Treatment of HER2-overexpressing breast cancer

J. Baselga*
Massachusetts General Hospital Cancer Center, Boston, MA, USA

The HER family of receptors consists of four closely related type 1 transmembrane TK receptors: HER1 (EGFR), HER2, HER3 and HER4. Signalling via the HER family of receptors underpins the majority of the intricate array of cellular activities on which cell survival and functionality depend. Aberrant HER2 expression and/or functionality have been implicated in the evolution of breast cancer and this receptor has proved to be a potent target for anticancer therapies, including antibody-based therapies to prevent ligand binding, dimer formation or the recruitment of antibody-dependent cell-mediated cytotoxicity, and direct kinase inhibition to prevent molecular activation and recruitment of downstream signalling partners. Novel strategies against HER2 include HER tyrosine kinase inhibitors, HSP90 inhibitors and antibody–chemotherapy conjugates. This latter approach is exemplified by T–DM1, a potent antibody that has a good safety profile and that has shown remarkable activity in patients with advanced disease. In addition, pertuzumab, an mAb that directly inhibits the formation of HER2 dimers including the HER2:HER3 dimer, offers a unique mechanism of HER3 inhibition. All these approaches have shown substantial clinical activity in patients refractory to trastuzumab. It is anticipated that with the increased availability of novel anti-HER2 agents together with a better understanding of the mechanisms of resistance to anti-HER2 agents we should be able to further improve the outcome of patients with HER2 breast cancer. There will also be an increasing tendency towards moving the study of these agents to earlier stages of the disease, namely in the adjuvant and neoadjuvant setting.

Key words: Breast cancer, HER2, monoclonal antibodies, tyrosine kinase inhibitors, resistance

The human epidermal growth factor (HER) family of transmembrane receptors are potent mediators of normal cell growth and development [1, 2]. This family of receptors consists of four closely related type 1 transmembrane tyrosine kinase (TK) receptors: HER1 (epidermal growth factor receptor; EGFR), HER2, HER3 and HER4. Each receptor comprises an extracellular domain where ligand binding occurs, an α-helical transmembrane segment and an intracellular protein TK domain. Receptor dimerization (pairing) is an essential requirement for HER function and for the signalling activity of all HER receptors. Dimerization can occur between two different HER receptors (heterodimerization) or between two molecules of the same receptor (homodimerization). However, HER receptors normally exist as inactive monomers with the molecules folded in such a way as to prevent dimerization [3]. Not all HER dimers offer equivalent signalling potency; homodimers achieve weak signal perpetuation compared with heterodimers. HER1, HER2 and HER3 are all implicated in the development and progression of cancer; the role of HER4 in oncogenesis remains less well defined. The HER2:HER3 heterodimer is considered the most potent HER receptor pair with respect to strength of interaction, ligand-induced tyrosine phosphorylation and downstream signalling, and functions as an oncogenic unit. Indeed, HER3 may be a necessary partner for HER2 to act as an oncogene in tumours overexpressing HER2. Taking together their oncogenic capacity and their frequently aberrant expression or dysregulation in human tumours, members of the HER family are established targets for approved therapeutics and continue to be targets for the development of novel anticancer agents, including monoclonal antibodies (mAbs) that target the extracellular regions of the receptor and small-molecule TK inhibitors (TKIs) that prevent signal transduction via the receptor TK domain.

HER2 overexpression occurs in ∼15%–20% of patients with breast cancer and is associated with aggressive disease and decreased survival [4]. As mentioned above, taking in consideration the role that HER2 plays in breast cancer, a number of therapeutic approaches have been developed against HER2 including monoclonal antibodies and small molecule TKIs. Trastuzumab, the first anti-HER2 agent that was developed, is a humanized mAb that binds to the extracellular, juxtamembrane portion of the HER2 receptor and suppresses HER2 signalling activity, resulting in inhibition of downstream signalling pathways, cell cycle arrest and a reduction in angiogenesis. As a result of antibody binding to the HER2 extracellular domain, trastuzumab also leads to antibody-dependent cell-mediated cytotoxicity (ADCC), and prevents HER2 receptor extracellular domain cleavage—an additional activation mechanism for HER2. In patients with HER2-amplified breast tumours, trastuzumab has anti-tumour activity [5, 6] and improves survival in the first-line setting when combined with chemotherapy in patients with advanced disease [7, 8]. The administration of trastuzumab in the initial postoperative (adjuvant) setting, in combination and/or sequentially after chemotherapy, results in an improvement in...
disease-free survival, with a 50% reduction in the risk of relapse, as well as improving the overall survival of patients with HER2-positive advanced and early-stage breast cancer [9, 10].

Small-molecule TKIs directly inhibit the kinase activity of HER receptors. These agents bind to the ATP binding site, preventing signal transduction of both the ras/Raf1 MAPK and PI3K/Akt pathways, leading to an increase in apoptosis and decrease in cellular proliferation. The most clinically advanced anti-HER2 TKI is lapatinib, a dual HER2 and HER1 TKI [11]. Lapatinib has shown activity as a single agent and in combination with chemotherapy in HER2-positive advanced breast cancer. In the registration phase III study, the addition of lapatinib was demonstrated to be superior to capecitabine alone in terms of time to progression (8.4 versus 4.4 months; \( P < 0.001 \)) [12]. In addition, although not statistically significant, a lower incidence of central nervous system metastases was noted in the lapatinib group. As lapatinib is a small molecule that could penetrate the blood–brain barrier, it is now being extensively studied for the treatment and prevention of central nervous system metastasis [13].

The results of this trial led to lapatinib’s regulatory approval for use in combination with capcitabine in patients with advanced HER2-positive breast cancer who have previously received chemotherapy with an anthracycline and a taxane or have received trastuzumab. Currently, the role of lapatinib in early disease is being explored in both the adjuvant and the neoadjuvant setting in two studies that are being conducted in parallel, the ALTTO and the NeoALTTO (Figure 1). Accrual to NeoALTTO has now been completed.

**novel anti-HER2 therapies**

Despite the advances that have been brought by trastuzumab and lapatinib, patients with HER2-positive metastatic breast cancer who initially respond to trastuzumab or lapatinib will eventually develop disease progression. There are an emerging number of alternatives on how to treat these patients (Figure 2). An option to be considered is retreatment with trastuzumab combined with a different chemothapeutic agent or regimen that the patient has progressed on. A randomized study in patients with documented disease progression while receiving trastuzumab compared the efficacy of continued administration of trastuzumab in combination with capecitabine versus capecitabine alone. The continuation of trastuzumab resulted in an increased response rate (48.9% versus 24.6%) and progression-free survival (PFS) (8.5 versus 5.6 months, hazard ratio (HR) = 0.71) [14]. In patients who have progressed to trastuzumab, improved clinical outcome has also been achieved with the combination trastuzumab and lapatinib in comparison with the administration of lapatinib alone [15]. This combination is of particular interest since it is devoid of chemotherapy.

Another strategy to overcome trastuzumab resistance is through the concurrent blockade of multiple HER family members. As mentioned above, HER2 becomes activated via the formation of homodimers with other HER2 receptors or by heterodimerization with other members of the HER receptor family as a result of ligand binding. Pertuzumab is a humanized mAb that binds to an epitope in domain II, the dimerization domain of the HER2 receptor extracellular domain, which is a region of HER2 distinct from the domain IV binding site of trastuzumab [16, 17]. Pertuzumab inhibits HER2 dimerization by sterically preventing HER2 pairing with other HER receptors, including HER3 [18, 19]. Pertuzumab has demonstrated potent activity in vitro and in vivo and the combination of pertuzumab with trastuzumab has been shown to synergistically inhibit the survival of breast tumour cells in vitro and in vivo [2]. Notable clinical benefit has been observed in patients with HER2-overexpressing breast cancer who had disease progression
during trastuzumab therapy [20, 21]. In the largest study, the efficacy of pertuzumab plus trastuzumab was evident by a clinical benefit rate of 50% and an overall response rate of 24% and this treatment combination did not result in enhanced cardiac toxicity [21]. This drug combination is now being studied in combination with chemotherapy in the Cleopatra study, a randomized phase III study in the first-line setting comparing trastuzumab and docetaxel 6 pertuzumab. It is also being studied in the neoadjuvant setting in the Neosphere trial.

A different approach to ‘naked’ antibody targeting of HER2 is the use of antibody–drug conjugates. Trastuzumab–DM1 (T–DM1) consists of the trastuzumab antibody conjugated to the potent anti-microtubule agent DM1 (a maytansine derivative) [22]. Upon binding to the HER2 receptor, T–DM1 is internalized and DM1 is released intracellularly, thereby delivering highly potent chemotherapy only to HER2-overexpressing cells. T–DM1 has demonstrated encouraging anti-tumour activity in preclinical and early clinical studies with response rates close to 50% and with very limited toxic effects [23]. These results have prompted the study of T–DM1 in the first-line and second-line settings where it is being compared with lapatinib plus capecitabine in a phase III randomized study. Inhibitors of the heat shock protein 90 (HSP90), a molecular chaperone required to maintain HER2 integrity and function, have also been shown to be active against HER2 breast cancer due to enhanced receptor degradation. Initial studies with the HSP90 inhibitor tanespimycin and other HSP90 inhibitors have demonstrated anti-tumour activity and tolerability in combination with trastuzumab in patients with trastuzumab-refractory breast cancer [24].

Second-generation TKIs include the HER2 irreversible inhibitor HKI-272 (neratinib). In a recently reported phase II study with single-agent neratinib, the median PFS was 23 weeks and the objective response rate was 26% in patients previously treated with trastuzumab. Of interest, in patients who had not received trastuzumab, the median PFS doubled to 40 weeks and the response rate reached 56% [25]. Neratinib is currently being studied in combination with chemotherapy.

**resistance to anti-HER2 agents**

Resistance to anti-HER2 agents may occur as a result of aberrant activation of signalling pathways downstream of the receptor, such as the presence of activating PI3K mutations or loss of function of the phosphatase PTEN [26, 27]. In those cases, the addition of PI3K and/or mTOR inhibitors restores sensitivity to anti-HER2 agents in preclinical models [28]. Results from two phase I trials in which the mTOR inhibitor everolimus was combined with trastuzumab and paclitaxel [29] or vinorelbine [30] indicate that the addition of everolimus may overcome resistance to trastuzumab. The combination of an mTOR inhibitor with chemotherapy or trastuzumab seems highly active, with complete responses achieved in a few patients and partial responses or stable disease in the majority of patients. Although combinations with mTOR inhibitors and trastuzumab are more advanced in the clinic, combinations with PI3K inhibitors and trastuzumab are also underway.

Another potential mechanism of resistance to HER2 mAbs is the presence of truncated forms of the HER2 receptor that lack the trastuzumab binding domain. Tumours that harbor the truncated receptor, also known as p95HER2, are not vulnerable to trastuzumab, but are sensitive to the HER1/HER2 TKI lapatinib, which binds the receptors intracellularly [31, 32]. These truncated receptors are also client receptors to HSP-90 and they remain sensitive to HSP90 inhibitors [33]. In a similar conceptual fashion, loss of HER2 amplification has recently been documented in patients with significant

![Figure 2. Novel anti-HER2 therapies.](image-url)
residual disease after neoadjuvant administration of trastuzumab, and this change is associated with poor relapse-free survival [34]. The implications of these findings are that tumour identified at the time of surgery should be reassessed for HER2 status.

**future directions**

In the last decade we have witnessed remarkable progress in the therapy of HER2-positive breast cancer with the availability of trastuzumab in the advanced and adjuvant disease settings. Yet, primary and acquired resistance to trastuzumab remains a formidable challenge. Improved insights into the biology of the HER family of receptors have led to novel and active anti-HER2 therapies including TKIs, antibody-based conjugates and HSP90 inhibitors. We have also learned that combined anti-HER2 therapies may be superior to single-agent strategies. For example, there is evidence that in patients who have progressed on trastuzumab, combining lapatinib and trastuzumab is superior to administering lapatinib alone [15]. The same may be true for the HSP90 inhibitors and for pertuzumab.

One considerable clinical challenge may be to overcome not only the genetic heterogeneity of human tumours, which rarely depends on the aberrant expression or functioning of a single receptor kinase or pathway, but also the considerable capacity for compensatory cross-talk between pathways. Combination therapy with more than one targeted agent may offer the most potent approach to tumour control and may delay or avoid the acquisition of resistance to individual therapies. An example of one such rational potential combination, based on complementary mechanisms of action, is that of trastuzumab and pertuzumab; trastuzumab binds to HER2 and suppresses its signalling capability as part of a dimer, and pertuzumab prevents HER2 dimers forming, including HER2:HER3. Indeed preclinical data support the synergistic activity of these two antibodies [35].

A rational approach is now needed to design and evaluate potential combinations that target multiple and/or pivotal ‘players’ in oncogenic signalling cascades. Promising results have been reported for PI3K hyperactivation-mediated resistance to lapatinib and trastuzumab [27], which was overcome by the addition of a dual inhibitor of both mTOR and PI3K. Such combinations with HER2-targeted agents should continue to be explored.

Finally, the early testing of new agents has been relegated to heavily pretreated patients, not an ideal setting as these tumours may have already evolved to a state of high resistance to any type of therapy. In this regard, pilot studies of novel anti-HER2 agents in the preoperative setting in breast cancer are increasingly being conducted because they satisfy the need for tumour profiling and for a molecular and clinical readout in a patient population unaffected by prior therapies. This is exemplified by the NeoALTTO study and within the Breast International Group, additional exploration of novel HER2 therapies are being planned in the neoadjuvant setting.

**disclosure**

The author has acted as a consultant to Exelixis, Novartis, Roche and Merck.

**references**


