Breast cancer treatment has entered the translational era with the increasing emergence of rationally designed molecular therapeutics, particularly those that target members of the epidermal growth factor receptor (EGFR) human epidermal growth factor receptor (HER) family. The HER-2-targeted agents trastuzumab and lapatinib are now in routine clinical practice and have significantly improved the prognosis for patients with HER-2-positive breast cancer. The development of trastuzumab (Herceptin™), the HER-2 monoclonal antibody, for the treatment of HER-2-positive breast cancer is one of the key examples of the success that can be achieved with rationally designed molecularly targeted therapeutics. In contrast, targeting EGFR in breast cancer has not, as yet, produced positive results in clinical trials. The success of trastuzumab is in part attributable to the identification of the appropriate HER-2-positive patient population for treatment with this agent, whereas appropriate molecularly defined subtypes have not yet been identified for EGFR-targeted therapy of breast cancer.

**EGFR and HER-2 in Breast Cancer**

The EGFR/HER family of tyrosine kinases plays an important role in the development and progression of breast cancer. It includes four known members: EGFR (HER-1 or erbB1), HER-2 (neu or erbB2), HER-3 (erbB3) and HER-4 (erbB4). Signalling from these receptor tyrosine kinases is triggered by binding of specific ligands, including EGF, transforming growth factor-α (TGF-α), amphiregulin, epiregulin, betacellulin, heparin-binding EGF-like growth factor (HB-EGF) and neuregulins 1–4. Ligands for EGFR, HER-3 and HER-4 are frequently expressed in breast cancer. No ligands for HER-2 have been identified, and analysis of the crystal structure of HER-2 suggests that the receptor is constitutively poised in an active conformation and is capable of forming heterodimers with other ligand-activated HER receptors.

The overexpression of both EGFR and HER-2 has been associated with poor prognosis in breast cancer. The HER-2 gene is amplified in approximately 20–25% of breast cancers, and these HER-2-positive tumours constitute a distinct subtype of breast cancer, as demonstrated by recent microarray-based classification of the disease. Although the EGFR protein is frequently overexpressed in breast cancer, EGFR gene amplification is reported in fewer than 10% of breast tumours. EGFR is frequently expressed with HER-2 in breast cancer and co-overexpression of both receptors is associated with worse outcome. EGFR is also frequently overexpressed in basal-like breast cancers, which lack the expression of oestrogen receptor (ER), progesterone receptor (PR) and HER-2 (‘triple-negative’). In ER-positive breast tumours, increased expression of EGFR is associated with resistance to endocrine therapy.

**HER-2 Inhibitors**

Trastuzumab (Herceptin, Genentech), a recombinant humanised monoclonal antibody against HER-2, binds to the extracellular domain of HER-2 and inhibits tumour cell proliferation, enhances response to chemotherapy and induces antibody-dependent cellular cytotoxicity. It is approved for the treatment of both metastatic and early-stage HER-2-positive breast cancer. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) recently issued guidelines to improve the accuracy of HER-2 testing in breast cancer. The guidelines define HER-2 positivity as an immunohistochemical staining (IHC) score above three, more than six copies of the HER-2 gene by fluorescence in situ hybridisation (FISH) or a FISH ratio (HER-2 gene to chromosome 17) greater than 2.2. Values of two plus for IHC, between four and six gene copies by FISH or FISH ratio of 1.8–2.2 are considered intermediate and require additional testing.

As a single agent, trastuzumab achieved overall clinical responses of 11–15% in patients with pre-treated HER-2-positive metastatic breast cancer. The pivotal phase III trial of trastuzumab in combination with chemotherapy demonstrated an overall response rate of approximately 50% (versus 32%), a longer duration of response (time to progression 7.4 versus 4.6 months), a longer survival (overall survival 25.1 versus 20.3 months) and a 20% reduction in risk of death compared with chemotherapy alone in HER-2-overexpressing metastatic breast cancer (see Table 1). As a single agent, trastuzumab achieved overall clinical responses of 11–15% in patients with pre-treated HER-2-positive metastatic breast cancer. The pivotal phase III trial of trastuzumab in combination with chemotherapy demonstrated an overall response rate of approximately 50% (versus 32%), a longer duration of response (time to progression 7.4 versus 4.6 months), a longer survival (overall survival 25.1 versus 20.3 months) and a 20% reduction in risk of death compared with chemotherapy alone in HER-2-overexpressing metastatic breast cancer (see Table 1). The combination of lapatinib with trastuzumab has led to the approval of a new treatment strategy for patients with HER-2-positive metastatic breast cancer.

**References**

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5. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


7. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

8. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


13. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


15. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


17. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

18. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


22. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

23. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


25. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


27. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

28. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

29. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

30. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

31. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

32. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

33. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

34. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

35. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

36. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

37. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

38. Crown Subbed EU.qxp 22/5/09 10:19 Page 50


40. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

41. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

42. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

43. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

44. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

45. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

46. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

47. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

48. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

49. Crown Subbed EU.qxp 22/5/09 10:19 Page 50

50. Crown Subbed EU.qxp 22/5/09 10:19 Page 50
and anthracyclines, which also cause cardiotoxicity. Therefore, the concurrent administration of trastuzumab and anthracyclines is not recommended. Pegylated liposomal doxorubicin (PLD) shows similar activity to conventional doxorubicin, but is associated with a significantly lower risk of cardiotoxicity.25 Two phase II studies have examined the concurrent administration of PLD and trastuzumab in HER-2-positive metastatic breast cancer and showed that while some patients experienced a reduction in left ventricular ejection fraction (LVEF), none of the patients developed congestive heart failure.26,27 A number of ongoing randomised trials are evaluating the combination of PLD and trastuzumab in HER-2-positive breast cancer.28

The greatest clinical impact of trastuzumab is in the treatment of HER-2-positive early-stage breast cancer, where data from five randomised trials demonstrated a benefit of trastuzumab. The addition of trastuzumab to adjuvant therapy resulted in a 39–52% reduction in disease progression (see Table 2).29–32 A recent meta-analysis of the five adjuvant trials comparing adjuvant trastuzumab plus chemotherapy versus chemotherapy alone showed a significant reduction in mortality (p < 0.00001), recurrence (p < 0.00001) and rates of metastasis (p < 0.00001) for the trastuzumab-containing regimens.33 The first negative trial of trastuzumab-containing regimens was the study comparing trastuzumab to adjuvant therapy resulted in a 39–52% reduction in disease progression.28

In the BCRG006 adjuvant study, trastuzumab, docetaxel and carboplatin (TCH) was compared with doxorubicin/cyclophosphamide followed by docetaxel alone (AC-T) or in combination with trastuzumab (AC-TH). The TCH combination was derived from laboratory observations of synergy,36 and at the second interim analysis it showed similar efficacy to the AC-TH arm.37 Topoisomerase II alpha (TOP2A) co-amplification was detected in one-third of the HER-2-amplified tumours in the BCRG006 study.38 The fact that there was no difference in disease-free progression between the anthracycline and non-anthracycline-containing arms of the study37 suggests that in tumours with co-amplification of both genes, targeting HER-2 with trastuzumab or sequential trastuzumab plus chemotherapy versus chemotherapy alone showed a significant reduction in mortality (p < 0.00001), recurrence (p < 0.00001) and rates of metastasis (p < 0.00001) for the trastuzumab-containing regimens.33 The first negative trial of trastuzumab in the adjuvant setting was presented at the 2007 San Antonio Breast Cancer Symposium. The PACS-04 study was a double randomisation study comparing fluorouracil plus epirubicin and cyclophosphamide with epirubicin and docetaxel and assessing trastuzumab for one year following adjuvant chemotherapy in HER-2-positive patients. At a mean follow-up time of four years there was no significant difference in disease-free survival (hazard ratio [HR] 0.86) or overall survival (HR 1.27) in the trastuzumab arm compared with the control arm.39 Examination of hazard estimates over four years indicated that HRs favoured the trastuzumab arm up until 18 months (HR 0.57), but this benefit was lost in the following 30 months (HR 1.04). Concurrent administration of trastuzumab with chemotherapy may be more beneficial in adjuvant therapy than sequential treatment.39 The unplanned interim analysis of the N9831 adjuvant trial, which randomised patients to trastuzumab, concurrent trastuzumab or sequential trastuzumab with chemotherapy, also suggested a greater benefit for concurrent trastuzumab; the results of this trial may provide an answer to the sequential versus concurrent question.

In the PACS-04 trial of trastuzumab plus anastrozole compared with anastrozole alone in post-menopausal women with ER-positive HER-2-positive metastatic disease (the Trastuzumab in Dual HER2-ER-positive metastatic breast cancer [TanDEM] study) showed improvements in progression-free survival, clinical response and time to progression in the trastuzumab plus anastrozole arm.40 However, the overall response rates were significantly lower than those observed for combinations of trastuzumab with chemotherapy.41

Combinations of trastuzumab with hormonal therapies such as tamoxifen and aromatase inhibitors are also currently under investigation.39 A phase III trial of trastuzumab plus anastrozole compared with anastrozole alone in post-menopausal women with ER-positive HER-2-positive metastatic disease (the Trastuzumab in Dual HER2-ER-positive metastatic breast cancer [TanDEM] study) showed improvements in progression-free survival, clinical response and time to progression in the trastuzumab plus anastrozole arm.40 However, the overall response rates were significantly lower than those observed for combinations of trastuzumab with chemotherapy.41

Induction of antibody-dependent cellular cytotoxicity (ADCC) may be an important mechanism of action for trastuzumab, and several studies are examining whether increasing natural killer cell numbers and activity using interleukin-2 or interleukin-12 could increase efficacy by enhancing the trastuzumab-induced ADCC.42,43 Other issues to be resolved regarding the use of trastuzumab in HER-2-positive breast cancer include scheduling...
Breast Cancer

Pertuzumab (Omnitarg™, Genentech) is also a humanised monoclonal antibody against HER-2, but it differs from trastuzumab in its mechanism of action. Pertuzumab binds to domain two of HER-2, stERICally blocking a binding pocket necessary for receptor dimerisation and signalling. In vitro studies have shown that pertuzumab combined with trastuzumab is synergistic in HER-2-overexpressing cell lines. A phase II study in patients with metastatic breast cancer with low expression of HER-2 reported that pertuzumab was safe but showed limited activity as a single agent in this population. A phase II trial of pertuzumab combined with trastuzumab in patients who did not respond to trastuzumab showed a complete response rate of 3% (one of 33 patients), a partial response rate of 15% (five of 33 patients) and stable disease in approximately 50% (17 of 33) patients. A phase III study to evaluate trastuzumab and docetaxel alone or in combination with pertuzumab in previously untreated HER-2-positive metastatic breast cancer is currently recruiting patients (www.clinicaltrials.gov).

Lapatinib (Tykerb™, GlaxoSmithKline) is an orally administered small-molecule tyrosine kinase inhibitor of both HER-2 and EGFR that binds reversibly to the adenosine triphosphate (ATP)-binding site of both receptors and blocks receptor phosphorylation and activation. A phase I study in heavily pre-treated patients with metastatic carcinomas established that lapatinib is well tolerated at doses of 550–1,600mg daily, and no lapatinib-related cardiac dysfunction was observed in the study. Two phase II trials of single-agent lapatinib have been conducted in refractory metastatic breast cancer: the first in HER-2-overexpressing metastatic breast cancer with progressive disease on prior trastuzumab-containing regimens, and the second in metastatic breast cancer patients who developed progressive disease following prior treatment with anthracyclines, taxanes or capecitabine (including HER-2-overexpressing trastuzumab-refractory and HER-2-non-overexpressing metastatic breast cancer in two separate arms). The overall response rates for these two studies were 22 and 14%, respectively. Combined biomarker analysis for the two studies suggested that metastatic breast cancer patients were more likely to respond if their tumours were ER- and PR-negative or HER-2-overexpressing.

A phase III trial of lapatinib plus capecitabine versus capecitabine alone was conducted in patients with HER-2-positive refractory advanced or metastatic breast cancer who were previously treated with anthracycline, taxane and trastuzumab (see Table 1). The study demonstrated a significant improvement in median time to progression for lapatinib and capecitabine versus capecitabine alone (6.2 versus 4.3 months; p=0.00013). Importantly, brain metastases were detected less frequently in patients in the combination arm than in the capecitabine-alone group (four versus 13 cases with central nervous system [CNS] involvement at first progression; p=0.045). This may be due to lapatinib’s ability to cross the blood-brain barrier. Trastuzumab cannot cross the blood-brain barrier, so is not effective for the treatment of brain metastasis. Cardiotoxicity was reported in only four of 160 patients receiving lapatinib and capecitabine. Thus, cardiotoxicity does not appear to be a significant problem with lapatinib treatment. In fact, a recent study has shown that lapatinib stimulated a metabolic stress response in human cardiac cells, which appears to offer protection against TNF-α-induced cell death. Diarrhoea is the most frequently reported adverse event in lapatinib clinical trials, and this may be due to gastrointestinal toxicity caused by EGFR inhibition. A recent analysis of 2,201 patients demonstrated that lapatinib-induced diarrhoea is usually low-grade, with grade 3 diarrhoea occurring in <10% of patients.

Single-agent lapatinib has also been evaluated in a phase II study in patients with relapsed or refractory inflammatory breast cancer. Patients were divided into two cohorts: cohort A included patients with HER-2-positive disease and cohort B included patients with EGFR-positive/HER-2-negative disease. A 50% (15 of 30 patients) response rate was reported in cohort A compared with a 7% (one of 15 patients) response rate in cohort B. Tumours co-expressing pHER-2 and pHER-3 were more likely to respond to lapatinib.

Several trials of lapatinib in combination with trastuzumab, chemotherapy and endocrine therapies in metastatic breast cancer are currently accruing patients. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) phase III study that commenced in 2007 will compare trastuzumab alone, lapatinib alone, trastuzumab followed by lapatinib and trastuzumab combined with lapatinib in women with HER-2-overexpressing primary breast cancer (www.alttotrials.com). The trial employs two study designs: in the first design, all (neo)adjuvant chemotherapy is completed prior to administration of the study treatments; in the second design, all anthracycline-based (neo)adjuvant chemotherapy is completed prior to the administration of the study treatments, while paclitaxel is given concurrently with the study treatments. A companion neo-adjuvant study, Neo-ALTTO, will compare treatment with lapatinib, trastuzumab and the combination with paclitaxel prior to surgery (www.alttotrials.com/nealto.php).

EGFR Inhibitors

Gefitinib (Iressa™, AstraZeneca) is a small-molecule tyrosine kinase inhibitor of EGFR that binds reversibly to the ATP-binding site of EGFR. Phase II trials of gefitinib in refractory metastatic breast cancer yielded disappointing response rates of 2–13%. An examination of biological profiles in the tumour tissues from a phase II study of gefitinib in advanced breast cancer suggested that the lack of activity was due to a lack of EGFR dependence in the tested population. A phase II study of gefitinib in combination with paclitaxel and carboplatin as first-line therapy for advanced breast cancer showed no benefit of addition of gefitinib based on previously reported response for the combination of paclitaxel and carboplatin alone.

A phase II trial of docetaxel in combination with gefitinib as first-line treatment was conducted in patients with metastatic breast cancer and produced an overall response rate of 54% (22 of 41 patients) with five complete responses, 17 partial responses and six patients with stable disease. The authors conclude that this is an active and generally
Developments in Breast Cancer Treatment – EGFR and HER-2 Inhibitors

Table 4: Novel EGFR and HER-2 Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Category</th>
<th>Targets</th>
<th>Status (<a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>)</th>
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<td>Panitumumab</td>
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<td>EGFR</td>
<td>Approved for colorectal cancer</td>
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<td>TKI – reversible</td>
<td>HER-2</td>
<td>Phase III trials in breast cancer</td>
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<tr>
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<td>HER-2</td>
<td>Phase I trials in breast cancer</td>
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<td>CI-1033</td>
<td>TKI – irreversible</td>
<td>Pan-HER</td>
<td>Phase II trials in breast and lung cancer</td>
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TKI = tyrosine kinase inhibitor; EGFR = epidermal growth factor receptor; VEGFR = vascular endothelial growth factor receptor; HER-2 = human epidermal growth factor receptor-2.

Table 4: Novel EGFR and HER-2 Inhibitors

Dual Targeting of EGFR and HER-2 in Breast Cancer

Evidence from cell line models and patient samples suggests that dual targeting of EGFR and HER-2 may be beneficial for HER-2-overexpressing breast cancer. EGFR is frequently expressed in HER-2-positive tumours and the co-expression of EGFR and HER-2 is associated with a worse prognosis. Combinations of the EGFR inhibitors gefitinib or cetuximab with trastuzumab have been tested in cell line models and show that the response to trastuzumab was enhanced by the dual targeting of EGFR and HER-2. A phase III study of trastuzumab and gefitinib in HER-2-overexpressing breast cancer was completed. Disappointingly, few responses were observed and these occurred only in previously untreated patients (two of 28). Time to progression was shorter than reported for trastuzumab alone. However, Normanno et al. argued that the dose used in the phase II part of the study may have been too low. A phase I/II trial of docetaxel in combination with gefitinib and trastuzumab for metastatic breast cancer is currently open. A phase II trial of erlotinib in combination with trastuzumab as first-line treatment for HER-2-positive metastatic breast cancer is currently ongoing, as is a phase I study of cetuximab in combination with trastuzumab. Combinations of trastuzumab and lapatinib might offer advantages in HER-2-positive breast cancer due to dual targeting of the extracellular and the kinase domains of HER-2 in addition to targeting EGFR. Results of a phase III trial of lapatinib in combination with trastuzumab versus lapatinib monotherapy in heavily pre-treated HER-2-positive metastatic breast cancer patients progressing on trastuzumab treatment were presented at the ASCO 2008 conference. Treatment with the combination of trastuzumab and lapatinib significantly improved progression-free survival (12.0 versus 8.1 weeks, HR 0.73; p=0.008) compared with lapatinib alone. Several trials of lapatinib and trastuzumab with chemotherapy and/or hormone therapy are under way (see Table 3).

Novel EGFR and HER-2 Inhibitors

Several novel EGFR and HER-2 inhibitors are currently in pre-clinical and clinical development. The inhibitors include monoclonal antibodies and both reversible and irreversible small-molecule tyrosine kinase inhibitors of HER-2, dual inhibitors of EGFR and HER-2 and pan-HER inhibitors (see Table 4).
Novel Strategies Targeting EGFR/HER-2 Signalling

**ADAM Protease Inhibition**

Signalling through EGFR is controlled by the release of ligands such as EGF, TGF-α, amphiregulin, HB-EGF and epigen. While these ligands do not bind directly to HER-2, they influence HER-2 signalling via heterodimerisation with EGFR and HER-3. The release of EGFR/HER ligands is mediated by a disintegrin and metalloproteases (ADAM) proteases. Recent findings suggest that increased production of the ligands confers resistance to both trastuzumab and EGFR inhibitors. ADAM17 is also responsible for cleavage of the extracellular domain of HER-2, which is associated with resistance to trastuzumab. Therefore, the inhibition of specific ADAMS could improve response to HER-2- and EGFR-targeted therapies. A dual ADAM10/ADAM17 inhibitor, INC87839 (inotec), is currently in phase I/II trials in HER-2-positive breast cancer.

**Hsp90 Inhibition**

Hsp90 is a molecular chaperone that regulates the stability and maturation of HER-2 and is expressed at higher levels in breast tumours than non-cancerous breast tissue. The inhibition of Hsp90 has been shown to downregulate HER-2 and improve responses to trastuzumab in vitro. A phase I study of tanezumab (17-AAG) plus trastuzumab has been completed. The combination was well tolerated and showed antitumour activity in patients with trastuzumab-refractory HER-2-positive breast cancers. Hsp90 inhibitors may also have therapeutic benefits in HER-2-negative breast cancers, as Hsp90 inhibition targets a number of key signalling pathways including Akt.

**Targeting Downstream Signalling Pathways**

The PI3 kinase/Akt pathway is activated by EGFR and HER-2 signalling, and is a key survival and antiapoptotic signal transduction pathway. Targeting components of the Akt pathway may inhibit the growth of EGFR or HER-2-dependent tumour cells and may enhance response to EGFR and HER-2 inhibitors. The mammalian target of rapamycin (mTOR) is a key downstream signalling intermediate in the Akt pathway. The inhibition of mTOR potentiates response to gefitinib and cetuximab in EGFR-positive cell lines and blocks multiple stages in HER-2-induced tumour progression in a transgenic mouse model of HER-2-positive breast cancer. Initial results from phase I studies show that the mTOR inhibitor everolimus (RAD001) is well tolerated in combination with trastuzumab and chemotherapy, and shows promising activity in heavily pre-treated patients with HER-2-overexpressing metastatic breast cancer. Combinations of everolimus with erlotinib, trastuzumab, lapatinib and chemotherapy are currently under investigation in clinical trials.

**Conclusions**

The role of HER-2 antagonists in the treatment of HER-2-positive breast cancer is now well established. Trastuzumab, and more recently lapatinib, have had a significant impact on improving outcome for HER-2-positive breast cancer patients. In addition to the studies examining combinations of trastuzumab and lapatinib, another exciting area in the development of therapies for HER-2-positive breast cancer will be the addition of antiangiogenic therapies such as bevacizumab to HER-2 inhibitors. Another key area in the development of treatment strategies for HER-2 breast cancer will be understanding mechanisms of resistance and developing strategies to overcome resistance. The future of EGFR inhibitors in breast cancer is less certain and requires better definition of the patient populations that are likely to benefit from EGFR inhibition. EGFR inhibition may play an important role in overcoming resistance to endocrine therapies and may provide the first targeted therapy option for the treatment of triple negative breast cancer. Dual targeting of EGFR and HER-2 may also provide added benefit for a subset of HER-2-positive patients whose tumours also express EGFR.