Developments in Breast Cancer Treatment—Epidermal Growth Factor Receptor and Human Epidermal Growth Factor Receptor 2 Inhibitors

a report by

Norma O'Donovan, PhD[1] *and* **John Crown, MD, MPH**[1,2]

1. National Institute for Cellular Biotechnology, Dublin City University; 2. Department of Medical Oncology, St Vincent's University Hospital, Dublin

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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.[1] It includes four known members: EGFR (HER-1 or erbB1), HER-2 (neu or erbB2), HER-3 (erbB3), and HER-4 (erbB4). Signaling 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.[2] Ligands for EGFR, HER-3, and HER-4 are frequently expressed in breast cancer.[3,4] 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.[5]

The overexpression of both EGFR and HER-2 has been associated with poor prognosis in breast cancer.[6–10] The HER-2 gene is amplified in approximately 20–25% of breast cancers, and these HER-2-positive tumors constitute a distinct subtype of breast cancer, as demonstrated by recent microarray-based classification of the disease.[11] Although the EGFR protein is frequently overexpressed in breast cancer, EGFR gene amplification is reported in fewer than 10% of breast tumors.[12,13] EGFR is frequently expressed with HER-2 in breast cancer and co-overexpression of both receptors is associated with worse outcome.[14] EGFR is also frequently overexpressed in basal-like breast cancers, which lack the expression of estrogen receptor (ER), progesterone receptor (PR), and HER-2 ('triple negative'). In ER-positive breast tumors, an increased expression of EGFR is associated with resistance to endocrine therapy.[15,16]

HER-2 Inhibitors

Trastuzumab (Herceptin™, Genentech), a recombinant humanised monoclonal antibody against HER-2, binds to the extracellular domain of HER-2 and inhibits tumor cell proliferation, enhances response to chemotherapy, and induces antibody dependent cellular cytotoxicity.[17] It is approved for the treatment of both metastatic and early-stage HER-2-positive breast cancer.[18] 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.[19] 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* hybridization (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 a FISH ratio of 1.8–2.2 are considered intermediate and require additional testing. As a single agent, trastuzumab achieved clinical overall responses of 11–15% in patients with pre-treated HER-2-positive metastatic breast cancer.[20–22] 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 for death compared with chemotherapy alone in HER-2-overexpressing metastatic breast cancer (see *Table 1*).[23]

Combinations of trastuzumab with taxanes, platinum compounds, or vinorelbine are safe and show favorable efficacy.[24] The only significant toxicity associated with trastuzumab is cardiac toxicity, and this is particularly problematic when trastuzumab is administered with or following 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 for 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 randomized 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 randomized trials demonstrated a benefit of trastuzumab. The addition of trastuzumab to adjuvant therapy resulted in a 39–52% reduction in disease recurrence (see

Table 1: Pivotal Trials of Trastuzumab and Lapatinib in HER-2-positive Metastatic Breast Cancer

Regimen	Setting	Phase	Number	ORR (%)	TTP (Months)	OS (Months)	References
H	MBC that had progressed after chemotherapy	II	222	15	9.1	13	Cobleigh et al.[22]
AC ± H or T ± H	First-line MBC	III	469	50 versus 32 p<0.001	7.4 versus 4.6 p<0.001	25.1 versus 20.3 p=0.01	Slamon et al.[23]
Capecitabine ± L	MBC that had progressed after hemotherapy plus H	III	324	24 versus 14 p=0.017	6.2 versus 4.3 p<0.001	15.6 versus 15.3 p=0.177	Geyer et al.[52] Cameron et al.[53]

ORR = overall response rate; TTP = time to progression; OS = overall survival; H = trastuzumab; A = anthracycline; C = cyclophosphamide; T = paclitaxel; L = lapatinib; MBC = metastatic breast cancer.

Table 2: Phase III Trials of Trastuzumab in Adjuvant Treatment of Early Breast Cancer

Trial	Regimen	Number	HR for DFS	HR for OS	Reference
HERA	Chemotherapy followed by observation or H (1 year)	3,387	0.54 (0.43–0.57) p<0.0001	0.74 (0.47–1.23) p=0.26	Piccart-Gebhart et al.[29]
B31 + N9831	AC-T ± H	3,351	0.48 (0.39–0.59) p<0.0001	0.67 (0.48–0.93) p=0.015	Romond et al.[30]
BCIRG006	AC-T ± H or TCarboH	3,222	AC-TH versus AC->T 0.61 (0.48–0.76) p<0.0001 TCH versus AC-T 0.67 (0.54–0.83) p=0.0003	AC-TH versus AC-T 0.59 (0.42–0.85) p=0.004 TCH versus AC-T 0.66 (0.47–0.93) p=0.017	Slamon et al.[31]
FinHER	D-FEC ± H or V-FEC ± H	231	0.42 (0.21–0.83) p=0.01	0.41 (0.16–1.08) p=0.07	Joensuu et al.[32]
PACS-04	FEC ± H or ED ± H	528	0.86 (0.61–1.22) p=0.41	1.27 (0.68–2.38) p=NA	Spielmann et al.[34]

HERA = the HERceptin® Adjuvant Trial; FinHER = the Finland Herceptin trial; HR = hazard ratio; DFS = disease-free survival; OS = overall survival; A = anthracycline; C = cyclophosphamide; T = paclitaxel; H = trastuzumab; Carbo = carboplatin; D = docetaxel; F = 5-fluorouracil; E = epirubicin; V = vinorelbine; NA = not available.

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 in the adjuvant setting was presented at the 2007 San Antonio Breast Cancer Symposium. The PACS-04 study was a double randomization study to compare fluorouracil plus epirubicin and cyclophosphamide with epirubicin and docetaxel, and to assess trastuzumab for one year following adjuvant chemotherapy in the 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.[34] Examination of hazard estimates over the four years indicated that HRs favored 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.[35] The unplanned interim analysis of the N9831 adjuvant trial, which randomized patients to no 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 for the sequential versus concurrent question.

In the BCIRG006 adjuvant study, trastuzumab, docetaxel, and carboplatin (TCH) was compared with doxorubicin/cyclophoshophamide 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.[31] Topoisomerase II alpha (TOP2A) co-amplification was detected in one-third of the HER-2-amplified tumors in the BCIRG006 study.[37] The fact that there was no difference in disease-free progression between the anthracycline and non-anthracycline-containing arms of the study[31] suggests that in tumors with co-amplification of both genes, targeting HER-2 with trastuzumab or TOP2A with anthracyclines achieves similar efficacy.[38] 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 (weekly versus every three weeks), the optimum duration of treatment, and whether to continue trastuzumab treatment beyond disease progression.[41]

Table 3: Ongoing Phase III Trials of Trastuzumab Compared or Combined with Lapatinib in HER-2-positive Breast Cancer

Regimen (NCI Identifier)	Setting
AC followed by T + H, L or H+L (NCT00486668)	Neoadjuvant therapy in operable invasive breast cancer
THL versus TH + placebo (NCT00272987)	Metastatic breast cancer
ALTTO – L, H, H followed by L or H+L (NCT00490139)	Adjuvant treatment in primary breast cancer
Neo-ALTTO – L+T versus H+T, versus concomitant LH+T (NCT00553358)	Neoadjuvant treatment in primary breast cancer

NCI = National Cancer Institute; A = anthracycline; C = cyclophosphamide; T = paclitaxel; H = trastuzumab; L = lapatinib.

Pertuzumab (Omnitarg™, Genentech) is also a humanized 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 dimerization and signaling.[44] *In vitro* studies have shown that pertuzumab combined with trastuzumab is synergistic in HER-2-overexpressing cell lines.[45] 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.[46] 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).[47] 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.[48] 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.[49] Two phase II trials of single-agent lapatinib have been conducted in refractory metastatic breast cancer: one 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, and 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.[50] Combined biomarker analysis for the two studies suggested that metastatic breast cancer patients were more likely to respond if their tumors were ER- and PR-negative, or HER-2-overexpressing.[51]

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*).[52] 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).[53] 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.[54] 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.[52] 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.[55] Diarrhea 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 diarrhea is usually low-grade, with grade 3 diarrhea occurring in <10% of patients.[56]

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. Tumors co-expressing pHER-2 and pHER-3 were more likely to respond to lapatinib.[57]

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/neoaltto.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%.[58] An examination of biological profiles in the tumor 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.[59] 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.[60]

A phase II trial of docetaxel in combination with gefitinib as first-line treatment was conducted in patients with metastatic breast cancer[61] 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 well-tolerated regimen in women with metastatic breast cancer who have not

Table 4: Novel EGFR and HER-2 Inhibitors

Inhibitor	Category	Targets	Status (www.clinicaltrials.gov)
Panitumumab	Monoclonal antibody	EGFR	Approved for colorectal cancer
CP-724,714	TKI—reversible	HER-2	Phase I/II trials in breast cancer
TAK165	TKI—irreversible	HER-2	Phase I trials in breast cancer
AEE-788	TKI—reversible	EGFR, HER-2 and VEGFR	Phase I/II trials in glioblastoma
BMS-599626	TKI—reversible	EGFR and HER-2	Phase I trials
Arry-334543	TKI—reversible	EGFR and HER-2	Phase I trials
BIBW2992	TKI—irreversible	EGFR and HER-2	Phase II trials in breast, lung, and head and neck cancer
HKI-272	TKI—irreversible	EGFR and HER-2	Phase II trials in breast and lung cancer
MP-412	TKI—irreversible	EGFR and HER-2	Phase I trials
CI-1033	TKI—irreversible	Pan-HER	Phase II trials in breast and lung cancer

TKI = tyrosine kinase inhibitor ; EGFR = epidermal growth factor receptor; VEGFR = vascular endothelial growth factor receptor; HER-2 = human epidermal growth factor receptor-2.

been previously treated for metastatic disease, and that the response rates observed are similar to those seen with taxanes combined with anthracyclines. Interestingly, ER-positive patients showed a 70% response rate, compared with a 21% rate in ER-negative patients, which may be attributable to the development of EGFR-dependent tamoxifen resistance following up to five years of tamoxifen treatment in the adjuvant setting.[61] A subsequent randomized phase II trial of docetaxel and gefitinib versus docetaxel plus placebo as first-line treatment in metastatic breast cancer showed no benefit for the addition of gefitinib.[62] A pre-operative trial of gefitinib alone or in combination with the aromatase inhibitor anastrozole was conducted in post-menopausal patients with ER- and EGFR-positive primary breast cancer.[63] Partial responses were observed in 50% of patients (14 of 28) and 54% of patients (12 of 22) assigned to gefitinib and anastrozole or gefitinib alone, respectively.

Erlotinib (Tarceva™, OSI Pharmaceuticals) is also a small-molecule inhibitor of EGFR and binds reversibly to the ATP-binding site of EGFR. Similar to gefitinib, preliminary phase II trials of erlotinib in combination with chemotherapy showed disappointing response rates.[64] Combined with docetaxel, erlotinib produced a partial response rate of 55% compared with response rates of 29–53% that have previously been reported for docetaxel alone in metastatic breast cancer.[65] A number of studies of erlotinib in combination with chemotherapy and hormone therapies are ongoing in breast cancer. Two phase II studies of erlotinib in triple-negative breast cancer are currently recruiting patients, one with erlotinib as a single agent in metastatic triple negative breast cancer and the second in combination with neoadjuvant chemotherapy.

Cetuximab (Erbitux™, ImClone Systems Incorporated) is a monoclonal antibody that binds with high affinity to the extracellular domain of EGFR, competes for ligand binding, and blocks activation of the receptor by EGF or TGFα. It also induces antibody-mediated receptor dimerization, resulting in receptor downregulation. Results of a phase I trial of cetuximab in combination with paclitaxel in advanced breast cancer were recently reported. However, based on prohibitive dermatological toxicities and disappointing preliminary efficacy, the combination of paclitaxel and cetuximab was not considered promising in this population.[66] Cetuximab alone has recently been shown to have little activity in stage IV triple-negative breast cancer, while the combination of cetuximab with carboplatin achieved a response rate of 17% with a clinical benefit of 29%.[67] A number of other studies of cetuximab plus chemotherapy in triple-negative breast cancer are ongoing. The disappointing results observed in trials of EGFR inhibitors in breast cancer may be partly attributable to the majority of the studies being conducted in unselected patient populations. There is still hope that EGFR inhibitors will provide clinical benefit in specific subgroups of breast cancers, such as HER-2 and EGFR-positive tumors, triple-negative breast cancers, and ER-positive tumors that have developed resistance to hormone therapy.

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.[68,69] EGFR is frequently expressed in HER-2-positive tumors and co-expression of EGFR and HER-2 is associated with a worse prognosis.[14,70] 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.[71,72] A phase I/II study of trastuzumab and gefitinib in HER-2-overexpressing breast cancer was completed.[73] Disappointingly, few responses were observed and only in previously untreated patients (two of 28), and time to progression was shorter than reported for trastuzumab alone. However, Normanno et al.[74] argued that the dose used in the phase II part of the study may have been too low to see any benefit. 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 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.[75] 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 currently 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 Signaling

ADAM Protease Inhibition

Signaling through EGFR is controlled by the release of ligands such as EGF, TGF-alpha, amphiregulin, HB-EGF, and epigen. While these ligands do not bind directly to HER-2, they influence HER-2 signaling via heterodimerization with EGFR and HER-3. The release of EGFR/HER ligands is mediated by a disintegrin and metalloproteases (ADAM) proteases.[76] Recent findings suggest that increased production of the ligands confers resistance to both trastuzumab and EGFR inhibitors.[77,78] ADAM17 is also responsible for cleavage of the extracellular domain of HER-2,[79] which is associated with resistance to trastuzumab.[80] Inhibition of specific ADAMs could therefore improve response to HER-2 and EGFR targeted therapies. A dual ADAM10/ADAM17 inhibitor, INCB7839 (Incyte), is currently in phase I/II trials in HER-2-positive breast cancer.[81]

Hsp90 Inhibition

Hsp90 is a molecular chaperone that regulates the stability and maturation of HER-2[82] and is expressed at higher levels in breast tumors than in non-cancerous breast tissue.[83] The inhibition of Hsp90 has been shown to downregulate HER-2 and improve responses to trastuzumab *in vitro*.[84] A phase I study of tanespimycin (17-AAG) plus trastuzumab has been completed.[85] The combination was well tolerated and showed antitumor 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 signaling pathways including Akt.

Targeting Downstream Signaling Pathways

The PI3 kinase/Akt pathway is activated by EGFR and HER-2 signaling, 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 tumor cells and may enhance response to EGFR and HER-2 inhibitors. The mammalian target of rapamycin (mTOR) is a key downstream signaling intermediate in the Akt pathway. The inhibition of mTOR potentiates response to gefitinib and cetuximab in EGFR positive cell lines[86] and blocks multiple stages in HER-2-induced tumor progression in a transgenic mouse model of HER-2-positive breast cancer.[87] 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.[88,89] 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 tumors also express EGFR. ■

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