New Strategies in HER2-Overexpressing Breast Cancer: Many Combinations of Targeted Drugs Available
Vandana Abramson1,2, and Carlos L. Arteaga1,2,3

Abstract
The anti-HER2 drugs trastuzumab and lapatinib are increasingly changing the natural history of early and metastatic HER2-overexpressing breast cancer. Many other agents targeted against the HER2 signaling network are in clinical development, and these are or will soon be combined with the currently approved anti-HER2 therapies. We review herein recent data in support of the early use of combinations of agents targeted to the HER2 network as the most rational approach against this subtype of breast cancer. We propose that the optimal combination or combinations of anti-HER2 agents delivered early in the natural history of HER2þ breast cancer should close to eliminate acquired drug resistance, shorten the duration of therapy, and potentially dispense with the need of concurrent chemotherapy. Clin Cancer Res; 17(5); 952–8. ©2011 AACR.

Background
The antibody trastuzumab and the tyrosine kinase inhibitor (TKI) lapatinib are approved by the U.S. Food and Drug Administration (FDA) for the treatment of HER2-overexpressing (HER2þ) metastatic breast cancer (MBC). Trastuzumab binds to an epitope in the juxtamembrane region of the HER2 receptor. This binding induces uncoupling of ligand-independent HER2-HER3 heterodimers, inhibition of downstream signaling (1), and antibody-dependent cell-mediated cytotoxicity (ADCC; ref. 2). Several randomized adjuvant trials (NCCTG N9831, NSABP B-31, BCIRG 006, and HERA) have shown that the addition of trastuzumab to standard chemotherapy reduces disease recurrence and the risk of death compared with chemotherapy alone in patients with surgically resected tumors (3–5). In N9831, a recent interim analysis showed that the benefit of concurrent trastuzumab and chemotherapy was more pronounced than that of chemotherapy followed by trastuzumab (6). On the basis of these data, the addition of trastuzumab to adjuvant chemotherapy has become standard of care in women with HER2þ breast cancer (7, 8), suggesting adjuvant trastuzumab should be considered for these patients. However, the amount and type of chemotherapy to combine with the antibody in this setting is undetermined. Most of the adjuvant trials used 1 year of trastuzumab. One study delivered only 9 weeks of the antibody, whereas the HERA trial included an arm in which it was given for 2 years. In the first study, patients in the trastuzumab arm exhibited fewer overall recurrences and improved overall survival compared with patients treated with chemotherapy alone (9). Results in the 2-year arm in HERA are pending.

The dual epidermal growth factor receptor (EGFR)/HER2 TKI lapatinib is active as first-line monotherapy in patients with HER2þ MBC and, in combination with capecitabine, improves progression-free survival (PFS) compared with capecitabine alone (10, 11). In the latter registration trial, fewer brain metastases occurred in women in the combination arm than in the monotherapy arm, suggesting a potential difference between lapatinib and trastuzumab as it applies to recurrences in the central nervous system (CNS; 11). In the registration study and in a second randomized trial of paclitaxel ÷ lapatinib in patients with MBC, the clinical benefit of lapatinib was limited to patients with HER2 overexpression by immunohistochemistry (IHC) and/or FISH (12).

On the Horizon
HER2 testing, discordance, and conversion
The clinical activity of anti-HER2 agents has been limited to patients with HER2þ tumors as defined by intense membrane staining with HER2 antibodies in the majority of tumor cells (3þ by IHC) or ≥2 copies of the HER2 gene determined by FISH. In general, HER2 IHC and FISH correlate with each other (13–15). FISH seems superior...
susceptible to tissue fixation. For these reasons, excess stable DNA, of which the loci are measured by FISH, is less of antigenicity of the HER2 protein. Conversely, the more clinical trials (16). Intrinsic limitations of IHC are the to IHC to reproducibly assess tumors for HER2 overexpression at outside and/or local laboratories for entry into clinical trials (16). Intrinsic limitations of IHC are the variability in fixation methods and the impact of fixation of antigenicity of the HER2 protein. Conversely, the more stable DNA, of which the loci are measured by FISH, is less susceptible to tissue fixation. For these reasons, excess copies of the HER2 gene (so-called HER2 positivity) defined by FISH have gained ground as the standard to define odds of tumor dependence on HER2 and, therefore, response to HER2 antagonists (17).

A reanalysis in a central laboratory of NSABP B-31 showed that 9.7% of patients enrolled on the basis of a test done in a local laboratory had tumors that did not meet criteria for HER2 amplification by FISH or IHC (18). Notably, these patients also benefited from trastuzumab. This finding suggests that the local laboratory was correct and/or there is discordance in the levels of HER2 expression between micrometastases, of which the clinical recurrence defines the endpoint of adjuvant trials, and the primary tumor, in which the HER2 alteration was measured. This possibility is further suggested by a study in which 9 out of 24 patients with breast cancer whose primary tumor was HER2–acquired HER2 amplification in their circulating tumor cells (CTC) during cancer progression (19). In another study, 10% of patients who recur on adjuvant tamoxifen converted from HER2–to HER2+ in the relapsing tumor (20). Of note, however, the HER2 status of CTCs has yet to be linked to clinical outcome. On the basis of these data, the NSABP is initiating a phase III trial in which patients with 1+ or 2+ HER2 by IHC and no HER2 amplification by FISH will be randomized to adjuvant chemotherapy followed by 1 year of trastuzumab versus placebo.

Several studies have shown changes in HER2 status in patients treated with trastuzumab. Pectasides and colleagues showed that 37% of patients with HER2+ primary tumors no longer exhibited HER2 amplification in their metastatic lesions. Further, these patients exhibited a shorter time to progression (TTP) than the group that remained HER2+ (21). Hurley and colleagues reported that following treatment with neoadjuvant trastuzumab and chemotherapy, 43% of HER2+ tumors became HER2–as measured by FISH (22). Finally, Mintendorf and colleagues also reported that 32% of HER2+ tumors treated with neoadjuvant chemotherapy and trastuzumab “converted” to HER2–by FISH. Notably, at 37 months, relapse-free survival (RFS) was statistically superior in patients whose residual tumors retained HER2 amplification (23). These results have several implications. First, the change in HER2 status may reflect heterogeneity in HER2 expression in the primary tumor; the antioncogene therapy eliminates the HER2+ compartment and enriches for HER2–clones. Second, patients with HER2+ breast cancer who relapse after adjuvant or neoadjuvant anti-HER2 therapy should considering having their recurrent disease biopsied for reassessment of the HER2 status. Third, patients with ER+/HER2+ tumors at diagnosis that “converted” to HER2–after treatment are at high risk of early recurrence. Further, there are no clear adjuvant (targeted) therapy standards for these patients who, as a result, may exhibit a poor outcome.

**Antibody-chemotherapy conjugates**

Trastuzumab (T)–derivative of maytansine 1 (DM1) is an antibody–drug conjugate in which 1 molecule of trastuzumab is covalently bonded via a noncleavable linker to 3 molecules of the microtubule polymerization inhibitor DM1 (24). T-DM1 binds to HER2 with similar affinity as trastuzumab. It is postulated that after binding, the T-DM1/HER2 complex is internalized followed by degradation in the lysosome, release of DM1, and subsequent cell lysis. Although used at lower doses and frequency than trastuzumab, T-DM1 retains the ability to inhibit signaling and engaging of immune effectors that mediate ADCC, and it is active against lapatinib-resistant xenografts (25). Phase I-II studies of T-DM1 showed mild, reversible toxicity and a remarkable clinical response rate in excess of 25% in patients with heavily pretreated HER2+ MBC who had progressed after trastuzumab and lapatinib (26, 27). T-DM1 is being further evaluated in 2 large phase III randomized studies. The first trial compares T-DM1 versus T-DM1 plus pertuzumab versus the standard of trastuzumab plus a taxane in patients with HER2+ MBC previously untreated in the metastatic setting. The second trial compares T-DM1 versus the standard of lapatinib and capecitabine in similar patients but who have previously received trastuzumab (Table 1).

**Combination of anti-HER2 therapies and abrogation of drug resistance**

**Dual HER2 blockade.** Many HER2-amplified breast cancers do not respond to or eventually escape trastuzumab, suggesting both de novo and acquired mechanisms of resistance. A possible mechanism of de novo resistance is expression of the HER2 receptor as a kinase-active 95-kDa cytosolic fragment that lacks the trastuzumab-binding epitope (28). Analysis of a cohort of patients with HER2+ MBC treated with trastuzumab and chemotherapy showed a very low response rate in tumors with cytosolic p95HER2 compared with those without (29). Lapatinib has been shown to inhibit the catalytic activity of p95HER2. Therefore, patients with p95HER2–positive breast cancers treated with lapatinib alone or in combination with capecitabine exhibited a similar PFS and overall response rate compared with p95HER2–negative tumors (30), suggesting a clinical setting in which a HER2 TKI might be advantageous.

Like lapatinib, the HER2/EGFR dual TKI neratinib (31) has shown clinical activity in patients with HER2+ MBC who have progressed on trastuzumab. These data suggest that trastuzumab-resistant tumors continue to be dependent on the HER2 tyrosine kinase. However, the response to each single-agent TKI tends to be short-lived (10, 11). Further, these patients may still need trastuzumab beyond progression as suggested by a recent study in which the combination of lapatinib and trastuzumab was superior to
<table>
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Abbreviations: H, herceptin; L, lapatinib; P, paclitaxel; D, docetaxel; TC, docetaxel, carboplatin; TCH, docetaxel, carboplatin, herceptin; DFS, disease-free survival; DRFS, distant relapse-free survival; OS, overall survival; QoL, quality of life; TTR, time to recurrence; TTDR, time to distant recurrence; DTF, distant failure-free survival; ORR, overall response rate; TTF, time to treatment failure; CBR, clinical benefit rate; AC, adriamycin/taxol; LABC, locally advanced breast cancer; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; LN, lymph node; EC, epirubicin and cyclophosphamide.
HER3 (40–42), thus partially maintaining PI3K activity.

Figure 1. Upregulation of H3R3 and resistance to anti-HER2 therapies. The kinase-dead HER3 receptor, but not EGFR or HER2, can couple directly to p85, the regulatory subunit to PI3K. HER2/HER3 heterodimers are the most potent signaling complexes of the HER receptor network. Upon inhibition of HER2 and PI3K (as with lapatinib in the figure), tumor cells upregulate expression of the HER3 protein. Other tyrosine kinases such as MET, FGFR2, Src, and EGFR present in HER2+ cancer cells can then phosphorylate tyrosines in the C terminus of HER3, which, in turn, couples to p85 to partially maintain PI3K activity and, thus, limits the antitumor effect of HER2 inhibitors. Alternatively, the cell can use other receptor networks, that is, IGF-IR, to activate the PI3K/Akt survival pathway.

In control of HER3-mediated signaling to apoptosis induced by PI3K inhibitors is generally accepted that HER3 is required for the viability of HER2-dependent cells (36, 37).

In HER2-dependent cells, the phosphoinositide 3-kinase (PI3K)/Akt pathway (1, 34, 35) is essential for the viability of HER2-dependent cells (36, 37). Indeed, HER2+ breast cancer cells are particularly sensitive to apoptosis induced by PI3K inhibitors (38), further underscoring the importance of HER3-mediated signaling in HER2-dependent cells. It is generally accepted that sustained inhibition of the output of HER2/HER3 to HER2/HER3 dimers is required for the antitumor effect of HER2 inhibitors. Interestingly, HER2+ breast cancer cells upregulate HER3 expression upon inhibition of HER2 with lapatinib (39). This upregulation is problematic because several kinases such as MET, EGFR, Src, and fibroblast growth factor receptor 2 (FGFR2) can phosphorylate HER3 (40–42), thus partially maintaining PI3K activity and limiting the antitumor effect of the HER2 inhibitor (Fig. 1).

Trastuzumab has been shown to block ligand-independent association between HER2 and HER3, whereas pertuzumab, an antibody that recognizes an epitope in ligand-induced HER2-HER3 dimerization domain II of HER2, blocks ligand-induced HER2-HER3 dimerization (43). Recent data using Clinical Laboratory Improvement Amendments (CLIA)-certified dimer assays suggest that levels of HER2-containing homo- and heterodimers (with EGFR and HER3) can be measured in situ and are highly variable among HER2+ tumors (44, 45). We hypothesize, for example, that a tumor with high levels of HER2/HER3 heterodimers would be relatively unresponsive to trastuzumab and, thus, may be a candidate for lapatinib or pertuzumab, each in combination with trastuzumab. These speculations and the question of whether the addition of quantitative dimer assays to FISH and IHC for HER2 will refine the selection of the type of anti-HER2 therapy remain to be investigated.

In trastuzumab-resistant xenografts and in patients with HER2+ breast cancer who have progressed on trastuzumab, only the combination of pertuzumab and trastuzumab, but not each antibody alone, exhibited clinical activity (46, 47). These data suggest that both HER2 antibodies might be required to completely inhibit HER2-HER3 dimerization in situ, potentially explaining their clinical activity in combination. To test this hypothesis, the phase III Cleopatra study (Table 1) is currently randomizing patients with HER2+ MBC to trastuzumab and docetaxel ± pertuzumab as first-line therapy in the metastatic setting using PFS as a primary endpoint. Of note, in the recently reported NeoSphere trial in patients with HER2+ primary breast cancer (Table 1), the pathologic complete response (pCR) rate was 45.8% versus 29% (P = 0.01) in patients treated with neoadjuvant docetaxel-trastuzumab-pertuzumab versus docetaxel-trastuzumab.
respectively (48). Currently, the HER3 monoclonal antibodies AMG-888 (49) and MM-121 (50) are completing phase I testing. We anticipate that, like pertuzumab, they may also exert a synergistic effect in combination with trastuzumab or lapatinib in patients with HER2+ MBC.

PI3K and drug resistance. Amplification of PI3K signaling as a result of coexpression of PIK3CA-activating mutations or loss of the lipid phosphatase PTEN in HER2+ breast cancer cells and primary tumors is associated with a lower response to trastuzumab and lapatinib (51–55). Several PI3K pathway antagonists are in clinical development and are the subject of recent reviews (56, 57). In preclinical studies, the addition of some of these inhibitors to trastuzumab or lapatinib has inhibited growth of HER2+ tumors resistant to anti-HER2 therapy (53, 54). Interestingly, inhibitors of mTOR, a serine-thereonine kinase downstream of PI3K, have shown activity after progression on trastuzumab. Dalenc and colleagues recently reported a multicenter phase II study of 55 women with HER2+ MBC whose tumors were resistant to trastuzumab and taxanes. Patients were treated with the TOR inhibitor everolimus, paclitaxel, and trastuzumab, exhibiting an impressive partial response rate of 19% and an overall clinical benefit rate of 81% (58).

Neoadjuvant therapy as a platform for clinical research. Trastuzumab has been administered with chemotherapy in the neoadjuvant setting with rates of pCR as high as 65% (22, 59–62). Achievement of pCR after neoadjuvant chemotherapy has been widely associated with improved long-term outcome. Although not yet clear, recent data suggest similar conclusions may eventually also apply to patients treated with neoadjuvant anti-HER2 therapy. The neoadjuvant herceptin (NOAH) trial tested the efficacy of chemotherapy ± trastuzumab in patients with HER2+ locally advanced or inflammatory breast cancer. pCR rate was 38% versus 19% in the trastuzumab versus the control group. There was a 71% versus 56% 3-year event-free survival in the trastuzumab versus control arms in all subgroups tested. Overall survival was not different between both arms, but this finding is qualified by the fact that a significant proportion of patients “crossed-over” to adjuvant trastuzumab (62). Nonetheless, NOAH is the first trial in patients with HER2+ tumors in which pCR mirrors longer term event-free survival, suggesting use of the neoadjuvant therapy space as a platform for clinical investigation, which we discuss below.

Neo-ALLOT is a 450-patient study in which HER2+ tumors ≥2 cm were randomized to trastuzumab, lapatinib, or the combination for 6 weeks, at which time paclitaxel is added to each of the arms for an additional 12 weeks. After surgery, all 3 arms will receive adjuvant chemotherapy with 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) followed by the respective HER2 inhibitor either alone or in combination for 34 weeks. About half of the patients enrolled had ER+ tumors. There was increased but manageable toxicity in the lapatinib arms (diarrhea, transaminitis). pCR, defined as no invasive cancer in the breast or only ductal carcinoma in situ (DCIS) in the breast specimen, was significantly higher in the combination arm (51.3%) versus 29.5% and 24.7% in the trastuzumab and lapatinib arms, respectively. In all 3 arms, the pCR rate was lower in the ER+ versus the ER– tumors (63). Whether pCR correlates with disease-free and overall survival is pending further follow-up.

Other combinations. The data summarized above suggest that, in addition to the combination of trastuzumab and lapatinib, many other rational combinations are or will soon be available for clinical testing. Examples of 2-drug combinations that will inhibit the HER2 network and its output to PI3K/Akt more comprehensively are trastuzumab plus pertuzumab, trastuzumab or lapatinib plus a HER3-neutralizing antibody, trastuzumab or lapatinib plus a PI3K or an Akt inhibitor, a PI3K pathway inhibitor plus a HER3 antibody, T-DM1 plus pertuzumab or a PI3K inhibitor, a combination of HER2 and insulin like growth factor-IR (IGF-IR) pathway antagonists, and others. Some of these combinations are shown in Table 1. We speculate that many or all of these will be well tolerated and effective against HER2+ early disease and the increasing limitation in patient resources, it will be difficult to move these combinations to the adjuvant setting to test their true anti-(micro)metastatic potency using survival as an endpoint.

However, the increasing use of preoperative therapy should provide a clinical research platform in which these combinations can be compared and triaged using pCR as a clinical endpoint predictive of long-term outcome. Another benefit of a preoperative platform is that residual tumor tissue is available at the time of surgery. These “drug-resistant” residual cancers may well reflect the molecular profile of drug-resistant micrometastases and can be interrogated with open-ended molecular approaches to identify biomarkers and/or effectors of resistance to anti-HER2 therapies. It would not be too surprising if the clinical activity of these combinations turns out to be equivalent. However, toxicity and cost may turn out to be important differentiating factors. If so, just like options for endocrine therapy in ER+ breast cancer, this scenario would provide a plethora of treatment choices for patients with HER2-overexpressing breast cancer who, in the end, will be the winners.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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