"Vertical" Inhibition of HER2 Yields Horizontal Gains in the Clinic

George W. Sledge and Mark D. Pegram

HER2-targeted therapy has moved beyond trastuzumab to include other monoclonals targeting the cell surface, receptor tyrosine kinase inhibitors of HER2, and antibody–drug conjugates. Afatinib, a small molecule receptor tyrosine kinase inhibitor, now joins the ranks of HER2-targeting agents in combination with trastuzumab. The combination brings new opportunities and challenges. Clin Cancer Res; 21(12): 2693–5. ©2015 AACR.

See related article by Ring et al., p. 2737

In this issue of Clinical Cancer Research (CCR), Ring and colleagues (1) present clinical data for the combination of trastuzumab with afatinib, a combination that demonstrates both the challenges and promises of combination vertical blockade of HER2.

Following the initial proof-of-concept studies with trastuzumab, investigators confronted the reality that although HER2-targeted monotherapy significantly improved outcome, it did not eliminate HER2-driven breast cancer. Indeed, an increasing understanding of HER2 biology has led to multiple new avenues of attack beyond trastuzumab. Given the evidence of trastuzumab’s manifest efficacy in the adjuvant and metastatic settings (2), these new approaches regularly involved “combinations” with trastuzumab.

These included drugs targeting the tyrosine kinase moiety of the HER2 molecule (e.g., lapatinib and neratinib), drugs preventing HER2 dimerization (e.g., pertuzumab), antibody–drug conjugates (e.g., T-DM1), and drugs targeting downstream pathway molecules (e.g., PI3K/AKT/mTOR; see Fig. 1). Afatinib now joins the list of agents combined with trastuzumab, as described in the phase I trial presented by in this issue of CCR. Afatinib is an irreversible, oral, 4-anilinoquinazoline small molecule that binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4), as well as selected EGFR exon 19 deletion mutations, or exon 21 L858R mutations, to inhibit their tyrosine kinase activity. It was FDA approved in 2013 as first-line monotherapy for patients with metastatic non–small cell lung cancer whose tumors have detectable EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. In that setting, common toxicities (≥20%; 40 mg, once daily dose) include diarrhea, rash, stomatitis, paronychia, dry skin, decreased appetite, and pruritus (3).

Ring and colleagues combined afatinib with trastuzumab in a phase I trial using a standard 3+3 dose escalation. Trastuzumab was used in its standard weekly dosing of 4 mg/kg for 1 week, then 2 mg/kg weekly thereafter. Afatinib ultimately was tested at just two dose levels, 20 mg and 30 mg once daily, with dose-limiting toxicity (DLT), namely grade 3 diarrhea, being common at both dose levels (4/13 and 2/2, respectively). In contrast, afatinib monotherapy is administered at a higher dose of 40 mg daily.

This experience mimics that seen previously with lapatinib, where full doses of the oral kinase inhibitor could not be administered with trastuzumab, due to DLT events defined by grade 3 fatigue and diarrhea, as well as nausea and vomiting (4). Whether this necessity for dose reduction to half the monotherapy dose will also decrease combinational efficacy is uncertain. At a dose of 20 mg daily, the reported afatinib Cmax and trough concentrations at steady state were 36.8 nmol/L and ~20.5 nmol/L, respectively, close to the published EC50 of afatinib for HER2 kinase (14 nmol/L) in enzymatic assays (5). However, the toxicities experienced by patients (in the form of diarrhea, rash, and fatigue) were certainly significant. As there was no obvious pharmacokinetic interaction between these two agents, the increased toxicity must be occurring at a pharmacodynamic level.

It is certainly premature, based on the results of a phase I trial, to predict the ultimate fate of the trastuzumab plus afatinib combination. How well have the other combinations fared? The results have been mixed.

Trastuzumab plus lapatinib was the first combination anti-HER2 therapy to be extensively tested. The rationale for “vertical” inhibition of the same receptor kinase target, in this case HER2, was based upon (i) demonstration of synergistic antiproliferative effects in vitro (6; (ii) lapatinib inhibition of truncated HER2 receptors that retain a highly functional HER2 kinase domain but lack the extracellular domain and results in intrinsic trastuzumab resistance (7); and (iii) accumulation of HER2 at the cell surface by lapatinib enhanced immune-mediated trastuzumab-dependent cytotoxicity (8).

Following early combinatorial trials in the metastatic HER2 setting, investigators rapidly moved this combination into the neoadjuvant and adjuvant settings. The preoperative trials were promising, with improved (sometimes numerically, NSABP B-41; sometimes statistically, neoALTTO) pCR rates for the combination over monotherapy. The results of lapatinib/trastuzumab combination in the adjuvant disease setting, first presented at the 2014 ASCO annual meeting, were therefore a shock to
some and a disappointment to all: a small, non-statistically improved disease-free survival (compared with trastuzumab) accompanied by substantial toxicity (9). However, it is important to note that just 555 disease-free events had occurred at 4.5 years, which fell far short of the 850 that were needed to achieve the desired power in the statistical plan. Moreover, a substantial number of subjects enrolled in the ALTTO trial were lymph node-negative (40%), or low T stage (40% < 2 cm), many of whom may never contribute events in the final analysis. Accordingly, further subset analysis of higher risk populations within the ALTTO cohort (i.e., stage II subjects) could still prove to be enlightening.

In contrast, the combination of trastuzumab with pertuzumab has offered impressive outcomes in both the neoadjuvant and metastatic settings. In the neoadjuvant setting, pCR rates were significantly improved with the combination (45.8% vs. 29%; P = 0.0141; ref. 10), and in the metastatic setting the combination of trastuzumab and pertuzumab resulted in an unprecedented 56.5-month median overall survival as first-line therapy in the CLEOPATRA trial, the longest ever recorded (4). The combination of pertuzumab and trastuzumab in combination with T-DM1 for the treatment of HER2-positive breast cancer, following surgery and anthracycline-based chemotherapy (NCT01966471).
Where will the combination of afatinib and trastuzumab ultimately land? The 11% response rate reported in this trial is unimpressive, but phase I trials are particularly poor places to judge a combination’s ultimate activity; the patients entered in such trials tend, as occurred in this trial, to be a highly selected and heavily pretreated population.

Predicting benefit for HER2-targeting combinations has been particularly difficult, and so far we have been reduced to the empiricism of large, expensive trials. This is a particular problem in the adjuvant setting, where the early hope that neoadjuvant trials would represent a simple step to predicting outcome has been called into question by the ALTTO trial results. Thus, we still need predictors of clinical benefit for HER2 combinations, and indeed may still need novel combinations of HER2-targeting agents, with agents affecting either other growth factor receptor pathways or the immune system.

Disclosure of Potential Conflicts of Interest
G.W. Sledge reports receiving a commercial research grant from Roche/Genetech and is on the Board of Directors for Syndax. M.D. Pegram is a consultant/advisory board member for Genetech. No other potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: G.W. Sledge
Writing, review, and/or revision of the manuscript: G.W. Sledge, M.D. Pegram

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Correction: "Vertical" Inhibition of HER2 Yields Horizontal Gains in the Clinic

In this article (Clin Cancer Res 2015;21:2663–5), which was published in the June 15, 2015, issue of Clinical Cancer Research (1), Fig. 1 was mistakenly omitted from the article. The figure and legend are provided below. In addition, the online version of the article has been revised to include this figure. The publisher regrets this error.

Reference

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Figure 1.
Target domains for combined receptor blockade of HER2. Left, HER2 has an extracellular domain (ECD), a single transmembrane domain (TM), and a cytoplasmic kinase domain (CD). The dimerization loop of HER2 is indicated by the dashed circle, and small green circles indicate segments for which the crystal structures have not yet been solved. On the upper right is a space-filling model of the HER2 ECD (ECD subdomains indicated by Roman numerals) with binding residues for Fab fragments of 2C4 (the murine precursor of pertuzumab) and 4D5 (the murine counterpart for trastuzumab) highlighted in magenta and red, respectively. Pertuzumab binds subdomain II of the HER2 ECD, causing steric inhibition of the dimerization interface. In contrast, trastuzumab binds to a juxtamembrane epitope in subdomain IV (T-DM1 binds the identical epitope). The insets on the lower right indicate modeling of lapatinib (purple) binding to the wild-type EGFR kinase domain, and afatinib binding to the EGFR kinase domain (green). The catalytic domains for HER2 and EGFR are 88% identical. Structural data for these kinase inhibitors binding to the HER2 kinase are not available, but covalent interaction for afatinib has been shown by mass spectrometry (4). HER2 structure (top left) reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer (ref. 13), copyright 2012. HER2 ECD structure (top right) reprinted by permission from Macmillan Publishers Ltd: Oncogene (ref. 14), copyright 2008. Afatinib structure (bottom right) reprinted from ref. 15: Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. J Pharmacol Exp Ther 2012;343:342–50. Lapatinib structure (bottom middle) reprinted from ref. 16.
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