Why Is This Effective HSP90 Inhibitor Not Being Developed in HER2+ Breast Cancer?

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Inhibition of the HSP90 chaperone leads to degradation of the HER2 receptor. The HSP90 inhibitor tanespimycin in combination with trastuzumab is active in patients with HER2-overexpressing metastatic breast cancer. This combination is one of several HER2-targeted therapies that will significantly improve the outcome of patients with this subtype of breast cancer. Clin Cancer Res; 17(15); 1–3. ©2011 AACR.

In this issue of Clinical Cancer Research, Modi and colleagues (1) report the clinical activity of tanespimycin with trastuzumab in patients with HER2-overexpressing metastatic breast cancer (MBC).

Approximately a quarter of breast cancers overexpress the HER2 (ErbB2) proto-oncogene. HER2 is a member of the ErbB family of transmembrane receptor tyrosine kinases (RTK), which also includes the epidermal growth factor receptor (EGFR), HER3, and HER4. Binding of ligands to EGFR, HER3, and HER4 induces the formation of receptor homodimers and heterodimers that contain HER2, activation of the receptors’ kinase activity, and engagement of signal transducers associated with enhanced tumor cell proliferation and survival. The antibody trastuzumab is currently approved for the treatment of early and metastatic HER2-overexpressing breast cancer. Trastuzumab binds to an epitope in the juxtamembrane region of the HER2 receptor. This binding induces uncoupling of ligand-independent HER2-HER3 heterodimers and inhibition of downstream signaling as well as antibody-dependent, cell-mediated cytotoxicity. Although many breast cancers with HER2 gene amplification respond to trastuzumab, a significant fraction of these eventually progress. Several mechanisms of resistance to the antibody have been reported. These mechanisms include enhanced signaling by RTKs in the ErbB family or in other receptor networks, amplification of phosphoinositide 3-kinase (PI3K) signaling as result of mutations in this pathway, and the presence of truncated forms of HER2 devoid of the antibody-binding epitope in the receptor’s ectodomain (reviewed in ref. 2).

The HER2 tyrosine kinase inhibitors (TKI) lapatinib and neratinib have shown clinical activity as single agents or in combination with chemotherapy in patients who have progressed on trastuzumab (2). These data suggest that trastuzumab-resistant tumors continue to depend on the HER2 tyrosine kinase. 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 lapatinib alone at improving progression-free survival, clinical response, and overall survival in patients with HER2+ MBC who had progressed on trastuzumab (3). These data imply that, even in advanced stages, HER2+ breast cancers remain dependent on HER2 and that combinations of drugs targeted to the HER2 receptor network will be required for better inhibition of this pathway and, hence, improved clinical activity.

Recent clinical evidence supports the efficacy of combinations of anti-HER2 therapies that improve the inhibition of HER2 by trastuzumab. For example, the combination of trastuzumab and pertuzumab, an antibody that blocks ligand-induced HER2 heterodimerization by binding to an epitope in HER2 different to that of trastuzumab, induces clinical responses in trastuzumab-resistant patients (4). The Neo-ALTTO study compared trastuzumab, lapatinib, or the combination, each arm together with paclitaxel in patients with HER2+ tumors >2 cm in the preoperative setting. A pathologic complete response, 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 (5).

Inhibitors of HSP90 are another rational approach against HER2+ breast cancers that progress on primary anti-HER2 therapy. HSP90 is an abundant molecular chaperone that is required for the refolding of proteins under conditions of environmental stress and for the conformational maturation of several proteins involved in signal transduction, such as steroid receptors, RAF-1, cyclin dependent kinase 4 (CDK4), AKT, MET, and HIF-1α, ...
among others (Fig. 1; ref. 6). The antitumor antibiotic geldanamycin binds to the ATP pocket of HSP90, thus inhibiting its function; this results in ubiquitination and proteasomal degradation of the HSP90 client proteins. HER2 is among the most sensitive HSP90 clients (7).

Indeed, treatment of HER2-overexpressing cancer cells and xenografts with geldanamycin causes potent and rapid degradation of HER2, concomitant inhibition of PI3K/AKT, and inhibition of tumor growth (6). Similar activity of HSP90 inhibitors has been observed against HER2+ tumors with either acquired resistance to trastuzumab, coexpression of mutant PI3KH1047R (p110α), expression of truncated p95-HER2, or upregulation of membrane-associated mucin 4 (8–10).

Tanespimycin [17-allylamino-17-demethoxy-geldanamycin (17-AAG)] is a geldanamycin derivative that potently inhibits HSP90 in preclinical cancer models. Its early clinical development was limited by poor aqueous solubility and pharmacokinetic properties. A formulation of 17-AAG, KOS-953, that contains polyethoxylated castor oil (Cremophor, BASF Corp.), was tested in a phase I trial in patients with advanced cancer (11). Inhibition of the drug target was supported by induction of HSP70, a marker of inhibition of HSP90, in patients’ lymphocytes at all dose levels. Tanespimycin was well tolerated overall and, in combination with trastuzumab, exhibited antitumor activity only in patients with HER2-overexpressing MBC who had progressed on prior trastuzumab.

In this issue of the *Clinical Cancer Research* and building on their phase I experience, Modi and colleagues (1) report the results of a phase II trial of tanespimycin plus trastuzumab in 31 patients with HER2+ MBC progressing on trastuzumab. Tanespimycin (KOS-953) was administered weekly at a dose of 450 mg/m² intravenously and trastuzumab at a conventional weekly dose. After 21 patients had been enrolled, a second formulation of tanespimycin without Cremophor was substituted to avoid hypersensitivity reactions. Therapy was continued until disease progression, with clinical response being assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The most common toxicities were diarrhea, nausea, headache, fatigue, and neuropathy (mostly grade 1 to 2). The overall response rate was 22%, with a clinical benefit rate of 59%. Median progression-free survival was 6 months, and the overall survival was 17 months. Of note, patients responding to the Cremophor-based formulation maintained this response after cross-over to the second formulation, and there was no significant cardiac toxicity observed. Drug-induced downregulation of HER2 in tumors was not reported.

This level of clinical activity is not inconsistent and, in some cases, may seem superior to that seen with lapatinib plus trastuzumab, pertuzumab plus trastuzumab, trastuzumab-DM1, or neratinib in patients with similar characteristics (reviewed in ref. 12). Whether trastuzumab is necessary for the antitumor activity of the combination...
cannot be ascertained without a randomized study. However, the clinical data supporting trastuzumab’s activity beyond progression (3, 13), its tolerability, the likely possibility that single-agent HSP90 inhibitors will be unable to completely downregulate HER2 (and other client proteins) in sustained fashion, and the preclinical data supporting synergy of both types of drugs (8, 9) would together argue for HSP90 inhibitors to be used in combination with trastuzumab or another HER2 (pathway) inhibitor in patients with HER2+ breast cancer. Thus, this rational combination is one of several HER2-targeted therapies that, pending further development and approval, should improve the outcome of patients with this subtype of breast cancer.

With the positive outcome of this trial, it is, then, disappointing to read in the report by Modi and colleagues that “the development of tanespimycin as a cancer therapy has been suspended by the sponsor for non-clinical reasons.” The usual roadblocks to drug development, such as lack of efficacy against its molecular target(s), undue toxicity, lack of clinical activity, and production issues, do not seem to be at play here (14). Hence, I am afraid that, given the potential of this drug to benefit cancer patients, this cryptic explanation might not be acceptable. Will other HSP90 inhibitors, for which to my knowledge no clinical efficacy data in HER2+ breast cancers are yet available, fill this niche? Through federal grants to academia and/or tax breaks to industry to support the entrepreneurial pursuit of projects that should help society, like the one discussed herein, (tax-paying) patients, advocates, and cancer care providers contribute to this research and, therefore, deserve a better explanation about why the development of this useful therapy is now truncated.

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