Clinical Cancer Research

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Pertuzumab Protects the Achilles' Heel of Trastuzumab—Emtansine

William R. Gwin and Neil L. Spector

Trastuzumab emtansine (T-DM1) represents a significant advancement in the treatment of HER2+ breast cancers. Its clinical efficacy however will be limited by the development of therapeutic resistance. In this report, the HER3 ligand neuregulin is shown to mediate T-DM1 resistance, which was overcome by administration of pertuzumab, a steric inhibitor of HER2 dimerization. Clin Cancer Res; 20(2); 278–80. ©2013 AACR.

In this issue of Clinical Cancer Research, Lewis Phillips and colleagues describe the first reported mechanism of therapeutic resistance to trastuzumab emtansine (T-DM1), an antibody–drug conjugate recently approved for the treatment of advanced stage HER2+ breast cancers that have progressed on prior trastuzumab-based treatment regimens. In this CCR article, the authors demonstrate that the HER3 ligand neuregulin β1 (NRG) can abrogate the antitumor activity of T-DM1 in a subset of tumor cell lines (1). Importantly, resistance to T-DM1 mediated by NRG was reversed when cells were treated with T-DM1 in combination with pertuzumab—a U.S. Food and Drug Administration–approved HER2 monoclonal antibody that blocks NRG-induced formation of HER3–HER2 dimers (Fig. 1; ref. 2). In addition to the preclinical data, Lewis Phillips and colleagues report data on the safety, tolerability, and clinical efficacy from a small phase Ib clinical trial (N = 9), evaluating the combination of pertuzumab and T-DM1. A dose of this combination was identified that will be taken forward in a phase II trial. Although primary objectives of phase I trials typically include a determination of safety/tolerability and pharmacokinetics, the authors also report encouraging objective clinical response rates. Efforts to identify mechanisms of T-DM1 resistance and strategies to overcome or delay its onset are critical, as primary and secondary therapeutic resistance to T-DM1 exists and will continue to limit the clinical efficacy of this exciting new drug.

Identification of NRG, also referred to as heregulin β1, as a mediator of therapeutic resistance to T-DM1 may not be surprising, as the role of the PI3K–Akt–mTOR signaling axis in promoting tumor cell survival and drug resistance to a variety of anticancer therapies is well established. HER3 contains six phosphotyrosine binding sites for the p85 regulatory subunit of phosphoinositide 3-kinase (PI3K), more than any other HER receptor, making it a highly potent activator of PI3K (3). Moreover, HER3 is primarily transactivated via a kinase active HER dimerization partner, e.g., HER2. Thus, in breast cancer, HER2–HER3 heterodimer signaling complexes represent one of the most potent activators of the PI3K pathway (3, 4). Spontaneous formation of HER2–HER3 heterodimers can occur in tumors where HER2 expression on the cell surface is dramatically increased as a consequence of gene amplification. In other settings, autocrine- or paracrine-derived NRG can trigger the formation of HER2–HER3 heterodimers, which are blocked by pertuzumab, but not trastuzumab (5). In preclinical models of HER2+ breast cancer, NRG has been shown to abrogate the antitumor effects of trastuzumab and lapatinib (6, 7). We recently demonstrated that autocrine production of NRG in HER2+ breast cancer cell lines can mediate acquired therapeutic resistance to lapatinib and other tyrosine kinase inhibitors in class, in addition to possibly mediating cross-resistance to the mitotic inhibitor paclitaxel (8, 9). Similarly, Lewis Phillips and colleagues show that NRG can mediate therapeutic resistance to mitotic inhibitors used in the treatment of breast cancer and other solid tumors. It will be interesting to determine whether chronic exposure to T-DM1 triggers autocrine induction of NRG, which can in turn, promote therapeutic resistance. An important potential clinical implication of these findings is that tumors that become resistant to T-DM1 as a consequence of NRG may also be cross-resistant to salvage regimens.

T-DM1 was developed to deliver DM1 (mertansine), a tubulin-binding mitotic inhibitor, directly to HER2+ breast cancer cells (10). In this CCR article, the authors show that phosphorylation of HER3 (tyrosine 1289) and Akt (threonine 308) was inhibited in HER2+ SKBR3 breast cancer cells treated with T-DM1 alone. However, these effects were blocked in the presence of NRG, but restored with the addition of pertuzumab (Fig. 1). One potential explanation for the enhanced antitumor effects observed following the

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doi: 10.1158/1078-0432.CCR-13-2628

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addition of pertuzumab is that antibody-dependent cell-mediated cytotoxicity (ADCC) is increased in the presence of two antibodies compared with T-DM1 alone. Using an engineered pertuzumab molecule that lacks ADCC activity, the authors demonstrate that the synergistic effects of adding pertuzumab to T-DM1 were not due to increased ADCC. These findings provide strong evidence that pertuzumab blocks the antiapoptotic HER2–HER3–PI3K signaling pathway that can promote T-DM1 resistance, particularly in the presence of NRG.

In addition, the authors showed that MDA-MB-175VII cells, a HER2 non-overexpressing breast cancer cell line that produces autocrine HRG-γ, were resistant to T-DM1. These cells were, however, sensitive to the antitumor effects of the combination of T-DM1 and pertuzumab. These findings, albeit preliminary, make it tempting to speculate that a subset of HER2 non-overexpressing tumors may respond to a T-DM1–containing regimen. Consistent with these findings are previous observations that a subset of patients with HER2 non-overexpressing breast cancers responds to pertuzumab.

Figure 1. NRG blocks the antitumor effects of T-DM1. A, T-DM1 binds to domain IV of HER2, which, in the absence of NRG, can lead to inhibition of HER2/HER3 phosphorylation and downstream mitogen-activated protein kinase (MAPK) and PI3K signaling. T-DM1 bound to HER2 is then internalized, and the mertansine, represented in pegged brown circles with the letter “D,” is released into the cell, which induces apoptosis. B, binding of NRG, derived from paracrine (e.g., tumor microenvironment) or autocrine sources, to its cognate receptor HER3 induces a conformational change in HER3 leading to dimerization with HER2. NRG maintains PI3K and MAPK signaling despite the presence of T-DM1. Persistent activation of the antiapoptosis NRG-HER3–HER2–PI3K signaling axis blocks mertansine-induced apoptosis. C, NRG binds HER3, but dimerization with HER2 is blocked by cotreatment with pertuzumab, which binds close to extracellular domain II of the HER2, preventing its interaction with HER3. Abrogation of tumor cell survival NRG–HER3–HER2–PI3K signaling pathway in response to pertuzumab sensitizes cells to mertansine–induced cell death.
trastuzumab therapy (11). Furthermore, pertuzumab can block ligand-induced HER2 dimerization in tumor cells that are either HER2 high or low expressers (2). Consequently, the relevance of these findings may extend beyond merely HER2+ breast cancers. The challenge however, is to develop the tools to identify those HER2 non-overexpressing breast cancers that are more likely to respond to T-DM1 alone or in combination with pertuzumab. Lewis Phillips and colleagues also show that HER2+ breast cancer cells that express an activating PI3KCA mutation remain sensitive to the antitumor effects of T-DM1, even in the presence of NRG. If one mechanism of resistance to T-DM1 is mediated through persistent activation of an NRG–HER3–HER2–PI3K signaling axis, then it seems counterintuitive that tumor cells driven by constitutive activation of the PI3K signaling pathway should remain sensitive to T-DM1. If these preliminary findings are confirmed in larger studies, then expression of activating PI3KCA mutations, which predict for resistance to trastuzumab (12), may predict for sensitivity to T-DM1, regardless of the presence or absence of NRG.

With the excitement generated by the successful development of each new HER2-targeted therapy comes the reality that therapeutic resistance remains a significant clinical dilemma. It turns out that T-DM1 is no exception to the rule. Here, Lewis Phillips and colleagues have provided the scientific rationale for a therapeutic strategy to overcome or prevent the development of resistance to T-DM1 that is mediated by NRG. By blocking the formation of HER2–HER3 heterodimers, pertuzumab can interrupt the anti-apoptotic NRG–HER2–HER3–PI3K signaling axis. It will be interesting to see whether other therapies targeting this signaling axis, e.g., HER3 antibodies, PI3K inhibitors, and as we recently showed, certain EGFR/HER2 tyrosine kinase inhibitors (8), have similar effects. Although the preclinical findings presented here are intriguing, the role of NRG in mediating T-DM1 resistance has not been clinically validated. Moreover, NRG-independent mechanisms of T-DM1 resistance are also likely to exist, which may require a different therapeutic intervention. Therefore, we should avoid the temptation to empirically treat all T-DM1-resistant breast cancers with pertuzumab until we can identify those patients who are more likely to respond to the combination. Creating a personalized treatment approach to overcome, delay, or ideally prevent T-DM1 resistance will require further research, and clinical confirmation, into the molecular mechanisms underlying its development.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: W.R. Gwin, N.L. Spector
Development of methodology: N.L. Spector
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W.R. Gwin, N.L. Spector
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W.R. Gwin

Grant Support
This work was supported by the Susan G. Komen Foundation (SAC110033; to N.L. Spector).

Received October 16, 2013; accepted November 7, 2013; published OnlineFirst November 15, 2013.

References
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doi:10.1158/1078-0432.CCR-13-2626

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