

Molecular Pathways: Targeting *NRG1* Fusions in Lung Cancer

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Abstract

The four members of the ERBB (HER) family of transmembrane receptor tyrosine kinases are frequently activated in cancer by several mechanisms, such as mutation, amplification, or autocrine ligand–receptor stimulation. We recently identified gene fusions involving the ERBB ligand gene, *NRG1*, which represent a novel mechanism for ERBB pathway deregulation. These fusions lead to expression and presentation of the EGF-like domain of *NRG1* on the cell surface, which binds to ERBB3 in an autocrine and juxtacrine manner, thus inducing the formation of ERBB2–ERBB3 heterodimers, and subsequent activation of the PI3K–AKT

and MAPK signaling pathways. These fusion genes were exclusively detected in lung adenocarcinomas of never smokers of the invasive mucinous subtype, which usually presents as a multifocal and unresectable disease, for which no effective treatment exists. Considering the large amount of drugs that target ERBB2 (HER2) and ERBB3 (HER3), and which are currently in different stages of clinical development, detecting and targeting *NRG1* fusions in invasive mucinous lung adenocarcinomas may represent a therapeutic opportunity for this aggressive disease. *Clin Cancer Res*; 21(9); 1989–94. ©2014 AACR.

Background

ERBB1 (EGFR; ref. 1), ERBB2 (HER2; ref. 2), ERBB3 (3, 4), and ERBB4 (5) constitute the ERBB family of transmembrane receptor tyrosine kinases (RTK). These RTKs are composed of a large extracellular ligand-binding domain, a transmembrane domain, a small intracellular juxtamembrane domain, a kinase domain, and a C-terminal tail (6). Upon ligand binding, these receptors form hetero- or homodimers, which induce the phosphorylation of their intrinsic kinase domain, resulting in the activation of the downstream PI3K–AKT and MAPK pathways (7–9). There are 13 polypeptide extracellular ligands for these RTK, all of them carrying an EGF-like consensus sequence, consisting of six cysteine residues. These ligands can be subdivided in those that specifically bind EGFR and ERBB4 (such as EGF, TGF- α , amphiregulin, epiregulin, BTC, HB-EGF, and EPR), and the neuregulins (NRG), which bind to ERBB3 (*NRG1* and *NRG4*) and to ERBB4 (*NRG1*–*NRG4*; ref. 10). ERBB receptors are expressed in many cells of the epithelial, mesenchymal, and neuronal lineages, in which they have diverse roles in development, proliferation, and differentiation (11). Aberrant tyrosine kinase activity of ERBB receptors owing to gene amplification and mutations (EGFR and ERBB2; refs. 12–14), or autocrine ligand–receptor stimulation (10) can result in growth stimulation and tumorigenesis in

various tumor types, including cancers of the breast, lung, brain, head and neck, and colon (12).

Contrary to ERBB1 and ERBB4, ERBB2 and ERBB3 are nonautonomous receptors and therefore their activation relies on their heterodimerization with other ERBB receptors: ERBB2 lacks the capacity to interact with growth factor ligands (15) but is the preferred dimerization partner of the other three receptors (16). ERBB3 is generally considered to be kinase deficient (17), although it has a low level of kinase activity (1,000-fold less than EGFR; refs. 18, 19). Interestingly, the heterodimer ERBB2–ERBB3 is considered the most transforming and mitogenic one (20–22), as suggested by the following: first, ERBB2-containing heterodimers undergo slow endocytosis, recycling more frequently back to the cell surface (23–25). Similarly, upon ligand binding and heterodimerization, ERBB3 undergoes tyrosine phosphorylation and can recruit PI3K but not GRB2, enabling ERBB3 to evade ligand-induced degradation (23, 26); and second, ERBB2–ERBB3 leads to the activation of both the PI3K–AKT and the MAPK pathways, strongly enhancing cellular proliferation and evasion of apoptosis (20, 21).

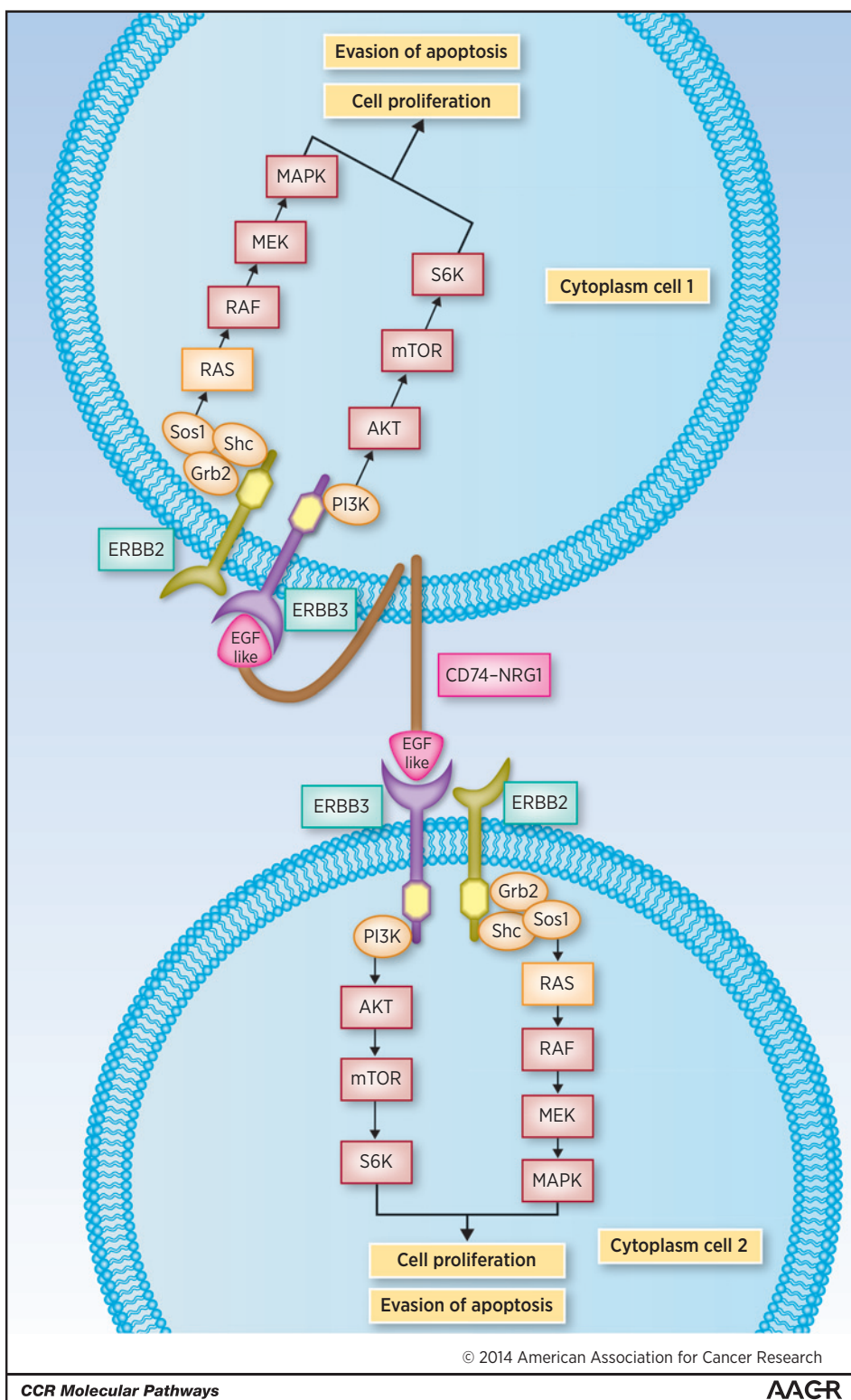
Because the main ligands for ERBB3 are NRGs, these molecules also activate ERBB2–ERBB3 heterodimers. In fact, coexpression of ERBB2 and ERBB3 constitutes a high-affinity receptor for these ligands (27). NRGs are signaling proteins mainly expressed in the nervous system, the heart, and the breast (28). They comprise a large family of growth factors that induce dimerization and activation of ERBB receptors (29). NRGs are encoded by four individual genes (*NRG1*–*4*), of which *NRG1* is the best characterized. *NRG1* generates six types of proteins (I–VI), and at least 31 isoforms (29). All of these isoforms have an extracellular EGF-like domain that induces activation of ERBB RTKs. Contrary to most *NRG1* isoforms that undergo proteolytic cleavage resulting in the release of the EGF-like domain, type III *NRG1*s have a membrane-tethered EGF-like domain that restricts the signaling to cell–cell interactions mainly, although a small amount of the EGF-like domain of these isoforms has been found secreted into the medium (30).

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**Figure 1.**

Schematic representation of the molecular pathways activated by CD74-NRG1. CD74-NRG1 provides the ligand for ERBB3 receptors inducing its heterodimerization with ERBB2, and subsequent activation of the PI3K-AKT and MAPK pathways, in an autocrine (cytoplasm cell 1) and juxtacrine (cytoplasm cell 2) manner, resulting in an abnormal cell proliferation. The mechanism of action is expected to be the same for SCL3A2-NRG1. In the CD74-NRG1 fusion protein, the part coming from CD74 is colored in brown and the part coming from NRG1, in pink. Kinase domains of ERBB2 and ERBB3 receptors are colored in yellow. Adaptor and enzymes are represented in orange and members of the signaling cascade, in red.

ERBB3 is not frequently affected by mutation or amplification in cancer (14); in contrast, overproduction of ligands is another mechanism by which cancers aberrantly activate ERBB receptors.

Several examples point toward the existence of an autocrine loop between ERBB3 and NRG1: in ovarian tumors that overexpressed NRG1 and ERBB3, inactivation of ERBB3 suppressed cancer

Table 1. Overview of ERBB3 inhibitors

Name (antibody)	Target	Biologic effect	Clinical status
MM-121 (SAR256212)	ERBB3	In combination with cetuximab, it blocks reactivation of ERBB3 in mice EGFR T790M-L858R, resulting in a sustained and durable response (31, 55, 56)	-Completed phase I safety and dose-finding trial -Several phase I and phase II studies ongoing -Refs 62–66
MM-111	ERBB2 and ERBB3	Antitumor activity in preclinical models that are dependent on ERBB2 overexpression (57)	-Completed phase I safety and dose-finding trial -Several phase II studies ongoing -Refs 52, 53
MM-141	IGF-IR and ERBB3	Prevents PI3K/AKT/mTOR network adaptation by blocking the redundant survival pathways and degrading the RTK complexes (58)	-Ongoing phase I study to establish the recommended dose and schedule -Ref. 67
MEHD7945A	EGFR and ERBB3	It has superior antitumor activity against multiple tumor models compared with monospecific antibodies (59)	-Completed phase I safety and dose-finding trial, with evidence of anti-tumor activity -Several phase I and phase II studies ongoing -Ref. 68
LJM716	ERBB3	It inhibits ligand-induced and ligand-independent ERBB3 dimerization (60)	-Completed phase I safety and dose-finding trial, with evidence of antitumor activity -Several phase I and phase II studies ongoing -Refs 69, 70
RG7116 (RO5479599)	ERBB3	It inhibits xenograft tumor growth and downregulates cell surface ERBB3. Its efficacy is further enhanced in combination with anti-ERBB2 (pertuzumab) antibodies (61)	-Completed phase I safety and dose-finding trial, with evidence of antitumor activity -Several phase I studies ongoing -Ref. 71
U3-1287 (AMG 888, patritumab)	ERBB3	It blocks the upregulation of total and phosphorylated ERBB3 that follows treatment with lapatinib and trastuzumab, and enhances the antitumor action of the combination against trastuzumab-sensitive and -resistant cells (48)	-Completed phase I safety and dose-finding trial -Several phase I, phase II, and phase III studies ongoing -Ref. 72

growth in laboratory models (31). Similarly, an *NRG1*-mediated autocrine loop inducing ERBB3 activation was also discovered in head and neck cancer cells lacking *ERBB2* amplification, and these cells were particularly sensitive to the EGFR/ERBB2 kinase inhibitor, lapatinib (32). Finally, analyses of prostate cancer cells and tumors suggest the existence of a paracrine loop involving *NRG1* and the ERBB2–ERBB3 heterodimer (33).

We recently discovered recurrent *CD74–NRG1* gene fusions, which result in the expression of the *NRG1* III- β isoform in the otherwise *NRG1*-negative invasive mucinous subtype of lung adenocarcinomas (34). *CD74–NRG1* activates ERBB3 as well as PI3K–AKT signaling (34), thus promoting anchorage-independent growth of NIH-3T3 cells (ref. 35; Fig. 1). Furthermore, *NRG1* fusion-mediated signaling could be suppressed by clinically approved kinase inhibitors (35). *NRG1* fusions are preferentially found in women who had never smoked, and whose tumors are negative for other known mutant oncogenic gene mutations such as those in *KRAS* [frequently mutated in invasive mucinous adenocarcinoma (IMA)], or *EGFR* (34, 35). In another study, *CD74–NRG1*-positive tumors displayed uncommon radiologic features in comparison with what it is usually seen in IMA (36).

Clinical-Translational Advances

Invasive mucinous adenocarcinoma accounts for 2% to 10% of all lung adenocarcinomas and is associated with an unfavorable clinical course because it usually presents as multifocal unresectable disease, for which no effective treatment exists (37–40). *KRAS* mutations were, until recently, the only recurrent oncogenic

mutations identified in IMA, with a frequency ranging from 50% in Asians to 80% in Caucasians. *NRG1* fusions are the first potentially treatable oncogenic driver alteration associated with a specific lung adenocarcinoma subtype and in contrary to *KRAS* mutations, which are associated with tobacco use, *NRG1* fusions occur in *KRAS*-negative IMA of never smokers. Taking all together, the discovery of recurrent, oncogenic, and possibly targetable *NRG1* fusions may represent a therapeutic opportunity for these tumors (34, 35).

Because *NRG1* fusions act through activation of ERBB2–ERBB3 heterodimers (34), blocking the activity of these receptors may be the best strategy to treat *NRG1*-rearranged tumors. Similar to EGFR and ERBB4, the extracellular domain of ERBB3 probably exists in two different conformations: a tethered autoinhibited form and an untethered ligand-bound form (41). In contrast, the crystal structure of ERBB2 reveals a constitutively activated conformation similar to that of ligand-bound EGFR. Although more mechanistic details exist for ERBB2 than for ERBB3 (14), and therefore more drugs are available for the former, blocking only this receptor might not be enough to completely shut down the signaling elicited by ERBB2–ERBB3. In fact, the effect of single-agent lapatinib or afatinib (irreversible small-molecule inhibitor of the ERBB2 and EGFR tyrosine kinases; ref. 42) has already been tested for *NRG1* fusions *in vitro*, and downstream signaling was not completely shut down, although an inhibitory effect was observed (35). Reactivation of ERBB3 has been observed as a resistance mechanism to EGFR and ERBB2 inhibitors (31, 43–49), and such mechanism might help *NRG1*-rearranged tumor cells escape exclusive targeting of ERBB2. A more successful approach could be to

block ERBB2–ERBB3 heterodimerization. In this context, ligand-induced ERBB2–ERBB3–PI3K complexes can be disrupted by pertuzumab (monoclonal antibody that recognizes an epitope in the heterodimerization domain II of ERBB2; ref. 50), whereas ligand-independent complexes might be dissociated by trastuzumab (51). However, it is important to note that the observed clinical efficacy of all therapeutic inhibitors against ERBB2 has been limited to breast cancer with overexpression of this gene (14).

Several ERBB3 inhibitors showing promising preclinical data are currently in different phases of clinical trials. A selection of those, for which substantial preclinical and clinical data exist, is presented in Table 1. Several of these are being tested in combination with ERBB2-targeting drugs in breast and gastric ERBB2-positive tumors (refs. 52, 53; Clinical trials: NTC01602406, NTC02167854, NTC01512199). However, although the outcome of these clinical trials will help gauge the benefit that dual ERBB2 and ERBB3 inhibition might have in cancer patients, a clinical trial in a selected cohort of *NRG1* fusion-positive cases is necessary to determine the benefit for this specific group of patients. Finally, given the activation of the PI3K–AKT signaling pathway, its inhibition may represent another therapeutic strategy. Inhibitors targeting PI3K itself or AKT have been in clinical development for several years now. Unfortunately, identification of the right patient population

is not as clear as anticipated from preclinical experiments (54). Thus, inhibition of the upstream ERBB family members, ERBB2 and ERBB3, might be more promising at this point.

Disclosure of Potential Conflicts of Interest

L. Fernandez-Cuesta and R.K. Thomas are listed as coinventors of a patent pending on *NRG1* fusions in lung cancer, which is owned by the University of Cologne. R.K. Thomas is a founder and shareholder of Blackfield AG/New Oncology; reports receiving commercial research grants from AstraZeneca, EOS, and Merck; and is a consultant/advisory board member for AstraZeneca, Bayer, Blackfield AG/New Oncology, Boehringer Ingelheim, Clovis Oncology, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, Puma, Roche, and Sanofi. No other potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Fernandez-Cuesta, R.K. Thomas
Development of methodology: L. Fernandez-Cuesta, R.K. Thomas
Writing, review, and/or revision of the manuscript: L. Fernandez-Cuesta, R.K. Thomas
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Fernandez-Cuesta, R.K. Thomas
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References

- Downward J, Yarden Y, Mayes E, Scrace G, Totty N, Stockwell P, et al. Close similarity of epidermal growth factor receptor and v-erb-B oncogene protein sequences. *Nature* 1984;307:521–7.
- Schechter A, Stern D, Vaidyanathan L, Decker S, Drebin J, Greene M, et al. The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumour antigen. *Nature* 1984;312:513–6.
- Kraus MH, Issing W, Miki T, Popescu NC, Aaronson SA. Isolation and characterization of ERBB3, a third member of the ERBB/epidermal growth factor receptor family: evidence for overexpression in a subset of human mammary tumors. *Proc Natl Acad Sci U S A* 1989;86:9193–7.
- Plowman GD, Whitney GS, Neubauer MG, Green JM, McDonald VL, Todaro GJ, et al. Molecular cloning and expression of an additional epidermal growth factor receptor-related gene. *Proc Natl Acad Sci U S A* 1990;87:4905–9.
- Plowman GD, Culouscou JM, Whitney GS, Green JM, Carlton GW, Foy L, et al. Ligand-specific activation of HER4/p180erbB4, a fourth member of the epidermal growth factor receptor family. *Proc Natl Acad Sci U S A* 1993;90:1746–50.
- Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. *Nat Rev Mol Cell Biol* 2006;7:505–16.
- Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol* 2001;2:127–37.
- Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J* 2000;19:3159–67.
- Schlessinger J. Common and distinct elements in cellular signaling via EGF and FGF receptors. *Science* 2004;306:1506–7.
- Hynes NE, MacDonald G. ErbB receptors and signaling pathways in cancer. *Curr Opin Cell Biol* 2009;21:177–84.
- Casalini P, Iorio MV, Galmozzi E, Ménard S. Role of HER receptors family in development and differentiation. *J Cell Physiol* 2004;200:343–50.
- Yarden Y, Pines G. The ERBB network: at last, cancer therapy meets systems biology. *Nat Rev Cancer* 2012;12:553–63.
- The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. *Nature* 2012;490:61–70.
- Arteaga C, Engelman J. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. *Cancer Cell* 2014;25:282–303.
- Klapper LN, Glathe S, Vaisman N, Hynes NE, Andrews GC, Sela M, et al. The ErbB-2/HER2 oncoprotein of human carcinomas may function solely as a shared coreceptor for multiple stroma-derived growth factors. *Proc Natl Acad Sci U S A* 1999;96:4995–5000.
- Tzahar E, Waterman H, Chen X, Levkowitz G, Karunakaran D, Lavi S, et al. A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. *Mol Cell Biol* 1996;16:5276–87.
- Guy PM, Platko JV, Cantley LC, Cerione RA, Carraway KL. Insect cell-expressed p180^{erbB3} possesses an impaired tyrosine kinase activity. *Proc Natl Acad Sci U S A* 1994;91:8132–6.
- Shi F, Telesco SE, Liu Y, Radhakrishnan R, Lemmon MA. ErbB3/HER3 intracellular domain is competent to bind ATP and catalyze autophosphorylation. *Proc Natl Acad Sci U S A* 2010;107:7692–7.
- Telesco SE, Shih AJ, Jia F, Radhakrishnan R. A multiscale modeling approach to investigate molecular mechanisms of pseudokinase activation and drug resistance in the HER3/ErbB3 receptor tyrosine kinase signaling network. *Mol Biosyst* 2011;7:2066–80.
- Alimandi M, Romano A, Curia M, Muraro R, Fedi P, Aaronson S, et al. Cooperative signaling of ErbB3 and ErbB2 in neoplastic transformation and human mammary carcinomas. *Oncogene* 1995;10:1813–21.
- Wallasch C, Weiss FU, Niederfellner G, Jallal B, Issing W, Ullrich A. Heregulin-dependent regulation of HER2/neu oncogenic signaling by heterodimerization with HER3. *EMBO J* 1995;14:4267–75.
- Pinkas-Kramarski R, Soussan L, Waterman H, Levkowitz G, Alroy I, Klapper L, et al. Diversification of Neu differentiation factor and epidermal growth factor signaling by combinatorial receptor interactions. *EMBO J* 1996;15:2452–67.
- Baulida J, Kraus MH, Alimandi M, Paolo Di Fiore P, Carpenter G. All ErbB receptors other than the epidermal growth factor receptor are endocytosis impaired. *J Biol Chem* 1996;271:5251–7.
- Worthylake R, Opresko LK, Wiley HS. ErbB-2 Amplification inhibits down-regulation and induces constitutive activation of both ErbB-2 and epidermal growth factor receptors. *J Biol Chem* 1999;274:8865–74.
- Lenferink AEG, Pinkas-Kramarski R, van de Poll MLM, van Vugt MJH, Klapper LN, Tzahar E, et al. Differential endocytic routing of homo- and hetero-dimeric ErbB tyrosine kinases confers signaling superiority to receptor heterodimers. *EMBO J* 1998;17:3385–97.
- Waterman H, Alroy I, Strano S, Seger R, Yarden Y. The C-terminus of the kinase-defective neuregulin receptor ErbB-3 confers mitogenic superiority and dictates endocytic routing. *EMBO J* 1999;18:3348–58.

27. Sliwkowski MX, Schaefer G, Akita W, Lofgrens JA, Fitzpatrick VD, Nuijens A, et al. Coexpression of erbB2 and erbB3 proteins reconstitutes a high affinity receptor for heregulin. *J Biol Chem* 1994;269:14661–5.
28. Falls D. Neuregulins: functions, forms, and signaling strategies. *Exp Cell Res* 2003;284:14–30.
29. Mei L, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nat Rev Neurosci* 2008;9:437–52.
30. Wang JY, Miller SJ, Falls DL. The N-terminal region of neuregulin isoforms determines the accumulation of cell surface and released neuregulin ectodomain. *J Biol Chem* 2001;276:2841–51.
31. Sheng Q, Liu X, Fleming E, Yuan K, Piao H, Chen J, et al. An activated ErbB3/*NRG1* autocrine loop supports in vivo proliferation in ovarian cancer cells. *Cancer Cell* 2010;17:298–310.
32. Wilson TR, Lee DY, Berry L, Shames DS, Settleman J. Neuregulin-1-mediated autocrine signaling underlies sensitivity to HER2 kinase inhibitors in a subset of human cancers. *Cancer Cell* 2011;20:158–72.
33. Lyne J, Melhem M, Finley C, Wen D, Liu N, Deng D, et al. Tissue expression of neu differentiation factor/hergulin and its receptor complex in prostate cancer and its biologic effects on prostate cancer cells in vitro. *Cancer J Sci Am* 1997;3:21–30.
34. Fernandez-Cuesta L, Plenker D, Osada H, Sun R, Menon R, Leenders F, et al. CD74-*NRG1* fusions in lung adenocarcinoma. *Cancer Discov* 2014;4:415–22.
35. Nakaoku T, Tsuta K, Ichikawa H, Shiraishi K, Sakamoto H, Enari M, et al. Druggable oncogene fusions in invasive mucinous lung adenocarcinoma. *Clin Cancer Res* 2014;20:3087–93.
36. Gow C, Wu S, Chang Y, Shih J. Multidriver mutation analysis in pulmonary mucinous adenocarcinoma in Taiwan: identification of a rare CD74-*NRG1* translocation case. *Med Oncol* 2014;31:34.
37. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. *J Thorac Oncol* 2011;8:381–5.
38. Tsuta K, Kawago M, Inoue E, Yoshida A, Takahashi F, Sakurai H, et al. The utility of the proposed IASLC/ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations. *Lung Cancer* 2013;81:371–6.
39. Warth A, Muley T, Meister M, Stenzinger A, Thomas M, Schirmacher P, et al. The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. *J Clin Oncol* 2012;30:1438–46.
40. Yoshizawa A, Motoi N, Riely GJ, Sima CS, Gerald WL, Kris MG, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. *Mod Pathol* 2011;24:653–64.
41. Bouyain S, Longo PA, Li S, Ferguson KM, Leahy DJ. The extracellular region of ErbB4 adopts a tethered conformation in the absence of ligand. *Proc Natl Acad Sci U S A* 2005;102:15024–9.
42. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chiriac LR, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in pre-clinical lung cancer models. *Oncogene* 2008;27:4702–11.
43. Konecny GE, Pegram MD, Venkatesan N, Finn R, Yang G, Rahmeh M, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res* 2006;66:1630–9.
44. Molina MA, Codony-servat J, Albanell J, Baselga J. Trastuzumab (Herceptin), a humanized anti-HER2 receptor monoclonal antibody, inhibits basal and activated HER2 ectodomain cleavage in breast cancer cells. *Cancer Res* 2001;61:4744–9.
45. Engelman JA, Janne PA, Mermel C, Pearlberg J, Mukohara T, Fleet C, et al. ErbB-3 mediates phosphoinositide 3-kinase activity in gefitinib-sensitive non-small cell lung cancer cell lines. *Proc Natl Acad Sci U S A* 2005;102:3788–93.
46. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;316:1039–43.
47. Scaltriti M, Verma C, Guzman M, Jimenez J, Parra JL, Pedersen K, et al. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. *Oncogene* 2009;28:803–14.
48. Garrett J, Sutton C, Kuba M, Cook R, Arteaga C. Dual blockade of HER2 in HER2-overexpressing tumor cells does not completely eliminate HER3 function. *Clin Cancer Res* 2013;19:610–9.
49. Garrett JT, Olivares MG, Rinehart C, Granja-Ingram ND, Sánchez V, Chakrabarty A, et al. Transcriptional and posttranslational up-regulation of HER3 (ErbB3) compensates for inhibition of the HER2 tyrosine kinase. *Proc Natl Acad Sci U S A* 2011;108:5021–6.
50. Agus DB, Akita RW, Fox WD, Lewis GD, Higgins B, Pisacane PI, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2002;2:127–37.
51. Junttila TT, Akita RW, Parsons K, Fields C, Phillips GDL, Friedman LS, et al. Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941. *Cancer Cell* 2009;15:429–40.
52. Richards DA, Braiteh FS, Garcia AA, Denlinger CS, Conkling PR, Edenfield WJ, et al. A phase 1 study of MM-111, a bispecific HER2/HER3 antibody fusion protein, combined with multiple treatment regimens in patients with advanced HER2-positive solid tumors. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 651).
53. Denlinger CS, Sym SJ, Bendell JC, Alsina M, Watkins D, Chao Y, et al. Randomized open-label phase 2 study of MM-111 and paclitaxel (PTX) with trastuzumab (TRAS) in patients with HER2-expressing carcinomas of the distal esophagus, gastroesophageal (GE) junction, and stomach who have failed front-line metastatic or locally advanced therapy. *J Clin Oncol* 32:5s, 2014 (suppl; abstr TPS4148).
54. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. *Nat Rev Drug Discov* 2014;13:140–56.
55. Schoeberl B, Pace E, Fitzgerald J, Harms B, Xu L, Nie L, et al. Therapeutically targeting ErbB3: a key node in ligand-induced activation of the ErbB receptor-PI3K axis. *Sci Signal* 2009;2:ra31.
56. Schoeberl B, Faber AC, Li D, Liang M-C, Crosby K, Onsum M, et al. An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation. *Cancer Res* 2010;70:2485–94.
57. McDonagh CF, Huhlov A, Harms BD, Adams S, Paragas V, Oyama S, et al. Antitumor activity of a novel bispecific antibody that targets the ErbB2/ErbB3 oncogenic unit and inhibits heregulin-induced activation of ErbB3. *Mol Cancer Ther* 2012;11:582–93.
58. Fitzgerald JB, Johnson BW, Baum J, Adams S, Iadevaia S, Tang J, et al. MM-141, an IGF-IR- and ErbB3-directed bispecific antibody, overcomes network adaptations that limit activity of IGF-IR inhibitors. *Mol Cancer Ther* 2014;13:410–25.
59. Schaefer G, Haber L, Crocker LM, Shia S, Shao L, Dowbenko D, et al. A two-in-one antibody against HER3 and EGFR has superior inhibitory activity compared with monospecific antibodies. *Cancer Cell* 2011;20:472–86.
60. Garrett JT, Sutton CR, Kurupi R, Bialucha CU, Ettenberg SA, Collins SD, et al. Combination of antibody that inhibits ligand-independent HER3 dimerization and a p110 α inhibitor potently blocks PI3K signaling and growth of HER2+ breast cancers. *Cancer Res* 2013;73:6013–23.
61. Mirschberger C, Schiller CB, Schröml M, Dimoudis N, Friess T, Gerdes CA, et al. RG7116, a therapeutic antibody that binds the inactive HER3 receptor and is optimized for immune effector activation. *Cancer Res* 2013;73:5183–94.
62. Arnedos M, Denlinger CS, Harb WA, Rixe O, Morris JC, Dy GK, et al. A phase I study of MM-121 in combination with multiple anticancer therapies in patients with advanced solid tumors. *J Clin Oncol* 31, 2013 (suppl; abstr 2609).
63. Cleary JM, McRee AJ, O'Neil BH, Sharma S, Pearlberg J, Manoli S, et al. A phase 1 study of MM-121 (a fully human monoclonal antibody targeting the epidermal growth factor receptor family member ErbB3) in combination with cetuximab and irinotecan in patients with advanced cancers. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 3076).
64. Liu J, Ray-Coquard IL, Selle F, Poveda A, Cibula D, Hirte HW, et al. A phase II randomized open-label study of MM-121, a fully human monoclonal antibody targeting ErbB3, in combination with weekly paclitaxel versus weekly paclitaxel in patients with platinum-resistant/refractory ovarian cancers. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5519).
65. Higgins MJ, Doyle C, Paepke S, Azaro A, Martin M, Semiglazov V, et al. A randomized, double-blind phase II trial of exemestane plus MM-121 (a monoclonal antibody targeting ErbB3) or placebo in postmenopausal

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- women with locally advanced or metastatic ER+/PR+, HER2-negative breast cancer. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 587).
66. Sequist LV, Lopez-Chavez A, Doebele RC, Gray JE, Harb WA, Modiano MR, et al. A randomized phase 2 trial of MM-121, a fully human monoclonal antibody targeting ErbB3, in combination with erlotinib in EGFR wild-type NSCLC patients. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 8051).
 67. Isakoff SJ, Saleh MN, Lugovskoy A, Manoli S, Czibere AG, LoRusso P, et al. First-in-human study of MM-141: a novel tetravalent monoclonal antibody targeting IGF-1R and ErbB3. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 3068).
 68. Cervantes-Ruiperez A, Juric D, Hidalgo M, Messersmith WA, Blumenschein GR, Baselga J, et al. A phase I study of MEHD7945A (MEHD), a first-in-class HER3/EGFR dual-action antibody, in patients (pts) with refractory/recurrent epithelial tumors: expansion cohorts. *J Clin Oncol* 30, 2012 (suppl; abstr 2568).
 69. Reynolds KL, Juric D, Baselga J, Alsina M, Tabernero J, et al. A phase 1 study of LJM716 in patients with esophageal squamous cell carcinoma, head and neck cancer, or HER2-overexpressing metastatic breast or gastric cancer. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 2517).
 70. Im SA, Juric D, Baselga J, Kong A, Martin P, Lin CC, et al. A phase 1 dose-escalation study of anti-HER3 monoclonal antibody LJM716 in combination with trastuzumab in patients with HER2-overexpressing metastatic breast or gastric cancer. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 2519).
 71. Meulendijks D, Lolkema MPJK, Voest EE, De Jonge MJ, Sleijfer S, Schellens JHM, et al. A first-in-human trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in patients with advanced/metastatic tumors of epithelial cell origin expressing HER3 protein. *J Clin Oncol* 31, 2013 (suppl; abstr 2522).
 72. Berlin J, Keedy VL, Janne PA, Yee L, Rizvi NA, Jin X, et al. A first-in-human phase I study of U3-1287 (AMG 888), a HER3 inhibitor, in patients (pts) with advanced solid tumors. *J Clin Oncol* 29: 2011 (suppl; abstr 3026).

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