Rationale for a Phase II Trial of Pertuzumab, a HER-2 Dimerization Inhibitor, in Patients with Non–Small Cell Lung Cancer

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Abstract

Background and Rationale: In non–small cell lung cancer (NSCLC) *HER-2* gene amplification and 3+ staining by immunohistochemistry are present in only 2% to 5% of the tumors. Therefore, relatively few patients with lung cancer are likely to benefit from treatment with trastuzumab, the humanized monoclonal antibody that is effective in the 20% of patients with breast cancer and *HER-2* gene amplification and/or 3+ staining by immunohistochemistry. Pertuzumab (rhuMAb 2C4), a humanized HER2 antibody, represents a new class of targeted therapeutics that inhibit dimerization of HER2 with ligand-activated EGFR (HER1), HER3, and HER-4. Pertuzumab can have antitumor activity in patients with HER-2 present on the tumor without gene amplification or 3+ staining by immunohistochemistry. Preclinical xenograft studies have shown efficacy of pertuzumab in treating NSCLC. Therefore, a trial was undertaken for patients with relapsed NSCLC.

Materials and Methods: Subjects with advanced or recurrent NSCLC treated previously with chemotherapy were treated with pertuzumab (840 mg i.v. loading dose then 420 mg every 3 weeks). Mandatory fresh tumor biopsies before treatment were obtained for biomarker analysis including HER-2 phosphorylation. Computed tomography scans were obtained every two cycles to assess tumor response. Tumor response (response evaluation criteria in solid tumors criteria) was the primary end point.

Results: As reported in a previous abstract, none of the 33 patients with NSCLC and evaluable disease had a response to the treatment.

Conclusions: Pertuzumab has an appropriate rationale for therapeutic use in patients with NSCLC. A phase II trial in patients with NSCLC has completed enrollment, and the details of the trial will be presented in a future publication. This article will review the preclinical rationale for undertaking a study of pertuzumab for patients with relapsed NSCLC.

There have been extensive efforts to develop agents effective against the HER family of tyrosine kinase receptors for the treatment of human solid tumors. The HER family of receptors is composed of four related receptors, the epidermal growth factor receptor (EGFR, HER-1, or ErbB1), HER-2 (ErbB2), HER-3 (ErbB3), and HER-4 (ErbB4) (1–3). These receptors are involved in cell signaling pathways that cause increased cell proliferation, cell motility, and cell survival (2, 3).

The most extensively studied HER family member in non–small cell lung cancer (NSCLC) is the EGFR and is the focus of this conference proceeding. The EGFR has been an attractive candidate for the development of antineoplastic agents because it is detected by immunohistochemistry in 50% to 80% of NSCLCs and is activated by amplification and/or mutations in a subset of these tumors (4–6). This biology prompted the development of small-molecule tyrosine kinase inhibitors that act on the intracellular portion of the EGFR (gefitinib and erlotinib) and of a monoclonal antibody directed against the extracellular portion of the EGFR (cetuximab). The efficacy of erlotinib has now been shown in NSCLC. A phase II trial for patients with previously treated NSCLC given erlotinib showed that 12% had a partial response and a median survival duration of 8 months (7). In addition, in patients with previously treated NSCLC, those treated with erlotinib have a median survival 2 months longer (6.7 versus 4.7 months) than those given placebo (8). This survival benefit has led to approval by the U.S. Food and Drug Administration of erlotinib for patients with relapsed NSCLC.

The other HER family member that has been successfully pursued as a therapeutic target in other solid tumors is HER-2 or ErbB2. HER-2 is amplified in a subset of human breast cancers, and women with amplified HER-2 have a shorter survival than women without amplification (9). This observation prompted the development of a humanized monoclonal antibody directed against the extracellular domain of the HER-2

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receptor, trastuzumab (10). This target has been validated because trastuzumab has shown single-agent antitumor activity against breast cancer with evidence of abundant HER-2, and the addition of trastuzumab to combination chemotherapy can prolong survival for patients with advanced breast cancer (10, 11).

Trastuzumab has also been tested in phase II trials as a single agent and in combination with cytotoxic chemotherapy for patients with NSCLC (12–16). A single-agent trial has been done for 22 evaluable patients whose tumors had 2+ to 3+ HER-2 staining by immunohistochemistry who were then treated with trastuzumab. There was a single response of 6 months, duration among the 22 patients treated with trastuzumab (5%). Trastuzumab, in combination with chemotherapy, has been tested in patients with previously untreated advanced NSCLC with HER-2 detectable by immunohistochemistry. These studies have documented the frequency of HER-2 detected by immunohistochemistry in NSCLC. More than 1,000 patients with previously untreated NSCLC have been screened for inclusion into prospective clinical trials, which required the presence of HER-2 to be eligible for potential treatment with trastuzumab (13, 14, 16, 17). Approximately 60% of the NSCLC tumor specimens had no detectable HER-2, 20% had 1+, 15% were 2+, and 5% were 3+. The trials did not produce an obvious increase in response rates or survival in the patients with detectable HER-2 whose treatment included trastuzumab compared with patients treated with chemotherapy alone (13, 14, 16, 17). Thus, the trials have not yet produced any convincing evidence of antitumor activity of trastuzumab in NSCLC. However, HER-2 may be involved in the sensitivity of NSCLC to treatment with gefitinib or erlotinib. Patients with EGFR mutations and increased HER-2 copy number assessed by fluorescent *in situ* hybridization had a significantly greater response rate to gefitinib compared with those with EGFR mutations but without an increase in HER-2 copy number (response rates 87.5% versus14.2%, respectively; $P = 0.01$; ref. 18).

Another therapeutic agent has been developed against the HER-2 target for solid tumors in adults. The monoclonal antibody pertuzumab is directed against the dimerization domain of the HER-2 molecule to inhibit the homodimerization and heterodimerization of HER-2 with other ErbB family members (19, 20). This agent has the potential to be active in the 40% of NSCLCs with detectable HER-2. A phase II trial has been completed in NSCLC but has yet to be published in full (21). This article will review mechanism of action of pertuzumab and its rationale for testing in NSCLC compared with other tumors, particularly breast cancer. We will also cover pharmacologic variables studied *in vitro, in vivo*, and in phase I testing to achieve the proposed therapeutic targets of the drug. The formal results of the phase II trial will be presented in an upcoming publication.

Mechanism of Action

HER-2 is the one member of the HER family of receptor tyrosine kinases that does not have a known ligand (1). The accumulation of excess HER-2 on the cell membrane causes constitutive activation via the homodimerization of the HER-2 molecules and thus drives tumor growth (19, 22). The HER-2 molecule preferentially dimerizes with the other members of the HER family after they undergo ligand activation. Pertuzumab is directed against the dimerization domain of the HER-2 molecule. It prevents the dimerization with HER-2 itself and other activated HER family receptors and thereby interrupts the growth signals mediated by the HER-2 homodimers and ligand-activated heterodimers (Fig. 1).

Rationale

As noted above, the HER-2 receptor is detectable by immunohistochemistry in ~40% of patients with untreated NSCLC. However, it is less common for the HER-2 receptor to be abundantly present or undergo gene amplification. The HER-2 receptor is detected and scored as 2+ or 3+ by immunohistochemical staining in ~20% of the specimens examined (13, 14, 16, 17, 23). Gene amplification and 3+ staining by immunohistochemistry is present in only 2% to 5% of the tumors (17, 23). Thus, the frequency of gene amplification and 3+ staining in human lung cancer is >5-fold less common than in breast cancer, the population in which trastuzumab has shown antitumor activity (9–11). Therefore, if the HER-2 therapeutic target in lung cancer is similar to that in breast cancer, it is probable that <5% of patients would clinically benefit from trastuzumab administration.

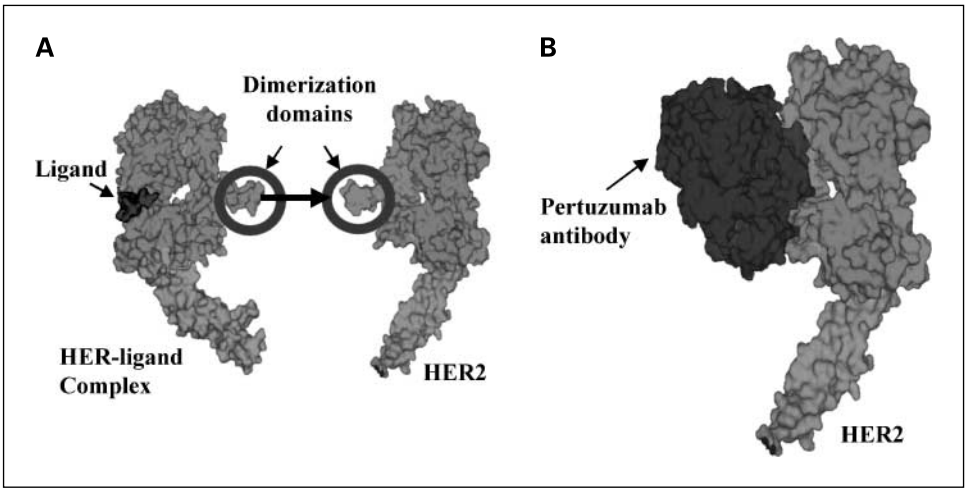

Fig. 1. Depiction of the HER family members, the ligand-binding site, the dimerization domain, and pertuzumab binding to the binding site. *A,* right, gray, HER-2 molecule; ligand (*light gray, left*) binds to the ligand-binding site of one of the partners of HER-2 (EGFR, HER-3, or HER-4) identified as the HER-ligand complex. The dimerization domains are represented by the projections inside the circles (*arrows*). *B,* the pertuzumab antibody (*black, arrow*) binds to the dimerization domain and therefore prevents the dimerization of HER-2 to the other HER family members. Figure provided by Genentech.

However, if a therapeutic agent could be effective against NSCLC with fewer HER-2 receptors (the 40% with detectable HER-2 receptors), an increased proportion of lung cancer patients could benefit. Therefore, preclinical testing has been done to determine if the HER-2 receptor and its dimerization partners can be effectively targeted with the pertuzumab antibody.

In vitro and *In vivo* Studies

Most of the *in vitro* studies have been done in breast cancer, prostate cancer, and colon cancer cell lines (20, 24, 25). Pertuzumab disrupted HER-2 dimerization with EGFR, HER-3, and HER-4 and led to decreased growth rates. Pertuzumab can inhibit the survival of the breast cancer cell line BT474, a cell line with abundant HER-2, and the GEO colon cancer cell line, a cell line with detectable HER-2 (20, 25). Pertuzumab blocked growth stimulation by the ligands heregulin and epidermal growth factor in four breast cancer cell lines, two prostate cancer cell lines, and one colon cancer cell line (19, 20, 25).

There has been relatively little published *in vivo* work on pertuzumab in NSCLC. It has been studied in two different lung cancer xenograft models, Calu-3 and QG56 (26). Calu-3 has abundant HER-2 with undetectable EGFR by immunohistochemistry of athymic nude mouse xenografts, whereas QG56 has abundant EGFR and undetectable HER-2. However, Western blot analyses of the NSCLC cell line, Calu-3, shows detectable EGFR (27). Pertuzumab caused a 75% growth inhibition of both Calu-3 and QG56 NSCLC xenografts despite the differences in their detectable EGFR and HER-2. Pertuzumab can also inhibit the growth of breast and prostate cancer xenografts. Breast cancer cell lines with both high HER-2 (BT474) and low HER-2 (MCF-7) treated with pertuzumab have ~75% growth inhibition (19). No information has yet been identified, which shows that pertuzumab is active against tumor cell lines that have become resistant to treatment with trastuzumab. The androgen-dependent and androgen-independent prostate cancer cells treated with pertuzumab have ~75% growth inhibition as well. Thus, the pertuzumab antibody has both *in vitro* and *in vivo* evidence of antitumor activity in breast cancer, prostate cancer, and NSCLC. Pertuzumab has antitumor activity against lung cancer xenografts with both abundant and relatively little evidence of HER-2. These preclinical findings support the potential use of pertuzumab in lung cancer where the HER-2 is typically less abundant than in breast cancer.

Phase I Trial of Pertuzumab

The phase I trial of pertuzumab has been completed and reported (28). The phase I trial was not designed to reach a maximum tolerated dose but rather to reach the serum concentration at which antitumor activity was observed in the *in vitro* and *in vivo* experiments. The terminal half-life of ~21 days supports the every 3-week schedule that has been used in the phase II trial. The phase I testing showed that patients were able to tolerate doses of 15 mg/kg every 3 weeks. Doses >5 mg/kg given every 3 weeks produce serum concentrations in excess of 20 μg/mL, the concentration at which tumor growth *in vivo* was inhibited by 75% or more. These observations have led to a recommended phase II dosing of 840 mg [equivalent to 12 mg/kg in a 70 kg (154 lb) individual] given as a loading dose followed by 420 mg (equivalent to 6 mg/kg in a 70 kg individual) given every 3 weeks. This dose was used in the phase II trial that was just completed (21). Two of 20 patients with evaluable disease in the phase I study had evidence of antitumor response. One patient with ovarian cancer had a response that lasted 6 months, and a patient with islet cell carcinoma also had a response.

Phase II Trials of Pertuzumab

There have been four phase II trials of pertuzumab for patients with relapsed solid tumors, including NSCLC and prostate, ovarian, and breast cancers. The trial in NSCLC has completed accrual and has been reported in abstract form at the 2005 meeting of the World Conference on Lung Cancer (21). Patients with advanced or recurrent NSCLC previously treated with chemotherapy were treated with pertuzumab (840 mg i.v. loading dose then 420 mg every 3 weeks). Mandatory fresh tumor biopsies before treatment were obtained for biomarker analysis, including HER-2 phosphorylation. Computerized tomography scans were obtained every two cycles to assess tumor response. A subset of the patients underwent fluorodeoxyglucose-positron emission tomography scans. Tumor response (response evaluation criteria in solid tumors) was the primary end point. There have been no objective responses observed in the 33 evaluable patients. Three of the 12 patients who underwent serial positron emission tomography scans had a decrease in the SUV_{max} of >25% following treatment with pertuzumab. Further biological correlates that are being studied include EGFR and HER-2 status, phosphorylated EGFR status, phosphorylated HER-2 status, and evidence of response by fluorodeoxyglucose-positron emission tomography scanning. These will be reported in an upcoming publication.

Summary

The HER-2 receptor is a valid therapeutic target in breast cancer. The humanized monoclonal antibody developed against the HER-2 receptor, trastuzumab, causes partial responses as a single agent and increases the survival of patients with metastatic breast cancer and HER-2 DNA amplification treated with chemotherapy (10, 11). HER-2 amplification is present in ~20% of breast cancers. In contrast, gene amplification and 3+ staining by immunohistochemistry is present in only 2% to 5% of the tumors (17, 23). Therefore, trastuzumab may be an effective therapy for a small minority of patients with NSCLC, so this option should continue to be pursued.

Pertuzumab is being studied as a therapeutic agent in patients who have less HER-2 receptor in their lung cancer than those who have levels of HER-2 associated with clinical responses to trastuzumab. Although *HER-2* gene amplification or 3+ staining by immunohistochemistry is only present in 2% to 5% of patients with NSCLC, HER-2 expression detectable by immunohistochemistry is present in ~25% of NSCLCs (29, 30). If a new agent has antitumor activity in lung cancer or other types of cancers where the receptor density is less than that needed for trastuzumab antitumor activity, the agent can be used in a larger percentage of lung cancers. Therefore, further

preclinical studies will be needed to identify the characteristics of the tumors needed for pertuzumab to be effective.

Open Discussion

Dr. Jeffrey Engelman: This is one of the best-designed trials I've seen because you actually tried to get some good information. I think assaying phospho-erbB2 is fraught with potential errors, and I would not rely on those data. Taking tumor out of the xenograft and putting it right into liquid nitrogen is different than getting it sucked out a few times in the radiology suite, putting it down on the pad, looking at it, and then 2 minutes later, throwing it into liquid nitrogen. Obviously, the data were not out at the time that you were developing this study, but the patients to look at would be those Dr. Bunn identified with the HER-2 amplifications. Apparently, there are maybe more patients with the amplification than we originally thought.

Dr. Bruce Johnson: It is our intent to work a little bit more with this agent. We would like to see some kind of evidence of a clinical signal. The other approach is to do some more xenografts and to take a look at the cell lines that have been characterized now. With regard to the analysis, they did consider this issue and set specific time criteria about how long the sample could be out. Whether those criteria were met or not is unclear, but they had gone through it to find out that their measurable end point could be done in such a setting.

Dr. John Heymach: In xenograft models after about a half hour, all the phosphorylation with the EGFR receptor is gone.

Dr. David Johnson: This drug was developed at the same time as trastuzumab. It was dropped because it didn't seem to be as effective in the HER-2-amplified patients. It turns out to be as effective in the nonamplified as it is in the HER-2-amplified tumors, at least in preclinical data. That is why they thought NSCLC would be a reasonable population to look at. I agree that it might be interesting to look at it in the patients with amplification and those with mutation as well.

Dr. Glenwood Goss: I'd like to suggest that the clinical responses that we are seeing due to EGFR inhibition are unrelated to HER-2. The reasons why I am suggesting this—obviously, I don't have proof—are 3-fold. First, in the original trastuzumab studies, very few patients responded. Secondly, we now have these supporting antibody data, and thirdly, we haven't seen the dramatic response that we expected with the dual inhibitors. There are three points of evidence now to suggest that, at least for EGFR activity, the HER-2 heterodimer may not be that important and that what we are seeing is a mechanism that is unrelated to the dimerization with that receptor.

Dr. Engelman: I think there are several problems with that line of logic. The best evidence just came out from Paul Bunn's data that, in the EGFR mutation–positive patients, 88% responded if they were HER-2 amplified and only 14% responded if they were not HER-2 amplified. The response rate to trastuzumab was quite low in the lung cancer trials but it also is for erlotinib, it is 8%. A TKI is not equivalent to an antibody, so the fact that you don't see the same response rate from trastuzumab that you do with an EGFR TKI doesn't mean HER-2 is not implicated in lung cancer. Finally, in this trial there was only one patient with EGFR mutation, so to say that we didn't get that one response in that one patient would be a bit premature.

Dr. Goss: I accept all of that; I just put the idea out for discussion.

Dr. Thomas Lynch: At these meetings, we always end up concluding that we need phase II trials with pre- and posttreatment biopsies and with tissue required at relapse. Having done this now, what is your take on the feasibility of requiring these biopsies?

Dr. Bruce Johnson: My first comment is that you need relatively robust preclinical data to test the hypothesis before you go into human trial. This study was based on 18 tumors with just 4 responders among them. I think we would be well served to spend more time on xenograft models and relatively well-characterized cell lines. There is now a large array of lung cancer lines that are extensively characterized for mutational status. As a second issue, our scientific review committee said that if we are going to do a biopsy that is not for clinical care purposes, then it needs to be for a testable hypothesis and the trial needs to be designed with adequate statistical power to answer that question.

References

1. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127–37.
2. Baselga J, Arteaga CL. Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. J Clin Oncol 2005;23:2445–59.
3. Herbst RS, Bunn PA, Jr. Targeting the epidermal growth factor receptor in non-small cell lung cancer. Clin Cancer Res 2003;9:5813–24.
4. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
5. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
6. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004;101:13306–11.
7. Perez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. J Clin Oncol 2004;22:3238–47.
8. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–32.
9. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. Science 1987;235:177–82.
10. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719–26.
11. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–92.
12. Clamon G, Herndon J, Kern J, et al. Lack of trastuzumab activity in nonsmall cell lung carcinoma with overexpression of erb-B2:39810: a phase II trial of Cancer and Leukemia Group B. Cancer 2005;103:1670–5.
13. Krug LM, Miller VA, Patel J, et al. Randomized phase II study of weekly docetaxel plus trastuzumab versus weekly paclitaxel plus trastuzumab in patients with previously untreated advanced nonsmall cell lung carcinoma. Cancer 2005;104:2149–55.
14. Langer CJ, Stephenson P, Thor A, et al. Trastuzumab in the treatment of advanced non-small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group study 2598. J Clin Oncol 2004;22:1180–7.
15. Gatzemeier U, Groth G, Butts C, et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Ann Oncol 2004;15:19–27.
16. Zinner RG, Glisson BS, Fossella FV, et al. Trastuzumab in combination with cisplatin and gemcitabine in patients with Her2-overexpressing, untreated, advanced non-small cell lung cancer: report of a phase II trial and findings regarding optimal identification of patients with Her2-overexpressing disease. Lung Cancer 2004;44:99–110.
17. Heinmoller P, Gross C, Beyser K, et al. HER2 status

in non-small cell lung cancer: results from patient screening for enrollment to a phase II study of herceptin. Clin Cancer Res 2003;9:5238–43.
18. Cappuzzo F, Varella-Garcia M, Shigematsu H, et al. Increased HER2 gene copy number is associated with response to gefitinib therapy in epidermal growth factor receptor-positive non-small-cell lung cancer patients. J Clin Oncol 2005;23:5007–18.
19. Agus DB, Akita RW, Fox WD, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. Cancer Cell 2002;2:127–37.
20. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. Cancer Res 2004;64:2343–6.
21. Herbst R, Davies A, Johnson B, et al. Efficacy and safety of single agent pertuzumab (rhuMAB 2C4), a HER dimerization inhibitor, in non-small cell lung cancer (NSCLC) patients after prior chemotherapy. In: 11th World Conference on Lung Cancer. Barcelona (Spain); 2005. p. S62.
22. Franklin MC, Carey KD, Vajdos FF, et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell 2004;5:317–28.
23. Hirsch FR, Varella-Garcia M, Franklin WA, et al. Evaluation of HER-2/*neu* gene amplification and protein expression in non-small cell lung carcinomas. Br J Cancer 2002;86:1449–56.
24. Nahta R, Yuan LX, Zhang B, et al. Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. Cancer Res 2005;65:11118–28.
25. Jackson JG, St Clair P, Sliwkowski MX, et al. Blockade of epidermal growth factor- or heregulin-dependent ErbB2 activation with the anti-ErbB2 monoclonal antibody 2C4 has divergent downstream signaling and growth effects. Cancer Res 2004;64:2601–9.
26. Friess T, Scheuer W, Hasmann M. Combination treatment with erlotinib and pertuzumab against human tumor xenografts is superior to monotherapy. Clin Cancer Res 2005;11:5300–9.
27. Engelman JA, Janne PA, Mermel 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.
28. Agus DB, Gordon MS, Taylor C, et al. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. J Clin Oncol 2005;23:2534–43.
29. Pelosi G, Del Curto B, Dell'Orto P, et al. Lack of prognostic implications of HER-2/*neu* abnormalities in 345 stage I non-small cell carcinomas (NSCLC) and 207 stage I-III neuroendocrine tumours (NET) of the lung. Int J Cancer 2005;113:101–8.
30. Nakamura H, Kawasaki N, Taguchi M, et al. Association of HER-2 overexpression with prognosis in nonsmall cell lung carcinoma: a metaanalysis. Cancer 2005;103:1865–73.

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