Her2-Targeted Therapies in Non–Small Cell Lung Cancer

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Abstract Sensitivity to Her2-directed therapies is complex and involves expression not only of Her2 but also of other epidermal growth factor receptor (EGFR) family members, their ligands, and molecules that influence pathway activity, such as insulin-like growth factor-1 receptor, PTEN, and p27. The EGFR experience has taught us that responses can easily be diluted in an unselected cohort of patients. To date, trials of Her2-targeted therapies, such as trastuzumab, have been insufficiently powered to determine whether patients with non–small cell lung cancer (NSCLC) with Her2 gene amplification (rather than overexpression by immunohistochemistry) may benefit from these agents. It is unclear whether agents targeting Her2 might prove successful in future clinical trials in a highly selected patient cohort, either with Her2 amplification or Her2 gene mutations. The frequency of Her2 mutations in NSCLC may be too low to justify a prospective clinical trial in this patient group. The frequency of Her2 amplification (2-23%) in NSCLC and the widespread availability of Her2 fluorescence *in situ* hybridization analysis may justify a final study of trastuzumab monotherapy in this patient population. The role played by Her2 as the obligate heterodimerization partner for the other EGFR family members renders Her2 an attractive target irrespective of receptor overexpression. The most promising Her2-targeted strategy will likely prove to be combinatorial approaches using an EGFR tyrosine kinase inhibitor together with Her2 dimerization inhibitors.

In 1984, Downward et al. showed the sequence similarity of the human epidermal growth factor receptor (EGFR) to sequences from the oncogenic v-erb-B transforming protein of avian erythroblastosis virus (1). This was one of the first reports of a connection between the human EGFR and cellular transformation. Since then, EGFR has been placed in the subclass I of the receptor tyrosine kinase superfamily along with three other members (Her2/ErbB2, ErbB3, and ErbB4). Altered expression of the EGFR family or their ligands has been observed in diverse tumor types and, in the case of EGFR and Her2, associated with poor prognosis (2).

The intrinsic oncogenic properties of the EGFR family resulting from receptor overexpression, together with their transmembrane localization, has made this family an attractive target for drug development. Current strategies can be divided into antibody therapies targeting the extracellular domain of the receptor and small molecules that compete with ATP for tyrosine kinase activation.

There are extensive clinical trial data in non–small cell lung cancer (NSCLC) with the small-molecule inhibitors of EGFR (gefitinib and erlotinib), with erlotinib showing a survival advantage following chemotherapy (3). In-depth analysis of clinical trial data, together with EGFR sequencing and gene expression data, has enabled a sensitive patient cohort to be better defined. Data from laboratory studies and clinical trials have shown that EGFR amplification, increased Her2 copy number, or mutations within the EGFR tyrosine kinase domain may increase sensitivity to EGFR small-molecule tyrosine kinase inhibitors (4–7).

Her2 receptor overexpression occurs in 11% to 32% of NSCLC tumors, with increased gene copy number (amplification) documented in 2% to 23% of cases. However, Her2-targeted agents in patients overexpressing this receptor tyrosine kinase have proven less successful in clinical trials. Trial data will be reviewed, and lessons learnt from the EGFR experience, together with mechanisms of resistance, will be discussed to define variables for future studies with Her2-targeted therapies.

EGFR Family Signal Transduction

Following the interaction of ligands (such as EGF, transforming growth factor-α, and amphiregulin) with EGFR, homodimerization or heterodimerization with other family members occurs, activating the inherent kinase activity of the protein, thereby promoting the autophosphorylation of tyrosine residues in the cytoplasmic COOH-terminal region (ref. 8; Fig. 1). The Her2 receptor is unusual in that it does not interact with the EGF ligand family. This is in keeping with the markedly different structure of the extracellular region of Her2, which has an inflexible conformation similar to the ligand-activated structure. This renders the Her2 receptor open for interaction with other ligand-bound members of the EGFR

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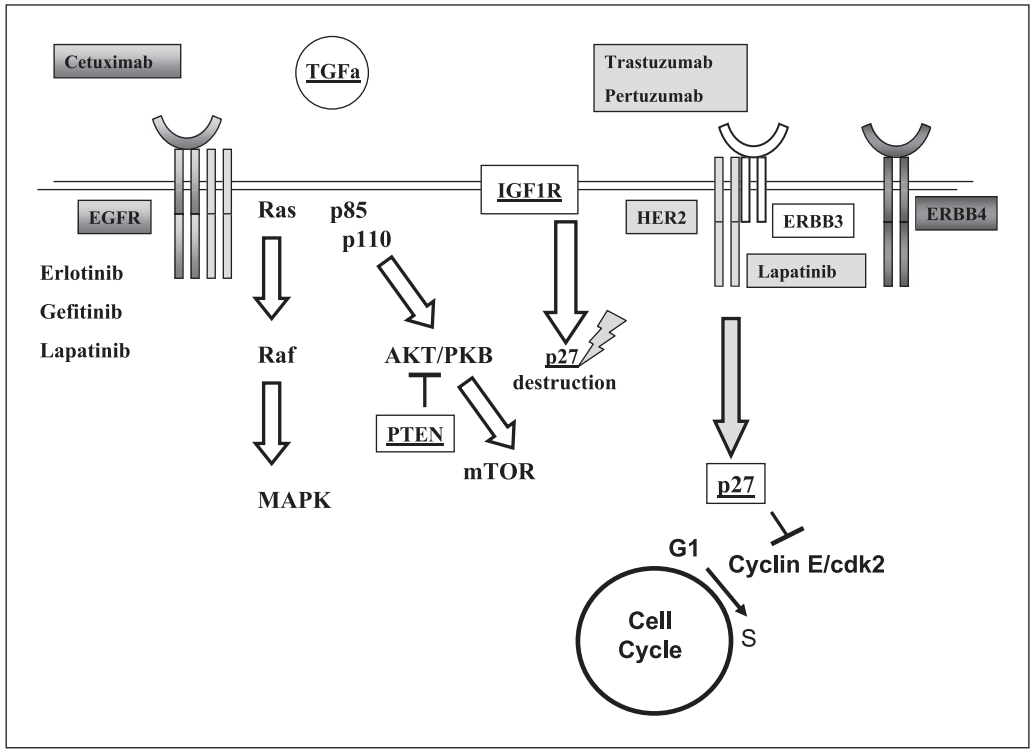

Fig. 1. EGFR family showing small-molecule tyrosine kinase inhibitors (intracellular) and monoclonal antibodies to EGFR and Her2 (extracellular). Molecules regulating sensitivity or resistance to trastuzumab are underlined.

family. It is likely that the unusual structural properties of Her2 are responsible for its status as the favored heterodimerization partner with other family members.

Following receptor dimerization, multiple downstream pathways may be activated, including the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin and mitogen-activated protein kinase pathways, along with activation of the signal transducer and activator of transcription proteins and the Src tyrosine kinases. Pathway activation is modulated by receptor specificity for interaction with downstream signaling targets.

Her2 is frequently overexpressed in breast, ovarian, and gastric malignancies. Overexpression is also observed in NSCLC, and a recent meta-analysis revealed a significantly poorer prognosis in this patient cohort (9). The association of Her2 overexpression with poor prognosis and the availability of EGFR family–targeted therapies has prompted interest in the use of these agents in the management of NSCLC.

Her2 Heterodimerization

Heterodimerization of EGFR family members enhances the repertoire of downstream signaling pathways that may be activated following ligand stimulation (10–12). No ligand has yet been identified for Her2, and evidence suggests that this receptor acts as the favored heterodimerization partner for other family members and may enhance EGFR family signaling (11, 13, 14).

Overexpression of EGFR and the rodent Her2 receptor act synergistically to promote cellular transformation in NIH-3T3 cells (15). In this cell system, either receptor alone fails to induce cellular transformation.

Intriguingly, ErbB3 has reduced tyrosine kinase activity due to sequence alterations in the kinase domain and is therefore critically dependent on receptor heterodimerization for signal initiation following ligand stimulation. In support of the role played by Her2 in facilitating ErbB3-mediated signal transduction (and mirroring results observed with EGFR), both receptors act synergistically in NIH-3T3 cellular transformation assays, and Her2/ErbB3 heterodimerization results in increased tyrosine phosphorylation of ErbB3 (16, 17). ErbB4 also requires either Her2 or EGFR to transform fibroblasts.

Her2 Receptor Abnormalities in NSCLC

The frequency of Her2 receptor overexpression defined by immunohistochemistry (2+/3+) in NSCLC ranges from 11% to 32%. Patients with Her2 3+ tumors (frequency, 0.5-10%) have a poorer prognosis and survival (18). Frequency of gene amplification defined by fluorescence *in situ* hybridization (FISH) ranges from 2% to 23%, depending on the study (5, 18, 19). Importantly, amplification of the Her2 locus is more frequent in tumors with bronchioloalveolar carcinoma histology, with 30% showing FISH positivity in one study (20). In the recent meta-analysis confirming the unfavorable prognosis associated with Her2 overexpression in NSCLC, the frequency of Her2 positivity was significantly increased in patients with adenocarcinoma histology (38% versus 16% in squamous cell carcinoma and 17.9% in large cell carcinoma; ref. 9).

Scientists from the Cancer Genome Project were the first to identify mutations within the tyrosine kinase domain of Her2 in patients with NSCLC (21). Somatic mutations were predominantly insertion/duplications between amino acids 774 and 779, with one tumor harboring a missense mutation at 755 (Fig. 2). Intriguingly, these in-frame insertions were found in a similar position to the deletion mutations observed

in EGFR in NSCLC. EGFR and Her2 mutations are located in the C-helix region of the kinase domain (Fig. 3).

All mutations occurred in tumors of adenocarcinoma histology (5 of 51, 10%), and four of five cases were current or ex smokers (whereas the majority of patients with EGFR mutations are never smokers). Mutations were not found in the presence of receptor overexpression or with EGFR/KRAS/NRAS or BRAF mutations.

In contrast, a follow-up study incorporating sequencing of EGFR/KRAS and Her2 in different populations identified similar Her2 mutations exclusively in NSCLC of adenocarcinoma histology at a lower frequency (adenocarcinoma, 11 of 394; ref. 22). Her2 mutation frequency seemed to be higher in the Japanese population (5.1% of adenocarcinomas versus 0% of a U.S. cohort). Furthermore, similar to EGFR mutation data, Her2 mutations were more common in female patients and never or light smokers. A recent Japanese study of 122 patients with surgically treated NSCLC documented only one insertion mutation in exon 20 (amino acids 775-776) of Her2 in a female nonsmoker with adenocarcinoma histology (23).

A study of 89 NSCLC patients revealed no mutations in exon 20 of Her2 (5). Similarly, Takano et al. failed to identify Her2 mutations in exons 18 to 24 of 66 patients with NSCLC, and data presented in abstract form by Han et al. failed to identify mutations in exons 19 and 20 in 59 patients studied (24, 25).

The reasons for the differences in frequency of both receptor mutations and smoking status are unclear. Nevertheless, the mutations observed in three studies appear in the same eight-codon region, and all occurred in adenocarcinomas. There are no reports of simultaneous mutations in EGFR, indicating that one mutation is sufficient for either adenocarcinoma tumor development or maintenance.

Her2 Receptor Targeting

The most widely used Her2 monoclonal antibody is trastuzumab (Herceptin). Trastuzumab induces Her2 down-regulation and cell cycle inhibition mediated by the cyclin-dependent kinase inhibitor $p27^{kip1}$. Pertuzumab (2C4, Omnitarg), a humanized monoclonal antibody to Her2, interacts with the receptor near domain II, thereby inhibiting receptor dimerization with EGFR, ErbB3, and ErbB4 (26). A phase II multicenter trial of single-agent pertuzumab in patients with advanced NSCLC that had progressed following first-line or second-line chemotherapy has recently been presented; 42% of patients experienced disease stabilization at 6 weeks (27).

Lapatinib (GW572016) is a reversible small-molecule inhibitor of both EGFR and Her2, attenuating downstream extracellular signal-regulated kinase 1/2 and AKT signaling (28). A phase II study of lapatinib in NSCLC has been closed to accrual due to a low overall response rate in a subset comprising patients with pure bronchioloalveolar carcinoma, adenocarcinoma with bronchioloalveolar carcinoma features, or no smoking history (29). Other small-molecule inhibitors that have reached phase I/II trials include PKI-166 and EKB-569 (dual inhibitors of EGFR and Her2) and CI-1033, an irreversible oral pan-EGFR family tyrosine kinase inhibitor.

Overview of Clinical Trials of Trastuzumab in NSCLC

Trastuzumab has been the predominant Her2-targeted agent studied in clinical trials in patients with NSCLC. This humanized monoclonal antibody directed against the extracellular domain of Her2 is thought to work through activation of antibody-dependent cellular cytotoxicity and by promoting the down-regulation and degradation of the Her2 receptor. Trastuzumab may also prevent the cleavage and subsequent production of an active truncated form of Her2, p95 (30). Trastuzumab may also inhibit the phosphatidylinositol 3-kinase/AKT pathway by promoting PTEN activation (31).

Gatzemeier et al. reported a randomized phase II trial of gemcitabine/cisplatin ± trastuzumab in patients with untreated stage IIIB/IV NSCLC that was positive for Her2 by

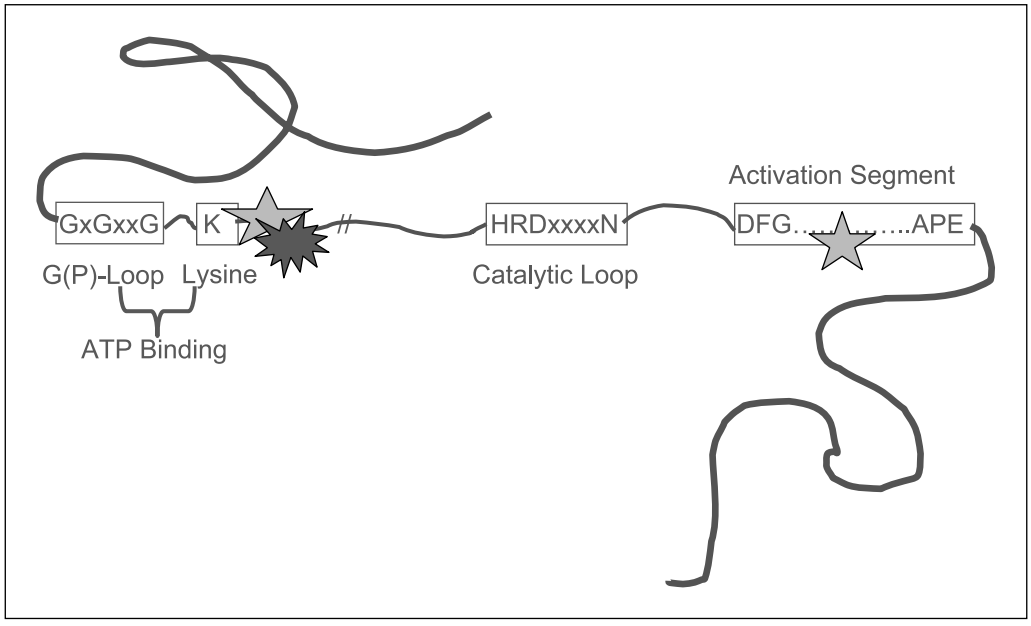

Fig. 2. General kinase domain structure: EGFR and Her2 mutations. Kinase domain structure of EGFR and Her2, illustrating sites where mutations have been identified in human tumors. Five-pointed star: sites of EGFR mutations; Dark star: site of ERBB2 mutations.

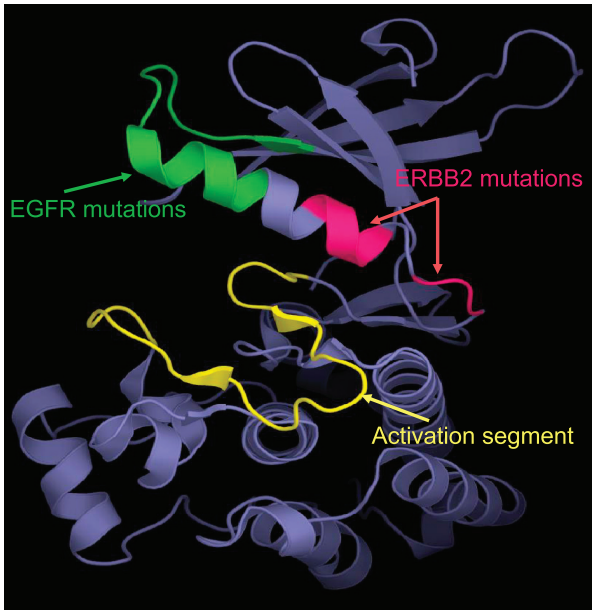

Fig. 3. EGFR and Her2 mutations are located in the C-helix region of the kinase domain. Ribbon diagram of COOH-terminal helix, showing relationship of mutation sites to activation segment of EGFR/Her2.

immunohistochemistry 2+/3+ (DAKO HercepTest), FISH (PathVysion Her-2 DNA Probe kit), or serum-shed extracellular domain (15 ng/mL; ref. 32). There was no statistical difference in response rates between the two arms. Subset analysis revealed that the six trastuzumab-treated patients with Her2 3+ or FISH-positive disease had a higher response rate (83%) and longer progression-free survival (8.5 months) compared with an overall response rate in the trastuzumab arm of 36% and 6.1-month progression-free survival. In this study, the addition of trastuzumab to gemcitabine and cisplatin led to a higher incidence of fatigue. Three patients in the trastuzumab arm developed a decrease in left ventricular ejection fraction of >15% with symptomatic cardiac toxicity (New York Heart Association class IV) observed in one patient.

A phase II study examined the combination of paclitaxel, carboplatin, and trastuzumab in 139 patients with stage IIIB/IV NSCLC (33). Eligible patients (immunohistochemistry 1+, 2+, or 3+ by DAKO HercepTest) were treated with chemotherapy and weekly trastuzumab until progression with the option of continuing trastuzumab for up to 1 year after completion of chemotherapy. There was no statistically significant difference in overall survival or progression-free survival among any of the immunohistochemistry-positive subgroups. Cautious interpretation should be given to the eight patients with Her2 3+ disease in this study who experienced improved survival compared with historical controls.

Zinner et al. reported a phase II study of gemcitabine/cisplatin and trastuzumab in patients with Her2 immunohistochemistry 1+ to 3+ disease or Her2 serum-shed antigen >15 ng/mL, stage IIIB/IV NSCLC. Of the 21 patients, eight achieved a partial response to treatment, with disease stabilization observed in a further nine patients (34). In this small study, there was no relationship between intensity of Her2 expression and response (only 4 of 21 patients were immunohistochemistry 3+). The addition of trastuzumab to gemcitabine and cisplatin was well tolerated.

The most recent study reported by Clamon et al. (CALGB 39810) of single-agent trastuzumab in 24 patients with Her2 immunohistochemistry 2+ or 3+ stage IIIB/IV NSCLC showed one partial response and one treatment-related death due to pulmonary toxicity (35). This patient had received prior chemotherapy and radiotherapy, and a pre-trial chest X-ray showed pneumonitis, which was thought to be exacerbated by trastuzumab. Two further patients had grade 3 hypoxia, and one patient experienced grade 1 pneumonitis. One patient developed a decrease in left ventricular ejection fraction from 52% to 45%, and two patients suffered from fatigue. Individual patients experienced episodes of grade 3 constipation, hyponatremia, rigors, muscle weakness, or hallucinations. It is noteworthy that 209 patients had to be screened to recruit 24 eligible patients with 2+ or 3+ receptor overexpression. The authors concluded that further studies of trastuzumab in patients with Her2 0 to 2+ expression were not justifiable.

Therefore, no trial has yet proven a benefit to the addition of trastuzumab in patients with Her2 immunohistochemistry- or FISH-positive disease. Clinical trials are required to address whether a subpopulation of Her2 FISH-positive patients or patients with Her2 receptor mutations respond preferentially to Her2-targeted therapy either alone or in combination with chemotherapy. Trials to date have been too heterogeneous, enrolling too few patients with receptor amplification (FISH positive), to warrant any firm conclusions. It is conceivable that patients with Her2 FISH-positive disease harbor tumors that are more dependent on Her2 signaling (and potentially more sensitive to Her2-targeted therapy) than patients with immunohistochemistry 3+ disease, as receptor overexpression defined by immunohistochemistry can result from multiple transcriptional and translational aberrations in the cancer cell. Furthermore, patients with Her2 mutations may be more sensitive to antibody or small molecule receptor inhibition.

In attempting to define reasons for the disappointing clinical trial results with Her2-targeted therapies it is important to consider lessons learnt from EGFR tyrosine kinase inhibitor clinical trials and to review the pathways promoting resistance to Her2-directed agents.

Sensitivity to EGFR-Directed Therapies as a Model for Her2-Targeted Agents

Paez and Lynch were the first to document that mutations in EGFR correlate with sensitivity to EGFR tyrosine kinase inhibitors (6). More recently, EGFR gene copy number or high EGFR protein expression as well as EGFR mutation have been associated with sensitivity to gefitinib (36), with EGFR copy number associated with prolonged survival in multivariate analysis. Tsao et al. found that EGFR expression is also associated with response to erlotinib in multivariate analysis (4). There is also evidence in a small study that EGFR-positive patients with increased Her2 copy number have improved outcome compared with EGFR-positive/Her2 FISH-negative patients after gefitinib therapy (5). A similar study presented in abstract form documented improved response rates to

gefitinib and time to progression in patients with EGFR-positive/ErbB3-positive disease compared with those with EGFR-negative or ErbB3-negative disease (37).

Laboratory data indicate that forced expression of Her2 in a NSCLC line increases sensitivity to gefitinib. The authors speculate that this may result from the gefitinib-mediated inhibition of Her2/ErbB3 heterodimerization and ErbB3 phosphorylation (38). It might be expected that combinatorial approaches, such as EGFR inhibition in tandem with Her2 dimerization blockade, may be even more effective. Preclinical data indicate this may be the case, with the combination of erlotinib and pertuzumab promoting more than additive antitumor activity in the Calu-3 NSCLC cell line (39).

Phase I trials with combinatorial EGFR and Her2 blockade have recently been reported in advanced solid tumors. Britten et al. presented the results of a phase I study of weekly trastuzumab and escalating daily doses of erlotinib in patients with $Her2^+$ metastatic breast cancer. Following erlotinib dose escalation from 50 to 150 mg, the most common toxicities were grade 1 or 2 diarrhea and grade 1 rash. Grade 2/3 rash occurred in two patients at the 150 mg dose level requiring dose reductions. Two patients had reversible deterioration in left ventricular ejection fraction (40).

Patnaik et al. presented a study with erlotinib and trastuzumab in combination with weekly paclitaxel in patients with advanced Her2-positive (immunohistochemistry 1+ to 3+) solid tumors. The majority of these patients suffered from metastatic breast cancer. The combination was well tolerated. Intriguingly, responses were seen in patients with taxane and trastuzumab refractory breast cancer, indicating that EGFR inhibition may overcome resistance to trastuzumab therapy (41).

Therefore, preclinical and clinical trial data are accumulating that correlate sensitivity to EGFR-targeted therapy with expression levels of other dimerization partners. Two lessons may be learnt from these observations. First, the EGFR family target should not be considered in isolation without assessing expression levels of other dimerization partners. Second, targeting multiple members of the EGFR family, or dimerization inhibitory strategies (exemplified by pertuzumab), may be a more efficient mechanism of attenuating aberrant growth factor signaling in NSCLC.

Resistance to Her2-Targeted Therapies

It is critical to consider known pathways of resistance to Her2-targeted therapies to help explain the failure of clinical trials to show a benefit of trastuzumab in patients with NSCLC. A better understanding of both acquired and *de novo* resistance may enable trials to be designed to select a sensitive cohort.

Recent studies have shown that PTEN expression is an important predictor of sensitivity to trastuzumab in breast cancer cell lines and retrospectively from studies in patient tumor samples. Loss of PTEN expression results in AKT pathway activation and resistance to Her2-targeted therapy (31). In one study, PTEN expression was found to be absent in 24% of early-stage NSCLC patient samples (n = 125), and silencing was associated with promoter methylation in 35% of cases (42).

Transforming growth factor-α (a ligand for EGFR) expression may promote trastuzumab resistance by inhibiting trastuzumab-induced Her2 down-regulation (43). Valabrega et al. proposed a model whereby autocrine secretion of transforming growth factor-α stimulates the formation of a Her2/EGFR heterodimer that uncouples Her2 from degradation by the Cbl ubiquitin ligase, promoting resistance to trastuzumab. In one study of resectable NSCLC, transforming growth factor-α overexpression was observed in 48% of samples studied (n = 96; ref. 44). Furthermore, *in vitro* data have shown that the antiproliferative effects of a monoclonal antibody targeting Her2 are compromised in the presence of ligands for EGFR, a phenomenon not observed with PKI166, a dual EGFR/Her2 small-molecule tyrosine kinase inhibitor (45).

Given the influence of EGFR ligands in the response to trastuzumab, it is not surprising that the relative expression of other EGFR family dimerization partners may be important in determining sensitivity to agents targeting this protein family. Studies with EGFR-targeted agents have recently revealed that increased expression of Her2 and ErbB3 may enhance sensitivity to gefitinib (5, 37).

The cyclin-dependent kinase inhibitor p27 may play a role in trastuzumab sensitivity. Trastuzumab may induce p27, leading to the inhibition of cyclin E/cyclin-dependent kinase 2 and cell cycle arrest (for review, see ref. 46). Reduced p27 expression is associated with resistance to trastuzumab, which can be reversed by reexpression of p27 *in vitro* (47). Expression of the receptor tyrosine kinase insulin-like growth factor-1 receptor may promote resistance to trastuzumab in Her2-overexpressing breast cancer cells, and this may occur through insulin-like growth factor-1 receptor–induced proteasome-mediated degradation of p27 (48, 49).

Conclusions

Sensitivity to Her2-directed therapies is complex and involves the expression of not only Her2 but also other EGFR family members, their ligands, and molecules that influence pathway activity, such as insulin-like growth factor-1 receptor, PTEN, and p27. It is unclear whether agents targeting Her2 will prove successful in future clinical trials in a highly selected patient cohort, either with Her2 amplification or Her2 gene mutations. The frequency of Her2 mutations in NSCLC may be too low to justify a prospective clinical trial in this patient group. Nevertheless, the EGFR experience has taught us that responses can easily be diluted in an unselected cohort of patients.

Certainly, trials to date have been insufficiently powered to determine whether NSCLC patients with Her2 gene amplification (rather than overexpression by immunohistochemistry) benefit from Her2-targeted therapies. The frequency of Her2 amplification (2-23%) in NSCLC and the widespread availability of Her2 FISH analysis may justify a final study of trastuzumab monotherapy in this patient population.

The role played by Her2 as the obligate heterodimerization partner for the other EGFR family members renders Her2 an attractive target irrespective of receptor overexpression. Arguably, the most exciting Her2 approach will prove to be combinatorial approaches using an EGFR tyrosine kinase inhibitor together with Her2 dimerization inhibitors (e.g., pertuzumab).

Given the central part played by Her2 in receptor signaling, gene amplification witnessed in human malignancies, and the recent Her2 mutations documented in NSCLC, the failure of trastuzumab in clinical trials of NSCLC should not discourage further studies of these potentially important agents.

Open Discussion

Dr. Jeffrey Engelman: I would be curious about how the drugs worked in preclinical models. It is easier to define if the concept will work in the preclinical model before interpreting the clinical model to know if it is a failure of the concept or a failure of the agent. I would be curious specifically about the EGFR-driven lung cancer cell lines that are exquisitely sensitive to gefitinib. I am not too excited about the xenograft data.

Dr. Eisen: There are preclinical data with pertuzumab and erlotinib *in vitro* showing there does appear to be genuine synergy.

Dr. David Johnson: I'll take a little bit of a provocative perspective on the presentation. First of all, the Clamon data [Cancer 2005;103:1670-5] are the only data out there to look at the use of trastuzumab in human tumors, and they studied patients who had 2+ and 3+ expression using the HerceptTest. The response rate was 5%. As Dr. Bunn pointed out earlier, that is not arguably different than the 8% response we have seen with erlotinib. I would argue that maybe it is a better signal than we might imagine. As far as the Langer data go, in which admittedly trastuzumab was administered with chemotherapy, the 3+ patients treated with trastuzumab actually had a 25% 2 year survival rate. The numbers are small, but they are as large as what we saw in the IDEAL data that Dr. Haber presented, in terms of total numbers of patients. Thus, I am not convinced that we have demonstrated that this drug trastuzumab is not useful in this disease, particularly if we looked at FISH-positive patients, who appear to be different from those with the HER2 mutation. They actually may end up representing a larger percentage of non-small cell lung cancer patients than the 1% or 2% identified with the HerceptTest.

Dr. Eisen: I think that if we are going to do biological markers, it makes sense to do a panel because the economics of screening huge numbers of patients for a single signal do not make sense. I agree with you that the results with trastuzumab are not statistically significantly worse than what we get with erlotinib. These patients have received treatment in a semi targeted way, while erlotinib data are from patients treated in an untargeted way.

Dr. Daniel Haber: Just going back to proof of principle, is it fair to say that there haven't been cases with bona fide HER2-activating mutations treated with a dual tyrosine kinase inhibitor like lapatinib? So do we know whether there is a subset of lung cancer with HER2 mutations that might respond to kinase inhibition?

Dr. Eisen: We were hoping to do that.

Dr. Thomas Lynch: Dr. Eisen and our group had a trial with lapatinib ready to open for patients with previously treated lung cancer, but it was never begun. Some felt that the evidence to date with erlotinib did not yet clearly demonstrate activity in lung cancer. Of course, it might work in the small fraction of patients with HER2 mutations.

Dr. Bruce Johnson: I would like to bring the issue of assessing response rate in HER2-positive lung cancers. I have always been a skeptic of PET scans in assessing response because they are very expensive, and if using RECIST criteria is somewhat subjective, using the PET scan is an even greater leap. However, in the pertuzumab study, PET actually helped in identifying the people who by RECIST criteria had stable disease but on PET had a decrease in the SUV [standardized uptake value]. Thus, in this instance, PET gave a clue about how we can identify the subset of patients who have prolonged stable disease, and perhaps they have a different biology than the others.

Dr. Lynch: That is being done a lot with the small molecule VEGF inhibitors, isn't it? Using PET scans and other biologic imaging to try to correlate responses?

Dr. John Heymach: With VEGF pathway inhibitors, in particular, it is unlikely that you are going to see an early PET signal. That is because the endothelium is the target but endothelium is only 3% of a tumor. It is relatively far down the line before you are actually affecting the tumor cells in a way that you will see by PET. With agents where the tumor cells are the target, you are probably going to see an earlier FDG-PET signal first. For the anti angiogenesis agents, DC-MRI has the best data, and other new imaging modalities are being investigated.

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