Summary Statement: Novel Agents in the Treatment of Lung Cancer: Advances in Epidermal Growth Factor Receptor-Targeted Agents

Thomas J. Lynch,[1] Alex A. Adjei,[3] Paul A. Bunn, Jr.,[4] Tim G. Eisen,[5] Jeffrey Engelman,[2] Glenwood D. Goss,[6] Daniel A. Haber,[1] John V. Heymach,[7] Pasi A. Jänne,[2] Bruce E. Johnson,[2] David H. Johnson,[8] Rogerio C. Lilenbaum,[9] Matthew Meyerson,[2] Alan B. Sandler,[8] Lecia V. Sequist,[1] Jeffrey Settleman,[1] Kwok-Kin Wong,[2] and Carol S. Hart[10]

The Third Cambridge Conference on *Novel Agents in the Treatment of Lung Cancer* was convened in Cambridge, Massachusetts on September 23 to 24, 2005 to discuss ongoing research into the significance of the epidermal growth factor receptor (EGFR) pathway in the biology of non–small cell lung cancer (NSCLC) and the potential for novel therapies targeting this pathway. The conference format combined brief presentations with extended periods of open discussion. The conclusions reached over the course of the 2-day conference are summarized briefly below and presented at greater length in the individual articles and accompanying discussions that comprise the conference proceedings.

Clinicians who treat patients with NSCLC are aware that this is a highly heterogeneous disease. Until recently, we lacked the ability to use molecular profiles to classify patients into clinically meaningful subgroups, instead relying on classic histopathology and radiographic staging (Table 1). With the advent of targeted therapy and the discovery of a number of potential biological markers, such as sensitivity- and resistance-inferring mutations, and evaluation of gene copy number, it is becoming possible to define distinct patient populations. This hopefully will allow us to make predictions of treatment response and overall outcome. These recent advances have resulted from a collaborative effort of clinicians and researchers. Clinical observations have been central to stimulating investigations into the biological basis for the dramatic responses seen in a small number of patients treated with small-molecule EGFR tyrosine kinase inhibitors (TKIs), i.e., gefitinib and erlotinib.

Overall, these two agents produce partial responses in 10% to 20% of patients with NSCLC. The primary focus of the conference was to address three questions. First, what is the optimal way to predict benefit from EGFR TKI therapy and thus to identify patients who might benefit from first-line or even adjuvant treatment? Next, given what we have learned about EGFR biology, what strategies or combination therapies can be tried to extend and prolong the efficacy of the EGFR TKIs? Finally, will new classes of agents with different mechanisms of receptor inhibition or multiple targets have activity in patients not responsive to the currently available EGFR TKIs as monotherapy? These newer agents include, among others, panitumumab, an anti-EGFR fully humanized monoclonal antibody; ZD6474, a dual inhibitor of EGFR and vascular endothelial growth factor receptor (VEGFR); and lapatinib and HKI 272, which are irreversible inhibitors of EGFR and HER2. Table 2 provides an overview of currently ongoing late-phase clinical trials of EGFR-targeted agents.

EGFR Biology

EGFR is an important target for existing and emerging agents against NSCLC (Fig. 1). The EGF signaling system has four closely related members: HER1 (also known as erbB1), HER2 (erbB2), HER3 (erbB3), and HER4 (erbB4). Their downstream effects include activation of the STAT, MAPK, and phosphatidylinositol-3-OH kinase (PI3K)/Akt pathways. Tyrosine kinase receptors are activated by ligand binding to two adjacent receptors to form either a homodimer or a heterodimer. The HER2 receptor, which has no known ligand, is the preferred binding partner for the other three ErbB receptors. The biology of these receptor interactions and of the complexes that they form is still poorly understood.

Somatic activating mutations in the *EGFR* identify a subpopulation of patients with NSCLC who are more likely to respond to treatment with EGFR TKIs. These *EGFR* mutations seem to be transforming in NSCLC, based on *in vitro* studies. The sensitivity-conferring mutations are in exons 18 to 21 of the tyrosine kinase domain (Fig. 1). In virtually all studies to date, the presence of EGFR TK mutations has predicted for response to treatment. In all studies, these mutations predicted improved time to progression and overall survival on both chemotherapy, EGFR TKI therapy, and placebo therapy, demonstrating their biological and prognostic importance. In the largest randomized trial comparing EGFR TKI treatment to placebo, mutations were predictive of improved outcome (the BR.21 study population) irrespective of the type of therapy. Possible explanations for the inconsistencies in the data linking mutations with predicting survival benefit from EGFR TKIs are discussed in Patient Selection and Diagnostics. Exon 19 deletions seem to be the

Authors' Affiliations: [1]Division of Hematology/Oncology, Massachusetts General Hospital; [2]Dana-Farber Cancer Institute, The Lowe Center for Thoracic Oncology, Boston, Massachusetts; [3]Mayo Clinic Rochester, Rochester, Minnesota; [4]University of Colorado Cancer Center, Aurora, Colorado; [5]The Royal Marsden Hospital, Surrey, United Kingdom; [6]Ottawa Regional Cancer Centre, Ottawa, Ontario, Canada; [7]M.D. Anderson Cancer Center, Houston, Texas; [8]Vanderbilt-Ingram Cancer Center, Nashville, Tennessee; [9]Mount Sinai Cancer Center, Miami Beach, Florida; and [10]InforMEDical, Narberth, Pennsylvania

Received 4/24/06; revised 5/8/06; accepted 5/9/06.

Grant support: The symposium and educational proceedings publications were supported by educational grants provided by AstraZeneca Pharmaceuticals, Genentech and OSI Pharmaceuticals, and Bristol-Myers Squibb.

Requests for reprints: Thomas J. Lynch, Division of Hematology/Oncology, Massachusetts General Hospital, 100 Blossom Street, Cox 210, Boston, MA 02114. Phone: 617-724-1136; Fax: 617-724-1137; E-mail: tlynch@partners.org.

doi:10.1158/1078-0432.CCR-06-1005

Table 1. The new WHO/International Association for the Study of Lung Cancer: histologic classification of NSCLCs

1. Squamous cell carcinoma
   - Papillary
   - Clear cell
   - Small cell
   - Basaloid
2. Adenocarcinoma
   - Acinar
   - Papillary
   - Bronchioloalveolar carcinoma
     - Nonmucinous
     - Mucinous
     - Mixed mucinous and nonmucinous or indeterminate cell type
   - Solid adenocarcinoma with mucin
   - Adenocarcinoma with mixed subtypes
   - Variants
     - Well-differentiated fetal adenocarcinoma
     - Mucinous (colloid) adenocarcinoma
     - Mucinous cystadenocarcinoma
     - Signet ring adenocarcinoma
     - Clear cell adenocarcinoma
3. Large cell carcinoma
   - Variants
     - Large-cell neuroendocrine carcinoma
     - Combined large-cell neuroendocrine carcinoma
     - Basaloid carcinoma
     - Lymphoepithelioma-like carcinoma
     - Clear cell carcinoma
     - Large-cell carcinoma with rhabdoid phenotype
4. Adenosquamous carcinoma
5. Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
   - Carcinomas with spindle and/or giant cells
   - Spindle cell carcinoma
   - Giant cell carcinoma
   - Carcinosarcoma
   - Pulmonary blastoma
6. Carcinoid tumor
   - Typical carcinoid
   - Atypical carcinoid
7. Carcinomas of salivary-gland type
   - Mucoepidermoid carcinoma
   - Adenoid cystic carcinoma
   - Others
8. Unclassified carcinoma

most common, comprising ~60% of known *EGFR* mutations; a missense mutation in exon 21 accounts for another 25%. Preliminary evidence suggests that exon 19 deletions may respond better to EGFR TKI therapy, whereas exon 20 mutations may predict for an adverse outcome and potential resistance, based on laboratory and clinical findings. *EGFR* mutant cell lines exhibit increased autophosphorylation and altered signaling output that favors prosurvival pathways.

Acquisition of drug resistance in patients initially responsive to EGFR TKIs has been linked to a specific secondary somatic mutation, *EGFR* T790M. Germ line *EGFR* T790M mutations have recently been described in a family with multiple cases of lung cancer, another line of evidence to suggest that activating mutations of the EGFR may have a role in oncogenesis. Other ErbB family members, particularly ErbB3, may be involved in resistance mechanisms to EGFR TKIs that do not involve secondary *EGFR* T790M mutations. It is known, for example, that phosphorylated ErbB3 can directly activate phosphatidylinositol-3-OH kinase, implicated in the growth of many human cancers; thus, agents that target ErbB3 to block its phosphorylation might be an effective strategy in delaying or treating acquired resistance to EGFR inhibition. Continued research into the biology of resistance to EGFR inhibitors will potentially identify new molecular targets as well as strategies to enhance the efficacy of these agents.

Preclinical Studies and Models

Preclinical models include an ever-expanding number of cell lines, xenografts, and transgenic mouse models. Although there are certainly limitations to preclinical model systems that need to be considered when designing and interpreting preclinical studies, these models have an ongoing importance in the evaluation of targeted therapies. Properly used, preclinical models are crucial in determining whether an investigational agent is hitting its intended target and whether that target is in fact biologically relevant.

Some conference participants, particularly those who perform laboratory-based research, felt that the preclinical data put forward to support clinical development of some targeted agents have often come from inadequate and poorly designed studies in inappropriate models. Recent advances in modeling make it possible to test mechanistic hypotheses with far greater rigor, through manipulating pathways to create novel cell lines or systematically knocking in and knocking out the genes for putative target molecules in mouse models.

Given that molecular targeted cytostatic agents may produce responses only in specific tumor types and stages, it is important to test novel agents and combination therapies in multiple cell lines that have been rationally selected to present the presumed target and to replicate the clinical disease state in which the therapy will be studied. Testing in well-established models, such as the *in vitro* cell line screening panel of the National Cancer Institute, is advisable, because there is a large body of published data available for comparison. Novel cell lines should be used in addition to these when there is a biological rationale for their selection. There was significant discussion of the need for more robustness in the number and diversity of preclinical model systems that should be used when developing clinical studies. Typically, therapies that have shown efficacy in phase III trials had initially shown activity in an impressive variety of preclinical models.

Perhaps the most important conclusion from this portion of the conference was a feeling that clinical investigators need to consider the totality of the preclinical model data when making decisions about which agents and which combinations to pursue further. Often, important decisions are made based on one or two cell lines that show synergy while ignoring (or often not even having access to) experiments in dozens of cell lines that failed to show benefit. There was near consensus that enhanced communication between preclinical and clinical

researchers needs to occur to optimize this type of translational research.

Patient Selection and Diagnostics

Molecular profiling of lung cancer has considerable potential to improve the quality of patient care by identifying subtypes of cancer with specific vulnerabilities to targeted therapies, and by offering improved prognostic and predictive tools. Accurate and reproducible diagnostic approaches will enable researchers to determine which lesions are truly associated with clinical responses to specific regimens of care. These advances, however, are not yet reality, as there are issues with standardization and validation of molecular analyses that need to be resolved.

A key area of debate at this meeting was the relationship between *EGFR* mutation, increased *EGFR* gene copy number, EGFR protein expression, and outcome after treatment with TKIs. Despite the initial enthusiasm for using mutation status as the principal biomarker, it is now clear that *EGFR* copy number likely adds important additional predictive information for survival in a large group of patients. Embracing copy number as an important marker does not diminish the role of *EGFR* mutation status as a predictor of those patients who may have the very best response to treatment. The disparate findings of studies correlating *EGFR* mutation status with treatment outcome may be explained in part by differences in sequencing technology and techniques. These technologies include direct DNA sequencing, several PCR-based methods, and a recently developed screen that uses a DNA endonuclease. Specimen quality may also have an effect, with potential sources of error including false positives due to PCR artifacts (e.g., occurring with DNA amplification from a small starting sample), as well as false negatives due to impure samples (e.g., from paraffin-embedded specimens) masking mutant alleles. In addition, there may be differential effects of different mutations, with some conferring high levels of treatment sensitivity, others resistance, and still others having unknown effects.

High levels of EGFR protein expression, as determined by immunohistochemistry, are associated with response and survival in retrospective subsets of the BR.21 and Southwest Oncology Group 0126 trials and in the series of gefitinib-treated patients reported by Cappuzzo and colleagues (discussed in individual articles within these proceedings). This is in contrast to the findings in the initial gefitinib studies by Kris et al. (1) and to the large body of data in colorectal cancer patients treated with cetuximab. Some of the differences may be due to different methodologies and scoring systems. Because the methodologies used have not been standardized and have included different antibodies, different scoring systems, and different cutoffs for immunohistochemical positivity, we might be comparing very different biological phenomena. Protein expression is variably reported as either percentage of positive cells, intensity of staining (0, 1+, 2+, 3+), or the product of the percentage of positive cells and staining intensity.

Increased *EGFR* gene copy number correlated with survival benefit for second- and third-line EGFR TKI treatment in the BR.21 and Southwest Oncology Group trial data and in the Cappuzzo series. Copy number, measured by FISH or by quantitative PCR, is defined as including both gene amplification and polysomy. Efforts are ongoing to determine the appropriate cutoff for high versus low polysomy. A retrospective analysis of the data from the IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer) trials of single-agent gefitinib found that mutations and (to a more limited degree) amplification describe distinct subgroups of therapy responders. However, data from some of the Japanese groups suggest that the patients with increased copy number have a relatively high rate of mutation. Again, differences in methods and techniques used may explain some of this variation.

Several novel candidate markers were discussed during the conference as worthy of further study: (*a*) E-cadherin, with preclinical data and retrospective clinical data suggesting high levels correlate with increased response to EGFR therapy; (*b*) ErbB3, with preclinical data showing that higher protein expression levels correlate with sensitivity to EGFR therapy; and (*c*) increased *HER2* gene copy number, which, in conjunction with *EGFR* mutation, has been associated with sensitivity to gefitinib.

EGFR mutation testing is available for clinical use; however, the current 7- to 14-day time frame may limit the usefulness of the test for many patients with symptomatic or rapidly worsening disease. There are novel means of detecting mutations that might accelerate this process and improve the utility of mutation testing. These are detailed elsewhere in these proceedings.

To determine the value of upfront mutation testing in metastatic patients, investigators at Harvard have begun the TARGET trial (Trial to Assess Response to Gefitinib in EGFR-mutated Tumors) to prospectively investigate the efficacy of EGFR-targeted therapy in patients with a known mutation. Additional trials similar to the TARGET study are under way in Europe and Asia. FISH and immunohistochemistry are also feasible in clinical practice and these techniques offer faster turnaround times. Clinical trials in the United States and Europe are now either in planning stages or early activation that look at EGFR TKI therapy in patients with FISH positive disease (Table 2). Given the larger numbers of patients who are FISH positive, it may be more fruitful to examine this strategy for adjuvant settings as well.

Therapy Options

The availability of three approved agents in the setting of second-line therapy led to a vigorous discussion about the utility of each of these drugs in patients with previously treated lung cancer. Conference participants discussed their personal clinical criteria for selecting erlotinib over docetaxel or pemetrexed as second-line therapy for NSCLC, now that all three agents have been approved for this indication. In this context, participants felt that the most important clinical characteristic would be smoking status, as the never-smoker subset seemed most robustly associated with response to an EGFR TKI. Participants also suggested that a patient who progressed on first-line chemotherapy, or failed rapidly thereafter, might be more appropriately managed by an EGFR TKI rather than by a second chemotherapy regimen. However, it should be stressed that this is a clinical observation of the participants, and there are not sufficient data yet from studies to allow accurate selection of which patients should get treated with either chemotherapy or an EGFR TKI. Randomized trials addressing this question are ongoing and should be informative.

Table 2. Selected phase II/III trials of EGFR-targeted agents in NSCLC

Agents/modalities studied (National Cancer Institute trial identifier)	Phase	Projected accrual
Cetuximab		
1. Cisplatin/vinorelbine ± cetuximab (FLEX study; NCT00148798)	III	1,100
2. Docetaxel or pemetrexed ± cetuximab (NCT00095199)	III	800
3. Taxane/carboplatin ± cetuximab (NCT00112294)	III	660
4. Pemetrexed, carboplatin, and radiation therapy ± cetuximab (NCT00117962)	II	100
5. Cetuximab (NCT00103207)	II	71
6. Cetuximab + radiation (NCT00124618)	II	60
7. Cetuximab + vinorelbine (NCT00165334)	II	53
8. Cetuximab ± pemetrexed (NCT00203931)	II	80
9. Docetaxel + cetuximab or bortezomib (NCT00118183)	II	62
10. Cetuximab (NCT00118118)	II	120
Erlotinib		
11. Chemotherapy + bevacizumab followed by bevacizumab/erlotinib vs bevacizumab/placebo (NCT00257608)	III	1,150
12. Erlotinib ± bevacizumab (NCT00130728)	III	650
13. Stereotactic radiosurgery ± temozolomide or erlotinib (NCT00096265)	III	381
14. Erlotinib vs placebo following concurrent docetaxel, carboplatin and radiotherapy (NCT00153803)	III	380
15. Erlotinib ± combination chemotherapy (NCT00294762)	II	140
16. Neoadjuvant erlotinib (NCT00087269)	II	55-110
17. Erlotinib ± carboplatin/paclitaxel (NCT00126581)	II	180
18. Erlotinib in women with previously untreated adenocarcinoma of the lung (NCT00137839)	II	75
19. High- vs low-dose erlotinib + paclitaxel/carboplatin (NCT00287989)	II	58
20. Erlotinib (predictive biomarkers study; NCT00085280)	II	129
Gefitinib		
21. Gefitinib after chemotherapy (EORTC trial)	III	736
22. Gefitinib (Italy, Ministry of Health)	III	490
23. Neoadjuvant gefitinib (NCT00104728)	II	50
24. Docetaxel + gefitinib (NCT00231465)	II	55
ZD6474		
25. Docetaxel ± ZD6474 (NCT00312377)	III	1,240
26. ZD6474 (NCT00290537)	II	120
27. Carboplatin/paclitaxel ± ZD6474 (NCT00093392)	II	210-220

NOTE: All trials are open in the United States unless otherwise stated.
Abbreviations: PS, Eastern Cooperative Oncology Group performance status; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; BAC, bronchioloalveolar carcinoma; n/a, not applicable.

There was no consensus on the appropriateness of EGFR-targeted agents in first-line therapy, with some conference participants commenting that they would use an EGFR TKI off-protocol in patients (primarily never-smokers, EGFR mutation positive, or FISH positive) who had the clinical characteristics associated with response. Other felt that an EGFR TKI should be offered as first-line therapy only in the context of a clinical trial, given that chemotherapy (with or without bevacizumab) now has shown efficacy as a first-line modality. In Eastern Cooperative Oncology Group 4599, >800 patients with previously

Table 2. Selected phase II/III trials of EGFR-targeted agents in NSCLC (Cont'd)

Entry criteria	Projected time frame (as of 4/15/2006)
1. Stage IIIB (pleural effusion) or IV; immunohistochemical evidence of EGFR expression on tumor tissue; first-line therapy	11/2004-5/2007
2. Metastatic, unresectable, or locally advanced NSCLC; progression on prior platinum-based chemotherapy regimen	10/2004-11/2006
3. Advanced/metastatic NSCLC; first-line therapy	Currently recruiting; start: 12/2004
4. Stage III unresectable NSCLC	Currently recruiting; 10 to 13 mo time frame
5. Recurrent stage IIIB or IV; BAC or lung adenocarcinoma with BAC features; ≥1 unidimensional lesion ≥20 mm	Currently recruiting; 9–12 mo time frame
6. Stage III NSCLC	Currently recruiting 20 mo time frame
7. ≥70 y; stage IV or IIIB NSCLC	Currently recruiting; start: 6/2005
8. Stage III or IV NSCLC	Currently recruiting; start: 3/2005
9. Stage III or IV NSCLC; PS = 2; first-line therapy	Currently recruiting; 6-11 mo time frame
10. Recurrent or progressive metastatic NSCLC	Currently recruiting
11. Nonsquamous NSCLC; no prior systemic chemotherapy, EGFR inhibitor or antiangiogenesis therapy	Start: 12/2005
12. Advanced NSCLC, progressing after first-line chemotherapy	Start: 6/2005
13. NSCLC with brain metastases	Currently recruiting; 70 mo time frame
14. Stage III NSCLC	Start: 5/2005
15. Measurable or evaluable disease; one or two EGFR pathway markers positive at screening	1/2006-7/2007
16. Stage IA-IIIA resectable NSCLC	Currently recruiting; 11-22 mo
17. Stage III or IV chemotherapy-naïve NSCLC	Currently recruiting; 1.5 y time frame
18. Female; stage IV or IIIB NSCLC; nonsmoker or former smoker	Study start: 10/2004
19. Stage IIIB or IV or recurrent NSCLC; ≥100 cigarettes in his/her lifetime	Currently recruiting
20. Stage IIIB or IV or recurrent NSCLC	Currently recruiting; 6 mo time frame
21. Stage IIIB or IV NSCLC; no progression after two to six courses of platinum-based chemotherapy	2.5 y
22. Locally advanced NSCLC previously treated with combined therapy; maintenance therapy	Start: 1/2004
23. Stage I-III resectable NSCLC	12.5 mo
24. ≥70 y; stage IIIB (pleural effusions) or stage IV	Start: 7/2003
25. Locally advanced or metastatic NSCLC; failure of prior first line therapy	Start: 3/2006
26. Stage IIIB or IV NSCLC eligible for chemoradiation; at least one unidimensional lesion ≥20 mm; PS 0-1.	Start: 1/2006
27. Stage IIIB or IV or recurrent NSCLC	Currently recruiting; n/a

untreated advanced NSCLC were randomized to receive paclitaxel and carboplatin with or without bevacizumab. The bevacizumab-containing arm showed significant improvements in response rates, median progression-free survival, and 1- and 2-year survival rates. A phase III trial of erlotinib as first-line therapy in unselected patients with advanced disease not suitable for chemotherapy is currently being conducted in the United Kingdom. A phase II study of first-line erlotinib in patients who are light smokers is also being done by the Cancer and Leukemia Group B.

Ongoing Research

The currently available small-molecule EGFR TKIs do not seem capable of fully inhibiting EGFR at their clinically achievable dosages. It is not yet clear whether the irreversible

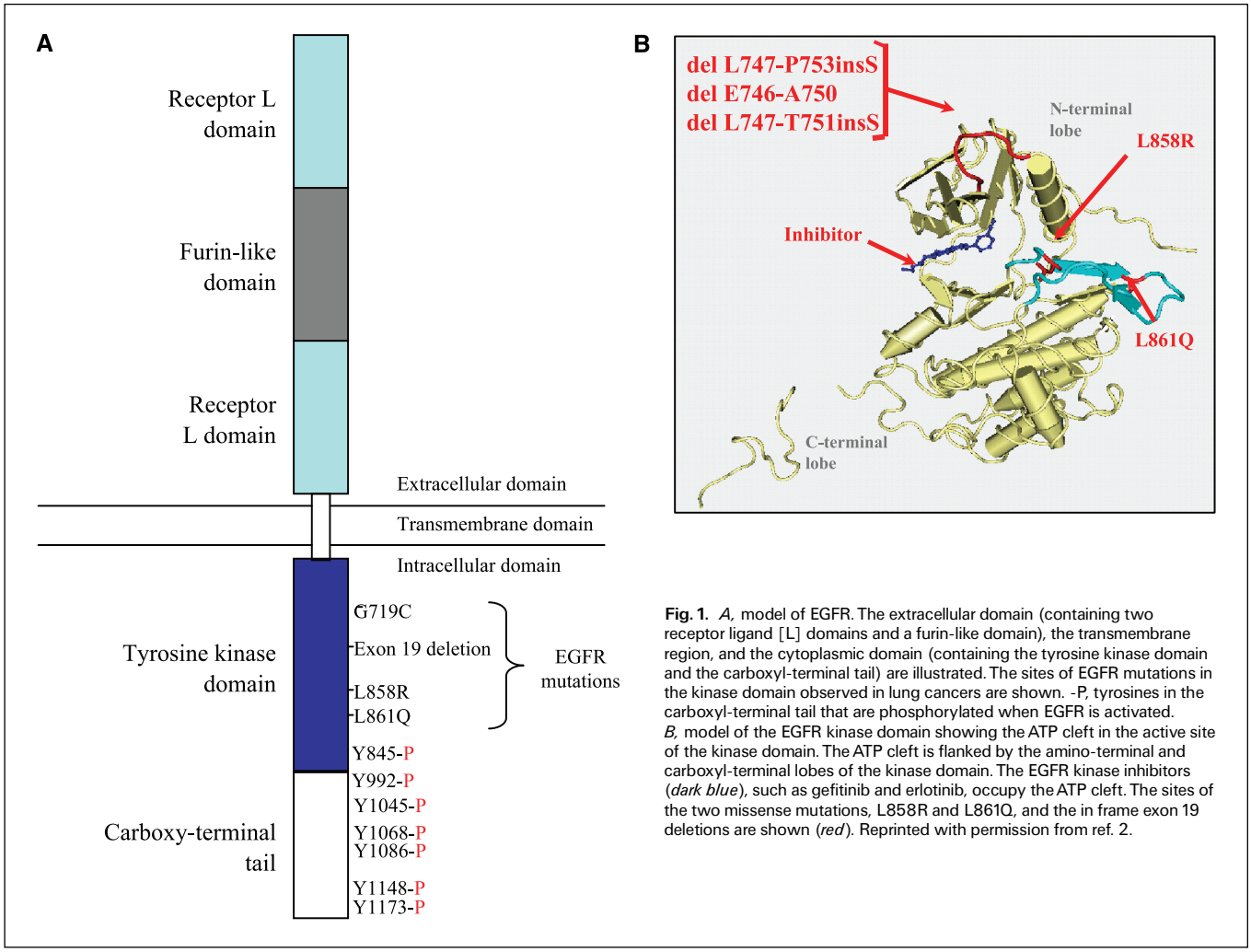

Fig. 1. *A,* model of EGFR. The extracellular domain (containing two receptor ligand [L] domains and a furin-like domain), the transmembrane region, and the cytoplasmic domain (containing the tyrosine kinase domain and the carboxyl-terminal tail) are illustrated. The sites of EGFR mutations in the kinase domain observed in lung cancers are shown. -P, tyrosines in the carboxyl-terminal tail that are phosphorylated when EGFR is activated. *B,* model of the EGFR kinase domain showing the ATP cleft in the active site of the kinase domain. The ATP cleft is flanked by the amino-terminal and carboxyl-terminal lobes of the kinase domain. The EGFR kinase inhibitors (*dark blue*), such as gefitinib and erlotinib, occupy the ATP cleft. The sites of the two missense mutations, L858R and L861Q, and the in frame exon 19 deletions are shown (*red*). Reprinted with permission from ref. 2.

EGFR inhibitors (such as EKB-569 or HKI 272) may be capable of producing a more prolonged response or a response in a larger proportion of patients. These two agents may have greater activity because of the irreversible nature of their binding to the EGFR tyrosine kinase or due to the fact that they have activity against both EGFR and HER2.

The participants were uniform in their feeling that, to date, the data do not support the routine use of erlotinib concurrent with chemotherapy in patients with lung cancer. Trials in selected patients (mutation, increased copy number, or never smokers) are warranted at this time to compare erlotinib to chemotherapy or chemotherapy plus erlotinib. There are lessons to be learned from an analysis of the failure of the INTACT trials, which evaluated gefitinib administered in conjunction with chemotherapy. Although responses had been seen in phase I and II trials of single-agent gefitinib, the mechanism of action had not been adequately characterized because EGFR overexpression did not correlate with activity. Importantly, the rationale for the combination with chemotherapy was not well supported. Conference participants commented on the need to better characterize phase II responders before launching a major phase III trial of a novel therapy; combination therapies also need more careful preclinical and phase I/II study to provide evidence of additive or synergistic effects.

How do we know if these agents are working? Some argue that we have overinterpreted the modest activity levels seen in some phase II trials of novel agents. Others feel that in the early-phase studies evidence of therapeutic benefit may have been missed because of the end points selected. Reliance on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria may prevent recognition of clinically meaningful responses, such as stable disease that is associated with symptom improvement. Fluorodeoxyglucose-PET scanning and the novel molecular targeted imaging technologies may prove their utility for more precise evaluation of activity in these phase I/II studies.

A number of important antibodies are under investigation that target the EGF pathway. These include cetuximab, panitumumab, and pertuzumab. Currently, phase III trials are under way with the anti-EGFR monoclonal antibody cetuximab. Although the phase II studies showed only modest activity, it is hoped that benefit may be seen in combination with chemotherapy. There are preclinical data to suggest cetuximab may have value in conjunction with radiotherapy, a combination that is now being investigated in phase II studies. Clear data in head and neck cancer show activity of cetuximab in combination with radiotherapy, which has stimulated hope in the lung cancer field. Pertuzumab, which is a HER dimerization inhibitor, showed less single-agent activity than anticipated

from the preclinical studies. However, by fluorodeoxyglucose-PET scanning, it seemed to achieve a biological effect in 25% of unselected NSCLC patients, which correlated with prolonged progression-free survival. Level of HER2 expression did not correlate with progression-free survival, suggesting that with this agent also the mechanism of action has not been adequately delineated. The pertuzumab phase II study (discussed in detail elsewhere in these proceedings) was important for demonstrating both the value and the challenge of performing lung cancer studies that require serial tissue biopsies.

Finally, ZD6474, a VEGFR-2 antagonist that also has some EGFR activity, has shown modest single-agent activity; however, studies in the second-line setting of ZD6474 in combination with docetaxel have shown a prolonged time to progression. The preclinical models would suggest that inhibition of the VEGF pathway is the predominant activity of this agent, but again it is not clear that the mechanism of action is fully understood. Phase III studies with this agent are now under way (Table 2).

Combining cytostatic targeted therapies is an area of growing research and clinical interest. A number of targeted agents with different mechanisms of activity have shown at least moderate activity, such as improved stable disease rates, raising hopes that rational combinations targeting different pathways might improve the clinical benefit achievable with these agents. Combination therapies might delay the onset of resistance in patients who show an initial response to EGFR inhibition, or block competing tumor growth pathways in patients who do not respond to single-agent treatment. In particular, there are now good data emerging in a number of disease settings to indicate that VEGF and EGFR inhibitors together might be a superior strategy to single-agent therapy. In addition, whereas HER2-targeted agents have not been shown to be effective for NSCLC in unselected patients, a case can be made for investigating them in combination with EGFR TKIs, to explore the possibility that HER2 may be implicated in resistance to EGFR therapy. At the conference, a number of agents with good rationale for their investigation in combination with EGFR TKIs were discussed, including (*a*) anti-VEGF agents (e.g., bevacizumab or small molecules such as sorafenib or ZD6474); (*b*) anti-EGFR monoclonal antibodies (e.g., cetuximab); (*c*) statins (e.g., lovastatin, rosuvastatin); (*d*) mTOR inhibitors (e.g., CCI-779, everolimus); and (*e*) proteosome inhibitors (e.g., bortezomib).

Future Research Directions

The development of the EGFR inhibitors has had a transforming effect on the fields of lung cancer research and clinical care. The understanding of EGFR biology that has developed as a consequence will further rational evaluation of combination therapies and exploration of the biology of related growth pathways. There is considerable reason for optimism that the benefit offered by EGFR TKI therapy in a small subset of patients can be prolonged or extended to other patient subgroups through the rational development and study of combination therapies.

Both scientific and clinical progress may be achieved by better characterization of the mutations that confer resistance versus those associated with sensitivity. More studies are also needed in tumors showing sensitivity to EGFR inhibition to better describe the biology of tumor response. Selective cell killing effects of gefitinib or erlotinib in mutation-positive NSCLC may result from the dependence of the tumor on EGFR-mediated survival signals ("oncogene addiction") and/or an increased sensitivity of the mutant receptors to the drug. Another possible mechanism, termed "oncogenic shock," is the subject of an article included in these proceedings.

The potential role of EGFR TKIs as adjuvant therapy following chemotherapy should be investigated, particularly in the population of patients with *EGFR* mutation, high *EGFR* gene copy number, and increased EGFR protein expression. A large trial of adjuvant erlotinib following chemotherapy in unselected patients is currently being planned. It will also be important to investigate prospectively the benefit of EGFR TKIs as first-line therapy in selected populations: patients with mutations in exons 19 to 21, those with the clinical characteristics associated with response (e.g., never smoker, adenocarcinoma/bronchioloalveolar carcinoma histology, or Asian ethnicity), and those with increased *EGFR* copy number and/or protein expression.

Acknowledgments

We thank InforMEDical Communications, Inc. (Carlisle, MA), for editorial assistance and Continuing Medical Education Sponsorship.

References

1. Kris MG, Natale, RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290:2149–58.
2. 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;350:2191–3.