



Assessment  
Program  
Volume 22, No. 6  
November 2007

# Epidermal Growth Factor Receptor Mutations and Tyrosine Kinase Inhibitor Therapy in Advanced Non-Small-Cell Lung Cancer

## Executive Summary

### Background

Traditional treatment options for advanced (stage IIIA/B, IV) non-small-cell lung cancer (NSCLC) depend on tumor stage and location at diagnosis. Outcomes are particularly poor, with often severe systemic toxicities in patients treated with current platinum-based chemotherapy. As a consequence, targeted therapies, including those specific to the epidermal growth factor receptor (EGFR), have been sought to improve outcomes and reduce systemic toxicities.

EGFR is a protein kinase involved in key cellular processes that include growth, differentiation, apoptosis, and morphogenesis. It is commonly overexpressed on the surface of cells in a variety of human epithelial cancers, including NSCLC. Genetic dysregulation in carcinogenesis has been associated with constitutive activation of EGFR TK and downstream signaling pathways. Anti-EGFR drugs, including the small-molecule tyrosine kinase inhibitors (TKI) gefitinib (Iressa®) and erlotinib (Tarceva®) inhibit EGFR activation. In the initial phase II and phase III monotherapy studies in patients with refractory NSCLC, gefitinib had no survival benefit, but improved intermediate outcomes; whereas, erlotinib produced a small, but statistically significant, improvement in survival compared to placebo. Subsequent phase III studies showed no benefit of adding gefitinib or erlotinib to standard chemotherapy regimens in first-line treatment of advanced NSCLC. However, subgroup analyses of several trials revealed consistent correlations between therapeutic response to TKI drugs and adenocarcinoma histology, female sex, never-smoking history, and East Asian ancestry.

These observations, in the context of earlier preclinical findings, led to the identification in 2004 of somatic gain-of-function mutations in the TK domain of the EGFR gene in tumor samples from patients who had objective response to TKI drugs. A corollary to identification of the TKI mechanism of action is that this also permits testing to predict response of individual patients' tumors to these agents. The ultimate goal of EGFR mutation testing in this setting is to select individuals who have increased probability of obtaining clinical benefit from EGFR TKI therapy and, if sufficiently predictive, to exclude individuals from such therapy who are highly unlikely to benefit from treatment.

This Assessment uses a conceptual framework that examines the analytical validity, clinical validity, and clinical utility of EGFR mutation analysis as a predictor of clinical response to either drug. As defined by the U.S. National Human Genome Research Institute, National Institutes of Health (<http://www.genome.gov/10002404>), the analytical validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest. The clinical validity of a genetic test defines its ability to detect or predict the presence or absence of the phenotype, which in the case of this Assessment is defined as response to treatment. The clinical utility of a genetic test refers to the likelihood that using the pretreatment test results to help make management decisions will lead to an improved outcome.

NOTICE OF PURPOSE: TEC Assessments are scientific opinions, provided solely for informational purposes. TEC Assessments should not be construed to suggest that the Blue Cross Blue Shield Association, Kaiser Permanente Medical Care Program or the TEC Program recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service; any particular course of treatment, procedure, or service; or the payment or non-payment of the technology or technologies evaluated.



An Association  
of Independent  
Blue Cross and  
Blue Shield Plans



**Objective**

The objective of this Assessment is to evaluate tumor cell EGFR gene mutation analysis as a means to select (or deselect) patients with advanced non-small-cell lung cancer (NSCLC) for therapy with the small-molecule tyrosine kinase inhibitor (TKI) erlotinib (Tarceva®).

Gefitinib (Iressa®), also a TKI, received accelerated marketing approval from the U.S. Food and Drug Administration (FDA) in May 2003; whereas, erlotinib received approval through the new drug approval (NDA) process in November 2004. On the basis of unanticipated poor results with gefitinib in a postapproval phase III monotherapy trial (ISEL), the FDA revised its labeling in mid-2005. Gefitinib is no longer available for routine use in new patients in the U.S. However, given the close pharmacologic and pharmacodynamic similarities of gefitinib and erlotinib, both agents were considered in the evidence review.

**Search Strategy**

A MEDLINE® search (via PubMed) was performed through May 2007 to obtain references to original reports on TKI therapy and mutation analysis in NSCLC, using keywords or phrases “EGFR,” “epidermal growth factor receptor,” “tyrosine kinase inhibitor,” “gefitinib,” “erlotinib,” and “mutation.” The electronic search was limited to English-language studies of human subjects. Review articles and meta-analyses provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search. The “related articles” function was used in conjunction with key articles to identify other papers that may have been missed by the search process. Manufacturers and other vendor websites were consulted for information on commercial laboratory assays.

**Selection Criteria**

Original full-length, peer-reviewed studies were selected for inclusion if they provided sufficient information to calculate the analytic performance of EGFR mutations in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and related those to clinical outcomes (e.g., objective response rate [ORR], overall survival [OS], progression-free survival [PFS]) with TKI therapy for advanced NSCLC.

**Main Results**

In 23 nonconcurrent or retrospective studies, investigators analyzed tumor samples from patients with advanced NSCLC who already had entered a TKI protocol or compassionate-use program (n=1,471 patients analyzed). The data for gefitinib consistently suggested that the presence of an EGFR gene mutation in tumors is associated with improved response, reflected in a median ORR of 72% in patients with mutations and 11% in patients with the wild-type gene. Calculation of the analytic performance of EGFR mutations as a predictor of ORR to gefitinib yields median values for sensitivity, specificity, PPV, and NPV of 75%, 91%, 72%, and 89%, respectively. Median ORR values for erlotinib were 34% and 12%, with sensitivity, specificity, PPV and NPV of 32%, 87%, 34%, and 88%, based on two reports. The presence of EGFR mutations generally correlated with longer PFS and OS, compared to results in tumors with wild-type EGFR, but the relationship between EGFR mutations and ORR is not absolute. A proportion of patients with wild-type EGFR did respond (median ORR=11%) and some with mutations did not respond (median ORR=28%).

Six subsequent peer-reviewed reports of phase II, nonrandomized studies presented results of first-line or greater TKI monotherapy in 397 patients with EGFR mutation-positive advanced NSCLC. EGFR mutations were found in 144 (36%) individual tumor samples ranging from 24% to 64% among the studies. An ORR of 81% is based on compiled mutation data from 112 patients who entered phase II treatment protocols using gefitinib. Individual study response rates ranged from 75% to 90%, with median PFS ranging from 8 months to more than 15 months and a median PPV of 82%. Comparable data on erlotinib alone are unavailable.

**Discussion**

The nonconcurrent and retrospective analyses of tumor cell EGFR gene TK domain mutations consistently suggest an association between the presence (or absence) of a mutation and therapeutic response (or nonresponse) to TKI drugs, primarily gefitinib. The magnitude and

consistency of the PPVs for EGFR mutation analysis among 6 prospective, single-arm phase II studies supports the conclusion that this test has clinical validity as a predictor of NSCLC response to gefitinib. However, no prospective data are available on the use of EGFR mutation analysis to reliably identify nonresponders (i.e., a high NPV) to gefitinib, such that mutation-negative patients could be excluded from therapy when it is otherwise likely to be prescribed. Therefore, the clinical utility of mutation analysis remains unproven for gefitinib. A scarcity of clinical data precludes conclusions on the clinical validity or utility of EGFR mutation analysis to predict response of advanced NSCLC to erlotinib.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether use of EGFR mutation analysis to predict TKI sensitivity meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

**1. The technology must have final approval from the appropriate governmental regulatory bodies.**

EGFR mutation analysis (PCR amplification and gene sequencing) is commercially available as a laboratory-developed test (Genzyme Genetics, Westborough, MA). Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

**2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

Evidence compiled from nonconcurrent and retrospective studies is sufficient to conclude that a gain-of-function somatic mutation in one of exons 18-24 of tumor cell EGFR gene tyrosine kinase domain reasonably predicts ORR to gefitinib therapy in patients with advanced NSCLC, based on the sensitivity, specificity, PPV, and NPV of mutation presence compared to absence, suggesting this marker has clinical validity in this setting. Results from single-arm prospective phase II studies are sufficient to conclude that the presence of a gain-of-function somatic mutation in one of exons 18-24 of the EGFR gene TK domain is a strong predictor of ORR based on the PPV, supporting clinical validity. Evidence from the prospective gefitinib studies cannot be used to determine the NPV, nor correlations with OS, and thus does not permit conclusions concerning the clinical utility of tumor cell EGFR mutation analysis to predict the net health outcome relative to standard therapy. Furthermore, because gefitinib is not available for routine use in the U.S., conclusions about the clinical utility of mutation analysis in guiding its use have little practical value.

Evidence is insufficient to permit conclusions about the clinical validity or utility of EGFR mutation testing to predict erlotinib sensitivity or guide therapy in patients with advanced NSCLC. There is no prospective evidence on the NPV of mutation analysis that could be used to justify withholding erlotinib therapy.

**3. The technology must improve the net health outcome; and**

**4. The technology must be as beneficial as any established alternatives.**

There is insufficient evidence to permit conclusions regarding the use of tumor cell EGFR mutation analysis results for managing advanced NSCLC treatment in the context of a standard of care in which erlotinib therapy would be offered to all endstage patients.

**5. The improvement must be attainable outside the investigational settings.**

Whether or not the use of tumor cell EGFR mutation analysis for managing advanced NSCLC treatment improves health outcomes has not been demonstrated in the investigational setting.

Based on the above, use of tumor cell EGFR mutation analysis to predict therapeutic sensitivity to erlotinib (Tarceva®) does not meet the TEC criteria.

**Contents**

|                                      |           |   |           |
|--------------------------------------|-----------|---|-----------|
| <b>Assessment Objective</b>          | <b>5</b>  | <b>Review of Evidence</b>   | <b>10</b> |
| <b>Background</b>                    | <b>5</b>  | <b>Summary of Application of the Technology Evaluation Criteria</b> | <b>17</b> |
| <b>Methods</b>                       | <b>9</b>  | <b>References</b>   | <b>19</b> |
| <b>Formulation of the Assessment</b> | <b>10</b> |   |           |

**Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.**

**TEC Staff Contributors**

**Author**—Thomas A. Ratko, Ph.D.; **TEC Executive Director**—Naomi Aronson, Ph.D.; **Managing Scientific Editor**—Kathleen M. Ziegler, Pharm.D.; **Research/Editorial Staff**—Claudia J. Bonnell, B.S.N., M.L.S.; Maxine A. Gere, M.S.

**Blue Cross and Blue Shield Association Medical Advisory Panel**

**Allan M. Korn, M.D., F.A.C.P.**—Chairman, *Senior Vice President, Clinical Affairs/Medical Director, Blue Cross and Blue Shield Association*; **Alan M. Garber, M.D., Ph.D.**—Scientific Advisor, *Staff Physician, U.S. Department of Veterans Affairs*; **Henry J. Kaiser, Jr., Professor, and Professor of Medicine, Economics, and Health Research and Policy, Stanford University**; **Steven N. Goodman, M.D., M.H.S., Ph.D.**—Scientific Advisor, *Associate Professor, Johns Hopkins School of Medicine, Department of Oncology, Division of Biostatistics (joint appointments in Epidemiology, Biostatistics, and Pediatrics)*—American Academy of Pediatrics Appointee. ■ **Panel Members** **Peter C. Albertsen, M.D.**, *Professor, Chief of Urology, and Residency Program Director, University of Connecticut Health Center*; **Sarah T. Corley, M.D.**, *Physician Consultant, NexGen Healthcare Information Systems, Inc.*—American College of Physicians Appointee; **Helen Darling, M.A.**, *President, National Business Group on Health*; **Josef E. Fischer, M.D., F.A.C.S., William V. McDermott Professor of Surgery, Harvard Medical School and Chair, Department of Surgery, Beth Israel Deaconess Medical Center—American College of Surgeons Appointee; **Willard K. Harms, M.D., M.M., M.H.P.E., F.A.C.P.**, *Senior Medical Director, Medical Policy and Adjudication, Blue Cross Blue Shield of Illinois*; **I. Craig Henderson, M.D.**, *Adjunct Professor of Medicine, University of California, San Francisco*; **Mark A. Hlatky, M.D.**, *Professor of Health Research and Policy and of Medicine (Cardiovascular Medicine), Stanford University School of Medicine*; **Walter A. Hollinger, M.D., M.M., M.H.P.E., F.A.C.P.**, *Senior Medical Director, Care Management, Blue Cross and Blue Shield of Florida*; **Bernard Lo, M.D.**, *Professor of Medicine and Director, Program in Medical Ethics, University of California, San Francisco*; **Barbara J. McNeil, M.D., Ph.D.**, *Ridley Watts Professor and Head of Health Care Policy, Harvard Medical School, Professor of Radiology, Brigham and Women's Hospital*; **Joel Owerbach, Pharm.D.**, *Vice President and Chief Pharmacy Officer, Excellus Health Plans*; **William R. Phillips, M.D., M.P.H.**, *Clinical Professor of Family Medicine, University of Washington*—American Academy of Family Physicians' Appointee; **Maren T. Scheuner, M.D., M.P.H.**, *Natural Scientist in the Division of Behavioral and Social Sciences, RAND Corporation; Adjunct Associate Professor, UCLA School of Public Health*—American College of Medical Genetics Appointee; **J. Sanford Schwartz, M.D.**, *Professor of Medicine, Department of Medicine, University of Pennsylvania School of Medicine and Professor, Health Care Systems, Health Management & Economics, The Wharton School*; **Earl P. Steinberg, M.D., M.P.P.**, *President and CEO, Resolution Health, Inc.*; **A. Eugene Washington, M.D., M.Sc.**, *Executive Vice Chancellor and Provost, University of California, San Francisco*; **Jed Weissberg, M.D.**, *Associate Executive Director for Quality and Performance Improvement, The Permanente Federation.***

CONFIDENTIAL: This document contains proprietary information that is intended solely for Blue Cross and Blue Shield Plans and other subscribers to the TEC Program. The contents of this document are not to be provided in any manner to any other parties without the express written consent of the Blue Cross and Blue Shield Association.

## Assessment Objective

The objective of this Assessment is to evaluate tumor cell epidermal growth factor receptor (EGFR) gene mutation analysis as a means to select (or deselect) patients with advanced non-small-cell lung cancer (NSCLC) for therapy with the small-molecule tyrosine kinase inhibitor (TKI) erlotinib (Tarceva®), which received approval through the U.S. Food and Drug Administration (FDA) new drug approval (NDA) process in November 2004.

Another TKI, gefitinib (Iressa®), received accelerated FDA marketing approval in May 2003 based on intermediate outcomes in the phase II studies. However, on the basis of unanticipated poor results with gefitinib in a subsequent phase III monotherapy trial (ISEL), the FDA revised its labeling in mid-2005. Gefitinib is no longer available for routine use in new patients in the U.S. Given the close pharmacologic and pharmacodynamic similarities of gefitinib and erlotinib, both agents were considered in the evidence review.

## Background

### Lung Cancer Therapy

Lung cancer is the second most commonly diagnosed cancer in the U.S., with nearly 175,000 new cases in 2005 (Jemal et al. 2005). It is the most common cause of cancer deaths in the U.S. among men and women, accounting for nearly 30% of all cancer-related mortality. Lung cancer is classified into two major histologic types, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The latter accounts for about 70–80% of all cases, with clinical characteristics and approaches to therapy that differ considerably from those of SCLC (Jemal et al. 2005).

Treatment options for NSCLC include surgery, chemotherapy, radiation therapy, and best supportive care, depending on tumor stage and location at diagnosis (Table 1). Surgery is the primary treatment for early stage disease, with an approximate 5-year survival range of between 35% (stage II) and 70% (completely resected stage I; Ginsberg et al. 1997). However, in about 80% of cases, cancer has spread beyond the lungs at diagnosis, precluding surgery, with low survival rates. Median survival time for untreated advanced NSCLC (stage IIIB/IV) with best supportive care is about 4 months from diagnosis, with fewer than 20% of patients surviving past the first year. Third-generation, first-line cytotoxic chemotherapy regimens for advanced NSCLC comprise primarily platinum-based (cisplatin, carboplatin) combinations with docetaxel, paclitaxel, or gemcitabine. Randomized trials have shown overall response rates of 19–33%, median survival time of about 8–10 months, and overall survival rates of 33–37% at 1 year and 11% at 2 years among patients with good performance status (Scagliotti et al. 2002; Schiller et al. 2002). Although patients may experience symptomatic palliation with these regimens, significant toxicities limit use to patients with good (<2) ECOG performance status. Recurrent or relapsed NSCLC is treated with docetaxel and pemetrexed supplemented with vitamin B12 and folate, yielding median survival of 7–8 months (Hanna et al. 2004; Shepherd et al. 2000).

The poor long-term outcomes and substantial toxicities of cytotoxic chemotherapy have stimulated investigation for more effective, less toxic alternative therapies for advanced NSCLC. Among those, agents that target the EGFR signaling pathway have been under investigation for more than 20 years (Dei Tos and Ellis 2005; Giaccone and Rodriguez 2005; Fruehauf 2006;

**Table 1.** Standard Treatment Outcomes for NSCLC

| Treatment   | Stage  | Median Survival   |                                |
|---|--|---|--------------------------------|
| Surgical resection<br>(Ginsberg et al. 1997)                                    | I  | – 70% at 5 years with complete resection                |                                |
|   | II   | – 35% at 5 years  |                                |
| Third-generation chemotherapy<br>(Scagliotti et al. 2002; Schiller et al. 2002) | IIIB/IV  | – 8–10 months<br>– 33–37% at 1 year<br>– 11% at 2 years |                                |
|   | Best supportive care<br>(Ginsberg et al. 1997) | IIIB/IV   | – 4 months<br>– <20% at 1 year |

Metro et al. 2006; Sharma et al. 2007; Toschi and Cappuzo 2007). EGFR is a member of a family of four closely related transmembrane receptors found on the surface of normal epithelial cells: EGFR/erbB-1, HER2/neu/erbB-2, HER3/erbB-3, and HER4/erbB-4 (first name in each set now preferred). It consists of an extracellular ligand-binding domain; a transmembrane domain; and, an intracellular cytoplasmic protein with tyrosine kinase (TK) activity. EGFR has a number of endogenous ligands that include EGF, transforming growth factor- $\alpha$ , amphiregulin, betacellulin, heparin-binding EGF, poxvirus mitogens, and epiregulin. Binding by EGFR of one of these ligands initiates a complex signaling cascade that is involved in several normal cellular processes including growth, differentiation, apoptosis, and morphogenesis.

Given the centrality of these processes in the physiologic regulation of normal epidermal tissues, it is not surprising that dysregulation of the EGFR pathway has been implicated in carcinogenesis. High levels of EGFR and its ligands have been detected in oral dysplasias and pre-malignant lesions of the lung, cervix, and prostate. The receptor is commonly overexpressed on the surface of cells in a variety of human epithelial cancers including NSCLC, colorectal cancer (CRC), head and neck, pancreatic, renal, breast, ovarian, glioma, and bladder cancers (Dei Tos and Ellis 2005). Aberrant EGFR expression in tumors has been associated with more aggressive disease, resistance to chemo- and radiotherapy, increased propensity for metastasis, angiogenesis, and decreased survival. At the molecular level, this has been attributed to a number of mechanisms that include EGFR overexpression secondary to transcriptional or translational modification or gene amplification; or, mutations in the EGFR TK gene that result in constitutive activation of downstream signaling (Bunn et al. 2006; Riely et al. 2006; Rosell et al. 2006; Thomas et al. 2006).

Laboratory and animal experiments have shown that therapeutic interdiction of the EGFR pathway could be used to halt cell cycle progression, cellular proliferation, and tumor growth in solid tumors that express EGFR (Fruehauf 2006). This concept led to the development of two main classes of anti-EGFR agents: small-molecule TK inhibitors (TKI) and monoclonal antibodies (MAbs) that block EGFR-ligand interaction (Heymach et al. 2006). Two orally administered EGFR-selec-

tive quinazolinamine derivatives have been developed for use in treating NSCLC: gefitinib (Iressa<sup>®</sup>) and erlotinib (Tarceva<sup>®</sup>). Gefitinib received accelerated FDA marketing approval in May 2003, whereas erlotinib received approval through the standard NDA process in November 2004. However, on the basis of unanticipated poor results with gefitinib in a postapproval phase III monotherapy trial (ISEL), the FDA revised its labeling in mid-2005, to the effect that gefitinib is no longer available for routine use in new patients in the U.S. (Sequist et al. 2007a). A third broader spectrum agent, lapatinib (Tykerb<sup>®</sup>; GW572016) is an EGFR and ErbB-2 (HER2/neu) dual tyrosine kinase inhibitor that is FDA-labeled for use in treatment-refractory metastatic breast cancer in combination with capecitabine (Xeloda<sup>®</sup>). Two anti-EGFR MAbs are commercially available in the U.S. Cetuximab (Erbix<sup>®</sup>) is a chimeric (mouse/human) molecule indicated to treat patients with metastatic colorectal cancer as a combination treatment to be given intravenously with irinotecan. Panitumumab (Vectibix<sup>™</sup>) is a totally human MAb indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

#### Tyrosine Kinase Inhibitor Therapy of NSCLC

A recent systematic review summarizes clinical results with gefitinib and erlotinib in advanced NSCLC (Feld et al. 2006). Initial phase I trials (not shown) that suggested efficacy were followed by a number of phase II and III randomized studies of gefitinib or erlotinib monotherapy in previously treated patients with advanced or recurrent NSCLC (Table 2).

The two IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer) trials tested different doses of gefitinib, with no dose-response effect evident in either trial (Fukuoka et al. 2003; Kris et al. 2003). Indirect comparison of the IDEAL results to third-generation chemotherapy outcomes suggested that gefitinib has clinical benefit in this setting, especially considering the relatively low toxicity of gefitinib compared to chemotherapy. The NCIC BR.21 trial in patients not eligible for further chemotherapy provided evidence that erlotinib monotherapy extends median OS by 2 months compared with placebo (Shepherd et al. 2005). However, the ISEL (Iressa Survival Evaluation in Lung Cancer) trial showed no statistically significant

**Table 2.** RCTs of TKI Monotherapy in Previously Treated Advanced NSCLC\*

| Study<br>(Investigator)              | Phase | TKI Dose<br>(mg/d) | No.<br>Pts | Median OS<br>(months) | 1-Year Survival<br>(%) |
|--------------------------------------|-------|--------------------|------------|-----------------------|------------------------|
| IDEAL 1<br>(Fukuoka et al. 2003)     | II    | gefitinib 250      | 104        | 7.6                   | 35                     |
|                                      |       | gefitinib 500      | 106        | 8.0                   | 29                     |
| IDEAL 2<br>(Kris et al. 2003)        | II    | gefitinib 250      | 102        | 7                     | 27                     |
|                                      |       | gefitinib 500      | 114        | 6                     | 24                     |
| ISEL<br>(Thatcher et al. 2005)       | III   | gefitinib 250      | 1,129      | 5.6                   | 27                     |
|                                      |       | placebo            | 563        | 5.1                   | 21                     |
| NCIC-BR.21<br>(Shepherd et al. 2005) | III   | erlotinib 150      | 488        | 6.7                   | 31                     |
|                                      |       | placebo            | 243        | 4.7                   | 22                     |

p&lt;0.001

\* All patients had failed 2 or more chemotherapy regimens and had stage IIIA/B or IV NSCLC  
TKI: tyrosine kinase inhibitor; OS: overall survival

effect of gefitinib compared with placebo (plus best supportive care) on OS in a sample of patients refractory to or intolerant of chemotherapy (Thatcher et al. 2005).

Preclinical studies demonstrated synergy between gefitinib and cytotoxic chemotherapy in human solid tumors, both in vitro and in vivo (Ciardiello et al. 2000; Sirotnak et al. 2000). Based on such preclinical findings and results from the BR.21 erlotinib trial, 4 large randomized phase III trials of first-line chemotherapy with or without a TKI in advanced NSCLC were undertaken (Table 3). However, neither gefitinib nor erlotinib provided additional benefit in OS when the data from each were considered as a whole.

Although the overall outcomes in most of the phase II and III TKI trials showed marginal or no improvement, exploratory subset analyses identified subgroups of patients with specific clinicopathologic characteristics who experienced significantly greater ORR or OS with TKI therapy compared to those without the traits. These identifiers included adenocarcinoma tumor histology (IDEAL 1, BR.21); female sex (IDEAL 1 and 2, BR.21); history of never having smoked (IDEAL 2, ISEL, TRIBUTE, BR.21); and, East Asian (i.e., Japanese, Korean, Chinese) origin or ancestry (BR.21, ISEL).

Because highly disparate clinicopathologic characteristics were associated with similar clinical response to TKI therapy in the pivotal trials, investigators surmised a possible genetic

basis for these associations (Pao and Miller 2005). The centrality of the EGFR pathway in regulating cellular proliferative processes further suggested a genetic component could be involved in differential response to TKI therapy. This idea was supported by earlier observations in transgenic animal models that demonstrated tumors could become dependent for growth and maintenance on signaling from aberrant TKs and other oncogenes—the “oncogene addiction hypothesis”—and that such mutated enzymes could be effectively targeted in cancer therapy (Weinstein 2002). Based on these concepts, several groups sought genetic correlates to TKI sensitivity, with the aim of using such markers to predict which patients would respond and which would not respond to anti-EGFR therapies. These are briefly described in the following section of this Assessment.

#### Genetic Correlates of EGFR TKI Sensitivity EGFR Gene Mutation Analysis.

In 2004, somatic mutations in the EGFR gene within NSCLC tissue samples were identified that were closely associated with favorable clinical response to gefitinib and erlotinib therapy in NSCLC patients (Lynch et al. 2004; Paez et al. 2004; Pao et al. 2004). These genetic changes consisted of small, in-frame deletions or point mutations in EGFR exons 18–24, which encode the kinase domain of the protein and are clustered in two hot spots in the EGFR gene. Most common were small deletions in exon 19 that delete amino acids 747–750, located around the kinase active site, and point mutations in exon

**Table 3.** RCTs of TKI Therapy Combined with First-Line Chemotherapy in Advanced NSCLC\*

| Study (Investigator)            | Phase | Chemotherapy Regimen     | TKI Dose (mg/d) | No. Pts | Median OS (months) | 1-Year Survival (%) |
|---------------------------------|-------|--------------------------|-----------------|---------|--------------------|---------------------|
| INTACT 1 (Giaccone et al. 2004) | III   | cisplatin + gemcitabine  | gefitinib 250   | 365     | 9.9                | 41                  |
|                                 |       |                          | gefitinib 500   | 365     | 9.9                | 43                  |
|                                 |       |                          | placebo         | 363     | 10.9               | 44                  |
| INTACT 2 (Herbst et al. 2004)   | III   | paclitaxel + carboplatin | gefitinib 250   | 345     | 9.8                | 41                  |
|                                 |       |                          | gefitinib 500   | 347     | 8.7                | 37                  |
|                                 |       |                          | placebo         | 345     | 9.9                | 42                  |
| TALENT (Gatzemeier et al. 2007) | III   | cisplatin + gemcitabine  | erlotinib 150   | 580     | 9.9                | 41                  |
|                                 |       |                          | placebo         | 579     | 10.1               | 42                  |
| TRIBUTE (Herbst et al. 2005)    | III   | paclitaxel + carboplatin | erlotinib 150   | 539     | 10.6               | 47                  |
|                                 |       |                          | placebo         | 540     | 10.5               | 44                  |

\* all patients had stage IIIA/B or IV NSCLC; monotherapy (TKI or placebo) was continued after completion of chemotherapy  
OS: overall survival; TKI: tyrosine kinase inhibitor

21 that result in the substitution of a leucine residue with arginine in the TK activation loop (Giaccone and Rodriguez 2005).

Mutation analysis involves two steps. The first, nucleic acid amplification (NAA) increases the amount of a target, probe, or signal. Polymerase chain reaction (PCR) is the most widely used NAA method. It can be performed on a variety of samples, including DNA or RNA (i.e., reverse-transcriptase PCR<sup>1</sup>) derived from whole blood, frozen cell pellets, or tissues. The second step, DNA sequencing, is used to determine the order of nucleotides within DNA. Conventional sequencing technologies based on Sanger dideoxy chain termination methods have been in widespread use by laboratories for many years (Metzker 2005). The technology is well developed; automated sequencers are marketed by several commercial suppliers, and can determine up to 96 independent DNA sequences about 400 to 500 nucleotides long in approximately 8 hours. These sequencing technologies have been proven in practice, and are accurate for most diagnostic applications. Furthermore, according to the American College of Medical Genetics 2006 *Standards and Guidelines for*

*Clinical Genetics Laboratories* ([http://www.acmg.net/Pages/ACMG\\_Activities/stds-2002/g.htm](http://www.acmg.net/Pages/ACMG_Activities/stds-2002/g.htm)). DNA sequencing is the “gold standard” for the analytic validation of DNA-based mutation tests.

**Other Predictive Biomarkers.** EGFR is frequently overexpressed on the surface of NSCLC cells. These receptors have an important role in tumor cell survival, with downstream signaling molecules controlling cell proliferation, invasion, metastasis, and inhibition of apoptosis. It is logical, therefore, that EGFR protein expression assayed using immunohistochemistry (IHC) methods has been investigated as a predictive factor for anti-EGFR therapy. However, clinical data on the correlation between tumor cell EGFR protein expression and clinical outcomes of TKI therapy are inconsistent (Clark et al. 2006; Cappuzzo et al. 2005; Han et al. 2005b; Hirsch et al. 2005; Parra et al. 2004; Perez-Soler et al. 2004). The conflicting results among these studies suggest that analysis of tumor cell surface EGFR expression is not an optimal method for predicting EGFR-targeted therapy response in NSCLC patients.

<sup>1</sup> The polymerase chain reaction (PCR) process uses multiple cycles of template denaturation, primer annealing, and primer elongation to amplify DNA sequences. It is an exponential process since amplified products from the previous cycle serve as templates for the next cycle of amplification, making it a highly sensitive technique for the detection of nucleic acids. RT-PCR combines cDNA synthesis from RNA templates with PCR to provide a rapid, sensitive method for analyzing gene expression. RT-PCR is used to detect or quantify the expression of messages, often from small amounts of RNA. In addition, the technique is used to analyze differential gene expression or clone cDNAs without constructing a cDNA library. RT-PCR is more sensitive and easier to perform than other RNA analysis techniques.

A second marker of constitutive EGFR pathway activation, increased EGFR gene copy number (genomic gain), has been investigated as a potential predictive marker for TKI sensitivity in advanced NSCLC. Fluorescence in-situ hybridization (FISH) has been used in 3 retrospective reports that suggest increased EGFR gene copy number is associated with enhanced TKI response in patients with advanced NSCLC (Cappuzzo et al. 2005; Hirsch et al. 2005; Tsao et al. 2005). However, other investigators who used quantitative PCR (qPCR) to assay EGFR gene copy number reported results that conflicted with the FISH findings (Hirsch et al. 2006; Dziadziuszko et al. 2006; Bell et al. 2005). Another report using qPCR showed that NSCLC patients with high EGFR mRNA expression, but not high EGFR gene copy number, had significantly longer PFS with TKI therapy compared to those who had low mRNA expression (Dziadziuszko et al. 2006). Finally, a recent retrospective study showed that the combination of increased EGFR FISH gene copy number and IHC-positive EGFR expression was an effective predictor of improved survival with gefitinib treatment in Western patients with previously treated advanced NSCLC (Hirsch et al. 2007).

In summary, the results of studies that examined potential relationships between tumor cell EGFR gene expression or copy number and clinical response to TKI therapy in NSCLC have been inconsistent, hampered by small numbers of cases, methodologic differences among laboratories, and subgroup bias. As a consequence, data are insufficient at present to draw meaningful conclusions about their routine clinical use in guiding clinical treatment with TKIs. Because of this, these predictive biomarkers will not be considered in this Assessment, which will focus on EGFR TK mutations and their use in predicting response to and guiding therapy with TKI drugs gefitinib and erlotinib.

**FDA Status.** EGFR gene mutation analysis is commercially available through Genzyme Genetics (<http://www.genzyme.com>) and regulated as a laboratory-developed test under the Clinical Laboratory Improvement Amendments (CLIA) regulation. Genzyme Genetics holds exclusive, worldwide diagnostic rights to the discovery of EGFR gene mutations in NSCLC tumors.<sup>2</sup> Premarket approval from

the FDA is not required when the assay is performed in a laboratory that observes the CLIA regulations.

## Methods

### Search Methods

A MEDLINE® search (via PubMed) was performed through June 2007 to obtain references to original reports on TKI therapy and mutation analysis in NSCLC, using keywords or phrases “EGFR,” “epidermal growth factor receptor,” “tyrosine kinase inhibitor,” “gefitinib,” “erlotinib,” and “mutation.” The electronic search was limited to English-language studies of human subjects. Review articles and meta-analyses provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search. The “related articles” function was used in conjunction with key articles to identify other papers that may have been missed by the search process. Manufacturers and other vendor Web sites were consulted for information on commercial laboratory assays.

### Study Selection

Original full-length, peer-reviewed studies were selected for inclusion if they provided sufficient information to calculate the analytic performance of EGFR mutations in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and related those to clinical outcomes (e.g., radiological ORR, OS, PFS) with TKI therapy for advanced NSCLC.

### Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 28, 2007. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

<sup>2</sup> Press Release: Genzyme Introduces New Genetic Test to Complement Lung Cancer Portfolio, December 4, 2006 (<http://www.genzyme.com/about/news/GENZ%20PR-120406.asp#TopOfPage>)

## Formulation of the Assessment

---

### Patient Indications

Individuals with advanced (stage IIIA/B or IV) metastatic or recurrent NSCLC are the target population for TKI therapy with erlotinib or gefitinib. Both drugs were initially labeled for use as second- or third-line treatment following failure of at least one course of cytotoxic chemotherapy. Due to unanticipated poor results in the ISEL trial, the FDA revised the approved label for gefitinib. Patients who were receiving gefitinib as of September 15, 2005 were allowed to continue to receive it, with prescription refills obtained through the Iressa Access Program after required patient and physician forms were filed. After September 15, 2005, no new patients have been allowed access to gefitinib unless part of a clinical study approved by an Institutional Review Board (IRB) prior to June 17, 2005 or they are part of a clinical study approved by an IRB after June 17, 2005 that is conducted under an Investigational New Drug (IND) application.

### Technologies to Be Compared

The technology of interest in this Assessment is EGFR mutation analysis to select (or to deselect) patients for TKI therapy in advanced NSCLC. The key comparison is the clinical response to TKI therapy observed in patients whose tumor samples carry somatic EGFR gene TK domain mutations versus the clinical response in patients with tumors that have the wild type EGFR gene.

### Health Outcomes

Health outcomes of primary interest are OS and radiologic ORR to assess the impact of EGFR mutation analysis as a means to select (or to deselect) patients with advanced NSCLC for TKI therapy.

### Specific Assessment Questions

This Assessment uses a conceptual evaluation framework that examines the analytical validity, the clinical validity, and the clinical utility of genetic tests, as defined by the U.S. National Human Genome Research Institute, National Institutes of Health (<http://www.genome.gov/10002404>). The analytical validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest in blood or tissue samples. The clinical validity of a genetic test defines its ability to detect or predict the presence or absence of the phenotype, which in the case of this review is

defined as clinical response to TKI treatment. The clinical utility of a genetic test refers to the likelihood that using the test results to help make management decisions will lead to an improved health outcome. This framework is used to assess the overall value of tumor cell EGFR gene mutation analysis as a means to select patients who have a high likelihood of response, and vice versa, to identify those unlikely to respond to TKI therapy with gefitinib or erlotinib.

**Key Question 1. What is the analytical validity of TK gene mutation analysis to predict response to TKI drugs in advanced NSCLC?**

**Key Question 2. What is the clinical validity of TK gene mutation analysis to predict response to TKI drugs in advanced NSCLC?**

**Key Question 3. What is the clinical utility of TK gene mutation analysis to predict response to TKI drugs in advanced NSCLC?**

## Review of Evidence

---

In this section, we evaluate the evidence supporting the use of tumor cell EGFR gene mutation analysis to identify patients with advanced NSCLC most likely to respond (or not respond) to TKI therapy.

**Key Question 1. What is the analytical validity of TK gene mutation analysis to predict response to TKI drugs in advanced NSCLC?**

Although analytical validity will ultimately be reflected in the evidence gathered to support clinical validity and clinical utility, a separate review allows estimation of its likely contribution to any uncertainty regarding clinical validity and utility, as well as information on routine laboratory performance and variation over time. FDA-approved tests are extensively reviewed for analytical validity, but laboratory-developed tests not subject to FDA review may have little publicly available documentation of technical performance. Usual components of analytical validity include analytic sensitivity (how often the marker of interest is detected when it is present), analytic specificity (how often the marker is not detected when it is absent), assay performance when potentially interfering substances are present in the specimen, and assay variability. Assay variability is usually examined within an assay run; between

runs; across reagent lot numbers; and across operators, automated instruments, and laboratories (where applicable).

EGFR gene mutation analysis is commercially available through Genzyme Genetics (<http://www.genzyme-genetics.com>) as a laboratory-developed test under CLIA regulation. Assessment of test technical performance characteristics is desirable to determine the accuracy and reliability of results in clinical practice. However, we did not identify any articles in which the analytical validity of EGFR mutation analysis was specifically reported, nor is information available on the analytic performance of the procedures used by Genzyme. Nonetheless, the methods used in the studies compiled in this Assessment, PCR followed by Sanger dideoxy DNA sequencing, concur with current, widespread clinical laboratory use. As noted in the background, Sanger dideoxy sequencing is the gold standard for other types of mutation analysis (Metzker 2005). Furthermore, the spectrum of mutations detected, in particular their consistency in locations and types (deletion, frameshift, point, etc.) within exons 18-24 of the EGFR TK domain reported among the numerous studies, in different types of tumor samples (frozen samples, paraffin-embedded slices, etc.), together comprise strong, indirect evidence supporting the analytical validity of mutation analysis as performed in the studies.

**Key Question 2. What is the clinical validity of TK gene mutation analysis to predict response to TKI drugs in advanced NSCLC?**

Twenty-three peer-reviewed publications provide data on EGFR mutations in tumor samples obtained from NSCLC patients in TKI clinical studies (Table 4). Among those, two involved erlotinib alone (Eberhard et al. 2005; Tsao et al. 2005), one reported on erlotinib or gefitinib (Sequist et al. 2007b), and the others involved gefitinib alone. Four of the reports are categorized as nonconcurrent, prospective studies because tumor samples originated from an already completed prospective clinical trial. The tumor samples, while not inclusive, demographically reflect the entire study population (Bell et al. 2005; Eberhard et al. 2005; Tsao et al. 2005; Hirsch et al. 2006). The others were retrospective, with tissue samples based on availability (14 reports) or that were inclusive (5 reports).

The clinical response data for gefitinib consistently suggest the presence of an EGFR gene mutation in tumors is associated with higher radiological ORR, reflected in medians of 72% with mutations and 11% with the wild type. Calculation of the analytic performance of EGFR mutations as a predictor of ORR to gefitinib yields median values for sensitivity, specificity, PPV, and NPV of 75%, 91%, 72%, and 89%, respectively. Median ORR values for erlotinib were 34% and 12%, with sensitivity, specificity, PPV, and NPV of 32%, 87%, 34%, and 88%, but these were based on two reports (Eberhard et al. 2005; Tsao et al. 2005). The presence of EGFR mutations correlates with longer PFS and OS with either agent, compared to results in tumors with wild-type EGFR. However, these outcomes were not consistently reported for either drug, precluding sound conclusions. Furthermore, for both drugs, the relationship between EGFR mutations and ORR is not absolute. A median 11% of patients with wild-type EGFR did respond and a median 28% with mutations did not respond. Nonetheless, the consistency in direction and magnitude of these nonconcurrent or retrospective findings suggest tumor cell EGFR gene mutation analysis has clinical validity as a predictor of NSCLC response to gefitinib and thus might be used to select patients for therapy. Data on erlotinib demonstrate a similar pattern, but the numbers of studies and patients are too small to compare indirectly to gefitinib or draw similar conclusions.

**Key Question 3. What is the clinical utility of TK gene mutation analysis to predict response to TKI drugs in advanced NSCLC?**

Table 5 shows results from 6 peer-reviewed publications of phase II, nonrandomized investigations of first-line or greater TKI monotherapy in patients with EGFR mutation-positive advanced NSCLC. EGFR mutations were found in 144 of a total 397 (36%) tumors, with a range of 24% to 64% among the studies. Among 112 patients with tumor mutation data who entered phase II TKI treatment, the overall ORR was 81%. Individual study response rates ranged from 75% to 90%, with median PFS ranging from 8 months to more than 15 months. Because all patients who entered phase II TKI therapy had EGFR mutation-positive tumors, it is possible to calculate only a PPV (median 82%) for EGFR mutations. The data do not permit calculation of a NPV for mutation testing

**Table 4.** Correlation of EGFR TK Gene Mutations with TKI Response in Advanced NSCLC\*

| Investigator<br>(Study)              | TKI                                 | Mutation Analysis<br>Study Design<br>(sample selection)      | Total TK Gene<br>Mutation<br>Assessable/<br>TKI-Treated<br>Patients (%) | TK Gene Mutation<br>Status of TK<br>Gene Mutation           |  | Analytic<br>Performance<br>of Mutation<br>Analysis for ORR | Median PFS/TTP<br>(mos)<br>[p-value] | Median OS<br>(mos)<br>[p-value] |
|--------------------------------------|-------------------------------------|--|---|---|--|--|--------------------------------------|---------------------------------|
|                                      |                                     |  |   | Assessable TKI-<br>Treated Patients**<br>(% assessable pts) | Objective<br>Response<br>to TKI (%)<br>[p-value] |  |                                      |                                 |
| Bell et al.<br>2005<br>(IDEAL I&II)  | gefitinib<br>Phase II               | nonconcurrent<br>prospective<br>(reported<br>representative) | 119/425 in<br>two studies<br>(28)                                       | Mutated: 13<br>Wt: 61<br>(62)                               | 46<br>10<br>[0.005]                              | Sens: 50%<br>Spec: 89%<br>PPV: 46%<br>NPV: 90%             | 4<br>2<br>[NS]                       | 8<br>6<br>[NS]                  |
| Bell et al.<br>2005<br>(INTACT I&II) | gefitinib ± chemo<br>Phase III      | nonconcurrent<br>prospective<br>(reported<br>representative) | 312/1,422 in<br>two studies<br>(22)                                     | Mutated: 18<br>Wt: 152<br>(54)                              | 72<br>55<br>[NS]                                 | Sens: 16%<br>Spec: 94%<br>PPV: 72%<br>NPV: 55%             | Not reached<br>5.5<br>[NS]           | 14.6<br>9.3<br>[NS]             |
| Hirsch et al.<br>2006<br>(ISEL)      | gefitinib ±<br>placebo<br>Phase III | nonconcurrent<br>prospective<br>(reported<br>representative) | 215/1,129<br>(19)   | Mutated: 16<br>Wt: 116<br>(61)                              | 38<br>3<br>[0.001]                               | Sens: 67%<br>Spec: 92%<br>PPV: 38%<br>NPV: 97%             | NR<br>[insufficient data]            | NR<br>[insufficient data]       |
| Eberhard<br>et al. 2005<br>(TRIBUTE) | erlotinib ± chemo<br>Phase III      | nonconcurrent<br>prospective<br>(reported<br>representative) | 274/539<br>(51)   | Mutated: 15<br>Wt: 99<br>(42)                               | 53<br>18<br>[<0.01]                              | Sens: 31%<br>Spec: 92%<br>PPV: 53%<br>NPV: 82%             | 12.5<br>5<br>[<0.001]                | Not reached<br>10<br>[<0.001]   |
| Tsao et al.<br>2005<br>(BR.21)       | erlotinib ±<br>placebo<br>Phase III | nonconcurrent<br>prospective<br>(reported<br>representative) | 177/488<br>(36)   | Mutated: 19<br>Wt: 81<br>(56)                               | 16<br>7<br>[NS]                                  | Sens: 33%<br>Spec: 82%<br>PPV: 16%<br>NPV: 93%             | NR<br>[NS]                           | NR<br>[NS]                      |
| Cappuzzo<br>et al. 2005              | gefitinib                           | retrospective<br>(tissue<br>availability)                    | 89/102<br>(87)  | Mutated: 15<br>Wt: 74<br>(100)                              | 53<br>5<br>[0.001]                               | Sens: 73%<br>Spec: 91%<br>PPV: 53%<br>NPV: 95%             | 10<br>3<br>[0.02]                    | 20.8<br>8.4<br>[NS]             |
| Chou et al.<br>2005                  | gefitinib                           | retrospective<br>(tissue<br>availability)                    | 54/146<br>(37)  | Mutated: 24<br>Wt: 13<br>(68)                               | 71<br>31<br>[0.02]                               | Sens: 81%<br>Spec: 56%<br>PPV: 71%<br>NPV: 69%             | 7.6<br>1.7<br>[0.01]                 | 14.7<br>4.7<br>[0.046]          |

Table 4. Correlation of EGFR TK Gene Mutations with TKI Response in Advanced NSCLC\* (cont'd)

| Investigator<br>(Study)     | TKI       | Mutation Analysis<br>Study Design<br>(sample selection) | Total TK Gene<br>Mutation<br>Assessable/<br>TKI-Treated<br>Patients (%) | TK Gene Mutation<br>Status of TK<br>Gene Mutation<br>Assessable TKI-<br>Treated Patients**<br>(% assessable pts) | Objective<br>Response<br>to TKI (%)<br>[p-value] | Analytic<br>Performance<br>of Mutation<br>Analysis for ORR | Median PFS/TTP<br>(mos)<br>[p-value] | Median OS<br>(mos)<br>[p-value] |
|-----------------------------|-----------|---|---|--|--|--|--------------------------------------|---------------------------------|
| Cortes-Funes<br>et al. 2005 | gefitinib | retrospective<br>(tissue<br>availability)               | 83/220<br>(38)  | Mutated: 10<br>Wt: 73<br>(100)   | 60<br>9<br>[0.001]                               | Sens: 46%<br>Spec: 94%<br>PPV: 60%<br>NPV: 91%             | 12.3<br>3.6<br>[0.002]               | 13<br>4.9<br>[0.02]             |
| Han et al.<br>2005a         | gefitinib | retrospective<br>(tissue<br>availability)               | 90/219<br>(41)  | Mutated: 17<br>Wt: 73<br>(100)   | 65<br>14<br>[0.001]                              | Sens: 52%<br>Spec: 91%<br>PPV: 65%<br>NPV: 86%             | 21.7<br>1.8<br>[<0.001]              | 30.5<br>6.6<br>[<0.001]         |
| Huang et al.<br>2004        | gefitinib | retrospective<br>(all patients)                         | 16/16<br>(100)  | Mutated: 8<br>Wt: 8<br>(100)   | 88<br>25<br>[0.012]                              | Sens: 78%<br>Spec: 86%<br>PPV: 88%<br>NPV: 75%             | NR                                   | 5.4<br>1.3<br>[NR]              |
| Kim et al.<br>2005          | gefitinib | retrospective<br>(tissue<br>availability)               | 27/98<br>(28)   | Mutated: 6<br>Wt: 21<br>(100)  | 100<br>10<br>[<0.001]                            | Sens: 75%<br>Spec: 100%<br>PPV: 100%<br>NPV: 90%           | 12.7<br>2.8<br>[0.003]               | 18.9<br>4.8<br>[0.008]          |
| Kondo et al.<br>2005        | gefitinib | retrospective<br>(all patients)                         | 12/12<br>(100)  | Mutated: 4<br>Wt: 8<br>(100)   | 100<br>0<br>[NR]                                 | Sens: 100%<br>Spec: 100%<br>PPV: 100%<br>NPV: 100%         | NR                                   | NR                              |
| Mitsudomi<br>et al. 2005    | gefitinib | retrospective<br>(tissue<br>availability)               | 59/75<br>(79)   | Mutated: 29<br>Wt: 21<br>(85)  | 83<br>10<br>[<0.001]                             | Sens: 92%<br>Spec: 79%<br>PPV: 83%<br>NPV: 90%             | NR                                   | Not reached<br>15<br>[0.005]    |
| Mu et al.<br>2005           | gefitinib | retrospective<br>(all patients)                         | 22/22<br>(100)  | Mutated: 10<br>Wt: 12<br>(100)   | 70<br>0<br>[0.0004]                              | Sens: 100%<br>Spec: 100%<br>PPV: 70%<br>NPV: 100%          | NR                                   | NR                              |

**Table 4.** Correlation of EGFR TK Gene Mutations with TKI Response in Advanced NSCLC\* (cont'd)

| Investigator<br>(Study) | TKI                          | Mutation Analysis<br>Study Design<br>(sample selection) | Total TK Gene<br>Mutation<br>Assessable/<br>TKI-Treated<br>Patients (%) | TK Gene Mutation<br>Status of TK<br>Gene Mutation           |                       | Objective<br>Response<br>to TKI (%)<br>[p-value]   | Analytic<br>Performance<br>of Mutation<br>Analysis for ORR | Median PFS/TTP<br>(mos)<br>[p-value] | Median OS<br>(mos)<br>[p-value] |
|-------------------------|------------------------------|---|---|---|-----------------------|--|--|--------------------------------------|---------------------------------|
|                         |                              |   |   | Assessable TKI-<br>Treated Patients**<br>(% assessable pts) | Wt: (n)               |  |  |                                      |                                 |
| Niho et al.<br>2006     | gefitinib                    | retrospective<br>(tissue<br>availability)               | 13/40<br>(32)   | Mutated: 4<br>Wt: 9<br>(100)                                | 100<br>0<br>[NR]      | Sens: 100%<br>Spec: 100%<br>PPV: 100%<br>NPV: 100% | NR   | 15.6<br>9.7<br>[NR]                  |                                 |
| Rosell et al.<br>2006   | gefitinib                    | retrospective<br>(tissue<br>availability)               | 34/34<br>(?)****  | Mutated: 7<br>Wt: 24<br>(91)                                | 86<br>12<br>[0.0003]  | Sens: 67%<br>Spec: 95%<br>PPV: 86%<br>NPV: 88%     | NR   | 15.6***<br>2.3<br>[0.04]             |                                 |
| Satouchi et al.<br>2007 | gefitinib                    | retrospective<br>(tissue<br>availability)               | 91/221<br>(41)  | Mutated: 28<br>Wt: 63<br>(100)                              | 71<br>11<br>[<0.001]  | Sens: 74%<br>Spec: 88%<br>PPV: 71%<br>NPV: 89%     | NR   | 24.9<br>7.4<br>[<0.001]              |                                 |
| Sequist et al.<br>2007b | gefitinib<br>or<br>erlotinib | retrospective<br>(all patients)                         | 59/59<br>(100)  | Mutated: 28<br>Wt: 31<br>(100)                              | 54<br>0<br>[<0.001]   | Sens: 100%<br>Spec: 70%<br>PPV: 54%<br>NPV: 100%   | NR   | Not reached<br>43.2<br>[0.001]       |                                 |
| Sone et al.<br>2007     | gefitinib                    | retrospective<br>(tissue<br>availability)               | 59/101<br>(58)  | Mutated: 17<br>Wt: 42<br>(29)                               | 59<br>14<br>[0.0005]  | Sens: 62%<br>Spec: 84%<br>PPV: 59%<br>NPV: 86%     | 7.3<br>1.8<br>[0.003]                                      | 18.9<br>6.4<br>[0.0092]              |                                 |
| Takano et al.<br>2005   | gefitinib                    | retrospective<br>(tissue<br>availability)               | 66/279<br>(24)  | Mutated: 37<br>Wt: 27<br>(97)                               | 84<br>11<br>[<0.0001] | Sens: 91%<br>Spec: 77%<br>PPV: 82%<br>NPV: 89%     | 12.6<br>1.7<br>[<0.0001]                                   | 20.4<br>6.9<br>[<0.0001]             |                                 |
| Taron et al.<br>2005    | gefitinib                    | retrospective<br>(tissue<br>availability)               | 68/68<br>(?)****  | Mutated: 17<br>Wt: 51<br>(100)                              | 94<br>12<br>[<0.0001] | Sens: 73%<br>Spec: 98%<br>PPV: 94%<br>NPV: 88%     | NR   | Not reached<br>9.9<br>[0.001]        |                                 |

**Table 4.** Correlation of EGFR TK Gene Mutations with TKI Response in Advanced NSCLC\* (cont'd)

| Investigator<br>(Study) | TKI       | Mutation Analysis<br>Study Design<br>(sample selection) | Total TK Gene<br>Mutation<br>Assessable/<br>TKI-Treated<br>Patients (%) | TK Gene Mutation<br>Status of TK<br>Gene Mutation           |                       | Objective<br>Response<br>to TKI (%)<br>[p-value] | Analytic<br>Performance<br>of Mutation<br>Analysis for ORR | Median PFS/TTP<br>(mos)<br>[p-value] | Median OS<br>(mos)<br>[p-value] |
|-------------------------|-----------|---|---|---|-----------------------|--|--|--------------------------------------|---------------------------------|
|                         |           |   |   | Assessable TKI-<br>Treated Patients**<br>(% assessable pts) | Wt: (n)               |  |  |                                      |                                 |
| Tokumo et al.<br>2005   | gefitinib | retrospective<br>(all patients)                         | 21/21<br>(100)  | Mutated: 9<br>Wt: 12<br>(100)                               | 89<br>17<br>[<0.01]   | Sens: 80%<br>Spec: 91%<br>PPV: 89%<br>NPV: 83%   | NR   | 25.1<br>14.0<br>[NS]                 |                                 |
| Tomizawa<br>et al. 2005 | gefitinib | retrospective<br>(tissue<br>availability)               | 20/82<br>(24)   | Mutated: 10<br>Wt: 9<br>(95)                                | 100<br>33<br>[0.0012] | Sens: 77%<br>Spec: 100%<br>PPV: 100%<br>NPV: 67% | NR   | NR                                   |                                 |
| Zhang et al.<br>2005    | gefitinib | retrospective<br>(tissue<br>availability)               | 30/98<br>(31)   | Mutated: 12<br>Wt: 18<br>(100)                              | 67<br>6<br>[0.0003]   | Sens: 89%<br>Spec: 81%<br>PPV: 67%<br>NPV: 94%   | 10.0<br>3.0<br>[0.045]                                     | Not reached<br>7.0<br>[0.002]        |                                 |

\* stage IIIA/B or IV metastatic or recurrent NSCLC;

\*\* refers to measurable, evaluable lesions only;

\*\*\* refers to Japanese patients only;

\*\*\*\* paper states patients selected per "tissue availability", not specifying total number of cases screened

NR: not reported; NS: not significant; ORR: objective response rate according to RECIST or ECOG criteria, comprising CR+PR; OS: overall survival; PFS/TTP: progression-free survival/time to progression; Wt: wild-type

**Table 5.** Clinical Response in Prospective Phase II Studies of TKI Therapy in Patients with TK Gene Mutation-Positive Advanced NSCLC\*

| Study (Yr)                 | No. Mutated/ No. Tested (%) | TKI Therapy (mg/d)                                 | Median PFS (months) [95% CI] | Clinical Response in Evaluable Pts | PPV |
|----------------------------|-----------------------------|--|------------------------------|------------------------------------|-----|
| Asahina et al. (2006)      | 20/82 (24)                  | First-line (gefitinib 250)                         | 8.9 [6.7–11.1]               | CR+PR: 2+10<br>SD+PD: 1+3          | 75% |
| Inoue et al. (2006)        | 25/75 (33)                  | First-line (gefitinib 250)                         | 9.7 [7.4–9.9]                | CR+PR: 0+12<br>SD+PD: 2+2          | 75% |
| Sutani et al. (2006)       | 38/100 (38)                 | First- or second-line (gefitinib 250)              | 15.4 [NR]                    | CR+PR: 1+20<br>SD+PD: 5+1          | 78% |
| Sunaga et al. (2007)       | 21/33 (64)                  | First-line or greater (gefitinib 250)              | 12.9 [NR]                    | CR+PR: 3+13<br>SD+PD: 3+0          | 84% |
| Yoshida et al. (2007)      | 27/66 (41)                  | First-line or greater (gefitinib 250)              | 7.7 [6.0–not reached]        | CR+PR: 3+16<br>SD+PD: 1+1          | 90% |
| Van Zandwijk et al. (2007) | 13/41 (32)                  | First-line or greater (gefitinib or erlotinib, NR) | 14.3 [9.8–18.9]              | CR+PR: 1+10<br>SD+PD: 2+0          | 85% |

\* all patients had stage IIIA/IV NSCLC;

CR: complete response; NR: not reported; PD: progressive disease; PFS: progression-free survival; PPV: positive predictive value; PR: partial response; SD: stable disease; TK: tyrosine kinase

as a predictor of ORR nor does the evidence directly compare TKI therapy to standard cytotoxic chemotherapy or placebo with respect to tumor mutation status or overall survival, leaving the clinical utility of mutation testing uncertain for gefitinib therapy. There are no individual prospective data to assess the clinical utility of EGFR mutation testing as a predictor of response to erlotinib.

### Summary and Conclusions

A substantial body of evidence from 25 nonconcurrent prospective and retrospective studies, and 6 prospective phase II studies, demonstrates a consistent, robust positive correlation between the presence of gain-of-function somatic mutations in one of exons 18–24 of tumor cell EGFR gene TK domain and clinical response to TKI therapy, primarily gefitinib, in patients with advanced NSCLC. These findings together strongly support the clinical validity of EGFR mutation analysis to predict individual clinical response to gefitinib therapy in patients with advanced NSCLC. By contrast, evidence on the relationship between EGFR TK mutations and response to erlotinib is insufficient to draw conclusions concerning test clinical validity.

While the body of data from the phase II prospective studies comprises the best available evidence supporting the clinical validity of EGFR mutation analysis to select TKI therapy, for several reasons it does not support clinical utility. First, because mutation positivity was an entry criterion for the prospective studies, one cannot calculate an NPV. Thus, evidence is missing regarding the ability of mutation analysis to identify individuals who could be excluded from this therapy because they have low probability of benefit. Given a standard of practice under which patients who fail cytotoxic chemotherapy would be offered salvage TKI therapy (erlotinib in the U.S.), the NPV must be known and of sufficient magnitude to confidently dissuade patients from further treatment. Second, the prospective data do not provide information on OS, or direct comparisons to outcomes with chemotherapy. Finally, the relevance of the prospective findings to clinical practice in the U.S. is uncertain, given the current FDA labeling status of gefitinib and that the majority of patients were of Eastern Asian origin. Therefore, while EGFR mutation analysis is feasible in the clinical laboratory, and test results appear to correlate with TKI

clinical outcomes, the available evidence is insufficient to support use of this test alone as the standard for clinical predictive practice in patients with advanced NSCLC.

The available evidence does provide a sound basis for further randomized, placebo-controlled phase III trials that would allocate advanced NSCLC patients into therapeutic groups on the basis of TK mutations or their absence, with stratification according to previously identified clinicopathologic characteristics. These types of trials would determine both positive and negative predictive values for TK gene mutations and therapeutic response in well-defined patient groups, confirm their relationship to clinicopathologic characteristics alone and together, and ultimately to define the clinical utility of mutation testing in oncology practice.

According to the National Cancer Institute, a few phase III randomized clinical trials are underway or in the planning stages to investigate TKI treatment in a population with advanced NSCLC defined by clinical or pharmacogenomic (TK mutation status) characteristics or in combination with chemotherapy in adjuvant and neoadjuvant therapy for earlier stage disease (<http://www.cancer.gov/clinicaltrials>; Table 6). These studies will provide additional evidence about EGFR mutation analysis in predicting clinical benefits of TKIs, although their design suggests no data will be forthcoming to determine the NPV of mutation analysis in advanced NSCLC. However, one trial (RADIANT) will examine the effect of erlotinib in resectable NSCLC, which could have potential value in changing practice to earlier use of TKI therapy.

## Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether use of EGFR mutation analysis to predict TKI sensitivity meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

### 1. The technology must have final approval from the appropriate governmental regulatory bodies.

EGFR mutation analysis (PCR amplification and gene sequencing) is commercially available as a laboratory-developed test (Genzyme Genetics, Westborough, MA). Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

### 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Evidence compiled from nonconcurrent and retrospective studies is sufficient to conclude that a gain-of-function somatic mutation in one of exons 18-24 of tumor cell EGFR gene tyrosine kinase domain reasonably predicts ORR to gefitinib therapy in patients with advanced NSCLC, based on the sensitivity, specificity, PPV, and NPV of mutation presence compared to absence, suggesting this marker has clinical validity in this setting. Results from single-arm

**Table 6.** Ongoing Clinical Trials of TKI Therapy and Advanced NSCLC

| TKI       | NCI Identifier         | Patient Population  | Treatment   | Primary Endpoint          |
|-----------|------------------------|---|---|---------------------------|
| erlotinib | NCT 00373425 (RADIANT) | resected stage IB-IIIa, EGFR mutation-positive              | erlotinib vs. placebo                                   | overall survival          |
| erlotinib | NCT 00446225           | first-line, stage IIIB/IV, EGFR mutation-positive           | erlotinib vs. chemotherapy                              | progression-free survival |
| erlotinib | NCT 00300586           | sequential following first-line chemotherapy, stage IIIB/IV | erlotinib vs. maintenance chemotherapy with gemcitabine | progression-free survival |
| gefitinib | NCT 00455936           | first-line, stage IIIB/IV, never-smokers                    | gefitinib vs. chemotherapy                              | progression-free survival |

prospective phase II studies are sufficient to conclude that the presence of a gain-of-function somatic mutation in one of exons 18-24 of the EGFR gene TK domain is a strong predictor of ORR based on the PPV, supporting clinical validity. Evidence from the prospective gefitinib studies cannot be used to determine the NPV, nor correlations with OS, and thus does not permit conclusions concerning the clinical utility of tumor cell EGFR mutation analysis to predict the net health outcome relative to standard therapy. Furthermore, because gefitinib is not available for routine use in the U.S., conclusions about the clinical utility of mutation analysis in guiding its use have little practical value.

Evidence is insufficient to permit conclusions about the clinical validity or utility of EGFR mutation testing to predict erlotinib sensitivity or guide therapy in patients with advanced NSCLC. There is no prospective evidence on the NPV of mutation analysis that could be used to justify withholding erlotinib therapy.

3. **The technology must improve the net health outcome; and**
4. **The technology must be as beneficial as any established alternatives.**

There is insufficient evidence to permit conclusions regarding the use of tumor cell EGFR mutation analysis results for managing advanced NSCLC treatment in the context of a standard of care in which erlotinib therapy would be offered to all endstage patients.

5. **The improvement must be attainable outside the investigational settings.**

Whether or not the use of tumor cell EGFR mutation analysis for managing advanced NSCLC treatment improves health outcomes has not been demonstrated in the investigational setting.

Based on the above, use of tumor cell EGFR mutation analysis to predict therapeutic sensitivity to erlotinib (Tarceva®) does not meet the TEC criteria.

---

NOTICE OF PURPOSE: TEC Assessments are scientific opinions, provided solely for informational purposes. TEC Assessments should not be construed to suggest that the Blue Cross Blue Shield Association, Kaiser Permanente Medical Care Program or the TEC Program recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service; any particular course of treatment, procedure, or service; or the payment or non-payment of the technology or technologies evaluated.

CONFIDENTIAL: This document contains proprietary information that is intended solely for Blue Cross and Blue Shield Plans and other subscribers to the TEC Program. The contents of this document are not to be provided in any manner to any other parties without the express written consent of the Blue Cross and Blue Shield Association.

# References

- Asahina H, Yamazaki K, Kinoshita I et al. (2006).** A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. *Br J Cancer*, 95(8): 998-1004.
- Bell DW, Lynch TJ, Haserlat SM et al. (2005).** Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol*, 23(31):8081-92.
- Bunn PA, Dziadziuszko R, Varella-Garcia M et al. (2006).** Biological markers for non-small cell lung cancer patient selection for epidermal growth factor receptor tyrosine kinase inhibitor therapy. *Clin Cancer Res*, 12:5652-56.
- Cappuzzo F, Hirsch FR, Rossi E et al. (2005).** Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst*, 97(9):645-55.
- Chou TY, Chiu CH, Li LH et al. (2005).** Mutation in the tyrosine kinase domain of epidermal growth factor receptor is a predictive and prognostic factor for gefitinib treatment in patients with non-small cell lung cancer. *Clin Cancer Res*, 11(10):3750-7.
- Ciardello F, Caputo R, Bianco R et al. (2000).** Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1859 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res*, 6:2053-63.
- Clark GM, Zborowski DM, Culbertson JL et al. (2006).** Clinical utility of epidermal growth factor receptor expression for selecting patients with advanced non-small cell lung cancer for treatment with erlotinib. *J Thoracic Oncol*, 1:837-46.
- Cortes-Funes H, Gomez C, Rosell R et al. (2005).** Epidermal growth factor receptor activating mutations in Spanish gefitinib-treated non-small-cell lung cancer patients. *Ann Oncol*, 16(7):1081-6.
- Dei Tos AP, Ellis I. (2005).** Assessing epidermal growth factor receptor expression in tumours: what is the value of current test methods? *Eur J Cancer*, 41:1585-92.
- Dziadziuszko R, Witta SE, Cappuzzo F, et al. (2006).** Epidermal growth factor receptor messenger RNA expression, gene dosage, and gefitinib sensitivity in non-small cell lung cancer. *Clin Cancer Res*, 12:5078-84.
- Eberhard DA, Johnson BE, Amler LC et al. (2005).** Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol*, 23(25):5900-9.
- Feld R, Sridhar SS, Shepherd FA et al. (2006).** Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a systematic review. *J Thorac Oncol*, 1:567-76.
- Fruehauf J. (2006).** EGFR function and detection in cancer therapy. *J Exp Ther Oncol*, 5:251-46.
- Fukuoka M, Yano S, Giaccone G et al. (2005).** Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). *J Clin Oncol*, 21(12):2237-46.
- Gatzemeier U, Pluzanska A, Szczesna A et al. (2007).** Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol*, 25:1545-52.
- Giaccone G, Herbst RS, Manegold C et al. (2004).** Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol*, 22(5):777-84.
- Giaccone G, Rodriguez JA. (2005).** EGFR inhibitors: what have we learned from the treatment of lung cancer? *Nat Clin Pract Oncol*, 2:554-61.
- Ginsberg RJ, Vokes EE, Raben A. (1997).** Non-small cell lung cancer. In: De Vita VT Jr, Hellman S, Rosenberg SA, Eds. *Cancer Principles and Practice of Oncology*. Philadelphia: Lippincott-Raven, 858-911.
- Han SW, Hwang PG, Chung DH et al. (2005b).** Epidermal growth factor receptor (EGFR) downstream molecules as response predictive markers for gefitinib (Iressa ZD1859) in chemotherapy-resistant non-small cell lung cancer. *Int J Cancer*, 115:109-15.
- Han SW, Kim TY, Hwang PG et al. (2005a).** Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol*, 23(11):2495-501.
- Hanna N, Shepherd FA, Fossella FV et al. (2004).** Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*, 22:1589-97.
- Herbst RS, Giaccone G, Schiller JH et al. (2004).** Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol*, 22(5):785-94.
- Herbst RS, Prager D, Hermann R et al. (2005).** TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol*, 23(25):5892-9.

- Heymach JV, Nilsson M, Blumenschein G et al. (2006).** Epidermal growth factor receptor inhibitors in development for the treatment of non-small cell lung cancer. *Clin Cancer Res*, 12(14 Suppl):4441s-45s.
- Hirsch FR, McCoy J, Cappuzzo F et al. (2005).** FISH and immunohistochemistry can be used to select NSCLC patients, who will not benefit from gefitinib treatment. *Lung Cancer*, 49:S58.
- Hirsch FR, Varella-Garcia M, Bunn PA Jr et al. (2006).** Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol*, 24:5034-42.
- Hirsch FR, Varella-Garcia M, Cappuzzo F et al. (2007).** Combination of EGFR gene copy number and protein expression predicts outcome for advanced non-small-cell lung cancer patients treated with gefitinib. *Ann Oncol*, 18:752-60.
- Huang S-F, Liu H-P, Li L-H, et al. (2004).** High frequency of epidermal growth factor receptor mutations with complex patterns in non-small cell lung cancers related to gefitinib responsiveness in Taiwan. *Clin Cancer Res*, 10:8195-8205.
- Inoue A, Suzuki T, Fukuhara T et al. (2006).** Prospective phase II study of gefitinib for chemotherapy-naïve patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. *J Clin Oncol*, 24(21):5340-6.
- Jemal A, Murray T, Ward E et al. (2005).** Cancer statistics, 2005. *CA Cancer J Clin*, 55:10-30.
- Joshi VA, Kucherlapati R. (2006).** Lung cancer genetics and pharmacogenomics. *Cytogenet Genome Res*, 115:298-302.
- Kim KS, Jeong JY, Kim YC et al. (2005).** Predictors of the response to gefitinib in refractory non-small cell lung cancer. *Clin Cancer Res*, 11(6):2244-51.
- Kondo M, Yokoyama T, Fukui T, et al. (2005).** Mutations of epidermal growth factor receptor of non-small cell lung cancer were associated with sensitivity to gefitinib in recurrence after surgery. *Lung Cancer*, 50:385-91.
- Kris MG, Natale RB, Herbst RS et al. (2005).** 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*, 290(16):2149-58.
- Lynch TJ, Bell DW, Sordella R et al. (2004).** Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*, 350(21):2129-59.
- Metro G, Giovanna F, Toschi L et al. (2006).** Epidermal growth factor receptor (EGFR) targeted therapies in non-small cell lung cancer (NSCLC). *Rev Recent Clin Trials*, 1:1-15.
- Metzker ML. (2005).** Emerging technologies in DNA sequencing. *Genome Res*, 15:1767-76.
- Mitsudomi T, Kosaka T, Endoh H et al. (2005).** Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol*, 25(11):2515-20.
- Mu XL, Li LY, Zhang XT, et al. (2005).** Gefitinib-sensitive mutations of the epidermal growth factor receptor tyrosine kinase domain in Chinese patients with non-small cell lung cancer. *Clin Cancer Res*, 11:4289-94.
- Niho S, Kubota K, Goto K, et al. (2006).** First-line single agent treatment with gefitinib in patients with advanced non-small-cell lung cancer: a phase II study. *J Clin Oncol*, 24:64-69.
- Paez JG, Janne PA, Lee JC et al. (2004).** EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*, 304(5676):1497-500.
- Pao W, Miller VA. (2005).** Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non-small-cell lung cancer: current knowledge and future directions. *J Clin Oncol*, 23:2556-68.
- Pao W, Miller V, Zakowski M et al. (2004).** 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 USA*, 101(36):13506-11.
- Parra HS, Cavina R, Latteri F et al. (2004).** Analysis of epidermal growth factor receptor expression as a predictive factor for response to gefitinib (‘Iressa’, ZD 1859) in non-small-cell lung cancer. *Br J Cancer*, 91:208-12.
- Perez-Soler R, Chachoua A, Hammond LA et al. (2004).** Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol*, 22:5258-47.
- Riely GJ, Politi KA, Miller VA et al. (2006).** Update on epidermal growth factor receptor mutations in non-small cell lung cancer. *Clin Cancer Res*, 12:7232-41.
- Rosell R, Taron M, Reguart N et al. (2006).** Epidermal growth factor receptor activation: how exon 19 and 21 mutations changed our understanding of the pathway. *Clin Cancer Res*, 12:7222-31.
- Satouchi M, Negoro S, Funada Y et al. (2007).** Predictive factors associated with prolonged survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib. *Br J Cancer*, 96:1191-96.
- Scagliotti GV, De Marinis F, Rinaldi M et al. (2002).** Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol*, 20:4285-91.
- Schiller JH, Harrington D, Belani CP et al. (2002).** Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*, 346:92-8.
- Sequist LV, Bell DW, Lynch TJ, et al. (2007a).** Molecular predictors of response to epidermal growth factor receptor antagonists in non-small-cell lung cancer. *J Clin Oncol*, 25:587-95.

- Sequist LV, Joshi VA, Janne PA et al. (2007b). Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. *Oncologist*, 12(1):90-8.
- Sharma S, Bell D, Settleman J et al. (2007). Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer*; 7:169-81.
- Shepherd FA, Dancey J, Ramlau R et al. (2000). Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*, 18:2095-2105.
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. (2005). Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*, 353(2):125-32.
- Sirotnak FM, Zakowski MF, Miller VA et al. (2000). Efficacy of cytotoxic agents against human tumor xenografts in markedly enhanced by coadministration of ZD1859 (Iressa), an inhibitor of EGFR tyrosine kinase. *Clin Cancer Res*, 6:4885-92.
- Sone T, Kasahara K, Kimura H, et al. (2007). Comparative analysis of epidermal growth factor receptor mutations and gene amplification as predictors of gefitinib efficacy in Japanese patients with nonsmall cell lung cancer. *Cancer*, 109:1856-44.
- Sunaga N, Tomizawa Y, Yanagitani N et al. (2007). Phase II prospective study of the efficacy of gefitinib for the treatment of stage III/IV non-small cell lung cancer with EGFR mutations, irrespective of previous chemotherapy. *Lung Cancer*, 56(3):583-9. Epub 2007 Mar 26.
- Sutani A, Nagai Y, Udagawa K et al. (2006). Gefitinib for non-small-cell lung cancer patients with epidermal growth factor receptor gene mutations screened by peptide nucleic acid-locked nucleic acid PCR clamp. *Br J Cancer*, 95(11):1483-9.
- Takano T, Ohe Y, Sakamoto H et al. (2005). Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. *J Clin Oncol*, 23:6829-37.
- Taron M, Ichinose Y, Rosell R et al. (2005). Activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor are associated with improved survival in gefitinib-treated chemorefractory lung adenocarcinomas. *Clin Cancer Res*, 11(16):5878-85.
- Thatcher N, Chang A, Parikh P et al. (2005). Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicenter study (Iressa Survival Evaluation in Lung Cancer). *Lancet*, 366:1527-37.
- Thomas RK, Weir B, Meyerson M. (2006). Genomic approaches to lung cancer. *Clin Cancer Res*, 12:4584-91.
- Tokumo M, Toyooka S, Kiura K et al. (2005). The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. *Clin Cancer Res*, 11(5):1167-75.
- Tomizawa Y, Iijima H, Sunaga N, et al. (2005). Clinicopathologic significance of the mutations of the epidermal growth factor receptor gene in patients with non-small cell lung cancer. *Clin Cancer Res*, 11:6816-22.
- Toschi L, Cappuzo F. (2007). Understanding the new genetics of responsiveness to epidermal growth factor receptor tyrosine kinase inhibitors. *Oncologist*, 12:211-20.
- Tsao MS, Sakurada A, Cutz JC et al. (2005). Erlotinib in lung cancer - molecular and clinical predictors of outcome. *N Engl J Med*, 353(2):133-44.
- van Zandwijk N, Mathy A, Boerrigter L et al. (2007). EGFR and KRAS mutations as criteria for treatment with tyrosine kinase inhibitors: retro- and prospective observations in non-small-cell lung cancer. *Ann Oncol*, 18(1):99-103.
- Weinstein I. (2002). Cancer. Addiction to oncogenes: the Achilles heel of cancer. *Science*, 297:64-4.
- Yoshida K, Yatabe Y, Park JY et al. (2007). Prospective validation for prediction of gefitinib sensitivity by epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer. *J Thorac Oncol*, 2(1):22-8.
- Zhang X-T, Li L-Y, Cui Q-C, et al. (2005). The EGFR mutation and its correlation with response of gefitinib in previously treated Chinese patients with advanced non-small-cell lung cancer. *Annals Oncol*, 16:1534-42.



**Technology  
Evaluation  
Center**

**Blue Cross and  
Blue Shield Association**  
225 North Michigan Avenue  
Chicago, Illinois 60601-7680  
[www.bcbs.com/tec](http://www.bcbs.com/tec)