

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



Assessment
Program
Volume 25, No. 6
March 2011

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 generally poor, and patients treated with current platinum-based chemotherapy often experience severe systemic toxicities. 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 tyrosine kinase and downstream signaling pathways. Anti-EGFR drugs, including the small-molecule tyrosine kinase inhibitors (TKI) gefitinib (Iressa[®], AstraZeneca; not commercially available for new patients in the U.S.) and erlotinib (Tarceva[®], Genentech BioOncology) 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. 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 tyrosine kinase domain of the *EGFR* gene—small deletions in exon 19 and point mutations in exon 21 (L858R)—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 distinguish patients who would benefit from *EGFR* TKI therapy from those who would not. In the U.S., the impact of *EGFR* mutation testing on erlotinib response is the particular focus of interest.

A Technology Evaluation Center (TEC) Assessment on this topic was first published in November 2007 (Vol. 22, No. 6). This Assessment used a conceptual framework that examined 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 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



An Association
of Independent
Blue Cross and
Blue Shield Plans



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.

using the pretreatment test results to help make management decisions will lead to an improved outcome. The 2007 Assessment concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of *EGFR* mutation testing to predict erlotinib sensitivity or to guide treatment in patients with advanced NSCLC.

Since that analysis there have been numerous new clinical studies evaluating the relationship between *EGFR* mutations and TKI responses, as well as a large number of additional reviews, editorials, and perspectives on this subject. This current Assessment evaluates new information available on this subject and updates the analysis using the same conceptual framework applied in 2007.

There are now over a dozen studies linking response to erlotinib to *EGFR* mutation status. Most of these studies are either nonconcurrent-prospective designs or one-arm prospective enrichment studies (i.e., evaluating response to erlotinib in test-positive or –negative patients only). While the statistical interpretations are variable, the studies are quite uniform in suggesting patients with *EGFR* mutation-positive tumors are likely to respond favorably to erlotinib, while patients with wild-type tumors are not. In addition, patients with *EGFR* mutation-positive tumors appear to show better tumor response to erlotinib than to standard chemotherapy. Taken together, these findings indicate that patients with *EGFR* mutation-positive tumors are ideal candidates for erlotinib treatment and have a high likelihood of responding favorably to this therapy. Patients with wild-type tumors are unlikely to respond to erlotinib therapy and should be considered candidates for alternative therapies without delay.

Objective

The objective of this Assessment is to evaluate *EGFR* testing as a predictor of tumor response to the small-molecule TKI erlotinib (Tarceva®). This would allow for targeted and optimized selection of patients for TKI therapy based on the *EGFR* genetic profile of the tumor being treated.

Search Strategy

A MEDLINE® search (via PubMed) was performed from May 2007 to December 2010 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,” “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 objective radiologic response rate, progression-free survival or in some cases, time to progression and/or the overall survival with erlotinib therapy for advanced NSCLC.

Main Results

Thirteen publications provide data on *EGFR* mutations in tumor samples obtained from NSCLC patients in erlotinib treatment studies. Nine of these were nonconcurrent-prospective studies of patients treated with erlotinib and then studied for the presence or absence of mutations. Four were prospective one-arm enrichment studies of patients with mutation-positive (3 studies) or wild-type (1 study) tumors that were treated with erlotinib.

A total of 630 patients were studied in the 9 nonconcurrent-prospective studies comparing erlotinib results in patients with *EGFR* mutation-positive versus wild-type tumors. The median objective radiologic response rates in patients with *EGFR* mutation-positive tumors was 45% compared to 5% in wild-type patients, median progression-free survival in patients with *EGFR*

mutation-positive tumors was 12.5 months compared to 2.5 months in wild-type patients, and median overall survival rate in patients with *EGFR* mutation-positive tumors was 21 months compared to 8.1 months in wild-type patients. According to the U.S. Food and Drug Administration (FDA) drug label, second-line treatment with erlotinib in untested patients results in a progression free survival of 2.8 months and an overall survival of 12 months.

In the 3 prospective studies of patients with *EGFR* mutation-positive tumors (n=465) treated with erlotinib, objective radiologic response rates ranged from 40 to 70%, progression-free survival times from 8 to 14 months, and overall survival times from 16 to 29 months. This performance was distinctly different than that observed in similarly treated patients with wild-type tumors who, in a small independent single-arm enrichment trial (n=30), exhibited an objective radiologic response of 3.3%, a progression-free survival of 2.1 months, and an overall survival of 9.2 months.

In the largest study, *EGFR* mutation status was measured in 2,105 patients and erlotinib administered to 217 patients with *EGFR* mutation-positive advanced NSCLC. In this *EGFR* mutation-positive, erlotinib-treated group, the objective radiologic response rate was 70%, median progression-free survival 14 months, and median overall survival 27 months. Adverse events were most commonly mild rashes and diarrhea. Only about 11% of patients experienced grade 3 (severe) toxic effects. The authors concluded that using historic benchmarks of response to chemotherapy (estimates of objective radiologic response of 30%, progression-free response of 5 months, and overall survival of 12 months) targeted use of erlotinib appeared to produce an improvement in net health outcome.

EGFR testing appears to identify a mutation-positive subset that is particularly sensitive to erlotinib treatment. These patients show superior response when compared to erlotinib treatment in patients with wild-type tumors. They also show superior response when compared to the use of standard chemotherapy in patients with mutation-positive tumors. Patients whose tumors are *EGFR* mutation positive thus appear to be ideal candidates for erlotinib treatment. Patients with wild-type tumors are much less likely to respond to erlotinib and are better served by exploring other therapeutic options.

One important final observation is that patients with *EGFR* mutation-positive tumors and who are treated with either erlotinib or with standard chemotherapy appear to exhibit better outcomes than patients with wild-type tumors with the same treatments. This suggests part of the predictive behavior of mutational testing is attributed to an underlying prognostic signal. Based on the information gathered so far, it is impossible to determine the relative magnitude of prognostic versus predictive effect observed as a result of testing.

Discussion

The studies of tumor-cell *EGFR* gene tyrosine kinase domain mutations consistently demonstrate an association between the presence (or absence) of a mutation and therapeutic response (or nonresponse) to erlotinib. Patients with *EGFR* mutation-positive tumors are also likely to show better response when treated with erlotinib than with standard chemotherapy and to exhibit an improved prognosis, regardless of therapy.

While to date there have been no prospective, randomized clinical trials specifically looking at how *EGFR*-directed therapy affects patient outcomes, there is strong evidence that response to erlotinib can be predicted based on *EGFR* mutation status. In evaluating patients with NSCLC, a serious disease with a poor overall prognosis, use of *EGFR* mutation testing appears to be a valuable tool in assisting physicians in making optimal treatment choices and improving their ability to identify patients likely to benefit or not benefit from erlotinib treatment.

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 response to erlotinib (Tarceva®) 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 is commercially available at both academic medical centers and commercial laboratories. The tests available are being offered as laboratory-developed tests, and at the current time, the FDA is not actively regulating these as a matter of enforcement discretion. The laboratories performing these tests must meet quality standards as prescribed under the Clinical Laboratory Improvement Amendments (CLIA).

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

Evidence compiled from nonconcurrent-prospective studies and one-arm prospective enrichment studies is sufficient to conclude that a gain-of-function somatic mutation in the tumor-cell *EGFR* gene tyrosine kinase domain identifies a population subset (patients with mutation-positive tumors) with advanced NSCLC who exhibit improved objective radiologic response, progression-free survival, and overall survival when treated with erlotinib compared to the same treatment in patients with wild-type tumors or to standard chemotherapy in patients with *EGFR* mutation-positive tumors.

Data are strongest for demonstrating differences in objective radiologic response, is less consistent, but strong, for progression-free survival, and is less consistent, but strong, for overall survival. Radiologic response is not generally viewed by itself as a meaningful endpoint, since its ability to predict standard and more established outcomes such as progression free survival, overall survival, or quality of life is not reliable. However, there is a published meta-analysis suggesting objective radiologic response is strongly associated with median overall survival in patients with NSCLC treated with TKIs. There is also growing discussion that overall survival may be a compromised endpoint for NSCLC due to the fact that NSCLC is a particularly aggressive disease with an increasing number of treatment choices, many specifically available for cross-over use in patients demonstrating resistance to earlier therapies. These cross-over therapies are likely to make evaluation of overall survival a challenging, and perhaps impossible, study endpoint.

3. The technology must improve the net health outcome.

Recent prospective and retrospective studies have shown convincing evidence that *EGFR* mutations can identify disease likely to respond to erlotinib. There is growing evidence that this information affects the net health outcome by identifying patients who are likely to exhibit good outcomes with this treatment with minimal toxicity. Recent reports suggest *EGFR* mutations also identify patients more likely to respond to erlotinib than to standard chemotherapy. In these patients, use of erlotinib therapy may be much more effective than alternative drug choices.

There is also growing information demonstrating that *EGFR* status can help physicians identify wild-type tumors in patients who are unlikely to respond to erlotinib. In these patients, alternative treatment choices should be considered. It is therefore prudent for physicians to evaluate patients with wild-type tumors carefully, considering the unique patient-specific variables and preferences at hand, to discuss these with the patient, and to use this information to make patient-informed, collaborative personalized treatment choices.

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

Alternatives—in particular, use of empiric therapy—appear to be less reliable at estimating likely objective response and progression-free and overall survival than testing using *EGFR* mutation analysis to select patients for erlotinib therapy. The role for use of clinical risk features (female sex, adenocarcinoma histology, nonsmoking history, or Asian heritage) requires further study to determine how this information might help in making accurate testing or treatment choices.

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

EGFR mutation testing is now widely available commercially, and studies have indicated that it is possible to utilize testing for improved decision making at multiple clinical sites. Testing is recognized to be of value in centers of oncology excellence, and the only impediment is the need for increased access to testing (an ongoing process) and introduction of more wide-scale use of tests with rapid turnaround time.

Based on the available evidence, use of tumor-cell *EGFR* mutation analysis to predict response to erlotinib (Tarceva®) in patients with advanced non-small-cell lung cancer meets the TEC criteria.

Contents

Assessment Objective	6	Review of Evidence	15
Background	6	Summary and Conclusions	23
Methods	14	Summary of Application of the Technology Evaluation Criteria	23
Formulation of the Assessment	14	References	25

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

TEC Staff Contributors

Author—Steven Gutman, M.D., M.B.A.; **TEC Executive Director**—Naomi Aronson, Ph.D.; **Director, Clinical Science Services**—Kathleen M. Ziegler, Pharm.D.; **Research/Editorial Staff**—Claudia J. Bonnell, B.S.N., M.L.S.; Kimberly L. Hines, 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, Professor, *Johns Hopkins School of Medicine, Department of Oncology, Division of Biostatistics (joint appointments in Epidemiology, Biostatistics, and Pediatrics)*.
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., F.A.C.P., Chief Medical Officer, *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*—American College of Surgeons Appointee; I. Craig Henderson, M.D., *Adjunct Professor of Medicine, University of California, San Francisco*; Jo Carol Hiatt, M.D., M.B.A., F.A.C.S. *Chair, Inter-Regional New Technology Committee, Kaiser Permanente*; Mark A. Hlatky, M.D., *Professor of Health Research and Policy and of Medicine (Cardiovascular Medicine), Stanford University School of Medicine*; Saira A. Jan, M.S., Pharm.D., *Associate Clinical Professor, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Residency Director and Director of Clinical Programs Pharmacy Management, Horizon Blue Cross and Blue Shield of New Jersey*; Leslie Levin, M.B., M.D., F.R.C.P.(Lon), F.R.C.P.C., *Head, Medical Advisory Secretariat and Senior Medical, Scientific and Health Technology Advisor, Ministry of Health and Long-Term Care, Ontario, Canada*; Bernard Lo, M.D., *Professor of Medicine and Director, Program in Medical Ethics, University of California, San Francisco*; Randall E. Marcus, M.D. *Charles H. Herndon Professor and Chairman, Department of Orthopaedic Surgery, Case Western Reserve University School of Medicine*; 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*; William R. Phillips, M.D., M.P.H., *Clinical Professor of Family Medicine, University of Washington*—American Academy of Family Physicians' Appointee; Alan B. Rosenberg, M.D., *Vice President, Medical Policy, Technology Assessment and Credentialing Programs, WellPoint, Inc.*; Maren T. Scheuner, M.D., M.P.H., F.A.C.M.G., *Director, Genomics Strategic Program Area, VA HSR&D Center of Excellence for the Study of Healthcare Provider Behavior, VA Greater Los Angeles Healthcare System; Natural Scientist, RAND Corporation; Adjunct Associate Professor, Department of Health Services, UCLA School of Public Health*; J. Sanford Schwartz, M.D., F.A.C.P., *Leon Hess Professor of Medicine and Health Management & Economics, School of Medicine and The Wharton School, University of Pennsylvania*; Earl P. Steinberg, M.D., M.P.P., *President and CEO, Resolution Health, Inc.*; Robert T. Wanovich, Pharm.D., *Vice-President, Pharmacy Affairs, Highmark, Inc.*

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 *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®).

Erlotinib was approved by the U.S. Food and Drug Administration (FDA) in November 2004 for use in locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen

Another TKI, gefitinib (Iressa®, AstraZeneca), received accelerated FDA marketing approval in May 2003 based on intermediate outcomes in Phase II studies. However, following a report of unanticipated poor results with gefitinib in a subsequent Phase III monotherapy trial (the Iressa Survival Evaluation in Lung Cancer trial–ISEL), the FDA revised its labeling to restrict use to patients already on this drug. As a result, gefitinib is no longer commercially available for use in newly diagnosed patients in the U.S., although this drug is widely used in Asia, Europe, and Canada. Therefore, evidence supporting *EGFR* gene mutation analysis for selecting advanced NSCLC patients for gefitinib therapy will be reviewed only in the Background section of this Assessment.

Background

Lung Cancer Therapy

Lung cancer is the most frequently diagnosed major cancer in the world and the leading cause of worldwide cancer mortality. In 2009 in the U.S. alone, there were an estimated 219,000 cases and more than 159,000 deaths (Jemal et al. 2010). Lung cancer is classified by the World Health Organization into two major types: small-cell lung cancer (SCLC) and NSCLC. The latter accounts for approximately 85% of cases and exhibits unique biologic, therapeutic, and prognostic features (U.S. Cancer Statistics Working Group 2009).

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. Unfortunately, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40%

of patients with NSCLC present with metastatic disease (Fathi et al. 2008). When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30 to 45% (Martoni et al. 2005; Rudd et al. 2005). These treatments are typically accompanied by significant toxicities, most commonly severe neutropenia and thrombocytopenia.

New, improved, and targeted treatment alternatives are being sought. Among the alternative agents of particular interest have been those that target the *EGFR* signaling pathway (Dei Tos and Ellis 2005; Giaccone and Rodriguez 2005; Fruehauf 2006; Metro et al. 2006; Sharma et al. 2007; Toschi and Cappuzzo 2007). *EGFR* is a transmembrane receptor found on the surface of normal epithelial cells. It consists of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular cytoplasmic protein with tyrosine kinase activity. *EGFR* has a number of endogenous ligands that upon binding with the receptor, initiate a complex signaling cascade that is involved in several normal cellular processes including growth, differentiation, apoptosis, and morphogenesis.

Laboratory and animal experiments have shown that therapeutic interdiction of the *EGFR* pathway could be used to halt tumor growth in solid tumors that express *EGFR* (Fruehauf 2006). These observations led to the development of two main classes of anti-*EGFR* agents for use in various types of cancer: small molecule TKIs and monoclonal antibodies (MAbs) that block *EGFR*-ligand interaction (Heymach et al. 2006).

Two orally administered *EGFR*-selective small molecules (quinazolinamine derivatives) were identified for use in treating NSCLC: gefitinib (Iressa®, AstraZeneca) and erlotinib (Tarceva®, Genentech BioOncology). While gefitinib is available in Europe, Canada, and Asia, as noted (see Assessment Objective), only erlotinib is available for use in new patients in the U.S.

Identifying Candidates for Tyrosine Kinase Treatment

During Phase II trials with both erlotinib and gefitinib, it was noted that clinical responses observed were usually seen in a subset of the population characterized by unique clinical and pathologic features. These unique characteristics included female sex, adenocarcinoma histology, Asian ethnicity and never-smoker

status (Govidan 2010). 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 made this pathway a logical target. This idea was supported by observations in transgenic animal models that demonstrated tumors could become dependent for growth and maintenance on signaling from aberrant tyrosine kinases and other oncogenes and that such mutated enzymes could be effectively targeted in cancer therapy (Weinstein 2002). Consequently, 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

Two publications (Lynch et al. 2004; Paez et al. 2004) demonstrated that the underlying molecular mechanism underpinning dramatic responses in these favorably prognostic groups was the presence of activating somatic mutations in the tyrosine kinase domain of the *EGFR* gene. The most reliable markers for this change appeared to be the presence of the mutations themselves detected by direct sequencing or polymerase chain reaction technologies. The two most frequently observed changes are small deletions in exon 19 and point mutations in exon 21 (L858R) (Giaccone and Rodriguez 2005).

A Technology Evaluation Center (TEC) Assessment on this topic was first published in November 2007 (Vol. 22, No. 6). This Assessment used a conceptual framework that examined 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 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. The 2007 Assessment concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of *EGFR* mutation testing to predict erlotinib sensitivity or to guide treatment in patients with NSCLC.

The study of the association between changes in *EGFR* gene status and tumor response was noted in 2007 to be complicated by the fact that there are alternative *EGFR* gene mutation measurement techniques including evaluation of gene copy number, most commonly measured by fluorescent in-situ hybridization (FISH) (Cappuzzo et al. 2005; Hirsch et al. 2005; Tsao et al. 2005), and protein expression, measured by standard immunohistochemistry staining (IHC) (Clark et al. 2006; Cappuzzo et al. 2005; Hirsch et al. 2005; Parra et al. 2004; Perez-Soler et al. 2004). To date these methodologies appear poorly standardized (Lee et al. 2010; Mathieu et al. 2009), and associations with drug response have been confusing and unpredictable (Hirsch et al. 2006; Dziadziuszko et al. 2006; Bell et al. 2005). For the sake of this Assessment update, as was true in the original 2007 Assessment, only mutational analysis (using sequencing or nucleic acid amplification methodologies) will be considered.

National Comprehensive Cancer Network Guidelines

The National Comprehensive Cancer Network (NCCN; 2010) in the V2.2010 guidelines on NSCLC makes several explicit recommendations or general comments with regard to *EGFR* testing and subsequent treatment including:

Systemic Therapy for Advanced or Metastatic Disease:

First line therapy: “Erlotinib for *EGFR* mutation positive patients.” Charts indicate use of the drug in patients of any performance status: 0–4.

Erlotinib is listed as a potential drug for recurrence or metastasis or third line therapy but without reference to *EGFR* testing.

In a section labeled “Principles of Pathologic Review—Molecular Diagnostic Studies in Lung Cancer,” they retain language in the 2009 guideline “There is a significant association between *EGFR* mutations, especially exon 19 deletions and response to TKIs.”

There is a section in this guideline on prognostic and predictive studies of *EGFR* testing, but no further explicit recommendations are made.

ASCO Publication Recommendations

In a 2009 publication by the American Society of Clinical Oncology (ASCO; Azzoli et al. 2009) on chemotherapy for stage IV NSCLC, there is a specific suggestion (Recommendation A7) that “The first-line use of gefitinib may be recommended to patients with known epidermal growth factor receptor (*EGFR*) mutation; for negative or unknown *EGFR* mutation status, cytotoxic chemotherapy is preferred.” There is a second suggestion (Recommendation D1) that states

“Evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment in patients with metastatic NSCLC.” A Provisional Clinical Opinion regarding the use of *EGFR* mutation testing in patients with advanced NSCLC is pending (ASCO 2010).

International Regulatory Approvals

In 2009, the European Medicine Agency (EMA) and Health Canada both approved use of gefitinib for treatment of patients with advanced-stage *EGFR* mutation-positive NSCLC.

Test Performance in Patients Treated with Gefitinib

In the 2007 Assessment, the overwhelming majority of studies identified to establish differential performance in *EGFR*-positive versus wild-type tumors (20 of 25) used gefitinib as the drug of choice. Only 3 studies were entirely or partially composed of patients receiving erlotinib.

It was noted at this time that while these drugs have a strikingly different regulatory status in the U.S., they are in many ways remarkably alike. As a result the impact of *EGFR* mutations on tumor response in patients treated with gefitinib was used as a surrogate for patients receiving erlotinib.

In the 2007 Assessment in studies of 1,471 patients treated with gefitinib, a mean objective radiologic response was observed in 72% of patients with mutations but only 11% of patients with the wild-type gene. Six prospective one-arm trials of gefitinib in patients with *EGFR* mutation-positive tumors demonstrated an objective radiologic response of 75 to 90%

and progression-free survival ranging from 8 to more than 15 months.

An update of the gefitinib data first summarized in 2007 is presented in Table 1. The median objective radiologic response is virtually unchanged since 2007—72% in patients with mutations and 12% in patients with the wild-type gene. Progression-free survival in gefitinib-treated patients with *EGFR* mutation-positive tumors ranged from 6 to 21.7 months (median of 12.5) and in patients with wild-type tumors from 1.7 to 5.5 months (median of 2.4). Overall survival in patients with *EGFR* mutation-positive tumors ranged from 4.5 to 30.4 months (median of 17.1) and in patients with wild-type tumors from 1.3 to 15 months (median of 7.4).

Of particular interest is the publication since 2007 of 5 separate reports (2 nonconcurrent-prospective and 3 single-arm enrichment studies) (Table 2) indicating that patients with *EGFR* mutation-positive tumors are likely to show a significantly improved objective radiologic response and improved progression-free survival when treated with gefitinib compared to standard chemotherapy. Improvements were not observed in overall survival, but as was noted in several cases, reasons for lack of improvement may have been that the data were immature (data collection was on-going) or that extensive post-study cross-over treatments were employed.

In 2 of the studies, response to TKI versus standard chemotherapy was evaluated in patients with wild-type tumors, as well as patients with mutation-positive tumors (Table 3). The study by Mok et al. (2009) was performed in Asian patients treated with first-line gefitinib; the study by Douillard et al. (2010) in predominantly non-Asian patients receiving second-line gefitinib. Both studies suggested *EGFR* mutations provided both prognostic and predictive information on patient response. In virtually all categories of analysis, outcome results (objective radiologic response, progression-free survival, overall survival) were superior in patients with *EGFR* mutations compared to wild-type patients. The Mok et al. study strongly suggested that the use of gefitinib in wild-type patients was largely ineffective; only 1.1% of patients showed a pharmacologic response in this setting compared to 23% of patients treated with standard chemotherapy. Although it is unclear how well this observation

Table 1. Studies Evaluating Outcomes According to *EGFR* Mutation Status in Patients with Advanced NSCLC* Treated with Gefitinib
(Note: cases in bold represent new reports since 2007)

Study	Tissue Available in Treated Patients/ Total Patients Treated (%)	Mutation Prevalence (%)	Objective Radiologic Response (%) in Mutation-positive Patients	Objective Radiologic Response (%) in Wild-type Patients	Median Progression-free Survival/Time to Progression (months) in Mutation-positive/ Wild-type Patients	Median Overall Survival (months) in Mutation-positive/ Wild-type Patients
Nonconcurrent-Pro prospective*						
Bell et al. (IDEAL) 2005	119/425 (28)	18	46	10 p<0.0005	6 2 NS	8 6 NS
Bell et al. (INTACT) 2005	312/1422 (22)	11	72	55 NS	Not reached 5.5 NS	14.6 9.3 NS
Douillard et al. (INTEREST) 2010	297/1446 (70)	15	42	7 NR	NR	14.2 7.4 NS
Hirsch et al. (ISEL) 2006	215/1129 (19)	11	38	3 p<0.001	NR	NR
Mok et al. 2009 (IPASS)	437/1038 (41)	60	71	1 NR	Longer PFS p<0.001	Overall survival NS
Retrospective Trials (tissue availability)						
Cappuzzo et al. 2005	89/102 (87)	17	53	5 NR	10 3 p<0.02	20.8 8.4 NS
Chou et al. 2005	54/145 (37)	64	71	31 NR	7.6 1.7 p<0.01	14.7 4.7 p<0.046
Cortes-Funes et al. 2005	83/220 (38)	12	60	9 p<0.001	12.3 3.6 p<0.002	13 4.9 p<0.02

* This refers to studies in which treatment information has been collected in a standardized manner at some point in the past and mutation status is determined at the time a study of the interaction between these two elements is initiated.

Table 1. Studies Evaluating Outcomes According to *EGFR* Mutation Status in Patients with Advanced NSCLC* Treated with Gefitinib
(Note: cases in bold represent new reports since 2007) (cont'd)

Study	Tissue Available in Treated Patients/ Total Patients Treated (%)	Mutation Prevalence (%)	Objective Radiologic Response (%) in Mutation-positive Patients	Objective Radiologic Response (%) in Wild-type Patients	Median Progression-free Survival/Time to Progression (months) in Mutation-positive/ Wild-type Patients	Median Overall Survival (months) in Mutation-positive/ Wild-type Patients
Retrospective Trials (tissue availability) (cont'd)						
Dongiovanni et al. 2008	43/147 (29)	17	100	12 p<0.001	NR	14.9/5 p<0.05
Han et al. 2005	90/219 (41)	19	65	14 NR	21.7/1.8 p<0.001	30.5/6.6 p<0.001
Huang et al. 2004	16/16 (100)	50	88	25 p<0.012	NR	5.4/1.3 NR
Kim et al. 2005	22/98 (23)	27	100	10 p<0.001	12.7/2.8 p<0.003	18.9/4.8 p>0.008
Kondo et al. 2005	12/12 (100)	33	100	0 NR	NR	NR
Mitsudomi et al. 2005	50/75 (66)	28	83	10 p<0.001	NR	Not reached/ 15 p<0.005
Mu et al. 2005	22/22 (100)	45	70	0 p<0.0004	NR	NR
Niho et al. 2006	13/40 (32)	31	100	0 NR	NR	15.6/9.7 NR
Rosell et al. 2006	34/34 (100)	23	86	12 p<0.0003	NR	15/2.3 p<0.04
Sasaki et al. 2007	54/54 (100)	48	73	21 p<0.0001	NR	NR

Table 1. Studies Evaluating Outcomes According to *EGFR* Mutation Status in Patients with Advanced NSCLC* Treated with Gefitinib
(Note: cases in bold represent new reports since 2007) (cont'd)

Study	Tissue Available in Treated Patients/ Total Patients Treated (%)	Mutation Prevalence (%)	Objective Radiologic Response (%) in Mutation-positive Patients	Objective Radiologic Response (%) in Wild-type Patients	Median Progression-free Survival/Time to Progression (months) in Mutation-positive/ Wild-type Patients	Median Overall Survival (months) in Mutation-positive/ Wild-type Patients
Retrospective Trials (tissue availability) (cont'd)						
Satouchi et al. 2007	91/22 (41)	31	71	11 p<0.001	NR	24.9/7.4 p<0.001
Sone et al. 2007	59/101 (58)	28	59	14 p<0.0005	7.3/1.8 p<0.003	18.9/6.4 p<0.0092
Takano et al. 2007	66/279 (24)	41	84	11 p<0.0001	12.6/1.7 p<0.0001	20.4/6.9 p<0.0001
Taron et al. 2005	68/68 (100)	25	94	12 p<0.0001	NR	Not reached/9.9 p<0.001
Tokumo et al. 2005	21/21 (100)	43	89	17 p<0.01	NR	25.1/14 NS
Tomizawa et al. 2005	20/82 (24)	53	100	33 NR	NR	NR
Xu et al. 2009	106/106 (100)	30	72	13 NR	15/3 p<0.0001	18.5/6 p<0.0001
Yang et al. 2006	37/196 (12)	52	68	39 NR	NR	14/9.7 p=0.29
Median (range)			72 (46–100)	12 (1–39)	12.5 (6–21.7) 2.4 (1.7–5.5)	17.1 (4.5–30) 7.4 (1.3–15)

*Stage IIIA/B or IV metastatic or recurrent NSCLC
Abbreviations: NR: Not reported; NS: Not significant

Table 2. Clinical Trials Assessing *EGFR* Mutations as Predictors of Efficacy of Gefitinib Compared to Standard Chemotherapy

Study	Gefitinib Objective Radiologic Response (%)	Chemo Objective Radiologic Response (%)	Gefitinib Progression-free Survival (months)	Chemo progression-free Survival (months)	Gefitinib Overall Survival (months)	Chemo Overall Survival (months)
Douillard et al. 2010 n=297 Randomized by therapy, second-line therapy	42	21 p=0.040	Hazard ratio – gefitinib to docetaxel 0.16 with 95% CI (0.04 to 0.49)		14.2	16.6
Maemondo et al. 2010 n=230 Randomized by therapy, first-line therapy	74	31 p<0.001	10.8	5.4 p<0.001	30.5	23.6 p=0.31
Mitsudomi et al. 2010 WJTOG3405 n=172 Randomized by EGFR, first- and second-line therapy	62	32 p<0.0001	9.2	6.3 p<0.001	Follow-up incomplete	
Mok et al. 2009 (IPASS) n=261 Selected by clinical features, randomized by therapy, first-line therapy	71	47 p≤0.001	9.5	6.3 p<0.001	~20	~20 NS
Morita et al. 2009 n=148 Nonrandomized pooled analysis, first- and second-line therapy	79	25 p=0.001	10.7	6 Reported as significantly different	27.7	25.7 NS

Table 3. Clinical Trials Assessing *EGFR* Mutation-positive versus Wild-type Tumors as Predictors of Efficacy of Gefitinib (G) Compared to Standard Chemotherapy (CH)

Study	Mutation-Positive Objective Radiologic Response (%)		Wild-Type Objective Radiologic Response (%)		Mutation-Positive Progression-free Survival (months)		Wild-Type Progression-free Survival (months)		Mutation-Positive Overall Survival (months)		Wild-Type Overall Survival (months)	
	G	CH	G	CH	G	CH	G	CH	G	CH	G	CH
Douillard et al. 2010 n=297 Randomized by therapy, second-line therapy	42	21	6.6	9.8	7	4.1	1.7	2.6	14.2	16.6	6.4	6
Mok et al. 2009 (IPASS) n=261 Selected by clinical features, randomized by therapy, first-line therapy	71	47	1.1	23	G significantly longer than CH in mutation-positive		G significantly shorter than CH in wild type		NS		NS	

in gefitinib would translate to use of erlotinib, this is the reference cited in the recent National Comprehensive Cancer Network (NCCN) recommendation to utilize *EGFR* testing to select patients for treatment with erlotinib.

FDA Status. Genzyme Genetics holds exclusive diagnostic rights to the discovery of *EGFR* gene mutations in NSCLC tumors (Genzyme Genetics 2006). However, *EGFR* gene mutation analysis is currently commercially offered by a growing number of academic and commercial laboratories as a laboratory-developed test under Clinical Laboratory Improvement Amendments (CLIA) regulation. As a matter of enforcement discretion, premarket approval and clearance is currently not required by U.S. Food and Drug Administration (FDA) for laboratory-developed tests.

Methods

Search Methods

A MEDLINE® search (via PubMed) was performed from May 2007 (the date of the previous Assessment) through December 2010 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,” “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.

Study Selection

Original full-length, peer-reviewed studies were selected for inclusion if they provided sufficient information to calculate the radiologic objective response rate, progression-free survival or in some cases time to progression and/or the overall survival with erlotinib for advanced NSCLC. Several published abstracts at international cancer meetings were also included in this analysis.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on September 30, 2010. 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.

Formulation of the Assessment

Patient Indications

Individuals with locally advanced or metastatic (stage IIIA/B or IV) NSCLC are the target population for treatment with erlotinib. The drug is approved by the FDA for use after failure of at least one prior chemotherapy regimen. The studies evaluated in this Assessment contained a mix of both treatment-naïve patients and patients who had failed previous therapy.

Technologies to be Compared

The technology of interest in this Assessment is *EGFR* mutation testing as a predictor of tumor response to the small-molecule tyrosine kinase inhibitor (TKI) erlotinib (Tarceva®). This will allow for targeted selection of the best alternative treatment of each patient based on the *EGFR* genetic profile of the tumor.

The key comparison is the clinical response to erlotinib 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

The health outcomes of primary interest were objective radiologic response and progression-free survival. Most studies have been focused on comparisons of these outcomes in patients with classic *EGFR* mutations versus patients with wild-type genes treated with a TKI. To the extent that *EGFR* mutations are able to predict tumor response to a TKI, testing for these mutations can be used to optimize treatment choices in patients with advanced NSCLC.

The decision to utilize objective radiologic response as a co-primary endpoint is based on a meta-analysis evaluating data from more than 6,000 patients in 24 Phase II and 4 Phase III trials (Tsujino et al. 2009), which suggests that the association between objective radiologic response and median overall survival in patients with advanced lung cancer treated using TKI is very strong (area under the receiver-operating characteristic [ROC] curve of 0.92, where 0.5 is random performance and 1.0 is perfect performance).

The decision to utilize progression-free survival as a co-primary endpoint instead of overall survival was based on the aggressive nature of NSCLC and the recent shift to more aggressive therapy. Cross-over treatments of patients following clinical trial failures are the norm. As a result, overall survival is not a particularly reliable endpoint. This has been a topic of recent editorial interest (Govidan 2010; Shepherd and Tsao 2010). As a matter of research practice, progression-free survival has begun to appear as a regularly chosen endpoint in planned treatment trials of patients with NSCLC (Douillard et al. 2010; Mok et al. 2009; Mitsudomi et al. 2010). FDA published an abstract at the 2010 American Society of Clinical Oncology Annual Meeting (Malik et al. 2010) expressing the view that “an improvement in overall survival in randomized controlled trials has been the standard for establishing clinical benefit for drug approvals in advanced NSCLC.” The abstract noted that criteria for disease progression and tumor response can be difficult to evaluate and may not correlate with overall survival.

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 erlotinib.

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

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

Key Question 3. (a) What is the clinical utility of *EGFR* gene mutation analysis to predict response to erlotinib in advanced NSCLC? (b) What populations benefit from testing for *EGFR*?

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 erlotinib therapy.

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

As noted in the previous Assessment, sequencing is a well-described method often referred to as a “gold standard.” In an effort to expedite and improve the generation of testing results, a number of investigators have begun using rapid, polymerase chain reaction (PCR) assays targeted at the major identified mutations. These alternative techniques have been reported to have varying performance (Zhu et al. 2008; Gow et al. 2009). To date, no test for mutation analysis has been cleared or approved by the FDA, and there are no proficiency testing materials available to compare performance of mutation analysis across laboratories. Archival tissues can be used for testing in patients being considered for second- or third-line treatment if sufficient tissue is available.

A rapid response report on *EGFR* mutation analysis has recently been published by the Canadian Agency for Drugs and Technologies in Health (Mujoomdar et al. 2010). Based on an

analysis of 11 observational studies evaluating the use of PCR-based strategies to detect mutations in the *EGFR* gene, this report concluded PCR-based approaches are capable of identifying mutations in the *EGFR* gene with a sensitivity equivalent to that of direct sequencing.

Test analysis is complicated by the fact there is currently no single standardized technique for tissue processing with some studies based on use of samples with varying amounts of tumor cells present, others based on use of microdissection techniques, and others silent on tumor collection procurement methods or criteria. It is possible that some inconsistencies in *EGFR* predictive behavior observed in the literature may be a result of differing signals being generated by nonstandardized sampling or testing methodologies. Tumor heterogeneity has been reported as a potential confounder in patients undergoing mutational testing for *EGFR* (Nakano et al. 2008).

Of additional interest in understanding the relationship between *EGFR* mutation results and clinical outcomes is a recent publication by Gow et al. (2009). These investigators noted that mutational results from paired primary and metastatic tumors (each sampled in duplicate to minimize the impact of underlying tumor heterogeneity) did not always match. Discordant results were observed in 27% of the patients with changes from primary to metastatic tumor demonstrating both development and loss of relevant *EGFR* mutations.

A recurrent problem in evaluating patients for *EGFR* mutational status is difficulty in obtaining adequate samples. In both research studies and the clinical use of this marker, it may be necessary to rebiopsy patients in order to obtain adequate material. This obviously requires careful discussion with the patients about the benefits and risks of such an added procedure.

As suggested in the 2007 Assessment, analytical validity is ultimately reflected in the evidence gathered to support clinical validity and utility. While Mujoomdar et al. (2010) do note method-specific differences in test sensitivity and specificity, they clearly conclude PCR assays may be useful in selecting a population of patients with NSCLC who are likely to respond to treatment with a TKI.

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

The evidence consists of 13 publications providing data on *EGFR* mutations in tumor samples obtained from NSCLC patients in erlotinib treatment studies. Nine of these (Table 4) were nonconcurrent-prospective studies of patients treated with erlotinib and then studied for the presence or absence of mutations. Four (Table 5) were prospective one-arm enrichment studies of mutation-positive (3 studies) or wild-type (1 study) patients treated with erlotinib.

Data comparing erlotinib results in *EGFR* mutation-positive versus wild-type patients has been reported in 9 studies of 630 patients (Table 4). In studies of treatment with erlotinib, objective radiologic response rates in patients with *EGFR* mutation-positive tumors ranged from 0 to 83% (median 45%) compared to objective radiologic response rates in patients with wild-type tumors of from 0 to 18% (median 5.5%). In the 5 studies statistically evaluating results, patients with *EGFR* mutation-positive tumors always demonstrated statistically significant increases in objective radiologic response.

Progression-free survival in patients with *EGFR* mutation-positive tumors ranged from 6.8 to 13.1 months (median 12.5) and in wild type tumors ranged from 1.4 to 5 months (median 2.5). In all cases in which these data were reported, *EGFR* mutation-positive tumors showed a trend or a statistically significant increase in progression-free survival rate.

Overall survival in patients with *EGFR* mutation-positive tumors ranged from 10 to 35 months (median 21) and in wild-type tumors ranged from 3 to 12 months (median 8.1) In all cases in which these data were reported, *EGFR* mutation-positive tumors showed a trend or a statistically significant increase in survival rate.

In the 3 prospective studies of *EGFR* mutation-positive patients, objective radiologic response rates were 40 to 70%, progression-free survival times were 8 to 14 months, and overall survival times were 16 to 29 months. This performance was distinctly different than that observed in wild-type patients who exhibited an objective radiologic response of 3.3%, a progression-free survival of 2.1 months, and an overall survival of 9.2 months.

Table 4. Studies Evaluating Outcomes According to *EGFR* Mutation Status in Patients with Advanced NSCLC* Treated with Erlotinib
(Note: cases in bold represent new reports since 2007)

Study	Tissue Available in Treated Patients/Total Treated Patients (%)	Mutation Prevalence (%)	Objective Radiologic Response (%) in Mutation-Positive Patients (responders/total evaluated)	Objective Radiologic Response (%) in Wild-Type Patients (responders/total evaluated)	Median Progression-free Survival or Time to Progression in Patients with Mutation/Wild-Type (months)	Median Overall Survival in Patients with Mutation/Wild-Type (months)
Nonconcurrent-prospective						
Ahn et al. 2008 Prospective one-arm study of erlotinib; previous chemotherapy and chemotherapy naïve	92/120 (77)	15	58 14/24	16 11/68 p<0.001	8.6/2.5 p<0.003	Not reached/10.8 p<0.023
Amann et al. 2010 Prospective one-arm study of erlotinib; chemotherapy naïve	41 patients with tissue	7.3	0 0/3	2.6 1/38 NR	13.1/1.8 p<0.052	35/6 p<0.054
Eberhard et al. (TRIBUTE) 2005 Prospective randomized study of chemotherapy plus placebo versus chemotherapy plus erlotinib; chemotherapy naïve	114/539 (21)	13	53 8/15	18 18/99 p<0.01	12.5/5 p<0.01	Not reached/10 p<0.01
Felip et al. 2008 Prospective one-arm study of erlotinib; previous chemotherapy	39/71(55)	13	40 2/5	3 1/34 NR	205 days/43 days p(log rank) =0.0878	205 days/113 days p(log rank)=0846
Giaccone et al. 2006 Prospective one-arm study of erlotinib; previous chemotherapy	27/53(51)	18	80 4/5	4.5 1/22 NR	NR	>627 days/377 days p<0.15

Table 4. Studies Evaluating Outcomes According to *EGFR* Mutation Status in Patients with Advanced NSCLC* Treated with Erlotinib
(Note: cases in bold represent new reports since 2007) (cont'd)

Study	Tissue Available in Treated Patients/Total Treated Patients (%)	Mutation Prevalence (%)	Objective Radiologic Response (%) in Mutation-Positive Patients (responders/total evaluated)	Objective Radiologic Response (%) in Wild-Type Patients (responders/total evaluated)	Median Progression-free Survival or Time to Progression in Patients with Mutation/Wild-Type (months)	Median Overall Survival in Patients with Mutation/Wild-Type (months)
Nonconcurrent-prospective						
Jackman et al. 2007 Prospective one-arm study of erlotinib; chemotherapy naive patients age 70 or more	43/80 (54)	21%	33 3/9	6 2/34 NR	NR	>15/8.1 p<0.012
Miller et al. 2008 Prospective one-arm study of erlotinib; 75% of patients chemotherapy naïve; bronchoalveolar cell histology	88/101 (87)	22	83 15/18	7 4/63 p<0.01	13/2 p<0.01	23/17 Trend but p=0.24
Schneider et al. 2008 Prospective one-arm study or erlotinib; previous chemotherapy	72/393 (18)	40	50 2/4	3 2/68 p<0.014	~12.5/~2.5 p=<0.009**	~17.5/~4.3 p=<0.025**
Zhu et al. 2008 (BR.21) Prospective study of erlotinib versus placebo in patients with previous chemotherapy	204/731 (28)	13	27 4/15	7 7/101 p<0.035	NR	10./7.9 p=0.47

*Stage IIIA/B or IV metastatic or recurrent NSCLC; **Based on comparative hazard ratio
Abbreviations: NR: Not reported; NS: Not significant

Table 5. Outcomes in Patients According to *EGFR* Mutation Status in Response to Treatment with Erlotinib

Endpoint	Overall Radiologic Response Rate Median (range), %	Progression-Free Survival Median (range), months	Overall Survival Median (range), months
Patients with <i>EGFR</i> -Positive Tumors	45 (0–83)	12.5 (6.8–13.1)	21 (10–35)
Patients with Wild-Type Tumors	5.5 (0–18)	2.5 (1.4–5 months)	8.1 (3–12)
Untested Patients (Intent to Treat) – FDA Label		2.8 months	12 months

Of note, *EGFR* mutations appear to provide prognostic as well as predictive information about the behavior of tumors. In the study by Eberhard et al. (2005) improved outcome parameters were observed in patients with *EGFR* positive tumors compared to wild-type tumors for the population as a whole (standard chemotherapy and standard chemotherapy with erlotinib) in all measurement categories with objective radiologic response of 38% versus 23% ($p=0.01$), time to progression of 8 months versus 5 months ($p<0.001$) and overall survival (not reached versus 10 months ($p<0.001$)). Similar enhanced outcomes in patients with *EGFR*-positive tumors were observed regardless of treatment using gefitinib versus standard chemotherapy by Mok et al. (2010) and Douillard et al. (2009) (Table 5). To date no formal study has been performed evaluating the relative prognostic versus predictive effects. Given proven efficacy of a variety of both first- and second-line treatments, it is not clear a study to evaluate prognosis in untreated patients to determine the natural course of tumor progression will be performed. Nevertheless, *EGFR* mutations appear to demonstrate improved patient outcomes for patients treated with erlotinib as compared to standard chemotherapy. Patients with *EGFR* mutations appear to be ideal candidates for treatment with erlotinib, whereas wild-type patients appear to derive little detectable benefit from erlotinib.

Identification of patients likely to respond or to fail to respond to erlotinib treatment leads to tailored choices of treatment likely to result in predictable and desirable outcomes.

However, as is true for all tests, testing is likely to result in both false-positive and -negative results (the latter most likely a result of sampling or sensitivity of analytical methods) with the following results (Table 6).

While a true-positive result identifies patients who would benefit from erlotinib treatment and a true-negative result identifies patients who would be better served by immediately using an alternative therapy; the inevitable occurrence of incorrect results (both false positives and negatives) has the potential to confound treatment choices and result in harmful outcomes. In the case of false-positive results, patients will be treated with erlotinib when they are in fact not likely to be responsive to the drug. In the case of false-negative results, erlotinib may be withheld and benefit denied a patient who actually would be sensitive to the drug (Table 7).

Current techniques for analyzing diagnostic test performance make it relatively easy to define predictive values of testing in patients based on objective radiologic response rates. Based on the composite data in Table 4, it is estimated that results of *EGFR* testing (using tumor response as a gold standard) are:

Predictive value of a positive – 45%
 True-positive – 45%
 False-positive – 55%
 Predictive value of a negative – 94.5%
 True-negative – 94.5%
 False-negative – 5.5%

Results of both positive and negative testing have been corroborated in prospective enrichment studies, although to date no reports on randomized clinical trials evaluating the association between *EGFR* status and tumor response to erlotinib have been published. Fortunately, two are in progress (Paz-Ares et al. 2010).

Summary endpoints such as median progression-free survival or overall survival are more difficult to capture using traditional diagnostic parameters. However, in the context of patients being treated for advanced NSCLC, the

Table 6. Potential Impact of False-positive and False-negative Results in Responders and Nonresponders Based on Mutation Status

	<i>EGFR</i> Mutation-Positive Tumors	Wild-Type Tumors
Patients responding to erlotinib	True positive – Patients benefit from erlotinib treatment	False negative – Patients would respond to erlotinib; however treatment deferred based on test results
Nonresponders	False positive – Patients receive erlotinib but shows no benefit; alternative better drug choices are delayed	True negative – Patients expected to show poor response to erlotinib; alternative therapies are considered/used

Table 7. Clinical Response in Prospective Studies of Erlotinib Therapy in Patients with *EGFR* Gene Mutation-Positive Advanced NSCLC*

Study (Year)	No. Mutated/ No. Tested (%)	Mutation-Positive Objective Radiologic Response (%)	Median Progression-free Survival (months) [95% CI]	Median Overall Survival (months) [95% CI]
Jackman et al. 2009 Prospective one-arm treatment of patients with <i>EGFR</i> -positive tumors with erlotinib, chemotherapy naïve	84 enrolled	70	13	28.7
Rosell et al. 2009 Prospective one-arm treatment of patients with <i>EGFR</i> -positive tumors with erlotinib in treatment failure and chemotherapy naïve	350/2105 (16.6)	70	14 [11.3-16,7]	27 [24.9-33.1]
Sun et al. 2010 Prospective one-arm treatment of patients with <i>EGFR</i> -positive tumors with erlotinib in treatment failures	144/164 (32)	40	8	15.8
Yoshioka et al. 2010 Prospective one-arm treatment of patients with <i>EGFR</i> wild-type tumors with erlotinib in treatment failures	30 enrolled	Mutation negative 3.3	2.1	9.2

* all patients had stage IIIA/IV NSCLC

increases in survival times observed between *EGFR*-positive and wild-type tumors (10-month increase for progression-free survival and 13-month increase for overall survival) appear to be clinically meaningful.

The largest of 4 prospective enrichment studies is that performed by Rosell et al. (2009) in Spain. *EGFR* was measured in 2105 patients and erlotinib administered to 217 patients with advanced *EGFR* mutation-positive NSCLC. Patients received a mixture of first- and second-line therapy. Although no efforts at enrichment were made, patients referred for study appeared to include increased numbers of women and nonsmokers. Prevalence of mutation in the population referred was 16.6%.

In the *EGFR* mutation-positive, erlotinib-treated groups the objective radiologic response rate was 70%, median progression-free survival 14 months, and median overall survival 27 months. Adverse events were most commonly mild rashes and diarrhea. Only about 11% of patients experienced grade 3 (severe) toxic effects. The authors concluded that using historic benchmarks of response to chemotherapy (using estimates of objective radiologic response of 30%, progression-free response of 5 months, and overall survival of 12 months) targeted use of erlotinib appeared to produce an improvement in net health outcome.

Key Question 3 (a). What is the clinical utility of *EGFR* gene mutation analysis to predict response to erlotinib in advanced NSCLC?

The detection of *EGFR* gene mutations identifies patients who are likely to benefit from use of erlotinib and who, therefore, represent ideal candidates for treatment with this drug. Performance of erlotinib is likely to be superior to that observed in wild-type patients. Performance is also likely to be superior to that observed with treatments using standard chemotherapy providing superior performance with relatively little toxicity. Patients who are found to have wild-type tumors are unlikely to respond to erlotinib. They should be considered candidates for alternative therapies and benefit from testing by avoiding non-beneficial therapy and proceeding directly to better alternatives. *EGFR* mutation testing can be performed to identify patients who would

benefit from treatment with erlotinib and to distinguish these patients from those who should be considered for alternative treatment choices. Of note, while the FDA does not currently recommend use of erlotinib therapy for first-line treatment of advanced NSCLC and does not recommend use of *EGFR* mutational analysis as a prerequisite for second-line treatment with this drug, *EGFR* mutational analysis does appear to identify patients likely to show improved performance (*EGFR* mutation-positive tumors) versus suboptimal performance (wild-type tumors). In light of these striking differences in treatment response, the test appears to have value in making decisions about erlotinib use.

Key Question 3 (b). What populations benefit from testing for *EGFR*?

Rosell et al. (2009) reported mutations in 16.6% of the total patients studied but noted these were found more frequently in women (69.7%), in patients who had never smoked (66.6%), and in patients with adenocarcinomas (80.9%). Based on these findings, Rosell et al. recommended *EGFR* mutation screening in women with lung cancer with nonsquamous cell tumors who have never smoked. Other reports on the frequency of mutations have also revealed a higher prevalence in East Asians when compared to other ethnicities (38% versus 15%) (Zhu et al. 2008). An increased incidence of mutations is clearly seen in these special populations (women, patients with adenocarcinoma, nonsmokers, and/or Asians); however, it does appear that a substantial number of patients without these selected demographics still exhibit *EGFR* mutations and would benefit from erlotinib treatment.

In a comprehensive analysis of 14 studies involving 2,880 patients, Mitsudomi et al. (2006) noted mutations were observed in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, but in only 2% of patients with nonadenocarcinoma histologies. While histology appears to be the strongest discriminating factor, results are diverse across studies. Eberhardt et al. (2005) observed mutations in 6.4% of patients with squamous cell carcinomas and Rosell et al. (2009) in 11.5% of patients with large-cell carcinomas. Given the value in treatment decision making, it does not appear that testing should be reserved for patients with unique demographic characteristics.

Summary and Conclusions

While to date there have been no prospective randomized, clinical trials specifically looking at how *EGFR* mutation-directed erlotinib therapy has an impact on patient outcomes, there is strong evidence in nonconcurrent-prospective and one-arm enrichment prospective studies demonstrating an interaction between *EGFR* gene mutation test results and erlotinib responses.

In evaluating patients with NSCLC, a serious disease with a poor overall prognosis, use of *EGFR* mutation testing appears to be a valuable test in assisting physicians to make optimal treatment choices and to improve their ability to select patients likely to benefit from use of erlotinib as a treatment for patients with advanced NSCLC. Patients not likely to benefit from erlotinib would also receive the best alternative without delay.

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 response to erlotinib (Tarceva[®]) 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 is commercially available at both academic medical centers and commercial laboratories. The tests available are being offered as laboratory-developed tests and at the current time, the FDA is not actively regulating these as a matter of enforcement discretion. The laboratories performing these tests must meet quality standards as prescribed under the Clinical Laboratory Improvement Amendments (CLIA).

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

Evidence compiled from nonconcurrent-prospective studies and one-arm prospective enrichment studies is sufficient to conclude

that a gain-of-function somatic mutation in the tumor-cell *EGFR* gene tyrosine kinase domain identifies a population subset (patients with mutation-positive tumors) with advanced NSCLC who exhibit improved objective radiologic response, progression-free survival, and overall survival when treated with erlotinib compared to the same treatment in patients with wild-type tumors or to standard chemotherapy in patients with *EGFR* mutation-positive tumors.

Data are strongest for demonstrating differences in objective radiologic response, is less consistent, but strong, for progression-free survival, and is less consistent, but strong, for overall survival. Radiologic response is not generally viewed by itself as a meaningful endpoint, since its ability to predict standard and more established outcomes such as progression free survival, overall survival, or quality of life is not reliable. However, there is a published meta-analysis suggesting objective radiologic response is strongly associated with median overall survival in patients with NSCLC treated with TKIs. There is also growing discussion that overall survival may be a compromised endpoint for NSCLC due to the fact that NSCLC is a particularly aggressive disease with an increasing number of treatment choices, many specifically available for cross-over use in patients demonstrating resistance to earlier therapies. These cross-over therapies are likely to make evaluation of overall survival a challenging, and perhaps impossible, study endpoint.

3. The technology must improve the net health outcome.

Recent prospective and retrospective studies have shown convincing evidence that *EGFR* mutations can identify disease likely to respond to erlotinib. There is growing evidence that this information affects the net health outcome by identifying patients who are likely to exhibit good outcomes with this treatment with minimal toxicity. Recent reports suggest *EGFR* mutations also identify patients more likely to respond to erlotinib than to standard chemotherapy. In these patients, use of erlotinib therapy may be much more effective than alternative drug choices.

There is also growing information demonstrating that *EGFR* status can help physicians identify wild-type tumors in patients who are unlikely to respond to erlotinib. In these

patients, alternative treatment choices should be considered. It is therefore prudent for physicians to evaluate patients with wild-type tumors carefully, considering the unique patient-specific variables and preferences at hand, to discuss these with the patient, and to use this information to make patient informed, collaborative personalized treatment choices.

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

Alternatives—in particular, use of empiric therapy—appear to be less reliable at estimating likely objective response and progression-free and overall survival than testing using *EGFR* mutation analysis to select patients for erlotinib therapy. The role for use of clinical risk features (female sex, adenocarcinoma histology, nonsmoking history, or Asian heritage) requires further study to determine how this information might help in making accurate testing or treatment choices.

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

EGFR mutation testing is now widely available commercially and studies have indicated that it is possible to utilize testing for improved decision making at multiple clinical sites. Testing is recognized to be of value in centers of oncology excellence and the only impediment is the need for increased access to testing (an ongoing process) and introduction of more wide-scale use of tests with rapid turnaround time.

Based on the available evidence, use of tumor-cell *EGFR* mutation analysis to predict response to erlotinib (Tarceva®) in patients with advanced non-small-cell lung cancer meets 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

- Ahn MJ, Park BB, Ahn JS et al. (2008).** Are there any ethnic differences in molecular predictors of erlotinib efficacy in advanced non-small cell lung cancer? *Clin Cancer Res*, 14(12):5860-6.
- Amann JM, Lee JW, Roder H et al. (2010).** Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 5503. *J Thorac Oncol*, 5(2):169-178.
- American Society of Clinical Oncology (ASCO). (2009).** Original guidelines and guidelines updates in progress (last updated 10/06/09). Available online at: [http://www.asco.org/ASCO/Downloads/Cancer%20Policy%20and%20Clinical%20Affairs/Clinical%20Affairs%20\(derivative%20products\)/Guidelines%20in%20Progress%2010.6.09.pdf](http://www.asco.org/ASCO/Downloads/Cancer%20Policy%20and%20Clinical%20Affairs/Clinical%20Affairs%20(derivative%20products)/Guidelines%20in%20Progress%2010.6.09.pdf). Last accessed June 2010.
- Azzoli CG, Baker Jr S, Temin S et al. (2009).** American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small cell lung cancer. *J Clin Oncol*, 27(36):6251-66. Available online at <http://jco.ascpubs.org/cgi/reprint/27/36/6251>. Last accessed June 2010.
- 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.
- 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.
- 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 Thorac Oncol*, 8:837-46.
- 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(10):1585-92.
- Dongiovanni D, Daniele L, Barone C et al. (2008).** Gefitinib (ZD1859): therapy in selected patients with non-small cell lung cancer (NSCLC)? *Lung Cancer*, 61(1):73-81.
- Douillard J, Shepherd FA, Hirsh V et al. (2010).** Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. *J Clin Oncol*, 28(5):744-52.
- Dzadzadzko R, Hirsch FR, Varella-Garcia et al. (2006).** Selecting lung cancer patients for treatment with epidermal growth factor receptor tyrosine kinase inhibitors by immunohistochemistry and fluorescence in situ hybridization--why, when, and how? *Clin Cancer Res*, 12(14 Pt 2):4409s-4415s.
- 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.
- Fathi AT, Brahmer JR (2008).** Chemotherapy for advanced stage non-small cell lung cancer. *Semin Thorac Cardiovasc Surg*, 20(3):210-6.
- Felip E, Rojo F, Reck M et al. (2008).** A phase II pharmacodynamic study of erlotinib in patients with advanced non-small cell lung cancer previously treated with platinum-based chemotherapy. *Clin Cancer Res*, 14(12):3567-74.
- Freuhauf J. (2006).** EGFR function and detection in cancer therapy. *J Exp Ther Oncol*, 5(3):251-46.
- Genzyme Genetics. (2006).** Press release: Genzyme introduces new genetic test to complement lung cancer portfolio. Westborough, MA; December 4, 2006.
- Giaccone G, Rodriguez JA. (2005).** EGFR inhibitors: what have we learned from the treatment of lung cancer? *Nat Clin Pract Oncol*, 2(11):554-61.
- Giaccone G, Gallegos RM, Le Chevalier T. (2006).** Erlotinib for frontline treatment of advanced non-small cell lung cancer: a phase II study. *Clin Cancer Res*, 12(20 Pt 1):6049-55.
- Govidan R. (2010).** INTERESTing biomarker to select IDEAL patients for epidermal growth factor receptor tyrosine kinase inhibitors: Yes, for EGFR mutation analysis, others, I PASS. *J Clin Oncol*, 28(5):713-5.
- Gow CH, Chang YL, Hsu YC et al. (2009).** Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. *Ann Oncol*, 20(4):696-702.

- Han SW, Kim TY, Hwang PG et al. (2005).** 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.
- 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 Pt 2):4441s-4445s.
- 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(Suppl 2):S38.
- 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(31):5034-42.
- Huang SF, Liu HP, Li LH 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(24):8195-205.
- Jackman DM, Yeap BY, Lindeman NI et al. (2007).** Phase II clinical trial of chemotherapy naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell-lung cancer. *J Clin Oncol* 25(7):760-6.
- Jackman DM, Miller VA, Cioffredi L et al. (2009).** Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated Non-small cell lung cancer patients; results of an online tumor registry of clinical trials. *Clin Cancer Res*, 15(16):5267-75.
- Jemal A, Siegel R, Ward E et al. (2010).** Cancer statistics, 2009. *CA Cancer J Clin* 2010; 60(5):277-500.
- 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, Yoshioka H 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*; 2005 50(3):385-91.
- Lee JH, Xu X, Choe G et al. (2010).** Protein overexpression and gene amplification of epidermal growth factor receptor in nonsmall cell lung carcinomas: comparison of four commercially available antibodies by immunohistochemistry and fluorescence in situ hybridization study. *Lung Cancer*; 68(5):575-82.
- 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):2129-39.
- Maemondo M, Inoue A, Kobayashi et al. (2010).** Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*, 362(25):2380-8.
- Malik SM, Ibrahim R, Sridhara RI et al. (2010).** Use of progression-free survival (PFS) as an endpoint in advanced non-small cell lung cancer (NSCLC) trials: FDA perspective. 2010 ASCO Annual Meeting Abstract No: e18001.
- Martoni A, Marino A, Sperandi F et al. (2005).** Multicentre randomised phase III study comparing the same dose and schedule of cisplatin plus the same schedule of vinorelbine or gemcitabine in advanced non-small cell lung cancer. *Eur J Cancer* 41(1):81-92.
- Mathieu A, Weynand B, Verbeken E et al. (2009).** Comparison of four antibodies for immunohistochemical evaluation of epidermal growth factor receptor expression in non-small cell lung cancer. *Lung Cancer*, 2009 Sep 29. [Epub ahead of print]
- Metro G, Finocchiaro G, 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.
- Miller VA, Riely GJ, Zakowski MF et al. (2008)** Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. *J Clin Oncol*, 26(9):1472-1478.
- 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*, 23(11):2515-20.
- Mitsudomi T, Kosaka T, Yatabe Y. (2006)** Biological and clinical implications of EGFR mutations in lung cancer. *Int J Clin Oncol*, 11(5):190-8.
- Mitsudomi T, Morita S, Yatabe Y et al. (2010).** Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomized phase 3 trial. *Lancet Oncol*, 11(2):121-8.
- Mok TS, Wu YL, Thongprasert S et al. (2009).** Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*, 361(10); 947-857.
- Mujoomdar M, Moulton K, Spry C. (2010).** Epidermal growth factor receptor mutation analysis in advanced non-small cell lung cancer: a review of the clinical effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in health; 2010.
- Morita S, Okamoto I, Kobayashi K et al. (2009).** Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. *Clin Cancer Res*, 15(15):4495-8.
- 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(12):4289-94.

- Nakano H, Soda H, Takasu M, Tomonaga N et al. (2008).** Heterogeneity of epidermal growth factor receptor mutations within a mixed adenocarcinoma lung nodule. *Lung Cancer*, 60(1):156-40.
- National Comprehensive Cancer Network (NCCN). (2010).** NCCN Clinical Practice Guidelines in Oncology™: Non-small cell lung cancer (V.2.2010). Available online at: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf. Last accessed June 2010.
- 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(1):64-9.
- 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(11):2556-68.
- 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 1839) in non-small-cell lung cancer. *Br J Cancer*, 91(2):208-12.
- Paz-Ares, Soulieres D, Melezinek I et al. (2010).** Clinical outcomes in non-small-cell lung cancer patients with EGFR mutations: pooled analysis. *J Cell Mol Med*, 14(1-2):51-69.
- 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.
- 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(24):7222-51.
- Rosell R, Moran T, Queralt C et al. (2009).** Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med*, 361(10):958-967.
- Rudd RM, Gower NH, Spiro SG et al. (2005)** Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. *J Clin Oncol*, 23(1):142-55.
- Sasaki H, Endo K, Okuda K et al. (2007).** Epidermal growth factor receptor gene amplification and gefitinib sensitivity in patients with recurrent lung cancer. *J Cancer Res Clin Oncol*, 134(5):569-77
- 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(8):1191-96.
- Schneider CP, Heigener D, Schott-von-Romer K et al. (2008).** Epidermal growth factor receptor-related tumor markers and clinical outcomes with erlotinib in non-small cell lung cancer: an analysis of patients from german centers in the TRUST study. *J Thorac Oncol*, 3(12):1446-55.
- Sharma SV, Bell DW, Settleman J et al. (2007).** Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer*, 7(3):169-81.
- Shepherd FA, Tsao MS. (2010).** Epidermal growth factor receptor biomarkers in non-small-cell lung cancer: a riddle, wrapped in a mystery, inside an enigma. *J Clin Oncol*, 28(6):905-5.
- 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(9):1856-44.
- Sun JM, Won YW, Kim SJ et al. (2010).** The different efficacy of gefitinib or erlotinib according to epidermal growth factor receptor exon 19 and exon 2 mutations in Korean non-small cell lung cancer patients. *J Cancer Res Clin Oncol*, June 2010 epub.
- 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(28):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.
- Tokumo M, Toyooka S, Kiura K et al. (2005).** The relationship between epidermal growth factor receptor mutations and clinicopathological features in non-small cell lung cancer. *Clin Cancer Res*, 11(3):1167-75.
- Tomizawa Y, Iijama H, Sunaga N et al. (2005).** Clinicopathological significance of the mutations of the epidermal growth factor receptor gene in patients with non-small cell lung cancer. *Clin Cancer Res*, 11(19 Pt 1):6816-22.
- Toschi L, Cappuzzo F. (2007).** Understanding the new genetics of responsiveness to epidermal growth factor receptor tyrosine kinase inhibitors. *Oncologist*, 12(2):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):135-44.
- Tsujino K, Kawaguchi T, Kubo A et al. (2009).** Response rate is associated with prolonged survival in patients with advanced non-small-cell lung cancer treated with gefitinib or erlotinib. *J Thorac Oncol*, 4(8):994-1001.

U.S. Cancer Statistics Working Group. (2009). United States Cancer Statistics: 1999-2005 Incidence and Mortality Web-based Report. Atlanta, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. www.cdc.gov/uscs. Last viewed December 2009.

Weinstein IB. (2002). Cancer. Addiction to oncogenes: the Achilles heel of cancer. *Science*, 297(578):63-4.

Xu JM, Han Y, Duan HQ et al. (2009). EGFR mutations and HER2/3 protein expression and clinical outcome in Chinese advanced non-small cell lung cancer patients with gefitinib. *J Cancer Res Clin Oncol*, 135(6):771-782.

Yang C, Shih J, Chen K et al. (2006). Survival outcome and predictors of gefitinib antitumor activity in East Asian chemo-naïve patients with advanced non-small cell lung cancer. *Cancer*, 107(8):1875-82.

Yoshioka, H, Hotta Y, Kiura, et al. (2010). A phase II trial of erlotinib monotherapy in pretreated patients with advanced non-small cell lung cancer who do not possess active EGFR mutations: Okayama Lung Cancer Study Group trial 0705. *J Thorac Oncol*, 5(1):99-104.

Zhu CQ, da Cunha SG, Ding K et al. (2008). Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol*, 26(26):4268-4275.



**Technology
Evaluation
Center**

**Blue Cross and
Blue Shield Association**
225 North Michigan Avenue
Chicago, Illinois 60601-7680
www.bcbs.com/tec