Integration of Tissue Biomarker Assays into Protocol and Nonprotocol Management of Lung Cancer

Proceedings from a CME Symposium Held During the 13th World Conference on Lung Cancer

EDITOR

Neil Love, MD

FACULTY

Thomas J Lynch Jr, MD

Vincent A Miller, MD

Tony SK Mok, MD

Joan H Schiller, MD

Jean-Charles Soria, MD, PhD

This presentation was selected by the 13th World Conference on Lung Cancer Programme Committee as an independent educational activity held in conjunction with the 13th World Conference on Lung Cancer. This presentation is not sponsored or endorsed by the IASLC.

From the publishers of: Lung Cancer™ UPDATE

CME Certified

Integration of Tissue Biomarker Assays into Protocol and Nonprotocol Management of Lung Cancer

A Continuing Medical Education Program

OVERVIEW OF ACTIVITY

Lung cancer is the leading cause of cancer mortality in the United States in both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been limited, and approximately 85 percent of patients who develop lung cancer will die from it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on patient outcomes. However, with the advent of targeted biologic agents in addition to molecular and clinical biomarkers, recent improvements have been seen in time to progression and survival in lung cancer clinical trials. Published results from ongoing and completed studies lead to the continual emergence of novel therapeutic strategies and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with experts' perspectives on the findings, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Identify somatic gene mutations that may be utilized to predict lung tumor response or resistance to EGFR-directed therapy.
- Incorporate clinical and molecular biomarkers into the selection of optimal treatment strategies for patients with advanced non-small cell lung cancer (NSCLC).
- Recognize the role of target population enrichment in the tailored investigation of biologic therapy for localized and metastatic lung cancer.
- Explain how tumor histology and/or receptor expression profile may affect chemotherapy sensitivity.
- Apply the results of emerging research to refine the use of anti-angiogenic agents in the treatment of NSCLC.
- Recall the design and eligibility criteria for ongoing clinical trials in NSCLC, and counsel appropriate patients for study participation.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains audio, print and slide components. To receive credit, the participant should review the CME information, listen to the CD, review the monograph and slides and complete the Post-test and Educational Assessment and Credit Form located in the back of this monograph or on our website at **CME.ResearchToPractice.com**. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ResearchToPractice.com/WCLC09** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated within the text of the monograph in **blue, bold text**.

This program is supported by an educational grant from Genentech BioOncology & OSI Oncology.

Last review date: December 2009; Release date: December 2009; Expiration date: December 2010

TABLE OF CONTENTS

This presentation was selected by the 13th World Conference on Lung Cancer Programme Committee as an independent educational activity held in conjunction with the 13th World Conference on Lung Cancer. This presentation is not sponsored or endorsed by the IASLC.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Lynch** — Director, Yale Cancer Center; Physician-in-Chief, Smilow Cancer Hospital at Yale New Haven, New Haven, Connecticut. Consulting Agreements: AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Genentech BioOncology, Infinity Pharmaceuticals Inc, Merck and Company Inc; Royalties for EGFR Testing Patent: Genzyme Corporation. **Dr Miller** — Associate Attending Physician, Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York. Consulting Agreements: Abraxis BioScience, Agennix Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Facet Biotech Corporation, Genentech BioOncology, ImClone Systems Incorporated, Lilly USA LLC, Sanofi-Aventis; Scientific Advisory Board: Cylene Pharmaceuticals. **Dr Mok** — Professor, Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China. Advisory Committee: AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation, Eisai Inc, GlaxoSmithKline, Lilly USA LLC, Roche Laboratories Inc; Consulting Agreements: Pfizer Inc, Roche Laboratories Inc; Paid Research: AstraZeneca Pharmaceuticals LP; Speakers Bureau: Lilly USA LLC, Roche Laboratories Inc. **Dr Schiller** — Chief, Division of Hematology and Oncology; Deputy Director of Simmons Comprehensive Cancer Center; Andrea L Simmons Distinguished Chair in Cancer Research, University of Texas Southwestern Medical Center, Dallas, Texas. Advisory Committee: AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation, Bristol-Myers Squibb Company, Genentech BioOncology, Genomic Health Inc, ImClone Systems Incorporated, Lilly USA LLC, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi-Aventis; Paid Research: Pfizer Inc. **Prof Soria** — Full Professor, Paris University XI, Division of Cancer Medicine, Institut Gustave Roussy, Villejuif, France. Consulting Agreements: AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation, Biogen Idec, Bristol-Myers Squibb Company, Lilly USA LLC, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis, Wyeth. **Dr Schneider** (featured on the accompanying *Atlas of Molecular Oncology* PowerPoint CD) — Assistant Professor of Medicine, Departments of Medicine, Division of Hematology/Oncology, The Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, Indiana. Advisory Committee: Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline; Paid Research: Genentech BioOncology.

EDITOR — **Neil Love:** Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Centocor Ortho Biotech Services LLC, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Merck and Company Inc, Millennium Pharmaceuticals Inc, Monogram BioSciences Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Wyeth.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

PROGNOSTIC AND PREDICTIVE ROLE OF EGFR GENE MUTATIONS

DR LOVE: Tom, would you review some of the recent key findings in predicting response and resistance to EGFR TKIs?

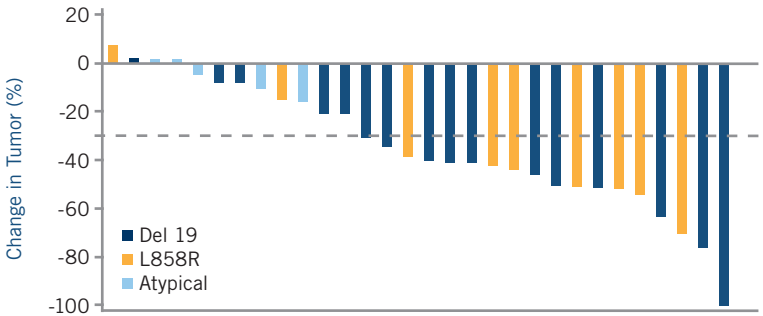
DR LYNCH: The identification of the EGFR mutations ushered in an era of molecular medicine in lung cancer. We now know that erlotinib and gefitinib can cause dramatic responses in a subset of patients and that EGFR tyrosine kinase mutations best predict this group. We also know that combining these agents with chemotherapy isn't likely to provide a great benefit.

Generally, two groups of mutations are important. These mutations occur in the tyrosine kinase domain. They tend to be either exon 19 deletions or exon 21 point mutations. Some mutations are found in exon 18, and some resistance mutations are found in exon 20. Through recent research we've been able to understand what most of these are, which has simplified testing and evaluation.

When one prospectively treats a patient with an EGFR mutation, one can see a dramatic response. In a study reported by Dr Sequist, 98 patients were screened, 35 percent of whom had EGFR mutations. The authors reported a 55 percent response rate, 9.2-month progression-free survival and 17.5-month overall survival among patients with EGFR mutations who received first-line gefitinib. A waterfall plot analysis showed that the vast majority of patients experienced notable

1.1

Tumor Response to First-Line Gefitinib in Patients with Advanced Non-Small Cell Lung Cancer Harboring Somatic EGFR Mutations



Response rate = 55%
Median progression-free survival = 9.2 months; median overall survival = 17.5 months

SOURCE: With permission from Sequist LV et al. *J Clin Oncol* 2008;26(15):2442-9.

shrinkage of their tumors (Sequist 2008; [1.1]).

We've learned not only from the Sequist study but also from other studies around the world that when you prospectively treat patients who have mutations, you obtain response rates of approximately 70 percent. Thus, approximately 30 percent of patients with EGFR mutations don't respond to treatment with EGFR TKIs. I would argue that this is one of the most important groups to evaluate and try to understand that inherent resistance.

BIOMARKERS OF RESISTANCE

DR LYNCH: We know that when you treat EGFR mutations with TKIs, resistance emerges relatively quickly. What are some of the ways by which the tumor cell can become resistant? T790M is a mutation that occurs in the active tyrosine kinase area and that essentially prevents gefitinib or erlotinib from inhibiting the enzyme, thus maintaining normal signaling. A second mechanism of resistance is MET amplification, in which the tumor cell, even with gefitinib or erlotinib on board, finds an alternative way to signal through AKT proteins and PI3 kinase. So MET amplification becomes an alternative mechanism for signaling the tumor cell to grow and proliferate. IGF-IR activation is another purported resistance mechanism, in which the insulin-like growth factor receptor is activated, creating another way for tumor cells to become resistant to EGFR tyrosine kinase activity (Engelman 2008).

Where are we now in terms of these resistance mechanisms? T790M mutation probably accounts for 50 percent of all known cases of acquired resistance, although some people have argued it's as high as 80 percent. Some people have argued that the nonkinase role of EGFR is important, and I believe a large group of cases would still fall under the category of "unknown." How do we overcome this resistance? A number of agents are under investigation in this area, such as dual kinase inhibitors for T790M, irreversible inhibitors, c-Met inhibitors and IGF-1-based treatments.

Another important clinical question is, what is the role of K-ras mutations? In my practice, I've seen probably one or two patients who had both K-ras and EGFR-activating mutations. It is remarkably unusual to see them together. No overlap is evident between K-ras mutations and EGFR-activating mutations.

DIAGNOSTIC CONSIDERATIONS: EGFR MUTATION TESTING IN CLINICAL PRACTICE

DR LYNCH: I would argue that EGFR mutation testing is "ready for prime time." The test can be performed reliably on 10 unstained slides from a core biopsy. You can almost always achieve an EGFR mutation test from a larger resection specimen. And as the technology improves, we're reaching the point at which performing EGFR mutation testing on a fine-needle aspirate is possible. Two- to three-week testing intervals remain a challenge, but we now know that the actual time

to perform the test can be brought down to only a day. Most of the time is spent simply gathering the specimens for testing. Rebiopsy is also an important trend we need to evaluate further. Vince Miller recently presented some excellent data reporting on the Memorial Sloan-Kettering experience rebiopsying when patients' disease became resistant (Arcila 2009), so we might be able to figure out why those patients have abnormalities.

DR LOVE: Tony, can you comment on your work on circulating DNA?

DR MOK: Everyone has circulating DNA. Our recent publication in *Clinical Cancer Research* reported on the use of a technique called *digital PCR* under development for the quantitative detection of the two common EGFR mutations — exon 19 and exon 21 — in the plasma and tumor tissue of patients with NSCLC (Yung 2009). This was a small study, but a larger, prospective study is under way and it is hoped that this will become an alternative method for detecting the plasma DNA of EGFR mutations.

DR LOVE: Tom, what do you think about circulating DNA, and would you comment on the circulating tumor cells study you reported in *The New England Journal of Medicine*?

DR LYNCH: I believe the detection and analysis of circulating DNA is promising and exciting. One of the advantages of identifying circulating tumor cells is the ability to characterize the cells and ultimately to create cell lines. From a research standpoint, that's an exciting tool.

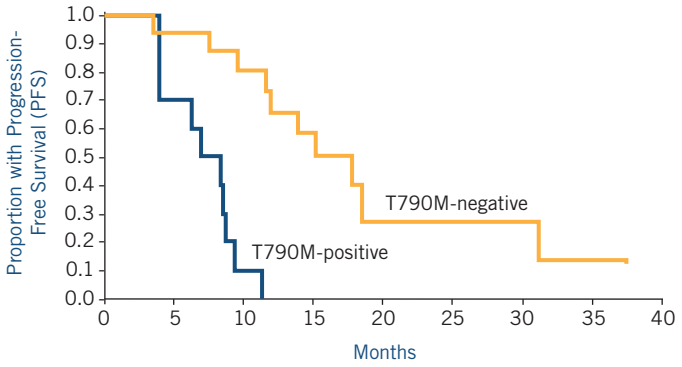
We believe that for a number of common cancer types, people who have metastatic disease will almost universally have circulating tumor cells. Even patients with early-stage disease probably have circulating tumor cells. The newer technologies enable us to assay the frequency of circulating tumor cells, which seems to correlate with benefit from therapy, and also to develop a profile of these cells.

A couple of hurdles and challenges are evident as we move forward. The first is that this technology is still being developed and it's not easily transported to different centers and sites. The second is that you don't know, when you collect circulating tumor cells, what they reflect. Are they reflective of cells that have already established metastasis, or are they reflective of cells that have metastatic potential because you might find pathways turned on and off in circulating tumor cells? What does that mean about areas that are resistant?

Jeff Engelman's work examining EGFR resistance has shown that lung metastases can develop with MET amplification and bone metastases with T790M mutation (Engelman 2007). What will the circulating tumor cells show? Will they show the lung metastasis, the bone metastasis or neither? So the approach is not perfect yet, but as a window to understanding easily accessible tumors, I believe that evaluation of circulating tumor cells and DNA does show a lot of promise and that the analysis will provide yet another way to look for evidence of resistance (Maheswaran 2008; [1.2]).

1.2

Correlation between the Presence of T790M Mutations in Tumor-Biopsy Specimens and Decreased Progression-Free Survival among Patients with NSCLC



No. at Risk

T790M-negative	16	15	11	7	2	2	2	1
T790M-positive	10	7	1	0				

	T790M-positive	T790M-negative	*p*-value
Median PFS	7.7 months	16.5 months	<0.001

"Molecular analysis of circulating tumor cells from the blood of patients with lung cancer offers the possibility of monitoring changes in epithelial tumor genotypes during the course of treatment."

SOURCE: With permission from Maheswaran S et al. *N Engl J Med* 2008;359(4):366-77.

A LANDMARK STUDY: IPASS

DR MOK: IPASS was a randomized trial conducted in Asia comparing gefitinib to carboplatin/paclitaxel for patients with pulmonary adenocarcinoma who were nonsmokers or oligosmokers. It had two clear populations of patients: those with EGFR mutation-positive disease and those with EGFR mutation-negative disease. The key feature of this clinical trial was that we were able to obtain sufficient tumor samples from 261 patients, or 60 percent. In this population, we reported a high objective response rate of about 70 percent for patients treated with gefitinib. The response rate was only 1.1 percent for patients with EGFR mutation-negative disease (Fukuoka 2009; [1.3]). The hazard ratio was 0.48 for mutation-positive disease and 2.85 for mutation-negative disease, indicating that it was hazardous for patients with EGFR mutation-negative disease to receive first-line gefitinib (Fukuoka 2009; [1.4]). Now that we've learned the importance of the EGFR mutation, I believe future studies should primarily be driven by mutation status.

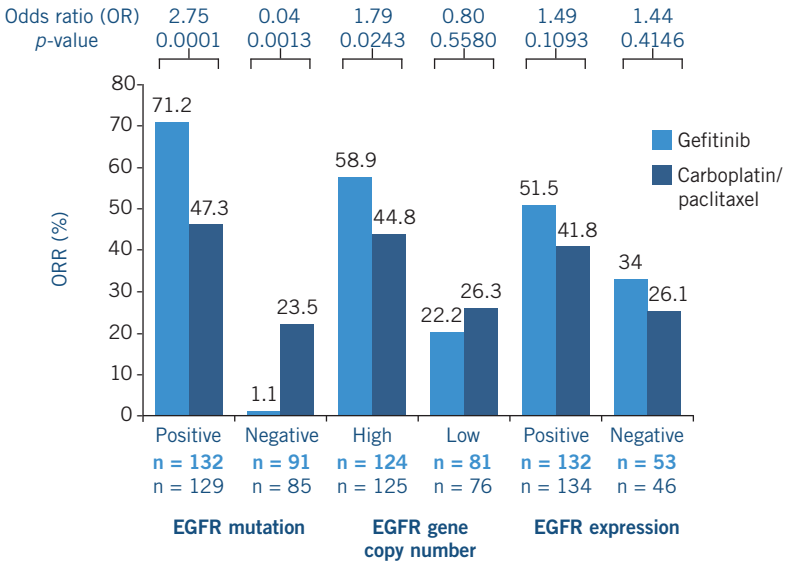
DR LOVE: Tom, which patients do you believe should undergo mutation

testing in clinical practice outside of a protocol setting?

DR LYNCH: I believe it would be important to order a test for a patient

1.3

IPASS Data: Objective Response Rate (ORR) by Treatment and Biomarker Status



OR > 1 implies greater chance of response to gefitinib; intent-to-treat population

SOURCE: Fukuoka M et al. *Proc ASCO* 2009;**Abstract 8006**.

1.4

IPASS Data: Progression-Free Survival (PFS) by Biomarker Status

	N	PFS hazard ratio*	*p*-value	PFS interaction by subgroup†
EGFR mutation status				
Mutation-positive	261	**0.48**	<0.0001	
Mutation-negative	176	**2.85**	<0.0001	<0.0001
Mutation-unknown	780	0.68	<0.0001	
EGFR gene copy number				
FISH-positive	249	0.66	0.0050	
Mutation-positive	190	**0.48**	—	
Mutation-negative	55	**3.85**	—	
FISH-negative	157	1.24	0.2368	0.0437
FISH-unknown	811	0.70	<0.0001	

* Hazard ratio (HR) < 1.0 favors gefitinib
† HR for positive biomarker versus HR for negative biomarker

SOURCE: Fukuoka M et al. *Proc ASCO* 2009;**Abstract 8006**.

with adenocarcinoma who is a light smoker or never smoker — a patient who you believe has a significant risk of harboring a mutation. Criteria should be broadened in the scope of a clinical trial, but outside of a trial I'd limit them to that.

PROF SORIA: I will argue that the European situation is a little different because we have approval for gefitinib in any line, based on the mutation. With the evolution of the technology, you should order mutation testing for every patient.

DR LOVE: Tom, does that mean you generally use erlotinib or an EGFR TKI up front as opposed to chemotherapy or chemotherapy with a biologic agent?

DR LYNCH: I've been doing this for a couple of years, so it won't completely change what I do. But I believe Tony's data should make people feel comfortable using a first-line EGFR TKI, be it erlotinib or gefitinib.

I believe a key question arises when you can't perform the test — when no tissue is available, for example. I still tend to use chemotherapy in that setting. One practice I've learned from Dr Mok's study is that if I don't have the mutation information, even if I have a woman from Tokyo who's a never smoker, I now use chemotherapy in that setting.

DR SCHILLER: I believe it should depend on your level of clinical suspicion, even though you might not be able to prove it.

DR MOK: In Hong Kong diagnoses are often made by cytology. One of the criteria we evaluate is how large the tumor load is. I would probably prefer chemotherapy in the possibility of an imminent problem. But if the patient has multiple small nodules and is not short of breath, we can have weeks or months to wait and see. Then I may lean more toward the use of TKIs. So the clinical situation may also change my decision.

DR LOVE: Vince, at this point, does any role exist currently or in the future for FISH or IHC?

DR MILLER: I don't see a role for these presently. If you consider the IPASS data, and evaluate the patients with EGFR mutations versus those with no mutations, this is surely the best indicator of treatment response (1.3). ■

SELECT PUBLICATIONS

Arcila ME et al. **Rebiopsy of patients (pts) with acquired resistance to epidermal growth factor tyrosine kinase inhibitors (EGFR-TKIs) in non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;**Abstract 8025**.

Engelman JA, Jänne PA. **Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer.** *Clin Cancer Res* 2008;14(10):2895-9.

Engelman JA et al. **MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling.** *Science* 2007;316(5827):1039-43.

Fukuoka M et al. **Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib vs carboplatin/paclitaxel in clinically selected patients with advanced non-small cell lung cancer in Asia (IPASS).** *Proc ASCO* 2009;**Abstract 8006**.

Maheswaran S et al. **Detection of mutations in EGFR in circulating lung-cancer cells.** *N Engl J Med* 2008;359(4):366-77.

Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009;361(10):947-57.

Sequist LV et al. **First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations.** *J Clin Oncol* 2008;26(15):2442-9.

Yung TK et al. **Single-molecule detection of epidermal growth factor receptor mutations in plasma by microfluidics digital PCR in non-small cell lung cancer patients.** *Clin Cancer Res* 2009;15(6):2076-84.

IDENTIFICATION OF NOVEL TARGETS AND AGENTS

EML4-ALK AND PF-02341066

DR LOVE: Vince, would you talk about the EML4-ALK fusion oncogene?

DR MILLER: ALK fusions in lung cancer are translocations that result in fusion genes, analogous to BCR-ABL. Multiple partners exist for the ALK protein, and the most common in lung cancer appears to be EML4, but nearly all the fusion proteins seem to involve the kinase domain, so they should be susceptible to kinase inhibition. This fusion involves the anaplastic lymphoma kinase — ALK — fused to the echinoderm microtubule-associated protein like 4 — EML4.

This phenomenon was first described two years ago. That's impressive because we've now built enough momentum in the field to be using this diagnostic marker and an active agent in trials. It took us five years to get the EGFR story to prime time.

Early data suggest that EML4-ALK may not be prognostic as EGFR mutations are. Similar to EGFR mutations, they appear to be essentially exclusive of K-ras mutations.

One of the ways we believe we can enrich a population for detecting this abnormality is to test the subgroup of patients who do not have EGFR and K-ras mutations and are never smokers. The incidence of EML4-ALK fusions in that patient population can be as high as 25 percent, as reported by Dr Shaw's group (Shaw 2009). In the initial papers, the frequency was reported to be about four or five percent among patients with adenocarcinomas (Horn 2009).

DR LYNCH: The recent publication by Alice Shaw evaluated about 150 patients at Massachusetts General Hospital and reported on clinical characteristics and treatment outcomes of patients with NSCLC and EML4-ALK fusions. They tend to be men, never smokers and younger (Shaw 2009; [2.1]).

DR MILLER: Eunice Kwak recently presented results with the investigational drug PF-02341066, which is not yet approved for lung cancer. This drug is an inhibitor of both MET and ALK, which is not necessarily characteristic of all agents in that class.

The trial began with unselected accrual of patients with differing histologies, diseases and histories and was then specified to include a cohort of patients with lung cancer and this ALK fusion.

To summarize the clinical and pathologic characteristics, patients in this trial tended to be former smokers or never smokers, and the majority had adenocarcinomas. Many patients had heavily pretreated disease.

The overall response rate was 53 percent (Kwak 2009; [2.2]), so this is a treatable target. We now routinely perform a FISH test for EML4-ALK at Memorial. And a Phase III trial of PF-02341066 is now recruiting patients with lung tumors and the EML4-ALK fusion oncogene (2.3).

2.1

Demographic Features of Patients by EML4-ALK and EGFR Mutation

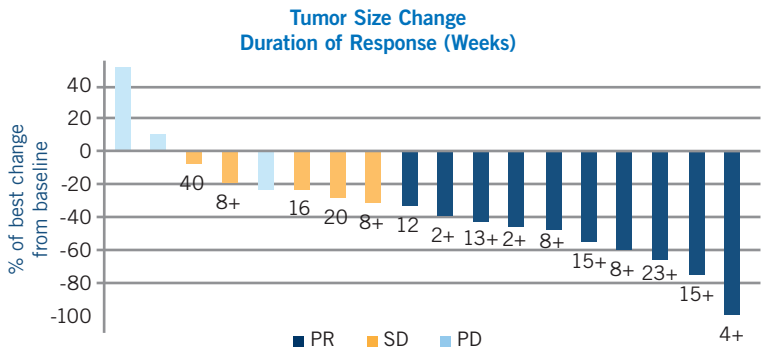
Characteristic	ALK+ (n = 19)	EGFR+ (n = 31)	ALK WT/WT*
Mutation-positive†	13%†	22%†	65%†
Age (median)	52 y	66 y	64 y
Male gender	58%	26%	32%
Never smoker	74%	68%	26%
Light smoker	26%	19%	16%
Smoker	0%	13%	57%

* ALK wild type/EGFR wild type
† ALK mutant tumors were nonoverlapping with EGFR mutant tumors.

SOURCE: Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

2.2

Tumor Response to PF-02341066 in 19 Patients with Pretreated NSCLC and ALK Fusion Oncogenes



One patient had clinical progression and discontinued without radiographic confirmation.

- PF-02341066, a selective ATP competitive oral inhibitor of MET and ALK kinases
  Overall response rate: 53%
  Disease control rate at 8 weeks: 79%

PR = partial response; SD = stable disease; PD = progressive disease

SOURCE: With permission from Kwak EL et al. *Proc ASCO* 2009;**Abstract 3509**.

DR LOVE: Joan, should oncologists in practice be considering the ALK fusion assays for their patients?

DR SCHILLER: It's exciting, but I believe we need to wait for clinical trial results.

PROF SORIA: Yes, and the Phase III trial that recently began recruiting patients is an extremely intelligently designed trial and will allow worldwide recruitment.

Patients will be randomly assigned to PF-02341066 or chemotherapy (2.3), but patients on the chemotherapy arm who experience disease progression will be able to cross over and receive PF-02341066. ■

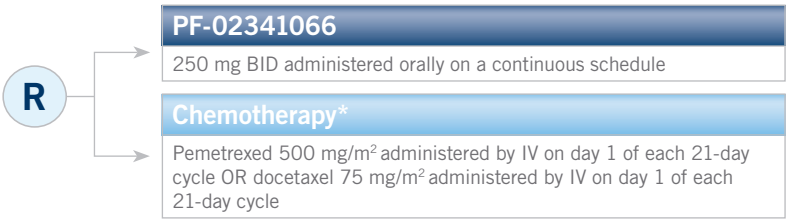
2.3

Phase III, Randomized, Open-Label Study of the Efficacy and Safety of PF-02341066 versus Standard Chemotherapy* for Patients with NSCLC Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus

Protocol ID: NCT00932893
Target Accrual: 318 (Open)

Eligibility

- Histologically or cytologically proven NSCLC
- Positive test results for the ALK fusion gene
- Disease progression after only one prior chemotherapy regimen that included one platinum agent
- No prior PF-02341066 treatment



* Investigator selection of pemetrexed or docetaxel

SOURCE: **www.clinicaltrials.gov**.

SELECT PUBLICATIONS

Horn L, Pao W. **EML4-ALK: Honing in on a new target in non-small-cell lung cancer.** *J Clin Oncol* 2009;27(26):4232-5.

Kwak EL et al. **Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066.** *Proc ASCO* 2009;**Abstract 3509**.

Shaw AT et al. **Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK.** *J Clin Oncol* 2009;27(26):4247-53.

Takahashi T et al. **Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene.** *Ann Surg Oncol* 2009;[Epub ahead of print].

TISSUE BIOMARKERS AND DECISIONS ABOUT SYSTEMIC THERAPY FOR ADVANCED NSCLC

DR LOVE: Vince, you were part of the faculty panel for our recent *Lung Cancer Update* Think Tank, which identified some tissue-based algorithms for NSCLC (3.1). Would you elaborate on some of the related issues?

DR MILLER: The identification of EGFR tyrosine kinase domain mutations in lung adenocarcinomas and their profound association with sensitivity to EGFR TKIs has revolutionized how we think about NSCLC. In the United States, we see about 60 percent adenocarcinomas, and about three in 10 patients have squamous cell carcinoma.

We ask all of our patients to bring 15 unstained slides or a pathology block, and we test for EGFR and K-ras mutations. For individuals with EGFR mutations, I consider EGFR TKI therapy initially. Chemotherapy may have a role for these patients, as suggested by work in the TRIBUTE study (Herbst 2005). This is not a standard approach, but it is a consideration in some settings. If the individual has K-ras mutations, I proceed with cytotoxic chemotherapy.

DR MILLER: For individuals without demonstrable EGFR and K-ras mutations, we now reflexively test for ALK FISH, looking for fusion partners of the ALK gene on the basis of the Kwak and Shaw data on the high efficacy of a kinase inhibitor for this fusion protein in appropriate patients with NSCLC. Individuals with positive test results for this marker are referred for a clinical trial (2.3, page 11). Patients with negative test results proceed to the chemotherapy/biologic leg of the algorithm.

The tough situation lies with those patients for whom no slides are available. If an individual has a low tumor burden and is relatively asymptomatic, we may consider rebiopsy. If rebiopsy is not considered — perhaps the patient's tumor burden is too high and he or she needs therapy quickly or the individual has declined additional biopsy — then the question in my mind is whether this patient is eligible to receive bevacizumab. I tend to use the more relaxed criteria to determine bevacizumab eligibility, which include patients with previously treated brain metastases, those receiving low-molecular-weight heparin and perhaps even extrathoracic or peripheral squamous cell tumors, although the latter is uncommon. For patients who are bevacizumab eligible, I typically administer bevacizumab with either cisplatin or carboplatin, often with pemetrexed also. Those patients who are ineligible for bevacizumab receive cisplatin or carboplatin with pemetrexed.

DR LOVE: Jean-Charles, another part of the algorithm I'm curious about relates to the use of chemotherapy/bevacizumab for patients who are bevacizumab eligible.

Based on the FLEX study results, some people believe chemotherapy/cetuximab should also be a consideration for such patients. What are your thoughts?

PROF SORIA: Currently bevacizumab is approved in both North America and Europe, and I believe it is a reasonable option. The FLEX data show an overall survival benefit in all histologies (Pirker 2009; [3.2]). In Europe we are awaiting appeal of the initial regulatory rejection of cetuximab.

DR LYNCH: I believe cetuximab works, and it works with chemotherapy. However, for the patient who is eligible for bevacizumab, I will continue to administer bevacizumab until I have more evidence. I believe cetuximab is a drug waiting desperately for a biomarker to identify whom to administer it to or for a way to select those patients who will benefit.

We need to find out which patients benefit, and we don't know that yet (Khambata-Ford 2008).

3.1

A Tissue Biomarker "Algorithm" for Advanced NSC

Editor: After reviewing relevant recent data sets, our 2009 clinical investigator think tank identified these treatment strategies (and others) as reasonable current first-/second-line options. *(Faculty: Thomas J Lynch Jr, MD (co-chair), F Anthony Greco, MD, John Heymach, MD, Rogerio C Lilenbaum, MD, Vincent A Miller, MD, Ronald B Natale, MD, Harvey I Pass, MD, Mark A Socinski, MD)*

	Rx	Tissue considerations
	Plat/TaxGemVin	—
	Plat/TaxGemVin >>> Pem	Nonsquamous
	Plat/Pem	Nonsquamous
	Plat/Pem >>> Pem	Nonsquamous
BIOLOGICS	Plat/TaxGemVinPem >>> TKI	Nonsquamous (? EGFR mutation)
BIOLOGICS	Plat/TaxGemVin/Cetux	? IHC, FISH EGFR+
BIOLOGICS	Plat/TaxGemVin/Cetux >>> Cetux	? IHC, FISH EGFR+
BIOLOGICS	Plat/TaxGemVinPem/Bev	Bev eligible
BIOLOGICS	Plat/TaxGemVin/Bev >>> Bev	Bev eligible
BIOLOGICS	Plat/TaxGemVin/Bev >>> Bev/TKI	Bev eligible, EGFR mutation
BIOLOGICS	Plat/Pem/Bev >>> Bev	Bev eligible
BIOLOGICS	Plat/Pem/Bev >>> Pem/Bev	Bev eligible
BIOLOGICS	EGFR TKI	EGFR mutation
BIOLOGICS	MET/ALK inhibitor trial	ALK fusion

Plat = cisplatin or carboplatin; TaxGemVin = taxane, or gemcitabine or vinorelbine; >>> = maintenance (immediate second-line) treatment; Pem = pemetrexed; TKI = erlotinib, gefitinib; Cetux = cetuximab; Bev = bevacizumab; Bev eligible = nonsquamous, no hemoptysis or untreated brain mets

SOURCE: Research To Practice. 2009 Clinical Investigator Think Tank Meeting. Available at: **www.ResearchToPractice.com/LCUTT109**.

DR LOVE: Vince, how do you evaluate the benefits of chemotherapy/bevacizumab versus chemotherapy/cetuximab?

DR MILLER: For a patient who's eligible for both, I believe the primary factor is the somewhat more robust survival benefit in the United States-performed trial ECOG-E4599 of chemotherapy/bevacizumab (Sandler 2006; [3.3]). ■

3.2

FLEX: Outcomes for Patients with EGFR-Expressing Advanced NSCLC Treated with Cisplatin/Vinorelbine (CV) with or without Cetuximab as First-Line Therapy

Efficacy	CV + cetuximab	CV	Hazard ratio (95% CI)	*p*-value
Median overall survival				
All patients	11.3 mo	10.1 mo	0.871 (0.762-0.996)	0.044
Caucasians	10.5 mo	9.1 mo	0.803 (0.694-0.928)	0.003
Progression-free survival	4.8 mo	4.8 mo	0.943 (0.825-1.077)	NS
Time to treatment failure	4.2 mo	3.7 mo	0.860 (0.761-0.971)	0.015

CI = confidence interval; NS = not significant

SOURCE: Pirker R et al. *Lancet* 2009;373(9674):1525-31.

3.3

ECOG-E4599: Overall and Progression-Free Survival of Patients with Previously Untreated Metastatic Nonsquamous NSCLC Treated with Bevacizumab (B) in Combination with Paclitaxel (P) and Carboplatin (C)

Endpoint	PC (n = 433)	PCB (n = 417)	HR	*p*-value
Median OS	10.3 mo	12.3 mo	0.79	0.003
Two-year OS	15%	23%	—	—
Median PFS	4.5 mo	6.2 mo	0.66	<0.001
Overall response	15%	35%	—	<0.001

HR = hazard ratio; OS = overall survival; PFS = progression-free survival

"In summary, the addition of bevacizumab to a standard, platin-based, two-agent chemotherapy regimen conferred a significant improvement in overall survival, progression-free survival, and response rate in patients with non-squamous-cell carcinoma and a good performance status. Increased toxic effects, particularly febrile neutropenia and pulmonary hemorrhage, were associated with the addition of bevacizumab. These risks must be considered within the context of the survival benefit conferred by the addition of bevacizumab to standard treatment for non-small-cell lung cancer."

SOURCE: Sandler A et al. *N Engl J Med* 2006;355(24):2542-50.

SELECT PUBLICATIONS

Herbst RS et al. **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* 2005;23(25):5892-9.

Khambata-Ford S et al. **K-ras mutations (mt) and EGFR-related markers as potential predictors of cetuximab benefit in 1st line advanced NSCLC: Results from the BMS099 study.** *J Thorac Oncol* 2008;3(Suppl 4):304.

Lynch T et al. **Overall survival (OS) results from the phase III trial BMS 099: Cetuximab + taxane/carboplatin as 1st-line treatment for advanced NSCLC.** *J Thorac Oncol* 2008;3(Suppl 4):305.

Manegold C et al. **Pemetrexed for the treatment of non-small-cell lung cancer.** *Expert Rev Anticancer Ther* 2009;9(9):1195-209.

Pirker R et al. **Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): An open-label randomised phase III trial.** *Lancet* 2009;373(9674):1525-31.

Sandler AB et al. **Treatment outcomes by tumor histology in Eastern Cooperative Group (ECOG) study E4599 of bevacizumab (BV) with paclitaxel/carboplatin (PC) for advanced non-small cell lung cancer (NSCLC).** Chicago Multidisciplinary Thoracic Oncology Meeting 2008;**Abstract 133**.

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50.

NOVEL BIOMARKERS AND GENOMIC PREDICTORS OF RESPONSE UNDER ACTIVE INVESTIGATION

PREDICTORS OF RESPONSE TO ANTI-ANGIOGENIC THERAPY

DR LOVE: Joan, what is known about predictors of response to bevacizumab?

DR SCHILLER: Clinical data suggest that the angiogenesis pathway is a potentially active target for the treatment of lung cancer.

The Phase III ECOG-E4599 trial reported improvements in response rate, progression-free survival and overall survival for patients with nonsquamous cell carcinoma of the lung treated in the first-line setting with carboplatin/paclitaxel and bevacizumab versus carboplatin/paclitaxel alone (3.3, page 14).

As with the EGFR pathway, one of the big questions now is, which biomarkers, if any, that we have can help guide us in terms of which patients are most likely to derive benefit from these types of therapies?

One current theory involves VEGF polymorphisms or VEGF single nucleotide polymorphisms (SNPs). VEGF polymorphisms may result in variable binding affinity to the receptor, possible altered binding affinity of the targeted agent to the ligand, variations in host response to the anti-angiogenic signals and/or potentially different VEGF levels.

A study presented at ASCO 2009 reported on a pharmacogenetic subset analysis of ECOG-E4599 and whether or not SNPs would predict benefit with bevacizumab. The study goal was to identify potential markers that could be proven in a larger study.

The authors evaluated a number of possible SNPs involving molecules in the angiogenesis pathway, the DNA repair pathway and WNK1 and identified four SNPs that did appear to predict for improved survival of

patients who received bevacizumab on the E4599 study (Zhang 2009; [4.1]).

DR LOVE: Would you comment on what is known about gender and age and response to bevacizumab?

DR SCHILLER: Unplanned subset analysis of ECOG-E4599 by gender showed that women had a greater response rate and progression-free survival if they were on the bevacizumab arm, but it did not show a benefit in overall survival for women (Brahmer 2006). This was puzzling.

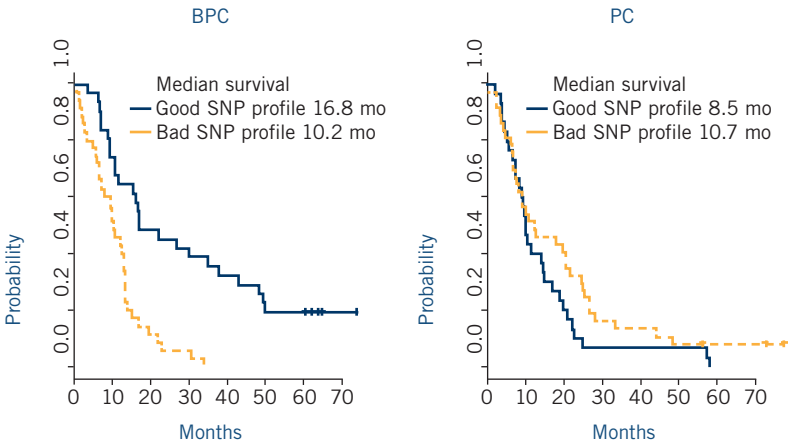
So Dr Heather Wakelee performed another retrospective analysis of patients on the ECOG-E4599 study evaluating age.

It is interesting that women younger than age 60 had a strong survival benefit in this unplanned, retrospective subset analysis, whereas those older than age 60 did not (Wakelee 2008).

This suggests a possible role for age as a surrogate for menopausal status and also some possible estrogen effects.

4.1

ECOG-E4599: SNP Profile as a Predictive Factor for Improved Survival for Patients Treated with Bevacizumab (B) in Combination with Paclitaxel (P) and Carboplatin (C)



- 4 SNPs identified that predicted for better survival:
  - ICAM469 TT & VEGF634 GG
  - ICAM469 ≠ TT & IL8251 ≠ TT

"Although exploratory, our preliminary results suggest germline SNPs in angiogenesis pathway may predict response, PFS and OS in NSCLC pts treated with BPC. Prospective trials based on these correlative studies are warranted."

SOURCE: With permission from Zhang W et al. *Proc ASCO* 2009;**Abstract 8032**.

4.2

Relationship between VEGF Levels and Response to Chemotherapy/Bevacizumab — ECOG-E4599

"Patients with low baseline ICAM (intercellular adhesion molecule) had a higher response rate (32% versus 14%; $P = 0.02$), better overall survival ($P = 0.00005$), and better 1-year survival (65% versus 25%) than those with high ICAM, respectively, regardless of treatment arm.

Patients with high VEGF levels were more likely to respond to BPC compared with PC, but this was not predictive of survival. The results also suggest a benefit from bevacizumab for patients with low baseline ICAM levels (53% reduction in the progression-free survival hazard rate)."

SOURCE: Dowlati A et al. *Clin Cancer Res* 2008;14(5):1407-12.

PREDICTORS OF RESPONSE TO CHEMOTHERAPY

DR LOVE: Jean-Charles, what about tissue predictors of response to chemotherapy in lung cancer?

PROF SORIA: I would say the most robust predictor of response for cisplatin, with in-depth preclinical and retrospective data from multiple clinical trials in different solid tumor types, is ERCC1 (Hsu 2007), but some other factors are also relevant — MSH2, RRM1 and BRCA1. Interest is active in RRM1 as a biomarker for response to gemcitabine, thymidylate synthase as a biomarker for response to pemetrexed and MAPtau and beta-tubulin III as biomarkers of response to paclitaxel and to vinorelbine, although beta-tubulin has been found to be more of a prognostic factor than a predictive one.

Biomarker expression with K-ras, EGFR or ERCC1 is discordant between the primary tumor and its corresponding metastasis in about one third of patients with NSCLC (Gomez-Roca 2009). This is different from breast and colorectal cancer, in which K-ras, for instance, is much more in line. ■

SELECT PUBLICATIONS

Brahmer JR et al. **ECOG 4599 phase III trial of carboplatin and paclitaxel ± bevacizumab: Subset analysis of survival by gender.** *Proc ASCO* 2006;**Abstract 7036**.

Dowlati A et al. **Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab — An Eastern Cooperative Oncology Group study.** *Clin Cancer Res* 2008;14(5):1407-12.

Gomez-Roca C et al. **Differential expression of biomarkers in primary non-small cell lung cancer and metastatic sites.** *J Thorac Oncol* 2009;[Epub ahead of print].

Hsu DS et al. **Pharmacogenomic strategies provide a rational approach to the treatment of cisplatin-resistant patients with advanced cancer.** *J Clin Oncol* 2007;25(28):4350-7.

Wakelee HA et al. **Increased benefit from bevacizumab (BEV) in younger women with advanced NSCLC on Eastern Cooperative Oncology Group (ECOG) E4599.** Chicago Multidisciplinary Thoracic Oncology Meeting 2008;**Abstract 131**.

Zhang W et al. **Genetic variants in angiogenesis pathway associated with clinical outcome in NSCLC patients (pts) treated with bevacizumab in combination with carboplatin and paclitaxel: Subset pharmacogenetic analysis of ECOG 4599.** *Proc ASCO* 2009;**Abstract 8032**.

POST-TEST

Integration of Tissue Biomarker Assays into Protocol and Nonprotocol Management of Lung Cancer

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In IPASS, first-line gefitinib resulted in a superior _____ compared to carboplatin/paclitaxel for patients who were clinically selected for enrichment of EGFR mutations.**
   a. Overall response rate
   b. Progression-free survival
   c. Overall survival
   d. All of the above
   e. Both a and b

2. **In IPASS, patients with EGFR _____ NSCLC appeared to benefit more from first-line therapy with gefitinib than from carboplatin/paclitaxel.**
   a. Mutation-positive
   b. Mutation-negative
   c. Neither a nor b

3. **Which of the following are clinical and/or pathological characteristics of patients with EML4-ALK mutated NSCLC?**
   a. Mostly with adenocarcinomas, signet-ring cell subtype
   b. Nonoverlapping with EGFR mutation
   c. Younger age
   d. Nonsmoking status or former/light smoking history
   e. All of the above

4. **The investigational drug PF-02341066 is an inhibitor of both MET and ALK.**
   a. True
   b. False

5. **In ECOG-E4599, which chemotherapy agents were combined with bevacizumab as first-line therapy for advanced NSCLC?**
   a. Paclitaxel/carboplatin
   b. Docetaxel/carboplatin
   c. Gemcitabine/cisplatin
   d. None of the above

6. **In ECOG-E4599, the addition of bevacizumab to first-line chemotherapy in patients with advanced nonsquamous NSCLC resulted in significant improvements in _____.**
   a. Overall response
   b. Progression-free survival
   c. Overall survival
   d. All of the above

7. **In a pharmacogenetic subset analysis of E4599, four single-nucleotide polymorphisms (SNPs) were identified that predicted for improved survival for patients who received bevacizumab in addition to chemotherapy.**
   a. True
   b. False

8. **In an unplanned subset analysis of E4599, women who were younger than age 60 and received bevacizumab experienced a significant survival advantage compared to older women, suggesting a potential interaction between anti-angiogenic therapy and the estrogen pathway.**
   a. True
   b. False

9. **The Phase III, randomized, open-label study for patients with NSCLC harboring a translocation or inversion involving the ALK gene locus will evaluate investigator selection of chemotherapy with _____ versus PF-02341066.**
   a. Cetuximab
   b. Docetaxel
   c. Pemetrexed
   d. Either a or b
   e. Either b or c

10. **Which of the following are purported mechanisms of resistance to EGFR TKIs?**
    a. T790M mutation
    b. MET amplification
    c. IGF-IR activation
    d. All of the above
    e. None of the above

Post-test answer key: 1e, 2a, 3e, 4a, 5a, 6d, 7a, 8a, 9e, 10d

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Integration of Tissue Biomarker Assays into Protocol and Nonprotocol Management of Lung Cancer

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Practical application of EGFR mutation testing in the community	4 3 2 1	4 3 2 1
Mechanisms of resistance to EGFR TKIs	4 3 2 1	4 3 2 1
Clinical features of patients with NSCLC who harbor EML4-ALK fusions and their response to an oral c-Met and ALK inhibitor	4 3 2 1	4 3 2 1
Predictors of response to bevacizumab in NSCLC	4 3 2 1	4 3 2 1
Biomarkers of response or resistance to chemotherapeutic agents in NSCLC	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Identify somatic gene mutations that may be utilized to predict lung tumor response or resistance to EGFR-directed therapy . . . . . 4 3 2 1 N/M N/A
- Incorporate clinical and molecular biomarkers into the selection of optimal treatment strategies for patients with advanced non-small cell lung cancer (NSCLC). . . . . 4 3 2 1 N/M N/A
- Recognize the role of target population enrichment in the tailored investigation of biologic therapy for localized and metastatic lung cancer . . . . . 4 3 2 1 N/M N/A
- Explain how tumor histology and/or receptor expression profile may affect chemotherapy sensitivity . . . . . 4 3 2 1 N/M N/A
- Apply the results of emerging research to refine the use of anti-angiogenic agents in the treatment of NSCLC . . . . . 4 3 2 1 N/M N/A
- Recall the design and eligibility criteria for ongoing clinical trials in NSCLC, and counsel appropriate patients for study participation . . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Thomas J Lynch Jr, MD	4 3 2 1	4 3 2 1
Vincent A Miller, MD	4 3 2 1	4 3 2 1
Tony SK Mok, MD	4 3 2 1	4 3 2 1
Joan H Schiller, MD	4 3 2 1	4 3 2 1
Jean-Charles Soria, MD, PhD	4 3 2 1	4 3 2 1
Bryan P Schneider, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name: ..... Specialty: .....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

Medical License/ME Number: ..... Last 4 Digits of SSN (required): .....

Street Address: ..... Box/Suite: .....

City, State, Zip: .....

Telephone: ..... Fax: .....

Email: .....

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.

WCLC09

Lung Cancer™ UPDATE

Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: DrNeilLove@ResearchToPractice.com
For CME/CNE Information	Email: CE@ResearchToPractice.com

Lung Cancer™ UPDATE

This program is supported by an educational grant from
Genentech BioOncology & OSI Oncology.

Research
To Practice®

Sponsored by Research To Practice.

Last review date: December 2009
Release date: December 2009
Expiration date: December 2010
Estimated time to complete: 3 hours