LCU | 2010 VOL 7 | ISSUE 2

Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Mark A Socinski, MD
Lecia V Sequist, MD, MPH
Eunice L Kwak, MD, PhD
F Anthony Greco, MD

EDITOR

Neil Love, MD

CME Certified

Subscribe to Podcasts or download MP3s of this program at ResearchToPractice.com/LCU210

Lung Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Lung cancer is the leading cause of cancer mortality in the United States for 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 of it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on long-term outcomes. However, the advent of biologic agents in lung cancer has led to recent improvements in disease-free and overall survival in select patient populations. 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 expert perspectives, this CME program is designed to assist medical oncologists and radiation oncologists with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Identify distinct subtypes of adenocarcinoma of the lung, including those with EGFR mutations and EML4-ALK gene fusions, and the investigational and approved treatment options for patients with these conditions.
- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible EGFR TKIs.
- Summarize controversies in the treatment of Stage III non-small cell lung cancer (NSCLC).
- Formulate individualized treatment plans addressing first-line therapy for recurrent or progressive NSCLC, considering unique patient and tumor characteristics.
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions.
- Counsel appropriately selected patients with lung cancer about participation in ongoing clinical trials.

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 both audio and print components. To receive credit, the participant should review the CME information, listen to the CDs, review the monograph 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/LCU210** 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 educational grants from Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc and Genentech BioOncology & OSI Oncology.

Last review date: September 2010; Release date: September 2010; Expiration date: September 2011

TABLE OF CONTENTS

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 — **Dr Kwak** had no real or apparent conflicts of interest to disclose. 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 Socinski** — Data and Safety Monitoring Board: Bayer HealthCare Pharmaceuticals; Paid Research: Abraxis BioScience, Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, Lilly USA LLC, Pfizer Inc; Speakers Bureau: Genentech BioOncology, GlaxoSmithKline, Lilly USA LLC, Sanofi-Aventis. **Dr Sequist** — Advisory Committee: Bristol-Myers Squibb Company; Consulting Agreement: Telik Inc. **Dr Greco** — Advisory Committee: Amgen Inc, Lilly USA LLC.

EDITOR — 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, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, Lilly USA LLC, Millennium Pharmaceuticals Inc, Monogram BioSciences Inc, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Spectrum Pharmaceuticals Inc.

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 grantors.

INTERVIEW

Mark A Socinski, MD

Dr Socinski is Professor of Medicine of the Multidisciplinary Thoracic Oncology Program at UNC's Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Tracks 1-17

Select Excerpts from the Interview

Tracks 7, 17

DR LOVE: How do you generally manage patients with advanced non-small cell lung cancer (NSCLC) and EGFR tumor mutations?

DR SOCINSKI: I am impressed with the IPASS trial findings (Mok 2009; [1.1]) and the recent CALGB data (Jänne 2010; [1.2]) in first-line sytemic treatment of advanced lung cancer positive for EGFR mutation, demonstrating the advantage of using an upfront EGFR TKI such as erlotinib without chemotherapy.

In IPASS, the rate of EGFR mutation was 60 percent in never or light smokers. As enthusiastic as we are about IPASS, one question that arose in the community was whether these data reflect the US population because the study population is Asian.

The CALGB-30406 data represent a mostly Caucasian population, and the incidence of EGFR mutation is close to 40 percent.

Although this is not as high as in IPASS, it is high enough that one should test for these mutations in nonsmokers, light smokers or former smokers. The incidence of the mutation is inversely related to smoking exposure.

In my practice, we evaluate EGFR mutation status in patients with advanced disease who have tumors with nonsquamous histology and a 40 pack-year or less smoking history. With this approach, we may not identify all tumors with EGFR mutations, but one must establish some criterion for testing, and that's our approach.

The ongoing RADIANT trial is evaluating erlotinib in the adjuvant setting, but it may be a long time before the results are available.

1.1

IPASS: A Phase III Randomized Trial of Gefitinib versus Carboplatin/Paclitaxel as First-Line Therapy for Clinically Selected (Asian, Nonsmokers or Former Light Smokers, Adenocarcinoma) Patients with Advanced Non-Small Cell Lung Cancer

Progression-free survival (Events)	Gefitinib	Carboplatin + paclitaxel	Hazard ratio* (95% CI)	*p*-value
Intent-to-treat population (n = 609; 608)	74.4%	81.7%	0.74 (0.65-0.85)	<0.001
EGFR mutation-positive (n = 132; 129)	73.5%	86.0%	0.48 (0.36-0.64)	<0.001
EGFR mutation-negative (n = 91; 85)	96.7%	82.4%	2.85 (2.05-3.98)	<0.001

* Hazard ratio < 1.0 favors gefitinib; CI = confidence interval

"The presence of an EGFR mutation was a robust predictor of improved progression-free survival with gefitinib, as compared with carboplatin-paclitaxel, and of the benefit of gefitinib with respect to the objective response rate, indicating that patients in whom an EGFR mutation has been identified will benefit most from first-line therapy with gefitinib.

Whenever possible, EGFR-mutation should be determined before the initial treatment of pulmonary adenocarcinoma."

Mok TS et al. *N Engl J Med* 2009;361(10):947-57.

1.2

CALGB-30406: Efficacy of Single-Agent Erlotinib (E) or Erlotinib with Carboplatin/Paclitaxel (ECP) in Never Smokers or Former Light Smokers with Advanced Lung Adenocarcinoma

Endpoint	E	ECP
Progression-free survival (n = 81, 100) EGFR mutant vs wild type*	6.7 mo 15.7 vs 2.7 mo $p < 0.0001$	6.6 mo 17.2 vs 4.8 mo $p < 0.0001$
Overall survival (n = 81, 100) EGFR mutant vs wild type*	24.3 mo 31.3 vs 18.1 mo $p = 0.0093$	19.6 mo 39.0 vs 13.7 mo $p = 0.0012$
Response rate (n = 81, 100) EGFR mutant vs wild type*	35% 67% vs 9% $p < 0.0001$	48% 73% vs 33% $p = 0.0004$

* E arm: n = 33 EGFR mutant, n = 44 EGFR wild type; ECP arm: n = 33 EGFR mutant, n = 54 EGFR wild type

"E and ECP have similar efficacy, but E is less toxic, in predominantly Caucasian never smokers with advanced NSCLC. *EGFR* mutations identify patients most likely to benefit from E and ECP."

Jänne PA et al. Presentation. ASCO 2010;**Abstract 7503**.

Tracks 12-16

DR LOVE: Can you discuss data you presented at ASCO on nanoparticle albumin-bound (*nab*) paclitaxel in the front-line treatment of NSCLC?

DR SOCINSKI: In the Phase III study comparing carboplatin/*nab* paclitaxel to carboplatin/paclitaxel, response rates in the *nab* paclitaxel arm were improved according to independent radiologic review (Socinski 2010; [1.3]). In both arms carboplatin was administered every three weeks. In the control arm paclitaxel was administered every three weeks, and in the investigational arm *nab* paclitaxel was administered weekly. Response rates by histology revealed a greater magnitude of benefit in the population with squamous cell NSCLC. Progression-free survival and overall survival results will be available later this year.

Regarding side effects, the major differences are the improved neuropathy and neutropenia on the *nab* paclitaxel arm (Socinski 2010) compared to the paclitaxel arm. I believe this difference in adverse events is real, but it would be difficult to know how much of it is a result of the formulation of *nab* paclitaxel and how much could be attributed to the weekly schedule.

Other benefits with *nab* paclitaxel include the lack of need for premedications and a much shorter infusion time — 30 minutes. In contrast, paclitaxel requires standard premedication, including steroids, and is administered over three hours. This is a real advantage in terms of convenience. I am optimistic that this is a more biologically potent way to administer a drug that has activity in breast, lung, ovarian and other types of cancer.

DR LOVE: What do we know about combining *nab* paclitaxel with bevacizumab?

DR SOCINSKI: A Phase II trial with a three-weekly schedule of carboplatin, *nab* paclitaxel and bevacizumab was published recently (Reynolds 2009; [1.4]). The response rates and other outcome measures are highly favorable. In view of these Phase II data — even in the absence of Phase III data — I personally would not hesitate to use it. ■

1.3

Efficacy of Carboplatin/*Nab* Paclitaxel versus Carboplatin/Paclitaxel as First-Line Therapy for Advanced Non-Small Cell Lung Cancer

Response by independent review	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
Response rate — **all patients**	25% (n = 531)	33% (n = 521)	1.31	0.005
Response rate — **squamous histology**	24% (n = 221)	41% (n = 228)	1.67	<0.001
Response rate — **nonsquamous histology**	25% (n = 310)	26% (n = 292)	—	0.808

* Response ratio > 1 favors *nab* paclitaxel

Socinski MA et al. Presentation. ASCO 2010;**Abstract LBA7511**.

1.4

Efficacy of Carboplatin/*Nab* Paclitaxel/Bevacizumab in a Phase II Study in Advanced Nonsquamous Non-Small Cell Lung Cancer (N = 48)

Response rate	Stable disease	Progression-free survival	Overall survival
31%	54%	9.8 months	16.8 months

Reynolds C et al. *J Thorac Oncol* 2009;4(12):1537-43.

SELECT PUBLICATIONS

Gazdar AF. **Personalized medicine and inhibition of EGFR signaling in lung cancer.** *N Engl J Med* 2009;361(10):1018-20.

Jänne PA et al. **Randomized phase II trial of erlotinib alone or in combination with carboplatin/paclitaxel in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406.** Presentation. ASCO 2010;**Abstract 7503**.

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

Reynolds C et al. **Phase II trial of nanoparticle albumin-bound paclitaxel, carboplatin, and bevacizumab in first-line patients with advanced non-squamous non-small cell lung cancer.** *J Thorac Oncol* 2009;4(12):1537-43.

Socinski MA et al. **Results of a randomized, phase III trial of *nab*-paclitaxel (*nab*-P) and carboplatin (C) compared with cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** Presentation. ASCO 2010;**Abstract LBA7511**.

INTERVIEW

Lecia V Sequist, MD, MPH

Dr Sequist is Assistant Professor of Medicine at Harvard Medical School and is a medical oncologist at the Center for Thoracic Cancers at Massachusetts General Hospital Cancer Center in Boston, Massachusetts.

Tracks 1-18

Track 1 Activity and tolerability of crizotinib in patients with NSCLC and the EML4-ALK fusion oncogene

Track 2 Assessment of EML4-ALK in clinical practice

Track 3 Erlotinib with the c-Met inhibitor ARQ 197 in advanced K-ras-mutant NSCLC

Track 4 Development of a clinical assay to rapidly perform targeted mutational analysis

Track 5 Tolerability and efficacy of *nab* paclitaxel/carboplatin as first-line therapy for advanced NSCLC

Track 6 CAN-NCIC-BR19: Results of a Phase III study of adjuvant gefitinib in Stage IB to IIIA NSCLC

Track 7 Efficacy, toxicity and quality of life with first-line EGFR TKIs versus chemotherapy for advanced EGFR-mutant NSCLC

Track 8 Mechanisms of resistance to EGFR TKIs and the potential role of irreversible TKIs

Track 9 LUX-Lung 1: A Phase IIb/III study of BIBW 2992 for patients with NSCLC who experience relapse after one or two lines of chemotherapy and erlotinib or gefitinib

Track 10 LUX-Lung 3: A Phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with Stage IIIB or IV NSCLC harboring EGFR mutations

Track 11 LUX-Lung 2: BIBW 2992 for patients with adenocarcinoma of the lung and EGFR mutations

Track 12 **Case discussion:** A 39-year-old woman and never smoker presents with an EGFR-mutant adenocarcinoma of the lung and multiple bone and central nervous system (CNS) metastases

Track 13 Efficacy of EGFR TKIs in patients with CNS metastases from EGFR-mutant NSCLC

Track 14 **Case discussion:** A 55-year-old man who is a smoker with cardiac disease and a prior pulmonary embolism is diagnosed with a Stage IV adenocarcinoma of the lung and achieves a near-complete response to six cycles of carboplatin/paclitaxel

Track 15 Lessons learned from a Gyneco-logic Oncology Group ovarian cancer trial: Role of maintenance bevacizumab after carboplatin/paclitaxel/bevacizumab

Track 16 **Case discussion:** An 86-year-old woman with resected Stage II lung cancer undergoes interventional radiation therapy with cement augmentation for a pathologic fracture of the acetabulum

Track 17 Treatment of advanced NSCLC in elderly patients: Single-agent versus platinum-based combination chemotherapy

Track 18 Effect of early palliative care on quality of life and survival in Stage IV NSCLC

Select Excerpts from the Interview

Track 6

DR LOVE: What are your thoughts on the BR19 trial results of adjuvant gefitinib for patients with Stage IB to IIIA NSCLC that were presented at ASCO this year?

DR SEQUIST: This study by NCI Canada was closed early in April 2005. At ASCO 2010, results after several years of follow-up were presented. No survival benefit was reported among patients who received adjuvant gefitinib versus placebo (Goss 2010). Of most concern with these data was the trend toward possible harm from gefitinib, which was observed to be consistent across different subgroups, including those with EGFR mutations. It's not clear what might cause this apparent detriment.

The number of patients who actually received gefitinib and for what period of time before accrual was halted was not reported. I am not sure what to make of these data, mainly because it wasn't clear how much gefitinib patients received or what might have caused the added toxicity. Although concern remains about using an EGFR TKI in the adjuvant setting, I believe that we still have many questions to answer.

DR LOVE: What ongoing trials are addressing this issue?

DR SEQUIST: I am chairing a Phase II single-arm clinical trial for patients with resected, early-stage NSCLC and EGFR mutations who have the option of chemotherapy and then afterward receive two years of erlotinib (NCT00567359). Also, we are awaiting the results of the RADIANT trial, which is evaluating adjuvant erlotinib versus placebo, but instead of taking "all comers," it requires patients to be positive for EGFR overexpression by either immunohistochemistry or FISH. We hope that in two years we will have an answer, and I am especially interested to see the results among patients with EGFR mutations.

Track 7

DR LOVE: What is your first-line approach for a patient with an EGFR mutation and metastatic disease, considering the recent report from the IPASS study?

DR SEQUIST: The use of an EGFR TKI as first-line therapy for patients with advanced, EGFR-mutant NSCLC is becoming the standard. How this approach affects survival is a topic of much discussion. The survival analysis of the IPASS data is not yet mature, but the progression-free survival curves were impressive as were the better quality-of-life data for patients with EGFR mutations whose disease was treated with gefitinib compared to carboplatin/paclitaxel (Mok 2009; [1.1, page 4]). I believe it to be reassuring for patients

who, even if they don't receive gefitinib in the first-line setting, are likely to gain a similar benefit by receiving gefitinib in the second-line setting.

Tracks 8-11

DR LOVE: What is known about mechanisms of resistance to erlotinib or gefitinib, and do the irreversible EGFR TKIs have a role for those patients?

DR SEQUIST: We know that EGFR TKIs work well for patients with EGFR mutations, but they don't cure the cancer. Most, if not all, patients will develop resistance after an average of 10 to 12 months. More and more major cancer centers have been making an effort to perform biopsies when these patients develop resistance to EGFR TKI therapy to learn more about the mechanisms of resistance.

Two main mechanisms of resistance that have been identified are the T790M mutation and MET amplification. T790M occurs in approximately 50 percent of patients and is another mutation in the EGFR that makes it more difficult for a drug such as gefitinib or erlotinib to bind to the receptor and inhibit it. MET is a parallel pathway to EGFR that gets turned up or amplified to compensate for the blocked EGFR signal. Several drugs in development focus on both of these mechanisms of EGFR TKI resistance.

One such drug is the irreversible dual HER2 and EGFR blocker BIBW 2992. We are awaiting results of the recently completed LUX-Lung 1 study, which randomly assigned patients who developed resistance to EGFR TKIs to BIBW 2992 or placebo.

BIBW 2992 is also being evaluated versus cisplatin/pemetrexed in the front-line setting in the LUX-Lung 3 study, which is enrolling patients in the United States and internationally. This is an important study because chemotherapy has evolved in the period since the IPASS study was developed. Pemetrexed has become a foundation of treatment, especially for patients with adenocarcinoma. So the LUX-Lung 3 study of BIBW 2992 versus cisplatin/pemetrexed is probably a more valid, modern chemotherapy comparison.

DR LOVE: What results have been reported to date with BIBW 2992?

DR SEQUIST: James Yang presented data from the LUX-Lung 2 trial at ASCO 2010, which evaluated BIBW 2992 in patients with TKI-naïve disease and EGFR mutations, and the results were good — a high response rate of approximately 60 percent and time to disease progression of more than one year (Yang 2010; [2.1]).

I believe that the irreversible EGFR TKIs are comparable to the first generation when it comes to patients with TKI-naïve disease. The question is, can they combat resistance?

2.1

LUX-Lung 2 Trial: Efficacy and Best Confirmed Response with BIBW 2992 According to RECIST and Type of EGFR Mutation in Patients with Adenocarcinoma

Survival	First-line therapy	Second-line therapy
Median progression-free survival	14.7 mo	11.8 mo
Median overall survival	NA	23.9 mo

Response*	EGFR mutation type		
	Del 19 + L858R (n = 106)	Other (n = 23)	All (n = 129)
Complete response + partial response	64%	43%	60%
Disease control rate	88%	78%	86%
Progressive disease	6%	13%	7%

* Investigator assessment

Yang C et al. *Proc ASCO* 2010;**Abstract 7521**.

Track 15

DR LOVE: How do you approach the use of bevacizumab in NSCLC?

DR SEQUIST: I try to assess every patient with advanced disease in terms of potentially receiving bevacizumab. The lung community is more hesitant about some of bevacizumab's relative contraindications than is the colon cancer community. One important emerging issue is duration of bevacizumab treatment.

An interesting data set reported at ASCO 2010 in ovarian cancer addressed the role of maintenance bevacizumab after chemotherapy. The ECOG-E4599 study, which established the use of bevacizumab in lung cancer, did not address that issue.

2.2

Maintenance Bevacizumab After Carboplatin/Paclitaxel/Bevacizumab for Patients with Advanced Ovarian Cancer

	Arm I CP (n = 625)	Arm II CP + Bev (n = 625)	Arm III CP + Bev → Bev (n = 623)
Patients with event (%)	67.7	66.9	57.8
Median progression-free survival	10.3 mo	11.2 mo	14.1 mo
Hazard ratio	Reference	0.908	0.717
One-sided *p*-value	Reference	0.080	<0.0001

CP = carboplatin/paclitaxel; Bev = bevacizumab

Burger RA et al. *Proc ASCO* 2010;**Abstract LBA1**.

The Gynecologic Oncology Group trial presented at ASCO evaluated carboplatin/paclitaxel versus carboplatin/paclitaxel/bevacizumab with maintenance bevacizumab versus carboplatin/paclitaxel/bevacizumab without maintenance bevacizumab. The authors reported that bevacizumab maintenance provided a significant benefit (Burger 2010; [2.2]).

Track 18

DR LOVE: What are your thoughts on the presentation by Dr Jennifer Temel at ASCO 2010 on the effect of early palliative care in advanced NSCLC?

DR SEQUIST: Dr Temel hypothesized that integrating palliative care when patients begin receiving chemotherapy for advanced NSCLC might improve quality of life for patients with metastatic lung cancer, which was demonstrated in this study.

However, the real buzz was the improvement in survival, despite the fact that patients on both arms received an equal number of chemotherapy regimens and the palliative care group received less aggressive care at end of life (Temel 2010). The Kaplan-Meier curves appeared similar to what was observed in the ECOG-E4599 study, which evaluated carboplatin/paclitaxel with or without bevacizumab (Sandler 2006).

A couple of factors may have contributed to the improvement in survival, including better treatment of depression, which we know occurs at a high rate in lung cancer and is associated with shorter survival. Additionally, better symptom control and faster recognition and treatment of problems may have played a role.

In the end we can't say what contributed to the survival improvement, but Dr Temel is planning a larger, more definitive study to determine whether these results can be replicated in a multicenter fashion. ■

SELECT PUBLICATIONS

Burger RA et al. **Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study.** *Proc ASCO* 2010;**Abstract LBA1**.

Goss GD et al. **A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinib in completely resected stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19.** *Proc ASCO* 2010;**Abstract LBA7005**.

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

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.

Temel JS et al. **Effect of early palliative care (PC) on quality of life (QOL), aggressive care at the end-of-life (EOL), and survival in stage IV NSCLC patients: Results of a phase III randomized trial.** *Proc ASCO* 2010;**Abstract 7509**.

Yang C et al. **Phase II study of BIBW 2992 in patients with adenocarcinoma of the lung and activating EGFR mutations (LUX-Lung 2).** *Proc ASCO* 2010;**Abstract 7521**.

INTERVIEW

Eunice L Kwak, MD, PhD

Dr Kwak is Assistant in Medicine at Massachusetts General Hospital and Instructor in Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-8

Track 1 Identification of the EML4-ALK fusion oncogene in NSCLC

Track 2 Clinical implications of the IPASS trial results for EGFR mutation testing in clinical practice

Track 3 BIBW 2992 as treatment for patients with EGFR mutations and those resistant to EGFR TKIs

Track 4 Mechanisms of resistance to erlotinib or gefitinib in EGFR-mutant NSCLC

Track 5 **Case discussion:** A 45-year-old woman and never smoker with biopsy-proven recurrent NSCLC who harbors EML4-ALK is enrolled on a clinical trial of the dual ALK/MET inhibitor crizotinib

Track 6 Efficacy, side effects and tolerability of crizotinib

Track 7 Incidence of EML4-ALK in unselected and selected patients with NSCLC

Track 8 Testing for the EGFR mutation and EML4-ALK

Select Excerpts from the Interview

Tracks 1, 5-7

DR LOVE: Would you summarize what we know about EML4-ALK rearrangements in NSCLC?

DR KWAK: Cancer with EML4-ALK rearrangement appears to be independent of cancer with EGFR mutation. In the EGFR-mutant NSCLC population, patients tend to have adenocarcinomas, be women, be of Asian ethnic descent and have a nonsmoking or light smoking history.

Some of those features are also common among patients with ALK rearrangement, in particular the adenocarcinoma histology and the light smoking or nonsmoking history. However, if you examine the gene status of a group of patients chosen phenotypically for those features, you'll find that EGFR mutation, ALK gene rearrangement and K-ras mutation are mutually exclusive in NSCLC (Shaw 2009).

DR LOVE: Would you discuss a patient you treated with the EML4-ALK inhibitor crizotinib (PF-02341066) on a clinical trial?

DR KWAK: I had a 45-year-old patient with no history of smoking who presented with a cough and hemoptysis. A CT scan revealed a 4-cm opacity in the left lower lobe, and biopsy confirmed an adenocarcinoma. She underwent a lobectomy that revealed 21 negative nodes, and she received adjuvant chemotherapy for Stage T2N0M0 NSCLC with wild-type EGFR.

About a year and a half later she developed recurrent disease and began receiving erlotinib. However, within two months of beginning erlotinib treatment, our lab tested her tumor and found ALK rearrangement. She was enrolled on the crizotinib trial and experienced a remarkable response. Prior to receiving this agent, CT had shown a diffuse distribution of tumor across the left side of her lung. At the first restaging, only two months after starting treatment, no disease was visible on a CT scan and she felt well.

Seventeen months later she's still on the trial. She's hiking, doing the things she likes to do and has a high quality of life. It's been rewarding to see patients such as this fare so well on this drug.

DR LOVE: Would you describe how the drug is administered and its tolerability?

DR KWAK: It's an oral drug that's currently administered twice a day at 250 mg. The most common side effects have been mild nausea and some vomiting, some of which can be modified with the intake of a small amount of food (Bang 2010). Other side effects we've seen include lower-extremity edema, fatigue and some visual symptoms. The visual disturbances are described as trails of light that follow objects, especially when people are waking up in the morning or during transitions from dark to light or light to dark.

Some of these patients are experiencing so many symptoms when they join the trial that, despite these side effects, they feel much better overall on the drug because of the improvement in their disease status, and the side effects of the drug seem relatively minor.

We've had some patients develop elevations of alanine transaminase, and in a few patients these increases have been dose limiting. For some, rechallenging with a lower dose can successfully keep the patient on the drug while minimizing the effects on liver function. All the elevated liver function test results have been reversible on withdrawal of the drug.

DR LOVE: What have you seen with regard to efficacy?

DR KWAK: The trial is ongoing so the number of patients receiving the treatment continues to increase, but as of December 2009 approximately 64 patients had received the drug and 50 of them were evaluable for response. At that time the objective response rate was 64 percent and 90 percent of patients had experienced either stable disease or response (Bang 2010; [3.1]). We find that notably few patients experience no response to the drug.

DR LOVE: What proportion of patients with NSCLC do you estimate have the ALK fusion gene, and what are the clinical implications?

3.1

Activity of Crizotinib in a Phase I Study for Patients with ALK-Positive Non-Small Cell Lung Cancer (N = 82)

Parameter		Outcome
Objective response rate (ORR)		57%
Number of prior regimens[1] and ORR	0	80%
	1	52%
	2	67%
	≥3	56%
Disease control rate (DCR) at eight weeks*		87%
Six-month progression-free survival probability[2]		72%

Toxicity: The most frequent adverse events were mild and moderate gastrointestinal events, including nausea (54%) and vomiting (44%), and mild visual disturbances (42%).

* DCR = complete responses + partial responses + stable disease at eight weeks
[1] Unknown for one patient; [2] Median follow-up for progression-free survival: 6.4 months

Bang Y et al. *Proc ASCO* 2010;**Abstract 3**.

DR KWAK: In an unselected NSCLC population, various groups have reported from a little more than one percent to as much as seven percent. Alice Shaw has described a 13 percent incidence of ALK fusion genes in a selected group of patients, particularly those with light smoking or nonsmoking histories and adenocarcinoma histology. In addition, if you exclude patients with EGFR mutations from that group, I believe that the incidence of ALK fusion genes could be as high as 33 percent in nonsmokers.

So if we analyze the genes that seem most likely to be abnormal within this demographically selected population, then I believe it's possible to prospectively identify these patients and administer appropriate therapy.

Although the majority of patients with this gene have light smoking or nonsmoking histories and adenocarcinoma histology, exceptions exist. For example, a few of our patients with ALK positivity had longer than 10-pack-year smoking histories, and although adenocarcinoma is by far the most common histology, one can encounter cases in which the histology is somewhat unclear.

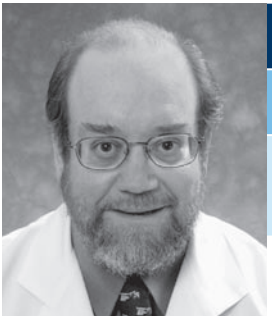
So I believe that if one suspects EML4-ALK positivity, particularly in young patients because that tends to be one of the demographic features, then it's worth testing the tumor. ■

SELECT PUBLICATIONS

Bang Y et al. **Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 3**.

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.

Soda M et al. **Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer.** *Nature* 2007;448(7153):561-6.



INTERVIEW

F Anthony Greco, MD

Dr Greco is Director of the Sarah Cannon Cancer Center in Nashville, Tennessee.

Tracks 1-10

Track 1 IFCT-0501: Carboplatin/paclitaxel versus single-agent therapy for patients age 70 or older with advanced NSCLC

Track 2 Clinical treatment algorithm for elderly patients with advanced NSCLC

Track 3 Perspective on *nab* paclitaxel/carboplatin as first-line therapy for advanced NSCLC

Track 4 A randomized Phase II study of first-line pemetrexed/bevacizumab with either gemcitabine or carboplatin as treatment for elderly patients with advanced NSCLC

Track 5 Activity of vandetanib compared to erlotinib as second- or third-line therapy for advanced NSCLC

Track 6 **Case discussion:** A 45-year-old woman and never smoker with resected Stage IIIA, EGFR wild-type NSCLC without EML4-ALK begins adjuvant chemotherapy with pemetrexed and carboplatin

Track 7 Selection of first-line therapy for patients with advanced EGFR-mutant NSCLC

Track 8 **Case discussion:** A 52-year-old man and heavy smoker undergoes resection of a single brain metastasis from EGFR-mutant NSCLC

Track 9 **Case discussion:** A 65-year-old man and never smoker presents with hepatic metastases from K-ras, EGFR and EML4-ALK wild-type NSCLC with uncertain histology

Track 10 Accuracy of tissue of origin prediction by molecular profiling in patients with unknown primary cancer

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the paper presented at ASCO on the use of a platinum doublet versus single-agent therapy for older patients with advanced NSCLC?

DR GRECO: Whether older patients with advanced NSCLC should receive single agents or combinations has often been a subject of debate, and the clinical trial results have been mixed. Recently, IFCT-0501, a large Phase III European study (Quoix 2010), compared single-agent therapy (gemcitabine or vinorelbine) to a two-drug regimen (paclitaxel weekly and carboplatin every four weeks)

for patients aged 70 to 89 years. The data clearly showed that the combination regimen was superior and was well tolerated overall (4.1), although toxicity was a little higher on the combination therapy arm than on the single-agent arm. I believe it's clear that elderly patients, particularly those without severe comorbidities, need to receive treatment as younger patients would. Many of us have believed this for years, and this study confirms that belief.

4.1

Safety and Efficacy of Combination versus Single-Agent Therapy in Elderly Patients with Advanced Non-Small Cell Lung Cancer

	Single agent (n = 211)	Doublet (n = 210)	*p*-value
Partial response	10.9%	29.1%	$<10^{-5}$
PFS, median	3.0 mo	6.1 mo	$<10^{-6}$
OS, mean	6.2 mo	10.3 mo	0.00004
Hematologic toxicity	(n = 210)	(n = 208)	
Neutropenia	4.7% (G)/37.7% (V)	54.3%	$<10^{-5}$
Febrile neutropenia	0% (G)/9.8% (V)	9.6%	0.004
Thrombocytopenia	1.3% (G)/0% (V)	6.3%	0.004

Single agent = G (gemcitabine) or V (vinorelbine); doublet = weekly paclitaxel and carboplatin q4wk; PFS = progression-free survival; OS = overall survival

Quoix EA et al. *Proc ASCO* 2010;**Abstract 2**.

Track 4

DR LOVE: Would you comment on your randomized Phase II study of pemetrexed, gemcitabine and bevacizumab versus pemetrexed, carboplatin and bevacizumab for elderly patients (Spigel 2010)?

DR GRECO: We noted a significant improvement in time to disease progression and even survival in the Phase II randomized trial in which elderly patients received carboplatin/pemetrexed with bevacizumab for nonsquamous advanced NSCLC (4.2).

DR LOVE: Many investigators utilize the combination of pemetrexed/carboplatin and bevacizumab, but no Phase III data compare that combination to other bevacizumab combinations, such as carboplatin/paclitaxel. What are your thoughts on this?

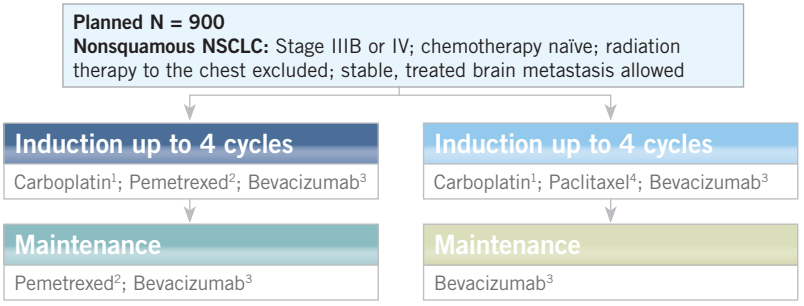
DR GRECO: An ongoing Phase III trial (4.3) is evaluating pemetrexed/carboplatin and bevacizumab versus paclitaxel/carboplatin and bevacizumab, the current standard treatment. The results of that trial should provide more information. My belief is that in disease with nonsquamous histology, pemetrexed/carboplatin and bevacizumab is an easier regimen to use, and I can't imagine it being inferior to paclitaxel/carboplatin and bevacizumab. ■

4.2 Randomized Phase II Study of Pemetrexed/Bevacizumab Combined with Carboplatin (PCB) or Gemcitabine (PGB) for Elderly Patients (≥70 years) with Nonsquamous Advanced Non-Small Cell Lung Cancer

	PCB (n = 211)	PGB (n = 210)	*p*-value
Objective response rate	34.5%	34.5%	—
Median time to progression	10.2 mo	4.7 mo	0.0011
Mean overall survival	14.8 mo	7.5 mo	0.0017

Spigel D et al. *Proc ASCO* 2010;**Abstract 7593**.

4.3 Phase III Study Comparing Carboplatin/Pemetrexed/Bevacizumab Followed by Pemetrexed and Bevacizumab Maintenance versus Carboplatin/Paclitaxel/Bevacizumab Followed by Bevacizumab Maintenance for Patients with Nonsquamous NSCLC



Primary endpoint is overall survival

[1] IV carboplatin is administered at AUC 6 during induction on day 1 every 21 days for up to four cycles; [2] IV pemetrexed is administered at 500 mg/m^2 on day 1 every 21 days for up to four cycles during induction and then as maintenance until disease progression or treatment discontinuation; [3] IV bevacizumab is administered at 15 mg/kg on day 1 every 21 days for up to four cycles during induction and then as maintenance until progressive disease or treatment discontinuation; [4] Paclitaxel is administered at 200 mg/m^2 during induction on day 1 every 21 days for up to four cycles

www.clinicaltrials.gov. Identifier NCT00762034.

SELECT PUBLICATIONS

Le Caer H et al. **A multicenter phase II randomized study of docetaxel/gemcitabine weekly followed by erlotinib after progression versus erlotinib followed by docetaxel/gemcitabine after progression in advanced non-small cell lung cancer in fit elderly patients selected with a comprehensive geriatric assessment. Groupe Français de Pneumocancerologie (GFPC) 0504.** *Proc ASCO* 2010;**Abstract 7536**.

Quoix EA et al. **Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 2**.

Spigel DR et al. **A randomized phase II trial of pemetrexed/gemcitabine/bevacizumab or pemetrexed/carboplatin/bevacizumab in the first-line treatment of elderly patients with advanced non-small cell lung cancer.** *Proc ASCO* 2010;**Abstract 7593**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the IPASS trial, patients with advanced, EGFR wild-type NSCLC who received gefitinib had a significantly improved progression-free survival compared to those who received carboplatin/paclitaxel.**
   a. True
   b. False

2. **In CALGB-30406, comparing single-agent erlotinib (E) to E with carboplatin/paclitaxel (ECP) for never smokers or light former smokers with advanced lung adenocarcinoma, _____.**
   a. Both regimens resulted in similar efficacy
   b. E was less toxic
   c. EGFR mutation status identified patients most likely to benefit from E or ECP
   d. All of the above

3. **Which of the following were observed in a Phase III study of carboplatin/paclitaxel versus carboplatin/*nab* paclitaxel as first-line therapy for advanced NSCLC?**
   a. Response rate was significantly better with carboplatin/*nab* paclitaxel for all patients
   b. Response rate was significantly better with carboplatin/*nab* paclitaxel for patients with squamous disease
   c. Rates of neuropathy and neutropenia were significantly improved with carboplatin/*nab* paclitaxel
   d. All of the above

4. **What is the overall survival in the Phase II study of first-line therapy with carboplatin/*nab* paclitaxel/bevacizumab for advanced nonsquamous NSCLC reported by Reynolds and colleagues?**
   a. 10.8 months
   b. 16.8 months
   c. 21.8 months
   d. 27.8 months

5. **In the LUX-Lung 2 trial, BIBW 2992 resulted in a high degree of efficacy (overall response rate of 43 percent to higher than 60 percent) in both the first- and second-line settings for patients with adenocarcinoma of the lung and activating EGFR mutations.**
   a. True
   b. False

6. **The T790M mutation accounts for approximately _____ percent of acquired resistance to EGFR TKIs.**
   a. 20
   b. 50
   c. 90

7. **In addition to the T790M mutation, MET amplification has been identified as another source of secondary resistance to EGFR TKIs.**
   a. True
   b. False

8. **In a Gynecologic Oncology Group study, carboplatin/paclitaxel and bevacizumab followed by maintenance bevacizumab resulted in a significant improvement in progression-free survival compared to carboplatin/paclitaxel in patients with advanced ovarian cancer.**
   a. True
   b. False

9. **Crizotinib is an oral targeted therapy that inhibits _____.**
   a. EML4-ALK
   b. MET
   c. Both a and b
   d. None of the above

10. **In a Phase I trial of crizotinib for patients with ALK-positive NSCLC, the disease control rate (complete responses, partial responses and stable disease) was _____.**
    a. 14 percent
    b. 33 percent
    c. 87 percent

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 2, 2010

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
Results of a Phase III trial of *nab* paclitaxel and carboplatin compared to Cremophor-based paclitaxel and carboplatin as first-line therapy for advanced NSCLC	4 3 2 1	4 3 2 1
Clinical activity of the oral ALK inhibitor crizotinib in patients with ALK-positive NSCLC	4 3 2 1	4 3 2 1
Results of a Phase III trial of the EGFR inhibitor gefitinib in completely resected Stage IB to IIIA NSCLC	4 3 2 1	4 3 2 1
Clinical trials of the irreversible EGFR/HER2 TKI BIBW 2992 for patients with advanced, EGFR-mutant NSCLC	4 3 2 1	4 3 2 1
Results of the Phase III study IFCT-0501: Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy for patients age 70 to 89 with advanced 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 distinct subtypes of adenocarcinoma of the lung, including those with EGFR mutations and EML4-ALK gene fusions, and the investigational and approved treatment options for patients with these conditions..... 4 3 2 1 N/M N/A
- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible EGFR TKIs..... 4 3 2 1 N/M N/A
- Summarize controversies in the treatment of Stage III non-small cell lung cancer (NSCLC)..... 4 3 2 1 N/M N/A
- Formulate individualized treatment plans addressing first-line therapy for recurrent or progressive NSCLC, considering unique patient and tumor characteristics..... 4 3 2 1 N/M N/A
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with lung cancer about participation in ongoing clinical trials..... 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?

.....

Additional comments about this activity:

.....

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
Mark A Socinski, MD	4 3 2 1	4 3 2 1
Lecia V Sequist, MD, MPH	4 3 2 1	4 3 2 1
Eunice L Kwak, MD, PhD	4 3 2 1	4 3 2 1
F Anthony Greco, 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 .....

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.

LCU210

Lung Cancer™ UPDATE

Lung Cancer™ UPDATE

This program is supported by educational grants from Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc and Genentech BioOncology & OSI Oncology.

Research To Practice®

Sponsored by Research To Practice.

Last review date: September 2010
Release date: September 2010
Expiration date: September 2011
Estimated time to complete: 3 hours