LCU | 2009 VOL 6 | ISSUE 4

# Lung Cancer™ UPDATE

## Conversations with Oncology Investigators
### Bridging the Gap between Research and Patient Care

**EDITOR**

Neil Love, MD

**INTERVIEWS**

Ronald B Natale, MD
Edward S Kim, MD
Jean-Charles Soria, MD, PhD
David M Jackman, MD
Tony SK Mok, MD

CME Certified

# *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

- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible TKIs.
- Summarize completed and ongoing clinical trials for the treatment of extensive small cell lung cancer.
- Develop a risk-adapted algorithm for the individualized use of adjuvant systemic therapy for patients with localized non-small cell lung cancer (NSCLC).
- Appraise the clinical application of emerging data on the combined use of biologic agents with chemoradiation therapy for Stage III NSCLC.
- Formulate individualized treatment plans addressing the first-, second- and third-line management of recurrent or progressive NSCLC, considering patient and tumor characteristics.
- Effectively utilize tumor histology and biomarkers when making evidence-based lung cancer treatment decisions.
- Discuss the rationale for the development of novel agents targeting DNA repair pathways.
- 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/LCU409** 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 Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Genentech BioOncology & OSI Oncology, ImClone Systems Incorporated and Sanofi-Aventis.***

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

# TABLE OF CONTENTS



*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.*

## 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 Jackman** 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 Natale** — Advisory Committee: Amgen Inc; Consulting Agreements: AstraZeneca Pharmaceuticals LP, Lilly USA LLC; Paid Research: Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation; Speakers Bureau: Genentech BioOncology, Lilly USA LLC, OSI Oncology. **Dr Kim** — Advisory Committee: AstraZeneca Pharmaceuticals LP, Genentech BioOncology, ImClone Systems Incorporated, Lilly USA LLC, OSI Oncology, Sanofi-Aventis; Paid Research: AstraZeneca Pharmaceuticals LP, Genentech BioOncology, ImClone Systems Incorporated, Lilly USA LLC, OSI Oncology. **Prof Soria** — 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 Mok** — 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.

**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.

INTERVIEW

## Ronald B Natale, MD

Dr Natale is Medical Oncologist at Cedars-Sinai Outpatient Cancer Center and Senior Research Advisor and Director at the National Lung Cancer Research Program for Aptium Oncology Inc in Los Angeles, California.

### Tracks 1-13

**Track 1** Mutations predictive of response and resistance to EGFR tyrosine kinase inhibitors (TKIs)

**Track 2** BIBW 2992: An irreversible EGFR/HER2 TKI and targeted agent against T790M mutations

**Track 3** JCOG-9511: Superiority of irinotecan/cisplatin versus etoposide/cisplatin for extensive small cell lung cancer (SCLC)

**Track 4** Outcomes with irinotecan/cisplatin for extensive-stage SCLC in two large US-based clinical trials

**Track 5** Current investigational objectives in SCLC

**Track 6** Adjuvant pemetrexed with cisplatin or carboplatin in younger and older patients with Stage II nonsquamous non-small cell lung cancer (NSCLC)

**Track 7** RADIANT: Erlotinib after complete resection with or without adjuvant chemotherapy for patients with Stage IB to IIIA NSCLC and EGFR-positive tumors

**Track 8** Clinical use of adjuvant erlotinib for patients with EGFR-mutant NSCLC

**Track 9** **Case discussion:** A 62-year-old man with locally advanced NSCLC is treated with concurrent cisplatin/pemetrexed and radiation therapy

**Track 10** Feasibility of combining chemotherapy/cetuximab with radiation therapy for locally advanced NSCLC

**Track 11** Clinical use of chemotherapy/cetuximab for patients with advanced NSCLC

**Track 12** A critical appraisal of studies with first-line chemotherapy/bevacizumab for advanced NSCLC

**Track 13** Proposed ECOG trial: First-line carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab, pemetrexed or the combination for advanced NSCLC

## Select Excerpts from the Interview

### Tracks 3-4

**DR LOVE:** Would you summarize the rationale for the study you chaired comparing cisplatin/irinotecan to cisplatin/etoposide for extensive small cell lung cancer (SWOG-S0124)?

**DR NATALE:** Irinotecan is an important agent that belongs to the camptothecin class of drugs. These drugs are potent inhibitors of DNA topoisomerase I

(TOPO I), and unlike many of our chemotherapy drugs that have target and off-target effects, the camptothecins are specific to TOPO I.

Japanese investigators conducted an important Phase III trial, JCOG-9511, comparing cisplatin/irinotecan to cisplatin/etoposide (Noda 2002). In that study, patients who received cisplatin/irinotecan had higher objective response and stable disease rates and an improved median one- and two-year survival.

This improvement in survival was extraordinary — the biggest gain recorded in small cell lung cancer in the past 20 years. Suddenly a new regimen simply substituted irinotecan for etoposide and improved survival by more than 25 to 30 percent.

The response and survival outcomes of the control arm, cisplatin/etoposide, appeared to be the same as those found in the United States cooperative group trials. The median survival was in the range of 9.5 to 10 months, whereas with cisplatin/irinotecan it reached beyond one year, and the difference was highly statistically significant with only 77 patients per arm.

**DR LOVE:** Your study, then, was one of two United States trials that attempted to confirm these data. What were the results?

**DR NATALE:** One was a North American trial in which they changed the dose and schedule of the cisplatin/etoposide regimen to make it more amenable to outpatient treatment in the United States (Hanna 2006). Also, because approximately 40 percent of patients in the Japanese study could not receive the irinotecan on day 15 because of hematologic toxicity, this trial dropped that dose and the combination was administered every three weeks rather than every four weeks.

Patients in the North American study received more platinum and irinotecan than the Japanese were able to deliver. Despite that, no difference was observed in the response rate, median survival or one- or two-year survival between the two study arms. Some differences were apparent with respect to toxicity, but in terms of efficacy it was a negative study.

Our study, SWOG-S0124, was a large Intergroup trial with more than 630 patients. We did not change the dose or schedule from that of the Japanese trial, and still our results were the same as those of the North American study — showing no significant efficacy benefit with cisplatin/irinotecan (Lara 2009; [1.1]).

We also collected blood to perform pharmacogenomic studies, hoping that we could identify a subpopulation of patients in North America who had similar camptothecin metabolic profiles to those of the patients in Japan and would possibly experience an important improvement in response rates and survival outcomes.

However, we were unable to identify a single subgroup based on demographics, patient characteristics or metabolic profile who benefited more from cisplatin/irinotecan than from cisplatin/etoposide.

**1.1**

**SWOG-S0124: A Phase III Trial of Cisplatin/Irinotecan versus Cisplatin/Etoposide in Extensive-Stage Small Cell Lung Cancer**

| | Cisplatin/irinotecan (n = 324) | Cisplatin/etoposide (n = 327) |
|---|---|---|
| Response rate | 60% | 57% |
| Median progression-free survival | 5.7 months | 5.2 months |
| Overall survival | 9.9 months | 9.1 months |

**SOURCE:** Lara PN Jr et al. *J Clin Oncol* 2009;27(15):2530-5.

## Track 11

**DR LOVE:** What is your approach to treating advanced squamous cell lung cancer?

**DR NATALE:** I'm participating in clinical trials that involve antibodies to the IGF-1 receptor. Of note, the emerging data with antibodies across the board show that these drugs don't work well alone. Rather, they need to be combined with chemotherapy.

I see few patients with squamous cell lung carcinoma, perhaps two or three per year. Outside of a clinical trial, I consider cetuximab for these patients. I find that the results with cetuximab for squamous cell cancer are at least encouraging in that the modest survival benefit recorded in the FLEX study occurred independent of histology (Pirker 2009; [1.2]). So that is one option, but it remains to be seen whether the FDA will approve cetuximab for this use and accept it as a standard.

## Tracks 12-13

**DR LOVE:** What is your approach to treating advanced adenocarcinoma of the lung?

**DR NATALE:** We have two FDA-approved treatments: platinum/pemetrexed and carboplatin/paclitaxel with bevacizumab. The NCCN guidelines recommend that bevacizumab be used with any first-line, platinum-based regimen for patients with adenocarcinoma and no contraindications to the agent. The regimen I often choose for patients with nonsquamous NSCLC, off protocol, is carboplatin/pemetrexed with bevacizumab.

Jyoti Patel at Northwestern University conducted an important pilot study in which she selected patients with nonsquamous NSCLC who met the eligibility criteria of ECOG-E4599 and administered first-line carboplatin/pemetrexed and bevacizumab (Patel 2009). The objective response rate was 55 percent, and the median survival rate was more than 14 months (1.3). That appears to be better than the results of the ECOG-E4599 study with carbopl-

atin/paclitaxel/bevacizumab, although we must remember that this pilot trial was an uncontrolled Phase II study with a select group of patients.

A randomized trial is in progress in which patients who are bevacizumab eligible are randomly assigned to carboplatin/paclitaxel/bevacizumab, the FDA-approved standard, or carboplatin/pemetrexed/bevacizumab. After four cycles of induction therapy, the patients receiving carboplatin/paclitaxel/bevacizumab who experience response or achieve stable disease then receive bevacizumab as maintenance therapy. The patients on the carboplatin/pemetrexed/bevacizumab arm receive maintenance bevacizumab/pemetrexed.

**DR LOVE:** What is emerging in practice with regard to bevacizumab and the risk of pulmonary hemorrhagic events?

**DR NATALE:** Large registration studies are taking place in the United States — the ARIES and the SAiL trials — in which community oncologists using a platinum-based regimen and front-line bevacizumab can register the outcomes of their cases. These studies are accumulating up to 3,000 patients, and it is interesting to note that the fatal pulmonary hemorrhage rate has dropped to 0.5 percent or lower.

Evidently, in the community the risk of a fatal pulmonary hemorrhagic event occurring with the use of bevacizumab is far lower than it was either in ECOG-E4599 or the AVAiL study for reasons that are unclear.

**DR LOVE:** What do you use for maintenance therapy in this setting?

**DR NATALE:** I continue to use bevacizumab as maintenance therapy after chemotherapy/bevacizumab, but this is an important question to which we need an answer. I'm grateful that ECOG is stepping to the fore. They are

**1.2**

**FLEX Efficacy Data: Intent-to-Treat Population and Histological Subgroups**

| | Number of patients | Cisplatin/vinorelbine and cetuximab | Cisplatin/vinorelbine |
|---|---|---|---|
| **Median overall survival** | | | |
| All histological subgroups | 1,125 | 11.3 months | 10.1 months |
| Adenocarcinoma | 413 | 12.0 months | 10.3 months |
| Squamous cell carcinoma | 347 | 10.2 months | 8.9 months |
| Other* | 185 | 9.0 months | 8.2 months |
| | **Number of patients** | **Hazard ratio (95% confidence interval)** | |
| **Hazard ratios for death** | | | |
| All histological subgroups | 1,125 | 0.87 (0.76-1.00) | |
| Adenocarcinoma | 532 | 0.94 (0.77-1.15) | |
| Squamous cell carcinoma | 377 | 0.80 (0.64-1.00) | |
| Other* | 216 | 0.81 (0.60-1.10) | |

* Other includes large cell, adenosquamous and undifferentiated carcinomas.

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

preparing a trial in which patients will receive the ECOG standard, carboplatin/paclitaxel/bevacizumab, in addition to three maintenance regimens (ECOG-5508; [1.4]).

On the standard maintenance arm patients will receive bevacizumab alone, on the second arm patients will receive pemetrexed alone and on the third arm they will receive the combination of pemetrexed and bevacizumab. ■

**1.3**

### Phase II Study of Pemetrexed/Carboplatin/Bevacizumab with Maintenance Pemetrexed and Bevacizumab as First-Line Therapy for Nonsquamous NSCLC (N = 49)

| Efficacy | |
|---|---|
| Overall response rate | 55% |
| Stable disease | 33% |
| Median progression-free survival | 7.8 mo |
| Median overall survival | 14.1 mo |

**SOURCE:** Patel JD et al. *J Clin Oncol* 2009;27(20):3284-9.

**1.4**

### Proposed ECOG-5508 Phase III Maintenance Therapy Trial

**Eligibility**

Patients with Stage IIIB/IV bevacizumab-eligible NSCLC who have received carboplatin/paclitaxel/bevacizumab x 4 cycles

**Accrual**

1,236 (864 expected to experience complete response, partial response or stable disease for randomization)


$B_{12}$, folate and dexamethasone administered to patients receiving pemetrexed

**SOURCE:** Khuri FR. Sixth Annual Atlanta Lung Cancer Symposium 2009.

## SELECT PUBLICATIONS


Hanna N et al. **Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer.** *J Clin Oncol* 2006;24(13):2038-43.

Lara PN Jr et al. **Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124.** *J Clin Oncol* 2009;27(15):2530-5.

Noda K et al. **Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer.** *N Engl J Med* 2002;346(2):85-91.

Patel JD et al. **Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2009;27(20):3284-9.

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.

INTERVIEW

## Edward S Kim, MD

Dr Kim is Associate Professor of Medicine in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

### Tracks 1-18



## Select Excerpts from the Interview

### Tracks 2-3

**DR LOVE:** What is your clinical approach to adjuvant therapy for NSCLC?

study will finish first, and I expect it will produce interesting information, especially regarding smokers versus nonsmokers, et cetera.

The other study, ECOG-E1505, is an Intergroup study evaluating four cycles of chemotherapy with or without bevacizumab for patients with Stage IB through Stage IIIA NSCLC. Patients on the pemetrexed/cisplatin arm cannot have nonsquamous cell histology, and for those with Stage IB cancer, the tumors must measure four centimeters or more. Patients who receive bevacizumab receive it during chemotherapy and then as maintenance for a total of one year.

Questions have arisen asking whether the duration of maintenance bevacizumab should be longer in light of the adjuvant colon cancer data. I believe that one year is adequate. We hope it will be enough to show an overall improvement.

## Tracks 14, 17

**DR LOVE:** What do you use as first-line therapy for patients with advanced-stage NSCLC?

**DR KIM:** Currently, the first choice is a bevacizumab-based chemotherapy regimen. For chemotherapy I prefer carboplatin/paclitaxel or carboplatin/docetaxel, although carboplatin/pemetrexed may be a future choice — we simply don't use it as much with bevacizumab. If the patient needs a gentle regimen because of age or comorbidities, I use carboplatin/pemetrexed.

If the histology is nonsquamous, not specifically adenocarcinoma, then I believe that any platinum-based doublet is fine. Carboplatin/pemetrexed is a relatively easy regimen to receive. I have not made the leap of faith reflecting Jyoti Patel's Phase II study by always combining bevacizumab with this regimen (Patel 2009; [1.3, page 7]). That's currently being tested in Phase III studies.

**DR LOVE:** What about cetuximab for advanced NSCLC?

**DR KIM:** I'm hopeful that cetuximab will be approved in the United States because I believe that having more options for patients is important and we're limited in the drugs that are available and work well in this setting. I believe that a platinum/taxane regimen with cetuximab is a good option for patients with squamous cell cancer, and I would like to be able to use cetuximab more often.

**DR LOVE:** Would you comment on trials evaluating cetuximab for advanced NSCLC and your experience with how patients tolerate cetuximab?

**DR KIM:** They tolerate it well. I chaired SWOG-S0536, a Phase II study of induction cetuximab, paclitaxel, carboplatin and bevacizumab for six cycles followed by maintenance cetuximab/bevacizumab for advanced NSCLC (Gandara 2009; [2.2]). The main problems patients experienced were skin peeling and nail changes. We had patients who were able to receive the maintenance therapy for more than 30 cycles, so it's clearly tolerated by some folks.

That trial led to the ongoing Phase III study SWOG-S0819, which evaluates carboplatin and paclitaxel or carboplatin, paclitaxel and bevacizumab, with or without concurrent cetuximab, for patients with Stage IV or recurrent NSCLC (2.3). The primary endpoint is efficacy, and planned subset analyses are examining whether patients with EGFR FISH-positive disease experience an additional benefit with cetuximab. ■

**2.2**

### SWOG-S0536: Phase II Study Results of Carboplatin (CB)/Paclitaxel (P) with Cetuximab (CX)/Bevacizumab (B) Followed by Maintenance CX + B in Advanced NSCLC (Median Follow-Up: 15 Months)

| | |
|---|---|
| Partial response (PR) | 54% |
| Stable disease (SD) | 23% |
| Disease control rate (PR + SD) | 77% |
| Progression-free survival | 7 months |
| Overall survival | 14 months |
| One-year survival | 57% |

**CB/P with CX/B demonstrates safety, tolerability and efficacy in advanced NSCLC and is the most active regimen studied to date by SWOG.**

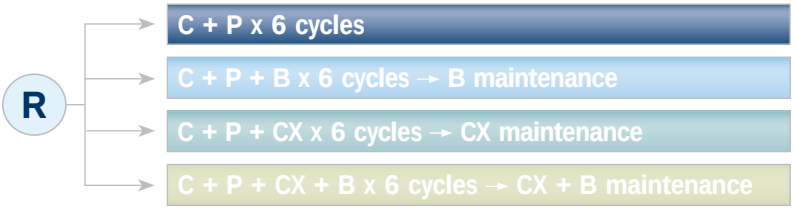
SOURCE: Gandara D et al. *Proc ASCO* 2009;**Abstract 8015**.

**2.3**

### Phase III Randomized Study of Carboplatin (C) and Paclitaxel (P) with or without Bevacizumab (B), with or without Concurrent Cetuximab (CX)

**Protocol IDs:** SWOG-S0819, NCT00946712 **Target Accrual:** 1,546 (Open)

**Eligibility:** Stage IV or recurrent NSCLC




SOURCE: **www.clinicaltrials.gov**. Accessed November 2009.

## SELECT PUBLICATIONS


Fossella F et al. **Randomized, multinational, Phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 Study Group.** *J Clin Oncol* 2003;21(16):3016-24.

Gandara D et al. **S0536: Carboplatin, paclitaxel, cetuximab, and bevacizumab followed by cetuximab and bevacizumab maintenance in advanced non-small cell lung cancer (NSCLC): A SWOG phase II study.** *Proc ASCO* 2009;**Abstract 8015**.

Patel JD et al. **Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2009;27(20):3284-9.

INTERVIEW

## Jean-Charles Soria, MD, PhD

Prof Soria is Full Professor at Paris University XI and serves in the Division of Cancer Medicine at the Institut Gustave Roussy in Villejuif, France.

### Tracks 1-9

| | |
|---|---|
| **Track 1** | Mechanisms of DNA damage and DNA repair pathways |
| **Track 2** | Base excision repair with poly(ADP-ribose) polymerase (PARP) |
| **Track 3** | Role of ERCC1 in interstrand DNA cross-link repair |
| **Track 4** | Synthetic lethality and individualized therapy in NSCLC |
| **Track 5** | ERCC1 and resistance to platinum-based adjuvant therapy |
| **Track 6** | Ongoing clinical trials evaluating adjuvant therapy based on ERCC1 status in NSCLC |
| **Track 7** | Use of ERCC1 in clinical decision-making about adjuvant therapy |
| **Track 8** | Microsatellite instability, mismatch repair dysfunction and benefit from adjuvant platinum-based chemotherapy |
| **Track 9** | Relationship between folate deficiency, homocysteine levels and response to platinums |

## Select Excerpts from the Interview

### Tracks 1-3, 5

**DR LOVE:** Would you provide a brief overview of the main DNA repair pathways?

**PROF SORIA:** When DNA becomes damaged — by UV light exposure, tobacco exposure, chemotherapy administration and so on — it requires repair. DNA is continually being monitored by proteins that run along the DNA, and when one of these continual sensors identifies DNA damage, it recruits other proteins to repair it.

Lesions or points of damage to the DNA can be in the form of single-strand breaks, double-strand breaks, interstrand lesions or DNA adducts. A DNA adduct is simply a molecule that creates a covalent bond with the DNA. When a covalent bond is formed, it can bond one strand or two strands, and when two strands are bound, it's usually called an interstrand adduct.

Parallel DNA repair pathways exist to deal with these different lesions. At least seven parallel DNA repair pathways exist, many of which, along with their respective major repair proteins, are familiar. They include the following: (1) base excision repair pathway, whose major player is PARP, (2) nuclear

excision pathway, whose major player is ERCC1, (3) homologous recombination pathway, whose major player is BRCA1, and (4) mismatch repair pathway, whose major player is MSH2.

**DR LOVE:** Would you describe the base excision repair pathway and PARP?

**PROF SORIA:** The base excision repair pathway and specifically the poly(ADP-ribose) polymerase (PARP) protein deal with single-strand DNA breaks. PARP-1 is the major player in base excision repair. PARP-2 is simply a duplication of PARP-1 without the capability of binding DNA. PARP-1 is a polymerase that binds to single-strand breaks in the DNA and recruits other proteins to repair the single-strand breaks.

**DR LOVE:** What about the nuclear excision pathway and ERCC1?

**PROF SORIA:** ERCC1 is an enzyme known as an endonuclease, which is important when a DNA adduct is created. This is the case when a large molecule, such as a platinum agent, bonds to your DNA. ERCC1 cuts the DNA and rids it of the adduct.

**DR LOVE:** What proportion of NSCLC cases are ERCC1 low versus ERCC1 normal?

**PROF SORIA:** About 40 percent of lung tumors in the adjuvant setting have low levels of ERCC1. The proportion is less clear in the metastatic setting.

**DR LOVE:** Are patients with high levels of ERCC1 less likely to respond to platinum agents?

**PROF SORIA:** Yes. High levels of ERCC1 indicate a tumor cell that is highly efficient at repairing DNA adducts. When you administer a platinum agent to a patient with such tumor characteristics, the tumor cell is more resistant because it can rid itself of the DNA adduct created by the platinum agent more rapidly (Olaussen 2007).

## Track 4

**DR LOVE:** What is synthetic lethality (Iglehart 2009; [3.1])?

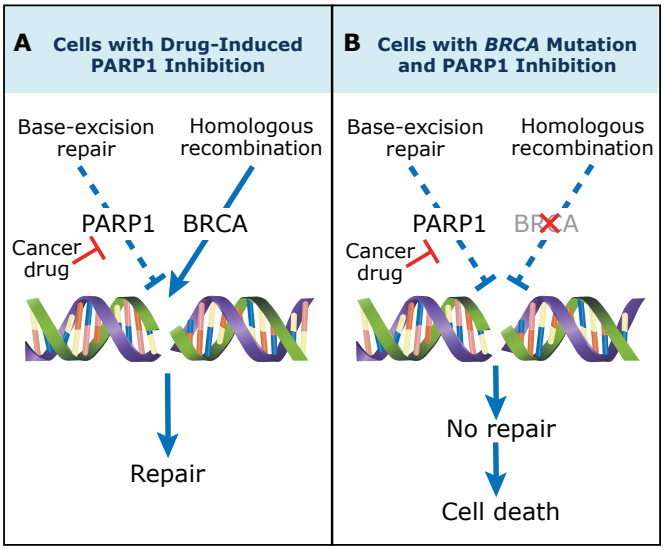
**PROF SORIA:** We now know that modulating these different DNA repair pathways increases the activity of chemotherapy. At this year's ASCO meeting, excellent Phase II data were reported evaluating carboplatin/gemcitabine with a PARP inhibitor for patients with triple-negative breast cancer. The authors reported a superb overall survival benefit with the combination (O'Shaughnessy 2009). By blocking PARP, you increase the lethal action of carboplatin and gemcitabine.

DNA repair proteins tend to be coexpressed. High levels of PARP tend to correlate with high levels of ERCC1, and so on. Imagine a tumor cell in which you are able to evaluate PARP levels and ERCC1 levels. If you find the tumor to have low levels of ERCC1 and low levels of PARP, it will be much more

sensitive to a platinum agent with a PARP inhibitor. We are on the bridge to an era of molecular medicine and personalized therapy in which we will be able to better select patients who are extremely sensitive to these compounds.

By manipulating the DNA repair pathways, we come to the synthetic lethality concept. When you target one repair pathway, the tumor cell is robust enough to survive because of the redundant pathways, but when you target a second key pathway, you can disrupt the system — this is the concept of synthetic lethality. ■

**3.1** **Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition**




In normal cells, both base-excision repair (BER) and homologous recombination (HR) are available for the repair of damaged DNA. In cells that have lost BER function because of PARP1 inhibition but retain at least one functioning copy of BRCA1 and BRCA2, HR is intact and can repair DNA damage, including damage left unrepaired because of the loss of BER (A). In the cancer cells of mutation carriers, all BRCA1 or BRCA2 function is absent, and when PARP1 is inhibited, cancer cells are unable to repair DNA damage by HR or BER, and cell death results (B).



## SELECT PUBLICATIONS

Iglehart JD, Silver DP. **Synthetic lethality — A new direction in cancer-drug development.** *N Engl J Med* 2009;361(2):189-91.

Olaussen KA et al. **ERCC1 as a risk stratifier in platinum-based chemotherapy for nonsmall-cell lung cancer.** *Curr Opin Pulm Med* 2007;13(4):284-9.

O'Shaughnessy J et al. **Efficacy of BSI-201, a PARP inhibitor, in combination with gemcitabine/carboplatin (GC) in triple negative metastatic breast cancer (mTNBC): Results of a Phase II study.** *Proc ASCO* 2009;**Abstract 3**.

INTERVIEW


## David M Jackman, MD

Dr Jackman is Instructor in Medicine at Harvard Medical School and Physician at the Lowe Center for Thoracic Oncology of Dana-Farber Cancer Institute in Boston, Massachusetts.


### Tracks 1-7

**Track 1** Mechanisms of acquired resistance to EGFR TKIs: t790M and c-MET

**Track 2** **Case discussion:** A 65-year-old never smoker presents with Stage IIIB NSCLC and exon 19 deletion with malignant pleural effusion

**Track 3** Tolerability and efficacy of irreversible EGFR TKIs, such as BIBW 2992

**Track 4** **Case discussion:** A 61-year-old woman who is a former light smoker presents with bulky, Stage IIIA squamous NSCLC and is treated with concurrent cisplatin/etoposide and radiation therapy

**Track 5** Clinical trials incorporating cetuximab with chemoradiation therapy for Stage IIIA/B NSCLC

**Track 6** **Case discussion:** A 50-year-old woman and former oligosmoker presents with EGFR wild-type, squamous cell NSCLC, mediastinal lymphadenopathy and hepatic metastases

**Track 7** Clinical approach to adjuvant therapy for patients with NSCLC

## Select Excerpts from the Interview

### Track 1

**DR LOVE:** What do we know about the mechanisms of resistance to EGFR TKIs?

**DR JACKMAN:** We are trying to uncover the potential causes of secondary resistance to EGFR TKIs in patients who initially respond to therapy, and we have good data for two sources of resistance. One is the T790M mutation. Michael Eck from Dana-Farber performed excellent protein crystallography work that showed that the T790M mutation does not create a steric inhibition caused by a conformational change, but rather the mutation changes the affinity of the receptor for ATP (Yun 2008; [4.1]). Because erlotinib and gefitinib are competitive inhibitors, the change in affinity reduces their effectiveness.

So for patients in whom T790M is the cause of secondary resistance, the irreversible EGFR/HER2 TKIs BIBW 2992 and PF-00299804 are currently

being evaluated in clinical trials to determine whether they can overcome this resistance (4.2).

**DR LOVE:** What about c-MET?

**DR JACKMAN:** The other cause for secondary resistance that has been identified is MET amplification (Bean 2007; Engelman 2007; [4.2]). In essence, a parallel pathway can activate downstream signaling independent of EGFR. For these patients, we hope to restore sensitivity by using an EGFR TKI and a MET inhibitor simultaneously.

**4.1**

### The T790M Mutation in EGFR Kinase Causes Drug Resistance by Increasing the Affinity for ATP

"Threonine 790 is the 'gatekeeper' residue, an important determinant of inhibitor specificity in the ATP binding pocket. The T790M mutation has been thought to cause resistance by sterically blocking binding of TKIs such as gefitinib and erlotinib, but this explanation is difficult to reconcile with the fact that it remains sensitive to structurally similar irreversible inhibitors...

[W]e show that the T790M mutation activates WT EGFR and that introduction of the T790M mutation increases the ATP affinity of the oncogenic L858R mutant by more than an order of magnitude. The increased ATP affinity is the primary mechanism by which the T790M mutation confers drug resistance...

We conclude that the T790M mutation is a 'generic' resistance mutation that will reduce the potency of any ATP-competitive kinase inhibitor and that irreversible inhibitors overcome this resistance simply through covalent binding, not as a result of an alternative binding mode."

**SOURCE:** Yun CH et al. *Proc Natl Acad Sci USA* 2008;105(6):2070-5.

**4.2**

### MET Amplification Occurs in EGFR-Mutant Lung Tumors with Acquired Resistance to Gefitinib or Erlotinib

"MET amplification was detected in 4 of 18 (22%) lung cancer specimens that had developed resistance to gefitinib or erlotinib...

MET amplification provides an example of a resistance mechanism characterized by gene amplification of a kinase that is not a direct or downstream target of gefitinib or erlotinib...

Our findings also suggest that irreversible EGFR inhibitors, which are currently under clinical development as treatments for patients whose tumors have developed acquired resistance to gefitinib and erlotinib, may be ineffective in the subset of tumors with a MET amplification even if they contain an EGFR T790M mutation. Therefore, combination therapies with MET kinase inhibitors, which are in early-stage clinical trials, and irreversible EGFR inhibitors should be considered for patients whose tumors have become resistant to gefitinib or erlotinib."

**SOURCE:** Engelman JA et al. *Science* 2007;316(5827):1039-43.

## Track 2

### Case discussion

A 65-year-old never smoker presents with Stage IIIB NSCLC and an exon 19 deletion and a malignant pleural effusion

**DR JACKMAN:** In light of this patient's never smoking status, we were interested in the possibility that he could have an EGFR mutation, so we tested and found that he had an exon 19 deletion. He was started on erlotinib and experienced wonderful improvements in his pleural effusion and his primary left upper lobe mass. He was able to continue receiving erlotinib for 10 months, but subsequently the disease progressed with a recurrence of the left pleural effusion and growth in the mediastinum and left upper lobe mass.

He was admitted to the hospital and underwent pleurodesis. Subsequently he received six cycles of carboplatin and pemetrexed and demonstrated another wonderful response. We discussed stopping therapy, which would be more in line with the standard treatment, versus using pemetrexed maintenance therapy. He wanted to proceed with treatment, and he has been receiving pemetrexed maintenance therapy with stable disease for more than one year.

**DR LOVE:** For a patient such as this one with an EGFR mutation and progressive disease after a response to erlotinib, are clinical trial options available?

**DR JACKMAN:** Yes, we have clinical trials with either an irreversible EGFR TKI or erlotinib in combination with a MET inhibitor. We had tissue available from his thoracentesis that we screened for the T790M mutation and MET amplification, but we found neither. He decided that he did not want to pursue clinical trials targeting mutations that we did not find, and he wanted conventional chemotherapy instead.

**DR LOVE:** What would you consider if he developed progressive disease?

**DR JACKMAN:** We've seen many patients with initial responses to EGFR TKIs who benefit from restarting the same agent in the future, so I would be inclined to consider EGFR-directed therapy. I would likely try a rebiopsy at that time to see if anything had emerged that might push us toward an irreversible TKI or another strategy. ■

### SELECT PUBLICATIONS


Bean J et al. **MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib.** *Proc Natl Acad Sci USA* 2007;104(52):20932-7.

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

Yun CH et al. **The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP.** *Proc Natl Acad Sci USA* 2008;105(6):2070-5.

INTERVIEW

## Tony SK Mok, MD

Dr Mok is Professor in the Department of Clinical Oncology at the Chinese University of Hong Kong in Hong Kong, China.

### Tracks 1-10



## Select Excerpts from the Interview

### Track 1

**DR LOVE:** Would you discuss the background of the IPASS trial, evaluating first-line gefitinib versus carboplatin/paclitaxel for Asian patients who were never smokers or oligosmokers?

**DR MOK:** We knew that patients with EGFR mutations would experience good responses to the EGFR TKIs, such as gefitinib. At the time this study was initiated in Asia it was difficult to select patients by EGFR mutation, so we chose to select a population enriched for EGFR mutations — nonsmokers or oligosmokers with adenocarcinoma. In the intent-to-treat population, the overall hazard ratio for the primary endpoint of progression-free survival was 0.74 (Mok 2009a; [5.1]) for gefitinib versus carboplatin/paclitaxel.

In a planned subgroup analysis, the hazard ratio for progression-free survival for patients with EGFR mutation-positive disease was 0.48 — a 50 percent reduction in the rate of disease progression (Mok 2009a). However, the hazard ratio for patients with EGFR mutation-negative disease was 2.85, so these patients fared much better with chemotherapy. On the basis of these data, I believe that we can consider using an EGFR TKI as first-line therapy for patients with EGFR-mutant NSCLC.

**DR LOVE:** Is the study powered to evaluate overall survival?

**DR MOK:** Yes. We presented the preliminary survival outcome at ESMO, but the data were only 36 percent mature and no difference was observed between the two curves. The final overall survival data will be analyzed in early 2010.

**DR LOVE:** What about acquired resistance after patients have been exposed to an EGFR TKI?

**DR MOK:** Originally, the T790M mutation was considered acquired resistance. However, in IPASS we identified the T790M mutation in patients who had not been treated.

**5.1**

**IPASS: Gefitinib versus Carboplatin/Paclitaxel as First-Line Therapy for Clinically Selected (Asian, Nonsmokers or Former Light Smokers, Adenocarcinoma) Patients with Advanced NSCLC**

| 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 |
| EGFR mutation unknown (n = 386; 394) | 69.4% | 80.2% | 0.68 (0.58-0.81) | <0.001 |

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

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

## Track 4

**DR LOVE:** What's the background for the study you recently published evaluating sequential erlotinib and chemotherapy for patients with advanced NSCLC?

**DR MOK:** We're trying to revisit the interesting concept of combining chemotherapy with an EGFR TKI. We conducted the First-line Asian Sequential Tarceva® And Chemotherapy Trial (FAST-ACT), in which we administered

carboplatin/gemcitabine on day one and day eight and then erlotinib on days 15 through 28 to patients with advanced NSCLC (Mok 2009b).

This study was based on preclinical work demonstrating that when the EGFR TKI and chemotherapy are administered together, they are antagonistic because erlotinib decreases apoptosis and therefore chemotherapy does not work well (Piperdi 2004).

Fred Hirsch and Paul Bunn conducted a similar study, but the sample size was small and it turned out to be negative except for patients with EGFR-mutant disease (Hirsch 2009). Our study included 150 patients in a randomized, placebo-controlled Phase II trial. This was a positive study demonstrating a significant improvement in progression-free survival for patients who received erlotinib sequentially with carboplatin/gemcitabine (Mok 2009b; [5.2]).

**DR LOVE:** Where are you heading with this strategy?

**DR MOK:** We are conducting a randomized, double-blind, placebo-controlled Phase III study with 450 Asian patients with advanced NSCLC (NCT00883779). These were "all comers" who were eligible regardless of smoking history, histology, gender and so on. They will be randomly assigned to carboplatin/gemcitabine on day one and day eight with intercalated placebo or erlotinib on days 15 through 28.

**5.2**

**Overall Response Rate (ORR) and Progression-Free Survival (PFS) for Patients with Advanced NSCLC Receiving First-Line Carboplatin/Gemcitabine (CG) with or without Intercalated Erlotinib**

| | CG/erlotinib | | | CG/placebo | | | |
|---|---|---|---|---|---|---|---|
| | No. | ORR | Median PFS | No. | ORR | Median PFS | PFS hazard ratio |
| All patients | 76 | 35.5% | 29.4 wk | 78 | 24.4% | 23.4 wk | 0.47 |
| Histology | | | | | | | |
| Adeno | 51 | 35.3% | 32.1 wk | 52 | 25.0% | 23.7 wk | 0.48 |
| Nonadeno | 25 | 36.0% | 23.4 wk | 26 | 23.1% | 19.6 wk | 0.66 |
| Smoking status | | | | | | | |
| Current | 33 | 30.3% | 25.1 wk | 36 | 13.9% | 17.5 wk | 0.58 |
| Former | 19 | 31.6% | 31.9 wk | 14 | 35.7% | 19.4 wk | 0.55 |
| Never | 24 | 45.8% | 48.1 wk | 28 | 32.1% | 28.0 wk | 0.37 |

**SOURCE:** Mok TS et al. *J Clin Oncol* 2009b;27(30):5080-7.

**Tracks 9-10**

## Case discussion

A 70-year-old woman with EGFR-mutant lung cancer presents with multiple bony metastases

**DR MOK:** This patient experienced a durable response with gefitinib before her disease progressed with a single sternal metastasis. We treated this with radiation therapy and readministered gefitinib, but six months later the disease progressed again.

This patient poses a frequent clinical problem that every oncologist encounters — a patient experiences a good duration of disease control with the EGFR TKI and then the disease progresses. What's the next step in treatment?

Ongoing studies are evaluating the irreversible TKIs, such as BIBW 2992 and PF-00299804 (5.3). Most of the patients have received a TKI before, but not all of them have EGFR mutations. The response rates are not high, but the majority of patients have stable disease. ■

**5.3**

**Phase III Studies of the Irreversible Dual EGFR/HER2 TKI BIBW 2992 and the Irreversible Small-Molecule Pan-HER TKI PF-00299804 for Patients with Advanced NSCLC**

| Protocol | Phase | N | Treatment | Eligibility |
|---|---|---|---|---|
| LUX-Lung 1 | III | 560 | BSC + BIBW 2992<br>BSC + placebo | • Stage IIIB (with pleural effusion) or IV<br>• 1 to 2 prior lines of chemotherapy<br>• PD ≥ 12 weeks of erlotinib or gefitinib |
| LUX-Lung 3 | III | 330 | BIBW 2992<br>Cisplatin/pemetrexed | • Stage IIIB (with pleural effusion) or IV<br>• EGFR mutation-positive<br>• No prior chemotherapy or EGFR-targeted therapy |
| CAN-NCIC-BR26 | III | 720 | PF-00299804 | • Stage IIIB or IV<br>• 1 to 2 prior lines of chemotherapy<br>• Prior erlotinib or gefitinib |

SOURCE: **www.clinicaltrials.gov**. Accessed December 2009.

## SELECT PUBLICATIONS


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

Hirsch FR et al. **Randomized phase II study of erlotinib (E) or intercalated E with carboplatin/paclitaxel (CP) in chemotherapy-naïve advanced NSCLC: Correlation of biomarker status and clinical benefit.** *Proc ASCO* 2009;**Abstract 8026**.

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

Mok TS et al. **Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer.** *J Clin Oncol* 2009b;27(30):5080-7.

Piperdi B et al. **Schedule-dependent interaction between epidermal growth factor inhibitors (EGFRI) and G2/M blocking chemotherapeutic agents (G2/MB) on human NSCLC cell lines in vitro.** *Proc ASCO* 2004;**Abstract 7028**.

## QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Data from SWOG-S0124, published by Lara and colleagues, failed to demonstrate a significant difference in _____ between cisplatin/irinotecan and cisplatin/etoposide for extensive-stage small cell lung cancer.**
   a. Response rate
   b. Median progression-free survival
   c. Overall survival
   d. All of the above

2. **In the FLEX trial, the addition of cetuximab to cisplatin/vinorelbine as first-line therapy for NSCLC demonstrated a significant improvement in overall survival in the subgroup of patients with squamous cell carcinoma.**
   a. True
   b. False

3. **In a Phase II study of pemetrexed/carboplatin/bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous NSCLC, the overall response rate was _____.**
   a. 25 percent
   b. 35 percent
   c. 45 percent
   d. 55 percent

4. **Data from the TAX-326 trial of a docetaxel/platinum combination versus vinorelbine/cisplatin for patients with previously untreated advanced NSCLC showed that docetaxel/cisplatin was inferior in efficacy to vinorelbine/cisplatin.**
   a. True
   b. False

5. **ECOG-E1505 is evaluating adjuvant _____ with or without bevacizumab for patients with completely resected Stage IB to Stage IIIA NSCLC.**
   a. Cisplatin/gemcitabine
   b. Cisplatin/vinorelbine
   c. Cisplatin/docetaxel
   d. All of the above

6. **_____ ERCC1 expression is predictive of resistance to platinum-based therapy.**
   a. Low
   b. Normal
   c. High

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

8. **In the IPASS trial, evaluating first-line gefitinib and carboplatin/paclitaxel for patients with advanced NSCLC, the hazard ratio for progression-free survival favoring gefitinib was _____ for patients with documented EGFR mutations.**
   a. 2.85
   b. 0.74
   c. 0.48

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

10. **For patients with previously untreated advanced NSCLC, the sequential administration of erlotinib after gemcitabine/platinum chemotherapy led to a significant improvement in _____.**
    a. Overall survival
    b. Progression-free survival
    c. Both a and b

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

## EDUCATIONAL ASSESSMENT AND CREDIT FORM

### *Lung Cancer Update* — Issue 4, 2009

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 |
|---|---|---|
| **IPASS: First-line gefitinib versus carboplatin/paclitaxel for Asian patients with adenocarcinoma of the lung in a population enriched for EGFR mutations** | 4 3 2 1 | 4 3 2 1 |
| **Mechanism of acquired resistance to EGFR TKIs in EGFR-mutant lung adenocarcinoma** | 4 3 2 1 | 4 3 2 1 |
| **Pilot study of neoadjuvant docetaxel and cisplatin followed by adjuvant erlotinib for Stage I to Stage III NSCLC** | 4 3 2 1 | 4 3 2 1 |
| **Feasibility of combining chemotherapy/cetuximab with radiation therapy for locally advanced NSCLC** | 4 3 2 1 | 4 3 2 1 |
| **RADIANT: Erlotinib after complete resection with or without adjuvant chemotherapy for patients with Stage IB to Stage IIIA NSCLC and EGFR-positive tumors** | 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:**

- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible TKIs . . . . . 4 3 2 1 N/M N/A
- Summarize completed and ongoing clinical trials for the treatment of extensive small cell lung cancer. . . . . 4 3 2 1 N/M N/A
- Develop a risk-adapted algorithm for the individualized use of adjuvant systemic therapy for patients with localized non-small cell lung cancer (NSCLC). . . . . 4 3 2 1 N/M N/A
- Appraise the clinical application of emerging data on the combined use of biologic agents with chemoradiation therapy for Stage III NSCLC . . . . . 4 3 2 1 N/M N/A
- Formulate individualized treatment plans addressing the first-, second- and third-line management of recurrent or progressive NSCLC, considering patient and tumor characteristics . . . . . 4 3 2 1 N/M N/A
- Effectively utilize tumor histology and biomarkers when making evidence-based lung cancer treatment decisions . . . . . 4 3 2 1 N/M N/A
- Discuss the rationale for the development of novel agents targeting DNA repair pathways. . . . . 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 |
|---|---|---|
| Ronald B Natale, MD | 4 3 2 1 | 4 3 2 1 |
| Edward S Kim, MD | 4 3 2 1 | 4 3 2 1 |
| Jean-Charles Soria, MD, PhD | 4 3 2 1 | 4 3 2 1 |
| David M Jackman, MD | 4 3 2 1 | 4 3 2 1 |
| Tony SK Mok, 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.**

LCU409

# Lung Cancer™ UPDATE



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

# Lung Cancer™ UPDATE


This program is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Genentech BioOncology & OSI Oncology, ImClone Systems Incorporated and Sanofi-Aventis.

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