LCU | 2011 VOL 8 | ISSUE 3

Lung Cancer™ UPDATE

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

FACULTY INTERVIEWS

Ronald B Natale, MD
David R Spigel, MD
Rafael Rosell, MD, PhD
Martin Reck, MD, PhD

EDITOR

Neil Love, MD

CME Certified

Subscribe to Podcasts or download MP3s of this program at ResearchToPractice.com/LCU311

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% 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

- Use case-based learning to formulate individualized strategies for the care of patients with lung cancer.
- Apply the results of emerging clinical research to the current and future treatment of non-small cell lung cancer (NSCLC).
- 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 biomarkers.
- Describe emerging efficacy and safety data on irreversible EGFR tyrosine kinase inhibitors, and identify patients who might benefit from participation in clinical trials evaluating these novel agents.
- Identify patients with metastatic NSCLC who may experience incremental benefit from maintenance biologic therapy and/or chemotherapy.
- Formulate an evidence-based treatment approach to adjuvant chemotherapy for NSCLC that recognizes the toxicities of different doublet regimens.
- Use biomarkers, clinical characteristics and tumor histology to select individualized front-line treatment approaches for patients with NSCLC.
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the 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, complete the Post-test with a score of 70% or better and fill out the Educational Assessment and Credit Form located in the back of this monograph or on our website at **ResearchToPractice.com/LCU311/CME**. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ResearchToPractice.com/LCU311** 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 activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Daiichi Sankyo Inc, EMD Serono Inc, Genentech BioOncology & OSI Oncology and Lilly USA LLC.

Last review date: January 2012; Release date: January 2012; Expiration date: January 2013

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 Spigel** 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, Boehringer Ingelheim Pharmaceuticals Inc, Pfizer Inc; Consulting Agreements: Genentech BioOncology, Lilly USA LLC; Paid Research: Lilly USA LLC, Novartis Pharmaceuticals Corporation. **Dr Rosell** — Stock Ownership: Pangaea Biotech. **Dr Reck** — Advisory Committee: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Lilly USA LLC, Pfizer Inc, Roche Laboratories Inc; Speakers Bureau: AstraZeneca Pharmaceuticals LP, Lilly USA LLC, Roche Laboratories Inc.

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: Abbott Laboratories, Allos Therapeutics, Amgen Inc, Astellas Pharma Global Development Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly USA LLC, Medivation Inc, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics and Teva Pharmaceuticals.

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

Ronald B Natale, MD

Dr Natale is Director of the Lung Cancer Clinical Research Program and Acting Director of the Phase I Clinical Trials Unit at the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute in Los Angeles, California.

Tracks 1-15

Track 1 **Case discussion:** A 71-year-old woman and never smoker with recurrent adenocarcinoma of the lung and brain metastases receives crizotinib

Track 2 Recent revision to NCCN guidelines regarding crizotinib for ALK-positive non-small cell lung cancer (NSCLC)

Track 3 High-dose weekly erlotinib for central nervous system (CNS) metastases from EGFR-mutant NSCLC

Track 4 Differential time course of NSCLC recurrence in nonsmokers and smokers and effect on follow-up surveillance

Track 5 Clinical decision-making regarding adjuvant therapy for lower-risk NSCLC

Track 6 **Case discussion:** A 79-year-old woman is diagnosed with recurrent EGFR-mutant adenocarcinoma of the lung 2 years after initial surgery

Track 7 Adjuvant treatment for patients with EGFR-mutant NSCLC

Track 8 **Case discussion:** A 76-year-old Chinese man and never smoker with EGFR-mutant, moderately differentiated adenocarcinoma experiences disease progression on erlotinib and is switched to carboplatin/pemetrexed (CP) followed by pemetrexed maintenance

Track 9 Perspective on combined EGFR targeting in NSCLC: Cetuximab with afatinib

Track 10 First-line and maintenance therapy options for patients with EGFR wild-type NSCLC

Track 11 Consideration of cetuximab for patients with squamous cell carcinoma

Track 12 BLP25: A liposomal MUC1 vaccine under investigation in unresectable Stage IIIB NSCLC

Track 13 Current available clinical trial data on BLP25

Track 14 Activity and side effects of the c-MET inhibitor tivantinib (ARQ 197) in NSCLC

Track 15 Improved survival for a subset of patients on the randomized Phase II OAM4558g trial evaluating MetMAb in combination with erlotinib for advanced NSCLC

Select Excerpts from the Interview

Track 2

DR LOVE: Would you comment on the recent revision of the NCCN guidelines with respect to crizotinib treatment for ALK-positive non-small cell lung cancer (NSCLC)?

DR NATALE: A few years ago, the guidelines were updated to state that if a patient had EGFR-mutated Stage IIIB/IV lung cancer the preferred first-line treatment was erlotinib. For EGFR wild-type adenocarcinoma, they recommended several different chemotherapies. They also stated that if you administered chemotherapy and subsequently found that the patient had an EGFR mutation, you should add erlotinib. Now they've updated the guidelines to state that if a patient has EML4-ALK-positive disease, the recommended first-line treatment is crizotinib before chemotherapy.

We're making the leap that crizotinib will play out in this setting like EGFR tyrosine kinase inhibitors (TKIs), and I believe it will. The objective response rate with crizotinib in patients with good performance status is 60% or higher (Bang 2010). The data we have are in the second-, third- and fourth-line settings, but the duration of response is 10 to 12 months. We continue to see patients from clinical trials who remain disease free at 2 years and beyond. Some patients fare remarkably well, mirroring what we've seen with EGFR-mutated disease treated with a TKI.

Track 10

DR LOVE: What are your thoughts on induction therapy and maintenance for EGFR wild-type adenocarcinoma?

DR NATALE: The paradigm has evolved to 4 cycles of induction therapy. I believe the preferred regimen is pemetrexed with a platinum agent. For patients with Stage IV disease, carboplatin is completely acceptable — cisplatin is not required — but I would never quibble that one is better than the other.

A randomized European trial is investigating the addition of bevacizumab to cisplatin/pemetrexed, and we will learn whether that results in a survival advantage. Although the AVAiL trial showed a progression-free survival (PFS) advantage, no overall survival (OS) advantage was evident when bevacizumab was added (Reck 2009). No lung cancer trial has proven that maintenance bevacizumab contributes to survival. Still, although we don't have definitive data I believe it could be continued as maintenance after 4 cycles if used as part of induction therapy.

One could also switch to erlotinib maintenance based on the SATURN trial, which reported that patients with EGFR wild-type disease experienced a statistically significant improvement in PFS and OS with maintenance erlotinib (Cappuzzo 2010). The survival advantage was modest, but the hazard ratio (HR) was 0.78, which is close to a 25% relative improvement in survival.

We've also heard preliminary results from the PARAMOUNT study, in which patients received 4 cycles of first-line cisplatin and pemetrexed as induction and were then randomly assigned to observation versus pemetrexed maintenance. The maintenance arm yielded a substantial improvement in PFS, with an HR of 0.6 (Paz-Ares 2011; [1.1]). We expect that to translate to an improvement in OS.

The ATLAS study that randomly assigned patients to maintenance bevacizumab, which was used with induction, alone or combined with erlotinib, did not demonstrate an improvement in survival with the addition of erlotinib to bevacizumab as maintenance therapy, whereas in the SATURN study maintenance with erlotinib demonstrated a modest improvement in survival compared to observation. So, paradoxically, erlotinib and bevacizumab maintenance was not of benefit there. This also mirrors the BeTa study, in which patients in the second-line setting were randomly assigned to erlotinib and placebo or erlotinib and bevacizumab. Although that study showed a PFS advantage, no OS advantage was evident (Herbst 2009).

So the concept of combining an anti-VEGF agent and an EGFR-targeted agent, at least in this population, has failed in 2 randomized clinical trials. For a patient who has received carboplatin/pemetrexed induction, maintenance erlotinib would be a consideration, but I'd be wary of simply adding erlotinib to bevacizumab if induction was with carboplatin/pemetrexed/bevacizumab.

1.1

PARAMOUNT: A Phase III Study of Maintenance Pemetrexed (Pem) with Best Supportive Care (BSC) versus Placebo with BSC Immediately After Induction Treatment with Pem and Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer

Efficacy — Independent review*	Pem + BSC (n = 316)	Placebo + BSC (n = 156)	Hazard ratio	*p*-value
Median progression-free survival	3.9 mo	2.6 mo	0.64	0.0002

Select Grade 3 or 4 adverse events	Pem (n = 359)	Placebo (n = 180)
Anemia†	4.5%	0.6%
Fatigue†	4.2%	0.6%
Neutropenia†	3.6%	0%
Leukopenia	1.7%	0%

* 88% of patient cases were independently reviewed (472/539)
† Statistically significant between arms ($p \leq 0.05$)

Paz-Ares LG et al. *Proc ASCO* 2011;**Abstract CRA7510**.

Track 12

DR LOVE: Would you discuss BLP25, the MUC1 vaccine currently under investigation?

DR NATALE: Randomized Phase II trials have been conducted with this agent in patients with Stage III disease, and a positive signal was observed (Butts 2011; [1.2]). It showed a potential effect on survival when this vaccine was administered to patients whose tumors expressed the antigen.

A Phase III trial that I participated in enrolled patients with Stage III disease who received chemotherapy and radiation therapy and randomly assigned

them to the vaccine or not after completing treatment (1.3). Presumably these patients had a greatly reduced tumor burden, a situation in which we believe immunotherapy has the best opportunity to affect outcome. ■

1.2

Efficacy of the BLP25 Liposome Vaccine (L-BLP25) in Patients with Stage IIIB or IV Non-Small Cell Lung Cancer

	L-BLP25 + best supportive care (BSC) (n = 88)	BSC alone (n = 83)	Hazard ratio	*p*-value
Median overall survival	17.2 mo	13.0 mo	0.745	NR
Three-year survival rate	31%	17%	—	0.035

Butts C et al. *J Cancer Res Clin Oncol* 2011;137(9):1337-42.

1.3

Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Cancer Vaccine Stimuvax® (L-BLP25 or BLP25 Liposome Vaccine) in Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT00409188
Target Accrual: 1,514

Eligibility
Unresectable Stage III NSCLC with documented stable disease or objective response after chemoradiation therapy

R

- Single infusion of cyclophosphamide → L-BLP25 qwk x 8 → maintenance L-BLP25
- Single infusion of placebo → placebo qwk x 8 → maintenance placebo

Treatment continues until disease progression.
Primary endpoint: Survival duration

www.clinicaltrials.gov. Accessed December 2011.

SELECT PUBLICATIONS

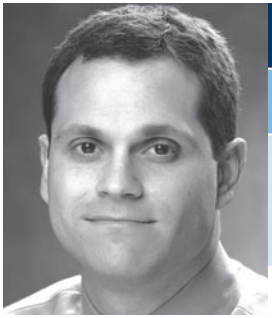
Bang Y et al. **Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 3**.

Butts C et al. **Updated survival analysis in patients with stage IIIB or IV non-small-cell lung cancer receiving BLP25 liposome vaccine (L-BLP25): Phase IIB randomized, multicenter, open-label trial.** *J Cancer Res Clin Oncol* 2011;137(9):1337-42.

Cappuzzo F et al. **Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study.** *Lancet Oncol* 2010;11(6):521-9.

Herbst RS et al. **Biomarker evaluation in the Phase III, placebo (P)-controlled, randomized BeTa trial of bevacizumab (B) and erlotinib (E) for patients (Pts) with advanced non-small cell lung cancer (NSCLC) after failure of standard 1st-line chemotherapy: Correlation with treatment outcomes.** *Proc World Conference on Lung Cancer* 2009;**Abstract B2.1**.

Reck M et al. **Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for non-squamous non-small cell lung cancer: AVAIL.** *J Clin Oncol* 2009;27:1227-34.



INTERVIEW

David R Spigel, MD

Dr Spigel is Program Director of Lung Cancer Research at the Sarah Cannon Research Institute in Nashville, Tennessee.

Tracks 1-15

Track 1 Final results from the OAM4558g trial

Track 2 MetMAb-associated edema

Track 3 Rationale for targeting the MET pathway in patients with EGFR activating mutations and acquired resistance to erlotinib

Track 4 Phase III trial of MetMAb and erlotinib for patients with MET diagnostic-positive NSCLC who have received chemotherapy for advanced disease

Track 5 Analysis of patients with MET amplification by FISH on the OAM4558g trial

Track 6 MET inhibitor-associated side effects

Track 7 Results of a Phase III trial of amrubicin versus topotecan as second-line treatment for small cell lung cancer

Track 8 **Case discussion:** A 37-year-old man and nonsmoker with ALK, EGFR and K-ras wild-type adenocarcinoma of the lung experiences disease progression while receiving CP

Track 9 Treatment approach for EGFR wild-type metastatic adenocarcinoma of the lung

Track 10 Updated survival results of a Phase III study comparing carboplatin/nanoparticle albumin-bound (*nab*) paclitaxel to carboplatin/paclitaxel as first-line therapy for advanced NSCLC

Track 11 **Case discussion:** A 63-year-old woman and nonsmoker with resected T2N1 Stage IIA NSCLC and an L858R EGFR activating mutation

Track 12 TREAT: A randomized Phase II trial on the refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin/pemetrexed versus cisplatin/vinorelbine

Track 13 Initial results and future role of immunotherapy in the treatment of lung cancer

Track 14 Perspective on the role of the irreversible EGFR tyrosine kinase inhibitor (TKI) afatinib for patients with newly diagnosed NSCLC and those with acquired resistance to erlotinib or gefitinib

Track 15 Phase II study of erlotinib/tivantinib versus erlotinib alone for previously treated NSCLC

Select Excerpts from the Interview

Tracks 1-2, 4-5

DR LOVE: Would you discuss the results you presented at ASCO 2011 evaluating MetMAb in combination with erlotinib for advanced NSCLC?

DR SPIGEL: We presented data from the Phase II OAM4558g trial, which evaluated MetMAb/erlotinib versus erlotinib/placebo. No advantage was observed with MetMAb/erlotinib compared to placebo/erlotinib for PFS or OS in the overall patient population, but a PFS advantage was evident for patients with MET diagnostic-positive disease treated with MetMAb/erlotinib. In the MET diagnostic-negative subgroup, the opposite was true — patients who received MetMAb/erlotinib experienced decreased PFS and OS (Spigel 2011; [2.1]).

No excess toxicity was observed with MetMAb except for edema. Peripheral edema was largely low grade and reversible, but a few patients experienced serious generalized edema, which appears to be a class effect. The other toxicities observed were what we'd expect with erlotinib — rash, diarrhea and fatigue. We did not witness any imbalances based on MetMAb exposure.

DR LOVE: Any indication as to why the MET diagnostic-negative group fared worse?

DR SPIGEL: We don't understand it. It's not simply that patients don't benefit — the suggestion is harm to the patients. If we know erlotinib offers so much benefit in the diagnostic-negative subgroup and worse outcomes are observed with the addition of MetMAb, the obvious connection is that MetMAb interferes with erlotinib's activity.

Crosstalk occurs among the MET pathway, hepatocyte growth factor signaling and the EGFR pathway, so it may have something to do with dependence on the pathway. Overall, it was felt that it was not a safe design for a Phase III study for these patients. However, I believe MetMAb and other agents

2.1

OAM4558g: A Phase II Trial of Erlotinib (E) with or without MetMAb in Advanced Non-Small Cell Lung Cancer

	Patients with positive c-MET immunohistochemistry			
	E + MetMAb	E + placebo	Hazard ratio	*p*-value
Median progression-free survival	2.9 mo	1.5 mo	0.53	0.04
Median overall survival	12.6 mo	3.8 mo	0.37	0.002
	Patients with negative c-MET immunohistochemistry			
Median progression-free survival	1.4 mo	2.7 mo	1.82	0.05
Median overall survival	8.1 mo	15.3 mo	1.78	0.16

Spigel DR et al. *Proc ASCO* 2011;**Abstract 7505**.

targeting this pathway should continue to be explored in solid tumors, and we shouldn't discount them for patients with MET-negative tumors until the studies have been completed.

DR LOVE: Would you expect erlotinib/MetMAb to be effective in EGFR mutation-positive disease, EGFR mutation-negative disease or both?

DR SPIGEL: We don't know yet. A prospective randomized Phase III study is in development that will focus on patients with MET diagnostic-positive disease, so patients will be selected up front for MET positivity. EGFR mutations are a source of continued debate, but it's unlikely that they will confound the data because of their low prevalence in the Western population.

Track 9

DR LOVE: How do you generally approach EGFR wild-type metastatic adenocarcinoma in terms of chemotherapy and maintenance therapy?

DR SPIGEL: Outside of a trial, when the results come back negative for EGFR and ALK, you turn to standard chemotherapy. I've been impressed with carboplatin/pemetrexed, not because of its efficacy but because I believe it's easier to administer than carboplatin/paclitaxel.

We participated in the PointBreak trial — jokingly referred to as "Sandler versus Patel" — as it evaluated the ECOG-E4599 regimen of carboplatin/paclitaxel/bevacizumab followed by bevacizumab versus carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab. We await those results to see if it makes sense to administer bevacizumab.

I discuss bevacizumab with all patients, and for some I administer it with pemetrexed and carboplatin. The question is, what do I do after 4 cycles? Do I stop and administer pemetrexed and bevacizumab, stop and administer pemetrexed alone, stop and administer bevacizumab alone or stop altogether?

I've done each of those based on patient preference and how they're faring overall. It's a big commitment to stay on pemetrexed and bevacizumab every 3 weeks indefinitely, but that may be where we're headed.

Track 10

DR LOVE: What are your thoughts on nanoparticle albumin-bound (*nab*) paclitaxel and the data presented this year at ASCO by Mark Socinski?

DR SPIGEL: I've been surprised by not only how easy *nab* paclitaxel is to administer but also by the amount of disease control. Dr Socinski presented results of a randomized Phase III study first presented last year, including updated survival data (2.2).

An advantage was observed in favor of *nab* paclitaxel in terms of response rate, although no advantage was evident for survival. Signals were observed

in subset analyses of patients with squamous cell carcinoma and in the elderly, and this agent probably offers the same activity as any second- or third-line monotherapy. It's well tolerated, patients can stay on it and it's a quick infusion.

2.2

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

Response rate by histologic subtype[1]	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
All patients (n = 531; 521)	25%	33%	1.31	0.005
Squamous (n = 221; 228)	24%	41%	—	<0.001
Nonsquamous (n = 310; 292)	25%	26%	—	0.808
Survival by histologic subtype and age[2]	**Carboplatin/ paclitaxel**	**Carboplatin/ *nab* paclitaxel**	**Hazard ratio**	***p*-value**
Median PFS — all patients (n = 531, 521)	5.8 mo	6.3 mo	0.902	0.214
Squamous (n = 221, 229)	5.7 mo	5.6 mo	0.865	0.245
Nonsquamous (n = 310, 292)	6.5 mo	6.9 mo	0.933	0.532
Median OS — all patients (n = 531, 521)	11.2 mo	12.1 mo	0.922	0.271
Age ≥70 years (n = 82, 74)	10.4 mo	19.9 mo	0.583	0.009

* Response ratio >1 favors *nab* paclitaxel

PFS = progression-free survival; OS = overall survival

[1] Socinski MA et al. *Proc ASCO* 2010;**Abstract LBA7511**.
[2] Socinski MA et al. *Proc ASCO* 2011;**Abstract 7551**.

Track 12

DR LOVE: Would you comment on the TREAT study of adjuvant cisplatin/vinorelbine versus cisplatin/pemetrexed for early-stage NSCLC?

DR SPIGEL: This is the first adjuvant data set to compare the so-called standard — cisplatin/vinorelbine — to what might be considered our most modern regimen, cisplatin/pemetrexed (Kreuter 2011; [2.3]). I was impressed that cisplatin/pemetrexed showed activity and safety, but I typically administer carboplatin/paclitaxel in this setting. I've considered pemetrexed and carboplatin, but I've only used it for about 5 patients.

Track 15

DR LOVE: What is known about the combination of erlotinib and tivantinib (ARQ 197) in previously treated NSCLC?

2.3

TREAT: A Phase II Trial on Refinement of Early-Stage Non-Small Cell Lung Cancer Adjuvant Chemotherapy with Cisplatin/Pemetrexed (CPx) versus Cisplatin/Vinorelbine (CVb)

	CPx (n = 67)	CVb (n = 65)	*p*-value
Clinical feasibility rate	95.5%	75.4%	0.001
Proportion of patients receiving planned cumulative dose	74.6%	20.0%	<0.0001
Grade 3 or 4 hematologic toxicity	10.5%	76.5%	<0.0001

Kreuter M et al. *Proc ASCO* 2011;**Abstract 7002**.

DR SPIGEL: ARQ 197 is an oral small-molecule inhibitor of MET. We recently saw the updated results from a randomized Phase II study of ARQ 197 in combination with erlotinib or placebo for patients with refractory disease (Sequist 2011). The initial intent-to-treat analysis didn't report a benefit, but an adjusted analysis favored ARQ 197 and erlotinib in terms of PFS.

A preplanned subset analysis evaluating patients with nonsquamous tumors showed that the advantage was even larger in that setting, which was true for PFS and OS. An unusual advantage was also observed in patients with K-ras mutations. That led to a randomized global Phase III study in which patients with nonsquamous tumors are randomly assigned to ARQ 197/erlotinib or erlotinib/placebo. The primary endpoint is OS, and total planned enrollment is nearly 1,000. ■

SELECT PUBLICATIONS

Adjei AA et al. **Early clinical development of ARQ 197, a selective, non-ATP-competitive inhibitor targeting MET tyrosine kinase for the treatment of advanced cancers.** *Oncologist* 2011;16(6):788-99.

Kreuter M et al. **Randomized phase II trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed (CPx) versus cisplatin and vinorelbine (CVb): TREAT.** *Proc ASCO* 2011;**Abstract 7002**.

Sequist LV et al. **Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer.** *J Clin Oncol* 2011;29(24):3307-15.

Socinski MA et al. **Survival results of a randomized, phase III trial of *nab*-paclitaxel and carboplatin compared with Cremophor-based paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer.** *Proc ASCO* 2011;**Abstract 7551**.

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).** *Proc ASCO* 2010;**Abstract LBA7511**.

Spigel DR et al. **Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC.** *Proc ASCO* 2011;**Abstract 7505**.

Surati M et al. **Role of MetMAb (OA-5D5) in c-MET active lung malignancies.** *Expert Opin Biol Ther* 2011;11(12):1655-62.

INTERVIEW

Rafael Rosell, MD, PhD

Dr Rosell is Professor at the Autonomous University of Barcelona and Head of Medical Oncology at the Catalan Institute of Oncology and the Oncology Institute Dr Rosell of USP Dexeus University Institute in Barcelona, Spain.

Tracks 1-7

Track 1 Erlotinib as first-line treatment for advanced EGFR-mutant NSCLC

Track 2 Forecasting future opportunities and challenges in the development of new therapeutic targets

Track 3 Potential use of the fibroblast growth factor receptor as a therapeutic target in patients with squamous cell carcinoma of the lung

Track 4 **Case discussion:** A 40-year-old woman and light smoker with EGFR-mutant adenocarcinoma of the lung with liver and multiple bone metastases rapidly develops acquired resistance to gefitinib

Track 5 Activity of afatinib/cetuximab in patients with NSCLC and acquired resistance to EGFR TKIs

Track 6 **Case discussion:** A 29-year-old woman and light smoker with EGFR wild-type, K-ras wild-type, ALK-negative metastatic adenocarcinoma of the lung is found to have ALK-positive disease upon tumor rebiopsy with IHC

Track 7 Perspective on the role of maintenance therapy in advanced NSCLC

Select Excerpts from the Interview

Track 1

DR LOVE: At ASCO 2011, you presented the findings of the EURTAC trial conducted in Europe, which compared the EGFR TKI erlotinib to chemotherapy as first-line treatment for EGFR mutation-positive disease. Would you discuss those findings?

DR ROSELL: The primary endpoint of the EURTAC trial was to demonstrate the superiority of EGFR TKI therapy with erlotinib compared to chemotherapy for PFS in patients who were screened for EGFR mutations.

The trial was positive, and I believe this could be of great relevance at the administrative level for health authorities to recognize that the new approach to first-line therapy for patients with EGFR-mutant NSCLC should be EGFR TKIs (Rosell 2011a; [3.1]).

3.1

EURTAC: A Phase III Trial of Erlotinib versus Chemotherapy for Patients with Advanced Non-Small Cell Lung Cancer with EGFR Activating Mutations

	Erlotinib (n = 86)	Chemotherapy (n = 87)	Hazard ratio	*p*-value
Median progression-free survival	9.7 mo	5.2 mo	0.37	<0.0001
Median overall survival	22.9 mo	18.8 mo	0.80	0.42
Best overall response rate	58%	15%	—	—
Complete response rate	2%	0%	—	—
Partial response rate	56%	15%	—	—
Disease control rate	79%	66%	—	—

Rosell R et al. *Proc ASCO* 2011a;**Abstract 7503**.

Track 5

DR LOVE: Some interesting data were also presented at ASCO 2011 on the irreversible TKI afatinib combined with cetuximab for patients with NSCLC and acquired resistance to erlotinib or gefitinib. What is your take on the biology of this combination?

DR ROSELL: That's an important question. Afatinib is a potent second-generation TKI that also targets HER2 and EGFR. We do not yet have enough information on the degree of efficacy of afatinib in patients with acquired resistance to erlotinib or gefitinib, nor do we have enough data on the benefit of afatinib in the presence of the T790M mutation. Other clinical trials with afatinib should be presented within the next year.

3.2

Activity of Afatinib and Cetuximab in Patients with Non-Small Cell Lung Cancer with Acquired Resistance to Erlotinib or Gefitinib

Best response	T790M-positive (n = 26)	T790M-negative (n = 14)	T790M unknown (n = 3)	No EGFR mutation (n = 2)
Any partial response (PR)	50%	57%	67%	—
Confirmed PR	35%	50%	67%	—
Stable disease (SD)	42%	36%	33%	—
Clinical response (any PR + SD)	92%	93%	100%	100%

Select adverse events (n = 47)	All grades	Grade ≥3
Rash	89%	6%
Diarrhea	74%	6%

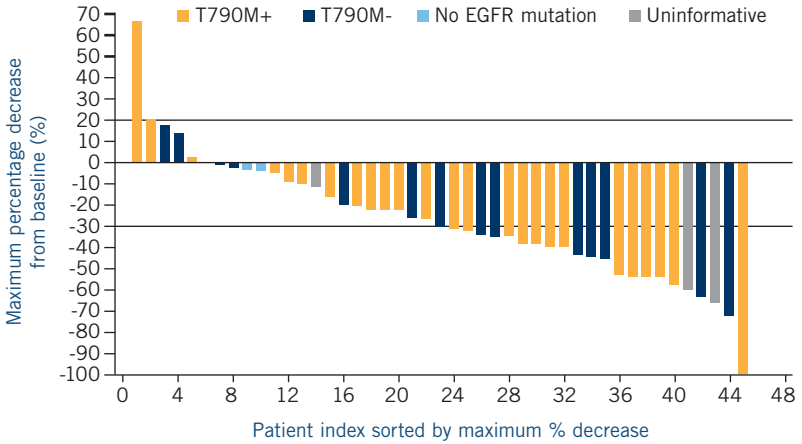
Janjigian YY et al. *Proc ASCO* 2011;**Abstract 7525**.

In this study of afatinib with cetuximab for patients in this setting, the authors were able to demonstrate an approximate 50% response rate. Interestingly, these responses were reported equally in patients with T790M acquired resistance mutations at the time of disease progression and those with clinical progression and no evidence of T790M mutations (Janjigian 2011; [3.2, 3.3]).

We have to keep in mind that other mechanisms of resistance to erlotinib or gefitinib are in the process of being identified, and we hope they will provide useful information regarding appropriate new forms of treatment. ■

3.3

Best Response at Maximum Tolerated Dose to Afatinib/Cetuximab for Patients with Advanced Non-Small Cell Lung Cancer and Resistance to an EGFR Tyrosine Kinase Inhibitor



With permission from Janjigian YY et al. *Proc ASCO* 2011;**Abstract 7525**.

SELECT PUBLICATIONS

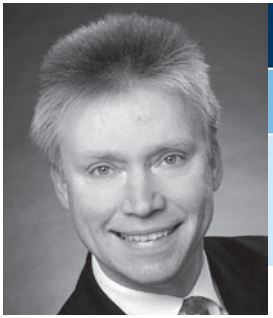
Janjigian YY et al. **Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib.** *Proc ASCO* 2011;**Abstract 7525**.

Metro G, Crinò L. **The LUX-Lung clinical trial program of afatinib for non-small-cell lung cancer.** *Expert Rev Anticancer Ther* 2011;11(5):673-82.

Murakami H et al. **Phase I study of continuous afatinib (BIBW 2992) in patients with advanced non-small cell lung cancer after prior chemotherapy/erlotinib/gefitinib (LUX-Lung 4).** *Cancer Chemother Pharmacol* 2011;[Epub ahead of print].

Rosell R et al. **Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European erlotinib versus chemotherapy (EURTAC) phase III randomized trial.** *Proc ASCO* 2011a;**Abstract 7503**.

Rosell R et al. **Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations.** *Clin Cancer Res* 2011b;17(5):1160-8.



INTERVIEW

Martin Reck, MD, PhD

Dr Reck is Head of the Thoracic Oncology and Clinical Trial Departments at Hospital Grosshansdorf in Grosshansdorf, Germany.

Tracks 1-13

Track 1 Safety and mechanism of action of BIBF 1120: A novel triple angiokinase inhibitor

Track 2 Revisiting contraindications to the use of bevacizumab in patients with squamous cell disease

Track 3 A Phase II trial of ipilimumab and paclitaxel/carboplatin as first-line therapy for Stage IIIB/IV NSCLC

Track 4 Vaccine-based therapies under investigation in NSCLC

Track 5 **Case discussion:** A 44-year-old woman and never smoker who presents with EGFR-mutant, Stage IV, TTF-1-positive adenocarcinoma of the lung and diffuse bone metastasis exhibits a dramatic response to EGFR TKI therapy

Track 6 Management of the cutaneous side effects of EGFR TKIs in NSCLC

Track 7 Cisplatin/pemetrexed as salvage therapy for patients with metastatic NSCLC and acquired resistance to EGFR TKIs

Track 8 **Case discussion:** A 62-year-old woman with Stage IV adenocarcinoma of the lung with pleural, pericardial and brain metastases receives carboplatin/vinorelbine/bevacizumab on a clinical trial

Track 9 Safety of bevacizumab for patients with NSCLC and CNS metastases

Track 10 Assessment of EGFR mutation status in nonsmokers and smokers with NSCLC

Track 11 **Case discussion:** A 68-year-old man with squamous cell carcinoma of the lung and multiple comorbidities receives cisplatin-based chemotherapy followed by radiation therapy

Track 12 Use of erlotinib as second-line or maintenance therapy for squamous cell carcinoma of the lung

Track 13 Disparity in identification of targeted agents for adenocarcinoma and squamous NSCLC

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the novel anti-angiogenic agent BIBF 1120, which you've been involved in studying?

DR RECK: BIBF 1120 is an oral VEGF TKI somewhat comparable to bevacizumab in that its action is anti-angiogenic. Bevacizumab is a direct inhibitor of VEGF, and BIBF 1120 is a direct inhibitor of the VEGF receptor.

Beyond this, BIBF 1120 is also an inhibitor of the PDGF and FGF receptors, so it's inhibiting crucial structures that are responsible for angiogenesis.

We have performed a Phase II trial of single-agent BIBF 1120 for patients with relapsed advanced NSCLC (Reck 2011; [4.1]), and we will soon present Phase III data from a second-line trial in which we combined BIBF 1120 with docetaxel for patients with advanced NSCLC (4.2).

We can say based on 2 interim analyses that we received recommendation from the data monitoring committee to move forward with the trials. We haven't seen any severe safety risks associated with treatment with BIBF 1120. We were able to fully recruit the trial. We have closed the database and await the final data.

DR LOVE: Did you observe any anti-angiogenic-like side effects such as hypertension or nosebleeds?

DR RECK: We did see some hypertension. We also saw a minimal increase in proteinuria but no severe or significant increase in bleeding events, especially in hemoptysis. So, in contrast to bevacizumab, we included all histologies with BIBF 1120, not only nonsquamous NSCLC. We included patients with squamous cell disease, who are excluded from treatment with bevacizumab. We didn't observe any increase in severe bleeding events in this group of patients.

4.1

Phase II Study of the Triple Angiokinase Inhibitor BIBF 1120 for Patients with Relapsed Advanced Non-Small Cell Lung Cancer

Efficacy	BIBF 1120 (n = 73)*
Median progression-free survival (PFS)	6.9 weeks
Median overall survival	21.9 weeks
Tumor stabilization	46%
Safety (most commonly reported drug-related adverse events)	
Nausea	57.5%
Diarrhea	47.9%
Vomiting	42.5%
Anorexia	28.8%
Abdominal pain	13.7%

* Patients for whom first- or second-line platinum-based chemotherapy failed were randomly assigned to 250 mg or 150 mg of BIBF 1120 BID.

Conclusion:

Continuous treatment with BIBF 1120 was well tolerated, with no difference in efficacy between treatment arms. PFS and objective response with single-agent treatment in advanced disease warrants further exploration.

Reck M et al. *Ann Oncol* 2011;22(6):1374–81.

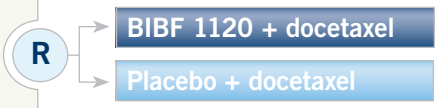
4.2

LUME Lung 1: A Randomized Phase III Trial of BIBF 1120 versus Placebo in Combination with Docetaxel for Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT00805194
Target Accrual: 1,300

Eligibility

- Locally advanced and/or metastatic NSCLC of Stage IIIB or IV or recurrent NSCLC
- Relapse or failure of 1 prior first-line chemotherapy
- ECOG PS 0 to 1



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. Accessed December 2011.

Track 9

DR LOVE: What are your thoughts on the issue of bevacizumab administration for patients with central nervous system (CNS) metastasis?

DR RECK: When we first started administering bevacizumab, some cases of CNS complications occurred. However, we now have data from a meta-analysis that indicate no increase in CNS adverse events with the use of bevacizumab in patients with CNS metastases (Besse 2010).

The European registration authority has now removed the label restriction on CNS metastases with the use of bevacizumab, and I personally have treated 15 or 20 cases of CNS metastasis and never observed any CNS event caused by the use of bevacizumab. ■

SELECT PUBLICATIONS

Besse B et al. **Bevacizumab safety in patients with central nervous system metastases.** *Clin Cancer Res* 2010;16(1):269-78.

Hilberg F et al. **BIBF 1120: Triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy.** *Cancer Res* 2008;68(12):4774-82.

Reck M et al. **A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer.** *Ann Oncol* 2011;22(6):1374-81.

Reck M. **BIBF 1120 for the treatment of non-small cell lung cancer.** *Expert Opin Investig Drugs* 2010;19(6):789-94.

Santos ES et al. **Targeting angiogenesis from multiple pathways simultaneously: BIBF 1120, an investigational novel triple angiokinase inhibitor.** *Invest New Drugs* 2011;[Epub ahead of print].

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The PARAMOUNT trial demonstrated a significant benefit in _____ for patients with advanced nonsquamous NSCLC who received maintenance pemetrexed compared to placebo.**
   a. OS
   b. PFS
   c. Overall response rate
   d. All of the above

2. **In the Phase III BeTa trial, evaluating erlotinib with or without bevacizumab as second-line therapy, which endpoint was significantly improved with the addition of bevacizumab?**
   a. PFS
   b. OS
   c. Both a and b
   d. None of the above

3. **The Phase II OAM4558g trial of erlotinib with MetMAb or placebo demonstrated a significant improvement in PFS and OS with MetMAb in the _____ population.**
   a. MET diagnostic-negative
   b. MET diagnostic-positive
   c. Intent-to-treat
   d. All of the above

4. **In the Phase II TREAT trial of adjuvant chemotherapy for patients with early-stage NSCLC, treatment with cisplatin/vinorelbine resulted in similar levels of clinical feasibility, treatment delivery and toxicity when compared to cisplatin/pemetrexed.**
   a. True
   b. False

5. **An updated adjusted analysis of the Phase II trial of erlotinib and tivantinib (ARQ 197) versus erlotinib and placebo for patients with refractory NSCLC showed that the addition of tivantinib to erlotinib _____ PFS when compared to erlotinib and placebo.**
   a. Prolonged
   b. Did not prolong

6. **The Phase III EURTAC trial of erlotinib versus chemotherapy for patients with advanced NSCLC and EGFR activating mutations reported statistically significant improvements in _____ for patients receiving erlotinib.**
   a. Median PFS
   b. Median OS
   c. Both a and b
   d. None of the above

7. **In a Phase II trial of afatinib with cetuximab for patients with NSCLC and acquired resistance to erlotinib or gefitinib, investigators reported confirmed responses in patients with _____.**
   a. T790M mutation-positive disease
   b. T790M mutation-negative disease
   c. Both of the above
   d. None of the above

8. **The novel anti-angiogenic agent BIBF 1120 inhibits the _____.**
   a. VEGF receptor
   b. PDGF receptor
   c. FGF receptor
   d. All of the above

9. **A Phase II study of the novel angiokinase inhibitor BIBF 1120 reported a median OS of approximately 22 weeks for patients with relapsed advanced NSCLC.**
   a. True
   b. False

10. **In a retrospective analysis of studies of bevacizumab for patients with CNS metastases from various solid tumors, the rate of CNS adverse events was _____ by the use of bevacizumab.**
    a. Increased
    b. Not increased

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 3, 2011

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 1 — 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 the EURTAC study: Erlotinib versus chemotherapy in advanced, EGFR-mutant NSCLC	4 3 2 1	4 3 2 1
Liposomal MUC1 vaccine BLP25 in Stage III NSCLC	4 3 2 1	4 3 2 1
PARAMOUNT study results with maintenance pemetrexed after cisplatin/pemetrexed for advanced nonsquamous NSCLC	4 3 2 1	4 3 2 1
Activity of afatinib/cetuximab in patients with NSCLC and acquired resistance to erlotinib or gefitinib	4 3 2 1	4 3 2 1
Results of studies combining MetMAb or tivantinib (ARQ 197) with erlotinib for advanced NSCLC	4 3 2 1	4 3 2 1
Results of a Phase III study of carboplatin with *nab* paclitaxel compared to standard-formulation paclitaxel as first-line therapy in 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: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ 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:

- Use case-based learning to formulate individualized strategies for the care of patients with lung cancer . . . . . 4 3 2 1 N/M N/A
- Apply the results of emerging clinical research to the current and future treatment of non-small cell lung cancer (NSCLC) . . . . . 4 3 2 1 N/M N/A
- 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 biomarkers . . . . . 4 3 2 1 N/M N/A
- Describe emerging efficacy and safety data on irreversible EGFR tyrosine kinase inhibitors, and identify patients who might benefit from participation in clinical trials evaluating these novel agents . . . . . 4 3 2 1 N/M N/A
- Identify patients with metastatic NSCLC who may experience incremental benefit from maintenance biologic therapy and/or chemotherapy . . . . . 4 3 2 1 N/M N/A
- Formulate an evidence-based treatment approach to adjuvant chemotherapy for NSCLC that recognizes the toxicities of different doublet regimens . . . . . 4 3 2 1 N/M N/A

- Use biomarkers, clinical characteristics and tumor histology to select individualized front-line treatment approaches for patients with NSCLC. . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation . . . . . 4 3 2 1 N/M N/A

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain: . . . . . .

. . . . . .

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 2 — 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
David R Spigel, MD	4 3 2 1	4 3 2 1
Rafael Rosell, MD, PhD	4 3 2 1	4 3 2 1
Martin Reck, MD, PhD	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

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 enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the 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 www.ResearchToPractice.com/LCU311/CME.

LCU311

Lung Cancer™ UPDATE

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

Lung Cancer™ UPDATE

This activity is supported by educational grants from
Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Daiichi Sankyo Inc,
EMD Serono Inc, Genentech BioOncology & OSI Oncology and Lilly USA LLC.

Research To Practice®

Sponsored by Research To Practice.

Last review date: January 2012
Release date: January 2012
Expiration date: January 2013
Estimated time to complete: 3 hours