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Lung Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

Roy S Herbst, MD, PhD

Edward S Kim, MD

SPECIAL EDITION:

Case-Based Roundtable Discussion

CME Certified

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A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Lung cancer is the leading cause of cancer mortality in the United States in both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been modest, and about 85 percent of patients who develop lung cancer will die from it. In addition, a sense of therapeutic nihilism has pervaded the medical community in the past. Chemotherapy, surgery and radiation therapy have had a modest effect on patient outcomes; however, recent improvements have been seen in time to progression and survival in lung cancer clinical trials. Published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist, radiation oncologist and pulmonologist must be well informed of these advances. To bridge the gap between research and patient care, *Lung Cancer Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists these physicians in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in lung cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, locally advanced and metastatic settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Develop and explain a management strategy for treatment of elderly patients and those with poor performance status in the adjuvant, neoadjuvant, locally advanced and metastatic settings.
- Integrate emerging data on utilization of targeted molecular therapies and molecular and genetic assays in the development of individual management strategies for patients with lung cancer.
- Counsel patients with localized primary lung cancer about the risks and benefits of adjuvant chemotherapy.
- Identify the impact of smoking-related comorbidities on the treatment of patients with lung cancer and integrate smoking cessation into the management strategy for these patients.

PURPOSE OF THIS ISSUE OF *LUNG CANCER UPDATE*

The purpose of Issue 2 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Herbst and Kim on the integration of emerging clinical research data into the management of lung cancer.

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FACULTY AFFILIATIONS

Roy S Herbst, MD, PhD
Chief, Section of Thoracic Medical Oncology
Associate Professor of Medicine
Co-Director, Phase I Clinical Trials Working Group
Department of Thoracic, Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Edward S Kim, MD
Assistant Professor of Medicine
Director, Educational Programs
Department of Thoracic, Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

MEDICAL ONCOLOGIST COMMUNITY PANEL

Stephen A Grabelsky, MD
Boca Raton, Florida

Atif M Hussein, MD
Hollywood, Florida

Leonard J Seigel, MD
Fort Lauderdale, Florida

Michael B Troner, MD
Miami, Florida

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EDITOR'S NOTE

Neil Love, MD

Vexing cases

QUESTION: What happens when you ask four astute community-based medical oncologists to present some of their most challenging lung cancer cases to two hotshot clinical investigators from Houston?

ANSWER: Lots of interesting stuff.

This program focuses on a tumor panel discussion that quickly narrowed in on the most controversial issues in contemporary lung cancer management. To hear how our faculty responded to the following research to practice questions, pop in the enclosed CDs and tapes into your car or download the MP3s to your iPod.

— Neil Love, MD
NLove@ResearchToPractice.net
April 7, 2006

Where do tyrosine kinase inhibitors (TKIs) fit into the management of a patient with non-small cell lung cancer (NSCLC) who is a nonsmoker or has an abnormality in tumor epidermal growth factor receptor? (Case 1)
Trials are under way to answer this critical question, but in the interim, which data set do we believe?

What is the optimal management of a patient with a short disease-free interval after receiving adjuvant chemotherapy for NSCLC? (Case 2)
This patient had mediastinal recurrence, which raised the issue of bevacizumab concurrent with radiation therapy, an untested strategy in lung cancer.

What is the optimal management of unresectable Stage III NSCLC? (Case 3)
Is the current "standard of care" the SWOG-S9504 strategy of etoposide/cisplatin/radiation therapy followed by docetaxel?

How should elderly and poor-performance status patients with metastatic NSCLC be managed? (Cases 4 and 5)
Is erlotinib a kinder, gentler first-line therapy for these patients? Does bevacizumab have a role? What about the combination?

How should patients with small cell lung cancer and an unknown primary tumor be managed? (Case 6)
In this case, our two faculty members and the treating physician all had different recommendations.

SELECT EXCERPTS FROM TUMOR PANEL DISCUSSION: DRS ROY S HERBST, MD, PHD AND EDWARD S KIM, MD

CASE 1: FROM THE PRACTICE OF LEONARD J SEIGEL, MD

Tracks 2-6

- 60-year-old woman who quit smoking in 1974 (four pack-year history)
- 2002: 1.5-centimeter left upper lobe nodule diagnosed via a screening CT scan
- PET scan demonstrated hypermetabolism concordant with CT abnormality
- Lobectomy revealed a T1, Grade II bronchoalveolar carcinoma with negative bronchial and aortopulmonary (AP) lymph nodes
- No other sites of disease
- March 2004: Malignant left pleural effusion
- Treated with carboplatin and gemcitabine: No response
- Responded to gefitinib but developed elevated LFTs (transaminase)
- Partial response to erlotinib for one and a half years

DR HERBST: Clearly, this patient is one of the 10 percent or so of patients who demonstrate response to these TKIs. I would bet, if we looked at her tumor, we would see either an EGFR mutation or FISH overexpression. The concern is how long this response will last.

People develop resistance to these agents, and she needs to be watched closely. I would probably order a scan for her every three or four months and think about adding something else at the first sign of progression.

DR KIM: I am extremely puzzled by this case. The liver toxicity humbles us. Erlotinib was branded, originally, as a more toxic version of gefitinib. Although we know of other inherent differences, it is puzzling to see similarly structured drugs with the lower-dosed drug causing the profound transaminitis and the higher-dosed drug being exceptionally tolerable.

That makes this a very interesting case. It teaches us a lesson that, indeed, these are different drugs, and even though the structural differences are minor, the distinction is not all dose related.

DR LOVE: Roy, what if she progressed objectively on erlotinib and was still clinically stable?

DR HERBST: She's received the EGFR inhibitors as second-line therapy, so one option if she were to progress would be to use another chemotherapeutic agent.

The agents one would consider would be pemetrexed or docetaxel (Hanna 2004), although I'm partial to the combination of bevacizumab and erlotinib (Herbst 2005a).

We recently published our Phase II experience at MD Anderson and Vanderbilt, in which that combination in second- or later-line therapy had a time to progression close to seven months, with a median survival of more than a year (Herbst 2005a; [1.1]). Those data are currently being confirmed.

At ASCO this year we'll hear about a large multicenter Phase II randomized trial that was conducted throughout the United States.

An ongoing trial is evaluating bevacizumab with erlotinib versus erlotinib alone in the second-line metastatic setting: the BETA-2 lung trial.

Based on my experience, if no contraindications were present — for example, disease in the brain — I probably would consider adding bevacizumab to the erlotinib if the tumor progresses.

DR LOVE: Are you more inclined to do

this because she's had such a great response to erlotinib?

DR HERBST: Yes, I probably wouldn't recommend it off study for someone "cold." If a patient comes in to whom you want to administer the combination of an EGFR inhibitor and an angiogenesis inhibitor, I'm a great proponent of clinical studies. But in this case, when you already have a patient who is responding to erlotinib, I think it would be reasonable to consider adding the angiogenesis inhibitor.

DR SEIGEL: If we didn't use bevacizumab and we were going to start chemotherapy with a taxane, would you still continue the erlotinib, even if she objectively progressed on it?

DR HERBST: That is a big question that we all grapple with as we see patients who benefit from the EGFR inhibitors. This is a group for which adding chemotherapy might provide a benefit. Certainly, we know that the never-smokers treated with chemotherapy and erlotinib had a wonderful outcome, a median survival of longer than 20 months, but it was a small group of patients (Herbst 2005b).

The problem here is that we might have missed our window. At the point when she's starting to progress, you have to assume that something has changed in her EGFR axis. The drug might still provide a benefit, but it's not a benefit in terms of apoptosis. I probably wouldn't mix the two. I would either add an anti-angiogenic agent or look for clinical trials. ■

1.1 Phase I/II Trial Combining Bevacizumab Plus Erlotinib in the Treatment of Recurrent Non-Small Cell Lung Cancer: Efficacy Data (N = 40)

Median survival	12.6 months
One-year survival	54.2%
Median progression-free survival	7.0 months
Median duration of response	32+ weeks

SOURCE: Herbst RS et al. *J Clin Oncol* 2005a;23(11):2544-55. **Abstract**

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Cappuzzo F et al. **Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer.** *J Natl Cancer Inst* 2005;97(9):643-55. **Abstract**

Hanna N et al. **Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.** *J Clin Oncol* 2004;22(9):1589-97. **Abstract**

Herbst RS et al. **Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer.** *J Clin Oncol* 2005a;23(11):2544-55. **Abstract**

Herbst RS et al; TRIBUTE Investigator Group. **TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer.** *J Clin Oncol* 2005b;23(25):5892-9. **Abstract**

Lynch TJ et al. **Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib.** *N Engl J Med* 2004;350(21):2129-39. **Abstract**

Pao W et al. **EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib.** *Proc Natl Acad Sci USA* 2004;101(36):13306-11. **Abstract**

SELECT EXCERPTS FROM TUMOR PANEL DISCUSSION: DRS ROY S HERBST, MD, PHD AND EDWARD S KIM, MD

CASE 2: FROM THE PRACTICE OF MICHAEL B TRONER, MD

Tracks 1-10

- 64-year-old man; extensive smoking history
- 2.5-centimeter right upper lobe pulmonary mass and no evidence of additional disease on a PET scan
- Stage IB nonsquamous cell NSCLC diagnosed on surgical resection
- Past medical history: Asymptomatic polycystic kidney disease with normal creatinine levels

DR LOVE: Ed, if this patient came to see you today postoperatively, what would you be likely to offer him?

DR KIM: If he were in very good shape, I probably would consider a carboplatin-based regimen, although the polycystic kidney disease does bother me. I prefer to use docetaxel rather than paclitaxel. It has fewer side effects, especially neuropathy.

DR LOVE: Mike, how did you treat this patient?

DR TRONER: He was treated with carboplatin and paclitaxel therapy and tolerated it reasonably well, although he did have some moderate toxicity. Dr Kim, I am intrigued by your comment about docetaxel being better tolerated than paclitaxel. My clinical impression from our patient population is that we tend to see more skin toxicity, peripheral edema and, most significantly, asthenia with docetaxel.

DR KIM: May I ask what dose of paclitaxel you're using?

DR TRONER: It's low. On an every three-week schedule, it is probably 135 to 150 mg/m^2.

DR KIM: That's the real issue. We tend to underdose paclitaxel a bit. If you used a similar dosing schedule with docetaxel, you would be dosing anywhere between 45 and 50 mg/m^2 every three weeks. So if you're using 75 mg/m^2 of docetaxel and you're not using 225 mg/m^2 of paclitaxel, I would totally agree with your statement that you would see better tolerability with paclitaxel. But I would challenge you that if you used 45 or 50 mg/m^2 of docetaxel, you would find it to be very well tolerated, with less asthenia as well.

DR LOVE: What happened with further follow-up?

DR TRONER: He did okay for a couple of months. I was about to restage him when he came into the office with increasing fatigability, some chest discomfort, dysphagia and esophageal pressure. Once again, he had an unremarkable physical exam, but a repeat PET/CT scan showed moderately extensive mediastinal disease with both paratracheal and subcarinal lymphadenopathy.

DR LOVE: Roy, what are your thoughts?

DR HERBST: This is a difficult situation, with a symptomatic patient who is primarily refractory to platinum-based therapy. My next step would be to consult a radiation oncologist right away. Then the decision is whether to treat him with radiation therapy alone or try to bring in some second-line chemotherapy in combination with radiation.

Not many good alternatives exist right now. We have some data on pemetrexed in combination with radiation (Seiwert 2005). It is pretty well tolerated, so one option might be to administer that in combination with carboplatin.

I've done that on a few occasions for patients like this. I still probably would use some carboplatin, too, and you can administer that with the radiation therapy. Radiation therapy would be the way to go here.

DR KIM: Assuming the MRI of the brain is negative, then we're looking at a local recurrence of his primary disease growing through chemotherapy, which is obviously of concern, but it's still local disease. I agree with Roy that radiation therapy is the first option we would consider.

If we wanted to treat with the best intention and take a risk, we could use a concurrent chemoradiation schedule because it is just local recurrence. That would be a multidisciplinary discussion between the surgeon, the radiation oncologist and the medical oncologist.

If we wanted to use chemotherapy with radiation therapy, then certainly docetaxel as a single agent is a possibility. The other regimen that I use often is cisplatin with docetaxel, both weekly. Hak Choy has conducted studies using carboplatin with docetaxel and radiation therapy (Choy 2001).

DR LOVE: Do you see bevacizumab fitting into this man's therapy, either now or in the future?

DR KIM: If we considered his disease metastatic and we used the radiation therapy as a local control measure because of his symptoms, then I wouldn't have a problem giving him bevacizumab afterward.

DR LOVE: Roy, what about the general concept of second- or third-line bevacizumab?

DR HERBST: I believe that, in most cases, bevacizumab should be used in the front-line setting. But in a case like this, one could consider a chemotherapy combination with bevacizumab once the radiation treatment is complete.

Trials combining bevacizumab with radiation therapy have developed slowly because of concerns about central lesions and about tumors of this type bleeding. The RTOG and SWOG both will soon have trials evaluating bevacizumab with and without radiation therapy.

Right now we do not have data, so I probably wouldn't add it to the radiation therapy, although every preclinical paper you read shows anti-angiogenic agents improving short-term oxygenation to the tumors, enhancing the radiation effect (Gerber 2005). In my opinion, that is going to be a real winner, but it's going to take some time.

I do think this patient is a great candidate for a second-line protocol that includes docetaxel with bevacizumab, pemetrexed with bevacizumab or erlotinib with bevacizumab. These trials are all out there.

DR LOVE: Mike, can you follow up with this patient?

DR TRONER: He will be seeing the radiation oncologist next week. My treatment plan was weekly docetaxel, but I am also considering bevacizumab. ■

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Choy H et al. **Phase I trial of outpatient weekly docetaxel, carboplatin and concurrent thoracic radiation therapy for stage III unresectable non-small-cell lung cancer: A Vanderbilt Cancer Center Affiliate Network (VCCAN) trial.** *Lung Cancer* 2001;34(3):441-9. **Abstract**

Gerber HP, Ferrara N. **Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies.** *Cancer Res* 2005;65(3):671-80. **Abstract**

Seiwert TY et al. **A phase I dose-escalating study of combination pemetrexed-based chemotherapy and concomitant radiotherapy for locally advanced or metastatic non-small cell lung or esophageal cancer.** *Proc ASCO* 2005;**Abstract 7062**.

SELECT EXCERPTS FROM TUMOR PANEL DISCUSSION: DRS ROY S HERBST, MD, PHD AND EDWARD S KIM, MD

CASE 3: FROM THE PRACTICE OF STEPHEN A GRABELSKY, MD

Tracks 1-5

- A 67-year-old man who is an ex-smoker
- 3.5-centimeter mass in the lower right lobe and a 1.5-centimeter hilar lymph node
- Mediastinoscopy and biopsy revealed poorly differentiated, large cell carcinoma with contralateral mediastinal adenopathy
- MRI of brain and CT scans were negative

DR LOVE: Ed, what treatment would you be thinking about for this patient?

DR KIM: We would talk with a radiation oncologist and plan on concurrent chemoradiation therapy. Many different agents are available that could be used.

The two regimens that I usually prefer are the SWOG-S9504 regimen — using cisplatin and etoposide followed by consolidation docetaxel — or cisplatin and docetaxel, each administered weekly (Gandara 2003, 2005; [2.1]).

Of course, you can also consider this patient for a clinical trial. He sounds like a fit person, and a trial with bevacizumab or some other agent, even cetuximab, is something to consider.

DR LOVE: What happened with this man?

DR GRABELSKY: He was treated a few months ago, so the bevacizumab trials were not yet open. He received etoposide and cisplatin with concurrent radiation therapy as in the SWOG study, followed by docetaxel every three weeks at 75 mg/m^2 (Gandara 2003, 2005a, 2005b; [2.1]).

He tolerated it fairly well. Toward the end of his combined-modality therapy, he had Grade II esophagitis and a moderate degree of anemia, which was treated with an erythropoietin agent. We decided to prophylactically treat him with pegfilgrastim with the docetaxel, and he had no significant problems with neutropenia.

2.1

Long-Term Survival in Stage IIIB NSCLC Treated with Docetaxel Consolidation Following Concurrent Chemoradiotherapy

Trial ID	Trial schema	Median survival (95% CI)	Two-year survival (95% CI)	Three-year survival (95% CI)	Four-year survival (95% CI)	Five-year survival (95% CI)
SWOG-S9504	PE/RT → D	26 months (18-35)	54% (43-65)	37% (24-55)	29% (19-29)	29% (19-29)
SWOG-S9019	PE/RT → PE	15 months (10-22)	34% (21-47)	17% (7-27)	17% (6-28)	17% (6-28)

Conclusion: "Long-term survival endpoints achieved in S9504 in documented Stage IIIB NSCLC compare favorably with the SWOG historical control of S9010 and published literature."

CI = confidence interval; P = cisplatin; E = etoposide; RT = radiation therapy; D = docetaxel

SOURCE: Gandara DR et al. Presentation. *Proc ASCO* 2005a;**Abstract 7059**.

He's now approximately six months out, and so far he is doing beautifully. A repeat PET scan on completion of therapy was negative, and CT scans and MRI of the brain were also negative.

DR LOVE: Roy, how do you approach the selection of a chemotherapeutic regimen to combine with radiation therapy in this situation?

DR HERBST: I believe the therapy this patient received was a good choice. The data from the SWOG Phase II report and the recent data from the Phase III report of SWOG-S0023 suggest that this combination continues to look like a winner (Kelly 2005).

I believe all the data over the last five or more years tell us that concurrent chemoradiation therapy is the way to go. One could do it with cisplatin and etoposide followed by docetaxel in the consolidation setting (2.2).

Many doctors in Houston at MD Anderson also use weekly carboplatin with paclitaxel during the radiation therapy, followed by two cycles of consolidation carboplatin and paclitaxel, because of the ease of administration.

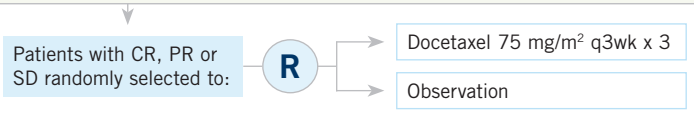
I think that's also reasonable. In the next year or so we'll start seeing bevacizumab brought into this setting as well. ■

2.2

A Phase III Study of Chemoradiation Therapy with or without Consolidation Docetaxel

Protocol IDs: HOG LUN01-24, NCT00216125
Target Accrual: 259

Eligibility
Unresectable Stage IIIA or Stage IIIB NSCLC, ECOG performance status 0 or 1
Patients receive cisplatin 50 mg/m^2 d1, 8, 29, 36 + etoposide 50 mg/m^2 d1-5, 29-33 + radiation therapy 5940 cGy (180 cGy/day)



SOURCE: NCI Physician Data Query, April 2006; ClinicalTrials.gov, April 2006.

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Gandara DR et al. **Long-term survival in stage IIIb non-small cell lung cancer (NSCLC) treated with consolidation docetaxel following concurrent chemoradiotherapy (SWOG S9504).** *Proc ASCO* 2005a;**Abstract 7059**.

Gandara DR et al. **Therapeutic strategies for combined-modality therapy of locally advanced non-small-cell lung cancer: Rationale for consolidation docetaxel therapy.** *Clin Lung Cancer* 2005b;7(Suppl 3):93-7. **Abstract**

Gandara DR et al. **Consolidation docetaxel after concurrent chemoradiotherapy in Stage IIIB non-small-cell lung cancer: Phase II Southwest Oncology Group Study S9504.** *J Clin Oncol* 2003;21(10):2004-10. **Abstract**

Kelly K et al. **Low incidence of pneumonitis on SWOG 0023: A preliminary analysis of an ongoing phase III trial of concurrent chemoradiotherapy followed by consolidation docetaxel and Iressa/placebo maintenance in patients with inoperable stage III non-small cell lung cancer**. *Proc ASCO* 2005;**Abstract 7058**.

SELECT EXCERPTS FROM TUMOR PANEL DISCUSSION: DRS ROY S HERBST, MD, PHD AND EDWARD S KIM, MD

CASE 4: FROM THE PRACTICE OF ATIF M HUSSEIN, MD

Tracks 1-4

- 71-year-old woman who is an ex-smoker with back pain
- Presented with a 2.5-centimeter subcutaneous mass on the skull, without parenchymal abnormalities
- CT revealed a three-centimeter lesion in the upper lobe of the left lung, three small (less than five millimeters) nodules in the right lung and multiple lytic lesions in the thoracic and lumbar spine
- Excisional biopsy of the skull mass revealed poorly differentiated adenocarcinoma
- Bone scan revealed abnormal accumulation in the spine and ribs, compatible with metastatic disease
- The patient was emotionally depressed and was losing weight

DR LOVE: Ed, once her mood and appetite improve, what therapy would you be considering for this patient?

DR KIM: I would consider this woman for combination chemotherapy with bevacizumab. If she were being treated at MD Anderson, I would put her on our Phase II trial of carboplatin/docetaxel and bevacizumab (3.1). Outside of a clinical trial, you have the option of using either taxane with carboplatin and bevacizumab.

DR HERBST: This is a patient who clearly should receive the best therapy available, which outside a clinical trial now includes

3.1 **A Phase II Evaluation of Bevacizumab in Combination with Chemotherapy**

Protocol ID: MDACC 2005-0224
Target Accrual: 50 (Open)

Eligibility
Metastatic NSCLC; ECOG performance status 0 or 1; without history of MI or stroke within past six months or NYHA Grade II or greater CHF; no clinically significant peripheral vascular disease, bleeding diathesis or coagulopathy, or CNS metastases

↓

Carboplatin + docetaxel + bevacizumab

- **Primary endpoint:** Progression-free survival
- **Secondary endpoints:** Overall survival, disease control rate, safety of triple-agent regimen, correlate primary and secondary objectives with biomarkers and immunohistochemistry

Study Contact:
Edward Kim, MD
Tel: 800-392-1611
MD Anderson Cancer Center
Houston, Texas

SOURCE: mdanderson.org.

bevacizumab. The median survival in the ECOG trial of carboplatin/paclitaxel/bevacizumab was more than 12 months for the group receiving bevacizumab (Sandler 2005; [3.2]). She doesn't have any contraindications to the drug, and I believe this is a reasonable approach.

DR LOVE: Dr Hussein, can you follow up on this patient?

DR HUSSEIN: I treated her with narcotics for her pain and sent her for a radiation oncology consult. She started radiation therapy to the spine immediately. The main trouble we are facing is her appetite. I put her on megestrol acetate, knowing it might increase the risk of deep vein thrombosis but not knowing what else to do. I think she would probably also benefit from an antidepressant.

In terms of chemotherapy, I started her on carboplatin and docetaxel, and I irradiated a large part of her spine. She also received pegfilgrastim and zoledronic acid. I did not want to start bevacizumab in the first cycle because I've administered so many drugs to her at the same time and because she has the incision in her scalp and a port. I will definitely be adding bevacizumab to her second cycle. ■

3.2

ECOG-E4599: A Phase III Trial Evaluating Paclitaxel (P)/Carboplatin (C) with or without Bevacizumab (B) in Patients with Previously Untreated Metastatic Nonsquamous NSCLC

	PCB (n = 434)	PC (n = 444)	HR (CI)	*p*-value
Median OS	12.5 months	10.2 months	0.77 (CI:0.65-0.93)	0.0075
Two-year OS	22.1%	16.9%	—	—
Median PFS	6.4 months	4.5 months	0.62 (CI:0.53-0.72)	<0.0001

OS = overall survival; PFS = progression-free survival

SOURCE: Sandler AB et al. Presentation. ASCO 2005;**Abstract 4**.

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Dornbusch D et al. **How do U.S. medical oncologists learn and apply new clinical trials information from press releases in nonmedical media? A case study based on ECOG 4599.** *Oncologist* 2006;11(1):31-8. **Abstract**

Herbst RS et al. **Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer.** *J Clin Oncol* 2005;23(11):2544-55. **Abstract**

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SELECT EXCERPTS FROM TUMOR PANEL DISCUSSION: DRS ROY S HERBST, MD, PHD AND EDWARD S KIM, MD

CASE 5: FROM THE PRACTICE OF DR SEIGEL

Tracks 1-4

- 79-year-old woman who is an ex-smoker
- Right upper lobe NSCLC and a two-centimeter contralateral axillary node, with widespread metastatic disease
- Multiple comorbidities, including diabetes
- ECOG performance status (PS) = 2

DR LOVE: Ed, can you talk about how you would think through this case?

DR KIM: Performance status and overall clinical health are important factors in how aggressively we can treat these types of patients. Her advanced age makes it difficult to even consider doublet chemotherapy, and I would not, even setting her performance status aside.

We have several options. We have to mention hospice. It may not be the right option at this time, but it has to be something that the patient and the family have heard about.

A second option is that we have oral drugs now, such as erlotinib, which are generally well tolerated with few side effects, although in a first-line setting, the overall benefit is unclear. Some benefit probably exists, but it's untested (4.1).

Chemotherapeutic agents such as pemetrexed or weekly docetaxel are options in patients with poorer performance status.

These agents have been tested in the elderly and are being tested in patients with poor performance status (Le Caer 2005; Gridelli 2005; Mainwaring 2005).

Her disease is everywhere, and her outcome will not be very good. It will be hard to manage her diabetes, especially with some of the chemotherapies that require steroids. I would probably start her on erlotinib as the single-agent choice right now.

DR HERBST: I agree completely. I think the most you can accomplish here is symptom control and supportive care.

No treatment is clearly a reasonable choice here, but this is a case where front-line erlotinib serves a good purpose. It's easy to administer, it is generally well tolerated, and the patient can take it at home.

You can give her a trial for a couple of months and see how she does.

DR LOVE: Roy, how would you approach this patient if she had no comorbidities and her poor performance status was directly related to the presence of the tumor?

DR HERBST: If, in fact, the tumor is causing the performance status decrease and you believe you have effective therapy for the tumor, I might want to be a bit more aggressive.

Potentially, you could treat the tumor and alleviate the symptoms at the same time, so I may lean more toward a cytotoxic chemotherapy up front.

DR LOVE: Would you start with a platinum doublet or single-agent chemotherapy?

DR HERBST: If a patient truly has a performance status of two, it is difficult to start with a platinum doublet. So I would probably recommend a single agent, either docetaxel or pemetrexed. ■

4.1

An Open-Label Phase II Study of First-Line Erlotinib in Elderly Patients with Previously Untreated, Stage IIIB/IV NSCLC

Patient characteristics (N = 76)

Median age, years (range)	ECOG performance status		Smoking status	
75 (70-91)	0	17%	Never	11%
	1	72%	Former	84%
	2	11%	Current	5%

Antitumor response (evaluable N = 66)

Response	N	%	95% CI	Median duration of response (range)	Median survival* (95% CI)
Complete response (CR)	0	0	—	—	—
Partial response (PR)	8	12	5-23	Not yet reached	Not yet reached
Stable disease (SD)	32	48	37-60	6.0 months (2-25+)	12 months (10-16)
Progressive disease	26	39	28-51	—	7 months (4-11)

Disease control rate (CR + PR + SD) = 60.6%

* Median survival (95% CI) for all patients = 11 months (8-14)

Adverse events (>5% occurrence)

Event	All Grades	Grades III-V	Event	All Grades	Grades III-V
Rash	75%	9%	Stomatitis	13%	0%
Diarrhea	61%	1%	Anorexia	12%	1%
Dry skin	36%	0%	Lacrimation	11%	1%
Elevated LFTs	28%	0%	Nausea/vomiting	8%	0%

SOURCE: Jackman DM et al. Presentation. ASCO 2005;**Abstract 7148**.

SELECT PUBLICATIONS

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Jackman DM et al. **Phase II study of the EGFR tyrosine kinase erlotinib in patients > 70 years of age with previously untreated advanced non-small cell lung carcinoma.** *Proc ASCO* 2005;**Abstract 7148**.

Le Caer H et al. **A multicenter phase II study of docetaxel (D) or docetaxel/gemcitabine (G) weekly in advanced non-small cell lung cancer (NSCLC) in elderly and/or poor performance status (PS) patients (pts). (GFPC 0202).** *Proc ASCO* 2005;**Abstract 7150**.

Mainwaring MG et al. **Weekly docetaxel versus weekly docetaxel/gemcitabine as first-line therapy for patients who are elderly or with poor performance status (PS) or with serious comorbidities with advanced non-small cell lung cancer (NSCLC): Interim safety analysis of a Minnie Pearl Cancer Research Network phase III trial.** *Proc ASCO* 2005;**Abstract 7151**.

SELECT EXCERPTS FROM TUMOR PANEL DISCUSSION: DRS ROY S HERBST, MD, PHD AND EDWARD S KIM, MD

CASE 6: FROM THE PRACTICE OF DR GRABELSKY

Tracks 1-3

- 82-year-old man who is an ex-smoker
- Presented with painless right supraclavicular lymphadenopathy
- Excisional biopsy revealed a neuroendocrine carcinoma consistent with small cell lung cancer (SCLC)
- CT scans and endoscopies were negative for disease outside the supraclavicular region
- PET not performed because of lack of reimbursement

DR KIM: You would almost call this an unknown primary because small cells can originate from many areas. Patients like this can be approached in several ways. If the cancer were small cell lung cancer, chemotherapy would almost be prophylactic in the sense that we don't know what we're treating, how many cycles to administer, etc.

If you delivered concurrent radiation therapy to the entire field, you would be adding excessive toxicity without knowing if you missed an extrathoracic primary. I would have a great deal of discussion with my colleagues about this case.

It might be that radiation therapy to the actual site of excision is the only thing needed at this point. Or you could watch and wait with close follow-up with scans to see if a primary manifests itself.

I had a similar situation with a patient who had a subcutaneous abdominal nodule that was excised, and it turned out to be non-small cell lung cancer with no obvious primary. We observed her for more than a year without any indication of a primary and without any additional therapy.

I would probably send this patient to receive radiation therapy in the specific area where the tumor was located and then just watch him closely.

DR HERBST: This is a tough case. Most of the time when small cell lung cancer is the pathologic diagnosis, it's assumed to be lung cancer, but I'm not so sure in this case. Clearly, it's extensive disease, wherever it came from. A search for a primary site, within reasonable limits, has not yielded much.

This is a case in which I'd sit down with the pathologist and carefully look at the pathology. If the best diagnosis is SCLC, one could have a number of different options.

This is an elderly gentleman, but it sounds as if his performance status is reasonable. He has extensive disease with an unknown primary, so I probably would opt for some chemotherapy, perhaps three or four cycles of carboplatin and etoposide. Although we don't know the origin of the primary, this should cover most primary sites. I would back off if he develops significant toxicity.

I've had a couple of recent cases like this, and they're difficult. One patient with presumed SCLC who had disease throughout his body came because of cord compression, but the patient had never smoked, which is unusual for SCLC. That patient ended up having a small bowel primary.

Radiation therapy certainly could be used, but if the surgical resection was good, this is presumably a systemic disease. So I would differ with that a little bit and go more toward systemic therapy.

Sometimes multiple options can be presented to the patient. In this case, I think options could vary from doing nothing to using radiation therapy to administering chemotherapy. As with anything else, you have to see this man in the office to make that decision.

DR LOVE: Steve, what happened with this patient?

DR GRABELSKY: We did have the pathology reviewed, and it confirmed the pathologic diagnosis. He was presented at our local hospital tumor board. On exam, it was unclear whether the biopsy site was indurated or just had residual tumor.

We elected to treat him with combined-modality therapy with etoposide and carboplatin along with involved-field radiation to the supraclavicular area and the adjacent anterior cervical lymph nodes. We did not radiate the lung area. He received an additional two cycles of etoposide/carboplatin after the radiation therapy was completed.

He did beautifully, with some minor radiation dermatitis, and resumed all his normal activities. I saw him just last week, and he's more than a year out and in complete remission. Still, no primary site has been discovered. ■

SELECT PUBLICATIONS

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INTERVIEW

Roy S Herbst, MD, PhD

Dr Herbst is Chief of the Section of Thoracic Medical Oncology, Associate Professor of Medicine and Co-Director of the Phase I Clinical Trials Working Group in the Department of Thoracic, Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-16

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: What are some of the anti-angiogenic agents in development right now that you believe are promising?

DR HERBST: So many different agents are emerging that I liken this period to when the taxanes were first introduced in lung cancer therapy. One of the agents that I think is most promising, or at least will make it to the more advanced stages sooner than others, is a drug called ZD6474. It's an oral agent, and it shows dual-receptor TKI activity against both the VEGF receptor 2 and the EGFR receptor.

It's somewhat like a combination bevacizumab and erlotinib in one molecule. It's reasonably well tolerated, and several trials have already shown promising

results (5.1). One trial has evaluated this drug versus gefitinib in a blinded fashion (Natale 2005) and showed a time to progression benefit in favor of ZD6474.

A second trial, which I led with John Haymack, showed that docetaxel with ZD6474 produced an improvement in time to progression versus docetaxel alone (Herbst 2005a). In the second-line lung cancer setting, that combination is about to be evaluated in Phase III trials.

5.1

Efficacy of ZD6474 in Randomized, Double-Blind Phase II Studies of Patients with Stage IIIB/IV NSCLC

Study of ZD6474 versus gefitinib

	ZD6474 (n = 83)	Gefitinib (n = 85)	Hazard ratio	95% CI	*p*-value
TTP	11.9 weeks	8.1 weeks	—	—	—
Prolongation of TTP*	58%	—	0.63	11% to 125%	0.011

Study of ZD6474 + D versus D alone†‡

	ZD6474 100 mg + D (n = 42)	ZD6474 300 mg + D (n = 44)	D alone (n = 41)
TTP	18.7 weeks	17 weeks	12 weeks
Hazard ratio	0.64	0.83	—
Prolongation of TTP§	57%	21%	—
95% CI	-4% to 160%	-27% to 99%	—
p-value	0.074	0.42	—

* Versus gefitinib; † median duration of follow-up was approximately nine months.
‡ D = docetaxel; § versus D alone; TTP = time to progression

SOURCES: Herbst R et al. Proceedings from the 11th World Conference on Lung Cancer 2005a;Abstract O-100; Natale R et al. Presentation. Proceedings from the 11th World Conference on Lung Cancer 2005;Abstract O-103.

DR LOVE: You said ZD6474 is like a combination of bevacizumab and erlotinib, yet its VEGF mechanism works from the inside rather than the outside of tumor cells, correct?

DR HERBST: It is a different mechanism than bevacizumab. Instead of trapping the ligand, VEGF, thereby preventing activation of the receptor on endothelial cells, these agents are working inside the cell at the level of the tyrosine kinase. If active, these types of agents have the potential for being more convenient, perhaps less expensive, and more active.

The downside would be that any combination molecule might not exhibit the optimal activity against both receptors. So you run the risk that perhaps this becomes a good inhibitor of angiogenesis, but maybe at the doses that are being used it's a weaker inhibitor of EGFR compared to the scenario in which you use two drugs that each show activity independently for one receptor or the other.

DR LOVE: What are the major toxicities associated with ZD6474?

DR HERBST: The toxicities are mostly related to EGFR inhibition, meaning some rash and mild diarrhea. However, the rash is a bit different than the rash one sees with a pure EGFR inhibitor.

The other issue is that many of these small molecules — and this agent is no exception — produce some asymptomatic prolongation of the cardiac QT interval, which has not been an issue in clinical trials, although followed closely. To my knowledge, no significant toxicity has been associated with that.

Track 10

DR LOVE: What questions do you commonly receive from medical oncologists about the use of bevacizumab?

DR HERBST: Oncologists want to use bevacizumab, but bleeding is of some concern. Right now, oncologists would probably not treat outside of the indications studied during the clinical trial because of the concern for bleeding. But the question often comes up, "Would you treat a patient with a centrally located adenocarcinoma?" We clearly need more data on that subject.

My approach is to discuss it with the patient. You need to follow these patients closely. What is a central lesion? Which lesions are most likely to bleed? I have treated some patients who have large tumors in the chest and I have gotten away with it, but a risk does exist that is probably somewhere in the range of one to two percent.

Track 14

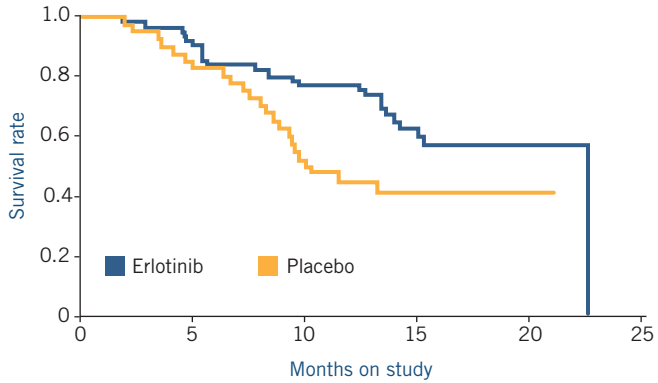
DR LOVE: Would you discuss your approach for NSCLC patients who have never smoked?

DR HERBST: I often receive questions from medical oncologists about the never-smokers and if they should use erlotinib with chemotherapy. I believe that's a reasonable approach; I've used it several times myself. For patients who have never smoked, our collaborative group showed a median survival of approximately 22 months versus 10 months for never-smokers who received carboplatin/paclitaxel/erlotinib versus carboplatin/paclitaxel, respectively (Herbst 2005b; [5.2]). The number of never-smokers in the trial was around 110 patients.

Vince Miller is leading a CALGB trial that will include larger numbers of patients to try to confirm this finding. But in a never-smoker with a good performance status — usually zero to one — it's reasonable to consider administering chemotherapy with erlotinib. Now, if the patient is a never-smoker with marginal performance status, you might not want to administer chemotherapy. This is a group for whom I've recommended erlotinib alone.

5.2

Overall Survival for Never-Smokers in the TRIBUTE Trial: Erlotinib or Placebo, Combined with Carboplatin and Paclitaxel



	Erlotinib	Placebo	*p*-value
Median survival (months)	22.5	10.1	0.01
Number of patients	72	44	—

SOURCE: Herbst RS et al. **TRIBUTE: A Phase III Trial of Erlotinib Hydrochloride (OSI-774) Combined with Carboplatin and Paclitaxel Chemotherapy in Advanced Non-Small-Cell Lung Cancer.** *J Clin Oncol* 2005b;23(25):5892-9. Reprinted with permission from the American Society of Clinical Oncology. **Abstract**

Track 15

DR LOVE: Can you discuss the combination of bevacizumab and erlotinib for NSCLC?

DR HERBST: I often receive calls from physicians about this combination, not only from clinicians, but also from investigators. It seems as if the combination is being used frequently. When we set out to do these trials, our goal was to pilot the combination of two targeted agents so we could then add chemotherapy in the future.

It always bothered me a little that we were using targeted therapy to reduce side effects with the ultimate goal of adding back all the chemotherapy. Of course, adding chemotherapy became less interesting when the gefitinib studies, including the INTACT studies (Herbst 2004; Giaccone 2004), and the erlotinib studies, including TRIBUTE (Gatzemeier 2004; Miller 2004; Herbst 2005b), didn't show a benefit when chemotherapy was added to EGFR inhibitors.

In our two-center study (MD Anderson and Vanderbilt), the combination of bevacizumab and erlotinib looked good, with a median survival of 12.6 months in patients who failed at least one platinum-based chemotherapy regimen for recurrent or metastatic disease: All patients had nonsquamous tumors, and all patients were without brain metastases (Herbst 2005c).

Those data made people take note, and now one agent is approved in lung cancer, and survival data for the other are looking good in randomized studies (Sandler 2005). This is a combination that has really taken off.

There is currently a Phase III trial being conducted in the United States that takes patients in the second-line setting and randomly assigns them to bevacizumab with erlotinib versus erlotinib alone (5.3). This combination is also being evaluated in clinical trials as neoadjuvant therapy, adjuvant therapy and maintenance therapy.

I often get calls from physicians in the community to ask how to use this combination. Should they add bevacizumab to erlotinib for someone whose disease might be progressing? Should they use the combination as standard second-line therapy? I try to encourage them to enter the patient on a clinical trial because the only way we're going to make progress is to test these combinations in a clinical study.

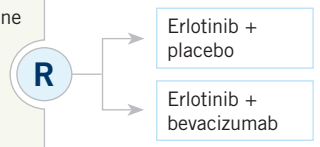
Occasionally, if someone is not a candidate for a study or has had too many prior therapies, then I'll advise the physician about how we've done it and refer them to our paper. ■

5.3

Phase III Study Evaluating the Efficacy of Bevacizumab with or without Erlotinib as Second-Line Treatment for Advanced NSCLC

Protocol IDs: OSI3364g, NCT00130728
Target Accrual: 650 (Open)

Eligibility
Clinical or radiographic progression during or after first-line chemotherapy or chemoradiotherapy for NSCLC
Consent to provide archival tissue for EGFR testing
ECOG PS 0-2
18 years of age or older
No squamous cell carcinoma with central pulmonary lesions



Study Contact:
Amy Graves
Genentech Incorporated
Graves.Amy@Gene.com

SOURCE: NCI Physician Data Query, March 2006.

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Among never-smokers in the TRIBUTE trial, the median survival was _____ for patients who received carboplatin/paclitaxel/erlotinib versus 10 months for those who received carboplatin/paclitaxel.**
   a. 36 months
   b. 22 months
   c. 12 months

2. **In a Phase I/II trial combining bevacizumab and erlotinib for the treatment of recurrent NSCLC, the median survival was greater than one year.**
   a. True
   b. False

3. **In the SWOG-S9504 trial, consolidation docetaxel was administered every three weeks after cisplatin/etoposide/radiation therapy.**
   a. True
   b. False

4. **Preclinical studies suggest that one mechanism of action of anti-angiogenic agents, such as bevacizumab, may be to improve short-term oxygenation to tumors, thus enhancing the effect of radiation therapy.**
   a. True
   b. False

5. **In the Phase III trial NCT00130728, erlotinib with placebo control is being compared to erlotinib with _____ for patients with progressive NSCLC.**
   a. Gefitinib
   b. Docetaxel
   c. Bevacizumab
   d. Radiation therapy

6. **The oral agent ZD6474 has dual-receptor TKI activity against both the VEGF receptor 2 and the EGFR receptor.**
   a. True
   b. False

7. **In ECOG-E4599, the Phase III trial evaluating paclitaxel/carboplatin with or without bevacizumab, the addition of bevacizumab significantly improved which of the following?**
   a. Overall survival
   b. Progression-free survival
   c. Both of the above
   d. None of the above

8. **Which of the following agents have been tested in the elderly and may be options for patients with poorer performance status?**
   a. Docetaxel
   b. Pemetrexed
   c. Both of the above
   d. None of the above

9. **In a double-blind, randomized, Phase II study of patients with Stage IIIB/IV non-small cell lung cancer, time to progression was _____ for patients who received ZD6474 and 8.1 weeks for those who received gefitinib (p = 0.011).**
   a. 5.4 weeks
   b. 11.9 weeks
   c. 8.9 weeks

10. **Toxicities associated with ZD6474 include:**
    a. Rash
    b. Increased cardiac QT interval
    c. Mild diarrhea
    d. All of the above
    e. None of the above

11. **In the SWOG-S9504 trial of cisplatin/etoposide with radiation therapy followed by docetaxel for the treatment of Stage IIIB NSCLC, the median survival was significantly _____ than that of SWOG-S9019, in which cisplatin/etoposide/radiation therapy was administered without docetaxel.**
    a. Longer
    b. Shorter

Post-test answer key: 1b, 2a, 3a, 4a, 5c, 6a, 7c, 8c, 9b, 10d, 11a

EVALUATION FORM

Lung Cancer Update — Issue 2, 2006

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Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = Not applicable to this issue of *LCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *LCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in lung cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, locally advanced and metastatic settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for treatment of elderly patients and those with poor performance status in the adjuvant, neoadjuvant, locally advanced and metastatic settings. . . . . 5 4 3 2 1 N/A
- Integrate emerging data on utilization of targeted molecular therapies and molecular and genetic assays in the development of individual management strategies for patients with lung cancer. . . . . 5 4 3 2 1 N/A
- Counsel patients with localized primary lung cancer about the risks and benefits of adjuvant chemotherapy. . . . . 5 4 3 2 1 N/A
- Identify the impact of smoking-related comorbidities on the treatment of patients with lung cancer and integrate smoking cessation into the management strategy for these patients. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Roy S Herbst, MD, PhD	5 4 3 2 1	5 4 3 2 1
Edward S Kim, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

Which of the following audio formats of this program did you use?

☐ Audio CDs ☐ Audio tapes ☐ Download MP3s from website

EVALUATION FORM

Lung Cancer Update — Issue 2, 2006

REQUEST FOR CREDIT — please print clearly

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

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ 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 Credit(s)™*. 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: .....

Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Additional comments about this activity:

.....

FOLLOW-UP

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.

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at LungCancerUpdate.com/CME.

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: NLove@ResearchToPractice.net
For CME Information	Email: CME@ResearchToPractice.net

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