LCU | 2007 VOL 4 | ISSUE 3

Lung Cancer™ UPDATE

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

EDITOR

Neil Love, MD

INTERVIEWS

Bruce E Johnson, MD

Mark A Socinski, MD

Heather A Wakelee, MD

CME Certified

Lung Cancer Update
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 and radiation oncologist 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 3 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Johnson, Socinski and Wakelee on the integration of emerging clinical research data into the management of lung cancer.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 2.75 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs, review the monograph and complete the Post-test and Evaluation Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **LungCancerUpdate.com** 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 here in **blue underlined text**.

This program is supported by education grants from Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology/OSI Pharmaceuticals Inc and Sanofi-Aventis.

TABLE OF CONTENTS

If you would like to discontinue your complimentary subscription to *Lung Cancer Update*, please email us at **Info@ResearchToPractice.com**, call us at (800) 648-8654 or fax us at (305) 377-9998. Please include your full name and address, and we will remove you from the mailing list.

IN THIS ISSUE OF *LUNG CANCER UPDATE*

- First presentation of data from the AVAiL trial evaluating bevacizumab, gemcitabine and cisplatin as first-line therapy for metastatic non-small cell lung cancer
- Update on EGFR tumor cell mutations and response to EGFR tyrosine kinase inhibitors
- New findings on prophylactic cranial irradiation in extensive-stage small cell cancer
- Launch of ECOG-E1505, an adjuvant trial evaluating chemotherapy (cisplatin/etoposide, cisplatin/docetaxel or cisplatin/gemcitabine) with or without bevacizumab

CONTENT VALIDATION AND DISCLOSURES

Research To Practice 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 by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest, either current or within the past 12 months, for themselves (or their spouses/partners) that have been resolved through a peer review process: John Brebner, Clayton Campbell, Anne Jacobson, MPH, Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Ginelle Suarez, Chris Thomson, MD, MS, Erin Wall and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Aviva Asnis-Alibozek, PA-C, MPAS — salary: AstraZeneca Pharmaceuticals LP; shareholder of AstraZeneca Pharmaceuticals LP; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc and Genentech BioOncology. Research To Practice receives education grants from Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Genentech BioOncology/OSI Pharmaceuticals Inc, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Johnson — Consulting Fees: Genzyme Corporation; Royalty: Patent EGFR testing. **Dr Socinski** — Contracted Research: Abraxis BioScience, Genentech BioOncology, Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: Abraxis BioScience, Genentech BioOncology, Sanofi-Aventis. **Dr Wakelee** — Consulting Fees: Sanofi-Aventis; Other (Research Funding): Eli Lilly and Company, Genentech BioOncology.

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

Bruce E Johnson, MD

Dr Johnson is Director of Dana-Farber Cancer Institute's Lowe Center for Thoracic Oncology and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-22

Select Excerpts from the Interview

Track 1

DR LOVE: Can you provide an overview of the tumor mutations that are associated with increased response to EGFR TKIs in non-small cell carcinoma?

DR JOHNSON: We were involved in the discovery of a correlation between

genetic changes in the epidermal growth factor receptor (EGFR) and the likelihood of response to treatment with either gefitinib or erlotinib (Lynch 2004; Jackman 2006).

We observed a subgroup of patients who had dramatic, long-lived responses (1.1), and that was unusual in NSCLC. Subsequently, my colleagues Dr Tom Lynch and Dr Lecia Sequist led a trial that prospectively identified EGFR mutations in patients with newly diagnosed, previously untreated NSCLC.

Patients with EGFR mutations were treated with gefitinib. We reported the results for 31 patients, with a response rate of approximately 60 percent and a time to progression of about one year (Sequist 2007). Whether those patients with mutations would have done just as well with chemotherapy remains unknown.

1.1

Association of EGFR Mutations and Response to Erlotinib or Gefitinib in Patients with NSCLC

	EGFR mutation	
	Exon 19 deletion (n = 22)	L858R point mutation (n = 10)
Response rate	73%	50%
One-year TTP	68%	40%
One-year OS	95%	80%

TTP = time to progression; OS = overall survival

SOURCE: Jackman DM et al. *Clin Cancer Res* 2006;12(13):3908-14. **Abstract**

Track 9

DR LOVE: Would you comment on the nonprotocol management of patients with EGFR mutations and phenotypic predictors of response, such as nonsmoking status?

DR JOHNSON: We believe the place to begin to answer that question is in first-line treatment of metastatic disease for patients with previously untreated NSCLC. Trials to answer that question — how patients fare with the EGFR TKIs versus those treated with conventional chemotherapy — will be available within the next two years.

That question may be more difficult to answer in that adjuvant setting.

DR LOVE: What about in the first-line metastatic setting, off protocol?

DR JOHNSON: The agents aren't approved for first-line therapy, but we have had trials with first-line erlotinib and gefitinib for the past five years in our institution. We've considered it when a patient tests mutation-positive and wouldn't otherwise qualify for a trial.

Tracks 10-12

DR LOVE: What's your algorithm for the management of metastatic disease in the clinical setting for patients who are not in the EGFR-enriched populations — an average patient, a smoker, et cetera?

DR JOHNSON: We follow the Eastern Cooperative Oncology Group (ECOG) algorithm. For patients with adenocarcinoma without brain metastasis, serious cardiovascular or cerebrovascular problems or clotting, we recommend paclitaxel, carboplatin and bevacizumab.

For patients with SCC, brain metastasis or hemoptysis, we administer paclitaxel and carboplatin. We try to utilize the same drugs off study as we do on study. For patients with a number of serious medical issues, we'll use a single agent such as vinorelbine.

DR LOVE: What's been your experience with the regimen of carboplatin/paclitaxel with bevacizumab, particularly in terms of the side effects and toxicity?

DR JOHNSON: Side effects include hypertension and an increased risk of clotting, bleeding and proteinuria, which are all manageable. We also see an increased risk of deep venous thrombosis and pulmonary emboli.

DR LOVE: How do you approach second-line therapy for patients with NSCLC?

DR JOHNSON: For patients in second-line therapy off study who have been treated with two agents — most commonly carboplatin/paclitaxel in our setting — and have a good response and go off therapy for an extended period, we'll commonly go back to docetaxel as second-line therapy.

For a patient who shows a mediocre response, we will commonly use erlotinib as the second agent. We often use pemetrexed as the third-line agent for the patients who don't quite fit into classic clinical response categories.

For almost everybody off study, we use one of the three approved agents for second-line treatment — pemetrexed, docetaxel or erlotinib.

Tracks 18-19

DR LOVE: Which of the new biologic agents show promise and may be coming into the clinic in the near future?

DR JOHNSON: One of the classes of agents I believe will likely find a place is the targeted kinases, such as those that include a VEGF receptor blockade. Sunitinib and sorafenib have been approved for kidney cancer, and a response rate of 10 to 12 percent has been recorded with sunitinib among previously treated patients with NSCLC (Socinski 2006).

The other agent I work with is vandetanib, which when combined with docetaxel reached its primary endpoint of prolonging progression-free survival

(Heymach 2006). It is now being tested in a large trial to find out if it increases response rates.

We have also found that a number of patients can be maintained on vandetanib from six months up to two years. We believe that represents a particularly sensitive subset, and we hope to identify what conveys such sensitivity in those particular tumors.

DR LOVE: What is the proposed mechanism of action of vandetanib?

DR JOHNSON: Vandetanib is an inhibitor of the VEGF receptor and the EGFR. It inhibits the VEGF receptor II at a level about five times lower than the EGFR.

When you use a higher dose of vandetanib, 300 milligrams a day, the patients don't do as well as when you administer a lower dose, 100 milligrams a day, within a randomized Phase II trial. Does that have to do with toxicity, in that if you use a lower dose you can administer it for a longer period of time, or is it that with the lower dose you block the VEGF II without blocking the EGFR? That's currently under investigation.

DR LOVE: What are the side effects and toxicities of vandetanib?

DR JOHNSON: Rash, diarrhea and, as with many of these agents, prolongation in the QTc interval — the length of time it takes for the heart to repolarize. Thus far, no clinical increased risk of arrhythmia has been recorded. Another effect that can occur is increased sensitivity to the sun. We also see elevation of blood pressure but less proteinuria than with bevacizumab.

In terms of bleeding, randomized Phase II studies have evaluated vandetanib at two different doses with docetaxel versus docetaxel alone (Heymach 2006), and an up-front study has been conducted of vandetanib alone versus vandetanib and paclitaxel/carboplatin or paclitaxel/carboplatin alone (Heymach 2007).

No increased risk of bleeding has been found among those patients, and that includes the subsets of patients with brain metastasis and SCC excluded from the trials with bevacizumab.

Track 22

DR LOVE: Can you discuss the ASCO presentation evaluating prophylactic cranial radiation in small cell lung cancer (Slotman 2007)?

DR JOHNSON: That study observed 286 patients who had extensive-stage small cell lung cancer.

Patients were randomly assigned to one of several different doses of prophylactic cranial radiation. Results showed a threefold reduction in the primary endpoint of cumulative incidence of symptomatic brain metastasis.

Even more impressive was that the risk of dying was reduced by more than 30 percent (1.2). ■

1.2

Prophylactic Cranial Irradiation (PCI) in Extensive-Disease Small Cell Lung Cancer (SCLC): EORTC 08993-22993

	PCI*	Control†	HR (95% CI)	*p*-value
12-month overall survival	27.1%	13.3%	0.68 (0.52-0.88)	0.003
Symptomatic brain metastases at 12 months	14.6%	40.4%	0.27 (0.16-0.44)	<0.001
Cumulative symptomatic brain metastases	16.8%	41.3%	—	—
Deaths due to SCLC	68.5%	80.4%	—	—

* Median follow-up: 170 days, n = 143

† Median follow-up: 156 days, n = 143

SOURCE: Slotman B et al. *Proc ASCO* 2007;**Abstract 4**.

SELECT PUBLICATIONS

Heymach J et al. **Randomized phase II study of vandetanib (VAN) alone or in combination with carboplatin and paclitaxel (CP) as first-line treatment for advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2007;**Abstract 7544**.

Heymach JV et al. **A phase II trial of ZD6474 plus docetaxel in patients with previously treated NSCLC: Follow-up results.** *Proc ASCO* 2006;**Abstract 7016**.

Jackman DM et al. **Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib.** *Clin Cancer Res* 2006;12(13):3908-14. **Abstract**

Kelly K et al. **Updated analysis of SWOG 0023: A randomized phase III trial of gefitinib versus placebo maintenance after definitive chemoradiation followed by docetaxel in patients with locally advanced stage III non-small cell lung cancer.** *Proc ASCO* 2007;**Abstract 7513**.

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**

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

Sandler A et al. **Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial — E4599.** *Proc ASCO* 2005;**Abstract 4**.

Sequist LV et al. **iTARGET: A phase II trial to assess the response to gefitinib in epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) tumors.** *Proc ASCO* 2007;**Abstract 7504**.

Shepherd F et al. **Erlotinib in previously treated non-small-cell lung cancer.** *N Engl J Med* 2005;353:123-32. **Abstract**

Slotman B et al. **A randomized trial of prophylactic cranial irradiation (PCI) versus no PCI in extensive disease small cell lung cancer after a response to chemotherapy (EORTC 08993-22993).** *Proc ASCO* 2007;**Abstract 4**.

Socinski MA et al. **Efficacy and safety of sunitinib in previously treated, advanced non-small cell lung cancer (NSCLC): Preliminary results of a multicenter phase II trial.** *Proc ASCO* 2006;**Abstract 7001**.

INTERVIEW

Mark A Socinski, MD

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

Tracks 1-21

Select Excerpts from the Interview

Track 1

DR LOVE: What common questions about adjuvant therapy are you asked by community-based oncologists?

DR SOCINSKI: The question I hear most frequently is regarding the approach to node-negative disease. Controversy has existed since ASCO 2006 about the role of chemotherapy for patients with Stage IB disease. These patients were included in the positive adjuvant trials, although the subset analyses were negative (Douillard 2006; Winton 2005).

I don't put much weight on the subset analyses not powered to show a difference. So if the trial had the eligibility criteria of Stage IB to IIIA disease and it was positive, then to me the patients with Stage IB to IIIA disease are eligible for that treatment.

I believe we will ultimately prove that the potential benefit of adjuvant chemotherapy for patients with Stage IB disease is as good as it is for patients with Stage II or Stage III disease in terms of the relative risk reduction. I'm banking on the precedent in other solid tumors that we'll see the same results.

So if you have a patient with a Stage IB tumor who is a good candidate for adjuvant therapy, it's reasonable to offer treatment. The next Intergroup trial (E1505) will include patients with Stage IB tumors larger than four centimeters.

Tracks 10-11

DR LOVE: What is your treatment approach for patients with Stage IV NSCLC?

DR SOCINSKI: I view patients with Stage IV disease and a good performance status as belonging to one of three major groups: patients who should receive bevacizumab, patients who shouldn't receive bevacizumab and "never smokers."

It's interesting to talk to physicians across the United States about the percentage of patients in their practices they consider eligible to receive bevacizumab. A wide spectrum is evident, ranging from around 20 percent to about 60 to 70 percent.

DR LOVE: When you start a patient on chemotherapy with bevacizumab, how long do you continue the bevacizumab?

DR SOCINSKI: In ECOG-E4599, patients were supposed to continue bevacizumab until disease progression (Sandler 2006). One of the philosophical debates we often have is whether the benefit of bevacizumab or anti-angiogenic drugs is maximized in the presence of chemotherapy, and do you obtain much benefit after the chemotherapy is stopped?

We've had trial designs in which bevacizumab was stopped when the chemotherapy was ended. I don't believe we have an answer.

I believe that if you conduct a Phase III trial and it's positive, then when you translate that into practice, you should follow the approach used in the Phase III trial. So I have continued my patients on bevacizumab after I've stopped the chemotherapy, which is typically carboplatin/paclitaxel.

Track 12

DR LOVE: What are your thoughts about the AVAiL trial evaluating cisplatin/gemcitabine with or without bevacizumab at two different dose levels?

DR SOCINSKI: As a purist, I'd point out that the AVAiL trial wasn't designed to address the dose question.

The way I interpret AVAiL is that it's a second positive trial evaluating the use of bevacizumab in combination with chemotherapy — in this case, cisplatin/gemcitabine. The regimen appears to be safe, and both the 7.5-mg/kg and the 15-mg/kg doses improved the primary endpoint of progression-free survival (Manegold 2007). No survival data were presented.

The 7.5-mg/kg dose did not appear to be less toxic, and I have continued to use 15 mg/kg, based on the survival results from ECOG-E4599 (Sandler 2006). I would bet that at least by ASCO 2008, we will see some survival data from the AVAiL trial, and perhaps that will change our minds about the dosing. For right now, in the absence of survival data in that trial, I've continued administering the 15-mg/kg dose.

Track 14

DR LOVE: What are your thoughts about the combination of bevacizumab and erlotinib?

DR SOCINSKI: The attractiveness of combining erlotinib and bevacizumab is that they target two new and validated pathways. Each of them by itself has been shown to improve survival. This also gets away from some of the traditional toxicities we see with chemotherapy, and I believe it makes biologic sense.

The initial data from MD Anderson and Vanderbilt were encouraging (Herbst 2005a). Those data were moved into the randomized Phase II trial, which suggested that bevacizumab in combination with either chemotherapy or erlotinib was better than chemotherapy alone.

They also suggested that the combination of erlotinib and bevacizumab appeared to be as good and had less toxicity compared to chemotherapy with bevacizumab (Fehrenbacher 2006; [2.1]).

I believe this opens up the possibility that some patients may be better served with a noncytotoxic approach by combining these novel targeted agents. We do have some ongoing Phase III trials that will answer this question about that combination.

We also have to remember that we may be able to identify with various biomarkers the patients who — at least from the erlotinib point of view — may be the best candidates for that approach.

2.1

Phase II Randomized Trial Comparing Bevacizumab with Either Chemotherapy (Docetaxel or Pemetrexed) or Erlotinib to Chemotherapy Alone as Second-Line Therapy for Nonsquamous NSCLC

	Chemotherapy alone (n = 41)	Chemotherapy + bevacizumab (n = 40)	Bevacizumab + erlotinib (n = 39)
Progression-free survival			
Median	3.0 months	4.8 months	4.4 months
Six-month rate	21.5%	30.5%	33.6%
Hazard ratio (95% CI)	NA	0.66 (0.38-1.16)	0.72 (0.42-1.23)
Overall survival			
Six-month rate	62.4%	72.1%	78.3%
Response rate			
CR/PR	12.2%	12.5%	17.9%
CR/PR/SD	39.0%	52.5%	51.3%

SOURCE: Fehrenbacher L et al. Presentation. ASCO 2006;**Abstract 7062**.

Track 16

DR LOVE: What questions are you asked by practicing oncologists about metastatic disease?

DR SOCINSKI: What to do for never smokers. The never smokers represent approximately 10 percent of the population. In my experience, if you use the cutoff of 10 to 15 pack years, the oligosmokers comprise approximately another 10 percent.

So one in five patients with lung cancer fall into this category. That's not insignificant when you consider the number of patients with lung cancer. The one observation I am convinced of in that population is that anti-EGFR therapy seems to be important.

The question I struggle with regarding the never smokers is that many of them are eligible for bevacizumab. What do you do in that setting? Are they candidates for erlotinib or bevacizumab? What's the role of chemotherapy?

One option is to treat these patients with chemotherapy and bevacizumab and then, as we continue the bevacizumab, perhaps add erlotinib. We have a lot of safety information, and I don't believe we're going to harm patients with that approach.

If patients are not bevacizumab candidates — let's say they have brain metastases — then the question is, should we use chemotherapy followed immediately by a maintenance strategy with erlotinib or chemotherapy with erlotinib or erlotinib alone?

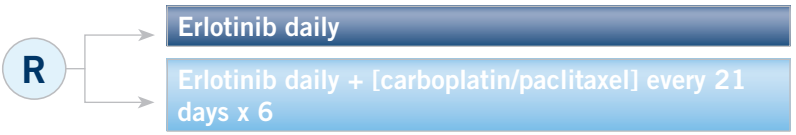
In CALGB, we currently have a trial (CALGB-30406; [2.2]) that randomly assigns these patients to erlotinib alone versus carboplatin/paclitaxel with erlotinib. It is exploring two of those three possibilities.

You might argue that we should have used four cycles of chemotherapy followed immediately by erlotinib or chemotherapy alone as a control arm, but there's only so much you can do in a randomized Phase II trial to sort out these issues.

2.2

Phase II Randomized Trial of Erlotinib with or without Carboplatin/Paclitaxel in Patients with Chemotherapy-Naïve Stage IIIB/IV NSCLC

Protocol ID: CALGB-30406
Target Accrual: 180 (Open)



Select Eligibility Criteria

- Adenocarcinoma
- Stage IIIB/IV
- Nonsmoker or former light smoker

Study Contacts

Cancer and Leukemia Group B
Pasi Janne, MD, PhD
Tel: 617-632-6076
Vincent Miller, MD
Tel: 212-639-7243

SOURCE: NCI Physician Data Query, August 2007.

Track 17

DR LOVE: What are your thoughts about nanoparticle albumin-bound (*nab*) paclitaxel?

DR SOCINSKI: The breast cancer data have encouraged me to be optimistic about *nab* paclitaxel. It is less toxic and an easier drug to administer in terms of infusion times compared to Cremophor®-based paclitaxel. That in itself is an advantage, and it may have greater antitumor activity compared to the parent compound or to other taxanes.

The data in lung cancer thus far are limited to Phase II trials (Reynolds 2007; Hawkins 2007), most of which are single-arm and not comparative trials. A plan is in place for a large Phase III trial comparing carboplatin/paclitaxel to carboplatin/*nab* paclitaxel.

Tracks 18-19

DR LOVE: Can you comment on your Phase II adjuvant trial evaluating docetaxel/carboplatin?

DR SOCINSKI: We conducted a feasibility study of that combination, and our endpoint was to determine whether we could deliver four cycles of therapy within 12 weeks to more than 80 percent of the patients.

The study included 72 patients and showed that 80 percent of them were able to receive four cycles. We allowed patients to receive growth factor support, and approximately one third of the patients received growth factors at some point during the four cycles.

No treatment-related deaths occurred (Stinchcombe 2007). Our conclusion was that this is a feasible regimen for the patient whom you consider not to be a good candidate for a cisplatin-based approach.

These Phase II safety data suggest that you can use that regimen. The data in our trial were similar to what the CALGB showed with carboplatin and paclitaxel. ■

SELECT PUBLICATIONS

Azzoli CG et al. **A phase II tolerability study of cisplatin plus docetaxel as adjuvant chemotherapy for resected non-small cell lung cancer.** *J Thorac Oncol* 2007;2(7):638-44. **Abstract**

Clark GM et al. **Smoking history and epidermal growth factor receptor expression as predictors of survival benefit from erlotinib for patients with non-small-cell lung cancer in the National Cancer Institute of Canada Clinical Trials Group study BR.21.** *Clin Lung Cancer* 2006;7(6):389-94. **Abstract**

Fehrenbacher L et al. **A phase II, multicenter, randomized clinical trial to evaluate the efficacy and safety of bevacizumab in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib hydrochloride compared with chemotherapy alone for treatment of recurrent or refractory non-small cell lung cancer.** *Proc ASCO* 2006;**Abstract 7062**.

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

Hawkins MJ et al. **Study of three weekly nab-paclitaxel regimens in combination with carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2007;**Abstract 7659**.

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: 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**

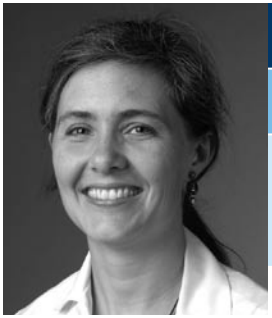
Manegold C et al. **Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704.** *Proc ASCO* 2007;**Abstract LBA7514**.

Reynolds C et al. **An open-label, phase II trial of nanoparticle albumin bound paclitaxel (*nab*-paclitaxel), carboplatin, and bevacizumab in first-line patients with advanced non-squamous non-small cell lung cancer (NSCLC).** *Proc ASCO* 2007;**Abstract 7610**.

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

Stinchcombe TE et al. **Feasibility of adjuvant carboplatin/docetaxel (C/D) in patients (pts) with resected stage I-IIIB non-small cell lung cancer (NSCLC): Preliminary report of a phase II trial.** *Proc ASCO* 2007;**Abstract 18069**.

Subramanian J, Govindan R. **Lung cancer in never smokers: A review.** *J Clin Oncol* 2007;25(5):561-70. **Abstract**



INTERVIEW

Heather A Wakelee, MD

Dr Wakelee is Assistant Professor of Medicine in the Division of Oncology at the Stanford School of Medicine in Stanford, California.

Tracks 1-12

Select Excerpts from the Interview

Track 1

DR LOVE: What were some of the practice-changing presentations at ASCO this year?

DR WAKELEE: The Hoosier Oncology Group (HOG) trial, which evaluated chemotherapy with cisplatin/etoposide and concurrent radiation therapy for unresectable Stage IIIA and IIIB disease, was the most practice-changing presentation in lung cancer at ASCO (Hanna 2007).

All patients in the study received chemotherapy and radiation therapy, and then they were randomly assigned to either consolidation docetaxel using the standard SWOG-S9504 protocol or nothing. The trial showed no difference in survival between the two arms, with strikingly overlapping survival curves.

Criticisms include the fact that it was a relatively small study, and it was stopped early because of an interim analysis showing that there was no way statistically

to obtain a separation of the curves. The study begs the question of what consolidation chemotherapy is achieving in that situation. Other studies that evaluated induction chemotherapy with additional chemoradiation therapy in a similar patient population also didn't show any benefit with chemotherapy. Again, it's bringing into the forefront this question of what to do with Stage III disease.

For several years, everyone has been comfortable with the SWOG-S9504 regimen. Now we have to question that. However, I have a hard time believing that two cycles of a platinum doublet with radiation therapy is enough to cure Stage III disease when we know we need more than that to improve survival for earlier stages. I don't believe the question is dead, but I believe we need to move away from simply building on S9504.

Many people are still using a weekly carboplatin-based regimen and a taxane with the radiation therapy. To say that we shouldn't administer any chemotherapy after that is a somewhat frightening proposition, considering that these patients are not receiving much chemotherapy at all during the radiation therapy.

The median survival from those Phase II trials, excluding the CALGB study, is in keeping with what we're seeing with these cisplatin/etoposide/radiation therapy regimens with or without docetaxel. We still have a lot of questions in Stage III disease, but as a general practice, consolidation docetaxel cannot be considered a standard anymore.

Track 3

DR LOVE: What are your thoughts on the AVAiL study data presented at ASCO?

DR WAKELEE: This was a European study of gemcitabine and cisplatin with or without bevacizumab (Manegold 2007; [3.1]). It evaluated two doses of bevacizumab: 7.5 mg/kg or 15 mg/kg. The 15-mg/kg dose was the dose used in the ECOG-E4599 carboplatin/paclitaxel study (Sandler 2005). AVAiL was initially an overall survival study, but they changed it to include progression-free survival.

A statistically significant improvement was demonstrated in progression-free survival — not a big difference, but a real difference statistically — with both the 7.5-mg/kg and the 15-mg/kg doses. The trial wasn't powered to compare 15 mg/kg to 7.5 mg/kg — only both of those doses to placebo. Overall survival data weren't mature yet.

DR LOVE: People may now question whether you can get away with using 7.5 mg/kg.

DR WAKELEE: That is the big question. I'm cautious still. We don't have the survival data yet. We have no real way of evaluating any difference between 15 mg/kg and 7.5 mg/kg, even if we could do it statistically. I don't believe it's wrong to consider using 7.5 mg/kg, but I'm not ready to make the change in my practice. Certainly we won't be making a change in the ECOG-E1505 adjuvant trial, in which we're still using the 15-mg/kg dose every three weeks.

3.1

Progression-Free Survival (PFS) Following Cisplatin/Gemcitabine with or without Bevacizumab in Chemotherapy-Naïve Patients with Advanced or Recurrent NSCLC

	Median PFS	Hazard ratio	*p*-value
Cisplatin/gemcitabine + placebo	6.1 months	Reference	Reference
Cisplatin/gemcitabine + bevacizumab 7.5 mg/kg	6.7 months	0.75	0.0026
Cisplatin/gemcitabine + bevacizumab 15 mg/kg	6.5 months	0.82	0.0301

SOURCE: Manegold C et al. *Proc ASCO* 2007;**Abstract LBA7514**.

Track 4

DR LOVE: What do you consider reasonable nonprotocol options for chemotherapy regimens to combine with bevacizumab for metastatic disease?

DR WAKELEE: In the United States, carboplatin/paclitaxel with bevacizumab is approved. Given the AVAiL data (Manegold 2007), gemcitabine/cisplatin would certainly be reasonable now.

We're conducting an ongoing trial with carboplatin/gemcitabine. I wouldn't say that regimen is "ready for prime time" — not until we have the toxicity data, given the increased thrombocytopenia and neutropenia with that regimen. Substituting docetaxel for paclitaxel is reasonable because we don't have any toxicity differences that would be of concern.

Track 6

DR LOVE: Will you provide an update on the ECOG-E1505 adjuvant study that you chair?

DR WAKELEE: We activated the study recently, and we are more comfortable than ever with our choice of regimens that investigators can select: cisplatin/gemcitabine, cisplatin/vinorelbine and cisplatin/docetaxel, all with and without bevacizumab (3.2).

At this point, we're still sticking with the 15-mg/kg dose of bevacizumab because that's the dose for which we have known survival benefit. The bevacizumab is administered at the 15-mg/kg dosing every three weeks starting with the first cycle of chemotherapy and then continuing for one year.

DR LOVE: Are patients with Stage IB disease included in the study?

DR WAKELEE: We are limiting patients with Stage IB disease to those whose tumors are four centimeters or larger. We know from subset analyses of the larger adjuvant trials that patients with Stage IB disease don't seem to benefit overall.

The CALGB IB trial was statistically negative overall, but those whose tumors were four centimeters or larger did show a survival benefit (Strauss 2006). That's why we came up with the 4-cm cutoff.

At this point we're not limiting to any NSC histology. We're also not excluding patients receiving anticoagulation. Based on the safety data that have emerged in colorectal cancer — and now hints that have emerged in the AVAiL study — patients who have had any sort of stroke or transient ischemic attack are excluded. Patients who have had any other arterial thrombotic events, such as myocardial infarction, within six months are also excluded. ■

3.2

Phase III Study of Adjuvant Chemotherapy with or without Bevacizumab for Patients with Completely Resected Stage IB-IIIA NSCLC

Protocol ID: ECOG-E1505
Target Accrual: 1,500

* Patients are stratified according to type of chemotherapy, stage, histology and gender.

Eligibility

- Resection within the past six to 12 weeks
- ECOG performance status 0-1
- No history of CVA or TIA
- History of MI or angina acceptable if no evidence of active disease within the past 12 months

Study Contact

Heather Wakelee, MD, Protocol Chair
Tel: 650-723-9094; 800-756-9000

SOURCE: NCI Physician Data Query, August 2007.

SELECT PUBLICATIONS

Hanna NH et al. **Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023.** *Proc ASCO* 2007;**Abstract 7512**.

Manegold C et al. **Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704.** *Proc ASCO* 2007;**Abstract LBA7514**.

Sandler AB et al. **Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC #704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial — E4599.** *Proc ASCO* 2005;**Abstract 4**.

Strauss GM et al. **Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol 9633.** *Proc ASCO* 2006;**Abstract 7007**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the study by David Jackman and colleagues, over 70 percent of patients with NSCLC and EGFR exon 19 deletions responded to erlotinib or gefitinib, with a one-year overall survival of _____.**
   a. 65 percent
   b. 75 percent
   c. 85 percent
   d. 95 percent

2. **Vandetanib (ZD6474) is a novel, orally administered, active inhibitor of _____.**
   a. VEGFR
   b. EGFR
   c. Both VEGFR and EGFR

3. **Among patients with extensive small cell lung cancer who achieved response to chemotherapy, prophylactic cranial irradiation (PCI) resulted in _____ compared to those who did not receive PCI.**
   a. Reduced risk of symptomatic brain metastases
   b. Improved overall survival
   c. Both a and b

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

5. **In a Phase II feasibility study, Dr Socinski and colleagues demonstrated that more than ____ percent of patients could complete four cycles of adjuvant carboplatin/docetaxel.**
   a. 50
   b. 60
   c. 70
   d. 80

6. **The Hoosier Oncology Group showed that consolidation docetaxel did not improve survival among patients with unresectable Stage IIIA and IIIB NSCLC undergoing treatment with cisplatin/etoposide and concurrent radiation therapy.**
   a. True
   b. False

7. **In AVAiL, the addition of _____ improved progression-free survival among chemotherapy-naïve patients with advanced or recurrent NSCLC undergoing treatment with cisplatin/gemcitabine.**
   a. Bevacizumab at 7.5 mg/kg
   b. Bevacizumab at 15 mg/kg
   c. Both a and b

8. **In ECOG-E4599, bevacizumab was _____.**
   a. Discontinued after three doses
   b. Discontinued at the same time as carboplatin/paclitaxel
   c. Discontinued at the time of disease progression
   d. Discontinued at the investigator's discretion
   e. None of the above

9. **In a Phase II, multicenter trial, Fehrenbacher and colleagues compared _____ to chemotherapy alone.**
   a. Bevacizumab with chemotherapy (pemetrexed or docetaxel)
   b. Bevacizumab with erlotinib
   c. Both a and b

10. **For patients with metastatic NSCLC who are nonsmokers or oligosmokers, CALGB-30406 will evaluate _____.**
    a. Erlotinib alone
    b. Erlotinib in combination with chemotherapy
    c. Chemotherapy alone
    d. Both a and b
    e. All of the above

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

EVALUATION FORM

Lung Cancer Update — Issue 3, 2007

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this Evaluation Form. A certificate of completion will be issued upon receipt of your completed Post-test and Evaluation Form.

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
Bruce E Johnson, MD	5 4 3 2 1	5 4 3 2 1
Mark A Socinski, MD	5 4 3 2 1	5 4 3 2 1
Heather A Wakelee, 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 ☐ Downloaded MP3s from website

EVALUATION FORM

Lung Cancer Update — Issue 3, 2007

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 2.75 *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 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 Evaluation online at www.LungCancerUpdate.com/CME.

LCU307

Lung Cancer™ UPDATE

Editor/CME Director	Neil Love, MD
Managing Editor	Kathryn Ault Ziel, PhD
Scientific Director	Richard Kaderman, PhD
Senior Director, Medical Affairs	Aviva Asnis-Alibozek, PA-C, MPAS
Writers	Lilliam Sklaver Poltorack, PharmD Douglas Paley Clayton Campbell Anne Jacobson, MPH
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng John Brebner Ginelle Suarez Erin Wall
Director, Creative and Copy Editing	Aura Herrmann
Creative Manager	Fernando Rendina
Graphic Designers	Jason Cunnius Tamara Dabney Shantia Daniel Elisa Stambouli
Senior Production Editor	Alexis Oneca
Traffic Manager	Tere Sosa
Copy Editors	Dave Amber Margo Harris Rosemary Hulce Kirsten Miller Pat Morrissey/Havlin Carol Peschke Susan Petrone
Production Manager	Rena Chiarelli
Audio Production	Frank Cesarano
Web Master	John Ribeiro
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.com
For CME Information	Email: CME@ResearchToPractice.com

Lung Cancer™ UPDATE

This program is supported by education grants from
Abraxis BioScience, AstraZeneca Pharmaceuticals LP,
Genentech BioOncology/OSI Pharmaceuticals Inc and Sanofi-Aventis.

Research To Practice®

Sponsored by Research To Practice.

Last review date: August 2007
Release date: August 2007
Expiration date: August 2008
Estimated time to complete: 2.75 hours