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Lung Cancer™ UPDATE

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

EDITOR

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INTERVIEWS

Corey J Langer, MD

Joan H Schiller, MD

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ROUNDTABLE DISCUSSION

Corey J Langer, MD

Vincent A Miller, MD

Peter M Ravdin, MD, PhD

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 2 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Langer, Miller, Ravdin, Reynolds and Schiller on the integration of emerging clinical research data into the management of lung cancer.

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UPCOMING EDUCATIONAL EVENTS

Canadian Association of Medical Oncologists Annual Meeting
April 26-29, 2007
Toronto, Ontario
Website: **www.cos.ca/camo/meeting.asp**

SWOG Spring Group Meeting
May 2-6, 2007
Chicago, Illinois
Website: **www.swog.org/Visitors/Spring07GpMtg.asp**

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Website: **www.asco.org**

ECOG Semi-Annual Meeting
June 8-10, 2007
Washington, DC
Website: **www.ecog.org/general/meeting_dates.html**

RTOG Semi-Annual Meeting
June 21-24, 2007
Philadelphia, Pennsylvania
Website: **www.rtog.org/index.html**

12th World Conference on Lung Cancer
September 2-6, 2007
Seoul, Korea
Website: **www.2007worldlungcancer.org**

INTERVIEW

Corey J Langer, MD

Dr Langer is Medical Director of Thoracic Oncology and Head and Neck Oncology and Vice Chair of the Radiation Therapy Oncology Group at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Tracks 1-17

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Can you describe the study design of CALGB-9633 (Strauss 2006) and discuss the outcomes?

DR LANGER: The CALGB-9633 study was an adjuvant trial of paclitaxel/carboplatin versus observation for patients with Stage IB disease. The trial specifically evaluated patients without nodal involvement in tumors that were at least three centimeters or when there was invasion of the main-stem bronchus through the visceral pleura.

The initial report from two years ago (Strauss 2004) showed a statistically significant survival improvement in patients who received chemotherapy. About a 12 percent improvement was seen in four-year survival. In the control arm, the four-year overall survival was 59 percent. For the intervention arm it was 71 percent ($p = 0.028$). The majority of patients were actually able to get all four cycles at or near full dose.

The update at the 2006 ASCO meeting (Strauss 2006) was tremendously disappointing — the p-value increased to 0.1. The five-year absolute survival difference was two to three percent (1.1).

DR LOVE: How do you interpret those findings?

DR LANGER: Because the investigators had not observed the predetermined number of events, this may be a premature reporting of a Phase III trial.

Another interesting caveat is that, according to a retrospective analysis, patients whose tumors were four centimeters or larger actually had a survival benefit. Those results have left us in a therapeutic quandary. What do we do with Stage IB patients? Do we treat them? Do we observe them? Do we replicate this regimen in this group of patients? Do we segregate them by tumor size, using four centimeters as our cutoff? And if we do treat them, do we use paclitaxel and carboplatin or a cisplatin-containing regimen?

People have evaluated the data and dismissed the role of carboplatin. Frankly, I don't believe we have sufficient data. Only one trial evaluated carboplatin in the adjuvant treatment of patients with Stage IB disease only. Carboplatin was not evaluated in patients with Stage II or Stage IIIA disease.

1.1

CALGB-9633: Efficacy of Adjuvant Chemotherapy (Paclitaxel and Carboplatin) or Observation for Patients with Stage IB Lung Cancer

	HR (90% CI)	*p*-value
Primary analysis*		
Overall survival	0.80 (0.60-1.07)	0.10
Disease-free survival	0.74 (0.57-0.96)	0.03
Exploratory analysis		
Overall survival among patients with tumors ≥4 cm	0.66 (0.45-0.97)	0.04
Disease-free survival among patients with tumors ≥4 cm	0.62 (0.44-0.89)	0.01

* DSMB recommended early termination of trial; median follow-up = 57 months

SOURCE: Strauss GM et al. *Proc ASCO* 2006;**Abstract 7007**.

I must confess that since ASCO, at least for patients with Stage II or IIIA disease, I've started using cisplatin. For patients with tumors that are four centimeters or larger in size with Stage IB disease, I'm still using paclitaxel and carboplatin.

Track 4

DR LOVE: Can you discuss the data from the meta-analysis of trials evaluating adjuvant cisplatin?

DR LANGER: The Lung Adjuvant Cisplatin Evaluation (Pignon 2006) evaluated three positive platinum trials — ANITA, JBR.10 and the IAL trial — and two other trials: the ALPI trial from Italy and the BLT trial, primarily from the United Kingdom — both of which were negative. So in fairness, it evaluated both positive and negative trials, and in aggregate, despite the inclusion of the negative trials, a robust, statistically significant improvement in survival with a platinum-based regimen was seen — overall about a five percent difference at five years (1.2).

In their further analysis, that benefit was essentially confined to patients with Stage II or IIIA disease. When the investigators evaluated Stage IA disease, chemotherapy seemed to be associated with a detrimental outcome, and the effect in Stage IB disease wasn't significant. It was trending in the right direction, but the *p*-value wasn't significant and the confidence intervals clearly overlapped.

1.2

Overall Survival in Adjuvant Trials of Cisplatin-Based Chemotherapy: Lung Adjuvant Cisplatin Evaluation (LACE)

	Mortality	HR (95% CI)
ALPI	569/1,088	0.95 (0.81-1.12)
ANITA	458/840	0.82 (0.68-0.98)
BLT	152/307	1.00 (0.72-1.38)
IALT	980/1,867	0.91 (0.80-1.03)
JBR.10	197/482	0.71 (0.54-0.94)
Total	2,356/4,584	0.89 (0.82-0.96)

Chemotherapy effect: $p = 0.004$

Three-year survival: With chemotherapy, 61.0%; without chemotherapy, 57.1%

Five-year survival: With chemotherapy, 48.8%; without chemotherapy, 43.5%

SOURCE: Pignon JP et al. Presentation. ASCO 2006;**Abstract 7008**.

Track 5

DR LOVE: Can you discuss the analysis of the Canadian JBR.10 study that reported data on adjuvant treatment in the elderly (Pepe 2006)?

DR LANGER: It was one of the first analyses of the elderly in the adjuvant setting. The JBR.10 trial subanalysis of elderly patients was presented by Carmella Pepe at the 2006 ASCO meeting during the lung plenary session. They used 65 years of age as their cutoff.

Patients who were older than 65 years of age constituted a third of the total accrual to JBR.10, so it was a fairly large group. Among the elderly, a higher percentage of patients had squamous histology, which is no surprise because it's probably a result of the use of cigarettes.

The upshot was that the elderly had a significant survival benefit. The younger patients did better across the board, but relatively speaking, comparing chemotherapy to observation, there was still a survival benefit among the elderly (1.3). ■

1.3

Overall Survival and Disease-Free Survival among Elderly (>65 Years) and Young (≤65 Years) Patients Who Participated in JBR.10 (Adjuvant Vinorelbine and Cisplatin versus Observation)

Outcome measure	≤65 years	>65 years
Overall survival		
Treatment	70%	66%
Observation	58%	46%
HR (*p*-value)	0.77 (0.14)	0.61 (0.04)
Disease-free survival		
Treatment	72%	73%
Observation	60%	56%
HR (*p*-value)	0.69 (0.05)	0.66 (0.13)

SOURCE: Pepe C et al. *Proc ASCO* 2006;**Abstract 7009**.

SELECT PUBLICATIONS

Pepe C et al. **Adjuvant chemotherapy in elderly patients: An analysis of National Cancer Institute of Canada Clinical Trials Group and Intergroup BR.10.** *Proc ASCO* 2006;**Abstract 7009**.

Pignon JP et al. **Lung Adjuvant Cisplatin Evaluation (LACE): A pooled analysis of five randomized clinical trials including 4,584 patients.** Presentation. ASCO 2006;**Abstract 7008**.

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

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

Strauss GM et al. **Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633.** *Proc ASCO* 2004;**Abstract 7019**.

Winton T et al; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. **Vinorelbine plus cisplatin vs observation in resected non-small-cell lung cancer.** *N Engl J Med* 2005;352(25):2589-97. **Abstract**

ROUNDTABLE DISCUSSION

Corey J Langer, MD, Vincent A Miller, MD, Peter M Ravdin, MD, PhD

Tracks 1-14

Select Excerpts from the Discussion

Track 2

DR LOVE: Peter, can you comment on the competing causes of mortality in patients with lung cancer?

DR RAVDIN: The default estimates of competing mortality by age are higher in patients with lung cancer than with other solid tumors. In the SEER data, patients with lung cancer did slightly worse than an age-matched group for competing mortality, which isn't surprising. You see increased deaths from cardiovascular disease and COPD-like illnesses in these patients.

DR LOVE: Vince, in breast cancer we use the concept of relative risk reduction in the Adjuvant! Online model. Do we have enough data in lung cancer to do the same?

DR MILLER: We have a body of data with which we can start to do it, but the quality of the data is not great. I think we need to enhance the data. We always lag behind breast cancer by a few years, and this may be no exception.

DR LOVE: Corey, according to our Patterns of Care surveys, more than half of the oncologists in the United States are using Adjuvant! Online for breast cancer. The use in colon cancer is about one quarter of what it is in breast cancer. Do you think Adjuvant! Online is going to have a future in lung cancer in the next couple of years?

DR LANGER: I expect it will, but we need more trials. It's not so much that the quality of the data is not good — it's the quantity of data that's lacking. In the modern era, we only have five or six trials.

Many nuances factor into our therapeutic decision-making, particularly in lung cancer — the patient's comorbidities and performance status. This is a population that's generally older and a bit more ill than patients with breast cancer. So the data from a cooperative group or a European trial do not necessarily extrapolate to our patients.

DR RAVDIN: The average patients with lung cancer behave as if they're three to five years older than they actually are. Adjuvant! Online was designed to be used in the adjuvant setting, but the majority of lung cancer patients never have completely resected disease. Patients who were in good enough shape to undergo at least a lobectomy are not your average patients with lung cancer.

Patients with Stage I disease have a ferocious mortality. Then you have therapies — and there's great debate as to whether it applies to those patients — with 20 percent efficacy. That's a substantial benefit. In breast cancer, we would always treat without any question. In lung cancer, it's less obvious to the patient.

Track 6

DR LOVE: Lowell, what are your thoughts on the cisplatin regimens for treatment of non-small cell lung cancer (NSCLC) in community practice?

DR HART: In the advanced disease setting, I believe cisplatin/docetaxel is better than cisplatin/vinorelbine. I am wondering, does that have any bearing on any of your decisions about the selection of adjuvant therapy?

DR MILLER: Your overall impression is that of the oncology community. In the paper evaluating cisplatin/docetaxel versus cisplatin/vinorelbine, the *p*-value for survival is 0.044 (Fossella 2003). Do I think that makes it reasonable to extrapolate and use cisplatin/docetaxel in the adjuvant setting? Yes, I believe it's a reasonable thing to do. However, I don't know that it's any easier when you administer it every three weeks as opposed to smaller, divided doses of cisplatin/vinorelbine.

DR LANGER: I have no personal experience with docetaxel/cisplatin in the

adjuvant setting. A lot of my colleagues are using it because in advanced disease it was noninferior to vinorelbine/cisplatin. I believe most of us would interpret that it is at least as good, if not better.

Having said that, there are no Phase III data with that combination in the adjuvant setting. All of the data are with vinorelbine/cisplatin or paclitaxel/carboplatin. So it's all by extrapolation. I don't think it's going to be worse, and I doubt it's going to be significantly better.

The upcoming ECOG trial (ECOG-E1505; [3.2, page 14]) is going to feature a "chemo du jour," with a menu of options to pick from. I don't feel we're as caught up in lung cancer as the breast cancer world is in comparing minute changes in regimens. The presumption is that various platinum cocktails are probably going to achieve the same result. We have to ask other questions, particularly about the introduction of targeted agents.

Tracks 7-8

DR LOVE: Corey, can you update us on the toxicity associated with bevacizumab in patients with lung cancer and, from a safety perspective, how you think bevacizumab is going to play out in the adjuvant setting in lung cancer?

DR LANGER: In ECOG-E4599, the addition of bevacizumab to paclitaxel/carboplatin demonstrated a two-month improvement in median overall survival and about a six to eight percent improvement in one- and two-year survival. It also showed more toxicity, particularly pulmonary hemorrhage (Sandler 2006a; [2.1]).

In the bevacizumab/paclitaxel/carboplatin arm, 15 treatment-related deaths occurred out of 305 patients. Not all were related to hemorrhage — some were from neutropenic fever or other causes. In the control group, two treatment-related deaths occurred out of 344 patients. So, although we excluded patients with squamous histology, brain metastases, ongoing thromboembolic phenomena, anticoagulation use or antecedent hemoptysis, we still saw a heightened treatment-related death rate (Sandler 2006a).

I believe many of those concerns are going to fall by the wayside in the adjuvant trial. The tumors have been resected. By definition, these patients have no residual tumor in the chest. Ideally, they should not have pulmonary hemorrhage.

Track 12

DR LOVE: Do you think the cavitation and bleeding associated with bevacizumab are related to its mechanism of action or to the response to therapy?

DR LANGER: Definitely the response. Many of the patients in whom we've seen some of the more worrisome bleeding episodes have actually demon-

strated tumor response. So it could be that these patients are, in fact, responding too quickly. Whether it has something to do with the mechanism of action is unclear to me. It's conceivable that these folks may have more vascular tumors and, therefore, we see more necrosis, but that's purely speculative.

DR LOVE: Vince, what do you think is happening with these patients?

DR MILLER: Although the data have not yet been presented, it's widely known from the folks at ECOG that in a Phase II trial (ECOG-E3501) of patients with small cell lung cancer, which had an interim analysis with 50 or 60 patients, there were essentially no Grade IV or V pulmonary events. Those are centrally located tumors, which are often endobronchial and change rapidly in response to chemotherapy. So I believe it's something largely peculiar to squamous cell histology. ■

2.1

ECOG-E4599: Grade III or Higher Adverse Events

	PC (n = 440)			PCB (n = 427)			*p*-value
	Grade III	Grade IV	Grade V	Grade III	Grade IV	Grade V	
Neutropenia		16.8%			25.5%		0.002
Thrombocytopenia		0.2%			1.6%		0.04
Febrile neutropenia	1.8%		0.2%	4.0%		1.2%	0.02
Hyponatremia	0.9%	0.2%		2.6%	0.9%		0.02
Hypertension	0.5%	0.2%		6.8%	0.2%		<0.001
Proteinuria				2.6%	0.5%		<0.001
Headache	0.5%			3.0%			0.003
Rash or desquamation	0.5%			2.3%			0.02
Bleeding events	0.7%			4.4%			<0.001
CNS hemorrhage					0.7%		
Epistaxis	0.2%			0.7%			
Hematemesis						0.5%	
Hemoptysis	0.2%			0.5%	0.2%	1.2%	
Melena or GI bleed	0.2%		0.2%	0.7%	0.2%		
Other hemorrhage				0.2%	0.2%		

PC = paclitaxel + carboplatin; PCB = paclitaxel + carboplatin + bevacizumab

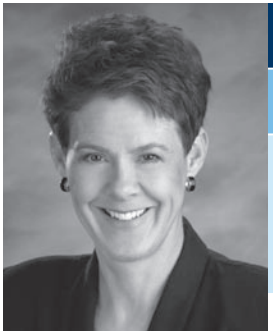
SOURCE: Sandler A et al. *N Engl J Med* 2006;355(24):2542-50. **Abstract**

SELECT PUBLICATIONS

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

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

Sandler AB et al. **Retrospective study of clinical and radiographic risk factors associated with early onset, severe pulmonary hemorrhage in bevacizumab-treated patients with advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2006b;**Abstract 7068**.



INTERVIEW

Joan H Schiller, MD

Dr Schiller is Professor and Division Chief of Hematology/Oncology and Deputy Director at Simmons Comprehensive Cancer Center at UT Southwestern Medical Center in Dallas, Texas.

Tracks 1-14

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss ECOG-E4599, which was the basis for the new adjuvant trial evaluating chemotherapy and bevacizumab?

DR SCHILLER: Based on the Phase II study that came out of Vanderbilt (Johnson 2004), ECOG recently completed and published our randomized Phase III study (E4599) in the first-line metastatic setting, in which patients with nonsquamous non-small cell carcinoma of the lung who had undergone

no prior chemotherapy were randomly assigned to receive either carboplatin/paclitaxel or carboplatin/paclitaxel and bevacizumab. A few more than 870 patients were assigned. We found a significant improvement in response rate, progression-free survival and overall survival for the bevacizumab-containing arm (Sandler 2006; [3.1]).

DR LOVE: Can you discuss the side effects and toxicity?

DR SCHILLER: We were concerned about hemoptysis. In the randomized Phase II study, the incidence of severe or fatal hemoptysis was greater than 30 percent among patients with squamous cell carcinoma (SCC). For that reason, we excluded patients with SCC. The rate of clinically significant bleeding was 4.4 percent in the bevacizumab arm compared to 0.7 percent in the chemotherapy arm. This is not what we would like it to be, but it is potentially manageable in this group of patients with fatal disease.

The incidence of hypertension and proteinuria, which are class effects associated with these agents, was also higher. It is interesting that neutropenia and febrile neutropenia also occurred more in the bevacizumab arm. That's not something we were expecting. In preclinical models, VEGF has been shown to be an immune stimulator, so it enhances the activity of immune cells. We're hypothesizing that bevacizumab inhibits that activity, thus increasing the incidence of neutropenia.

3.1

ECOG-E4599: Efficacy of the Addition of Bevacizumab (B) to Paclitaxel (P) and Carboplatin (C) in Previously Untreated Metastatic Nonsquamous NSCLC

Endpoint	PC (n = 433)	PCB (n = 417)	HR (95% CI)	*p*-value
Median OS	10.3 months	12.3 months	0.79 (0.67-0.92)	0.003
Two-year OS	15%	23%	—	—
Median PFS	4.5 months	6.2 months	0.66 (0.57-0.77)	<0.001
Overall response	15%	35%	—	<0.001

OS = overall survival; PFS = progression-free survival

SOURCE: Sandler A et al. *N Engl J Med* 2006;355(24):2542-50. **Abstract**

Tracks 4-5

DR LOVE: What is your clinical approach to the use of bevacizumab for metastatic disease?

DR SCHILLER: I use the ECOG-E4599 eligibility criteria: no brain metastases, no SCC, no hemoptysis, no thromboembolic abnormalities and no anticoagulants. Off study, for patients who meet the eligibility criteria, I routinely offer bevacizumab as part of the treatment.

Bevacizumab has been well tolerated, with the possible exception of hyperten-

sion, but that's always been easily manageable. We've had no problems in that regard, and we follow the typical hypertension management.

DR LOVE: For what duration do you continue chemotherapy and bevacizumab?

DR SCHILLER: I follow the E4599 guidelines: Stop the chemotherapy after six cycles and continue the bevacizumab. A big question, which is currently unanswered, is what to do when the disease progresses. If the patient is already on bevacizumab, do you continue it? Clearly we need clinical studies to answer that, particularly given the expense of this drug.

DR LOVE: What about the use of other chemotherapeutic agents in combination with bevacizumab?

DR SCHILLER: Bevacizumab appears to work in colorectal carcinoma and in breast cancer. I don't believe it's specific to any one type of chemotherapy, so I have no problem using it with other drugs besides carboplatin and paclitaxel.

Track 8

DR LOVE: Can you discuss the upcoming adjuvant trial that will be conducted by ECOG?

DR SCHILLER: ECOG-E1505 will be a Phase III trial for patients with selected Stage IB to IIIA NSCLC, who will be randomly assigned to four cycles of chemotherapy versus four cycles of chemotherapy and up to one year of bevacizumab (3.2).

Eligible patients will have Stage IB to IIIA disease, with IB tumors greater than four centimeters in size. The reason for that is based on a subset analysis CALGB conducted of their adjuvant study, in which patients with larger Stage IB tumors were the ones who seemed to benefit (Strauss 2006). We'll apply the typical bevacizumab exclusion criteria. Patients will be allowed to have had SCC, however, because the disease will be removed. It is hoped that the histology will not be important if it's not there.

DR LOVE: What kind of chemotherapy will be allowed?

DR SCHILLER: To some degree, it's "dealer's choice." The referring physician can choose among cisplatin/gemcitabine, cisplatin/docetaxel and cisplatin/vinorelbine.

Track 14

DR LOVE: Let's talk about another targeted therapy, erlotinib. To what extent do you consider factors such as nonsmoking and EGFR mutation status in deciding when to use erlotinib?

DR SCHILLER: We have not been obtaining EGFR mutation status as a standard rule because of all the other data that seem to suggest that EGFR overexpression, determined either by protein or by FISH analysis, is also

a strong predictor of benefit (Tsao 2005; Paez 2004). It may not predict dramatic response rates, but it seems to predict stable disease and improved survival. So we've been using erlotinib in our second-line therapy.

We've been utilizing clinical factors along with how well patients responded to first-line therapy. If someone's disease progresses through first-line therapy, we are more likely to use erlotinib in the second line rather than go on to a second-line cytotoxic. Or if the patient is a woman, a nonsmoker, is of Asian descent or has bronchoalveolar carcinoma, that too would push us to use erlotinib as a second- or third-line therapy. ■

3.2

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

Protocol IDs: ECOG-E1505
Target Accrual: 1,500 (Approved — not yet active)

* 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

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

SOURCE: NCI Physician Data Query, January 2007.

SELECT PUBLICATIONS

Johnson DH et al. **Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.** *J Clin Oncol* 2004;22(11):2184-91. **Abstract**

Paez JG et al. **EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy.** *Science* 2004;304(5676):1497-500. **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**

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**.

Tsao MS et al. **Erlotinib in lung cancer — Molecular and clinical predictors of outcome.** *N Engl J Med* 2005;353(2):133-44. **Abstract**

INTERVIEW

Craig Reynolds, MD

Dr Reynolds is Development Chair of the Lung Cancer Research Committee of US Oncology Research at the Ocala Oncology Center in Ocala, Florida.

Tracks 1-11

Select Excerpts from the Interview

Track 4

DR LOVE: Can you summarize where we are right now in terms of predictors of patient response to tyrosine kinase inhibitors, particularly erlotinib?

DR REYNOLDS: I believe there are a couple ways you can look at it. One is to view it from a clinical physician standpoint and say female patients are more likely to respond than male patients, Asians are more likely to respond than non-Asians and nonsmokers are much more likely to respond than smokers. In general, using these clinical factors can provide a good estimate of the likelihood of response. That does not mean that a male smoker with squamous cell carcinoma has no chance of benefit from erlotinib, but the likelihood of a huge benefit is much less.

Another view is from the biology perspective, and a few ideas have been

investigated. One is EGFR gene amplification. That work has been conducted predominantly by Fred Hirsch at Colorado, and his team has shown fairly compellingly that overexpression of the EGFR gene in tumors predicts response and survival in lung cancer.

The other part of the biology equation has been EGFR mutations, with research pioneered primarily by Tom Lynch at Harvard. He has been able to show certain mutations, particularly an exon 19 deletion, for example, that tend to predict good response to therapy (Jackman 2006; [4.1]).

Every clinician who has used erlotinib or gefitinib extensively has most likely had one or two patients who have done incredibly well on the drug. I feel that gene amplification is a better predictor of the group of patients that derives meaningful benefit from the drug but not the spectacular home run we occasionally see.

4.1

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**

Tracks 5-6

DR LOVE: Can you discuss the study you just reported evaluating bevacizumab, *nab* paclitaxel and carboplatin?

DR REYNOLDS: We conducted a single-arm Phase II trial evaluating the combination of bevacizumab, *nab* paclitaxel and carboplatin in nonsquamous NSCLC, and this trial was developed after the results of ECOG-E4599 became available (Sandler 2006). In fact, we were developing the trial without bevacizumab and then thought the combination of *nab* paclitaxel and bevacizumab offered promise for lung cancer patients.

Rakesh Jain compellingly suggested with his research (Willett 2004) that one of the major roles of bevacizumab in improving outcomes has to do with improving drug delivery into tumors by changing tumor oncotic pressure and normalizing vasculature. Compelling preclinical and early clinical data with *nab* paclitaxel show that the formulation of *nab* paclitaxel does a better job of tumor drug delivery, so we thought the combination of these two drugs would potentially improve outcomes.

We embarked on a single-arm Phase II trial with entry criteria that were fairly similar to those used in ECOG-E4599, and the results we have seen are promising. Thus far with 50 patients, response rates are in the range of 30 percent, and we did not see any toxicity different from what we would expect based on ECOG-E4599.

DR LOVE: How much of an advantage is the shorter infusion time with *nab* paclitaxel (4.2)?

DR REYNOLDS: The shortened time in the office is significant, especially when you are dealing with patients who will only live about another year.

DR LOVE: What is the next step in terms of studying *nab* paclitaxel?

DR REYNOLDS: The current strategy is to embark on a Phase III trial. Whether that trial will involve bevacizumab is still a matter of debate, although I believe the study that will go forward is standard paclitaxel with carboplatin versus *nab* paclitaxel with carboplatin for advanced lung cancer treatment. The possibility of a study in the adjuvant setting has also been discussed.

4.2

Novel Paclitaxel Formulation: *Nab* Paclitaxel (Abraxane®)

"ABI-007…is a novel, biologically interactive, nanometer-sized albumin-bound paclitaxel particle initially developed to avoid the toxicities associated with polyethylated castor oil. It is the first of a new class of anticancer agents that incorporate albumin particle technology and exploit the unique properties of albumin, a natural carrier of lipophilic molecules in humans.

Administered as a colloidal suspension of 130 nanometer particles, ABI-007 allows the safe infusion of significantly higher doses of paclitaxel than the doses used with standard paclitaxel therapy, with shorter infusion schedules (30 minutes v 3 hours, respectively) and no premedication."

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

We have to be careful to ask questions that benefit our patients, and my enthusiasm for using these engineered taxanes in general has to do with the possibility of improving outcomes. Compelling data with at least a couple of these drugs indicate better delivery into the tumor and therefore potentially improved outcomes. ■

SELECT PUBLICATIONS

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

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**

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**

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004;10(2):145-7. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A trial of adjuvant chemotherapy in patients with Stage IB lung cancer (CALGB-9633) reported that overall survival was significantly improved in _____.**
   a. All patients
   b. Patients with tumors <4 cm
   c. Patients with tumors ≥4 cm
   d. None of the above

2. **A meta-analysis of overall survival in adjuvant trials of cisplatin in lung cancer (LACE) showed that the absolute difference in five-year survival with or without chemotherapy was ____ percent.**
   a. Five
   b. 10
   c. 15
   d. 20

3. **A retrospective analysis of elderly (older than 65 years of age) patients from the JBR.10 study reported that treatment was associated with significant advantages in _____.**
   a. Overall survival
   b. Disease-free survival
   c. Both a and b
   d. None of the above

4. **Cisplatin/gemcitabine has been extensively evaluated as adjuvant therapy in randomized Phase III clinical trials.**
   a. True
   b. False

5. **Which of the following has been found to predict for bevacizumab-related pulmonary hemorrhage?**
   a. Cavitation
   b. The patient's age
   c. The patient's performance status
   d. Both a and c
   e. All of the above

6. **Which of the following were exclusion criteria for ECOG-E4599?**
   a. Brain metastases
   b. Squamous histology
   c. History of hemoptysis
   d. All of the above
   e. None of the above

7. **In ECOG-E4599, fatal hemoptysis occurred in approximately one percent of patients.**
   a. True
   b. False

8. **Predictors of response to erlotinib therapy in patients with NSCLC include _____.**
   a. Female sex
   b. Nonsmoker status
   c. Asian descent
   d. All of the above

9. **Eligibility criteria for ECOG-E1505 include _____.**
   a. Stage IB (tumor size greater than four centimeters) to Stage IIIA NSCLC
   b. No bleeding
   c. Both a and b

10. **_____ levels of caveolin-1 and SPARC expression tend to correlate with increased metastatic potential and poor outcomes in lung cancer and other diseases.**
    a. Lower
    b. Higher

11. **Potential benefits of *nab* paclitaxel compared to standard formulation paclitaxel include no need for steroid premedication and shorter infusion time.**
    a. True
    b. False

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

EVALUATION FORM

Lung Cancer Update — Issue 2, 2007

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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
Corey J Langer, MD	5 4 3 2 1	5 4 3 2 1
Vincent A Miller, MD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
Craig Reynolds, MD	5 4 3 2 1	5 4 3 2 1
Joan H Schiller, 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

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

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.....

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LCU207

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UPDATE

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