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Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

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

ACCREDITATION STATEMENT

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UPCOMING EDUCATIONAL EVENTS

UICC World Cancer Congress 2006
July 8-12, 2006
Washington, DC
Event website: **worldcancercongress.org**

Asia Pacific Perspectives in Lung Cancer
August 4-5, 2006
Shanghai, China
Event website: **imedex.com/calendars/oncology.asp**

7th European Conference: Perspectives in Lung Cancer
September 8-9, 2006
Athens, Greece
Event website: **imedex.com/calendars/oncology.asp**

31st ESMO Congress
September 29-October 3, 2006
Istanbul, Turkey
Event website: **esmo.org**

Oncology Congress
October 19-21, 2006
New York, New York
Event website: **oncologycongress.com**

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: **astro.org**

American Association for Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **aacr.org**

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **asco.org/portal/site/ASCO**

INTERVIEW

Mark A Socinski, MD

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

Tracks 1-18

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Can you provide an overview of clinical trial data of nanoparticle albumin-bound *(nab)* paclitaxel in lung cancer?

DR SOCINSKI: One of the mainstays of treatment in not only lung cancer but also breast, ovarian and other cancers has been taxane-based therapy. However, we know that taxanes are relatively insoluble in aqueous solution

— they require the use of solvents, of which Cremophor® is probably the most notable.

The toxicities associated with the taxanes are not only hematologic. More problematic, typically, are the nonhematologic toxicities, including myalgias, arthralgias, neuropathy and hypersensitivity reactions.

Most of these toxicities may not be mediated by the parent taxane compound but by some of the solvents in which they're dissolved. Recently published evidence suggests that Cremophor has a direct neurotoxic effect.

Nanoparticle paclitaxel is a formulation of paclitaxel suspended in albumin (1.1). These nanoparticles — micelles — are soluble in water; therefore, they don't require the use of solvents.

They are administered relatively quickly with a very low incidence of hypersensitivity reactions compared to either docetaxel or paclitaxel. We have what appears to be safer and more convenient administration with less toxicity.

Nab paclitaxel received FDA approval because it provided an improved time to progression in breast cancer in a comparative trial versus paclitaxel (Gradishar 2005; [1.2]).

We conducted a Phase I trial that was presented at the 2005 San Antonio Breast Cancer Symposium, combining *nab* paclitaxel with carboplatin on either an every three-week or a weekly (days one, eight and 15 every 28 days) schedule (Stinchcombe 2005). It appears to be well tolerated and convenient.

1.1

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

"ABI-007 (Abraxane; American BioScience Inc, Santa Monica, CA) 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**

DR LOVE: Two of the potential advantages of *nab* paclitaxel are a shorter infusion time and the lack of premedication. How do those play out in lung cancer?

DR SOCINSKI: My view is that this agent has a bright future. If the breast cancer data were to be projected on other tumors — and it looks as if the *nab* formulation delivers the active cytotoxic to the tumor more effectively — and those data coupled with convenience, less toxicity and no need for premedication will impact how we prioritize first-line treatment regimens.

1.2

Phase III Randomized Trial Comparing *Nab* Paclitaxel to Paclitaxel as First-, Second-, Third- or Fourth-Line Therapy for Women with Metastatic Breast Cancer

	Nab paclitaxel (n = 229)	Paclitaxel (n = 225)	*p*-value
Complete response + partial response			
Overall	33%	19%	0.001
First-line therapy	42%	27%	0.029
Median time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival			
Overall	65 weeks	55.7 weeks	0.374
≥Second-line therapy	56.4 weeks	46.7 weeks	0.024
Neutropenia (Grade IV)	9%	22%	<0.001
Sensory neuropathy (Grade III)	10%	2%	<0.001
Hypersensitivity (any Grade)	<1%	2%	Not reported

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

Tracks 14-15

DR LOVE: Can you discuss the tyrosine kinase inhibitors ZD6474 and AZD2171?

DR SOCINSKI: ZD6474 is purported to have anti-VEGF as well as anti-EGFR properties. It's a small-molecule tyrosine kinase inhibitor, and it appears to inhibit the VEGF receptor at lower concentrations, but it will also inhibit the EGFR at a slightly higher concentration.

AZD2171 is also a VEGF inhibitor. The NCIC is conducting an interesting Phase II/III trial evaluating carboplatin/paclitaxel with or without this agent. They are entering 150 patients in the Phase II trial and evaluating time to progression. If that endpoint is met, the trial will shift into a larger Phase III trial with approximately 600 patients.

DR LOVE: What do we know about the efficacy of these agents?

DR SOCINSKI: Currently we have a little more data with ZD6474 than with AZD2171. A second-line trial is comparing docetaxel as the control arm to docetaxel combined with two different doses of ZD6474, either 100 or 300 milligrams (Heymach 2005; Herbst 2005c; [1.3]).

In the initial data, the progression-free survival curves were dramatically better for the 100- versus the 300-milligram dose combined with docetaxel, and remember, with the lower dose you're probably getting primarily VEGF inhibition, whereas with the 300-milligram dose, you're getting some EGFR inhibition.

This trial is reminiscent of the trials in which combining EGFR drugs with

chemotherapy didn't make a difference. No major toxicity issues were associated with the drug, so this is not a result of patients not receiving the therapy. Rather, it suggests that, based on the mechanism of action, we don't know that anti-EGFR inhibition in combination with chemotherapy is a good thing. After all, the INTACT, TRIBUTE and TALENT trials were all negative in that population (Giaccone 2004; Herbst 2004; Herbst 2005b; Gatzemeier 2004).

However, because the Phase II trial showed an impressive difference in the progression-free survival of patients treated with the 100-milligram dose of ZD6474, I believe the signal is sufficient to go on to Phase III.

1.3

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.

Tracks 16-17

DR LOVE: What are your thoughts on combining erlotinib and bevacizumab to block both EGFR and VEGF?

DR SOCINSKI: We only have one experience thus far and that's the study reported by MD Anderson and Vanderbilt (Herbst 2005a; [1.4]). They treated 40 patients in the refractory setting and produced impressive outcome data. The response rate was 20 percent and the stable disease rate was 65 percent in a group of relatively refractory patients. The median survival was approximately 12 months.

DR LOVE: Can you comment on what we know about clinical or tissue predictors of response to TKIs?

DR SOCINSKI: In my mind, the data from the BR-21, TALENT, TRIBUTE and other trials are hypothesis generating, but they haven't changed my practice (Shepherd 2005; Gatzemeier 2004; Herbst 2005b). We don't have good standardized methodologies to stain a tumor for EGFR; however, they will evolve.

This is reminiscent of the initial HER2 experience with trastuzumab, when investigators attempted to determine how to screen patients for therapy and whether IHC or FISH is better to measure HER2. We're going through the same process with the targeted agents for non-small cell lung cancer.

We do have a current CALGB trial targeting patients who have never smoked that randomly assigns them to single-agent erlotinib or erlotinib with carboplatin/paclitaxel in the first-line setting (CALGB-30406).

The data from a number of trials now suggest that EGFR-directed therapy is important for never smokers. The trial includes mandatory tissue collection, so we're studying all the molecular markers, IHC and FISH in a prospective manner.

In practice, if I have a patient with a good performance status who has failed a first-line platinum-based doublet, he or she is going to receive erlotinib and pemetrexed.

The question is, which one comes first? I use clinical parameters, such as smoking status, histology, and sometimes gender and ethnicity, to guide my selection of EGFR-based therapy in the second-line setting, and if the patient isn't demonstrating clinical benefit within four to six weeks, I switch to the other agent. ■

1.4

Phase I/II Trial Evaluating Bevacizumab in Combination with Erlotinib for Patients with Recurrent Non-Small Cell Lung Cancer

"Combined erlotinib and bevacizumab therapy was well tolerated in both phase I and II of this study. AEs were rarely more than mild to moderate and were easily managed, suggesting that treatment with this combination is feasible. The most common AEs were rash, diarrhea, infection, hematuria, and proteinuria....

The antitumor activity and survival data reported in this trial were very encouraging. The disease control rate (CR + PR + SD) for the entire study population was 85%; overall response rate was 20.0% with a median response duration of >35 weeks. Median OS and PFS for the 34 patients treated at the phase II dose were 12.6 months and 6.2 months, respectively. Similar results were noted for the entire population (n = 40), with a median OS of 12.6 months and PFS of 7.0 months."

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

SELECT PUBLICATIONS

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* 2005;**Abstract 7059**.

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**

Gatzemeier U et al. **Results of a phase III trial of erlotinib (OSI-774) combined with cisplatin and gemcitabine (GC) chemotherapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2004;**Abstract 7010**.

Giaccone G et al. **Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: A phase III trial — INTACT 1.** *J Clin Oncol* 2004;22(5):777-84. **Abstract**

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**

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**

Herbst R et al. **ZD6474 plus docetaxel in patients with previously treated NSCLC: Results of a randomized placebo-controlled Phase II trial.** Presentation. Proceedings from the 11th World Conference on Lung Cancer 2005c;Abstract O-100.

Herbst RS, Sandler AB. **Non-small cell lung cancer and antiangiogenic therapy: What can be expected of bevacizumab?** *Oncologist* 2004;9(Suppl 1):19-26. **Abstract**

Heymach JV et al. **A randomized, placebo-controlled phase II trial of ZD6474 plus docetaxel in patients with NSCLC.** *Proc ASCO* 2005;**Abstract 3023**.

Johnson BE et al. **Preliminary phase II safety evaluation of ZD6474, in combination with carboplatin and paclitaxel, as 1st-line treatment in patients with NSCLC.** *Proc ASCO* 2005;**Abstract 7102**.

Natale R et al. **A comparison of the antitumour efficacy of ZD6474 and gefitinib (Iressa) in patients with NSCLC: Results of a randomized, double-blind Phase II study.** Presentation. Proceedings from the 11th World Conference on Lung Cancer 2005;Abstract O-103.

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.** Presentation. ASCO 2005;**Abstract 4**.

Shepherd FA et al; National Cancer Institute of Canada Clinical Trials Group. **Erlotinib in previously treated non-small-cell lung cancer.** *N Engl J Med* 2005;353(2):123-32. **Abstract**

Sparreboom A et al. **Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol).** *Clin Cancer Res* 2005;11(11):4136-43. **Abstract**

Stinchcombe TE et al. **Preliminary results of phase I trial of carboplatin (CP) in combination with ABI-007 administered weekly or every 3 weeks in patients (pts) with solid tumors.** San Antonio Breast Cancer Symposium 2005;**Abstract 1092**.

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

Nasser H Hanna, MD

Dr Hanna is Assistant Professor in the Department of Medicine, Division of Hematology/Oncology in the School of Medicine at Indiana University Medical Center in Indianapolis, Indiana.

Tracks 1-17

Select Excerpts from the Interview

Track 4

DR LOVE: Can you summarize your impression of the trial conducted by Drs Sandler and Herbst evaluating erlotinib in combination with bevacizumab?

DR HANNA: It's an important study because once patients are in the second-

line setting their survival times are usually very short. The vast majority of patients in this setting do not survive one year.

It's unacceptable to induce toxicities in this patient population, particularly when the goal is palliation. So a regimen that is well tolerated and effective in this group of patients would be ideal.

In the second-line setting, one would expect the response rate with chemotherapy agents to be about 10 percent, with a median survival time of six to eight months. In the trial combining erlotinib with bevacizumab, the response rate was 20 percent and the median survival time exceeded a year (Herbst 2005; [2.1]).

It was a Phase II, two-institution study, but the results are still remarkable. So I believe it's appropriate to conduct the randomized Phase III study, the design of which is erlotinib with or without bevacizumab.

The combination appears to be well tolerated because these agents don't have the same side-effect profiles as chemotherapy drugs. They usually don't cause nausea, vomiting, alopecia, diarrhea, mucositis, myelosuppression, et cetera.

2.1

Phase I/II Trial Evaluating Erlotinib with Bevacizumab in Patients with Previously Treated Nonsquamous NSCLC (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
Partial response rate	20%

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

Track 9

DR LOVE: Can you review your trial in Stage III non-small cell lung cancer?

DR HANNA: For the last three and a half years, the Hoosier Oncology Group, in collaboration with US Oncology, has been conducting a Phase III randomized trial (HOG LUN01-24; [2.2]) for patients with Stage IIIA/IIIB disease who have a performance status of zero or one.

All cases are considered unresectable, and they're all treated with cisplatin and etoposide with chest radiation, just as SWOG has done for years.

After the completion of that therapy — as long as they haven't experienced disease progression or undue toxicity and they have maintained a performance status of zero, one or two — patients are randomly assigned either to be

observed or to receive three cycles of docetaxel.

At ASCO this year, we will be presenting some initial data regarding consolidation therapy. The issues at hand in our patient population are: what percentage of patients were able to be randomly assigned, what percentage of patients who were treated with docetaxel received all three cycles, what percentage needed dose reductions or dose omissions, what percentage required growth factor support, and what were the complication rates of patients, including hospitalization rates, blood transfusion rates and such. These are all important to consider.

A major difference between our trial and the Southwest Oncology Group 9504 trial is that the pulmonary function of patients only had to be an FEV1 (forced expiratory volume in one second) of greater than one liter.

I believe that that represents the smoking lung cancer population to a greater degree than an FEV1 of greater than two liters. In fact, we evaluated our data, and based upon that criteria alone, half of the patients who entered our trial would not have been eligible for the SWOG trial.

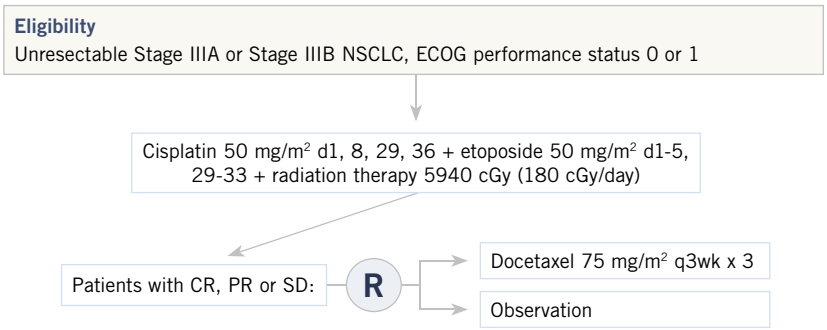
I believe patients who have better pulmonary function probably have better cardiac function and are more fit. It's also important when viewing rates of pneumonitis and late complications of therapy that we understand the baseline pulmonary function of patients. If somebody's baseline pulmonary function is excellent, they can take some pneumonitis and pulmonary fibrosis.

However, if baseline FEV1 is borderline and you start causing fibrosis, that patient will likely remain on oxygen and be chronically short of breath, which is unpleasant for patients. So with that criteria, our trial will represent a more representative group of patients in the general community.

2.2

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

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



SOURCES: NCI Physician Data Query, June 2006; ClinicalTrials.gov, June 2006.

Track 14

DR LOVE: How do you approach adjuvant systemic therapy for non-small cell lung cancer?

DR HANNA: The regimen that was used in the US Intergroup/NCI Canada study JBR.10 (Winton 2005; [2.3]) was vinorelbine with cisplatin. The large 800-patient ANITA trial (Douillard 2005; [2.3]) also evaluated vinorelbine and cisplatin, so I believe it's perfectly appropriate to use that regimen.

Also, it's appropriate to administer etoposide with cisplatin because more than 50 percent of the patients who received chemotherapy on the International Adjuvant Lung Trial received this combination (Arriagada 2004; [2.3]).

My preference is to use docetaxel plus carboplatin because three randomized trials in metastatic disease indicate that docetaxel is a superior drug to vinorelbine.

The first was a second-line trial, which Dr Fossella reported seven years ago, evaluating docetaxel with either ifosfamide or vinorelbine. Docetaxel showed a superior one-year survival compared to vinorelbine.

The second trial was the TAX-326 trial, which Dr Fossella also reported and which led to the registration of docetaxel as first-line therapy for NSCLC.

The control arm on that study administered vinorelbine and cisplatin versus docetaxel and cisplatin. In that study, docetaxel/cisplatin was superior to vinorelbine/cisplatin (Fossella 2003; [2.4]).

2.3

Trials Evaluating Adjuvant Cisplatin-Based Regimens versus Observation in NSCLC

	IALT[1]	JBR.10[2]	ANITA[3]
N	1,867	482	840
Stage	I, II, III	IB & II	I, II & IIIA
Therapy	Cis-based* Some RT	Cis/vinorelbine No RT	Cis/vinorelbine Some RT
Five-year RFS	39.4% vs 34.3%	61% vs 49%	Not reported
Five-year OS	44.55% vs 40.4%	69% vs 54%	51.2% vs 42.6%

Cis = cisplatin; RT = radiation therapy; RFS = relapse-free survival; OS = overall survival

*Cisplatin + vinca alkaloid or etoposide

SOURCES: [1] Arriagada R et al; International Adjuvant Lung Cancer Trial Collaborative Group. *N Engl J Med* 2004;350(4):351-60. **Abstract**; [2] Winton T et al; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. *N Engl J Med* 2005;352(25):2589-97. **Abstract**; [3] Douillard J et al. Presentation. ASCO 2005;**Abstract 7013**.

The third was a study from Japan, reported at ASCO 2005, observing an elderly group of patients treated with first-line docetaxel versus vinorelbine. Docetaxel was significantly superior to vinorelbine.

I believe docetaxel and cisplatin are better than vinorelbine and cisplatin in the adjuvant setting. Again, vinorelbine/cisplatin and etoposide/cisplatin are reasonable, but I consider our most effective agents to be docetaxel and cisplatin. ■

2.4

Phase III Randomized Trial (TAX-326) of Docetaxel with Platinum Combination versus Vinorelbine/Cisplatin in Patients with Previously Untreated Advanced NSCLC: Comparison of Docetaxel/Cisplatin and Vinorelbine/Cisplatin*

	Docetaxel/cisplatin (n = 408)	Vinorelbine/cisplatin (n = 404)	*p*-value
Overall median survival (95% CI)	11.3 months (10.1-12.4)	10.1 months (9.2-11.3)	0.044†‡
Estimated one-year survival (95% CI)	46% (42%-51%)	41% (36%-46%)	—
Estimated two-year survival (95% CI)	21% (16%-25%)	14% (10%-18%)	—
Overall response rate (95% CI)	31.6% (27.1%-36.4%)	24.5% (20.4%-29.0%)	0.029§

CI = confidence interval
* Comparison of docetaxel/carboplatin and vinorelbine/cisplatin not presented in this table
† Nonparametric covariate-adjusted log-ranked test; ‡ hazard ratio = 1.183;
§ Fischer's exact test

SOURCE: Fossella F et al. *J Clin Oncol* 2003;21(16):3016-24. **Abstract**

SELECT PUBLICATIONS

Arriagada R et al; International Adjuvant Lung Cancer Trial Collaborative Group. **Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer.** *N Engl J Med* 2004;350(4):351-60. **Abstract**

Douillard J et al. **ANITA: Phase III adjuvant vinorelbine (N) and cisplatin (P) versus observation (OBS) in completely resected (stage I-III) non-small-cell lung cancer (NSCLC) patients (PTS): Final results after 70-month median follow-up. On behalf of the Adjuvant Navelbine International Trialists Association.** *Proc ASCO* 2005;**Abstract 7013**.

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**

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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INTERVIEW

Edward S Kim, MD

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

Tracks 1-19

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the ECOG-E4599 trial and your study with bevacizumab?

DR KIM: ECOG-E4599 was a two-arm randomized trial of carboplatin/paclitaxel with or without bevacizumab. Patients received up to six cycles of chemotherapy. Patients on the bevacizumab arm received it concurrently with chemotherapy and then as maintenance after completing six cycles (Sandler 2005).

ECOG-E4599 included more than 800 patients, and the results indicated a survival benefit of greater than two months (3.1). It's the first trial in NSCLC to add an agent to an existing chemotherapy regimen and show a survival advantage. Median survival was more than 12 months, which is the first time that's been demonstrated (Sandler 2005).

The study we are conducting at MD Anderson evaluates carboplatin/docetaxel and bevacizumab as first-line therapy for patients with NSCLC (3.2). This trial will supplement the data from ECOG-E4599 to show feasibility of bevacizumab with other platinum-based doublets.

3.1

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**.

3.2

A Phase II Evaluation of Bevacizumab in Combination with Chemotherapy

Protocol ID: MDACC 2005-0224, NCT00271505
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

Protocol therapy: 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

SOURCES: **mdanderson.org**; NCI Physician Data Query, June 2006.

Track 3

DR LOVE: What agents are currently being used in combination with bevacizumab for the treatment of non-small cell lung cancer?

DR KIM: Currently, to my knowledge, docetaxel and paclitaxel are the only taxanes evaluated in combination with bevacizumab in lung cancer. Data for gemcitabine/cisplatin in combination with bevacizumab may be available by the end of the year. We're not sure yet if any carboplatin with gemcitabine data will become available, although I'm sure that trial is planned. I'm unsure whether any of the *nab* paclitaxel studies are ready to evaluate bevacizumab.

Track 7

DR LOVE: What deliberations are going on within MD Anderson and the SWOG Lung Committee with regard to lung cancer clinical research?

DR KIM: At MD Anderson, in cooperation with Dana-Farber and Emory, we are planning to perform a series of Phase II trials. We will mandate that patients receiving second-line therapy undergo two core biopsies. After completing the biopsies, we are asking them to wait for two weeks. At that point, we will conduct a litany of biomarker tests, including VEGF-related, EGF-related, including mutation and amplification, and others, like cyclin D1, RAS and RAF kinase.

We will put these data into a statistical model that's being developed by one of our top statisticians, Dr Jack Lee at MD Anderson, and derive a hypothetical score. If the patient's tumor, based on preclinical data, favors a VEGF type of inhibition, that patient will then be randomly assigned to a VEGF trial we have open.

The four drugs we will be evaluating are erlotinib, ZD6474 (Zactima), erlotinib plus bexarotene — because we've seen synergistic activities described at Dartmouth (Dragnev 2004) — and then sorafenib, as the final arm. So, based on the characteristics of a patient's tissue, we will hypothetically try to place them in a drug arm that is most favorable to their tumor. The best-case scenario is that we get much higher response rates and disease control than has been described in other Phase II studies. The worst-case scenario is that we've randomly placed a patient into a trial with one of four very active drugs for non-small cell lung cancer. So it's a "win-win" from that standpoint.

DR LOVE: How much extra morbidity or risk will there be in getting more tissue?

DR KIM: There's always a risk any time you perform a procedure on a patient. In breast cancer they have made major strides because they were able to obtain tissue and do validated arrays. The problem we have in lung cancer is that we have no validation of arrays, because, frankly, we don't have much tissue to test in these metastatic patients.

We tell patients that they will have an opportunity to receive one of these four promising drugs and be followed closely. In fact, if they progress on one of these arms, we retest their tissue, if they allow us, and see if they may fit into a different arm.

DR LOVE: What if the patient asks, "How much extra risk am I going to take, and what are the risks of those procedures?"

DR KIM: The major risk is doing a core biopsy. That may be a bronchoscopy or a CT-guided core biopsy. The risks — particularly at our center for doing these in lesions that are reasonably sized, greater than one centimeter, somewhat peripheral — as far as pneumothorax or lung collapse — are very low, in the realm of one percent.

Track 12

DR LOVE: What are the key clinical issues in new trials evaluating bevacizumab as adjuvant therapy for non-small cell lung cancer?

DR KIM: Bevacizumab works well in the metastatic setting, so there is a rationale to move our best metastatic regimen to adjuvant therapy. If you go with the published data, cisplatin/vinorelbine is the regimen that you would choose to add bevacizumab to in the adjuvant setting. However, not many people are using cisplatin/vinorelbine as adjuvant therapy. I personally prefer cisplatin/docetaxel.

With bevacizumab, you need to consider the problems that could occur in a postoperative setting. We have to derive that from the colon trials. We're not sure if there will be any wound dehiscence in lung cancer patients who have had surgery. ■

SELECT PUBLICATIONS

Dragnev KH et al. **A phase I/II study of bexarotene (B) and erlotinib (E): A novel targeted combination therapy for lung cancer and other aerodigestive tract (ADT) tumors.** *Proc ASCO* 2004;**Abstract 3092**.

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Lee D. **Phase II data with ZD6474, a small-molecule kinase inhibitor of epidermal growth factor receptor and vascular endothelial growth factor receptor, in previously treated advanced non-small-cell lung cancer.** *Clin Lung Cancer* 2005;7(2):89-91. No abstract available.

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**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. ***Nab* paclitaxel is FDA approved for the treatment of _____ cancer.**
   a. Breast
   b. Non-small cell lung
   c. Ovarian
   d. Gastric
   e. All of the above

2. **The oral agent ZD6474 has dual-receptor tyrosine kinase inhibitor activity against both the VEGF and the EGFR receptors.**
   a. True
   b. False

3. **In the trial evaluating docetaxel versus docetaxel with ZD6474, the 100-milligram dose, versus docetaxel/ZD6474, the 300-milligram dose, which arm demonstrated superior progression-free survival?**
   a. Single-agent docetaxel
   b. Docetaxel with the 100-milligram dose of ZD6474
   c. Docetaxel with the 300-milligram dose of ZD6474

4. **In a small Phase II trial of erlotinib in combination with bevacizumab as second-line therapy for metastatic NSCLC, the median survival was about _____.**
   a. Four months
   b. Six months
   c. Eight months
   d. Twelve months

5. **Which of the following adjuvant regimens was evaluated in both the US Intergroup/NCI Canada study and the ANITA trial?**
   a. Cisplatin/docetaxel
   b. Cisplatin/paclitaxel
   c. Cisplatin/vinorelbine
   d. Carboplatin/paclitaxel
   e. All of the above

6. **Among patients with previously untreated NSCLC, bevacizumab in combination with _____ improved median overall survival by approximately two months.**
   a. Carboplatin and paclitaxel
   b. Carboplatin and docetaxel
   c. Carboplatin and *nab* paclitaxel
   d. Cisplatin and paclitaxel
   e. Cisplatin and docetaxel

7. **Patients enrolled in ECOG-E4599 were allowed to continue on maintenance bevacizumab after completing _____ cycles of chemotherapy and bevacizumab.**
   a. Two
   b. Four
   c. Six
   d. Eight

8. **In the Phase III randomized TAX-326 trial, the combination of _____ was superior to the combination of vinorelbine/cisplatin in patients with previously untreated metastatic NSCLC.**
   a. Docetaxel/carboplatin
   b. Docetaxel/cisplatin
   c. Paclitaxel/carboplatin/bevacizumab
   d. Erlotinib/bevacizumab

9. **The MD Anderson Cancer Center is conducting a phase II trial evaluating the combination of carboplatin/docetaxel/bevacizumab in patients with metastatic NSCLC.**
   a. True
   b. False

10. **Potential advantages for *nab* paclitaxel include _____.**
    a. Shorter infusion time
    b. No premedication
    c. Less neurotoxicity
    d. Both a and b
    e. All of the above

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

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Lung Cancer Update — Issue 3, 2006

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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

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Faculty	Knowledge of subject matter	Effectiveness as an educator
Mark A Socinski, MD	5 4 3 2 1	5 4 3 2 1
Nasser H Hanna, MD	5 4 3 2 1	5 4 3 2 1
Edward S Kim, MD	5 4 3 2 1	5 4 3 2 1

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