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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 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 1 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Greco, Belani and Natale 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**.

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UPCOMING EDUCATIONAL EVENTS

Fourth Annual Winter Lung Cancer Conference

March 16-18, 2007
Miami Beach, Florida
Event website: **www.thecbce.com**

Third Annual Multidisciplinary Interactive Thoracic Oncology Conference

April 20-21, 2007
Seattle, Washington
Event website: **www.thecbce.com**

National Lung Cancer Partnership Annual Meeting

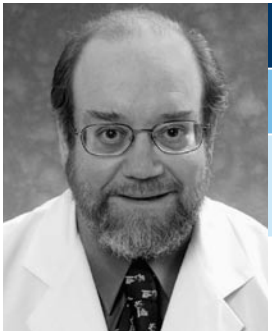
June 1, 2007
Chicago, Illinois
Event website: **www.thecbce.com**

2007 ASCO Annual Meeting

June 1-5, 2007
Chicago, Illinois
Event website: **www.asco.org**

12th World Conference on Lung Cancer — IASLC

September 2-6, 2007
Seoul, Korea
Event website: **www.2007worldlungcancer.org**



INTERVIEW

F Anthony Greco, MD

Dr Greco is Medical Director at the Sarah Cannon Cancer Center in Nashville, Tennessee.

Tracks 1-19

Select Excerpts from the Interview

Track 2

DR LOVE: Can you describe the pathogenesis of cancer of unknown primary?

DR GRECO: I don't believe there's one explanation for all patients with cancer of unknown primary, but the most attractive theory is what I call an

embryologic theory. Basically, cells are misplaced during embryologic migration. The cells in our body that make up all the tissues migrated from a small blastosphere and grew and differentiated into our organs, and we know that cells may be misplaced during this process. In other words, pancreas cells could end up in a lymph node when most of their brethren formed the pancreas.

DR LOVE: Can you describe a clinical scenario to illustrate this theory?

DR GRECO: Consider a man who has an enlarged lymph node in his left neck and no other abnormality anywhere else. A biopsy indicates an adenocarcinoma, but he's otherwise healthy. After a full workup, including endoscopy, CT scanning and PET scanning, everything's normal.

He may have an occult small primary in another site that has spread into the bloodstream and migrated into a lymph node in his neck, which is the traditional thinking. The embryologic theory is that the misplaced cell was in his neck from the time he was born.

Track 3

DR LOVE: Roughly how many cases of cancer of unknown primary appear in a year in the United States?

DR GRECO: Approximately 50,000. It's not rare, and let me clarify that. Probably a third to a half of the cases are identified as something else. For example, a patient has liver metastases and an elevated CA19-9 — a marker associated with pancreatic cancer — but the pancreas is absolutely normal. More than half of the time, that person's death certificate will say the patient died of pancreatic cancer.

About 70 to 80 percent of the cases are adenocarcinoma, and the majority of the rest are poorly differentiated carcinoma. A minority present with one tumor site, and they have a better prognosis. This is not one group of patients but rather a heterogeneous group, and several of these patient subgroups are highly treatable.

DR LOVE: If you consider the entire heterogeneous group of patients with unknown primaries, what's the long-term prognosis?

DR GRECO: It's poor overall. If you treat patients with adenocarcinoma of unknown etiology, the one-year survival is as good as, if not a little better than, advanced lung cancer. The two-year survival is around 20 percent of the patients, and as you go out to five years it settles into 10 to 15 percent.

Track 6

DR LOVE: Can you describe the study of *nab* paclitaxel that you conducted in non-small cell lung cancer (Allerton 2006)?

DR GRECO: The study consisted of a weekly schedule of *nab* paclitaxel and was designed for patients with advanced or recurrent non-small cell lung cancer. The patients had to be in reasonable health overall and have normal organ function. The dose of *nab* paclitaxel was 100 mg/m^2 per week on days one, eight and 15, and the dose of carboplatin was calculated for an AUC of six and administered on day one.

The courses were repeated every 28 days. We treated approximately 60 patients with advanced non-small cell lung cancer, and the response rate was around 45 percent with confidence intervals that were reasonably tight (Allerton 2006; [1.1]).

It was a well-tolerated regimen — neutropenia was the most common side effect, but it wasn't prolonged or particularly severe in most patients (1.1). The most troublesome side effect was sensory neuropathy. Unlike the traditional paclitaxel formulation (Belani 2003), however, the neuropathy associated with *nab* paclitaxel was more transient, which has also been observed in breast cancer clinical trials.

It often resolved within several weeks — sometimes it markedly decreased within several days. So this Phase II trial showed activity, safety and a relatively high response rate.

1.1

Trials of Paclitaxel and *Nab* Paclitaxel with Carboplatin as First-Line Treatment for Advanced Non-Small Cell Lung Cancer

	Efficacy	
	Paclitaxel[1] + carboplatin (n = 132)	*Nab* paclitaxel[2] + carboplatin (n = 56)
Objective response rate (CR + PR)	32%	48%
Stable disease (SD) 12-39 weeks	NR	30%
Median time to progression	30 weeks	30 weeks
	Grade III/IV adverse events	
	Paclitaxel[1] + carboplatin	*Nab* paclitaxel[2] + carboplatin
Neutropenia	22%	30%
Thrombocytopenia	5%	18%
Anemia	7%	7%
Neuropathy	5%	0%*

* Thirteen percent had Grade I neuropathy, and five percent had Grade II neuropathy.

Both paclitaxel and *nab* paclitaxel administered at 100 mg/m^2 weekly x 3 and carboplatin AUC = 6 mg/mL x min

SOURCES: [1] Belani CP et al. *J Clin Oncol* 2003;21(15):2933-9. **Abstract**
[2] Greco A et al. *Proc Chemotherapy Foundation Symposium XXIV* 2006. No abstract available

Track 12

DR LOVE: What's your treatment algorithm for patients with metastatic NSCLC who are nonsmokers or oligo-smokers with a 15 pack per year history?

DR GRECO: Usually erlotinib is on top of the list, either before or combined with chemotherapy. The data with chemotherapy did not show a benefit, but those data were from unselected or unenriched populations (Herbst 2005; [1.2]).

We have only anecdotal data for chemotherapy combined with erlotinib for nonsmokers. My bias is that the combination will be even better than monotherapy but you will not cure these patients, and erlotinib alone would be a reasonable first choice for a nonsmoking woman with adenocarcinoma.

DR LOVE: In the adjuvant setting, would you consider the use of erlotinib for a nonsmoker?

DR GRECO: Yes I would — again, we don't have good data, but the scientific logic of it is more important right now. In that situation, I would use erlotinib.

1.2

TRIBUTE Trial: Phase III Randomized Study of Carboplatin/Paclitaxel (C/P) with or without Erlotinib in Patients with Previously Untreated NSCLC

	All patients		Nonsmokers	
	C/P + erlotinib (n = 539)	C/P alone (n = 540)	C/P + erlotinib (n = 72)	C/P alone (n = 44)
Median overall survival	10.6 months	10.5 months*	22.5 months	10.1 months†
Median TTP	5.1 months	4.9 months*	6.0 months	4.3 months‡

* p = NS; † p = 0.01; ‡ p = 0.02; TTP = time to progression

SOURCE: Herbst RS et al. *J Clin Oncol* 2005;23(25):5892-9. **Abstract**

Track 13

DR LOVE: A lot of controversy has emerged since the last ASCO meeting as a result of the CALGB-9633 data. What's your take on that?

DR GRECO: CALGB-9633 was a study conducted to evaluate patients with Stage IB NSCLC in the postoperative setting. The trial evaluated paclitaxel/carboplatin versus no further treatment, and the study was stopped early after an interim analysis because the overall and failure-free survival appeared to be significantly better for the patients receiving adjuvant chemotherapy (Strauss 2006). With additional follow-up, it turned out that the five-year overall survival was not any different, although progression-free survival still favored the group receiving adjuvant chemotherapy (Strauss 2006).

The total number of patients on the trial was relatively small, and finding a certain survival benefit was not statistically likely. In my view, it is hard to prove this because the power of the study was too low to detect an important clinical difference. Some would say that is not the reason because other studies of patients with Stage IB disease showed no benefit, and those studies were larger — and there's truth to that.

In the ANITA trial, patients with Stage IB disease did not benefit (Douillard 2005). Some believe the reason patients didn't benefit was that the ANITA trial used cisplatin instead of carboplatin.

The Canadian trial, led by Dr Francis Shepherd (Winton 2005), showed a benefit using vinorelbine and cisplatin for patients with Stage IB disease. It was probably related to the size of the tumors. A retrospective subgroup analysis of CALGB-9633 (Strauss 2006) suggested that patients with tumors four centimeters or greater did benefit (1.3).

1.3

Adjuvant Paclitaxel/Carboplatin versus Observation for Patients with Stage IB Non-Small Cell Lung Cancer (CALGB-9633): Exploratory Analysis of Survival Benefits According to Tumor Size (≥4 Centimeters or <4 Centimeters)

	Hazard ratio (90% CI)	*p*-value
Tumor ≥ 4.0 cm		
Disease-free survival	0.62 (0.44-0.89)	0.01
Overall survival	0.66 (0.45-0.97)	0.04
Tumor < 4.0 cm		
Disease-free survival	0.91 (0.62-1.32)	0.42
Overall survival	1.02 (0.67-1.55)	0.51

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

Track 14

DR LOVE: What kind of data would you want to see in order to use carboplatin/*nab* paclitaxel instead of carboplatin/paclitaxel in the adjuvant setting?

DR GRECO: I'd like to see Phase III efficacy data, but toxicity is not a trivial concern for patients with lung cancer. They're older, and they tend to have comorbid conditions. Therefore, I believe that *nab* paclitaxel could have a role because the drug is less toxic, particularly in terms of the neuropathy in the postoperative setting. It combines well with platinum agents, so I believe it could have a role there.

DR LOVE: Would a Phase III trial in metastatic disease with favorable findings be enough to adopt *nab* paclitaxel in the adjuvant setting?

DR GRECO: Yes. Perhaps I jump quicker, and some would say too quickly, but

if I had those data in the metastatic setting, I would translate those findings into the adjuvant setting.

DR LOVE: So what specifically are you doing first line off protocol in the adjuvant setting right now?

DR GRECO: I usually use carboplatin/paclitaxel. The myth is still out there that cisplatin and carboplatin are really different drugs. In my opinion, they're not different except in the rare instance of germ-cell tumors. I'm a proponent for therapy that doesn't debilitate patients in the adjuvant setting after thoracic surgery, and carboplatin is better tolerated in this setting than cisplatin. I know I am going to get major arguments from some of the purists who've conducted the studies, but that's okay — I can deal with it. ■

SELECT PUBLICATIONS

Allerton JP, Greco FA et al. **A phase II evaluation of the combination of paclitaxel protein-bound and carboplatin in the first-line treatment of advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2006;**Abstract 7127**.

Belani CP et al. **Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation.** *J Clin Oncol* 2003;21(15):2933-9. **Abstract**

Blum JL et al. **Long term disease control in taxane-refractory metastatic breast cancer treated with *nab* paclitaxel.** *Proc ASCO* 2004;**Abstract 543**.

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 Trialist Association.** ASCO 2005;**Abstract 7013**.

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**

Gradishar WJ. **Albumin-bound paclitaxel: A next-generation taxane.** *Expert Opin Pharmacother* 2006;7(8):1041-53. **Abstract**

Greco FA et al. **Paclitaxel/carboplatin/etoposide versus paclitaxel/topotecan for extensive-stage small cell lung cancer: A Minnie Pearl Cancer Research Network randomized, prospective phase II trial.** *Oncologist* 2005;10(9):728-33. **Abstract**

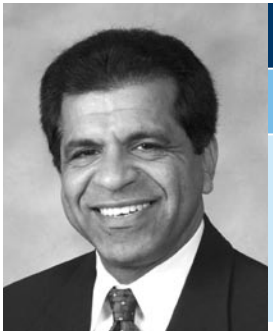
Greco FA et al. **Carcinoma of unknown primary site: Sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan: A Minnie Pearl Cancer Research Network phase II trial.** *Oncologist* 2004;9(6):644-52. **Abstract**

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* 2005;23(25):5892-9. **Abstract**

Miller VA et al. **Long survival of never smoking non-small cell lung cancer (NSCLC) patients (pts) treated with erlotinib HCl (OSI-774) and chemotherapy: Sub-group analysis of TRIBUTE.** Presentation. ASCO 2004;**Abstract 7061**.

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**.

Winton T et al. **Vinorelbine plus cisplatin vs observation in resected non-small-cell lung cancer.** *N Engl J Med* 2005;352(25):2589-97. **Abstract**



INTERVIEW

Chandra P Belani, MD

Dr Belani is Professor of Medicine at the University of Pittsburgh School of Medicine and Co-Director of the Lung and Thoracic Malignancies Program at the University of Pittsburgh Cancer Institute in Pittsburgh, Pennsylvania.

Tracks 1-16

Select Excerpts from the Interview

Track 2

DR LOVE: Can you summarize the current available data on adjuvant therapy for non-small cell lung cancer?

DR BELANI: I believe adjuvant therapy has become the standard for patients with resected non-small cell lung cancer. After 2005, it was the standard for patients with Stage IB to IIIA disease. Now we have a brewing controversy regarding whether we should administer adjuvant therapy to patients with Stage IB disease.

One issue in the controversy is whether or not it was carboplatin that caused

the failure of the carboplatin and paclitaxel regimen for patients with Stage IB disease in CALGB-9633 (Strauss 2006). At long-term follow-up, the data failed to show an improvement in overall survival because the hazard ratio fell from 0.62 to 0.80 and the *p*-value was not significant. As a word of caution, that was a small trial, and it is still not completed.

In general, considering the results of the other clinical trials, the JBR.10 study (Winton 2005), the IALT study (Arriagada 2004) and the ANITA trial (Douillard 2006), adjuvant chemotherapy did play a role in Stage IB disease because in those trials the chemotherapy was cisplatin based (2.1).

The CALGB-9633 trial has shown in a subset analysis that among patients who have tumors greater than four centimeters, a benefit still exists (Strauss 2006; [1.3]). But again, we may be reading too much into these subset analyses, which were not clear endpoints of these clinical studies.

In the clinical setting, for Stage IB disease, I offer chemotherapy to patients, informing them that in a small subset it has shown a benefit and in another subset it has not shown a benefit. I let the patient decide whether he or she wants to receive adjuvant chemotherapy. If the tumor is greater than four centimeters in size, then I usually suggest that the patient receive it.

DR LOVE: What about the older patient who has some comorbid conditions but is still healthy enough to consider therapy?

DR BELANI: The older patient should be considered for adjuvant chemotherapy because the JBR.10 trial reported on the elderly subset of patients. About 155 patients in the JBR.10 trial were elderly (Winton 2005; Pepe 2006), and a significant benefit was still evident in that population. The numbers are actually higher than they were in the total patient population: A 20 percent benefit appeared with adjuvant chemotherapy in the elderly population, and a 15 percent benefit appeared in the overall population.

2.1

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	44.5% 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. *N Engl J Med* 2004;350(4):351-60. **Abstract**; [2] Winton T et al. *N Engl J Med* 2005;352(25):2589-97. **Abstract**; [3] Douillard J et al. Presentation. ASCO 2005;**Abstract 7013**.

Five-year overall survival was 69 percent in the overall population versus 66 percent in the elderly population. So if the performance status was good and a patient didn't have any significant problems, I would offer cisplatin-based chemotherapy to an older patient.

Tracks 3-4

DR LOVE: Where are we in terms of the next generation of adjuvant trials, particularly with regard to the issue of evaluating bevacizumab?

DR BELANI: The next adjuvant bevacizumab trial will be ECOG-E1505 (2.2), and it includes three regimens — cisplatin/vinorelbine, cisplatin/docetaxel and cisplatin/gemcitabine — all with or without bevacizumab. Eligible patients will include those with Stage IB disease who have tumors that

2.2

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

Protocol IDs: ECOG-E1505, SWOG-E1505, CALGB-E1505, CAN-NCIC-E1505, NCCTG-E1505
Target Accrual: 1,500 (Approved — not yet active)

* Patients are stratified according to type of chemotherapy (cisplatin/vinorelbine vs cisplatin/docetaxel vs cisplatin/gemcitabine), stage (IB vs II vs IIIa [N2] vs IIIA [T3N1]), histology (squamous cell vs other) and gender.

Eligibility

- Resection (lobectomy, sleeve lobectomy, bilobectomy or pneumonectomy) within the past six to 12 weeks
- INR ≤ 1.5 or INR ≤ 3.0 with therapeutic anticoagulation
- ECOG performance status 0-1
- No history of CVA or TIA
- History of MI or angina acceptable if no evidence of active disease within past 12 months

Study Contacts

ECOG
Heather Wakelee, MD, Protocol Chair
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Tel: 916-734-3772

CALGB
Stephen Graziano, MD, Protocol Chair
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SOURCE: NCI Physician Data Query, January 2007.

are greater than four centimeters in size and those with Stage II or Stage IIIA disease without mediastinal nodes.

DR LOVE: What were your thoughts about the ECOG-E4599 study (Sandler 2005) evaluating carboplatin/paclitaxel with or without bevacizumab in patients with metastatic disease?

DR BELANI: That's an excellent trial that has shown a significant but modest benefit for bevacizumab in combination with carboplatin and paclitaxel. A two-month survival difference appeared, and this is the only trial that has shown a one-year survival greater than 50 percent in a select group of patients with metastatic NSCLC.

DR LOVE: How have those data affected your practice?

DR BELANI: We are using bevacizumab for patients with metastatic non-squamous cell carcinoma outside of a study. We are still following the ECOG-E4599 criteria. Outside of a study context, I would not recommend its use for patients with squamous cell carcinoma, patients with brain metastases or patients taking anticoagulants.

Track 6

DR LOVE: What are your thoughts about the combination of erlotinib and bevacizumab and the data that were presented at ASCO (2.3)?

DR BELANI: I consider it a combination worth pursuing further. A Phase III trial is definitely warranted in the second-line setting. A second-line trial

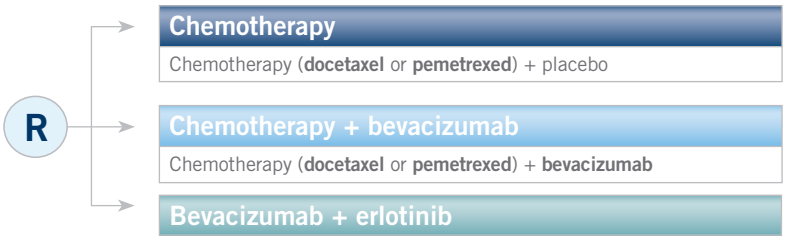
2.3

Phase II Trial of Bevacizumab with Chemotherapy or Erlotinib Compared to Chemotherapy Alone in Recurrent or Refractory Non-Small Cell Lung Cancer

Accrual: 120 (Closed)

Eligibility

Histologically or cytologically proven nonsquamous, recurrent or unresectable NSCLC with no antiangiogenic treatment, history of hemoptysis, recent history of hematemesis or stroke, ongoing treatment with full-dose anticoagulation agents, history of brain metastases, central lesion, presence of cavitation or a lesion abutting a major blood vessel



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

(Fehrenbacher 2006) compared chemotherapy to chemotherapy with bevacizumab to erlotinib with bevacizumab. The trial showed that the progression-free survival is superior in the chemotherapy with bevacizumab arm and in the erlotinib with bevacizumab arm by about 50 percent compared to chemotherapy alone (2.4). ■

2.4

Phase II Trial of Bevacizumab with Chemotherapy or Erlotinib Compared to Chemotherapy Alone in Recurrent or Refractory Non-Small Cell Lung Cancer: Efficacy Data

	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**.

SELECT PUBLICATIONS

Bedano PM et al. **Phase III study of cisplatin (P) plus etoposide (E) with concurrent chest radiation (XRT) followed by docetaxel (D) vs observation in patients (pts) with stage III non-small cell lung cancer (NSCLC): An interim toxicity analysis of consolidation therapy.** *Proc ASCO* 2006;**Abstract 7043**.

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 Trialist Association.** Presentation. ASCO 2005;**Abstract 7013**.

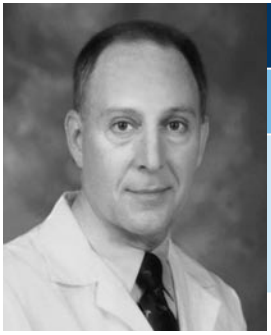
Fehrenbacher L et al. **A phase II, multicenter, randomized clinical trial to evaluate the efficacy and safety of bevacizumab in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib hydrochloride compared with chemotherapy alone for treatment of recurrent or refractory non-small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

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**.

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 on Cancer and Leukemia Group B (CALGB) Protocol 9633.** *Proc ASCO* 2006;**Abstract 7007**.

Winton T et al. **Vinorelbine plus cisplatin vs observation in resected non-small-cell lung cancer.** *N Engl J Med* 2005;352(25):2589-97. **Abstract**



INTERVIEW

Ronald B Natale, MD

Dr Natale is Medical Oncologist at Cedars-Sinai Outpatient Cancer Center and Senior Research Advisor and Director of the National Lung Cancer Research Program of Aptium Oncology Inc in Los Angeles, California.

Tracks 1-19

Select Excerpts from the Interview

Tracks 2-5, 7

DR LOVE: Can you discuss the mechanism of action of ZD6474 and the trial you presented at ASCO?

DR NATALE: ZD6474 is one of a growing list of multitargeted kinase inhibitors. This is an oral agent that targets vascular endothelial growth factor receptors (VEGFR) 1 and 2. It ranks among one of the most potent inhibitors

of the VEGFR kinases. It is also a moderately potent inhibitor of the EGFR tyrosine kinase.

Our objective was to evaluate the effectiveness of ZD6474 in patients with NSCLC. The question was, if ZD6474 is active in lung cancer, is it active because of its EGFR-targeted properties or because of its VEGFR-targeted properties? To answer that question, we designed a randomized, blinded study to compare ZD6474 head to head with gefitinib (Natale 2006; [3.1]).

Patients with NSCLC who had received one or, in a few cases, two prior chemotherapy regimens were eligible. Patients were evaluated at four-week intervals with follow-up CT scans. If evidence of disease progression was found, treatment was stopped. We allowed a four-week period for washout because both drugs have a long half-life, and then treatment was switched while we maintained the blinding. So patients who were first treated with gefitinib were switched to ZD6474 if their cancer progressed, and patients treated with ZD6474 first were then switched to gefitinib.

In the ZD6474 group, the objective response rate was eight percent and the stable disease rate was around 35 percent — a little better than a 40 percent overall benefit rate.

In terms of progression-free survival, the outcome with gefitinib was exactly the same as has been seen in other studies, with a median of a little more than two months. The progression-free survival with ZD6474 was significantly better statistically, at about 11 weeks (Natale 2006; [3.1]). That was the signal we were looking for to tell us whether it would be worthwhile pursuing more costly, larger and more definitive clinical trials.

The crossover part of the study was also important. More than 35 patients in the gefitinib arm made the crossover to ZD6474, and about 30 patients in the ZD6474 arm made the crossover to gefitinib. Crossing over from gefitinib to ZD6474, we had a disease control rate — meaning confirmed stabilization for eight weeks or longer — of around 35 to 40 percent. We would interpret that as meaning that these patients clearly did not have tumors that were sensitive to EGFR inhibition and that their disease stabilization pointed to the VEGFR-targeted properties of ZD6474.

Track 8

DR LOVE: What other studies are currently being conducted with ZD6474?

DR NATALE: At ASCO 2006, another important study was presented combining ZD6474 with docetaxel in the second-line setting (Heymach 2006; [3.1]). We had concerns because in the past, whenever we've combined an EGFR inhibitor with chemotherapy, we've observed inhibitory effects. Whatever might have been gained by EGFR inhibition was lost because EGFR inhibition slowed the proliferation of the cancer and probably rendered it less chemotherapy sensitive.

In this Phase II trial, patients were randomly assigned to receive docetaxel, combined with placebo, 100 milligrams of ZD6474 or 300 milligrams of ZD6474. The 100-mg dose was probably taking advantage only of ZD6474's VEGFR inhibitory properties because that dose is probably too low to have any significant EGFR inhibition. The 300-mg dose, however, probably causes some EGFR inhibition.

It is interesting that the results showed that the 100-mg dose was more effective. It had a higher response rate — 26 percent compared to about 10 or 11 percent with docetaxel alone. The 300-mg dose was intermediate between the 100-mg dose and the placebo in terms of progression-free survival, suggesting that once you get some EGFR inhibitory properties at that 300-mg dose, you begin to lose a little bit of what you gained by combining VEGFR inhibitory properties with chemotherapy.

The second reason we believe the 100-mg dose was better is that it was simply less toxic. When you combine a VEGFR-targeted agent — especially an agent that causes skin rash, mild nausea and mild hypertension — with docetaxel, you begin to see an increase in overall toxicity. You also begin to see increased intolerance, especially with respect to fatigue and asthenia, as we saw in our study.

3.1 **ZD6474 (Vandetanib) in Treatment of Patients with Advanced Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy**

	ZD6474[1] (n = 83)	Gefitinib[1] (n = 85)	Docetaxel + placebo[2] (n = 41)	Docetaxel + ZD6474 100 mg[2] (n = 42)	Docetaxel + ZD6474 300 mg[2] (n = 44)
Median PFS	11.0 wks	8.1 wks	12.0 wks	18.7 wks	17.0 wks
Hazard ratio (95% CI)	0.69 (0.50-0.96)		NA	0.64 (0.38-1.05)	0.83 (0.50-1.36)
p-value[1]	0.025		NA	0.074	0.416

SOURCES: [1] Natale RB et al. *Proc ASCO* 2006;**Abstract 7000**; [2] Heymach JV et al. *Proc ASCO* 2006;**Abstract 7016**.

Track 11

DR LOVE: Can you review what we know about the predictors of response to EGFR small-molecule tyrosine kinase inhibitors?

DR NATALE: Patients who have mutations in exon 19 and 21 of the EGFR gene appear to be the subgroup with the best chance of showing a major radiographic response to an EGFR-targeted agent such as erlotinib. Among patients with those mutations, objective responses to gefitinib occur at a rate of around 70 to 80 percent, and they have a median survival of more than a year (Hirsch 2006).

However, only a minority of patients have those types of specific EGFR mutations. In the population of patients with lung cancer as a whole, 12 percent have any mutations, and about half to two thirds of those have specific mutations of exon 19 or 21. Therefore, we're talking about selecting less than 10 percent of patients to be treated with these agents on the basis of mutations.

Clearly, many other patients can show major radiographic responses or clinical benefits from these drugs that mutations do not predict. Some can be identified by fluorescence in situ hybridization (FISH) analysis of EGFR gene copy number. Upwards of 30 to 35 percent of patients will be so-called FISH-positive, which is predictive of objective responses or some slowing of progression that results in a survival benefit. However, one of the problems with FISH is that many of these patients will not benefit from these agents. So we still don't have a test that is highly specific and sensitive.

Smoking status remains one of the best criteria you can use at the bedside to enrich the population of patients you select for treatment with an EGFR-targeted agent. In the first-line setting, 12 to 15 percent of patients in North America are never smokers. They smoked fewer than a hundred cigarettes in their lifetime. Some of us believe that the never smokers group can be extended to include patients who smoked less than a pack per day for less than 20 years and stopped smoking 15 or 20 years ago.

Someone who has a limited history of cigarette smoking — stopped smoking 15 or 20 years ago and now presents with lung cancer — has about a 50-50 chance that the cancer is the result of cigarette smoking.

DR LOVE: What fraction would you estimate this group of smokers represents in the first-line setting, in addition to the 10 or 12 percent nonsmokers?

DR NATALE: Probably another 10 percent or so. ■

SELECT PUBLICATIONS

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**.

Gatzemeier U et al. **Phase II trial of single-agent sorafenib in patients with advanced non-small cell lung carcinoma.** *Proc ASCO* 2006;**Abstract 7002**.

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**.

Hirsch FR et al. **Predicting clinical benefit from EGFR TKIs: Not all EGFR mutations are equal.** *Proc ASCO* 2006;**Abstract 7072**.

Natale RB et al. **ZD6474 versus gefitinib in patients with advanced NSCLC: Final results from a two-part, double-blind, randomized phase II trial.** *Proc ASCO* 2006;**Abstract 7000**.

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**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A Phase II study of patients with advanced NSCLC showed that the use of weekly *nab* paclitaxel combined with carboplatin was associated with _____ neuropathy.**
   a. Grade I
   b. Grade II
   c. Grade III/IV
   d. All of the above
   e. Only a and b

2. **An exploratory analysis of survival from CALGB-9633 showed that adjuvant carboplatin/paclitaxel conferred a significant benefit for patients with Stage IB disease who had tumors greater than _____ centimeters in size.**
   a. Five
   b. Three
   c. Four
   d. Two and a half

3. **In the TRIBUTE trial, no significant benefits were observed when erlotinib was added to chemotherapy in unselected patients with previously untreated NSCLC.**
   a. True
   b. False

4. **At this time, controversies in the adjuvant treatment of NSCLC include the following issues:**
   a. Whether or not to treat Stage IA disease
   b. Whether or not to treat Stage IB disease
   c. The use of carboplatin-based regimens
   d. Both b and c

5. **ECOG-E1505 will evaluate the use of _____ with or without bevacizumab for patients with resected Stage IB-IIIA NSCLC.**
   a. Vinorelbine and cisplatin
   b. Docetaxel and cisplatin
   c. Gemcitabine and cisplatin
   d. All of the above

6. **During treatment with bevacizumab, the risk of fatal pulmonary hemorrhage for patients with NSCLC (excluding predominant squamous histology) is approximately _____.**
   a. 3.2 percent
   b. 2.3 percent
   c. 5.0 percent
   d. None of the above

7. **Pulmonary hemorrhage has been seen following treatment with _____.**
   a. Sunitinib
   b. Sorafenib
   c. ZD6474
   d. Both a and b

8. **Which of the following has been shown to predict response to EGFR tyrosine kinase inhibitors?**
   a. Exon 19 or 21 mutation
   b. EGFR overexpression confirmed by FISH
   c. Never smoker status
   d. All of the above

9. **In a Phase II trial of docetaxel combined with placebo or ZD6474, which treatment was associated with the highest response rate and best progression-free survival?**
   a. Placebo
   b. 100 milligrams of ZD6474
   c. 300 milligrams of ZD6474

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

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Lung Cancer Update — Issue 1, 2007

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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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
F Anthony Greco, MD	5 4 3 2 1	5 4 3 2 1
Chandra P Belani, MD	5 4 3 2 1	5 4 3 2 1
Ronald B Natale, 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
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