LCU | 2007 VOL 4 | ISSUE 4

Lung Cancer™ UPDATE

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

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INTERVIEWS

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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 4 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Curran, Lilenbaum and Edelman 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 3 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs, review the monograph and complete the Post-test and Evaluation Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **LungCancerUpdate.com** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**.

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

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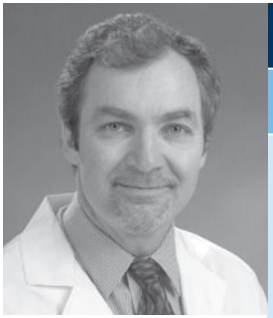

INTERVIEW

Walter J Curran Jr, MD

Dr Curran is Professor and Chairman in the Department of Radiation Oncology and Deputy Director for Clinical Sciences at the Kimmel Cancer Center of Jefferson Medical College at Thomas Jefferson University in Philadelphia, Pennsylvania.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What is your take on the plenary presentation at ASCO on the EORTC study of PCI for extensive-disease SCLC (Slotman 2007)?

DR CURRAN: PCI is a standard approach for patients with limited-stage SCLC who achieve a complete or near-complete response to chest radiation therapy and chemotherapy. At least two meta-analyses demonstrated an overall absolute increase in survival of five percent with that approach over a series of

1.1

EORTC Randomized Trial of Prophylactic Cranial Irradiation (PCI) versus No PCI in Extensive-Disease SCLC After Response to Chemotherapy

Endpoints	PCI (n = 143)	Control (n = 143)	Hazard ratio (95% CI), *p*-value
One-year symptomatic brain metastases	16.8%	41.3%	0.27 (0.16-0.44), $p < 0.001$
Extracranial progression	88.8%	92.8%	Not significant
Disease-free survival	23.4% 14.7 wk	15.5% 12.0 wk	0.76 (0.59-0.96), $p = 0.02$
One-year overall survival	27.1% 6.7 mo	13.3% 5.4 mo	0.68 (0.52-0.88), $p = 0.003$

SOURCE: Slotman B et al. *N Engl J Med* 2007;357:664-72. **Abstract**

studies and, in general, approximately a 50 percent or greater reduction in the development of central nervous system metastases (Aupérin 1999; Fried 2004).

The decision was made by the EORTC to conduct a trial to determine whether PCI could confer the same level of benefit to patients with extensive-stage disease who had a response to chemotherapy (Slotman 2007; [1.1]). The random assignment of 286 patients was between the administration of PCI at an aggressive fractionation of 20 Gray in five 4-Gray fractions versus observation. An important factor was that no brain imaging was required to confirm eligibility, so it's possible that patients already had asymptomatic metastases at the time of randomization. One interpretation of the study was: could this PCI have been early treatment of subclinical disease?

A statistically significant improvement was seen, not only in progression-free survival but also overall survival, which was a startling observation considering the fact that patients with extensive-stage SCLC, even those who experienced a good response to chemotherapy, have so many competing risks for mortality.

One can interpret these data in several ways: (1) It was a positive study, which defines a new paradigm of treatment for extensive-stage SCLC, (2) It was a positive study that is so counterintuitive that it needs confirmation or (3) It was a positive study that has to do with design methodology — for example, lack of careful restaging of the patients to assess response or evaluate the CNS and perhaps asymmetry in the actual randomization and stratification.

DR LOVE: How were you approaching these patients before the EORTC study was presented, and what are you doing now?

DR CURRAN: These patients have extensive-stage disease — that's an old VA Lung Cancer Group definition based on being encompassable or not in a reasonable radiation field. Some have extensive-stage disease and what I call oligometastases with an excellent complete response or near-complete response to chemotherapy or chemoradiation therapy, with whom I have a discussion about an aggressive therapeutic approach, including PCI. However, this is dependent on them having a normal brain MRI after staging. I have been

doing that for highly selected patients, and I will continue to. As far as the broader group of patients with extensive-stage SCLC, I have not changed my practice.

DR LOVE: What was the overall consensus within the RTOG regarding the EORTC study results?

DR CURRAN: The responses span the spectrum. Some members say it has changed how they approach these patients, whereas others found the design so different from our standards that they don't know how to apply the data.

I have never used the specific radiation regimen from the EORTC study, nor has any American study ever used it for PCI. This was administered in a week in five 4-Gray fractions (1.2), and the only time I see that in the US is for patients with cerebral metastases who are in poor condition, for whom there's a desire to complete treatment rapidly. For PCI, the usual treatment I administer is 2.5 Gray in 10 fractions.

1.2

Cranial Irradiation Dose in the EORTC PCI Study

"The question of the optimal dose for cranial irradiation in limited small-cell lung cancer is unresolved. A dose-response relationship was reported for radiobiologically equivalent doses of up to 30 to 35 Gy (in 2-Gy fractions) but not for higher doses, provided that radiotherapy was started early after chemotherapy…

The majority of patients in our study (88 of 143) received only 20 Gy in five fractions, and an impressive reduction in the risk of brain metastases was still seen."

SOURCE: Slotman B et al. *N Engl J Med* 2007;357:664-72. **Abstract**

Tracks 5-6

DR LOVE: What do you think about the clinical research strategy of combining radiation therapy with bevacizumab?

DR CURRAN: The landmark paper by Chris Willett and Rakesh Jain showed that in a small number of rectal cancer patients, bevacizumab alone had a physiologic effect in terms of the vasculature and showed clinical effect when combined with radiation therapy (Willett 2004).

DR LOVE: The other major discovery from that study was not only is there an anti-angiogenic effect, but there is also a normalization of the tumor vasculature, which has big implications in chemotherapy and radiation therapy.

DR CURRAN: Yes, because tumor hypoxia is thought to be one of the primary mechanisms of resistance to radiation therapy — you're right. SWOG initiated a study in Stage III NSCLC that is integrating bevacizumab into chemoradiation therapy, dividing patients between high- and low-risk groups according to whether they have central tumors, squamous histology, history of hemoptysis and other factors (SWOG-S0533; [1.3]). Due to cautious enrollment, a

small number of patients have enrolled. Episodes of tracheoesophageal (TE) fistula were reported in parallel ongoing studies in SCLC with bevacizumab and chemoradiation therapy. That required SWOG to stop S0533 and evaluate safety.

DR LOVE: What's your perspective on the potential benefits and risks of bevacizumab combined with chemoradiation therapy in lung cancer?

DR CURRAN: My gut feeling is that it can be an active addition to chemoradiation therapy. My biggest concern is that people will become legitimately concerned about the risk of catastrophic complications, and that will slow the clinical development. TE fistulas are obviously serious, life-threatening events. Originally with thoracic malignancies, we saw these when we started combining chemotherapy with radiation therapy decades ago, and it made some people back away from that paradigm. However, once we learned how to administer it, it revolutionized the care for those patients.

Even further back in the radiation therapy–alone era of unresected thoracic malignancies, we were taught that if someone had a tumor potentially

1.3

Multicenter Pilot Trial of Cisplatin/Etoposide/Radiation Therapy Followed by Consolidation Docetaxel and Bevacizumab in Three Cohorts of Patients with Inoperable, Locally Advanced Stage III NSCLC

Protocol ID: SWOG-S0533
Target Accrual: 182 (Open) Trial Start Date: June 15, 2006

Induction therapy

- **Cisplatin/etoposide** + **thoracic radiation therapy**
- **Cisplatin/etoposide** + **thoracic radiation therapy** + **bevacizumab** (d15, 36, 57)
- **Cisplatin/etoposide** + **thoracic radiation therapy** + **bevacizumab** (d1, 22, 43)

Three to six weeks after completion of induction therapy

Consolidation therapy

- **Docetaxel** + **bevacizumab** (with **filgrastim** or **pegfilgrastim**) q3wk x 3

Primary Endpoints
Frequency and severity of toxicity

Secondary Endpoints
Progression-free survival, overall survival and response

Stratification
High- versus low-risk

Eligibility

- Stage IIIA (N2) disease meeting the following criteria:
  - N2 mediastinal lymph nodes must be multiple and/or bulky on CT scan or x-ray so that the patient is not a candidate for induction chemotherapy or chemoradiation therapy followed by surgical resection
  - Stage IIIB disease with histologically or radiographically confirmed positive N3 nodes
  - T4 lesions of any size that invade the mediastinum, heart, great vessels, trachea, esophagus, vertebral body or crania

SOURCE: NCI Physician Data Query, October 2007.

invading the esophagus, we were to use a lower dose per fraction to avoid a TE fistula. So I view the TE fistula as a surrogate for excellent tumor response. We just need to figure out how to calibrate the antitumor action so it doesn't have a catastrophic effect.

Tracks 9-10

DR LOVE: Can you discuss what we know about predictors of response to EGFR tyrosine kinase inhibitors (TKIs), specifically erlotinib?

DR CURRAN: There are molecular and epidemiologic predictors of response to EGFR TKIs in second- and third-line treatment of NSCLC. Patients who are never smokers, women and of Asian descent have a higher likelihood of responding to a TKI than men who are heavy smokers and non-Asian.

In searching for predictors of response at the molecular level, the focus is on mutations in chromosomes 18 and 22. Work is also being conducted at Harvard, Sloan-Kettering and Colorado showing that EGFR mutational analysis is extremely helpful, in the right hands. The FISH-type analysis by Fred Hirsch and others has also been useful for predicting response (Cappuzzo 2005a, 2005b; Hirsch 2003, 2005, 2007).

Recently, we've seen interest in whether the presence of a K-ras mutation is a sufficiently adverse predictor of response to warrant not using TKIs. I reviewed data suggesting that, although the overall response rate using RECIST is lower in patients with K-ras mutation-positive disease, waterfall-type trends clearly suggest that the range of responses does not appear different in those patients with K-ras mutations from those with non-K-ras mutations.

DR LOVE: What do you see in terms of quality of life with chemotherapy versus erlotinib?

DR CURRAN: In general, erlotinib is better tolerated, especially compared to doublet-based chemotherapy. If erlotinib provides the same palliation and arrest of symptoms as doublet chemotherapy in the older, never smoker or oligosmoker with a poor performance status at diagnosis, I would like to have data to support erlotinib as initial treatment for that patient. That's an option that many patients and families would prefer. ■

SELECT PUBLICATIONS

Aupérin A et al. **Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group.** *N Engl J Med* 1999;341(7):476-84. **Abstract**

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Willett C et al. **Direct evidence that the VEGF-specific antibody bevacizumab has anti-vascular effects in human rectal cancer.** *Nat Med* 2004;10:145-7. **Abstract**

INTERVIEW

Rogerio C Lilenbaum, MD

Dr Lilenbaum is Clinical Associate Professor of Medicine at the University of Miami School of Medicine and Director of the Thoracic Oncology Program at The Mount Sinai Comprehensive Cancer Center in Miami Beach, Florida.

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Select Excerpts from the Interview

Tracks 1-6

Case Discussion 1

A 62-year-old woman with mild hypertension and a history of smoking two packs per day for 45 years presented with persistent cough, weight loss, fatigue, dyspnea on exertion and right-sided chest pain. Diagnostic workup reveals Stage IV small cell lung cancer with a large, right-sided perihilar mass, extensive mediastinal adenopathy and hepatic metastases.

DR LOVE: What was your approach with this patient?

DR LILENBAUM: We enrolled her in the CALGB-30306 trial evaluating cisplatin/irinotecan in combination with bevacizumab as front-line therapy for extensive-stage SCLC. Two cooperative group Phase II trials were studying chemotherapy with bevacizumab in this population. The other was ECOG-E3501, evaluating cisplatin/etoposide with bevacizumab.

Both trials have since been completed, and preliminary data were presented at ASCO (Ready 2007; Sandler 2007). The reaction to the data was mixed, and some were disappointed with the ECOG results. I don't believe they were bad — they just weren't as good as we had expected.

DR LOVE: How did she tolerate the cisplatin/irinotecan/bevacizumab regimen?

DR LILENBAUM: She was able to complete six cycles and only encountered a mild hematological toxicity, which was compounded by the bevacizumab. I believe bevacizumab enhances the delivery of the chemotherapy to the bone marrow, so it's more myelosuppressive.

Prior to therapy, the patient was coughing a lot, breathless upon minimal exertion and losing weight. While receiving treatment, she gained 10 to 15 pounds and all of her respiratory symptoms resolved. Within two cycles, she was back to baseline.

She had a near complete response. Imaging studies revealed only small hypodensities in the liver, and the disease in her chest was essentially gone. It was remarkable.

DR LOVE: Did you consider PCI at that point?

DR LILENBAUM: We talked about it, but she wasn't enthusiastic about the idea of receiving radiation therapy to her brain. This is a problem we face with every patient when we discuss PCI. This patient had just completed six cycles of chemotherapy, so she was feeling good and wanted a break.

I did not push the issue because this was in 2006, and we didn't have substantial data in extensive-disease SCLC at that time. So she did not receive PCI and within three months of completing chemotherapy, she developed brain metastases.

DR LOVE: If she presented today, would you be more inclined to recommend PCI?

DR LILENBAUM: Definitely. Based on the EORTC trial data, I believe that if this patient had received PCI, it may have been six months before she relapsed systemically (Slotman 2007; [1.1, page 4]). In the meantime, we would have prevented the development of CNS disease, which had an incredible impact not only on her outcome in general but also on her psyche.

DR LOVE: In your practice, what percent of your patients with small cell lung cancer respond to the extent that you could consider PCI?

DR LILENBAUM: With standard platinum/etoposide doublets, 15 to 25 percent of patients with extensive disease have a complete response and possibly another 15 to 25 percent experience good partial or near-complete responses. So anywhere from 25 to 50 percent of patients with extensive disease may qualify for this treatment.

DR LOVE: Of those patients who have a good response to chemotherapy, what percent relapse primarily in the brain?

DR LILENBAUM: According to the data, it can be as high as 25 percent for patients with limited-stage disease, and if the patient does not relapse systemically within six to 12 months, that number can reach almost 50 percent. I'm not sure it would be any different for patients with extensive disease (Aupérin 1999; Komaki 1981).

Tracks 7-10

Case Discussion 2

A 73-year-old woman who never smoked and had mild hypertension and well-compensated CAD presented with persistent cough and dyspnea on exertion. She underwent a thoracentesis for a large left-sided pleural effusion, and cytology was positive for adenocarcinoma. She was diagnosed with Stage IIIB NSCLC in the upper left lobe, with mediastinal adenopathy and no other evidence of disease.

DR LOVE: Can you comment on how you treated this patient and whether you tested the tumor for the presence of an EGFR mutation?

DR LILENBAUM: I did not test her tumor for a mutation. From a clinical research standpoint, I believe that information is important because it will help us design new trials and new drugs. However, in practice I don't believe it's necessary when deciding on therapy — with few exceptions.

We enrolled this patient on a Phase II trial of gemcitabine, oxaliplatin and bevacizumab. However, after two cycles we saw no response and she was more symptomatic. We stopped the chemotherapy and initiated single-agent erlotinib.

We started with 150 milligrams and within two weeks she had a Grade III rash on her face, scalp and upper chest in addition to oral mucositis, which I tend to see more often in elderly patients. We gradually tapered the dose to 75 milligrams, and she's been on that for the past 18 months without progression of her disease.

The rash stabilized, as you see in the literature, within the first two to three months, as did the mucositis. Neither has been a problem for her since. Upon examination, you still see a few macular lesions and a little facial erythema, but she's comfortable.

DR LOVE: What will be your approach if she develops disease progression?

DR LILENBAUM: I will probably administer a taxane or pemetrexed, and I'm tempted to continue the erlotinib. This is an unorthodox approach, but in the retrospective analyses of the TRIBUTE study, never smokers seemed to benefit from the combination of chemotherapy with erlotinib as opposed to chemotherapy alone and, anecdotally, I believe I see this in practice also (Herbst 2005).

Another option would be to add bevacizumab to the erlotinib when she progresses. I believe there's a positive interaction with this combination, so it may be sufficient to stabilize her disease. However, if I chose this type of approach, I would probably add a cytotoxic agent and bevacizumab, and then after a while stop the cytotoxic agent, continuing just the erlotinib and bevacizumab.

Tracks 11-16

Case Discussion 3

An otherwise-healthy 30-year-old woman who never smoked developed persistent hip pain due to lytic lesions, which were determined to be squamous cell carcinoma. PET scan revealed multiple bony lesions, a left perihilar mass and hepatic metastases. Biopsy via bronchoscopy revealed adenocarcinoma.

DR LOVE: Can you talk about your approach to this young woman?

DR LILENBAUM: When this patient presented with bone pain, imaging studies revealed disease in her femur and pelvis, and a biopsy was positive for squamous cell carcinoma. I was troubled by her presentation in the setting of this histology, so we biopsied the chest lesion and it revealed adenocarcinoma.

The staging studies then revealed liver lesions and extensive disease in the chest, so she received radiation therapy to the bone and then I treated her with cisplatin and docetaxel.

I told her that I believed it would be beneficial to add bevacizumab to that regimen but that there were risks for patients with squamous cell carcinoma, including pulmonary hemorrhage. She and her family asked questions and then she looked me in the eye and said, "I'm ready."

She received five to six cycles of this regimen and had a nice partial response but still had measurable disease in her chest and liver. At that point, I decided that rather than waiting for a relapse, I would start her on erlotinib as soon as she finished her chemotherapy and keep her on bevacizumab also.

DR LOVE: Have you used this regimen before?

DR LILENBAUM: In similar cases, I have used all four drugs concurrently. This case required an intense thought process and, although I'm not sure exactly why, I felt that starting the erlotinib after finishing the chemotherapy was a better strategy. After she went on erlotinib and maintenance bevacizumab, she had a phenomenal response. Her PET scan three or four months later was negative in the chest, liver and bones.

DR LOVE: How did she tolerate the combination of erlotinib and bevacizumab?

DR LILENBAUM: She had no side effects from the bevacizumab. As for erlotinib, we started her on 150 milligrams, which was tough, so we reduced her to 75 milligrams. She's been on this regimen for a year, and she's comfortable and has almost no rash.

I know that some of my colleagues insist on keeping patients on higher doses of erlotinib, believing the rash will eventually improve. However, I feel that once you get them through the first two or three months, you should adjust the dose accordingly.

DR LOVE: How would you have treated her if she had presented with a Stage II tumor?

DR LILENBAUM: I would still have used cisplatin and docetaxel but not bevacizumab outside of a clinical trial. As for the erlotinib, I would discuss it with the patient after she completed her four cycles of adjuvant chemotherapy. This is a difficult position to be in because we're not supposed to make decisions emotionally, but if it were me in that situation, I would want the drug.

Tracks 17-19

Case Discussion 4

A 77-year-old man with a 30 pack-year smoking history with well-compensated CHF, hypertension and diabetes mellitus but otherwise had an excellent performance status, who underwent a lobectomy and mediastinal dissection for Stage IIB NSCLC.

DR LOVE: How healthy did this 77-year-old man appear?

DR LILENBAUM: This patient was extremely fit. He had coronary heart disease, hypertension and diabetes mellitus, all under excellent control. He had a 30 pack-year history of smoking and had quit about 25 years before his diagnosis. He was focused on his health and was determined to do well.

He underwent a sleeve lobectomy and then we waited two months for him to recover before initiating adjuvant cisplatin/docetaxel, each at 75 mg/m^2.

He completed three cycles with growth factor support and experienced no major complications. However, by the fourth cycle he was unhappy — which is the best word I can use to describe him — and asked if he could stop treatment.

I told him that in the clinical trials, the average number of cycles was three and that I wasn't surprised that someone his age would want to stop then, even though his performance status was excellent. It's been almost 15 months since his last cycle of chemotherapy, and he remains disease-free.

DR LOVE: Why did you use a combination of cisplatin and docetaxel?

DR LILENBAUM: In the adjuvant setting, I believe this is a more convenient regimen. It's once every three weeks, and it's only four cycles. In addition, I don't recommend a port — rather, we're able to complete four cycles with peripheral IV access.

In the Stage IV setting, we have evidence that this regimen is not inferior to cisplatin/vinorelbine (Fossella 2003), and I'm comfortable extrapolating that information to the adjuvant setting. I'm also comfortable with the routine prophylactic use of growth factors.

If you use cisplatin/vinorelbine, the patient will need a port and it requires weekly administration. I have used cisplatin/gemcitabine, but I haven't incorporated that in my practice in the adjuvant setting. In patients for whom hair loss is a deal breaker in the adjuvant setting, I would feel comfortable with that combination. ■

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

INTERVIEW

Martin J Edelman, MD

Dr Edelman is Professor of Medicine and Director of Medical Thoracic Oncology at the University of Maryland Greenebaum Cancer Center in Baltimore, Maryland.

Tracks 1-16

Select Excerpts from the Interview

Tracks 4-5

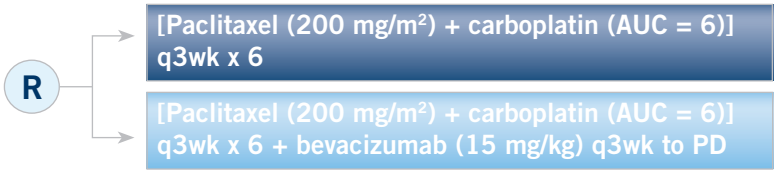
DR LOVE: What do you think about the trials that are evaluating the adjuvant use of erlotinib in enriched populations (ie, those with EGFR-positive tumors)?

DR EDELMAN: Erlotinib is a fascinating agent because it has shown efficacy in nonsmokers, never smokers and women with adenocarcinomas and bronchoalveolar carcinoma features. Patients with these characteristics are coming into my office with increasing frequency. I'm seeing two to three never smokers a month in my clinic and an increasing number of patients who smoked for

2.1

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

Protocol IDs: ECOG-4599, CTSU, NCT00021060, CALGB-E4599
Accrual: 878 (Closed)



Eligibility

- Histologically confirmed nonsquamous NSCLC
- Stage IIIB/IV or recurrent ECOG PS 0-1
- No anticoagulation
- No CNS metastases
- No hemoptysis
- No medically uncontrolled hypertension
- No clinically significant cardiovascular disease

	PCB (n = 434)	PC (n = 444)	HR (CI)	*p*-value
Median OS	12.3 months	10.3 months	0.79 (CI: 0.67-0.92)	0.003
Two-year OS	23%	15%	—	—
Median PFS	6.2 months	4.5 months	0.66 (CI: 0.57-0.77)	<0.001

AUC = area under the curve; PD = disease progression; OS = overall survival; PFS = progression-free survival

SOURCES: NCI Physician Data Query, October 2007; Sandler A et al. *N Engl J Med* 2006;355:2542-50. **Abstract**

only one year or so. For an enriched population in which you believe that the EGFR marker is present — either because of positive prognostic factors or because you've actually tested for it — adjuvant study of erlotinib is reasonable. We need to approach the use of these drugs in a more intelligent fashion, and I believe this is the way to do it.

Obviously in a resected population, you can test for the presence of EGFR by FISH or gene mutations — whatever your favorite method is.

Track 8

DR LOVE: How do you approach the clinical use of bevacizumab in metastatic NSCLC?

DR EDELMAN: I've held fairly closely to the ECOG-E4599 eligibility criteria (Sandler 2005; [2.1]). Patients are concerned about the risk of hemoptysis, but again, viewing this in the aggregate, patients fared better with bevacizumab.

They live longer, so if we have patients who would have been eligible for that, we approach them about the use of bevacizumab.

I have used bevacizumab pretty much as it was used on E4599 with carboplatin/paclitaxel. The only difference is that I tend to use less cytotoxic chemotherapy — I use four cycles, not six, and I base that on my belief that the evidence is pretty compelling that cytotoxics do not aid you after four courses of therapy. I could certainly be criticized, but I believe it's a reasonable approach and it's well tolerated.

Track 15

DR LOVE: What chemotherapy regimen do you usually utilize as adjuvant therapy?

DR EDELMAN: Generally, cisplatin and docetaxel because I believe the weight of data supports a cisplatin-based regimen (2.2). If one wants to be completely data driven, cisplatin/vinorelbine is probably the most validated regimen out there, but it's difficult to administer. In Stage IV disease, cisplatin/docetaxel is at least as good, possibly even superior, and probably better tolerated than cisplatin/vinorelbine, so I consider that a reasonable regimen.

If someone told me that he or she intended to administer cisplatin/vinorelbine, I would not argue. The combination of cisplatin/gemcitabine is also reasonable. The crucial component in this combination is the platinum.

Despite all the controversy, I believe carboplatin/paclitaxel is also reasonable. Another key issue is adjuvant therapy for Stage IB disease. It has been pointed out that to conduct an adequately powered study of patients with Stage IB disease, you'd have to enroll about 2,000 patients.

2.2 Positive Studies of Adjuvant Chemotherapy versus Observation in NSCLC

	IALT[1] (ASCO 2003)	JBR.10[2] (ASCO 2004)	ANITA[3] (ASCO 2005)	CALGB-9633[4] (ASCO 2006)
N	1,867	482	840	344
Stage	I, II & III	IB & II	I, II & IIIA	IB
Therapy	Cis-based Some RT	Cis/vinorelbine No RT	Cis/vinorelbine Some RT	Carbo/paclitaxel No RT
Five-year RFS	39.4% vs 34.3%	61% vs 49%	54% vs 42%*	52% vs 48%*
Five-year OS	44.5% vs 40.4%	69% vs 54%	49% vs 42%*	59% vs 57%*

Cis = cisplatin; carbo = carboplatin; RT = radiation therapy;
RFS = relapse-free survival; OS = overall survival
* Five-year RFS and OS

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. *Lancet Oncol* 2006;7:719-27. **Abstract**; [4] Strauss GM et al. Presentation. ASCO 2006;**Abstract 7007**.

So the CALGB carboplatin/paclitaxel study (Strauss 2006) that showed an improvement in progression-free survival in Stage IB disease was probably underpowered.

If you consider the subgroup of patients with tumors of four centimeters or greater (Strauss 2006), those patients clearly fared better with the chemotherapy. I don't believe carboplatin/paclitaxel is inactive in this setting — occasionally we use that. We use it because some patients cannot tolerate cisplatin-based therapy.

It is not unusual for us to start with a cisplatin-based therapy and switch the patient after one or two cycles because he or she cannot tolerate it. So for their final couple of cycles, these patients are switched to a carboplatin-based regimen. ■

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. **Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial.** *Lancet Oncol* 2006;7:719-27. **Abstract**

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

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

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

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

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

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

Wakelee HA et al. **Lung cancer incidence in never smokers.** *J Clin Oncol* 2007;25:472-8. **Abstract**

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;352:2589-97. **Abstract**

Winton TL et al. **A prospective randomised trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non small cell lung cancer (NSCLC) Intergroup JBR. 10.** *Proc ASCO* 2004;**Abstract 7018**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Clinical predictors of erlotinib response include _____.**
   a. Nonsmoking status
   b. Female gender
   c. Adenocarcinoma
   d. All of the above
2. **SWOG-S0023 evaluated the use of gefitinib maintenance therapy after cisplatin-based therapy in _____ patients with Stage IIIA or IIIB lung cancer.**
   a. Selected (based on EGFR status)
   b. Unselected (regardless of EGFR status)
3. **In ECOG-E4599, what dose and schedule of bevacizumab was utilized?**
   a. 5 mg/kg every three weeks
   b. 7.5 mg/kg every three weeks
   c. 15 mg/kg every three weeks
   d. 15 mg/kg weekly
4. **Primary outcome(s) for the SWOG-S0533 trial evaluating the integration of bevacizumab into chemoradiation therapy for patients with Stage III NSCLC is/are _____.**
   a. Frequency and severity of toxicity
   b. Progression-free and overall survival
   c. Response rate
5. **The EORTC study of PCI versus no PCI for patients with extensive-disease small cell lung cancer showed significant improvement in both disease-free and overall survival with PCI.**
   a. True
   b. False
6. **The one-year survival rate for patients receiving PCI on the EORTC study was _____ versus 13 percent for the control arm.**
   a. Three percent
   b. 27 percent
   c. 67 percent
7. **A retrospective subset analysis from the TRIBUTE trial revealed that in never smokers with advanced NSCLC, the addition of erlotinib to carboplatin/paclitaxel conferred an efficacy benefit versus chemotherapy alone.**
   a. True
   b. False
8. **Which of the following were exclusionary criteria of ECOG-E4599 evaluating paclitaxel/carboplatin with or without bevacizumab in patients with previously untreated advanced NSCLC?**
   a. Squamous cell carcinoma
   b. CNS metastases
   c. Hemoptysis
   d. Anticoagulation therapy
   e. All of the above
9. **The AVAiL trial evaluated the safety and efficacy of _____ with our without bevacizumab as first-line treatment for metastatic nonsquamous NSCLC.**
   a. Paclitaxel/carboplatin
   b. Paclitaxel/cisplatin
   c. Gemcitabine/cisplatin
   d. Docetaxel/cisplatin
10. **Data from trials evaluating adjuvant chemotherapy versus observation in patients with NSCLC indicate that a greater improvement in relapse-free survival and overall survival was associated with _____ -based regimens.**
    a. Carboplatin
    b. Cisplatin
    c. Carboplatin and cisplatin

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

EVALUATION FORM

Lung Cancer Update — Issue 4, 2007

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

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Walter J Curran Jr, MD	5 4 3 2 1	5 4 3 2 1
Rogerio C Lilenbaum, MD	5 4 3 2 1	5 4 3 2 1
Martin J Edelman, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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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

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Lung Cancer™ UPDATE

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

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Last review date: November 2007
Release date: November 2007
Expiration date: November 2008
Estimated time to complete: 3 hours