LCU | 2006 VOL 3 | ISSUE 1

Lung Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

Thomas J Lynch, MD

Kathy Albain, MD

Richard J Gralla, MD

CME Certified

www.LungCancerUpdate.com

Lung Cancer Update
A CME Audio Series and Activity

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 Lynch, Albain and Gralla 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.

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 or tapes, 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**.

TABLE OF CONTENTS

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

CONTENT VALIDATION AND DISCLOSURES

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest for themselves (or their spouses/partners) that have been resolved through a peer review process: Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Michelle Paley, MD, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Carol R Regueiro, MD, MSc and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Marie Bialek, PharmD — freelancer/contractor: McNeil Consumer & Specialty Pharmaceuticals, Janssen Pharmaceutica Products LP; salary (spouse): AstraZeneca Pharmaceuticals LP; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc. Research To Practice receives education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Biogen Idec, Genentech BioOncology, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

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

Dr Lynch — Consulting Fees: Genentech BioOncology, Sanofi-Aventis. Fees for Non-CME Services Received Directly from Commercial Interest of their Agents: Genentech BioOncology, Sanofi-Aventis. **Dr Albain** — No financial interests or affiliations to disclose. **Dr Gralla** — Consulting Fees: Eli Lilly and Company, Genentech BioOncology, GlaxoSmithKline, Sanofi-Aventis; Contracted Research: Eli Lilly and Company, Sanofi-Aventis.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

UPCOMING EDUCATIONAL EVENTS

American Association for Cancer Research
97th Annual Meeting
April 1-5, 2006
Washington, DC
Event website: **www.aacr.org**

NSABP Group Meeting
April 28-May 1, 2006
Denver, Colorado
Event website: **www.nsabp.pitt.edu**

American Society of Clinical Oncology
42nd Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **www.asco.org**

American College of Surgeons Oncology Group (ACOSOG) Semiannual Meeting
June 22-24, 2006
Chicago, Illinois
Event website: **www.acosog.org**

ECOG Semiannual Meeting
June 23-25, 2006
Washington, DC
Event website: **www.ecog.org**

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

2nd Annual Oncology Congress
October 19-21, 2006
New York, New York
Event website: **www.oncologycongress.com**

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

INTERVIEW

Thomas J Lynch, MD

Dr Lynch is Director of the MGH Thoracic Oncology Center, Deputy Chief of Hematology Oncology and Associate Professor of Medicine at Massachusetts General Hospital in Boston, Massachusetts.

Tracks 1-21

Select Excerpts from the Interview

Track 2

DR LOVE: Would you provide an overview of the predictors of response to EGFR tyrosine kinase inhibitors?

DR LYNCH: The field has progressed rapidly in the past 10 to 12 months in terms of what we know about predicting response to EGFR TKIs. We've seen a remarkable number of studies, which have been very consistent in demonstrating a particularly dramatic response to erlotinib and gefitinib in patients with mutations in the tyrosine kinase domain of the EGFR gene.

However, when looking at a retrospective subset (Tsao 2005) from the large randomized trial BR-21 from Canada (Shepherd 2005), we are not able to associate patient survival with mutations (1.1). Rather, what appeared to be more important in the BR-21 subset is gene copy number, as measured by FISH, and immunohistochemistry (IHC) of the EGFR protein.

These are very important measures and may reflect tumors that have a certain degree of dependence on the epidermal growth factors.

DR LOVE: Is this information of practical use to an oncologist currently?

DR LYNCH: Right now, it's a little unclear. When I see a patient with an adenocarcinoma — basically, all patients with nonsquamous cell tumors — I frequently obtain EGFR sequencing up front. If the disease is mutation positive, the patient qualifies for a clinical trial looking at EGFR TKI therapy in the first line.

1.1

Molecular Predictors of EGFR TKI Response in a Subgroup of Patients from BR-21

Factor	Patients evaluated	% Response	HR (95% CI)	*p*-value
EGFR IHC				
Positive*	106/184	11% (n = 12)	0.68 (0.49-0.95)	0.02
Negative	80/141	4% (n = 3)	0.93 (0.63-1.36)	0.70
FISH status				
Amplified†	25/56	20% (n = 5)	0.44 (0.23-0.82)	0.008
Not amplified	41/69	2% (n = 1)	0.85 (0.48-1.51)	0.59
Mutational status				
Wild type	81/137	7% (n = 6)	0.73 (0.49-1.10)	0.13
Mutation	19/40	16% (n = 3)	0.77 (0.40-1.50)	0.45

* 10% or more cells with membranous staining; † High polysomy and amplification
IHC = Immunohistochemistry

SOURCE: Tsao M-S et al. *N Engl J Med* 2005;353(2):133-44. **Abstract**

Track 8

DR LOVE: Right now, when you're evaluating a patient for adjuvant therapy, do you offer adjuvant erlotinib off trial to a younger patient in his or her fifties who is either a nonsmoker or has the mutation?

DR LYNCH: I don't, but that's one of the questions we frequently debate. The reason I don't offer a TKI off protocol is based on the results of the SWOG-

S0023 study (Kelly 2005), which randomly assigned patients to gefitinib or placebo after chemoradiation for Stage III lung cancer (1.2). That study showed patients who received adjuvant gefitinib had a worse outcome, not statistically significant but very close to being statistically significant, than patients who received placebo.

DR LOVE: I remember asking you previously what you would do if you were in that situation — a nonsmoker with a mutation in the adjuvant setting. As I recall, you said you'd probably opt for treatment.

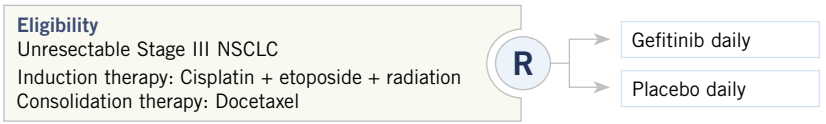
DR LYNCH: I said that I would probably choose treatment because I'd be willing to accept that risk for myself. So it is something we need to discuss with patients, to see if they're willing to accept the risk — which may be an increased risk of death in this setting.

To be quite frank, we're not going to have this answer for seven to 10 years.

1.2

Phase III Randomized Study of Cisplatin, Etoposide, Radiotherapy and Docetaxel with or without Gefitinib in Patients with Unresectable Stage III Non-Small Cell Lung Cancer

Protocol IDs: SWOG-S0023, CAN-NCIC-BR.15, CTSU, NCCTG-S0023
Accrual: 620 (Closed)



SOURCES: NCI Physician Data Query, October 2005; Kelly K et al. Presentation. ASCO 2005;**Abstract 7058**.

Track 15

DR LOVE: Where are we right now in terms of trials evaluating bevacizumab in the adjuvant setting? Can you speculate whether bevacizumab might be more or less effective in the adjuvant compared to the metastatic setting?

DR LYNCH: We have a trial just starting at Massachusetts General Hospital and at the Dana-Farber Cancer Institute in which we're treating patients with chemotherapy and bevacizumab in the adjuvant setting.

It's a pilot study and the design is straightforward: 50 people, Phase II, and just getting off the ground now. We're looking at the use of bevacizumab/carboplatin/paclitaxel in the adjuvant setting. Patients must be treated within eight weeks of surgery, they can't show any evidence of hemoptysis, and they must have T2 tumors or greater. Patients with Stage IA disease are not eligible.

DR LOVE: Do you include patients with squamous cell disease in the trial?

DR LYNCH: In completely resected lung cancer, no squamous cells should remain so there is no theoretical reason that patients should bleed. I don't think there's any reason to believe bevacizumab would not be beneficial in that group of patients, so we will be including patients with squamous cell disease in the trial.

Track 20

DR LOVE: Do you use chemotherapy after chemoradiotherapy in patients with Stage IIIB disease? The SWOG regimen utilizing docetaxel maintenance has generated a lot of excitement. Can you talk a little bit about that and discuss the updated data (Gandara 2005) that were presented at ASCO?

DR LYNCH: The SWOG-S9504 data look very encouraging. Etoposide/platinum was used in a 50-50 combination in which you administer 50 mg/m^2 of platinum on day one and day eight and 50 mg/m^2 of etoposide on days one to five. That way, full doses of etoposide/platinum are received in cycle one and cycle two. When you administer that combination with radiation, you have 12 days of overlap. I believe that's a very good regimen. Cisplatin/etoposide with radiation is followed by three cycles of docetaxel, and I believe this is a very good approach. The SWOG data showed a median survival of 26 months at 32 months follow-up (1.3).

However, I tend to use weekly carboplatin with a taxane for patients with reasonable functional status who either have impaired organ function or marginal performance status, or for people who I don't think can tolerate cisplatin. Generally, I tend to be a very big believer in the SWOG trial until convinced otherwise.

1.3

Long-Term Survival of a Phase II Study of Consolidation Docetaxel after Definitive Chemoradiation: SWOG-S9504

Protocol ID: SWOG-9504
Accrual: 83 (Closed)

Eligibility
- Stage IIIB NSCLC
- No prior chemo
- PS 0-2

PROTOCOL → Cisplatin d1, 8, 29, 36/ etoposide d1-5, 29-33 + concurrent XRT 1.8 Gy/d → Docetaxel 75-100 mg/m^2 q3wk x 3 cycles

MST (months)	Two years	Three years	Four years	Five years
26 (18%-35%)*	54% (43%-65%)*	37% (24%-55%)*	29% (19%-29%)*	29% (19%-29%)*

* 95% CI
MST = median survival time; CI = confidence interval

SOURCE: Gandara DR et al. *J Clin Oncol* 2003;21(10):2004-10. **Abstract**

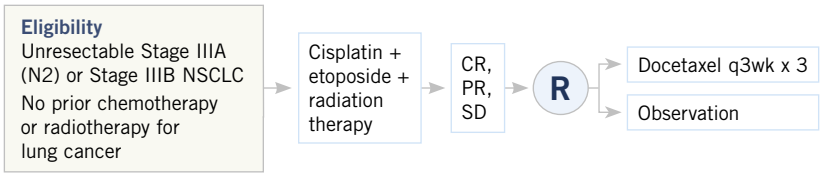
We'll have some data coming out from a Hoosier Oncology Group study (LUN01-24; [1.4]) which evaluated etoposide and cisplatin with radiation therapy followed by docetaxel, asking whether the posterior docetaxel is important in that setting.

This will be a very important trial. Some subsets of Karen Kelly's SWOG-0023 trial do suggest that the cisplatin/etoposide followed by docetaxel arm appears to be holding up pretty well. ■

1.4

Etoposide and Cisplatin with Radiotherapy with or without Consolidation Docetaxel in Advanced Stage III Non-Small Cell Lung Cancer

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



SOURCE: NCI Physician Data Query, February 2006.

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**

Hussain S et al. **Correlation of EGFR and KRAS mutation status, response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and survival with histologic subtypes of adenocarcinoma of the lung.** *Proc ASCO* 2005;**Abstract 7080**.

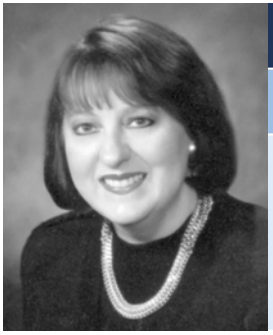
Kelly K et al. **Low incidence of pneumonitis on SWOG 0023: A preliminary analysis of an ongoing phase III trial of concurrent chemoradiotherapy followed by consolidation docetaxel and Iressa/placebo maintenance in patients with inoperable stage III non-small cell lung cancer.** *Proc ASCO* 2005;**Abstract 7058**.

Lynch TJ et al. **Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib.** *N Engl J Med* 2004;350(21):2129-39. **Abstract**

Lynch TS et al. **Correlation of molecular markers including mutations with clinical outcomes in advanced non small cell lung cancer (NSCLC) patients (pts) treated with gefitinib, chemotherapy or chemotherapy and gefitinib in IDEAL and INTACT clinical trials.** *Proc ASCO* 2005;**Abstract 7006**.

Shepherd FA et al. **Erlotinib in previously treated non-small-cell lung cancer.** *N Engl J Med* 2005;353(2):123-32. **Abstract**

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



INTERVIEW

Kathy S Albain, MD

Dr Albain is Professor of Medicine at Loyola University Stritch School of Medicine, Clinical Director of Breast Cancer Research, Co-Director of Breast Care Center and Director of the Thoracic Oncology Center in Chicago, Illinois.

Tracks 1-13

Select Excerpts from the Interview

Track 2

DR LOVE: Would you comment on ECOG-E4599, which evaluated bevacizumab in combination with chemotherapy in patients with metastatic disease?

DR ALBAIN: The addition of bevacizumab makes carboplatin/paclitaxel a better regimen. If you want to utilize carboplatin and paclitaxel in the front-line setting and the patient meets the criteria for ECOG-E4599 (nonsquamous histology and no history of uncontrolled hypertension, bleeding or clotting), you should probably also administer bevacizumab (Sandler 2005; [2.1]).

DR LOVE: How do you approach the selection of chemotherapy in the first-line setting for patients with metastatic NSCLC, and where does bevacizumab fit in?

DR ALBAIN: Our goal is to enroll our patients on clinical trials. In the Southwest Oncology Group, we've just finished a study (SWOG-S0342) with cetuximab, either concurrent with or sequenced after carboplatin and paclitaxel.

As I mentioned previously, if you want to use carboplatin and paclitaxel as your main regimen in this patient population, then you should add bevacizumab (Sandler 2005).

There is a preclinical rationale for the combination of bevacizumab with a taxane, and a lot of work is being done to evaluate other potentially additive and/or synergistic combinations. So, hopefully, there'll be more agents to work with. I also use other regimens: cisplatin/docetaxel, cisplatin/gemcitabine, and a number of others.

DR LOVE: How do you decide between those options on a case-by-case basis? What are some of the factors you consider?

DR ALBAIN: I consider the patient's overall performance status and comorbid illnesses. So if the patient, for example, has diabetes that's quite difficult to control, you may stay away from a regimen that requires steroids for a few days. There are a lot of things that play into the decision-making in advanced lung cancer. Patients often have a spectrum of other illnesses that go along with prior smoking — poor lung function, et cetera.

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

Primary endpoints	BCP (n = 434)	CP (n = 444)	HR (CI)	*p*-value
Median overall survival	12.5 months	10.2 months	0.77 (CI: 0.65-0.93)	0.007
Median progression-free survival	6.4 months	4.5 months	0.62 (CI: 0.53-0.72)	<0.0001
Secondary endpoints	**BCP (n = 357)**	**CP (n = 350)**	**HR (CI)**	***p*-value**
Overall response	27.2%	10.0%	—	<0.0001
Complete response	1.4%	0.0%	—	—
Partial response	25.8%	10.0%	—	—

CI = 95% confidence interval

SOURCE: Sandler AB et al. Presentation. ASCO 2005;**Abstract 4**.

Track 7

DR LOVE: Where do you see things heading with the next generation of adjuvant trials in NSCLC?

DR ALBAIN: We do need an adjuvant bevacizumab trial, and one is being designed right now and will be conducted by the Intergroup. I believe that

we also have to get erlotinib back in trials, because I can't imagine that it wouldn't be helpful for minimal residual disease as opposed to very advanced chemotherapy-refractory disease.

DR LOVE: What are your thoughts about the report by Herbst and Sandler evaluating the combination of bevacizumab and erlotinib (Herbst 2005; [2.2])?

DR ALBAIN: That's a very interesting trial, and we're participating in the follow-up study. It's an extremely provocative result, and it is worth testing the combination of agents. Combining targeted agents is going to be important for those tumors that aren't driven by a dominant single pathway.

2.2

Efficacy Results from a Phase I/II Trial Evaluating Erlotinib Plus Bevacizumab in Patients with Previously Treated Stage IIIB/IV Nonsquamous NSCLC

	Total population (N = 40)	Phase II population (n = 28)
Median survival	12.6 months	12.6 months*
One-year survival	54.2%	51.8%*
Median progression-free survival	7.0 months	6.2 months*
Partial response	20.0%	14.3%
Stable disease	65.0%	71.4%

* Includes patients treated at the Phase II dose in the Phase I portion of the trial (n = 34)

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

Tracks 9-10

DR LOVE: Would you talk about the RTOG-9309 study?

DR ALBAIN: RTOG-9309 evolved because of the large number of Phase II trials conducted in the late 1980s and early 1990s that showed the feasibility of sending patients for a resection following chemoradiotherapy.

Other trials were studying chemotherapy alone, but at least in the Southwest Oncology Group's series of pilot studies, we were evaluating a concurrent chemoradiotherapy program that showed a lot of promise.

That was brought into two studies — the first a trimodality study with surgery after the chemoradiation and the second with straight chemoradiation. These trials not only showed feasibility, but they also raised some concerns about a higher rate of acute respiratory distress syndrome (ARDS) after surgery.

Additionally, these trials identified a group of patients who — even though they had high-volume disease prior to therapy — at the time of surgery would have no remaining disease in their mediastinal nodes. The pilot study observed

patients with Stage IIIA (pN2) and IIIB (nonpleural effusion) disease. The big debate, then, was whether surgery really contributes to survival.

Thus, SWOG started a Phase III trial while several other Phase III trials were going on. The Intergroup decided to shut all of them down and start a new one (RTOG-9309), which was identical to the SWOG design but was run by the RTOG. RTOG-9309 limped along in its accrual for a number of years.

It was an extremely difficult study to discuss with patients because you had to inform them of the possibility of a higher rate of postoperative death. The trial finally recorded enough events for reporting, which were fewer than projected because of the long duration of accrual.

The first report showed a marked improvement in progression-free survival with the addition of surgery. Reproducing what we had seen in the pilot study, those patients with mediastinal nodes that were no longer positive after chemoradiotherapy seemed to have the best outcome.

The overall survival, however, showed no difference; the tail of the curve was a little bit separated, but the *p*-value was not significant (Albain 2003).

A final survival report was planned when more data were available, and we presented it at ASCO 2005. We showed the same overall results in terms of progression-free survival and overall survival (Albain 2005; [2.3]).

We looked very carefully at the postoperative deaths. We found — just as we had in the pilot trial — that the majority of the postoperative deaths occurred in patients who had undergone a pneumonectomy. These deaths were predominantly from ARDS, just as other postoperative deaths we have reported. The trial was not able to show an overall survival advantage because of these postoperative deaths (Albain 2005).

2.3

RTOG-9309: Phase III Randomized Trial Comparing Chemoradiotherapy with or without Surgical Resection in Patients with Stage IIIA (pN2) NSCLC

	Chemoradiotherapy + surgery (n = 202)	Chemoradiotherapy alone (n = 194)	Hazard/ odds ratio (95% CI)	*p*-value
Median progression-free survival (PFS)	12.8 months	10.5 months	0.77 (0.62-0.96)	0.017
Five-year PFS	22.4%	11.1%	—	—
Median overall survival	23.6 months	22.2 months	0.87 (0.70-1.10)	0.24
Five-year overall survival	27.2%	20.3%	0.63 (0.36-1.10)	0.10

CI = confidence interval

SOURCE: Albain KS et al. Presentation. ASCO 2005;**Abstract 7014**.

Our statistician performed an exploratory analysis matching the patients who had undergone pneumonectomies to a similar group in the nonsurgical arm.

The same process was followed with the patients who had undergone lobectomies. A dramatic split favored the lobectomy group over chemoradiotherapy alone, whereas the patients who had pneumonectomies had a worse survival rate than a matched group that did not receive surgery (Albain 2005; [2.4]).

That analysis was exploratory, but it answered the question, "What do I do in practice?" These were the types of patients for whom the standard of care would be chemotherapy and radiation. These were not the patients with very minimal N2 disease, who could still undergo surgery.

If I see a patient with mediastinal disease who fits the criteria for the study, is suited to undergoing a lobectomy, is fit and has a good performance status and good pulmonary function, we discuss the study results. ■

2.4 RTOG-9309: Exploratory Survival Analysis According to Type of Surgery

	Pneumonectomy		Lobectomy	
	Chemo/XRT + surgery (n = 51)	Chemo/XRT alone* (n = 51)	Chemo/XRT + surgery (n = 90)	Chemo/XRT alone* (n = 90)
Median survival	19 months	29 months	34 months	22 months
Five-year overall survival	22%	24%	36%	18%
p-value (log-rank)	NS		0.002	

* Patients on chemoradiotherapy + surgery arm were matched with those on chemoradiotherapy alone arm for four prestudy factors (Karnofsky performance status, age, sex and T stage)

NS = not significant; chemo/XRT = chemoradiotherapy

SOURCE: Albain KS et al. Presentation. ASCO 2005;**Abstract 7014**.

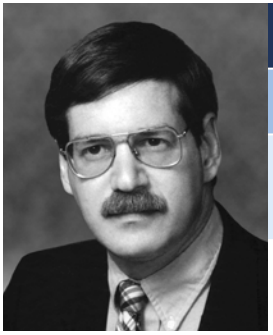
SELECT PUBLICATIONS

Albain KS et al. **Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for Stage IIIA (PN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309).** Presentation. ASCO 2005;**Abstract 7014**.

Albain KS et al. **Phase III comparison of concurrent chemotherapy plus radiotherapy (CT/RT) and CT/RT followed by surgical resection for Stage IIIA (PN2) non-small cell lung cancer (NSCLC): Initial results from the intergroup trial 0139 (RTOG 93-09).** Presentation. ASCO 2003;**Abstract 2497**.

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**

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**.



INTERVIEW

Richard J Gralla, MD

Dr Gralla is President of the New York Lung Cancer Alliance in New York, New York.

Tracks 1-17

Select Excerpts from the Interview

Track 3

DR LOVE: What's your take on the issue of cisplatin versus carboplatin for metastatic disease?

DR GRALLA: At the ASCO 2005 meeting, a meta-analysis that demonstrated two-drug combinations containing a platinum agent are better than nonplatinum-containing regimens also showed the cisplatin-based combinations to be more effective (Barlesi 2005). This analysis showed approximately a 12 percent

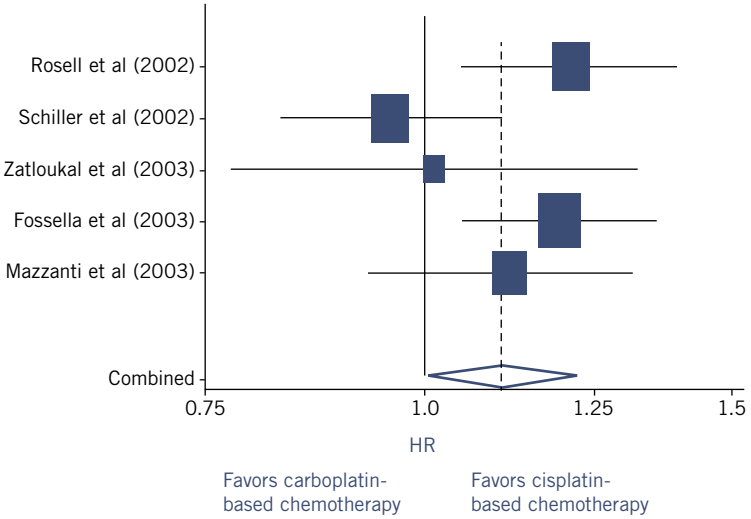
survival advantage among patients treated with a cisplatin-based regimen. A bit more toxicity occurred with the cisplatin-containing combinations, but the toxicity was classified as acceptable.

In the past year, two other meta-analyses have examined cisplatin versus carboplatin with newer agents, including a Japanese meta-analysis published by Hotta (Hotta 2005; [3.1]).

They both showed that adding the same newer agent to both platinums resulted in a 12 to 15 percent survival advantage for cisplatin. So survival appears to be a bit better with the platinum combinations versus nonplatinum, and while nobody particularly likes cisplatin, it appears to be superior to carboplatin.

3.1

Overall Survival with Cisplatin and New Agents versus Carboplatin and New Agents



"Cisplatin-based chemotherapy was associated with only a 5% improvement in overall survival as compared with carboplatin-based chemotherapy, and this difference was not statistically significant (HR, 1.050; 95% CI, 0.907 to 1.216; P = .515). A funnel plot and rank correlation test regarding survival confirmed the absence of publication bias (Z = 0.37; P = .71). On the other hand, subset analysis of the five trials revealed that the combination chemotherapy consisting of cisplatin plus a new agent yielded an 11% superior survival as compared with that of carboplatin plus a new agent. This difference was statistically significant (HR, 1.106; 95% CI, 1.005 to 1.218; P = .039)."

SOURCE: Reprinted with permission from the American Society of Clinical Oncology. Hotta K et al. **Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer.** *J Clin Oncol* 2004;22(19):3852-9. **Abstract**

Track 5

DR LOVE: What were your thoughts on the ECOG-E4599 study with bevacizumab presented by Alan Sandler (Sandler 2005)?

DR GRALLA: The big winner at ASCO 2005 was bevacizumab. The ECOG-E4599 trial was certainly an interesting study. It consisted of nearly 900 patients with nonsquamous cell lung cancers, and all the patients received paclitaxel/carboplatin. They were then randomly assigned to receive bevacizumab at 15 mg/kg every three weeks or not.

The data demonstrated approximately a 10.2-month survival with paclitaxel/carboplatin, which is probably the best rate we have seen reported for that combination, and a 12.5-month survival with the bevacizumab, which indicates a 15 to 18 percent benefit to adding bevacizumab.

DR LOVE: What are the clinical implications of these data?

DR GRALLA: The difference in efficacy between the two arms was highly significant. Actually, both arms of the study did better than expected, so it's not as though the bevacizumab arm did well because the chemotherapy-only arm did poorly.

I think this is likely to be a true finding, and I expect a lot of patients will receive bevacizumab as a result.

This is at least the seventh large trial, each with a minimum of 600 patients, that has examined a standard chemotherapy regimen combined with a molecularly targeted agent. All of them have been negative with the exception of the bevacizumab trial, so I think the chances of this being correct are relatively high.

DR LOVE: In the clinical setting, what agent would you combine with bevacizumab?

DR GRALLA: We have seen an advantage reported with bevacizumab and a variety of chemotherapies in several other malignancies. Its efficacy appears to be more tumor related than chemotherapy related; obviously, a second trial using different drugs from those used in E4599 would answer that question, but my prediction is that its effectiveness is not chemotherapy specific.

Track 10

DR LOVE: In your practice, how do you treat nonsmoking female patients with metastatic adenocarcinoma?

DR GRALLA: Any nonsmoking woman with adenocarcinoma has a high likelihood of doing well with a TKI. I have treated many of these patients with a TKI as monotherapy, and within three to four weeks I expect to see symptomatic relief and some hint of a response on a simple imaging study like a chest x-ray.

We don't know whether it's better to administer a TKI or chemotherapy first, and we need to conduct research to answer that question. As for using chemotherapy with erlotinib, the results of the two trials evaluating that weren't so good.

DR LOVE: What new agents or combinations are being evaluated for treatment of recurrent non-small cell lung cancer?

DR GRALLA: Many second-line agents have been studied, but docetaxel remains the agent that is used as the comparator and nothing has beaten it to date, although there are other candidates. It also has shown good evidence in the first line and is one of our many reasonable choices in that setting.

An article in the *Journal of Clinical Oncology* indicated that the combination of bevacizumab and erlotinib can be used but we need to identify the specific patient population for this combination (Herbst 2005).

I don't believe we can have great confidence that we have found the target population for bevacizumab, whereas with erlotinib or gefitinib, maybe we have.

Track 11

DR LOVE: Would you discuss the use of adjuvant chemotherapy in the treatment of non-small cell lung cancer?

DR GRALLA: The most recent study was reported at the 2005 ASCO meeting. The ANITA trial was a large, well-executed international trial, with more than 800 patients who were randomly assigned to postoperative vinorelbine and cisplatin or no chemotherapy (Douillard 2005).

The distribution of Stage I, II and III disease was almost equal, with slightly fewer patients having Stage II disease. This study demonstrated, as have others, a significant advantage to receiving adjuvant chemotherapy.

At the ASCO meeting in 2005, Emilio Bria presented a pooled analysis of 11 randomized trials and one meta-analysis with 6,494 patients (Bria 2005; [3.2]). No matter how the data were segregated — all studies, only those studies published in peer-review journals, earlier versus later stage — the data showed a significant advantage with adjuvant chemotherapy.

So I don't think the question is whether adjuvant chemotherapy improves survival but rather, what is the magnitude of benefit? Dr Bria's analysis provided evidence of an absolute benefit in the three to four percent range, which is not very much. In breast cancer, the meta-analysis of adjuvant chemotherapy showed a six percent absolute benefit.

DR LOVE: What's the relative risk reduction in lung cancer?

DR GRALLA: Interestingly, the smaller the study, the larger the benefit and vice versa. In individual trials, relative risk benefits or hazard ratios reduced to 0.69 or 0.74. In the ANITA study, the number was 0.79 (Douillard 2005). In

the largest study of all, the IALT study, it was 0.86 (Arriagada 2004). When you look at them all together, the hazard ratio is about 0.9.

Dr Bria has also observed how many patients must be treated for one patient to benefit, which is probably a good way to look at the issue. In his studies, depending on which stage and which group of patients you look at, that number is somewhere between 20 and 30 patients. ■

3.2

Pooled Analysis Examining Survival and Magnitude of Benefit of Adjuvant Chemotherapy in the Treatment of NSCLC

Parameter	Number of trials	Number of patients	RR* (95% CI)	*p*-value	Absolute benefit	NNT† benefit
Disease-free survival‡	8	4,835	0.90 (0.86-0.95)	<0.001	5.5%	16
Overall survival‡						
All patients	12	6,494	0.93 (0.89-0.95)	0.01	3.1	26
Stage I/II§	8	3,172	0.87 (0.80-0.95)	0.002	5.5	17
Stage III§	5	1,341	0.93 (0.87-1.00)	0.07	5	19

* Event-based relative risk ratio; † number needed to treat for one patient to benefit; ‡ sensitivity analyses — fixed-effect model; § not all studies specified or analyzed patients by stage.

SOURCE: Bria E et al. Presentation. ASCO 2005;**Abstract 7140**.

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**

Barlesi F et al. **Should chemotherapy (Cx) for advanced non-small cell lung cancer (NSCLC) be platinum-based? A literature-based meta-analysis of randomized trials.** *Proc ASCO* 2005;**Abstract 7213**.

Bria E et al. **Does adjuvant chemotherapy improve survival in non small cell lung cancer (NSCLC)? A pooled-analysis of 6494 patients in 12 studies, examining survival and magnitude of benefit.** Presentation. ASCO 2005;**Abstract 7140**.

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.** *Proc ASCO* 2005;**Abstract 7013**.

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**

Hotta K et al. **Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer.** *J Clin Oncol* 2004;22(19):3852-9. **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**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **According to exploratory analyses conducted in a subgroup of patients from BR-21, the molecular characteristic predictive of survival during treatment with erlotinib was _____.**
   a. Mutation in the tyrosine kinase domain of the EGFR gene
   b. EGFR gene copy number
   c. Both a and b
   d. Neither a nor b

2. **Clinical predictors of erlotinib response include _____.**
   a. Nonsmoking status
   b. Female gender
   c. Adenocarcinoma
   d. All of the above

3. **Among patients with Stage IIIB disease who received consolidation docetaxel after definitive chemoradiation (SWOG-S9504), the median survival time was _____ months.**
   a. 12
   b. 20
   c. 26
   d. 35

4. **In ECOG-E4599, bevacizumab improved the efficacy of _____ as front-line therapy for patients with metastatic NSCLC.**
   a. Paclitaxel
   b. Capecitabine
   c. Paclitaxel/carboplatin
   d. Capecitabine/docetaxel
   e. None of the above

5. **Sandler and Herbst reported the results of a trial that combined bevacizumab with _____.**
   a. Gefitinib
   b. Erlotinib
   c. Trastuzumab
   d. Either a or b
   e. All of the above

6. **RTOG-9309 compared chemoradiotherapy alone to chemoradiotherapy with surgery in the management of Stage III NSCLC.**
   a. True
   b. False

7. **According to the results from RTOG-9309, chemoradiotherapy with surgery improved progression-free survival but not overall survival.**
   a. True
   b. False

8. **In a meta-analysis presented at ASCO by Barlesi, which combinations showed a survival advantage in the treatment of advanced NSCLC?**
   a. Platinum-based combinations
   b. Nonplatinum-based combinations

9. **In ECOG-E4599, the median overall survival in the carboplatin/paclitaxel with bevacizumab arm was _____.**
   a. 10 months
   b. 12.5 months
   c. 15 months
   d. 17.5 months

10. **At ASCO in 2005, Bria presented a pooled analysis of 11 randomized trials and one meta-analysis with 6,494 patients that showed a significant advantage with adjuvant chemotherapy.**
    a. True
    b. False

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

EVALUATION FORM

Lung Cancer Update — Issue 1, 2006

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Thomas J Lynch, MD	5 4 3 2 1	5 4 3 2 1
Kathy S Albain, MD	5 4 3 2 1	5 4 3 2 1
Richard J Gralla, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

EVALUATION FORM

Lung Cancer Update — Issue 1, 2006

REQUEST FOR CREDIT — please print clearly

Name: ..... Specialty: .....

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other .....

Medical License/ME Number: ..... Last 4 Digits of SSN (required): .....

Street Address: ..... Box/Suite: .....

City, State, Zip: .....

Telephone: ..... Fax: .....

Email: .....

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

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

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Additional comments about this activity:

.....

FOLLOW-UP

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.LungCancerUpdate.com/CME.

Lung Cancer™ UPDATE

Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Email: CME@ResearchToPractice.net

This program is supported by education grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology and Sanofi-Aventis.

Lung Cancer™ UPDATE

This program is supported by education grants from
AstraZeneca Pharmaceuticals LP, Genentech BioOncology and Sanofi-Aventis.

Research To Practice™

Sponsored by Research To Practice.

Last review date: February 2006
Release date: February 2006
Expiration date: February 2007
Estimated time to complete: 3 hours