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Lung Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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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, radiation oncologist and pulmonologist must be well informed of these advances. To bridge the gap between research and patient care, *Lung Cancer Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists these physicians in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *LUNG CANCER UPDATE*

The purpose of Issue 3 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Sandler, Lilenbaum and West 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 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

HOW TO USE THIS MONOGRAPH

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. **www.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

The 11th World Conference on Lung Cancer — International Association for the Study of Lung Cancer
July 3-6, 2005
Barcelona, Spain
Event website: **www.2005worldlungcancer.com/2005WLC/**

47th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
October 16-20, 2005
Denver, Colorado
Event website: **www.astro.org**

ECCO13 — The European Cancer Conference
October 30-November 3, 2005
Paris, France
Event website: **www.fecs.be/emc.asp?pageId=10&Type=P**

Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow Symposium XXIII
November 2-5, 2005
New York, New York
Event website: **www.mssm.edu/tcf/index.shtml**

Oncology World Congress
November 16-19, 2005
New York, New York
Event website: **www.oncologycongress.com**

Editor's Note

Same question; very different answer

March 4, 2004

DR LOVE: What, in general, is your clinical approach to first-line therapy for Stage IV non-small cell lung cancer in younger patients with good performance status?

DR LILENBAUM: I use a platinum-based regimen — usually a carboplatin doublet — even though there may be a slight efficacy advantage for cisplatin.

April 13, 2005

DR LOVE: What, in general, is your clinical approach to first-line therapy for Stage IV non-small cell lung cancer in younger patients with good performance status?

DR LILENBAUM: In the past, I have used platinum-based doublets, and at this point, I would combine this with bevacizumab. Because of potential bleeding complications, I am more likely to use a taxane rather than gemcitabine with carboplatin/bevacizumab.

Most patients will finish chemotherapy and continue on bevacizumab, and eventually the disease will progress. At that point, the question is: Do you consider adding erlotinib to the bevacizumab as a promising second-line intervention? And my answer to that is, "Yes, I would."

DR LOVE: What about patients with known EGFR mutations or those with mutation phenotypic characteristics, such as being a nonsmoker?

DR LILENBAUM: Based on Vince Miller's data from the TRIBUTE trial, demonstrating a very impressive doubling of overall survival in nonsmokers who received erlotinib plus chemotherapy, for those patients, I would use four cycles of chemotherapy plus bevacizumab, and then stop the chemotherapy and add in erlotinib.

After years of stagnation, clinical research in non-small cell lung cancer is rapidly gaining momentum. The above conversations with Rogerio Lilenbaum capsulize the striking impact these research advances are having on daily patient care.

During the lung cancer oral sessions at this year's ASCO meeting, I was happy to observe that there were fewer monotonous presentations of Stage IV chemo comparison trials and many more encouraging and innovative research approaches to this disease.

Of course, topping the list was Alan Sandler's blockbuster presentation of ECOG-E4599, demonstrating a survival advantage when bevacizumab was added to carbo/paclitaxel as first-line therapy for Stage IV non-small cell disease. Alan is interviewed on this issue of *Lung Cancer Update*, and his simple conclusion delivered to the multitudinous throng in Orlando left no doubt as to how he and ECOG interpret these data:

> *"To conclude, bevacizumab improves survival when added to paclitaxel/carboplatin chemotherapy in patients with nonsquamous non-small cell lung cancer. Bevacizumab also improves response rate and progression-free survival. Bevacizumab is associated with a small increase in serious bleeding, including hemoptysis. PCB (paclitaxel, carboplatinum, bevacizumab) is now the ECOG reference standard for the first-line treatment of advanced nonsquamous non-small cell lung cancer. Future plans include combining bevacizumab with chemotherapy and radiotherapy in locally advanced disease, combining bevacizumab with other targeted agents, and considering the use of bevacizumab with chemotherapy in either the neoadjuvant or adjuvant settings in the hopes of curing even more lung cancer patients."*
>
> ***— Alan Sandler, MD, 2005 ASCO meeting plenary session***

In his interview for this issue, Rogerio Lilenbaum describes two patients he treated on E4599, both of whom experienced rapid and complete tumor responses to PCB. In the first patient, treatment resulted in a near vaporization of the tumor, which unfortunately led to fatal hemoptysis. With that experience in mind, when Rogerio observed a cavitary response to treatment in the second patient, he stopped therapy with Alan's input and support. Eighteen months later, this patient now continues off all treatment without disease progression.

There were also multiple ASCO presentations, posters and seminars on the correlations between the presence of EGFR mutations and tumor responses to tyrosine kinase inhibitors. Listening to paper after paper on this fascinating phenomenon, it was difficult for me to grasp that the very first data report about this mutation was published in the spring of 2004.

The 2005 ASCO meeting also marked the transition from gefitinib to erlotinib as the preferred tyrosine kinase inhibitor for non-small cell lung cancer. This important shift also occurred within an accelerated timeline that began in 2004 with Frances Shepherd's ASCO presentation of CAN-NCIC-BR21 demonstrating a survival advantage to erlotinib versus best supportive care.

This unexpected data set was then followed by a report in December 2004 demonstrating a disappointing lack of similar benefit with gefitinib in the ISEL trial. The final "nail in the coffin" for gefitinib came with Karen Kelly's ASCO presentation on the results of SWOG-S0023, which again demonstrated a lack of

survival benefit for the gefitinib versus control, this time as a maintenance treatment after chemo-radiation therapy for Stage III disease.

The changes in the algorithm for management of advanced non-small cell disease reflect a general acceleration of clinical research in lung cancer, and advances in adjuvant chemotherapy have similarly led to important changes in management of patients with early-stage disease. During the ASCO meeting, another major adjuvant study, the ANITA trial, demonstrated an advantage to treatment and the picture that has clearly emerged from the last three ASCO meetings is that the absolute benefit of this therapeutic strategy significantly exceeds what is seen in breast and colorectal cancer.

Our CME group has a dedicated computer server that warehouses thousands of hours of interviews and recording sessions. These chronicle what has, until recently, been the gradual evolution of cancer clinical research, but as is clearly evident in the two interviews with Rogerio Lilenbaum, the sudden increase in clinically relevant trial findings in lung cancer is part of an overall acceleration of progress that now provides more than a glimmer of optimism for the future.

— Neil Love, MD
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Select publications

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. **TRIBUTE — A phase III trial of erlotinib HCl (OSI-774) combined with carboplatin and paclitaxel (CP) chemotherapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2004;**Abstract 7011**.

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**.

Miller VA et al. **EGFR mutation, immunohistochemistry (IHC) and chromogenic in situ hybridization (CISH) as predictors of sensitivity to erlotinib and gefitinib in patients (pts) with NSCLC.** *Proc ASCO* 2005;**Abstract 7031**.

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.** *Proc ASCO* 2004;**Abstract 7061**.

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 LBA4**.

Shepherd FA et al. **A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial.** *Proc ASCO* 2004;**Abstract 7022**.

Alan B Sandler, MD

EDITED COMMENTS

Clinical trials comparing carboplatin/paclitaxel with or without bevacizumab in patients with metastatic NSCLC

Efficacy data

ECOG-E4599 was based on results from a randomized, Phase II, limited-institution study in which we participated. The trial enrolled 99 patients who were randomly assigned to paclitaxel/carboplatin alone versus paclitaxel/carboplatin with bevacizumab 7.5 mg/kg versus paclitaxel/carboplatin with bevacizumab 15 mg/kg every three weeks (Johnson 2004).

With the addition of bevacizumab, the results were interesting in terms of improvement in response rate, time to progression and survival. While only time to progression was statistically significant, the data suggest bevacizumab added some benefit to chemotherapy. ECOG-E4599 then evaluated carboplatin/paclitaxel with or without bevacizumab, and the top-line data revealed that the median survival increased from 10.2 months to 12.6 months in patients receiving bevacizumab (Sandler 2005; [1.2]). A 25 percent improvement in survival is important, both statistically and clinically. I believe that as a result of the data, the new standard for patients who fit the criteria of ECOG-E4599 will be chemotherapy combined with bevacizumab.

Toxicity data

In the Phase II trial, issues arose with pulmonary hemorrhage and hemoptysis that seemed to be associated with squamous cell cancers. ECOG-E4599 excluded patients with these tumors, patients with brain metastases and patients on therapeutic anticoagulation. When we designed the Phase III trial, we paid particular attention to toxicity (Sandler 2005; [1.1]). As the protocol chair, I received toxicity data on a real-time basis, and the study was stopped after 112 patients for an interim analysis.

The interim data presented at ASCO in 2003 showed that while a difference occurred in the incidence of Grade V hemoptysis for patients on bevacizumab, it

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was not statistically significant and was lower than that seen in the Phase II trial (Gray 2003). The study was then amended to accrue approximately 840 patients in hopes of detecting a 25 percent difference in survival. The last patient was enrolled in April 2004.

1.1 ECOG-E4599: Hematologic and Nonhematologic Toxicity

	CPB (n = 420)	CP (n = 427)	*p*-value
Hematologic toxicity (Grade IV)			
Neutropenia	24.0%	16.4%	0.006
Thrombocytopenia	1.4%	0%	0.01
Anemia	0%	0.7%	NS
Febrile neutropenia	3.3%	1.9%	NS
Nonhematologic toxicity (>Grade III)			
Hemorrhage	4.5%	0.7%	<0.001
Hemoptysis	1.9%	0.2%	0.04
CNS	1.0%	0%	0.03
GI	1.2%	0.5%	NS
Other	1.0%	0.2%	NS
Hypertension	6.0%	0.7%	<0.001
Venous thrombosis	3.8%	3.0%	NS
Arterial thrombosis	1.9%	1.0%	NS
Number of treatment-related deaths			
Hemorrhage			
Hemoptysis	5	0	
GI bleed	2	1	
Neutropenic fever	1	1	

CPB = carboplatin + paclitaxel + bevacizumab
CP = carboplatin + paclitaxel

SOURCE: Sandler AB et al. **A randomized phase III trial of paclitaxel plus carboplatin with or without bevacizumab in patients with advanced non-squamous non-small cell lung cancer: An Eastern Cooperative Oncology Group Trial - E4599.** Presentation. ASCO 2005;**Abstract LBA4**.

Clinical impact

An interesting question raised by ECOG-E4599 is whether the FDA will approve bevacizumab in combination with only carboplatin/paclitaxel, with all platin-based chemotherapy or with all doublet chemotherapy. I doubt that combining it with other chemotherapies would be problematic, as bevacizumab is an antibody and is not metabolized by the liver. The only potential issue, given the concern for bleeding, would be combining it with an agent known to cause thrombocytopenia, although the thrombocytopenia associated with bevacizumab is more of a paper toxicity in that it doesn't usually get below 50,000/µL.

Selecting adjuvant chemotherapy in the nonprotocol setting

In the adjuvant setting, I tend to use a cisplatin-based doublet such as cisplatin/gemcitabine, although I have used paclitaxel/carboplatin. Cisplatin/docetaxel is also reasonable, as is cisplatin/vinorelbine, which was studied in the French

trial. We have a wide range of choices that can be utilized, and they appear to be somewhat equivalent. Adjuvant therapy for patients with Stage III disease remains controversial, so for the unresectable patients I've used cisplatin/etoposide with concurrent radiation therapy followed by docetaxel, as in the SWOG study. I like cisplatin/etoposide because I can administer it in full dose with radiation therapy. With weekly paclitaxel and weekly carboplatin, some of the data, such as from the CALGB study, were not as exciting as we had hoped. However, I still think that is a reasonable approach and have used that also. There remain a number of choices for adjuvant therapy, and without any head-to-head studies, we're left with a lot of open-ended decisions.

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

Primary endpoint	CPB (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)	0.0075
Median progression-free survival	6.4 months	4.5 months	0.62 (CI: 0.53-0.72)	<0.0001

Secondary endpoint	CPB (n = 357)	CP (n = 350)	HR (CI)	*p*-value
Overall response	27.2%	10.0%	—	—
Complete response	1.4%	0.0%	—	—
Partial response	25.8%	10.0%	—	<0.0001

HR = hazard ratio; CI = confidence interval

SOURCE: Sandler AB et al. **A randomized phase III trial of paclitaxel plus carboplatin with or without bevacizumab in patients with advanced non-squamous non-small cell lung cancer: An Eastern Cooperative Oncology Group Trial - E4599.** Presentation. ASCO 2005;Abstract LBA4.

Use of erlotinib in patients with metastatic disease

We now have essentially three approved agents in the second-line metastatic setting — docetaxel, pemetrexed and erlotinib — and I'm comfortable with each of these. Erlotinib is approved for second- and third-line therapy, and I'm content to use it in either setting. In patients who have received and done well with front-line chemotherapy, it's reasonable to consider chemotherapy again, although I would use a different agent. In patients who have not fared well with chemotherapy in the front-line setting (either they progressed or were unable to tolerate it), I tend to use erlotinib. In patients with poor performance status — maybe a PS 2+, someone who's not interested in chemotherapy, an older octogenarian-plus or a nonsmoking, Asian female with adenocarcinoma — it's tempting to consider first-line therapy with erlotinib. However, chemotherapy has a more proven track record in that setting, so I still prefer to use chemotherapy.

The question is whether erlotinib adds to chemotherapy given concurrently or sequentially. Vince Miller's data from the TRIBUTE trial showed a survival advantage for chemotherapy and erlotinib versus chemotherapy alone in nonsmokers. However, the curve suggests that the improvement is seen in the first few months after the chemotherapy is finished, whereas when they're given together they seem similar. For that reason, I have on occasion used chemotherapy followed by maintenance therapy, with a tyrosine kinase inhibitor, particularly in an Asian patient with adenocarcinoma who never smoked.

The data on bronchioloalveolar carcinoma (BAC) from Adi Gazdar at the University of Texas Southwestern show that the pure BACs, which represent a small minority, do not seem to have the EGFR mutation (Shigematsu 2005). However, adenocarcinomas with varying degrees of BAC do have the mutation, and those patients tend to do very well. So that's another group in which erlotinib alone could be beneficial. We participated in a Memorial Sloan-Kettering study of erlotinib in first- and second-line treatment of patients with some degree of BAC, and the response rates were around 26 percent.

1.3 Correlation of Response to Erlotinib and Histological BAC Pathologic Type

Histological BAC type	Response to erlotinib
Pure BAC (n = 19)	2 (10.5%)
BAC with focal invasion (n = 1)	0
Adenocarcinoma with BAC features (n = 58)	17 (29.3%)
All patients with BAC features (n = 78)	19 (24.4%)

SOURCE: Kris MG et al. **Cigarette smoking history predicts sensitivity to erlotinib: Results of a phase II trial in patients with bronchioloalveolar carcinoma (BAC).** Presentation. ASCO 2004;**Abstract 7062**.

Phase I/II trial of bevacizumab in combination with erlotinib

Roy Herbst and I conducted a Phase I/II trial at MD Anderson and Vanderbilt, respectively, evaluating the combination of bevacizumab and erlotinib in patients with previously treated non-small cell lung cancer (Herbst 2005). We excluded patients with squamous cell tumors and brain metastases. It wasn't an official Phase I trial in that we didn't push for maximum tolerated dose. Rather, we wanted to evaluate whether we could reach the full dose of each single agent when combined, and we did. We treated 40 patients overall, and 34 patients received the Phase II doses of erlotinib 150 mg and bevacizumab 15 mg/kg.

In this study, the response rate was 20 percent with a median survival of 12.6 months, and time to progression was over six months. Although we didn't know at the time that it was a good thing to do, we now recognize that the study had an enriched population for erlotinib because we excluded squamous cell tumors. What was interesting is that we saw responses in patients whom we did not expect to respond to erlotinib alone, such as smokers, males and African-

American males. In addition, 65 percent of patients experienced stable disease, which is double what one would expect.

Randomized trials of combination chemotherapy in SCLC

Data were published in 2002 from a Japanese trial comparing etoposide/cisplatin versus irinotecan/cisplatin in 154 previously untreated patients with extensive SCLC (Noda 2002; [1.3]). The data showed the irinotecan combination significantly improved survival, and the trial was closed early because of the survival advantage. The patients who received the irinotecan-containing regimen had a median overall survival of approximately 12.75 months versus approximately 9.3 months for the patients on the standard etoposide/cisplatin regimen. We then conducted a larger, Phase III study of etoposide/cisplatin versus irinotecan/cisplatin with 330 patients, using a three-week schedule for cisplatin/irinotecan rather than the four-week schedule used in the Japanese trial. Our study was designed to detect a survival advantage of 33 percent with irinotecan, and we expect to have the data by ASCO 2005.

Select publications

Blackhall FH et al. **Erlotinib in non-small cell lung cancer: A review.** *Expert Opin Pharmacother* 2005;6(6):995-1002. **Abstract**

Byrne BJ, Garst J. **Epidermal growth factor receptor inhibitors and their role in non-small-cell lung cancer.** *Curr Oncol Rep* 2005;7(4):241-7. **Abstract**

Di Maio M et al. **Trying to compose the puzzle with all the pieces: Epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer.** *J Cell Physiol* 2005;[Epub ahead of print]. **Abstract**

Gray R et al. **The safety of adding angiogenesis inhibition into treatment for colorectal, breast, and lung cancer: The Eastern Cooperative Oncology Group's (ECOG) experience with bevacizumab (anti-VEGF).** *Proc ASCO* 2003;**Abstract 825**.

Hanna NH et al. **Randomized, phase III trial comparing irinotecan/cisplatin (IP) with etoposide/cisplatin (EP) in patients (pts) with previously untreated, extensive-stage (ES) small cell lung cancer (SCLC).** *Proc ASCO* 2005;**Abstract LBA7004**.

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**

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

Noda K et al; Japan Clinical Oncology Group. **Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer.** *N Engl J Med* 2002;346(2):85-91. **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 LBA4**.

Shigematsu H et al. **Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers.** *J Natl Cancer Inst* 2005;97(5):339-46. **Abstract**

ECOG trial E4599: Carboplatin/paclitaxel with or without bevacizumab

Until now, every time we talked about clinical research in advanced non-small cell lung cancer, we would have to say, "We've been on a plateau for at least the last five years, if not longer, with platinum doublets and benchmark median one-year survival rates, etcetera, with a small percentage of people who would live two years from the time of diagnosis."

The bevacizumab trial breaks through that plateau for the very first time (Sandler 2005). Our group in Miami entered over 30 patients in the ECOG-E4599 trial, and we had the largest accrual in CTSU. So we had a lot of exposure to that regimen. What the study shows is not unlike the data we saw in colon and breast cancer. I'm not sure exactly how, but something about bevacizumab enhances the activity of chemotherapy regimens. We all know about the anti-VEGF properties and the role they may play in either the development or the cessation of growth of the tumor, but I'm not sure this explains what we see.

The message is that bevacizumab is a very exciting drug. This is an agent that will be in every Phase III study we develop or design in non-small cell lung cancer, and it should be widely available for patients with this disease. However, we need to be careful about some rather unique complications, including cavitation and hemoptysis, that we're not accustomed to seeing in patients with non-small cell lung cancer. The other aspect of this drug is that it still does not apply to a substantial percentage of patients with this disease: patients with squamous cell carcinomas, those with cavitating lesions at presentation or who have hemoptysis of almost any degree at presentation. Corey Langer looked at his data from Fox-Chase and asked, "How many patients would not qualify for the ECOG trial?" The number they came up with was approximately 30 percent.

Nonprotocol first-line chemotherapy regimens

I almost always use carboplatin as opposed to cisplatin in the Stage IV population. I have used carboplatin with gemcitabine, docetaxel or paclitaxel. I have

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used carboplatin/vinorelbine in the past, but not recently. The specific choice is based on the toxicities of the chemotherapy regimen. I discuss the toxicities and issues of convenience with the patient because there are different schedules for carboplatin/gemcitabine. You have to come back for day eight, and then you have the advantage of less hair loss and other benefits, but hematologic toxicity may be somewhat more pronounced. Then you run into the taxane issues of neuropathy, myalgias, arthralgias, hair loss, etcetera. It may sound unusual, but I really make an effort to go in with an open mind. I almost never make that decision a priori, even though I may know the patient.

I have not yet utilized bevacizumab off study, but if I were to use it, I would probably be more reluctant to use it with carboplatin and gemcitabine than I would with the taxane regimens. The bleeding complications from the bevacizumab are not related to hematologic toxicity, but carbo-gemcitabine-related thrombocytopenia is obviously something you would like to avoid in a regimen that can cause bleeding.

Incorporating bevacizumab into adjuvant therapy

A couple of months ago, the leaders of the major cooperative groups met to discuss adjuvant trials. At that time, people were waiting for the ECOG data to be released, and it's my impression that there will now be an adjuvant study with bevacizumab. As we move into the adjuvant setting with bevacizumab, we may not have such a restricted population because the tumor will be resected. So I believe the risk of bleeding, cavitation and other side effects will be much less.

Off protocol, especially in the adjuvant setting, because we're dealing with curable patients, the dogma is that an agent shouldn't be utilized unless Phase III evidence exists. I abide by that dogma, but I have no doubts that we will be tempted in patients at high risk to use the bevacizumab in addition to the standard regimen that we use in the adjuvant setting. As long as an honest and frank discussion occurs with the patient about the potential complications, I think that is reasonable, but personally, I don't think I will be bringing that topic up very often.

Combining bevacizumab with erlotinib

The ECOG study published in the *JCO* by Roy Herbst and Alan Sandler was very exciting, not just because of the results but because this is a proof of principle (Herbst 2005; [2.1]). They published data from a study evaluating the combination of bevacizumab and erlotinib in previously treated patients with non-small cell lung cancer. The study demonstrated a nice response rate and a median survival that was close to 12 months. Obviously, it's a selected population and this is not the type of survival rate that we see for all of our patients, but it's enough to justify taking this regimen ahead, and I believe the erlotinib/bevacizumab will be used in various settings. The idea that two different biologic agents can be combined means we can get away from standard chemotherapy completely and hopefully obtain the results they published. That is exciting.

2.1 Combining Biologic Therapies without Chemotherapy in NSCLC

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

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

AEs = adverse events

	Adverse Events* (%)				
	All	Grade I	Grade II	Grade III	Grade IV
Rash†	29/(85)	18/(53)	9/(26)	2/(6)	0
Diarrhea	22/(65)	19/(56)	3/(9)	0	0
Infection	10/(29)	0	7/(21)	2/(6)	1/(3)
Hematuria	11/(32)	10/(29)	1/(3)	0	0

* Occurring in ≥10% of patients treated at the Phase II dose (n = 34)
† Includes pruritus

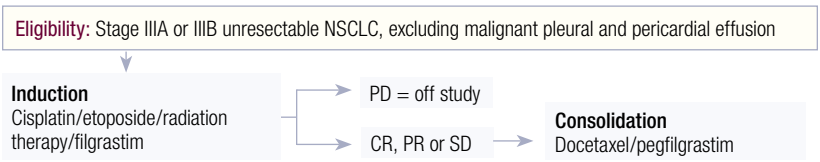
SOURCE: Herbst RS et al. **Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer.** *J Clin Oncol* 2005;23(11):2544-55. **Abstract**

Chemotherapy and radiation therapy in Stage III disease

Our group is conducting a trial (2.2) based on the SWOG model using cisplatin and etoposide for two cycles during thoracic radiotherapy followed by three cycles of docetaxel. In the SWOG study S9504, which utilized this regimen, significant hematologic toxicity occurred, which mandated a substantial dose reduction (Gandara 2003). This was more important in the docetaxel consolidation, but it was also significant during the combined portion of the trial. We're adding growth factors to that combined modality portion to see if we can minimize dose reduction and maintain dose intensity, which we believe is important in Stage III disease. Data from an old small cell trial that Paul Bunn published indicated that growth factors did abbreviate hematologic toxicity, but thrombocytopenia and pulmonary toxicity were more pronounced (Bunn 1995). Therefore, growth factors are not used with combined modality. We are evaluating this to see if it's feasible and beneficial.

2.2 Phase II Trial of Combined Modality Therapy with Growth Factor Support

Protocol ID: LUN-07
Target Accrual: 28 patients



PD = progressive disease; CR = complete response; PR = partial response; SD = stable disease

SOURCE: LUN-07 protocol, June 2005.

TRIBUTE trial: Chemotherapy with or without erlotinib

Vince Miller performed a subset analysis from the TRIBUTE trial (Miller 2004). They looked at the nonsmokers who received chemotherapy plus the TKI versus those who received chemotherapy only. The difference in median survival was one of the most impressive and overwhelming I have ever seen in a lung cancer study. In fact, when I first looked at the curves, it didn't look like a non-small cell lung cancer curve. It was 22 versus 10 months. I've had the opportunity to apply the data to a couple of patients. My only question was whether I should have done the chemotherapy first, followed by a TKI after four cycles, or if I should have done it exactly the way it was done in the TRIBUTE trial, which was to start the three drugs at the same time.

Select publications

Bunn PA Jr et al. **Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: A prospective phase III randomized study of the Southwest Oncology Group.** *J Clin Oncol* 1995;13(7):1632-41. **Abstract**

Gandara DR et al; Southwest Oncology Group. **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**

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**

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

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.** *Proc ASCO* 2004;**Abstract 7061**.

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 LBA4**.

CAN-NCIC-BR21: Randomized trial of erlotinib versus observation in patients with previously treated advanced NSCLC

CAN-NCIC-BR21 (3.1), with over 600 patients, evaluated subsets of patients and demonstrated an interesting dissociation between response rates, which were clearly and consistently higher in women, nonsmokers, Asians and patients with adenocarcinoma, and survival benefit associated with erlotinib 150 mg, which seemed to extend over a much broader range. The survival curves shifted the same, regardless of whether the patients were male or female and had squamous or adenocarcinoma. The hazard ratios and relative benefits were essentially identical.

It's also interesting that a response was not necessary for a survival benefit. This was suggested from the second-line trials of docetaxel, which demonstrated a single-digit response rate but a better one-year survival compared to best supportive care (Shepherd 2000). Also, pemetrexed, when compared to docetaxel, has superimposable activities and, presumably, the same clinical benefit with an almost negligible response rate (Hanna 2004). Perhaps the bar is too high, at least in advanced lung cancer, to expect that a 50 percent reduction in tumor size is necessary to translate into a survival benefit. Prolonged stable disease also helps.

ISEL: Randomized trial of gefitinib versus observation in patients with previously treated advanced NSCLC

I think everyone in the field was stunned that the ISEL trial of gefitinib 250 mg, which had a similar design to CAN-NCI-BR21, was negative. Nearly 1,700 patients were enrolled (Price 2005; [3.1]). Everyone suspected that the two drugs — erlotinib and gefitinib — were close enough to interchange and that the ISEL trial would have a positive result. ISEL was a large trial, and it had a very good trial design. It was surprising to us that it was negative, with only trends in the right direction.

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3.1 TK Inhibitors in the Treatment of Advanced Non-Small Cell Lung Cancer: Survival Data from the CAN-NCIC-BR21 and ISEL Trials

CAN-NCIC-BR21: Erlotinib versus placebo (N = 731)[1]

Survival parameter	Erlotinib	Placebo	Hazard ratio	*p*-value
Overall survival	6.7 months	4.7 months	0.71	<0.0001
Progression-free survival	2.2 months	1.8 months	0.61	<0.0001

ISEL: Gefitinib versus placebo (N = 1,692)[2,3]

Survival parameter	Gefitinib	Placebo	Hazard ratio	*p*-value
Overall survival	5.6 months	5.1 months	0.89	0.11
Patients with adenocarcinoma	6.3 months	5.4 months	0.83	0.07

SOURCES: [1] Shepherd FA et al. **A randomized placebo controlled study of erlotinib (OSI-774) versus placebo in patients with incurable non-small cell lung cancer who have failed standard therapy for advanced or metastatic disease.** Presentation. ASCO 2004;**Abstract 7022**.

[2] Price N, Belani C. **Clinical development of gefitinib in non-small-cell lung cancer and the Iressa Survival Evaluation in Lung Cancer trial.** *Clin Lung Cancer* 2005;6(4):214-6. No abstract available

[3] Iressa (ZD1839, gefitinib) tablets. **Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document.** AstraZeneca, January 2005. **www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2_01_01-AstraZeneca-Iressa.pdf**

Rash and antitumor effect of EGFR inhibitors

The association between rash and survival has been noted with erlotinib for years and across a wide range of tumor types. Roman Perez-Soler demonstrated a striking difference in median survival — 1.5 months for patients who had no rash versus 19.6 months for patients who had a Grade II or III rash. The median survival for patients with a Grade I rash fell right in between (Perez-Soler 2004; [3.2]). Many trials have shown a similar "rash-dependent" stratification with survival.

It is less clear with gefitinib, and I think that has contributed to the concept of using lower doses of gefitinib. In SWOG-S0126, the gefitinib trial in patients with BAC that I led, we found that the development of rash was significantly associated with better survival. There was some stepwise association with a higher degree of rash, but it was not as clear (West 2004). I have been struck by the consistency of the data in a wide range of trials with EGFR inhibitors, especially erlotinib. Even in other settings, trials of cetuximab have shown similar trends (Saltz 2003).

In terms of the relationship between rash and response rates, some trials have evaluated it and others have not. In both SWOG-S0126 (West 2004) and a trial of erlotinib in 78 evaluable patients with BAC presented by Mark Kris at ASCO (Kris 2004), we saw no responses among the patients who failed to develop a

rash. A fundamental question is whether you can obtain a better response by increasing the dose of the drug and dosing to rash. My take is that it seems to be more indigenous to the patient. If you consider the Phase I gefitinib trials, not everyone developed a rash by increasing the dose to 800 or 1,000 mg.

3.2 Phase II Trial of Erlotinib in Patients with Previously Treated HER1/EGFR-Positive NSCLC: Correlation between Survival and Rash

Grade of rash	Number of patients	Median survival (95% CI)
0	14	1.5 (1-2.2) months
I	26	8.5 (4.8-14.8) months
II/III	17	19.6 (10.8+) months

SOURCE: Perez-Soler R et al. **Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer.** *J Clin Oncol* 2004;22(16):3238-47. **Abstract**

Management of patients with BAC

We held a consensus conference about BAC in New York in November 2004. Our consensus was that there were no data to define the value of chemotherapy. Anecdotally, in clinical experience, chemotherapy is viewed as less effective for patients with BAC than other forms of lung cancer. These days, chemotherapy is often skipped in favor of EGFR-TK inhibitors.

I think that is an acceptable potential standard of care. However, in patients with a good performance status, I still treat them first with standard chemotherapy and move on immediately to erlotinib. In a patient with a more marginal performance status, I might use an EGFR-TK inhibitor immediately.

Integration of erlotinib into the management of patients with Stage IV NSCLC

Certainly, for patients who either have clinical or molecular evidence of carrying the EGFR gene mutation, you might make a strong argument to use erlotinib as first-line therapy. The TRIBUTE trial, which evaluated carboplatin/paclitaxel with or without erlotinib as first-line therapy, demonstrated a survival benefit for nonsmokers who received erlotinib (Miller 2004). I believe some institutions, including Memorial Sloan-Kettering, are using chemotherapy plus concurrent erlotinib for nonsmokers.

Although a survival benefit was seen in the nonsmokers in the TRIBUTE trial, I don't think that answers the question of how well these patients would have done with a sequential, instead of concurrent, approach. I think the data suggesting an antagonistic interaction between conventional chemotherapy and the EGFR-TK inhibitors (ie, the INTACT [Herbst 2004a, Giaccone 2004], TALENT [Gatzemeier 2004] and TRIBUTE [Herbst 2004b] trials) would dissuade me from using concurrent chemotherapy and an EGFR-TK inhibitor as first-line therapy.

Obviously, a much larger population of patients will be receiving erlotinib in the second- or third-line setting or beyond. In that situation, we have other approved agents — docetaxel and pemetrexed. For patients with a performance status that allows more chemotherapy, I tend to use chemotherapy in the second-line setting and sometimes in the third-line setting because you don't need a huge physiologic reserve to tolerate the EGFR-TK inhibitors. Some patients may be able to receive chemotherapy second line and erlotinib as third-line therapy, but they may not be able to do the reverse.

I would generally choose between chemotherapy and an EGFR-TK inhibitor as salvage therapy, based on factors like performance status and smoking status. I usually give nonsmokers an EGFR-TK inhibitor early on to determine if they would have a prolonged benefit with minimal toxicity. Another important potential factor is the patient's prior response to chemotherapy.

In patients who have had a response or prolonged stable disease and a good performance status, I would be more inclined to use chemotherapy before an EGFR-TK inhibitor even in the salvage setting. In patients who have had rapid progression on chemotherapy, I might be inclined to try a different approach and switch over to an EGFR-TK inhibitor earlier.

SWOG-S9504: Consolidation docetaxel after concurrent chemoradiation therapy in patients with Stage III disease

I use the SWOG-S9504 docetaxel consolidation approach in patients with Stage III disease. Although S9504 was a Phase II trial, there aren't enough Phase III trials with contemporary approaches in patients with Stage III lung cancer to guide us. By necessity, we need to extrapolate from the available data. To me, the data from SWOG-S9504 have been strikingly superior to those preceding that trial (Gandara 2003; [3.3]).

3.3 Comparison of SWOG Phase II Trials Evaluating Induction Chemoradiation Therapy Followed by Consolidation Chemotherapy in Patients with Stage IIIB NSCLC

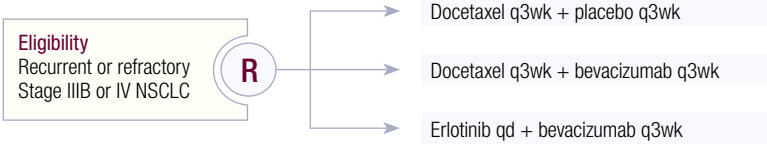
Study	MST (months)	2 year	3 year	4 year	5 year
S9504 (PE/RT → D)	26 (18-35)*	54% (43-65)*	37% (24-55)*	29% (19-29)*	29% (19-29)*
S9019 (PE/RT → PE)	15 (10-22)*	34% (21-47)*	17% (7-27)*	17% (6-28)*	17% (6-28)*

* 95% CI
MST = median survival time; PE = cisplatin/etoposide; RT = radiotherapy (61 Gy); D = docetaxel

SOURCE: 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).** Presentation. ASCO 2005;**Abstract 7059**.

3.4 Phase II Randomized Study of Bevacizumab Combined with Either Docetaxel or Erlotinib versus Docetaxel Alone

Protocol IDs: PRA-OSI2950g, GENENTECH-OSI2950g, UCLA-0408116-01, NCT00098410
Target Accrual: 150 (Open)



In all arms, courses repeat for up to 52 weeks in the absence of unacceptable toxicity or disease progression.

Patients in arms I and II who experience disease progression may be eligible to receive single-agent oral erlotinib once daily for the remainder of the study.

SOURCE: NCI Physician Data Query, May 2005.

Continuation of bevacizumab on disease progression

If bevacizumab becomes integrated into first-line therapy, it will raise the ongoing question that we have in a huge range of oncology practice: How long should targeted therapies be continued, even in patients who progress on a combination of targeted therapy plus conventional chemotherapy?

There has been one prominent Phase II trial of bevacizumab and erlotinib that looked encouraging (Herbst 2005), and further study with that combination is ongoing. That combination may be employed as a salvage therapy in patients who have already been on bevacizumab in the first-line setting. The Southwest Oncology Group is planning to undertake a trial of pemetrexed with bevacizumab in the salvage setting, so that will provide important clinical activity and toxicity data for that combination. I'm sure docetaxel and bevacizumab will also be studied extensively (3.4).

It would be nice to actually see some suggestion of a survival benefit beyond that seen with chemotherapy or erlotinib alone. Another key component will be showing that there isn't prohibitive toxicity from these combinations. I would be very cautious about combining bevacizumab with anything that hasn't been extensively tested.

Evolution of clinical trial data with adjuvant chemotherapy

At ASCO 2003 (Le Chevalier 2003), the IALT trial data were presented at a plenary session with statistically and arguably clinically significant results. A four percent overall survival benefit was enough to convince the people who already believed in the concept of systemic therapy for early-stage lung cancer. The skeptics remained largely unconvinced, and we still debated questions about treating patients with Stage IB disease. These patients seemed to derive a little less benefit in the IALT trial than patients with Stage II or III disease. It was

still very much an open question: Which patients should be recommended for adjuvant chemotherapy? Much of that debate was laid to rest at ASCO in 2004, when two trials — presented back to back in oral sessions — showed double-digit survival benefits (Strauss 2004; Winton 2004). Everyone would have to agree that these data were quite clinically significant. One trial was with a chemotherapy regimen that was widely used in the United States — carboplatin and paclitaxel — and that same trial specifically evaluated patients with Stage IB disease.

We believed it would be difficult to demonstrate a survival benefit in patients with Stage IB disease in the adjuvant setting; however, a double-digit survival benefit of 12 percent was demonstrated at four years. So at this point, I believe adjuvant chemotherapy has become the clear standard of practice and just about every patient should at least have systemic therapy discussed, if not implemented. For some patients, getting through a thoracotomy alone is a challenge. Those patients who were enrolled on the trial had already been selected as potential candidates. So it is not necessarily for everybody, but with the magnitude of the benefits it deserves to be discussed. I would find fault with the rare surgeon or practitioner who dissuades their patient after surgery from at least considering a consultation with a medical oncologist to consider adjuvant chemotherapy.

Selection of adjuvant chemotherapeutic regimens

The potential curability of the disease makes me try to adhere as much as possible to regimens with maximum efficacy. The clinical trials have used a range of cisplatin-based chemotherapy in addition to carboplatin and paclitaxel.

The few trials that have directly compared cisplatin- and carboplatin-based regimens in other settings in lung cancer have suggested a slight efficacy advantage for cisplatin-based chemotherapy. I favor cisplatin-based regimens if a patient's performance status would allow it, which is really a subset of patients. Although it may seem anachronistic, I use as much cisplatin and vinorelbine as any other regimen in this setting, based on it being one of the leading regimens in the IALT trial and the regimen that was employed in the NCI Canada JBR.10 trial.

I would have no trouble using almost any platinum-based doublet, and probably in around 50 percent of my patients, carboplatin-based doublets are a much more feasible choice. I would have no reluctance in utilizing carboplatin and paclitaxel now that there are data supporting its comparability in this setting. If feasible, I'd prefer to use the regimens that have supporting data. However, given the large volume of data in advanced disease that show essentially complete comparability of these platinum doublets, most physicians in the field would consider them to be interchangeable.

Select publications

Gandara DR et al; Southwest Oncology Group. **Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: Phase II Southwest Oncology Group Study S9504.** *J Clin Oncol* 2003;21(10):2004-10. **Abstract**

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

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

Hanna N et al. **Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.** *J Clin Oncol* 2004;22(9):1589-97. **Abstract**

Herbst RS et al. **Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: A phase III trial — INTACT 2.** *J Clin Oncol* 2004b;22(5):785-94. **Abstract**

Herbst RS et al. **Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer.** *J Clin Oncol* 2005;23(11):2544-55. **Abstract**

Herbst RS et al. **TRIBUTE — A phase III trial of erlotinib HCl (OSI-774) combined with carboplatin and paclitaxel (CP) chemotherapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2004a;**Abstract 7011**.

Kris MG et al. **Cigarette smoking history predicts sensitivity to erlotinib: Results of a phase II trial in patients with bronchioloalveolar carcinoma (BAC).** *Proc ASCO* 2004;**Abstract 7062**.

Le Chevalier T et al. **Results of the Randomized International Adjuvant Lung Cancer Trial (IALT): Cisplatin-based chemotherapy (CT) vs no CT in 1867 patients (pts) with resected non-small cell lung cancer (NSCLC).** *Proc ASCO* 2003;**Abstract 6**.

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.** *Proc ASCO* 2004;**Abstract 7061**.

Perez-Soler R et al. **Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer.** *J Clin Oncol* 2004;22(16):3238-47. **Abstract**

Price N, Belani C. **Clinical development of gefitinib in non-small-cell lung cancer and the Iressa Survival Evaluation in Lung Cancer trial.** *Clin Lung Cancer* 2005;6(4):214-6. No abstract available

Saltz L et al. **The presence and intensity of the cetuximab-induced acne-like rash predicts increased survival in studies across multiple malignancies.** *Proc ASCO* 2003;**Abstract 817**.

Shepherd FA et al. **A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial.** *Proc ASCO* 2004;**Abstract 7022**.

Shepherd FA et al. **Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy.** *J Clin Oncol* 2000;18(10):2095-103. **Abstract**

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

West H et al. **Gefitinib (ZD1839) therapy for advanced bronchioloalveolar lung cancer (BAC): Southwest Oncology Group (SWOG) Study S0126.** *Proc ASCO* 2004;**Abstract 7014**.

Winton TL et al. **A prospective randomised trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage 1B and II non small cell lung cancer (NSCLC) Intergroup JBR.10.** *Proc ASCO* 2004;**Abstract 7018**.

Post-test:
Lung Cancer Update — Issue 3, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. What was the dose of bevacizumab utilized in ECOG trial E4599 that evaluated carboplatin/paclitaxel with or without bevacizumab?
   a. 5 mg/kg
   b. 10 mg/kg
   c. 15 mg/kg
   d. 20 mg/kg
2. In ECOG-E4599, the addition of bevacizumab to carboplatin/paclitaxel resulted in an improvement in median progression-free and overall survival in patients with previously untreated metastatic NSCLC.
   a. True
   b. False
3. Patients with which of the following conditions were excluded from ECOG-E4599?
   a. Pulmonary hemorrhage
   b. Hemoptysis
   c. Squamous cell carcinoma
   d. Brain metastases
   e. a and b
   f. All of the above
4. In ECOG-E4599, which of the following adverse events were more common with the addition of bevacizumab to carboplatin/paclitaxel?
   a. Neutropenia
   b. Thrombocytopenia
   c. Hemoptysis
   d. Hypertension
   e. All of the above
5. In ECOG-E4599, life-threatening or fatal hemoptysis was observed as a potential complication associated with bevacizumab, but it did not compromise the survival benefit conferred by the addition of bevacizumab to chemotherapy.
   a. True
   b. False
6. The TRIBUTE trial failed to demonstrate a survival advantage to adding erlotinib to chemotherapy in nonsmokers.
   a. True
   b. False
7. Patients who develop a rash when treated for non-small cell lung cancer with erlotinib have a better median survival compared to those who do not develop a rash.
   a. True
   b. False
8. In a Phase I/II trial evaluating erlotinib/bevacizumab in the treatment of previously treated patients with recurrent NSCLC, the disease control rate (CR + PR + SD) was:
   a. 20 percent
   b. 45 percent
   c. 65 percent
   d. 85 percent
9. Noda and colleagues demonstrated that cisplatin plus irinotecan versus etoposide resulted in a significant survival advantage in previously untreated patients with extensive SCLC.
   a. True
   b. False
10. In CAN-NCIC trial BR21, patients treated with erlotinib experienced a survival benefit.
    a. True
    b. False
11. Which of the following trial(s) were associated with a survival advantage for a TKI in highly refractory patients with NSCLC?
    a. ISEL trial (gefitinib versus placebo)
    b. CAN-NCIC-BR21 (erlotinib versus placebo)
    c. Both a and b
12. In SWOG trial S9504, patients with unresectable Stage III NSCLC who underwent induction chemoradiation therapy experienced an improvement in survival from consolidation docetaxel compared to historical comparison with consolidation cisplatin/etoposide in SWOG-S9019.
    a. True
    b. False

Post-test Answer Key: 1c, 2a, 3f, 4e, 5a, 6b, 7a, 8d, 9a, 10a, 11b, 12a

Evaluation Form:
Lung Cancer Update — Issue 3, 2005

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 will be 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 a management strategy 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
Alan B Sandler, 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
Howard West, 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 3, 2005

REQUEST FOR CREDIT — please print clearly

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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?

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Additional comments about this activity:

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Degree:

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

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

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