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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 4 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Miller, Socinski and Perez-Soler 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

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

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

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

Sixth Annual Targeted Therapies for the Treatment of Lung Cancer Conference
January 26-28, 2006
Santa Monica, California
Event website: **www.thecbce.com/currentactivities.asp**

Third Annual Winter Lung Cancer Conference
March 10-12, 2006
Aventura, Florida
Event website: **www.thecbce.com/currentactivities.asp**

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

Editor's Note

Disease within a disease

"Breast cancer is more than one disease, and HER2-positive breast cancer may be as different from HER2-negative breast cancer as acute myeloid leukemia is from acute lymphocytic leukemia or as different as pneumococcal pneumonia is from staphylococcal pneumonia. We finally have the tools to show us those differences, and even more exciting, we have therapies to take advantage of those differences. I predict that in a couple of years, we're going to have to rethink all of the major conceptual paradigms that we use right now to treat breast cancer."

— ***Harold J Burstein, MD,*** **Breast Cancer Update** ***Audio Series***

Hal Burstein's prediction about breast cancer came true on the afternoon of May 16th in Orlando during the ASCO meeting with a succession of four stunning presentations on the effects of adjuvant trastuzumab in major Phase III randomized trials. In an instant, clinical practice had undergone a revolution for the approximately 40,000 to 50,000 patients with HER2-positive breast cancer. From a research perspective, a new model of targeted treatment had achieved its pinnacle. An unspoken undercurrent was that Hal Burstein's vision of a "disease within a disease" had come to pass. Not only will day-to-day care for these patients be altered radically, but current and future clinical trials are now also being reconsidered.

For example, ongoing randomized studies of various forms of chemotherapy — such as NSABP-B-38 and SWOG-S0221 — have now essentially become studies for patients with HER2-negative breast cancer because patients with HER2-positive disease will undoubtedly receive adjuvant trastuzumab and thus will not be eligible. What about adjuvant endocrine trials? Will they need to be altered to allow trastuzumab for ER-positive, HER2-positive cases? In the three adjuvant trastuzumab trials presented on May 16th, about half of the patients had ER-positive, HER2-positive tumors.

Sometimes it seems like breast cancer is the wise grandmother who serves as a role model to other less developed oncologic clinical research cultures. Our CME group has uncovered repeated instances in which it has been helpful to make comparisons between breast cancer and other tumors. At the moment, the best analogy I see to the HER2/trastuzumab story in solid tumor oncology relates to non-small cell lung cancer — specifically, the 10 to 20 percent of the NSCLC

population that can be differentiated by a high rate of tumor response to tyrosine kinase inhibitors. Let's call these tumors TKIR (tyrosine kinase inhibitor responsive). From what I can gather in chatting with pulmonary oncology mavens interviewed for this series, it seems that these lung cancer tumors respond to TKIs at least as robustly (favorite new word for researchers replacing "signal") as HER2-positive breast cancer responds to trastuzumab in the metastatic setting (eg, Chuck Vogel's key trial demonstrating a 35 percent objective tumor response rate in patients with FISH-positive tumors).

Here's the problem and concern: It was not until many years after studies in the metastatic setting that clinical trials proved adjuvant trastuzumab was relatively safe and added an impressive level of tumor control combined with or following chemotherapy. With perhaps 15,000 people a year dying of TKIR NSCLC, I don't much like the idea of waiting that long for an answer. Perhaps the most significant challenge facing investigators leading the next wave of trials focusing on the TKIRs is figuring out who fits into this important group. From what I could ascertain at ASCO by attending sessions and speaking with the three interviewees on this program, the first step is to focus on nonsmokers and perhaps former smokers who have less than a yet-to-be-defined amount of tobacco exposure — perhaps 10 pack years.

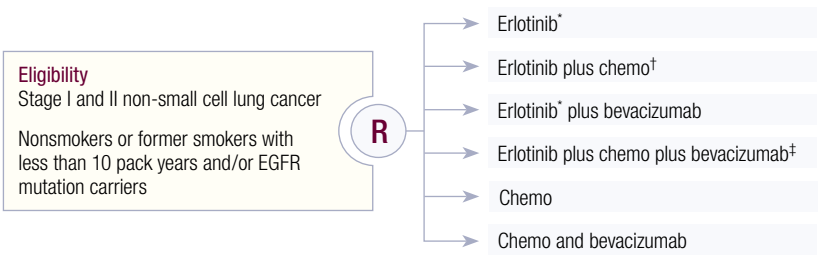
Additional phenotypic qualities of the TKIR group are female gender, Asian background and adenocarcinoma histology, particularly with BAC features. Of course, another key identifying factor is the presence of an EGFR mutation in the tumor. However, I left ASCO believing that quality control with the assay is lacking and the mutation's correlation with response to TKIs is far from a given. FISH and IHC assays of EGFR may turn out to be better predictors. Future clinical trials focusing on TKIR NSCLC might have smoking history as a primary eligibility factor. Other patients might enter based on documented gene mutations and phenotypic factors. The question is: What kind of adjuvant trial design makes sense?

In that regard, another major card tossed on the table at ASCO was the anti-VEGF agent bevacizumab. As discussed on the last issue of *Lung Cancer Update* by principal investigator Alan Sandler, ECOG trial E4599 — presented by Dr Sandler at a major plenary session — demonstrated for the first time in NSCLC that the use of three systemic agents as first-line therapy resulted in greater progression-free and overall survival than two agents. In this case, the third partner was bevacizumab, which provided a clinically meaningful improvement in tumor control with a minimal increase in side effects and toxicity when combined with paclitaxel-carboplatin in carefully selected patients (eligibility criteria: Stage IIIB, IV or recurrent nonsquamous NSCLC with a PS of 0-1).

As with colorectal cancer and breast cancer, bevacizumab now deserves to be rapidly studied in the adjuvant setting, and it will be interesting to see if new adjuvant trials in lung cancer divide patients into TKIR and non-TKIR subsets. In this regard, my "dream trial" (1.1) would have six randomization arms — some of which would undoubtedly be squashed by CTEP, the FDA and other powers that be. If this type of trial has merit, a major issue would be accrual, specifically

related to the question of whether oncologists and patients would be comfortable with the two arms not containing erlotinib. If I were a nonsmoker with NSCLC or had a tumor with an EGFR mutation, this would give me cause for great concern, but maybe others will feel differently. Whatever is decided, I sure as hell want to see these studies get done quickly. This disease is devastating thousands of lives a year, but the rapid progression rate and high mortality also means that answers could come sooner, for example, than in breast and colon cancer.

1.1 Theoretical Adjuvant Trial Design



* For a total of two years; † doctor's choice of menu of common regimens; ‡ for a total of one year

To focus on 10 percent of patients in a disease that decimates the lives of 160,000 people annually may seem questionable, but the mortality in patients with TKIR tumors exceeds that of other important cancers such as gastric cancer, soft tissue sarcoma and melanoma. With trastuzumab, it took many years to find an answer, but my take is that now we know how to execute adjuvant trials more effectively, and maybe that time frame can be cut in half.

As long as I am rambling on about things that maybe I don't know enough about, here's another suggestion: Get the NSABP involved. Call it the NSABLP (National Surgical Breast and Bowel and Lung Project). Yes, I know that Norm Wolmark and colleagues have their hands full, but those guys know how to get surgeons on board. They did it in breast, colon, and rectal cancer, and when the casualties are this brutal, we should pull out all the stops.

It is well documented that many or most trial participants join studies primarily to help future patients, although we also know that there is often a direct benefit to those in the trials (witness the participants in the trastuzumab studies who avoided relapse and death via participation). I don't see any reason why lung cancer patients would be less interested in making a contribution to the greater good than breast cancer patients. Let's give them that chance now, and maybe there will be another May 16th at a future ASCO meeting with more good news — this time in a disease (NSCLC) that perhaps three years ago was considered stuck in the 1980s but now has the opportunity to take a leadership role in the research-to-practice translation of molecular targeted therapy.

— Neil Love, MD
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ECOG-E4599: Carboplatin/paclitaxel with or without bevacizumab in patients with previously untreated advanced nonsquamous NSCLC

This study was a major stepping stone in the therapy for patients with NSCLC. We've never had a three-drug combination beat a two-drug combination.

In large US cooperative group studies of patients with Stage IV disease, we've also never had a median survival greater than one year. In ECOG-E4599, at two years, we now have survival of about 20 percent of the patients treated with carboplatin/paclitaxel and bevacizumab (Sandler 2005; [2.1]).

This has been "soft pedaled" or felt to be a modest benefit by some, but for those of us who have worked in the field for a while, this is important proof of principle that we can do better for our patients. E1594 was described as the plateau trial, with the belief that we couldn't obtain a median survival beyond eight months (Schiller 2002).

Interestingly, patients in the carboplatin/paclitaxel arm of E4599 did better than those in E1594. Perhaps some patients are doing better with our second- and third-line therapies. Pemetrexed, gefitinib and erlotinib were available to some patients on this study.

Even though these drugs may not be a home run, they are a series of walks, infield hits and singles. We're scoring points and having people live longer with this disease.

We all wanted to see the data to make sure there were no unusual patterns predictive of toxicity or groups that were particularly sensitive or insensitive to the combination, and we have been reassured that the safety profile is robust. The drug may have different toxicities than cytotoxic agents, but that doesn't mean it has more or worse toxicities. Overall, it's a tolerable regimen. We are interested in using bevacizumab in our patients who fit the profile of the patients treated in E4599.*

* Note: Nonsquamous cell Stage IIIB or IV NSCLC; no history of hemoptysis; no CNS metastasis.

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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

	PCB (n = 434)	PC (n = 444)	HR (CI)	*p*-value
Median OS	12.5 months	10.2 months	0.77 (CI:0.65-0.93)	0.0075
Two-year OS	22.1%	16.9%	—	—
Median PFS	6.4 months	4.5 months	0.62 (CI:0.53-0.72)	<0.0001

OS = overall survival; PFS = progression-free survival

SOURCE: Sandler AB et al. **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 (ECOG) Trial — E4599.** Presentation. ASCO 2005;**Abstract LBA4**.

Phase I/II trial of erlotinib and bevacizumab in patients with recurrent Stage IIIB/IV nonsquamous NSCLC

In this trial, it was nice to see that the drugs were safe to administer together at the full doses (150 mg daily for erlotinib and 15 mg/kg every three weeks for bevacizumab). We saw clear activity of the combination (Herbst 2005; [2.2]). Another trial will compare bevacizumab plus erlotinib to erlotinib alone in patients with adenocarcinomas. Among patients with adenocarcinomas, two obvious sets of patients exist. Patients who have a negligible or no smoking history are likely to have EGFR gene mutations. Those patients will benefit greatly from erlotinib and may or may not need bevacizumab. At the other end are patients who are heavy smokers in whom erlotinib may not be helpful and bevacizumab may be a key drug. Our task is to characterize them by a testing or stratification process so we can deliver the best therapies on a patient-specific basis.

2.2 Efficacy Results from a Phase I/II Trial of Erlotinib and Bevacizumab in Patients with Recurrent Stage IIIB/IV Nonsquamous NSCLC

	Phase I cohort (n = 12)	Phase II cohort (n = 34)*
Median survival	14.9 months	12.6 months
One-year survival	66.7%	51.8%
Median PFS	10.1 months	6.2 months

* Phase II cohort includes six patients from the Phase I study treated with the Phase II dose.
PFS = progression-free survival

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**

First-line therapy for patients with metastatic NSCLC and an EGFR gene mutation

We're big believers in the positive predictive value of EGFR gene mutations, particularly in exons 19 and 21. We are also privileged to have the EGFR gene mutation test available at Memorial Sloan-Kettering. If I have a patient with an EGFR gene mutation, I treat them initially with chemotherapy and erlotinib, based on the subgroup analysis of the never-smokers from the TRIBUTE trial (Miller 2004; [2.3]). We don't have much data on mutations from large series of patients in terms of response and whether chemotherapy is necessary, but my intuition is that it's a reasonable course of action.

I'm not sure my approach to these patients would change because of the results of ECOG-E4599. You could, however, envision bevacizumab/erlotinib or the four drugs (carboplatin/paclitaxel/bevacizumab/erlotinib) as first-line therapy in that subset of patients. A number of different scenarios exist. In that modest-sized subset, I would probably use carboplatin/paclitaxel and erlotinib. For the patients who aren't likely to benefit from erlotinib, I would use bevacizumab.

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

	All patients[1]		Nonsmokers[2]	
	C/P + erlotinib (n = 539)	C/P alone (n = 540)	C/P + erlotinib (n = 64)	C/P alone (n = 41)
Overall median survival	10.6 months	10.5 months*	22.5 months	10.1 months†
Median TTP	5.1 months	4.9 months*	6.0 months	4.3 months†

* P = NS; † P = not reported; TTP = time to progression

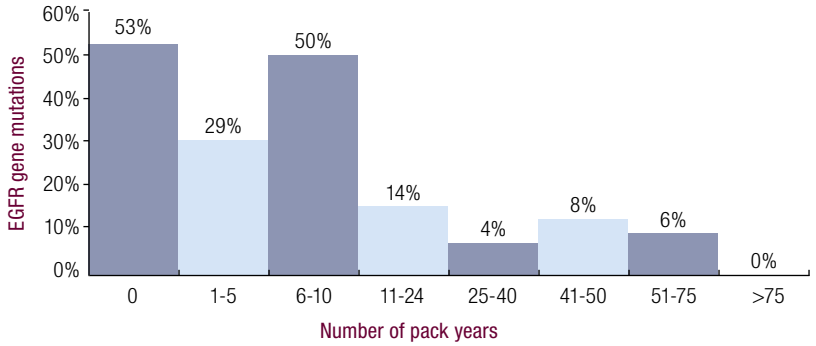
SOURCES: [1] Herbst RS et al. **TRIBUTE — A phase III trial of erlotinib HC1 (OSI-774) combined with carboplatin and paclitaxel (CP) chemotherapy in advanced non-small cell lung cancer (NSCLC).** Presentation. ASCO 2004;**Abstract 7011**.

[2] Miller VA et al. **Long survival of never smoking non-small cell lung cancer (NSCLC) patients (pts) treated with erlotinib HC1 (OSI-774) and chemotherapy: Sub-group analysis of TRIBUTE.** Presentation. ASCO 2004;**Abstract 7061**.

Relationship between smoking history and EGFR gene mutation

We evaluated patients who had smoking histories of varying degrees to determine the frequency of EGFR gene mutations. We arbitrarily divided patients according to units of pack years. Patients with a smoking history of 10 pack years or less, particularly those who had quit many years ago (≥25 years ago), had a likelihood of having an EGFR gene mutation that was as high as the individual who never smoked (Pham 2005; [2.4]). This observation helps the clinician who doesn't have access to the EGFR gene mutation test or doesn't want to wait three weeks for the results. If you believe in the EGFR gene mutation like we do, it's a guiding feature that helps in clinical decision-making.

2.4 Incidence of EGFR Gene Mutations by Pack Years of Smoking



SOURCE: Pham D et al. **Estimation of the likelihood of epidermal growth factor receptor (EGFR) mutations based on cigarette smoking history in patients with adenocarcinoma of the lung.** *Proc ASCO* 2005;**Abstract 7069**.

Adjuvant therapy for patients with EGFR gene mutations

In certain adjuvant therapies, it is more important to know if the EGFR gene mutations are predictive. If a therapy works 50 or 70 percent of the time in the metastatic setting in patients with the EGFR gene mutation, it will be that much more efficacious in locoregional disease. If I were a patient with an EGFR gene mutation who had a surgical resection, I'd be running to take erlotinib.

I would use one of two approaches: (1) chemotherapy alone for four cycles, followed by erlotinib for a few years or (2) erlotinib and chemotherapy concomitantly from the beginning, as in the TRIBUTE trial in patients with metastatic disease. Either approach would be acceptable. In my most recent patients, I've used chemotherapy alone first, followed by erlotinib.

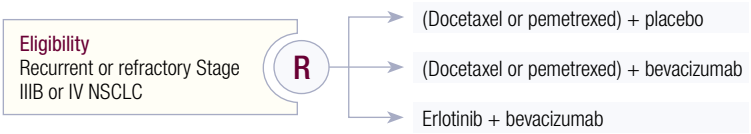
Incorporation of bevacizumab with docetaxel or pemetrexed

In an important ongoing study, patients are randomly assigned to one of three arms: (1) placebo plus either docetaxel or pemetrexed (according to the physician's choice), (2) bevacizumab plus either docetaxel or pemetrexed or (3) bevacizumab plus erlotinib (2.5). That's an important question that speaks to the potential use of bevacizumab in the second-line setting.

For example, if you saw a much higher response rate in patients who received pemetrexed with bevacizumab versus pemetrexed alone, given how powerful bevacizumab was in the first-line setting, that would indicate that this approach is reasonable. If there were no safety and insurance issues, I would certainly consider that doublet in the second-line setting.

2.5 Bevacizumab Combined with Docetaxel, Pemetrexed or Erlotinib Compared to Docetaxel or Pemetrexed Alone

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



Patients randomly assigned to receive pemetrexed disodium also receive cyanocobalamin (vitamin B) intramuscularly once every nine weeks and a low-dose oral folic acid preparation or a multivitamin with folic acid once daily during study participation.

In all arms, courses repeat approximately every three weeks for up to 52 weeks in the absence of unacceptable toxicity or disease progression. Patients in arms I and II who experience disease progression or unacceptable toxicity may be eligible to receive single-agent oral erlotinib once daily for the remainder of the study.

SOURCE: NCI Physician Data Query, July 2005.

Select publications

FDA Alert for Healthcare Professionals. **Gefitinib**. Available at **www.fda.gov/cder/drug/InfoSheets/HCP/gefitinibHCP.pdf**. Accessed on June 24, 2005.

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 HC1 (OSI-774) combined with carboplatin and paclitaxel (CP) chemotherapy in advanced non-small cell lung cancer (NSCLC).** Presentation. ASCO 2004;**Abstract 7011**.

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**

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

Pham D et al. **Estimation of the likelihood of epidermal growth factor receptor (EGFR) mutations based on cigarette smoking history in patients with adenocarcinoma of the lung.** *Proc ASCO* 2005;**Abstract 7069**.

Sandler AB et al. **Anti-vascular endothelial growth factor monoclonals in non-small cell lung cancer**. *Clin Cancer Res* 2004;10(12 Pt 2):4258-62. **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 LBA4**.

Schiller JH et al; Eastern Cooperative Oncology Group. **Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.** *N Engl J Med* 2002;346(2):92-8. **Abstract**

Mark A Socinski, MD

EDITED COMMENTS

ECOG-E4599: Phase III randomized trial of carboplatin/paclitaxel with or without bevacizumab

One of the biggest stories presented at ASCO 2005 was that of bevacizumab in the ECOG-E4599 trial (Sandler 2005). The trial design was simple — paclitaxel plus carboplatin with or without bevacizumab. E4599 was based on impressive, favorable findings from a Phase II experience, which were published last year in the *JCO* (Johnson 2004).

A review of the eligibility criteria for the Phase III trial is important because the population studied had nonsquamous cell tumors, no brain metastases, a PS from 0-1, no anticoagulation therapy and no recent history of hemoptysis. Therefore, this was a clinically selected population of patients, first and foremost for safety issues.

Response rates and survival benefits

In the control arm, paclitaxel plus carboplatin alone was associated with a median survival of just over 10 months, which is more favorable than the median survival of approximately eight months for paclitaxel plus carboplatin in E1594 (Schiller 2002). In the investigational arm, the addition of bevacizumab to paclitaxel plus carboplatin resulted in significant improvements in both median and progression-free one-year survival of approximately two months and an approximate eight percent increase in absolute one-year survival.

One-year survival in the bevacizumab arm was just over 50 percent, which is a major milestone in terms of one-year survival in NSCLC. The response rate in the control arm of ECOG-E4599 was approximately 10 percent and approximately 27 percent in the bevacizumab arm.

Toxicity

In the bevacizumab arm, slightly more myelosuppression occurred. An approximate 4.5 percent incidence of hemorrhagic complications also occurred — mostly hemoptysis — compared to an incidence of 0.8 percent in the control arm, which translates to roughly a five-fold increase in risk (Sandler 2005; [3.1]). We have to learn how to identify patients at high risk. A review of which patients

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suffered the fatal hemorrhagic complications could provide insight into how these patients were different from others.

We must be careful extrapolating these data to the general population, because the results suggest that hemorrhagic complications may occur in one of every 20 or 25 patients who are treated. As we take the positive findings from E4599 and integrate them into everyday practice, we must be as selective in treating patients as the eligibility criteria were in the trial for determining to whom we offer this regimen as a standard of care.

3.1 ECOG-E4599: Grade IV Hematologic and Grade III-IV Nonhematologic Toxicity

	PCB (n = 420)	PC (n = 427)	*p*-value
Neutropenia	24%	16.4%	0.006
Thrombocytopenia	1.4%	0%	0.01
Anemia	0%	0.7%	NS
Febrile neutropenia*	3.3%	1.9%	NS
Hemorrhage	4.5%	0.7%	<0.001
Hemoptysis	1.9%	0.2%	0.04
CNS	1.0%	0%	0.03
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

* Includes one death on each arm due to neutropenic fever
P = paclitaxel; C = carboplatin; B = bevacizumab

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 (ECOG) Trial — E4599.** Presentation. ASCO 2005;**Abstract LBA4**.

Potential risk factors for bevacizumab-associated bleeding

Patients with large central lesions who possibly undergo early cavitation may have a heightened risk for bleeding complications. The CT scans of such patients provide a sense that the tumor might be making up part of the pulmonary arterial wall or that it might be adjacent to another vital vascular structure. It's not known whether bevacizumab should be discontinued in these patients. We must use our best clinical judgment, as no clear guidelines exist for these circumstances.

Bleeding complications might be related to the manifestation of an anti-VEGF effect or a profound tumor response. The other issue that has been frequently discussed involves determining the unique predisposing aspects of the squamous cell tumor population. We know that the squamous cell population tends to have more centrally located tumors and perhaps more bulky central tumors that are associated with increased local invasion.

A patient with a central, bulky adenocarcinoma that appears similar radiographically to a squamous cell tumor may have the same risk of bleeding as those with squamous cell tumors. I'm not convinced that increased bleeding complications relate to histology; rather, the anatomical location of tumors may play an important role.

3.2 Results of a Phase I/II Trial of Erlotinib Plus Bevacizumab in Patients with Nonsquamous, IIIB/IV NSCLC Who Had Prior Chemotherapy

"Forty patients were enrolled and treated in this study (34 patients at phase II dose); the median age was 59 years (range, 36 to 72 years), 21 were female, 30 had adenocarcinoma histology, nine were never-smokers, and 22 had ≥ two prior regimens (three patients had ≥ four prior regimens). The most common adverse events were mild to moderate rash, diarrhea, and proteinuria. Preliminary data showed no pharmacokinetic interaction between A T. Eight patients (20.0%; 95% CI, 7.6% to 32.4%) had partial responses and 26 (65.0%; 95% CI, 50.2% to 79.8%) had stable disease as their best response. The median overall survival for the 34 patients treated at the phase II dose was 12.6 months, with progression-free survival of 6.2 months."

A = bevacizumab; T = erlotinib

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**

Combining bevacizumab with erlotinib

The concept of using two targeted agents, such as anti-EGFR and anti-VEGF agents, is intriguing. Over the past year, the BR21 data have validated the EGFR pathway as significant and therapeutic (Shepherd 2004). The angiogenesis pathway has also emerged as an important pathway in lung cancer. Therefore, targeting both pathways makes sense.

Drs Sandler and Herbst reported interesting Phase I/II data that described a 20 percent response rate and favorable survival outcomes among patients who received erlotinib and bevacizumab (Herbst 2005; [3.2]). Once again, the caveat was that the study group was comprised of a select group of patients with nonsquamous cell tumors and no brain metastases. Both bevacizumab and erlotinib may be administered at full doses. Grade III or IV toxicities were not observed using erlotinib plus bevacizumab.

If bevacizumab is used following chemotherapy in the first-line setting, one might argue that it would be appropriate to add erlotinib, which is FDA approved in the second-line setting. By initiating this regimen soon after chemotherapy, you may be instituting your second-line therapy earlier. This should be studied to compare the value of earlier therapy versus delayed treatment in the second-line setting. Another question is: In a patient receiving maintenance bevacizumab,

should bevacizumab be discontinued, or should erlotinib be added to the bevacizumab upon disease progression?

Combining bevacizumab with different chemotherapy regimens

It is not known whether the benefits of bevacizumab are restricted to the treatment regimen used in E4599. I don't believe one standard therapy exists; there are probably three to five reasonable platinum-based doublets. However, we should evaluate safety data from Phase I/II trials before combining bevacizumab with other regimens.

Another issue is determining which treatment to utilize in patients progressing after first-line platinum-based therapy. Typically, in the second-line setting, my cytotoxic drug of choice is pemetrexed. However, it is unknown if bevacizumab should be combined with pemetrexed or if bevacizumab will work as well in the second-line setting or beyond. Ongoing exploratory, randomized Phase II trials in the second-line setting are evaluating the use of bevacizumab with pemetrexed. The magnitude of benefit is difficult to estimate, but I believe the benefit of bevacizumab in the second-line setting will be similar to that observed in the first-line setting.

Most likely, docetaxel and bevacizumab could be combined safely, but additional data are needed to ensure that the toxicity profile of docetaxel is not dramatically different from that of paclitaxel when used in combination. Considering the safety and efficacy data from E4599, switching from carboplatin plus docetaxel to carboplatin plus paclitaxel is an option.

Selection of chemotherapy in patients with metastatic disease and a contraindication to anti-VEGF therapy

In patients with metastatic disease who do not meet the eligibility criteria for ECOG-E4599, my approach has been to utilize a platinum-based therapy for four cycles. Depending on a patient's concerns about toxicity, I treat half of my patients with carboplatin and a taxane and the other half with carboplatin and gemcitabine in the first-line setting.

The Coalition trial (Treat 2005) was the first head-to-head comparison of carboplatin/paclitaxel versus carboplatin/gemcitabine. The survival and response outcomes were similar between those two regimens, but the toxicity profiles were different. Carboplatin/gemcitabine was associated with more bone marrow toxicity (anemia, neutropenia and thrombocytopenia), while carboplatin/paclitaxel had more nonhematologic toxicity, particularly neuropathy and alopecia.

I've been using carboplatin/paclitaxel for a long time, and that's typically what I use outside of a clinical trial. My use of carboplatin/docetaxel has mostly been restricted to use in clinical trials, but I believe carboplatin/docetaxel is a reasonable regimen.

Role of adjuvant erlotinib in patients with an EGFR mutation

In Stage III disease, a compelling argument can be made to use erlotinib as adjuvant therapy following chemotherapy in patients with known genetic mutations. However, the duration of therapy, the duration of response and the true magnitude of benefit are unknown in this setting. Although select patients, such as those with genetic mutations, are more sensitive to oral tyrosine kinase inhibitors, not all patients with genetic mutations are sensitive to these agents. Due to the lack of data, one must make the best clinical judgment.

I would not administer erlotinib alone as adjuvant therapy in a patient with a known genetic mutation, as the standard is platinum-based doublet therapy for three or four cycles. However, based on current data, I would talk to the patient about the potential benefits of receiving sequential erlotinib. Because most patients who relapse after lung cancer surgery do so within two to three years, I would probably limit treatment to three years, when the patient is at the highest risk for disease recurrence.

3.3 Studies of Adjuvant Chemotherapy versus Observation in NSCLC (2003-2005)

	IALT[1] (ASCO 2003)	JBR.10[2] (ASCO 2004)	CALGB-9633[3] (ASCO 2004)	ANITA[4] (ASCO 2005)
N	1,867	482	344	840
Stage	I, II & III	IB & II	IB	I, II & IIIA
Therapy	Cis-based Some RT	Cis/vinorelbine No RT	Carbo/paclitaxel No RT	Cis/vinorelbine Some RT
Five-year RFS	39.4% vs 34.3%	61% vs 49%	61% vs 50%*	Not reported
Five-year OS	44.5% vs 40.4%	69% vs 54%	71% vs 59%*	51.2% vs 42.6%

RFS = relapse-free survival; OS = overall survival; RT = radiation therapy
* Four-year RFS and OS

SOURCES: [1] 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

[2] Winton T et al; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. **Vinorelbine plus cisplatin vs observation in resected non-small-cell lung cancer.** *N Engl J Med* 2005;352(25):2589-97. Abstract

[3] 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.** Presentation. ASCO 2004;Abstract 7019.

[4] Douillard J et al. **ANITA: A prospective randomized study of adjuvant chemotherapy with vinorelbine + cisplatin in completely resected non small cell lung cancer (on behalf of the Adjuvant Navelbine International Trialist Association).** Presentation. ASCO 2005;Abstract 7013.

ANITA trial

The Adjuvant Navelbine International Trialist Association (ANITA) results presented at the 2005 ASCO meeting were similar to those of the NCIC CTG

BR10 study and confirmed the survival data presented by the Canadian group at ASCO 2004 and data from CALGB-9633, which showed a clear survival benefit associated with adjuvant treatment (Douillard 2005; [3.3]). Both ANITA and BR10 studied the same regimen, and the magnitude of benefit was roughly the same. The ANITA trial included patients with Stage IB through IIIA disease, whereas the Canadian study did not include patients with Stage IIIA disease.

ANITA is the fourth straight large adjuvant trial to show a clear survival benefit in resected NSCLC. I believe the book is closed on this, and we can begin debating the optimal adjuvant strategy.

Chemoradiation versus chemoradiotherapy followed by surgery

At ASCO, Kathy Albain updated the Intergroup trial 0139 evaluating chemoradiotherapy versus chemoradiotherapy followed by surgery (Albain 2005; [3.4]). The bottom line from that trial is not different than it was a year or two ago: Survival is the same on both arms. An advantage in progression-free survival seems to exist for the surgical arm, but that does not translate into a survival advantage.

The one observation they've refined somewhat is the risk that patients who require a pneumonectomy are undertaking. The "punch line" from that trial is that if a pneumonectomy is required, surgery is probably not the right thing to do in this population.

The subsequent trial that will be done by the Intergroup will take a more select group of patients, probably those with less bulky IIIA disease and good staging (3.5). The trial will evaluate chemotherapy followed by surgery versus chemotherapy/radiation induction followed by surgery. On the chemotherapy-alone arm, it will be cisplatin and docetaxel for two or three cycles, while on the chemoradiotherapy arm, they will use cisplatin and docetaxel at attenuated doses in order to administer it with radiation therapy. After surgery, patients are supposed to receive three cycles of docetaxel.

3.4 INT 0139/RTOG 9309 Survival Endpoints

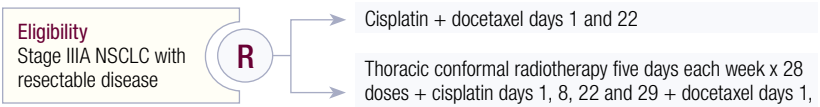
Endpoint	CT + RT + S	CT + RT
Progression-free survival*		
Median	12.8 months	10.5 months
Five-year (±95% CI)	22.4% (±6%)	11.1% (±5%)
Overall survival*		
Median	23.6 months	22.2 months
Five-year (±95% CI)	27.2% (±6%)	20.3% (±6%)

* Crossing survival curves due to treatment-related deaths, 96 (24.2%) alive/censored
CT = chemotherapy; RT = radiotherapy; S = surgical resection

SOURCE: Albain KS et al. **Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) versus CT/RT followed by surgical resection for stage IIIA (pN2) NSCLC. Outcomes update of North American Intergroup trial 0139 (R9309).** Presentation. ASCO 2005;**Abstract 7014**.

3.5 Cisplatin and Docetaxel with or without Radiation Therapy in Treating Patients Who Are Undergoing Surgery for Newly Diagnosed Stage III Non-Small Cell Lung Cancer

Protocol IDs: RTOG-0412, NCT00113386, SWOG-S0332
Accrual: 574 (Open)



Surgery
Within four to eight weeks after completion of induction therapy, patients with stable disease or better undergo a lobectomy or pneumonectomy with a formal systematic mediastinal lymph node dissection.

Consolidation therapy
Beginning four to six weeks after surgery, patients receive docetaxel IV over one hour on days 1, 22 and 43 and pegfilgrastim subcutaneously on days 2, 23 and 44.

Study Contacts:

Maria Werner-Wasik, MD, PI	Howard West, MD, PI
Radiation Therapy Oncology Group	Southwest Oncology Group
Tel: 215-955-7679; 800-533-3669	Tel: 206-386-2882

SOURCE: NCI Physician Data Query, July 2005.

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. **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**

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 LBA4**.

Schiller JH et al; Eastern Cooperative Oncology Group. **Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.** *N Engl J Med* 2002;346(2):92-8. **Abstract**

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.** Presentation. ASCO 2004;**Abstract 7022**.

Treat J et al. **A randomized phase III trial of gemcitabine (G) in combination with carboplatin (C) or paclitaxel (P) versus paclitaxel plus carboplatin in advanced (Stage IIIB, IV) Non-Small Cell Lung Cancer (NSCLC): Update of the Alpha Oncology trial (A1-99002L).** *Proc ASCO* 2005;**Abstract LBA7025**.

Hemorrhagic complications in E4599

The big news from ASCO this year is that in ECOG-E4599, bevacizumab prolongs median survival by about two months when added to carboplatin/paclitaxel (Sandler 2005). Attempts to create a triplet drug combination have been a big frustration in thoracic oncology for years.

These are modest improvements, but they are a step up. Based on this information, people will and should use the combination. The main concern, which might be overstated, is bleeding.

However, in E4599, the numbers were four percent for bleeding and one percent for death related to bleeding (Sandler 2005). These numbers are small, so I'm not too concerned.

From time to time in the clinic, we have patients who die by exsanguination. It's rare, but it happens, and we don't know if the bleeding in E4599 is a manifestation of tumor response. It probably is because it tends to occur more in tumors that are necrotic. By disturbing the vascularity in those tumors, they bleed more. I cannot tell you that spontaneous bleeding occurs more often in patients with squamous cell cancer; however, it certainly happens more often in patients with central tumors — those close to the bronchus — than when a tumor is in the parenchyma, because the parenchyma contains the bleeding.

We will learn how to handle the toxicity associated with bevacizumab. I'm driven more by efficacy, and the toxicity is manageable. Obviously, we should also be evaluating — and we've started seeing data — which groups of patients may benefit the most.

From the analysis, it seems that males derive more benefit than females, which is intriguing (Sandler 2005). I don't think it will turn out to be true because in patients with breast cancer, bevacizumab works well.

Comparing the ISEL and CAN-NCIC-BR21 trials

I believe gefitinib is underdosed, and that's probably why the ISEL trial failed (4.1). The incidence of rash was 35 percent (Carroll 2004) in the ISEL

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trial and 75 percent in CAN-NCIC-BR21 (Shepherd 2004). For the extremely sensitive mutated tumor that's going to respond, dose doesn't make a difference. But for the older male patient with squamous cell carcinoma and a poor performance status, the tumor is sensitive to dose. Those are the patients in whom you must maximize the dose to block as many of the receptors as possible.

4.1 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	0.70	<0.001
Progression-free survival	2.2 months	1.8 months	0.61	<0.001

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

[2] **Gefitinib (Iressa™) lung cancer ISEL trial shows no overall survival advantage in a highly refractory population.** AstraZeneca press release, 17 December 2004. **http://www.astrazeneca.com/pressrelease/4245.aspx**

[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**

Adjuvant therapy for nonsmokers or patients with EGFR gene mutations

I would bring up the issue of adjuvant erlotinib with these patients. I tend to be liberal in terms of how to use therapies. Patients have the right to make choices, not just based on randomized trials but rather on emerging evidence. If I were a patient, I would pick the latest treatment that looks promising. I don't need a randomized study to accept a therapy, particularly if I know the risk is low. Obviously, if a risk of death existed, I would think twice. So I would discuss adjuvant erlotinib with any patient who is young with children, female, a nonsmoker and has adenocarcinoma that is being resected.

I would explain to the patient that adjuvant chemotherapy has been shown to work, and I would do an EGFR gene mutation analysis. If it were positive, maintenance erlotinib would be reasonable after adjuvant chemotherapy, based on our current knowledge. I would probably use maintenance erlotinib for six months or one year. It would be completely intuitive medicine, and you cannot

practice that way unless the patient understands exactly what you are doing. If the patient does not and is skeptical, I wouldn't push. If I'm not comfortable that the patient understands, I would use the standard of care.

Predictors of response and survival with erlotinib

In CAN-NCIC-BR21, out of roughly 700 patients, one third received placebo and two thirds received erlotinib. Dr Tsao presented data at ASCO 2005 from approximately 160 samples obtained from that study. They found that approximately 20 percent of the samples had EGFR gene mutations. However, half of those mutations were the ones reported by the Harvard group, and the other half were new ones that no one has described (Tsao 2005). We don't know if they were sensitizing mutations or if it might have been the result of technological problems. The frequency of the mutations was more or less what we would have expected, but half of them were strange mutations.

Based on the data from the Harvard and Memorial groups, you would expect at least a 60 percent response rate for the patients with the EGFR gene mutation, and the response rate was 16 percent (Tsao 2005). The study also evaluated the survival of patients with the mutated EGFR gene, and erlotinib had no impact on survival in those patients (Tsao 2005). That's the bad news, which leaves us with the question, should we send tumors for mutation testing? Maybe not. If the patient has all the clinical characteristics, you already have a sense of the probability of response.

In the same study, the amplification of the EGFR gene by FISH was evaluated. They found clearly that if the patient had an amplified EGFR gene, the chance of response and survival was much better. The hazard ratio for survival was 0.4 for the patients with amplified EGFR genes. That was as strong as the results for the nonsmoking patients in that trial. Nonsmoking status was number one clinically, and now EGFR gene amplification is number one pathologically — both with a 0.4 hazard ratio (Tsao 2005). No data were reported on nonsmokers with EGFR gene amplification. That hazard ratio may be even lower.

Rash and response to the EGFR tyrosine kinase inhibitors

The lack of rash at 30 days is another negative predictor of response to the EGFR tyrosine kinase inhibitors. I have always been "the rash person." I'm a strong believer that rash is correlated with survival. If a patient doesn't develop a rash after 30 days of erlotinib at full doses, the curves show their median survival is about two months (Perez-Soler 2004; [4.2]).

The lack of rash always indicates you've selected a group of patients who do poorly. If I don't see any rash at 30 days, I use a higher dose. I start with a dose of 150 mg of erlotinib and at one month, if the patient does not have a rash or diarrhea, I escalate the dose to 200 mg. I've done it up to 250 mg. If I don't see any rash with a higher dose, I start to think I'm wasting time.

4.2 Grade of Rash Is Related to Survival of Patients Treated with Erlotinib

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

"The median time to the first occurrence of rash, regardless of severity, was 10 days (range, 2 to 44 days), whereas the median duration of erlotinib exposure was 9 weeks (range, 2 to 131 weeks). Therefore, it is unlikely that the relationship between rash and increased survival can be explained simply by longer exposure to erlotinib. However, to investigate this possibility, we performed an additional multivariate analysis in which rash, regardless of severity, was included as a time-dependent variable, and cumulative dose of erlotinib was included...

"Rash continued to be a significant predictor of survival, with a hazard ratio of 0.24 (95% CI, 0.10 to 0.56)... ."

SOURCE: Perez-Soler R et al. *J Clin Oncol* 2004;22(16):3238-47. **Abstract**

Select publications

Carroll K et al. **Trial 709. The ISEL study (Iressa® Survival Evaluation in Lung Cancer). Summary of data as of December 16, 2004.** FDA presentation. Available at **www.fda.gov/ohrms/dockets/ac/05/slides/2005-4095S2_01_02-AstraZeneca-709-Survival_files/frame.htm**. Accessed June 20, 2005.

Gefitinib (Iressa™) lung cancer ISEL trial shows no overall survival advantage in a highly refractory population. AstraZeneca press release, 17 December 2004. **http://www.astrazeneca.com/pressrelease/4245.aspx**

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**.

Pao W et al. **KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib.** *PLoS Med* 2005;2(1):e17. **Abstract**

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**

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 LBA4**.

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

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

Post-test:
Lung Cancer Update — Issue 4, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In patients with previously untreated advanced nonsquamous NSCLC, a Phase III randomized trial (ECOG-E4599) demonstrated that the addition of bevacizumab to _____ prolonged survival by about two months.
   a. Cisplatin/etoposide
   b. Cisplatin/paclitaxel
   c. Carboplatin/etoposide
   d. Carboplatin/paclitaxel
   e. None of the above

2. In ECOG-E4599, approximately _____ percent of the patients with nonsquamous NSCLC who received carboplatin/paclitaxel and bevacizumab as first-line therapy were alive at two years.
   a. 80
   b. 60
   c. 40
   d. 20

3. Which of the following were exclusionary criteria in ECOG-E4599?
   a. Squamous cell histology
   b. Brain metastases
   c. Use of anticoagulation therapy
   d. Recent hemoptysis
   e. All of the above

4. In ECOG-E4599, bevacizumab was associated with a statistically significant increase in _____.
   a. Hemorrhage
   b. Hypertension
   c. Neutropenia
   d. All of the above

5. The likelihood of an EGFR gene mutation increases as the number of pack years smoked increases.
   a. True
   b. False

6. In a Phase I/II trial combining erlotinib and bevacizumab in patients with nonsquamous, Stage IIIB/IV NSCLC who had received more than one prior chemotherapy, the response rate was 20 percent, and 65 percent of patients had stable disease.
   a. True
   b. False

7. In the subset analysis of the nonsmokers in the TRIBUTE trial, the median overall survival for patients treated with carboplatin/paclitaxel and erlotinib was prolonged compared to patients receiving carboplatin/paclitaxel alone.
   a. True
   b. False

8. Four large Phase III trials have demonstrated an improvement in overall survival associated with adjuvant chemotherapy.
   a. True
   b. False

9. In the CAN-NCIC trial BR21, patients with advanced NSCLC treated with erlotinib experienced improvements in _____.
   a. Progression-free survival
   b. Overall survival
   c. Both a and b

10. In an analysis of approximately 160 patients from the CAN-NCIC-BR21 trial, the response rate for erlotinib in patients with an EGFR gene mutation was _____.
    a. Sixty percent
    b. Sixteen percent
    c. Six percent
    d. None of the above

11. Dr Perez-Soler and colleagues demonstrated that likelihood of response, but not survival, is related to grade of rash in response to erlotinib.
    a. True
    b. False

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

Evaluation Form:
Lung Cancer Update — Issue 4, 2005

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in lung cancer treatment and incorporate these data into 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
Vincent A Miller, MD	5 4 3 2 1	5 4 3 2 1
Mark A Socinski, MD	5 4 3 2 1	5 4 3 2 1
Roman Perez-Soler, 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 4, 2005

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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:

.....

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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