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Lung Cancer™ UPDATE

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

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INTERVIEWS

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CME Certified

Lung Cancer Update
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Lung cancer is the leading cause of cancer mortality in the United States in both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been modest, and about 85 percent of patients who develop lung cancer will die from it. In addition, a sense of therapeutic nihilism has pervaded the medical community in the past. Chemotherapy, surgery and radiation therapy have had modest effects 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 — practicing medical oncologists, radiation oncologists, hematologists and hematology-oncology fellows must be well informed of these advances. To bridge the gap between research and patient care, *Lung Cancer Update* features 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 with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Formulate an evidence-based algorithm for the use of adjuvant chemotherapy in localized NSCLC.
- Develop a treatment approach incorporating neoadjuvant chemotherapy and radiation therapy for patients with Stage III NSCLC.
- Evaluate the role of prognostic and predictive factors in selecting treatment for patients in the adjuvant and metastatic settings.
- Develop an evidence-based algorithm for first-line and later-line therapies in patients with advanced NSCLC.
- Assess the emerging clinical research data and ongoing trials evaluating the future roles of novel molecular targeted agents in lung cancer.
- Counsel appropriately selected patients about the availability of ongoing clinical trials for which they may be eligible to participate.

PURPOSE OF THIS ISSUE OF *LUNG CANCER UPDATE*

The purpose of Issue 2 of *Lung Cancer Update* is to support the learning objectives by offering the perspectives of Drs Kris, Perez-Soler, Brahmer and Bonomi on the integration of emerging clinical research data into the management of lung cancer.

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INTERVIEW

Mark G Kris, MD

Dr Kris is Chief of Thoracic Oncology Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-20

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you discuss the recently published practice guidelines on adjuvant therapy developed by Cancer Care Ontario and the American Society of Clinical Oncology (Pisters 2007)?

DR KRIS: First I would like to point out the unanimity of the group in agreeing that adjuvant therapy — particularly adjuvant cisplatin-based chemotherapy — improves survival. It is important to deliver that message.

The devil is in the details. Agreement was reached that the data are strong for Stage II and Stage IIIA disease, and the guidelines represent a standard. However, in some areas the recommendations are not as strong. One of these areas is Stage IB disease — only one clinical trial specifically addressed that group (CALGB-9633), and it did not show a survival benefit (Strauss 2006).

In other adjuvant trials that did show a benefit — IALT, CAN-NCIC-BR10 and the ANITA trial — the primary endpoint was improvement in five-year survival for the entire study population. All those trials included patients with Stage IB disease, and they were all convincingly positive (Arriagada 2004; Winton 2005; Douillard 2006).

DR LOVE: How do you treat patients with Stage IB disease in your practice?

DR KRIS: I believe these patients should be offered adjuvant therapy, and I would probably offer it to patients with Stage IA disease also. Even with the new staging system, the five-year survival for these patients is such that we'd recommend adjuvant therapy if it were breast cancer.

Track 4

DR LOVE: What are your thoughts about ECOG-E1505, an ongoing trial evaluating three different types of cisplatin-based chemotherapy with or without bevacizumab?

DR KRIS: This trial evaluates cisplatin in combination with vinorelbine, gemcitabine or docetaxel, with or without bevacizumab (1.1).

We need to consider that this trial has a couple of caveats. One is our ability to administer each of those regimens. I expected that docetaxel/cisplatin might be superior because in the TAX-326 trial, that regimen showed improved survival and response over vinorelbine/cisplatin in the metastatic setting (Fossella 2003). However, we conducted two trials with the docetaxel/cisplatin regimen used in the ECOG trial, and while we thought it was a great idea, we were not able to deliver it.

The other caveat is the likelihood for greater myelosuppression when combining bevacizumab with chemotherapy, as seen in the Sandler trial, so we need to watch out for that (Sandler 2006).

Track 14

DR LOVE: What are your thoughts about nanoparticle albumin-bound (*nab*) paclitaxel in non-small cell lung cancer?

DR KRIS: The use of *nab* paclitaxel in breast cancer is fairly extensive, suggest-

ing that it is at least equivalent and probably better than paclitaxel. Additionally, it has one clear toxicity advantage, which is the lack of hypersensitivity reactions that are frightening to patients and, on rare occasions, can be lethal.

The other toxicities — alopecia, neutropenia and neurotoxicity — are comparable. To me, if good evidence of equivalence were available, with the safety advantage, *nab* paclitaxel would have an edge over the other taxanes.

1.1

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

Protocol ID: ECOG-E1505; Target Accrual: 1,500

* Patients are stratified according to type of chemotherapy, stage, histology and gender.

Eligibility

- Resection within the past six to 12 weeks
- ECOG performance status 0 to 1
- No history of CVA or TIA
- History of myocardial infarction or angina acceptable if no evidence of active disease within the past 12 months

SOURCE: NCI Physician Data Query, May 2008.

Track 16

DR LOVE: What are your thoughts about the combination of an EGFR tyrosine kinase inhibitor like erlotinib with bevacizumab?

DR KRIS: Much empirical evidence supports that approach — they are two active agents with completely different side-effect profiles and mechanisms of action. Clearly it can be done, and many combine them routinely.

DR LOVE: In what clinical scenarios are they combined?

DR KRIS: Physicians use it as second-line therapy, although that was more common before bevacizumab was widely available. The safety of combining these agents is clear in the studies that have been reported (Herbst 2007; [1.2]). We also use the combination up front for some patients who are candidates for both agents.

It makes sense, particularly for a patient who has an EGFR mutation or a high likelihood of having an EGFR mutation, such as a woman who's a never smoker. That patient has at least a 50-50 chance of having a mutation, and it makes sense to administer chemotherapy with bevacizumab and erlotinib. ■

1.2

Phase II Trial of Bevacizumab with Chemotherapy or Erlotinib Compared to Chemotherapy Alone in Recurrent or Refractory NSCLC: Efficacy Data

	Chemotherapy* alone (n = 41)	Chemotherapy* + bevacizumab (n = 40)	Bevacizumab + erlotinib (n = 39)
Progression-free survival			
Median	3.0 months	4.8 months	4.4 months
Six-month rate	21.5%	30.5%	33.6%
Hazard ratio (95% CI)	NA	0.66 (0.38 to 1.16)	0.72 (0.42 to 1.23)
Overall survival			
Median	8.6 months	12.6 months	13.7 months
One-year survival rate	33.1%	53.8%	57.4%
Hazard ratio (95% CI)	NA	0.71 (0.41 to 1.21)	0.78 (0.46 to 1.31)
Response rate			
CR/PR	12.2%	12.5%	17.9%
CR/PR/SD	39.0%	52.5%	51.3%

* Docetaxel or pemetrexed

CI = confidence interval; NA = not applicable; CR = complete response; PR = partial response; SD = stable disease

SOURCE: Herbst RS et al. *J Clin Oncol* 2007;25(30):4743-50. **Abstract**

SELECT PUBLICATIONS

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Fossella F et al. **Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group.** *J Clin Oncol* 2003;21(16):3016-24. **Abstract**

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Pisters KM et al. **Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non small-cell lung cancer guideline.** *J Clin Oncol* 2007;25(34):5506-18. **Abstract**

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50. **Abstract**

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

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

INTERVIEW

Roman Perez-Soler, MD

Dr Perez-Soler is Chairman of the Department of Oncology at the Montefiore Medical Center and is Gutman Professor of Medicine at Albert Einstein College of Medicine in Bronx, New York.

Tracks 1-19

Select Excerpts from the Interview

Tracks 1, 8

DR LOVE: What are your thoughts about the selection of a chemotherapy regimen to be combined with bevacizumab in advanced NSCLC?

DR PEREZ-SOLER: The AVAiL study results, reported at ASCO 2007, demonstrated that bevacizumab adds benefit to the cisplatin/gemcitabine chemotherapy regimen (2.1). Improvements in response rate and progression-free survival have been observed with the addition of bevacizumab (2.2).

The hazard ratios were good (Manegold 2007) but not as good as what was seen in ECOG-E4599, which evaluated the addition of bevacizumab to carboplatin/paclitaxel (Sandler 2006; [3.2, page 14]).

Initially, the premise was that bevacizumab would work independently of the chemotherapy used. I believe we are starting to learn that may not be true. Some chemotherapy regimens are better than others. For example, cisplatin/gemcitabine — which was used in AVAiL — may not be as good of a backbone as carboplatin/paclitaxel.

Some chemotherapeutic agents, particularly taxanes, are toxic to endothelial cells. They destroy blood vessels, which may help an anti-angiogenic agent and might explain why a taxane, at least in lung cancer, may be better. So it seems that a taxane-based regimen is probably a better option.

2.1

AVAiL Trial: Progression-Free Survival (PFS) with Cisplatin/Gemcitabine with or without Bevacizumab as First-Line Therapy for Patients with Advanced or Recurrent Nonsquamous NSCLC

	Median PFS	Hazard ratio	*p*-value
Cisplatin/gemcitabine + placebo	6.1 months	Reference	Reference
Cisplatin/gemcitabine + bevacizumab 7.5 mg/kg	6.7 months	0.75	0.0026
Cisplatin/gemcitabine + bevacizumab 15 mg/kg	6.5 months	0.82	0.0301

SOURCE: Manegold C et al. *Proc ASCO* 2007;**Abstract LBA7514**.

2.2

Update of the AVAiL Study: A Randomized Phase III Clinical Trial of Cisplatin/Gemcitabine with or without Bevacizumab in Patients with Advanced Nonsquamous NSCLC

"The update confirmed the clinically and statistically significant improvement in the primary endpoint of progression free survival (PFS) for the two different doses of bevacizumab studied in the trial (15 mg/kg and 7.5 mg/kg) compared to chemotherapy alone.

The study did not demonstrate a statistically significant prolongation of overall survival, a secondary endpoint, for either dose in combination with gemcitabine and cisplatin chemotherapy compared to chemotherapy alone. Median survival of patients in all arms of the study exceeded one year, longer than previously reported survival times in this indication."

SOURCE: Genentech BioOncology. Press release. April 20, 2008.

DR LOVE: What are your thoughts on bevacizumab/erlotinib?

DR PEREZ-SOLER: The data so far are encouraging. In the initial study by Roy Herbst with about 30 patients who failed at least one platinum-based regimen, the overall survival was one year with bevacizumab/erlotinib (Herbst 2005b). In CAN-NCIC-BR21, the overall survival was about eight months for that group when treated with erlotinib alone (Shepherd 2005).

In the study by Fehrenbacher, bevacizumab added benefit to erlotinib (Herbst 2007; [1.2, page 6]). The good news was that this combination of two nonchemotherapeutic agents — bevacizumab and erlotinib — was superior to single-agent chemotherapy (docetaxel or pemetrexed).

Bevacizumab also added benefit to single-agent docetaxel or pemetrexed, so you could also combine pemetrexed or docetaxel with bevacizumab as second-line therapy for a better regimen (Herbst 2007).

However, the key issue is that patients who receive bevacizumab will receive it as front-line therapy. Once their disease has progressed, who will have the guts to keep pushing bevacizumab without data?

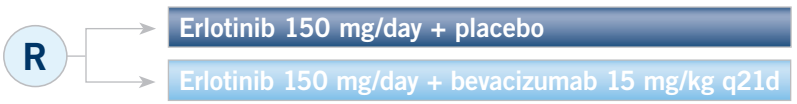
The BeTa trial, comparing erlotinib to erlotinib/bevacizumab, is being conducted only with patients who have never received bevacizumab as front-line therapy (2.3). It will probably be positive for the combination, but then the question will be how relevant this study is in practice because none of the patients in the trial received bevacizumab as front-line therapy.

I believe many people will conclude that it doesn't mean anything. We need to determine whether bevacizumab is a good drug as second-line therapy for patients who have received bevacizumab as front-line therapy.

2.3

BeTa: A Phase III Placebo-Controlled Randomized Study of Erlotinib with or without Bevacizumab as Second-Line Therapy for Advanced Nonsquamous NSCLC

Protocol IDs: OSI3364g, NCT00130728
Target Accrual: 650 (Open)



Eligibility

- Nonsquamous NSCLC with clinical or radiographic progression during or after first-line chemotherapy or chemoradiation therapy
- No prior therapy with an EGFR inhibitor or anti-angiogenesis agent

SOURCES: NCI Physician Data Query, March 2008; Gridelli C et al. *Oncologist* 2007;12(10):1183-93. **Abstract**

Tracks 12-13

DR LOVE: Can you review the RADIANT study?

DR PEREZ-SOLER: RADIANT is evaluating adjuvant chemotherapy followed by erlotinib administered for two years (2.4). It selects patients with EGFR-positive disease as determined by IHC or FISH.

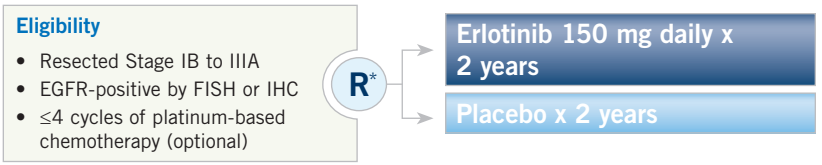
The RADIANT trial is a good study for any patient who clearly has EGFR-positive disease. The issue will be whether a patient can receive erlotinib for two years — if that would be tolerable.

I believe it will be tolerable for most patients. The first two months may be rough, but after two months of erlotinib, the majority will find that the toxicity subsides and the skin rash improves. A minority will need a dose reduction or will not be able to tolerate the drug.

2.4

RADIANT: A Phase III Study of Erlotinib or Placebo with or without Adjuvant Chemotherapy for Patients with Resected, EGFR-Positive NSCLC

Protocol IDs: OSI-774-302, NCT00373425
Target accrual: 945 (Open)



* Stratified by histology (squamous versus other), gender, age, EGFR status, smoking status and adjuvant chemotherapy

SOURCES: NCI Physician Data Query, April 2008; Wakelee H et al. *Oncologist* 2007;12(3):331-7. **Abstract**

Track 15

DR LOVE: Can you discuss the INTEREST study comparing gefitinib to docetaxel as second-line therapy?

DR PEREZ-SOLER: The trial met the noninferiority criteria (2.5) in that the curves were the same. The most interesting finding was that all the subsets that traditionally had been identified as good candidates for an EGFR inhibitor were also good candidates for docetaxel, as the nonsmokers and those with FISH-positive disease fared equally well with docetaxel as they had with gefitinib (Douillard 2007). ■

2.5

INTEREST: Gefitinib versus Docetaxel in Platinum-Treated Non-Small Cell Lung Cancer

Efficacy endpoints	Gefitinib (n = 723)	Docetaxel (n = 710)	HR (96% CI)
Events	593 (82%)	576 (81.1%)	1.02 (0.91-1.15)
Median overall survival	7.6mo	8.0mo	—
One-year survival	32%	34%	—
Treatment-related adverse event (AE) summary			
Grade III/IV AEs	8.5%	40.7%	—
Serious AEs	3.8%	18.2%	—
Deaths caused by AEs	0.8%	2.1%	—
Study discontinuations caused by AEs	4.1%	10.9%	—

HR = hazard ratio; CI = confidence interval

SOURCE: Douillard J-Y et al. *Proc 12th World Conference on Lung Cancer* 2007;**Abstract PRS-02**.

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Douillard J-Y et al. **Gefitinib (IRESSA) versus docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer pre-treated with platinum-based chemotherapy: A randomized, open-label Phase III study (INTEREST).** *Proc 12th World Conference on Lung Cancer* 2007;**Abstract PRS-02**.

Gridelli C et al. **The role of bevacizumab in the treatment of non-small cell lung cancer: Current indications and future developments.** *Oncologist* 2007;12(10):1183-93. **Abstract**

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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* 2005b;23(11):2544-55. **Abstract**

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

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50. **Abstract**

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

Wakelee H et al. **Optimal adjuvant therapy for non-small cell lung cancer — How to handle stage I disease.** *Oncologist* 2007;12(3):331-7. **Abstract**

INTERVIEW

Julie R Brahmer, MD

Dr Brahmer is Assistant Professor of Oncology at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland.

Tracks 1-13

Select Excerpts from the Interview

Track 1

DR LOVE: Can you comment on predictors of response to EGFR TKIs?

DR BRAHMER: Some investigators believe that EGFR mutations are the major predictors of response, while others believe that EGFR gene expression, as measured by FISH, determines benefit from tyrosine kinase inhibitors. We know that patients treated with EGFR inhibitors will respond better if they have an EGFR mutation, but will they live longer? The large Canadian trial CAN-NCIC-BR21, which evaluated erlotinib versus placebo, retrospectively addressed this issue, and patients with EGFR mutations did not live any longer than those without the mutation when treated with erlotinib (Shepherd 2007).

However, patients treated with erlotinib who had increased EGFR gene expression as determined by FISH did live longer (Shepherd 2007). Data from

the INTEREST study, evaluating gefitinib versus docetaxel, may reverse those findings (Douillard 2007).

The first-line trials evaluating erlotinib in patients with EGFR mutations will answer whether we should move erlotinib to the first-line setting for those patients. I don't believe the mutations will indicate whether a patient will live longer with erlotinib versus another treatment, but those patients with EGFR mutations probably need erlotinib up front rather than chemotherapy.

Track 4

DR LOVE: Can you discuss the data in NSCLC with vandetanib, which targets both the EGFR and VEGF pathways?

DR BRAHMER: Dr John Heymach from MD Anderson has led much of the research on this agent and has presented interesting data combining chemotherapy and vandetanib. Vandetanib is both an anti-angiogenic and an inhibitor of EGFR, depending on the dose. Vandetanib at 100 milligrams per day has both anti-EGFR and anti-VEGF activity.

The higher dose of 300 milligrams per day — at least when combined with chemotherapy — did not improve progression-free survival (Heymach 2007b; [3.1]). These findings have led to a large Phase III trial, which will be evaluating vandetanib at 100 milligrams per day with chemotherapy versus chemotherapy alone as second-line therapy.

3.1

Randomized Phase II Study of Carboplatin/Paclitaxel (CP) with or without Vandetanib (300 Mg/Day) as First-Line Treatment for Patients with Advanced NSCLC

	Vandetanib + CP (n = 56)	CP (n = 52)
Median progression-free survival	24 weeks	23.1 weeks
Men	18.7 weeks	23.1 weeks
Women	28.6 weeks	11.7 weeks
Median overall survival	10.2 months	11.9 months
Men	8.9 months	13.0 months
Women	≥8.6 months	5.8 months

SOURCE: Heymach J et al. *Proc ASCO* 2007b;**Abstract 7544**.

Tracks 6, 8

DR LOVE: Can you provide an update on the ECOG-E4599 trial, which evaluated bevacizumab in advanced NSCLC (Sandler 2006)?

DR BRAHMER: Patients with nonsquamous cell metastatic NSCLC were randomly assigned to first-line therapy with carboplatin/paclitaxel with or

without bevacizumab at 15 mg/kg. The patients treated with carboplatin/paclitaxel/bevacizumab experienced a significant improvement in overall survival compared to those who received chemotherapy alone (Sandler 2006; [3.2]).

However, in this study, elderly patients who were treated with chemotherapy and bevacizumab experienced increased toxicities with no improvement in survival compared to those treated with chemotherapy alone. For patients who are more prone to complications because of a drop in blood counts or any sign that they might be prone to bleeding, I would avoid using the three-drug regimen, not particularly because of age but certainly because of comorbidities, lower physical activity and the potential for bleeding.

DR LOVE: If you see a patient in his or her seventies who otherwise meets the criteria for E4599, do you have any hesitation about using bevacizumab?

DR BRAHMER: Absolutely not. I'd have more hesitation if they were in their fifties and had a history of active coronary artery disease or even leg claudication. I'd be more worried about those patients than the active 70-year-old with no other health problems. ■

3.2

ECOG-E4599: Efficacy of the Addition of Bevacizumab (B) to Paclitaxel (P) and Carboplatin (C) in Previously Untreated Metastatic Nonsquamous NSCLC

Endpoint	PC (n = 433)	PCB (n = 417)	HR (95% CI)	*p*-value
Median OS	10.3 months	12.3 months	0.79 (0.67-0.92)	0.003
Two-year OS	15%	23%	—	—
Median PFS	4.5 months	6.2 months	0.66 (0.57-0.77)	<0.001
Overall response	15%	35%	—	<0.001

HR = hazard ratio; CI = confidence interval; OS = overall survival; PFS = progression-free survival

SOURCE: Sandler A et al. *N Engl J Med* 2006;355(24):2542-50. **Abstract**

SELECT PUBLICATIONS

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Heymach JV et al. **Randomized, placebo-controlled Phase II study of vandetanib plus docetaxel in previously treated non-small-cell lung cancer.** *J Clin Oncol* 2007a;25(27):4270-7. **Abstract**

Heymach J et al. **Randomized phase II study of vandetanib (VAN) alone or in combination with carboplatin and paclitaxel (CP) as first-line treatment for advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2007b;**Abstract 7544**.

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50. **Abstract**

Shepherd FA et al. **Updated molecular analyses of exons 19 and 21 of the epidermal growth factor receptor (EGFR) gene and codons 12 and 13 of the KRAS gene in non-small cell lung cancer (NSCLC) patients treated with erlotinib in National Cancer Institute of Canada.** *Proc ASCO* 2007;**Abstract 7571**.

INTERVIEW

Philip Bonomi, MD

Dr Bonomi is Director of the Division of Hematology/Oncology and is Alice Pirie Wirtz Professor of Medicine at Rush University Medical Center in Chicago, Illinois.

Tracks 1-8

Select Excerpts from the Interview

Track 1

DR LOVE: Can you describe the recent results of the trial evaluating cisplatin with either pemetrexed or gemcitabine in advanced disease?

DR BONOMI: As we move forward, chemotherapy will be used in different, more targeted fashions as was seen in the Phase III randomized study of pemetrexed/cisplatin versus gemcitabine/cisplatin.

This was a 1,700-patient study, of which approximately 1,200 patients had a nonsquamous cell diagnosis. A subset analysis of patients with adenocarcinomas and large cell histology reported significantly longer overall survival with pemetrexed versus gemcitabine (Scagliotti 2007; [4.1]).

It has always been said that histology doesn't make any difference to the effectiveness of chemotherapy in relation to response or survival. These results flew in the face of convention and made everybody say, "Wait a minute." Many people remain skeptical, but increasing data will suggest that pemetrexed works better in adenocarcinoma.

The hazard ratio was approximately 0.8, which wasn't a home run. However, without doing anything differently except selecting the patients, there seems to be an advantage with pemetrexed (Hanauske 2007).

Treatment of Stage IV disease has always been about trying to relieve symptoms and prolong life. It is a testing ground for new ideas that we hope to move into earlier-stage disease — locally advanced disease and ultimately into the adjuvant setting — which we hope will translate into longer survival.

4.1 **Randomized Phase III Trial of Cisplatin and Pemetrexed versus Cisplatin and Gemcitabine in Locally Advanced or Metastatic NSCLC: Efficacy Data**

	Cisplatin + pemetrexed (n = 862)	Cisplatin + gemcitabine (n = 863)	Adjusted HR (95% CI)
Median overall survival (OS)	10.3 months	10.3 months	0.94 (0.84-1.05)
OS subset analysis*	11.8 months	10.4 months	0.81 (0.70-0.94)
Median progression-free survival (PFS)	4.8 months	5.1 months	1.04 (0.94-1.15)
PFS subset analysis*	5.3 months	4.7 months	0.90 (0.79-1.02)

* Patients with adenocarcinoma or large cell carcinoma; CP n = 512; CG n = 488

HR = hazard ratio; CI = confidence interval; CP = cisplatin + pemetrexed; CG = cisplatin + gemcitabine

SOURCE: Scagliotti G et al. *Proc IASLC* 2007;**Abstract PRS-03**.

Track 2

DR LOVE: About what fraction of patients with extensive NSCLC meet the entry criteria for the trials evaluating bevacizumab?

DR BONOMI: ECOG-E4599 reported longer progression-free survival with chemotherapy and bevacizumab versus chemotherapy alone (Sandler 2006). The most important consideration, however, is the current exclusion criteria. We don't use bevacizumab to treat patients with brain metastases, squamous cell carcinoma, hemoptysis or those on anticoagulation.

My impression, though, is that only 35 or 40 percent of the people who walk through your door with Stage IV disease meet these criteria. However, this might change because current studies are evaluating bevacizumab in patients with brain metastasis.

And although improvements were modest on ECOG-E4599, we are now moving into the adjuvant setting with the ongoing ECOG-E1505 Intergroup study of postoperative chemotherapy with or without bevacizumab (1.1, page 5).

On that study, we do not have as many exclusions, and the issue is whether or not bevacizumab will have a greater impact in the treatment of early-stage disease.

Track 3

DR LOVE: What's your treatment algorithm for patients with advanced NSCLC who are nonsmokers or who have EGFR mutations?

DR BONOMI: We don't know the answer yet, but I and many other people would treat such patients with an EGFR TKI first, then proceed to chemotherapy later. I wouldn't administer them together, although some clinicians would consider using the combination.

I would treat with the EGFR TKI and evaluate the response. Not all patients respond, but they have a relatively high response rate — higher than with chemotherapy.

DR LOVE: For the patient who responds, what would you do after disease progression?

DR BONOMI: I would use chemotherapy with bevacizumab, if appropriate.

DR LOVE: Have you used erlotinib with bevacizumab?

DR BONOMI: Yes. In fact, I had a patient who had a large mass in his lung, multiple nodules, PS 1.5 and extensive bone metastases.

A friend advised him to opt for erlotinib and bevacizumab with no chemotherapy, and we did that. He had an unbelievable response and went into a remission for a year and a half. ■

SELECT PUBLICATIONS

Bonomi PD et al. **Selecting patients for treatment with epidermal growth factor tyrosine kinase inhibitors.** *Clin Cancer Res* 2007;13(15 Pt 2):s4606-12. **Abstract**

Fong T et al. **EGFR inhibitors as first-line therapy in advanced non-small cell lung cancer.** *J Thorac Oncol* 2008;3(3):303-10. **Abstract**

Hanauske AR et al. **In vitro chemosensitivity of freshly explanted tumor cells to pemetrexed is correlated with target gene expression.** *Invest New Drugs* 2007;25(5):417-23. **Abstract**

Herbst RS et al. **Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer.** *J Clin Oncol* 2007;25(30):4743-50. **Abstract**

Ramalingam SS et al. **Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: Analysis of Eastern Cooperative Oncology Group Trial 4599.** *J Clin Oncol* 2008;26(1):60-5. **Abstract**

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50. **Abstract**

Scagliotti G et al. **Phase III study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaïve patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).** *Proc IASLC* 2007;**Abstract PRS-03**.

Seiwert TY et al. **A phase I dose-escalating study of combination pemetrexed-based chemotherapy and concomitant radiotherapy for locally advanced or metastatic non-small cell lung or esophageal cancer.** *Proc ASCO* 2005;**Abstract 7062**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following chemotherapy regimens are included in the ECOG-E1505 trial evaluating chemotherapy with or without bevacizumab for patients with completely resected Stage IB to IIIA NSCLC?**
   a. Vinorelbine/cisplatin
   b. Docetaxel/cisplatin
   c. Pemetrexed/cisplatin
   d. Both a and b
2. **In the randomized Phase III trial of pemetrexed/cisplatin versus gemcitabine/cisplatin, which regimen was superior in median overall and progression-free survival for patients with adenocarcinoma or large cell carcinoma?**
   a. Pemetrexed/cisplatin
   b. Gemcitabine/cisplatin
3. **The AVAiL trial demonstrated that the addition of _____ to chemotherapy as first-line therapy for NSCLC improved the response rate and progression-free survival rate.**
   a. Erlotinib
   b. Bevacizumab
   c. Cetuximab
   d. Panitumumab
4. **Vandetanib is a once-daily oral inhibitor of _____.**
   a. VEGF receptor
   b. EGFR kinase activity
   c. Both a and b
5. **The BeTa trial will compare erlotinib to erlotinib/bevacizumab as _____ for patients with advanced NSCLC.**
   a. First-line therapy
   b. Second-line therapy
   c. Third-line therapy
6. **The RADIANT study will evaluate adjuvant _____ with or without chemotherapy in patients with EGFR-positive disease.**
   a. Erlotinib
   b. Bevacizumab
   c. Cetuximab
   d. Panitumumab
7. **The INTEREST study demonstrated that _____ was equivalent to docetaxel as second-line therapy for NSCLC.**
   a. Erlotinib
   b. Gefitinib
   c. Cetuximab
   d. Pemetrexed
8. **In ECOG-E4599, the addition of bevacizumab to carboplatin/paclitaxel for patients with previously untreated metastatic nonsquamous NSCLC resulted in a significant two-month improvement in overall survival.**
   a. True
   b. False
9. **Recently published practice guidelines on adjuvant therapy developed by Cancer Care Ontario and the American Society of Clinical Oncology represent a standard for treatment of Stage II and Stage IIIA disease but not for Stage IB disease, for which recommendations are not as strong.**
   a. True
   b. False
10. **Bevacizumab administration is contra-indicated for patients with which of the following?**
    a. Brain metastases
    b. Hemoptysis
    c. Anticoagulant therapy
    d. All of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 2, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **ASCO practice guidelines for adjuvant therapy** 4 3 2 1
- **AVAiL and ECOG-E4599: Use of bevacizumab as first-line therapy** 4 3 2 1
- **Phase III trial results of cisplatin with either gemcitabine or pemetrexed for metastatic NSCLC** 4 3 2 1
- **Emerging role of EGFR inhibitors in the adjuvant and metastatic settings** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **ASCO practice guidelines for adjuvant therapy** 4 3 2 1
- **AVAiL and ECOG-E4599: Use of bevacizumab as first-line therapy** 4 3 2 1
- **Phase III trial results of cisplatin with either gemcitabine or pemetrexed for metastatic NSCLC** 4 3 2 1
- **Emerging role of EGFR inhibitors in the adjuvant and metastatic settings** 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

Please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will:

- Formulate an evidence-based algorithm for the use of adjuvant chemotherapy in localized NSCLC. ..... 4 3 2 1 N/M N/A
- Develop a treatment approach incorporating neoadjuvant chemotherapy and radiation therapy for patients with Stage III NSCLC. ..... 4 3 2 1 N/M N/A
- Evaluate the role of prognostic and predictive factors in selecting treatment for patients in the adjuvant and metastatic settings. ..... 4 3 2 1 N/M N/A
- Develop an evidence-based algorithm for first-line and later-line therapies in patients with advanced NSCLC. ..... 4 3 2 1 N/M N/A
- Assess the emerging clinical research data and ongoing trials evaluating the future roles of novel molecular targeted agents in lung cancer. ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials for which they may be eligible to participate. ..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

Additional comments about this activity:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

PART TWO — Please tell us about the faculty for this educational activity

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Faculty	Knowledge of subject matter	Effectiveness as an educator
Mark G Kris, MD	4 3 2 1	4 3 2 1
Roman Perez-Soler, MD	4 3 2 1	4 3 2 1
Julie R Brahmer, MD	4 3 2 1	4 3 2 1
Philip Bonomi, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Degree:

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

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

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

City, State, Zip:.....

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

Email:.....

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

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

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

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.LungCancerUpdate.com/CME.

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