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Lung Cancer™ UPDATE

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

EDITOR

Neil Love, MD

INTERVIEWS

Thomas J Lynch, MD

F Anthony Greco, MD

Rogerio C Lilenbaum, MD

Robert Pirker, MD

CME Certified

Lung Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

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 disease 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 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 non-small cell lung cancer (NSCLC).
- Consider the benefits and risks of induction chemotherapy and of concurrent chemoradiation therapy when devising treatment strategies for patients with Stage III NSCLC.
- Incorporate prognostic and predictive factors when utilizing EGFR-targeted therapy for patients with lung cancer.
- Utilize emerging data on the combined use of chemotherapy and biologics when making treatment decisions for the first-line and subsequent care of patients with advanced NSCLC.
- Appraise the current role of maintenance pemetrexed for patients with advanced NSCLC who respond to front-line chemotherapy.
- Recall the emerging data and ongoing trials evaluating novel targeted agents in lung cancer, and assess the implications for present and future clinical practice.
- Counsel appropriately selected patients with lung cancer about the availability of ongoing clinical trials in which they may be eligible to participate.

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INTERVIEW

Thomas J Lynch, MD

Dr Lynch is Chief of Hematology Oncology and Director of the Center for Thoracic Cancers at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-19

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss the FLEX trial that was presented by Robert Pirker at ASCO?

DR LYNCH: The FLEX study was a Phase III randomized trial for patients with advanced NSCLC, who were randomly assigned to treatment with cisplatin/vinorelbine alone or cisplatin/vinorelbine with weekly cetuximab (Pirker 2008; [1.1]). The key selection criteria in FLEX were different from those in a number of other trials. Patients were selected on the basis of positive EGFR staining by immunohistochemistry (IHC). At least one cell had to be EGFR-positive, which is a fairly liberal criterion. This excluded the approximately 15 percent of patients who did not have detectable EGFR expression.

A statistically significant difference in response rate favored cetuximab. Most importantly, survival was prolonged, with median survival increasing from approximately 10.1 months to approximately 11.3 months for patients treated with chemotherapy and cetuximab.

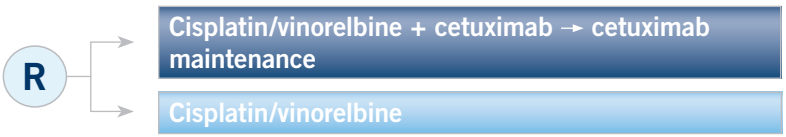
Interestingly, no difference was apparent in progression-free survival between the two arms (4.1). That was a big surprise because an expectation exists for progression-free survival to trend in the same direction as overall survival. Still, I believe this was an important but somewhat modest benefit in the first study of cetuximab in this setting.

In my podium discussion of Professor Pirker's presentation at ASCO, I raised the question of whether we should be using IHC staining. In the future, we will probably move away from that. However, right now, after a study with such a close margin of benefit, following the entrance criteria is important. I believe I'll be using IHC in my practice to exclude patients who may not benefit from cetuximab.

1.1

FLEX: A Randomized, Multicenter, Phase III Study of Cisplatin/Vinorelbine (CV) with Cetuximab versus CV Alone in the First-Line Treatment of Advanced NSCLC

Accrual: 1,125



Cetuximab 400 mg/m^2 initial dose then 250 mg/m^2 weekly

Eligibility

- Wet IIIB/IV NSCLC
- All histologic subtypes
- EGFR expression by IHC (≥1 positive tumor cell)
- ECOG PS 0/1 and 2
- No known brain metastases
- No prior chemotherapy or anti-EGFR therapy

SOURCE: Pirker R et al. *Proc ASCO* 2008;**Abstract 3**.

Tracks 3-4

DR LOVE: What are the practical clinical implications of the FLEX trial?

DR LYNCH: I believe cetuximab will be used for NSCLC. Patients and doctors want options that improve outcome. Cetuximab with chemotherapy improves outcome, similar to the way that bevacizumab with chemotherapy improves outcome. I believe we'll see bevacizumab used for bevacizumab-eligible patients and cetuximab used for patients for whom bevacizumab is not an option. Learning more about which biomarkers identify those who might benefit from therapy may broaden the group of patients who are treated with cetuximab.

DR LOVE: What are your thoughts on the risks and benefits of using cetuximab for bevacizumab-eligible patients?

DR LYNCH: I still believe bevacizumab is a good drug. American oncologists have shown a remarkable ability to use it safely. The toxicity reports on the ARIES study, a registry trial of thousands of patients who have been treated with chemotherapy and bevacizumab, are consistently better than those from either ECOG-E4599 or AVAiL (Lynch 2008; Sandler 2006; Manegold 2007). That suggests practicing physicians are selecting the right patients to treat with bevacizumab. Bevacizumab is safe and active in patients with lung cancer, so I don't think that we should give up on bevacizumab at this point.

In the subset of Caucasian patients with adenocarcinomas who were treated with cetuximab in the FLEX trial, the benefit appears to be similar to that in ECOG-E4599 (Sandler 2006). However, that's not a head-to-head comparison, so I believe one must be cautious. The real question is how we use them in combination, and that's what the SWOG-S0819 trial will evaluate.

SWOG-S0819 is currently before the NCI, and according to the current design, bevacizumab-eligible patients will be randomly assigned to carboplatin/paclitaxel and bevacizumab or carboplatin/paclitaxel and bevacizumab/cetuximab. Bevacizumab-ineligible patients will be randomly assigned to carboplatin/paclitaxel or carboplatin/paclitaxel and cetuximab. This is a confirmatory study for carboplatin/paclitaxel, but in the bevacizumab-eligible population, we'll learn whether two antibodies are better than one.

Track 12

DR LOVE: What are your thoughts on vandetanib? How does it work and where do you think it's heading clinically?

DR LYNCH: Vandetanib is another drug that's generating interest. It is a dual kinase inhibitor, inhibiting both EGF and VEGF, though I believe most of its activity comes from its VEGF inhibition. Vandetanib is being evaluated in Phase III trials in two settings: First, as monotherapy compared to erlotinib in a large trial led by Ron Natale (Study 57) and second, in a trial led by John

Heymach of docetaxel versus docetaxel/vandetanib in the second-line setting (ZODIAC).

Personally, I have confidence that the docetaxel/vandetanib trial will be positive. It's a lot to ask of vandetanib to be better than erlotinib. However, the docetaxel/vandetanib trial is exciting, and if it's positive, this could end up setting a new standard for second-line lung cancer.

Tracks 16-18

DR LOVE: Let's talk about adjuvant therapy. First, how are you approaching the decision of what chemotherapy to utilize?

DR LYNCH: As my default, I prefer cisplatin/docetaxel because it can be administered relatively easily, one day every three weeks, and it's well tolerated. We do use carboplatin-based regimens with some patients. In a real-world situation, such as when you're seeing a patient who is 76 years old, has a creatinine level of 1.7 milligrams per deciliter and perhaps had a myocardial infarction and a stroke, you will not necessarily administer cisplatin. I believe more carboplatin is being used than people may recognize.

DR LOVE: What about patients with EGFR mutations?

DR LYNCH: We are accruing to a study evaluating the role of adjuvant erlotinib for patients with EGFR mutations (NCT00567359). Fortunately, the trial's inclusion criteria are fairly liberal, and I'm encouraging all of our eligible patients to enroll. The trial involves two years of adjuvant erlotinib.

Outside the setting of a study, I believe it is permissible to consider a treatment like this. We know the response rates in this population are extraordinarily high. The issue is, we don't know what the long-term side effects are or the optimal duration of therapy. Patients develop significant rash. Many people experience loose bowels. For patients who are really benefiting, the rash will burn out. It will not stay at that same level of intensity that you find in the first two months. In advanced disease, I have patients who have been on gefitinib and erlotinib for four, five, six, seven years. ■

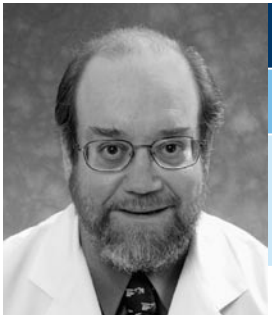
SELECT PUBLICATIONS

Lynch TJ et al. **Preliminary treatment patterns and safety outcomes for non-small cell lung cancer (NSCLC) from ARIES, a bevacizumab treatment observational cohort study (OCS).** *Proc ASCO* 2008;**Abstract 8077**.

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**.

Pirker R et al. **FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2008;**Abstract 3**.

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**



INTERVIEW

F Anthony Greco, MD

Dr Greco is Director of the Sarah Cannon Cancer Center in Nashville, Tennessee.

Tracks 1-20

Select Excerpts from the Interview

Tracks 6-7

DR LOVE: In clinical practice, how do you treat the patient with metastatic NSCLC who is a nonsmoker?

DR GRECO: I believe those patients should first receive oral tyrosine kinase drugs — the EGFR inhibitors — and I prefer erlotinib. No cure exists for these patients, and if they have an exon 19 or 21 mutation, which most of them have, the median survival is close to two years with this agent (Riely 2006).

One could argue that we should administer chemotherapy first, but I don't agree. Chemotherapy is more toxic, in general, and I'm not sure we gain anything by using it first. We need studies to determine whether we should use sequential therapies or combinations, but right now I would use erlotinib for these patients as a single drug for primary therapy.

DR LOVE: How would you treat that same population in the adjuvant setting?

DR GRECO: We have no data in the adjuvant setting, but I believe tumor cells don't care whether they're in an overt metastatic or an adjuvant setting. Micrometastatic disease is highly likely to respond to an agent like erlotinib if the mutation is present, so I would somehow incorporate erlotinib.

However, in the adjuvant setting I would not use erlotinib as a single drug because we have data suggesting that chemotherapy improves survival in this setting, for instance, in Stage IIB NSCLC. Therefore, for such patients I would use chemotherapy and then add erlotinib, probably for a year.

DR LOVE: Are you concerned about using a drug in practice that is being studied in adjuvant clinical trials but has not yet been approved in that setting?

DR GRECO: When you have a patient in front of you asking for advice, to be disciplined to the point of saying he or she must either go on study or may not receive the drug to me is like "copping out." That would be essentially not giving the patient an opinion about what to do.

One might hold the opinion that patients should not receive adjuvant erlotinib off study, but considering the data with this drug in the metastatic setting, I believe it would be inconsistent not to administer it in the adjuvant setting for micrometastatic disease. If it's proven to be harmful, then I won't use it in that setting anymore. However, I won't second-guess myself now because I don't have evidence that it will be harmful and, indeed, it might help.

Track 12

DR LOVE: Can you comment on the data with maintenance pemetrexed that were presented by Ciuleanu at ASCO?

DR GRECO: This trial evaluated pemetrexed in patients whose disease had not progressed after platinum-based induction chemotherapy. The patients were randomly assigned to receive pemetrexed or no maintenance therapy. The trial demonstrated an advantage with pemetrexed maintenance for the patients with nonsquamous cell cancer (2.1).

I found the data interesting and important considering the advanced disease trial that was presented at the International Association for the Study of Lung

Cancer in Korea in September 2007 (Scagliotti 2007). That study showed that in advanced disease, first-line pemetrexed/cisplatin was superior to gemcitabine/cisplatin for patients with nonsquamous histologies.

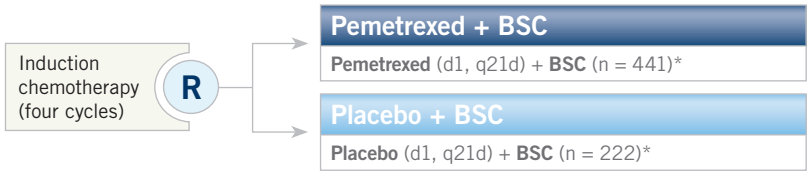
I believe pemetrexed is likely to play a major role in the treatment of nonsquamous cell cancer, as first-line therapy and perhaps as maintenance therapy as well. It might be that because we're using a better drug, we could use it in either setting and still obtain the same overall survival benefit. That's my bias.

DR LOVE: What chemotherapy regimen do you currently use for front-line therapy in your practice?

DR GRECO: I favor either gemcitabine/carboplatin or pemetrexed/carboplatin. While I do use taxanes with carboplatin, I'm using them less often now off study because of the toxicity issues.

2.1

Phase III Study of Pemetrexed with Best Supportive Care (BSC) versus Placebo with BSC for Patients with Stage IIIB/IV NSCLC without Disease Progression After Four Cycles of Platinum-Containing Induction Therapy



* B_{12}, folate and dexamethasone administered in both arms

Efficacy

Endpoint	Pemetrexed	Placebo	HR (95% CI)	*p*-value
Progression-free survival (N = 581)	4.04mo	1.97mo	0.599 (0.49-0.73)	<0.00001
Nonsquamous (n = 482)	4.37	1.84		<0.00001
Adenocarcinoma (n = 329)	4.60	2.66		<0.00001
Large cell (n = 20)	4.53	1.45		0.104
Other (n = 133)	4.11	1.58		0.0001
Squamous (n = 181)	2.43	2.50		0.896
Overall survival (N = 663)*	13.01mo	10.18mo	0.798 (0.63-1.01)	0.060
Nonsquamous (n = 482)	14.4	9.4		0.005
Adenocarcinoma (n = 329)	16.4	11.7		0.091
Large cell (n = 20)	9.1	5.5		0.154
Other (n = 133)	11.3	7.0		0.005
Squamous (n = 181)	9.6	11.9		0.231

* Preliminary data; final OS expected early 2009

HR = hazard ratio; CI = confidence interval

SOURCE: Ciuleanu T et al. *Proc ASCO* 2008;**Abstract 8011**.

Gemcitabine/carboplatin is one of my preferred chemotherapy combinations because it's as effective as other regimens and it's well tolerated. Based on the emerging data, I also like pemetrexed/carboplatin for patients with nonsquamous histologies. I believe that combination is even better tolerated than gemcitabine/carboplatin and the results are equally good, if not better, in that population.

Maintenance pemetrexed will probably increase the survival of patients with nonsquamous histologies, so I would also consider that therapy for selected patients. However, to me, what we use in the front line is probably more important, and this is evolving. Pemetrexed will likely be one of the major drugs to use with a platinum in front-line therapy for nonsquamous cancer, and it's likely to be soon.

Track 13

DR LOVE: How do paclitaxel, docetaxel and *nab* paclitaxel compare in terms of treating NSCLC?

DR GRECO: I believe the verdict is still out on *nab* paclitaxel, but it may end up being a better taxane than paclitaxel. I'm awaiting the data from the Phase III CA031 trial comparing carboplatin/*nab* paclitaxel to carboplatin/paclitaxel for patients with advanced NSCLC. *Nab* paclitaxel is easier to use and can be administered over a shorter period of time.

In breast cancer, *nab* paclitaxel clearly appears to be superior to paclitaxel, at least in the second-line setting, and maybe to docetaxel. While the verdict's not been reached on *nab* paclitaxel, I expect that before long we will see a major dip in the use of the other taxanes in lung cancer. This is my opinion, and it's partly because of the data that are emerging with the pemetrexed combinations. ■

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**

Bunn PA Jr, Thatcher N. **Systemic treatment for advanced (stage IIIb/IV) non-small cell lung cancer: More treatment options; more things to consider. Conclusion.** *Oncologist* 2008;13(Suppl 1):37-46. **Abstract**

Ciuleanu T et al. **Maintenance pemetrexed plus best supportive care (BCS) versus placebo plus BSC: A phase III study.** *Proc ASCO* 2008;**Abstract 8011**.

Riely GJ et al. **Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and 21 mutations treated with gefitinib or erlotinib.** *Clin Cancer Res* 2006;12(3 Pt 1):839-44. **Abstract**

Scagliotti GV et al. **Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer.** *J Clin Oncol* 2008;26(21):3543-51. **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) which may impact future treatment decisions.** 12th World Conference on Lung Cancer 2007;**Abstract PRS-03**.

INTERVIEW

Rogerio C Lilenbaum, MD

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

Tracks 1-12

Select Excerpts from the Interview

Track 4

DR LOVE: Can you discuss the results of the AVAiL study?

DR LILENBAUM: AVAiL was a European trial evaluating cisplatin/gemcitabine with or without bevacizumab at two different doses, 7.5 milligrams per kilogram and 15 milligrams per kilogram (Manegold 2007). There was a statistically significant difference in the study's main endpoint of progression-free survival. Although the difference in the median progression-free survival among the three arms was modest, the improvement was statistically significant. The hazard ratio wasn't as positive as the hazard ratio for the ECOG-E4599 trial (Sandler 2006).

A recent press release regarding the AVAiL study indicated that no difference appeared in overall survival (Genentech 2008), but we have yet to see the data.

We were hoping to see results at ASCO, but I believe we'll have to wait until the fall European meeting.

Track 5

DR LOVE: Bevacizumab is commonly being used in NSCLC. How do the issues of hemoptysis and pulmonary hemorrhage play out in your practice?

DR LILENBAUM: I have the sense that physicians have become more comfortable with bevacizumab. They use it in NSCLC, colorectal cancer and in breast cancer. People are aware of the pulmonary hemorrhage issue, but it doesn't seem to be an impediment the way it was when ECOG-E4599 was first presented.

The limited analysis presented by the E4599 authors at ASCO 2008 indicated a trend toward a higher rate of pulmonary hemorrhage for people with cavitation, but it wasn't statistically significant (Sandler 2008). We were dealing with small numbers overall. I believe that raises a concern, but I don't know that this means that patients who receive bevacizumab and develop cavitation within the tumor should not receive it.

I believe other issues with regard to bevacizumab have been overcome. Solid data now exist to support the use of bevacizumab for patients with brain metastases after they've received definitive treatment and are neurologically stable (Akerley 2008; [3.1]). I find that to be a significant step forward because we were excluding a large group of patients from receiving bevacizumab.

DR LOVE: Can you review the issue of anticoagulation in terms of AVAiL versus ECOG-E4599?

DR LILENBAUM: The main difference was that although patients who'd had thromboembolic phenomena were not eligible for either trial, if patients on AVAiL developed one of these complications while receiving bevacizumab, they were allowed to continue the bevacizumab with full anticoagulation. These individuals did not have significantly higher rates of pulmonary hemorrhages or bleeding complications.

3.1

Acceptable Safety of Bevacizumab in Patients with Brain Metastases Due to NSCLC — Analyses of ATLAS and PASSPORT Studies

- No symptomatic CNS hemorrhage events observed among 83 patients treated with bevacizumab at doses of 15 mg/kg q3wk
- One symptomatic CNS bleed (Grade II) observed in a patient on postprogression therapy who was treated with 14 cycles of bevacizumab

SOURCE: Akerley WL et al. *Proc ASCO* 2008;**Abstract 8043**.

Track 7

DR LOVE: What are your thoughts on the adjuvant ECOG-E1505 trial evaluating bevacizumab with chemotherapy?

DR LILENBAUM: We have five patients on this study, and we've had no major complications so far. Interestingly, I believe only one of those five patients was randomly assigned to bevacizumab, so we haven't had to deal with maintenance yet.

DR LOVE: That study allows docetaxel, vinorelbine or gemcitabine in combination with cisplatin. What are you generally using?

DR LILENBAUM: I administer either cisplatin/docetaxel, with prophylactic growth factors, or cisplatin/gemcitabine. Cisplatin/docetaxel is a once every three-week regimen, and most patients will not require a port.

The typical cisplatin/vinorelbine regimen is 12 doses and is difficult to administer without an indwelling catheter, which adds complexity and inconvenience. I'm surprised by how many lung cancer investigators and institutions have adopted the cisplatin/vinorelbine combination, although I can understand why — because of the data from the international adjuvant trials.

Track 11

DR LOVE: Would you discuss the CALGB trial in Stage III disease that you are chairing?

DR LILENBAUM: CALGB has just opened a study evaluating patients with poor-risk Stage III disease treated with induction carboplatin/*nab* paclitaxel followed by radiation therapy and erlotinib (3.2).

Nab paclitaxel is arguably a more tolerable taxane for patients susceptible to toxicity. Erlotinib is used only for the duration of the radiation therapy — it is not used for maintenance. This is a pure radiosensitizing question independent of clinical or molecular predictors.

This is a neglected subset of patients. If you examine the Stage III literature, you see that it is restricted essentially to patients with PS 0 to 1 and no significant weight loss.

This is less than five percent of patients. An enormous group of patients don't fit the eligibility for the major clinical trials, and that has led, directly or indirectly, to our current positions on combined modality therapies.

A past CALGB trial evaluating gefitinib in a small number of patients with PS 2 or greater showed promising results (Zinner 2004). A precedent exists for trying to develop a regimen for patients who are not felt to be good candidates for combined chemotherapy and radiation therapy. ■

3.2 Phase II Study of Induction Chemotherapy Comprising Carboplatin and *Nab* Paclitaxel Followed by Concurrent Thoracic Radiation Therapy and Erlotinib Hydrochloride for Patients with Poor-Risk, Unresectable Stage IIIA or IIIB NSCLC

Protocol IDs: CALGB-30605, NCT00553462
Target Accrual: 76 (Open)

Eligibility

- Histologically or cytologically confirmed NSCLC, including the following histologies: squamous cell carcinoma, adenocarcinoma, large cell anaplastic carcinoma
- Must meet the following criteria: T1-3 with N2 and selected N3*, T4 with N0, N1, N2 and selected N3*, M0 (no M1 patients)
- Must have measurable disease, defined as ≥1 unidimensionally measurable lesion ≥20 millimeters by conventional techniques or ≥10 millimeters by spiral CT scan
- Poor-risk with NCI CTC performance status (PS) 2 OR PS 0-1 and ≥10 percent weight loss within the past three months

* Patients with contralateral mediastinal disease (ie, N3) are eligible provided all gross disease can be encompassed within the radiation boost field in accordance with the homogeneity criteria.

† Induction chemotherapy comprising *nab* paclitaxel (days 1, 8 and 15) and carboplatin (day 1). Treatment repeats every 28 days for two courses. Beginning on day 57, oral erlotinib once daily and concurrent radiation therapy five days per week for up to seven weeks.

Study Contact

Rogerio Lilenbaum, MD, Protocol Chair Tel: 305-535-3323

SOURCE: NCI Physician Data Query, August 2008.

SELECT PUBLICATIONS

Akerley WL et al. **Acceptable safety of bevacizumab therapy in patients with brain metastases due to non-small cell lung cancer.** *Proc ASCO* 2008;**Abstract 8043**.

Genentech. **Update on "AVAiL" phase III study of Avastin plus chemotherapy in first-line, advanced, non-squamous, non-small cell lung cancer** [press release]. April 2008. Available at: **www.gene.com/gene/news/press-releases/display.do?method=detail&id=11207**

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 AB et al. **Retrospective study of clinical and radiographic risk factors associated with early onset, severe pulmonary hemorrhage in bevacizumab-treated patients with advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2008;**Abstract 8074**.

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**

Zinner R et al. **Compassionate use experience with gefitinib in poor performance (PS) patients with advanced non-small-cell lung cancer (NSCLC) treated in an expanded access program (EAP).** *Proc ASCO* 2004;**Abstract 7082**.

INTERVIEW

Robert Pirker, MD

Professor Pirker is Professor of Medicine in the Department of Medicine I at the Medical University of Vienna in Vienna, Austria.

Tracks 1-11

Select Excerpts from the Interview

Tracks 1-2, 4

DR LOVE: Would you discuss the FLEX study you presented at ASCO?

PROF PIRKER: This trial aimed to demonstrate superior survival for chemotherapy with cetuximab compared to chemotherapy alone in advanced NSCLC (Pirker 2008; [1.1, 4.1]).

The eligibility criteria included documented Stage IIIB disease with malignant pleural effusion or Stage IV disease. We attempted to evaluate EGFR expression by IHC in at least 100 cells from each patient. Patients with any positive EGFR expression in a tumor, as defined by positivity in one or more cells, were eligible. The assessment of EGFR expression was performed for 1,688 patients, of whom 85 percent fulfilled the criterion of at least one positive cell.

Patients with all histological subtypes were eligible. We included patients with ECOG PS 0 to 2. The other main inclusion criterion was that we did not

screen for brain metastases. In the case of known brain metastases, patients were excluded. So it was a broad patient population.

Cetuximab with chemotherapy demonstrated superior overall survival compared to chemotherapy alone, with a hazard ratio of 0.87 and a 30 percent risk reduction.

The median survival in the cetuximab arm was 11.3 months versus 10.1 months, and the one-year survival in the cetuximab/chemotherapy arm was 47 percent compared to 42 percent in the chemotherapy-alone arm for the overall population (4.1).

We did not see a significant difference in progression-free survival, however. We also analyzed time to treatment failure, and we observed a significant difference in favor of the cetuximab arm.

We conducted an exploratory subgroup analysis that indicated a benefit in all the subgroups analyzed except the Asian patients, which was a small population. The forest plot for the Asian subgroup was to the right, slightly above one, but with a broad confidence interval, so we can't make any statement from it. For all the other groups, it was to the left.

4.1

FLEX: Efficacy Analysis and Adverse Event Results

Efficacy	CV + cetuximab (n = 557)	CV (n = 568)	Hazard ratio (95% CI)	*p*-value
Overall survival (OS)	11.3mo	10.1mo	0.871 (0.762-0.996)	0.044
One-year OS	47%	42%	—	—
Caucasian subgroup (n = 946)	10.5mo	9.1mo	0.803 (0.694-0.928)	0.003
Asian subgroup (n = 121)	17.6mo	20.4mo	1.179 (0.703-1.905)	ns
Progression-free survival	4.8mo	4.8mo	0.943 (0.825-1.077)	ns
Time to treatment failure	4.2mo	3.7mo	0.860 (0.761-0.971)	0.015
Overall response rate	36%	29%	—	0.012
Grade III/IV adverse events	(n = 548)	(n = 562)	—	—
Neutropenia	53%	51%	—	—
Febrile neutropenia	22%	15%	—	—
Anemia	14%	17%	—	—
Acne-like rash	10%	<1%	—	—
Diarrhea	5%	2%	—	—
Infusion reactions	4%	<1%	—	—
Treatment-related deaths	3%	2%	—	—

CV = cisplatin/vinorelbine; CI = confidence interval; ns = not significant

SOURCE: Pirker R et al. *Proc ASCO* 2008;**Abstract 3**.

DR LOVE: What do you think about the clinical implications of this study?

PROF PIRKER: I believe that the implications are that it will become one of the standard treatments in the future, if not the standard treatment, at least in Europe. I anticipate this because of the survival advantage reported with cetuximab in such a broad population with all histological subtypes.

It's also of importance to note that a cisplatin-based protocol was used, and I believe that cisplatin-based protocols are slightly superior to carboplatin-based protocols, particularly with regard to patient survival.

The addition of cetuximab to optimal chemotherapy further improves survival. I would consider cetuximab with cisplatin-based therapy as a new standard.

DR LOVE: What about patients who would have met the eligibility criteria for the ECOG-E4599 trial of paclitaxel/carboplatin with or without bevacizumab (Sandler 2006)?

PROF PIRKER: Compared to the inclusion criteria for the ECOG trial of chemotherapy with bevacizumab, we reached the same median survival in this population of patients with adenocarcinomas.

We reported an improvement of nearly two months, from 10.3 months median in the control arm to 12 months in the chemotherapy/cetuximab arm.

In this patient population, I would use cisplatin-based chemotherapy with cetuximab, based on the data with cetuximab improving survival with a cisplatin-based protocol and based on the fact that bevacizumab did not significantly improve overall survival in the AVAiL trial (Manegold 2007). ■

SELECT PUBLICATIONS

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**.

Pirker R et al. **FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2008;**Abstract 3**.

Rosell R et al. **Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer.** *Ann Oncol* 2008;19(2):362-9. **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**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the FLEX trial, adding cetuximab to cisplatin/vinorelbine improved _____ among patients with advanced, EGFR-positive NSCLC.**
   a. Response rates
   b. Progression-free survival
   c. Overall survival
   d. Both a and b
   e. Both a and c

2. **Patients who met which of the following entry criteria were eligible for the randomized Phase III FLEX study?**
   a. Wet IIIB/IV NSCLC
   b. Any histologic subtype
   c. EGFR expression by IHC (≥1 positive tumor cell)
   d. ECOG PS 0 to 2
   e. All of the above

3. **The SWOG-S0819 trial will examine _____ in advanced NSCLC.**
   a. Carboplatin/paclitaxel
   b. Bevacizumab with or without cetuximab for bevacizumab-eligible patients
   c. Chemotherapy with or without cetuximab for bevacizumab-ineligible patients
   d. All of the above

4. **The Phase III ZODIAC trial will compare _____ as second-line treatment for NSCLC.**
   a. Erlotinib to vandetanib
   b. Docetaxel to docetaxel/vandetanib

5. **Long-term findings from IALT showed _____ among patients who received adjuvant chemotherapy for NSCLC.**
   a. Continued overall survival benefit after five years
   b. Continued disease-free survival benefit after five years
   c. An increase in noncancer deaths
   d. All of the above

6. **In a Phase III study of pemetrexed versus placebo as maintenance therapy for patients with Stage IIIB/IV NSCLC without disease progression after platinum-based induction therapy, pemetrexed _____ associated with improved survival among patients with nonsquamous histologies.**
   a. Was
   b. Was not

7. **Vandetanib is an oral inhibitor of _____.**
   a. VEGF receptor
   b. EGFR kinase activity
   c. Both a and b

8. **In the AVAiL trial, the addition of _____ to cisplatin/gemcitabine improved progression-free survival for patients with chemotherapy-naïve, advanced or recurrent NSCLC.**
   a. Bevacizumab at 2.5 milligrams per kilogram
   b. Bevacizumab at 7.5 milligrams per kilogram
   c. Bevacizumab at 15 milligrams per kilogram
   d. Both a and b
   e. Both b and c

9. **The addition of bevacizumab to paclitaxel/carboplatin in the ECOG-E4599 trial for previously untreated patients with metastatic nonsquamous NSCLC increased median overall survival by _____.**
   a. 2.0 months
   b. 4.5 months
   c. 6.0 months

10. **CALGB-30605 will evaluate induction chemotherapy of carboplatin and _____ followed by radiation therapy and oral erlotinib for patients with poor-risk, unresectable Stage IIIA or IIIB NSCLC.**
    a. Paclitaxel
    b. *Nab* paclitaxel
    c. Docetaxel

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 3, 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 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Efficacy, side effects and perspectives on the use of cetuximab in clinical practice based on the FLEX trial in advanced NSCLC 4 3 2 1
Perspectives on the earlier use of erlotinib for patients with EGFR mutations 4 3 2 1
Phase III placebo-controlled trial of maintenance pemetrexed in Stage IIIB/IV NSCLC 4 3 2 1
Perspectives on bevacizumab contraindications 4 3 2 1

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

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Efficacy, side effects and perspectives on the use of cetuximab in clinical practice based on the FLEX trial in advanced NSCLC 4 3 2 1
Perspectives on the earlier use of erlotinib for patients with EGFR mutations 4 3 2 1
Phase III placebo-controlled trial of maintenance pemetrexed in Stage IIIB/IV NSCLC 4 3 2 1
Perspectives on bevacizumab contraindications 4 3 2 1

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

☐ Yes ☐ No

If 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 be able to:

- Formulate an evidence-based algorithm for the use of adjuvant chemotherapy in localized non-small cell lung cancer (NSCLC). ..... 4 3 2 1 N/M N/A
- Consider the benefits and risks of induction chemotherapy and of concurrent chemoradiation therapy when devising treatment strategies for patients with Stage III NSCLC. ..... 4 3 2 1 N/M N/A
- Incorporate prognostic and predictive factors when utilizing EGFR-targeted therapy for patients with lung cancer. ..... 4 3 2 1 N/M N/A
- Utilize emerging data on the combined use of chemotherapy and biologics when making treatment decisions for the first-line and subsequent care of patients with advanced NSCLC. ..... 4 3 2 1 N/M N/A
- Appraise the current role of maintenance pemetrexed for patients with advanced NSCLC who respond to front-line chemotherapy. ..... 4 3 2 1 N/M N/A
- Recall the emerging data and ongoing trials evaluating novel targeted agents in lung cancer, and assess the implications for present and future clinical practice. ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with lung cancer about the availability of ongoing clinical trials in 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?

.....

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

.....

Additional comments about this activity:

.....

.....

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.

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

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Thomas J Lynch, MD	4 3 2 1	4 3 2 1
F Anthony Greco, MD	4 3 2 1	4 3 2 1
Rogerio C Lilenbaum, MD	4 3 2 1	4 3 2 1
Robert Pirker, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. 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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