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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

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 limited, and about 85 percent of patients who develop lung cancer will die from it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on patient outcomes. However, with the advent of biologic agents, recent improvements have been seen in time to progression and survival in lung cancer clinical trials. Published results from ongoing and completed studies lead to the continual emergence of novel therapeutic strategies and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with experts' perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Summarize the benefits and risks of alternative surgical approaches for patients with localized or resectable locally advanced non-small cell lung cancer (NSCLC).
- Utilize tumor characteristics and molecular biomarkers in treatment decision-making for patients with lung cancer.
- Communicate the benefits and risks of induction chemotherapy and concurrent chemoradiation therapy when devising treatment strategies for Stage III NSCLC.
- Integrate emerging data on the combined use of cytotoxics and biologics when selecting first-line therapy and subsequent care for patients with advanced NSCLC.
- Identify patients with NSCLC who are most likely to benefit from treatment with EGFR tyrosine kinase inhibitors.
- Appraise the current role of maintenance pemetrexed for patients with advanced NSCLC that responds 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

David Jablons, MD

Dr Jablons is Professor and Chief in the Division of General Thoracic Surgery and Ada Distinguished Professor and Program Leader in Thoracic Oncology at UCSF Helen Diller Family Comprehensive Cancer Center at the University of California in San Francisco, California.

Tracks 1-15

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the role of surgery in the management of Stage III NSCLC?

DR JABLONS: Stage III is probably the most confusing of all the stages of lung cancer for medical oncologists, resulting in endless debates at tumor boards.

Unfortunately, in 2005 data from a Phase III study of concurrent chemotherapy and radiation therapy with or without surgical resection for patients with Stage IIIA NSCLC were presented, and it was concluded to be a negative trial for surgery (Albain 2005; [1.1]).

However, if you carefully examined the subset analysis, you could see that surgery was beneficial, in terms of local control and survival, for patients who avoided pneumonectomy. Although it was a good trial with approximately 400 patients, I believe the conclusion was misconstrued, and as a result, many patients are not obtaining surgical opinions or undergoing surgery.

An enormous number of patients present with Stage III disease, particularly Stage IIIA, each year. Approximately 30,000 to 35,000 cases are reported annually. In centers with experienced surgeons, the morbidity and mortality of surgical resection can be reduced to one percent or less. Yet many of those patients are not offered a surgical option.

The problem is that the local failure rate with chemoradiation therapy in clinical trials is 30 to 40 percent, and when the cancer recurs a year later, surgery is all but impossible. I believe that most aggressive oncologists still feel surgery is the best local control for patients with Stage IIIA lung cancer.

Of course, I'm not suggesting surgery for patients who experience disease progression on chemoradiation therapy or patients with bulky, multistation, N2 disease. Those patients will not fare well either way, and surgery has little to offer. However, for patients with limited N2 burden and a good performance status who can get by with lobectomy, surgery can be beneficial.

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

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

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

Chemo/XRT = chemoradiation therapy; NS = not significant

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

Tracks 2-4, 8

DR LOVE: Would you discuss a patient from your practice for whom you recommended preoperative treatment?

DR JABLONS: I recently treated a 60-year-old, otherwise healthy man who had no symptoms despite a 5-cm, left upper lobe, moderately differentiated adenocarcinoma. His PET/CT scan revealed nodal involvement, and the disease was staged as T2/N2, Stage IIIA. We have ordered a brain MRI, and if it is negative, I will refer him to a medical oncologist for systemic induction chemotherapy with the goal of maximizing the radiologic response.

After two cycles, we'll restage. If he's showing a good response, he'll receive a third cycle, presuming he's tolerating it. Then we'll let him recover for three to four weeks and perform a lobectomy, which is associated with a one percent or less mortality.

DR LOVE: Which chemotherapy do you think should be used?

DR JABLONS: I believe the best regimen for this patient is a pemetrexed-based platinum regimen, probably pemetrexed/cisplatin based on clinical trial data in Stage IV disease (Shepherd 2001). Also, in the absence of brain metastases, we might administer bevacizumab preoperatively. We've done this off study with numerous patients, and they fare well. They have good response rates and proceed to surgery without complications.

Many physicians would choose to administer paclitaxel/carboplatin, which is an active regimen. Historically we have administered a lot of gemcitabine/carboplatin, which patients tolerate well. However, we now know that gemcitabine is a little better in tumors with squamous histologies.

For an adenocarcinoma, I administer either pemetrexed/carboplatin or pemetrexed/cisplatin, if the performance status is good. I believe that in the future patients with Stage IIIA disease will receive a pemetrexed-based platinum regimen with full-dose radiation therapy. These regimens are well tolerated, or better tolerated than etoposide/cisplatin, and you can use full-dose radiation therapy with pemetrexed-based platinum regimens, unlike paclitaxel/carboplatin.

Patients have an excellent chance of responding to the pemetrexed-based platinum regimens. Currently, ongoing Intergroup trials through the RTOG are evaluating these combinations with full-dose radiation therapy. ■

SELECT PUBLICATIONS

Albain KS et al. **Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309).** *Proc ASCO* 2005;**Abstract 7014**.

Cullen MH et al. **A randomized phase III trial comparing standard and high-dose pemetrexed as second-line treatment in patients with locally advanced or metastatic non-small-cell lung cancer.** *Ann Oncol* 2008;19(5):939-45. **Abstract**

Scagliotti GV et al. **Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.** *J Clin Oncol* 2008;26(21):3543-51. **Abstract**

Shepherd FA et al. **Phase II study of pemetrexed disodium, a multitargeted antifolate, and cisplatin as first-line therapy in patients with advanced nonsmall cell lung carcinoma: A study of the National Cancer Institute of Canada Clinical Trials Group.** *Cancer* 2001;92(3):595-600. **Abstract**

INTERVIEW

Gregory J Riely, MD, PhD

Dr Riely is Assistant Attending at Memorial Sloan-Kettering Cancer Center in New York, New York.

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Track 1 Clinical and molecular predictors of response to EGFR tyrosine kinase inhibitors (TKIs)

Track 2 Single-agent activity of EGFR monoclonal antibodies in NSCLC

Track 3 EGFR protein expression, gene amplification and mutation status as predictors of response to EGFR TKIs

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Select Excerpts from the Interview

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DR LOVE: Can you discuss the assays for molecular markers that have been studied for predicting response to the EGFR TKIs?

DR RIELY: A number of retrospective evaluations have been conducted of tumor sets from large randomized trials evaluating EGFR overexpression with immunohistochemistry (IHC) and FISH in addition to evaluating EGFR mutations. It's complicated, but I would break it down to an issue of sensitivity and specificity. Patients with EGFR IHC-positive tumors represent the majority of lung cancer patients, and these patients may or may not respond to EGFR TKIs. IHC does not serve as much of an enrichment for patients likely to respond to erlotinib.

Fewer patients have true FISH-positive tumors. Among unselected patients, the overall response rate with erlotinib is approximately nine percent. If you identify those patients with FISH-positive tumors, the response rate jumps significantly and is closer to 40 percent. Approximately 10 percent of patients with lung cancer have EGFR mutations, but the response rate for those tumors is closer to 80 percent (van Zandwijk 2007).

The EGFR mutation represents the most specific predictor of response to EGFR TKIs, whereas EGFR overexpression as determined by IHC and FISH describes a larger number of patients, but those patients are less likely to respond to erlotinib (Jackman 2008; Zhu 2008).

Tracks 6, 8

DR LOVE: What is your approach to treatment for a patient with an EGFR mutation in the adjuvant setting? Do you offer erlotinib?

DR RIELY: It is difficult to argue against the idea of using erlotinib — with a response rate of more than 80 percent — for a patient with an EGFR mutation. However, it's unclear whether the EGFR mutation is a predictive factor or a prognostic factor. Retrospective analyses of patients with EGFR mutations have shown that they fare relatively well after resection in comparison to those with EGFR wild-type tumors, and these patients may go on to fare better overall, whether we administer erlotinib or not.

At the same time, lung cancer is a difficult diagnosis. For a patient with early-stage resected lung cancer who has a known EGFR mutation, I explain that no data exist to demonstrate improvements in overall survival with erlotinib, but my scientific estimation is that it will.

DR LOVE: For patients with metastatic NSCLC who have the EGFR mutation, do you recommend erlotinib up front?

DR RIELY: You can make a perfectly reasonable argument to start patients with known EGFR mutations or with clinical characteristics that are likely to be associated with mutations — such as never smokers with adenocarcinomas — on erlotinib monotherapy, which is what I generally do off protocol.

Track 9

DR LOVE: Can you summarize the FLEX trial results that were presented at ASCO (2.1)?

DR RIELY: In the FLEX study, patients were randomly assigned to receive either cisplatin/vinorelbine alone or cisplatin/vinorelbine with cetuximab (Pirker 2008). Patients received cetuximab on a weekly basis, and after six cycles of chemotherapy, those patients who were on cetuximab continued it as maintenance therapy.

Approximately a one-month improvement in overall survival was observed, without a marked difference in progression-free survival, for patients treated with cetuximab. Subset analysis revealed that cetuximab was equally efficacious in squamous cell tumors and adenocarcinomas. As such, chemotherapy with cetuximab would be a reasonable choice for patients with squamous cell tumors, for which we are unable to use bevacizumab safely.

2.1 **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%	—	—
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

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

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

Tracks 12-13

DR LOVE: Do you think cetuximab has a positive risk-benefit ratio for patients with advanced squamous cell NSCLC?

DR RIELY: It's reasonable to consider cetuximab for patients with squamous cell tumors. The side effects of cetuximab are real, including the rash and the side effect that is rarely talked about, which is weekly therapy. Patients must come to the doctor's office once a week for the first six cycles of therapy, which is a burden for a patient with Stage IV NSCLC.

DR LOVE: How do you approach patients with adenocarcinomas who meet the entry criteria for ECOG-E4599, which evaluated carboplatin/paclitaxel and bevacizumab?

DR RIELY: Chemotherapy with cetuximab is an option, but carboplatin/paclitaxel and bevacizumab led to a two-month improvement in overall survival, compared to somewhat less improvement in overall survival in the FLEX trial. Therefore, it's reasonable to consider bevacizumab as probably superior, acknowledging the caveats about cross-trial comparisons. Additionally, we have much greater experience administering bevacizumab for a large number of patients.

Track 14

DR LOVE: How do you treat the patient with an EGFR mutation who responds to erlotinib and then experiences disease progression?

DR RIELY: This is an important question, to which we don't have an answer. The direct analogy is a patient with HER2-positive breast cancer who responds to trastuzumab and then develops progressive disease. The standard approach to those patients without evidence from a randomized trial is to continue trastuzumab and add chemotherapy.

We investigated this situation with a relatively small study, in which we took 10 patients with what we defined as acquired resistance to erlotinib or gefitinib (Riely 2007). Those patients had all been treated with erlotinib or gefitinib for more than six months and all had responded to therapy. If we couldn't document a response to therapy, we verified that the tumor had an EGFR mutation.

So we took this relatively select group of patients and performed scans on them. We discontinued therapy at disease progression and rescanned them. As you would expect, most of the tumors grew. FDG avidity also rose on the PET scan because disease was progressing in all cases beforehand, so it's reasonable to presume that it would continue to progress off treatment. We restarted gefitinib or erlotinib for another three weeks and then reassessed. Somewhat surprisingly, all of the tumors stabilized in their growth rate and FDG uptake on PET scan. These data suggest that these patients are continuing to benefit from erlotinib therapy, so our standard treatment is to continue erlotinib and add chemotherapy.

Track 17

DR LOVE: Can you discuss the study you were involved with evaluating nanoparticle albumin-bound (*nab*) paclitaxel in patients with previously untreated NSCLC (Rizvi 2008)?

DR RIELY: This was a Phase I/II trial. After initially identifying the maximum tolerated dose (MTD), we treated patients with the MTD of *nab*

paclitaxel on a weekly administration schedule. The response rate with single-agent *nab* paclitaxel was 30 percent, and the overall survival was acceptable for up-front treatment in NSCLC (Rizvi 2008; [2.2]).

Nab paclitaxel is clearly an effective drug, and compared to conventional taxanes, its benefits are apparent, such as the absence of hypersensitivity reactions in patients who are receiving the taxane without steroid premedication. ■

2.2

Activity of Single-Agent *Nab* Paclitaxel as Initial Chemotherapy for Patients with Stage IV NSCLC

"A total of 40 patients were treated at 125 mg/m^2. The objective response rate was 30% (12 of 40 patients; 95% CI, 16% to 44%), median time to progression was 5 months (95% CI, 3 to 8 months), and median overall survival was 11 months (95% CI, 7 months to not reached). The 1-year survival was 41%...

NAB-paclitaxel 125 mg/m^2 administered on days 1, 8, and 15 of a 28-day cycle was well tolerated and demonstrated encouraging single-agent activity. No corticosteroid premedication was administered and no hypersensitivity reactions were seen."

SOURCE: Rizvi NA et al. *J Clin Oncol* 2008;26(4):639-43. **Abstract**

SELECT PUBLICATIONS

Jackman DM et al. **Impact of EGFR and KRAS genotype on outcomes in a clinical trial registry of NSCLC patients initially treated with erlotinib or gefitinib.** *Proc ASCO* 2008;**Abstract 8035**.

Patel JD et al. **Pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for advanced non-squamous non-small cell lung cancer (NSCLC).** *Proc ASCO* 2008;**Abstract 8004**.

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**.

Riely GJ et al. **Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus.** *Clin Cancer Res* 2007;13(17):5150-5. **Abstract**

Rizvi NA et al. **Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer.** *J Clin Oncol* 2008;26(4):639-43. **Abstract**

Scagliotti GV et al. **Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.** *J Clin Oncol* 2008;26(21):3543-51. **Abstract**

Van Zandwijk N et al. **EGFR and KRAS mutations as criteria for treatment with tyrosine kinase inhibitors: Retro- and prospective observations in non-small-cell lung cancer.** *Ann Oncol* 2007;18(1):99-103. **Abstract**

Zhu CQ et al; National Cancer Institute of Canada Clinical Trials Group Study BR.21. **Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21.** *J Clin Oncol* 2008;26(26):4268-75. **Abstract**

INTERVIEW

Alan B Sandler, MD

Dr Sandler is Associate Professor of Medicine and Medical Director of Thoracic Oncology in the Division of Hematology/Oncology at Vanderbilt University Medical Center in Nashville, Tennessee.

Tracks 1-12

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the current treatment options for patients with advanced NSCLC?

DR SANDLER: We have two positive studies evaluating regimens for metastatic NSCLC in somewhat similar groups of patients (Manegold 2008; Sandler 2006), and cisplatin/vinorelbine with cetuximab is now another option (Pirker 2008; [2.1, page 8]). However, three issues need to be addressed with cetuximab. The dermatologic reaction is not a life-threatening toxicity,

but it is one that certain patients find difficult to live with. Another issue is the inconvenience of a weekly injection.

Finally, in certain parts of the country, an increased risk of anaphylactic reactions to cetuximab exists, although a recent *New England Journal of Medicine* article reported on the prospect of identifying patients who may be at risk for anaphylactic reactions (Chung 2008).

Tracks 2-4

DR LOVE: What data sets have been reported in the past year addressing chemotherapy in combination with bevacizumab?

DR SANDLER: A subset analysis of the ECOG-E4599 trial evaluated outcomes for the elderly population because one fourth of the patients on the trial were older than age 70.

A little more toxicity occurred in these older patients, which is not unexpected, but it was manageable. The response rate was better for patients treated with bevacizumab, and progression-free survival trended upward with a *p*-value close to 0.06 (Ramalingam 2008).

DR LOVE: What do we know about bevacizumab-associated hemoptysis?

DR SANDLER: We learned in the Phase II study (AVF0757g) that patients with squamous cell histology should not receive bevacizumab because of the risk of hemoptysis. We've gone back and evaluated data from various studies, including E4599, and only baseline cavitation emerged as a potential risk factor (Sandler 2008).

Interestingly, tumor size and location have not panned out as risk factors. Location may well be part of the squamous cell histology, but it's difficult to tease the two apart.

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

DR SANDLER: The AVAiL study was the European counterpart of ECOG-E4599. It used a three-arm design to evaluate cisplatin/gemcitabine with or without bevacizumab at two different doses, 7.5 mg/kg and 15 mg/kg.

Response rate and progression-free survival endpoints were met in both the bevacizumab arms. Bevacizumab did not add significant benefit to survival, although overall survival was good in all three arms (Manegold 2008; [3.1]).

DR LOVE: If someone were to say to you, "Why not use the lower dose of bevacizumab," how would you respond?

DR SANDLER: The AVAiL study is compelling. The hazard ratio for progression-free survival was 0.75 with the low dose and about 0.8 with the higher dose, but E4599 is the only study to date that shows a survival advantage, which is with the 15-mg/kg dose (3.1), so I am still administering that dose.

3.1

Efficacy of Bevacizumab (Bev) with Chemotherapy as First-Line Therapy for Patients with Advanced or Recurrent Nonsquamous NSCLC

	ECOG-E4599		AVAiL		
	PC[1]	PC + bev[1]	CG + placebo[2]	CG + bev 7.5 mg/kg[2]	CG + bev 15 mg/kg[2]
Median PFS	4.5mo	6.2mo HR = 0.66 $p < 0.001$	6.2mo	6.8mo HR = 0.75 $p = 0.0003$	6.6mo HR = 0.85 $p = 0.0456$
Median OS	10.3mo	12.3mo HR = 0.79 $p = 0.003$	13.1mo	13.6mo HR = 0.93 $p = 0.42$	13.4mo HR = 1.03 $p = 0.76$

PC = paclitaxel/carboplatin; CG = cisplatin/gemcitabine; PFS = progression-free survival; OS = overall survival; HR = hazard ratio

SOURCES: [1] Sandler A et al. *N Engl J Med* 2006;355(24):2542-50. **Abstract**; [2] Manegold C et al. *Proc ESMO* 2008;**Abstract LBA1**.

Track 9

DR LOVE: What do we know about the multikinase inhibitor vandetanib?

DR SANDLER: Vandetanib inhibits both VEGF and EGFR to different degrees. The low dose is more of a VEGF inhibitor, and the higher dose is more of a combination of VEGF and EGFR inhibition.

As a single agent, the higher dose may be better, but in combination with chemotherapy, the lower dose may be preferable because of the potential antagonism between an EGFR agent and chemotherapy. Phase II studies suggest that the addition of vandetanib to either docetaxel or gefitinib may provide benefit (3.2).

3.2

Vandetanib in the Treatment of Patients with Advanced Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

	Vandetanib[1] (n = 83)	Gefitinib[1] (n = 85)	Docetaxel + placebo[2] (n = 41)	Docetaxel + vandetanib 100 mg[2] (n = 42)	Docetaxel + vandetanib 300 mg[2] (n = 44)
Median PFS	11.0wk	8.1wk	12.0wk	18.7wk	17.0wk
Hazard ratio (95% CI)	0.69 (0.50-0.96)	—	NA	0.64 (0.38-1.05)	0.83 (0.50-1.36)
p-value (two-sided)	0.025	—	NA	0.074	0.461

PFS = progression-free survival; CI = confidence interval

SOURCES: [1] Natale RB et al. *Proc ASCO* 2006;**Abstract 7000**; [2] Heymach JV et al. *J Clin Oncol* 2007;25(27):4270-7. **Abstract**

Track 10

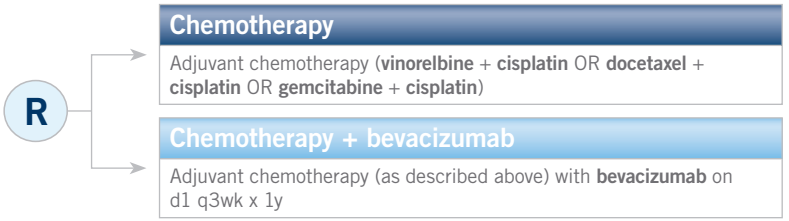
DR LOVE: Could you provide an update on the adjuvant ECOG-E1505 trial evaluating chemotherapy with or without bevacizumab (3.3)?

DR SANDLER: This study is evaluating cisplatin-based chemotherapy with or without a year of bevacizumab in patients with tumors of all histologies. The study has a target accrual of 1,500 patients with survival as the endpoint. The study is not accruing nearly as fast as it should, with only about 250 patients enrolled. ■

3.3

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



SOURCE: NCI Physician Data Query, November 2008.

SELECT PUBLICATIONS

Chung CH et al. **Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose.** *N Engl J Med* 2008;358(11):1109-17. **Abstract**

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* 2007;25(27):4270-7. **Abstract**

Manegold C et al. **(AVAIL): A Phase III randomised study of first-line bevacizumab combined with cisplatin/gemcitabine in patients with advanced or recurrent non-squamous, non-small-cell-lung cancer.** *Proc ESMO* 2008;**Abstract LBA1**.

Natale RB et al. **ZD6474 versus gefitinib in patients with advanced NSCLC: Final results from a two-part, double-blind, randomized phase II trial.** *Proc ASCO* 2006;**Abstract 7000**.

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**.

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 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**.

INTERVIEW

David S Ettinger, MD

Dr Ettinger is Alex Grass Professor of Oncology at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland.

Tracks 1-7

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on tumor tissue type and treatment selection in NSCLC?

DR ETTINGER: Practice-changing data have emerged regarding the use of histology to predict the effectiveness of different therapeutic agents.

Dr Scagliotti recently published data in the *Journal of Clinical Oncology* from a study of gemcitabine/cisplatin versus pemetrexed/cisplatin in chemotherapy-naïve patients with advanced stage NSCLC, which demonstrated that patients with squamous cell histology had better outcomes with gemcitabine/cisplatin and those with adenocarcinoma fared better with pemetrexed/cisplatin (Scagliotti 2008; [4.1]).

As another example, Karp and colleagues presented a study at ASCO evaluating paclitaxel and carboplatin with CP-751,871 — a monoclonal antibody against insulin-like growth factor type 1 receptor (IGF-IR) — in patients with advanced, treatment-naïve NSCLC (Karp 2008). The highest levels of IGF1 occur in squamous cell NSCLC. In patients with squamous cell tumors, 11 out of 14 patients responded, or 78 percent, whereas 57 percent of patients with adenocarcinomas demonstrated responses.

4.1

Randomized Phase III Trial of Cisplatin/Pemetrexed (CP) versus Cisplatin/Gemcitabine (CG) in Locally Advanced or Metastatic NSCLC: Efficacy Data

Endpoint	CP (n = 862)	CG (n = 863)	Adjusted HR (95% CI)
Median overall survival	10.3 months	10.3 months	0.94 (0.84-1.05)
Nonsquamous cell (n = 1,000)	11.8 months	10.4 months	0.81 (0.70-0.94)
Adenocarcinoma (n = 847)	12.6 months	10.9 months	0.84 (0.71-0.99)
Large cell carcinoma (n = 153)	10.4 months	6.7 months	0.67 (0.48-0.96)
Squamous cell (n = 473)	9.4 months	10.8 months	1.23 (1.00-1.51)
Median progression-free survival	5.3 months	4.7 months	0.90 (0.79-1.02)

HR = hazard ratio; CI = confidence interval

SOURCE: Scagliotti GV et al. *J Clin Oncol* 2008;26(21):3543-51. **Abstract**

Track 3

DR LOVE: What are your thoughts about ECOG-E1505 and the incorporation of bevacizumab in the adjuvant setting?

DR ETTINGER: ECOG-E1505 is a great study because we haven't seen advances in adjuvant therapy for a while. In fact, at ASCO this year, Le Chevalier presented the eight-year follow-up data for the IALT study and showed that the survival advantage was no longer evident for chemotherapy (Le Chevalier 2008; [4.2]). Interestingly, ERCC1 status remained predictive for survival benefit from adjuvant chemotherapy (4.2).

DR LOVE: How do you approach selection of adjuvant chemotherapy off study?

4.2

Long-Term Results of the International Adjuvant Lung Cancer Trial (IALT) Evaluating Cisplatin-Based Chemotherapy for NSCLC

	Number of events			
Endpoint	Chemo	Control	Hazard ratio (CI)	*p*-value
Overall survival	578	590	0.91 (0.81-1.02)	0.10
ERCC status				
ERCC1-negative	NR	NR	0.76 (0.59-0.98)	NR
ERCC1-positive	NR	NR	1.20 (0.91-1.59)	NR
Time period of analysis				
First five years	495	534	0.86 (0.76-0.97)	NR
After five years	83	56	1.45 (1.02-2.07)	NR
Disease-free survival	606	631	0.88 (0.78-0.98)	0.02

CI = confidence interval; NR = not reported

SOURCE: Le Chevalier T et al. *Proc ASCO* 2008;**Abstract 7507**.

DR ETTINGER: I use cisplatin paired with gemcitabine. If patients are intolerant of cisplatin, I use carboplatin. The bigger issue is where pemetrexed will fit in when it's approved, especially for patients with adenocarcinomas.

Tracks 4-5

DR LOVE: Can you discuss new research approaches to locally advanced disease, particularly chemoradiation therapy and maintenance therapy?

DR ETTINGER: A study presented by Blumenschein and colleagues at ASCO revealed a median survival of 22.7 months with concurrent chemoradiation therapy and cetuximab, which is the longest survival observed in RTOG trials with Stage III NSCLC (Blumenschein 2008; [4.3]). Sequential chemoradiation therapy is associated with a 14-month median survival, and with concurrent chemoradiation therapy it's about 17 months.

4.3

RTOG-0324: A Phase II Study of Cetuximab in Combination with Chemoradiation Therapy in Patients (N = 93) with Stage IIIA/B NSCLC: Two-Year Follow-Up

Median overall survival[1]	22.7 months
Two-year overall survival[1]	49.3%
FISH-positive[2]	61.9%
FISH-negative[2]	53.8%
Response rate[1]	62%

SOURCES: [1] Blumenschein GR Jr et al. *Proc ASCO* 2008;**Abstract 7516**; [2] Olsen CC et al. *Proc ASCO* 2008;**Abstract 7607**.

The Intergroup study (RTOG-0617) of concurrent chemoradiation therapy, comparing two different doses of radiation therapy — 74 and 60 Gray — has added cetuximab. Based on our experience with cetuximab and chemotherapy (Vermorken 2008) combined with radiation therapy (Bonner 2006) in head and neck malignancies, we expect that cetuximab will be effective. ■

SELECT PUBLICATIONS

Blumenschein GR Jr et al. **A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (PTS) with stage IIIA/B non-small cell lung cancer (NSCLC): A report of the 2 year and median survival (MS) for the RTOG 0324 trial.** *Proc ASCO* 2008;**Abstract 7516**.

Bonner JA et al. **Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.** *N Engl J Med* 2006;354(6):567-78. **Abstract**

Karp DD et al. **High activity of the anti-IGF-IR antibody CP-751,871 in combination with paclitaxel and carboplatin in squamous NSCLC.** *Proc ASCO* 2008;**Abstract 8015**.

Le Chevalier T et al. **Long-term results of the International Adjuvant Lung Cancer Trial (IALT) evaluating adjuvant cisplatin-based chemotherapy in resected non-small cell lung cancer (NSCLC).** *Proc ASCO* 2008;**Abstract 7507**.

Scagliotti GV et al. **Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.** *J Clin Oncol* 2008;26(21):3543-51. **Abstract**

Vermorken JB et al. **Platinum-based chemotherapy plus cetuximab in head and neck cancer.** *N Engl J Med* 2008;359(11):1116-27. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Results of the International Adjuvant Lung Cancer Trial (IALT) revealed a differential effect on overall survival for patients who received cisplatin-based chemotherapy for NSCLC, based on ERCC1 status.**
   a. True
   b. False

2. **ECOG-E1505 is evaluating adjuvant _____ with or without bevacizumab for patients with completely resected, Stage IB to IIIA NSCLC.**
   a. Cisplatin/gemcitabine
   b. Cisplatin/vinorelbine
   c. Cisplatin/docetaxel
   d. All of the above

3. **In the Phase III Intergroup trial 0139 (RTOG-9309), which evaluated concurrent chemoradiation therapy (CT/RT) versus CT/RT followed by surgical resection for Stage IIIA NSCLC, subset analysis revealed a survival benefit with surgery for those patients who underwent a lobectomy as opposed to a pneumonectomy.**
   a. True
   b. False

4. **Approximately what percent of patients with NSCLC whose tumors have an EGFR mutation respond to erlotinib?**
   a. Nine percent
   b. 20 percent
   c. 40 percent
   d. 80 percent

5. **Data suggest that patients with acquired resistance to TKIs respond to re-treatment with erlotinib or gefitinib as assessed by tumor size, tumor FDG uptake and symptomatic disease progression.**
   a. True
   b. False

6. **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 adenocarcinomas or large cell carcinomas?**
   a. Pemetrexed/cisplatin
   b. Gemcitabine/cisplatin

7. **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

8. **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

9. **In the AVAiL trial, the addition of bevacizumab to first-line cisplatin/gemcitabine for patients with advanced or recurrent nonsquamous NSCLC resulted in significant improvements in _____.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b
   d. Neither a nor b

10. **In a Phase II trial, the objective response rate for patients with previously untreated Stage IV NSCLC who received single-agent *nab* paclitaxel as first-line therapy was _____.**
    a. Eight percent
    b. 14 percent
    c. 30 percent

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 4, 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

- **FLEX trial of cisplatin/vinorelbine with or without cetuximab as first-line therapy for advanced NSCLC** 4 3 2 1
- **ECOG-E4599 and AVAiL studies of chemotherapy and bevacizumab as first-line therapy for advanced nonsquamous cell NSCLC** 4 3 2 1
- **Clinical and molecular predictors of response to EGFR TKIs and monoclonal antibodies** 4 3 2 1
- **Role of maintenance pemetrexed for Stage IIIB/IV NSCLC** 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

- **FLEX trial of cisplatin/vinorelbine with or without cetuximab as first-line therapy for advanced NSCLC** 4 3 2 1
- **ECOG-E4599 and AVAiL studies of chemotherapy and bevacizumab as first-line therapy for advanced nonsquamous cell NSCLC** 4 3 2 1
- **Clinical and molecular predictors of response to EGFR TKIs and monoclonal antibodies** 4 3 2 1
- **Role of maintenance pemetrexed for Stage IIIB/IV NSCLC** 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

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☐ Yes ☐ No

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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:

- Summarize the benefits and risks of alternative surgical approaches for patients with localized or resectable locally advanced non-small cell lung cancer (NSCLC). ..... 4 3 2 1 N/M N/A
- Utilize tumor characteristics and molecular biomarkers in treatment decision-making for patients with lung cancer. ..... 4 3 2 1 N/M N/A
- Communicate the benefits and risks of induction chemotherapy and concurrent chemoradiation therapy when devising treatment strategies for Stage III NSCLC. ..... 4 3 2 1 N/M N/A
- Integrate emerging data on the combined use of cytotoxics and biologics when selecting first-line therapy and subsequent care for patients with advanced NSCLC. ..... 4 3 2 1 N/M N/A
- Identify patients with NSCLC who are most likely to benefit from treatment with EGFR tyrosine kinase inhibitors. ..... 4 3 2 1 N/M N/A
- Appraise the current role of maintenance pemetrexed for patients with advanced NSCLC that responds 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?

.....

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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

.....

Additional comments about this activity:

.....

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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

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David Jablons, MD	4 3 2 1	4 3 2 1
Gregory J Riely, MD, PhD	4 3 2 1	4 3 2 1
Alan B Sandler, MD	4 3 2 1	4 3 2 1
David S Ettinger, 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:

.....

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