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Lung Cancer™ UPDATE

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

FACULTY INTERVIEWS

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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 for 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 approximately 85 percent of patients who develop lung cancer will die of it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on long-term outcomes. However, the advent of biologic agents in lung cancer has led to recent improvements in disease-free and overall survival in select patient populations. 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 expert perspectives, this CME program is designed to assist medical oncologists and radiation oncologists with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Identify distinct subtypes of adenocarcinoma of the lung, including those with EGFR mutations and those with EML4-ALK gene fusions, and the investigational and approved treatment options for patients with these conditions.
- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible EGFR TKIs.
- Apply the results of recent clinical research to the rational selection of EGFR- or VEGF-inhibiting agents for patients with metastatic non-small cell lung cancer (NSCLC).
- Formulate individualized treatment plans addressing first-line therapy for recurrent or progressive NSCLC, considering unique patient and tumor characteristics.
- Identify patients with metastatic NSCLC who may benefit from individualized maintenance treatment approaches after successful completion of first-line systemic therapy.
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions.

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INTERVIEW

Nasser H Hanna, MD

Dr Hanna is Associate Professor of Medicine at the Indiana University Medical Center School of Medicine in Indianapolis, Indiana.

Tracks 1-13

Select Excerpts from the Interview

Track 5

DR LOVE: The IPASS paradigm of using an EGFR tyrosine kinase inhibitor (TKI) up front in EGFR mutation-positive, advanced non-small cell lung cancer (NSCLC) is now well established. What about patients with wild-type tumors?

DR HANNA: Obviously erlotinib is not the preferred first-line therapy for these patients, but I believe it's reasonable to administer erlotinib to them as second-, third- and sometimes fourth-line therapy. If you evaluate the IPASS

data, those patients who were never smokers with EGFR wild-type adenocarcinoma had a significant early drop-off in terms of response if they received the EGFR inhibitor gefitinib (Mok 2009; [1.1]) instead of chemotherapy. Some patients who received gefitinib experienced rapid disease progression, and unfortunately, a significant number of patients died. These data support the use of chemotherapy rather than an EGFR inhibitor for never smokers with EGFR wild-type disease.

For a patient with an EGFR mutation, the preponderance of the data supports administering an EGFR inhibitor in the first-line setting. But we don't see a rapid drop-off in progression-free survival or overall survival in the first three months if we administer chemotherapy to those patients. So I don't believe you're wrong to administer chemotherapy in the front line for these patients, but a drug like erlotinib is preferred in this setting.

1.1

IPASS: A Phase III Randomized Trial of Gefitinib versus Carboplatin/Paclitaxel as First-Line Therapy for Clinically Selected (Asian, Nonsmokers or Former Light Smokers, Adenocarcinoma) Patients with Advanced Non-Small Cell Lung Cancer

Progression-free survival (events)	Gefitinib	Carboplatin + paclitaxel	Hazard ratio* (95% CI)	*p*-value
Intent-to-treat population (n = 609; 608)	74.4%	81.7%	0.74 (0.65-0.85)	<0.001
EGFR mutation-positive (n = 132; 129)	73.5%	86.0%	0.48 (0.36-0.64)	<0.001
EGFR mutation-negative (n = 91; 85)	96.7%	82.4%	2.85 (2.05-3.98)	<0.001

* Hazard ratio < 1.0 favors gefitinib; CI = confidence interval

Conclusions:
"The presence of an EGFR mutation was a robust predictor of improved progression-free survival with gefitinib, as compared with carboplatin-paclitaxel, and of the benefit of gefitinib with respect to the objective response rate, indicating that patients in whom an EGFR mutation has been identified will benefit most from first-line therapy with gefitinib.

Whenever possible, EGFR-mutation status should be determined before the initial treatment of pulmonary adenocarcinoma."

Mok TS et al. *N Engl J Med* 2009;361(10):947-57.

Track 10

DR LOVE: Would you discuss the clinical data we have with crizotinib, the small-molecule inhibitor that targets the EML4-ALK fusion oncogene?

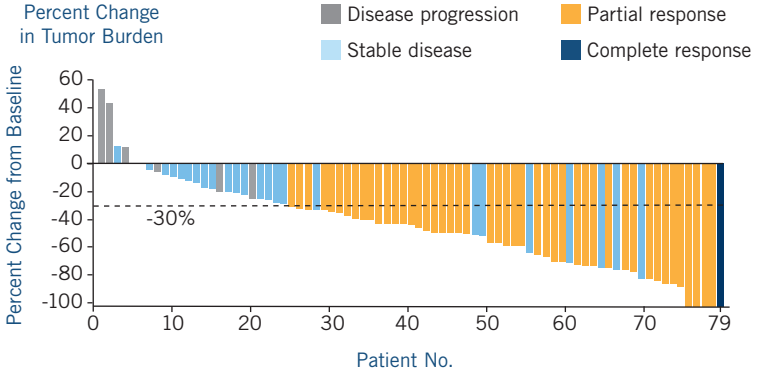
DR HANNA: Many advances in cancer treatment have taken decades to develop, but the EML4-ALK mutation story in lung cancer has developed rapidly. Phase II results presented in the plenary session at ASCO 2010

reported that nearly 60 percent of patients with ALK rearrangements had an objective response to crizotinib (Kwak 2010; [1.2]).

Activation of a worldwide, Phase III study occurred a few months afterward. Other protocols are now under way in the first- and second-line settings. Another study is evaluating crizotinib as a single agent for patients who

1.2

Tumor Response to Crizotinib in Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer



Overall response rate: 57%; stable disease: 33%; median progression-free survival: Not yet reached

Kwak EL et al. *N Engl J Med* 2010;363(18):1693-703.

1.3

Ongoing Studies of Crizotinib for Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer

Protocol	Phase	N	Treatment/ randomization	Eligibility
NCT00932451	II	400	• Crizotinib	• EML4-ALK-positive • Progressive disease on pemetrexed or docetaxel from previous Phase III trial (A8081007) • >1 prior chemotherapy
NCT00932893	III	318	• Crizotinib • Pemetrexed or docetaxel	• EML4-ALK-positive • 1 prior platinum-based regimen
NCT01154140	III	334	• Crizotinib • Pemetrexed/cisplatin or pemetrexed/carboplatin	• EML4-ALK-positive • Metastatic nonsquamous cell lung carcinoma • No prior treatment

www.clinicaltrials.gov. Accessed February 2011.

experienced disease progression while receiving chemotherapy on a prior second-line study or for patients who never entered any of the trials because of eligibility issues (1.3).

Crizotinib is clearly active in patients with ALK mutations. I expect that even though this mutation only occurs in three to four percent of patients, it is such an exciting field that physicians and patients are highly motivated to gain access to these studies. Hopefully, within six months to a year we'll have data, and if they remain positive, I expect rapid approval.

Track 13

DR LOVE: What is your take on the Phase II trial data presented at ASCO 2010 of erlotinib alone or in combination with the oral c-MET inhibitor ARQ 197 for patients with previously treated, EGFR inhibitor-naïve advanced NSCLC?

DR HANNA: This was one of the more interesting trials presented at ASCO 2010. ARQ 197 combined with erlotinib seemed to have better efficacy compared to erlotinib alone in patients with advanced NSCLC (Schiller 2010; [1.4]).

c-MET amplification is observed in approximately one third of patients who have acquired resistance to drugs such as erlotinib, so it is logical to combine a drug that inhibits c-MET with a drug that inhibits EGFR.

We and others will be participating in a Phase III trial of ARQ 197, which is probably at the forefront of newer classes of drugs that are furthest along in development. ■

1.4

Efficacy of the Oral c-MET Inhibitor ARQ 197 (A) in Combination with Erlotinib (E) for Patients with Previously Treated, EGFR Inhibitor-Naïve Advanced Non-Small Cell Lung Cancer

	E + A (n = 84)	E + placebo (n = 83)	Hazard ratio	*p*-value
Median progression-free survival	16.1 weeks	9.7 weeks	0.68	<0.05

Schiller JH et al. *Proc ASCO* 2010;**Abstract LBA7502**.

SELECT PUBLICATIONS

Kwak EL et al. **Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer.** *N Engl J Med* 2010;363(18):1693-703.

Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009;361(10):947-57.

Schiller JH et al. **Results from ARQ 197-209: A global randomized placebo-controlled phase II clinical trial of erlotinib plus ARQ 197 versus erlotinib plus placebo in previously treated EGFR inhibitor-naive patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract LBA7502**.

INTERVIEW

Naiyer A Rizvi, MD

Dr Rizvi is Associate Attending at Memorial Sloan-Kettering Cancer Center's Thoracic Oncology Service in New York, New York.

Tracks 1-12

Track 1 **Case discussion:** A physician and never smoker presents with a large pleural effusion and is diagnosed with EGFR-mutant adenocarcinoma of the lung and bone metastases

Track 2 Dosing of erlotinib for patients with EGFR mutations

Track 3 Afatinib in patients with the T790M mutation and acquired resistance to erlotinib

Track 4 Reinitiation versus continuation of erlotinib in patients who are sensitive or resistant to EGFR TKIs

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Track 7 Increasing number of targets for biomarker assessment in NSCLC

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Track 10 Antitumor activity of bevacizumab alone in NSCLC

Track 11 Clinical approach to first-line and maintenance therapy for advanced NSCLC

Track 12 Therapeutic options for adjuvant chemotherapy in NSCLC

Select Excerpts from the Interview

Tracks 2, 4

DR LOVE: How do you approach dosing of erlotinib for patients with EGFR-mutant NSCLC?

DR RIZVI: Our goal by and large is for patients to receive full-dose erlotinib at 150 mg per day. We are able to manage cutaneous toxicities reasonably well in conjunction with our dermatology department. Even though erlotinib is an oral agent, the side effects are real and can be as significant as those with intravenous chemotherapy.

Many of our patients are not able to tolerate full-dose therapy, and we probably have about the same number of patients at 100 mg per day as their maximally tolerated dose as we do at 150 mg per day. We don't know whether

patients are more apt to develop resistance at 100 mg versus 150 mg, so we try to administer as full a dose as possible.

DR LOVE: What are your thoughts on the issue of re-treatment with erlotinib? What do we know about repeat responses in patients who've previously received an EGFR TKI?

DR RIZVI: Two scenarios relate to that. I have a patient with clinical Stage IIIA NSCLC and an EGFR mutation who chose erlotinib as adjuvant treatment.

No data support that, but with Stage IIIA disease and a high risk of recurrence, we chose to administer it. At two years we stopped the erlotinib, and approximately one year later he experienced a recurrence in the lung and lymph nodes.

At that point we resumed the erlotinib, and he was sensitive to it. He has been receiving it for about a year now and is maintaining a response to therapy. So he never was truly resistant to erlotinib — it was stopped at two years empirically and then, when he experienced a recurrence, we resumed it and he was sensitive again.

The second situation is someone who is receiving erlotinib for advanced-stage disease and experiences disease progression while receiving it. What do you do in that situation? Our experience has been that, to some extent, if you stop it, you may see a flare effect — the tumor may grow because a sensitive population of cells may remain (Riely 2007; [2.1]).

By and large, for patients who had initially sensitive but subsequently resistant disease we continue the erlotinib and add whatever our next course of chemotherapy might be to that regimen.

2.1

Changes in Tumor on CT and FDG-PET After EGFR Tyrosine Kinase Inhibitor (TKI) Discontinuation and Reinitiation in Patients with Non-Small Cell Lung Cancer Previously Responding to Erlotinib or Gefitinib

Median/mean change in:	After stopping EGFR TKI	After restarting EGFR TKI
Tumor diameter	+9%/+9%	-1%/1%
Tumor volume	+50%/+61%	-1%/-4%
Tumor SUV(max)	+18%/+23%	-4%/-11%

"In patients who develop acquired resistance, stopping erlotinib or gefitinib results in symptomatic progression, increase in SUV(max), and increase in tumor size.

Symptoms improve and SUV(max) decreases after restarting erlotinib or gefitinib, suggesting that some tumor cells remain sensitive to epidermal growth factor receptor blockade."

Riely GJ et al. *Clin Cancer Res* 2007;13(17):5150-5.

Track 3

DR LOVE: Would you comment on what we know about the "irreversible" EGFR TKI BIBW 2992, or afatinib?

DR RIZVI: Afatinib is an irreversible TKI affecting EGFR and HER2, and earlier Phase I trials provided evidence that this agent may be more effective at targeting the T790M acquired-resistance mutation. The belief is that patients with a "sensitivity" EGFR mutation will invariably respond to erlotinib. However, with time eventually everyone will develop resistance through emergence of a secondary acquired-resistance mutation, which changes the conformation of the protein further and makes the cancer cell resistant to erlotinib.

Afatinib may be a more effective agent in terms of targeting that acquired-resistance mutation (Shih 2010). One trial is ongoing with afatinib as first-line therapy for patients with known sensitivity EGFR mutations. Another study is combining afatinib with cetuximab for patients who have developed acquired resistance to erlotinib.

Track 8

DR LOVE: What are your thoughts on the recent data with nanoparticle albumin-bound (*nab*) paclitaxel in NSCLC, particularly the favorable results seen in advanced squamous cell NSCLC?

DR RIZVI: Our own earlier Phase II experience was as a first-line, single-agent, weekly therapy in the older, not as good performance status (PS)-type of patient population with advanced NSCLC. We experienced a good outcome (Rizvi 2008).

The more recent data with *nab* paclitaxel — particularly in patients with squamous histology — show an extremely important result (Socinski 2010b). I don't know how to explain it, and we are not routinely using *nab* paclitaxel for our patients, but I believe it would be worth studying *nab* paclitaxel for the population of patients with squamous cell disease.

Our institutional guidelines limit the use of *nab* paclitaxel to patients with an intolerance or a reaction to standard taxane therapy. However, our threshold is low and we switch to *nab* paclitaxel if patients experience any sort of reaction with paclitaxel.

Track 11

DR LOVE: How do you generally approach first-line treatment for patients with advanced NSCLC?

DR RIZVI: Our group has been fairly uniform in terms of our approach to first-line therapy for Stage IV non-EGFR-mutated adenocarcinoma of the

lung. Most of our patients are receiving pemetrexed/cisplatin or pemetrexed/carboplatin with bevacizumab as first-line therapy.

For patients with squamous cell disease, most are receiving gemcitabine and a platinum agent or a taxane and a platinum agent as first-line treatment. We've always favored cisplatin as opposed to carboplatin as first-line therapy, although it's more difficult to administer taxanes in combination with cisplatin because patients encounter problems with diarrhea from docetaxel, renal compromise from cisplatin and neuropathy from both.

Pemetrexed has been fairly easy to combine with cisplatin, and we've found that patients fare extremely well while receiving this therapy. It's been a nice match in terms of tolerability.

Patients with adenocarcinoma receive pemetrexed/cisplatin and bevacizumab as first-line therapy. My practice has been to drop the cisplatin after four to six cycles and continue the pemetrexed and bevacizumab as maintenance therapy. Patients can continue with this combination for a long time.

I am currently treating a couple of 80-year-old patients who are receiving pemetrexed/bevacizumab maintenance therapy, and they've been responsive. As long as the PS is reasonable, even the elderly patients have been faring well.

Most patients prefer receiving maintenance therapy. I believe that more patients have conceptual difficulties with discontinuing chemotherapy after four or six cycles. The discontinuation is unsettling for patients, and our patients welcome being able to continue active maintenance treatment. ■

SELECT PUBLICATIONS

Patel JD et al. **Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2009;27(20):3284-9.

Reynolds C et al. **Phase II trial of nanoparticle albumin-bound paclitaxel, carboplatin, and bevacizumab in first-line patients with advanced nonsquamous non-small cell lung cancer.** *J Thorac Oncol* 2009;4(12):1537-43.

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.

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.

Shih J et al. **Activity of BIBW2992, an irreversible EGFR/HER1 and HER2 TKI, in lung adenocarcinoma patients harboring less common EGFR mutations.** *Proc ESMO* 2010;**Abstract 415P**.

Socinski MA et al. **A dose finding study of weekly and every-3-week *nab*-paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer.** *J Thorac Oncol* 2010a;5(6):852-61.

Socinski MA et al. **Results of a randomized, phase III trial of *nab*-paclitaxel (*nab*-P) and carboplatin (C) compared with Cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010b;**Abstract LBA7511**.

INTERVIEW

Jyoti D Patel, MD

Dr Patel is Associate Professor of Medicine at Northwestern University in Chicago, Illinois.

Tracks 1-12

Track 1 Gender-related differences in the incidence, biology, prognosis and response/toxicity to treatment in NSCLC

Track 2 Phase II study results with pemetrexed/carboplatin and bevacizumab with maintenance pemetrexed/bevacizumab as first-line therapy for nonsquamous NSCLC

Track 3 PointBreak: A Phase III study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC

Track 4 "Switch" and "continuation" maintenance therapy for NSCLC

Track 5 Approach to biomarker assessment and treatment for NSCLC

Track 6 Erlotinib-associated dermatologic toxicity, trichomegaly and metabolic changes

Track 7 ECOG-E6508: A Phase II study of BLP25 and bevacizumab in unresectable Stage IIIA/B nonsquamous NSCLC after definitive chemoradiation therapy

Track 8 **Case discussion:** A 63-year-old man and never smoker with adenocarcinoma of the lung and a solitary brain metastasis undergoes stereotactic radiosurgery followed by treatment with carboplatin/pemetrexed and bevacizumab on a clinical trial

Track 9 **Case discussion:** A 50-year-old woman and never smoker has an EGFR-mutant adenocarcinoma of the lung and cardiac tamponade with extreme shortness of breath

Track 10 **Case discussion:** A 48-year-old woman with a remote smoking history is diagnosed with EGFR wild-type metastatic NSCLC and receives carboplatin/paclitaxel and bevacizumab followed by bevacizumab on the PointBreak study

Track 11 Mutual exclusivity of K-ras, EGFR and ALK mutations in NSCLC

Track 12 Preferred adjuvant chemotherapy regimens in NSCLC

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss your study that evaluated the combination of pemetrexed/carboplatin and bevacizumab as first-line therapy for NSCLC and the ongoing Phase III trial with this regimen?

DR PATEL: We developed a single-arm Phase II study of the combination of pemetrexed/carboplatin and bevacizumab (Patel 2009). The eligibility criteria were similar to the ECOG-E4599 study of carboplatin/paclitaxel and bevacizumab — no brain metastasis, no anticoagulation, PS 0 to 1 and no squamous histology. Patients received six cycles of chemotherapy followed by continued pemetrexed and bevacizumab maintenance therapy.

The idea was that pemetrexed was a little gentler. It doesn't yield the taxane toxicities, such as neuropathy and myelosuppression, so we could administer prolonged therapy and improve outcomes.

We were impressed with the toxicity profile, but more impressive were the tremendous radiographic responses we observed in more than half of the patients. The median survival was approximately 14 months (3.1). It is interesting to note that three patients developed diverticulitis, but it didn't seem to be a vasculitic phenomenon, so we amended the study such that patients with a history of diverticulitis could no longer enroll. After that, we saw no further issues.

We've now developed a Phase III trial that has completed accrual. The PointBreak study includes 900 patients randomly assigned to four cycles of carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance therapy or carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance therapy (3.2).

DR LOVE: Do you have initial data from this trial in terms of quality-of-life side effects, particularly on the maintenance phase with pemetrexed/bevacizumab versus bevacizumab?

DR PATEL: We have not yet shared the data, but I can speak from anecdotal experience. Patients who have controlled disease tend to fare well with prolonged pemetrexed treatment. Five to seven percent experience a tremendous amount of fatigue, and we usually identify those patients early. I'm most excited about this approach because, in almost 20 percent of patients, after we stopped the carboplatin we continued to see a response with only pemetrexed and bevacizumab.

3.1

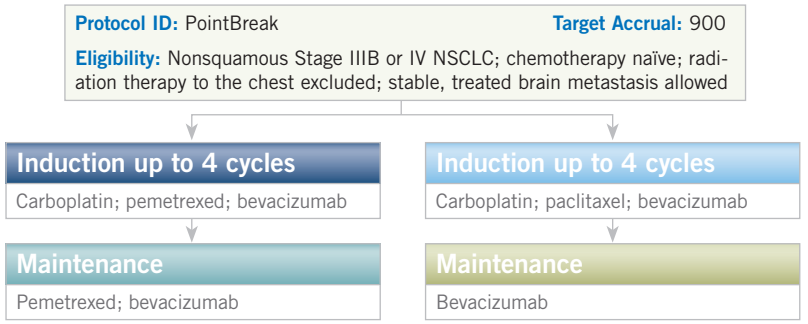
Efficacy Results from a Phase II Study of First-Line Carboplatin, Pemetrexed and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab in Nonsquamous Non-Small Cell Lung Cancer

Treatment outcomes	N = 49	Percent
Objective response	27	55%
Complete response	1	2%
Partial response	26	53%
Progression-free survival	7.8 mo (5.2-11.5)	—
Overall survival	14.1 mo (10.8-19.6)	—

Patel JD et al. *J Clin Oncol* 2009;27(20):3284-9.

3.2

Phase III Study of Chemotherapy/Bevacizumab Followed by Maintenance Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)



Primary endpoint: Overall survival

www.clinicaltrials.gov. Identifier NCT00762034.

DR LOVE: Do you have any other thoughts on the issue of maintenance therapy in general?

DR PATEL: Another approach is called "switch maintenance," although it may more accurately be early second-line therapy. Induction therapy is administered, and then at the completion of four to six cycles it is followed with an agent that has been approved using the switch paradigm — either erlotinib or pemetrexed. Survival benefits were observed in studies using this tactic (Ciuleanu 2009; Cappuzzo 2010), and it is a reasonable approach. Many would argue that if a patient is followed closely and scans or chest x-rays are conducted fairly often, you would be able to find minimal disease progression before the patient became symptomatic and thus administer equal amounts of a second drug with a similar survival outcome. However, catastrophic events can occur and 30 percent of patients may never move on to that second-line agent using this strategy.

For patients who have demonstrated responses to initial therapy, often I find that continuation of the first drug makes sense. With pemetrexed many of us have been doing just that. We don't have enough data on true "continuation maintenance" to make a good argument for it, but intuitively it makes sense — and it works.

Track 7

DR LOVE: Would you describe the BLP25 liposomal vaccine and how it is being studied in NSCLC?

DR PATEL: BLP25 is a vaccine targeting the mucinous — or MUC — glycoproteins expressed in almost all NSCLC tumors. A randomized Phase II study evaluated patients with at least localized cancer and some radiation therapy

(Butts 2005, 2007). When they evaluated patients with locally advanced disease, they found a survival improvement. That led to a large Phase III trial, the START trial, which is currently ongoing in patients with locally advanced NSCLC who receive definitive chemoradiation therapy (3.3).

Administration of the vaccine is interesting because a small amount of cyclophosphamide is administered prior to the vaccine to increase its immunogenicity. The vaccine is administered in four injections every three weeks initially and then every six weeks.

We are conducting a Phase I/II study evaluating bevacizumab in combination with the vaccine among patients who've undergone definitive chemoradiation therapy with weekly paclitaxel and carboplatin followed by two cycles of consolidation carboplatin and paclitaxel. We then administer a combination of bevacizumab for two years with the vaccine. The rationale for this approach stems from evidence that bevacizumab increases T-cell function and antigen presentation. We believe it may make the vaccine more effective. ■

3.3

Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Cancer Vaccine Stimuvax® (L-BLP25 or BLP25 Liposome Vaccine) in Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT00409188
Target Accrual: 1,476

Eligibility
Unresectable Stage III NSCLC with documented stable disease or objective response after chemoradiation therapy

R

Single infusion of cyclophosphamide → L-BLP25 qwk x 8 → maintenance L-BLP25

Single infusion of placebo → placebo qwk x 8 → maintenance placebo

Treatment continues until disease progression.
Primary endpoint: Survival

www.clinicaltrials.gov. Accessed February 24, 2011.

SELECT PUBLICATIONS

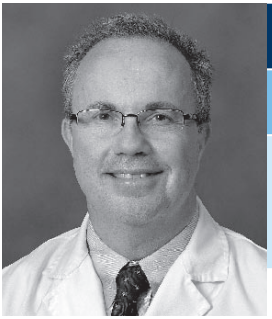
Butts C et al. **A multi-centre phase IIB randomized controlled study of BLP25 liposome vaccine (L-BLP25 or Stimuvax) for active specific immunotherapy of non-small cell lung cancer (NSCLC): Updated survival analysis B1–01.** *J Thorac Oncol* 2007;2(Suppl 4):332-3.

Butts C et al. **Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer.** *J Clin Oncol* 2005;23(27):6674-81.

Cappuzzo F et al. **Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study.** *Lancet Oncol* 2010;11(6):521-9.

Ciuleanu T et al. **Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study.** *Lancet* 2009;374(9699):1432-40.

Patel JD et al. **Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2009;27(20):3284-9.



INTERVIEW

Alan B Sandler, MD

Dr Sandler is Professor of Medicine and Division Chief of Hematology and Medical Oncology at Oregon Health and Science University in Portland, Oregon.

Tracks 1-16

Select Excerpts from the Interview

Track 2

DR LOVE: Would you comment on your recent data with advanced NSCLC correlating tumor-related outcome with the presence of hypertension during treatment with carboplatin/paclitaxel and bevacizumab?

DR SANDLER: Hypertension as a potential predictor of benefit from bevacizumab is an interesting concept. In a landmark analysis, patients with hypertension were compared to patients without hypertension. High blood pressure by the end of cycle one was defined as blood pressure greater than 150/100 at any previous time or an increase of at least 20 mm Hg in diastolic blood pressure from baseline. It appears that the development of high blood pressure may be associated with improved outcomes (Dahlberg 2010; [4.1]).

4.1 **Blood Pressure and Outcome After One Cycle of Bevacizumab (Bev) and Carboplatin (C)/Paclitaxel (P) in Advanced Non-Small Cell Lung Cancer**

	CP		CP + bev		*p*-value
	No HBP	HBP	No HBP	HBP	
Median overall survival	10.1 mo	10.3 mo	11.5 mo	15.9 mo	0.0002
Median progression-free survival	4.2 mo	3.6 mo	5.5 mo	7.0 mo	<0.0001

HBP = high blood pressure

Dahlberg SE et al. *J Clin Oncol* 2010;28(6):949-54.

Track 5

DR LOVE: Considering the additional data presented on the use of bevacizumab in NSCLC since the ECOG-E4599 study was first presented, would you revisit the contraindications to bevacizumab in NSCLC?

DR SANDLER: The ECOG-E4599 trial did not include patients with squamous cell histology, and that's still an absolute contraindication. Since that time, data from studies such as PASSPORT have shown that patients with previously treated brain metastases can safely receive bevacizumab (Socinski 2009). Registry trials, such as ARIES and SAiL, have reported that patients with stable anticoagulation seem to fare well while receiving bevacizumab (Wozniak 2010; Lynch 2008).

The issue that challenges me is treatment for a patient with hemoptysis. Who truly has hemoptysis, and who doesn't? I would urge physicians to be conservative. We somewhat empirically use the half-teaspoon measurement as the defining point. My intent is to have something quantifiable to make a distinction between individuals who truly have hemoptysis and gross blood and those who perhaps have a little bronchitis or a recent bronchoscopy and have pink-tinged sputum. If a patient truly has hemoptysis, play it conservatively and do not administer bevacizumab.

DR LOVE: Where are we today in terms of understanding the potential risk factors for pulmonary hemorrhage and cavitation, for example?

DR SANDLER: We and others have attempted to define which patients with nonsquamous NSCLC are at higher risk. In a retrospective analysis of ECOG

Phase II and Phase III data, the only potential risk factor for pulmonary hemorrhage that stood out was baseline hemoptysis (Sandler 2009). During analysis of the ARIES and SAiL data a number of potential factors were investigated, including tumor size larger or smaller than three centimeters, tumor location — central versus peripheral — and baseline cavitation. None of those panned out (Kumar 2010; Wozniak 2010).

Track 8

DR LOVE: What are your thoughts on Mark Socinski's presentation at ASCO 2010 comparing carboplatin/*nab* paclitaxel to carboplatin/paclitaxel in the front-line treatment of metastatic NSCLC?

DR SANDLER: This large randomized study reported improved response rates on the *nab* paclitaxel arm. Patients with squamous cell histology also fared well on *nab* paclitaxel (Socinski 2010; [4.2]). We await data on progression-free and overall survival, which may be presented at ASCO 2011. ■

4.2

Efficacy of Carboplatin/*Nab* Paclitaxel versus Carboplatin/Paclitaxel as First-Line Therapy for Advanced Non-Small Cell Lung Cancer

Response by independent review	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
Response rate — **all patients**	25% (n = 531)	33% (n = 521)	1.31	0.005
Response rate — **squamous histology**	24% (n = 221)	41% (n = 228)	—	<0.001
Response rate — **nonsquamous histology**	25% (n = 310)	26% (n = 292)	—	0.808

* Response ratio > 1 favors *nab* paclitaxel

Socinski MA et al. *Proc ASCO* 2010;**Abstract LBA7511**.

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**.

Kumar P et al. **Baseline (BL) radiographic characteristics and severe pulmonary hemorrhage (SPH) in bevacizumab (BV)-treated non-small cell lung cancer (NSCLC) patients (pt): Results from ARIES, an observational cohort study (OCS).** *Proc ASCO* 2010;**Abstract 7619**.

Sandler AB et al. **Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with carboplatin and paclitaxel plus bevacizumab.** *J Clin Oncol* 2009;27(9):1405-12.

Socinski MA et al. **Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases.** *J Clin Oncol* 2009;27(31):5255-61.

Wozniak AJ et al. **Clinical outcomes (CO) for special populations of patients (pts) with advanced non-small cell lung cancer (NSCLC): Results from ARIES, a bevacizumab (BV) observational cohort study (OCS).** *Proc ASCO* 2010;**Abstract 7618**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the IPASS trial, patients with advanced, EGFR wild-type NSCLC who received gefitinib had a significantly improved progression-free survival compared to those who received carboplatin/paclitaxel.**
   a. True
   b. False

2. **In a Phase I trial of crizotinib for patients with ALK-positive NSCLC, the objective response rate was _____.**
   a. 14 percent
   b. 33 percent
   c. 57 percent

3. **A Phase II trial of erlotinib and ARQ 197 versus erlotinib and placebo for patients with previously treated, EGFR inhibitor-naïve locally advanced or metastatic NSCLC reported that the addition of ARQ 197 to erlotinib _____ progression-free survival when compared to erlotinib and placebo.**
   a. Prolonged
   b. Did not prolong

4. **In the Memorial Sloan-Kettering Cancer Center experience, patients who developed acquired resistance to erlotinib or gefitinib had improvement in symptoms and decreases in SUVmax after restarting the EGFR TKI.**
   a. True
   b. False

5. **A Phase III study is currently evaluating BIBW 2992 (afatinib) versus _____ as first-line therapy for patients with Stage IIIB or IV adenocarcinoma of the lung harboring EGFR activating mutations.**
   a. Carboplatin/paclitaxel in combination with bevacizumab
   b. Gefitinib
   c. Cisplatin/pemetrexed

6. **In the Phase II study of first-line carboplatin/pemetrexed/bevacizumab followed by maintenance therapy for NSCLC reported by Patel and colleagues, maintenance therapy consisted of _____.**
   a. Bevacizumab
   b. Pemetrexed
   c. Bevacizumab and pemetrexed

7. **Which subset of patients experienced a survival improvement in a Phase II, randomized study of the liposomal vaccine BLP25, which prompted the ongoing Phase III START study?**
   a. Stage II
   b. Stage IIIB
   c. Stage IV

8. **A retrospective analysis of data from the ECOG-E4599 trial evaluating the addition of bevacizumab to carboplatin/paclitaxel for patients with advanced NSCLC reported that onset of high blood pressure during treatment with carboplatin/paclitaxel/bevacizumab may be associated with improved outcomes.**
   a. True
   b. False

9. **The ARIES study has shown safety with bevacizumab in which subgroup(s) of patients with NSCLC?**
   a. Elderly patients (older than age 70)
   b. Patients with central nervous system metastases
   c. Patients receiving concurrent anticoagulation therapy
   d. Patients with ECOG PS 2 disease
   e. All of the above

10. **Carboplatin/*nab* paclitaxel has shown an improvement in response rates in the _____ subtype of NSCLC when compared to standard carboplatin/paclitaxel.**
    a. Squamous
    b. Nonsquamous
    c. Both squamous and nonsquamous

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 1, 2011

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

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Development and use of reversible and irreversible EGFR TKIs in NSCLC	4 3 2 1	4 3 2 1
Liposomal MUC1 vaccine BLP25 in Stage III NSCLC	4 3 2 1	4 3 2 1
Results of a Phase III study of first-line carboplatin with *nab* paclitaxel compared to paclitaxel in advanced NSCLC	4 3 2 1	4 3 2 1
Gender-related differences in the incidence, biology and outcomes of NSCLC	4 3 2 1	4 3 2 1
PointBreak: A Phase III study of pemetrexed/carboplatin/bevacizumab → maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen in Stage IIIB/IV nonsquamous NSCLC	4 3 2 1	4 3 2 1
Safety of bevacizumab in patient subsets with advanced NSCLC	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain:.....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

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

As a result of this activity, I will be able to:

- Identify distinct subtypes of adenocarcinoma of the lung, including those with EGFR mutations and those with EML4-ALK gene fusions, and the investigational and approved treatment options for patients with these conditions..... 4 3 2 1 N/M N/A
- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible EGFR TKIs..... 4 3 2 1 N/M N/A
- Apply the results of recent clinical research to the rational selection of EGFR- or VEGF-inhibiting agents for patients with metastatic non-small cell lung cancer (NSCLC) ..... 4 3 2 1 N/M N/A
- Formulate individualized treatment plans addressing first-line therapy for recurrent or progressive NSCLC, considering unique patient and tumor characteristics. ..... 4 3 2 1 N/M N/A
- Identify patients with metastatic NSCLC who may benefit from individualized maintenance treatment approaches after successful completion of first-line systemic therapy..... 4 3 2 1 N/M N/A
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions..... 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

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 faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Nasser H Hanna, MD	4 3 2 1	4 3 2 1
Naiyer A Rizvi, MD	4 3 2 1	4 3 2 1
Jyoti D Patel, MD	4 3 2 1	4 3 2 1
Alan B Sandler, 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 faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

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

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Lung Cancer™ UPDATE

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Lung Cancer™ UPDATE

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