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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 EML4-ALK gene fusions, and the investigational and approved treatment options for patients with these biomarkers.
- Describe emerging efficacy and safety data on irreversible EGFR tyrosine kinase inhibitors, and identify patients who might benefit from participation in clinical trials evaluating these novel agents.
- 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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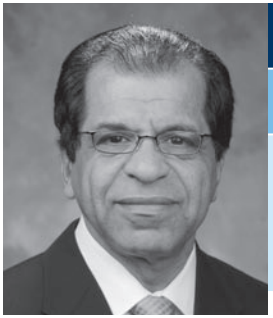


INTERVIEW

Chandra P Belani, MD

Dr Belani is Miriam Beckner Distinguished Professor of Medicine at Penn State College of Medicine and Deputy Director of the Penn State Hershey Cancer Institute in Hershey, Pennsylvania.

Tracks 1-13

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What are your thoughts on maintenance treatment for patients with metastatic non-small cell lung cancer (NSCLC)?

DR BELANI: I believe maintenance therapy is a new treatment paradigm in advanced NSCLC, but some skepticism still exists regarding its role.

In our recent study, the use of maintenance pemetrexed after four cycles of platinum-based chemotherapy was associated with significant improvements in progression-free survival and overall survival compared to placebo maintenance. The preplanned subset analysis of patients with nonsquamous cell

histology revealed a provocative 5.2-month improvement in median overall survival. In this intent-to-treat analysis, significant survival advantages were observed in the entire population.

DR LOVE: How do you approach maintenance treatment for patients with EGFR mutation-positive advanced NSCLC?

DR BELANI: In the SATURN study of erlotinib as maintenance treatment for patients with advanced NSCLC, erlotinib was associated with a significant improvement in median progression-free survival and highly significant survival advantages in patients with EGFR mutations, with a *p*-value of less than 0.0001 (Cappuzzo 2010). Based on these data, patients with EGFR mutations should receive maintenance treatment with erlotinib. Otherwise, patients with

1.1

PARAMOUNT: Efficacy and Safety of Maintenance Pemetrexed (Pem) with Best Supportive Care (BSC) versus Placebo with BSC Immediately After Induction Therapy with Pem and Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer

Efficacy — Independent review*	Pem + BSC (n = 316)	Placebo + BSC (n = 156)
Median progression-free survival (PFS), from maintenance	3.9 months	2.6 months
Response rate	2.8%	0.6%
Complete response	0%	0%
Partial response	2.8%	0.6%
Stable disease	69%	59%
Select Grade 3 or 4 adverse events	**Pem (n = 359)**	**Placebo (n = 180)**
Fatigue†	4.2%	0.6%
Anemia†	4.5%	0.6%
Neutropenia†	3.6%	0%
Leukopenia	1.7%	0%
Sensory neuropathy	0.3%	0.6%
Mucositis/stomatitis	0.3%	0%
ALT (SGPT)	0.3%	0%

Conclusions

- The trial met its primary PFS endpoint with pem continuation maintenance therapy resulting in a significant benefit compared to placebo for patients with advanced nonsquamous non-small cell lung cancer.
- Pem maintenance was well tolerated.
- Mature overall survival data are pending.

* 88% of patients were independently reviewed (472/539)
† Statistically significant between arms ($p \leq 0.05$)

Paz-Ares LG et al. *Proc ASCO* 2011;**Abstract CRA7510**.

nonsquamous cell disease are good candidates for pemetrexed maintenance, and patients with a poor performance status should not receive maintenance therapy.

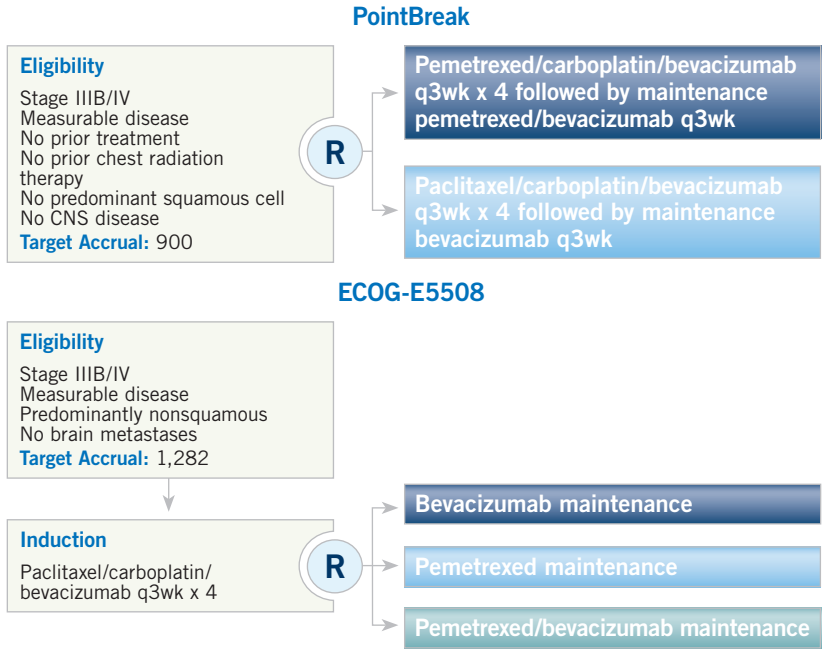
DR LOVE: How do you approach maintenance in patients with nonsquamous tumors who receive pemetrexed in the up-front setting?

DR BELANI: In clinical practice, pemetrexed is being continued into the maintenance setting, and the platinum agent is being discontinued. The PARAMOUNT trial (Paz-Ares 2011; [1.1]) is evaluating induction therapy with cisplatin/pemetrexed followed by maintenance with pemetrexed versus placebo.

The PointBreak study (Patel 2009) is evaluating the combination of carboplatin, pemetrexed and bevacizumab followed by maintenance with bevacizumab and pemetrexed compared to the investigational regimen used in the ECOG-E4599 trial — carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance (1.2). The PointBreak study is attempting to answer two different questions. One question is in the up-front setting and the other is in the maintenance setting.

1.2

Key Trials of Maintenance Therapy in Advanced Non-Small Cell Lung Cancer



CNS = central nervous system

www.clinicaltrials.gov. Identifiers NCT00762034 and NCT01107626.

Another maintenance therapy trial, ECOG-E5508, is studying the use of combination pemetrexed and bevacizumab (1.2). Patients are randomly assigned to maintenance with single-agent bevacizumab, single-agent pemetrexed or the combination of pemetrexed and bevacizumab.

DR LOVE: Outside of a research setting, how do you treat metastatic, EGFR-negative, EML4-ALK-negative adenocarcinoma?

DR BELANI: As a member of ECOG, I generally recommend either carboplatin/paclitaxel with or without bevacizumab followed by maintenance therapy with bevacizumab or the ECOG-E4599 regimen (Sandler 2006). The alternative is to administer carboplatin and pemetrexed, which I usually use without bevacizumab, and then use single-agent pemetrexed as maintenance therapy.

In North America, we substitute carboplatin for cisplatin, as the age-old controversy continues about which platinum agent is optimal.

DR LOVE: What is your approach to the treatment of metastatic squamous cell lung cancer?

DR BELANI: We tend to use carboplatin/paclitaxel or carboplatin/docetaxel. Carboplatin/gemcitabine is also available, but I don't favor it because of the associated thrombocytopenia.

Tracks 5-6

DR LOVE: What do we know about resistance to EGFR inhibitors?

DR BELANI: Sometime during treatment with reversible EGFR inhibitors, the disease eventually progresses. We are unsure whether this is attributable to MET gene amplification or the development of T790 mutation in the EGFR gene, which may be present at disease onset, but this type of disease stops responding to reversible EGFR inhibitors (Belani 2010).

For patients with EGFR mutations, the debate is whether to continue using the EGFR TKI while adding a new drug or whether an irreversible inhibitor of EGFR should be used instead.

Afatinib is an irreversible inhibitor of both EGFR — or HER1 — and HER2. A hint of activity has been seen in the Phase IIb/III clinical trial, in which afatinib was administered to patients whose disease progressed after 12 weeks or more of erlotinib or gefitinib.

Compared to placebo, a provocative and significant 2.2-month improvement in progression-free survival was observed with afatinib (Miller 2010; [1.3]), but no improvement in survival was evident because the patients on the placebo arm were crossed over to active treatment after only three to six weeks.

I believe afatinib is quite active, and the ongoing clinical trials for patients with EGFR mutations will probably show efficacy compared to combination chemotherapy in the front-line setting. ■

1.3

LUX-Lung 1: A Phase IIb/III Trial of Afatinib (BIBW 2992) with Best Supportive Care (BSC) versus Placebo and BSC for Patients with Non-Small Cell Lung Cancer Progressing on Chemotherapy and Erlotinib/Gefitinib

	Afatinib + BSC (n = 390)	Placebo + BSC (n = 195)	Hazard ratio	*p*-value
Efficacy				
Median overall survival	10.78 months	11.96 months	1.08	NS
Median progression-free survival	3.3 months	1.1 months	0.38	<0.0001
Disease control rate at eight weeks	58%	19%	—	<0.0001
Overall response rate	7.4%	0.5%	—	<0.01

NS = not significant

Miller VA et al. *Proc ESMO* 2010;**Abstract LBA1**.

SELECT PUBLICATIONS

Belani CP. **The role of irreversible EGFR inhibitors in the treatment of non-small cell lung cancer: Overcoming resistance to reversible EGFR inhibitors.** *Cancer Invest* 2010;28(4):413-23.

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.

Miller VA et al. **Phase IIB/III double-blind randomized trial of afatinib (BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2) + best supportive care (BSC) versus placebo + BSC in patients with NSCLC failing 1–2 lines of chemotherapy and erlotinib or gefitinib (LUX-Lung 1).** *Proc ESMO* 2010;**Abstract LBA1**.

Patel JD et al. **Treatment rationale and study design for the PointBreak study: A randomized, open-label phase III study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.** *Clin Lung Cancer* 2009;10(4):252-6.

Paz-Ares LG et al. **PARAMOUNT: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC).** *Proc ASCO* 2011;**Abstract CRA7510**.

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

INTERVIEW

Harvey I Pass, MD

Dr Pass is Professor of Surgery and Cardiothoracic Surgery and Director of the Division of Thoracic Surgery at NYU Langone Medical Center in New York, New York.

Tracks 1-12

Track 1 **Case discussion:** A 72-year-old man and prior smoker who underwent partial laryngectomy for ENT cancer three years ago is diagnosed with Stage IIIA squamous cell NSCLC and receives concurrent cisplatin/etoposide and radiation therapy

Track 2 Endobronchial ultrasound biopsy for staging mediastinal lymph nodes

Track 3 Objectives of induction chemo-radiation therapy for patients with operable Stage III NSCLC

Track 4 Interaction between induction chemotherapy with or without radiation therapy and operative procedure on surgical morbidity

Track 5 Effectiveness of chemotherapy and definitive radiation therapy versus chemoradiation therapy and surgery in NSCLC

Track 6 **Case discussion:** A 58-year-old woman and former smoker with adenocarcinoma of the left upper lung and positive N2 disease in the aortopulmonary window receives concurrent chemoradiation therapy

Track 7 Obtaining adequate tissue from needle aspirates for biomarker assessment

Track 8 **Case discussion:** A 65-year-old man with a smoking history diagnosed with EGFR-mutant, metastatic NSCLC experiences disease progression while receiving carboplatin/pemetrexed and has a complete response with erlotinib

Track 9 Toxicity of chemotherapy with definitive radiation therapy prior to surgical resection

Track 10 Clinical investigations of stereotactic body radiation therapy (SBRT) versus segmentectomy for the local treatment of NSCLC

Track 11 Use of SBRT for elderly patients with NSCLC

Track 12 New developments in the treatment of mesothelioma

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: For a patient with suspicious mediastinal lymph nodes, do you typically biopsy the primary tumor first, or do you immediately evaluate the lymph nodes?

DR PASS: For a patient with suspicious mediastinal lymph nodes, we go directly to the nodes, and we do so with endobronchial ultrasound (EBUS) rather than mediastinoscopy.

EBUS is necessary in cases of large, PET-positive lymph nodes. The learning curve for this approach requires about 50 cases, but as you gain experience the technique also improves.

DR LOVE: How would you compare the morbidity of EBUS to mediastinoscopy?

DR PASS: The morbidity with EBUS is certainly lower than it is with mediastinoscopy. Surprisingly, ascending mediastinitis has been reported with EBUS a couple of times. This occurs when the lymph node was biopsied and the mediastinum subsequently became infected. However, compared to the concerns regarding bleeding and recurrent laryngeal nerve injuries with mediastinoscopy, the morbidity is much lower.

It is definitely a user-directed procedure. Certain people have used EBUS considerably and are absolute experts, and that is the trend. Eventually, this initial evaluation will be conducted by people who've performed it so many times that the sensitivity will be extremely high.

DR LOVE: How long does the procedure typically take?

DR PASS: It can take 40 minutes to an hour and a half with multiple lymph nodes because you're aspirating the nodes. You're performing at least three aspirations — finding the lymph nodes, preparing the slides and reading the slides. It can take as long as a mediastinoscopy, if not longer.

DR LOVE: After performing EBUS on a patient, how do you assess the next steps?

DR PASS: At our institution, if we identify a positive lymph node, we prefer to administer induction therapy first and then operate. We have different protocols, but most of the time patients receive as induction cisplatin/etoposide with radiation therapy.

DR LOVE: What's the objective of induction therapy? Can it change the procedure?

DR PASS: In a randomized trial for patients with Stage IIIA disease, no significant difference was observed in the number of pneumonectomies between the induction arm and the surgery arm (Nagai 2003).

I believe one of the more important prognostic signs in all the studies is that if you're able to obtain a robust response to induction therapy in the mediastinum, then those patients seem to benefit from a doubled survival rate in the surgical series. The goal of induction therapy is a response that is histologically proven to be a near-complete response in the mediastinum.

Track 4

DR LOVE: What are your thoughts on the effects of induction therapy on surgical morbidity?

DR PASS: It depends on the type of surgical procedure, which is controversial. In the literature, postinduction right pneumonectomies particularly have been associated with an increased chance of postoperative death (Martin 2001; [2.1]). Some recent papers have stated that we can perform pneumonectomies, but we need to define whether that decision should be revisited for patients who have undergone induction therapy. A poll of the NCCN centers posed the question, would you perform a pneumonectomy for a patient for whom you could perform an R0 resection after induction therapy? Fifty-five percent of the centers replied that they would. So oncologists disagree about what to do for a patient who may undergo a pneumonectomy after induction therapy.

2.1

Morbidity and Mortality with Right Pneumonectomy After Induction Therapy for Lung Cancer

Surgical intervention	Total mortality, n (%)
Pneumonectomy (n = 97)	11 (11.3%)
Right pneumonectomy (n = 46)	11 (23.9%)
Lobectomy (n = 297)	7 (2.4%)

Martin J et al. *Ann Thorac Surg* 2001;72(4):1149-54.

Track 8

DR LOVE: Have you used an EGFR TKI, such as erlotinib, as part of induction therapy for any patients with EGFR mutations?

DR PASS: I recently had a patient whose initial presentation was not for induction. Rather, he presented with a large left upper lobe lesion with no mediastinal disease, and we thought he had an isolated site of metastasis to the rib. The disease progressed right through treatment with pemetrexed and carboplatin. We had the rib lesion biopsied because a large soft tissue component was present around it, and excellent core biopsies were obtained. We sent the samples out for mutational analysis, and the results came back as EGFR mutation-positive. After switching to erlotinib, the patient experienced a complete response and has been receiving it continuously for six months. ■

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INTERVIEW

Gregory J Riely, MD, PhD

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

Tracks 1-17

Track 1 **Case discussion:** A 70-year-old woman and never smoker with metastatic EGFR-mutant NSCLC receives afatinib on a clinical trial and remains progression free two years later

Track 2 Mutual exclusivity of K-ras, EGFR and ALK mutations in NSCLC

Track 3 Biomarker evaluation in lieu of smoking status

Track 4 Duration of disease control with reversible and irreversible EGFR TKIs in advanced, EGFR-mutant NSCLC

Track 5 Tolerability and side effects of afatinib

Track 6 Activity of afatinib in patients with advanced NSCLC after chemotherapy and an EGFR TKI in the LUX-Lung 1 study

Track 7 **Case discussion:** A 55-year-old woman and oligosmoker with EGFR and K-ras wild-type, Stage IV adenocarcinoma of the lung involving pleura and bone receives carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab for two years

Track 8 Crizotinib for ALK-positive advanced NSCLC

Track 9 Continuation of EGFR TKI therapy in responding patients who experience disease progression while receiving erlotinib

Track 10 Zoledronic acid, bevacizumab and osteonecrosis of the jaw

Track 11 Choice of first-line therapy and continuation or switch maintenance therapy for advanced NSCLC in the current era

Track 12 Potential role of *nab* paclitaxel as treatment for advanced squamous cell NSCLC

Track 13 Lack of concordance among pathologists in identification of adenocarcinoma, squamous cell and mixed histology NSCLC

Track 14 Treatment decision-making for adjuvant chemotherapy doublets in NSCLC

Track 15 Evaluating targeted agents as adjuvant therapy for EGFR-mutant and ALK-mutant NSCLC

Track 16 Ongoing neoadjuvant and adjuvant strategies evaluating the role of bevacizumab in early-stage NSCLC

Track 17 **Case discussion:** A 55-year-old woman and smoker with a Stage IIIA, EGFR wild-type adenocarcinoma of the lung receives neoadjuvant cisplatin/docetaxel, refuses surgery and remains disease free two years after definitive radiation therapy

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What is the approach to biomarker evaluation at your institution? Do you await results on EGFR mutation status before testing for ALK translocation?

DR RIELY: We use a staged evaluation system in which we initially evaluate patients for EGFR and K-ras mutations in parallel. If a patient has either an EGFR mutation or a K-ras mutation, we stop there because we know that those are driver mutations, which are unlikely to occur in tandem with an ALK translocation. If both of those results are negative, then we perform ALK FISH analysis, testing for a variety of rearrangements that can lead to activation of ALK, with EML4-ALK being the most common rearrangement.

DR LOVE: Does smoking history alter your approach to workup?

DR RIELY: No, we don't assume bias based on smoking history. We realize that even patients with significant smoking histories can have EGFR mutations or ALK rearrangements. Because patients with heavy smoking histories represent such a large proportion of our patients, we'd be missing a large number of patients if we didn't test them.

Track 9

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

DR RIELY: For patients with EGFR mutation-positive disease who respond well to erlotinib and then develop progressive disease, our first-line management would be enrollment on a clinical trial, but even at a large center like ours, a clinical trial is not always available. You have to come up with treatment decisions off protocol. For patients with EGFR mutations who experience a clear response to erlotinib, I continue erlotinib and add chemotherapy.

3.1

Changes in Tumor After EGFR 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%

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

In the absence of a randomized trial, I rely on results from a small study performed at our institution in which we selected patients with EGFR mutations who were developing resistance to EGFR TKI therapy. When we stopped treatment, we saw a relatively clear flare in tumor size. Their tumors grew and became more FDG avid on PET scans.

When we restarted erlotinib or gefitinib, the tumors either shrank or stabilized, and a number of patients again experienced some improvement in symptoms (Riely 2007; [3.1]).

Track 12

DR LOVE: What role do you envision for nanoparticle albumin-bound (*nab*) paclitaxel in advanced NSCLC?

DR RIELY: *Nab* paclitaxel is as efficacious as paclitaxel in NSCLC, and reported data are beginning to suggest that *nab* paclitaxel may work a little better for patients with squamous cell lung cancer (Socinski 2010; [3.2]). As we move forward, we need some prospective trials for patients with squamous cell lung cancer only.

Many of the big advancements in lung cancer — EGFR mutations, ALK, pemetrexed, bevacizumab — are for the most part restricted to patients with adenocarcinoma. Although the number of patients with squamous cell carcinoma is small, they still make up a significant proportion of patients with NSCLC, and an agent like *nab* paclitaxel may be a good option in that setting.

DR LOVE: What tends to be your initial systemic therapy for metastatic squamous cell carcinoma? Do you currently use *nab* paclitaxel in this setting?

DR RIELY: I typically administer gemcitabine/cisplatin if possible, but gemcitabine/carboplatin is also a reasonable option. I prefer that approach to carboplatin/paclitaxel. Our institution is somewhat restrictive in allowing us to use albumin-bound paclitaxel. The setting in which I've used it a number of times is for patients who have a hypersensitivity reaction to paclitaxel or docetaxel. Then I make the switch to *nab* paclitaxel.

3.2

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

Response rate by histological subtype	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
All patients (n = 531; 521)	25%	33%	1.31	0.005
Squamous (n = 221; 228)	24%	41%	—	<0.001
Nonsquamous (n = 310; 292)	25%	26%	—	0.808

* Response ratio >1 favors *nab* paclitaxel

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

Track 16

DR LOVE: What are your thoughts on ongoing research strategies evaluating the role of bevacizumab in early-stage NSCLC?

DR RIELY: The ECOG-E1505 trial is evaluating whether the addition of bevacizumab in the adjuvant setting provides a benefit. The study randomly assigns patients with resected lung cancer to chemotherapy alone or chemotherapy and bevacizumab. That's certainly the biggest trial ongoing in the adjuvant arena and certainly one with the most anticipated results.

At our institution, we've considered incorporating bevacizumab into induction chemotherapy. We know from the ECOG-E4599 study data that the addition of bevacizumab to carboplatin/paclitaxel significantly increases response rate, progression-free survival and overall survival (Sandler 2006).

We are evaluating bevacizumab with cisplatin/docetaxel (BEACON, NCT00130780). One interesting aspect of this trial is that we administer the first dose of bevacizumab a few weeks before the first dose of chemotherapy to study what effect bevacizumab has on its own. Tumor shrinkage with single-agent bevacizumab has been reported (Price 2009).

These are not partial responses by any measure for most patients, although the occasional patient has a tumor that cavitates as a result of that dose of bevacizumab.

After that single dose of bevacizumab, patients receive four cycles of neoadjuvant cisplatin/docetaxel and bevacizumab, followed by surgery and adjuvant bevacizumab alone. Not many significant toxicities have been associated with preoperative bevacizumab. ■

SELECT PUBLICATIONS

Miller VA et al. **Phase IIB/III double-blind randomized trial of afatinib (BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2) + best supportive care (BSC) versus placebo + BSC in patients with NSCLC failing 1–2 lines of chemotherapy and erlotinib or gefitinib (LUX-Lung 1).** *Proc ESMO* 2010;**Abstract LBA1**.

Price K et al. **Phase II study of induction and adjuvant bevacizumab in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) receiving induction docetaxel and cisplatin.** *Proc ASCO* 2009;**Abstract 7531**.

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.

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.

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* 2010;**Abstract LBA7511**.

INTERVIEW

Everett E Vokes, MD

Dr Vokes is John E Ultmann Professor of Medicine and Radiation and Cellular Oncology and Chairman of The University of Chicago's Department of Medicine in Chicago, Illinois.

Tracks 1-10

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the recent evolution of tissue biomarkers in the management of NSCLC?

DR VOKES: For approximately five years we've known that EGFR biomarkers matter, but we were debating which ones. The IPASS trial was the first instance in which we could say, "This means that a patient who does not have this biomarker should not receive the targeted agent in the first line and vice versa" (Mok 2009; [4.1]).

That has been solidified in the past year with the ALK fusion oncogene, for which a second targeted agent has become available — crizotinib. Crizotinib is associated with high response rates and seemingly good disease progression rates and perhaps overall survival as well, although that is somewhat premature.

4.1

IPASS: A Phase III Study of Up-Front Gefitinib versus Carboplatin/Paclitaxel in a Population of Asian Patients with Non-Small Cell Lung Cancer Phenotypically Enriched for EGFR Mutation

	Gefitinib	Carboplatin/ paclitaxel	Hazard ratio	*p*-value
PFS events (intent-to-treat population, N = 609; 608)	74.4%	81.7%	0.74	<0.001
PFS events (EGFR mutation-positive population, N = 132; 129)	73.5%	86.0%	0.48	<0.001
Response rates (EGFR mutation-positive population, N = 132; 129)	71.2%	47.3%	—	<0.001

PFS = progression-free survival

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

Dave Spigel presented data at ESMO on erlotinib with or without a c-MET inhibitor in the second- and third-line settings. Overall, no significant difference was observed in progression-free or overall survival, but a benefit was seen among c-MET overexpressors, although for those who had no or weak c-MET expression, addition of the agent was detrimental (Spigel 2010).

DR LOVE: What exactly is c-MET, and what's the epidemiology? How often do you see it, and where do you see it?

DR VOKES: c-MET is another receptor that has been shown to be overexpressed in tumors. It can also be mutated, but it's not mutated frequently and we're not sure yet, functionally, what the mutations mean. However, overexpression is observed commonly, and it can be inhibited. Inhibition can be achieved either by targeting an antibody to the ligand or by inhibiting the receptor directly. Two agents have been tested, including the receptor inhibitor ARQ 197 (Sandler 2011; [4.2, 4.3]), which showed a slight benefit as second-line treatment for c-MET overexpressors. Subset analysis of a second agent under development suggests that if you add it to erlotinib for overexpressors they will experience benefit.

4.2

Phase II Trial 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

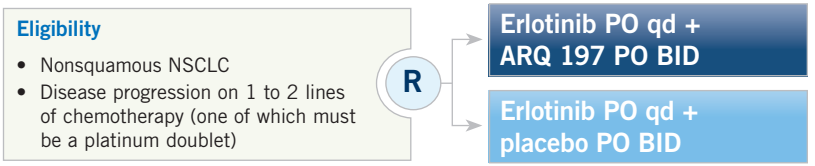
	E + A (n = 84)	E + placebo (n = 83)	Hazard ratio	*p*-value
Median progression-free survival	3.7 months	2.2 months	0.68	<0.05
Median overall survival	8.4 months	6.8 months	0.88	<0.52

Sandler A et al. *Proc ASCO* 2011;**Abstract TPS217**.

4.3

MARQUEE: A Phase III Trial of Erlotinib with ARQ 197 versus Erlotinib with Placebo for Patients with Previously Treated, Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT01244191 **Target Accrual:** 988 (Open)



Sandler A et al. *Proc ASCO* 2011;**Abstract TPS217**; **www.clinicaltrials.gov**, July 2011.

Track 5

DR LOVE: What are your thoughts on the selection of first-line therapy for squamous cell and nonsquamous cell metastatic NSCLC?

DR VOKES: I believe that it has become difficult for us to point to progress in squamous cell NSCLC in recent years. We don't have a good target in that population. Cetuximab may be of benefit, but the data aren't clear yet. We do know that pemetrexed is not the best agent for these patients, so we're left with carboplatin/paclitaxel or docetaxel and, based on Giorgio Scagliotti's trial evaluating cisplatin/gemcitabine versus cisplatin/pemetrexed, cisplatin and gemcitabine for patients with squamous cell NSCLC (Scagliotti 2008).

Also based on the Scagliotti study, I believe pemetrexed is the preferred agent for patients with adenocarcinoma (Scagliotti 2008). Bevacizumab is also a candidate for these patients.

DR LOVE: How do you make the decision about whether to use bevacizumab?

DR VOKES: It's a difficult decision. If you have a clear-cut bevacizumab case — adenocarcinoma, no EGFR mutation — administering carboplatin/paclitaxel/bevacizumab is perfectly reasonable. The alternative is carboplatin or cisplatin/pemetrexed. We have Phase II data supporting the use of carboplatin/pemetrexed/bevacizumab, but the data with that regimen compared to carboplatin/paclitaxel/bevacizumab are pending. Until then, these are equally valid options. I prefer cisplatin or carboplatin and pemetrexed. ■

SELECT PUBLICATIONS

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.

Spigel D et al. **Randomized multicenter double-blind placebo-controlled Phase III study evaluating METMAB, an antibody to MET receptor, in combination with erlotinib, in patients with advanced non-small-cell lung cancer.** *Proc ESMO* 2010;**Abstract LBA15**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The following trials are evaluating the use of maintenance therapy for patients with advanced NSCLC.**
   a. PointBreak
   b. PARAMOUNT
   c. ECOG-E5508
   d. All of the above

2. **During a Phase IIb/III trial for patients with NSCLC whose disease progressed on prior chemotherapy and an EGFR TKI, the use of afatinib was associated with significant differences in _____ compared to placebo.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b

3. **In the Memorial Sloan-Kettering Cancer Center experience, patients with acquired resistance to erlotinib or gefitinib experienced improvement in symptoms and decreases in tumor size after restarting the EGFR TKI.**
   a. True
   b. False

4. **Carboplatin/*nab* paclitaxel has demonstrated 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

5. **The ECOG-E1505 study 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

6. **For patients with resectable NSCLC, the BEACON trial is evaluating preoperative chemotherapy with _____.**
   a. Gefitinib
   b. Erlotinib
   c. Bevacizumab
   d. Both b and c
   e. None of the above

7. **A randomized trial for patients with Stage IIIA disease showed no significant difference in the number of pneumonectomies between the induction therapy arm and the surgery arm.**
   a. True
   b. False

8. **Crizotinib is a targeted agent used in the treatment of ALK-positive NSCLC.**
   a. True
   b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 2, 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
Phase III trial results with maintenance pemetrexed in advanced NSCLC	4 3 2 1	4 3 2 1
PointBreak and ECOG-E5508 studies evaluating maintenance bevacizumab and pemetrexed in advanced NSCLC	4 3 2 1	4 3 2 1
LUX-Lung 1 Phase III study results with afatinib in advanced NSCLC	4 3 2 1	4 3 2 1
Phase III trial results with carboplatin and either *nab* paclitaxel or standard-formulation paclitaxel as first-line therapy for advanced NSCLC	4 3 2 1	4 3 2 1
Reliability of histologic diagnosis of 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 EML4-ALK gene fusions, and the investigational and approved treatment options for patients with these biomarkers..... 4 3 2 1 N/M N/A
- Describe emerging efficacy and safety data on irreversible EGFR tyrosine kinase inhibitors, and identify patients who might benefit from participation in clinical trials evaluating these novel agents..... 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:.....

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 faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Chandra P Belani, MD	4 3 2 1	4 3 2 1
Harvey I Pass, MD	4 3 2 1	4 3 2 1
Gregory J Riely, MD, PhD	4 3 2 1	4 3 2 1
Everett E Vokes, 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).

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

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Lung Cancer™ UPDATE

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Lung Cancer™ UPDATE

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