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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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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 from 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

- Recognize the effect of quality disease staging on long-term clinical outcome for patients with non-small cell lung cancer (NSCLC).
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions.
- Appraise the role of definitive lung cancer surgery for Stage III NSCLC treated with preoperative therapy.
- Apply the results of recent clinical research to the rational selection of EGFR- or VEGF-inhibiting agents for patients with metastatic NSCLC.
- Identify patients with metastatic NSCLC who may benefit from individualized maintenance treatment approaches after successful completion of first-line systemic therapy.
- 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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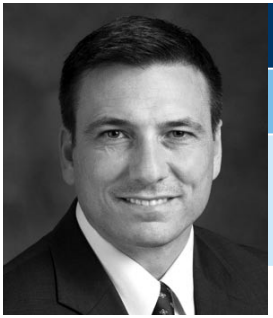

INTERVIEW

John Heymach, MD, PhD

Dr Heymach is Assistant Professor of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

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Track 2 Clinical use of tumor histology to identify patients to receive pemetrexed

Track 3 Reliability and accuracy of histologic diagnosis in NSCLC

Track 4 Ongoing studies with carboplatin/bevacizumab and pemetrexed in Stage IV adenocarcinoma of the lung

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Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Where are we today in terms of research on maintenance therapy for lung cancer?

DR HEYMACH: A long history exists of testing maintenance therapy for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and up until this past year we've had few successes. This year at ASCO, three different studies tested maintenance therapy — JMEN (Belani 2009), ATLAS (Miller 2009) and SATURN (Cappuzzo 2009) — and at some level, we'd have to say that all three were positive.

The JMEN trial was a large, well-designed, randomized study that evaluated the use of pemetrexed as maintenance therapy for patients with advanced NSCLC that had not progressed after four cycles of first-line platinum-containing doublet chemotherapy (Belani 2009). This demonstrated not only an improvement in progression-free survival but also a substantial prolongation in survival (1.1).

DR LOVE: An association was observed between tumor histology and outcome with maintenance pemetrexed (1.1), which has also been seen in other studies, and all of the benefit was observed in patients with adenocarcinoma of the lung.

DR HEYMACH: That's right. It was a confirmation of earlier studies and was consistent with the Scagliotti study, wherein patients with nonsquamous histology responded better to cisplatin/pemetrexed than to cisplatin/gemcitabine (Scagliotti 2008).

The best biological explanation for this association was also elucidated by Scagliotti's group in Italy. They identified several years ago that the levels of thymidylate synthase, which is one of the enzymes involved in metabolizing pemetrexed, was much higher in squamous cell carcinoma than in nonsquamous cell carcinoma (Ceppi 2006). Other differences are also present between

1.1

JMEN: Progression-Free and Overall Survival with Maintenance Pemetrexed (N = 663)

	Placebo	Pemetrexed	Hazard ratio	*p*-value
Progression-free survival	2.0mo	4.0mo	0.60	<0.00001
Nonsquamous (n = 481)	1.8mo	4.4mo	0.47	<0.00001
Squamous (n = 182)	2.5mo	2.4mo	1.03	0.896
Overall survival	10.6mo	13.4mo	0.79	0.012
Nonsquamous (n = 481)	10.3mo	15.5mo	0.70	0.002
Squamous (n = 182)	10.8mo	9.9mo	1.07	0.678

SOURCE: Belani CP et al. *Proc ASCO* 2009;**Abstract CRA8000**.

squamous and nonsquamous cell carcinoma in terms of the machinery for metabolizing pemetrexed. So these at least provide a plausible biologic mechanism for the association.

This is something we've adopted in practice, and of course the FDA label states that pemetrexed should be used for nonsquamous cell NSCLC.

Tracks 3-5

DR LOVE: What do we know about the accuracy of basic histologic diagnosis in non-small cell?

DR HEYMACH: Until recently, diagnosing the histology correctly wasn't critical once it was established that the disease was NSCLC because we did not treat adenocarcinoma or squamous cell carcinoma differently as long as the distinction between NSCLC and SCLC was clear.

However, as of this year histology makes a difference in treatment decision-making. A study presented at ASCO that looked into this issue has been characterized as disturbing. It compared the fidelity of histologic diagnoses among "expert" pathologists at major medical centers to that of community pathologists (Grilley-Olson 2009).

The concordance was lower than one would expect — approximately 70 percent. So in 30 percent of the cases disagreement prevails among pathologists about the histology, and that's not taking into account the substantial number of cases that are diagnosed as not otherwise specified. That puts us in a bind because the labels for pemetrexed and bevacizumab reflect histology.

DR LOVE: That raises an issue with the Belani study, which didn't use bevacizumab. Many patients with nonsquamous cell NSCLC would receive first-line chemotherapy with bevacizumab.

Do you think the strategy of using maintenance pemetrexed applies with bevacizumab on board?

DR HEYMACH: That's an excellent question. Can we extrapolate from the carboplatin/paclitaxel with bevacizumab triplet to pemetrexed/carboplatin with bevacizumab?

Jyoti Patel's Phase II study of carboplatin/pemetrexed/bevacizumab with maintenance pemetrexed and bevacizumab showed promising activity (Patel

1.2

Phase II Study of Pemetrexed/Carboplatin/Bevacizumab with Maintenance Pemetrexed and Bevacizumab as First-Line Therapy for Nonsquamous NSCLC (N = 49)

Efficacy	
Overall response rate	55%
Stable disease	33%
Median progression-free survival	7.8mo
Median overall survival	14.1mo

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

2009; [1.2]), and Phase III studies are ongoing. However, carboplatin/pemetrexed in combination with bevacizumab is not yet an established triplet regimen.

DR LOVE: For patients who receive carboplatin/paclitaxel/bevacizumab, once the carboplatin/paclitaxel is stopped do you continue the bevacizumab, and if so, do you bring in pemetrexed?

DR HEYMACH: Randomized Phase II data suggest a trend in favor of pemetrexed/bevacizumab compared to pemetrexed alone in the second-line setting (Herbst 2007), but that isn't the same as saying it will be better in the maintenance setting, in which patients may be receiving the drug for a longer period.

Studies are underway testing pemetrexed and bevacizumab as maintenance therapy. I discuss it with younger patients with nonsquamous cell NSCLC who want aggressive treatment, making it clear that we don't have Phase III data to support it yet.

Track 6

DR LOVE: Do you think these TKI maintenance studies are outdated because of the IPASS study? Shouldn't patients with mutations receive a TKI up front?

DR HEYMACH: That's another excellent question because in the IPASS trial they studied carboplatin/paclitaxel versus gefitinib in an Asian population enriched for EGFR mutations, and the response rate was dramatically higher for patients with EGFR mutations who received gefitinib compared to chemotherapy (Mok 2009; [1.3]).

Survival has not yet proved to be better for patients receiving the EGFR TKI, so sequencing may or may not make a difference. In light of the much better response rate with gefitinib, all patients with EGFR mutations should receive an EGFR TKI.

DR LOVE: Clearly the TKI should result in better quality of life than with chemotherapy.

DR HEYMACH: That's correct, especially with long-term treatment. We have patients who have received the EGFR TKIs for years. I have a handful of patients who have been treated for five or six years and are faring well. That's not the majority, but a substantial number of patients with EGFR mutations go on for years.

The biggest mistake that we could make would be administering a therapy to which patients are less likely to respond and then losing an opportunity to administer an EGFR TKI. Therefore, we always try to administer the EGFR TKI as first-line therapy for patients with EGFR mutations. ■

1.3

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 NSCLC

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
EGFR mutation unknown (n = 386; 394)	69.4%	80.2%	0.68 (0.58-0.81)	<0.001

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

"The efficacy of gefitinib seen in this study was coupled with lower incidences of alopecia, nausea, vomiting, neurotoxic symptoms, and myelosuppression than those seen with carboplatin-paclitaxel."

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

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INTERVIEW

Vincent A Miller, MD

Dr Miller is Associate Attending Physician of the Thoracic Oncology Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-13

Track 1 ATLAS: Bevacizumab with or without erlotinib after completion of first-line chemotherapy and bevacizumab for locally advanced, recurrent or metastatic NSCLC

Track 2 Clinical implications of the ATLAS trial

Track 3 Rebiopsy for patients with acquired resistance to EGFR TKIs in NSCLC

Track 4 K-ras mutations and response to EGFR TKIs in adenocarcinoma of the lung

Track 5 LUX-Lung 2: A Phase II study of BIBW 2992 for patients with adenocarcinoma of the lung and activating EGFR mutations after failure of one line of chemotherapy

Track 6 LUX-Lung 1: A Phase IIB/III trial of BIBW 2992 and best supportive care for patients with NSCLC failing on one to two lines of chemotherapy and an EGFR TKI

Track 7 Planned trial of BIBW 2992 versus chemotherapy in the first-line setting for patients with adenocarcinoma of the lung and EGFR mutations

Track 8 **Case discussion:** An 82-year-old woman, a never smoker, with left-sided, EGFR wild-type and right-sided, EGFR mutation-positive adenocarcinoma of the lung and right hilar adenopathy

Track 9 **Case discussion:** A 62-year-old woman with a 20-pack-year history of smoking underwent resection of a T1N0 adenocarcinoma one and a half years ago and subsequently developed multiple bone metastases

Track 10 Association between number of pack-years smoked and likelihood of EGFR mutation

Track 11 **Case discussion:** A 38-year-old woman who never smoked and developed symptomatic, EGFR and K-ras wild-type adenocarcinoma of the lung and bone, brain and visceral metastases and initially received pemetrexed/cisplatin/bevacizumab/erlotinib

Track 12 FLEX biomarker analysis: K-ras mutation and response to cetuximab in NSCLC

Track 13 Testing for EML4-ALK mutation in clinical practice for patients with NSCLC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the ATLAS trial results that you presented at ASCO this year?

DR MILLER: In the ATLAS trial, patients who were bevacizumab eligible received four cycles of a platinum-based doublet with bevacizumab (Miller 2009). Afterward, patients who had not experienced disease progression were randomly assigned to treatment with bevacizumab and either erlotinib or placebo.

We demonstrated that the median progression-free survival was improved by slightly more than one month — from 3.75 to 4.8 months — with a hazard ratio of 0.72 in favor of the combination arm (Miller 2009; [2.1]). The curves appear robust, with a clear separation early and sustained over time. The number of patients who could be evaluated at a one-year benchmark was small, but the difference appeared to be maintained. So this was an interesting and encouraging result.

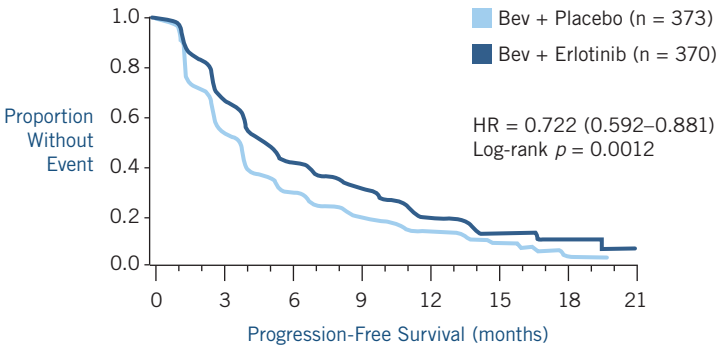
DR LOVE: What are the clinical implications of these results?

DR MILLER: The consensus is that this is not a uniformly applicable strategy unless we see a clear survival benefit with the combination. The number of events that were available at the time of analysis was too small for a comment on survival, but an assessment is expected by year's end.

In my mind, this strategy might be chosen if a patient is about to start maintenance therapy with bevacizumab and the cancer has responded somewhat yet the patient remains symptomatic from the disease.

2.1

ATLAS: Progression-Free Survival (ITT Population, Investigator Assessment)



	Bevacizumab + placebo	Bevacizumab + erlotinib
Median PFS	3.75 months	4.76 months
PFS rate		
Three months	53.4%	67.7%
Six months	28.4%	40.3%

SOURCE: With permission from Miller VA et al. *Proc ASCO* 2009;**Abstract LBA8002**.

Tracks 5-7

DR LOVE: Would you describe the new agent BIBW 2992 and the trial that you presented at ASCO?

DR MILLER: BIBW 2992 is a dual inhibitor of EGFR and HER2. It binds irreversibly in the ATP binding pocket, in contrast to erlotinib or gefitinib, which bind reversibly. Preclinically, it has demonstrated activity against what we call the T790M gatekeeper mutation or resistance mutation that arises commonly in the patients with EGFR-addicted disease when it progresses on treatment. So a key clinical question is whether BIBW 2992 will play a role for patients with EGFR-mutant lung cancer that has acquired resistance to the TKIs.

The Phase II trial (LUX-Lung 2) asked, how active is BIBW 2992 in patients with EGFR mutations who have not previously received a kinase inhibitor (Shih 2009; [2.2])? We observed a nice response rate and progression-free survival, which I believe will make this agent "a player" in the field.

DR LOVE: Do the data appear to be comparable, indirectly, to what's been observed with erlotinib?

DR MILLER: They appear to be in the same ballpark. It's difficult to interpret too much across studies, but it may be that in patients with exon 19 and exon 21 EGFR mutations, BIBW 2992 will be better because they are sensitive.

DR LOVE: What about the other trial evaluating BIBW 2992 with the patients who had experienced disease progression on erlotinib?

DR MILLER: That's a challenging group. The Phase IIB/III (LUX-Lung 1) trial attempts to salvage patients for whom one or two lines of platinum-containing chemotherapy had failed and who had experienced disease progression on gefitinib or erlotinib (Yang 2009). After disease progression, patients

2.2

LUX-Lung 2 Trial: Best Response According to RECIST and Type of EGFR Mutation in Patients Receiving Second-Line BIBW 2992 (N = 67 Evaluable)

	Mutation type			
	Del 19	L858R	Other	Total
Partial reponse (PR) + complete response (CR)	75%	66%	36%	**64%**
Stable disease (SD)	25%	28%	55%	31%
Disease control rate (PR + CR + SD)	100%	94%	91%	**95%**
Progressive disease	0%	6%	9%	4%

Median progression-free survival (second line): 10.2 months

SOURCE: Shih J et al. *Proc ASCO* 2009;**Abstract 8013**.

are randomly assigned to receive best supportive care and BIBW 2992 or a placebo in a two-to-one fashion. This trial has not completed accrual, so the results are unknown.

DR LOVE: Where do you think we're heading with BIBW 2992?

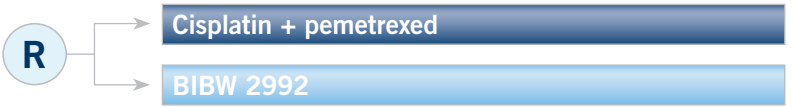
DR MILLER: We need the results of the Phase III pivotal trial, and we hope it does something for these patients with acquired resistance to the TKIs because we need an agent for them.

One planned study will be analogous to the IPASS study (LUX-Lung 3; [2.3]), with the exception that patients will be genotyped beforehand. Patients with the EGFR-activating mutations will be randomly assigned to either chemotherapy or BIBW 2992.

2.3

LUX-Lung 3: A Phase III Trial of First-Line Chemotherapy versus BIBW 2992 for Patients with Stage IIIB/IV Adenocarcinoma of the Lung with EGFR-Activating Mutations

Protocol ID: EUDRACT 2008-005615-18; **Target Accrual:** 330



Eligibility

Untreated Stage IIIB or IV adenocarcinoma of the lung; EGFR-activating mutation by central laboratory; no active brain metastases; no preexisting interstitial lung disease; no significant or recent acute GI disorders with diarrhea as a major symptom; no history or presence of clinically relevant cardiovascular abnormalities

SOURCE: **www.clinicaltrials.gov**.

Track 13

DR LOVE: Would you discuss the emerging data with the anaplastic lymphoma kinase (ALK) fusion mutation and clinical implications?

DR MILLER: The frequency of this abnormality in patients who are never smokers is as high as 22 percent (Shaw 2009). At some point we may be able to test for this more widely, but if there's a patient for whom you should lobby for testing, it's the young patient, particularly a nonsmoker or a never smoker who had no demonstrable EGFR or K-ras mutation.

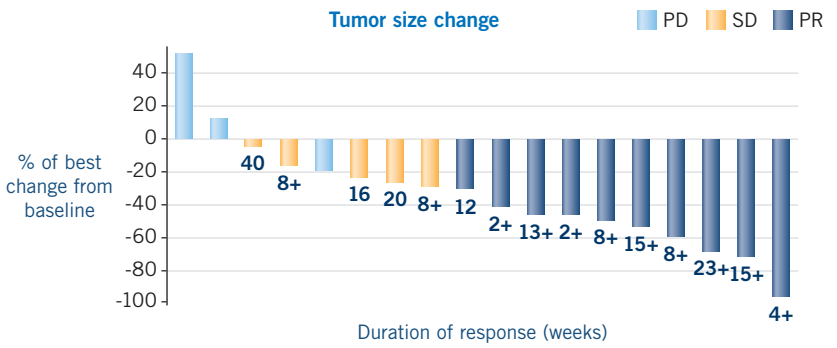
DR LOVE: If you do identify a patient with this ALK fusion mutation, how do you approach treatment?

DR MILLER: I would look for trials of PF-02341066, which is the drug that targets the ALK fusion mutation (Kwak 2009; [2.4]).

PF-02341066 was designed initially for tumors that were either mutated or amplified for MET, and it was serendipity that it was also found to inhibit this other mutated kinase, EML4-ALK. ■

2.4

Tumor Response to PF-02341066 in 19 Patients with Pretreated NSCLC and ALK Fusion Mutations



One patient had clinical progression and discontinued without radiographic confirmation.

Overall response rate: 53% Disease control rate at 8 weeks: 79%

SOURCE: With permission from Kwak EL et al. *Proc ASCO* 2009;**Abstract 3509**.

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INTERVIEW

Mark A Socinski, MD

Dr Socinski is Professor of Medicine of the Multidisciplinary Thoracic Oncology Program at the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Tracks 1-13

Select Excerpts from the Interview

Tracks 3, 6

DR LOVE: What's your treatment approach for advanced squamous cell NSCLC?

DR SOCINSKI: For a patient with a good performance status, I consider two assessments: What's the best chemotherapy doublet for this patient, and could a targeted agent add benefit to the chemotherapy?

I typically use carboplatin and paclitaxel for advanced disease, although I believe that docetaxel is perfectly fine. Currently, the one targeted agent that bears consideration for patients with squamous cell NSCLC is cetuximab.

The FLEX trial demonstrated that cetuximab can have a clear effect independent of histology (Pirker 2009). The hazard ratio for patients with squamous cell NSCLC versus adenocarcinomas was the same. In the Caucasian patient population, the hazard ratio calculated in the FLEX trial was 0.8 (3.1), which is similar to the hazard ratio with bevacizumab in ECOG-E4599 (Sandler 2006; [3.2]).

DR LOVE: How do you approach the duration of treatment and maintenance therapy?

DR SOCINSKI: I administer four cycles. I tend to continue cetuximab as maintenance until disease progression. I use the same approach with bevacizumab.

3.1

FLEX: Outcome for Patients with EGFR-Expressing Advanced NSCLC Treated with Cisplatin/Vinorelbine (CV) with or without Cetuximab as First-Line Therapy

Efficacy	CV + cetuximab	CV	Hazard ratio (95% CI)	*p*-value
Median overall survival				
All patients	11.3mo	10.1mo	0.871 (0.762-0.996)	0.044
Caucasians	10.5mo	9.1mo	0.803 (0.694-0.928)	0.003
Asians	17.6mo	20.4mo	—	NS
Progression-free survival	4.8mo	4.8mo	0.943 (0.825-1.077)	NS
Time to treatment failure	4.2mo	3.7mo	0.860 (0.761-0.971)	0.015

CI = confidence interval; NS = not significant

SOURCE: Pirker R et al. *Lancet* 2009;373(9674):1525-31.

3.2

ECOG-E4599: Overall and Progression-Free Survival of Patients with Previously Untreated Metastatic Nonsquamous NSCLC Treated with Bevacizumab (B) in Combination with Paclitaxel (P) and Carboplatin (C)

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

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

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

Track 8

DR LOVE: What's your approach for patients with advanced adenocarcinoma of the lung who are bevacizumab eligible?

DR SOCINSKI: I've treated the majority of these patients with carboplatin/paclitaxel and bevacizumab, but I'm intrigued by the carboplatin/pemetrexed/bevacizumab combination. We have Phase III data indicating that first-line cisplatin/pemetrexed is superior to cisplatin/gemcitabine (Scagliotti 2008), and Phase II randomized trial data indicate that carboplatin/pemetrexed is superior to carboplatin/docetaxel for patients with previously untreated Stage IIIB/IV NSCLC (Obasaju 2009).

We are also running a Phase III trial, JMHD, that compares carboplatin/paclitaxel and bevacizumab to carboplatin/pemetrexed and bevacizumab.

Tracks 10-11

DR LOVE: What's your treatment approach for patients with advanced adenocarcinoma of the lung whose disease is EGFR mutation-positive?

DR SOCINSKI: First off, I do believe we need to do more EGFR mutation testing in lung cancer. I was influenced by the IPASS trial results (Mok 2009), so for a patient with an EGFR mutation, particularly in exon 19 or exon 21, I begin with erlotinib.

If the patient's disease is progressing rapidly, I'll switch to chemotherapy. Patients with adenocarcinomas and EGFR mutations are well suited for a carboplatin/pemetrexed and bevacizumab regimen. ■

SELECT PUBLICATIONS

Einhorn LH. **First-line chemotherapy for non-small-cell lung cancer: Is there a superior regimen based on histology?** *J Clin Oncol* 2008;26(21):3485-6.

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Herbst RS, Hirsch FR. **Patient selection criteria and the FLEX study.** *Lancet* 2009;373(9674):1497-8.

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

Obasaju CK et al. **Final results of a randomized phase II trial of pemetrexed (P) + carboplatin (Cb) ± enzastaurin (E) versus docetaxel (D) + Cb as first-line treatment of patients (pts) with stage IIIB/IV non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;**Abstract 8037**.

Pirker R et al. **Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): An open-label randomized phase III trial.** *Lancet* 2009;373(9674):1525-31.

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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.

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.

INTERVIEW

Kenneth O'Byrne, MD

Dr O'Byrne is Professor in Medical Oncology at St James's Hospital in Dublin, Ireland.

Tracks 1-5

Track 1 Overview of the results of clinical trials evaluating first-line chemotherapy plus cetuximab for advanced NSCLC

Track 2 FLEX analysis of molecular predictors of outcome with cetuximab in NSCLC

Track 3 Association between rash and outcome in patients treated with cetuximab

Track 4 First-line treatment algorithm for patients with advanced NSCLC

Track 5 Tolerability of cetuximab-induced rash

Select Excerpts from the Interview

Track 1

DR LOVE: Would you provide an overview of the clinical trial results with first-line chemotherapy and cetuximab in advanced NSCLC?

DR O'BYRNE: The FLEX trial, an international trial that recruited more than 1,000 patients, demonstrated a five-week overall survival benefit with the addition of cetuximab to chemotherapy (Pirker 2009; [3.1]). Three other randomized controlled trials — two Phase II and one Phase III — reported similar magnitudes of overall survival benefit, and the results seem to be consistent across studies (Butts 2007; Lynch 2008; Rosell 2008).

DR LOVE: One issue with the FLEX trial was that even though a survival benefit was reported, no progression-free survival benefit was evident.

DR O'BYRNE: I believe that should be put in context with the other studies. It depends on how you define progression-free survival. In my view, progression-free survival is not as firm an endpoint as overall survival.

I believe the consistency of results across the four studies — survival benefit of approximately five to six weeks across all the studies with more than 2,000 patients — is encouraging. If the magnitude of survival benefit varied from trial to trial, then we would have a reason for concern. A formal meta-analysis was performed for these four trials, evaluating the overall issues such

as progression-free survival and overall survival. The results were presented at the 2009 World Conference on Lung Cancer (Thatcher 2009; [4.1]).

4.1

Meta-Analysis of Randomized Phase II/III Trials of Cetuximab with Platinum-Based Chemotherapy (CT) as First-Line Treatment of NSCLC

	Hazard ratio*/ odds ratio†	95% CI	*p*-value
Overall survival	0.878*	0.795-0.969	0.010
Progression-free survival	0.899*	0.814-0.993	0.036
Objective response rate	1.463†	1.201-1.783	<0.001

"The meta-analysis based on 1003 patients treated with CT + cetuximab and 1015 patients treated with CT alone demonstrated a significant benefit across all investigated efficacy endpoints for the cetuximab combination over CT alone."

SOURCE: Thatcher N et al. *Proc IASLC* 2009;**Abstract A3.7**.

Tracks 2-4

DR LOVE: Would you discuss your presentation at ASCO 2009 analyzing predictors of benefit with cetuximab in the FLEX trial?

DR O'BYRNE: Summarizing the data, K-ras mutation status did not predict for benefit and EGFR gene copy number measured by FISH showed no predictive value (O'Byrne 2009; [4.2]). Likewise, we believe that EGFR immunohistochemistry shows no predictive value, and two other markers that are being studied will be presented at subsequent meetings. So we don't have a predictive marker in the areas we would expect.

Importantly, this analysis also studied the relationship between rash and outcome for patients treated with cetuximab. At the end of the first cycle of treatment, approximately 60 percent of patients had a skin rash. Patients who developed a skin rash after the first cycle had a 15-month median survival, and patients who did not develop a skin rash had about an eight and a half-month median survival.

In the control arm, the median survival at the 21-day cutoff was approximately 10 months. So patients who have a skin rash on cetuximab demonstrate a five-month better survival than the control arm and a seven-month better survival than those who don't develop a skin rash (4.2).

We can safely say that this is a marker for outcome. It doesn't imply that it's a predictor of response to cetuximab, but it is a factor that we can use when patients develop rash to tell them that their prognosis is better than it was at baseline.

If the skin rash is a marker for benefit, what treatment should we offer to patients who don't experience a skin rash? Should we increase the dose of

cetuximab to induce a skin rash and find out if we can enhance patient outcomes? Future work will study that question.

DR LOVE: What is your first-line treatment algorithm for advanced NSCLC?

DR O'BYRNE: I would administer cisplatin/gemcitabine with cetuximab as my first line of treatment for squamous cell disease and adenocarcinoma. I don't use bevacizumab because it's not adding a huge amount to the treatment paradigm. We know that cetuximab can be used for all histologies, and we also know that when a patient develops rash at the end of the first cycle, the outcome will be significantly better. That's encouraging. ■

4.2

FLEX: First-Cycle Rash as a Clinical Biomarker for Overall Survival Benefit for Patients with Advanced NSCLC Treated with Cetuximab

Efficacy	CT + cetuximab without rash (n = 228)	CT + cetuximab with rash (n = 290)	CT (n = 540)
Median overall survival	8.8 months	15.0 months	10.3 months
	Hazard ratio: 0.63; $p < 0.001$		

"Clinical data from the FLEX study do not support the hypothesis that KRAS mutation status is predictive for cetuximab efficacy when combined with 1st-line chemotherapy in advanced NSCLC, whereas early acne-like rash of any grade appears to be associated with better outcome in pts treated with platinum-based chemotherapy plus cetuximab in this setting."

SOURCE: O'Byrne KJ et al. *Proc ASCO* 2009;**Abstract 8007**.

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Butts CA et al. **Randomized phase II study of gemcitabine plus cisplatin or carboplatin, with or without cetuximab, as first-line therapy for patients with advanced or metastatic non small-cell lung cancer.** *J Clin Oncol* 2007;25(36):5777-84.

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Lynch T et al. **Overall survival (OS) results from the phase III trial BMS 099: Cetuximab taxane/carboplatin as 1st-line treatment for advanced NSCLC.** *J Thorac Oncol* 2008;3(Suppl 4):305.

O'Byrne KJ et al. **Molecular and clinical predictors of outcome for cetuximab in non-small cell lung cancer (NSCLC): Data from the FLEX study.** *Proc ASCO* 2009;**Abstract 8007**.

Pirker R et al. **Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): An open-label randomised phase III trial.** *Lancet* 2009;373(9674):1525-31.

Pirker R. **Cetuximab: Potential role as first-line treatment for advanced non-small cell lung cancer.** *Clin Adv Hematol Oncol* 2008;6(10):735-6.

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

Thatcher N et al. **Cetuximab plus platinum-based chemotherapy as 1st-line treatment in patients with non-small cell lung cancer (NSCLC): A meta-analysis of randomized phase II/III trials.** *Proc IASLC* 2009;**Abstract A3.7**.

INTERVIEW

Frank C Detterbeck, MD

Dr Detterbeck is Professor and Chief in the Section of Thoracic Surgery, Associate Director of the Yale Cancer Center and Surgical Director of the Thoracic Oncology Program at Yale University School of Medicine in New Haven, Connecticut.

Tracks 1-9

Track 1	**Case discussion:** A 68-year-old woman with bilateral upper lobe densities on CT — 1.5 centimeters with ground glass opacities and a small solid component and 1.2 centimeters with pure ground glass opacities, respectively — diagnosed at surgery as adenocarcinoma of the lung
Track 2	Characterization of multifocal lung lesions with a ground glass component
Track 3	ACOSOG and CALGB Phase III studies evaluating sublobar resection for small NSCLC
Track 4	Quality of staging procedures in NSCLC and impact on survival
Track 5	Estimating prognosis for patients with multifocal lung cancer
Track 6	Postsurgical treatment approach for patients with multifocal lung cancer with primarily ground glass components
Track 7	Role of endobronchial ultrasound in diagnosing and staging NSCLC
Track 8	Perspective on approach to preoperative systemic therapy
Track 9	Controversies in the treatment approach for Stage III NSCLC

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss your treatment approach for patients presenting with ground glass opacities?

DR DETTERBECK: We commonly see patients with small ground glass opacities found on routine CT. The guidelines we use are as follows: If a lesion is smaller than five millimeters, we watch the patient and perform a follow-up scan in one year. With lesions between five and 10 millimeters, we worry a bit more but if it's a pure ground glass area, the majority of cases turn out to be atypical adenomatous hyperplasia, which is benign. So if a lesion is smaller than a centimeter and doesn't have a solid component, we generally watch it.

Once a ground glass lesion is larger than one centimeter, the chance is approximately 20 percent that it will be a bronchoalveolar carcinoma (BAC), perhaps with a small focus of invasive adenocarcinoma, and we worry about those more. When the ground glass area develops a solid component, the chance is high that it will be an invasive adenocarcinoma with peripheral BAC features.

Track 3

DR LOVE: Would you discuss the ongoing studies evaluating sublobar resection for patients with small NSCLC (5.1)?

DR DETTERBECK: The American College of Surgeons is conducting a trial in which patients are randomly assigned to sublobar resection with or without brachytherapy. This study is geared more toward patients who are undergoing a sublobar resection as a compromise procedure.

The CALGB is also running a trial for patients with lesions that are smaller than two centimeters. Patients are randomly assigned to either lobectomy or a sublobar resection. We are participating in the CALGB study but not in the ACOSOG study.

DR LOVE: What do you think those two studies will find?

DR DETTERBECK: My guess is that the CALGB study will find that lobectomy is still better, although I believe that study cast the net too broadly. A 2-cm solid tumor is different than a 1.2-cm ground glass lesion. However, I believe that some tumors may be well treated with a sublobar resection.

5.1

Ongoing Phase III Randomized Studies of Sublobar Resection for Patients with Small Non-Small Cell Lung Cancer

	ACOSOG-Z4032	CALGB-140503
Target accrual	226	1,297
Stage	I	IA
Tumor size	≤3 cm	≤2 cm
Randomization	Sublobar resection ± brachytherapy	Sublobar resection versus lobectomy

SOURCE: **www.clinicaltrials.gov**.

Track 4

DR LOVE: How do you approach surgical staging of lung cancer?

DR DETTERBECK: We always perform at least a systematic sampling of mediastinal nodes. Usually I perform a mediastinal node dissection. The goal with systematic sampling is to try to excise a node from each node station — left and right paratracheal and subcarinal, biopsy-representative nodes. This is standard for lung cancer surgery. Unfortunately, it's not necessarily practiced as broadly as we would like.

Many surgeons grew up with a more nihilistic attitude toward lung cancer and haven't focused on paying attention to details. They perform lobectomies and then say, "If the patients are lucky, they'll fare well. If they're unlucky, it won't

matter because we have nothing else to do." Perhaps that was the case 30 years ago, but that's not true today. We now have other therapies for lung cancer.

I believe that the majority of surgeries are being performed by cardiothoracic surgeons who may be focused on cardiac surgery and not as much on thoracic surgery or by general surgeons who deal with many types of procedures. A minority of the surgeries are performed by dedicated thoracic surgeons who have a focused interest.

DR LOVE: What do you think about the quality, not only of the surgery technically but also of the decision-making by surgeons?

DR DETTERBECK: This is an area of crucial importance. I believe that a huge disparity exists in quality across the country. A recent study evaluating staging procedures for patients with lung cancer was conducted using SEER Medicare data. Patients who underwent only one staging test — CT — had a statistically significant worse survival than patients who underwent bimodal staging — CT and PET — or trimodal staging — CT, PET and mediastinoscopy or endobronchial ultrasound with biopsy (Farjah 2009a; [5.2]).

The increase in survival was dramatic — three or four times what we obtain from other clinical approaches that we are excited about. For example, we're excited that we have adjuvant chemotherapy for early-stage lung cancer, and yet simply performing better staging gives you three or four times as much benefit as adjuvant chemotherapy.

If we're serious about doing a better job for our patients, we must get our hands around this quality issue. ■

5.2 **Effect of Multimodality Staging for Lung Cancer on Patient Survival**

"The use of a greater number of staging modalities was associated with a lower risk of death (bi- versus single modality: hazard ratio [HR] 0.58, 99% confidence interval [CI] 0.56-0.60; tri- versus single modality; HR 0.49, 99% CI 0.45-0.54; tri- versus bi-modality: HR 0.85, 99% CI 0.77-0.93).

The use of multimodality mediastinal staging increased over time and was associated with better survival…Health policy directed at optimizing lung cancer staging should take high priority since improved staging may have a greater effect on survival than incremental improvements in surgery, radiation, or chemotherapy."

SOURCE: Farjah F et al. *J Thorac Oncol* 2009a;4(3):355-63.

SELECT PUBLICATIONS

Detterbeck F. **What is quality and does it matter?** *J Thorac Oncol* 2009;4(3):279-80.

Farjah F et al. **Multi-modality mediastinal staging for lung cancer among Medicare beneficiaries.** *J Thorac Oncol* 2009a;4(3):355-63.

Farjah F et al. **Surgeon specialty and long-term survival after pulmonary resection for lung cancer.** *Ann Thorac Surg* 2009b;87(4):995-1004.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the JMEN study, maintenance pemetrexed resulted in a significant progression-free and overall survival benefit for patients with nonprogressive, advanced _____ after first-line platinum-containing doublet chemotherapy.**
   a. Nonsquamous cell NSCLC
   b. Squamous cell NSCLC
   c. Both a and b

2. **At ASCO 2009, Grilley-Olson and colleagues reported that the concordance in histologic diagnosis of NSCLC between pathologists at major medical centers and community pathologists was _____.**
   a. More than 90 percent
   b. 85 percent
   c. 70 percent
   d. Less than 50 percent

3. **In the IPASS study, for patients who were clinically selected for enrichment of EGFR mutations, use of first-line gefitinib resulted in a superior progression-free survival compared to carboplatin/paclitaxel.**
   a. True
   b. False

4. **The ATLAS trial demonstrated an improvement in progression-free survival with the addition of erlotinib to maintenance bevacizumab for patients who had completed first-line therapy for advanced NSCLC.**
   a. True
   b. False

5. **Among patients with adenocarcinomas of the lung and EGFR mutations, the disease control rate (PR + CR + SD) with BIBW 2992 as second-line therapy was _____.**
   a. 20 percent
   b. 40 percent
   c. 60 percent
   d. More than 90 percent

6. **The frequency of ALK mutations in nonsmokers is approximately _____.**
   a. Five percent
   b. 10 percent
   c. 22 percent
   d. 60 percent

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. **A meta-analysis of randomized Phase II/III trials of cetuximab with platinum-based chemotherapy (CT) as first-line treatment for NSCLC reported benefit in _____ with cetuximab and CT compared to CT alone.**
   a. Overall survival
   b. Progression-free survival
   c. Objective response rate
   d. All of the above

9. **In an analysis of the FLEX study, early acne-like rash of any grade was associated with better outcomes for patients who received platinum-based chemotherapy with cetuximab for advanced NSCLC.**
   a. True
   b. False

10. **A recent publication using SEER Medicare data to evaluate staging procedures for patients with lung cancer reported no association between multimodal staging versus single-modality staging and survival for patients with NSCLC.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 3, 2009

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
Results of recent studies with maintenance therapy (pemetrexed, erlotinib with or without bevacizumab) in advanced NSCLC	4 3 2 1	4 3 2 1
Clinical trial results for the use of first-line EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy for patients with EGFR mutations	4 3 2 1	4 3 2 1
Clinical investigator treatment algorithms for advanced NSCLC based on tumor histology and mutation status	4 3 2 1	4 3 2 1
LUX-Lung 1 and 2: Clinical trial results with BIBW 2992 — an irreversible EGFR TKI and targeted agent against secondary T790M mutations — in advanced NSCLC	4 3 2 1	4 3 2 1
FLEX analysis of molecular predictors of outcome for cetuximab in NSCLC	4 3 2 1	4 3 2 1
Overview of the results of clinical trials evaluating first-line chemotherapy in combination with cetuximab in advanced NSCLC	4 3 2 1	4 3 2 1
Staging procedures in NSCLC and effect on survival	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:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following 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:

- Recognize the effect of quality disease staging on long-term clinical outcome for patients with non-small cell lung cancer (NSCLC) . . . . . 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
- Appraise the role for definitive lung cancer surgery in Stage III NSCLC treated with preoperative therapy. . . . . 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 NSCLC . . . . . 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
- 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?

.....

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

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ⬭ Yes, I am willing to participate in a follow-up survey.
- ⬭ No, I am not willing to participate in a follow-up survey.

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

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
John Heymach, MD, PhD	4 3 2 1	4 3 2 1
Vincent A Miller, MD	4 3 2 1	4 3 2 1
Mark A Socinski, MD	4 3 2 1	4 3 2 1
Kenneth O'Byrne, MD	4 3 2 1	4 3 2 1
Frank C Detterbeck, 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:

.....

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LCU309

Lung Cancer™ UPDATE

Lung Cancer™ UPDATE

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