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Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Thomas J Lynch Jr, MD
Roy S Herbst, MD, PhD
John Heymach, MD, PhD
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CME Certified

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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 conditions.
- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible EGFR TKIs.
- Recall the effects of early palliative care for patients with metastatic non-small cell lung cancer (NSCLC).
- 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.
- Appraise the clinical application of emerging data on the combined use of biologic agents and chemoradiation therapy for Stage III NSCLC.
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions.
- Counsel appropriately selected patients with lung cancer about participation in ongoing clinical trials.

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TABLE OF CONTENTS

FACULTY INTERVIEWS

3 **Thomas J Lynch Jr, MD**
Director, Yale Cancer Center
Physician-in-Chief, Smilow Cancer Hospital at Yale New Haven
New Haven, Connecticut

7 **Roy S Herbst, MD, PhD**
Professor of Medicine
Chief, Section of Thoracic Medical Oncology
Department of Thoracic/Head and Neck Medical Oncology
Barnhart Family Distinguished Professor in Targeted Therapies
The University of Texas MD Anderson Cancer Center
Houston, Texas

11 **John Heymach, MD, PhD**
Associate Professor of Thoracic/Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

15 **Roman Perez-Soler, MD**
Guttman Professor of Medicine
Chair, Department of Oncology
Montefiore Medical Center
Chief, Division of Medical Oncology
Associate Director for Clinical Research
Albert Einstein Cancer Center
Bronx, New York

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

CONTENT VALIDATION AND DISCLOSURES

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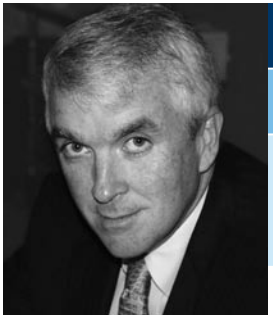

INTERVIEW

Thomas J Lynch Jr, MD

Dr Lynch is Director of the Yale Cancer Center and Physician-in-Chief at Smilow Cancer Hospital at Yale New Haven in New Haven, Connecticut.

Tracks 1-17

Track 1 Early palliative care for patients with metastatic non-small cell lung cancer (NSCLC)

Track 2 ARIES: An observational cohort study of bevacizumab-based treatment in advanced NSCLC

Track 3 Rates of severe pulmonary hemorrhage in patients receiving bevacizumab on the ARIES trial

Track 4 In vivo assessment of the effects of bevacizumab in advanced NSCLC

Track 5 Results of a Phase III Gyneco-logic Oncology Group study in advanced ovarian cancer: Role of maintenance bevacizumab after carboplatin/paclitaxel/ bevacizumab

Track 6 CAN-NCIC-BR19: Results of a Phase III study of adjuvant gefitinib in Stage IB to IIIA NSCLC

Track 7 Effect of EGFR and K-ras mutations on clinical outcomes in previously untreated NSCLC

Track 8 Activity of the irreversible EGFR tyrosine kinase inhibitor (TKI) afatinib (BIBW 2992) in patients with advanced NSCLC progressing on erlotinib or gefitinib

Track 9 Clinical features and outcomes of patients with NSCLC who harbor EML4-ALK and clinical activity of the oral ALK inhibitor crizotinib (PF-02341066)

Track 10 Phase III study of second-line crizotinib versus pemetrexed or docetaxel for patients with advanced NSCLC and a specific gene profile involving ALK

Track 11 Phase II trial of ipilimumab and paclitaxel/carboplatin as first-line therapy for Stage IIIB to IV NSCLC

Track 12 Results of a Phase III trial of nanoparticle albumin-bound (*nab*) paclitaxel/carboplatin compared to Cremophor®-based paclitaxel/ carboplatin as first-line therapy for advanced NSCLC

Track 13 Perspective on the role of immune-based therapy in NSCLC and other solid tumors

Track 14 **Case discussion:** A 68-year-old never smoker is diagnosed with NSCLC and an exon 19 mutation while receiving active treatment for chronic myelogenous leukemia

Track 15 **Case discussion:** A 55-year-old woman who received treatment five years ago for BRCA-mutant breast cancer presents with adenocarcinoma of the lung

Track 16 ECOG-E5508: A Phase III study of maintenance therapy with bevacizumab, pemetrexed or both after carboplatin/paclitaxel/ bevacizumab for advanced-stage nonsquamous NSCLC

Track 17 Clinical decision-making regarding the use of maintenance therapy in advanced NSCLC

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the paper you coauthored on early palliative care for patients with metastatic non-small cell lung cancer (NSCLC)?

DR LYNCH: Patients randomly assigned to the early palliative care arm received outstanding palliative care from a team of palliative care doctors, social workers and nurse practitioners. Patients met with the palliative care team once a month. I believe it was the psychosocial support that made the patients on the early palliative care arm stronger. We expected to find that early palliative care improves quality of life and also helps with depression and anxiety, which was demonstrated, but the most shocking finding was that a survival benefit emerged with early palliative care (Temel 2010; [1.1]).

Although some people could argue that survival was not the primary endpoint, I believe we could easily conclude that early palliative care did not adversely affect survival and that patients fare well when early palliative care is integrated. Perhaps with better control of depression and anxiety, patients make better decisions and are therefore benefitting from other therapies. It is important to remember that this was a single-center study and to consider what will happen when we do this across several centers with different palliative care units. The other issue will be whether this approach is applicable to other cancer types.

1.1

Phase III Study Investigating Early Palliative Care in Metastatic Non-Small Cell Lung Cancer

	Standard care (n = 74)	Early palliative care (n = 77)	*p*-value
Depressive symptoms	38%	16%	0.01
Aggressive end-of-life care	54%	33%	0.05
Median survival	8.9 months	11.6 months	0.02

Temel JS et al. *N Engl J Med* 2010;363(8):733-42.

Tracks 2-3

DR LOVE: Would you comment on the ARIES study you reported, which is examining bevacizumab use in advanced NSCLC in the community setting?

DR LYNCH: ARIES is a prospective observational cohort study evaluating the efficacy and safety of bevacizumab in the real-world setting and has enrolled approximately 2,000 patients so far. To enroll in the ARIES study, a patient

must be receiving a bevacizumab-containing regimen for the initial management of nonsquamous NSCLC.

The goal of the ARIES study is to evaluate how bevacizumab is performing in the real world as opposed to in clinical trials. In clinical trials, many patients, such as those with brain metastases, those receiving anticoagulation, those older than age 70 and those with a performance status of 2, are either not represented or are under-represented. Real concern exists about how bevacizumab will perform for these subpopulations.

Results from the ARIES study show that bevacizumab can be safely used for all of these subpopulations and that community oncologists are good at using bevacizumab and selecting appropriate patients (Wozniak 2010; [1.2]). The incidence of pulmonary hemorrhage is also small, which is fantastic, and might suggest that the location of the primary tumor might not be driving the rate of pulmonary hemorrhage (Kumar 2010). I am impressed that the toxicity profile of bevacizumab in the ARIES study is better than it was in the pivotal ECOG-E4599 study.

1.2

ARIES: Observational Cohort Study of Bevacizumab for Nonsquamous Non-Small Cell Lung Cancer in the Community Setting

	All patients (n = 1,970)	Age ≥70 (n = 650)	PS ≥2 (n = 182)	CNS metastasis (n = 150)
Progression-free survival (median)	6.7 months	6.8 months	5.8 months	6.0 months
Overall survival (median)	13.6 months	12.6 months	8.1 months	11.7 months
Severe pulmonary hemorrhage (PH)	0.8%	0.3%	1.0%	—
Grade 3 to 5 bleeding (excluding PH)	3%	3%	4%	—
Arterial thromboembolism	2%	3%	3%	—
Grade 3 to 5 CNS bleeding	0.1%	0%	0.5%	0%

These results suggest that advanced age, poor performance status and CNS metastasis are not necessarily contraindications for bevacizumab therapy.

Wozniak AJ et al. *Proc ASCO* 2010;**Abstract 7618**.

Tracks 9-10

DR LOVE: Would you summarize the EML4-ALK story in lung cancer?

DR LYNCH: I believe this is probably the most important development in lung cancer this year — or even during the past five years. When we learned about the EML4-ALK translocation, we started screening patients for this mutation

with a homegrown FISH assay that could reliably identify it. We found that, overall, approximately five percent of patients with NSCLC harbor the EML4-ALK translocation. It also appears in nonsmokers, but unlike the EGFR mutation, it is a little more common in men than in women. Also, patients with this translocation appear to be a bit younger than the patients who have EGFR mutations.

The Phase I study of crizotinib presented at ASCO 2010 featured one of the most incredible waterfall plots I have ever seen in lung cancer, with response rates in excess of 60 to 65 percent and good progression-free survival (PFS) (Bang 2010; [1.3]). I believe the story of EML4-ALK will be similar to the story of EGFR mutations — after 18 to 24 months, we will begin to see emergence of resistance to therapy.

From the perspective of the practicing oncologist, I believe that for now screening for the EML4-ALK oncogene in never smokers or former smokers makes sense, although one can make a valid argument for screening all patients. An ongoing Phase III trial is open and is randomly assigning patients to crizotinib or chemotherapy in the second-line setting (NCT00932893). The issue will be that inevitably some patients will receive chemotherapy and will not receive the ALK inhibitor in the subsequent line, and I believe one could make a strong argument for approving the drug based on the data that we have right now. ■

1.3

Activity of Crizotinib in a Phase I Study for Patients with ALK Fusion-Positive Non-Small Cell Lung Cancer (N = 82)

Parameter	Outcome
Objective response rate	57%
Disease control rate (DCR)* at eight weeks	87%
Six-month progression-free survival probability	72%

Toxicity: The most frequent adverse events were mild and moderate gastrointestinal events, including nausea (54%) and vomiting (44%), and mild visual disturbances (42%).

* DCR = complete responses + partial responses + stable disease

Bang Y et al. *Proc ASCO* 2010;**Abstract 3**.

SELECT PUBLICATIONS

Bang Y et al. **Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 3**.

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**.

Temel JS et al. **Early palliative care for patients with metastatic non-small cell lung cancer.** *N Engl J Med* 2010;363(8):733-42.

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**.

INTERVIEW

Roy S Herbst, MD, PhD

Dr Herbst is Professor of Medicine, Chief of the Department of Thoracic/Head and Neck Medical Oncology's Section of Thoracic Medical Oncology and Barnhart Family Distinguished Professor in Targeted Therapies at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-11

Track 1 Mutations associated with resistance to EGFR TKIs: T790M and c-MET

Track 2 Efficacy and safety of *nab* paclitaxel/carboplatin as first-line therapy for advanced NSCLC

Track 3 BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination) study

Track 4 ZODIAC: A Phase III trial of docetaxel with or without vandetanib as second-line treatment for advanced NSCLC

Track 5 Comparison of BATTLE and ZODIAC trial results to other ongoing clinical trials evaluating vandetanib-based therapy in advanced NSCLC

Track 6 Novel multikinase inhibitors — cediranib, pazopanib and axitinib — in advanced NSCLC

Track 7 Physician and patient acceptance of biopsy and molecular testing in the BATTLE study

Track 8 Lung Cancer Mutation Consortium Protocol: An observational study to determine the frequency of oncogenic mutations in Stage IIIB/IV adenocarcinoma

Track 9 BeTA study: Improvement in progression-free survival with the addition of bevacizumab to erlotinib as second-line therapy for advanced NSCLC

Track 10 ATLAS (erlotinib/bevacizumab versus bevacizumab) and SATURN (erlotinib versus placebo) studies of maintenance therapy

Track 11 Inhibition of the phosphatidylinositol 3-kinase pathway as a therapeutic target in NSCLC and other solid tumors

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the development of resistance to EGFR tyrosine kinase inhibitors (TKIs) and the recent development of agents with the potential to overcome this resistance?

DR HERBST: The most exciting aspect of the EGFR TKIs for patients with EGFR-mutant lung cancer is that unprecedented responses are observed with minimal toxicity. However, the median duration of response is probably less than one year because resistance is either present initially or develops quickly. This resistance tends to fall into predefined categories, one of which is due

to a secondary mutation known as T790M, which is another mutation in the EGFR gene. The reason why patients with EGFR mutation in exons 19 and 21 are so sensitive to erlotinib and gefitinib is that these agents can block ATP binding precisely with a high affinity.

However, when the T790M mutation develops, it abrogates that effect, and the irreversible EFGR TKIs, such as BIBW 2992, may be effective in that setting.

A large clinical trial has compared BIBW to placebo for patients with EGFR resistance, which will be an important study and may provide a new agent for the treatment armamentarium (Miller 2010; [3.1]). One might even consider using BIBW 2992 in the up-front treatment setting (Yang 2010; [2.1]).

This is a small population of patients because it's 10 percent of all patients with lung cancer and then a smaller percentage of those who have the specific mutations resulting in resistance to EGFR TKIs. But these are patients for whom we may be able to achieve significant control of their disease without using chemotherapy. So this is a fertile and important area of research.

2.1

LUX-Lung 2: A Phase II Study of BIBW 2992 for Patients with Adenocarcinoma of the Lung and Activating EGFR/HER1 Mutations (N = 129)

Overall response rate	Disease control rate	Median progression-free survival	Median overall survival
67%	86%	14 months	24 months

Comparable efficacy was observed in the first- and second-line settings.

Yang C et al. *Proc ESMO* 2010;**Abstract 367PD**.

Track 2

DR LOVE: Would you comment on the Phase III data with *nab* paclitaxel in advanced NSCLC presented at ASCO 2010?

DR HERBST: This was a large trial with more than 1,000 patients that compared carboplatin and *nab* paclitaxel to the standard carboplatin/paclitaxel combination for the initial management of NSCLC. Paclitaxel is relatively insoluble and therefore has to be mixed with Cremophor. *Nab* paclitaxel uses nanotechnology to deliver paclitaxel and does not require Cremophor. An approach such as this, which has been approved in breast cancer, could potentially be more effective and less toxic because Cremophor causes some serious side effects, such as anaphylaxis.

One facet to keep in mind is that the schedules were somewhat different — *nab* paclitaxel was administered weekly and standard paclitaxel was administered every three weeks. According to an independent review, response rates were higher for the patients who received carboplatin with *nab* paclitaxel than for those who received standard carboplatin/paclitaxel (Socinski 2010; [2.2]).

An interesting observation is that when efficacy is broken down by histologic subtype, the greatest effect was observed in patients with squamous cell carcinoma. I believe that is important because a number of advances in nonsquamous NSCLC, such as pemetrexed and bevacizumab, have been made without any recent advancement in the squamous subtype of NSCLC.

In addition, I believe we need to be aware that in lung cancer, other endpoints, such as PFS and overall survival (OS), are important. The PFS and OS data are currently maturing, and it is understandable that it is taking some time to gather those data, considering that this is an international, multicenter trial.

The toxicity data seemed to favor the *nab* paclitaxel arm, especially in terms of neurotoxicity and some of the other parameters, but we are comparing weekly *nab* paclitaxel to an every three-week paclitaxel regimen. We know that when paclitaxel is administered on a weekly basis, the neurotoxicity can be modulated by the schedule.

We need to keep our eye on the follow-up data because it is desirable for the baseline combination chemotherapy to be as minimally toxic as possible when we are adding a targeted agent to doublet chemotherapy. Certainly carboplatin and *nab* paclitaxel could serve as the backbone regimen in the future, especially for patients with squamous histology.

2.2

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

Objective response by independent review	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
All patients	25% (n = 531)	33% (n = 521)	1.31	0.005
Squamous histology	24% (n = 221)	41% (n = 228)	1.67	<0.001
Nonsquamous histology	25% (n = 310)	26% (n = 292)	—	0.808

* Response ratio > 1 favors *nab* paclitaxel

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

Track 10

DR LOVE: What about maintenance strategies that combine drugs that inhibit EGFR with those that inhibit VEGF, for example, erlotinib and bevacizumab?

DR HERBST: The rationale behind such combinations is attacking both the tumor cells and the microenvironment. The most potent way I have ever approached such a strategy in the clinic is to combine the two approved agents, erlotinib and bevacizumab. The erlotinib/bevacizumab combina-

tion has been taken forward in the ATLAS study as maintenance therapy and has shown an improvement in PFS after completion of an initial platinum-based doublet in combination with bevacizumab (Miller 2009; [2.3]). The SATURN study evaluated single-agent erlotinib for patients who received a platinum-based doublet, and because of a significant improvement in PFS with single-agent erlotinib, the drug just received FDA approval and now can be used in the maintenance setting (Cappuzzo 2010; [2.4]). ■

2.3

ATLAS Phase III Randomized, Double-Blind, Placebo-Controlled Study Evaluating Bevacizumab with or without Erlotinib After Initial Treatment for Advanced Non-Small Cell Lung Cancer

	Bevacizumab + erlotinib (n = 373)	Bevacizumab + placebo (n = 370)	Hazard ratio	*p*-value
Progression-free survival	3.2 months	4.0 months	0.79	<0.0001

Miller VA et al. *Proc ASCO* 2009;**Abstract LBA8002**.

2.4

SATURN Phase III Randomized, Double-Blind, Placebo-Controlled Study Evaluating Erlotinib After First-Line Platinum-Based Doublet Chemotherapy for Advanced Non-Small Cell Lung Cancer

	Erlotinib (n = 437)	Placebo (n = 447)	Hazard ratio	*p*-value
Progression-free survival	12.3 weeks	11.1 weeks	0.71	<0.0001

Cappuzzo F et al. *Lancet Oncol* 2010;11(6):521-9.

SELECT PUBLICATIONS

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.

Miller V 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**.

Miller VA et al. **A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;**Abstract LBA8002**.

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**.

Yang C et al. **A Phase II study of BIBW 2992 in patients with adenocarcinoma of the lung and activating EGFR/HER1 mutations (LUX-Lung 2).** *Proc ESMO* 2010;**Abstract 367PD**.

INTERVIEW

John Heymach, MD, PhD

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

Tracks 1-12

Track 1 Rationale for clinical investigations of anti-angiogenic agents in the adjuvant setting

Track 2 NSABP-C-08 trial results of adjuvant FOLFOX and bevacizumab in colorectal cancer: Perspective on duration of anti-angiogenic treatment

Track 3 Potential effect of host response to EGFR and VEGF inhibitors on tumor growth

Track 4 Theoretical underpinnings for the differential activity of bevacizumab monotherapy in solid tumors

Track 5 BATTLE-2 program: A biomarker-integrated targeted therapy study for patients with previously treated advanced NSCLC

Track 6 K-ras mutation as a predictor of response to sorafenib in advanced NSCLC

Track 7 Raf and ras mutations in NSCLC and other solid tumors

Track 8 Predictive utility of VEGFR2 and VEGF to vandetanib in advanced NSCLC

Track 9 Advantages for a Bayesian adaptive randomization design in the BATTLE study

Track 10 Evaluation of primary, discovery and blood-based biomarkers in the BATTLE study

Track 11 Afatinib: An irreversible EGFR/HER2 TKI targeted against secondary T790M mutations in NSCLC

Track 12 Targeted delivery of *nab* paclitaxel in cancer to enhance activity and reduce toxicity

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Would you discuss some of the issues involved in improving the effects of anti-angiogenic drugs for the treatment of NSCLC and other solid tumors?

DR HEYMACH: One initial notion was that angiogenesis inhibitors that were easier to administer, such as the oral TKIs, might be more viable options for long-term dosing, but an issue that wasn't anticipated was that the angiogenesis inhibitors themselves induce changes in the host.

Work from Bob Kerbel's lab in mouse models has shown that angiogenic factors and cytokines induced by TKIs are partly dependent on the tumor and partly dependent on the host.

A publication by this group reported on the use of the VEGF TKI sunitinib in mice in which the investigators had implanted tumors. They reported that pretreatment with the angiogenesis inhibitor accelerated the growth of the tumors (Ebos 2009). This raises the theoretical possibility that the TKI could be ramping up the tumor or accelerating it in some way by increasing host production of angiogenic factors, and when you discontinue the drug that may have a biologic effect.

DR LOVE: Another issue I hear about as I talk with investigators from various areas of expertise is that angiogenesis inhibitors have different efficacies in different tumor types.

DR HEYMACH: That's an extremely important issue, and we can make the initial observation that response rates to single-agent angiogenesis inhibitor therapy are different in different diseases. The best single-agent responses to angiogenesis inhibitors have been observed in renal cell cancer. Renal cell cancer — at least clear cell renal cell cancer — tends to have an angiogenic driver that seems to predominately come from a single pathway, the HIF-1 alpha pathway.

We believe other tumors may have more factors driving angiogenesis — such as the NF-kappa B pathway or inflammatory pathways — but a wider diversity of angiogenic factors is apparent in some of the other disease types. Some tumor types do not respond to anti-angiogenic therapy, and we don't understand why. We don't have the tools to predict which tumors will respond. In pancreatic cancer, no benefit is evident whatsoever with the addition of bevacizumab to chemotherapy. It seems that the tumors can develop bypass pathways to VEGF.

Tracks 5-6, 8-10

DR LOVE: Would you discuss the design of the BATTLE study and the results recently reported at AACR (Kim 2010) and ASCO 2010 (Herbst 2010)?

DR HEYMACH: The BATTLE study randomly assigned more than 300 patients with platinum-refractory disease to one of four arms: erlotinib, erlotinib with the retinoid RXR inhibitor bexarotene, sorafenib or vandetanib. When the study began in 2005 or so, these were the agents that we believed were either standards or had the potential to become standards.

This study is unique and is one of the first of this size and scope to incorporate tumor markers using what we call a Bayesian adaptive randomization design. Every patient underwent a new biopsy, an approach for which oncologists' resistance was the biggest obstacle. After more than 200 biopsies, only one overnight hospitalization occurred, and that patient fared well. This

study demonstrates the feasibility of performing a biomarker-driven, biopsy-requiring study among patients with platinum-refractory lung cancer.

The way the randomization design worked was if the patient had a certain marker profile and experienced a great response to agent number one, then the subsequent randomization favored that marker toward agent number one. It didn't guarantee that the patient would receive agent number one, but it increased the probability.

With time we hope that the drugs become more and more closely associated with the markers that they're more likely to have a response to in real time, so we're learning as we go.

I'd also like to point out that we used a set of what we call primary markers embedded in the study, and the patients were randomly assigned based on these markers. They included obvious factors — EGFR mutations, K-ras mutations and EGFR amplification. Also included were blood-based biomarkers and a rich host of what we call discovery markers. Discovery markers are markers that are not established, but we were evaluating and looking for new predictors of response.

We are still analyzing the data, but initial results were presented at ASCO 2010. Sorafenib appears to have intriguing activity in patients with K-ras mutations (Herbst 2010). We typically think of K-ras mutations as markers of resistance to EGFR inhibitors, and approximately 20 percent of patients with NSCLC harbor K-ras mutations.

DR LOVE: Do you have any theories as to why patients with K-ras-positive tumors would fare better while receiving sorafenib?

DR HEYMACH: K-ras is one of the important pathways downstream of EGFR, but activation of the K-ras pathway is not dependent on EGFR. Constitutive activation of that pathway can occur that essentially bypasses EGFR. Downstream from ras are raf, MEK and ERK. Sorafenib was initially designed and tested as a B-raf inhibitor, and it has some B-raf activity. So you can imagine, if the ras pathway is active, inhibiting downstream of ras at the level of raf or MEK might be an effective strategy.

Another interesting finding related to patients on the vandetanib and erlotinib arms is that patients with high VEGFR2 and VEGF appeared to fare better while receiving vandetanib than the patients who didn't exhibit those markers, whereas high levels of VEGFR2 didn't have the same effects for patients who received erlotinib.

Track 11

DR LOVE: What are your thoughts on the irreversible EGFR TKIs?

DR HEYMACH: Irreversible EGFR inhibitors are potentially an important development in the field. We know that EGFR TKIs, such as gefitinib and erlotinib, bind reversibly to the ATP-binding pocket of the EGFR tyrosine

kinase. The irreversible inhibitors bind to the pocket in a different way, creating an irreversible bond.

We are eagerly awaiting data from a couple of large randomized studies with BIBW 2992, the irreversible EGFR/HER2 TKI. The Phase II data with this agent are impressive, and it may provide another alternative to using reversible EGFR inhibitors. I suspect that BIBW 2992 will become a valuable tool that we'll eventually use in addition to reversible inhibitors. ■

3.1

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 Failing 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	11.0%	0.5%	—	<0.01
Adverse events				
Diarrhea (Grade 3)	87.0%	17.0%	—	—
Rash/acne (Grade 3)	78.0%	14.0%	—	—

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

SELECT PUBLICATIONS

Doebele RC et al. **New strategies to overcome limitations of reversible EGFR tyrosine kinase inhibitor therapy in non-small cell lung cancer.** *Lung Cancer* 2010;69(1):1-12.

Herbst RS et al. **Sorafenib treatment efficacy and KRAS biomarker status in the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial.** *Proc ASCO* 2010;**Abstract 7609**.

Kim ES et al. **The BATTLE trial (Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination): Personalizing therapy for lung cancer.** *Proc AACR* 2010;**Abstract LB-1**.

Miller V 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**.

Printz C. **BATTLE to personalize lung cancer treatment. Novel clinical trial design and tissue gathering procedures drive biomarker discovery.** *Cancer* 2010;116(14):3307-8.

Yang C et al. **A Phase II study of BIBW 2992 in patients with adenocarcinoma of the lung and activating EGFR/HER1 mutations (LUX-Lung 2).** *Proc ESMO* 2010;**Abstract 367PD**.

Yap TA et al. **Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors.** *J Clin Oncol* 2010;28(25):3965-72.

INTERVIEW

Roman Perez-Soler, MD

Dr Perez-Soler is Guttman Professor of Medicine, Chair of the Department of Oncology at Montefiore Medical Center, Chief of the Division of Medical Oncology and Associate Director for Clinical Research at the Albert Einstein Cancer Center in Bronx, New York.

Tracks 1-10

Track 1 Clinical algorithm for locally advanced NSCLC

Track 2 Treatment of locally advanced, EGFR-mutant NSCLC

Track 3 Perspective on the results of the CAN-NCIC-BR19 study of adjuvant gefitinib

Track 4 Correlation between skin rash and antitumor activity of EGFR TKIs

Track 5 Adjuvant treatment options for Stage I to IIIA NSCLC

Track 6 Age versus performance status in treatment decision-making

Track 7 Selection of chemotherapy to combine with bevacizumab as first-line therapy for advanced NSCLC

Track 8 Bevacizumab, erlotinib or pemetrexed as maintenance therapy options for advanced NSCLC

Track 9 Rationale for the development of the irreversible EGFR TKI afatinib in lung cancer

Track 10 Phase II study of amrubicin as second-line therapy for platinum-refractory small cell lung cancer

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: What are your thoughts on the data from the recent Canadian trial of adjuvant gefitinib for unselected patients with completely resected NSCLC?

DR PEREZ-SOLER: In the CAN-NCIC-BR19 study of adjuvant gefitinib, no advantage was evident with the use of gefitinib, and patients who received gefitinib may have experienced a disadvantage (Goss 2010; [4.1]). In patients with EGFR and K-ras mutations, the outcomes were not predictive or prognostic of survival. When we analyze data among patients with EGFR-mutated tumors, many times I question whether the assay technologies are appropriate or even correct. I believe a technical aspect exists that we need to consider.

DR LOVE: What's new in terms of the skin rash associated with the use of EGFR TKIs, both as a predictor of response and in terms of management?

4.1

Trial Schema and Outcomes in CAN-NCIC-BR19: A Phase III Study of Adjuvant Gefitinib for Patients with Completely Resected Non-Small Cell Lung Cancer (NSCLC)

Accrual: 503 (Closed)[1]

Eligibility

- Resected Stage IB, II or IIIA NSCLC
- ECOG PS 0 to 2

R

Gefitinib (n = 251)
Daily x 2 years

Placebo (n = 252)
Daily x 2 years

[1] Accrual was closed in April 2005 because of the inferiority of the gefitinib arm.

Patients were stratified by stage, histology, postoperative radiation therapy, sex and adjuvant chemotherapy.

Overall survival and disease-free survival

	Gefitinib (n = 251)	Placebo (n = 252)	Hazard ratio	*p*-value
Median overall survival	5.1 years	Not reached	1.23	0.136
Median disease-free survival	4.2 years	Not reached	1.22	0.152

Multivariate analysis

- Age ≥ 65 years and tumor size ≥ 4 cm ($p = 0.0003$) were significantly associated with shorter survival.
- Gefitinib remained not significant, but a trend suggested that it may be harmful ($p = 0.097$).

Goss GD et al. *Proc ASCO* 2010;**Abstract LBA7005**.

DR PEREZ-SOLER: Oral tetracyclines seem to reduce the incidence of severe rashes without affecting the outcome. Reducing the dose of the EGFR TKI may be another option, as such high doses may not be necessary.

Several analyses have shown that patients who develop severe rashes have better outcomes. These findings led to the thinking that dose intensity may be important or that responders have a predisposition to developing bad rashes. An interesting question that has not been addressed is whether the intensity of the rash correlates with outcome in the patients with mutations. I believe this is an area we should study further.

DR LOVE: I understand you've been involved in developing a specific cream to treat this rash.

DR PEREZ-SOLER: We developed phosphatase inhibitors. Theoretically, the alteration of balance between kinase and phosphatase by a phosphate inhibitor should rescue the skin. We selected menadione — vitamin K3 — and formulated it into a cream. The cream has been licensed to a company that is developing it and conducting the appropriate studies.

Tracks 7-8

DR LOVE: How do you approach the use of bevacizumab as first-line therapy for metastatic NSCLC?

DR PEREZ-SOLER: I administer bevacizumab regularly as front-line therapy. In general, I use bevacizumab with carboplatin/paclitaxel because the AVAiL data — bevacizumab with gemcitabine/cisplatin — were not robust (Reck 2009). With certain patients I may also discuss the possibility of using bevacizumab with pemetrexed. I believe the probability is high that the pemetrexed regimen will be the best regimen, although the data have not yet been shown.

DR LOVE: How do you approach the issue of maintenance therapy, particularly for patients who are receiving carboplatin/paclitaxel/bevacizumab or carboplatin/pemetrexed/bevacizumab?

DR PEREZ-SOLER: We normally administer bevacizumab as maintenance therapy because it makes biological sense to do so, although no study ever compared bevacizumab maintenance therapy to no maintenance therapy.

Two other agents now approved for maintenance treatment of locally advanced or advanced NSCLC are pemetrexed (Belani 2009) and erlotinib (Cappuzzo 2010). We all believe that the associated data are positive, but what do they mean? I believe the results of the maintenance trials are positive because many patients on the control arms never receive further therapy. Many patients don't receive maintenance therapy because they develop bone metastases, spinal cord compressions, et cetera.

If I see a patient who I believe is at high risk of never returning or is noncompliant or if the individual may have an EGFR mutation — for example, a former light smoker who cannot be tested for the mutation — I might administer erlotinib maintenance therapy. If the patient is a heavy smoker and I believe I will lose the patient to follow-up, I may administer pemetrexed. I believe pemetrexed is an option, but most thoracic oncologists will not administer it as a rule. It's something we consider on a case-by-case basis. ■

SELECT PUBLICATIONS

Belani CP et al. **Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care: A randomized phase III study in advanced NSCLC.** *Proc ASCO* 2009;**Abstract CRA8000**.

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.

Goss GD et al. **A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinib in completely resected stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19.** *Proc ASCO* 2010;**Abstract LBA7005**.

Reck M et al. **Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil.** *J Clin Oncol* 2009;27(8):1227-34.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following has been shown with the incorporation of early palliative care into the management of metastatic NSCLC?**
   a. Improvement in OS
   b. More aggressive end-of-life care
   c. Improvement in pain control

2. **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 CNS metastasis
   c. Patients receiving concurrent anticoagulation
   d. Patients with ECOG PS 2
   e. All of the above

3. **In an unselected population with NSCLC, approximately ____ percent of patients are positive for the EML4-ALK translocation.**
   a. Five
   b. 40
   c. 80

4. **EML4-ALK translocation is more common in _____.**
   a. Current smokers
   b. Nonsmokers or light smokers

5. **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

6. **Vandetanib is an inhibitor of _____.**
   a. VEGF
   b. EGFR
   c. Both VEGF and EGFR
   d. Neither VEGF nor EGFR

7. **The BATTLE study randomly assigned more than 300 patients with advanced platinum-refractory NSCLC to _____.**
   a. Erlotinib
   b. Erlotinib with bexarotene
   c. Sorafenib
   d. Vandetanib
   e. Both a and d
   f. All of the above

8. **The LUX-Lung 1 Phase III placebo-controlled trial of afatinib (BIBW 2992) combined with best supportive care for patients with NSCLC failing on prior chemotherapy and erlotinib/gefitinib reported an improvement in response rates and PFS but not OS with the addition of afatinib.**
   a. True
   b. False

9. **During the CAN-NCIC-BR19 trial, patients with completely resected NSCLC treated with adjuvant gefitinib experienced _____ compared to those who received placebo.**
   a. No significant difference in OS
   b. No significant difference in disease-free survival
   c. Possible harmful effects
   d. All of the above

10. **FDA-approved maintenance therapy agents for advanced NSCLC include _____.**
    a. Erlotinib
    b. Pemetrexed
    c. Both a and b
    d. None of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 3

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
CAN-NCIC-BR19: A Phase III study of adjuvant gefitinib for NSCLC	4 3 2 1	4 3 2 1
Benefits of early palliative therapy for patients with advanced NSCLC	4 3 2 1	4 3 2 1
ATLAS (erlotinib/bevacizumab versus bevacizumab) and SATURN (erlotinib versus placebo) studies of maintenance therapy	4 3 2 1	4 3 2 1
ZODIAC: A Phase III trial of vandetanib with docetaxel versus docetaxel alone as second-line treatment for advanced NSCLC	4 3 2 1	4 3 2 1
Efficacy and tolerability of first-line *nab* paclitaxel/carboplatin compared to paclitaxel/carboplatin in advanced NSCLC	4 3 2 1	4 3 2 1
Clinical trials of the irreversible EGFR TKI afatinib (BIBW 2992) for patients with advanced, EGFR-mutant NSCLC	4 3 2 1	4 3 2 1
BATTLE studies in 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:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

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☐ Yes ☐ No

If no, please explain:.....

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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 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
- Recall the effects of early palliative care for patients with metastatic non-small cell lung cancer (NSCLC) . . . . . 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
- Appraise the clinical application of emerging data on the combined use of biologic agents and chemoradiation therapy for Stage III 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
- Counsel appropriately selected patients with lung cancer about participation in ongoing clinical trials. . . . . 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?

.....

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.....

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Thomas J Lynch Jr, MD	4 3 2 1	4 3 2 1
Roy S Herbst, MD, PhD	4 3 2 1	4 3 2 1
John Heymach, MD, PhD	4 3 2 1	4 3 2 1
Roman Perez-Soler, 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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Lung Cancer™ UPDATE

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