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Lung Cancer™ UPDATE

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

EDITOR

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INTERVIEWS

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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 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

- Identify distinct subtypes of adenocarcinoma of the lung, including those with EGFR mutations and EML4-ALK gene fusions, and the investigational and treatment options for these patients.
- Describe mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) and emerging data on irreversible EGFR TKIs.
- Summarize clinical trial data on the treatment of extensive small cell lung cancer.
- Appraise the outcomes of molecular analysis-directed individualized therapy (MADeIT) for advanced NSCLC.
- Formulate individualized treatment plans addressing the first-line and maintenance management of recurrent or progressive non-small cell lung cancer, considering unique patient and tumor characteristics.
- 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

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INTERVIEW

Corey J Langer, MD

Dr Langer is Professor of Medicine at the University of Pennsylvania and Vice Chair for the Radiation Therapy Oncology Group in Philadelphia, Pennsylvania.

Tracks 1-13

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on your trial evaluating the safety of bevacizumab in patients with brain metastases?

DR LANGER: The Phase II/III trial ECOG-E4599, which evaluated carboplatin/paclitaxel with or without bevacizumab, excluded patients with brain metastases, but that exclusion was orchestrated out of fear. No instances of intracranial bleeding occurred in the original Phase I efforts. In the E4599

trial, some of the patients experienced central nervous system (CNS) progression, but no untoward incidents of CNS hemorrhage occurred in that group.

Probably 15 to 25 percent of patients who present with de novo Stage IV NSCLC have brain metastases. Our study addressed whether bevacizumab could be combined safely with first- or second-line therapy for patients with advanced NSCLC and treated brain metastases.

The bottom line is that with more than 100 patients enrolled in our trial, no unexpected safety signals were noted (Socinski 2009; [1.1]). One episode of bleeding occurred prior to the data cut, and that was probably unrelated to the bevacizumab. As a result of this trial and others, the indication for bevacizumab has expanded to include patients with treated brain metastases.

1.1

Safety of Bevacizumab Combined with Chemotherapy for Patients with NSCLC and Brain Metastases

Adverse events	Total (n = 106)	Carboplatin + paclitaxel (n = 37)	Carboplatin + other (n = 30)	Pemetrexed (n = 19)	Erlotinib (n = 11)	Other (n = 9)
CNS hemorrhage (Grade II+)	0	0	0	0	0	0
Pulmonary hemorrhage (Grade III+)	3	1	1	0	1	0
Non-CNS/nonpulmonary hemorrhage (Grade III+)	2	0	2	0	0	0
Arterial thromboembolic events (any grade)	0	0	0	0	0	0
New or exacerbated hypertension (Grade III+)	3	1	0	1	0	1

Socinski MA et al. *J Clin Oncol* 2009;27(31):5255-61.

Track 6

DR LOVE: Would you comment on your editorial in the *JCO* about the response to gefitinib that was reported by Inoue and colleagues, which you termed the "Lazarus response" (Langer 2009)?

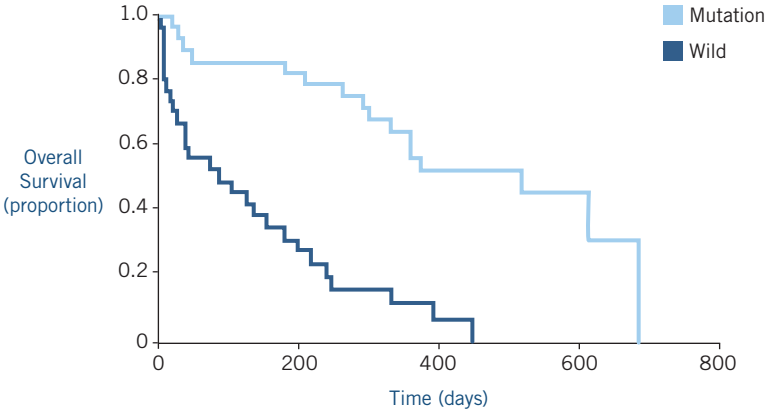
DR LANGER: They published an amazing paper in which they reported on first-line gefitinib in patients with advanced NSCLC harboring EGFR mutations who were ineligible for chemotherapy as a result of poor performance status. Their data showed that outcomes for the patients with mutation-positive disease who received gefitinib were nearly as good as what we see in patients with a performance status of 0 or 1.

The notion that a single oral agent, which 10 years ago was hardly on our radar screen, can induce response and "resurrect" these patients is novel. Although they were not cured, it provided these patients with a meaningful

quality of life and extended their survival from eight months to about one and a half years (Inoue 2009; [1.2]). It's clear that if a patient with mutation-positive, advanced NSCLC is not a candidate for chemotherapy, one should have no compunction whatsoever about administering an EGFR TKI.

1.2

Multicenter, Phase II Trial of First-Line Gefitinib for Patients with Advanced NSCLC Harboring EGFR Mutations with Poor Performance Status



"The median PFS, median survival time, and 1-year survival rate of the patients with sensitive EGFR mutations were 6.5 months, 17.8 months, and 63%, respectively. [This graphic] also shows a survival curve of 31 patients without EGFR mutations. Their median survival time was 3.5 months."

Originally published by the American Society of Clinical Oncology. Inoue A et al. *J Clin Oncol* 2009;27:1394-400.

Track 7

DR LOVE: How do you select therapy in the first-line metastatic setting based on EGFR mutation testing?

DR LANGER: Considering the IPASS data, I believe that patients who test positive for EGFR mutations should be offered the opportunity to receive an EGFR TKI up front. I wouldn't say that it's mandatory. If you examine the survival data in Dr Mok's paper, which are still somewhat immature, the profound response and progression-free survival (PFS) advantages have not yet translated into a survival benefit (Mok 2009). In some cases, the PFS exceeds one year or more. I can think of no cytotoxic combination that can generate a RECIST response rate of 65 to 80 percent.

Also, gefitinib spares patients the toxicity of chemotherapy. Patients still have to deal with diarrhea and rash, but I believe with time that we will learn how to manage these side effects more effectively.

DR LOVE: At ASCO a biomarker analysis from the IPASS study was presented that examined the significance of EGFR mutations, EGFR gene copy number by FISH and EGFR protein expression (1.3). Based on these data, it appears that if a patient's mutation status was negative but FISH-positive, gefitinib was not beneficial. What are your thoughts about that?

DR LANGER: Yes — clearly the key predictor was EGFR mutation status.

1.3

Phase III Trial Comparing First-Line Gefitinib to Carboplatin/Paclitaxel in Patients with Advanced NSCLC: Progression-Free Survival (PFS) by Biomarker Status

	PFS, HR[1]	*p*-value	PFS, Rx x subgroup interaction[2]
EGFR mutation status			
M+ (n = 261)	0.48	<0.0001	<0.0001
M- (n = 176)	2.85	<0.0001	
EGFR gene copy number			
FISH+ (n = 249)	0.66	0.0050	
FISH+, M+ (n = 190)	**0.48**	—	0.0437
FISH+, M- (n = 55)	**3.85**	—	
FISH- (n = 157)	1.24	0.2368	

[1] HR (hazard ratio) < 1.0 favors gefitinib; [2] HR in biomarker-positive versus HR in biomarker-negative

Fukuoka M et al. *Proc ASCO* 2009;**Abstract 8006**.

Track 8

DR LOVE: How do you approach selection of first-line systemic therapy for patients with advanced disease?

DR LANGER: For standard patients who present with de novo metastatic NSCLC with squamous histology, I prefer gemcitabine generally in combination with carboplatin.

For patients with predominantly adenocarcinomas, my preference is carboplatin in combination with paclitaxel or pemetrexed. If the patient is bevacizumab eligible, we've been grafting that onto the combination also.

I've been particularly impressed with the data reported by Patel and colleagues evaluating first-line carboplatin/pemetrexed and bevacizumab with maintenance pemetrexed and bevacizumab for NSCLC. Granted, they're Phase II data and come from a limited number of institutions, but these are still some of the more impressive data we've seen (Patel 2009; [1.4]).

An ongoing Phase III trial for patients eligible for bevacizumab is comparing carboplatin/pemetrexed/bevacizumab followed by maintenance bevacizumab and pemetrexed to carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab in patients with Stage IIIB or IV NSCLC.

ECOG has a trial that we hope will open soon for patients who've already received the ECOG-E4599 regimen of carboplatin/paclitaxel/bevacizumab and are free of disease progression after four cycles. They will be randomly assigned to receive maintenance with bevacizumab versus pemetrexed versus the combination.

A purist could argue for a fourth arm, offering observation alone with crossover to the combination perhaps at the time of disease progression, but such a trial would not be able to accrue patients in the United States.

DR LOVE: In clinical practice in this situation, are you using bevacizumab alone for maintenance therapy, or are you combining it with pemetrexed?

DR LANGER: I have patterned my approach based on the Patel data, combining bevacizumab and pemetrexed. We have no Phase III data that prove this regimen is superior. Those data are pending, and the ongoing Phase III trial comparing maintenance bevacizumab to bevacizumab and pemetrexed will help determine whether adding pemetrexed is advantageous. ■

1.4

Pemetrexed/Carboplatin/Bevacizumab with Maintenance Pemetrexed and Bevacizumab for NSCLC

"The regimen achieved a median PFS of 7.8 months, and the entire PFS 95% CI exceeded the a priori assumption of a median PFS of 4.2 months. Additional outcomes included a response rate of 55% and median OS of 14.1 months. At a median follow-up of 13.0 months, 18 patients (36%) were still alive. Importantly, the regimen had a favorable toxicity profile. The majority of adverse events were observed during the initial six cycles of therapy, and the continuation of pemetrexed and bevacizumab beyond initial treatment was feasible."

PFS = progression-free survival; CI = confidence interval; OS = overall survival

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

SELECT PUBLICATIONS

Fukuoka M et al. **Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS).** *Proc ASCO* 2009;**Abstract 8006**.

Inoue A et al. **First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy.** *J Clin Oncol* 2009;27:1394-400.

Langer CJ. **The "Lazarus response" in treatment-naïve, poor performance status patients with non-small-cell lung cancer and epidermal growth factor receptor mutation.** *J Clin Oncol* 2009;27(9):1350-4.

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

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

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

INTERVIEW

Alice Shaw, MD, PhD

Dr Shaw is Assistant Professor of Medicine at Harvard Medical School and Physician for the Center for Thoracic Cancers at Massachusetts General Hospital in Boston, Massachusetts.

Tracks 1-14

Select Excerpts from the Interview

Track 6

DR LOVE: What is known now about the clinical features of patients with NSCLC who harbor the EML4-ALK fusion gene, which is one of the newest molecular targets in lung cancer?

DR SHAW: They share certain features with patients who have EGFR mutations, in particular never smoker or light smoker status, and almost all have adenocarcinoma histology (Shaw 2009; [2.1]). A slight enrichment of

ALK translocations probably exists in Asians, although it is not as significant as with EGFR mutations.

In evaluating our study along with data from several studies published in other countries, overall the frequency of ALK in NSCLC is roughly three to four percent of all patients (Shaw 2009). When we evaluated the patient population at Massachusetts General Hospital and studied the patients who were never smokers or light smokers, we found the frequency of ALK translocations to be higher — roughly 10 to 15 percent (Shaw 2009).

You can enrich further if you isolate the patients who are never smokers or light smokers and are known not to harbor EGFR mutations. In that subset, we see ALK translocations in approximately 30 percent of patients.

2.1

Demographic Features of Patients by EML4-ALK and EGFR Mutation

Characteristic	ALK+ (n = 19)	EGFR+ (n = 31)	ALK WT/WT*
Mutation-positive†	13%†	22%†	65%†
Age (median)	52 y	66 y	64 y
Male gender	58%	26%	32%
Never smoker	74%	68%	26%
Light smoker	26%	19%	16%
Smoker	0%	13%	57%

* ALK wild type/EGFR wild type
† ALK-mutant tumors were nonoverlapping with EGFR-mutant tumors.

The majority of tumors were **adenocarcinomas**, with ALK but not EGFR-mutant tumors strongly associated with **signet-ring cell subtype**.

Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

Tracks 7, 11

DR LOVE: Would you discuss the data on the clinical activity observed with PF-02341066, the small-molecule c-MET inhibitor that targets the EML4-ALK fusion gene, that your group recently reported?

DR SHAW: The first data on the safety/toxicity and efficacy were reported by Dr Eunice Kwak at ASCO 2009. The vast majority of patients had stable disease or a response, although a handful of patients did not respond to PF-02341066 despite having the ALK translocation.

The waterfall plot of the initial 18 patients or so was impressive. The response rate was close to 60 percent, and the disease control rate — which is equivalent to the number of complete responses, partial responses (PR) and stable disease — was approximately 80 percent (Kwak 2009).

At the recent AACR-IASLC joint meeting, Dr Camidge presented the most up-to-date results on efficacy. We have now enrolled more than 70 patients with metastatic NSCLC harboring the ALK translocation.

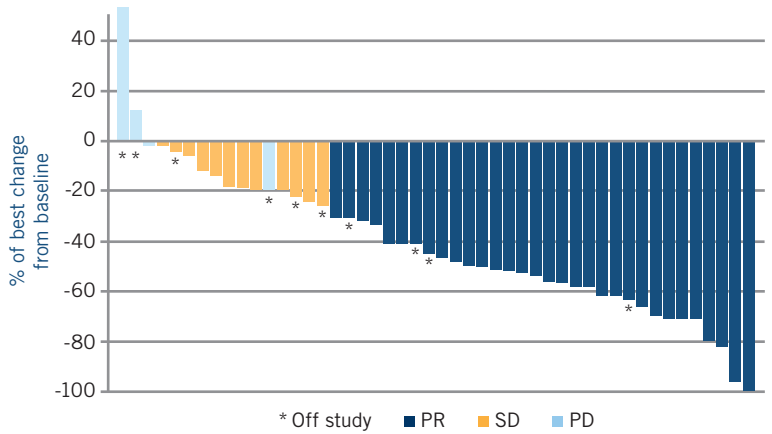
The objective response rate among these patients is now 64 percent, and the disease control rate is close to 90 percent (Camidge 2010; [2.2]). The median duration of treatment to date has been about 28 weeks, but most of the patients who have achieved a PR are still on the trial and are faring well. One patient is now approaching 15 months of PF-02341066 treatment.

DR LOVE: What is the current status of clinical research with this agent?

DR SHAW: We have now moved into a second-line Phase III trial for patients with metastatic NSCLC and proven ALK translocations. Patients will be randomly assigned to receive either PF-02341066 or standard chemotherapy, which on this trial will be pemetrexed or docetaxel. ■

2.2

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



Objective response rate = 64% CR + PR + SD = 95%

Median progression-free survival not yet reached

With permission from Camidge DR et al. *Proc AACR-IASLC* 2010. No abstract available

SELECT PUBLICATIONS

Camidge DR et al. **Addressing right drug-right target-right patients in phase I studies to accelerate bench to clinical benefit time: ALK gene rearrangements and the development of PF-02341066 in NSCLC.** *Proc AACR-IASLC* 2010. No abstract available

Kwak EL et al. **Clinical activity observed in a phase I dose escalation trial of an oral c-Met and ALK inhibitor, PF-02341066.** *Proc ASCO* 2009;**Abstract 3509**.

Shaw AT et al. **Clinical features and outcomes of patients with non-small-cell lung cancer who harbor EML4-ALK.** *J Clin Oncol* 2009;27(26):4247-53.

INTERVIEW

Suresh Ramalingam, MD

Dr Ramalingam is Associate Professor of Hematology and Medical Oncology, Director for the Division of Medical Oncology and Chief of Thoracic Oncology at the Winship Cancer Institute of Emory University in Atlanta, Georgia.

Tracks 1-16

Select Excerpts from the Interview

Track 3

DR LOVE: Would you discuss the IPASS trial, which evaluated first-line gefitinib versus carboplatin/paclitaxel as treatment for metastatic NSCLC?

DR RAMALINGAM: The IPASS study evaluated more than 1,000 patients with adenocarcinomas who had no smoking history or less than a 10 pack-year smoking history. Patients were randomly assigned to treatment with a standard doublet of carboplatin/paclitaxel versus gefitinib.

The primary endpoint was PFS, and for the overall patient population, the PFS was superior, with gefitinib compared to chemotherapy with a hazard ratio of 0.74. When the data were evaluated by EGFR mutation status in the patients for whom they had tumor tissue — approximately 500 patients — PFS was far superior in favor of gefitinib for the patients with EGFR mutations, with a trend toward a survival benefit compared to chemotherapy (Mok 2009; [3.1]).

On the flip side of this analysis, chemotherapy resulted in much better outcomes for patients without EGFR mutations (3.1). As a result, we might conclude that if you know that the patient's EGFR mutation status is positive, gefitinib or EGFR TKIs are optimal as front-line therapy. However, if you don't know the mutation status or the patient does not have the mutation, then administering chemotherapy might be the better approach.

3.1

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

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

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

Tracks 4-5, 12

DR LOVE: Where are we with maintenance erlotinib for NSCLC?

DR RAMALINGAM: In the SATURN trial — which compared maintenance erlotinib to placebo in patients who had received four cycles of front-line chemotherapy — the improvement in the primary PFS endpoint was significant, and for patients with EGFR mutations, the improvement in PFS in favor of erlotinib was dramatic — the hazard ratio was 0.1. So for patients with EGFR mutations, it is a fairly straightforward decision. If the patient has not received front-line erlotinib, then after four to six cycles of chemotherapy I switch to an EGFR inhibitor. A PFS benefit was also noted in patients with

EGFR wild-type disease. So erlotinib is a reasonable option to consider even for patients without EGFR mutations, although the benefit may not be quite as large as reported with EGFR-mutated tumors (Cappuzzo 2009; [3.2]).

DR LOVE: What about erlotinib and bevacizumab as maintenance?

DR RAMALINGAM: That approach was evaluated in the ATLAS trial in which patients who initially received four cycles of chemotherapy with bevacizumab were then randomly assigned to bevacizumab with erlotinib versus continuation on bevacizumab alone.

The PFS was 4.8 months for the combination versus 3.7 months for bevacizumab, which was a significant improvement that met the primary endpoint of the trial. The survival data have not yet been formally presented (Miller 2009). Considering the survival benefits reported in the pemetrexed trial (Ciuleanu 2009) and the erlotinib trial, we need to see the survival data from this study before we can use this approach. ■

3.2

SATURN: Efficacy of Maintenance Erlotinib versus Placebo After Nonprogression with First-Line Platinum-Based Chemotherapy for Patients with Advanced NSCLC

Progression-free survival	Erlotinib vs placebo HR (95% CI)	*p*-value
ITT population (n = 437; 447)	0.71 (0.62-0.82)	<0.0001
EGFR IHC-positive (n = 307; 311)	0.69 (0.58-0.82)	<0.0001
EGFR mutation-positive (n = 22; 27)	0.10 (0.04-0.25)	<0.0001
EGFR wild type (n = 199; 189)	0.78 (0.63-0.96)	0.0185
Adenocarcinoma (n = 204; 197)	0.60 (0.48-0.75)	<0.0001
Squamous cell (n = 166; 193)	0.76 (0.60-0.95)	0.0148

HR = hazard ratio; CI = confidence interval; ITT = intent-to-treat; IHC = immunohistochemistry

Cappuzzo F et al. *Proc ASCO* 2009;**Abstract 8001**.

SELECT PUBLICATIONS

Cappuzzo F et al. **SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC.** *Proc ASCO* 2009;**Abstract 8001**.

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

Miller VA et al. **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**.

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

INTERVIEW

George R Simon, MD

Dr Simon is Director of the Thoracic Oncology Program at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Tracks 1-15

Track 1 Molecular analysis-directed individualized therapy (MADeIT) in advanced NSCLC

Track 2 Effect of personalized therapy based on ERCC1 and RRM1 on overall survival in advanced NSCLC

Track 3 Studies evaluating chemotherapy based on ERCC1 and RRM1 expression status

Track 4 ERCC1 and RRM1 in lung cancer treatment decision-making

Track 5 Clinical benefit of ERCC1- and RRM1-based chemotherapy in advanced NSCLC

Track 6 Bevacizumab/erlotinib for elderly patients (>70 years old) with treatment-naïve advanced NSCLC

Track 7 EGFR mutation testing in clinical practice

Track 8 Clinical studies of the irreversible EGFR TKI BIBW 2992 in EGFR-mutant NSCLC

Track 9 BIBW 2992-associated side effects

Track 10 Commonly observed bevacizumab-associated toxicities in NSCLC

Track 11 Management of dermatologic toxicities from EGFR inhibitors

Track 12 **Case discussion:** A 65-year-old woman and former smoker has large, EGFR mutation-negative, K-ras-negative lung cancer with asymptomatic adrenal gland and brain metastases

Track 13 Predictive scoring systems for brain metastasis at diagnosis and at recurrence in NSCLC

Track 14 **Case discussion:** A 62-year-old man with completely resected T2N1 squamous cell NSCLC

Track 15 Perspective on the ECOG-E1505 study of adjuvant chemotherapy/bevacizumab in NSCLC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss your research related to the molecular markers ERCC1 and RRM1, presented at the World Lung Congress 2009?

DR SIMON: At the Moffitt Cancer Center, we completed four Phase II studies, and one of these — the MADeIT trial — involved the use of molecular analysis to individualize therapy based on DNA repair proteins as molecular markers — ERCC1 and RRM1 — in patients with Stage IV NSCLC and good performance status.

ERCC1 is used to predict platinum sensitivity or resistance, and RRM1 predicts for gemcitabine sensitivity or resistance. Based on the levels of these markers, patients were assigned to four different regimens (4.1): carboplatin/gemcitabine, carboplatin/docetaxel, gemcitabine/docetaxel or docetaxel/vinorelbine (Simon 2007).

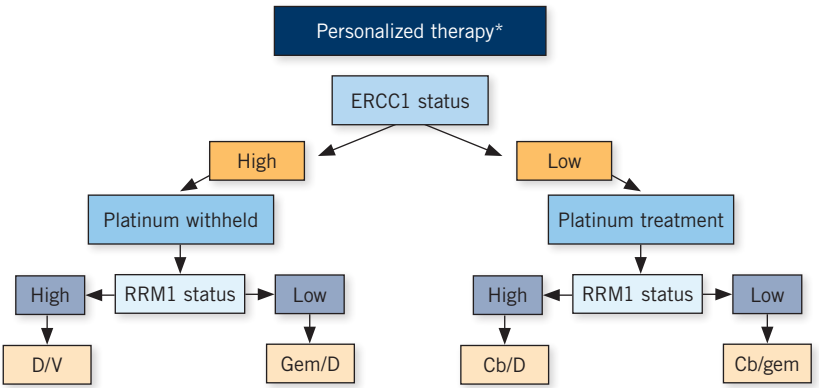
After the results of the other Phase II studies were published, we updated the data on PFS and overall survival. We divided the entire data set from all four studies into a personalized therapy group — patients from the MADeIT study — and a standard therapy group — the other three studies. According to data from up to 48 months of follow-up, patients who received personalized therapy had a better overall survival, 12.3 months, compared to patients in the standard therapy group, with 8.1 months (4.1; [Simon 2009]).

We hypothesized that the administration of platinum-based chemotherapy to patients with low ERCC1 will kill most or all of the cells with low ERCC1. However, the remaining cells are forced to adapt to platinum exposure by upregulating ERCC1 to survive. Similarly, we believe that patients with low RRM1 who are exposed to gemcitabine upregulate RRM1 to survive the

4.1

Personalized Therapy (MADeIT Study) versus Standard Therapy in Advanced NSCLC

Efficacy	Personalized therapy* (N = 58)	Standard therapy† (N = 128)
Median OS	12.3 mo (10.1 to 17.1)	8.1 mo (6.1 to 11.4)
Median PFS	7.0 mo (4.8 to 9.0)	4.5 mo (3.2 to 5.3)



OS = overall survival; PFS = progression-free survival; D/V = docetaxel/vinorelbine; Gem/D = gemcitabine/docetaxel; Cb/D = carboplatin/docetaxel; Cb/gem = carboplatin/gemcitabine

Standardized treatment† = carboplatin/gemcitabine → docetaxel OR carboplatin/paclitaxel/atrasentan OR docetaxel/gefitinib

* Data from the Phase II study 13208 (MADeIT; Simon 2007); † Data from the Phase II studies 12621 (Chiappori 2005), 13303 (Chiappori 2008) and 12905 (Simon 2008)

Simon G et al. *Proc IASLC* 2009;**Abstract D7.6**.

onslaught of gemcitabine-based chemotherapy. Patients with high ERCC1 and high RRM1, although they may not respond to a platinum agent or gemcitabine, have more indolent disease.

Therefore, we hypothesized that when we expose patients to personalized therapy, based on ERCC1 and RRM1, we are forcing the upregulation of these markers, consequently causing more indolent disease behavior.

Track 8

DR LOVE: What are your thoughts on the newer so-called irreversible EGFR TKIs, such as BIBW 2992?

DR SIMON: BIBW 2992 is an irreversible inhibitor of HER1/HER2. When a compound is irreversibly bound to a receptor, that receptor is blocked. Therefore, to survive, cells dependent on EGFR signaling make additional receptors. Consequently, we administer irreversible TKIs using a continuous dosing schedule to keep blocking the newly formed receptors. Generally speaking, these irreversible agents bind tightly.

In a Phase II study of BIBW 2992, the disease control rate was 95 percent in a cohort of patients with EGFR mutation-positive disease (Shih 2009; [4.2]). At this time, a randomized Phase III trial is comparing BIBW 2992 to cisplatin/pemetrexed as first-line treatment for patients with EGFR mutation-positive disease (4.3). It is also being evaluated in the third-line setting in a cohort of patients who have failed on erlotinib. These patients are being randomly assigned to BIBW 2992 or placebo (4.3).

In cell lines, resistance to erlotinib or gefitinib can be attributed to the T790 mutation. T790 adds a bulky methionine group in the ATP-binding pocket. Because the group is bulky, it sterically hinders the attachment of the TKI to the ATP-binding pocket (Kobayashi 2005; [4.4]). Some of the irreversible inhibitors are still able to bind despite the presence of the steric hindrance, which could be an advantage for agents like BIBW 2992. ■

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

	Mutation type			
	Del 19	L858R	Other	Total
Partial response (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

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

4.3

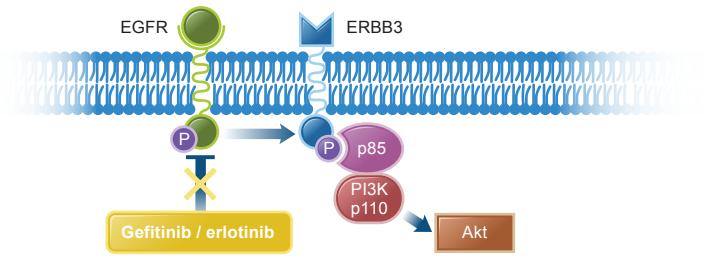
Phase III Studies of the Irreversible EGFR/HER2 TKI BIBW 2992 in Advanced NSCLC

Protocol	Phase	N	Treatment	Eligibility
LUX-Lung 1	III	560	BSC + BIBW 2992 BSC + placebo	• Stage IIIB (with pleural effusion)-IV • 1 to 2 prior lines of chemotherapy • PD ≥ 12 weeks of erlotinib or gefitinib
LUX-Lung 3	III	330	BIBW 2992 Cisplatin/pemetrexed	• Stage IIIB (with pleural effusion)-IV • EGFR mutation-positive • No prior chemotherapy or EGFR-targeted therapy

www.clinicaltrials.gov. Accessed December 2009.

4.4

Steric Hindrance Associated with T790M Mutation Results in Acquired Resistance to Gefitinib or Erlotinib



T790M adds a bulky methionine group in the ATP-binding pocket, which sterically hinders the attachment of EGFR TKIs. Gefitinib and erlotinib are unable to inhibit EGFR phosphorylation in the presence of EGFR T790M. EGFR signaling persists in the presence of gefitinib or erlotinib, leading to persistent erbB3 and Akt phosphorylation. The irreversible EGFR TKIs, such as BIBW 2992, are still able to bind despite the presence of steric hindrance and may be able to prevent EGFR phosphorylation and overcome resistance.

Adapted by permission from Macmillan Publishers Ltd. (Arteaga CL. **HER3 and mutant EGFR meet MET.** *Nat Med* 13:675-7), copyright 2007.

SELECT PUBLICATIONS

Kobayashi S et al. **EGFR mutation and resistance of non-small-cell lung cancer to gefitinib.** *N Engl J Med* 2005;352:786-92.

Shih J et al. **A phase II study of BIBW 2992, a novel irreversible dual EGFR and HER2 tyrosine kinase inhibitor (TKI), in patients with adenocarcinoma of the lung and activating EGFR mutations after failure of one line of chemotherapy (LUX-Lung 2).** *Proc ASCO* 2009;**Abstract 8013**.

Simon GR et al. **Personalized chemotherapy may favorably alter intrinsic disease biology to produce a higher proportion of long term survivors in patients with advanced NSCLC. Oral prognostic and predictive markers.** *Proc IASLC* 2009;**Abstract D7.6**.

Simon G et al. **Feasibility and efficacy of molecular analysis-directed individualized therapy in advanced non-small-cell lung cancer.** *J Clin Oncol* 2007;25:2741-6.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a multicenter, Phase II trial of first-line gefitinib for patients with advanced NSCLC and poor performance status, gefitinib significantly improved overall survival for patients harboring EGFR mutations compared to those who did not have the mutation.**
   a. True
   b. False

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

3. **The frequency of ALK mutations in the overall population of patients with NSCLC is approximately _____.**
   a. Four percent
   b. 10 percent
   c. 22 percent
   d. 60 percent

4. **Which of the following are clinical and/or pathological characteristics seen in patients with EML4-ALK-mutated NSCLC?**
   a. Mostly with adenocarcinomas, signet-ring cell subtype
   b. Nonoverlapping with EGFR mutations
   c. Nonsmoking status or former/light smoking history
   d. All of the above

5. **The disease control rate for patients on a Phase I dose-escalation trial of PF-02341066 in patients with NSCLC with EML4-ALK translocations was reported to be approximately _____.**
   a. 15 percent
   b. 30 percent
   c. 60 percent
   d. 80 percent

6. **The Phase III, randomized, open-label study for patients with NSCLC harboring a translocation or inversion involving the ALK gene locus will evaluate investigator selection of chemotherapy with _____ versus PF-02341066.**
   a. Cetuximab
   b. Docetaxel
   c. Pemetrexed
   d. Either a or b
   e. Either b or c

7. **IPASS demonstrated that progression-free survival (PFS) was longer for patients with NSCLC whose tumors had EGFR mutations when treated with _____ than with chemotherapy.**
   a. Gefitinib
   b. Bevacizumab
   c. Cetuximab
   d. All of the above

8. **The SATURN trial evaluated which of the following strategies as maintenance therapy after nonprogression with first-line platinum-based chemotherapy for patients with advanced NSCLC?**
   a. Bevacizumab versus erlotinib
   b. Bevacizumab versus pemetrexed
   c. Erlotinib versus placebo

9. **The ATLAS trial demonstrated an improvement in PFS with the addition of _____ to maintenance bevacizumab for patients who had completed first-line therapy for advanced NSCLC.**
   a. Erlotinib
   b. Cetuximab
   c. Pemetrexed

10. **The mechanism of BIBW 2992 involves _____.**
    a. Irreversible inhibition of HER1
    b. Irreversible inhibition of HER2
    c. Both a and b
    d. None of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 1, 2010

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
Safety of bevacizumab in patients with treated brain metastases	4 3 2 1	4 3 2 1
Clinical implications of IPASS for EGFR mutation testing and selection of first-line therapy for advanced NSCLC	4 3 2 1	4 3 2 1
Resistance to EGFR TKIs and ongoing studies with the irreversible TKI BIBW 2992	4 3 2 1	4 3 2 1
Clinicopathologic characteristics of patients harboring EML4-ALK and outcomes with the oral c-MET and ALK inhibitor PF-02341066	4 3 2 1	4 3 2 1
Maintenance therapy for advanced NSCLC	4 3 2 1	4 3 2 1
Molecular analysis-directed individualized therapy (MADeIT) in advanced NSCLC	4 3 2 1	4 3 2 1
Gefitinib in patients with treatment-naïve EGFR-mutant NSCLC and poor performance status	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:

- Identify distinct subtypes of adenocarcinoma of the lung, including those with EGFR mutations and EML4-ALK gene fusions, and the investigational and treatment options for these patients . . . . . 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
- Summarize clinical trial data on the treatment of extensive small cell lung cancer . . . . . 4 3 2 1 N/M N/A
- Appraise the outcomes of molecular analysis-directed individualized therapy (MADeIT) for advanced NSCLC . . . . . 4 3 2 1 N/M N/A
- Formulate individualized treatment plans addressing the first-line and maintenance management of recurrent or progressive non-small cell lung cancer (NSCLC), considering unique patient and tumor characteristics. . . . . 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?

.....

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
Corey J Langer, MD	4 3 2 1	4 3 2 1
Alice Shaw, MD, PhD	4 3 2 1	4 3 2 1
Suresh Ramalingam, MD	4 3 2 1	4 3 2 1
George R Simon, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.

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Lung Cancer™ UPDATE

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Lung Cancer™ UPDATE

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