

# Lung Cancer™

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U P D A T E

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

**FACULTY INTERVIEWS**

Rogério C Lilenbaum, MD  
Lecia V Sequist, MD, MPH  
John Heymach, MD, PhD  
Chandra P Belani, MD

**EDITOR**

Neil Love, MD

**CONTENTS**

2 Audio CDs  
Monograph



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## Lung Cancer Update

### A Continuing Medical Education Audio Series

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#### 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% 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

- Apply the results of emerging clinical research to the current and future treatment of non-small cell lung cancer (NSCLC).
- Develop an evidence-based strategy for the initial diagnosis and treatment of localized NSCLC.
- Apply the results of existing and emerging clinical research to the multimodality management of patients with Stage III NSCLC.
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced NSCLC.
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangement and other recently identified driver mutations — and the approved and investigational treatment options for patients with these mutations.
- Review emerging research evidence with the use of the irreversible EGFR tyrosine kinase inhibitor afatinib alone or in combination with an EGFR monoclonal antibody for patients with advanced EGFR mutation-positive NSCLC.
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

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## EDITOR



**Neil Love, MD**  
Research To Practice  
Miami, Florida

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## INTERVIEW

### Rogerio C Lilenbaum, MD

Dr Lilenbaum is Chief Medical Officer at the Smilow Cancer Hospital and Professor of Medicine at Yale University School of Medicine in New Haven, Connecticut.

## Tracks 1-14

### Lung Cancer Highlights of ASCO 2013

- Track 1** Results of the Phase III RTOG-0617 trial evaluating standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiation therapy with or without cetuximab for Stage III non-small cell lung cancer (NSCLC)
- Track 2** Increased toxicity with high-dose chemoradiation therapy in combination with cetuximab on the RTOG-0617 study
- Track 3** Results of the Phase II IFCT-0801/TASTE trial of customized adjuvant therapy for NSCLC
- Track 4** Investigation of anti-programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) antibodies
- Track 5** Clinical activity and safety of the PD-L1 antibody MPDL3280A in locally advanced or metastatic NSCLC
- Track 6** BRAF V600E mutations in NSCLC
- Track 7** BRF113928: Interim results of a Phase II study of dabrafenib in BRAF V600E mutation-positive, advanced NSCLC
- Track 8** Results of routine EGFR, HER2, KRAS, BRAF and PI3KCA mutation detection and EML4-ALK gene fusion assessment in 10,000 French patients with NSCLC
- Track 9** Clinical activity of the second-generation ALK inhibitor LDK378 in advanced, ALK-positive NSCLC
- Track 10** Efficacy and safety of crizotinib in patients with advanced ROS1-rearranged NSCLC
- Track 11** Results of PROSE: A Phase III trial of proteomic-stratified (VeriStrat®) second-line erlotinib versus chemotherapy for patients with inoperable, EGFR wild-type or unknown NSCLC
- Track 12** PRONOUNCE: Results of a Phase III study of pemetrexed/carboplatin → maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab → maintenance bevacizumab for advanced nonsquamous NSCLC
- Track 13** Subset analysis of elderly patients on the PointBreak study: Pemetrexed/carboplatin/bevacizumab → maintenance pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab → maintenance bevacizumab in Stage IIIB or IV nonsquamous NSCLC
- Track 14** Front-line therapeutic options for pan-wild-type metastatic adenocarcinoma of the lung

## Select Excerpts from the Interview

### Track 1

► **DR LOVE:** What are your thoughts about the Phase III RTOG study reported at ASCO comparing high-dose to standard-dose radiation therapy (RT) with chemotherapy for patients with Stage IIIA/B non-small cell lung cancer (NSCLC)?

► **DR LILENBAUM:** RT at a dose of around 60 Gy is the standard for patients with Stage III NSCLC. Previous Phase II data had suggested that higher doses of RT could be beneficial. The RTOG-0617 study was designed to determine whether high-dose RT (74 Gy) would be superior to standard-dose RT (60 Gy). Patients received RT at 60 Gy or 74 Gy with weekly carboplatin/paclitaxel followed by 2 cycles of consolidation carboplatin/paclitaxel. An evaluation of chemoradiation therapy with or without cetuximab was also part of the study design, but those data were not reported. The results showed that high-dose RT was inferior to standard-dose RT in terms of survival, progression-free survival (PFS) and, perhaps of greatest interest, local recurrence rates (Bradley 2013).

► **DR LOVE:** What dose of RT is being used most frequently in practice, and how will the results of this study affect practice?

► **DR LILENBAUM:** I believe 63 to 66 Gy is the dose most frequently used in practice. I don't believe that the 74-Gy dose is used outside of a clinical trial. However, if oncologists are using this dose, they need to stop immediately because the clear message from this trial was that 60 Gy should be the standard dose for unresectable Stage III NSCLC, irrespective of the chemotherapy regimen.

### Track 3

► **DR LOVE:** Another presentation on local treatment that I'd like your take on was from the TASTE study (Soria 2013). What was reported on that trial?

► **DR LILENBAUM:** TASTE was a customized adjuvant trial in which patients were tested for EGFR mutation and then ERCC1 overexpression. The Phase II feasibility component of that trial was reported at ASCO 2013. The authors reported, much to everybody's surprise, that the ERCC1 assay that they were using was simply not reliable enough for a prospective Phase III trial.

► **DR LOVE:** Even though the assay didn't work, the other interesting aspect of the trial was that the control regimen was cisplatin/pemetrexed, which is being used more now in the United States in the adjuvant setting. This aspect of TASTE was similar to reports from the TREAT trial (Kreuter 2013).

► **DR LILENBAUM:** Yes, this was an important finding. The authors reported that more than 80% of patients were able to complete 4 cycles of treatment with cisplatin/pemetrexed. This was similar to the finding from the TREAT study, which compared cisplatin/pemetrexed to cisplatin/vinorelbine. I believe cisplatin/pemetrexed is emerging as the adjuvant regimen of choice for patients with nonsquamous NSCLC.

### Tracks 4-5

► **DR LOVE:** Another exciting data set from ASCO 2013 evaluated an anti-programmed death ligand-1 (PD-L1) antibody in patients with locally advanced or metastatic NSCLC. Would you talk about that study?

► **DR LILENBAUM:** It is incredibly exciting how immunotherapy is evolving and the difference it is likely to make for patients for whom we had no new therapies. The results with the anti-PD-L1 antibody (MPDL3280A) in NSCLC were dramatic. The overall response rate was 22% for patients with NSCLC, and a response was observed in patients with both nonsquamous and squamous cell histologies. A significant differ-

ence in response rate was reported between those whose tumors were PD-L1-positive versus those whose tumors were not (80% versus 14%) (Spigel 2013; [1.1]). I believe that it would be reasonable to evaluate this agent even in patients whose tumors do not express PD-L1 because of the lack of options for these patients. One of the remarkable features of this agent is that no significant toxicity was observed in this group of patients with heavily pretreated disease.

## 1.1

### Clinical Activity and Safety of the PD-L1 Antibody MPDL3280A in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Efficacy*	ORR*	SD ≥24 wk	PFS at 24 wk
NSCLC (n = 41) <sup>†‡</sup>	22%	12%	46%
Nonsquamous (n = 31)	19%	13%	44%
Squamous (n = 9)	33%	11%	44%
Response by PD-L1 status	PD-L1-positive	PD-L1-negative	
NSCLC (n = 41) <sup>†</sup>	80%	14%	
Nonsquamous (n = 31)	67%	14%	
Squamous (n = 9)	100%	17%	

\* Investigator assessed; <sup>†</sup> One patient had undetermined histology status; <sup>‡</sup> Number of prior systemic regimens: 1 (15%), 2 (21%), ≥3 (62%)

ORR = objective response rate; SD = stable disease; PFS = progression-free survival

Spigel DR et al. *Proc ASCO* 2013; **Abstract 8008**.

## Track 9

► **DR LOVE:** What are your thoughts on the Phase I trial of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC?

► **DR LILENBAUM:** ALK rearrangements are present in 3% to 7% of patients with NSCLC, and crizotinib is quite active for these patients. However, most patients eventually develop resistance to crizotinib. This is the first clinical trial to demonstrate that LDK378 is active in crizotinib-resistant disease. A response rate of approximately 60% was reported with this agent (Shaw 2013; [1.2]). LDK378 now provides an option other than conventional chemotherapy for these patients. Additionally, in a subset of patients the mechanisms of resistance were identified and LDK378 was also found to be active against tumors with the L1196 mutation. The study also included patients with crizotinib-naïve disease, and LDK378 had excellent activity in that group of patients.

## Track 11

► **DR LOVE:** Would you discuss the Phase III study on the predictive value of VeriStrat classification on the survival of patients with advanced NSCLC treated with second-line chemotherapy or erlotinib?

► **DR LILENBAUM:** VeriStrat is a serum proteomic signature that can be used to classify patients with NSCLC into VeriStrat good and VeriStrat poor groups based on 8 mass spectral peaks. In the study reported by Lazzari and colleagues, patients with NSCLC had their VeriStrat status determined upon registration and were then randomly

## 1.2

### Phase I Trial of the ALK Inhibitor LDK378 in Advanced, ALK-Positive Non-Small Cell Lung Cancer

	All patients (n = 114)	CRZ pretreated (n = 79)*	CRZ naïve (n = 35) <sup>†</sup>
<b>Overall response rate</b>	58%	57%	60%
Complete response	1%	1%	0%
Partial response	57%	56%	60%
<b>Median progression-free survival</b> (≥400 mg/d) (n = 114)	8.6 mo		

The most common adverse events among all patients were nausea (73%), diarrhea (72%), vomiting (58%) and fatigue (41%).

CRZ = crizotinib; \* 1 response unknown; † 4 responses unknown

Shaw AT et al. *Proc ASCO* 2013; **Abstract 8010**.

assigned to either chemotherapy with pemetrexed or docetaxel or to erlotinib. The results indicated that, as expected, the test is prognostic and patients with good VeriStrat status fared much better than those with poor status.

Additionally, the results indicated that the survival of patients with good VeriStrat status (65% to 70% of patients) was similar with chemotherapy and erlotinib. However, patients with poor VeriStrat status had a higher median overall survival with chemotherapy than with erlotinib (Lazzari 2013; [1.3]).

## 1.3

### Results of PROSE: A Prospective Phase III Trial of Proteomic-Stratified (VeriStrat) Second-Line Erlotinib versus Chemotherapy for Patients with Inoperable Non-Small Cell Lung Cancer

Median overall survival	Chemotherapy	Erlotinib	Hazard ratio	p-value
All patients (n = 129, 134)	9.0 mo	7.7 mo	1.14	0.313
VeriStrat good (n = 96, 88)	10.92 mo	10.95 mo	1.06	0.714
VeriStrat poor (n = 38, 41)	6.38 mo	2.98 mo	1.72	0.022

- Overall, patients with VeriStrat good status have better outcomes than those with VeriStrat poor status.
- VeriStrat classification is useful in guiding second-line treatment decision-making for patients with EGFR wild type or unknown EGFR status.

Lazzari C et al. *Proc ASCO* 2013; **Abstract LBA8005**.

## Tracks 12-13

► **DR LOVE:** What are your thoughts on the Phase III PRONOUNCE study in advanced nonsquamous cancers (Zinner 2013)?

► **DR LILENBAUM:** In this study, patients were randomly assigned to either carboplatin/pemetrexed with pemetrexed maintenance or the ECOG-E4599 regimen, which is carboplatin/paclitaxel/bevacizumab with bevacizumab maintenance. The primary endpoint was Grade 4 PFS, which means survival free of progression or death but also free of Grade 4 adverse events.



The results indicated no difference in Grade 4 PFS between the 2 regimens. Hematologic toxicity was not that much more favorable for carboplatin/pemetrexed versus carboplatin/paclitaxel/bevacizumab. In fact, anemia and thrombocytopenia were worse on the carboplatin/pemetrexed arm. Neutropenia was worse on the bevacizumab arm, as you would expect. Alopecia and peripheral neuropathy were also more common on the bevacizumab arm.

The data suggest that either regimen can be used, but the small size and unusual endpoint must be considered in comparison to the large data set for the addition of bevacizumab to chemotherapy. I am a little unclear about how a trial like this advances the field.

► **DR LOVE:** Mark Socinski presented a subset analysis of the PointBreak trial at ASCO 2013. Can you also discuss those data?

► **DR LILENBAUM:** PointBreak was a Phase III study comparing 2 regimens — carboplatin/pemetrexed/bevacizumab with maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen. The results showed no significant difference between the 2 regimens with respect to overall survival, the primary endpoint (Patel 2012). Both regimens were tolerable, suggesting that either regimen can be used.

At ASCO 2013 Dr Socinski presented the results of a subgroup analysis of elderly patients from the PointBreak trial using age 70 or 75 as a cutoff. No significant difference in overall survival was observed between patients in the different age groups (Socinski 2013).

Based on data from earlier studies, concerns were raised about the use of bevacizumab in elderly patients. This subset analysis indicated that you can administer bevacizumab to elderly patients without significant additional toxicity compared to younger patients. ■

## SELECT PUBLICATIONS

Bradley JD et al. **A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617.** *Proc ASCO* 2013;**Abstract 7501.**

Kreuter M et al. **Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: The TREAT study.** *Ann Oncol* 2013;24(4):986-92.

Patel J et al. **A randomized, open-label, Phase III, superiority study of pemetrexed (Pem) + carboplatin (Cb) + bevacizumab (Bev) followed by maintenance Pem + Bev versus paclitaxel (Pac) + Cb + Bev followed by maintenance Bev in patients with Stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC).** Chicago Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract LBPL1.**

Socinski M et al. **A phase III study of pemetrexed (Pem) plus carboplatin (Cb) plus bevacizumab (Bev) followed by maintenance pem plus bev versus paclitaxel (Pac) plus cb plus bev followed by maintenance bev in stage IIIB or IV nonsquamous non-small cell lung cancer (NS-NSCLC): Overall and age group results.** *Proc ASCO* 2013;**Abstract 8004.**

Soria JC et al. **Results of the prospective, randomized, and customized NSCLC adjuvant phase II trial (IFCT-0801, TASTE trial) from the French Collaborative Intergroup.** *Proc ASCO* 2013;**Abstract 7505.**

Spigel DR et al. **Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2013;**Abstract 8008.**

Zinner R et al. **Randomized, open-label, phase III study of pemetrexed plus carboplatin (PemC) followed by maintenance pemetrexed versus paclitaxel (Pac) + carboplatin + bevacizumab (Bev) followed by maintenance bevacizumab in patients with advanced nonsquamous non-small cell lung cancer (NS-NSCLC).** *Proc ASCO* 2013;**Abstract LBA8003.**



## INTERVIEW

### Lecia V Sequist, MD, MPH

Dr Sequist is Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

#### Tracks 1-14

- Track 1** Treatment options on discovery of EGFR mutation positivity after initiation of chemotherapy for advanced NSCLC
- Track 2** **Case discussion:** A 62-year-old patient and former smoker with advanced, EGFR-mutant NSCLC experiences disease progression after 10 months of response to erlotinib
- Track 3** First-line therapy for advanced, EGFR-mutant NSCLC
- Track 4** Erlotinib dosing in advanced, EGFR mutation-positive NSCLC
- Track 5** Continuation of erlotinib after disease progression in patients with advanced, EGFR-mutant NSCLC
- Track 6** Mechanisms of action of the second-generation pan-HER inhibitors afatinib and dacomitinib
- Track 7** Results of the LUX-Lung 3 study comparing the irreversible pan-HER inhibitor afatinib to cisplatin/pemetrexed as first-line treatment in advanced, EGFR-mutant NSCLC
- Track 8** Activity and tolerability of afatinib/cetuximab in patients with advanced NSCLC and acquired resistance to EGFR TKIs
- Track 9** Results of the SELECT study: A multicenter Phase II trial of adjuvant erlotinib in resected EGFR-mutant NSCLC
- Track 10** Clinical experience with adjuvant erlotinib
- Track 11** A dose-finding study of adjuvant afatinib in combination with cisplatin or carboplatin/pemetrexed for patients with EGFR-mutant NSCLC undergoing definitive chemoradiation therapy
- Track 12** **Case discussion:** A 59-year-old patient and heavy smoker with advanced squamous cell carcinoma of the lung who achieves stable disease after 4 cycles of carboplatin/paclitaxel
- Track 13** Investigation of checkpoint inhibitors in NSCLC
- Track 14** **Case discussion:** A 41-year-old patient and former moderate smoker with recurrent, pan-wild-type adenocarcinoma less than 1 year after completing definitive chemoradiation therapy for Stage IIIB NSCLC

#### Select Excerpts from the Interview

##### Track 6

- ▶ **DR LOVE:** Would you discuss the mechanism of action of various EGFR tyrosine kinase inhibitors (TKIs)?
- ▶ **DR SEQUIST:** There are 3 generations of EGFR TKIs. Gefitinib and erlotinib are first-generation, reversible TKIs that compete for receptor-binding with ATP. I explain to my patients that both of these TKIs bind tightly to EGFR like a strong magnet, but the binding is not permanent. If one pulls hard enough, the connection can be dissociated.

The second-generation TKIs, like afatinib and dacomitinib, covalently bind, irreversibly, to the ATP-binding site of the receptor. Afatinib and dacomitinib are both pan-HER inhibitors with strong binding affinities for both HER2 and EGFR. In laboratory experiments, second-generation TKIs can overcome the EGFR T790M mutation, the most common acquired secondary EGFR mutation. Several clinical studies are ongoing to provide definitive answers about whether this effect applies in patients.

In general, the degree of activity of the second-generation TKIs in patients with erlotinib-resistant NSCLC has been somewhat disheartening. Because of the strong covalent binding nature of these TKIs, some of the side effects can prohibit the administration of the required dose needed to prevent or overcome the EGFR T790M mutation. With these agents, patients seem to develop more rash and diarrhea than with the first-generation TKIs. They are effective in treatment-naïve NSCLC but not quite as efficacious for patients with drug-resistant disease.

A third generation of TKIs is currently being clinically investigated. The difference is that these agents do not block wild-type EGFR. They do not cause rash or diarrhea because they do not inhibit EGFR in noncancerous cells. Rather, they target EGFR-activating mutations like T790M. Many third-generation TKIs are currently in Phase I clinical trials. It will be exciting to see the results from these studies in the coming years.

 **Track 7**

► **DR LOVE:** Would you discuss the results of the Phase III LUX-Lung 3 trial?

► **DR SEQUIST:** The LUX-Lung 3 trial evaluated afatinib versus cisplatin/pemetrexed as first-line therapy for patients with advanced EGFR-mutant NSCLC (Sequist 2013; [2.1]). It's the first trial to compare second- or third-generation TKIs to a pemetrexed-based regimen. Pemetrexed has evolved into one of our favorite agents, at least in the United States, for patients with lung adenocarcinoma. So a randomized trial of an EGFR TKI versus a pemetrexed-based chemotherapeutic regimen was needed.

Patients received 6 cycles of cisplatin/pemetrexed or daily afatinib. PFS and quality of life were significantly improved with afatinib. The majority of patients on the trial had NSCLC harboring EGFR mutations with exon 19 deletion or L858R mutation. Approximately 11% of patients on the trial had atypical mutations that are less responsive to EGFR TKIs.

**2.1 LUX-Lung 3: A Phase III Trial Evaluating Afatinib versus Cisplatin/Pemetrexed (Cis/Pem) as First-Line Therapy for Advanced EGFR-Mutant Non-Small Cell Lung Cancer**

Efficacy	Afatinib (n = 230)	Cis/pem (n = 115)	Hazard ratio	p-value
Median PFS: All patients	11.1 mo	6.9 mo	0.58	<0.001
Median PFS: Patients with del(19)/L858R	13.6 mo	6.9 mo	0.47	<0.001
Objective response rate	56.1%	22.6%	—	0.001
Median duration of response	11.1 mo	5.5 mo	—	—

PFS = progression-free survival

Sequist LV et al. *J Clin Oncol* 2013;[Epub ahead of print].

In the entire study population, the median PFS was approximately 11 months with afatinib. A subgroup analysis of patients with the classical EGFR mutations demonstrated a median PFS of 13.6 months with first-line afatinib. If these results are compared across trials to the observations in the IPASS trial of gefitinib (Mok 2009) or the EURTAC trial, which resulted in a median PFS of 9.7 months with erlotinib (Rosell 2012), it appears that second-generation TKIs such as afatinib may yield a longer median PFS by an average of 2 to 4 months. However, the first- and second-generation TKIs have yet to be compared head to head.

## Tracks 9-10

► **DR LOVE:** Based on the preliminary results of the Phase II SELECT trial, what is your perspective on the current role of adjuvant TKI therapy in NSCLC (Neal 2012)?

► **DR SEQUIST:** The single-arm SELECT trial evaluated 100 patients with resected, EGFR-mutant NSCLC who received adjuvant erlotinib for 2 years. The study is ongoing, and the mature results are not yet available. At ASCO 2012 we presented the fairly mature data for the first 36 patients enrolled on the study. It took several years to accrue 100 patients. By the time the hundredth patient was enrolled, the first 36 patients had been followed for a good amount of time.

Analysis of results for the first 36 patients reported a low rate of disease progression during treatment. Only 1 patient in that group experienced disease progression while receiving adjuvant erlotinib. A handful of patients experienced progressive disease within 6 months of discontinuing therapy.

This observation may be reflected in the mature data from 100 patients, demonstrating that this strategy is not curative but instead delays the appearance or emergence of metastatic disease.

When you consider patients with advanced disease and you see the response rate with chemotherapy in the neighborhood of 30% and the response rate with TKIs in the neighborhood of 75%, it seems obvious that if chemotherapy helps in the adjuvant setting, an EGFR TKI should help more. But many concepts in medicine seem obvious until you test them. In order to know whether a small group of patients exists whom you are moving from recurrence to cure, you need a randomized study. So together with the NCI, CALGB is now working on a randomized trial in which patients would receive either placebo or erlotinib. In addition, we are opening another trial at Mass General, Memorial Sloan-Kettering and Stanford University evaluating adjuvant afatinib for patients with fully resected EGFR-mutant tumors. ■

## SELECT PUBLICATIONS

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

Neal JW et al. **The SELECT study: A multicenter Phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).** Multidisciplinary Symposium in Thoracic Oncology 2012; **Abstract 16.**

Rosell R et al. **Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial.** *Lancet Oncol* 2012;3(3):239-46.

Sequist LV et al. **Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.** *J Clin Oncol* 2013;[Epub ahead of print].



## INTERVIEW

### John Heymach, MD, PhD

Dr Heymach is Chief of Thoracic Medical Oncology and 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** The Cancer Genome Atlas consortium's identification of mutations in squamous cell lung cancer
- Track 2** Potential role of *nab* paclitaxel as treatment for advanced squamous cell lung cancer
- Track 3** Perspective on targeting MET in NSCLC
- Track 4** MetLung: A Phase III study of onartuzumab (MetMAB)/erlotinib versus erlotinib/placebo in advanced MET diagnostic-positive NSCLC after failure of 1 to 2 platinum-based regimens
- Track 5** Use of erlotinib in EGFR wild-type, squamous cell lung cancer
- Track 6** Targeting angiogenesis in NSCLC
- Track 7** **Case discussion:** A 66-year-old patient and never smoker with resected Stage IB NSCLC and 2 uncommon EGFR mutations (E709A, G719C)
- Track 8** Adjuvant chemotherapy options for Stage IB NSCLC
- Track 9** TREAT: Results of a Phase II trial on the refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin/pemetrexed versus cisplatin/vinorelbine
- Track 10** **Case discussion:** A 50-year-old patient and never smoker with EGFR wild-type, ALK-negative, HER2-positive Stage IV adenocarcinoma of the lung
- Track 11** Incidence of HER2 mutations in NSCLC
- Track 12** Perspective on the PointBreak trial results: Pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC

#### Select Excerpts from the Interview

##### Track 2

► **DR LOVE:** Nanoparticle albumin-bound (*nab*) paclitaxel was recently approved by the FDA in combination with carboplatin for the first-line treatment of locally advanced or metastatic NSCLC in patients who are not eligible for curative surgery or RT. What role does it play in patients with squamous cell lung cancer?

► **DR HEYMACH:** According to some preclinical suggestions, *nab* paclitaxel may be more active in squamous cell lung cancer than it is in nonsquamous histology because the receptor that *nab* paclitaxel binds to seems to be more highly expressed in squamous cell carcinoma. Mark Socinski confirmed this in a Phase III trial in which the response rate was significantly higher with *nab* paclitaxel/carboplatin compared to solvent-based paclitaxel/carboplatin in patients with squamous cell carcinoma (Socinski 2012; [3.1]). Although overall survival — which wasn't the primary endpoint of the study — wasn't significantly longer, *nab* paclitaxel did appear to be more active. We also know that this agent may be better tolerated than conventional paclitaxel.

**Phase III Trial of *Nab* Paclitaxel/Carboplatin (*Nab*-PC) versus Solvent-Based Paclitaxel/Carboplatin (sb-PC) as First-Line Therapy for Patients with Advanced Non-Small Cell Lung Cancer**

	<i>Nab</i> -PC	sb-PC	<i>p</i> -value
<b>Overall response rate</b>			
All patients (n = 521, 531)	33%	25%	0.005
Squamous (n = 229, 221)	41%	24%	<0.001
Nonsquamous (n = 292, 310)	26%	25%	0.808
<b>Median progression-free survival</b>			
All patients (n = 521, 531)	6.3 mo	5.8 mo	0.214
Patients aged ≥70 y (n = 74, 82)	8.0 mo	6.8 mo	0.134
<b>Median overall survival</b>			
All patients (n = 521, 531)	12.1 mo	11.2 mo	0.271
Patients aged ≥70 y (n = 74, 82)	19.9 mo	10.4 mo	0.009

Socinski MA et al. *Ann Oncol* 2013;24(2):314–21; Socinski MA et al. *J Clin Oncol* 2012;30(17):2055–62.

Often I'll administer *nab* paclitaxel when I'm concerned about neuropathy or other toxicity in patients with squamous cell carcinoma. Additional research is now under way evaluating the receptors that bind *nab* paclitaxel as well as other proteins involved in that cascade that seem to be more prevalent in squamous cell carcinoma. It is possible that this agent could be combined with targeted therapies, and we are currently trying to ascertain whether we can combine *nab* paclitaxel on an every 3-week basis with targeted agents and whether that works as well as combining it with other drugs.

We know *nab* paclitaxel combined with platinum alone won't dramatically change outcomes in lung cancer as compared to standard chemotherapy, but it has advantages. And if it becomes a platform for combining targeted agents, it's possible that it will become more widely used.

### Tracks 3-4

► **DR LOVE:** What are your thoughts on the strategy of targeting MET in NSCLC?

► **DR HEYMACH:** MET is an interesting target for lung cancer for a number of reasons. MET is often amplified in tumors that have become resistant to EGFR inhibitors. Also, after you radiate a tumor, it can upregulate MET even if the tumor didn't express MET initially. MET is a protein that not only drives resistance to EGFR inhibitors and other pathways, but it also drives metastases — that's how it was initially characterized in different types of cancer.

Onartuzumab (MetMab) is one of the advanced MET-targeted agents in terms of investigations on clinical trials. In a Phase II study, it appeared as though the combination of onartuzumab and erlotinib provided a significant benefit in the subgroup of patients who expressed MET by either FISH or immunohistochemistry compared to those who didn't express MET (Spigel 2011; [3.2]).

Those results prompted a large Phase III trial, which is ongoing (3.3). We're eagerly awaiting results from this study because it's clear that MET is a key player in resistance to EGFR inhibitors. We believe it may also be a mediator of resistance to angiogenesis inhibitors and other agents. In my mind I see no question that targeting MET will be part of future therapeutic strategies.

## 3.2

### OAM4558g: A Phase II Trial of Erlotinib (E) with or without Onartuzumab as Second- or Third-Line Therapy for Advanced Non-Small Cell Lung Cancer

	Patients with positive c-MET immunohistochemistry			
	E + onartuzumab	E + placebo	Hazard ratio	p-value
Median progression-free survival	2.9 mo	1.5 mo	0.53	0.04
Median overall survival	12.6 mo	3.8 mo	0.37	0.002
Patients with negative c-MET immunohistochemistry				
Median progression-free survival	1.4 mo	2.7 mo	1.82	0.05
Median overall survival	8.1 mo	15.3 mo	1.78	0.16
Intent-to-treat population				
Median progression-free survival	2.2 mo	2.5 mo	1.09	0.69
Median overall survival	8.9 mo	7.4 mo	0.80	0.34

Spigel DR et al. *Proc ASCO* 2011; **Abstract 7505**.

## 3.3

### MetLung: A Phase III, Randomized Study of Onartuzumab with Erlotinib versus Placebo with Erlotinib in Advanced, MET-Positive Non-Small Cell Lung Cancer (NSCLC)

**Protocol ID:** NCT01456325

**Target Accrual:** 480

**Eligibility:** MET-positive NSCLC; disease progression on 1 to 2 lines of platinum-based chemotherapy; patients stratified by MET expression (2+ versus 3+), prior lines of therapy (1 versus 2) and EGFR-activating mutation status (yes versus no)

Onartuzumab + erlotinib

Placebo + erlotinib

**Primary endpoint:** Overall survival

Spigel DR et al. *Proc ASCO* 2012; **Abstract TPS7616**.

## Track 6

► **DR LOVE:** Bevacizumab is very much a part of clinical practice, but what other anti-angiogenic agents are on the horizon in NSCLC?

► **DR HEYMACH:** One is ramucirumab, a monoclonal antibody that targets VEGF receptor 2 instead of targeting the VEGF ligand as bevacizumab does. We've also discovered recently that not only is VEGF receptor 2 a key driver of angiogenesis, but it also is often on tumor cells themselves so it may be a tumor-derived target in lung cancer.

You may ask why you would want to target the receptor instead of the ligand. A couple of different ligands can bind to VEGF receptor 2. So it may be the case that if you block VEGF, these other VEGF ligands may become upregulated and still activate VEGF receptor 2 even though VEGF is blocked, whereas if you block the receptor itself it may not matter which ligands are upregulated. Phase III studies evaluating ramucirumab are ongoing in lung cancer (3.4), and we're eagerly awaiting those results to ascertain if this adds something different than targeting VEGF by itself.

Nintedanib (BIBF 1120) is another agent undergoing Phase III testing in combination with pemetrexed (NCT00806819) and docetaxel (NCT00805194). (Editor's note: Subsequent to this interview the initial results of these studies were presented [3.5].) The exciting aspect about this agent is that it not only blocks the VEGF receptor pathways, but it also blocks multiple FGF receptors and a couple of other targets such as the PDGF receptor and RET. So we have reason to be hopeful that, either by targeting the VEGF pathway more effectively or by targeting the VEGF pathway and some of these other pathways, we may make anti-angiogenic therapy more effective. ■

### 3.4

#### REVEL: A Phase III Study Evaluating Docetaxel and Ramucirumab versus Docetaxel and Placebo for Stage IV Non-Small Cell Lung Cancer (NSCLC) Progressing After 1 Prior Platinum-Based Therapy Regimen

Protocol ID: NCT01168973

Target Accrual: 1,242

##### Eligibility

- Histologically or cytologically confirmed Stage IV NSCLC
- ECOG PS 0 to 1



Docetaxel + ramucirumab

Docetaxel + placebo

[www.clinicaltrials.gov](http://www.clinicaltrials.gov), July 2013.

### 3.5

#### Phase III Trials Evaluating Nintedanib-Based Therapy for Non-Small Cell Lung Cancer Progressing After 1 Prior Chemotherapy Regimen

	LUME-Lung 1 <sup>1</sup>		LUME-Lung 2 <sup>2</sup>	
	Nintedanib + docetaxel (n = 655)	Placebo + docetaxel (n = 659)	Nintedanib + pemetrexed (n = 353)	Placebo + pemetrexed (n = 360)
Median progression-free survival	3.4 mo	2.7 mo	4.4 mo	3.6 mo
	HR 0.79; <i>p</i> -value 0.0019		HR 0.83; <i>p</i> -value 0.0435	

HR = hazard ratio

<sup>1</sup>Reck M et al. *Proc ASCO* 2013; **Abstract LBA8011**; <sup>2</sup>Hanna NH et al. *Proc ASCO* 2013; **Abstract 8034**.

## SELECT PUBLICATIONS

Fossella F et al. **Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group.** *J Clin Oncol* 2003;21(16):3016-24.

Kreuter M et al. **Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: The TREAT study.** *Ann Oncol* 2013;24(4):986-92.

Socinski MA et al. **Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase III trial.** *J Clin Oncol* 2012;30(17):2055-62.

Spigel DR et al. **The MetLUNG study: A randomized, double-blind, phase III study of onartuzumab (MetMAB) plus erlotinib versus placebo plus erlotinib in patients with advanced, MET-positive non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012; **Abstract TPS7616**.

Spigel DR et al. **Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAB or placebo in combination with erlotinib in advanced NSCLC.** *Proc ASCO* 2011; **Abstract 7505**.





## INTERVIEW

### Chandra P Belani, MD

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

#### Tracks 1-9

- |   |   |
|---|---|
| <b>Track 1</b> Practical benefits of maintenance therapy compared to second-line chemotherapy   | <b>Track 5</b> Management of hypomagnesemia and azotemia in patients receiving cisplatin/pemetrexed   |
| <b>Track 2</b> Viewpoint on the results of the PointBreak study comparing pemetrexed/carboplatin/bevacizumab → maintenance pemetrexed/bevacizumab to the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC | <b>Track 6</b> <b>Case discussion:</b> A 37-year-old patient and never smoker with a 3.9-cm adenocarcinoma of the lung and an EGFR exon 19 mutation |
| <b>Track 3</b> ECOG-E5508: A Phase III study of maintenance bevacizumab, pemetrexed or the combination in advanced NSCLC  | <b>Track 7</b> Surgical resection versus neoadjuvant chemoradiation therapy for Stage III NSCLC   |
| <b>Track 4</b> <b>Case discussion:</b> A 61-year-old patient and smoker with a Stage IIIA (T2N2M0) moderately differentiated adenocarcinoma of the lung   | <b>Track 8</b> Multidisciplinary management of malignant pleural effusion   |
|   | <b>Track 9</b> Approach to maintenance therapy for elderly patients with advanced NSCLC   |

#### Select Excerpts from the Interview

##### Track 1

► **DR LOVE:** Would you discuss the role of maintenance therapy for patients with advanced NSCLC?

► **DR BELANI:** Currently, approximately 45% of eligible patients with advanced NSCLC receive maintenance therapy. Although the remaining 50% are eligible, they don't receive maintenance therapy because of physician skepticism.

Pemetrexed and erlotinib are the 2 FDA-approved agents for maintenance therapy in advanced NSCLC. Patients with nonsquamous NSCLC primarily receive maintenance pemetrexed, the indication for which it is approved. Patients who've received up-front platinum-based chemotherapy with or without pemetrexed are generally receiving maintenance pemetrexed, which is the most commonly administered maintenance agent based on the results of the Phase III JMEN (Ciuleanu 2009) and PARAMOUNT trials (Paz-Ares 2012, 2013), which reported that maintenance pemetrexed significantly improves overall survival and PFS.

Maintenance erlotinib is used to a lesser extent because it is primarily used as first-line therapy for patients with EGFR mutation-positive disease. Few patients with wild-type

disease receive it as maintenance therapy. They usually receive it as second- or third-line therapy instead of maintenance therapy.

► **DR LOVE:** What are the most common arguments against the use of maintenance therapy?

► **DR BELANI:** A key argument against maintenance therapy is that although about 60% of the patients on the placebo arm of the JMEN trial received second-line therapy, only a few received pemetrexed. However, in the Phase III study of maintenance versus second-line docetaxel, about 60% of the patients made it to second-line therapy, and almost all received maintenance docetaxel (Fidias 2009).

The overall survival was the same for patients who received maintenance and those who received second-line therapy. So some investigators believe that proper selection of patients for second-line therapy will result in survival benefits similar to those with maintenance therapy. However, those who favor second-line versus maintenance therapy discount the fact that a third of the patients on that study discontinued treatment before second-line intervention.

## Tracks 2-3

► **DR LOVE:** What is your perspective on the results of the Phase III PointBreak trial?

► **DR BELANI:** The PointBreak study was not a maintenance trial per se — it was a comparison of 2 regimens. It compared the ECOG-E4599 regimen of paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab to pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab (Patel 2012). As the trial was designed, one can't make an argument for maintenance bevacizumab because all patients received it. Maintenance pemetrexed/bevacizumab received after the 3-drug combination was not significantly beneficial in terms of overall survival when compared to the ECOG-E4599 regimen.

Initially we thought that maintenance pemetrexed/bevacizumab increased toxicity, which in turn reduced survival, preventing the study from meeting its primary endpoint. However, a breakdown of the induction and maintenance phases of the study revealed that some benefit was observed with the 2-drug maintenance therapy, although it was associated with slightly increased toxicity. Failure to meet the primary endpoint, therefore, was not due to a reduction in survival in response to pemetrexed/bevacizumab in the maintenance phase of the trial.

The Phase III AVAPERL1 trial demonstrated that maintenance pemetrexed/bevacizumab was superior in terms of PFS versus bevacizumab alone, but no significant difference in overall survival was observed (Barlesi 2013). Though I may be biased because I have been involved in maintenance pemetrexed studies, I believe maintenance pemetrexed has a role based on the results of the JMEN and PARAMOUNT studies.

► **DR LOVE:** Any comments on the ongoing Phase III ECOG-E5508 trial?

► **DR BELANI:** This study is evaluating maintenance bevacizumab, pemetrexed or the combination after responsive or stable disease on carboplatin/paclitaxel/bevacizumab induction therapy for patients with advanced nonsquamous NSCLC (4.1). Enrollment is currently about half of the target accrual. ■

## ECOG-E5508: A Phase III Trial of Bevacizumab or Pemetrexed Alone or in Combination After Induction Therapy with Carboplatin, Paclitaxel and Bevacizumab for Patients with Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

Target Accrual (n = 1,282)

### Eligibility

- Stage IIIB-T4Nx, Stage IV (including M1a, M1b) or recurrent NSCLC
- Nonsquamous histology
- No prior systemic chemotherapy for advanced NSCLC
- No prior paclitaxel, pemetrexed or bevacizumab

### Induction therapy

Paclitaxel: 200 mg/m<sup>2</sup> IV  
Carboplatin: AUC 6 mg/mL IV  
Bevacizumab: 15 mg/kg IV  
d1 of cycles 1-4

R

CR/PR/SD

Maintenance therapy  
(cycles 1 and beyond)

Bevacizumab  
15 mg/kg IV  
d1 of every cycle

Pemetrexed  
500 mg/m<sup>2</sup> IV  
d1 of every cycle

Pemetrexed +  
bevacizumab  
Same dose  
d1 of every cycle

[www.clinicaltrials.gov](http://www.clinicaltrials.gov), July 2013; [www.ecog.org](http://www.ecog.org), July 2013.

## SELECT PUBLICATIONS

Barlesi F et al. **Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089).** *J Clin Oncol* 2013;[Epub ahead of print].

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.

Fidias PM et al. **Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer.** *J Clin Oncol* 2009;27(4):591-8.

Karayama M et al. **Maintenance therapy with pemetrexed versus docetaxel after induction therapy with carboplatin and pemetrexed in chemotherapy-naïve patients with advanced non-squamous non-small-cell lung cancer: A randomized, phase II study.** *Cancer Chemother Pharmacol* 2013;72(2): 445-52.

Patel JD et al. **A randomized, open-label, phase III, superiority study of pemetrexed (pem) + carboplatin (cb) + bevacizumab (bev) followed by maintenance pem + bev versus paclitaxel (pac) + cb + bev followed by maintenance bev in patients with stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC).** Chicago Multidisciplinary Symposium in Thoracic Oncology 2012; **Abstract LBPL1.**

Paz-Ares LG et al. **PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;[Epub ahead of print].

Paz-Ares L et al. **Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): A double-blind, phase 3, randomised controlled trial.** *Lancet Oncol* 2012;13(3):247-55.

## QUESTIONS (PLEASE CIRCLE ANSWER):

1. The Phase III RTOG-0617 trial evaluating standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiation therapy for Stage III NSCLC reported that high-dose RT was \_\_\_\_\_ to standard-dose RT in terms of survival, progression-free survival and local recurrence rates.
  - a. Equivalent
  - b. Inferior
  - c. Superior
2. A Phase I trial of the novel ALK inhibitor LDK378 in advanced, ALK-positive NSCLC demonstrated that patients with crizotinib-resistant and those with crizotinib-naïve disease experienced about a 60% response rate to the ALK inhibitor.
  - a. True
  - b. False
3. The Phase III ECOG-E5508 trial is evaluating maintenance therapy with bevacizumab or \_\_\_\_\_ alone or in combination after induction therapy with carboplatin, paclitaxel and bevacizumab for patients with advanced nonsquamous NSCLC.
  - a. Erlotinib
  - b. Pemetrexed
  - c. Afatinib
4. The Phase III PRONOUNCE study comparing carboplatin/pemetrexed with pemetrexed maintenance to carboplatin/paclitaxel/bevacizumab with bevacizumab maintenance for the first-line treatment of advanced nonsquamous NSCLC reported a significant difference in Grade 4 PFS between the 2 arms.
  - a. True
  - b. False
5. \_\_\_\_\_ is a second-generation TKI that targets both EGFR and HER2 and acts by covalently binding, irreversibly, to the ATP-binding site of the receptor.
  - a. Erlotinib
  - b. Afatinib
  - c. Gefitinib
  - d. Dacomitinib
  - e. Both b and d
  - f. All of the above
6. The results of the Phase III LUX-Lung 3 trial of afatinib versus cisplatin/pemetrexed as first-line therapy for patients with advanced EGFR mutation-positive NSCLC demonstrated statistically significant improvements in \_\_\_\_\_ with afatinib therapy.
  - a. Median PFS
  - b. Objective response rate
  - c. Both a and b
7. A Phase III trial of *nab* paclitaxel/carboplatin versus solvent-based paclitaxel/carboplatin as first-line therapy for patients with advanced NSCLC demonstrated a significantly higher overall response rate with *nab* paclitaxel for patients with squamous cell histology.
  - a. True
  - b. False
8. Which of the following statements is true of the Phase III PROSE study evaluating the predictive utility of VeriStrat on the survival outcome of patients with inoperable NSCLC treated with second-line erlotinib versus chemotherapy?
  - a. Patients with VeriStrat good status have better outcomes than those with VeriStrat poor status
  - b. The survival of patients with good VeriStrat status was similar with chemotherapy and erlotinib
  - c. Patients with poor VeriStrat status experienced longer median overall survival with chemotherapy compared to erlotinib
  - d. All of the above
9. In the Phase II TREAT trial of adjuvant chemotherapy for patients with early-stage NSCLC, treatment with cisplatin/vinorelbine resulted in similar levels of clinical feasibility, treatment delivery and toxicity when compared to cisplatin/pemetrexed.
  - a. True
  - b. False
10. The Phase III MetLung study is investigating \_\_\_\_\_ with erlotinib versus placebo with erlotinib for patients with advanced MET-positive NSCLC.
  - a. Tivantinib
  - b. Onartuzumab
  - c. Gefitinib

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**PART 1 — 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
RTOG-0617: Results of a Phase III trial evaluating standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiation therapy with or without cetuximab for Stage III NSCLC	4 3 2 1	4 3 2 1
Clinical activity of the second-generation ALK inhibitor LDK378 in advanced, ALK-positive NSCLC	4 3 2 1	4 3 2 1
Results of PROSE: A Phase III trial of proteomic-stratified (VeriStrat) second-line erlotinib versus chemotherapy for patients with inoperable NSCLC	4 3 2 1	4 3 2 1
Phase III study results (PointBreak, PRONOUNCE) and ongoing studies (ECOG-E5508) evaluating maintenance therapeutic approaches for advanced nonsquamous NSCLC	4 3 2 1	4 3 2 1
Clinical activity of <i>nab</i> paclitaxel compared to solvent-based paclitaxel in patients with squamous histology enrolled on the Phase III trial evaluating these 2 approaches in NSCLC	4 3 2 1	4 3 2 1
MetLung: A Phase III study of onartuzumab/erlotinib in advanced MET diagnostic-positive NSCLC	4 3 2 1	4 3 2 1

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

Yes     No    If no, please explain: .....

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

- This activity validated my current practice
- Create/revise protocols, policies and/or procedures
- Change the management and/or treatment of my patients
- Other (please explain): .....

**If you intend to implement any changes in your practice, please provide 1 or more examples:**

.....

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

Yes     No    If no, please explain: .....

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

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

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

- Apply the results of emerging clinical research to the current and future treatment of non-small cell lung cancer (NSCLC). . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based strategy for the initial diagnosis and treatment of localized NSCLC. . . . . 4 3 2 1 N/M N/A
- Apply the results of existing and emerging clinical research to the multimodality management of patients with Stage III NSCLC. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced NSCLC. . . . . 4 3 2 1 N/M N/A
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangement and other recently identified driver mutations — and the approved and investigational treatment options for patients with these mutations. . . . . 4 3 2 1 N/M N/A
- Review emerging research evidence with the use of the irreversible EGFR tyrosine kinase inhibitor afatinib alone or in combination with an EGFR monoclonal antibody for patients with advanced EGFR mutation-positive NSCLC. . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation . . . . . 4 3 2 1 N/M N/A

**EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)**

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

Would you recommend this activity to a colleague?

Yes  No

If no, please explain:

Additional comments about this activity:

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

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

**PART 2 — Please tell us about the faculty and editor for this educational activity**

	4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal					
<b>Faculty</b>	<b>Knowledge of subject matter</b>				<b>Effectiveness as an educator</b>				
Rogério C Lilenbaum, MD	4	3	2	1	4	3	2	1	
Lecia V Sequist, MD, MPH	4	3	2	1	4	3	2	1	
John Heymach, MD, PhD	4	3	2	1	4	3	2	1	
Chandra P Belani, MD	4	3	2	1	4	3	2	1	
<b>Editor</b>	<b>Knowledge of subject matter</b>				<b>Effectiveness as an educator</b>				
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**

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Neil Love, MD  
Research To Practice  
One Biscayne Tower  
2 South Biscayne Boulevard, Suite 3600  
Miami, FL 33131

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