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Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Julie R Brahmer, MD
Roy S Herbst, MD, PhD
Jeffrey Bradley, MD
David P Carbone, MD, PhD

EDITOR

Neil Love, MD

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2 Audio CDs
Monograph

CME Certified

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. However, progress in the screening, prevention and treatment of this disease has been limited. In 2012 it is estimated that 226,160 new cases will be diagnosed and 160,340 deaths will occur in the United States. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on long-term outcomes. With the advent of biologic agents in lung cancer, the field has seen 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 strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Describe emerging data on the efficacy and safety of tumor immunotherapy directed at the PD-1/PD-L1 pathway in lung cancer, and consider this information when counseling patients regarding clinical trial options.
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, MET amplifications and other recently identified driver mutations — and the investigational and approved treatment strategies available to patients expressing these biomarkers.
- Use clinical characteristics and tumor histology to develop personalized treatment algorithms for patients with early-stage and advanced non-small cell lung cancer (NSCLC).
- Develop an evidence-based treatment approach to the selection of induction and maintenance biologic therapy and/or chemotherapy in patients with advanced NSCLC.
- 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.
- Consider the use of high-dose radiation therapy (RT) with concurrent chemotherapy, with or without EGFR inhibitors, in addition to positron emission tomography/computed tomography (PET/CT)-guided RT in selected patients with locally advanced 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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FACULTY INTERVIEWS

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EDITOR

Neil Love, MD
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INTERVIEW

Julie R Brahmer, MD

Dr Brahmer is Associate Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at John Hopkins in Baltimore, Maryland.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you discuss the data you reported with the monoclonal antibody anti-PD-1 in non-small cell lung cancer (NSCLC)?

DR BRAHMER: These data are exciting in that this is the first time we've observed robust responses to antibody therapy in patients with lung cancer. For 76 patients with lung cancer, the reported response rate with the anti-PD-1 antibody was 18% (Brahmer 2012a; [1.1]).

If you break this down by histology, the response rate among patients with squamous cell histology was approximately 33% and the response rate for patients with nonsquamous cell histology was approximately 11%. But it is important to realize that most of these patients' disease was heavily pretreated — this Phase I trial allowed patients to have received 2 to 5 prior therapies. The majority of the patients had received 3 or more therapies.

So the fact that we saw long-lasting responses is interesting. The progression-free survival rate for the patients who were followed for 6 months was higher than 20%. The responses are maintained with time and, in my experience, are longer than those in patients who receive chemotherapy, particularly among those with heavily pretreated disease.

DR LOVE: In the "spider plot" from your presentation, 1 patient was a year out from stopping therapy but the response continued (Brahmer 2012a; [1.2]). How many patients like that have you seen?

DR BRAHMER: In the lung cancer group a handful of patients are beyond 2 years without needing therapy. We saw more patients with melanoma and renal cell carcinoma in that situation, but they've been followed longer. On this trial patients started therapy and if they achieved a response or stable disease, they received treatment for up to 2 years. At that point if the response was maintained, therapy was stopped.

1.1

Efficacy and Tolerability of the Anti-PD-1 Antibody in Patients with Advanced Non-Small Cell Lung Cancer

Efficacy

	Dose mg/kg	Patients n	ORR n (%)	Duration of response, months	SD ≥24 wk n (%)	PFSR at 24 wk %
All evaluable patients	1-10	76	14 (18)	1.9+ to 30.8+	5 (7)	26
Dose levels evaluated	1	18	1 (6)	9.2+	1 (6)	16
	3	19	6 (32)	1.9+ to 30.8+	2 (11)	41
	10	39	7 (18)	3.7 to 14.8+	2 (5)	24

Select drug-related adverse events (AEs) occurring in ≥5% of the population

	All grades	Grades 3 and 4*
	Number (%) of patients, all doses	
Any AE	78 (64)	10 (8)
Fatigue	22 (18)	2 (2)
Rash	5 (4)	—
Diarrhea	7 (6)	1 (1)

ORR was assessed using modified RECIST v1.0. The response rate was higher for patients with squamous cell histology.
* The most common Grade 3 and 4 AEs were fatigue, pneumonitis and elevated AST (2 patients each). An additional 16 Grade 3 and 4 drug-related AEs were observed, 1 or more occurring in a single patient.
ORR = overall response rate; SD = stable disease; PFSR = progression-free survival rate

Brahmer JR et al. *Proc ASCO* 2012a;**Abstract 7509**.

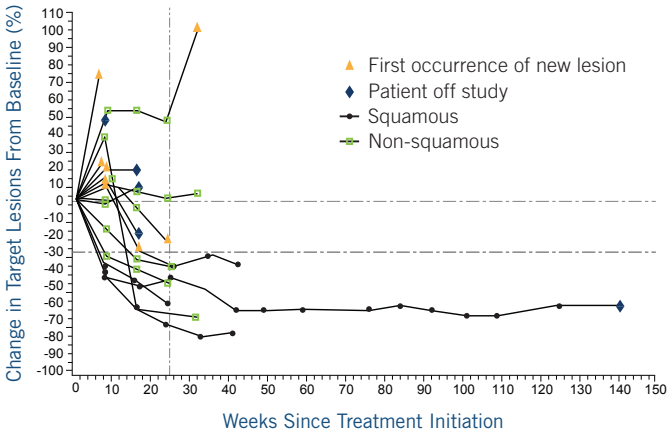
DR LOVE: Another aspect of the spider plot that caught my attention was that in at least a couple of patients the disease progressed and then responded. What are your thoughts on the issue of monitoring responses for patients receiving immune-based therapies?

DR BRAHMER: The hardest aspect for us to get used to is leaving patients on therapy while their disease is radiographically worsening. In this trial and in other immunotherapy trials we're moving toward immune-related response criteria with which clinically stable patients are allowed to remain on study while the disease is getting worse. We do observe the disease decreasing in size with time. In some patients a new lesion is found, and in other studies treatment would be discontinued but they're allowed to stay on this trial.

DR LOVE: What are the side effects observed with the anti-PD-1 antibody?

DR BRAHMER: In terms of side effects, we observed immune-related toxicities such as colitis, hepatitis, hypophysitis and thyroiditis. Probably the most worrisome was pneumonitis, and 3 patients on this study died from complications related to pneumonia. The most common toxicity was fatigue (1.1). That being said, in general the side effects are easier to tolerate than those of chemotherapy, which is in part why the anti-PD-1 antibody can be administered for so long.

1.2 **Clinical Activity of the Anti-PD-1 Antibody in Advanced Non-Small Cell Lung Cancer**



Changes from baseline in the tumor burden, measured as the sum of the longest diameters of target lesions, in patients with NSCLC who received anti-PD-1 antibody at a dose of 3.0 mg/kg.

With permission from Brahmer JR et al. *Proc ASCO* 2012a;**Abstract 7509**.

Track 8

DR LOVE: Would you discuss the LUX-Lung 3 data from ASCO on afatinib, which demonstrated superiority to cisplatin/pemetrexed as first-line therapy for patients with advanced disease harboring EGFR mutations?

DR BRAHMER: The data are tantalizing and indicate that irreversible EGFR tyrosine kinase inhibitors (TKIs) also delay disease progression for longer and outperform chemotherapy in those patients with EGFR mutations (Yang 2012; [1.3]). You can't

compare these data directly to those from similar trials with reversible TKIs, but the progression-free survival here is impressive.

1.3

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

Efficacy	Afatinib (n = 230)	Cis/pem (n = 115)	Hazard ratio	*p*-value
Median progression-free survival	11.1 mo	6.9 mo	0.58	0.0004
Objective response rate	56.1%	22.6%	—	<0.001

Yang JC et al. *Proc ASCO* 2012;**Abstract LBA7500**.

Track 9

DR LOVE: How do you approach patients with EGFR mutations who have good responses to erlotinib and then experience disease progression?

DR BRAHMER: I try to find a clinical trial for these patients, and in the past 6 months I've started obtaining a biopsy to ascertain if a T790 mutation has developed. We have trials for that, and other mechanisms of resistance are being discovered also, including MET amplification. A Phase I trial is combining 2 oral agents that may block these pathways.

Other trials use oral TKIs that bind to the pocket of the T790 mutation, and MET amplification, MET inhibitors or MEK inhibitors may play a role in these patients. Six months ago I wouldn't have biopsied the disease, but now I do when it's progressing in patients with previous EGFR mutations to determine whether they're developing resistance mutations.

If we don't have a clinical trial, I don't stop the erlotinib but I add chemotherapy. If patients are not tolerating erlotinib, I may stop and switch to chemotherapy, but I consider the afatinib/cetuximab data from Memorial, which initially included a long washout period (Janjigian 2011).

Many patients' disease progressed quickly, and that's part of the reason the washout period was shortened in that trial. In taking patients off the erlotinib, a rebound was observed. Maintaining the response to the EGFR TKI is important for these patients. ■

SELECT PUBLICATIONS

Brahmer JR et al. **Clinical activity and safety of anti-PD1 (BMS-936558, MDX-1106) in patients with advanced non-small-cell lung cancer (NSCLC).** *Proc ASCO* 2012a;**Abstract 7509**.

Brahmer JR et al. **Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.** *N Engl J Med* 2012b;366(26):2455-65.

Janjigian YY et al. **Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib.** *Proc ASCO* 2011;**Abstract 7525**.

Topalian SL et al. **Anti-PD-1 (BMS-936558, MDX-1106) in patients with advanced solid tumors: Clinical activity, safety, and a potential biomarker for response.** *Proc ASCO* 2012a;**Abstract CRA2509**.

Topalian SL et al. **Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.** *N Engl J Med* 2012b;366(26):2443-54.

INTERVIEW

Roy S Herbst, MD, PhD

Dr Herbst is Chief of Medical Oncology at the Yale Comprehensive Cancer Center's Smilow Cancer Hospital at Yale-New Haven/Yale School of Medicine in New Haven, Connecticut.

Tracks 1-15

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the current role of cetuximab in NSCLC?

DR HERBST: Over the years there have been several trials of cetuximab for NSCLC in the front- and second-line settings. The FLEX trial evaluated cisplatin/vinorelbine with or without cetuximab in more than 1,000 patients with advanced NSCLC. Although the FLEX trial had a positive overall survival endpoint, the hazard ratio

associated with this benefit was not impressive (Pirker 2011, 2012; [2.1]). So one wonders whether a population of patients exists who might benefit more from cetuximab. If we can identify these patients prospectively, we will be able to administer treatment to only those patients who truly benefit.

In the past decade the Southwest Oncology Group has been involved with studies investigating cetuximab in combination with chemotherapy. We found that patients with the best treatment outcomes in terms of response rate, progression-free survival and overall survival were those with an EGFR gene copy number greater than or equal to 4, as measured by fluorescence in situ hybridization (FISH). A patient with multiple copies of the EGFR gene will make more of the protein. Presumably, those patients are more sensitive to EGFR inhibition with cetuximab.

We conducted some studies, including SWOG-S0342 and SWOG-S0536, which investigated cetuximab with chemotherapy in advanced NSCLC. In both trials, it appeared that patients with an increased EGFR gene copy number had improved outcomes with cetuximab (Hirsch 2008).

DR LOVE: What were the histology criteria for inclusion in these trials?

DR HERBST: The histological subtypes included mixed, squamous cell carcinoma and adenocarcinoma. This is important because it allows for the inclusion of all NSCLC subtypes.

2.1

EGFR Expression as a Predictor of Survival with First-Line Chemotherapy (CT) with Cetuximab (Cet) in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) on the Phase III FLEX Study

	ITT population		Low EGFR expression		High EGFR expression	
	CT (n = 568)	**CT + cet** (n = 557)	**CT** (n = 399)	**CT + cet** (n = 377)	**CT** (n = 167)	**CT + cet** (n = 178)
Median overall survival	10.1 mo	11.3 mo	10.3 mo	9.8 mo	9.6 mo	12.0 mo
	HR = 0.87; $p = 0.044$		HR = 0.99; $p = 0.88$		HR = 0.73; $p = 0.011$	

"High EGFR expression is a tumour biomarker that can predict survival benefit from the addition of cetuximab to first-line chemotherapy in patients with advanced NSCLC. Assessment of EGFR expression could offer a personalised treatment approach in this setting."

Pirker R et al. *Lancet Oncol* 2012;13(1):33-42.

Track 2

DR LOVE: Would you discuss your ongoing SWOG-S0819 Phase III trial?

DR HERBST: I am the national principal investigator on the SWOG-S0819 trial. It's designed to evaluate a population of patients who have an increase in the EGFR gene copy number by FISH (2.2). It is an important trial to determine a more specific role for cetuximab in lung cancer. All patients have tissue samples taken at the time of enrollment.

Patients are randomly assigned to carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab, with or without cetuximab. The question of the percent of patients with an increased EGFR gene copy number will be investigated prospectively. Patients will

not be stratified based on the EGFR marker. We're making sure that we have the results so that we can look back to see if, in fact, that marker is predictive of outcome.

To make the trial more user friendly and to allow physicians to administer treatment to patients as they would off study, bevacizumab is allowed for those who have not experienced any problems with bleeding and have nonsquamous NSCLC or brain metastases, if treated. The trial will have 4 treatment arms — 2 control arms of carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab and 2 experimental arms including cetuximab.

Patients receive a combination of chemotherapy and cetuximab for 6 cycles followed by cetuximab maintenance therapy, which is a bit rigorous. Cetuximab is administered on a weekly basis, which is one of the issues with the drug. Patients who are receiving cetuximab/bevacizumab would receive weekly cetuximab with bevacizumab administration every 3 weeks. Some patients on the control arm will receive no maintenance therapy.

DR LOVE: So far, what have you observed in terms of toxicity?

DR HERBST: Overall, we have not observed any major issues with severe toxicity on any of the treatment arms. It is especially good news that we have not encountered such problems with the patients on the carboplatin/paclitaxel/bevacizumab/cetuximab arm. The most frequently observed side effects are dermatologic, with skin toxicity being the biggest issue with cetuximab.

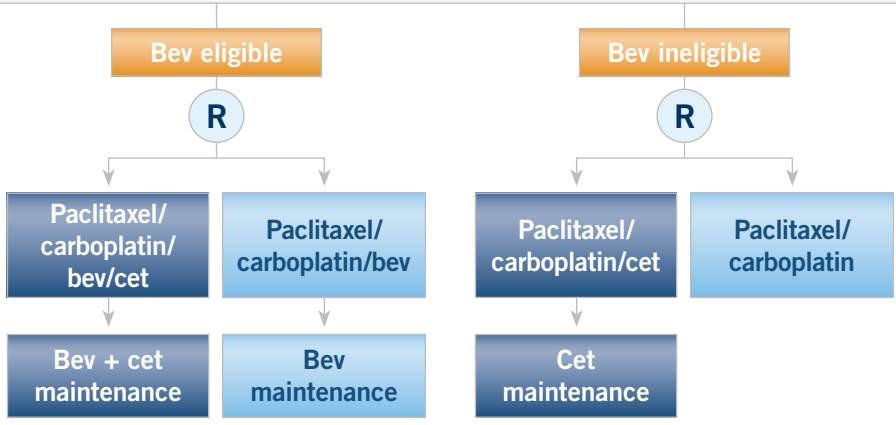
That being said, based on my own experience and those of other investigators here at Yale and at Vanderbilt, I believe that cetuximab will have a major role in lung cancer, either in combination with chemotherapy as we're testing in the SWOG-S0819 trial

2.2

SWOG-S0819: A Randomized Phase III Trial of Carboplatin/ Paclitaxel with or without Bevacizumab (Bev) and/or Cetuximab (Cet) in Advanced Non-Small Cell Lung Cancer (NSCLC)

Protocol IDs: SWOG-S0819; NCT00946712 **Target Accrual:** 1,546

Eligibility: Newly diagnosed Stage IV NSCLC or recurrent NSCLC after prior surgery and/or irradiation; histologically/cytologically confirmed adenocarcinoma, large cell, squamous cell carcinomas and unspecified subtypes; no prior chemotherapy for NSCLC; brain metastases controlled for ≥2 weeks after treatment; available tumor tissue



www.clinicaltrials.gov, December 2012.

or as it was evaluated recently in combination with afatinib (BIBW 2992), the oral irreversible EGFR blocker.

The data evaluating the cetuximab/afatinib combination in patients with NSCLC and acquired resistance to EGFR therapy are compelling. Responses were reported among patients with the T790M mutation and in patients who did not harbor this specific resistance mutation (Janjigian 2011).

I believe we need to continue to closely examine cetuximab in lung cancer. It's a weapon that we shouldn't discard just because of the limited results from the FLEX study.

At the 2011 World Lung Cancer Conference in Amsterdam, I heard a lot of excitement about the use of the H score, which is a quantitative method of determining the intensity of immunostaining over the course of the entire tissue section, to evaluate EGFR expression. High tumor EGFR expression appeared to correlate with better outcome (Pirker 2011, 2012; [2.1]). We've added prospective evaluation of this marker to the SWOG-S0819 trial.

Track 3

DR LOVE: Where do you believe the combination of cetuximab with afatinib fits in the treatment of refractory NSCLC?

DR HERBST: I would say that this combination not only offers an opportunity for patients with refractory NSCLC but would also have a role in the up-front setting. As exciting as it may be to administer EGFR inhibitors to patients harboring EGFR gene mutations, the reality is that all patients will at some point develop resistance. Therefore, it would be great if targeted therapy could be used with the most potent combination from the start, assuming that patients can tolerate the dual skin toxicity.

I believe that investigators will be interested in follow-up clinical trials of the cetuximab/afatinib combination because the data presented at ASCO 2011 are so compelling (Janjigian 2011). It's important to figure out the exact mechanism of action behind this effect. I believe that if we can figure out how the combination works and identify the subgroup of patients who will benefit the most, the combination could be that much more effective. ■

SELECT PUBLICATIONS

Franklin WA et al. **SWOG S0342 and S0536: Expression of EGFR protein and markers of epithelial-mesenchymal transformation (EMT) in cetuximab/chemotherapy-treated non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;**Abstract 11076**.

Hirsch FR et al. **Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy.** *J Clin Oncol* 2008;26(20):3351-7.

Janjigian YY et al. **Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib.** *Proc ASCO* 2011;**Abstract 7525**.

Pirker R et al. **EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: Analysis of data from the phase 3 FLEX study.** *Lancet Oncol* 2012;13(1):33-42.

Pirker R et al. **Epidermal growth factor receptor (EGFR) expression as a predictor of survival for first-line chemotherapy plus cetuximab in FLEX study patients with advanced non-small cell lung cancer (NSCLC).** *Proc IASLC* 2011;**Abstract 1557**.

INTERVIEW

Jeffrey Bradley, MD

Dr Bradley is S Lee Kling Professor of Radiation Oncology at the Alvin J Siteman Cancer Center in the Washington University School of Medicine in St Louis, Missouri.

Tracks 1-14

Select Excerpts from the Interview

Track 7

DR LOVE: Would you discuss the results of the RTOG-0229 study evaluating concurrent neoadjuvant chemotherapy and high-dose radiation therapy followed by resection and consolidation therapy for Stage III NSCLC?

DR BRADLEY: The RTOG-0229 study evaluated patients with operable Stage III lung cancer who received chemotherapy and radiation therapy prior to surgery (Suntharal-

ingam 2012; [3.1]). The intent of the study was to clear the mediastinal lymph nodes using a radiation dose of 60 Gray with chemotherapy before surgery. The results demonstrated that mediastinal nodal clearance was achieved in 63% of the patients enrolled on the study. For patients who achieved mediastinal nodal clearance, the 2-year survival rate was 75%. For patients with residual nodal disease, the 2-year survival rate was 52%.

3.1

RTOG-0229: A Phase II Trial of Neoadjuvant Therapy with Concurrent Chemotherapy and Full-Dose Radiation Therapy Followed by Resection and Consolidative Therapy for Locally Advanced Non-Small Cell Lung Cancer

Response	N = 43
Mediastinal node clearance (MNC)	63%
Overall survival rate (2 y)	54%
Patients with MNC	75%
Patients with residual nodal disease	52%
Progression-free survival rate (2 y)	33%
Grade 3 and 4 toxicities	
Hematologic	35%
Gastrointestinal	14%
Pulmonary	23%

Median follow-up: 24 mo

Suntharalingam M et al. *Int J Radiat Oncol Biol Phys* 2012;84(2):456-63.

Track 9

DR LOVE: What are your thoughts on the National Lung Screening Trial?

DR BRADLEY: Our institution is strongly in favor of lung cancer screening, and we were instrumental in accruing patients to several screening trials, including the National Lung Cancer Screening Trial. A 20% reduction in mortality was observed among patients who had a smoking history of at least 30 pack-years and who were screened using low-dose computed tomography (CT) (3.2).

This is impressive, even with the limitation of only 3 rounds of screening. We have never observed a 20% drop in mortality from an intervention in lung cancer, so that's a huge advantage. I believe screening is probably *the* most important development in lung cancer in the past several years.

DR LOVE: How significant is the issue of false-positive results?

DR BRADLEY: False-positive results can be a problem in carrying out screening and determining which nodules are of concern. The question arises as to whose responsibility it is to follow up with patients who have nodules that are found to be positive by screening. We established a clinic for that patient population to determine how they should be cared for. The use of 3-dimensional software might be helpful in determining which nodules are of concern, but we have a lot more to learn before we implement something like that globally.

DR LOVE: What criteria do you use to determine whether to biopsy a tumor?

DR BRADLEY: If a tumor is growing and approaches a centimeter or so, I would recommend a biopsy and a PET scan to get some idea of the FDG activity. We typically recommend that these patients undergo scans approximately every 6 months to detect growth.

3.2

National Lung Screening Trial (NLST): Reduced Lung Cancer Mortality with Low-Dose CT Screening

	Low-dose CT group (n = 26,722)	Radiography group (n = 26,732)	Relative reduction in mortality
Rate of positive screening results	24.2%	6.9%	—
Incidence of lung cancer (cases per 100,000 person-years)	645	572	—
Deaths from lung cancer (no. per 100,000 person-years)	356 247	443 309	20.0% $p = 0.004$
Deaths from any cause	1,877	2,000	6.7% $p = 0.02$

"The cost-effectiveness of low-dose CT screening must also be considered in the context of competing interventions, particularly smoking cessation. NLST investigators are currently analyzing the quality-of-life effects, costs, and cost-effectiveness of screening in the NLST and are planning collaborations with the Cancer Intervention and Surveillance Modeling Network to investigate the potential effect of low-dose CT screening in a wide range of scenarios."

National Lung Screening Trial Research Team et al. *N Engl J Med* 2011;365(5):395–409.

Track 12

DR LOVE: What are the indications for stereotactic radiation therapy in NSCLC?

DR BRADLEY: The question of whether stereotactic radiation therapy is applicable arises in a number of different situations. The trials we have conducted have demonstrated that it is highly applicable for tumors that are in the periphery, not next to a major bronchus or a blood vessel like the aorta or pulmonary artery, where the risk may be higher. Results from a number of studies have also demonstrated that stereotactic radiation therapy is applicable for patients with Stage I lung tumors that are central and within 2 centimeters of a primary bronchus. However, the radiation dose must be lowered and 5 fractions must be administered instead of 3. We do not observe much toxicity in that setting.

Another setting in which the question of stereotactic radiation therapy arises is with a patient whose disease progresses on standard chemoradiation therapy for Stage III disease and who has a persistent lung nodule. Stereotactic radiation therapy in these situations is the subject of ongoing trials. ■

SELECT PUBLICATIONS

National Lung Screening Trial Research Team et al. **Reduced lung-cancer mortality with low-dose computed tomographic screening.** *N Engl J Med* 2011;365(5):395–409.

Suntharalingam M et al. **Radiation Therapy Oncology Group protocol 02-29: A phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung.** *Int J Radiat Oncol Biol Phys* 2012;84(2):456–63.

INTERVIEW

David P Carbone, MD, PhD

Dr Carbone is Professor of Medicine and Director of the James Thoracic Center in Columbus, Ohio.

Tracks 1-11

Track 1 Prognostic and predictive role of the VeriStrat® serum proteomic test in patients with advanced NSCLC treated with erlotinib

Track 2 Impact of EGFR mutation status on the predictive accuracy of VeriStrat

Track 3 Technological foundation of the VeriStrat test

Track 4 Perspective on the Phase III PointBreak trial

Track 5 **Case discussion:** A 60-year-old man with PET-avid bilateral hilar adenopathy and subcentimeter contralateral pulmonary nodules underwent lobectomy and remains disease free 5 years later

Track 6 A physician's personal experience with the diagnosis and treatment of diffuse large B-cell lymphoma

Track 7 **Case discussion:** A 65-year-old never smoker with resected Stage I NSCLC receives repeated stereotactic RT for multiple recurrences of brain metastases and develops multisite EGFR mutation-positive disease 10 years later

Track 8 Approach to systemic treatment for patients with asymptomatic metastatic NSCLC

Track 9 Treatment options for patients with progressive EGFR-mutant NSCLC after sustained response to erlotinib

Track 10 Geographic differences in anaphylactic reactions to cetuximab versus panitumumab

Track 11 **Case discussion:** A 60-year-old smoker who underwent resection of Stage I NSCLC presents with recurrent brain metastasis

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you discuss the role of the VeriStrat test in identifying patients with advanced NSCLC who may benefit from EGFR TKI therapy?

DR CARBONE: The idea behind the VeriStrat plasma test was to ascertain, using a minimally invasive approach, whether we could identify which patients would benefit from EGFR-targeted therapies. It's clear that patients with EGFR mutations benefit from such targeted therapies, although ultimately they all develop resistant disease.

However, evidence shows that some subsets of patients with NSCLC without detectable EGFR mutations demonstrate several months of minimal responses or progression-free survival with EGFR-targeted therapies. Hence, we set out to determine a protein signature that was able to classify patients as those with good or poor survival outcomes after treatment with erlotinib.

The Canadian Phase III BR.21 study, which evaluated erlotinib versus placebo for previously treated NSCLC, was conducted about a decade ago and reported a survival advantage in an unselected patient population (Shepherd 2005). We performed a retrospective analysis of blood samples from patients enrolled on the BR.21 trial (Carbone 2012; [4.1]).

The median overall survival in the subset of patients receiving erlotinib that we identified with the good-outcome protein signature was 10.5 months. Without that signature, the median overall survival was 3.98 months. So the protein signature seemed to provide prognostic information in patients on the BR.21 trial who received erlotinib by identifying patients with a better chance of survival.

The majority of patients on the BR.21 study were not tested for EGFR mutations, so we don't know how that fits in. Of the blood samples subjected to VeriStrat testing, about 60% were classified as having a good protein signature (4.1). No more than 10% of patients in the Western population harbor EGFR mutations, so clearly the protein signature is not dependent on EGFR mutation status.

In fact, the result of our study was not correlated with EGFR mutations. Out of 19 patients with objective responses, 18 had a good proteomic signature, and that was a statistically significant predictive factor for response (4.1).

We also concluded that in certain circumstances the VeriStrat test might be able to identify subsets of patients with a better chance of survival. Of note, some data suggest that patients with squamous cell carcinomas may have better outcomes than those with adenocarcinomas.

4.1

Prognostic and Predictive Roles of the VeriStrat Plasma Test in Patients with Advanced Non-Small Cell Lung Cancer Treated with Erlotinib or Placebo on the BR.21 Phase III Trial

Outcome	Patients with good protein signature		Patients with poor protein signature	
	Erlotinib (n = 183)	Placebo (n = 83)	Erlotinib (n = 109)	Placebo (n = 61)
Overall survival	10.5 mo	6.6 mo	3.98 mo	3.09 mo
	HR = 0.63; $p = 0.002$		HR = 0.77; $p = 0.1071$	
Progression-free survival	3.68 mo	1.84 mo	1.76 mo	1.71 mo
	HR = 0.54; $p = 0.0000$		HR = 0.73; $p = 0.0495$	
	Erlotinib-treated patients with good protein signature (n = 157*)		Erlotinib-treated patients with poor protein signature (n = 95*)	
PR/CR (ORR)	18 (11%)		1 (1%)	
PD/SD	139 (89%)		94 (99%)	

* Evaluable patients
PR = partial response; CR = complete response; ORR = objective response rate; PD = progressive disease; SD = stable disease

"Of 252 erlotinib-treated patients evaluable for response, 157 (62%) were classified as Good and 95 (38%) as Poor."

Carbone DP et al. *J Thorac Oncol* 2012;7(11):1653-60.

In a set of data yet to be published, we observed a 6-fold difference in median survival for patients with squamous cell carcinoma treated with erlotinib between the patient groups classified as having good and poor proteomic signatures.

If patients with a poor chance of survival after erlotinib therapy are removed, it may be possible to identify a subset of patients with squamous cell carcinoma with excellent progression-free and overall survival with erlotinib. This concept is currently being studied in a prospective European randomized trial (ETOP 3-12 EMPHASIS-lung).

I need to make it clear that I'm not stating that the VeriStrat assay will replace EGFR mutation tests. It would be wrong to say so. All patients with lung cancer should have a mutation analysis performed for EGFR, ALK and other targetable genetic abnormalities. In Western populations, however, most patients with lung cancer don't have clinically validated targets that can be detected by genetic analysis. Therefore, the purpose of our study was to find markers that might correlate with benefit from EGFR TKIs.

DR LOVE: Would you discuss the technology behind the VeriStrat test?

DR CARBONE: The VeriStrat test is a protein-based assay that utilizes the matrix-assisted laser desorption ionization mass spectrometric technique (Taguchi 2007). It is conducted using only a few microliters of plasma or serum. The VeriStrat test can be performed by spotting the plasma onto a paper card and mailing the card for mass spectrometric analysis.

Track 4

DR LOVE: Would you summarize the results of the much-anticipated Phase III PointBreak trial and provide your perspective on it?

DR CARBONE: This study evaluated pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab versus paclitaxel, carboplatin and bevacizumab followed by bevacizumab maintenance for patients with advanced NSCLC (Patel 2012; [4.2]). The paclitaxel, carboplatin and bevacizumab arm of the trial is the same as the positive treatment arm from the ECOG-E4599 study (Sandler 2006).

We have ample data to show that pemetrexed is an extremely active agent in nonsquamous tumors, and many believe that it may be a superior regimen to carboplatin/paclitaxel. Also, the addition of maintenance pemetrexed has demonstrated improvements in progression-free survival. So it was reasonable to compare the ECOG-E4599 regimen to a pemetrexed-based regimen followed by pemetrexed/bevacizumab maintenance.

Many predicted that the pemetrexed/bevacizumab combination would be substantially better than bevacizumab alone as maintenance therapy. However, no difference was observed.

This was disappointing in that it would have been nice to have a documented regimen that was more beneficial than the E4599 regimen. It would have been a costly regimen, however, given that the PointBreak trial used both bevacizumab and pemetrexed as maintenance therapy. Even though the PointBreak trial results validate the E4599 data, it was disappointing that these data didn't point the way toward improving outcomes over the earlier study, which is now almost 10 years old. ■

4.2

PointBreak: A Phase III Trial of Pemetrexed (Pem)/Carboplatin (Cb)/Bevacizumab (B) Followed by Maintenance Pem + B versus Paclitaxel (Pac)/Cb/B Followed by Maintenance B for Patients with Advanced Nonsquamous Non-Small Cell Lung Cancer

All patients	Pem/Cb/B (n = 472)	Pac/Cb/B (n = 467)	HR	*p*-value
Median PFS	6.0 mo	5.6 mo	0.83	0.012
Median OS	12.6 mo	13.4 mo	1.00	0.949
Overall response rate	34.1%	33.0%	NR	NR
Maintenance patients	(n = 292)	(n = 298)		
Median PFS	8.6 mo	6.9 mo	NR	NR
Median OS	17.7 mo	15.7 mo	NR	NR
Adverse events	**Pem/Cb/B** (n = 442)		**Pac/Cb/B** (n = 443)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Anemia*	31.0%	14.5%	24.4%	2.7%
Thrombocytopenia*	17.9%	23.3%	17.2%	5.6%
Neutropenia*	14.7%	25.8%	8.4%	40.6%
Hemorrhage – GI/pulmonary†	3.6%	1.8%	3.8%	0.5%
Thromboembolic event	0.5%	3.2%	0.2%	2.0%

* Significant difference between arms for Grade 3 and 4 toxicities
† Grade 5 events: Pac/Cb/B = 0.7%; Pem/Cb/B = 0.5%
PFS = progression-free survival; OS = overall survival; NR = not reported

Conclusion: The primary endpoint of superior OS was not met in this trial, although Pem/Cb/B improved PFS. Toxicity profiles differed and both regimens demonstrated tolerability.

Patel J et al. Chicago Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract LBPL1**.

SELECT PUBLICATIONS

Carbone DP et al. **Prognostic and predictive role of the VeriStrat plasma test in patients with advanced non-small-cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial.** *J Thorac Oncol* 2012;7(11):1653-60.

Gautschi O et al. **VeriStrat® has a prognostic value for patients with advanced non-small cell lung cancer treated with erlotinib and bevacizumab in the first line: Pooled analysis of SAKK19/05 and NTR528.** *Lung Cancer* 2013;79(1):59-64.

Lazzari C et al. **Prospective correlative study of FDG-PET SUV and proteomic profile (VeriStrat) of non-small cell lung cancer patients treated with erlotinib.** *Proc ASCO* 2012;**Abstract e18096**.

Patel J et al. **A randomized, open-label, Phase 3, superiority study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (B) followed by maintenance Pem+B versus paclitaxel (Pac)+Cb+B followed by maintenance B in patients (Pts) with stage IIIB or IV non-squamous nonsmall cell lung cancer (Ns-Nsclc).** Chicago Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract LBPL1**.

Salmon JS et al. **VeriStrat predicts survival in patients with non-small cell lung cancer (NSCLC) treated with erlotinib and bevacizumab.** *Proc ASCO* 2008;**Abstract 8008**.

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50.

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

Taguchi F et al. **Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: A multicohort cross-institutional study.** *J Natl Cancer Inst* 2007;99(11):838-46.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Responses to the anti-PD-1 antibody are more frequent among patients with squamous cell NSCLC than among those with nonsquamous cell histology.**
   a. True
   b. False

2. **In a trial with 76 patients who received anti-PD-1 antibody therapy for advanced NSCLC, the overall response rate was approximately _____.**
   a. 6%
   b. 18%
   c. 34%

3. **Analysis of data from the Phase III FLEX study, which evaluated cisplatin and vinorelbine with or without cetuximab, demonstrated that high EGFR expression is a tumor biomarker that can predict survival benefit from the addition of cetuximab to first-line chemotherapy for patients with advanced NSCLC.**
   a. True
   b. False

4. **The Phase III SWOG-S0819 trial randomly assigns patients with Stage IV NSCLC to receive carboplatin in combination with paclitaxel with or without bevacizumab and/or _____ as initial therapy.**
   a. Afatinib
   b. Cetuximab
   c. Both a and b

5. **The major adverse events (AEs) associated with cetuximab therapy for patients with advanced NSCLC include _____.**
   a. Gastrointestinal AEs
   b. Dermatologic AEs
   c. Both a and b

6. **The National Lung Screening Trial reported a 20% relative reduction in mortality from lung cancer with low-dose CT screening versus chest radiography.**
   a. True
   b. False

7. **Patients with Stage III NSCLC treated on the RTOG-0229 trial experienced a 2-year survival rate of 75% if they experienced mediastinal nodal clearance after chemotherapy and full-dose radiation therapy prior to surgery.**
   a. True
   b. False

8. **The VeriStrat serum test predicts response to erlotinib therapy only for patients with advanced NSCLC harboring EGFR mutations based on a proteomic signature that uses the matrix-assisted laser desorption/ionization mass spectrometric technique.**
   a. True
   b. False

9. **A recent analysis with the VeriStrat assay of blood samples from patients enrolled in the Phase III BR.21 trial demonstrated that the good protein signature is _____ for progression-free and overall survival in patients with advanced NSCLC.**
   a. Prognostic
   b. Predictive
   c. Neither prognostic nor predictive

10. **Analysis of the Phase III PointBreak study reported a significant improvement in _____ with pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab in comparison to the ECOG-E4599 regimen of paclitaxel, carboplatin and bevacizumab followed by bevacizumab maintenance for patients with advanced NSCLC.**
    a. Overall survival
    b. Progression-free survival
    c. Overall response rate
    d. None of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 3, 2012

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 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
Roles of pulse erlotinib and dose escalation in patients with EGFR-mutant, advanced NSCLC with brain metastases or disease progression, respectively	4 3 2 1	4 3 2 1
Clinical benefits, tolerability and planned and ongoing clinical trials of the anti-PD-1 antibody in advanced NSCLC	4 3 2 1	4 3 2 1
Results from the Phase III PointBreak trial of pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC	4 3 2 1	4 3 2 1
Utility of the VeriStrat test in predicting benefit from erlotinib therapy	4 3 2 1	4 3 2 1
SWOG-S0819 study: Carboplatin/paclitaxel with or without bevacizumab and/or cetuximab for newly diagnosed Stage IV or recurrent NSCLC	4 3 2 1	4 3 2 1
Importance of rebiopsy at the time of disease progression	4 3 2 1	4 3 2 1
RTOG-1106 Phase II study: PET/CT in guiding radiation therapy for Stage III 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):.....

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:

- Describe emerging data on the efficacy and safety of tumor immunotherapy directed at the PD-1/PD-L1 pathway in lung cancer, and consider this information when counseling patients regarding clinical trial options..... 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, MET amplifications and other recently identified driver mutations — and the investigational and approved treatment strategies available to patients expressing these biomarkers..... 4 3 2 1 N/M N/A
- Use clinical characteristics and tumor histology to develop personalized treatment algorithms for patients with early-stage and advanced non-small cell lung cancer (NSCLC)..... 4 3 2 1 N/M N/A
- Develop an evidence-based treatment approach to the selection of induction and maintenance biologic therapy and/or chemotherapy in patients with advanced NSCLC..... 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
- Consider the use of high-dose radiation therapy (RT) with concurrent chemotherapy, with or without EGFR inhibitors, in addition to positron emission tomography/computed tomography (PET/CT)-guided RT in selected patients with locally advanced 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

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 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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Julie R Brahmer, MD	4 3 2 1	4 3 2 1
Roy S Herbst, MD, PhD	4 3 2 1	4 3 2 1
Jeffrey Bradley, MD	4 3 2 1	4 3 2 1
David P Carbone, MD, PhD	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

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Lung Cancer™ UPDATE

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