LCU | 2012 VOL 9 | ISSUE 1

# Lung Cancer™ UPDATE

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

**FACULTY INTERVIEWS**

Mark G Kris, MD
Heather Wakelee, MD
Ramaswamy Govindan, MD
David Jablons, MD

**EDITOR**

Neil Love, MD

**CONTENTS**

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. 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).
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions and other recently identified driver mutations — and the investigational and approved treatment options for patients with these biomarkers.
- Describe emerging efficacy and tolerability data with combined EGFR targeting for patients with NSCLC and acquired resistance to EGFR tyrosine kinase inhibitors.
- Identify patients with metastatic NSCLC who may experience clinical benefit from the addition of continuation or switch maintenance biologic therapy and/or chemotherapy.
- Consider the use of low-dose CT screening in evaluating appropriately selected patients for early-stage lung cancer.
- Individualize adjuvant chemotherapy for patients with early-stage NSCLC, with consideration of the efficacy and unique side-effect and tolerability profiles of guideline-endorsed regimens.
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.
- Use case-based learning to formulate individualized strategies for the care of patients with lung cancer.

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***This activity is supported by educational grants from Astellas, Celgene Corporation, Daiichi Sankyo Inc, Genentech BioOncology and Lilly USA LLC.***

Last review date: May 2012; Release date: May 2012; Expiration date: May 2013

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## EDITOR

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Miami, Florida

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INTERVIEW

## Mark G Kris, MD

Dr Kris is Chief of the Thoracic Oncology Service at Memorial Sloan-Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

### Tracks 1-17



## Select Excerpts from the Interview

### Tracks 2, 12-13

**DR LOVE:** Would you comment on EGFR mutations, EML4-ALK translocations and which patients should be tested for both?

**DR KRIS:** It makes sense at the diagnosis of metastatic disease to test for EGFR mutations. In the trial reported by Tony Mok in the *New England Journal of Medicine*, even if patients with adenocarcinoma had characteristics that predicted sensitivity

to erlotinib or gefitinib — women, Asians, never smokers — if they didn't have the mutation, there was a 1% chance that gefitinib would shrink the tumor (Mok 2009).

That changed how people approach patients at diagnosis and, as often as possible, patients undergo biopsies to determine whether EGFR mutations are present. If so, they receive erlotinib. If not, they receive chemotherapy. Now that we have crizotinib for patients with ALK rearrangements, it's been added to the repertoire. So at diagnosis tumors are tested for EGFR and ALK status. If you don't find either or are unable to obtain results, you administer chemotherapy. These concepts have been encoded and are standard in the NCCN guidelines.

I believe that every patient with metastatic adenocarcinoma of the lung should undergo testing, although I wouldn't recommend routine testing for patients with small cell lung cancer. I also wouldn't recommend it routinely for patients with squamous cell tumors, with a few exceptions. Never smokers with squamous cell tumors should be tested. Also, if the squamous cell diagnosis is based on a small biopsy specimen, it makes sense to test because of the possibility that it's actually adenocarcinoma. The NCCN guidelines don't say you should never test squamous cell tumors — only that you shouldn't do so routinely.

We've completed work that will be presented at ASCO indicating that roughly the same proportion of driver molecular lesions exist in squamous cell carcinoma as in adenocarcinoma. However, the mutations are different (Rekhtman 2012). We find amplification of the FGFR1 gene, a loss of PTEN and mutations in FGFR2, PI3 kinase and DDR1. If you add them up, it totals about 55%. So I believe that within the next 1 to 2 years we'll have a testing panel for squamous cell lung cancer that will differ from adenocarcinoma. The treatments directed at those targets are currently under investigation.

## Track 9

**DR LOVE:** How do you manage the side effects of EGFR TKIs?

**DR KRIS:** We are extremely fortunate to have dermatologist Dr Mario Lacouture at Memorial. He has dedicated his career to researching the optimal treatment for EGFR TKI dermatologic side effects, and not just the rashes but also the skin dryness, fingertip cracking and pruritus. It's a great resource for patients facing these toxicities. We have a whole repertoire of ways to ameliorate them, and Dr Lacouture approaches his patients in the same way — by using emollients, topical corticosteroids and antibiotics to treat secondary infections and trying to minimize the side effects.

I've also learned that you can use a much lower dose of the TKI and still obtain a good result. Dr Dan Costa from Beth Israel Deaconess in Boston reported on a series of patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC) who received 25 mg of erlotinib, one sixth of the maximum tolerated dose (Yeo 2010). Basic scientific literature also indicates that mutated kinases are much more sensitive to the effects of TKIs like erlotinib and gefitinib, so you often can use a lower dose.

For patients with severe toxicities I often stop treatment until the toxicity resolves or is more tolerable, then I start back at a lower dose and try to titrate upward. In addition, I routinely start erlotinib at 100 mg per day. Among all the patients receiving erlotinib, that's the dose the majority tolerate. You can increase it if it's well tolerated or decrease even that dose if not.

## Track 16

**DR LOVE:** What are your thoughts on where nanoparticle albumin-bound (*nab*) paclitaxel is headed in lung cancer?

**DR KRIS:** The agent has distinct advantages. It doesn't have to be administered with dexamethasone, which can be difficult for many patients, particularly those with diabetes and those who are uncomfortable after receiving the high-dose steroids necessary to safely administer paclitaxel and docetaxel. It's also tremendously helpful for patients who experience hypersensitivity reactions to paclitaxel or docetaxel.

The NCCN guidelines permit you to recommend *nab* paclitaxel for patients who can't tolerate dexamethasone or have experienced hypersensitivity reactions, so our standard in those cases is to discontinue paclitaxel or docetaxel and substitute with *nab* paclitaxel. With an extra hour of infusion you can reduce the incidence of neutropenia.

With a 2-hour infusion the degree of neuropathy, which can otherwise be dose limiting, is also diminished. I've had patients receive this drug for years without neuropathy. Although preliminary, the data are compelling that a 2-hour infusion is better, and that's how we routinely administer this agent (Paik 2011; [1.1]). ■

**1.1**

**Phase II Study of a 2-Hour versus 30-Minute Infusion of Weekly *Nab* Paclitaxel for Patients with Advanced Non-Small Cell Lung Cancer**

| | ***Nab* paclitaxel 2-hour infusion (n = 25)** | ***Nab* paclitaxel 30-minute infusion (n = 40)** |
|---|---|---|
| Safety | | |
| Grade 3 or 4 neuropathy | 4 (16%) | 9 (23%) |
| Grade 3 or 4 neutropenia | 3 (12%) | 8 (20%) |
| Efficacy | | |
| Median progression-free survival | 5.3 months | 5.3 months |
| Median overall survival | 11 months | 11 months |

Paik PK et al. *Cancer Chemother Pharmacol* 2011;68(5):1331-7.

## SELECT PUBLICATIONS


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

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology. Non-small cell lung cancer — Version 3.2012.** Available at **www.nccn.org/professionals/physician_gls/pdf/nscl.pdf**.

Paik PK et al. **A phase 2 study of weekly albumin-bound paclitaxel (Abraxane®) given as a two-hour infusion.** *Cancer Chemother Pharmacol* 2011;68(5):1331-7.

Rekhtman N et al. **Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: Lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations.** *Clin Cancer Res* 2012;18(4):1167-76.

Yeo WL et al. **Erlotinib at a dose of 25 mg daily for non-small cell lung cancers with EGFR mutations.** *J Thorac Oncol* 2010;5(7):1048-53.

INTERVIEW

## Heather Wakelee, MD

Dr Wakelee is Assistant Professor of Medicine in the Division of Oncology at the Stanford University School of Medicine in Stanford, California.

## Tracks 1-18

**Track 1** Second opinion recommendation regarding adjuvant chemotherapy in NSCLC

**Track 2** Tolerability of adjuvant cisplatin/pemetrexed versus cisplatin/vinorelbine in the randomized Phase II TREAT study

**Track 3** Ongoing ECOG-E1505 Phase III trial of adjuvant chemotherapy with or without bevacizumab in Stage IB (≥4 cm) to IIIA NSCLC

**Track 4** Second opinions on the treatment approach for patients with Stage III NSCLC

**Track 5** **Case discussion:** A 52-year-old Asian man with a light smoking history is diagnosed with Stage IIIA mixed adenosquamous NSCLC and receives cisplatin/docetaxel in combination with bevacizumab on the ECOG-E1505 study

**Track 6** EGFR and ALK testing in lung cancer

**Track 7** Use of erlotinib off-protocol as a component of adjuvant therapy for EGFR-mutant, early NSCLC

**Track 8** Clinical decision-making regarding adjuvant chemotherapy and radiation therapy (RT) for Stage IIIA NSCLC

**Track 9** Perspective on the optimal duration of adjuvant bevacizumab in lung cancer and other solid tumors

**Track 10** Continuation of bevacizumab after disease progression

**Track 11** Continuation of erlotinib after disease progression in patients with EGFR-mutant advanced NSCLC

**Track 12** **Case discussion:** A 57-year-old Asian woman and never smoker presents with sudden left eye visual loss and has possible leptomeningeal enhancement on brain MRI and a right lung mass with multiple pulmonary nodules biopsy proven to be EGFR, K-ras, BRAF and ALK wild-type adenocarcinoma

**Track 13** ROS1 translocation as a driver mutation in lung cancer potentially responsive to crizotinib

**Track 14** PointBreak: A Phase III trial of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC

**Track 15** **Case discussion:** A 55-year-old woman with a 15 pack-year smoking history presents with EGFR wild-type multifocal lung disease 1 year after completion of adjuvant chemotherapy and receives erlotinib followed by pemetrexed, gemcitabine and fourth-line cabozantinib on a clinical trial

**Track 16** Cabozantinib — an oral, potent inhibitor of VEGFR2, RET and MET with single-agent activity in lung cancer

**Track 17** Results of clinical trials combining MET inhibitors — tivantinib or onartuzumab — with erlotinib in advanced NSCLC

**Track 18** Efficacy and side effects of the irreversible EGFR TKI afatinib in combination with cetuximab in patients with advanced NSCLC and acquired resistance to erlotinib or gefitinib

## Select Excerpts from the Interview

### Tracks 1-3

**DR LOVE:** In which common clinical situations have you evaluated patients seeking second opinions and made significantly different recommendations from those of the initial oncologist?

**DR WAKELEE:** That has happened quite a bit recently with regard to adjuvant chemotherapy. I discuss the ECOG-E1505 trial with eligible patients (NCT00324805). The trial design allows for 4 different chemotherapy backbones to assess whether bevacizumab improves adjuvant chemotherapy — cisplatin/vinorelbine, cisplatin/docetaxel, cisplatin/gemcitabine and, for patients with nonsquamous cell histology, cisplatin/pemetrexed. We are starting to generate considerable comparative data on these different regimens in that setting (Wakelee 2011).

I find that a push is still felt for cisplatin/vinorelbine in our community. I usually treat patients with nonsquamous cell histology with cisplatin/pemetrexed, and for patients with squamous cell histology I tend to use cisplatin/gemcitabine.

The Phase II TREAT trial is the only randomized study that has evaluated cisplatin/pemetrexed in the adjuvant setting. It reported that cisplatin/pemetrexed was better tolerated than cisplatin/vinorelbine (Kreuter 2011; [2.1]). Higher doses of cisplatin/pemetrexed were administered without treatment discontinuations due to neutropenia or other complications.

**2.1**

**TREAT: A Phase II Trial on Refinement of Early-Stage Non-Small Cell Lung Cancer Adjuvant Chemotherapy with Cisplatin/Pemetrexed (CPx) versus Cisplatin/Vinorelbine (CVb)**

| | **CPx** (n = 67) | **CVb** (n = 65) | *p*-value |
|---|---|---|---|
| Clinical feasibility rate*† | 95.5% | 75.4% | 0.001 |
| Delivery of absolute intended dose | 74.6% | 20.0% | <0.0001 |
| Grade 3 or 4 hematologic toxicity | 10.5% | 76.5% | <0.0001 |

* No death due to cancer, toxicity or comorbidity; no nonacceptance by patients leading to premature withdrawal; no observation of dose-limiting toxicity
† Primary endpoint; secondary efficacy endpoints not yet reported — awaiting longer follow-up

Kreuter M et al. *Proc ASCO* 2011;**Abstract 7002**.

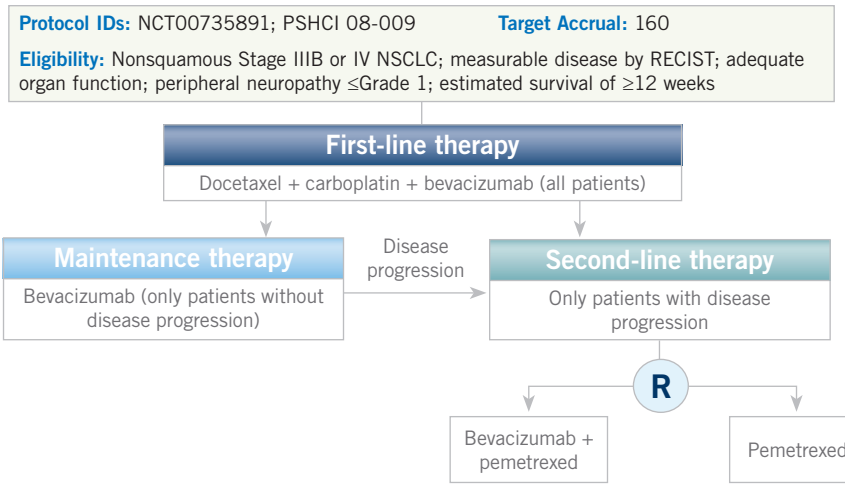
### Track 10

**DR LOVE:** How do you approach the patient with metastatic disease who develops slow progression after having a long response to chemotherapy/bevacizumab?

**DR WAKELEE:** Currently we have a trial in which patients with metastatic disease receiving bevacizumab maintenance are randomly assigned to continue with bevacizumab or not when a new agent is added to second-line therapy upon disease progression (2.2). This will provide important information about the utility of bevacizumab continuation in patients with lung cancer, but I don't currently use the continuation approach outside a trial setting.

**2.2**

**Phase II Trial to Determine the Potential Benefit of Continued Bevacizumab Therapy After Disease Progression or Treatment Failure in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)**




**www.clinicaltrials.gov**, May 2012.

## Track 14

**DR LOVE:** Would you discuss the "Patel regimen" as first-line therapy for NSCLC and the ongoing Phase III trial evaluating this regimen?

**DR WAKELEE:** A Phase II trial of patients who received the "Patel regimen" of 4 cycles of carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab had encouraging progression-free and overall survival (Patel 2009). The Phase III PointBreak trial is now comparing that regimen to the standard ECOG-E4599 regimen, and those results should be available soon (2.3).

## Track 17

**DR LOVE:** Would you talk about the new research strategy of combining MET inhibitors and erlotinib for patients with advanced NSCLC?

**DR WAKELEE:** In 2 randomized Phase II trials, patients with erlotinib-naïve disease received erlotinib with or without one of the MET inhibitors onartuzumab (a monoclonal antibody) or tivantinib (a TKI). Onartuzumab and tivantinib inhibit MET but by different mechanisms. A progression-free survival benefit and an overall survival advantage trend were observed in patients who received tivantinib (Sequist 2011; [2.4]). Thus a Phase III trial has been initiated (NCT01244191).

On evaluation of all patients in the intention-to-treat population treated on the Phase II trial of onartuzumab, no progression-free or overall survival advantage was seen. However, in the subgroup of patients with high MET expression, a substantial benefit occurred. Patients without high MET expression did not benefit. If anything, there

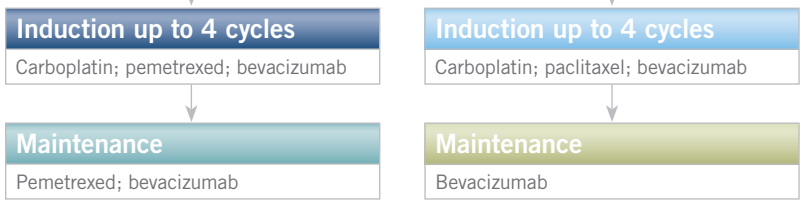
was potential harm (Spigel 2011; [2.5]). This has led to a focused Phase III trial in a subpopulation of patients with high MET expression (NCT01456325).

**2.3**

### PointBreak: A Phase III Study of Chemotherapy/Bevacizumab Followed by Maintenance Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)

**Protocol ID:** NCT00762034 **Target Accrual:** 900

**Eligibility:** Nonsquamous Stage IIIB or IV NSCLC; no prior treatment allowed, excluding radiation therapy to <25% of bone marrow; stable, treated brain metastasis allowed




**Primary endpoint:** Overall survival

**www.clinicaltrials.gov**, May 2012.

**2.4**

### Phase II Trial of Erlotinib and Tivantinib (ET) versus Erlotinib and Placebo (EP) for Patients with Erlotinib-Naïve, Previously Treated Advanced Non-Small Cell Lung Cancer

| Outcome | **ET** (n = 84) | **EP** (n = 83) | Hazard ratio | *p*-value |
|---|---|---|---|---|
| Median PFS (INV) | 3.8 mo | 2.3 mo | 0.81 | 0.24 |
| Median PFS (IRR) | 3.6 mo | 2.0 mo | 0.74 | 0.09 |
| Median OS (INV) | 8.5 mo | 6.9 mo | 0.87 | 0.47 |

PFS = progression-free survival; INV = investigator assessment; IRR = independent central radiology review; OS = overall survival
Hazard ratio <1 favors ET.

Sequist LV et al. *J Clin Oncol* 2011;29(24):3307-15.

## Track 18

**DR LOVE:** What are your thoughts on new trials evaluating the use of the irreversible TKI afatinib in combination with cetuximab for patients with advanced NSCLC who experience progression on erlotinib?

**DR WAKELEE:** The combination of afatinib/cetuximab in patients with NSCLC and acquired EGFR resistance produced striking results (Horn 2011; [2.6]). Most patients with EGFR mutation-positive NSCLC demonstrated a good response to erlotinib for a while and then developed resistance. In this study most of the patients responded to treatment regardless of whether the disease was T790M mutation positive. ■

## 2.5 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 |

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

## 2.6 Efficacy of Combined EGFR Targeting with Afatinib and Cetuximab by T790M Mutation Status in Patients with Advanced Non-Small Cell Lung Cancer and Resistance to an EGFR Tyrosine Kinase Inhibitor

| Best response | T790M-positive (n = 35) | T790M-negative (n = 16) | T790M uninformative (n = 2) | No EGFR mutation (n = 2) |
|---|---|---|---|---|
| Any partial response (PR) | 51% | 56% | 50% | — |
| Confirmed PR | 31% | 32% | 50% | — |
| Stable disease (SD) | 43% | 38% | 50% | 100% |
| Clinical response (any PR + SD) | 94% | 94% | 100% | 100% |
| Progressive disease | 6% | 6% | — | — |

Dose: Afatinib 40 mg PO per day, cetuximab 500 mg/m$^2$ IV

Horn H et al. *Proc IASLC* 2011;**Abstract O19.07**.

## SELECT PUBLICATIONS


Horn L et al. **Activity and tolerability of combined EGFR targeting with afatinib (BIBW 2992) and cetuximab in T790M+ NSCLC patients.** *Proc IASLC* 2011;**Abstract O19.07**.

Janjigian YY et al. **Phase I/II trial of cetuximab and erlotinib in patients with lung adenocarcinoma and acquired resistance to erlotinib.** *Clin Cancer Res* 2011;17(8):2521-7.

Kreuter M et al. **Randomized phase II trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed (CPx) versus cisplatin and vinorelbine (CVb): TREAT.** *Proc ASCO* 2011;**Abstract 7002**.

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

Sequist LV et al. **Randomized Phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non–small-cell lung cancer.** *J Clin Oncol* 2011;29(24):3307-15.

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**.

Wakelee HA et al. **Interim report of on-study demographics and toxicity from E1505, a phase III randomized trial of adjuvant (adj) chemotherapy (chemo) with or without bevacizumab (B) for completely resected early-stage non-small cell lung cancer (NSCLC).** *Proc ASCO* 2011;**Abstract 7013**.

INTERVIEW

## Ramaswamy Govindan, MD

Dr Govindan is Professor of Medicine and Co-Director of the Section of Medical Oncology in the Division of Oncology at Washington University School of Medicine in St Louis, Missouri.

### Tracks 1-18



## Select Excerpts from the Interview

### Tracks 3-6

**DR LOVE:** What is your usual treatment approach for locally advanced NSCLC?

**DR GOVINDAN:** My principle is to make decisions about surgery early on because with a nonoperative therapy, full rather than interrupted doses of thoracic radiation therapy (TRT) can be administered. Next I would advocate for FDG-PET scanning because about 10% to 15% of patients with Stage III disease have occult Stage IV NSCLC, and we do not want these patients to be subjected to needless combined modality therapy.

Also, it is important to choose the right chemotherapy regimen. I would administer cisplatin rather than carboplatin in the definitive setting of chemoradiation therapy. The most time-tested regimen for which we have Phase III data is cisplatin/etoposide. I tend to use 2 cycles of cisplatin/etoposide with concurrent radiation therapy. In a Phase III study patients with Stage III NSCLC were randomly assigned to either 2 cycles of cisplatin/etoposide and TRT or the same regimen followed by 3 cycles of docetaxel. No improvement in survival was observed in patients who received docetaxel, but a 5% increase in death rate occurred (Hanna 2007).

**DR LOVE:** What other chemotherapy regimens are being used with radiation therapy?

**DR GOVINDAN:** For many years, weekly paclitaxel/carboplatin concurrent with radiation therapy and 2 cycles of induction and consolidation systemic therapy were administered. The use of systemic doses of paclitaxel/carboplatin with radiation therapy is another option. Paclitaxel/carboplatin every 3 weeks in combination with TRT is well tolerated. I've used that on occasions when cisplatin was not an option.

We have been studying pemetrexed in this setting because it has the advantage that it can be administered at full doses with radiation therapy. The Phase II CALGB-30407 trial evaluated pemetrexed/carboplatin every 3 weeks in combination with TRT. Four additional cycles of pemetrexed alone in the consolidation setting were administered after 4 cycles of doublet therapy in an attempt to optimize systemic therapy. Remarkably, approximately 50% of patients were able to receive all 8 cycles with a median survival of about 22 months (Govindan 2011).

**DR LOVE:** Do you approach chemoradiation therapy differently for squamous and nonsquamous NSCLC?

**DR GOVINDAN:** Regardless of histology, I currently use cisplatin/etoposide/radiation therapy off protocol. The Phase III PROCLAIM study will compare pemetrexed/cisplatin/radiation therapy followed by consolidation pemetrexed to etoposide/cisplatin/radiation therapy followed by consolidation cytotoxic chemotherapy of choice for locally advanced Stage III nonsquamous NSCLC.

## Tracks 9-10

**DR LOVE:** What is your initial treatment strategy for an otherwise healthy, young patient with nonsquamous, EGFR wild-type, ALK wild-type, advanced NSCLC?

**DR GOVINDAN:** If the patient meets the eligibility criteria for the ECOG-E4599 study, I would administer bevacizumab (Sandler 2006). For the vast majority of patients, pemetrexed seems to be appropriate. In terms of side effects, pemetrexed/carboplatin is better tolerated.

If I chose not to administer bevacizumab, I would opt for 2 cycles of pemetrexed/carboplatin, reevaluate the patient, add 2 more cycles if chemotherapy is well tolerated and then continue with pemetrexed maintenance therapy. In patients who have received prolonged pemetrexed, I observe 3 common side effects: fatigue, leg edema

and cytopenia. The leg edema is quite symptomatic, and I tend to manage it with diuretics, particularly furosemide. Occasionally, I've used short courses of steroids. I believe the pathophysiology involves vascular endothelial damage leading to leaky vessels, either in the lymphatics or in the venous circulation.

## Tracks 13, 15-16

**DR LOVE:** When you interact with medical oncologists in community practice, what are some of the most common questions they ask about NSCLC?

**DR GOVINDAN:** One common question I am asked is what to do for a symptomatic patient with metastatic NSCLC for whom chemotherapy has been initiated before EGFR mutation test results were available: If the EGFR mutation test results are found to be positive, what do I do?

My typical approach is to continue chemotherapy and administer erlotinib in the maintenance setting as long as patients are tolerating the chemotherapy well with no major side effects. No hard data indicate that this is the only acceptable approach. Some investigators feel compelled to change therapy right away to erlotinib. I suppose that's an option, but I have not done so.

On the other hand, if I have the EGFR mutation data before I start chemotherapy, I opt to go straight to erlotinib in the front-line setting. We now have a number of studies indicating that administering EGFR TKIs in the front-line setting improves response rates two- to threefold and increases progression-free survival compared to chemotherapy (Mok 2009; Rosell 2011; [3.1]).

**DR LOVE:** Would you administer chemotherapy or erlotinib to a patient with highly symptomatic EGFR-mutant advanced NSCLC in need of a rapid response?

**DR GOVINDAN:** When you administer an EGFR TKI to a patient with EGFR mutation-positive NSCLC, especially in the case of an exon 19 deletion, you see responses within days. I've had patients with impressive radiographic resolution within a week — multiple nodules in the lung disappearing within just a week.

Keep in mind, however, that even with the exon 19 deletion, the response rate with EGFR TKI inhibitors is not 100%. Even though the patient may have an EGFR mutation, other factors may be present that can influence response to EGFR TKI therapy. We don't have a good handle on the genomic landscape of EGFR-mutant NSCLC. Planning is under way for studies for patients with EGFR mutation-positive disease to evaluate all the other mutations that are coexistent in that patient population.

**DR LOVE:** What is your approach for a patient who has an EGFR mutation and has a great response to erlotinib but then slowly experiences disease progression?

**DR GOVINDAN:** I believe we should be performing rebiopsy for these patients because about half of them will have a T790M mutation (Oxnard 2011), for which we have some interesting trials in development. About 20% may have the MET amplification, and then other oncogenes may be active in this population. Outside a trial setting, I would consider continuing erlotinib in spite of disease progression and then adding chemotherapy. The idea is that different clones of cancer cells exist, and the EGFR mutant clone could resurface in the absence of erlotinib (Riely 2007; [3.2]). Unfortunately, these patients are likely to experience progression again fairly soon. ■

**3.1**

## EURTAC: A Phase III Trial of First-Line Erlotinib versus Chemotherapy for Patients with Advanced Non-Small Cell Lung Cancer with EGFR Activating Mutations

| | Erlotinib (n = 86) | Chemotherapy (n = 87) | Hazard ratio | *p*-value |
|---|---|---|---|---|
| Median progression-free survival | 9.7 mo | 5.2 mo | 0.37 | <0.0001 |
| Median overall survival | 22.9 mo | 18.8 mo | 0.80 | 0.42 |
| Best overall response rate | 58% | 15% | — | — |
| Complete response rate | 2% | 0% | — | — |
| Partial response rate | 56% | 15% | — | — |
| Disease control rate | 79% | 66% | — | — |

Rosell R et al. *Proc ASCO* 2011;**Abstract 7503**.

**3.2**

## Changes in Tumor on CT and FDG-PET After EGFR Tyrosine Kinase Inhibitor (TKI) Discontinuation and Reinitiation in Patients with Non-Small Cell Lung Cancer Previously Responding to Erlotinib or Gefitinib

| Median/mean change in: | After stopping EGFR TKI | After restarting EGFR TKI |
|---|---|---|
| Tumor diameter | +9%/+9% | -1%/1% |
| Tumor volume | +50%/+61% | -1%/-4% |
| Tumor SUV(max) | +18%/+23% | -4%/-11% |

"In patients who develop acquired resistance, stopping erlotinib or gefitinib results in symptomatic progression, increase in SUV(max), and increase in tumor size.

Symptoms improve and SUV(max) decreases after restarting erlotinib or gefitinib, suggesting that some tumor cells remain sensitive to epidermal growth factor receptor blockade."

Riely GJ et al. *Clin Cancer Res* 2007;13(17):5150-5.

## SELECT PUBLICATIONS


Govindan R et al. **Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407.** *J Clin Oncol* 2011;29(23):3120-5.

Hanna NH et al. **Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023.** *Proc ASCO* 2007;**Abstract 7512**.

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

Oxnard GR et al. **Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation.** *Clin Cancer Res* 2011;17(6):1616-22.

Rosell R et al. **Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European erlotinib versus chemotherapy (EURTAC) phase III randomized trial.** *Proc ASCO* 2011;**Abstract 7503**.

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.

INTERVIEW

## David Jablons, MD

Dr Jablons is Professor and Chief in the Division of General Thoracic Surgery at the UCSF Helen Diller Family Comprehensive Cancer Center in San Francisco, California.

### Tracks 1-7

| | |
|---|---|
| Track 1 | Modest historic improvements in lung cancer survival |
| Track 2 | Results from the National Lung Screening Trial (NLST): Reduced lung cancer mortality with low-dose CT screening |
| Track 3 | Incidence of negative biopsies and complications in the NLST |
| Track 4 | Development of a molecular assay to predict survival in resected nonsquamous NSCLC |
| Track 5 | A practical 14-gene assay that uses quantitative PCR and runs on formalin-fixed paraffin-embedded tissue samples in patients with nonsquamous NSCLC |
| Track 6 | Proposed international, prospective randomized study to establish the predictive value of the multigene lung cancer assay |
| Track 7 | Prognostic value of the multigene assay in nonsquamous NSCLC |

## Select Excerpts from the Interview

### Track 2

**DR LOVE:** Would you discuss the National Lung Screening Trial, which aimed to determine whether screening with low-dose CT could reduce mortality from lung cancer?

**DR JABLONS:** We can make significant strides if we can identify patients at the early stages of disease. The predominant risk factor for the development of lung cancer is smoking. We can identify this risk factor, and we should be able to screen these patients. CT scans are an effective tool for finding nodules in the lung.

The National Lung Screening Trial accrued about 53,000 patients, half of whom were randomly assigned to undergo screening with the standard, which is a chest x-ray. The other half underwent screening with low-dose CT. Eligible participants were patients at high risk who were older than age 55 and had a history of smoking of at least 30 pack-years. These patients were monitored and if a suspicious nodule was found, the CT scan was repeated. Lung tumors, with the exception of low-grade adenocarcinoma in situ, will grow in time. If growth was observed, it was biopsied. If cancer was detected, it was resected.

Early analysis reported a dramatic 20% survival benefit in patients who were screened with low-dose, noncontrast CT (National Lung Screening Trial Research Team 2011; [4.1]). This was the first time a prospective, randomized trial indicating the benefit of

cancer screening was conducted. This was a brilliantly conducted multicenter trial that should yield a wealth of useful information over the next few years.

**4.1**

### National Lung Screening Trial: 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<br>247 | 443<br>309 | 20.0%<br>$p = 0.004$ |
| Deaths from any cause | 1,877 | 2,000 | 6.7%<br>$p = 0.02$ |

"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.

## Tracks 4-7

**DR LOVE:** Would you discuss your recently published paper describing a genomic assay to predict survival in patients with resected NSCLC?

**DR JABLONS:** The technology for the study came from our laboratory at UCSF. The idea was to try to find a molecular biomarker or a collection of genes that could provide a signature to identify high-risk early-stage lung cancer. About 50,000 patients with Stage I and II disease would be eligible to benefit from this analysis in the United States.

The overall survival for patients with Stage I disease after resection in the United States is approximately 60% to 65%. That means 35% to 50% of patients fail to survive as a result of occult micrometastasis. The biology of the tumor can inform us whether a lesion is truly localized or if occult micrometastatic disease may be present, which we cannot image. The purpose of this study was to be able to identify the group of patients at high risk for mortality.

The current test is a 14-gene test based on an algorithm. The assay was developed in a cohort of about 360 patients with early-stage nonsquamous NSCLC at UCSF. It was then independently validated in 433 patients with Stage I lung cancer at the Kaiser Permanente Northern California hospitals and 1,006 patients with Stage I to III lung cancer resected in several Chinese cancer centers.

The results showed that in about 1,000 patients in the United States with Stage I nonsquamous NSCLC, the survival was 71% for the group of patients at low risk versus 49% for those at high risk, with a *p*-value of 0.0003. In China the results were similar with 74% for the patients at low risk versus 44% for the patients at high risk, with a

*p*-value less than 0.0001 (Kratz 2012; [4.2]). The fact that similar results were obtained on 2 continents is one of the remarkable aspects of this study.

The test currently is purely prognostic, but we are about to embark on a large-scale, international, prospective, randomized trial that will enroll 1,500 patients with nonsquamous NSCLC that has been completely resected and has adequate surgical and clinical staging. The 14-gene assay will be performed, and patients in the high-risk category will be randomly assigned to systemic chemotherapy with a platinum doublet or pemetrexed/cisplatin. The patients will be followed for time to progression and survival.

We hope to accrue quickly and within the next 3 to 4 years be able to not only validate the prognostic value, but also establish whether a predictive benefit can be observed for administering chemotherapy in patients at high risk for mortality after surgical resection. ■

**4.2**

### Practical Molecular Assay to Predict Survival for Patients with Resected Nonsquamous Non-Small Cell Lung Cancer

| | 5-year overall survival | *p*-value |
|---|---|---|
| **Kaiser validation cohort** (n = 433) | | |
| Low risk | 71.4% | |
| Intermediate risk | 58.3% | 0.0003 |
| High risk | 49.2% | |
| **Chinese validation cohort** (n = 1,006) | | |
| Low risk | 74.1% | |
| Intermediate risk | 57.4% | <0.0001 |
| High risk | 44.6% | |

**Methods:** A 14-gene expression assay that uses quantitative PCR, runs on formalin-fixed, paraffin-embedded tissue samples and differentiates patients with heterogeneous statistical prognoses was developed in a cohort of 361 patients with nonsquamous NSCLC resected at UCSF. The assay was then independently validated by 2 separate cohorts.

**Conclusion:** This practical, quantitative PCR-based assay reliably identified patients with early-stage non-squamous non-small cell lung cancer at high risk for mortality after surgical resection.

Kratz JR et al. *Lancet* 2012;379(9818):823-32.

## SELECT PUBLICATIONS


Chen DT et al. **Prognostic and predictive value of a malignancy-risk gene signature in early-stage non-small cell lung cancer.** *J Natl Cancer Inst* 2011;103(24):1859-70.

Ding L et al. **Somatic mutations affect key pathways in lung adenocarcinoma.** *Nature* 2008;455(7216):1069-75.

Hou J et al. **Expression profiling-based subtyping identifies novel non-small cell lung cancer subgroups and implicates putative resistance to pemetrexed therapy.** *J Thorac Oncol* 2012;7(1):105-14.

Hutchinson L. **Lung cancer: Practical assay to predict survival.** *Nat Rev Clin Oncol* 2012;9(3):127.

Kratz JR et al. **A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: Development and international validation studies.** *Lancet* 2012;379(9818):823-32.

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.

Siegel R et al. **Cancer statistics, 2012.** *CA Cancer J Clin* 2012;62(1):10-29.

Sox HC. **Better evidence about screening for lung cancer.** *N Engl J Med* 2011;365(5):455-7.

Xie Y, Minna JD. **A lung cancer molecular prognostic test ready for prime time.** *Lancet* 2012;379(9818):785-7.

## QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Patients with squamous cell NSCLC and those with adenocarcinoma should be tested, routinely, for both EGFR mutations and EML4-ALK translocations.**
   a. True
   b. False

2. **Data from a Phase II study of *nab* paclitaxel in NSCLC suggest that the 2-hour infusion time results in a lower incidence of _____ compared to a 30-minute infusion.**
   a. Neuropathy
   b. Neutropenia
   c. Both of the above
   d. None of the above

3. **The results of the Phase II TREAT trial demonstrated that the combination of cisplatin and vinorelbine was better tolerated than cisplatin and pemetrexed for patients with early-stage NSCLC.**
   a. True
   b. False

4. **In the Phase II OAM4558g trial of erlotinib with or without onartuzumab (MetMAb) as second- or third-line therapy for advanced NSCLC, the addition of onartuzumab yielded benefits in _____ in a subpopulation of patients with high MET expression by immunohistochemistry.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b
   d. None of the above

5. **In a study of afatinib with cetuximab for patients with NSCLC and disease progression on erlotinib or gefitinib, investigators reported confirmed responses in _____.**
   a. T790M mutation-positive disease
   b. T790M mutation-negative disease
   c. Both of the above
   d. None of the above

6. **In a report published by Riely and colleagues, patients who developed acquired resistance to erlotinib or gefitinib experienced improvement in symptoms and decreases in SUVmax after restarting the EGFR TKI.**
   a. True
   b. False

7. **The Phase III PROCLAIM trial will compare cisplatin/etoposide to cisplatin/_____ for patients with locally advanced unresectable Stage III nonsquamous NSCLC.**
   a. Paclitaxel
   b. Vinorelbine
   c. Pemetrexed

8. **The Phase III EURTAC trial of erlotinib versus chemotherapy for patients with advanced NSCLC and EGFR-activating mutations reported statistically significant improvements in _____ for patients receiving erlotinib.**
   a. Median progression-free survival
   b. Median overall survival
   c. Overall response rate
   d. Both a and c

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

10. **Kratz and colleagues report that a practical molecular assay to predict survival in patients with resected nonsquamous NSCLC indicated a 5-year overall survival of approximately 70% in validation cohorts of patients at low risk from both the United States and China.**
    a. True
    b. False

## EDUCATIONAL ASSESSMENT AND CREDIT FORM

### *Lung Cancer Update* — Issue 1, 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 |
|---|---|---|
| Decreased neutropenia and peripheral neuropathy with 2-hour infusions of *nab* paclitaxel | 4 3 2 1 | 4 3 2 1 |
| PointBreak: A Phase III study of pemetrexed/carboplatin/bevacizumab → maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC | 4 3 2 1 | 4 3 2 1 |
| Activity of afatinib/cetuximab in patients with NSCLC and acquired resistance to erlotinib or gefitinib | 4 3 2 1 | 4 3 2 1 |
| Results of studies combining onartuzumab (MetMAb) or tivantinib (ARQ 197) with erlotinib for advanced NSCLC | 4 3 2 1 | 4 3 2 1 |
| Background and prognostic value of a multigene lung cancer assay | 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
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions and other recently identified driver mutations — and the investigational and approved treatment options for patients with these biomarkers..... 4 3 2 1 N/M N/A
- Describe emerging efficacy and tolerability data with combined EGFR targeting for patients with NSCLC and acquired resistance to EGFR tyrosine kinase inhibitors..... 4 3 2 1 N/M N/A
- Identify patients with metastatic NSCLC who may experience clinical benefit from the addition of continuation or switch maintenance biologic therapy and/or chemotherapy..... 4 3 2 1 N/M N/A
- Consider the use of low-dose CT screening in evaluating appropriately selected patients for early-stage lung cancer..... 4 3 2 1 N/M N/A
- Individualize adjuvant chemotherapy for patients with early-stage NSCLC, with consideration of the efficacy and unique side-effect and tolerability profiles of guideline-endorsed regimens... 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
- Use case-based learning to formulate individualized strategies for the care of patients with lung cancer..... 4 3 2 1 N/M N/A

**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 |
|---|---|---|
| Mark G Kris, MD | 4 3 2 1 | 4 3 2 1 |
| Heather Wakelee, MD | 4 3 2 1 | 4 3 2 1 |
| Ramaswamy Govindan, MD | 4 3 2 1 | 4 3 2 1 |
| David Jablons, MD | 4 3 2 1 | 4 3 2 1 |
| **Editor** | **Knowledge of subject matter** | **Effectiveness as an educator** |
| Neil Love, MD | 4 3 2 1 | 4 3 2 1 |

**Please recommend additional faculty for future activities:**

.....

**Other comments about the faculty and editor for this activity:**

.....

.....

.....

## REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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This activity is supported by educational grants from
Astellas, Celgene Corporation, Daiichi Sankyo Inc, Genentech
BioOncology and Lilly USA LLC.

Research
To Practice®

Sponsored by Research To Practice.

Last review date: May 2012
Release date: May 2012
Expiration date: May 2013
Estimated time to complete: 3 hours

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