

Lung Cancer™

U P D A T E

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

EDITOR

Neil Love, MD

INTERVIEWS

Harvey I Pass, MD

Jeffrey A Engelman, MD, PhD

Ritsuko Komaki, MD

Renato G Martins, MD, MPH



Lung Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Lung cancer is the leading cause of cancer mortality in the United States for both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been limited, and approximately 85 percent of patients who develop lung cancer will die from it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on long-term outcomes. However, the advent of biologic agents in lung cancer has led to recent improvements in disease-free and overall survival in select patient populations. Published results from ongoing and completed studies lead to the continual emergence of novel therapeutic strategies and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with expert perspectives, this CME program is designed to assist medical oncologists and radiation oncologists with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Identify innovative surgical techniques currently being evaluated for lung cancer, and summarize their effect on operative morbidity and mortality.
- Communicate the risks and benefits of stereotactic body radiation therapy (SBRT) to appropriate patients with non-small cell lung cancer (NSCLC).
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions.
- Appraise the clinical application of emerging data on the combined use of biologic agents with chemoradiation therapy for Stage III NSCLC.
- Formulate a risk-adapted algorithm for the individualized use of adjuvant systemic therapy for patients with localized NSCLC.
- Apply the results of recent clinical research to the rational selection of EGFR- or VEGF-inhibiting agents for patients with metastatic NSCLC.
- Describe the oncogene addiction hypothesis in relation to the genesis of cancer and the mechanism of action of biologic agents.
- Counsel appropriately selected patients with lung cancer about the availability of ongoing clinical trials in which they may be eligible to participate.

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3 INTERVIEWS

Harvey I Pass, MD

Professor of Surgery and Cardiothoracic Surgery
Director, Division of Thoracic Surgery
NYU Langone Medical Center
New York, New York

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Director of Lung Cancer Research
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Professor of Radiation Oncology
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As an added bonus, please visit www.ResearchToPractice.com for additional discussion among our faculty and practicing oncologists. An additional 13 minutes from the interview with Dr Martins is available for download or online listening.



INTERVIEW

Harvey I Pass, MD

Dr Pass is Professor of Surgery and Cardiothoracic Surgery and is Director of the Division of Thoracic Surgery at NYU Langone Medical Center in New York, New York.

Tracks 1-17

- Track 1** Lobectomy versus segmental resection for non-small cell lung cancer (NSCLC)
- Track 2** Impairment of cellular immune function and type of surgery
- Track 3** Role of the surgeon in translational research
- Track 4** Use of biomarker analyses in lung cancer
- Track 5** Genomic tests to determine prognosis in lung cancer
- Track 6** Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) for restaging NSCLC in the mediastinum
- Track 7** Cetuximab in combination with chemoradiation therapy for Stage IIIA/B NSCLC
- Track 8** Clinical use of EBUS-TBNA
- Track 9** National Mesothelioma Virtual Tumor Bank
- Track 10** Developing a new staging system for mesothelioma
- Track 11** Stereotactic body radiation therapy (SBRT) for lung cancer
- Track 12** **Case Discussion:** An 82-year-old woman, who is a nonsmoker, underwent video-assisted thoracoscopic surgery (VATS) for an invasive adenocarcinoma with an EGFR mutation
- Track 13** Clinical research on the use of adjuvant erlotinib for patients with NSCLC and an EGFR mutation
- Track 14** Resection of pulmonary metastases associated with nonlung primary cancer
- Track 15** **Case Discussion:** A 57-year-old man, who is a nonsmoker, was treated with chemoradiation followed by surgery and consolidation docetaxel for a left hilar mass and a lymph node metastasis
- Track 16** Excision repair cross-complementation group 1 (ERCC1) and ribonucleotide reductase subunit M1 (RRM1) as predictors of chemotherapy resistance
- Track 17** ECOG-E1505: A Phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for patients with completely resected Stage IB (≥ 4 cm) to IIIA NSCLC

Select Excerpts from the Interview

Track 1

▶ **DR LOVE:** Would you comment on the issue of segmentectomy versus lobectomy for resectable non-small cell lung cancer?

► **DR PASS:** An important shift is occurring right now toward individualized local management of lung cancer. The question of performing a lobectomy for every patient is evolving because we are recognizing that variation exists among pulmonary nodules. They differ with regard to appearance — whether they're solid or partially solid — which may indicate variations in histology, and that translates into differences in natural history.

We are also aware of the importance of lesion size, which is incorporated into the new staging system. Patients with smaller lesions within the Stage I category do much better than those with larger lesions, so they're segregated according to size.

As a result, I've seen great interest in determining whether we can perform fewer lobectomies — using, for example, sublobar resections — for certain patients. That issue is under active investigation in trials in the United States and abroad.

CALGB-140503 is evaluating surgical options for patients with node-negative disease and lesions smaller than two centimeters. In the operating room, patients are randomly assigned to either a lobectomy, which is the standard approach, or a sublobar resection (1.1). That trial is ongoing and may reveal that for small lesions, a segmental resection is as successful as a lobectomy. Of course, in those cases a complete mediastinal lymph node dissection must be conducted for staging purposes.

► **DR LOVE:** Can a segmental resection be performed via a video-assisted thoracic surgery (VATS)?

1.1 Phase III Trial of Lobectomy versus Sublobar Resection

Protocol IDs: CALGB-140503, ECOG-40503, NCT00499330; Target Accrual: 1,297 (Open)

R → Lobectomy by open thoracotomy or video-assisted thoracoscopic surgery (VATS)

→ Wedge resection or anatomical segmentectomy by open thoracotomy or VATS

Eligibility

- Stage IA NSCLC
- Peripheral lung nodule ≤ 2 cm by CT scan
- No prior chemotherapy or radiation therapy for this tumor

Study Contacts

Cancer and Leukemia Group B, Nasser Altorki, MD, Tel: 212-746-5156
Radiation Therapy Oncology Group, Harvey I Pass, MD, Tel: 212-263-7417
ACOSOG, Daniel Miller, MD, Tel: 404-778-3755
Southwest Oncology Group, Kemp Kernstine, MD, Tel: 319-356-3407

SOURCE: NCI Physician Data Query, March 2009.

▶ **DR PASS:** Yes it can, and I do that in my practice. I believe that in the future segmentectomy by VATS will be standard.

Track 6

▶ **DR LOVE:** Would you summarize your editorial on using endobronchial ultrasound (EBUS) for staging the mediastinum (Pass 2008b)?

▶ **DR PASS:** The question is how best to preoperatively restage the disease in patients with Stage IIIA lung cancer who have received induction therapy. A number of studies, beginning with Albain's data from the Intergroup trial 0139 (RTOG-9309), have demonstrated that persistent positive mediastinal nodes are a poor prognostic factor (Albain 2005). These patients do not fare as well, even if they undergo surgery and chemoradiation therapy. So we need to accurately identify them to decide whether they should undergo this potentially dangerous operation.

A mediastinoscopy is used to initially biopsy mediastinal nodes, and it can be repeated preoperatively, after induction therapy, to determine whether the nodes are still positive. Although that has been achieved by European and American surgeons, it is difficult — we need a better strategy.

The EBUS enables us to bronchoscope the patient, visualize the nodes using a transducer on the outside, insert a needle, aspirate the node and determine whether that lymph node is involved without having to violate the mediastinum. However, Herth and colleagues showed that the accuracy of EBUS was not that great compared to mediastinoscopy (Herth 2008). For some patients, surgery revealed lymph node disease that was not detected by EBUS.

I believe a better way to preoperatively restage disease after induction therapy is to begin by performing an EBUS when initially staging the disease and save the mediastinoscopy for restaging immediately prior to surgery. Why? Most patients have undergone a PET scan, which provides a detailed roadmap of where the positive lymph node or nodes are located. If we initially combine that with an EBUS and go directly to the area identified by PET, we can sample as many nodes as we want — being careful to include the PET scan-positive nodes — and determine whether the patient has N2 disease.

Then we save the gold standard, mediastinoscopy, to restage the patient preoperatively. That's the most important time to decide whether that patient has demonstrated a great response to chemotherapy or chemoradiation therapy — when you are deciding whether to operate.

Track 11

▶ **DR LOVE:** Would you describe your trial evaluating stereotactic body radiation therapy (SBRT)?

▶ **DR PASS:** Bob Timmerman and I are the primary investigators of a carefully constructed national Phase II trial in which patients with lesions smaller than

five centimeters in size who would otherwise have a lobectomy receive SBRT to the lesion, with PET and CAT scans before and after treatment.

The data for patients with unresectable disease have been promising, with superb control rates at two years of 95 percent (Timmerman 2006; [1.2]). I believe we're moving toward using SBRT for patients who otherwise may have resectable disease. It's a logical step, but surgeons are a little reticent to accept this. Surgeons need to understand that there's still a surgical option after SBRT if the patient experiences a recurrence. The associated morbidity is not bad, particularly if SBRT is limited to treating peripheral lesions.

- ▶ **DR LOVE:** For a patient who is not eligible for surgery, or simply doesn't want to undergo surgery, do you feel this is a reasonable option?
- ▶ **DR PASS:** Absolutely. For patients who have peripheral lesions in the outer third zone of the lung but refuse surgery or are not surgical candidates, this is a good option. We do not have 10-year follow-up data on these patients at this point, but the intermediate results are promising.

1.2 **Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer (N = 70)**

Efficacy data*	
Three-month major response	60%
Local control at two years	95%
Median overall survival	32.6 months
Two-year overall survival	54.7%

* Median follow-up was 17.5 months.

SOURCE: Timmerman R et al. *J Clin Oncol* 2006;24(30):4833-9. [Abstract](#)

Track 17

- ▶ **DR LOVE:** What are your thoughts on the ECOG-E1505 trial, evaluating adjuvant chemotherapy with or without bevacizumab for patients with completely resected Stage IB-IIIa NSCLC (1.3)?
- ▶ **DR PASS:** The initial study in metastatic disease demonstrated that bevacizumab can improve survival in the metastatic setting (Sandler 2006), so the next step is to determine whether it also will show a survival benefit in the adjuvant setting.

Administering an antibody can be difficult for patients, but it's manageable. Bevacizumab will be safer in the adjuvant setting because the primary lesion is removed, and we are able to control any associated hypertension. However, the fact that it's intravenous and costly concerns me. I would be more excited if a larger survival advantage had been seen in the completed studies that justified this trial.

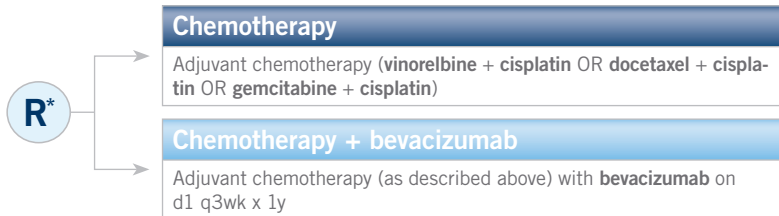
► **DR LOVE:** What about the issue of wound healing?

► **DR PASS:** We wait four to six weeks after bevacizumab before performing surgery, and I haven't seen any problems in my patients. I've also operated on patients who had mesothelioma and received bevacizumab up front with no problems. ■

1.3

Phase III Study of Adjuvant Chemotherapy with or without Bevacizumab for Patients with Completely Resected Stage IB to IIIA NSCLC

Protocol ID: ECOG-E1505; Target Accrual: 1,500



* Patients are stratified according to type of chemotherapy, stage, histology and gender.

Eligibility

- Resection within the past six to 12 weeks
- ECOG performance status 0 to 1
- No history of CVA or TIA
- History of myocardial infarction or angina acceptable if no evidence of active disease within the past 12 months

SOURCE: NCI Physician Data Query, March 2009.

SELECT PUBLICATIONS

Albain KS. **Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for Stage IIIA (pN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309).** *Proc ASCO* 2005;[Abstract 7014](#).

Herth FJ et al. **Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and PET normal mediastinum in patients with lung cancer.** *Chest* 2008;133:887-91. [Abstract](#)

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INTERVIEW

Jeffrey A Engelman, MD, PhD

Dr Engelman is Director of Lung Cancer Research at Massachusetts General Hospital and Assistant Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-17

- Track 1 Oncogene addiction hypothesis
- Track 2 Role of EGFR mutations in the development of lung cancer
- Track 3 Mechanisms of resistance to tyrosine kinase inhibitors (TKIs)
- Track 4 TKIs: Dose selection and correlation between rash and efficacy
- Track 5 Benefits associated with TKIs in patients without EGFR mutations
- Track 6 Clinical use of EGFR mutation testing
- Track 7 Incidence of EGFR and K-ras mutations in smokers and nonsmokers
- Track 8 Clinical research on cetuximab in NSCLC
- Track 9 NSCLC as a biologically heterogeneous disease
- Track 10 Normalization of vasculature by bevacizumab
- Track 11 Anaplastic lymphoma kinase (ALK) translocations in lung cancer
- Track 12 **Case Discussion:** A 45-year-old woman who is a nonsmoker with metastatic adenocarcinoma and an ALK translocation
- Track 13 Frequency of and testing for ALK translocations in NSCLC
- Track 14 TKI-associated toxicities
- Track 15 **Case Discussion:** A 54-year-old woman with a metastatic adenocarcinoma and an exon 19 deletion who received erlotinib for 18 months
- Track 16 Continuation of erlotinib upon disease progression
- Track 17 Erlotinib for the treatment of CNS metastases

Select Excerpts from the Interview

Tracks 1-2

► **DR LOVE:** Would you review the oncogene addiction hypothesis?

► **DR ENGELMAN:** It's a simple concept meaning that a cancer cell relies on the activity of one specific protein, and if you block the activity or function of that protein, the cancer cell dies. The oncogene is the gene or DNA that encodes for that protein. Without the oncogene being active and functional, the protein is not produced.

This goes hand in hand with targeted therapies because they can inhibit the protein. Everyone wants to go after these oncogene addictions, these “Achilles’ heels.” The cancer can’t survive without that protein being functional.

We have a few great examples of this hypothesis. The best one is imatinib for BCR-ABL translocated Philadelphia chromosome-positive chronic myelogenous leukemia (CML), which requires ABL kinase to be active or the cells won’t survive (Hughes 2003). HER2-amplified breast cancer is another model. If you use trastuzumab or lapatinib to block HER2 function, the cells die. I’ve been working on EGFR-driven lung cancer cases in which, when using an EGFR inhibitor, the cells die.

This occurs because EGFR is a receptor tyrosine kinase, a protein that spans the plasma membrane. It has kinase activity and phosphorylates other proteins. It is at the top of a huge cascade of events that occur inside the cell when it is active. All the events EGFR triggers promotes cancer cell growth and survival. So when you inhibit EGFR, you block its ability to transduce those signals and the cell dies.

► **DR LOVE:** Would you discuss what we know about EGFR mutations?

► **DR ENGELMAN:** EGFR mutations increase the activity of the receptor. The EGFR mutations pump the kinase activity that phosphorylates proteins and rev it into a higher gear.

The EGFR mutation probably allowed the cancer cell to develop in the first place, which is why it’s addicted to it. So when you inhibit EGFR, the kinase activity stops and the cell dies. These mutations are specific genetic changes resulting in amino acid substitutions in the kinase, leading to the increase in activity.

Tracks 4-5

► **DR LOVE:** What about the issue of dose escalation with EGFR tyrosine kinase inhibitors and the correlation between rash and clinical benefit (2.1)?

► **DR ENGELMAN:** We generally do not move forward with dose escalations. Patients who have cancer with EGFR mutations require much less drug for a response because the drug fortuitously inhibits these mutant receptors with a higher potency than the wild-type receptors as a result of the structural changes induced by these mutations.

If patients respond, we often reduce the dose if they experience too much toxicity. Patients without EGFR mutations can also benefit from these agents. For those patients, the full dose is likely required.

I like to see a little rash — not so much that it becomes intolerable — because the rash is a consequence of inhibiting EGFR in the skin. It’s what we call a pharmacodynamic marker. It tells you that you have enough drug in the blood to inhibit the receptor in the skin.

We believe that the development of a rash is a favorable event because some patients might metabolize the drug so quickly or absorb the drug so poorly that they don't attain adequate levels in the blood. They don't develop a rash, yet their tumor also isn't inhibited. So the rash provides comfort that you're reaching a reasonable blood level that will inhibit the receptor.

2.1

Correlation between Development of Rash and Efficacy of Erlotinib in Two Large Phase III Studies

"The analyses presented here suggest physicians and patients should view the development of rash as a desirable outcome, perhaps as a sign of erlotinib-induced biological effect. The patient who does not develop a characteristic rash within 2 to 4 weeks is less likely to benefit from erlotinib.

There is a need to develop methods for managing the rash without interfering with improvement in outcomes associated with the rash. Further studies are needed to identify which patients are more likely to develop rash and whether increasing the dose of erlotinib can induce rash in patients without rash at the standard dose and improve outcome."

SOURCE: Wacker B et al. *Clin Cancer Res* 2007;13(13):3913-21. [Abstract](#)

- ▶ **DR LOVE:** What about the use of EGFR TKIs in patients whose tumors do not have EGFR mutations? How many of those patients benefit?
- ▶ **DR ENGELMAN:** I believe that it's safe to say some patients without EGFR mutations benefit from EGFR inhibitors. My guess, based on laboratory models, is that those patients have normal EGFR levels, but it is still driving the cell to a large extent. In the patients with EGFR mutations, massive apoptosis, cell death and tumor shrinkage occur with the TKIs.
- ▶ **DR LOVE:** Is it your impression that EGFR mutation testing is not being conducted outside of tertiary care centers?
- ▶ **DR ENGELMAN:** Yes. However, I believe that EGFR mutation testing will become standard in less than a few years at most centers. We're conducting genetic analyses on every tumor.

We analyze for EGFR mutations — among other mutations that we can't even act on now because we want the information for retrospective analyses as we make our way through this new era of clinical trials with targeted therapies.

The whole panoply of genetic testing costs less than one CT scan. So it seems ridiculous that we wouldn't have this information about a patient's tumor when it could affect therapy.

The Iressa® Pan ASia Study (IPASS) demonstrated that patients with NSCLC whose tumors had EGFR mutations fared better when treated with an EGFR inhibitor than with chemotherapy. Patients whose tumors had wild-type EGFR, however, fared better when treated with chemotherapy than with an EGFR inhibitor (Mok 2008; [2.2]).

IPASS: A Phase III Randomized Trial of Gefitinib versus Carboplatin/Paclitaxel as First-Line Therapy for Clinically Selected* Patients with Advanced NSCLC

	Gefitinib	Carboplatin + paclitaxel	Hazard ratio (95% CI)	p-value
Progression-free survival events				
Intent-to-treat population (n = 609; 608)	74.4%	81.7%	0.74 (0.65-0.84)	<0.0001
EGFR mutation-positive (n = 132; 129)	73.5%	86.0%	0.48 (0.36-0.64)	<0.0001
EGFR mutation-negative (n = 91; 85)	96.7%	82.4%	2.85 (2.05-3.98)	<0.0001

* Asian patients with adenocarcinomas who were never smokers or past light smokers

CI = confidence interval

SOURCE: Mok T et al. *Proc ESMO* 2008; [Abstract LBA2](#).



Track 16

▶ **DR LOVE:** How do you decide whether to continue erlotinib for a patient with an EGFR mutation whose disease is progressing?

▶ **DR ENGELMAN:** I often continue the drug. Patients who responded to erlotinib or had a mutation and are now experiencing disease progression need to stay on some sort of EGFR inhibition. The model now involves either switching to a different EGFR inhibitor that may be able to inhibit the new mutation or adding new therapy to erlotinib.

So I don't discontinue erlotinib. If the patient's disease is progressing on erlotinib and it's time for chemotherapy, I add chemotherapy to the erlotinib. This is not proven in any way, but it seems like the right thing to do. ■

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Mok T et al. **Phase III, randomised, open-label, first-line study of gefitinib (G) vs carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non small-cell lung cancer (NSCLC) (IPASS).** *Proc ESMO* 2008; [Abstract LBA2](#).

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INTERVIEW

Ritsuko Komaki, MD

Dr Komaki is Professor of Radiation Oncology and Gloria Lupton Tennison Endowed Professor in Lung Cancer Research at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-10

- | | | | |
|----------------|---|-----------------|---|
| Track 1 | Case Discussion: A 76-year-old man treated with SBRT for a second squamous cell carcinoma | Track 7 | Case Discussion: A 62-year-old man with Stage IIIA NSCLC who was treated with cetuximab in combination with chemoradiation therapy |
| Track 2 | Risks and benefits associated with SBRT | Track 8 | RTOG-0324: A Phase II trial of cetuximab in combination with chemoradiation therapy for Stage IIIA/B NSCLC |
| Track 3 | Randomized trial evaluating SBRT versus surgery | Track 9 | Clinical use of cetuximab in combination with chemoradiation therapy |
| Track 4 | Clinical use of SBRT | Track 10 | Use of tumor histology and biomarkers in the selection of EGFR or VEGF inhibitors for the treatment of solid tumors |
| Track 5 | Case Discussion: A 51-year-old man with limited-stage small cell lung cancer (SCLC) and Eaton-Lambert syndrome who had a complete response to chemoradiation therapy | | |
| Track 6 | Neurocognitive impairment associated with prophylactic cranial irradiation | | |

Select Excerpts from the Interview

Track 2

► **DR LOVE:** Would you discuss the risks and benefits associated with SBRT?

► **DR KOMAKI:** We perform this treatment for patients with tumors smaller than three centimeters. If a tumor is large, it's difficult to perform SBRT, and damage to the surrounding normal tissue can be detrimental. Some centers apply this type of treatment to tumors as large as four centimeters.

Many physicians are using this type of treatment in the community radiation oncology setting. In fact, interest has developed in the use of SBRT for some patients traditionally considered for surgery. Patients are interested in this treatment because of the lack of postoperative complications and pain associated with surgery.

SBRT is now becoming popular among radiation oncologists who treat a number of elderly patients in Japan and certain places in the United States. Advancements in diagnostic screening such as spiral CT scans have started to pick up many T1 or smaller T2 lesions. We see it in patients who are 80 or 85 years old and undergoing routine check-ups or follow-up on a previous tumor and are found to have small lesions in the lung.

► **DR LOVE:** What data sets are available in terms of this technique?

► **DR KOMAKI:** The RTOG has published Phase II trial data reporting excellent local control and survival (Fakiris 2009), and Japanese studies have reported long-term outcome data indicating 10-year survival rates equivalent to surgical resection (Uematsu 2008). So it's comparable if we administer an adequate dose of stereotactic body radiation therapy to the patients in favor of surgical resection. Five-year survival outcomes are approximately 85 percent, and local control is approximately 90 percent.

An international study (NCT00840749) is now open to accrual in 20 centers across China, Japan and the United States comparing SBRT to surgical resection. The principal investigator is thoracic surgeon Jack Roth from the MD Anderson Cancer Center, and I serve as Co-PI. All patients must be considered reasonable candidates for surgical resection. A PET/CT scan is required, and the tumor size has to be four centimeters or smaller. Patients must have adequate lung function.

Track 8

► **DR LOVE:** Would you discuss the results of your Phase II trial of cetuximab in combination with chemoradiation therapy?

► **DR KOMAKI:** The results of this trial were presented at the 2008 ASCO meeting, evaluating the combination of cetuximab with paclitaxel/carboplatin and radiation therapy for 87 patients with Stage III NSCLC. We reported a median survival rate of 23 months and a two-year survival rate of 50 percent (Blumenschein 2008; [3.1]), which is better than previous Phase III RTOG-9410 trial results (Curran 2003).

Reported toxicities were also mild. The frequency of Grade III/IV pneumonitis and esophagitis was less than nine percent. I am certain that the use of the sophisticated 3D conformal radiation therapy technique contributed to less toxicity to the lung.

We are encouraged by the addition of cetuximab to paclitaxel/carboplatin and radiation treatment. This could become standard nationwide for patients with good performance status, Stage III disease. Based on the excellent outcome and minimal toxicity results from our Phase II trial, we will be opening a Phase III study requiring 700 patients who will be randomly assigned to paclitaxel/carboplatin and radiation therapy with or without cetuximab.

► **DR LOVE:** What are your thoughts on the possibility of using this strategy outside of a protocol setting?

► **DR KOMAKI:** We are not using cetuximab off protocol despite the positive Phase II trial results. ■

3.1

RTOG-0324: A Phase II Study of Cetuximab in Combination with Chemoradiation Therapy (CRT) for Patients with Stage IIIA/B NSCLC

	Cetuximab + CRT* (n = 87)
Efficacy	
Median survival (MS), months	22.7
Two-year overall survival (OS), %	49.3
Response rate, n (%)	54 (62)
Adverse events (Grade III/IV)	
Hematologic toxicities, n (%)	17 (20)
Esophagitis, n (%)	7 (8)
Pneumonitis, n (%)	6 (7)

Conclusions

“The combination of [cetuximab] with CRT is feasible and active with MS and OS better than any previously reported by the RTOG. These results warrant confirmation in a randomized trial.”

* Initial cetuximab dose of 400 mg/m² on day 1 of week 1, then weekly doses of 250 mg/m² until completion of therapy (weeks 2-17). During week 2, patients began CRT (63 Gy/35 fractions) with weekly carboplatin (C) AUC 2 and paclitaxel (P) 45 mg/m² x 6 doses followed by C (AUC 6) and P (200 mg/m²) x 2 cycles (weeks 12-17).

SOURCE: Blumenschein GR et al. *Proc ASCO* 2008; [Abstract 7516](#).

SELECT PUBLICATIONS

Blumenschein GR et al. **A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (PTS) with stage IIIA/B non-small cell lung cancer (NSCLC): A report of the 2 year and median survival (MS) for the RTOG 0324 trial.** *Proc ASCO* 2008; [Abstract 7516](#).

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Hughes S et al. **A brief report on the safety study of induction chemotherapy followed by synchronous radiotherapy and cetuximab in stage III non-small cell lung cancer (NSCLC): SCRATCH study.** *J Thorac Oncol* 2008;3(6):648-51. [Abstract](#)

Timmerman R et al. **Toxicity analysis of RTOG 0236 using stereotactic body radiation therapy to treat medically inoperable early stage lung cancer patients.** *Proc ASTRO* 2007; [Abstract 151](#).

Uematsu M et al. **Long-term results of computed tomography guided hypofractionated stereotactic radiotherapy for Stage I non-small cell lung cancers.** *Proc ASTRO* 2008; [Abstract 79](#).

Xiao Y et al. **Dosimetric evaluation of heterogeneity corrections for RTOG 0236: Hypofractionated radiotherapy of inoperable Stage I/II non-small cell lung cancer.** *Proc ASTRO* 2007; [Abstract 82](#).



INTERVIEW

Renato G Martins, MD, MPH

Dr Martins is Associate Professor and Medical Director of Outpatient Services at Seattle Cancer Care Alliance and Medical Director of the Thoracic/Head and Neck Cancer Program at the University of Washington in Seattle, Washington.

Tracks 1-8

- Track 1** **Case Discussion:** A 58-year-old man who is a former smoker with a Stage II adenocarcinoma treated with adjuvant cisplatin/pemetrexed
- Track 2** Tissue biomarkers as predictors of benefit from adjuvant chemotherapy for NSCLC
- Track 3** Tumor histology as a predictor of benefit from adjuvant chemotherapy for NSCLC
- Track 4** Monitoring patients after completion of adjuvant therapy for NSCLC
- Track 5** Clinical use of neoadjuvant therapy for NSCLC
- Track 6** Role of adjuvant chemotherapy for Stage IB NSCLC
- Track 7** Ongoing adjuvant trials with bevacizumab or erlotinib
- Track 8** Clinical use of adjuvant erlotinib in patients with NSCLC and EGFR mutations

WEB TRACKS

- 1 Case Discussion:** A 64-year-old woman and former smoker with a biopsy-confirmed TTF1-positive adenocarcinoma of the lumbar spine from non-small cell lung cancer (NSCLC)
- 2** Perspective on the FLEX trial results of cisplatin/vinorelbine with or without cetuximab as first-line therapy for patients with advanced NSCLC
- 3** Rationale for cisplatin/pemetrexed with or without bevacizumab as first-line therapy for patients with nonsquamous cell NSCLC
- 4 Case Discussion:** A 66-year-old woman, a nonsmoker, with biopsy-proven hepatic metastases from adenocarcinoma of the lung with EGFR exon 19 deletion who demonstrated a sustained complete response with erlotinib
- 5** Use of erlotinib for patients with NSCLC and suspected EGFR mutations
- 6** Detection of mutations in EGFR in circulating lung cancer cells
- 7** T790M mutation-associated resistance to EGFR inhibition

Select Excerpts from the Interview

Track 2

► **DR LOVE:** Would you discuss what we know about predictors of benefit from adjuvant chemotherapy?

► **DR MARTINS:** The strongest data in patient selection are from IALT, the International Adjuvant Lung Cancer Trial (Olaussen 2006; [4.1]). IALT postulated that patients with high levels of expression of the excision repair cross-

complementing 1 (ERCC1) gene, which is involved in repair of cisplatin-related DNA damage, would be resistant to adjuvant cisplatin chemotherapy. Sure enough, all of the benefit among evaluable patients appeared in those with ERCC1-negative disease. Patients with ERCC1-positive disease were able to repair the damage from cisplatin and, consequently, were less sensitive to the adjuvant chemotherapy (Olaussen 2006; [4.1]).

ERCC1 is an interesting biomarker because patients with ERCC1-positive disease also seem to have a better prognosis. In IALT, although patients with ERCC1-positive disease didn't benefit from adjuvant chemotherapy, their overall outcome was almost identical to those with ERCC1-negative disease who received adjuvant therapy, and both were superior to patients with ERCC1-negative disease who did not receive adjuvant therapy.

► **DR LOVE:** Do you think ERCC1 is ready for prime time?

► **DR MARTINS:** No. I would love to see the IALT data reproduced by other groups before we can embrace it as a definitive biomarker.

4.1

Overall Survival in the International Adjuvant Lung Cancer Trial (IALT) Evaluating Adjuvant Cisplatin-Based Chemotherapy According to ERCC1 Status

Group	All patients	Chemotherapy	Control	Hazard ratio (95% CI)*	p-value
ERCC1-negative				0.65 (0.50-0.86)	0.002
Five-year survival rate	44%	47%	39%		
Median survival	48mo	56mo	42mo		
ERCC1-positive				1.14 (0.84-1.55)	0.40
Five-year survival rate	43%	40%	46%		
Median survival	52mo	50mo	55mo		

* Hazard ratios are for the comparison of the chemotherapy group to the control group.

SOURCE: Olaussen KA et al. *N Engl J Med* 2006;355(10):983-91. [Abstract](#)

Track 3

► **DR LOVE:** How do you decide which adjuvant chemotherapy regimen to use?

► **DR MARTINS:** From an academic standpoint, cisplatin/vinorelbine is the regimen with the greatest amount of support. It was one of the regimens evaluated in the IALT trial (Le Chevalier 2008), and it is in the Canadian-led trial and the ANITA trial (Douillard 2006). Before the histology data with pemetrexed became more solid, our tendency outside of a clinical trial was to use cisplatin/gemcitabine. We still do for patients with squamous cell histology. Now we tend to use cisplatin/pemetrexed for patients with nonsquamous cell histology. We choose an every 21-day regimen such as cisplatin/docetaxel when travel is an issue for the patient. None of these regimens is FDA approved for

use in the adjuvant setting, but I find it difficult to imagine a substantial difference among any of them.

Tracks 7-8

▶ **DR LOVE:** Would you discuss some of the important ongoing adjuvant trials with biologic agents in NSCLC?

▶ **DR MARTINS:** Bevacizumab has been demonstrated to be effective in the metastatic setting (Reck 2009; Sandler 2006), so we want to determine whether it will have a positive effect in the curative setting. Currently, ECOG-E1505 is evaluating adjuvant chemotherapy with or without bevacizumab (1.3, page 7). Another important, ongoing study (RADIANT) is evaluating erlotinib in the adjuvant setting. This trial is open to all patients with NSCLC, irrespective of histology or biologic markers. Patients have to express EGFR via immunohistochemistry, but that represents a large percentage of patients.

▶ **DR LOVE:** In a clinical setting are you comfortable using adjuvant erlotinib for patients with EGFR mutations?

▶ **DR MARTINS:** It's not FDA approved in that setting, but for patients who cannot participate or are uncomfortable participating in a clinical trial, it is a reasonable topic to discuss. Having said that, it is possible for a treatment to make intuitive sense but then result in an adverse effect. I don't believe that applies to the use of EGFR TKIs in patients with EGFR mutation-positive advanced NSCLC, in whom response rates are 60 to 80 percent (Inoue 2009) and even approaching 90 percent (Yang 2008). ■

SELECT PUBLICATIONS

Douillard JY et al. **Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial.** *Lancet Oncol* 2006;7(9):19-27. [Abstract](#)

Inoue A et al. **First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy.** *J Clin Oncol* 2009;27(9):1394-400. [Abstract](#)

Le Chevalier T et al. **Long-term results of the International Adjuvant Lung Cancer Trial (IALT) evaluating adjuvant cisplatin-based chemotherapy in resected non-small cell lung cancer (NSCLC).** *Proc ASCO* 2008;[Abstract 7507](#).

Olaussen KA et al. **DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy.** *N Engl J Med* 2006;355(10):983-91. [Abstract](#)

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

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. [Abstract](#)

Yang CH et al. **Specific EGFR mutations predict treatment outcome of stage IIIB/IV patients with chemotherapy-naïve non-small-cell lung cancer receiving first-line gefitinib monotherapy.** *J Clin Oncol* 2008;26(16):2745-53. [Abstract](#)

QUESTIONS (PLEASE CIRCLE ANSWER):

- In CALGB-140503, the Phase III randomized trial of lobectomy versus sublobar resections in patients with early NSCLC, lesions must be less than or equal to _____ in size.
 - One centimeter
 - Two centimeters
 - Three centimeters
- ECOG-E1505 is evaluating adjuvant _____ with or without bevacizumab for patients with completely resected, Stage IB to IIIA NSCLC.
 - Cisplatin/gemcitabine
 - Cisplatin/vinorelbine
 - Cisplatin/docetaxel
 - All of the above
- In a Phase II study of stereotactic body radiation therapy (SBRT) for inoperable early-stage lung cancer, the local control rate at two years with this modality was _____.
 - 15 percent
 - 45 percent
 - 75 percent
 - 95 percent
- Studies have reported long-term outcome data indicating 10-year survival rates with stereotactic body radiation therapy equivalent to surgical resection.
 - True
 - False
- Results from the Phase II RTOG-0324 study of cetuximab in combination with chemoradiation therapy for patients with Stage IIIA/B NSCLC reported a two-year overall survival rate of approximately _____.
 - 20 percent
 - 35 percent
 - 50 percent
- Results from the Phase II RTOG-0324 study of cetuximab in combination with chemoradiation therapy for patients with Stage IIIA/B NSCLC reported a median survival rate of approximately _____.
 - 12 months
 - 23 months
 - 36 months
- Which of the following is an example of a targeted therapy that takes advantage of the oncogene addiction hypothesis?
 - Imatinib
 - Trastuzumab
 - Lapatinib
 - Both b and c
 - All of the above
- IPASS demonstrated that patients with NSCLC whose tumors had EGFR mutations fared better when treated with _____ than with chemotherapy.
 - Gefitinib
 - Bevacizumab
 - Cetuximab
 - All of the above
- The rash associated with the EGFR inhibitors is a potential pharmacodynamic marker.
 - True
 - False
- In IALT, the benefit of adjuvant cisplatin therapy was observed primarily in patients with _____ disease.
 - ERCC1-negative
 - ERCC1-positive
- Clinical trial data show that adjuvant chemotherapy improves overall survival for patients with Stage IB NSCLC.
 - True
 - False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 2, 2009

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

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

Trial design for CALGB-140503 comparing lobectomy to segmental resection	4	3	2	1
Role of endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) for staging or restaging the mediastinum in NSCLC	4	3	2	1
Results from RTOG-0324 evaluating cetuximab in combination with chemoradiation therapy for Stage IIIA/B NSCLC	4	3	2	1
Data with stereotactic body radiation therapy (SBRT) for NSCLC	4	3	2	1
Oncogene addiction hypothesis	4	3	2	1
Value of tumor histology and biomarkers in making treatment decisions for NSCLC	4	3	2	1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

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

Trial design for CALGB-140503 comparing lobectomy to segmental resection	4	3	2	1
Role of endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) for staging or restaging the mediastinum in NSCLC	4	3	2	1
Results from RTOG-0324 evaluating cetuximab in combination with chemoradiation therapy for Stage IIIA/B NSCLC	4	3	2	1
Data with stereotactic body radiation therapy (SBRT) for NSCLC	4	3	2	1
Oncogene addiction hypothesis	4	3	2	1
Value of tumor histology and biomarkers in making treatment decisions for NSCLC	4	3	2	1

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

Yes No

If no, please explain:

Will this activity help you improve patient care?

Yes No Not applicable

If no, please explain:

Did the activity meet your educational needs and expectations?

Yes No

If no, please explain:

Please respond to the following LEARNER statements by circling the appropriate selection:

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

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

- Identify innovative surgical techniques currently being evaluated for lung cancer, and summarize their effect on operative morbidity and mortality.....4 3 2 1 N/M N/A
- Communicate the risks and benefits of stereotactic body radiation therapy (SBRT) to appropriate patients with non-small cell lung cancer (NSCLC).....4 3 2 1 N/M N/A
- Effectively utilize tumor histology and biomarkers in making evidence-based lung cancer treatment decisions.....4 3 2 1 N/M N/A
- Appraise the clinical application of emerging data on the combined use of biologic agents with chemoradiation therapy for Stage III NSCLC.....4 3 2 1 N/M N/A
- Formulate a risk-adapted algorithm for the individualized use of adjuvant systemic therapy for patients with localized NSCLC.....4 3 2 1 N/M N/A
- Apply the results of recent clinical research to the rational selection of EGFR- or VEGF-inhibiting agents for patients with metastatic NSCLC.....4 3 2 1 N/M N/A
- Describe the oncogene addiction hypothesis in relation to the genesis of cancer and the mechanism of action of biologic agents.....4 3 2 1 N/M N/A
- Counsel appropriately selected patients with lung cancer about the availability of ongoing clinical trials in which they may be eligible to participate.....4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

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.....

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Jeffrey A Engelman, MD, PhD	4	3	2	1	4	3	2	1
Ritsuko Komaki, MD	4	3	2	1	4	3	2	1
Renato G Martins, MD, MPH	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 editor and faculty for this activity:

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Lung Cancer™

U P D A T E

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