LCU | 2013 VOL 10 | ISSUE 1

Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Alice Shaw, MD, PhD
Suresh S Ramalingam, MD
Jennifer S Temel, MD
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EDITOR

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Lung Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Lung cancer is the leading cause of cancer mortality in the United States for both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been limited, and approximately 85% 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 activity is designed to assist medical 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).
- Assess emerging research on the benefits of early palliative care for patients with metastatic NSCLC, and integrate this information, where appropriate, into patient consultations.
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangement and other recently identified driver mutations — and the investigational and approved treatment options for patients with these biomarkers.
- Review emerging research evidence with the use of the irreversible EGFR tyrosine kinase inhibitor afatinib alone or in combination with an EGFR monoclonal antibody for patients with advanced EGFR mutation-positive NSCLC.
- Develop an evidence-based treatment approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced NSCLC.
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

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This activity is supported by educational grants from Astellas, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology, Lilly USA LLC and Novartis Pharmaceuticals Corporation.

Last review date: July 2013; Release date: July 2013; Expiration date: July 2014

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EDITOR

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FACULTY — **Dr Temel** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Shaw** — Advisory Committee and Consulting Agreements: ARIAD Pharmaceuticals Inc, Chugai Pharmaceutical Co Ltd, Novartis Pharmaceuticals Corporation, Pfizer Inc. **Dr Ramalingam** — Advisory Committee: Pfizer Inc; Consulting Agreements: Agennix Inc, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology, Lilly USA LLC, Teva Oncology. **Dr Sandler** — Advisory Committee: Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Genentech BioOncology, GlaxoSmithKline, Lilly USA LLC, Novartis Pharmaceuticals Corporation, OSI Oncology, Pfizer Inc, Roche Laboratories Inc; Consulting Agreements: Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Daiichi Sankyo Inc, Genentech BioOncology, Lilly USA LLC, Pfizer Inc, Roche Laboratories Inc; Legal Consultant: Genentech BioOncology, OSI Oncology, Pfizer Inc; Speakers Bureau: Celgene Corporation, Genentech BioOncology, Lilly USA LLC, Pfizer Inc, Roche Laboratories Inc.

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INTERVIEW

Alice Shaw, MD, PhD

Dr Shaw is Assistant Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What is your practical algorithm for testing for tumor driver mutations in non-small cell lung cancer (NSCLC)?

DR SHAW: In addition to alterations in KRAS, EGFR, ALK and ROS1 genes, a slew of small subsets of lung adenocarcinomas are defined by key oncogenic drivers, against which targeted therapies may be on the horizon. Currently, the NCCN guidelines recommend testing for EGFR and ALK at the time of diagnosis, regardless of smoking history, for patients with nonsquamous NSCLC.

This is important for the appropriate selection of first-line therapy. The NCCN recommendation is for patients with unresectable or advanced NSCLC. Presumably, patients

with resectable disease have undergone curative therapy, either with surgery or definitive radiation therapy. Targeted therapies have no role in that setting.

DR LOVE: What about testing for ROS1 gene rearrangements in terms of treatment decision-making?

DR SHAW: ROS1 is one of the newest targets in NSCLC. Preliminary data indicate that ROS1 represents another good target for crizotinib. Results from the Phase I study of crizotinib for patients with advanced NSCLC harboring ROS1 rearrangements demonstrated a response rate of about 60% (Shaw 2012; [1.1]). The durability of response was as impressive as that in ALK-positive NSCLC. Fewer patients were enrolled because ROS1 rearrangements are rarer than ALK rearrangements. I believe that crizotinib will become a standard therapy for patients with ROS1 rearrangements.

In our institution, we perform up-front testing for the common mutations, EGFR and ALK. If the results are negative, we test for ROS1. Although ROS1 rearrangements are tightly associated with never and light smokers, it is possible for a smoker to have this genetic abnormality. Therefore, regardless of smoking history, if a patient's adenocarcinoma is negative for the more common mutations, we then screen for ROS1 rearrangements.

1.1

Clinical Activity of Crizotinib in Advanced Non-Small Cell Lung Cancer Harboring ROS1 Gene Rearrangements

Best response	n = 14
Overall response rate	57.1%
Complete response	7.1%
Partial response	50%
Stable disease	28.6%
Progressive disease	14.3%

Shaw AT et al. *Proc ASCO* 2012;**Abstract 7508**.

Track 4

DR LOVE: Would you discuss the results of the Phase II SELECT study of adjuvant erlotinib?

DR SHAW: This was a single-arm, multicenter study in which patients with resected EGFR-mutant NSCLC received 2 years of adjuvant erlotinib at the standard dose (Neal 2012; [1.2]).

The expected toxicities of erlotinib were observed, with rash and diarrhea being the most common. The remarkable observation was that the disease-free survival was extremely high at 2 years. This was much higher than expected for such a population of patients with resected tumors. Unfortunately, some patients experienced relapse when erlotinib was discontinued at 2 years. Some of my patients experienced relapse with CNS metastases.

One idea is that patients whose cancer was supposedly completely resected had micrometastatic disease that was kept under control with adjuvant erlotinib. So once treat-

ment was discontinued, the disease progressed. I believe these results are promising. However, a larger, controlled study with longer follow-up is needed to determine the true benefit of adjuvant erlotinib in this setting.

1.2

SELECT: Efficacy and Safety Results of a Multicenter Phase II Trial of Adjuvant Erlotinib in Resected EGFR Mutation-Positive Non-Small Cell Lung Cancer

Efficacy	n = 36	
Two-year disease-free survival	94%	
Adverse events	All grades	Grade 3*
Rash†	89%	17%
Diarrhea†	78%	3%
Fatigue†	61%	6%

* No Grade 4 adverse events reported; † Toxicities leading to dose reductions

Neal JW et al. Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract 16**.

Tracks 7-8

DR LOVE: Would you talk about some of the clinical trial data that have been reported with crizotinib in ALK-positive NSCLC?

DR SHAW: Recently we reported the results of the Phase III PROFILE 1007 trial, which was the first randomized study of second-line crizotinib versus chemotherapy in ALK-positive NSCLC. All patients received first-line platinum-based chemotherapy, and ALK testing was done using the standard diagnostic FISH assay. Patients received either second-line crizotinib or chemotherapy with pemetrexed or docetaxel.

This was a 1-to-1 randomization in which patients who received chemotherapy were allowed to cross over upon disease progression to receive third-line crizotinib on a separate Phase II study. The primary endpoint of PFS was met, demonstrating that crizotinib is statistically superior to standard chemotherapy, with a PFS of 7.7 months versus 3 months with chemotherapy. We also observed a significant improvement in response rates with a 3-fold increase with crizotinib over chemotherapy.

This was not surprising given what was observed in the Phase I and II trials of crizotinib. No difference in overall survival was observed at the time of final PFS analysis (Shaw 2013b). Because many patients were still receiving treatment at the time, the censoring rate was high. We didn't expect any difference in overall survival because most patients crossed over to receive crizotinib.

One of the most important observations was that crizotinib was associated with significant improvements over chemotherapy in terms of disease-related symptoms, functioning and quality of life. This trial supports the full approval of crizotinib in the United States and was necessary for its approval in other countries, including Europe.

DR LOVE: What is known about the activity of crizotinib in the first-line setting?

DR SHAW: Data on the use of first-line crizotinib in NSCLC are limited. A Phase I trial enrolled 24 patients with untreated, advanced ALK-positive NSCLC. These patients achieved similar response rates — about 60%. The median PFS was 18 months.

The Phase III PROFILE 1014 trial of first-line crizotinib versus platinum/pemetrexed is ongoing and open to accrual (NCT01154140). We hope the target enrollment will be met in about 6 months, soon providing definitive data on the efficacy of first-line crizotinib.

Tracks 10-11

DR LOVE: Would you discuss some of the newer agents being investigated for patients with ALK-positive advanced NSCLC who have developed resistance to crizotinib?

DR SHAW: The second-generation ALK inhibitors are the most exciting agents for patients who have experienced relapse while receiving crizotinib. These oral TKIs — including LDK378, AP26113 and AF802 — are more potent and usually more selective than crizotinib, and in Phase I studies they are already showing promising activity in patients with crizotinib resistance.

LDK378 is the furthest along in clinical development (1.3). This agent is 5 to 10 times more potent and more selective than crizotinib. We already have solid efficacy data, with an overall response rate of approximately 60% for patients with crizotinib-refractory or resistant advanced NSCLC (Shaw 2013a). The duration of response — more than 8 months — is also impressive. So LDK378 seems as though it will be a highly effective salvage treatment once crizotinib is no longer effective. ■

1.3

Editor's Note: FDA Grants Breakthrough Therapy Designation for LDK378 for ALK-Positive Metastatic NSCLC with Progression on or Intolerance to Crizotinib

On March 15, 2013 the investigational compound LDK378 received Breakthrough Therapy designation by the Food and Drug Administration for patients with anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer who experienced disease progression during treatment with, or were intolerant to, crizotinib.

Breakthrough Therapy designation is intended to expedite the development and review of drugs that treat serious or life-threatening conditions if the therapy has demonstrated substantial improvement over an available therapy on at least 1 clinically significant endpoint.

SELECT PUBLICATIONS

Bos M et al. **Complete metabolic response in a patient with repeatedly relapsed non-small cell lung cancer harboring ROS1 gene rearrangement after treatment with crizotinib.** *Lung Cancer* 2013;81(1):142-3.

Camidge DR et al. **Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: Updated results from a phase 1 study.** *Lancet Oncol* 2012;13(10):1011-9.

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

Oxnard GR et al. **New targetable oncogenes in non-small-cell lung cancer.** *J Clin Oncol* 2013;31(8):1097-104.

Shaw AT et al. **Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC.** *Proc ASCO* 2013a;**Abstract 8010**.

Shaw AT et al. **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.** *N Engl J Med* 2013b;368(25):2385-94.

Shaw AT, Engelman JA. **ALK in lung cancer: Past, present, and future.** *J Clin Oncol* 2013;31(8):1105-11.

INTERVIEW

Suresh S Ramalingam, MD

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

Tracks 1-11

Track 1 **Case discussion:** A 61-year-old man with metastatic, EGFR-mutant adenocarcinoma of the lung whose disease progresses on erlotinib

Track 2 Activity and tolerability of afatinib/cetuximab in patients with metastatic NSCLC and acquired resistance to EGFR tyrosine kinase inhibitors

Track 3 Mechanism of action and single-agent activity of afatinib as first-line therapy for advanced NSCLC

Track 4 Cisplatin/pemetrexed with continuation of erlotinib in patients with acquired EGFR T790 mutation

Track 5 Results from a Phase II study of the irreversible EGFR inhibitor dacomitinib versus erlotinib in advanced NSCLC

Track 6 **Case discussion:** A 64-year-old woman with KRAS-, EGFR- and ALK-negative metastatic NSCLC

Track 7 Results from the Phase III PointBreak trial of pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC

Track 8 ECOG-E5508: A Phase III study of maintenance bevacizumab, pemetrexed or the combination in advanced NSCLC

Track 9 First-line and maintenance therapy for patients with pan-wild-type adenocarcinoma who are eligible to receive bevacizumab

Track 10 Results of clinical trials combining MET inhibitors — onartuzumab or tivantinib — with erlotinib in advanced NSCLC

Track 11 Ongoing clinical studies of investigational agents in small cell lung cancer

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss the activity and tolerability of afatinib/cetuximab for patients with NSCLC with acquired resistance to EGFR tyrosine kinase inhibitors (TKIs)?

DR RAMALINGAM: About 60% of patients with NSCLC will develop resistance to EGFR TKIs as a result of the T790M mutation. The remaining 40% will acquire resistance by other mechanisms, such as MET amplification. For patients with the T790M mutation, afatinib/cetuximab has shown the most promising results, with a response rate of approximately 30% (Janjigian 2012; [2.1]). Based on Phase Ib trial results, a Phase III study of afatinib/cetuximab for disease that is resistant to EGFR TKIs has been proposed.

DR LOVE: Would you also discuss what is known about up-front afatinib for patients with advanced NSCLC?

2.1

Phase Ib Trial Evaluating the Activity and Safety of Afatinib/Cetuximab for Patients with EGFR-Mutant, Advanced Non-Small Cell Lung Cancer and Acquired Resistance to Erlotinib or Gefitinib

	T790M mutation status		Total*
Best response	**T790M-positive** (n = 53)	**T790M-negative** (n = 39)	(n = 96)
Confirmed PR	32%	28%	30%
CBR	81%	64%	75%

PR = partial response; CBR = clinical benefit rate

* Four patients had NSCLC with EGFR wild type or unknown T790M mutation status.

Janjigian YY et al. *Proc ESMO* 2012;**Abstract 1227O**.

DR RAMALINGAM: In the Phase III LUX-Lung 3 trial, first-line afatinib was superior to cisplatin/pemetrexed in terms of PFS (Yang 2012; [2.2]). For patients with exons 19 and 21 EGFR mutations, the median PFS was about 14 months, which is longer than previously observed with gefitinib or erlotinib (Maemondo 2010; Mok 2009). However, afatinib is associated with a higher incidence of GI toxicities. Although it has not yet been compared head to head to gefitinib or erlotinib, the data with afatinib are suggestive of a greater effect on EGFR-mutated tumors.

2.2

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

Efficacy	**Afatinib** (n = 230)	**Cis/pem** (n = 115)	Hazard ratio	*p*-value
Median PFS: All patients	11.1 mo	6.9 mo	0.58	0.0004
Median PFS: Patients with del(19)/L858R	13.6 mo	6.9 mo	0.47	<0.001
Objective response rate	56.1%	22.6%	—	<0.001
Median duration of response	11.1 mo	5.5 mo	—	—
	Afatinib (n = 229)		**Cis/pem** (n = 111)	
Select adverse events	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Diarrhea	95.2%	14.4%	15.3%	0%
Rash/acne	89.1%	16.2%	6.3%	0%
Paronychia	56.8%	11.4%	0%	0%
Stomatitis/mucositis	72.1%	8.7%	15.3%	0.9%
Dry skin	29.3%	0.4%	1.8%	0%
Nausea	17.9%	0.9%	65.8%	3.6%
Decreased appetite	20.5%	3.1%	53.2%	2.7%
Fatigue	17.5%	1.3%	46.8%	12.6%
Vomiting	17.0%	3.1%	42.3%	2.7%
Neutropenia	0.9%	0.4%	31.5%	18.0%
Anemia	3.1%	0.4%	27.9%	6.3%

PFS = progression-free survival

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

Track 5

DR LOVE: What is known about the novel irreversible EGFR inhibitor dacomitinib in advanced NSCLC?

DR RAMALINGAM: In a Phase II trial comparing dacomitinib to erlotinib for patients with advanced NSCLC and disease progression on 1 to 2 prior regimens, dacomitinib improved PFS (Ramalingam 2012a). Evaluation of tumor specimens from this trial revealed that patients with KRAS wild-type tumors had about a 2-fold increase in PFS with dacomitinib compared to erlotinib. However, dacomitinib induced a higher incidence of diarrhea and skin toxicities.

In a subset of 30 patients with EGFR-mutant NSCLC, dacomitinib improved PFS compared to erlotinib (Ramalingam 2012b). Although this represents a small number of patients, the data suggest that dacomitinib may be associated with favorable outcomes in EGFR-mutant NSCLC. In support of these data, results of a Phase II trial of up-front dacomitinib demonstrated a PFS of approximately 17 months for patients with EGFR-mutant NSCLC (Janne 2012). This is longer than the PFS observed with erlotinib or gefitinib in Phase III trials. We need more head-to-head comparative studies, however.

The Phase III ARCHER 1009 trial evaluating second- or third-line dacomitinib versus erlotinib in advanced NSCLC (NCT01360554) is ongoing. The primary endpoint is PFS in 2 coprimary populations: all enrolled patients and those with KRAS wild-type NSCLC.

Track 9

DR LOVE: What is your usual first-line therapy and your usual maintenance treatment, if any, for younger patients with metastatic adenocarcinoma of the lung?

DR RAMALINGAM: Our standard approach for such patients has been to use the ECOG regimen of carboplatin/paclitaxel/bevacizumab and continue with bevacizumab maintenance. For patients who have some comorbid illnesses or contraindications to bevacizumab, we often administer pemetrexed-based regimens. What is different now that the PointBreak results have been reported is that we are experiencing some resistance from some of our payers regarding carboplatin/pemetrexed/bevacizumab, so that combination may not be as readily available.

With a younger patient for whom our goal is to achieve a response for improvement of symptoms, we feel more strongly about administering either cisplatin/pemetrexed or the carboplatin/paclitaxel/bevacizumab regimen.

Track 10

DR LOVE: Would you discuss the therapeutic approach of targeting MET in NSCLC?

DR RAMALINGAM: The mechanism of resistance to EGFR TKIs includes the activation of the MET pathway. Targeting MET and EGFR to delay resistance is an attractive strategy. A randomized Phase II study of erlotinib with or without onartuzumab, a monoclonal antibody against the MET receptor, reported no significant difference in

survival in the overall population (Spigel 2011; [2.3]). However, survival was significantly higher with onartuzumab/erlotinib for patients with tumors expressing MET.

A Phase III trial of erlotinib with or without onartuzumab for patients with MET diagnostic-positive NSCLC who have received standard chemotherapy for advanced disease (NCT01456325) is ongoing. Unlike onartuzumab, tivantinib is a MET TKI, which demonstrated favorable outcomes when combined with erlotinib and compared to erlotinib alone in a Phase II trial (Sequist 2011). This study also reported a trend toward PFS and overall survival benefit for patients with nonsquamous cell histology.

The follow-up Phase III study of erlotinib with or without tivantinib for previously treated advanced nonsquamous NSCLC did not select for patients with MET expression (NCT01244191). (Editor's note: This Phase III trial was halted after an interim analysis concluded it would not meet its primary endpoint of improved overall survival.) We await the data to determine if exploratory/post hoc analysis will show a benefit with tivantinib/erlotinib for patients with high MET expression. ■

2.3

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

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

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

SELECT PUBLICATIONS

Janne PA et al. **Dacomitinib (PF-00299804), an irreversible pan-HER tyrosine kinase inhibitor (TKI), for first-line treatment of EGFR-mutant or HER2-mutant or -amplified lung cancers.** *Proc ESMO* 2012;**Abstract 1228**.

Maemondo M et al. **Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR.** *N Engl J Med* 2010;362(25):2380-8.

Mok TS et al. **Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer.** *J Clin Oncol* 2009;27(30):5080-7.

Ramalingam SS et al. **Randomized Phase II study of dacomitinib (PF-00299804), an irreversible pan–human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non–small-cell lung cancer.** *J Clin Oncol* 2012a;30(27):3337-44.

Ramalingam SS et al. **Dacomitinib (D) versus erlotinib (E) in patients (pt) with EGFR-mutated (mu) advanced non-small cell lung cancer (NSCLC): Analyses from a randomized, Phase 2 Trial.** Multidisciplinary Symposium in Thoracic Oncology 2012b;**Abstract 2**.

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.

INTERVIEW

Jennifer S Temel, MD

Dr Temel is Associate Professor of Medicine at Harvard Medical School and Clinical Director of Thoracic Oncology at Massachusetts General Hospital in Boston, Massachusetts.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-2, 4, 11

DR LOVE: Would you comment on the paper you published on early palliative care for patients with metastatic NSCLC (Temel 2010)?

DR TEMEL: This study started from my clinical observation that the traditional model of an oncologist taking care of a patient with advanced disease was not sufficient. An oncologist does a great job of managing cancer, but patients and their families go through so much more when facing a cancer diagnosis. Palliative care was a growing specialty when we started this research 10 years ago, so we hypothesized that palliative care could play a complementary role in caring for patients receiving standard oncology treatment.

We randomly assigned approximately 150 patients with newly diagnosed metastatic NSCLC to standard care or the same approach integrated with early palliative care. Patients assigned to the palliative care arm met with a palliative care physician or nurse practitioner at least monthly during their clinical course. The palliative care clinicians evaluated the patient and focused on the issues that were most salient for the patient and family at that time.

3.1

Phase III Study Investigating Early Palliative Care in Metastatic Non-Small Cell Lung Cancer

	Standard care alone	Early palliative care with standard care	*p*-value
Quality of life* (n = 47, 60)	91.5	98.0	0.03
Depressive symptoms (n = 47, 57)	38%	16%	0.01
Aggressive end-of-life care (n = 56, 49)	54%	33%	0.05
Median overall survival (n = 74, 77)	8.9 mo	11.6 mo	0.02

* Assessed by the Functional Assessment of Cancer Therapy — Lung scale (scores range from 0 to 136; higher scores indicate better quality of life)

CONCLUSIONS: "Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival."

Temel JS et al. *N Engl J Med* 2010;363(8):733–42.

The results indicated that patients on the palliative care arm experienced improvement in their quality of life, had lower rates of depression and were more likely to assess their illness and prognosis accurately. With such a small population, the study was not powered for survival, but a median increase in survival of more than 2 months was observed in the palliative care arm (Temel 2010; [3.1]; Kelley 2010; [3.2]) Previous studies also suggest that palliative care can affect survival (Bakitas 2009).

DR LOVE: What role does the palliative care clinician play?

DR TEMEL: The biggest role that the palliative care clinician plays is helping patients and families cope with a life-threatening illness (Irwin 2013; [3.3]). It is incredibly challenging for patients to find the right balance between planning for the future and living each day to the fullest.

Patients need to know about the effects of chemotherapy on life expectancy and quality of life. Palliative care clinicians are more comfortable and experienced in giving patients the information they need and helping them make decisions about their care.

DR LOVE: How do you approach end-of-life care decisions for patients with metastatic NSCLC?

3.2

Editorial: Palliative Care — A Shifting Paradigm

"The study by Temel et al represents an important step in confirming the beneficial outcomes of a simultaneous care model that provides both palliative care and disease-specific therapies beginning at the time of diagnosis. This study is an example of research that shifts a long-held paradigm that has limited access to palliative care to patients who were predictably and clearly dying. The new approach recognizes that life-threatening illness, whether it can be cured or controlled, carries with it significant burdens of suffering for patients and their families and that this suffering can be effectively addressed by modern palliative care teams. Perhaps unsurprisingly, reducing patients' misery may help them live longer. We now have both the means and the knowledge to make palliative care an essential and routine component of evidence-based, high-quality care for the management of serious illness."

Kelley AS, Meier DE. *N Engl J Med* 2010;363(8):781–2.

DR TEMEL: Unfortunately, most conversations about end-of-life care happen when patients are in the hospital. Oncologists should initiate conversations about end-of-life care preferences earlier in the ambulatory care setting and make sure that these preferences are documented and accessible.

These are difficult conversations to have. I believe the appropriate way to handle end-of-life care discussions is to ask patients about their resuscitation preferences. I explain to them that if a life-threatening event occurs, the chance of them having a good quality of life would be small, so I do not recommend heroic measures, and that usually develops into a conversation about the appropriate timing for initiation of hospice care.

DR LOVE: How do you deal with the grief associated with treating patients who are terminally ill?

DR TEMEL: One of the best things about being an oncologist is that you develop incredibly close relationships with patients. My approach to dealing with grief might be a little different from others, but I'm comfortable with showing some emotion.

The thoracic oncology group at Massachusetts General Hospital conducts a yearly memorial service for the families of the patients who have passed away within the previous year. This helps the caregivers, and I believe it is important for us to have that time and space to think about all the patients who have passed away and about the families that we miss. ■

3.3

Early Palliative Care (EPC) and Metastatic Non-Small Cell Lung Cancer: Potential Mechanisms of Prolonged Survival

- As a result of EPC, patients may experience improved quality of life and mood, develop a more realistic understanding of their disease and goals of therapy, and enhance adaptive coping behaviors, all of which in turn can influence treatment adherence and end-of-life decisions.
- The authors hypothesize that EPC has the potential to have an impact on overall survival by directly affecting the patient's well-being and experience of suffering, increasing social support, improving understanding of the illness and informing decision-making, which subsequently contribute to less aggressive care at the end of life and earlier referral to hospice.

Irwin K et al. *Chronic Respir Dis* 2013;10(1):35-47.

SELECT PUBLICATIONS

Bakitas M et al. **Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: The Project ENABLE II randomized controlled trial.** *JAMA* 2009;302(7):741-9.

Irwin K et al. **Early palliative care and metastatic non-small cell lung cancer: Potential mechanisms of prolonged survival.** *Chronic Respir Dis* 2013;10(1):35-47.

Kamal AH et al. **Integrating technology into palliative care research.** *Curr Opin Support Palliat Care* 2012;6(4):525-32.

Kelley AS, Meier DE. **Palliative care — A shifting paradigm.** *N Engl J Med* 2010;363(8):781-2.

Neal JW et al. **The SELECT study: A multicenter phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract 7010**.

Pirl WF et al. **Depression and survival in metastatic non-small-cell lung cancer: Effects of early palliative care.** *J Clin Oncol* 2012;30(12):1310-5.

Temel JS et al. **Early palliative care for patients with metastatic non-small-cell lung cancer.** *N Engl J Med* 2010;363(8):733-42.

INTERVIEW

Alan B Sandler, MD

Dr Sandler is Professor of Medicine in the Division of Hematology and Medical Oncology at Oregon Health and Science University in Portland, Oregon.

Tracks 1-11

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: The Phase III ECOG-E4599 study previously demonstrated a significant survival advantage with the addition of bevacizumab to carboplatin/paclitaxel versus chemotherapy alone for patients with untreated advanced NSCLC (Sandler 2006). Would you talk about your recent paper on the clinical outcomes with maintenance bevacizumab for patients on that study (Lopez-Chavez 2012)?

DR SANDLER: After the ECOG-E4599 study, a question arose about the contribution of the induction regimen versus maintenance bevacizumab to the survival advantage. This was a retrospective analysis to address the role of maintenance bevacizumab in the ECOG-E4599 study.

A landmark analysis was conducted for patients in both groups who were progression free after completing 6 cycles of induction therapy. The survival of patients who received bevacizumab maintenance after induction with carboplatin/paclitaxel/

bevacizumab was compared to that of those patients who received induction with carboplatin/paclitaxel alone. The results indicated that patients who received bevacizumab maintenance had significantly better progression-free and overall survival (Lopez-Chavez 2012; [4.1]).

4.1

Bevacizumab (Bev) Maintenance Therapy for Patients with Advanced Non-Small Cell Lung Cancer in the ECOG-E4599 Study: Results of an Exploratory Analysis

Survival	CP + bev induction followed by bev maintenance (n = 217)	CP induction + no maintenance (n = 134)
Progression-free survival	4.4 mo	2.8 mo
	HR = 0.64, $p < 0.001$	
Overall survival	12.8 mo	11.4 mo
	HR = 0.75, $p = 0.03$	

C = carboplatin; P = paclitaxel; HR = hazard ratio

Lopez-Chavez A et al. *J Thorac Oncol* 2012;7(11):1707.

4.2

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

All patients	Pem/Cb/B (n = 472)	Pac/Cb/B (n = 467)	HR	*p*-value
Median PFS	6.0 mo	5.6 mo	0.83	0.012
Median OS	12.6 mo	13.4 mo	1.00	0.949
Overall response rate	34.1%	33.0%	NR	NR
Maintenance phase	(n = 292)	(n = 298)		
Median PFS	8.6 mo	6.9 mo	NR	NR
Median OS	17.7 mo	15.7 mo	NR	NR
	Pem/Cb/B (n = 442)		**Pac/Cb/B** (n = 443)	
Adverse events	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Anemia*	31.0%	14.5%	24.4%	2.7%
Thrombocytopenia*	17.9%	23.3%	17.2%	5.6%
Neutropenia*	14.7%	25.8%	8.4%	40.6%
Hemorrhage – GI/pulmonary†	3.6%	1.8%	3.8%	0.5%
Thromboembolic event	0.5%	3.2%	0.2%	2.0%
Neuropathy/sensory*	11.8%	0%	35.7%	4.1%
Alopecia‡	6.6%	—	36.8%	—

HR = hazard ratio; PFS = progression-free survival; OS = overall survival; NR = not reported
* Significant difference between arms for Grade 3 and 4 toxicities
† Grade 5 events: Pac/Cb/B = 0.7%; Pem/Cb/B = 0.5%
‡ Maximum grade is Grade 2

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

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

DR LOVE: Would you also discuss the results from the PointBreak trial for patients with advanced NSCLC?

DR SANDLER: The PointBreak study evaluated pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen of paclitaxel, carboplatin and bevacizumab followed by bevacizumab maintenance (Patel 2012; [4.2]). The study reported no difference between the 2 arms with respect to overall survival, the primary endpoint.

The toxicities between the 2 arms were different, and overall both regimens were well tolerated. The taxane arm had a higher incidence of neurologic toxicity and alopecia, whereas the pemetrexed group experienced more hematologic toxicity.

The taxane regimen uses fewer drugs and is less expensive, so one could argue that it is superior. However, the pemetrexed regimen has a role for patients who don't want a taxane because of the side effects, such as hair loss and neuropathy.

Of course, in the maintenance phase you do have 2 agents versus 1, the latter of which is obviously less expensive. Both were well tolerated. These are both still reasonable options. And I don't necessarily look at the cost as much as my role as a physician to administer the best therapy for the patient.

Track 5

DR LOVE: You recently published a review of the incidence of CNS bleeding with anti-VEGF therapy in patients with NSCLC and brain metastases (Sandler 2012; [4.3]). What are your thoughts on the use of bevacizumab for patients with brain metastases?

DR SANDLER: Patients with brain metastases were previously considered ineligible for bevacizumab because of the concern about cerebral and pulmonary hemorrhage. Subsequently, studies have clearly shown that patients with treated brain metastases are eligible for treatment with bevacizumab (4.3). However, we have less evidence to support its use for patients with untreated brain metastases.

DR LOVE: Do you delay starting bevacizumab for patients who are receiving radiation therapy?

4.3

An Evidence-Based Review of the Incidence of CNS Bleeding with Anti-VEGF Therapy in Patients with Non-Small Cell Lung Cancer and Brain Metastases

- Recently, the prospective, randomized Phase III ATLAS trial, the open-label Phase II PASSPORT trial, the single-arm Phase IV SAiL study and the observational cohort study ARIES in NSCLC have provided data on the incidence of CNS hemorrhage in large patient populations, reflective of community practice.
- This literature review of patients with NSCLC and brain metastases receiving anti-VEGF therapy **showed no significantly increased risk of CNS hemorrhage for patients** with emerging (previously untreated) or pretreated CNS metastases.
- Clinical trial data indicate that anti-VEGF therapy can be considered for patients with NSCLC with emerging or pretreated CNS metastases.

Sandler A et al. *Lung Cancer* 2012;78(1):1-7.

DR SANDLER: For patients with an isolated lesion who are receiving stereotactic radiation therapy and have not had any problems with bleeding, I would start bevacizumab relatively soon after the radiation therapy. With patients who have multiple lesions or if there is a concern that would require a follow-up scan, I would consider waiting until the second cycle of chemotherapy before adding bevacizumab.

Tracks 7-8

DR LOVE: Nanoparticle albumin-bound (*nab*) paclitaxel was recently approved in combination with carboplatin for the first-line treatment of locally advanced or metastatic NSCLC in patients who are not eligible for curative surgery or radiation therapy. What is your take on the role of this agent in lung cancer?

DR SANDLER: *Nab* paclitaxel is a reformulation of paclitaxel without the Cremophor® vehicle. With *nab* paclitaxel, hypersensitivity reactions are less of a concern. Additionally, it does not have to be administered with steroids and is thought to penetrate the tumor better.

Higher response rates were achieved with *nab* paclitaxel versus solvent-based paclitaxel, particularly for patients with squamous cell histology. No difference was observed in terms of progression-free and overall survival (Socinski 2012, 2013; [4.4]).

For elderly patients, those with diabetes who want to avoid steroids or those who may not be eligible for pemetrexed based on poor renal function, *nab* paclitaxel has a role. It would also be a consideration for patients with squamous cell carcinoma. ■

4.4

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

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

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

SELECT PUBLICATIONS

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.

Socinski MA et al. **Safety and efficacy of weekly *nab*®-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer.** *Ann Oncol* 2013;24(2):314-21.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase II SELECT trial of adjuvant erlotinib therapy for patients with resected EGFR mutation-positive NSCLC demonstrated a disease-free survival of 94% at 2 years.**
   a. True
   b. False

2. **Which of the following adverse events led to dose reductions of erlotinib on the Phase II SELECT trial?**
   a. Rash
   b. Diarrhea
   c. Fatigue
   d. All of the above

3. **The results of the Phase III PROFILE 1007 trial for patients with advanced ALK-positive NSCLC demonstrated a statistically significant improvement in _____ with crizotinib versus standard chemotherapy with pemetrexed or docetaxel as second-line therapy.**
   a. PFS
   b. Overall survival
   c. Objective response rate
   d. Both a and c
   e. All of the above

4. **The results of a Phase Ib trial of afatinib and cetuximab for patients with EGFR mutation-positive, advanced NSCLC and acquired resistance to EGFR inhibitors demonstrated similar partial response rates between patients with and without the EGFR T790M mutation.**
   a. True
   b. False

5. **The Phase III LUX-Lung 3 trial evaluating afatinib versus cisplatin/pemetrexed as first-line therapy for patients with advanced EGFR-mutant NSCLC reported improvements in which of the following for patients who received afatinib?**
   a. Median PFS
   b. Median duration of response
   c. Objective response rate
   d. Both a and c
   e. All of the above

6. **In the Phase II OAM4558g trial of erlotinib with or without onartuzumab as second- or third-line therapy for patients with advanced NSCLC, the combination of onartuzumab with erlotinib significantly improved _____ versus erlotinib alone in the subpopulation of patients with high MET expression.**
   a. PFS
   b. Overall survival
   c. Both a and b
   d. Neither a nor b

7. **A Phase III study investigating early palliative care in combination with standard oncology treatment for patients with metastatic NSCLC demonstrated that palliative care improved _____ over standard care alone.**
   a. Quality of life
   b. Symptoms of depression
   c. Median overall survival
   d. All of the above

8. **A Phase III trial of *nab* paclitaxel/carboplatin versus paclitaxel/carboplatin as first-line therapy for patients with advanced NSCLC demonstrated a significantly higher overall response rate with *nab* paclitaxel for patients with squamous cell histology.**
   a. True
   b. False

9. **An exploratory analysis of patients in the ECOG-E4599 study demonstrated a significant advantage in _____ with induction chemotherapy followed by bevacizumab maintenance compared to chemotherapy alone.**
   a. PFS
   b. Overall survival
   c. Both a and b

10. **The Phase III PointBreak study reported a significant improvement in overall survival with pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab in comparison to the ECOG-E4599 regimen for patients with advanced NSCLC.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 1, 2013

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PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

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

	BEFORE	AFTER
PROFILE 1007: Results from a Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy as second-line therapy for advanced ALK-positive NSCLC	4 3 2 1	4 3 2 1
Activity and tolerability of afatinib/cetuximab for patients with NSCLC and acquired resistance to EGFR TKIs	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
Benefits of early palliative therapy for patients with advanced NSCLC	4 3 2 1	4 3 2 1
Results of an exploratory analysis of ECOG-E4599 evaluating bevacizumab maintenance in advanced NSCLC	4 3 2 1	4 3 2 1

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

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If no, please explain: .....

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☐ 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

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

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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
- Assess emerging research on the benefits of early palliative care for patients with metastatic NSCLC, and integrate this information, where appropriate, into patient consultations. . . . . 4 3 2 1 N/M N/A
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangement and other recently identified driver mutations — and the investigational and approved treatment options for patients with these biomarkers. . . . . 4 3 2 1 N/M N/A
- Review emerging research evidence with the use of the irreversible EGFR tyrosine kinase inhibitor afatinib alone or in combination with an EGFR monoclonal antibody for patients with advanced EGFR mutation-positive NSCLC. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based treatment approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced NSCLC. . . . . 4 3 2 1 N/M N/A
- 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

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

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Suresh S Ramalingam, MD	4 3 2 1	4 3 2 1
Jennifer S Temel, MD	4 3 2 1	4 3 2 1
Alan B Sandler, 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:

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This activity is supported by educational grants from
Astellas, Boehringer Ingelheim Pharmaceuticals Inc,
Celgene Corporation, Genentech BioOncology, Lilly USA LLC
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Last review date: July 2013
Release date: July 2013
Expiration date: July 2014
Estimated time to complete: 3 hours

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