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Lung Cancer™ UPDATE

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

FACULTY INTERVIEWS

Thomas J Lynch Jr, MD
Billy W Loo Jr, MD, PhD, DABR
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EDITOR

Neil Love, MD

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2 Audio CDs
Monograph

CME Certified

Lung Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

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

LEARNING OBJECTIVES

- Critically appraise the efficacy and safety of stereotactic ablative radiation therapy for the local treatment of early-stage NSCLC.
- Apply the results of existing and emerging clinical research to the multimodality treatment of Stage III NSCLC.
- Formulate a rational approach to identifying molecular determinates from tumor specimens that may be used to refine lung cancer prognosis and/or predict therapeutic response to an individual treatment.
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced NSCLC.
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangements and other recently identified driver mutations — and the approved and investigational treatment options for patients with these mutations.
- Review emerging research evidence with the use of the irreversible EGFR tyrosine kinase inhibitor afatinib alone or in combination with an EGFR monoclonal antibody for patients with advanced EGFR mutation-positive NSCLC.
- Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

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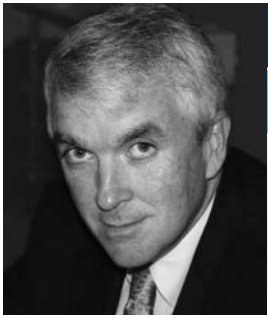

INTERVIEW

Thomas J Lynch Jr, MD

Dr Lynch is Director at Yale Cancer Center, Physician-in-Chief at Smilow Cancer Hospital at Yale-New Haven and Richard and Jonathan Sackler Professor of Internal Medicine at New Haven, Connecticut.

Tracks 1-10

Select Excerpts from the Interview

Tracks 1, 10

DR LOVE: What is the current status of research on EGFR and non-small cell lung cancer (NSCLC)?

DR LYNCH: At the large cancer centers, tests using 409-gene panels and whole exome sequencing are used. The questions are, what is evidence based, and what should be done in the community? In the community, I believe all patients with nonsquamous lung cancer should undergo specific testing for EGFR, ALK, ROS, RAF and HER2 expression, and gene panel testing should be performed at diagnosis. For patients with squamous cell NSCLC, it is more difficult to be dogmatic because we don't have specific agents in this setting that would drive treatment decision-making.

DR LOVE: Would you discuss the importance of the presence or absence of EGFR mutations in NSCLC?

DR LYNCH: It is important to know if the disease harbors the exon 19 deletion mutation or exon 21 point mutation. These 2 mutations are the most predictive of benefit from TKIs. Tumors with exon 19 deletions probably respond better, with a longer survival on TKIs. With more testing and sequencing studies, the frequency

of finding T790M increases. A concurrent T790M mutation at diagnosis is crucial because it is a negative prognostic factor that predicts worse outcome.

For patients with disease harboring exon 20 mutations, TKIs show no great evidence of benefit, and that may not be the correct initial treatment even though many anecdotal stories exist of benefit from erlotinib or gefitinib. It is important to review the specific eligibility criteria of the mutation type for trial entry when analyzing outcomes with afatinib, erlotinib or gefitinib. Not all mutations are activating, and not all activating mutations are likely to respond to TKIs.

Tracks 2-3

DR LOVE: How do you think the recently FDA-approved TKI afatinib will be integrated into clinical practice (Sequist 2013)?

DR LYNCH: Afatinib offers great promise in multiple ways. It's an irreversible EGFR inhibitor. In addition, it has activity against HER2. Afatinib offers a degree of benefit similar to that of erlotinib or gefitinib in patients with up-front EGFR mutations, so it's another first-line option. I'm most excited about its combination with cetuximab in TKI-resistant disease. Terrific evidence suggests that cetuximab/afatinib can produce responses in patients with acquired resistance (Janjigian 2012; [1.1]). This will lead to several trials evaluating whether that response improves survival or if it's reasonable to treat with up-front afatinib/cetuximab.

1.1

Initial Efficacy and Safety Results from a Phase Ib Trial of Afatinib/Cetuximab for Patients with EGFR-Mutant Non-Small Cell Lung Cancer and Acquired Resistance to Erlotinib or Gefitinib

	T790M mutation status		
Clinical outcome	**T790M+** (n = 53)	**T790M-** (n = 39)	**Total** (n = 96)
Confirmed PR	32%	28%	30%
Median DoR	6.4 mo	9 mo	8 mo
Stable disease	49%	36%	45%
Clinical benefit rate	81%	64%	75%
Progressive disease	13%	21%	16%
Not evaluable	6%	15%	9%
Median PFS	NR	NR	4.7 mo
Adverse events (n = 100)	**All grades**	**Grade 1 or 2**	**Grade ≥3**
Rash	97%	79%	18%
Diarrhea	71%	64%	7%
Fatigue	61%	52%	9%
Nausea	53%	50%	3%
Xerosis	52%	49%	3%
Stomatitis	51%	50%	1%
Nail effect	48%	48%	0%

PR = partial response; DoR = duration of response; PFS = progression-free survival; NR = not reported

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

DR LOVE: How would you compare the toxicity profile of afatinib alone or in combination with cetuximab to erlotinib or gefitinib?

DR LYNCH: As a single agent, afatinib causes diarrhea and rash, similar to erlotinib or gefitinib. Slightly more rash or diarrhea may occur with afatinib, although that's not been proven.

In comparison to single-agent afatinib, erlotinib or gefitinib, afatinib/cetuximab is associated with more GI toxicities, diarrhea, rash, paronychia and skin lesions on fingernails and toenails. So the use of afatinib/cetuximab may be a trade-off of toxicity versus improved efficacy.

Track 7

DR LOVE: What is your view on the use of immune checkpoint inhibitors in NSCLC?

DR LYNCH: We have evidence of terrific single-agent activity with anti-PD-1 and anti-PD-L1 antibodies. The major questions are, how do you determine who will respond, what are the biomarkers to predict response, is PD-1 expression the most important predictor of outcome and is anti-PD-L1 antibody as good as anti-PD-1 antibody? At this point we don't know the answers to these questions. It's also too early to know if one has more specificity or toxicity than the other.

I'm excited about combination immunotherapy with ipilimumab and an anti-PD-1 antibody. That's in development and was reported to have activity with an acceptable toxicity profile in melanoma (Wolchok 2013). These agents have the potential to be game changers in early-stage and metastatic disease.

DR LOVE: What is your clinical experience with anti-PD-1 or anti-PD-L1 monotherapy?

DR LYNCH: The single-agent benefits with both agents are remarkable. The side-effect profile is dramatically less than what we see with chemotherapy or TKIs. The prolongation of benefit appears to be longer. ■

SELECT PUBLICATIONS

Lynch TJ et al. **Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study.** *J Clin Oncol* 2012;30(17):2046-54.

Ramalingam SS et al. **Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: Analysis of Eastern Cooperative Oncology Group Trial 4599.** *J Clin Oncol* 2008;26(1):60-5.

Reck M et al. **Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase 2 trial.** *Ann Oncol* 2013;24(1):75-83.

Sequist LV et al. **Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.** *J Clin Oncol* 2013;31(27):3327-34.

Wolchok JD et al. **Safety and clinical activity of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients (pts) with advanced melanoma (MEL).** *Proc ASCO* 2013;**Abstract 9012**.

Wozniak AJ et al. **Clinical outcomes (CO) for special populations of patients (pts) with advanced non-small cell lung cancer (NSCLC): Results from ARIES, a bevacizumab (BV) observational cohort study (OCS).** *Proc ASCO* 2010;**Abstract 7618**.

INTERVIEW

Billy W Loo Jr, MD, PhD, DABR

Dr Loo is Assistant Professor, Thoracic Radiation Oncology Program Leader and New Technologies Committee Co-Chair in the Department of Radiation Oncology at Stanford University and Cancer Institute in Stanford, California.

Tracks 1-12

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Would you discuss the use of stereotactic ablative radiotherapy (SABR) for patients with Stage I NSCLC?

DR LOO: The advent of SABR has changed standard treatment for patients with inoperable tumors. This technology makes it possible to sharply focus the radiation field precisely on the tumor by using several beams at different angles. An intensive course of radiation therapy can be administered safely with minimum exposure to the surrounding organs. A course of radiation therapy (RT) can be compressed into a small number of treatments or even a single treatment with a higher biologically effective dose.

Higher rates of primary tumor control can be achieved than with conventional radiation therapy. Phase II studies have demonstrated primary tumor control rates of 85% to 90%. The landmark Phase II RTOG-0236 study, which evaluated SABR for patients with inoperable early-stage lung cancer, reported the highest primary tumor control rate at 3 years — approximately 98% (Timmerman 2010).

DR LOVE: What are the main complications associated with SABR?

DR LOO: The most common problems that we observe in patients with peripheral tumors are mild chest wall pain or rib fractures, which may or may not be symptomatic. Inflammatory changes surrounding the area of the target may be observed on follow-up CT or PET scans. This generally manifests a few months after treatment and is not of clinical consequence but may persist for a while before resolving. It is often interpreted as tumor recurrence, even though it is not. This is something to be aware of to avoid invasive biopsies.

DR LOVE: How do you determine the dose of SABR?

DR LOO: One of the factors predictive of tumor control is the dose intensity expressed in terms of a biologically effective dose, which could be achieved in a single fraction or multiple fractions. Many nuances exist in terms of how you calculate a biologically effective dose, but it is possible to compare different dosing regimens in the conversion to a biologically effective dose.

At Stanford we're performing a Phase II study of what we refer to as individualized stereotactic ablative radiation therapy, where we adapt the dose and the number of fractions to both the volume of the tumor and the location (NCT00551369). The idea is to optimize the balance between tumor ablation and normal tissue complications.

Tracks 7-8

DR LOVE: Would you discuss the Phase III RTOG study reported at ASCO 2013 comparing high-dose to standard-dose RT with chemotherapy for patients with Stage IIIA/B NSCLC (Bradley 2013a)?

DR LOO: RTOG-0617 was a randomized trial evaluating conformal RT with the standard dose of 60 Gy versus 74 Gy in combination with concurrent and consolidation chemotherapy. The results demonstrated that survival was worse for the 74-Gy arm than for the 60-Gy arm (Bradley 2013a; [2.1]). Patients on the 60-Gy arm had outcomes that were comparable to or better than those observed in any other cooperative group trial. This suggests that modern RT with excellent quality assurance may account for the good results with the standard dose of 60 Gy. It's difficult to understand why higher doses of RT do not result in better outcomes, including local control. Follow-up studies are ongoing based on the suggestion that a higher dose to the heart may correlate with worse outcome in the high-dose arm.

A secondary randomization to the addition of cetuximab or not occurred, but those results were not reported. It will be interesting to know if the combination of cetuximab with chemoradiation therapy results in higher toxicity. Anecdotally, from my own experience, there seems to be a higher rate of esophagitis, mucositis and dermatitis with cetuximab. (Editors note: Subsequent to this interview results from this secondary randomization were presented at the 15th World Conference on Lung Cancer. The authors reported no survival benefit and increased toxicity with the addition of cetuximab to chemoradiation therapy for patients with Stage III NSCLC [Bradley 2013b].)

Track 11

DR LOVE: Would you discuss the use of 4-dimensional computed tomography (4D CT) for radiation treatment planning?

2.1

RTOG-0617: A Phase III Trial Evaluating Standard-Dose (60 Gy) versus High-Dose (74 Gy) Conformal Chemoradiation Therapy for Stage III Non-Small Cell Lung Cancer

Efficacy	**Standard dose**	**High dose**	Hazard ratio	*p*-value
Median overall survival (n = 213, 206)	28.7 mo	19.5 mo	1.56	0.0007
18-mo PFS rate (n = 213, 205)	36.6%	26.3%	1.3	0.0116
18-mo local failure rate (n = 213, 206)	25.1%	34.3%	1.37	0.0319
Select adverse events				
60 Gy (n = 213)	Grade 2	Grade 3	Grade 4	Grade 5
Worst nonhematologic	NR	46%	9.9%	0.9%
Worst overall	NR	46.5%	26.8%	0.9%
Esophagitis/dysphagia	93%	7%	NR	NR
74 Gy (n = 206)	Grade 2	Grade 3	Grade 4	Grade 5
Worst nonhematologic	NR	46.1%	11.2%	4.9%
Worst overall	NR	41.7%	31.6%	4.9%
Esophagitis/dysphagia	79.1%	20.9%	NR	NR

PFS = progression-free survival; NR = not recorded

Bradley JD et al. *Proc ASCO* 2013a;**Abstract 7501**.

DR LOO: 4D CT scanning represents the next step after 3D scanning, which was the last revolution in RT, going from having full spatial information to now having full spatial information and time. Body motion, particularly respiratory motion, makes it difficult to accurately target the tumor.

The 4D scan is essentially a CT movie that we can acquire during treatment planning. We can characterize the motion of tumors as the patient breathes and then develop motion compensation or motion management strategies. The radiation field can be individually adjusted to cover the range of motion of the tumor, if it's limited. If the motion is large, we can employ a technique called respiratory gating, by which we turn on the beam only for a certain portion of the breathing cycle to avoid radiation to normal lung tissue. The key is to make sure that's being done accurately at the time of radiation delivery.

Biofeedback techniques can be used with 4D CT scanning. We can show patients their breathing pattern so that they can hit certain breathing targets, either as a breath hold or a kind of voluntary free breathing, and turn on the beam only at the appropriate time. ■

SELECT PUBLICATIONS

Bradley J et al. **An Intergroup randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) chemoradiotherapy (CRT) +/- cetuximab (CETUX) for stage III non-small cell lung cancer (NSCLC): Results on CETUX from RTOG 0617.** *Proc WCLC* 2013b;**Abstract PL03.05**.

Shirvani SM et al. **Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly.** *Int J Radiat Oncol Biol Phys* 2012;84(5):1060-70.

Timmerman R et al. **Stereotactic body radiation therapy for inoperable early stage lung cancer.** *JAMA* 2010;303(11):1070-6.

INTERVIEW

Nathan A Pennell, MD, PhD

Dr Pennell is Assistant Professor of Solid Tumor Oncology at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and Director of the Cleveland Clinic Lung Cancer Medical Oncology Program in Cleveland, Ohio.

Tracks 1-14

Select Excerpts from the Interview

Track 9

DR LOVE: What are your thoughts on the recent data presented on the novel ALK inhibitor LDK378 in advanced, ALK-positive NSCLC (Shaw 2013; [3.1])?

DR PENNELL: In this trial, LDK378 was administered to patients with crizotinib-naïve disease and to patients who had experienced disease progression while receiving crizotinib. The response rate was the same in both groups, approximately 60%. The progression-free survival (PFS) was also the same in both groups, and that raises the question of sequencing. Should we be administering crizotinib first line and upon

3.1

Phase I Trial of the ALK Inhibitor LDK378 at 400 mg to 750 mg Daily in Advanced, ALK-Positive Non-Small Cell Lung Cancer

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

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

Conclusion: LDK378 induces durable responses in the majority of patients with advanced, ALK-positive non-small cell lung cancer, including patients with crizotinib-resistant disease with and without crizotinib resistance mutations. These results suggest that more potent ALK inhibition by LDK378 represents a highly efficacious therapeutic strategy for patients with ALK-positive disease, particularly those who experience relapse on crizotinib.

CRZ = crizotinib; * 1 response unknown; † 4 responses unknown; ‡ Median PFS at 750 mg/d not reached

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

disease progression switch to LDK378 to see a potentially longer PFS? We need a head-to-head first-line trial to compare the 2 agents.

Track 11

DR LOVE: Your group presented a poster at ASCO on erlotinib beyond disease progression (Halmos 2013). What is your take on erlotinib/chemotherapy versus chemotherapy alone for patients who experience disease progression after response to a TKI?

DR PENNELL: When disease progression occurs, it makes sense to maintain TKI therapy as long as possible. However, many patients have been receiving treatment for a while, and when it is general disease progression, it is necessary to change therapy. If they've never received chemotherapy, or if they have and it has been more than a year since then, switching to chemotherapy makes sense. But should we stop the erlotinib?

The trial we presented at ASCO was for patients who had received first-line chemotherapy and developed acquired resistance to erlotinib. Patients either stopped the erlotinib and moved on to second-line chemotherapy or continued the erlotinib with chemotherapy to see if the combination helped. Unfortunately, we did not find a difference in response rates or PFS between the 2 arms. Some argue that one should continue the TKI therapy because of the risk of disease flare after discontinuation of erlotinib for patients with EGFR-mutant disease and acquired resistance to erlotinib, but I ask patients to stop erlotinib the day before they start the chemotherapy.

Track 13

DR LOVE: Data were recently presented on the VeriStrat assay (Lazzari 2013). Would you discuss what was presented and what you believe is significant?

DR PENNELL: PROSE was a randomized Phase III trial for patients unselected for the presence of EGFR mutations or EGFR wild-type disease (Lazzari 2013; [3.2]). They were randomly assigned to second-line chemotherapy with docetaxel or pemetrexed or to erlotinib. All of the patients were tested up front with the VeriStrat assay, which is a proteomic profile test developed in retrospective patient samples to categorize patients into either a good- or a poor-prognosis group when receiving an EGFR TKI such as erlotinib.

Patients received erlotinib or chemotherapy, and the trial reported no significant difference in efficacy in the overall population between the arms. However, a difference was observed depending on VeriStrat status. Patients with good VeriStrat status, approximately 70% of patients, fared equally on both arms, but patients with poor VeriStrat status fared worse with the TKI. The assay was both predictive of patients who didn't benefit from erlotinib and prognostic — patients with poor VeriStrat status didn't live as long as patients with good VeriStrat status.

How can we use this in practice? I can see it being used if you are undecided about administering erlotinib versus chemotherapy and the patient feels strongly about erlotinib but is willing to receive chemotherapy. If you plan to use chemotherapy no matter what, the assay doesn't matter. If the patient isn't fit enough to receive chemotherapy, again the assay doesn't matter because you'd use erlotinib anyway. ■

3.2

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

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

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

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

SELECT PUBLICATIONS

Chen J et al. **LDK378: A promising anaplastic lymphoma kinase (ALK) inhibitor.** *J Med Chem* 2013;[Epub ahead of print].

Halmos B et al. **Erlotinib beyond progression study: Randomized phase II study comparing chemotherapy plus erlotinib with chemotherapy alone in EGFR tyrosine kinase inhibitor (TKI)-responsive, non-small cell lung cancer (NSCLC) that subsequently progresses.** *Proc ASCO* 2013;**Abstract 8114**.

Hashemi-Sadraei N, Pennell NA. **Advanced non-small cell lung cancer (NSCLC): Maintenance therapy for all?** *Curr Treat Options Oncol* 2012;13(4):478-90.

Lazzari C et al. **Randomized proteomic stratified phase III study of second-line erlotinib (E) versus chemotherapy (CT) in patients with inoperable non-small cell lung cancer (PROSE).** *Proc ASCO* 2013;**Abstract LBA8005**.

Pennell NA. **Selection of chemotherapy for patients with advanced non-small cell lung cancer.** *Cleve Clin J Med* 2012;79(Electronic Suppl 1):46-50.

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

INTERVIEW

Karen L Reckamp, MD, MS

Dr Reckamp is Associate Professor and Co-Director in the Lung Cancer and Thoracic Oncology Program at the City of Hope Comprehensive Cancer Center in Duarte, California.

Tracks 1-13

Track 1 Maintenance therapy with pemetrexed (JMEN and PARAMOUNT) or erlotinib (SATURN) in advanced NSCLC

Track 2 PointBreak study: Pemetrexed/carboplatin/bevacizumab → maintenance pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab → maintenance bevacizumab in Stage IIIB or IV nonsquamous NSCLC

Track 3 ECOG-E5508 trial: Maintenance pemetrexed, bevacizumab or the combination after first-line carboplatin/paclitaxel/bevacizumab in advanced nonsquamous NSCLC

Track 4 Approach to maintenance therapy for bevacizumab-eligible patients in clinical practice

Track 5 **Case discussion:** A 72-year-old patient with EGFR/ALK wild-type, KRAS-mutant advanced NSCLC who receives an anti-PD-1 antibody on a clinical trial after disease progression on carboplatin/pemetrexed → maintenance pemetrexed

Track 6 Efficacy and side effects of the PD-1 and PD-L1 checkpoint inhibitors in lung cancer

Track 7 **Case discussion:** A 50-year-old patient and never smoker with EGFR/KRAS/ALK/ROS1 wild-type advanced NSCLC receives multiple lines of systemic treatment followed by dabrafenib after identification of a BRAF mutation on retesting

Track 8 **Case discussion:** A 48-year-old Vietnamese patient with EGFR-mutant advanced NSCLC receives systemic and local therapies to manage multiple metastatic sites

Track 9 Studies of the multikinase inhibitor cabozantinib in lung cancer

Track 10 Afatinib/cetuximab in patients with EGFR-mutant advanced NSCLC progressing on erlotinib

Track 11 Treatment for patients with EGFR-mutant, advanced NSCLC who are experiencing slow disease progression on erlotinib

Track 12 **Case discussion:** A 74-year-old patient with symptomatic, p63-positive, advanced squamous cell carcinoma (SCC) of the lung receives 2 lines of chemotherapy and stereotactic body radiation therapy for localized brain metastases prior to hospice referral

Track 13 Role of nanoparticle albumin-bound (*nab*) paclitaxel in the treatment of advanced SCC of the lung

Select Excerpts from the Interview

Tracks 1-2, 4

DR LOVE: You recently authored an editorial in *Lancet Oncology* about maintenance therapy for NSCLC (Reckamp 2012). Can you talk about some key points of the paper?

DR RECKAMP: The issue of maintenance therapy in lung cancer has exploded in the past few years, and in some ways we are more confused than we are clear. The first study that brought the issue of maintenance therapy to us was the JMEN trial, in which carboplatin with a nonpemetrexed-containing platinum-based doublet was administered for 4 cycles and patients who did not experience disease progression went on to receive either maintenance pemetrexed or placebo. That study demonstrated an improvement in progression-free survival (Ciuleanu 2009; [4.1]), which you would expect with an active agent in lung cancer, and an overall survival benefit was also observed among the patients who received pemetrexed maintenance.

Then the PARAMOUNT study evaluated a platinum-based doublet with pemetrexed for 4 cycles followed by continuation pemetrexed maintenance versus nonpemetrexed maintenance, or "switch maintenance." Here we also observed an improvement in progression-free survival (Paz-Ares 2012; [4.1]), and recently published data indicated an improvement in overall survival for patients who received pemetrexed maintenance after a platinum-based doublet with pemetrexed (Paz-Ares 2013). These results clearly indicate that pemetrexed has a role as maintenance therapy in NSCLC as switch maintenance or continuation maintenance.

For another cohort of patients one can use erlotinib maintenance, as in the SATURN trial (4.1). That study was similar to the JMEN trial in that patients received a platinum-based doublet for 4 cycles, and the patients who did not experience disease progression went on to receive erlotinib or placebo. In this study a small but statistically significant improvement in both progression-free survival and overall survival was observed across all subgroups. However, the subgroup that benefitted most was that of the patients with EGFR mutations. So erlotinib does potentially have a role, especially if patients can't receive chemotherapy.

DR LOVE: Would you discuss the design of the PointBreak trial and how that relates to your approach to maintenance therapy?

DR RECKAMP: In the PointBreak trial patients received either carboplatin, paclitaxel and bevacizumab, as in the ECOG-E4599 trial (Sandler 2006), followed by bevacizumab maintenance, or carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance. The results showed no overall survival differ-

4.1

Key Phase III Trials of Maintenance Therapy in Advanced Non-Small Cell Lung Cancer

PARAMOUNT[1,2]	Pem + BSC	Placebo + BSC	Hazard ratio	*p*-value
Median PFS*	4.1 months	2.8 months	0.62	<0.0001
Median OS	13.9 months	11.0 months	0.78	0.0195
JMEN[3]	Pem + BSC	Placebo + BSC	Hazard ratio	*p*-value
Median PFS	4.3 months	2.6 months	0.50	<0.0001
SATURN[4]	Erlotinib	Placebo	Hazard ratio	*p*-value
Median PFS	12.3 weeks	11.1 weeks	0.71	<0.0001

* By independent review

Pem = pemetrexed; BSC = best supportive care; PFS = progression-free survival; OS = overall survival

[1] Paz-Ares L et al. *Lancet Oncol* 2012;13(3):247-55. [2] Paz-Ares LG et al. *J Clin Oncol* 2013;31(23):2895-902.
[3] Ciuleanu T et al. *Lancet* 2009;374(9699):1432-40. [4] Cappuzzo F et al. *Lancet Oncol* 2010;11(6):521-9.

ence between the 2 arms. A slight benefit was suggested among patients who received pemetrexed/bevacizumab maintenance, but it was a prespecified exploratory analysis (Patel 2012; [4.2]).

I believe you can interpret the data in almost any way you want. Because no difference in efficacy was apparent, I consider the side effects, and that usually favors pemetrexed. If you consider the cost, however, pemetrexed/bevacizumab doesn't make sense.

DR LOVE: What's your usual approach in terms of maintenance therapy for the average bevacizumab-eligible patient presenting with metastatic adenocarcinoma of the lung?

DR RECKAMP: For patients who are bevacizumab eligible and age 75 or younger I tend to use carboplatin/pemetrexed/bevacizumab. Peripheral neuropathy is much less of an issue than it is with paclitaxel. As far as maintenance, if I use bevacizumab up front I tend to continue it in the absence of specific bevacizumab-related toxicities because we don't have any data on discontinuation. ■

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

HR = hazard ratio; PFS = progression-free survival; OS = overall survival; NR = not reported

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

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

SELECT PUBLICATIONS

Cappuzzo F et al. **Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study.** *Lancet Oncol* 2010;11(6):521-9.

Ciuleanu T et al. **Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study.** *Lancet* 2009;374(9699):1432-40.

Paz-Ares LG et al. **PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(23):2895-902.

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

Reckamp KL. **Is benefit of maintenance therapy for NSCLC best defined by progression-free survival?** *Lancet Oncol* 2012;13(5):435-6.

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

INTERVIEW

Vera Hirsh, MD

Dr Hirsh is Associate Professor in the Department of Medicine and Oncology and Chair of the Lung Cancer Committee at McGill University in Montreal, Canada.

Tracks 1-8

Select Excerpts from the Interview

Track 6

DR LOVE: Would you talk about your research involving bone-targeted therapies in general and specifically what's been going on recently in lung cancer?

DR HIRSH: We have known for many years that patients with NSCLC and bone metastases have poor prognoses. The reason for that is their performance status rapidly deteriorates because of pain and complications such as spinal cord compression, fractures and hypercalcemia. These complications are collectively known as skeletal-related events (SREs).

We've been involved in a number of trials in attempts to prevent SREs, and zoledronic acid was the first agent established to try to address them. When zoledronic acid was compared to placebo, it delayed SREs and the percent of patients who developed these events was smaller (Rosen 2004). Anticancer activity was also reported with zoledronic acid, as it produced a pro-apoptotic effect against the growth of cancer cells and stimulated the immune system against the cancer cells.

We now have a new agent, denosumab, which is a monoclonal antibody against RANKL, which also shows antiresorptive bone activity. We participated in a Phase

III trial that evaluated denosumab versus zoledronic acid in patients with advanced solid tumors — excluding breast and prostate cancer — or multiple myeloma and bone metastases, which reported superiority of denosumab compared to zoledronic acid.

We observed prolonged survival and improved pain control in patients who received denosumab. Noninferiority was reached in the overall patient population (Henry 2011). But when we excluded the patients with multiple myeloma and evaluated only those with solid tumors, we noted superiority with denosumab compared to zoledronic acid.

Also, a subgroup analysis we performed of patients with metastatic lung cancer in this Phase III trial reported superiority with denosumab compared to zoledronic acid not only for SREs but also for overall survival (Scagliotti 2012; [5.1]).

5.1

Overall Survival Improvement in Patients with Lung Cancer and Bone Metastases Treated with Denosumab versus Zoledronic Acid: Subgroup Analysis from a Phase III Trial

Efficacy	Denosumab (n = 411)	Zoledronic acid (n = 400)	Hazard ratio	*p*-value
Median overall survival	8.9 mo	7.7 mo	0.80	0.01
Adverse events (AEs)	**Denosumab** (n = 406)		**Zoledronic acid** (n = 395)	
Serious AEs	66.0%		72.9%	
Hypocalcemia	8.6%		3.8%	
Osteonecrosis of the jaw	0.7%		0.8%	

Scagliotti GV et al. *J Thorac Oncol* 2012;7(12):1823-9.

Tracks 7-8

DR LOVE: Nanoparticle albumin-bound (*nab*) paclitaxel, an agent already approved for breast cancer, was recently approved by the FDA in combination with carboplatin for patients with untreated locally advanced or metastatic NSCLC. What is known about this agent in lung cancer?

DR HIRSH: *Nab* paclitaxel is albumin-bound paclitaxel. It enables the drug to better penetrate the cancer cell, and we observe higher concentrations of the agent in the cancer cells (Desai 2006). Another advantage of *nab* paclitaxel is that steroid premedications are not required as they are with paclitaxel.

A Phase III trial that I was involved in evaluated paclitaxel/carboplatin versus *nab* paclitaxel/carboplatin as first-line therapy for advanced NSCLC. *Nab* paclitaxel was administered weekly with carboplatin as opposed to an every 3-week schedule for paclitaxel. The primary endpoint of the trial was overall response rate, and we reported an advantage for the patients who received *nab* paclitaxel/carboplatin. A trend for improved overall survival was also observed, but it was not statistically significant (Socinski 2012).

We noted a number of signals in certain subgroups of patients that I believe to be of importance. These groups seemed to benefit more from *nab* paclitaxel with regard to progression-free and overall survival than did the overall patient population. One

such group was elderly patients older than age 70, and another included patients with squamous cell histology (5.2).

Another big advantage with *nab* paclitaxel are the symptoms. Peripheral sensory neuropathy, which can be significant with paclitaxel, occurred less with *nab* paclitaxel and was faster to reverse once the agent was stopped. Another important aspect is that patients receiving paclitaxel can experience arthralgias or myalgias. These side effects also occurred with less frequency in patients receiving *nab* paclitaxel, as did edema and hearing loss. ■

5.2

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

Efficacy	*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
Patients aged ≥70 y (n = 74, 82)	34%		24%		0.196
Median progression-free survival					
All patients (n = 521, 531)	6.3 mo		5.8 mo		0.214
Squamous (n = 229, 221)	5.6 mo		5.7 mo		0.245
Nonsquamous (n = 292, 310)	6.9 mo		6.5 mo		0.532
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
Squamous (n = 229, 221)	10.7 mo		9.5 mo		0.284
Nonsquamous (n = 292, 310)	13.1 mo		13.0 mo		0.611
Patients aged ≥70 y (n = 74, 82)	19.9 mo		10.4 mo		0.009
Select adverse events	Grade 3	Grade 4	Grade 3	Grade 4	*p*-value
Neutropenia	33%	14%	32%	26%	<0.001
Thrombocytopenia	13%	5%	7%	2%	<0.001
Sensory neuropathy	3%	0%	11%	<1%	<0.001
Myalgia	<1%	0%	2%	0%	0.011
Arthralgia	0%	0%	2%	0%	0.008

Socinski MA et al. *Ann Oncol* 2013;24(9):2390-6; Socinski MA et al. *Ann Oncol* 2013;24(2):314-21; Socinski MA et al. *J Clin Oncol* 2012;30(17):2055-62.

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Desai N et al. **Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of Cremophor-free, albumin-bound paclitaxel, ABI-007, compared with Cremophor-based paclitaxel.** *Clin Cancer Res* 2006;12(4):1317-24.

Henry DH et al. **Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.** *J Clin Oncol* 2011;29(9):1125-32.

Rosen LS et al. **Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: A randomized, Phase III, double-blind, placebo-controlled trial.** *Cancer* 2004;100(12):2613-21.

Socinski MA et al. **Safety and efficacy analysis by histology of weekly *nab*-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer.** *Ann Oncol* 2013;24(9):2390-6.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The presence of _____ EGFR mutation in NSCLC is predictive of benefit from treatment with tyrosine kinase inhibitors.**
   a. Exon 19 deletion mutation
   b. Exon 21 point mutation
   c. Exon 20 insertion mutation
   d. Both a and b

2. **The initial analysis of the Phase Ib trial of combined EGFR-targeted therapies with afatinib and cetuximab for patients with EGFR mutation-positive NSCLC with progression on erlotinib or gefitinib demonstrated _____.**
   a. Similar confirmed partial response rates between patients with and without EGFR T790M mutation
   b. Efficacy in terms of progression-free survival for all patients
   c. That Grade 3 toxicities associated with combination therapy include diarrhea, rash and fatigue
   d. All of the above

3. **The results of the Phase III PROSE trial for patients with inoperable NSCLC demonstrated that patients with disease classified as VeriStrat poor had a better survival outcome with chemotherapy than with erlotinib in the second-line setting.**
   a. True
   b. False

4. **The Phase II RTOG-0236 study that evaluated stereotactic ablative radiation therapy for patients with inoperable early-stage lung cancer reported a primary tumor control rate of approximately 98%.**
   a. True
   b. False

5. **A Phase I trial of the novel ALK inhibitor LDK378 in advanced, ALK-positive NSCLC demonstrated that patients with _____ disease experienced an approximate 60% response rate to the ALK inhibitor.**
   a. Crizotinib-resistant
   b. Crizotinib-naïve
   c. Both a and b
   d. Neither a nor b

6. **The Phase III PointBreak trial evaluating carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance therapy versus carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance therapy demonstrated a statistically significant difference in overall survival between the 2 arms.**
   a. True
   b. False

7. **The Phase III RTOG-0617 trial evaluating standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiation therapy for Stage III NSCLC reported that high-dose RT was _____ to standard-dose RT in terms of overall survival, progression-free survival and local failure rates.**
   a. Equivalent
   b. Inferior
   c. Superior

8. **The Phase III PARAMOUNT trial demonstrated improvements in _____ with the addition of pemetrexed maintenance therapy among patients who received a platinum-based doublet with pemetrexed for 4 cycles.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b
   d. None of the above

9. **A subanalysis of patients with lung cancer treated on a Phase III study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer reported an overall survival advantage for patients who received zoledronic acid.**
   a. True
   b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 3, 2013

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

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

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

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

	BEFORE	AFTER
Efficacy and side effects of afatinib, alone or in combination with cetuximab	4 3 2 1	4 3 2 1
Effectiveness of the investigational agent LDK378 in patients with crizotinib-naïve and crizotinib-resistant ALK-positive, advanced NSCLC	4 3 2 1	4 3 2 1
Results of a subgroup analysis of patients with lung cancer treated on a Phase III study evaluating denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer	4 3 2 1	4 3 2 1
Outcomes with SABR compared to other local treatments in Stage I NSCLC	4 3 2 1	4 3 2 1
Early data with dabrafenib for BRAF-mutant, advanced NSCLC	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain: .....

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

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

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

.....

.....

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

☐ Yes ☐ No

If no, please explain: .....

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

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

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

- Critically appraise the efficacy and safety of stereotactic ablative radiation therapy for the local treatment of early-stage NSCLC. . . . . 4 3 2 1 N/M N/A
- Apply the results of existing and emerging clinical research to the multimodality treatment of Stage III NSCLC. . . . . 4 3 2 1 N/M N/A
- Formulate a rational approach to identifying molecular determinates from tumor specimens that may be used to refine lung cancer prognosis and/or predict therapeutic response to an individual treatment. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced NSCLC. . . . . 4 3 2 1 N/M N/A
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangements and other recently identified driver mutations — and the approved and investigational treatment options for patients with these mutations. . . . . 4 3 2 1 N/M N/A
- Review emerging research evidence with the use of the irreversible EGFR tyrosine kinase inhibitor afatinib alone or in combination with an EGFR monoclonal antibody for patients with advanced EGFR mutation-positive NSCLC. . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic 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:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

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

☐ Yes, I am willing to participate in a follow-up survey.

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

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

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
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Billy W Loo Jr, MD, PhD, DABR	4	3	2	1	4	3	2	1
Nathan A Pennell, MD, PhD	4	3	2	1	4	3	2	1
Karen L Reckamp, MD, MS	4	3	2	1	4	3	2	1
Vera Hirsh, 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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