Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

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SPECIAL ISSUE

Proceedings from a Clinical Investigator Think Tank

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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 in both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been limited, and approximately 85 percent of patients who develop lung cancer will die of it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on patient outcomes. However, with the advent of biologic agents, recent improvements have been seen in time to progression and survival in lung cancer clinical trials. 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 experts' perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Effectively utilize tumor histology and biomarkers when making evidence-based lung cancer treatment decisions.
- Formulate individualized treatment plans addressing the first-, second- and third-line management of recurrent or progressive non-small cell lung cancer (NSCLC), considering unique patient and tumor characteristics.
- Appraise the side effects and perioperative complications of bevacizumab to assess its safety in the systemic management of early- and late-stage lung cancer.
- Communicate the benefits and risks of maintenance cytotoxic and/or biologic treatment to patients with metastatic NSCLC who successfully complete first-line systemic therapy.
- Summarize the early clinical findings and ongoing research strategies with novel multikinase inhibitors exhibiting activity in NSCLC.
- Recall the design and rationale of ongoing studies incorporating biologic agents into the neoadjuvant therapy of NSCLC.
- Counsel appropriately selected patients with lung cancer about participation in ongoing clinical trials.

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SELECT EXCERPTS FROM THE DISCUSSION

DR LOVE: Tom, would you comment on the ECOG-E1505 adjuvant trial for patients with Stage IB to IIIA non-small cell lung cancer (NSCLC)?

DR LYNCH: In this trial, patients are randomly assigned to a cisplatin-based chemotherapy regimen with or without bevacizumab for one year (1.1). Due to the duration of the bevacizumab, it is a challenging trial for patients to consider because of the potential toxicities associated with bevacizumab.

This trial was not accruing well even before data were released from the adjuvant colon cancer study NSABP-C-08 (Wolmark 2009).

DR LOVE: Tony, C-08 investigators reported that in the first year of the trial, while the patients were receiving bevacizumab, a 40 percent reduction in relapse occurred, but by three years the difference between the arms was not significant. What is your take on this trial and its relevance, if any, to lung cancer?

DR GRECO: It was a powerful study with more than 1,300 patients per arm. Biologically, differences exist between breast, lung and colorectal cancer, and although I believe using adjuvant therapy for patients at high risk makes sense, the benefits, or lack thereof, of individual therapies don't necessarily translate from one tumor type to another.

DR HEYMACH: One way to interpret the C-08 trial data is that they are entirely consistent with what we believe to be the mechanism of action of bevacizumab.

With anti-angiogenic therapy, the micrometastatic cells don't disappear. They're still viable, but they simply don't have a blood supply and they don't grow. However, if you stop the inhibition, they can start growing again.

Unlike adjuvant chemotherapy, which is administered for a set period, we would want to continue therapy with bevacizumab, and if we stopped the drug, we would expect the tumor to start growing again. Thus, I believe the idea of an adjuvant trial with a longer duration of bevacizumab is rational.

DR SOCINSKI: One of the biggest sources of resistance we've encountered with the adjuvant ECOG-E1505 trial is the difference between receiving four cycles of chemotherapy in one arm and continuing the bevacizumab treatment for a year on the other arm. That's been a problem.

Adjuvant therapy is supposed to be of short duration — it either accomplishes the goal or it doesn't accomplish the goal.

I believe that most of us consider the concept of targeting angiogenesis in the adjuvant setting a good idea. However, bevacizumab may not be the best drug with which to do that due to the nature of the agent. ■

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

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

SOURCE: NCI Physician Data Query, October 2009.

SELECT PUBLICATION

Wolmark N et al. **A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08.** *Proc ASCO* 2009;**Abstract LBA4**.

GENOMIC MARKERS AND PREDICTORS OF RELAPSE AND RESPONSE

DR LOVE: What are some of the key research questions that need to be asked in the adjuvant setting?

DR LILENBAUM: A field that's growing in the adjuvant setting is the evaluation of gene profiles, trying to stratify patients according to risk and identify those who will derive significant benefit from adjuvant therapy.

DR LOVE: Are any trials currently evaluating tissue biomarkers in the adjuvant setting?

DR SOCINSKI: A Phase II trial is being conducted by SWOG, the S0720 study, which is evaluating the feasibility of assigning adjuvant treatment based on tumoral RRM1 and ERCC1 gene expression.

DR PASS: I find the idea of using tissue to examine genetic profiles and potential biomarkers, such as ERCC1 and RRM1, appealing and exciting. TS is another biomarker I believe is of importance.

The question is, how do we do this and get the answers quickly? How do we do it on a major scale? We'll get some answers from the current trials, but thousands of patients are out there and we haven't come to grips with completing this sort of study.

DR LOVE: Tom, the IPASS study evaluated EGFR mutations as a predictive factor for EGFR tyrosine kinase inhibitor (TKI) therapy. Would you discuss those data?

DR LYNCH: The IPASS trial was probably the most important study in lung cancer to come out in the past year (Mok 2009). It was a terrific example of how molecular profiling can affect outcome and the way we care for patients.

The study was conducted principally in East Asia and consisted of 1,200 patients with adenocarcinoma who were light or never smokers. The patients were randomly assigned to first-line gefitinib versus carboplatin/paclitaxel, and overall, the group who received gefitinib had a better progression-free survival and a benefit in terms of symptom management and quality of life (Mok 2009; [2.1]).

The exciting news was that the EGFR mutation analysis conducted in 437 cases showed that EGFR mutation positivity is an important factor in selecting front-line therapy (Fukuoka 2009; [2.2]). In patients with tumors positive for mutation, the benefit from gefitinib compared to chemotherapy was clear. More importantly, in my opinion, it demonstrated that patients with EGFR mutation-negative disease fared worse with gefitinib, even if they were Asian, female and had never smoked.

The data also suggested that FISH was a positive predictive marker, but the FISH and EGFR mutation groups overlap substantially, which is probably why FISH appeared to be an important predictor of outcome (2.2).

I believe that if you have a patient with an adenocarcinoma and a light smoking history, you should order an EGFR mutation assay.

DR LOVE: Vince, are FISH and IHC testing of value in this setting?

DR MILLER: I agree with Tom that the IPASS biomarker data were perhaps illustrative in explaining the challenges in interpreting the FISH data because so many patients who have EGFR mutations also have a high gene copy number. If you examine the cases that were mutation-negative and had a high EGFR copy number, you find that the hazard ratio was around four for

2.1

IPASS: A Phase III Randomized Trial of Gefitinib versus Carboplatin/Paclitaxel as First-Line Therapy for Clinically Selected (Asian, Nonsmokers or Former Light Smokers, Adenocarcinoma) Patients with Advanced NSCLC

Progression-free survival events	Gefitinib	Carboplatin + paclitaxel	Hazard ratio* (95% CI)	*p*-value
Intent-to-treat population (n = 609; 608)	74.4%	81.7%	0.74 (0.65-0.85)	<0.001
EGFR mutation-positive (n = 132; 129)	73.5%	86.0%	0.48 (0.36-0.64)	<0.001
EGFR mutation-negative (n = 91; 85)	96.7%	82.4%	2.85 (2.05-3.98)	<0.001
EGFR mutation unknown (n = 386; 394)	69.4%	80.2%	0.68 (0.58-0.81)	<0.001

* Hazard ratio < 1.0 favors gefitinib; CI = confidence interval

"The efficacy of gefitinib seen in this study was coupled with lower incidences of alopecia, nausea, vomiting, neurotoxic symptoms, and myelosuppression than those seen with carboplatin-paclitaxel."

SOURCE: Mok TS et al. *N Engl J Med* 2009;361(10):947-57.

gefitinib (2.2), so the benefit clearly tracks with mutation status.

I don't see a role for IHC or FISH testing for EGFR. Instead, mutation testing is critical in this setting.

DR LOVE: What are the clinical implications of the IPASS data?

DR NATALE: In the past I would have included erlotinib in my front-line treatment for a young woman with Stage IV lung cancer and a light smoking history. However, the results of the IPASS study have changed that for me.

One of the most striking aspects of the IPASS study was the rate of disease progression in nonsmoking women or women with light smoking histories and EGFR mutation-negative adenocarcinoma who received first-line gefitinib. More than 50 percent of them experienced progression of their lung cancer by RECIST — more than 30 percent growth within the first six weeks of starting treatment. That's a frightening rate of progression in a patient population that we would have considered as having good demographics for treatment with an EGFR TKI.

DR LOVE: How long does the EGFR mutation testing take?

DR NATALE: We conduct it internally, so at our institution it takes about five days. If you have archival tissue available to send out, the turnaround is probably seven to 10 days with any of the commercially available testing laboratories. ■

2.2

IPASS Data: Progression-Free Survival (PFS) by Biomarker Status

	N	PFS hazard ratio*	*p*-value	PFS interaction by subgroup†
EGFR mutation status				
M-positive	261	**0.48**	<0.0001	
M-negative	176	**2.85**	<0.0001	<0.0001
M-unknown	780	0.68	<0.0001	
EGFR gene copy number				
FISH-positive	249	0.66	0.0050	
M-positive	190	**0.48**	—	
M-negative	55	**3.85**	—	
FISH-negative	157	1.24	0.2368	0.0437
FISH-unknown	811	0.70	<0.0001	

* Hazard ratio (HR) < 1.0 favors gefitinib
† HR in positive biomarker versus HR in negative biomarker

SOURCE: Fukuoka M et al. *Proc ASCO* 2009;**Abstract 8006**.

SELECT PUBLICATIONS

Fukuoka M et al. **Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS).** *Proc ASCO* 2009;**Abstract 8006**.

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

DR LOVE: Vince, the BEACON trial evaluated preoperative and adjuvant bevacizumab for patients with Stage IB to IIIA NSCLC receiving induction cisplatin or docetaxel. Can you elaborate on the study design?

DR MILLER: The trial was divided into two cohorts of patients. Those for whom we thought induction bevacizumab would not be safe — such as patients with squamous cell tumors — received cisplatin or docetaxel preoperatively and then, after surgery, they received bevacizumab for one year.

The study was amended and now those patients receiving bevacizumab for one year receive pemetrexed instead of docetaxel.

The second cohort of patients — those who were bevacizumab eligible — received a dose of bevacizumab alone, then two cycles synchronized with the cisplatin or docetaxel and then one cycle of chemotherapy without bevacizumab in anticipation of planned surgery.

DR LOVE: Harvey, what do we know about the safety of using bevacizumab before lung resection?

DR PASS: I believe the precautions that we're taking currently are fine. I have operated on patients like this and had no problems. We are careful to ensure that problems like hypertension or proteinuria are resolved, and we find that by waiting three weeks before going to surgery, we do not encounter significant problems.

DR LOVE: Vince, what did the trial data show?

DR MILLER: The response rate was substantially higher for the patients who received bevacizumab, approximately 50 percent versus 30 percent. The incidence of complications and side effects was comparable between the two cohorts of patients. We do believe a subtle increase may occur in the severity of certain toxicities with bevacizumab, such as pulmonary hemorrhage and bronchopleural fistula, so that bears watching.

DR LOVE: How did you evaluate the impact of the single dose of bevacizumab administered alone?

DR MILLER: Scans were performed on day one, then patients received a dose of bevacizumab only and the scans were repeated two weeks later. As illustrated in a waterfall plot, we found that by bidimensional or volumetric measurements, almost all the patients had a reduction in tumor volume (Price 2009; [3.1]). We are not sure if this represents a decrease in tumor cells or interstitial edema, but a reduction in size did occur. I don't know the clinical implications of that.

DR LOVE: John, what do you think about these data?

DR HEYMACH: In metastatic disease, we are not able to examine tumors in the same way and observe this, but these data do illustrate that bevacizumab has single-agent activity.

We've been involved in the biomarker analysis of a similar trial evaluating

neoadjuvant pazopanib. The patients were those from a screening study in which early-stage lung cancer was detected. They received four to six weeks of pazopanib and, similarly, 86 percent had a reduction in their tumor volume, and in some cases it was quite large (Altorki 2008). We've identified some baseline angiogenic factors that can predict who will or will not respond.

DR LOVE: What kinds of trials should we be considering in the neoadjuvant setting?

DR PASS: I believe we need to study induction therapy for patients who have larger tumors, perhaps with negative mediastinoscopy and PET scans and no evidence of nodal involvement. I don't know where else to go with induction therapy, but I believe there's gold somewhere in this approach.

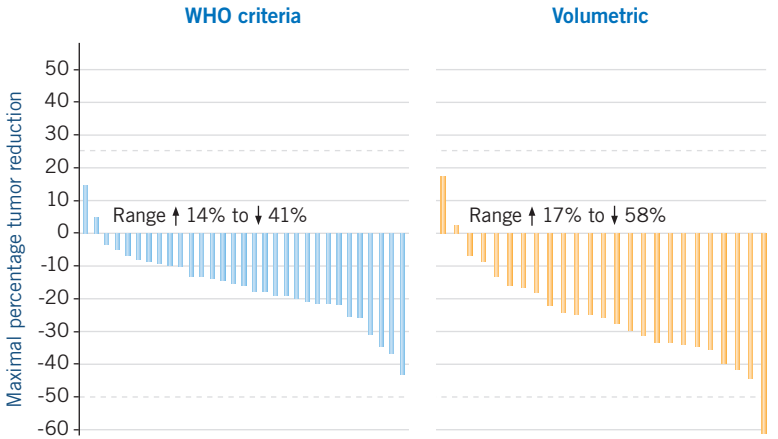
DR LOVE: In this setting, should we be studying chemotherapy or biologic agents, or both?

DR PASS: Frankly, I believe it can be both, but we have to choose the right population in which we can identify a signal. The trials conducted have included a heterogeneous mix of patients, instead of taking the patients who are at highest risk and would benefit from induction therapy.

DR LILENBAUM: Neoadjuvant chemotherapy has been evaluated for at least a decade, and I don't believe its use will increase significantly unless, in specific cases, such as T4 lesions, minimal mediastinal or N2 disease, the surgeon goes back to the medical oncologist and says, "I would like you to treat this patient with induction therapy. It may change my surgical plan and it may be in the patient's best interest." Also, it might be useful for

3.1

BEACON: Tumor Reduction After Two Weeks of Single-Agent Neoadjuvant Bevacizumab in Patients with Stage IB to IIIA NSCLC



WHO criteria for progression of disease: ≥25% increase
WHO criteria for response: ≥50% decrease

SOURCE: With permission from Price K et al. *Proc ASCO* 2009;**Abstract 7531**.

patients who you suspect may not be able to receive full adjuvant chemotherapy postoperatively and you want to treat them ahead of time. ■

SELECT PUBLICATIONS

Altorki NK et al. **Phase II study of pazopanib (GW786034) given preoperatively in stage I-II non-small cell lung cancer (NSCLC): A proof-of-concept study.** *Proc ESMO* 2008;**Abstract 2250**.

Price K et al. **Phase II study of induction and adjuvant bevacizumab in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) receiving induction docetaxel and cisplatin.** *Proc ASCO* 2009;**Abstract 7531**.

MANAGEMENT OF METASTATIC DISEASE

DR LOVE: Vince, could you describe the ongoing CALGB-30406 trial for never or former light smokers with advanced NSCLC?

DR MILLER: This is a randomized Phase II trial enrolling 180 patients with a 10 pack-year or less smoking history, and it evaluates erlotinib with or without carboplatin/paclitaxel. The study requires tissue from either a resection or a core biopsy, which will be sent to Dana-Farber for hierarchical testing, starting with an EGFR mutation test.

This trial was based on the TRIBUTE data, in which the median survival for never smokers with advanced NSCLC treated with erlotinib and chemotherapy was an encouraging 22 months (Herbst 2005).

On the basis of the demographics, we predict that 30 to 40 percent of patients in each arm will have an EGFR mutation, so we expect around 30 to 35 patients in each arm will receive erlotinib alone. We are confident that we know how that group will fare. We're hoping to have the data for ASCO 2010.

DR LOVE: Tom, what do you expect the data will show?

DR LYNCH: I don't know, but my bias is that erlotinib alone will be tough to beat.

DR LOVE: Vince, can you summarize the data from the ATLAS and SATURN trials, which evaluated maintenance therapy with biologic agents after first-line systemic treatment?

DR MILLER: The ATLAS trial evaluated bevacizumab with or without erlotinib after completion of first-line chemotherapy/bevacizumab for locally advanced, recurrent or metastatic NSCLC (Miller 2009).

The SATURN trial evaluated erlotinib versus placebo after no disease progression with first-line platinum-based chemotherapy in patients with advanced NSCLC. It is examining maintenance therapy in a population with EGFR-positive disease as determined by IHC (Cappuzzo 2009).

In both of these trials the hazard ratio in favor of the maintenance TKI was approximately 0.7 (4.1; 4.2). The median progression-free

survival differed by one week in the SATURN trial and by one month in the ATLAS study. Unlike IPASS and CALGB-30406, these studies included unselected patients. They are not genotypically enriched by any biomarker that I feel is relevant, so they address a different question of maintenance.

DR LOVE: Tom, what are the practical implications of these data?

DR LYNCH: We have to view these results in relationship to the maintenance pemetrexed and maintenance docetaxel studies (Ciuleanu 2009; Fidias 2009). All four of these trials evaluated maintenance or early second-line therapy, referring to the

4.1

ATLAS: A Phase III Randomized Trial Evaluating Maintenance Bevacizumab (B) with Erlotinib (E) or Placebo (P) After Completion of First-Line Therapy with Chemotherapy/Bevacizumab for Locally Advanced, Recurrent or Metastatic NSCLC

	B + E (n = 373)	B + P (n = 370)
Median progression-free survival	4.8 months	3.8 months
Progression-free survival (3 months)	68%	53%
Progression-free survival (6 months)	40%	28%
Hazard ratio (95% confidence interval)	0.72 (0.59-0.88)	
p-value	0.0012	

"E added to B treatment after chemotherapy with B significantly improves the PFS [progression-free survival] of patients treated in the first-line setting for locally advanced, recurrent, or metastatic NSCLC."

SOURCE: Miller VA et al. *Proc ASCO* 2009;**Abstract LBA8002**.

4.2

SATURN: A Phase III Randomized Trial of Maintenance Erlotinib versus Placebo After Nonprogression with First-Line Platinum-Based Chemotherapy for Advanced NSCLC

	Erlotinib (n = 437)	Placebo (n = 447)
Median progression-free survival	12.3 weeks	11.1 weeks
Progression-free survival (12 weeks)	53%	40%
Progression-free survival (24 weeks)	31%	17%
Hazard ratio (95% confidence interval)	0.71 (0.62-0.82)	
p-value	<0.0001	

"The SATURN study met its primary and co-primary endpoints with high statistical significance. Erlotinib in the 1st-line maintenance setting is well tolerated, and significantly improves disease control and delays progression versus placebo across patient subgroups."

SOURCE: Cappuzzo F et al. ASCO 2009;**Abstract 8001**.

practice of switching to a second agent after patients complete a front-line regimen for advanced disease, and they all consistently showed that progression-free survival is prolonged with the additional therapy. In the pemetrexed study, overall survival was also prolonged (Ciuleanu 2009; [4.3]).

The problem for physicians is how these data are assembled and interpreted. I'm concerned because many clinical investigators believe that second-line therapy is as good as maintenance therapy and that they as physicians are able to determine which patients will experience relapse and that therefore they can provide some patients with a break from therapy.

I was one of the physicians who treated these patients on study, and I would argue that we weren't able to identify these patients. The maintenance pemetrexed study showed a survival difference (Ciuleanu 2009; [4.3]), so I believe that we have to take the data more seriously. These data have changed my approach to treatment in this setting.

DR LOVE: Vince, with all the data on new biomarkers in NSCLC, what's your current approach to incorporating the data into the treatment algorithm for patients outside a protocol setting?

DR MILLER: My algorithm is first to determine whether we have tissue for analysis. If we do and the patient has a mutation, then I treat with either erlotinib alone or erlotinib/chemotherapy for the first line. My preference is erlotinib alone.

DR LOVE: Mark, how would you treat a patient with a Stage IV adenocarcinoma who is eligible to receive bevacizumab?

DR SOCINSKI: The FDA-approved choice is carboplatin/paclitaxel/bevacizumab, but I've also treated a number of these patients with carboplatin/pemetrexed/bevacizumab. Typically I administer four cycles and then continue the bevacizumab as so-called prolonged duration or maintenance therapy.

I use these two regimens fairly equally, depending on the patients and their comorbidities.

DR GRECO: In treating adenocarcinoma, I believe that the trend is to use pemetrexed with a platinum and bevacizumab, and I agree with this.

4.3

JMEN: Progression-Free and Overall Survival (PFS and OS) with Maintenance Pemetrexed for Patients with Advanced NSCLC (N = 663)

Efficacy parameter	Pemetrexed	Placebo	Hazard ratio	*p*-value
PFS	4.3 mo	2.6 mo	0.50	<0.0001
Nonsquamous (n = 481)	4.5 mo	2.6 mo	0.44	<0.0001
Squamous (n = 182)	2.8 mo	2.6 mo	0.69	0.039
OS (ITT population)	13.4 mo	10.6 mo	0.79	0.012
Nonsquamous	15.5 mo	10.3 mo	0.70	0.002
Squamous	9.9 mo	10.8 mo	1.07	0.678

SOURCE: Ciuleanu T et al. *Lancet* 2009;374(9699):1432-40.

DR LOVE: Tony, if a patient receives up-front carboplatin/pemetrexed/bevacizumab, what's your longer-term strategy?

DR GRECO: I'm using mixed data here, but I would probably administer four cycles of up-front therapy, then pemetrexed perhaps with bevacizumab for four more cycles, and then continue bevacizumab for a total of a year.

DR LOVE: Mark, what is your approach?

DR SOCINSKI: I continue bevacizumab until disease progression, but I'm comfortable with the tapering and, although I may be in the minority here, I'm also comfortable with no maintenance therapy. We have had a number of patients who question how much benefit they will obtain from prolonged bevacizumab and choose to stop it.

DR LOVE: Vince, what's your maintenance strategy?

DR MILLER: I follow the ECOG-E4599 regimen and continue bevacizumab for selected patients. I could certainly envision adding erlotinib or pemetrexed according to clinical or molecular features.

DR LOVE: Rogerio, if you had a patient who had received four cycles of carboplatin/pemetrexed/bevacizumab, what would you do in terms of maintenance?

DR LILENBAUM: I would usually continue the bevacizumab with or without the pemetrexed.

DR LYNCH: I believe the current practice pattern is that most physicians are using bevacizumab for maintenance unless it's contraindicated.

DR HEYMACH: Like Vince, I follow the ECOG-E4599 paradigm, starting with carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance.

However, based on Belani's data (Ciuleanu 2009), an interesting question is whether we should add pemetrexed for patients who can tolerate it.

We do have randomized Phase II data with second-line docetaxel versus pemetrexed, with or without bevacizumab (Herbst 2007). They demonstrated a progression-free survival trend favoring the addition of bevacizumab to either of those two drugs.

So if you view this as early second line, the data support using both pemetrexed and bevacizumab.

DR SOCINSKI: I was impressed by the maintenance pemetrexed data, particularly for patients with the right histology (Ciuleanu 2009). These are impressive curves, both for progression-free and overall survival, and I believe that's meaningful. ■

SELECT PUBLICATIONS

Cappuzzo F et al. **SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC.** ASCO 2009;**Abstract 8001**.

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.

Fidias PM et al. **Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer.** *J Clin Oncol* 2009;27(4):591-8.

Herbst RS et al. **Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer.** *J Clin Oncol* 2007;25(30):4743-50.

Herbst RS et al. **TRIBUTE: A Phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer.** *J Clin Oncol* 2005;23(25):5892-9.

Miller VA et al. **A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic NSCLC.** *Proc ASCO* 2009;**Abstract LBA8002**.

NOVEL TARGETED AGENTS CURRENTLY IN DEVELOPMENT

DR LOVE: What do we know about genomic mutations that cause lung cancer initially responsive to small molecule TKIs to become resistant?

DR HEYMACH: A growing list of molecular mechanisms can lead to resistance to an EGFR TKI, including T790M, MET amplification and ras mutation. We recently reported in *Clinical Cancer Research* that in preclinical models, VEGF can be upregulated as part of EGFR TKI resistance and blocking that upregulation can overcome resistance (Naumov 2009). Ultimately we will need to tailor our therapies to target these mechanisms.

We may be able to use the irreversible EGFR inhibitors. BIBW 2992 is the most advanced in its development. It is an oral dual EGFR-HER2 inhibitor, and it has certainly shown evidence of activity.

DR LOVE: How does it compare chemically to erlotinib and gefitinib?

DR HEYMACH: It's a multiring structure, but it has a rearrangement so it does not fit into the ATP binding pocket in the same way. BIBW 2992 is a tyrosine kinase inhibitor, but it has a different profile of activity than erlotinib and gefitinib.

William Pao from the Memorial Sloan-Kettering group conducted a study in which patients underwent further biopsies after the development of EGFR TKI resistance, and they observed one patient who had a mutation that prevented erlotinib or gefitinib to enter the binding pocket. In the same way that BIBW 2992 inhibits the T790M mutation, it also inhibited this mutation.

DR LOVE: Vince, do you think the irreversible binding of BIBW 2992 marks an advantage?

DR LYNCH: Theoretically, it may be advantageous, but I am not yet convinced that we have data demonstrating that it has changed outcomes for patients.

DR LOVE: What do we know about the role of BIBW 2992 for patients with acquired resistance to erlotinib or gefitinib?

DR MILLER: BIBW 2992 is an oral dual EGFR-HER2 inhibitor.

Data have been presented from the LUX-Lung 2 trial, a Phase II study conducted largely with Asian patients prospectively screened for EGFR mutations. Patients received second-line BIBW 2992, and the data indicate positive activity (Shih 2009; [5.1]).

In an ongoing Phase IIb/III study, LUX-Lung 1, patients with NSCLC who have experienced disease progression after receiving chemotherapy and erlotinib or gefitinib are randomly assigned to BIBW 2992 or placebo, with no crossover.

DR LOVE: Where do you think this agent is heading, Tom?

DR LYNCH: If this drug proves effective in patients whose disease progressed on erlotinib or gefitinib, that would be one niche for BIBW 2992. As for use in the front-line setting, the question is whether drugs like this improve progression-free survival. It may be that by targeting T790M earlier, by treating the disease before resistance emerges, we may prolong the time before we see resistance. That's one outcome we are hoping to achieve in these trials.

DR LOVE: So this agent targets T790M?

DR LYNCH: Yes, it also has activity against T790M.

DR LOVE: Is BIBW 2992 being investigated as first-line therapy?

DR MILLER: Yes, James Yang is the principle investigator of that trial (5.2). The progression-free survival data are early but did not appear markedly superior to what we would expect to see with erlotinib (Yang 2009).

DR HEYMACH: Using the analogy of HIV treatment strategies of combining the primary treatment with an agent meant to circumvent resistance, what would you think about combining erlotinib, which is potent against the EGFR mutation, with an irreversible inhibitor such as BIBW 2992?

DR LYNCH: BIBW should be as effective against the native EGFR mutation as erlotinib, but your point is well taken.

DR LOVE: Another agent that targets multiple pathways is vandetanib. What do we know about its mechanism of action?

5.1

LUX-Lung 2: Second-Line Efficacy Data from the Phase II Study of BIBW 2992 for Patients with Adenocarcinoma of the Lung and Activating EGFR Mutations

Parameter	Data	95% confidence interval
Overall response rate	64%	52-76%
Disease control rate	96%	87-99%
Median progression-free survival	10.2 months	7.5-17.7 months

"A Phase III trial (LUX-Lung 3) comparing BIBW 2992 with chemotherapy in chemo-naïve NSCLC patients harboring EGFR mutations will start recruitment shortly."

SOURCE: Shih J et al. *Proc ASCO* 2009;**Abstract 8013**.

DR NATALE: Vandetanib is an oral agent that has both EGFR- and VEGFR-inhibitory properties. Compared to erlotinib or gefitinib, its EGFR inhibitory properties are a little more modest, but it's a fairly potent VEGFR 1 and 2 inhibitor, and it's also a potent inhibitor of RET kinase.

DR LOVE: John, can you comment on the effects of the 100-mg dose versus the 300-mg dose of vandetanib?

DR HEYMACH: The full dose of 300 milligrams per day, which is essentially the maximum tolerated dose, has clear EGFR inhibitor activity and we see the related acneiform rash. At the lower dose of 100 milligrams, it appears that we're primarily obtaining VEGF inhibitory activity, with some hypertension and some other biomarker changes, but little EGFR inhibitory activity (Heymach 2007).

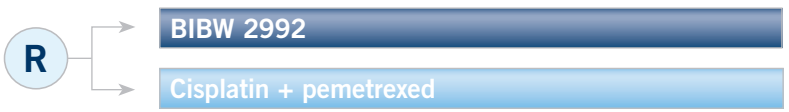
DR LOVE: Would you summarize your Phase II trial evaluating vandetanib with or without carboplatin/paclitaxel (Heymach 2008)?

DR HEYMACH: This trial randomly assigned 181 patients to vandetanib or carboplatin/paclitaxel or the combination of all three agents. Unfortunately, we didn't have the data suggesting the 100-mg dose of vandetanib was better with chemotherapy (Heymach 2007), so we used the 300-mg dose.

At the interim analysis, we found vandetanib monotherapy was inferior to chemotherapy among unselected patients. This is reminiscent of other studies comparing an EGFR TKI to chemotherapy, and I believe it

5.2

LUX-Lung 3: A Randomized, Open-Label, Phase III Study of BIBW 2992 versus Chemotherapy as First-Line Treatment for Patients with Stage IIIB or IV Adenocarcinoma of the Lung Harboring an EGFR-Activating Mutation



Key Facts

Eligibility

- Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is the predominant histology.
- EGFR mutation detected by central laboratory analysis of tumor biopsy material.

Estimated Enrollment: 330
Study Start Date: August 2009
Estimated Primary Completion Date: August 2011

ClinicalTrials.gov Identifier: NCT00949650

SOURCE: **www.clinicaltrials.gov**, October 2009.

tells us that in the absence of an EGFR mutation, or for unselected patients, chemotherapy is still better than an EGFR TKI. However, the patients with EGFR mutations fared extremely well with vandetanib monotherapy.

The three-drug combination was better than carboplatin/paclitaxel, with a hazard ratio of 0.76, which is in the range of what we're finding in other combination studies.

DR LOVE: How does vandetanib compare to gefitinib?

DR NATALE: In a blinded Phase II trial, in which patients were randomly assigned to receive second- or third-line gefitinib or vandetanib, the initial response and stable disease rates were higher with vandetanib (Natale 2009b).

At the time of disease progression, patients underwent a washout period and then switched to the alternate therapy. The proportion of patients who then experienced clinical benefit, measured as response or stable disease, was a little higher among those who received gefitinib first and then switched to vandetanib than among those who initially received vandetanib and crossed over to gefitinib.

So we found that after gefitinib exposure, vandetanib retained some apparent efficacy but the opposite was not true. These data support the dual action of vandetanib, which can perhaps be exploited as a single agent, administered at the full dose.

At a lower dose, it loses that EGFR inhibitory action and retains only its VEGFR inhibitory action, which may be complementary in combination with chemotherapy.

DR LOVE: Several studies evaluating vandetanib in the second-line setting were presented at ASCO. Would you summarize those data?

DR NATALE: ZEST was a worldwide, randomized, blinded comparison of second-line, and sometimes third-line, vandetanib at 300 milligrams per day to erlotinib, with 1,240 patients. We saw no differences in response rate, progression-free survival or overall survival between the two arms (Natale 2009a).

Although vandetanib performed as well as erlotinib did, some may find it disappointing given the results of the BeTa trial, in which combined EGFR and anti-angiogenic actions at least improved progression-free survival, with a slight trend toward an improvement in overall survival (Hainsworth 2008).

ZODIAC, another Phase III trial, compared docetaxel/placebo to docetaxel/vandetanib, using the lower 100-mg per day dose of vandetanib, with which we would expect to see only VEGFR inhibition.

This also was a large trial, with more than 1,300 patients, and investigators reported a statistically significant improvement in progression-free survival with at least a trend toward an improvement in overall survival, although not statistically significant (Herbst 2009; [5.3]).

DR LOVE: What was reported in terms of side effects and toxicity?

DR NATALE: In the trial of vandetanib at 300 milligrams per day, we recorded some skin toxicity and hypertension. We did not observe

severe anti-angiogenic class side effects or significant pulmonary hemorrhage.

In the trial combining the lower dose of vandetanib with docetaxel, a little increase was apparent in skin rash and anti-angiogenic side effects. ■

5.3

ZODIAC: Docetaxel (D) with or without Vandetanib (V) for Advanced Non-Small Cell Lung Cancer

Clinical response	V + D (N = 697)	Placebo + D (N = 694)	Hazard ratio	*p*-value
ORR	17%	10%	NR	<0.001
Median PFS	4 months	3.2 months	0.79	<0.001
Median OS	10.6 months	10.0 months	0.91	0.196
TDS	NR	NR	0.77	<0.001

ORR = objective response rate; PFS = progression-free survival; OS = overall survival; TDS = time to deterioration of symptoms

SOURCE: Herbst RS et al. ASCO 2009;**Abstract CRA8003**.

SELECT PUBLICATIONS

Hainsworth J, Herbst R. **A Phase III, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of bevacizumab (Avastin®) in combination with erlotinib (Tarceva®) compared with erlotinib alone for treatment of advanced non-small cell lung cancer after failure of standard first-line chemotherapy (BETA).** *J Thorac Oncol* 2008;3(11 Suppl 4);**Abstract LBA1**.

Herbst RS et al. **Vandetanib plus docetaxel vs docetaxel as 2nd-line treatment for patients with advanced NSCLC: A randomized, double-blind Phase III trial (ZODIAC).** ASCO 2009;**Abstract CRA8003**.

Heymach JV et al. **Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer.** *J Clin Oncol* 2008;26(33):5407-15.

Heymach JV et al. **Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer.** *J Clin Oncol* 2007;25(27):4270-7.

Natale RB et al. **Vandetanib versus erlotinib in patients with advanced NSCLC after failure of at least one prior cytotoxic chemotherapy: A randomized, double-blind phase III trial (ZEST).** ASCO 2009a;**Abstract 8009**.

Natale RB et al. **Vandetanib versus gefitinib in patients with advanced non-small-cell lung cancer: Results from a two-part, double-blind, randomized phase II study.** *J Clin Oncol* 2009b;27(15):2523-9.

Naumov GN et al. **Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance.** *Clin Cancer Res* 2009;15(10):3484-94.

Shih J et al. **A phase II study of BIBW 2992, a novel irreversible dual EGFR and HER2 tyrosine kinase inhibitor (TKI), in patients with adenocarcinoma of the lung and activating EGFR mutations after failure of one line of chemotherapy (LUX-Lung 2).** *Proc ASCO* 2009;**Abstract 8013**.

Yang CH et al. **BIBW 2992, a novel irreversible EGFR/HER2 tyrosine kinase inhibitor, in chemonaïve patients with adenocarcinoma of the lung and activating EGFR mutations.** *Proc International Association for the Study of Lung Cancer* 2009;**Abstract A3.3**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **ECOG-E1505 is evaluating adjuvant _____ with or without bevacizumab for patients with completely resected Stage IB to IIIA non-small cell lung cancer (NSCLC).**
   a. Cisplatin/gemcitabine
   b. Cisplatin/vinorelbine
   c. Cisplatin/docetaxel
   d. All of the above
2. **In the BEACON trial, evaluating induction and adjuvant bevacizumab in patients with Stage IB to IIIA NSCLC, the majority of patients who received one dose of single-agent bevacizumab preoperatively _____ experience a reduction in tumor size.**
   a. Did
   b. Did not
3. **In the IPASS trial, which first-line therapy resulted in greater efficacy for patients with advanced NSCLC and EGFR mutations?**
   a. Chemotherapy (carboplatin/paclitaxel)
   b. Gefitinib
   c. Neither a nor b
4. **SWOG-S0720 is a Phase II study evaluating the feasibility of assigning adjuvant treatment based on tumoral RRM1 and ERCC1 gene expression for patients with completely resected Stage I NSCLC.**
   a. True
   b. False
5. **The ATLAS trial demonstrated an improvement in progression-free survival with the addition of _____ to maintenance bevacizumab for patients who had completed first-line therapy for advanced NSCLC.**
   a. Cetuximab
   b. Erlotinib
   c. Pemetrexed
6. **The SATURN trial compared which of the following strategies as maintenance therapy for NSCLC?**
   a. Bevacizumab to erlotinib
   b. Bevacizumab to pemetrexed
   c. Erlotinib to placebo
7. **In a Phase III trial reported by Belani and colleagues evaluating maintenance pemetrexed versus placebo in advanced NSCLC, pemetrexed improved _____.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b
   d. None of the above
8. **Among patients with adenocarcinoma of the lung and EGFR mutations, the disease control rate with BIBW 2992 as second-line therapy was _____.**
   a. 20 percent
   b. 40 percent
   c. 60 percent
   d. Higher than 90 percent
9. **The Phase III ZODIAC trial of vandetanib and docetaxel versus docetaxel and placebo as second-line treatment for advanced NSCLC showed an improvement in progression-free survival for patients who received vandetanib.**
   a. True
   b. False
10. **Vandetanib is an oral inhibitor of _____.**
    a. VEGF receptor
    b. EGF receptor
    c. Both a and b

Post-test answer key: 1d, 2a, 3b, 4a, 5b, 6c, 7c, 8d, 9a, 10c

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Think Tank Issue 1, 2009

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

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

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

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

	BEFORE	AFTER
Awareness of ECOG-E1505: An ongoing Phase III study of adjuvant chemotherapy with or without bevacizumab for patients with resected Stage IB (≥4 cm) to IIIA NSCLC	4 3 2 1	4 3 2 1
NSABP-C-08 trial results and the evaluation of longer-duration adjuvant anti-angiogenic therapy	4 3 2 1	4 3 2 1
Results of BEACON: Induction and adjuvant bevacizumab for patients with Stage IB to IIIA NSCLC receiving induction docetaxel and cisplatin	4 3 2 1	4 3 2 1
Results of IPASS: First-line carboplatin/paclitaxel versus gefitinib for patients of Asian ethnicity selected for EGFR mutations	4 3 2 1	4 3 2 1
Results of the ATLAS (erlotinib/bevacizumab versus bevacizumab) and SATURN (erlotinib versus placebo) studies of maintenance therapy	4 3 2 1	4 3 2 1
Mechanisms of resistance to EGFR tyrosine kinase inhibitors	4 3 2 1	4 3 2 1
Clinical development of the irreversible EGFR-HER2-targeted agent BIBW 2992	4 3 2 1	4 3 2 1
Mechanisms of action and clinical trial results with the multikinase inhibitor vandetanib in lung cancer	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:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following 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:

- Effectively utilize tumor histology and biomarkers when making evidence-based lung cancer treatment decisions . . . . . 4 3 2 1 N/M N/A
- Formulate individualized treatment plans addressing the first-, second- and third-line management of recurrent or progressive non-small cell lung cancer (NSCLC), considering unique patient and tumor characteristics . . . . . 4 3 2 1 N/M N/A
- Appraise the side effects and perioperative complications of bevacizumab to assess its safety in the systemic management of early- and late-stage lung cancer.. . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of maintenance cytotoxic and/or biologic treatment to patients with metastatic NSCLC who successfully complete first-line systemic therapy . . . . . 4 3 2 1 N/M N/A
- Summarize the early clinical findings and ongoing research strategies with novel multikinase inhibitors exhibiting activity in NSCLC. . . . . 4 3 2 1 N/M N/A
- Recall the design and rationale of ongoing studies incorporating biologic agents into the neoadjuvant therapy of NSCLC . . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with lung cancer about participation in ongoing clinical trials . . . . . 4 3 2 1 N/M N/A

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

.....

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

.....

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 TWO — Please tell us about the faculty and moderator for this educational activity

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
F Anthony Greco, MD	4	3	2	1	4	3	2	1
John Heymach, MD, PhD	4	3	2	1	4	3	2	1
Rogerio C Lilenbaum, MD	4	3	2	1	4	3	2	1
Thomas J Lynch Jr, MD	4	3	2	1	4	3	2	1
Vincent A Miller, MD	4	3	2	1	4	3	2	1
Ronald B Natale, MD	4	3	2	1	4	3	2	1
Harvey I Pass, MD	4	3	2	1	4	3	2	1
Mark A Socinski, MD	4	3	2	1	4	3	2	1
Moderator	**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 moderator for this activity:

.....

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LCUTT109

Lung Cancer™ UPDATE

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Lung Cancer™ UPDATE

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