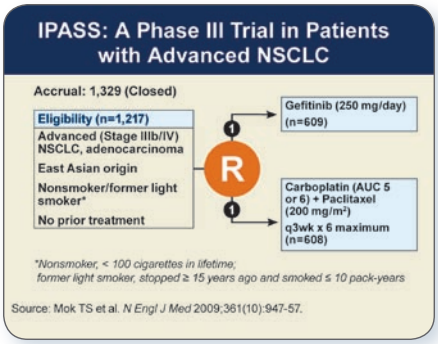
Year in Review

Lung Cancer: 2009

A CME monograph and web-based speaker's slide kit summarizing the year's most important meeting presentations and journal articles



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Web-based PowerPoint slide kit

FROM THE PUBLISHERS OF:
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Year in Review — Lung Cancer: 2009 CME Information

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 published or presented during the past year, along with experts' perspectives on these data, 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

- Compare and contrast the efficacy and toxicity profiles of bevacizumab and cetuximab when selecting a front-line chemobiologic regimen for patients with metastatic non-small cell lung cancer (NSCLC).
- Define the relative and absolute contraindications for the safe use of bevacizumab in the systemic management of lung cancer.
- Apply the results of recent clinical research to the rational selection of EGFR- or VEGF-inhibiting agents for patients with metastatic NSCLC.
- 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.
- Counsel appropriately selected patients with lung cancer about participation in ongoing clinical trials.

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Fischbach N et al. **Preliminary safety and effectiveness of bevacizumab-(BV) based treatment in subpopulations of patients with non-small cell lung cancer (NSCLC) from the ARIES study: A BV treatment observational cohort study (OCS).** *Proc World Conference on Lung Cancer* 2009;Abstract C2.7.

Pirker R et al; FLEX Study Team. **Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): An open-label randomised phase III trial.** *Lancet* 2009;373(9674):1525-31.

Scagliotti G et al. **Pemetrexed is more effective in patients with nonsquamous non-small cell lung cancer (NSCLC) histology: An analysis of three large, randomized, phase III trials.** *Proc World Conference on Lung Cancer* 2009;Abstract B2.6.

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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.

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

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.** *Proc ASCO* 2009;Abstract 8001.

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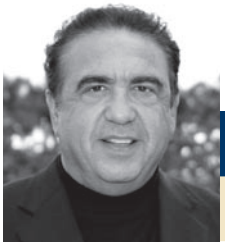

NEIL LOVE, MD

Papers of the year

I never thought the day would arrive when clinical research developments in breast cancer would be eclipsed by another tumor type, but oncology devotees might argue that in 2009 lung cancer provided more important steps forward than any other type of cancer.

To hone down this explosion of new findings for super-busy oncologists in practice, we once again (as in our prior *YiR* adventures) asked a panel of clinical investigators and community-based oncologists (see page 1) to provide analog ratings of 38 lung cancer journal articles and meeting presentations selected from 259 published or presented in the past year (Figure 1). Based on these ratings, we were able to identify 13 reports deemed to be of the greatest relevance to practicing physicians (Tier 1) and 21 additional papers that are also considered valuable (Tier 2). Highlights of all are included in this monograph.

Although there was general consensus in terms of which of these publications were most significant, everyone has their own opinion. So here are my personal nominees for the top 3 papers of the year:

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

Five years after the discovery that EGFR tumor mutations were associated with response to EGFR TKIs, this study defines a new algorithm in advanced NSCLC. Simply stated: Nonsmokers or oligosmokers and maybe all people with adenocarcinoma need to have their tumors genotyped in order to determine first-line therapy for metastatic disease. FISH and IHC seem not to be necessary, but this landmark study makes it abundantly clear that tumor genotyping needs to be part of every oncology practice, as patients with EGFR mutations clearly do better up front with an EGFR TKI than with chemotherapy, and it is not sufficient to rely on phenotypic factors like nonsmoking status to make this clinical decision.

2. Kwak EL et al. **Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066.** *Proc ASCO* 2009;Abstract 3509. Oral Presentation

Although the ASCO 2009 theme of personalized oncology leaves a faint whiff of hype in the air, two breathtaking presentations in Orlando were truly emblematic of the concept — this lung cancer report and Keith Flaherty's stunner on a B-raf inhibitor in melanoma. Both papers included waterfall plots to die for, and each was based on a simple logical pharmacologic solution to tumor oncogene addiction.

The EML4-ALK fusion oncogene — as with EGFR tumor mutations — is more common in nonsmokers and is estimated to occur in about five percent of all patients with NSCLC (ie, about as many cases as testicular cancer). Physicians in practice will need to soon figure out how to get this assay done — particularly for nonsmoking patients without EGFR mutations — and attempt to find trials with new agents for these patients.

3. Grilley-Olson JE et al. **Diagnostic reproducibility of squamous cell carcinoma in the era of histology-directed chemotherapy: A large prospective study.** *Proc ASCO* 2009;Abstract 8008.

Our reviewers weren't as impressed with this paper as it only managed to reach Tier 2 status, and I confess that other than the title and conclusion, my overworked and probably atrophied brain could make little sense out of the ASCO abstract or virtual presentation, but what I think this unique study demonstrated was that in an era in which the determination of lung cancer histology has become critical with regard to the safety of bevacizumab and efficacy of pemetrexed, even with primary tumor specimens in their hands (no FNAs or core biopsies), pathologists pretty much could not agree and had little confidence in defining whether a tumor was squamous or nonsquamous, creating perhaps more of a mess than ER and HER2 in breast cancer, and maybe, as with these two critical breast cancer tissue biomarkers, it will take another combined effort of ASCO and the American College of Pathology to find some practical solutions.

So although it's been exhilarating to watch lung cancer maybe leapfrog breast cancer with regard to new research findings, it is also disheartening to once again consider that with many of our positive steps forward, we are also taking one step (or at least a half) back.

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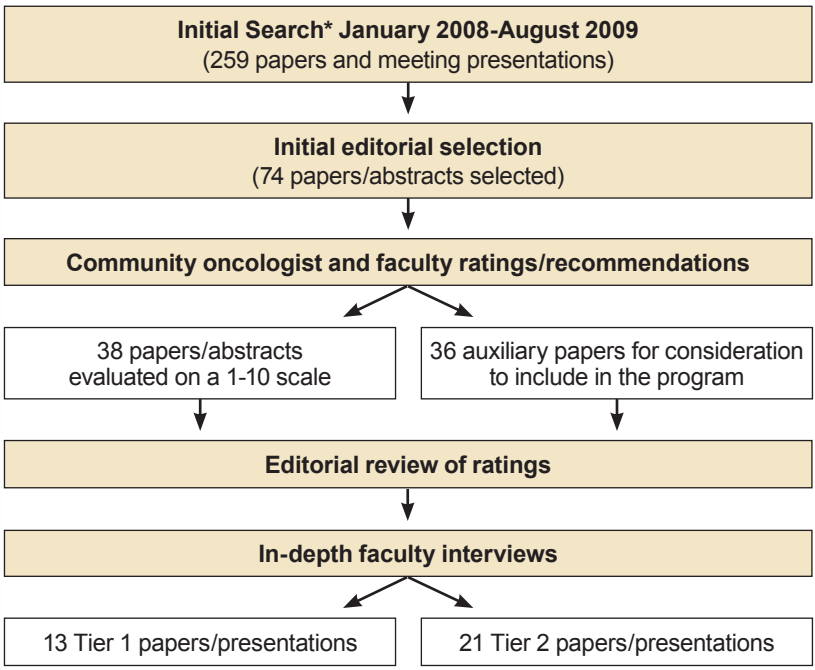
November 23, 2009

1 Processes for Identifying and Selecting Key Recent Reports on the Management of Non-Small Cell Lung Cancer



*** PubMed. January 1, 2008 to August 19, 2009, English language, clinical trials, randomized controlled trials, meta-analysis, practice guidelines for lung cancer, ASCO 2009, oral presentations, poster discussion papers and FWCLC 2008 and 2009, oral presentations.**

Gefitinib or Carboplatin/ Paclitaxel (C/P) in Pulmonary Adenocarcinoma

Mok TS et al

N Engl J Med 2009;361(10):947-57.

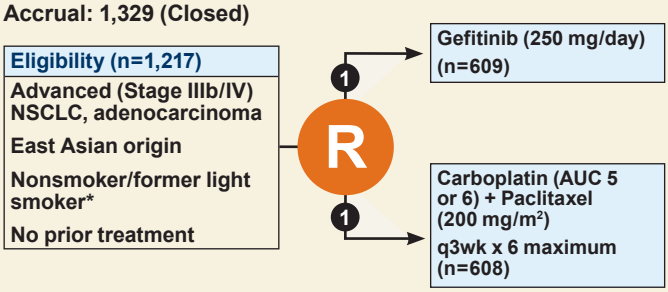
Introduction

- **EGFR tyrosine kinase inhibitors demonstrate improved efficacy in advanced non-small-cell lung cancer (NSCLC) in populations enriched for the presence of EGFR mutations**
  - **— Women**
  - **— Non-smokers**
  - **— Patients with lung adenocarcinomas**
  - **— Patients of Asian origin**
- **Current study objectives:**
  - **— Assess the efficacy and safety of first-line gefitinib versus C/P in EGFR mutation-enriched population with advanced NSCLC**
  - **— Assess the role of EGFR mutation as a predictor of treatment efficacy**

Sources: Mok TS et al. *N Engl J Med* 2009;361(10):947-57; Kim ES et al. *Lancet* 2008;372(9652):1809-18; Kosaka T et al. *Cancer Res* 2004;64(24):8919-23.

IPASS: A Phase III Trial in Patients with Advanced NSCLC

Accrual: 1,329 (Closed)



**Nonsmoker, < 100 cigarettes in lifetime; former light smoker, stopped ≥ 15 years ago and smoked ≤ 10 pack-years*

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

Efficacy of Gefitinib vs C/P in East Asian Patients with NSCLC

Objective Response Rate (ORR)	Gefitinib	C/P	*P*-value
Intent-to-treat population (n=609; 608)	43.0%	32.2%	<0.001
EGFR mutation-positive (n=132; 129)	**71.2%**	47.3%	<0.001
EGFR mutation-negative (n=91; 85)	**1.1%**	23.5%	0.001

Progression-Free Survival	Hazard Ratio	*P*-value
Intent-to-treat population	0.74	<0.001
EGFR mutation-positive	**0.48**	<0.001
EGFR mutation-negative	2.85	<0.001

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

Summary and Conclusions

- **Gefitinib is superior to C/P as 1st-line therapy in a selected EGFR mutation-rich population with pulmonary adenocarcinomas.**
  - **— Prolonged PFS and increased ORR**
  - **— Improved side effects and quality of life (data not shown)**
- **EGFR mutation status is a predictive biomarker in a selected EGFR mutation-rich population for responsiveness of pulmonary adenocarcinomas to 1st-line gefitinib treatment.**
  - **— PFS and ORR were significantly improved in patients who were positive for EGFR mutations**

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

FACULTY COMMENTS

DR HANNA: The IPASS data demonstrated that the population of never smokers that had EGFR mutations disproportionately benefited from gefitinib.

These data are practice changing. It is the first time in lung cancer that a biomarker has determined which therapy to use. Relying on clinical characteristics alone to determine treatment was flawed. In the past, one would have been tempted to administer an EGFR inhibitor to all never smokers, but clearly some never smokers should preferentially receive chemotherapy. In my clinical practice, if a patient has the clinical characteristics that indicate an EGFR mutation is possible, I test for the mutation up front.

DR LARA: It is remarkable that in this patient population that one would think is enriched for EGFR mutations, only 59 percent had a mutation. This tells you how insufficient a clinical profile is for selecting therapy, because a big proportion of patients will not have the target.

18 **Related reference on page 33**

Biomarker Analyses from a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib vs Carboplatin/Paclitaxel in Clinically Selected Patients with Advanced Non-Small Cell Lung Cancer in Asia (IPASS)

Fukuoka M et al

ASCO 2009;Abstract 8006.

Introduction

- **IPASS demonstrated overall superiority of first-line gefitinib (G) to carboplatin/paclitaxel (C/P) in selected East Asian population of nonsmokers/ex-light smokers with advanced pulmonary adenocarcinomas (see p 7).**
- **Current study objectives:**
  - **Evaluate progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) by EGFR mutation status, EGFR-gene-copy number and EGFR protein expression**
  - **IPASS (n = 1,217 randomized)**
    - **Biomarker consent (n = 1,038)**
    - **Provided tumor samples (n = 683)**

Source: Fukuoka M et al. ASCO 2009;Abstract 8006.

Biomarker Data in Evaluable Patients

Biomarker	Status	N (%)
EGFR mutation status (n=437)	Positive	261 (60%)
	Negative	176 (40%)
EGFR gene copy number (n=406)	High[1]	249 (61%)
	Low	157 (39%)
EGFR protein expression (n=365)	Positive[2]	266 (73%)
	Negative	99 (27%)

[1]High EGFR-gene-copy number was defined as high polysomy (≥ 4 copies in ≥ 40% of cells) or gene amplification (ratio of gene:chromosome per cell ≥ 2, or ≥ 15 copies of EGFR per cell in ≥ 10% of cells)
[2]Positive EGFR protein expression status defined as ≥ 10% of cells stained for EGFR protein

Source: Fukuoka M et al. ASCO 2009;Abstract 8006.

Progression-Free Survival by Biomarker Status

	PFS, HR[1]	P-value	PFS, Rx x Subgroup Interaction[2]
EGFR mutation status			
M+ (n=261)	0.48	<0.0001	<0.0001
M- (n=176)	2.85	<0.0001	
EGFR gene copy number			
FISH+ (n=249)	0.66	0.0050	
FISH+, M+ (n=190)	**0.48**	—	0.0437
FISH+, M- (n=55)	**3.85**	—	
FISH- (n=157)	1.24	0.2368	

[1]HR (hazard ratio) < 1.0 favors gefitinib; [2]HR in biomarker+ vs HR in biomarker-

Source: Fukuoka M et al. ASCO 2009;Abstract 8006.

Summary and Conclusions

- **EGFR mutation status is a predictive biomarker in a selected East Asian population for responsiveness of pulmonary adenocarcinomas to first-line gefitinib treatment ($p < 0.0001$).**
- **EGFR-gene-copy number was not as predictive of a differential PFS of gefitinib vs C/P ($p < 0.0437$).**
  - **— Patients with FISH+, EGFR mutation-negative disease did not benefit from gefitinib.**
- **EGFR protein expression was the least predictive (data not shown).**
- **Analysis of OS by EGFR mutation status is immature but trending toward improvement for EGFR mutation-positive disease treated with gefitinib (data not shown).**

Source: Fukuoka M et al. ASCO 2009;Abstract 8006.

FACULTY COMMENTS

DR HANNA: We already know that patients with a gene amplification of the EGFR family member ERB2 may benefit from trastuzumab treatment. Similarly, one could ask whether a patient with a gene amplification in ERB1 as detected by FISH would preferentially benefit from treatment with an EGFR inhibitor.

In this study, patients with positive FISH results seemed to benefit more from gefitinib than those with negative FISH results. The take-home message, however, was that EGFR mutation status trumped FISH status. Patients whose tumors were FISH-positive but EGFR mutation-negative did not preferentially benefit from gefitinib. FISH positivity is helpful to know about, but if patients do not have the EGFR mutation, they still should not preferentially receive gefitinib.

DR KRIS: I believe that this study shows that no other test is as good as the mutation test. The FISH assay, which has been the most discussed, is much less discriminating. If you test tumor tissue, then you should test for EGFR mutations.

3 **Related reference on page 31**

Phase III Trial of Cisplatin plus Gemcitabine with Either Placebo or Bevacizumab as First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer: AVAiL

Reck M et al

J Clin Oncol 2009;27(8):1227-34.

Introduction

- **Phase III ECOG-E4599 trial (*NEJM* 2006;355(24):2542) showed substantial clinical benefit of 1st-line bevacizumab (bev) plus carboplatin/paclitaxel in patients with nonsquamous non-small-cell lung cancer (NSCLC).**
- **Effectiveness of 1st-line bev plus cisplatin/gemcitabine (CG) regimen commonly used to treat NSCLC is not known.**
- **Current study objective:**
  - **Assess the efficacy and safety of the addition of 1st-line bev to the CG chemotherapy regimen in patients with advanced or recurrent nonsquamous NSCLC**

Source: Reck M et al. *J Clin Oncol* 2009;27(8):1227-34.

Phase III Randomized Trial of 1st-Line Bev plus CG

Accrual: 1,043 (Closed)

Eligibility
Advanced (Stage IIIb/IV) or recurrent nonsquamous NSCLC
No grade ≥2 hemoptysis
No CNS metastases
No history of thrombotic or hemorrhagic disorders
No non-healing wounds

R

- High- or Low-Dose Placebo + CG q3wk x 6 (n=347)
- Low-Dose Bev (7.5 mg/kg) + CG q3wk x 6 (n=345)
- High-Dose Bev (15 mg/kg) + CG q3wk x 6 (n=351)

All patients completing six treatment cycles assigned to continued Bev or placebo

Source: Reck M et al. *J Clin Oncol* 2009;27(8):1227-34.

Summary of Results

Efficacy Endpoints	Placebo+CG (n=347)	L-D Bev+CG (n=345)	H-D Bev+CG (n=351)
Objective response rate (ORR)	20.1% (reference)	34.1% (p<0.0001)	30.4% (p=0.0023)
Median PFS	6.1 mos (reference)	6.7 mos (HR=0.75)	6.5 mos (HR=0.82)
Severe AEs of Interest	**Placebo+CG (n=327)**	**L-D Bev+CG (n=330)**	**H-D Bev+CG (n=329)**
GI Perforation	<1%	—	<1%
FPH	0.3%	1.2%	0.9%

L-D low-dose; H-D high-dose; FPH fatal pulmonary hemorrhage

Source: Reck M et al. *J Clin Oncol* 2009;27(8):1227-34.

Summary and Conclusions

- **AVAiL is second randomized Phase III trial to demonstrate clinical benefit of bev plus platinum-based chemotherapy in patients with advanced NSCLC who are bev-eligible.**
  - **— PFS and ORR were increased**
- **Safety appeared similar to that seen in other studies of bev in NSCLC (*JCO* 2004;22(11):2184; *NEJM* 2006;355(24):2542)**
  - **— Severe pulmonary hemorrhage was increased in the bev arms of the current study with seven fatal events**
- **Although the study was not powered to compare the two doses of bevacizumab, no apparent efficacy or safety differences were observed.**

Source: Reck M et al. *J Clin Oncol* 2009;27(8):1227-34.

FACULTY COMMENTS

DR HANNA: This is an update of the data reported in 2008, with survival data reported in 2009. A slight improvement is evident in median progression-free survival, but the hazard ratio for the entire curve showed a benefit favoring the two bevacizumab arms versus the nonbevacizumab arm. The authors later reported that no difference had emerged in overall survival, a secondary endpoint of the trial. AVAiL simply reinforces the fact that bevacizumab improves response rates and progression-free survival when used with other chemotherapy — the effect is not specific to carboplatin and paclitaxel.

DR LARA: Although a benefit was recorded in progression-free survival in the AVAiL trial, it was extremely modest. That coupled with the fact that the overall survival endpoint was not met brings a sense of disappointment. Because the benefits were modest, we probably need to dig a little deeper and find out the molecular basis for identifying which patients will benefit, and this was not addressed in the trial.

15 **Related reference on page 33**

Safety and Effectiveness of Bevacizumab (BV) Based Treatment in Subpopulations of Patients with Non-Small Cell Lung Cancer (NSCLC) from the ARIES Study: A BV Treatment Observational Cohort Study (OCS)

Fischbach N et al

Proc World Conference on Lung Cancer 2009;Abstract C2.7.

Introduction

- **The ECOG-E4599 trial demonstrated that bevacizumab (BV) added to chemotherapy improves overall survival (OS) and progression-free survival (PFS) in patients with metastatic or locally-advanced NSCLC (*NEJM* 2006;355:2542).**
- **Current study objectives:**
  - **Assess efficacy and safety of BV added to chemotherapy in subpopulations of patients with NSCLC that were excluded or underrepresented in prior trials:**
    - **Patients with known brain metastases**
    - **Patients with history of hemoptysis**
    - **Elderly (≥70 years)**

Source: Fischbach N et al. *Proc World Conference on Lung Cancer* 2009;Abstract C2.7.

ARIES: Prospective Observational Cohort Study of Patients with NSCLC Treated with BV

- **Accrual: 1,758/2,000 targeted (as of February 9, 2009)**
  - **244 sites accruing patients; median follow-up: 8.4 months**
- **Eligibility (Primary Analysis Population)**
  - **Locally advanced/metastatic NSCLC (nonsquamous cell)**
  - **BV treatment with any first-line chemotherapy regimen**
  - **Start of BV-containing therapy <3 months prior to enrollment was allowed**
- **Descriptive safety analyses conducted for overall cohort and subpopulations**

Source: Fischbach N et al. *Proc World Conference on Lung Cancer* 2009;Abstract C2.7.

Summary of Results

Median PFS	6.67 mos (95% CI:6.28, 6.90)
Select Adverse Events	**Grade 3 or Above, n(%)**
Pulmonary Hemorrhage Overall cohort (n=1,758) History of hemoptysis (n=124)	 12 (0.7) 4 (3.2)
CNS Hemorrhage Overall cohort (n=1,758) Brain mets at baseline (n=126)	 2 (0.1) 0
Gastrointestinal Perforation Overall cohort (n=1,758)	 14 (0.8)

Source: Fischbach N et al. *Proc World Conference on Lung Cancer* 2009;Abstract C2.7.

Summary and Conclusions

- **Interim report of BV plus chemotherapy in "real-world" population of patients with NSCLC demonstrates:**
  - **— Multiple first-line chemotherapy regimens are used in combination with BV, with an apparent decreased usage of platinum-based regimens with increasing patient age (data not shown).**
  - **— Preliminary effectiveness and toxicity profiles are consistent with results of prior trials**
    - **— No reports of CNS bleeding in patients with brain metastases or of pulmonary hemorrhage in patients with cavitation in measurable tumors at baseline.**
- **Outcomes in specific patient subpopulations will be analyzed once the data is mature.**

Source: Fischbach N et al. *Proc World Conference on Lung Cancer* 2009;Abstract C2.7.

FACULTY COMMENTS

DR KRIS: The message that I take home from the ARIES trial is that it is safe to administer bevacizumab to patients who have brain metastases. The concern regarding the safety of using this drug in the treatment of brain metastases was derived from the extrapolation of experiences with another disease. The drug is now approved for patients with primary brain tumors.

DR NATALE: In terms of risks from bevacizumab, large registrational studies — ARIES and SAIL — have been performed in the United States, where community oncologists administering platinum-based regimens combined with bevacizumab as first-line therapy can register the outcomes of their patients.

These studies have now accumulated up to 3,000 patients, and interestingly the rate of fatal pulmonary hemorrhage is one half of a percent or lower.

So, clearly, in the community oncologists' hands the risks of a fatal pulmonary hemorrhagic event occurring with the use of bevacizumab is far lower than it was in either ECOG-E4599 or the AVAiL study for reasons that are not clear.

Cetuximab plus Chemotherapy in Patients with Advanced Non-Small-Cell Lung Cancer (FLEX): An Open-Label Randomised Phase III Trial

Pirker R et al

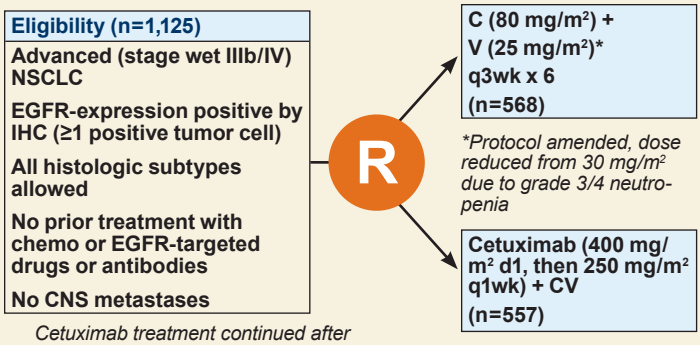
Lancet 2009;373(9674):1525-31.

Introduction

- Targeted drugs added to chemotherapy may improve the survival of patients with non-small-cell lung cancer (NSCLC) (*JCI* 2007;117(10):2740).
- Phase II trial in patients with advanced, EGFR-positive NSCLC suggested that the addition of cetuximab to cisplatin/vinorelbine (CV) improved survival and increased the response rate (*Ann Oncol* 2008;19(2):362).
- **Current study objective:**
  - Assess the efficacy and safety of cetuximab added to CV chemotherapy in the first-line in patients with advanced EGFR-positive NSCLC

Source: Pirker R et al. *Lancet* 2009;373(9674):1525-31.

Phase III Randomized Trial of First-Line Cetuximab plus CV



Cetuximab treatment continued after chemotherapy until disease progression or unacceptable toxicity occurred

Source: Pirker R et al. *Lancet* 2009;373(9674):1525-31.

Efficacy Results

Efficacy Parameter	Cetux + CV (n=557)	CV (n=568)	HR (95% CI)	*P*-value
Median OS				
All patients	11.3 mos	10.1 mos	0.87 (0.76-1.00)	0.044
Nonsquamous	12.0 mos	10.3 mos	0.94 (0.77-1.55)	
Squamous	10.2 mos	8.9 mos	0.80 (0.64-1.00)	
Median PFS	4.8 mos	4.8 mos	0.94 (0.83-1.08)	0.39
ORR	36%	29%	—	0.010

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; ORR = overall response rate

Source: Pirker R et al. *Lancet* 2009;373(9674):1525-31.

Summary and Conclusions

- **The addition of cetuximab improved the efficacy of first-line platinum-based chemotherapy in the treatment of EGFR-positive advanced NSCLC.**
  - **— OS was prolonged across all histological subtypes**
  - **— Tumor response rates were increased**
  - **— PFS, however, was unchanged**
- **Safety profile consistent with known patterns of side effects for individual treatment agents (data not shown).**
  - **— Main cetuximab-related adverse event was acne-like rash (10%, grade 3)**
  - **— High rate of febrile neutropenia observed (22%, grade 3/4)**

Source: Pirker R et al. *Lancet* 2009;373(9674):1525-31.

FACULTY COMMENTS

DR LARA: The trial demonstrated that the monoclonal antibody cetuximab improved clinical outcomes when added to chemotherapy. However, the benefit was modest and was coupled with a 22 percent rate of febrile neutropenia. I believe that the FLEX experience tells us that if you have a modest benefit and it seems to be confined to a subset of patients, it's necessary to characterize who composes that subset of patients. Studies presented at ASCO and the World Conference on Lung Cancer indicated that K-ras may not be the biomarker for cetuximab benefit or resistance in lung cancer. The open SWOG-S0819 trial will test the concept, and this trial is suitably powered to evaluate molecular subsets of patients, which may define who will benefit from cetuximab.

DR HERBST: This trial was positive, yet the hazard ratio was only 0.87. That's a benefit, but it's a small benefit. Clinicians have been using it in practice, especially for patients with squamous cell tumors who can't receive bevacizumab, and I also administer it in that setting.

2 **Related reference on page 31**

Pemetrexed is More Effective in Patients with Nonsquamous Non-Small-Cell Lung Cancer (NSCLC) Histology: An Analysis of Three Large, Randomized, Phase III Trials

Scagliotti G et al

Proc World Conference on Lung Cancer 2009;Abstract B2.6.

Introduction

- **Phase III studies indicate that nonsquamous tumor histology is a predictive factor for pemetrexed efficacy in treatment of advanced NSCLC.**
- **Current study objectives:**
  - **Evaluate the reproducibility and consistency of the increased efficacy of pemetrexed observed in three prior studies**
    - **Treatment-By-Histology Interaction (THI) model used to estimate the effect of histology on pemetrexed efficacy**

Source: Scagliotti G et al. *Proc World Conference on Lung Cancer* 2009;Abstract B2.6.

Statistical Analysis

- **Data analyzed by squamous (Sq) and nonsquamous (NSq) cell histology for three Phase III studies:**
  - **First Study (n = 571): 2nd-line pemetrexed vs docetaxel (P vs D) (*Oncologist* 2009;14:253)**
  - **Second Study (n = 1,725): 1st-line pemetrexed/cisplatin vs gemcitabine/cisplatin (P/C vs G/C) (*JCO* 2008;26:3543)**
  - **Third Study (n = 663): Maintenance pemetrexed vs placebo (mx-P vs PBO) (*Lancet* 2009;374:1432)**
- **THI model measures hazard ratio (HR) for histology effect in P arm relative to histology effect in control arm**

Source: Scagliotti G et al. *Proc World Conference on Lung Cancer* 2009;Abstract B2.6.

Efficacy of Pemetrexed by Tumor Histology and THI Interactions

Efficacy Parameter	P vs D		P/C vs G/C		Mx-P vs PBO	
Histologic Group (N)	NSq (399)	Sq (172)	NSq (1,252)	Sq (473)	NSq (481)	Sq (182)
Adjusted HR for OS	0.78	1.56	0.84	1.23	0.66	1.28
THI HR (*p*-value)	0.48 (0.001)		0.69 (0.002)		0.52 (0.033)	

THI HR<1, efficacy of P relative to control arm is greater in patients with NSq histology

Source: Scagliotti G et al. *Proc World Conference on Lung Cancer* 2009;Abstract B2.6.

Summary and Conclusions

- **Nonsquamous tumor histology is predictive of the improved efficacy of pemetrexed in patients with advanced NSCLC.**
- **Treatment advantage of pemetrexed is consistent and reproducible across three different studies and lines of therapy.**
- **Pemetrexed should be considered as the preferred treatment regimen for patients with nonsquamous advanced NSCLC.**

Source: Scagliotti G et al. *Proc World Conference on Lung Cancer* 2009;Abstract B2.6.

FACULTY COMMENTS

DR LILENBAUM: These data show that decisions pertaining to the optimal chemotherapy regimen in advanced NSCLC must include the consideration of histology. Pemetrexed-based regimens seem to offer an advantage to patients with nonsquamous histology. I believe that histology is a kind of epiphenomenon, a tip of the iceberg. We will eventually determine on a genomic level what underlies the phenotypic expression of a certain tumor.

DR LARA: The issue to me is the biology that underlies the nonsquamous histology. At the World Conference on Lung Cancer this year, David Gandara presented a study of mRNA levels of thymidylate synthase, the enzyme that pemetrexed is targeted against, in NSCLC. The mRNA levels varied across histologies, but both non-small cell adenocarcinoma and the squamous cell type included low mRNA levels in their value ranges. Are we excluding patients with squamous histology from benefiting from pemetrexed on the basis of histology alone? We need to find the true marker for pemetrexed beyond histology.

1 **Related reference on page 31**

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

Ciuleanu T et al

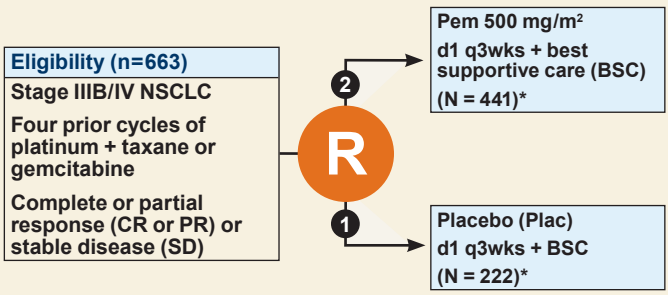
Lancet 2009;374(9699):1432-40.

Introduction

- Treatment guidelines for patients with advanced non-small-cell lung cancer (NSCLC) recommend waiting until disease progression to administer approved 2nd-line treatment agents such as docetaxel and pemetrexed.
- Recent Phase III studies (*Lung Cancer* 2006;52:155; *JNCI* 2005;97:499) of maintenance therapies after 1st-line chemotherapy in advanced NSCLC have not demonstrated an overall survival (OS) benefit.
- **Current study objective:**
  - Evaluate pemetrexed (Pem) as maintenance therapy in patients with advanced NSCLC that has not progressed on four cycles of 1st-line platinum-based chemotherapy

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

Phase III Randomized, Double-Blind, Placebo-Controlled Trial



**B12, folate and dexamethasone prophylaxis administered in both arms*

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

Summary of Results

Efficacy Parameter	Pem	Plac	HR	*P*-value
Progression-free survival	4.3 mos	2.6 mos	0.50	<0.0001
Nonsquamous (n=481)	4.5 mos	2.6 mos	0.44	<0.0001
Squamous (n=182)	2.8 mos	2.6 mos	0.69	0.039
Overall survival	13.4 mos	10.6 mos	0.79	0.012
Nonsquamous	15.5 mos	10.3 mos	0.70	0.002
Squamous	9.9 mos	10.8 mos	1.07	0.678
Select Grade 3/4 AEs				
Fatigue	5%	<1%	—	0.001
Neutropenia	3%	0%	—	0.006

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

Summary and Conclusions

- **Significant PFS and OS benefit was demonstrated with pemetrexed maintenance therapy in advanced NSCLC.**
- **Nonsquamous histology was predictive of improved PFS and OS benefit with pemetrexed maintenance.**
- **Overall rate of drug-related grade 3 or 4 AEs, including neutropenia and fatigue, was higher in the pemetrexed arm.**
  - **— Treatment discontinuation due to drug-related toxic effects was higher in pemetrexed arm (data not shown, 5% vs 1%).**
- **Pemetrexed maintenance therapy may be a new treatment option for patients with advanced nonsquamous NSCLC.**

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

FACULTY COMMENTS

DR KRIS: How to define maintenance therapy is an issue, but to me this is a practice-changing paper that establishes a new standard, and the FDA has agreed. This trial showed a huge overall survival improvement for patients with nonsquamous tumors who received maintenance pemetrexed. No benefit had been demonstrated in overall survival with other maintenance therapies in the treatment of advanced NSCLC.

DR HANNA: In my view, this study and the Cappuzzo study are somewhat flawed because post-study therapy was not balanced between the arms. In this trial published by Ciuleanu, only 18 percent of the patients on the placebo arm received pemetrexed. So we don't know whether delayed administration of pemetrexed is equally as good as immediate administration followed by its continuation as maintenance therapy. The disadvantage to not providing treatment breaks is that you'll never identify the cohort of patients who can go for a good period off treatment without experiencing disease progression.

17 **Related reference on page 33**

Phase II Study of Pemetrexed and Carboplatin plus Bevacizumab with Maintenance Pemetrexed and Bevacizumab as First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer

Patel JD et al

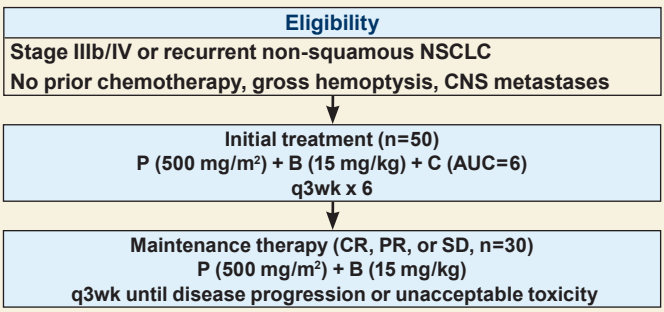
J Clin Oncol 2009;27(20):3284-9.

Introduction

- **Pemetrexed-containing chemotherapy regimens for NSCLC are noninferior to standard chemotherapy treatments and have greater tolerability (*JCO* 2004;22(9):1589; *JCO* 2008;26(21):3543).**
- **Phase III trials ECOG-E4599 (*NEJM* 2006;355(24):2542) and AVAiL (*JCO* 2007;18S:388) demonstrated a differential clinical benefit with bevacizumab added to chemotherapy for advanced nonsquamous NSCLC.**
- **Current study objective:**
  - **Assess the efficacy and safety of first-line pem/bev/carbo (P/B/C) treatment followed by P/B maintenance in patients with advanced nonsquamous NSCLC**

Source: Patel JD et al. *J Clin Oncol* 2009;27(20):3284-9.

Phase II Study of Pemetrexed in First-Line and Maintenance Therapies for NSCLC



Source: Patel JD et al. *J Clin Oncol* 2009;27(20):3284-9.

Summary of Results (ITT Population)

Efficacy Endpoints		
Median PFS at 13-month follow-up	7.8 mos	
Objective response rate	55%	
Select Adverse Events	**Grade 3**	**Grade 4**
Diverticulitis[1]	**6%**	**2%**
Thrombocytopenia	0%	8%
Neutropenia	4%	0%
Venous thrombosis	4%	2%

[1] *One case of Grade IV diverticulitis with bowel perforation*

Source: Patel JD et al. *J Clin Oncol* 2009;27(20):3284-9.

Summary and Conclusions

- **First-line carboplatin/pemetrexed and bevacizumab followed by maintenance pemetrexed/bevacizumab was effective, safe and tolerable.**
  - **— Median PFS and ORR compared favorably to other first-line NSCLC treatments**
  - **— No febrile neutropenia or pulmonary hemorrhage**
- **Grade 3 or 4 diverticulitis was an unexpected toxicity.**
- **PointBreak study (NCT00762034) will compare first-line P/B/C followed by P/B maintenance to standard treatment for advanced nonsquamous NSCLC.**

Sources: Patel JD et al. *J Clin Oncol* 2009;27(20):3284-9; Patel JD et al. *Clin Lung Cancer* 2009;10(4):252-6.

FACULTY COMMENTS

DR HANNA: This regimen appears to be an active regimen and to have a better side-effect profile than the Sandler regimen in ECOG-E4599. However, it is a Phase II trial, so it warrants further study.

A Phase III trial is ongoing in which patients receive both bevacizumab and pemetrexed as maintenance therapy.

Again, the value of that is still unanswered and at this point, this is similar to many Phase II studies that show promising data and are worth further study.

DR LARA: This is a single-arm, Phase II experience that needs to be further verified. I believe that this has received attention because it tells you that bevacizumab is potentially combinable with carboplatin and pemetrexed and that you could deliver maintenance pemetrexed and bevacizumab. In my mind, this ought to be considered investigational and maintenance pemetrexed/bevacizumab should not be used outside of a clinical trial. I am comfortable with the safety of using any platinum-based doublet with bevacizumab.

SATURN: A Double-Blind, Randomized, Phase III Study of Maintenance Erlotinib versus Placebo Following Non-Progression with 1st-Line Platinum-Based Chemotherapy in Patients with Advanced NSCLC

Cappuzzo F et al

ASCO 2009;Abstract 8001.

Introduction

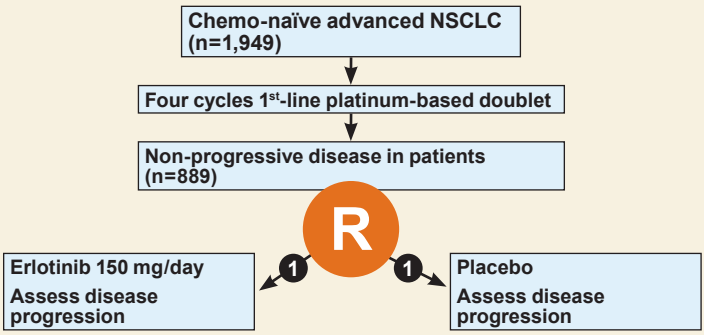
- **Efficacy and tolerability profile of erlotinib for NSCLC has been demonstrated in a large, phase III, placebo-controlled trial (*NEJM* 2005;353:123).**
- **Phase III TALENT study demonstrated a trend toward improved time to progression (TTP) or death in patients with NSCLC who continued to receive erlotinib after six cycles of 1st-line erlotinib with concurrent chemotherapy (*JCO* 2007;25:1545).**

Current study objectives:

Assess if erlotinib given right after 1st-line chemo prolongs progression-free survival (PFS) of patients with advanced NSCLC. Assess PFS in EGFR-positive subset of patients.

Source: Cappuzzo F et al. ASCO 2009;Abstract 8001.

Phase III, Placebo-Controlled Trial of Maintenance Erlotinib



Source: Cappuzzo F et al. ASCO 2009;Abstract 8001.

Efficacy Results

Progression-Free Survival	Erlotinib vs Placebo HR (95% CI)	*P*-value
ITT population (n=437; 447)	0.71 (0.62-0.82)	<0.0001
EGFR IHC-positive (n=307; 311)	0.69 (0.58-0.82)	<0.0001
EGFR mutation-positive (n=22; 27)	0.10 (0.04-0.25)	<0.0001
EGFR wild-type (n=199; 189)	0.78 (0.63-0.96)	0.0185
Adenocarcinoma (n=204; 197)	0.60 (0.48-0.75)	<0.0001
Squamous cell (n=166; 193)	0.76 (0.60-0.95)	0.0148

Source: Cappuzzo F et al. ASCO 2009;Abstract 8001.

Summary and Conclusions

- **Erlotinib maintenance therapy significantly improved PFS in patients with advanced NSCLC.**
- **Erlotinib treatment effect was independent of several clinical/biological characteristics, including tumor histology, gender and smoking status (data not shown).**
  - **— Greatest benefit in PFS seen in patients with EGFR mutation-positive disease (hazard ratio=0.10, p<0.0001)**
- **The effect on overall survival remains to be determined.**

Source: Cappuzzo F et al. ASCO 2009;Abstract 8001.

FACULTY COMMENTS

DR LARA: In SATURN, the post-study treatment differed according to the study arms. Only 16 percent of patients in the placebo arm received subsequent tyrosine kinase inhibitor therapy and many never received subsequent third-line therapy, as opposed to those in the erlotinib arm. That may have overemphasized the survival benefit.

SATURN tells us that erlotinib does improve outcomes in non-small cell lung cancer. Whether or not to use it in the maintenance setting depends on several factors, including whether the patient has an EGFR mutation.

DR KRIS: It's interesting that SATURN and ATLAS had similar trial designs except that patients in ATLAS received bevacizumab with their chemotherapy and maintenance therapy.

In SATURN, only 46 percent of patients had nonprogressed disease after chemotherapy, and 66 percent of patients in ATLAS had nonprogressed disease. That is an extraordinary testimonial for bevacizumab.

4 **Related reference on page 31**

ATLAS: A Randomized, Phase III Trial Comparing Bevacizumab with or without Erlotinib After Completion of Chemotherapy plus Bevacizumab for 1st-Line Treatment of Locally-Advanced, Recurrent, or Metastatic NSCLC

Miller VA et al

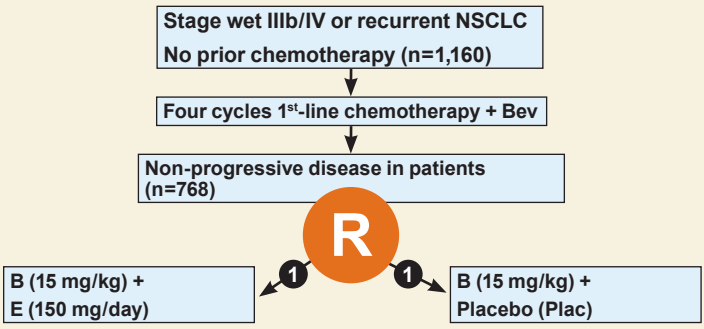
ASCO 2009;Abstract LBA8002.

Introduction

- **Phase III trials have demonstrated significant improvement in the survival of patients with advanced NSCLC treated with bevacizumab (bev) plus chemotherapy (*NEJM* 2006;355:2542) or with erlotinib monotherapy (*NEJM* 2005;353:123).**
- **Phase II data suggests that progression-free survival (PFS) may be prolonged when bev is combined with erlotinib after initial chemotherapy with bev (*JCO* 2007;25:4743).**
- **Current study objective: Assess if maintenance erlotinib with bev (E + B) after 1st-line therapy with chemotherapy/bev prolongs PFS in patients with advanced NSCLC**

Source: Miller VA et al. ASCO 2009;Abstract LBA8002.

Phase IIIb, Placebo-Controlled Trial of Maintenance Bev plus Erlotinib



Source: Miller VA et al. ASCO 2009;Abstract LBA8002.

Summary of Results

PFS (ITT Population)	B + E (n = 370)	B + Plac (n = 373)	HR (95% CI), *p*-value
Median PFS (median follow-up 8.3 mos)	4.8 mos	3.8 mos	0.722 (0.592-0.881), 0.0012
PFS rate, 3 mos PFS rate, 6 mos	68% 40%	53% 28%	—
Summary AE (grade≥3)	**B + E (n=368)**		**B + Plac (n=367)**
Grade 3-4	44.1%		30.4%
Grade 5	2.2%		1.1%

HR = hazard ratio

Source: Miller VA et al. ASCO 2009;Abstract LBA8002.

Summary and Conclusions

- **B + E maintenance therapy after four cycles of chemotherapy/bev significantly improved PFS in patients with advanced NSCLC.**
- **Improvement in PFS observed across multiple subgroups (data not shown).**
- **Toxicity profile consistent with known AE profiles for each agent, though occurrence of more serious AEs was increased in the B + E arm.**

Source: Miller VA et al. ASCO 2009;Abstract LBA8002.

FACULTY COMMENTS

DR LARA: Similar to the SATURN trial, ATLAS tells us that erlotinib is active as a second-line agent. I'm not sure, though, what the uptake of this strategy would be in the community. In my own practice, if I used bevacizumab in the front-line setting, I would continue with it as a single agent as maintenance. If the disease progressed, then I would switch to other active second- and third-line treatments.

The benefits that I saw from ATLAS were too modest for me to routinely combine treatments. I also have to consider the cost of combining biologic agents compared to the clinical benefit obtained from their use.

DR LILENBAUM: ATLAS adds to the literature arguing that early initiation of an alternative treatment is of potential benefit to patients. We need to be cautious about this trial because it is early and the trial was terminated early because it met its primary endpoint. Longer follow-up and more mature data are needed.

5 **Related reference on page 31**

Vandetanib plus Docetaxel vs Docetaxel as 2nd-Line Treatment for Patients with Advanced Non-Small-Cell-Lung Cancer (NSCLC): A Randomized, Double-Blind Phase III Trial (ZODIAC)

Herbst RS et al

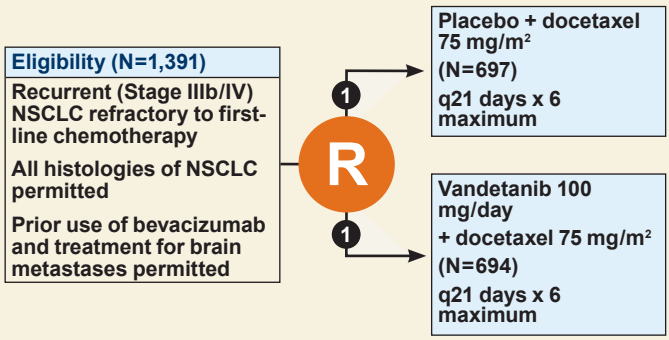
ASCO 2009;Abstract CRA8003.

Introduction

- Data from Phase II trial demonstrated an increase in PFS with vandetanib/docetaxel as second-line treatment of NSCLC (*JCO* 2007;25(27):4270).
- **Current study objectives:**
  - Assess the efficacy and safety of second-line vandetanib plus docetaxel versus docetaxel alone in patients with advanced, recurrent NSCLC
  - Assess efficacy and safety in female subgroup

Source: Herbst RS et al. ASCO 2009;Abstract CRA8003.

ZODIAC: A Phase III Trial of Vandetanib/Docetaxel vs Docetaxel Alone



Source: Herbst RS et al. ASCO 2009;Abstract CRA8003.

Efficacy Results

Clinical Response	Vandetanib + docetaxel (N=694)	Placebo + docetaxel (N=697)	HR, *P*-value
Objective response rate (ORR)	17%	10%	NR, <0.001
Median PFS	4 mos	3.2 mos	0.79, <0.001
Time to deterioration of symptoms (TDS)	NR	NR	0.77, <0.001

NR = not reported

Source: Herbst RS et al. ASCO 2009;Abstract CRA8003.

Summary and Conclusions

- **Vandetanib is the first oral targeted therapy to show significant clinical benefit in Phase III trials when added to standard chemotherapy in patients with previously treated NSCLC.**
  — Increased PFS, ORR and TDS
- **Significant clinical effect was not observed for PFS or OS in women (data not shown).**
- **Adverse events were similar to those seen in other NSCLC vandetanib studies (data not shown).**

Source: Herbst RS et al. ASCO 2009;Abstract CRA8003.

FACULTY COMMENTS

DR KRIS: I believe that you cannot view the vandetanib trials in isolation. These trials have led to inconsistent results, and the usefulness of this drug is unclear at this time. We have drugs available that clearly block EGFR efficiently and seem to block VEGF. It's still only a theoretical concept that it is advantageous to put together into one pill two drugs that do not block EGFR or VEGF as well as bevacizumab and erlotinib. It may be that you're inadequately blocking both targets. Doctors already have FDA-approved drugs that effectively block both targets.

DR HANNA: I believe that it's important for vandetanib to receive FDA approval because of the lack of effective treatments for lung cancer. The FDA will have to decide if there is value to the modest clinical benefit, increased side effects and higher cost with vandetanib.

If it is approved, I believe that other physicians and I will use it. It depends on whether other drugs are available and whether discoveries are made regarding patient subpopulations that can preferentially benefit.

16 **Related reference on page 33**

Clinical Features and Outcome of Patients with Non-Small-Cell Lung Cancer Who Harbor EML4-ALK

Shaw AT et al

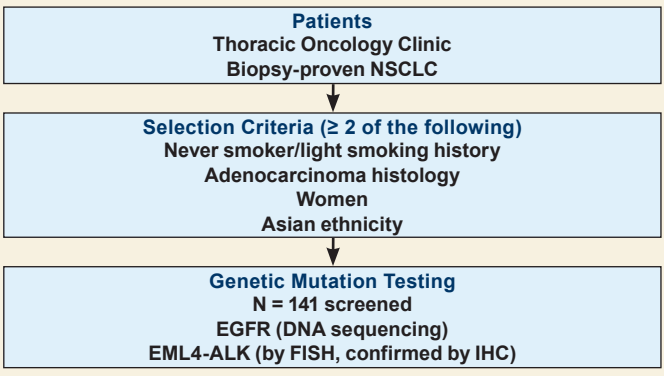
J Clin Oncol 2009;27(26):4247-53.

Introduction

- **EML4-ALK is a constitutively activated, chimeric tyrosine kinase encoded by a novel oncogene created by a small inversion within chromosome 2p.**
- **EML4-ALK inversion appears to be unique to NSCLC (*Clin Cancer Res* 2008;14:6618; *Br J Cancer* 2008;98:1536)**
  - **— Mostly in adenocarcinoma**
  - **— Non-overlapping with EGFR mutation**
- **Current study objective:**
  - **— Define clinicopathologic features, treatment response and survival of patients with and without EML4-ALK mutated NSCLC**

Source: Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

Patients and Methods



Source: Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

Demographic Features of Patients by EML4-ALK and EGFR Mutation

Characteristic	ALK+ (n = 19)	EGFR+ (n = 31)	ALK WT/WT*
Mutation-positive†	13%†	22%†	65%†
Age (median)	52 yrs	66 yrs	64 yrs
Male gender	58%	26%	32%
Never smoker Light smoker Smoker	74% 26% 0%	68% 19% 13%	26% 16% 57%

** ALK wild type/EGFR wild type*
† ALK mutant tumors were non-overlapping with EGFR mutant tumors

Source: Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

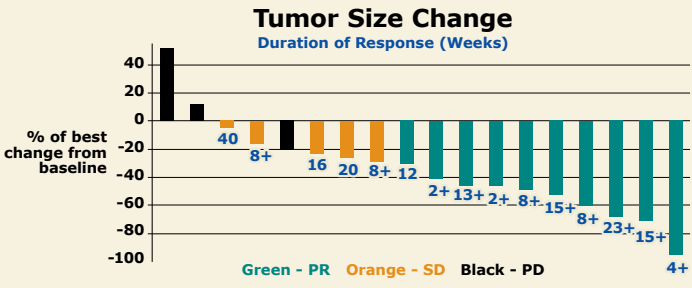
Clinical Outcome by EML4-ALK and EGFR Mutation Status

	ALK+	EGFR+	ALK WT/WT*
Chemotherapy† Response rate Time to progression	 25% 8-10 mos	 50% 8-10 mos	 35% 8-10 mos
EGFR TKI Response rate Time to progression	 0% 5 mos	 70% 16 mos	 13% 6 mos
Median overall survival	20 mos	32 mos	16 mos

** ALK wild type/EGFR wild type; † Platinum doublet*

Source: Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

Tumor Response to PF-02341066 in 19 Pretreated Patients with NSCLC and ALK Fusion Mutations



Overall response rate: 53%
Disease control rate at 8 weeks: 79%

Source: With permission from Kwak EL et al. ASCO 2009;Abstract 3509.

Summary and Conclusions

- **EML4-ALK+ defines a new molecular subset of NSCLC**
  - **— Non-overlapping with EGFR mutation**
  - **— Mostly signet-ring cell adenocarcinomas**
  - **— Younger age and more likely to be men**
  - **— High frequency in light/never smokers without EGFR mutations**
- **These patients receive no benefit from EGFR TKIs (ORR = 0%) and have similar response to chemotherapy to those with wild-type tumors.**
- **Novel ALK and MET kinase inhibitors may offer promising treatment options for patients with ALK mutant NSCLC (Kwak EL et al, ASCO 2009)**

Source: Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

FACULTY COMMENTS

DR HANNA: I believe that the Shaw and the Kwak trials are the most important trials and areas of study in lung cancer since the discovery of the EGFR mutation. We now have a never smoking population in which three distinct molecular subgroups may be identifiable. It is logical to test never smokers for EGFR and K-ras mutations.

If their tumor tissue is positive for either of those, there's no point in testing for the EML-ALK fusion protein. If the test results are negative for both, then it is certainly worthwhile to test for the EML-ALK fusion protein and preferentially treat those patients who test positive with an ALK inhibitor, which at this point means enrolling them on a clinical trial.

DR LARA: These two papers are remarkable advances in lung cancer, even though they benefit a minor portion of the patient population. An agent that is well targeted against the biology of that disease can produce remarkable benefits.

These papers are informative of the new era that we are in of integrating molecular selection into the clinical setting.

TIER 2 PAPERS/PRESENTATIONS — ANNOTATED BIBLIOGRAPHY

PATHOLOGY AND BIOMARKERS

1 Grilley-Olson JE et al. **Diagnostic reproducibility of squamous cell carcinoma in the era of histology-directed non-small cell lung cancer (NSCLC) chemotherapy: A large prospective study.** *Proc ASCO* 2009;Abstract 8008

The reproducible diagnosis of squamous cell versus nonsquamous cell classification based on H&E morphology is inadequate, highlighting the need for strict diagnostic criteria and confirmatory IHC stains.

2 O'Byrne KJ et al. **Molecular and clinical predictors of outcome for cetuximab in non-small cell lung cancer (NSCLC): Data from the FLEX study.** *Proc ASCO* 2009;Abstract 8007

Neither K-ras mutation status nor EGFR gene copy number differentially predicted response or benefit from cetuximab, although the development of early acne-like rash was associated with improvement in overall survival.

3 Hirsch FR et al. **Randomized phase II study of erlotinib (E) or intercalated E with carboplatin/paclitaxel (CP) in chemotherapy-naïve advanced NSCLC: Correlation of biomarker status and clinical benefit.** *Proc ASCO* 2009;Abstract 8026

Activating EGFR mutations are associated with improvement in six-month progression-free survival, whereas EGFR FISH positivity and absence of K-ras mutation were associated with a trend toward increased PFS.

4 Brugger W et al. **Biomarker analyses from the phase III placebo-controlled SATURN study of maintenance erlotinib following first-line chemotherapy for advanced NSCLC.** *Proc ASCO* 2009;Abstract 8020

EGFR gene protein expression, copy number and K-ras mutation were not predictive of benefit from erlotinib. Patients achieved a PFS benefit from erlotinib regardless of EGFR mutation status, although those with mutant disease experienced a greater benefit.

5 Herbst RS et al. **Biomarker evaluation in the Phase III, placebo (P)-controlled, randomized BeTa trial of bevacizumab (B) and erlotinib (E) for patients (Pts) with advanced non-small cell lung cancer (NSCLC) after failure of standard 1st-line chemotherapy: Correlation with treatment outcomes.** *Proc World Conference on Lung Cancer* 2009;Abstract B2.1

In the BeTa trial evaluating erlotinib with or without bevacizumab after failure of first-line chemotherapy for advanced NSCLC, none of the biomarkers assessed (EGFR mutation, gene copy number or K-ras mutation) were predictive of benefit from the combination.

6 Zhang W et al. **Genetic variants in angiogenesis pathway associated with clinical outcome in NSCLC patients (pts) treated with bevacizumab in combination with carboplatin and paclitaxel: Subset pharmacogenetic analysis of ECOG 4599.** *Proc ASCO* 2009;Abstract 8032

Preliminary results suggest that germline SNPs in the angiogenesis pathway may predict response, PFS and OS for patients with NSCLC treated with carboplatin/paclitaxel in combination with bevacizumab in ECOG-E4599.

LOCALIZED LUNG CANCER

7 Fischer B et al. **Preoperative staging of lung cancer with combined PET-CT.** *N Engl J Med* 2009;361(1):32-9.

The use of PET-CT for preoperative staging of NSCLC reduced both the total number of thoracotomies and the number of futile thoracotomies but did not affect overall mortality.

8 Vincent MD et al. **Updated survival analysis of JBR.10: A randomized phase III trial of vinorelbine/cisplatin versus observation in completely resected stage IB and II non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;Abstract 7501

Prolonged, nine-year median follow-up of the JBR.10 trial continues to show a survival benefit from adjuvant cisplatin-based chemotherapy, which appears to be confined to patients with N1 disease (OS = 6.8 years versus 3.6 years, HR = 0.68).

9 Felip E et al. **A phase III randomized trial of surgery (S) alone, or preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy followed by S, or S followed by adjuvant (adj) PC chemotherapy in early stage non-small cell lung cancer (NSCLC): NATCH follow-up data.** *Proc World Conference on Lung Cancer* 2009;Abstract PRS.3

More patients treated with preoperative versus adjuvant therapy received the planned chemotherapy, but no differences were observed in five-year DFS.

10 Janjigian YY et al. **Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor epidermal growth factor receptor (EGFR) mutations.** *Proc ASCO* 2009;Abstract 7523

Adjuvant gefitinib or erlotinib improves DFS for patients with completely resected Stage I to Stage III lung adenocarcinomas with mutations in EGFR exons 19 and 21.

11 Kris MG et al. **Phase II trial of induction and adjuvant bevacizumab with cisplatin and docetaxel in patients with locally advanced NSCLC.** *Proc World Conference on Lung Cancer* 2009;Abstract C6.3

All patients received induction cisplatin/docetaxel and bevacizumab, except those with squamous cell NSCLC or hemoptysis who received only induction chemotherapy. The addition of bevacizumab to induction cisplatin/docetaxel appeared to increase response rate (58 percent versus 40 percent), pathologic downstaging (47 percent versus 28 percent) and R0 resection rate (91 percent versus 82 percent) for patients with locally advanced NSCLC.

12 Socinski MA et al. **Incorporation of bevacizumab (B) and erlotinib (Er) with induction (Ind) and concurrent (Conc) carboplatin (Cb)/paclitaxel (P) and 74 Gy of thoracic radiotherapy in stage III non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;Abstract 7528

The incorporation of bevacizumab and erlotinib with induction carboplatin/paclitaxel and thoracic radiation therapy appears feasible, with promising overall survival (estimated one-year OS = 76 percent) and esophagitis as the primary toxicity in Stage III NSCLC.

13 Gore EM et al. **A phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small cell lung cancer: Initial analysis of Radiation Therapy Oncology Group 0214.** *Proc ASCO* 2009;Abstract 7506

PCI in patients without progressive disease after locoregional therapy for Stage III NSCLC significantly decreases the rate of CNS metastases but does not result in improvements in OS or DFS.

ADVANCED LUNG CANCER

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In a meta-analysis of four trials (N = 2,018) of first-line chemotherapy in combination with cetuximab, significant improvements in OS, PFS and overall response rate were demonstrated.

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Carboplatin/paclitaxel in combination with cetuximab/bevacizumab demonstrates safety, tolerability and efficacy in advanced NSCLC and is the most active regimen studied to date in SWOG for patients with advanced, nonsquamous cell, treatment-naïve NSCLC.

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

In patients with previously treated advanced NSCLC, vandetanib and erlotinib showed equivalent efficacy for PFS and OS in a planned noninferiority analysis.

17 De Boer R et al. **Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer (NSCLC): A randomized, double-blind phase III trial (ZEAL).** *Proc ASCO* 2009;Abstract 8010

Vandetanib with pemetrexed demonstrated evidence of a clinical benefit for patients with pretreated advanced NSCLC but no statistically significant PFS prolongation compared to pemetrexed alone.

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In patients with advanced NSCLC harboring an EGFR mutation, first-line gefitinib resulted in significantly higher ORR (74.5 percent versus 29.0 percent) and PFS (10.4 months versus 5.5 months) than carboplatin/paclitaxel. OS analysis is pending.

19 Inoue A et al; North East Japan Gefitinib Study Group. **First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy.** *J Clin Oncol* 2009;27(9):1394-400.

Patients with EGFR-mutant NSCLC and poor performance status benefited from treatment with first-line gefitinib (ORR = 66 percent, PS improvement rate = 79 percent, median PFS = 6.5 months and median OS = 17.8 months).

20 Rosell R et al; Spanish Lung Cancer Group. **Screening for epidermal growth factor receptor mutations in lung cancer.** *N Engl J Med* 2009;361(10):958-67.

Large-scale screening of patients for EGFR mutations with subsequent erlotinib treatment is feasible and leads to impressive outcomes, with median progression-free survival and overall survival of 14 months and 27 months, respectively.

21 Laurie SA et al. **Overall survival [OS] results of NCIC Clinical Trials Group [CTG] BR.24: A randomized, double-blind trial of carboplatin + paclitaxel [C+P] with either daily oral cediranib, a potent inhibitor of all vascular endothelial growth factor receptor tyrosine kinases, or placebo, in advanced non-small cell lung cancer [NSCLC]**. *Proc World Conference on Lung Cancer* 2009;Abstract C1.1

The addition of cediranib to carboplatin/paclitaxel resulted in improved ORR and PFS but not OS, possibly as a result of early fatal adverse events associated with the dose of cediranib used in this study.

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Rosell R et al. **Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer.** *Ann Oncol* 2008;19(2):362-9.

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Brodowicz T et al. **Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: A phase III trial.** *Lung Cancer* 2006;52(2):155-63.

Westeel V et al. **Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer.** *J Natl Cancer Inst* 2005;97(7):499-506.

Hanna N et al. **Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.** *J Clin Oncol* 2004;22(9):1589-97.

Manegold C et al. **Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704.** *Proc ASCO* 2007;Abstract LBA7514.

Shepherd FA et al. **Erlotinib in previously treated non-small-cell lung cancer.** *N Engl J Med* 2005;353(2):123-32.

Gatzemeier U et al. **Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: The Tarceva Lung Cancer Investigation Trial.** *J Clin Oncol* 2007;25(12):1545-52.

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.

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.

Takeuchi K et al. **Multiplex reverse transcription-PCR screening for EML4-ALK fusion transcripts.** *Clin Cancer Res* 2008;14(20):6618-24.

Fukuyoshi Y et al. **EML4-ALK fusion transcript is not found in gastrointestinal and breast cancers.** *Br J Cancer* 2008;98(9):1536-9.

Post-Test

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the IPASS trial, first-line gefitinib resulted in a superior _____ compared to carboplatin/paclitaxel in a population that was clinically selected for enrichment of EGFR mutations.**
   a. Overall response rate (ORR)
   b. Progression-free survival (PFS)
   c. Overall survival (OS)
   d. All of the above
   e. Both a and b
2. **In biomarker analyses of IPASS, which of the following was the most strongly predictive of a differential PFS and ORR benefit with first-line gefitinib versus carboplatin/paclitaxel?**
   a. EGFR mutation status
   b. EGFR gene copy number
   c. EGFR protein expression
3. **In the Phase III AVAiL study, the addition of bevacizumab to first-line cisplatin/gemcitabine resulted in significant improvement in _____ for patients with nonsquamous cell non-small cell lung cancer (NSCLC).**
   a. ORR
   b. PFS
   c. OS
   d. All of the above
   e. Both a and b
4. **ARIES is an observational cohort study that examines "real world" patients who received chemotherapy and bevacizumab for locally advanced or metastatic, nonsquamous cell NSCLC, including those with _____.**
   a. Known brain metastases
   b. History of hemoptysis
   c. Advanced age (>70 years old)
   d. All of the above
5. **In the FLEX trial, adding cetuximab to cisplatin/vinorelbine improved _____ among patients with advanced EGFR-positive NSCLC.**
   a. ORR
   b. PFS
   c. OS
   d. Both a and b
   e. Both a and c
6. **In the FLEX trial, the clinical benefits of adding cetuximab to cisplatin/vinorelbine for patients with advanced EGFR-positive NSCLC were observed regardless of histology.**
   a. True
   b. False
7. **In a meta-analysis of three large, randomized Phase III trials, which histology type was predictive of benefit from pemetrexed in patients with advanced NSCLC?**
   a. Squamous cell NSCLC
   b. Nonsquamous cell NSCLC
   c. Histology was not predictive of benefit from pemetrexed
8. **In the study published by Ciuleanu and colleagues, maintenance pemetrexed resulted in a significant PFS and OS benefit for patients with nonprogressive, advanced _____ after first-line platinum-containing doublet chemotherapy.**
   a. Nonsquamous cell NSCLC
   b. Squamous cell NSCLC
   c. Both a and b
9. **The SATURN trial evaluated which of the following strategies as maintenance therapy after nonprogression with first-line platinum-based chemotherapy for patients with advanced NSCLC?**
   a. Bevacizumab versus erlotinib
   b. Bevacizumab versus pemetrexed
   c. Erlotinib versus placebo
10. **The ATLAS trial demonstrated an improvement in PFS with the addition of _____ to maintenance bevacizumab for patients who had completed first-line therapy for advanced NSCLC.**
    a. Erlotinib
    b. Cetuximab
    c. Pemetrexed
11. **In the randomized Phase III ZODIAC trial, the addition of vandetanib to second-line docetaxel resulted in a significant improvement in _____ for patients with advanced NSCLC.**
    a. ORR
    b. PFS
    c. OS
    d. All of the above
    e. Both a and b
12. **Which of the following are clinical and pathological characteristics of patients with EML4-ALK-positive NSCLC?**
    a. Mostly with adenocarcinomas, signet-ring cell subtype
    b. Nonoverlapping with EGFR mutation
    c. Younger age
    d. Nonsmoking status or former light smoking history
    e. All of the above

Post-test answer key: 1e, 2a, 3e, 4d, 5e, 6a, 7b, 8a, 9c, 10a, 11e, 12e

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IPASS: Clinical trial results and biomarker analyses in a study of first-line therapy with gefitinib versus carboplatin/paclitaxel in advanced NSCLC	4 3 2 1	4 3 2 1
Clinical trial results with first-line chemotherapy/bevacizumab (AVAiL, ARIES) and with chemotherapy/cetuximab (FLEX) in patients with advanced NSCLC	4 3 2 1	4 3 2 1
Recent clinical trial results (ATLAS, SATURN, JMEN) of maintenance therapy for patients with advanced NSCLC	4 3 2 1	4 3 2 1
Second-line therapy with vandetanib/docetaxel versus docetaxel alone for patients with advanced NSCLC	4 3 2 1	4 3 2 1
Clinical features and outcomes for patients with advanced NSCLC harboring EML4-ALK	4 3 2 1	4 3 2 1
Efficacy of pemetrexed in patients with advanced nonsquamous NSCLC	4 3 2 1	4 3 2 1

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- Apply the results of recent clinical research to the rational selection of EGFR- or VEGF-inhibiting agents for patients with metastatic NSCLC. . . . . 4 3 2 1 N/M N/A
- 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
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Lung Cancer: 2009

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Lung Cancer™
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