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Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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Panos Fidias, MD
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CONTENTS

2 Audio CDs
Monograph

CME Certified

Lung Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

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

LEARNING OBJECTIVES

- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR or K-ras mutations, EML4-ALK gene fusions, ROS1 rearrangements and other recently identified driver mutations — and the investigational and approved treatment options for patients expressing these biomarkers.
- Describe emerging efficacy and tolerability data with irreversible EGFR tyrosine kinase inhibitor therapy for patients with advanced EGFR-mutant NSCLC and combined EGFR targeting in patients with acquired resistance to EGFR tyrosine kinase inhibitors.
- Develop an evidence-based approach to the selection of induction and continuation maintenance biologic therapy and/or chemotherapy in patients with advanced NSCLC.
- Describe the rationale for and emerging data with tumor immunotherapy directed at PD-1 in lung cancer and other solid tumors.
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

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TABLE OF CONTENTS

FACULTY INTERVIEWS

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EDITOR

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INTERVIEW

D Ross Camidge, MD, PhD

Dr Camidge is Director of the Thoracic Oncology Clinical Program at the University of Colorado Cancer Center in Aurora, Colorado.

Tracks 1-19

Track 1 Development of crizotinib for the treatment of advanced non-small cell lung cancer (NSCLC) with ALK gene rearrangements

Track 2 CNS progression and duration of response with crizotinib in ALK-positive NSCLC

Track 3 Mechanisms underlying the development of resistance to crizotinib

Track 4 Frequency of crizotinib-associated visual effects and impact on activities of daily living in patients with ALK-positive NSCLC

Track 5 Rapid-onset hypogonadism secondary to crizotinib use in men with advanced NSCLC

Track 6 Clinical activity of crizotinib in advanced NSCLC harboring ROS1 gene rearrangement

Track 7 Clinical approaches to patients with EGFR-mutant NSCLC who experience disease progression while receiving an EGFR tyrosine kinase inhibitor (TKI)

Track 8 Results of the LUX-Lung 3 study comparing the irreversible pan-HER inhibitor afatinib to cisplatin/pemetrexed as first-line treatment in advanced EGFR-mutant NSCLC

Track 9 Activity and tolerability of afatinib/cetuximab in patients with advanced NSCLC and acquired resistance to erlotinib or gefitinib

Track 10 Safety and activity of anti-programmed death-1 (PD-1) antibody in lung cancer and other solid tumors

Track 11 **Case discussion:** A 59-year-old man and never smoker with resected TTF1-positive M1a N2 adenocarcinoma of the lung without evidence of disease on PET-CT scans receives "pseudo-adjuvant" cisplatin/docetaxel

Track 12 Long-term control of brain and bone metastases in EGFR-mutant NSCLC with continued erlotinib treatment and radiation therapy

Track 13 Results of the SELECT study: A multicenter Phase II trial of adjuvant erlotinib in resected EGFR-mutant NSCLC

Track 14 **Case discussion:** A 59-year-old woman and never smoker with widespread, asymptomatic adrenal, renal and liver metastases from ALK-positive adenocarcinoma of the lung receives crizotinib on a clinical trial

Track 15 Prolonged progression-free survival with pemetrexed in advanced ALK-positive NSCLC

Track 16 Crizotinib-associated side effects

Track 17 Clinical benefit from pemetrexed before and after crizotinib exposure in advanced ALK-positive NSCLC

Track 18 **Case discussion:** A 54-year-old Asian man with a 5 pack-year smoking history has asymptomatic EGFR, K-ras, PI3 kinase, ROS1, ALK and MET wild-type metastatic NSCLC and receives carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance therapy

Track 19 AVAPERL study: Continuation maintenance therapy with pemetrexed/bevacizumab after first-line cisplatin/pemetrexed/bevacizumab in advanced nonsquamous NSCLC

Select Excerpts from the Interview

Tracks 2, 4-5

DR LOVE: What is the typical duration of response in patients with ALK-positive non-small cell lung cancer (NSCLC) receiving crizotinib?

DR CAMIDGE: The median progression-free survival (PFS) is between 9 and 10 months, but "the devil's very much in the details." We reported at ASCO 2012 that in about 46% of patients with ALK-positive NSCLC when crizotinib stops working, it does so due to disease progression within the brain.

Of note, in about 85% of cases, the brain was the only site of progression. The brain is standing out as the Achilles heel for crizotinib. When we administered radiation therapy to patients with CNS-only progression and continued crizotinib, it took an average of 7 months before patients experienced another progression outside of the brain (Weickhardt 2012a).

DR LOVE: Would you discuss the recent data your group has reported on crizotinib-related visual and gonadal effects?

DR CAMIDGE: Visual effects can manifest within days of a patient receiving crizotinib. They are classically at the edges of the patient's vision, usually in low-light conditions. Patients see either flashing lights or smearing of lights (Salgia 2012). Occasionally, patients see high-contrast images, such as banisters on the staircase, invert their registrations of dark and light. These issues improve over time, and that may be because the visual system slowly adapts. These visual effects are not harmful in any way. They don't prohibit people from driving or watching TV. However, I warn patients about them because otherwise they are concerned that it may be a more serious problem.

The hypogonadism story goes back to a 35-year-old patient of mine who was faring fantastically on crizotinib and whose cancer had melted away. He came in for a follow-up visit feeling absolutely exhausted. Patients typically get a bit of fatigue on crizotinib but not to this extent. We ended up checking his testosterone level and it was low. We're aware that testosterone levels can drop with advanced cancer if you've been through chemotherapy, so we began evaluating testosterone levels in both the patients receiving crizotinib and in a "control group" of my other patients with advanced NSCLC who were receiving standard therapies.

Consistent with the literature, we found low testosterone levels in about 30% of patients receiving standard therapy, but levels were low in 100% of the men who were receiving crizotinib. When we tracked the levels longitudinally, they were generally normal before patients began receiving crizotinib but would drop to below the lower limit of normal within about 3 weeks of initiating crizotinib (Weickhardt 2012b). I send these patients receiving crizotinib to the endocrinologist, where they discuss the pros and cons of testosterone replacement.

Track 6

DR LOVE: Would you comment on another major story that has evolved recently with evidence that crizotinib has clinical activity in patients with advanced NSCLC harboring ROS1 gene rearrangement?

DR CAMIDGE: This year at ASCO we saw a report of crizotinib for patients with ROS1 gene rearrangements, which are similar to ALK translocations. Although ROS1 rearrangements occur in fewer than 1% of lung cancer cases, patients with these mutations respond as well to crizotinib as do the patients with ALK positivity. I believe that will probably lead to a slight label expansion for crizotinib.

DR LOVE: Have you administered crizotinib to any patients with ROS1 rearrangements?

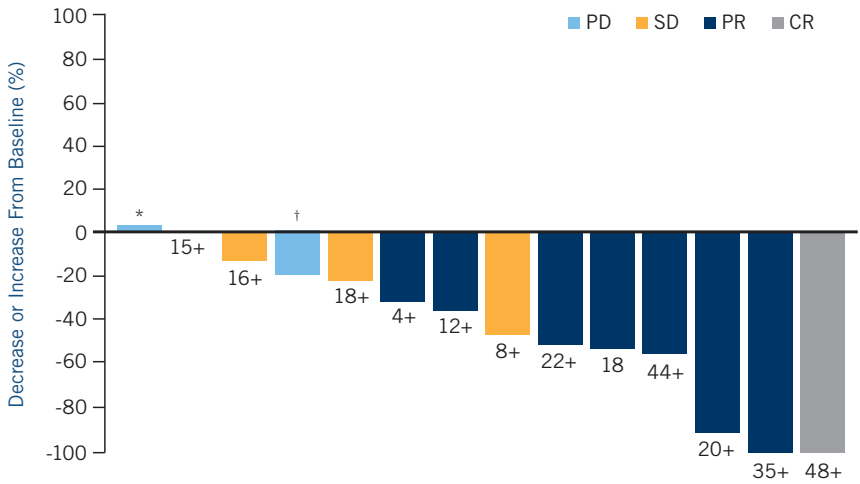
DR CAMIDGE: I had a patient, a medical oncologist actually, who had me test him for everything, all of which was negative. The ROS1 story had only broken a few months prior. We developed our own assay, and his was the first positive result.

He'd experienced a minimal response to carboplatin/pemetrexed/bevacizumab, and we placed him on our crizotinib study. He experienced a rapid, excellent response. We had to discontinue crizotinib about 6 weeks later for an unrelated bowel perforation. He was unwell and in intensive care.

Afterward, per study protocol, his first CT scan indicated progression. He'd been off crizotinib for many weeks, and if you look at the waterfall plot that Dr Alice Shaw presented at ASCO 2012, he is one of the patients who experienced progression (Shaw 2012; [1.1]). We were able to rechallenge with crizotinib when he'd recovered from his bowel operation, and he experienced another 6 to 7 months of disease control on crizotinib.

1.1

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



Overall response rate	Median duration of treatment	Disease control rate at 8 weeks
57.1%	25.7 weeks	79.0%

* Tumor ROS1 FISH-positive but negative for ROS1 gene fusion expression; † Crizotinib held >6 weeks prior to first scans that indicated PD; + Treatment ongoing (in weeks)
PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response

With permission from Camidge DR, Shaw AT et al. *Proc ASCO* 2012;**Abstract 7508**.

Track 8

DR LOVE: What are your thoughts on the recently reported results from the LUX-Lung 3 study evaluating the irreversible EGFR tyrosine kinase inhibitor (TKI) afatinib versus cisplatin/pemetrexed as first-line therapy for advanced EGFR-mutant NSCLC?

DR CAMIDGE: These results appear to corroborate the existing data that patients with EGFR mutation benefit from up-front targeted therapy with an EGFR TKI. Patients who received afatinib on the LUX-Lung 3 study experienced a PFS benefit compared to those who received standard therapy (Yang 2012; [1.2]). Because the study included patients with other rare, less responsive types of EGFR mutations, not just the classic L858R and exon 19 deletions, the authors performed a subset analysis in which they analyzed patients with only those common mutations. In the afatinib arm, the PFS was a little more than 13 months in patients with L858R/del 19 mutations, although that may be mild massaging of the data.

Now we ask, what does that mean? If and when afatinib receives an FDA license, will it be the first to be mutation specific in the EGFR category? What will cause somebody to use afatinib rather than erlotinib in that setting, even though erlotinib doesn't technically have a mutation-specific license? Some people are worried that the toxicity with afatinib appears to be greater than that with erlotinib. The Grade 3 rates of diarrhea, rash and paronychia are in the 10% to 20% range. These are severely toxic agents in some individuals and may require dose reductions. An ongoing head-to-head study in the Far East of afatinib versus gefitinib will help toward ascertaining the side effects and finding out whether afatinib is any better or worse than the traditional reversible EGFR TKIs. ■

1.2

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

Efficacy	Afatinib (n = 230)	Cis/pem (n = 115)	Hazard ratio	*p*-value
Median progression-free survival	11.1 mo	6.9 mo	0.58	0.0004
Objective response rate	56.1%	22.6%	—	<0.001
	Afatinib (n = 229)		**Cis/pem** (n = 111)	
Select adverse events	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	95.2%	14.4%	15.3%	0%
Rash/ache	89.1%	16.2%	6.3%	0%
Paronychia	56.8%	11.4%	0%	0%

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

SELECT PUBLICATIONS

Salgia R et al. **Visual effects in anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) patients treated with crizotinib.** *Proc ASCO* 2012;**Abstract 7596**.

Weickhardt AJ et al. **Continuation of EGFR/ALK inhibition after local therapy of oligoprogressive disease in EGFR mutant (Mt) and ALK+ non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012a;**Abstract 7526**.

Weickhardt AJ et al. **Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic nonsmall cell lung cancer.** *Cancer* 2012b;[Epub ahead of print].

INTERVIEW

Bruce E Johnson, MD

Dr Johnson is Professor of Medicine at Harvard Medical School and Program Director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-15

Track 1 Epidemiology of EGFR mutations and ALK rearrangements in adenocarcinomas of the lung

Track 2 Response to crizotinib in ROS1-rearranged advanced NSCLC

Track 3 Development of a next-generation sequencing platform to simultaneously test for multiple targetable genetic abnormalities in NSCLC

Track 4 Identification of sensitizing versus nonsensitizing EGFR mutations in NSCLC

Track 5 Mechanisms of acquired resistance to crizotinib in advanced ALK-positive NSCLC

Track 6 Selection of patients with NSCLC to test for EGFR mutations and ALK rearrangements

Track 7 Challenges in the genomic characterization of small cell carcinoma of the lung

Track 8 Combination therapy with neratinib and the mTOR inhibitor temsirolimus for advanced HER2-mutant NSCLC

Track 9 Targeting BRAF mutations in NSCLC

Track 10 Results of a Phase II, double-blind, randomized study of docetaxel with or without selumetinib in advanced K-ras-mutant NSCLC

Track 11 Clinical activity with inhibition of immune checkpoint PD-1 in advanced NSCLC

Track 12 Anti-MET monoclonal antibody onartuzumab (MetMAb) in combination with erlotinib in MET-positive advanced NSCLC

Track 13 Perspective on the SELECT study and proposed US cooperative group trials of adjuvant erlotinib in EGFR-mutant NSCLC

Track 14 Activity of afatinib/cetuximab in patients with advanced NSCLC and acquired resistance to erlotinib or gefitinib

Track 15 Perspective on the LUX-Lung 3 results comparing afatinib to cisplatin/pemetrexed as first-line treatment for advanced adenocarcinoma of the lung harboring EGFR-activating mutations

Select Excerpts from the Interview

Track 4

DR LOVE: What is known about the clinical behavior of tumors based on the type of EGFR mutation present?

DR JOHNSON: Not all EGFR mutations respond in the same way. The most common are exon 19 deletions, which are associated with the highest response rate of about 80%. Patients with exon 19 deletions who receive EGFR TKI therapy experience a median PFS in the 15- to 18-month range. The second most common is a L858R mutation, which has response rates of approximately 60% and median PFS of about 12 months.

One EGFR mutation that's dramatically different is called an insertion mutation of exon 20, meaning several amino acids are inserted into the epidermal growth factor receptor. Tumors with this mutation are resistant to EGFR TKI therapy. So we typically don't administer erlotinib to patients with this mutation.

It's important for an oncologist in practice to know whether a mutation sensitizes a tumor to a specific inhibitor or makes it resistant. We also believe it is important for oncologists who don't work with these agents every day to have a tool that will allow them to provide additional information to the patient as to why this is the case. Perhaps the leading site for providing this information is an academic site developed by Dr William Pao at Vanderbilt. It is called My Cancer Genome. I believe it provides unbiased information and is probably the leading site we use for both defining the mutations and determining whether these mutations are sensitizing or nonsensitizing.

Track 9

DR LOVE: Would you discuss what is currently known about BRAF mutations in melanoma and lung cancer and how agents like vemurafenib might fit into the management of these patients?

DR JOHNSON: BRAF mutations are present in about half of melanoma cases. As was published last year, vemurafenib is active in melanoma and is FDA approved for patients with BRAF mutations. Vemurafenib has produced a response rate in excess of 50% with a PFS of 8 to 10 months in patients with BRAF V600-mutant advanced melanoma (Sosman 2012). It demonstrates dramatic activity, particularly because this disease historically has not been highly responsive. The majority of BRAF mutations in melanoma are at one specific amino acid location, and they typically cause the V600E mutation.

BRAF mutations occur in 2% of patients with lung cancer, with a smaller proportion being V600E mutant (Paik 2011). In our current trial of a BRAF inhibitor for patients with NSCLC with BRAF mutations, only 1 out of the 7 patients has had to discontinue therapy, and that was due to the development of an allergic reaction.

In contrast, BRAF mutations are apparently not as active in colon cancer. Even though findings were similar in lung cancer and melanoma, thus far the same is not true for colon cancer. So it appears that the tumor type makes a difference. In terms of treating all tumors based on mutation expression, that approach has been used with selumetinib (AZD-6244), a MEK inhibitor, in an attempt to control BRAF-mutant disease.

Track 10

DR LOVE: What is known about agents directed at K-ras mutations?

DR JOHNSON: We were encouraged by the results of a randomized Phase II trial of docetaxel with or without selumetinib as second-line treatment for advanced K-ras-mutant NSCLC (Jänne 2012). The addition of selumetinib to docetaxel produced dramatic benefits with 37% response rates, a longer PFS and a median overall survival of 9 months. In comparison, patients who received docetaxel in combination with placebo had a median overall survival of 5 months without responses. The hazard ratio for survival was about 0.8, which was disappointing because the lines crossed over at the end. But the response rates and the PFS were encouraging. Based on these results, a randomized Phase III trial with approximately 80 patients is being discussed.

Track 11

DR LOVE: What other novel agents for lung cancer are you excited about?

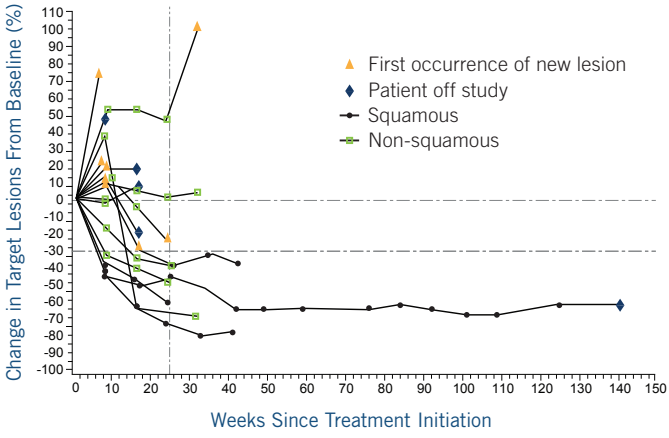
DR JOHNSON: Anti-PD-1 is a monoclonal antibody that inhibits an immune checkpoint, and we have had personal experience with it. It has demonstrated dramatic antitumor activity in melanoma, for which it was initially developed (Topalian 2012).

The recent report of 3 different dose levels — 1, 3 and 10 mg/kg — with approximately 70 patients with NSCLC showed clinical responses to 3 and 10 mg/kg in approximately 20% of the patients (Brahmer 2012). Some of these responses are encouraging (2.1), with the patients continuing therapy for years. A disproportionate share of responses were observed in patients with squamous cell carcinomas, and further trials of this agent versus chemotherapy are under consideration.

In our experience we've observed dramatic and prolonged responses in subsets of patients with NSCLC. We don't yet have a predictive biomarker to identify the patients who will benefit from such therapy, but the overall response rate in lung cancer at 3

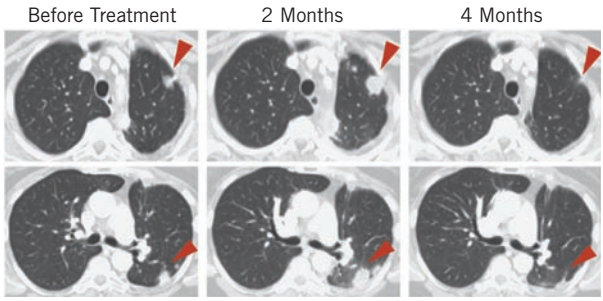
2.1 **Clinical Activity of Anti-PD-1 in Advanced Non-Small Cell Lung Cancer**

1



Changes from baseline in the tumor burden, measured as the sum of the longest diameters of target lesions, in patients with NSCLC who received anti-PD-1 antibody at a dose of 3.0 mg/kg.

2



Partial response in a patient with metastatic nonsquamous NSCLC who received anti-PD-1 antibody at a dose of 10.0 mg/kg. The arrows show initial progression in pulmonary lesions, followed by regression (an immune-related pattern of response).

[1] With permission from Brahmer JR et al. *Proc ASCO* 2012;**Abstract 7509**; [2] From *New England Journal of Medicine*, Topalian SL et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer, 366:2443-54. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

or 10 mg/kg appears to be approximately 20%. This would be as high or even higher than the 10% response rate observed with the conventional agents pemetrexed and docetaxel as second-line therapy.

Track 14

DR LOVE: Do you have any comments on the research strategy of using afatinib in combination with cetuximab for patients who previously received an EGFR TKI?

DR JOHNSON: One promising trial of the irreversible inhibitor afatinib in combination with cetuximab demonstrated response rates in excess of 50% (Janjigian 2011; [2.2]). This combination is believed to have the ability to inhibit the tyrosine kinase domain of EGFR and block agonist binding. The original hypothesis was that this combination would work in patients with disease harboring the T790M mutation, which is the most common mutation associated with resistance. However, antitumor activity has been observed in patients with acquired resistance as well as in other patients. So it's by far the most promising combination that we've seen in the acquired-resistance setting, and it's one that we as an institution are trying to get involved with for our patients. ■

2.2

Phase Ib Study of Afatinib and Cetuximab for Patients with Non-Small Cell Lung Cancer with Acquired Resistance to Erlotinib or Gefitinib

Best response at MTD	T790M-positive (n = 26)	T790M-negative (n = 14)	T790M unknown (n = 3)	No EGFR mutation (n = 2)
Any partial response (PR)	50%	57%	67%	—
Confirmed PR	35%	50%	67%	—
Stable disease (SD)	42%	36%	33%	100%
Clinical response (any PR + SD)	92%	93%	100%	100%
Select adverse events at MTD (n = 47)	All grades		Grade ≥3	
Rash	89%		6%	
Diarrhea	74%		6%	

MTD = maximum tolerated dose

Janjigian YY et al. *Proc ASCO* 2011;**Abstract 7525**.

SELECT PUBLICATIONS

Brahmer JR et al. **Clinical activity and safety of anti-PD1 (BMS-936558, MDX-1106) in patients with advanced non-small-cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract 7509**.

Janjigian YY et al. **Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib.** *Proc ASCO* 2011;**Abstract 7525**.

Jänne PA et al. **Phase II double-blind, randomized study of selumetinib (SEL) plus docetaxel (DOC) versus DOC plus placebo as second-line treatment for advanced KRAS mutant non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract 7503**.

Paik PK et al. **Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations.** *J Clin Oncol* 2011;29(15):2046-51.

Sosman JA et al. **Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib.** *N Engl J Med* 2012;366(8):707-14.

Topalian SL et al. **Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.** *N Engl J Med* 2012;366(26):2443-54.

INTERVIEW

Panos Fidias, MD

Dr Fidias is Assistant Professor of Medicine at Harvard Medical School and Medical Director of the Inpatient Oncology Unit at Massachusetts General Hospital's Thoracic Oncology Service in Boston, Massachusetts.

Tracks 1-15

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the issue of multiplex genomic testing and the approach used in your oncology group at Mass General?

DR FIDIAS: The platform we use is called SNaPshot. It's a multiplex DNA sequencing platform that began as a research tool in an effort to identify oncogenic drivers, with EGFR being the most frequent. Several years ago we thought it should not be simply a research tool. We believed it should be integrated into clinical practice because

being applicable strictly as a research tool requires a protocol and can therefore only be utilized in 15% to 20% of the population.

We believe that every patient with lung cancer who comes into the clinic should undergo genotyping. The SNaPshot platform has now been supplemented by FISH analysis, primarily for the ALK-translocated gene and, more recently, ROS1 rearrangement. We also test everyone who comes to the clinic for MET and other less common rearrangements and mutations.

This model proved to be successful in clinical practice (Sequist 2011; [3.1]). We obtain a lot of data, many of which are unexpected — you would not have predicted these patients to have tumors with these types of mutations. The model has now spread to other disease centers, where breast cancer and colorectal cancer are screened.

3.1

Multiplex Genotyping of Non-Small Cell Lung Cancer (NSCLC) in Clinical Practice

"While widely agreed that it is important to identify patients with EGFR and ALK given the availability of effective therapeutics, it is also noteworthy that in a short time frame at a single institution, we identified over 30 patients with less common mutations like BRAF, PIK3CA and HER2, which also have relevant candidate targeted therapies.

Among the patients with advanced or recurrent NSCLC seen within these 15 months, 22% began a genotype-specific therapy in response to SNaPshot results. We anticipate that this proportion should increase further in the future, as the scope of genotype-specific clinical trial efforts is rapidly broadening.... Overall, we have demonstrated that broad clinical genotyping with SNaPshot can be tightly integrated into clinical practice and we believe it can make a real difference for patients."

Sequist LV et al. *Ann Oncol* 2011;22(12):2616-24.

Track 11

DR LOVE: Your group reported on a variation of the ECOG-E4599 regimen with carboplatin/*nab* paclitaxel and bevacizumab. What did you see, and do you have any sense of whether the regimens differ?

DR FIDIAS: In general, no overall survival benefit is evident with *nab* paclitaxel compared to paclitaxel, but we have recorded the highest response rate to date with any regimen (Heist 2011; [3.2]), although this one is more intense and causes more myelo-

3.2

Response to Carboplatin, Nanoparticle Albumin-Bound (*Nab*) Paclitaxel and Bevacizumab in Patients with Previously Untreated Advanced Nonsquamous Non-Small Cell Lung Cancer (n = 25)

Disease control rate	17/23 (74%)
Partial response	8/23 (35%)
Stable disease	9/23 (39%)

One patient is in cycle 1, and 1 dropped out without receiving any study drug. Four patients came off study prior to first restaging: 1 for painful bony disease requiring radiation therapy and 3 for toxicity (perforated diverticulitis, liver function abnormalities and nausea and vomiting).

Heist RS et al. *Proc ASCO* 2012;**Abstract e18016**.

suppression and fatigue. A motivated person can get through it, but it's too early to tell whether *nab* paclitaxel should replace regular paclitaxel.

Track 15

DR LOVE: Would you discuss the SELECT study, which you worked on with Dr Lecia Sequist? What did you report, and how do you interpret those results?

DR FIDIAS: This is an adjuvant trial for patients with EGFR mutation-positive disease, up to Stage IIIA, who can receive erlotinib either immediately if they don't receive chemotherapy or at the end of chemotherapy if the standard treatment for their tumor stage is to receive adjuvant chemotherapy after resection. It's a single-arm Phase II study, so it will not be conclusive, but the disease-free survival rate appears to be remarkably good at 94% after 2 years (Neal 2012; [3.3]).

It's still early for this population, and we have to see how the results fall along historical lines, but I would not be surprised if this regimen became a new standard. My sense is that EGFR TKI therapy will be moved earlier in the treatment algorithm. It's effective, and I can envision using TKIs in both the adjuvant and the metastatic settings. Eventually we'll need a Phase III study to find out whether we have a new standard. Until such time, I would not use this approach outside of a trial setting. ■

3.3

SELECT Study: A Multicenter Phase II Trial of Adjuvant Erlotinib for Patients with EGFR Mutation-Positive Non-Small Cell Lung Cancer

Disease-free survival	94% (95% CI: 79.5%-98.5%)*	
Select adverse events	Any (%)	Grade ≥3 (%)
Rash†	89	17
Diarrhea†	78	3
Fatigue†	61	6

* Median duration of follow-up: 2.5 years; † Toxicities leading to dose reductions

Neal JW et al. *Proc ASCO* 2012;**Abstract 7010**.

SELECT PUBLICATIONS

Heist RS et al. **Phase II trial of carboplatin, Abraxane, and bevacizumab in NSCLC.** *Proc ASCO* 2011;**Abstract e18016**.

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

Oxnard GR et al. **Maintained sensitivity to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer recurring after adjuvant erlotinib or gefitinib.** *Clin Cancer Res* 2011;17(19):6322-8.

Sequist LV et al. **Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice.** *Ann Oncol* 2011;22(12):2616-24.

Shao H et al. **Improved response to *nab*-paclitaxel compared with Cremophor-solubilized paclitaxel is independent of secreted protein acidic and rich in cysteine expression in non-small cell lung cancer.** *J Thorac Oncol* 2011;6(6):998-1005.

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

Su Z et al. **A platform for rapid detection of multiple oncogenic mutations with relevance to targeted therapy in non-small-cell lung cancer.** *J Mol Diagn* 2011;13(1):74-84.

INTERVIEW

Luis Paz-Ares, MD, PhD

Dr Paz-Ares is Professor of Medicine and Chair of the Oncology Department at Hospital Universitario Virgen del Rocío in Seville, Spain.

Tracks 1-8

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the MetLung study evaluating the addition of onartuzumab (MetMAb) to erlotinib for advanced MET-positive NSCLC?

DR PAZ-ARES: The design of the Phase III study was similar to the Phase II study except that it focused on patients with high MET expression (Spigel 2012; [4.1]). In this well-powered study, patients with advanced NSCLC are randomly assigned to erlotinib with or without onartuzumab.

DR LOVE: What is the rationale for combining erlotinib and onartuzumab, and does onartuzumab have a role as a single agent for patients with NSCLC?

DR PAZ-ARES: In tumors that are not dependent on driver mutations it may be important to block 2 or 3 signaling pathways. From 10% to 20% of tumors in patients with mutations may develop a MET amplification as a resistance mechanism after treatment with erlotinib or gefitinib. A similar proportion of patients may experience an autocrine or paracrine increase in hepatocyte growth factor levels, the natural ligand of c-MET. I believe that agents like onartuzumab have a role for EGFR-mutated tumors.

It would be logical to study onartuzumab as a single agent for tumors addicted to MET signaling. Onartuzumab alone could have a role in some forms of lung cancer in which MET mutations arise sporadically.

DR LOVE: What is known about the toxicity of onartuzumab?

DR PAZ-ARES: The Phase II study recorded some cases of edema and mild nausea and vomiting. No significant increase in toxicity was evident in the combination arm with onartuzumab versus the erlotinib-alone arm (Spigel 2011).

4.1

MetLung: A Phase III, Randomized Study of Onartuzumab with Erlotinib versus Placebo with Erlotinib in Advanced, MET-Positive Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT01456325 **Target Accrual:** 480

Eligibility: MET-positive NSCLC; disease progression on 1 to 2 lines platinum-based chemotherapy; patients stratified by MET expression (2+ versus 3+), prior lines of therapy (1 versus 2), EGFR-activating mutation status (yes or no)

Primary endpoint: Overall survival

Spigel DR et al. *Proc ASCO* 2012;**Abstract TPS7616**.

Track 2

DR LOVE: Would you talk about the small-molecule MET inhibitor ARQ 197 (tivantinib) for patients with advanced NSCLC?

DR PAZ-ARES: Tivantinib has demonstrated activity in combination with erlotinib in a randomized Phase II trial (Sequist 2011; [4.2]). A Phase III trial of this agent in NSCLC has recently completed accrual. The level of MET expression was not among the criteria for enrollment, but tissue will be collected for a retrospective analysis of biomarkers.

DR LOVE: Have you observed any toxicity with tivantinib in patients you placed on a trial?

4.2

Phase II Trial of Erlotinib and Tivantinib (ET) versus Erlotinib and Placebo (EP) for Patients with Erlotinib-Naïve, Previously Treated Advanced Non-Small Cell Lung Cancer

Outcome	ET (n = 84)	EP (n = 83)	Hazard ratio	*p*-value
Median PFS (INV)	3.8 mo	2.3 mo	0.81	0.24
Median PFS (IRR)	3.6 mo	2.0 mo	0.74	0.09
Median OS (INV)	8.5 mo	6.9 mo	0.87	0.47

PFS = progression-free survival; INV = investigator assessment; IRR = independent central radiology review; OS = overall survival

Sequist LV et al. *J Clin Oncol* 2011;29(24):3307-15.

DR PAZ-ARES: In general I have not observed a significant increase in toxicity, although some patients had more severe skin toxicity. It is difficult to tell whether patients are receiving erlotinib alone or with tivantinib.

Track 3

DR LOVE: Would you discuss the PARAMOUNT trial and the final results you presented at ASCO 2012?

DR PAZ-ARES: PARAMOUNT is a Phase III study in which patients with NSCLC received 4 cycles of induction therapy with cisplatin and pemetrexed. Patients without disease progression were then randomly assigned to continuation maintenance with pemetrexed or placebo at a ratio of 2 to 1.

At ASCO 2012, we presented the final analysis of overall survival (Paz-Ares 2012; [4.3]). It confirmed the earlier PFS results and the interim analysis of overall survival. The median overall survival from randomization improved from 11 to 14 months. As measured from the time of induction it improved from 14 to 17 months. The hazard ratio was 0.78 whether overall survival was measured from randomization or from the time of induction.

Prior to this trial, no study was adequately powered to demonstrate an increase in overall survival. Now that we have agents with better toxicity profiles, I believe we should maximize the benefit from the drug with continuous maintenance.

4.3

PARAMOUNT: A Phase III Study of Maintenance Pemetrexed (Pem) with Best Supportive Care (BSC) versus Placebo with BSC After Induction with Pem and Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer

	Pem + BSC (n = 359)	Placebo + BSC (n = 180)	Hazard ratio	*p*-value
Median overall survival				
From randomization	13.9 mo	11.0 mo	0.78	0.0195
From induction	16.9 mo	14.0 mo	0.78	0.0191

Median follow-up = 12.5 mo

Paz-Ares L et al. *Proc ASCO* 2012;**Abstract LBA7507**.

Track 5

DR LOVE: Would you comment on the AVAPERL trial evaluating maintenance therapy with pemetrexed and bevacizumab for patients with advanced nonsquamous NSCLC?

DR PAZ-ARES: The AVAPERL trial had an induction phase of 4 cycles of cisplatin/pemetrexed and bevacizumab (Barlesi 2011). Patients who did not experience disease progression after induction were randomly assigned to receive bevacizumab alone or pemetrexed with bevacizumab. PFS from randomization was 7 months versus 3.5 months favoring the combination of pemetrexed and bevacizumab with a hazard ratio of approximately 0.5. When calculated from the time of induction, PFS was 10 months

for maintenance pemetrexed and bevacizumab as compared to about 7 months on the control arm. I believe that these results are encouraging for patients with NSCLC.

DR LOVE: Would you also comment on the PointBreak trial evaluating the "Patel regimen" for advanced NSCLC?

DR PAZ-ARES: The experimental arm of the PointBreak trial is evaluating the Patel regimen of carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab. This treatment is being compared to the conventional ECOG-E4599 regimen of carboplatin/paclitaxel/bevacizumab followed by maintenance therapy with bevacizumab alone. The induction arm and the maintenance arm both include different regimens.

The confounding factor is that if the results are different between the 2 arms, we will not know whether those differences result from differences in the induction or the maintenance phase or both. This study has recently completed accrual, and results should be available soon (Editor's note: Subsequent to this interview the initial results of this study were presented; see figure 4.4). ■

4.4

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

All patients	Pac/Cb/B (n = 84)	Pem/Cb/B (n = 472)	HR	*p*-value
Median PFS	5.6 mo	6.0 mo	0.83	0.012
Median OS	13.4 mo	12.6 mo	—	1.0
Maintenance patients	(n = 296)	(n = 292)		
Median PFS	6.9 mo	8.6 mo	NR	NR
Median OS	15.7 mo	17.7 mo	NR	NR

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

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

SELECT PUBLICATIONS

Barlesi F et al. **Final efficacy outcomes for patients with advanced nonsquamous nonsmall cell lung cancer randomized to continuation maintenance with bevacizumab or bevacizumab plus pemetrexed after first-line bevacizumab-cisplatin-pemetrexed treatment.** ECCO-ESMO 2011;**Abstract LBA34**.

Paz-Ares L et al. **PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced nonsquamous (NS) non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract LBA7507**.

Sequist L et al. **Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small cell lung cancer.** *J Clin Oncol* 2011;29(24):3307-15.

Spigel DR et al. **The MetLUNG study: A randomized, double-blind, phase III study of onartuzumab (MetMAb) plus erlotinib versus placebo plus erlotinib in patients with advanced, MET-positive non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract TPS7616**.

Spigel DR et al. **Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC.** *Proc ASCO* 2011;**Abstract 7505**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Crizotinib, a targeted agent recently approved for use in the treatment of ALK-positive NSCLC, was recently shown to also exhibit antitumor activity in patients with NSCLC harboring ROS1 gene rearrangement.**
   a. True
   b. False

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

3. **Favorable responses have been reported with the anti-PD-1 antibody in patients with _____ NSCLC.**
   a. Adenocarcinoma
   b. Squamous cell
   c. Neither a nor b
   d. Both a and b

4. **The addition of selumetinib to docetaxel in the second line significantly prolonged PFS compared to placebo in a Phase II trial for patients with _____ advanced NSCLC.**
   a. EGFR-mutant
   b. K-ras-mutant
   c. BRAF-mutant

5. **In a Phase II trial of afatinib with cetuximab for patients with NSCLC and acquired resistance to erlotinib or gefitinib, investigators reported confirmed responses in _____.**
   a. T790M mutation-positive disease
   b. T790M mutation-negative disease
   c. Both a and b
   d. Neither a nor b

6. **A Phase II trial evaluating carboplatin, *nab* paclitaxel and bevacizumab for patients with untreated advanced nonsquamous NSCLC reported a near 75% disease control rate with this combination.**
   a. True
   b. False

7. **The Phase II SELECT study evaluating adjuvant _____ for patients with resected EGFR mutation-positive NSCLC reported a disease-free survival rate of 94% after more than 2 years of follow-up.**
   a. Afatinib
   b. Erlotinib
   c. Gefitinib

8. **The Phase III MetLung study will investigate _____ with erlotinib versus placebo with erlotinib for patients with advanced MET-positive NSCLC.**
   a. Tivantinib
   b. Onartuzumab
   c. Gefitinib

9. **The AVAPERL trial demonstrated that the addition of pemetrexed to maintenance therapy with bevacizumab significantly increased PFS for patients with advanced nonsquamous NSCLC.**
   a. True
   b. False

10. **Final analysis of overall survival in the PARAMOUNT study demonstrated a significant increase in overall survival with the addition of pemetrexed to best supportive care for patients with advanced nonsquamous NSCLC.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 2, 2012

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

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

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

	BEFORE	AFTER
Results of the SELECT study: A multicenter Phase II trial of adjuvant erlotinib in resected EGFR mutation-positive NSCLC	4 3 2 1	4 3 2 1
Clinical benefits of pemetrexed in ALK-positive advanced NSCLC	4 3 2 1	4 3 2 1
Clinical activity of crizotinib in advanced NSCLC harboring ROS1 gene rearrangement or ALK positivity	4 3 2 1	4 3 2 1
Activity of afatinib/cetuximab in advanced NSCLC with acquired resistance to erlotinib	4 3 2 1	4 3 2 1
LUX-Lung 3: A randomized, open-label, Phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for advanced adenocarcinoma of the lung harboring EGFR-activating mutations	4 3 2 1	4 3 2 1
Anti-PD-1 antibody in lung cancer and other solid tumors	4 3 2 1	4 3 2 1
AVAPERL: Continuation maintenance therapy with pemetrexed/bevacizumab in advanced nonsquamous NSCLC	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain: .....

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

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

.....

.....

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

☐ Yes ☐ No

If no, please explain: .....

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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:

- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR or K-ras mutations, EML4-ALK gene fusions, ROS1 rearrangements and other recently identified driver mutations — and the investigational and approved treatment options for patients expressing these biomarkers. . . . . 4 3 2 1 N/M N/A
- Describe emerging efficacy and tolerability data with irreversible EGFR tyrosine kinase inhibitor therapy for patients with advanced EGFR-mutant NSCLC and combined EGFR targeting in patients with acquired resistance to EGFR tyrosine kinase inhibitors. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based approach to the selection of induction and continuation maintenance biologic therapy and/or chemotherapy in patients with advanced NSCLC. . . . . 4 3 2 1 N/M N/A
- Describe the rationale for and emerging data with tumor immunotherapy directed at PD-1 in lung cancer and other solid tumors. . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation. . . . . 4 3 2 1 N/M N/A

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.....

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Bruce E Johnson, MD	4	3	2	1	4	3	2	1
Panos Fidias, MD	4	3	2	1	4	3	2	1
Luis Paz-Ares, MD, PhD	4	3	2	1	4	3	2	1
Editor	**Knowledge of subject matter**				**Effectiveness as an educator**			
Neil Love, MD	4	3	2	1	4	3	2	1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

.....

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