# LUNG CANCER TUMOR BOARD

## Clinical Investigators Provide Perspectives on Current Cases and Key Publications in Non-Small Cell Lung Cancer

## CME INFORMATION

### TARGET AUDIENCE

This activity is intended for medical oncologists, hematology-oncology fellows and other healthcare providers involved in the treatment of non-small cell lung cancer (NSCLC).

### OVERVIEW OF ACTIVITY

Lung cancer is a devastating disease with a broad-reaching impact on public health, accounting for 14% of all new cancer cases in the United States and the most cancer-related deaths among both men and women. Development of new therapeutic strategies beyond cytotoxic chemotherapy has been the focus of extensive recent research and has led to an explosion in lung cancer genetic and biologic knowledge. The advent of these next-generation targeted treatments presents new promise of both efficacy and enhanced safety for patients with lung cancer but also challenges practicing oncologists to appropriately select individuals who may benefit from these agents and to determine how to integrate such therapies, as they become available, into standard lung cancer treatment algorithms. Several consensus- and evidence-based treatment guidelines are available and aim to assist clinicians with making lung cancer management decisions in the face of this dynamic clinical environment, but despite the existence of these tools, many areas of controversy persist within academic and community settings. This program uses a review of recent relevant publications and other relevant presentations, ongoing clinical trials, actual patient case discussions and Q&A to assist medical oncologists, hematology-oncology fellows and other healthcare providers with the formulation of up-to-date clinical management strategies, including referral of appropriate patients to ongoing pivotal clinical trials.

### LEARNING OBJECTIVES

- Develop an evidence-based strategy for the systemic treatment of localized NSCLC.
- Apply the results of emerging clinical research to the multimodality management of Stage III NSCLC.
- Employ an understanding of personalized medicine to individualize the use of available EGFR inhibitors in the treatment of NSCLC.
- Communicate the efficacy and safety of crizotinib and other emerging ALK inhibitors to appropriate patients with NSCLC, considering the predictive utility of ALK and ROS1 mutation testing.
- Devise an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced pan-wild-type NSCLC.
- Describe emerging data on the efficacy and safety of immunotherapy directed at the PD-1/PD-L1 pathway in lung cancer, and consider this information when counseling patients regarding clinical trial participation.
- Assess new oncogenic pathways mediating the growth of unique NSCLC tumor subsets, and recall emerging data and ongoing trials with experimental agents exploiting these targets.

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Ensign Professor of Medicine (Oncology)
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Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Director for Translational Research
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**Consulting Agreements:** Astellas, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Merck; **Contracted Research:** GlaxoSmithKline; **Data and Safety Monitoring Board:** Pfizer Inc.

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**Contracted Research:** Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, Lilly, Merrimack Pharmaceuticals, Onyx Pharmaceuticals Inc, Pfizer Inc; **Data and Safety Monitoring Board:** Millennium: The Takeda Oncology Company; **Speakers Bureau:** Celgene Corporation, Genentech BioOncology.

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Full Professor, Paris University XI
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**Hardware/Software Requirements:**
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

**Last review date:** August 2014

**Expiration date:** August 2015

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# Lung Cancer Tumor Board
## Clinical Investigators Provide Perspectives on Current Cases and Key Publications in Non-Small Cell Lung Cancer

**Friday, May 30, 2014**
**7:00 PM – 9:00 PM**
**Chicago, Illinois**

### Faculty

**Roy S Herbst, MD, PhD**
**John V Heymach, MD, PhD**
**Alice Shaw, MD, PhD**
**Mark A Socinski, MD**
**Jean-Charles Soria, MD, PhD**

### Moderator

**Neil Love, MD**

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## Within the past 12 months…

| | # New Patients (Median) | # Patient Deaths (Median) |
|---|---|---|
| **Lung Cancer** | **40** | **15** |
| Colon Cancer | 32 | 5 |
| MM | 15 | 2 |
| NHL/CLL | 53 | 7 |
| Breast Cancer | 60 | 7 |

RTP survey of 101 randomly selected US-based oncologists; February 2014.

## Agenda

**Module 1 –** *Adjuvant Therapy for Localized Non-Small Cell Lung Cancer; Management of Locally Advanced Disease*

**Module 2 –** *Management of Metastatic Pan-Wild-Type Adenocarcinoma*

**Module 3 –** *Current and Emerging Treatment of Metastatic Squamous Cell Carcinoma*

**Module 4 –** *Therapeutic Decision-Making for Patients with EGFR Mutations*

**Module 5 –** *Management of ALK- and ROS1-Positive NSCLC*

## Adjuvant Therapy for Localized NSCLC & Management of Locally Advanced Disease

Pr Jean-Charles SORIA

IOT

DITEP
Drug Development Department

Institute Gustave Roussy Inserm
U981
Institut national de la santé et de la recherche médicale

## *Management of the Metastatic Pan-Wild-Type (PWT) Adenocarcinoma*

**Mark A. Socinski, MD**

Professor of Medicine and Thoracic Surgery
Director, Lung Cancer Section, Division of Hematology/Oncology
Co-Director, UPMC Lung Cancer Center of Excellence and Lung and Thoracic Malignancies Program
University of Pittsburgh

# Current and Emerging Treatment of Metastatic Squamous Cell Carcinoma (SCC)

**Roy S Herbst, MD, PhD**
Ensign Professor of Medicine (Oncology)
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Director for Translational Research
Yale Comprehensive Cancer Center
Yale School of Medicine
New Haven, Connecticut

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

# Therapeutic Decision-Making for Patients with EGFR Mutations

**John Heymach, MD, PhD**
Chairman and Professor
Thoracic/Head and Neck Medical Oncology and Cancer Biology

ASCO Satellite Conference with Dr. Neil Love
May 30, 2014

Disclosures: Advisory boards for Genentech, AstraZeneca, Pfizer, Boehringer-Ingelheim
Research support from AstraZeneca, Bayer

# Management of ALK- and ROS1-Positive NSCLC

Alice T. Shaw, MD, PhD
Associate Professor of Medicine
Massachusetts General Hospital Cancer Center
Harvard Medical School
May 30, 2014

## Patient n°1, 76 yo male patient

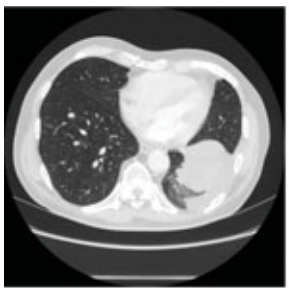
August 2010 | September 7th 2010 | October 26th-December 7th 2010 | April 30th 2014

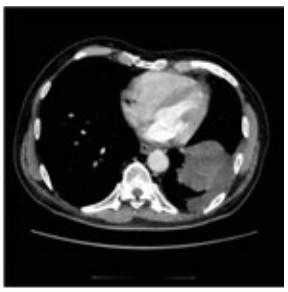
-**Smoking 42 pack-years**
-Type II diabetes
-Hemochromatosis
-Hypertension, LVEF 45%

## Patient n°1, 76 yo male patient

August 2010 | September 7th 2010 | October 26th-December 7th 2010 | April 30th 2014

Chronic coughing
➔Diagnosis of
**Squamous cell carcinoma TTF1-pT2N1M0, stage IIA**





Absence of EGFR, KRAS, BRAF, PI3K and HER2 mutations

GUSTAVE ROUSSY

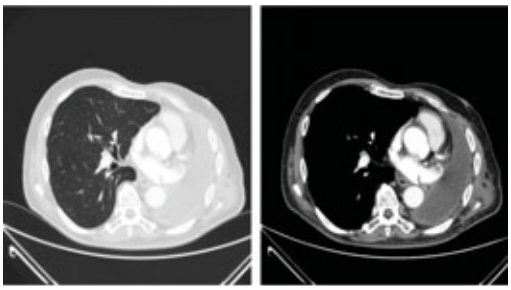
DITEP Drug Development Department

## Patient n°1, 76 yo male patient

August 2010 → September 7th 2010 → October 26th-December 7th 2010 → April 30th 2014

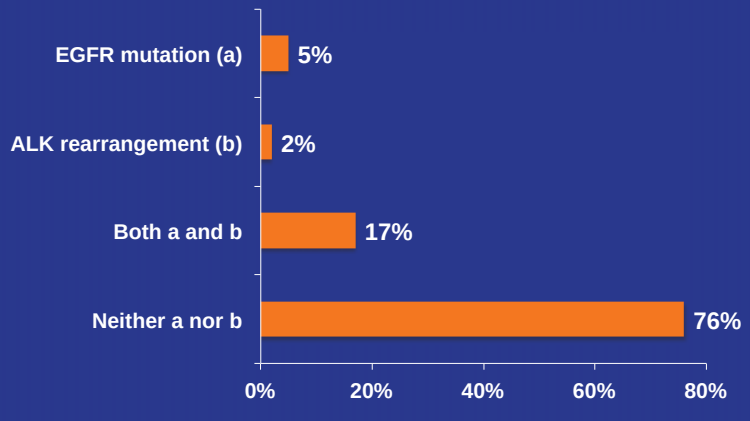
**SURGERY**

Left pneumonectomy

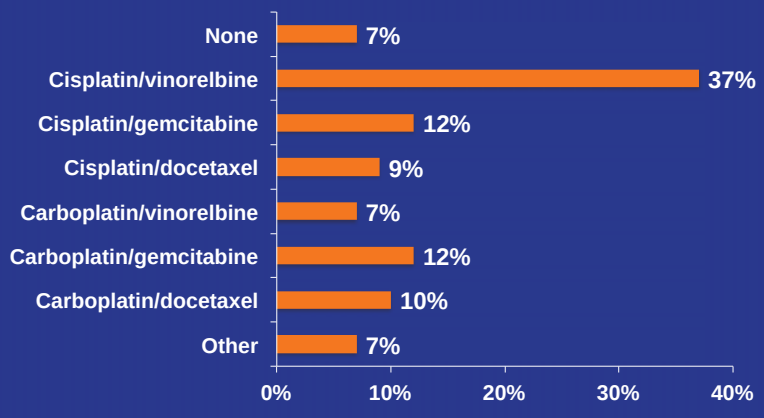


Early recovery from surgery; PS=0

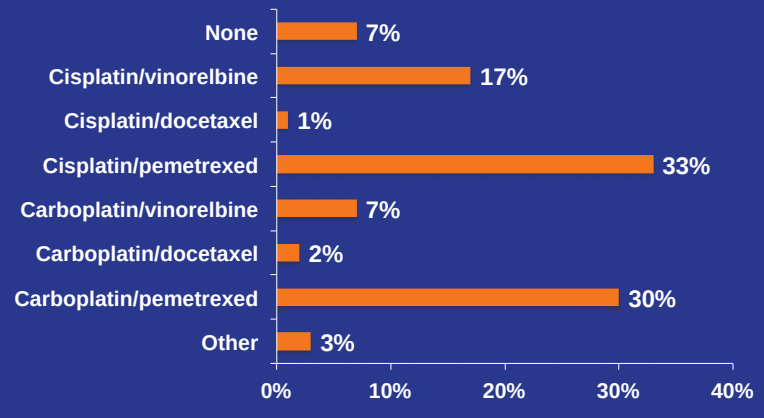
**A 76-year-old man and former heavy smoker s/p pneumonectomy (PS = 0) is diagnosed with Stage IIA (pT2pN1M0) squamous cell carcinoma of the lung. Which of the following would you test for in this patient?**



**What adjuvant chemotherapy would you recommend for a 76-year-old man s/p pneumonectomy (PS = 0) with Stage IIA (pT2pN1M0) squamous cell cancer of the lung?**




**What adjuvant chemotherapy would you recommend for a 76-year-old man s/p pneumonectomy (PS = 0) with Stage IIA (pT2pN1M0) adenocarcinoma of the lung?**



## Patient n°1, 76 yo male patient

August 2010 → September 7th 2010 → October 26th-December 7th 2010 → April 30th 2014

**ADJUVANT CHEMOTHERAPY**

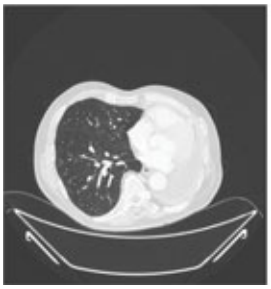
**-Carboplatin AUC5**
**-Paclitaxel 175mg/m²**
Day1-Day21

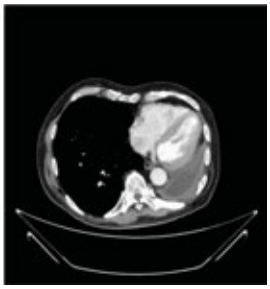
**4 cycles of chemotherapy**
Absence of grade III or IV toxicities

## Patient n°1, 76 yo male patient

August 2010 → September 7th 2010 → October 26th-December 7th 2010 → April 30th 2014

Complete remission and no sign of relapse at 4 years after the adjuvant chemotherapy





Excellent physical state with regular sport activities

# Adjuvant Therapy for Localized NSCLC & Management of Locally Advanced Disease

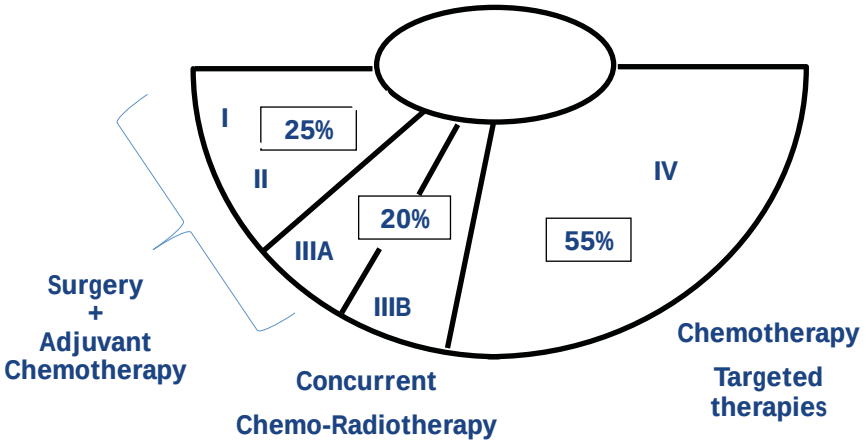
Pr Jean-Charles SORIA

IOT DITEP Drug Development Department Inserm U981

# Disclosures

| | |
|---|---|
| **Consulting Agreements** | AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Celgene Corporation, EMD Serono Inc, Genentech BioOncology, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly, Merck, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Sanofi |

## Therapeutic strategies in NSCLC




## What we know

### Resectable disease

- Some patients are cured (60%)
- Definitive surgery is SOC
- Adjuvant chemotherapy
  - → For stage II and IIIA
  - → Option for IB
  - → Debated for IA
- Adjuvant chemo
  - → Within 2 months of surgery
  - → Age < 75 years in trials
  - → Vinorelbine is favored by LACE meta-analysis

Pignon et al *J Clin Oncol* 2008
*Lancet* 2010; 375: 1267–77

### Locally advanced disease

- Some patients are cured (20%)
- Induction and concurrent chemoradiotherapy are each superior to radiotherapy alone
- Concurrent is superior to Induction
- Vinorelbine or Cis-Eto or Carbo-paclitaxel are the preferred regimens
- No role for adding induction or consolidation chemotherapy to concurrent chemoradiotherapy (incl unselected maintenance EGFR TKI)

# What we will discuss

**Resectable disease**

- Molecular profiling of patients (ie EGFR and ALK status)
- Value and use of molecular predictors of chemo efficacy (ie ERCC1)
- Modifying adjuvant therapy for such patients
  - → TASTE trial
  - → RADIANT trial
  - → ALCHEMIST trial

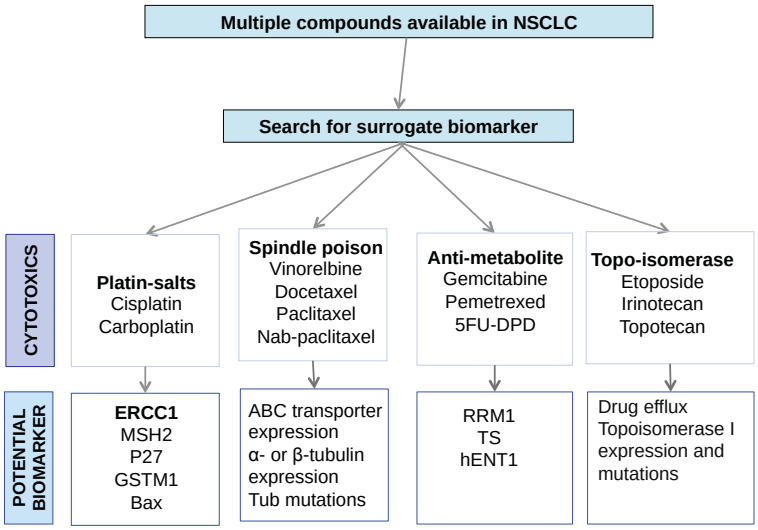
**Locally advanced disease**

- Optimal dose of radiotherapy
- Added value of EGFR blockade with chemoradiotherapy
  - → RTOG-0617 trial
- Integrating EGFR/ALK status in IIIB disease management
  - → RTOG 1306/Alliance 31101 trials

# Targetable molecular alterations: clinical benefit

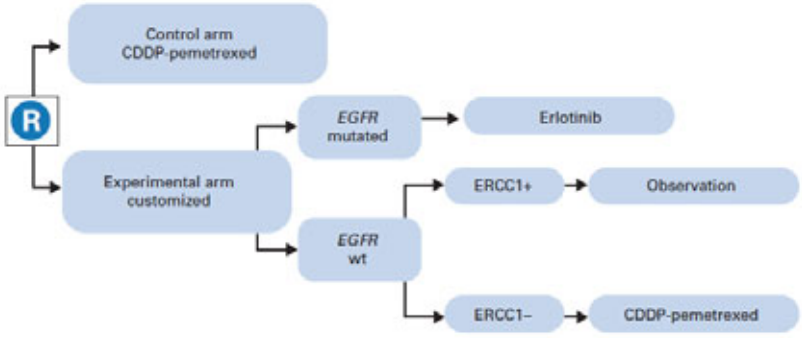
Research To Practice could not obtain permission to reproduce this slide at the time of publication. For further information, please see the following: Rosell R et al. **Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial.** *Lancet Oncol* 2012;13:239-46; Shaw AT et al. **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.** *N Engl J Med* 2013;368:2385-94 (Supplementary Appendix).

## Predictive markers for cytotoxic chemotherapy




## TASTE: data

- TAilored post-Surgical Therapy in Early stage NSCLC
  - is a prospective, randomized, and customized trial
  - incorporating ERCC1 IHC status and EGFR mutational status




Stage II and IIIA (non-N2) NSCLC patients with non-SCC histology were allowed
This French nationwide initiative (IFCT) recruited 150 pts in 3 years

Wislez M et al JCO 2014;32(12):1256-61.

## TASTE: Conclusions

- This adjuvant trial met its primary end point
  - for its phase II component
  - demonstrating the feasibility of a national biology-driven trial in the adjuvant setting.
- Safety data demonstrated an excellent tolerability profile for cisplatin-pemetrexed (as compared to cisplatin-vinorelbine).
- The phase III component was canceled due to the unexpected unreliability of the ERCC1 IHC read-out.
- **ERCC1 IHC read-outs need to be refined before a prospective phase III trial is launched.**



## Molecular predictors for Chemo efficacy…

4 fields of Caveats

- Inadequate number of samples
- Lack of control arm
- Lack of validation set

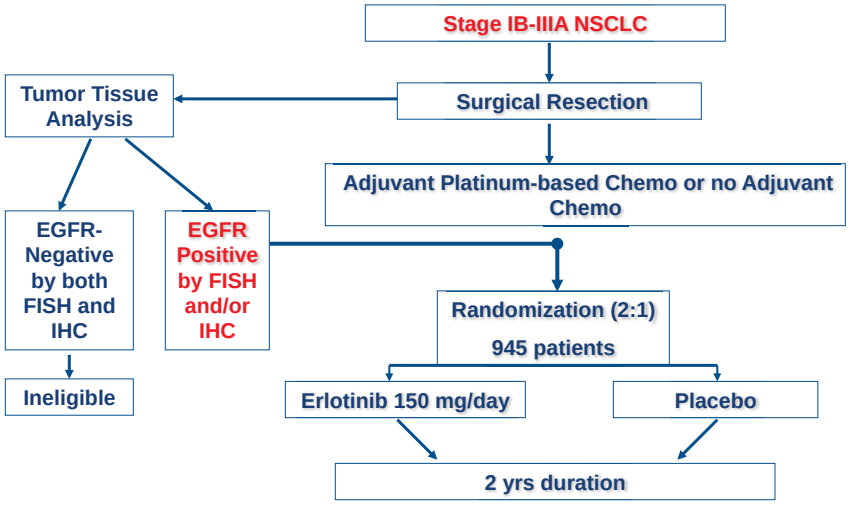
- Lack of biological validation (functional assays)

- Inappropriate use of new technologies
- Technical biases on FFPE samples

- Lack of commitment for prospective validation

Ioannidis, PLoS Med, 2005

# RADIANT: Adjuvant Erlotinib Study




**Primary Endpoint: Progression free survival**

www.clinicaltrials.gov. Identifier NCT00373425.

# BR19: gefitinib vs placebo (OS)

| Overall survival | Gefitinib versus Placebo: HR (95% CI) | Log rank p-value |
|---|---|---|
| Wild-type EGFR | 1.21 (0.84-1.73) | 0.30 |
| Sensitizing EGFR mutation | 1.58 (0.83-3.00) | 0.16 |

- Effect on normal tissue ?
- Effect on preneoplasic tissue ?

Goss ASCO 2010 and JCO 2013

# ALChEMIST Adjuvant Lung Cancer Enrichment Marker Identification Sequencing Trial

| | ALCHEMIST SCREEN Component A151216 | ALK+ E4512 | EGFR-mutant A081105 |
|---|---|---|---|
| Target | Registry | ALK+ | EGFRmut |
| Prevalence | All comers | ~5% | ~10% |
| n | 6000-8000 | 336 | 410 |
| Primary Endpt | -- | DFS-OS | OS |
| Power | -- | 80% | 85% |
| One-sided α | -- | 0.025 | 0.05 |
| HR | -- | 0.67 | 0.67 |
| Adjunct | Extended sequencing for additional targets (TCGA); correlation with local testing | Peripheral screening for ALK; RTPCR to identify fusion partners | Targeted sequence and kinome analysis; PRO and QOL |

**An Intergroup Randomized Phase III Comparison of Standard-Dose (60 Gy) Versus High-Dose (74 Gy) Chemoradiotherapy +/- Cetuximab for Unresectable Stage III Non-Small Cell Lung Cancer**

## RTOG 0617

**STRATIFY**

**RT Technique**
1. 3D-CRT
2. IMRT

**Zubrod**
1. 0
2. 1

**PET Staging**
1. No
2. Yes

**Histology**
1. Squamous
2. Non-Squamous

**RANDOMIZE**

| Concurrent Treatment | Consolidation Treatment |
|---|---|
| **Arm A**<br>Concurrent chemotherapy*<br>RT to **60 Gy**, 5 x per wk for 6 wks | Arm A<br>Consolidation chemotherapy* |
| **Arm B**<br>Concurrent chemotherapy*<br>RT to **74 Gy**, 5 x per wk for 7.5 wks | Arm B<br>Consolidation chemotherapy* |
| **Arm C**<br>Concurrent chemotherapy* and **Cetuximab**<br>RT to **60 Gy**, 5 x per wk for 6 wks | Arm C<br>Consolidation chemotherapy* and Cetuximab |
| **Arm D**<br>Concurrent chemotherapy* and **Cetuximab**<br>RT to **74 Gy**, 5 x per wk for 7.5 wks | Arm D<br>Consolidation chemotherapy* and Cetuximab |

*Carboplatin and paclitaxel

Proc IASLC 2013;Abstract PL03.05.

# Conclusions

- Cetuximab did not improve OS or PFS when added to chemo-radiotherapy for unresectable stage III NSCLC
- Cetuximab increases overall grade 3-5 toxicities (85% v. 69%, p<0.0001), and grade 3-5 non-heme toxicities
- Higher dose RT is not superior to standard-dose RT in unresectable stage III NSCLC
  - → Patients on the high-dose (74 Gy) arms had a 56% greater risk of death than patients on the standard-dose (60 Gy) arms.
  - → There was a 37% increased risk of developing local failure in the high-dose arms.
  - → There was a higher rate of esophagitis in the high-dose arms (21% vs. 7%).

## Individualized Combined Modality Therapy for Stage III NSCLC RTOG 1306/Alliance 31101

**Stratification**

| **Mutation Type** | **Weight Loss** (in prior 6 mos.) |
|---|---|
| 1. EGFR | 1. ≤ 5% |
| 2. ALK | 2. > 5% |

**EGFR TK Mutation Cohort**

**Arm 1**: Erlotinib, 150 mg/day for 12 weeks → Concurrent chemotherapy and radiation, 64 Gy

**Arm 2**: Concurrent Chemotherapy and radiation, 64 Gy

Courtesy E Vokes

# Adjuvant Therapy for Localized NSCLC & Management of Locally Advanced Disease

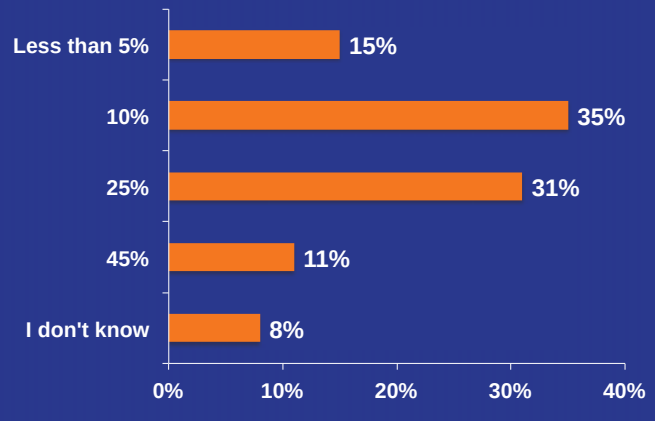
Pr Jean-Charles SORIA

IOT

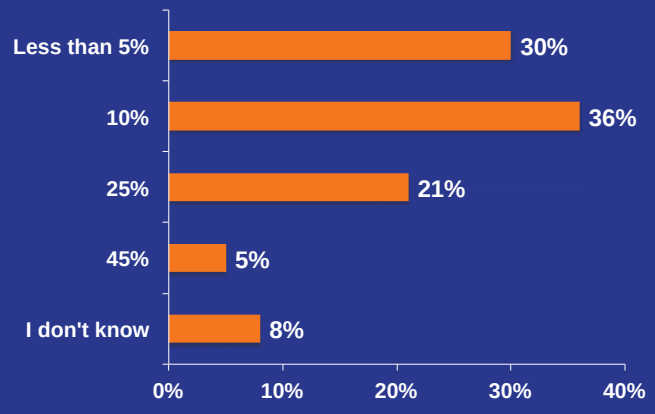
DITEP
Drug Development Department

Inserm
U981

**What is the likelihood that an otherwise fit patient with non-small cell lung cancer (NSCLC) will not be able to complete 4 cycles of adjuvant cisplatin/vinorelbine?**



**What is the likelihood that an otherwise fit patient with non-small cell lung cancer (NSCLC) will not be able to complete 4 cycles of adjuvant cisplatin/pemetrexed?**

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Jean-Charles Soria, MD, PhD

### Moderator

Neil Love, MD

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## Patient n°2, 75 yo male patient

October 2011 → October 23rd 2011 → November 15th 2011- March 27th 2012 → April 4th 2014

**-Never smoker**
No significant past medical history

## Patient n°2, 75 yo male patient

October 2011 → October 23rd 2011 → November 15th 2011- March 27th 2012 → April 4th 2014

Shortness of breath
➔Diagnosis of
**Squamous cell carcinoma**
**T4(atrium)N2(subcarinal)M0**
**stage IIIB**

- Atypical exon 19 EGFR (V742I) mutation
- HER2 amplification
- FGFR1 amplification
- KRAS neg, HER2 neg, PI3K neg, BRAF neg

## Patient n°2, 75 yo male patient

October 2011 → October 23rd 2011 → November 15th 2011- March 27th 2012 → April 4th 2014

Lateral thoracotomy

➔ Invasion of the atrium
➔ No pneumonectomy possible

## Patient n°2, 75 yo male patient

October 2011 → October 23rd 2011 → November 15th 2011- March 27th 2012 → April 4th 2014

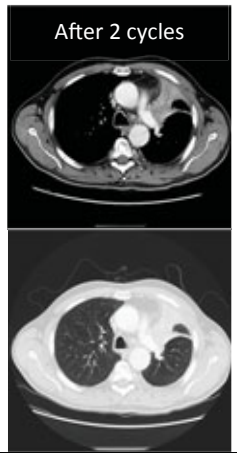
Baseline

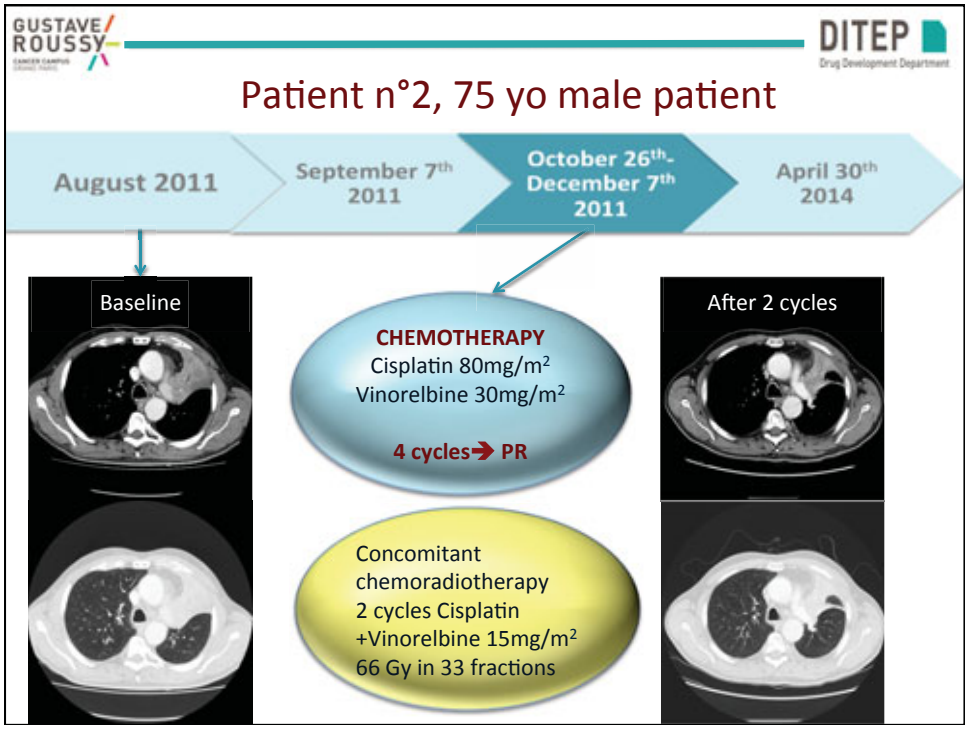
**CHEMOTHERAPY**
Cisplatin 80mg/m²
Vinorelbine 30mg/m²

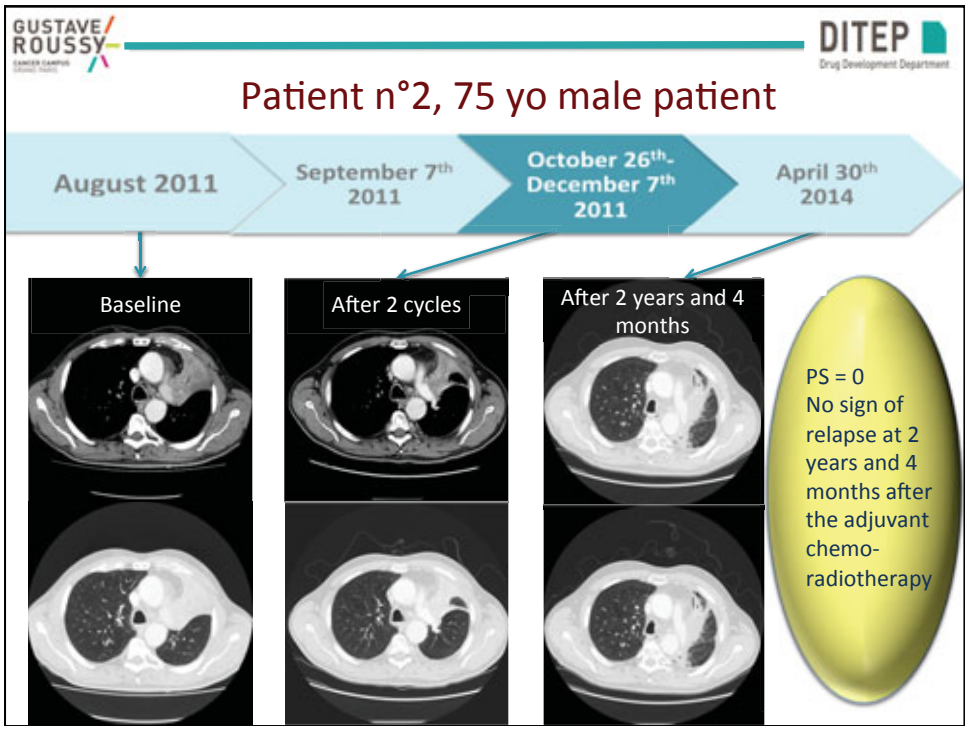
**4 cycles➔ PR**

Concomitant chemoradiotherapy
2 cycles Cisplatin +Vinorelbine 15mg/m²
66 Gy in 33 fractions

After 2 cycles




GUSTAVE ROUSSY
DITEP
Drug Development Department
Patient n°2, 75 yo male patient
August 2011
September 7th 2011
October 26th- December 7th 2011
April 30th 2014
Baseline
CHEMOTHERAPY
Cisplatin 80mg/m2
Vinorelbine 30mg/m2
4 cycles → PR
Concomitant chemoradiotherapy
2 cycles Cisplatin +Vinorelbine 15mg/m2
66 Gy in 33 fractions
After 2 cycles


GUSTAVE ROUSSY
DITEP
Drug Development Department
Patient n°2, 75 yo male patient
August 2011
September 7th 2011
October 26th- December 7th 2011
April 30th 2014
Baseline
After 2 cycles
After 2 years and 4 months
PS = 0
No sign of relapse at 2 years and 4 months after the adjuvant chemo-radiotherapy

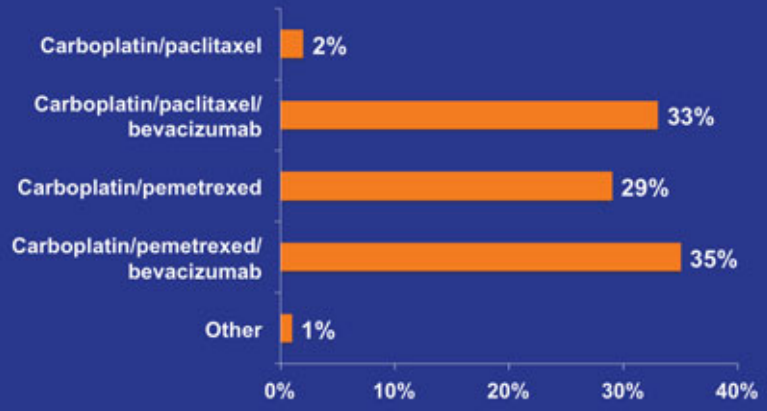
# Case 1

- A 55-year-old gentleman presented with shortness of breath
- Previous smoker (2 PPD for 25 years but quit at age 41)
- Seen in local ER where a CXR revealed a large R pleural effusion
- CT scan subsequently showed a 9.5 cm RUL mass, moderate R pleural as well as pericardial effusion
- Bone scan revealed multiple osseous mets

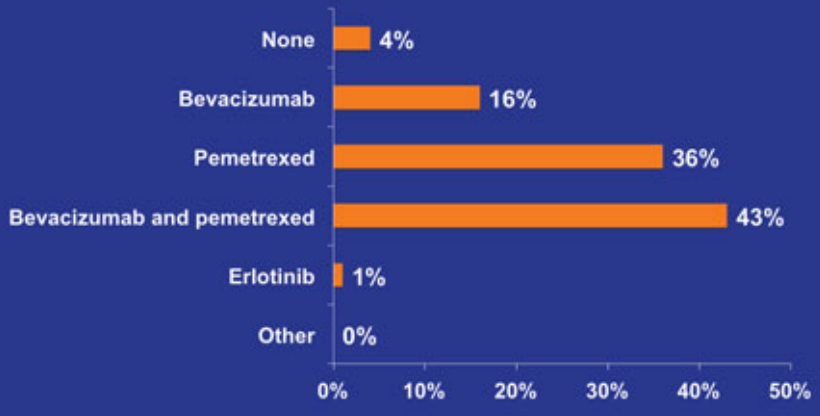
# Case 1

- Underwent a pericardiocentesis with window as well as pleurodesis
- Pathology from pleural biopsy – adenocarcinoma, acinar type (TTF-1 positive)
- Genotyping negative except for p53 mutation

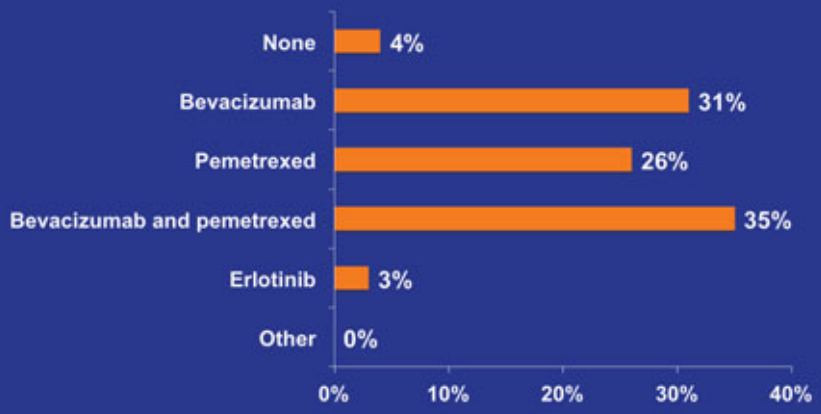
**A 55-year-old patient presents with large pleural and pericardial effusions, a 9.5-cm lung mass and multiple lesions on bone scan. Pathology reveals EGFR/ALK/ROS1-negative adenocarcinoma. Which initial systemic treatment would you most likely recommend?**




**The previous patient (55-year-old) receives carboplatin/ pemetrexed/bevacizumab for 4 cycles and achieves a significant response in the pleura and bones. What, if any, maintenance therapeutic approach would you recommend for this patient?**

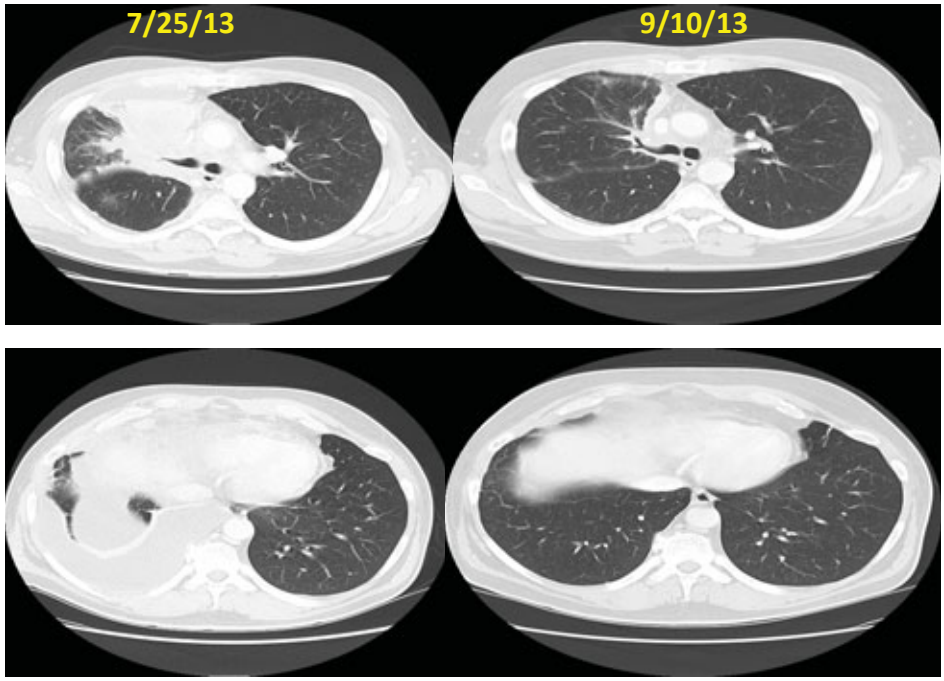


**The previous patient (55-year-old) receives carboplatin/ paclitaxel/bevacizumab for 4 cycles and achieves a significant response in the pleura and bones. What, if any, maintenance therapeutic approach would you recommend for this patient?**




# Case 1

- Enrolled on SWOG-S0819 trial and received
  - Carboplatin AUC 6
  - Paclitaxel 200 mg/m$^2$
  - Bevacizumab 15 mg/kg
  - Cetuximab 400 mg → 250 mg weekly




# Case 1

- Received 6 cycles of treatment followed by maintenance bevacizumab/cetuximab thru cycle 11
- Disease progression in liver, brain and bones documented
- WBRT delivered
- Went on to receive 2nd-line pemetrexed

# *Management of the Metastatic Pan-Wild-Type (PWT) Adenocarcinoma*

**Mark A. Socinski, MD**

Professor of Medicine and Thoracic Surgery
Director, Lung Cancer Section, Division of Hematology/ Oncology
Co-Director, UPMC Lung Cancer Center of Excellence and Lung and Thoracic Malignancies Program
University of Pittsburgh

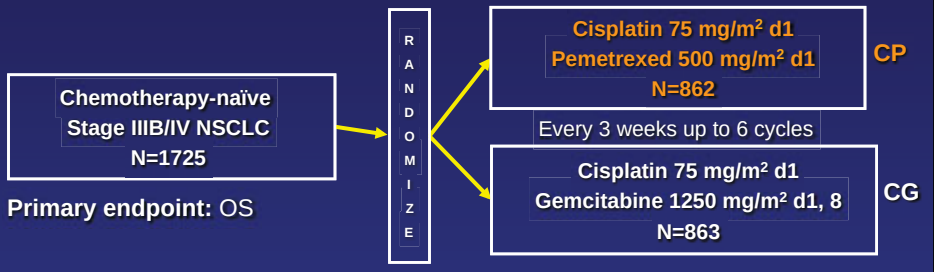
## Disclosures

| | |
|---|---|
| **Contracted Research** | Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, Lilly, Merrimack Pharmaceuticals, Onyx Pharmaceuticals Inc, Pfizer Inc |
| **Data and Safety Monitoring Board** | Millennium: The Takeda Oncology Company |
| **Speakers Bureau** | Celgene Corporation, Genentech BioOncology |

## Standard of Care in Patients without Identifiable Driver Mutations

- **Non-squamous**
  - Pemetrexed or taxane-based doublets
  - Bevacizumab in selected patients
  - 4 cycles (maybe 6?)
  - Maintenance considerations after 4 cycles
- **Squamous**
  - Taxane- or gemcitabine-based doublets
  - 4 cycles (maybe 6?)
  - Maintenance considerations after 4 cycles

## Phase III Trial: Cisplatin/Pemetrexed vs Cisplatin/Gemcitabine in Advanced NSCLC




| Clinical outcome | CP | CG |
|---|---|---|
| Median survival | 10.3 months | 10.3 months |
| Adjusted HR | 0.94 | |

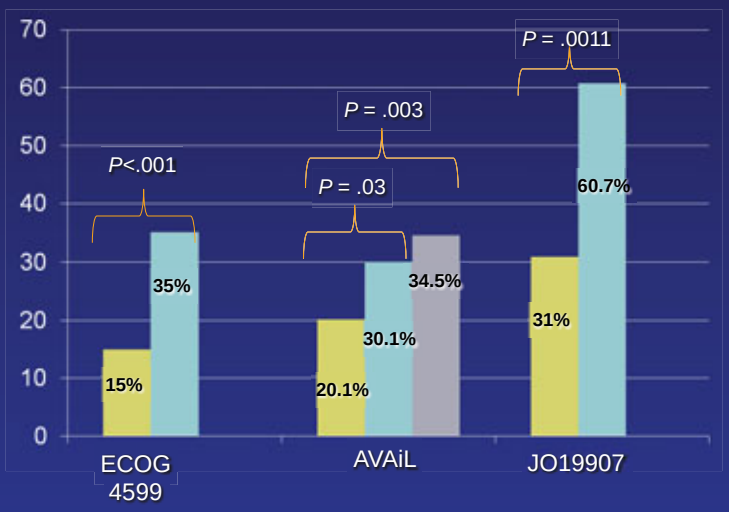
Scagliotti GV et al: *J Clin Oncol.* 26 (21), 2008: 3543-3551.

# Cisplatin/Pemetrexed vs Cisplatin/ Gemcitabine in Advanced NSCLC: Results

| Median survival | Cisplatin/ pemetrexed | Cisplatin/ gemcitabine | Adjusted HR |
|---|---|---|---|
| Nonsquamous | 11.8 mos | 10.4 mos | 0.81 |
| Squamous | 9.4 mos | 10.8 mos | 1.23 |

Scagliotti GV et al: *J Clin Oncol.* 26 (21), 2008: 3543-3551.

# Bevacizumab—Response




Sandler A, et al. *N Engl J Med.* 2006;355(24):2542-2550. Reck M, et al. *J Clin Oncol.* 2009;27(8):1227-1234. Reck M, et al. *Ann Oncol.* 2010;21(9):1804-1809. Niho S et al. *Lung Cancer.* 2012;76(3);362-367.

# Bevacizumab in Nonsquamous NSCLC: Key Results

| | E4599[1] | | AVAiL[2,3] | | | JO19907[4] | |
|---|---|---|---|---|---|---|---|
| Outcome | PCB | PC | CGB (7.5) | CGB (15) | PC | PCB | PC |
| ORR, % | 35 | 15 | 34.1 | 30.4 | 20.1 | 60.7 | 31.0 |
| | *P* <.001 | | *P* <.0001 | *P* = .0002 | | 0.001 | |
| HR for PFS | 0.66 (*P* <.001) | | 0.75 (*P* = .003) | 0.82 (*P* = .03) | | 0.61 (*P* = .009) | |
| Median PFS, months | 6.2 | 4.5 | 6.7 | 6.5 | 6.1 | 6.9 | 5.9 |
| HR for OS | 0.79 (*P* = .003) | | 0.93 (NS) | 1.03 (NS) | | 0.99 (*P* = .95) | |
| Median OS, months | 12.3 | 10.3 | 13.6 | 13.4 | 13.1 | 22.8 | 23.4 |

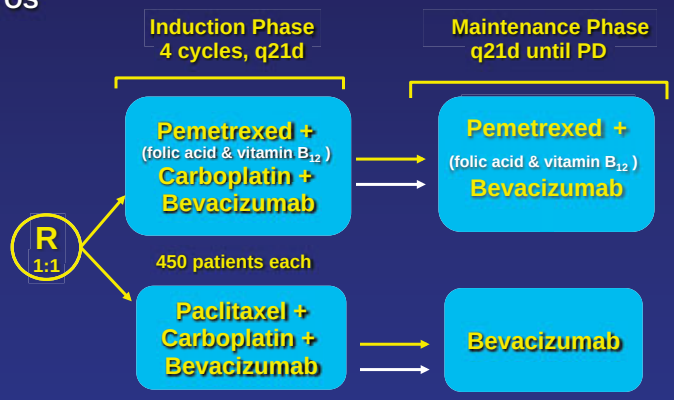
1. Sandler A, et al. *N Engl J Med.* 2006;355(24):2542-2550. 2. Reck M, et al. *J Clin Oncol.* 2009;27(8):1227-1234.
3. Reck M, et al. *Ann Oncol.* 2010;21(9):1804-1809. 4. Niho S et al. *Lung Cancer.* 2012;76(3);362-367.

# PointBreak: Study Design

- Randomized, open-label, phase III superiority study conducted in US
- Pemetrexed 500 mg/m$^2$; Carboplatin AUC 6; Bevacizumab 15 mg/kg
- Paclitaxel 200 mg/m$^2$; Carboplatin AUC 6; Bevacizumab 15 mg/kg
- Primary Endpoint: OS

Inclusion:- No prior systemic therapy for lung cancer
- ECOG PS 0/1
- Stage IIIB-IV NS-NSCLC
- Stable treated brain mets allowed

Exclusion:
- Peripheral neuropathy ≥Grade 1
- Uncontrolled pleural effusions




Stratified for:
PS (0 vs. 1) ; sex (M vs. F); disease stage (IIIB vs. IV); measurable vs. nonmeasurable disease

Patel J, Socinski MA, Garon EB et al. J Clin Oncol 31:4349-53, 2013

# PointBreak: PFS and OS (ITT Population)

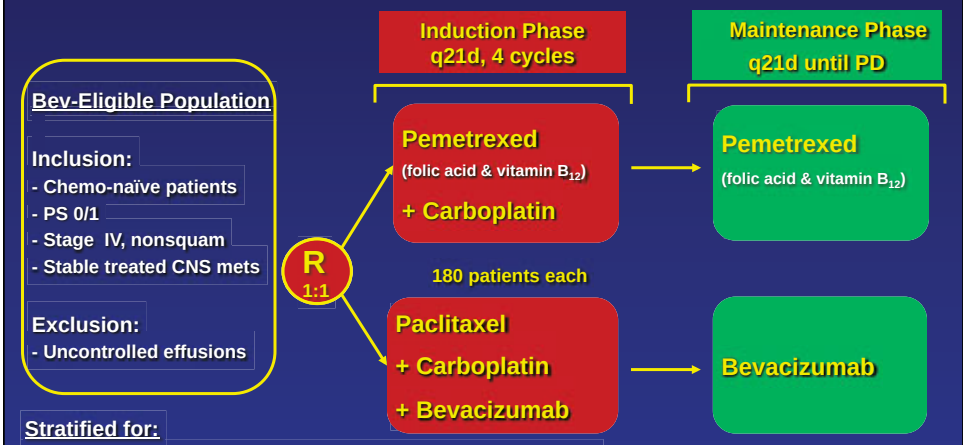
| | Pem+ Cb+Bev | Pac+ Cb+Bev |
|---|---|---|
| **PFS median (mo)** | **6.0** | **5.6** |
| HR (95% CI); *P* value | 0.83 (0.71, 0.96); *P*=0.012 | |
| **ORR (%)** | **34.1** | **33.0** |

| | Pem+ Cb+Bev | Pac+ Cb +Bev |
|---|---|---|
| **OS median (mo)** | **12.6** | **13.4** |
| HR (95% CI); *P* value | 1.00 (0.86, 1.16); *P*=0.949 | |
| **Survival rate (%)** | | |
| **1-year** | **52.7** | **54.1** |
| **2-year** | **24.4** | **21.2** |

Patel JD, Socinski MA, Garon EB et al. J Clin Oncol 31:4349-53, 2013

# PRONOUNCE: Study Design

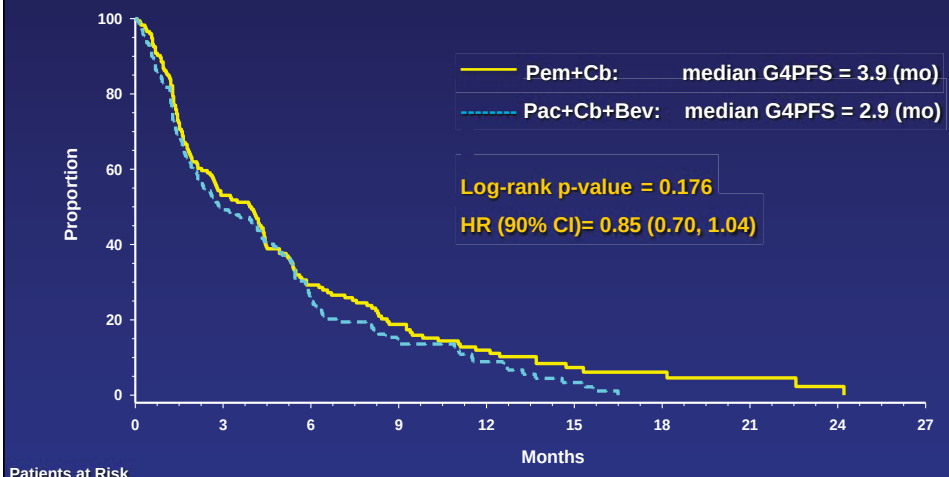
- Randomized, open-label, phase III superiority study conducted in US
- Pemetrexed 500 mg/m$^2$, Carboplatin AUC 6 (Pem+Cb)
- Paclitaxel 200 mg/m$^2$, Carboplatin AUC 6, Bevacizumab 15 mg/kg (Pac+Cb+Bev)




Stratified for:
PS (0 vs 1); gender (M vs F); disease stage (M1a vs M1b)

Primary Endpoint: PFS without grade 4 AE (Gr 4 PFS) – superiority of CbPem over CbP/Bev

# Primary Endpoint: G4PFS (ITT)

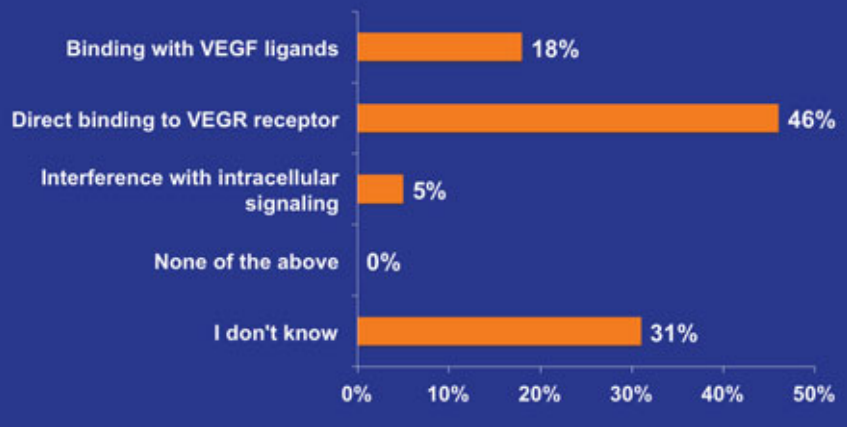



Patients at Risk

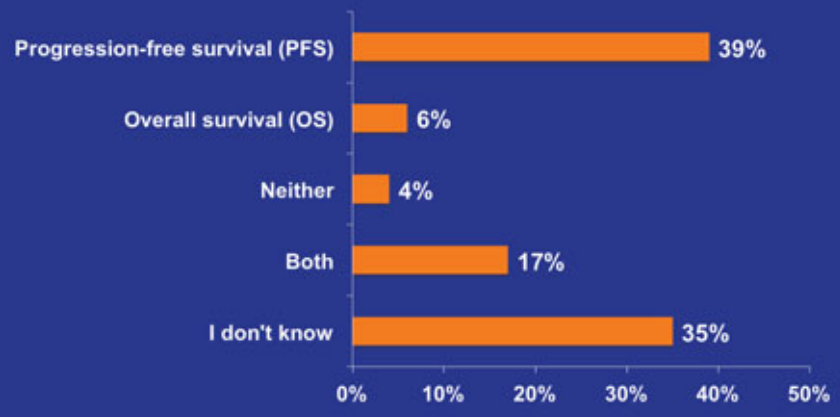
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pem+Cb | 182 | 87 | 44 | 26 | 14 | 7 | 5 | 3 | 1 | 0 |
| Pac+Cb+Bev | 179 | 75 | 33 | 17 | 9 | 3 | 0 | 0 | 0 | 0 |

With permission from Zinner R et al. Proc ASCO 2013;Abstract LBA8003.

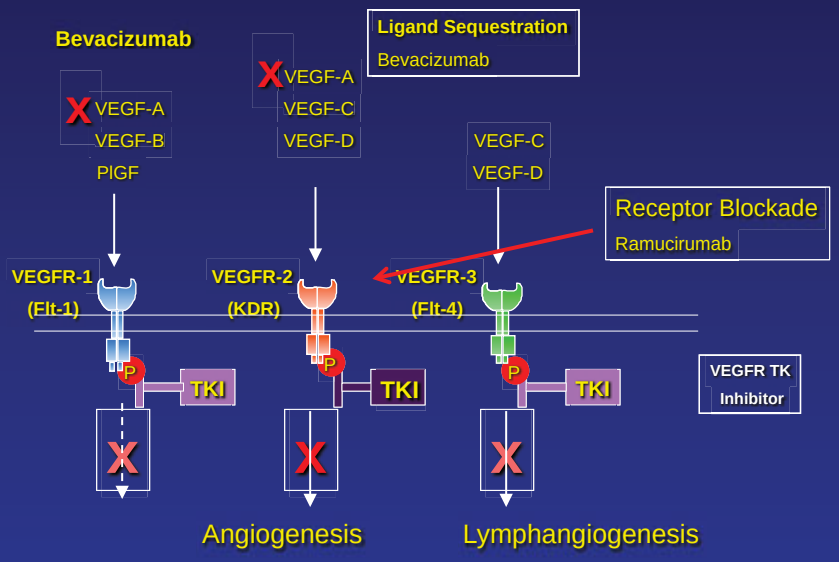
**What is the primary mechanism of action of ramucirumab?**

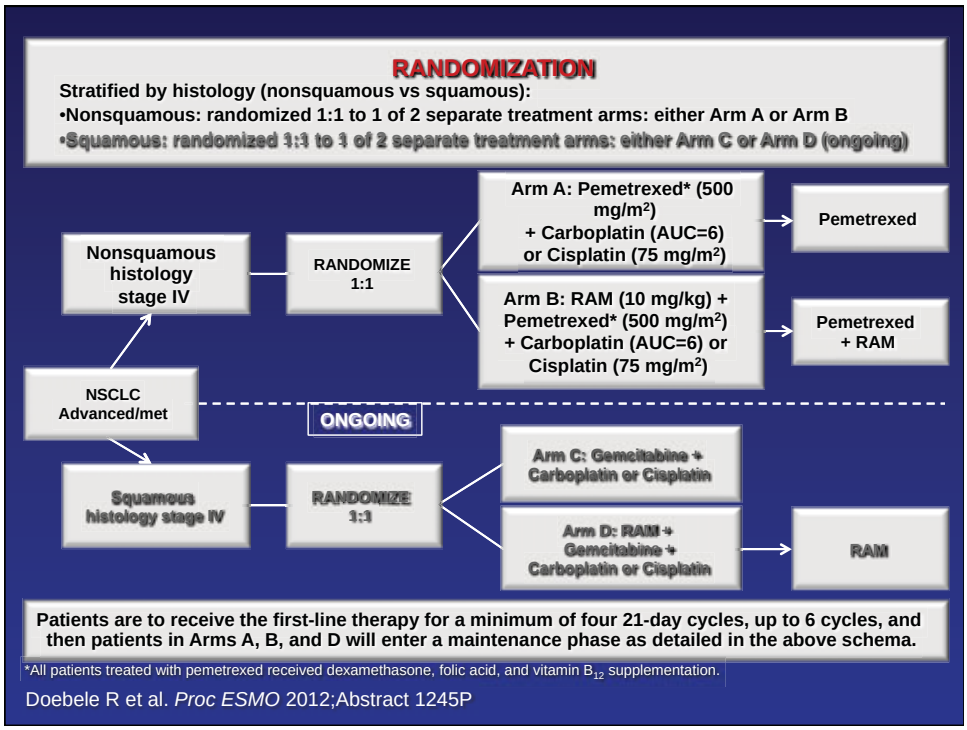


**Ramucirumab combined with docetaxel as second-line treatment in patients with metastatic NSCLC with disease progression on a platinum doublet resulted in a statistically significant improvement in…**




# MOA of Anti-angiogenic Agents






Doebele R et al. *Proc ESMO* 2012;Abstract 1245P

# Platinum/Pemetrexed ± Ramucirumab: Efficacy Results

**Median PFS**

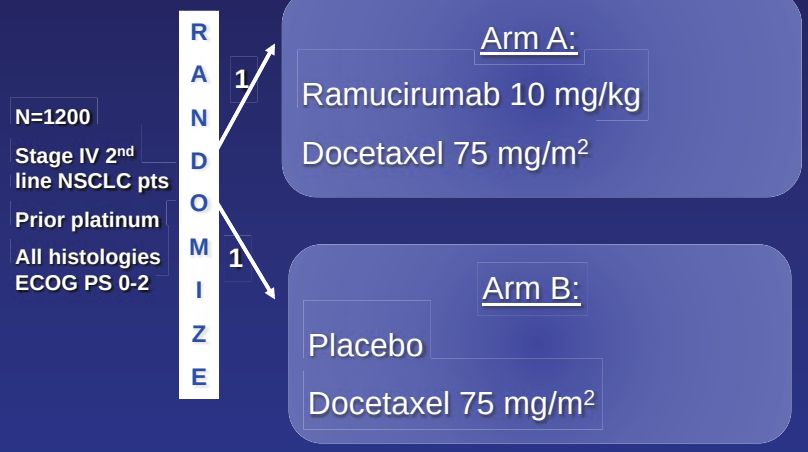
- Pem + carboplatin or cisplatin, 5.6 months
- Ramucirumab + pemetrexed + carboplatin or cisplatin, 7.2 months
- Hazard ratio = 0.75 (90% CI, 0.55-1.03)
- Log-rank p-value = 0.1318

**Median OS**

- Pem + carboplatin or cisplatin, 10.4 months
- Ramucirumab + pemetrexed + carboplatin or cisplatin, 13.9 months
- Hazard ratio = 1.03 (90% CI, 0.74-1.42)
- Log-rank p-value = 0.8916

- ORR (CR + PR) was 38% in Arm A and 49%, including one complete response, in Arm B (p = 0.180).
- Disease control rate was 70% in Arm A and 86% in Arm B (p = 0.032).

# REVEL: phase III, 2nd-line NSCLC




# REVEL: Phase III, 2nd line NSCLC

**Ramucirumab Phase III Lung Cancer Trial Meets Primary Endpoint of Overall Survival**

**— Ramucirumab Improved Survival in Second-Line Study of Patients with Non-Small Cell Lung Cancer —**

**INDIANAPOLIS, Feb. 19, 2014 /PRNewswire/ —**

**The REVEL trial, a global Phase III study of ramucirumab in combination with chemotherapy in patients with second-line non-small cell lung cancer (NSCLC), showed a statistically significant improvement in the primary endpoint of overall survival in the ramucirumab-plus-docetaxel arm compared to the control arm of placebo plus docetaxel. REVEL also showed a statistically significant improvement in progression-free survival in the ramucirumab arm compared to the control arm.**

## REVEL: Phase III, 2nd line NSCLC

**Ramucirumab Phase III Lung Cancer Trial Meets Primary Endpoint of Overall Survival**

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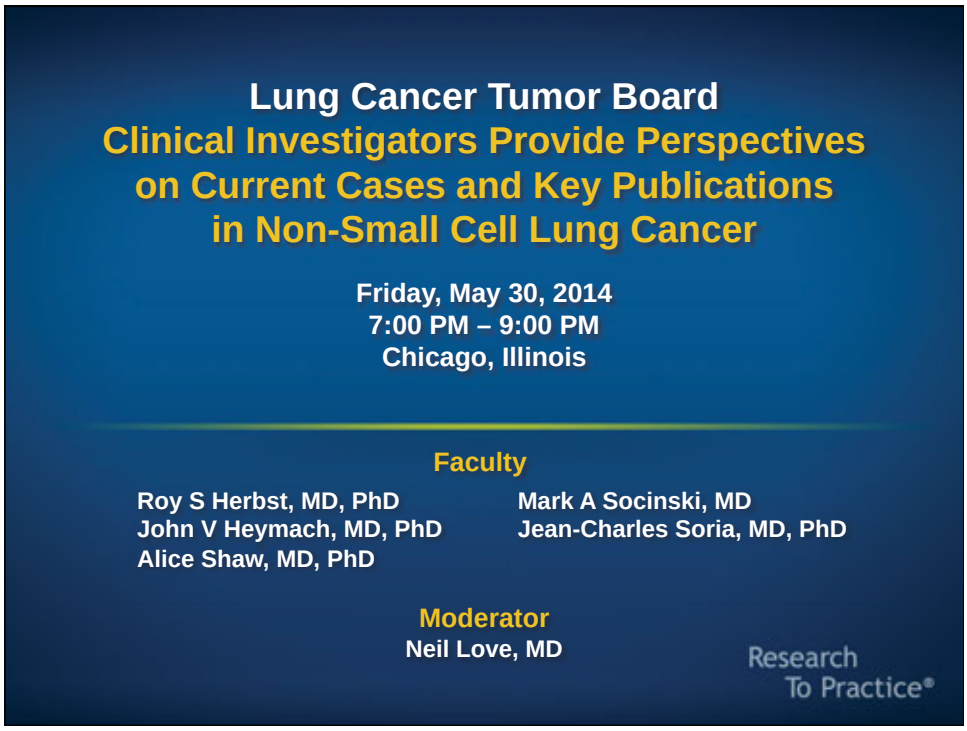
**LBA#8006 Monday June 2, 2014 Oral Presentation**

## Conclusions - PWT

- Platinum-based doublets remain the mainstay of therapy
- Choice of doublet depends on histology
- Bevacizumab an option for selected patients
- Duration of therapy – 4-6 cycles
- Maintenance commonly practiced with bevacizumab and pemetrexed
- 2nd line therapy improves survival – Ramucirumab may represent a new standard of care in this setting




# Case 2

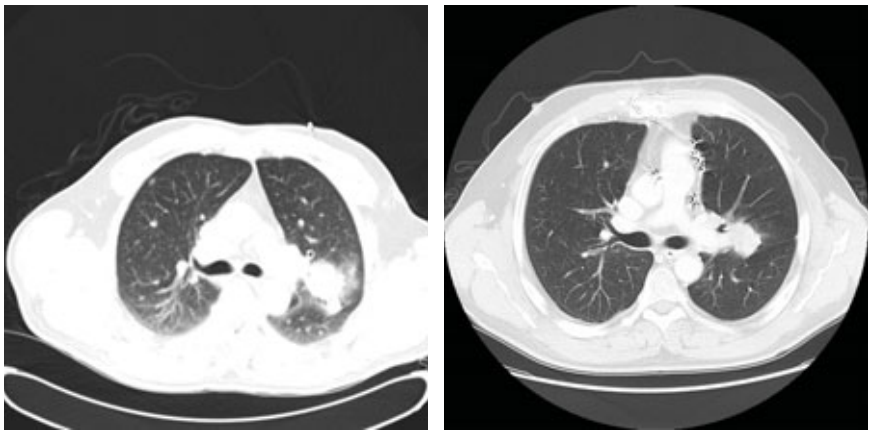
- A 62-year-old gentleman presented with back pain
- 5.5 cm infra-renal abdominal aortic aneurysm
- "Critical" coronary disease diagnosed and he underwent CABG 1 month previously
- During his work-up, he was found to have a LUL mass with hilar nodes and multiple pulmonary nodules
- 30 pack-year smoking history

# Case 2

- MRI brain and bone scan-negative
- Biopsy of LUL lesion – adenocarcinoma, TTF-1 positive
- EGFR wt, ALK-negative
- ECOG PS 0
- Bevacizumab-ineligible
- Treated with 4 cycles of carboplatin and pemetrexed

# Case 2

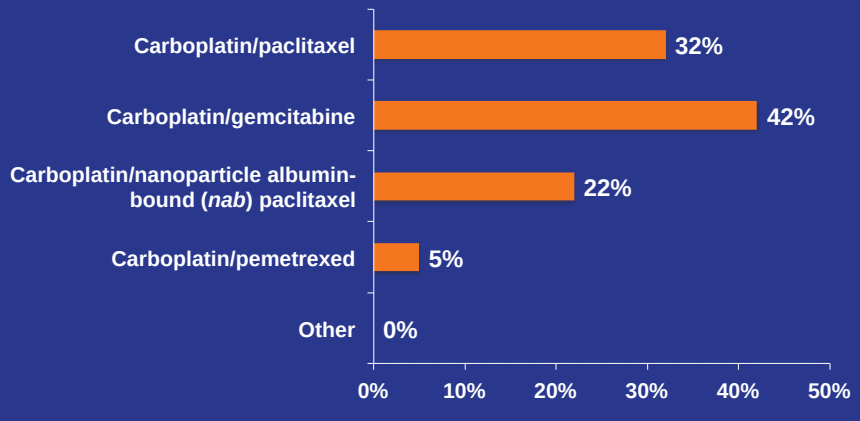
**Baseline** **s/p 4 cycles**



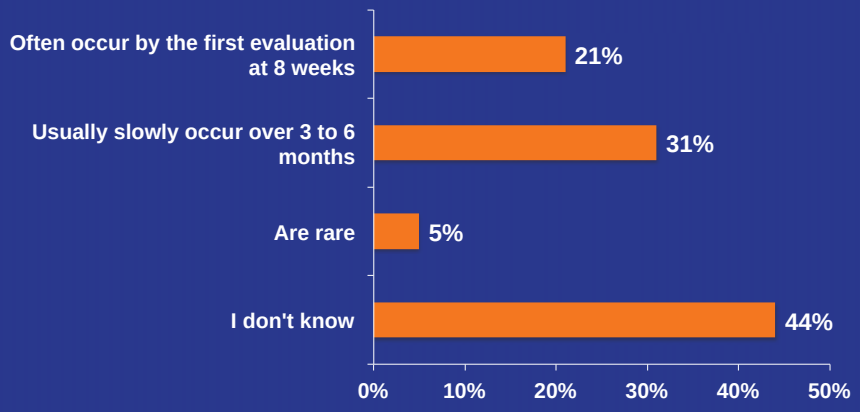
# Current and Emerging Treatment of Metastatic Squamous Cell Carcinoma (SCC)

**Roy S Herbst, MD, PhD**
Ensign Professor of Medicine (Oncology)
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Director for Translational Research
Yale Comprehensive Cancer Center
Yale School of Medicine
New Haven, Connecticut

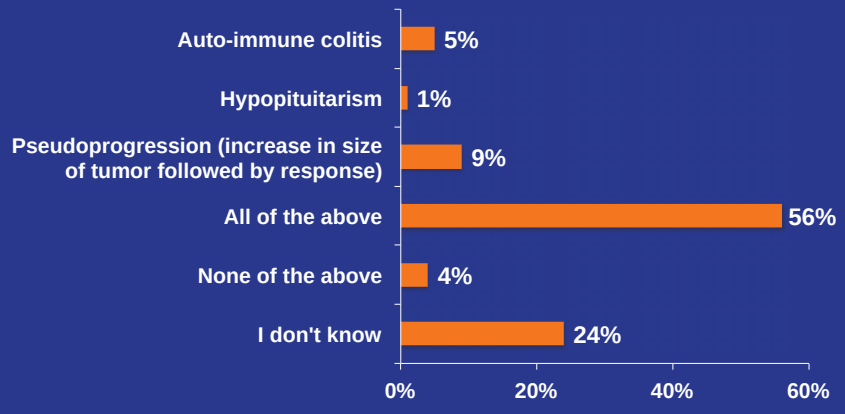
**In general, what first-line chemotherapy regimen would you most likely recommend for a 73-year-old patient (PS = 0) with metastatic squamous cell lung cancer?**



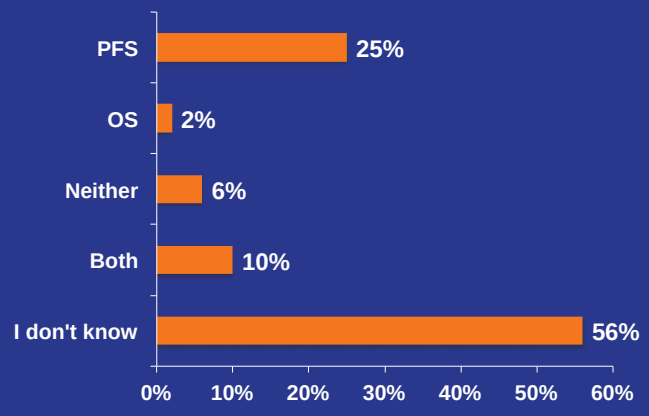
## Objective tumor responses to nivolumab in patients with NSCLC…




## Which of the following has been observed in patients who are enrolled in trials evaluating anti-PD-1 and anti-PDL-1 agents?



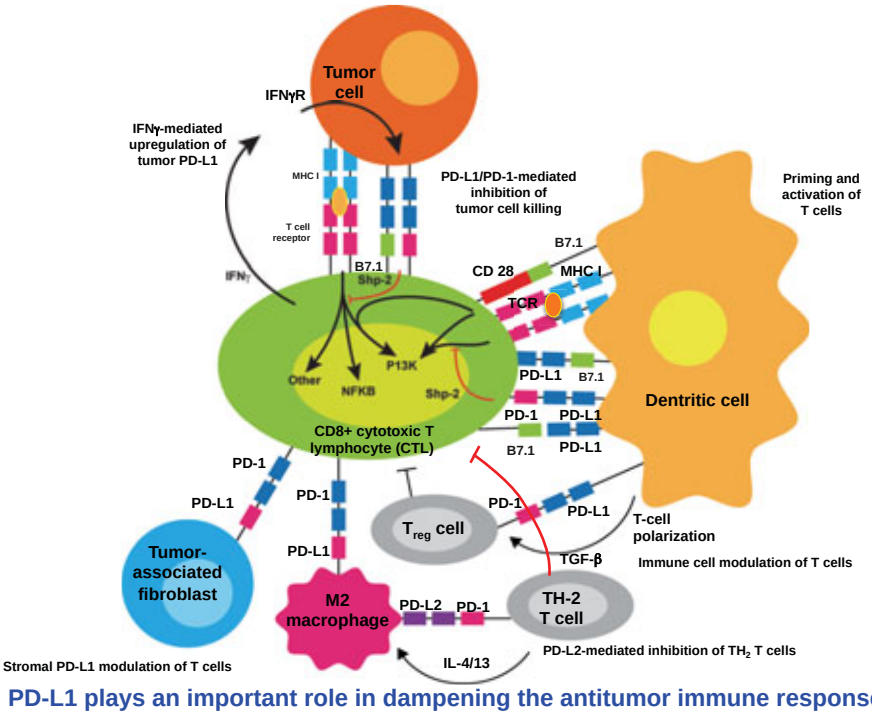
**Necitumumab combined with gemcitabine/carboplatin as first-line treatment of metastatic squamous cell cancer resulted in a statistically significant improvement in…**




# Disclosures

| | |
|---|---|
| **Consulting Agreements** | Astellas, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Merck |
| **Contracted Research** | GlaxoSmithKline |
| **Data and Safety Monitoring Board** | Pfizer Inc |

**A phase III comparative study of nivolumab versus docetaxel in patients with previously treated advanced or metastatic squamous cell NSCLC. Borghaei H et al.**
*Proc ASCO* 2013;Abstract TPS8122.




PD-L1 plays an important role in dampening the antitumor immune response

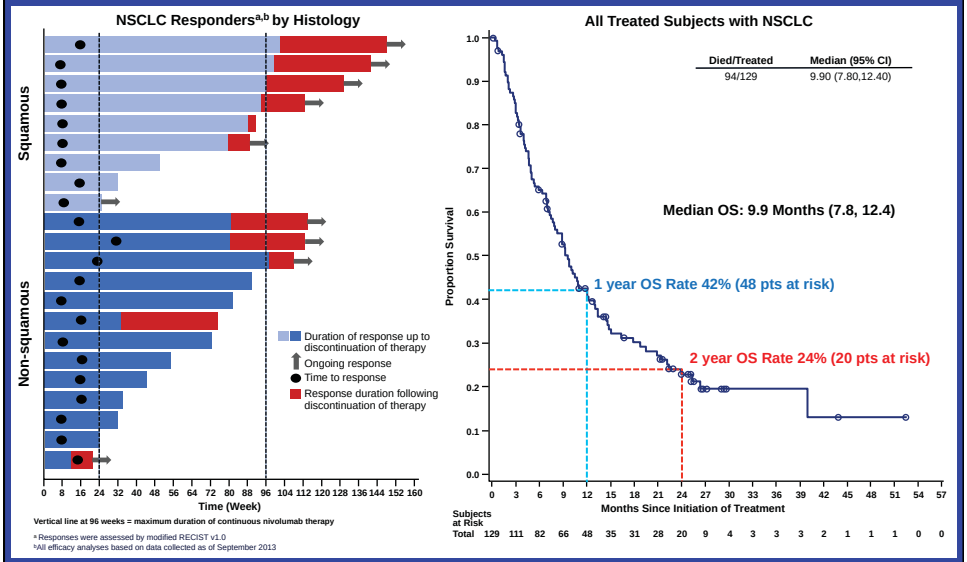
# Efficacy of Nivolumab Monotherapy in Patients (N=129) with NSCLC

| Dose mg/kg | ORR[a,b] % (n/N) | Estimated Median DOR Weeks (Range) | Stable Disease Rate ≥24 Wks % (n/N) | Median PFS Months (95% CI) | Median OS Months (95% CI) |
|---|---|---|---|---|---|
| All doses | 17.1 (22/129) | 74.0 (6.1+, 133.9+) | 10.1 (13/129) | 2.3 (1.9, 3.7) | 9.9 (7.8, 12.4) |
| 1 | 3.0 (1/33) | 63.9 (63.9, 63.9) | 15.2 (5/33) | 1.9 (1.8, 3.6) | 9.2 (5.3, 11.1) |
| 3 | 24.3 (9/37) | 74.0 (16.1+, 133.9+) | 8.1 (3/37) | 1.9 (1.7, 12.5) | 14.9 (7.3, NE) |
| 10 | 20.3 (12/59) | 83.1 (6.1+, 132.7+) | 8.5 (5/59) | 3.6 (1.9, 3.8) | 9.2 (5.2, 12.4) |

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
[a]Tumors and responses were assessed after each cycle per modified RECIST v1.0.
[b]All efficacy analyses based on data collected as of September 2013

- Durable responses were observed; responses are ongoing in 45% of patients (10/22)
- Higher ORRs observed at 3 and 10 mg/kg nivolumab doses relative to 1 mg/kg dose
- Rapid responses; 50% of patients (11/22) demonstrating response at first assessment (8 weeks)
- 7/16 responders who discontinued for reasons other than disease progression responded for ≥16 wks; 6/7 remain in response
- 6 patients with unconventional "immune-related" responses were not included as responders

# Duration of Response and Overall Survival




With permission from Brahmer J et al. Proc ASCO 2014;Abstract 8112.
Courtesy of Genentech BioOncology

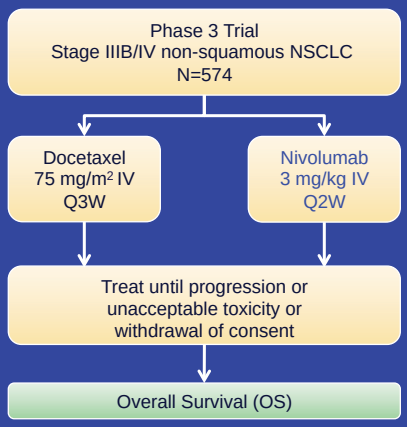
# Drug-Related Select Adverse Events (≥1%) Occurring in Patients with NSCLC (N=129) Treated with Nivolumab[a]

- No new safety signals emerging, with all patients now having ≥1 year of follow-up
- Select AE definition: AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention
- Drug-related pneumonitis (any grade) occurred in 8 patients with NSCLC (6%); 3 patients (2%) with NSCLC had grade 3-4 pneumonitis of which 2 cases were fatal

| Category | Treatment-related Select AE, % (n) | |
|---|---|---|
| | Any Grade % (n) | Grade 3-4 % (n) |
| Any treatment-related select AE | 41 (53) | 5 (6) |
| Skin | 16 (20) | 0 |
| Gastrointestinal | 12 (15) | 1 (1) |
| Pulmonary | 7 (9) | 2 (3) |
| Endocrinopathies | 6 (8) | 0 |
| Hepatic | 5 (6) | 1 (1) |
| Infusion reaction | 4 (5) | 1 (1) |
| Renal | 3 (4) | 0 |

[a]Safety data based on a March 2013 analysis

# Phase 3 Study of Nivolumab Compared to Docetaxel in 2nd/3rd-Line Advanced/Metastatic Non-Squamous Cell NSCLC (CA209-057/NCT01673867)




Start Date: November 2012
Estimated Study Completion Date: November 2014
Estimated Primary Completion Date: November 2014
Status: Ongoing

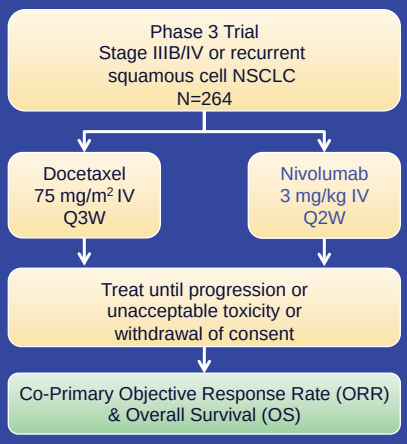
Primary Endpoints
- OS

Secondary Endpoints
- PFS
- ORR
- QoL

Key Eligibility Criteria
- ≥ 18 years of age
- Stage IIIB/IV non-squamous NSCLC
- Prior Pt-containing chemotherapy (2nd-line) required: additional TKI therapy allowed (3rd-line)
- Patient may have received continuous or switch maintenance with pemetrexed, erlotinib or bevacizumab post Pt-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation
- No prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 or other antibody targeting T-cell co-stimulation or checkpoint pathways

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; Pt, Platinum; QoL, Quality of life; TKI, Tyrosine kinase inhibitor

## Phase 3 Study of Nivolumab Compared to Docetaxel in 2nd-Line Advanced/Metastatic Squamous Cell NSCLC (CA209-017/NCT01642004)




Start Date: September 2012
Estimated Study Completion Date: August 2014
Estimated Primary Completion Date: August 2014
Status: Ongoing

Primary Endpoints
- ORR
- OS

Secondary Endpoints
- PFS
- ORR and OS in PD-L1$^{+}$ vs PD-L1$^{-}$ subgroups
- Duration of OR
- Time to OR
- Proportion of patients exhibiting disease-related symptom progression per Lung Cancer Symptom Scale

Key Eligibility Criteria
- ≥ 18 years of age
- Stage IIIB/IV squamous cell NSCLC or recurrent disease following RT or surgical resection
- Prior Pt-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

ECOG PS, Eastern Cooperative Oncology Group Performance Status; OR, objective response; PFS, progression-free survival; Pt, platinum; RT, radiotherapy

**Clinical activity, safety and biomarkers of PD-L1 blockade in NSCLC: Additional analyses from a clinical study of the engineered antibody MPDL3280A.**
**Soria JC.**
*Proc ECCO* 2013;Abstract 3408.

## Treatment-Related Adverse Events – NSCLC

| Adverse Event | Treatment-Related, n (%) n = 85 | |
|---|---|---|
| | Any Grade[a] | Grade 3-4[b] |
| Any AE | 56 (66%) | 9 (11%) |
| Fatigue | 17 (20%) | 2 (2%) |
| Nausea | 12 (14%) | 1 (1%) |
| Decreased appetite | 10 (12%) | 0 |
| Dyspnea | 8 (9%) | 1 (1%) |
| Diarrhea | 7 (8%) | 0 |
| Asthenia | 6 (7%) | 0 |
| Headache | 6 (7%) | 0 |
| Rash | 6 (7%) | 0 |
| Pyrexia | 5 (6%) | 0 |
| Vomiting | 5 (6%) | 1 (1%) |
| Upper respiratory tract infection | 4 (5%) | 0 |

- The majority of AEs were Grade 1-2 and did not require intervention
- No maximum tolerated dose or dose-limiting toxicities
- No Grade 3-5 pneumonitis observed
- One treatment-related death (cardio-respiratory arrest) in a patient with sinus thrombosis and large tumor mass invading the heart at baseline
- Immune-related Grade 3-4 AE observed in 1 patient with large cell neuroendocrine NSCLC (diabetes mellitus, 1%)

[a] AEs occurring in ≥ 5% of patients.
[b] Grade 3-4 treatment-related AEs listed include treatment-related AEs for which the any grade occurrence was ≥ 5% of patients.
Data cutoff Apr 30, 2013.

International Association for the Study of Lung Cancer
IASLC
IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

## MPDL3280A Phase Ia: Best Response by PD-L1 IHC Status, Histology and Duration of Treatment and Response – NSCLC

| PD-L1 Status (n = 53) | ORR[a] | PD Rate |
|---|---|---|
| IHC 3 (n = 6) | **83%** (5/6) | **17%** (1/6) |
| IHC 2 and 3 (n = 13) | **46%** (6/13) | **23%** (3/13) |
| IHC 1/2/3 (n = 26) | **31%** (8/26) | **38%** (10/26) |
| All patients (IHC 0/1/2/3 and 7 patients with diagnostic unknown; n = 53) | **23%** (12/53) | **40%** (21/53) |

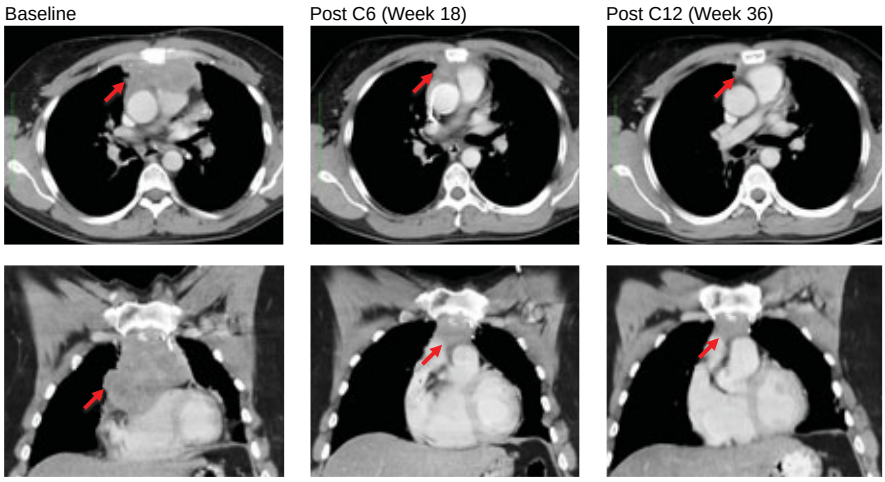
[a] ORR includes investigator-assessed unconfirmed and confirmed (u/c) PR per RECIST 1.1.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012. Data cutoff Apr 30, 2013.

# MPDL3280A Phase 1a Trial

- Larger trials, rapid responses
- Some patients may experience pseudoprogression before the tumors shrink

Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

# Clinical Activity of MPDL3280A in an NSCLC Patient




44-year-old male with NSCLC (adenocarcinoma), s/p radiotherapy, gemcitabine + cisplatin, temozolomide + docetaxel, pemetrexed, bevacizumab, CDX-1401, PD-L1-negative

Courtesy of Gettinger/Herbst

MPDL3280A Phase Ia

## Safety and efficacy analysis by histology of weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer.

**Socinski MA et al.**

*Ann Oncol* 2013;24(9):2390-6.

M. A. Socinski[1], I. Okamoto[2], J. K. Hon[3], V. Hirsh[4], S. R. Dakhil[5], R. D. Page[6], J. Orsini[7], N. Yamamoto[8], H. Zhang[9] & M. F. Renschler[9]

[1]Division of Hematology/Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, USA; [2]Department of Medical Oncology, Kinki University School of Medicine, Osaka-Sayama, Japan; [3]Stem Cell Transplant Program, Clearview Cancer Institute, Huntsville, USA; [4]Department of Oncology, McGill University, Montreal, Canada; [5]Cancer Center of Kansas, Wichita; [6]The Center for Cancer and Blood Disorders, Fort Worth; [7]Essex Oncology of New Jersey, Belleville, USA; [8]Shizuoka Cancer Center, Shizuoka, Japan; [9]Medical Affairs, Celgene, Summit, USA

## Blinded Radiology-Assessed Progression-Free Survival in Patients with NSCLC by Histology Subtype

**Squamous cell histology**

| | N/Events | Median PFS | Hazard ratio (*p*-value) |
|---|---|---|---|
| *nab*-P/C | 229/137 | 5.6 mo | 0.865 (0.245) |
| sb-P/C | 221/134 | 5.7 mo | |

**Adenocarcinoma**

| | N/Events | Median PFS | Hazard ratio (*p*-value) |
|---|---|---|---|
| *nab*-P/C | 254/137 | 6.9 mo | 0.991 (0.944) |
| sb-P/C | 264/151 | 6.9 mo | |

*nab*-P/C, *nab*-paclitaxel + carboplatin; sb-P/C, solvent-based paclitaxel + carboplatin

Socinski MA et al. *Ann Oncol* 2013;24(9):2390-6.

**Patient-Assessed Taxane-Related Symptoms by Functional Assessment of Cancer Therapy (FACT): Peripheral Neuropathy**

In patients with nonsquamous cell NSCLC, significant treatment effects favoring *nab*-P/C versus sb-P/C were noted for:

- Patient-reported neuropathy (1.77 versus 3.24; $P < 0.001$)
- Pain in hands/feet (0.75 versus 1.31; $P < 0.001$).

For both nonsquamous cell and squamous cell NSCLC, the change from baseline to final evaluation for all 16 questions included in the FACT-Taxane subscale and all 11-items included in the FACT-Taxane neuropathy subscale significantly favored the *nab*-P arm

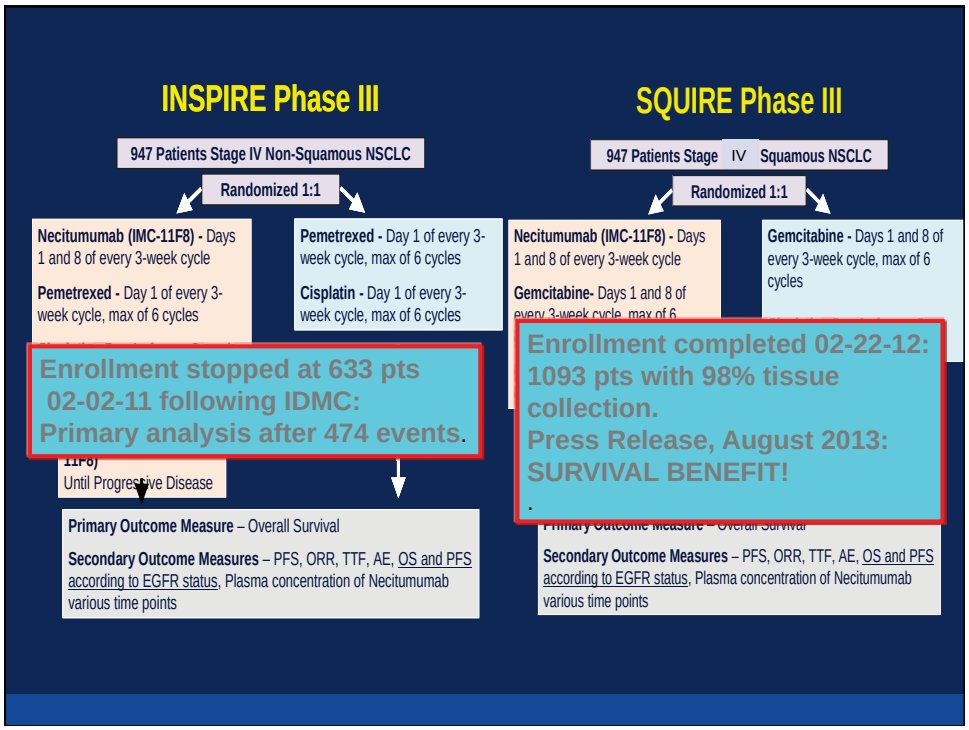
- $P < 0.001$ for all

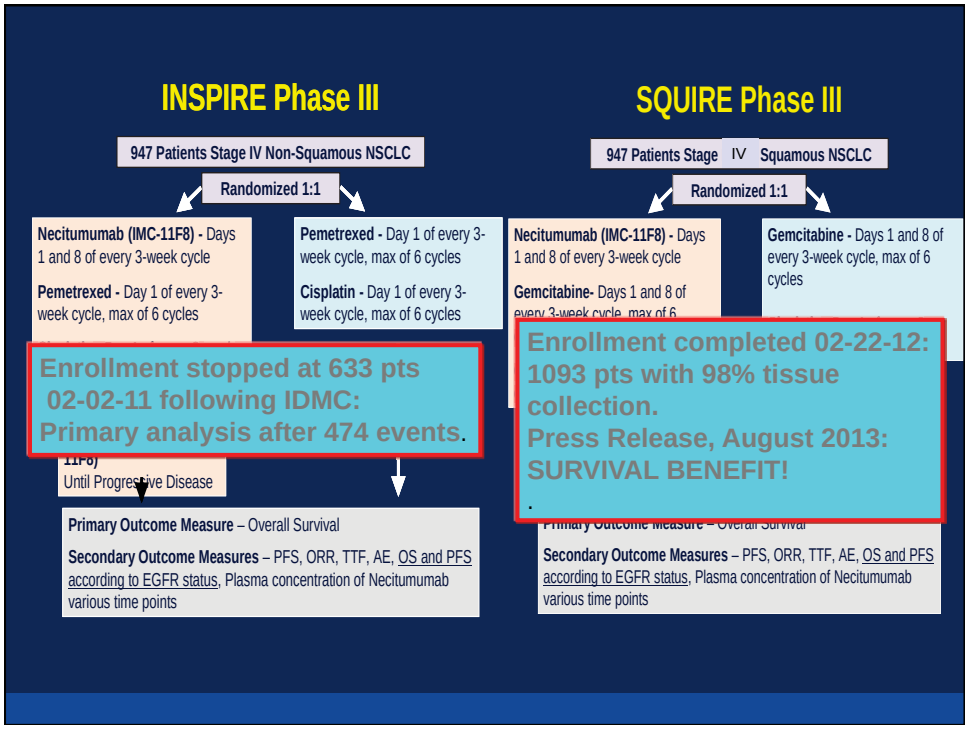
Socinski MA et al. *Ann Oncol* 2013;24(9):2390-6.

**SQUIRE: A randomized, multicenter, open-label phase 3 study of gemcitabine-cisplatin chemotherapy plus necitumumab (IMC-11F8) versus gemcitabine-cisplatin chemotherapy alone in the first-line treatment of patients with stage IV squamous NSCLC.**
www.clinicaltrials.gov.
Identifier NCT00981058.

# NECITUMUMAB (IMC-11F8, LY3012211)

- Necitumumab (IMC-11F8; LY3012211) is a human IgG1 monoclonal antibody designed to block the ligand binding site of the human epidermal growth factor receptor (EGFR)
- Necitumumab is being investigated in clinical trials in patients with NSCLC






# SQUIRE: Top-Line Results

- **SQUIRE met its primary endpoint of OS** in patients with Stage IV metastatic squamous NSCLC – hazard ratio 0.84
- Increased OS was observed when patients were administered necitumumab in combination with gemcitabine and cisplatin as first-line treatment compared to gemcitabine and cisplatin alone
- PFS improvement with the addition of necitumumab was also statistically significant (hazard ratio 0.85, $p = 0.020$)
- The most common adverse events occurring more frequently in patients on the necitumumab arm were rash and hypomagnesemia. Serious, but less frequent, adverse events occurring more often on the necitumumab arm included thromboembolism
- Results to be presented here at ASCO

# Lung Cancer Tumor Board

## Clinical Investigators Provide Perspectives on Current Cases and Key Publications in Non-Small Cell Lung Cancer

**Friday, May 30, 2014**
**7:00 PM – 9:00 PM**
**Chicago, Illinois**

**Faculty**

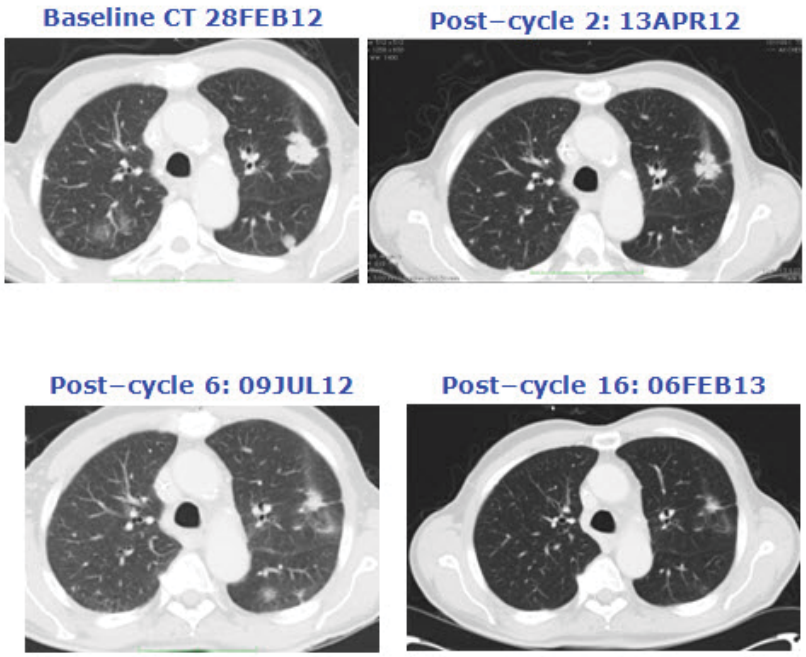

Roy S Herbst, MD, PhD
John V Heymach, MD, PhD
Alice Shaw, MD, PhD
Mark A Socinski, MD
Jean-Charles Soria, MD, PhD


**Moderator**
Neil Love, MD

Research To Practice®

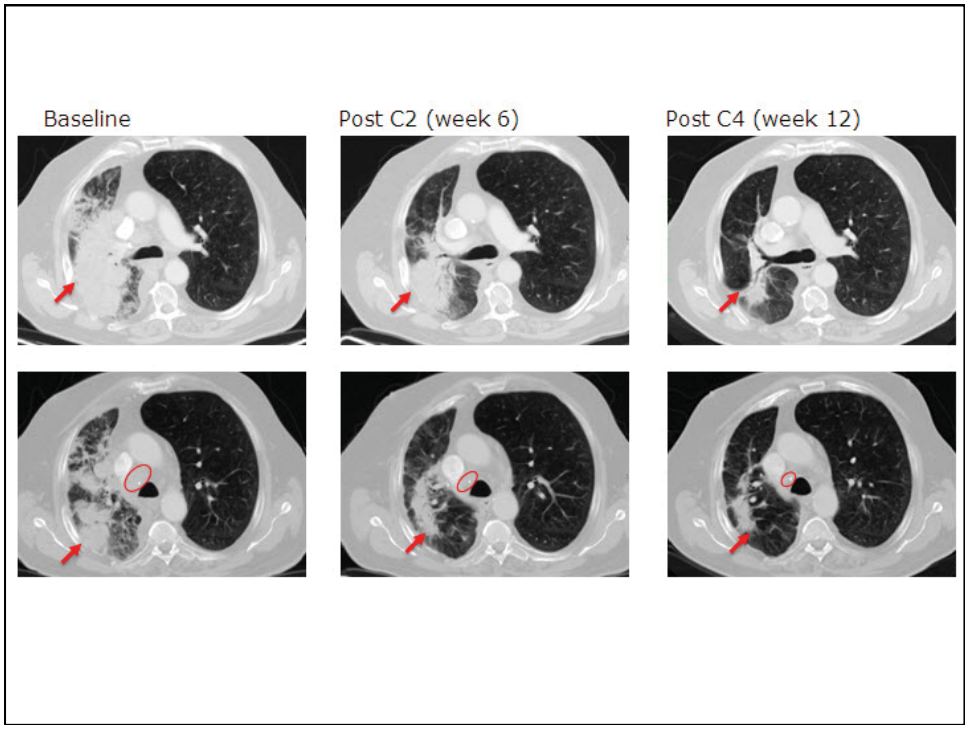
# Case 1: Squamous Cell Carcinoma

- 73-year-old male with Stage IV NSCLC (squamous)
- Diagnosed in 2011 with metastases to lung, mediastinum, lymph nodes and pleura
- Treated initially with Carboplatin and Paclitaxel with progressive disease
- Two cycles of Docetaxel
- Received an anti-PD-L1 agent on a clinical trial
- Response status: PR at C2 and remains in PR at C16 (1 out of 4 target lesions left). Percentage change in SLD of target lesions: -88.7%

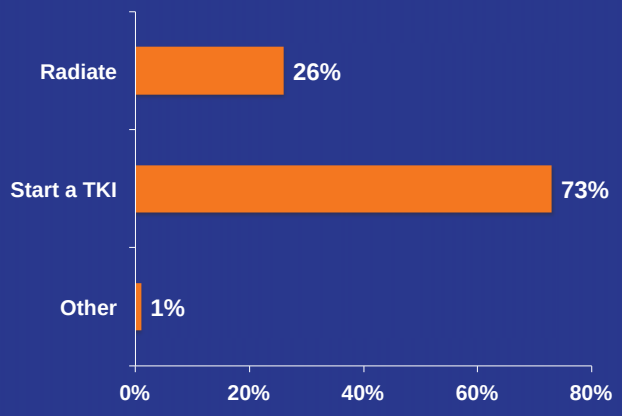



# Case 2: Squamous Cell Carcinoma

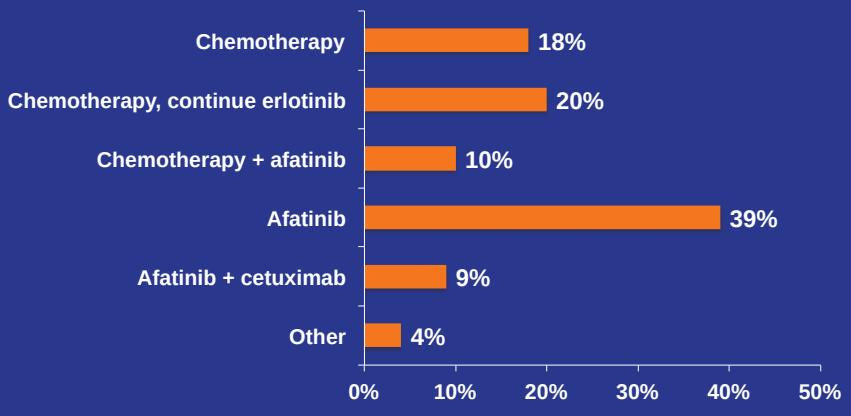
- 64 yo male squamous cell NSCLC
- s/p R lobectomy
- Treated with Cisplatin+Gemcitabine, Docetaxel, Erlotinib
- Tumor: PD-L1+
- Went on a clinical study with an anti-PD-L1 agent


Baseline
Post C2 (week 6)
Post C4 (week 12)

**A 39-year-old patient presents with EGFR mutation-positive (exon 19 deletion) adenocarcinoma of the lung and multiple, small, asymptomatic CNS metastases. Would you irradiate the brain now or initiate an EGFR TKI?**




**The 39-year-old patient in the previous question with EGFR mutation-positive (exon 19 deletion) adenocarcinoma of the lung is treated with erlotinib and has a 2-year response and then experiences slow, asymptomatic disease progression. What would be your most likely next systemic treatment, assuming the patient was not eligible for a clinical trial?**



# Case

- 39-year-old never-smoking engineer, h/o MS, dx in 2008 with metastatic adenocarcinoma and CNS mets. Exon 19 deletion
- Treated with erlotinib 2008 to 11/2010
- 3/2010  PD; started pem + erlotinib
- 7/2010 PD; T790M mutation
- 11/2010 started on afatinib + cetuximab
- 1/2011 — PD in CNS, given WBXRT, continued afatinib + cetuximab

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# Therapeutic Decision-Making for Patients with EGFR Mutations

**John Heymach, MD, PhD**
Chairman and Professor
Thoracic/Head and Neck Medical Oncology
and Cancer Biology

ASCO Satellite Conference with Dr. Neil Love
May 30, 2014

Disclosures: Advisory boards for Genentech, AstraZeneca, Pfizer, Boehringer-Ingelheim
Research support from AstraZeneca, Bayer

# Why do we need a new generation of EGFR inhibitors?

- Greater potency, bioavailability
  - CNS a frequent site of recurrence in patients with EGFR-mutant disease
- Target resistance mechanisms (e.g. T790M)
- Target uncommon mutations
- Different MOA
- More favorable toxicity profile
  - Off-target vs on-target effects

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# LUX-Lung 1: Improved PFS (but not OS) for afatinib vs placebo in EGFR TKI pretreated NSCLC

Stage IIIB/IV adeno with PD after ≥12 wks of erlotinib/gefitinib

**LUX-Lung 1: Ph 2b/3 of afatinib vs placebo**

**Central Review**

- Placebo (median 1.1 months [95% CI 0.95-1.68])
- Afatinib (median 3.3 months [95% CI 2.79-4.40])

- Hazard ratio 0.38 (95% CI 0.31-0.48)
- Log-rank test p value (one-sided) <0.0001

**Investigator Review**

- Placebo (median 0.95 months [95% CI 0.95-0.99])
- Afatinib (median 2.83 months [95% CI 2.73-4.01])

- Hazard ratio 0.37 (95% CI 0.30-0.44)
- Log-rank test p value (one-sided) <0.0001

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Miller et al, Lancet Oncology, 2012

## Afatinib in EGFR-mutant NSCLC with acquired resistance to reversible EGFR TKIs

- Overall goal of study:
  - evaluate clinical efficacy of afatinib in patients (pts) with EGFR-mutant NSCLC with secondary resistance to reversible EGFR TKIs.

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Cappuzzo F et al. Proc IASLC 2013;Abstract P1.11-033.

## Afatinib maintains its inhibitory activity in erlotinib/gefitinib resistant EGFR mutants

***In vitro* kinase assay**

| Kinases | Afatinib | Lapatinib | Gefitinib |
|---|---|---|---|
| EGFR wt | 0.5 | 3 | 3 |
| EGFR L858R | 0.4 | 8 | 0.8 |
| EGFR L858R/T790M | 10 | >4000 | 1013 |

**Anchorage independent growth**

| $EC_{50}$ [nM] | wild type H1666 | L858R H3255 | L858R+T790M NCI1975 | Target | Binding mode |
|---|---|---|---|---|---|
| Gefitinib | 157 | 5 | >4000 | EGFR | reversible |
| Erlotinib | 110 | 40 | >4000 | EGFR | reversible |
| Afatinib | 60 | 0.7 | 99 | EGFR/HER2 | irreversible |
| CP-724-714 | >4000 | 561 | >4000 | HER2 | reversible |
| Lapatinib | 534 | 63 | >4000 | EGFR/HER2 | reversible |

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## Secondary mutations in EGFR (T790M) lead to acquired resistance to EGFR TKIs

- T790M known as a major mechanism of acquired resistance
- Data suggest that it often is present at a low frequency at baseline and selected for after treatment with EGFR TKI
  - EGFR TKIs may kill non-T790M containing clones preferentially, enriching for T790M+ population

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Kobayashi et al, NEJM 2005

## Afatinib in EGFR-mutant NSCLC with acquired resistance to reversible EGFR-TKIs

**97 EGFR-mutant NSCLC**
**Afatinib 40-50 mg QD**
Pretreated w/ >3 therapy lines
ECOG PS 0-1

**87 patients evaluated**
- **RR: 11.5%**
- **Median PFS/OS: 3.9/7.3 months**

**Take Home: afatinib has modest effects in EGFR-TKI resistant NSCLC**

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Cappuzzo F et al. Proc IASLC 2013;Abstract P1.11-033.

EGFR TKIs are better than chemo for patients with EGFR M+ disease.

But what about chemo+EGFR TKI?

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Making Cancer History®

CALGB 30406: Randomized phase II trial of E vs ECP for first-line NSCLC in never or light former smokers.

**Progression-Free Survival (months)**

- Erlotinib: 14.1 (7.0–19.6)
- Erlotinib/CP: 17.2 (8.2–27.8)
  - P = 0.3490

**Overall Survival (months)**

- Erlotinib: 31.3 (23.8–NA)
- Erlotinib/CP: 38.1 (19.6–NA)
  - P = 0.9227

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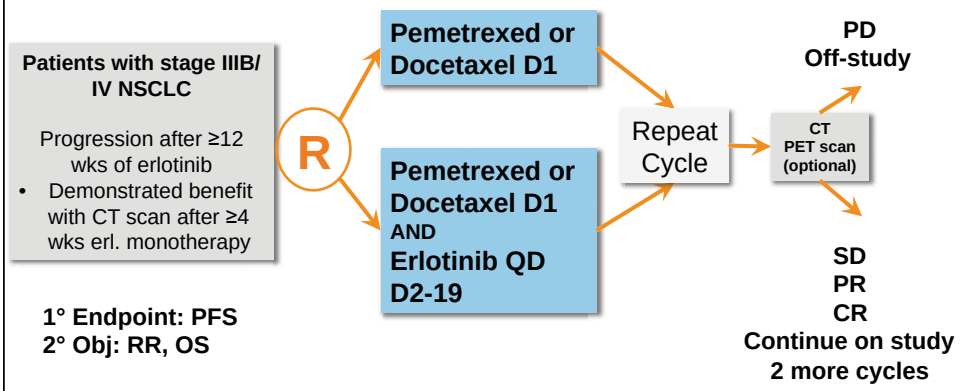
Making Cancer History®

Janne et al, J Clin Oncol, 2012

## Erlotinib beyond progression study: chemo plus erlotinib vs chemo alone in EGFR tyrosine kinase inhibitor (TKI)-responsive, NSCLC that subsequently progresses




Halmos B et al. *Proc ASCO* 2013;Abstract 8114; NCT00660816

## Erlotinib beyond progression study: chemo plus erlotinib vs chemo alone in EGFR tyrosine kinase inhibitor (TKI)-responsive, NSCLC that subsequently progresses

- Early termination due to slow enrollment
- No benefit seen with continuation of erlotinib+chemo vs chemo alone
- Significantly more toxicity in combo arm
- No benefit seen in M+ (39% vs 32% 6m PFS)

| | Pem/doc (N = 24) | Erlo+pem/doc (N = 22) | P |
|---|---|---|---|
| Median PFS (m) | 5.4 | 4.6 | .569 |
| Median OS (m) | 18.7 | 14.7 | .295 |
| EGFR M+ | 17 | 14 | |

Halmos B et al. *Proc ASCO* 2013;Abstract 8114; NCT00660816

# The LUX-Lung Trials

- **LUX-Lung 2:**
  - Ph II, EGFR-mutant Stage IIIb/IV NSCLC (2 doses afatinib)
  - Activity in pts with Exon 19 del and L858R mutations
- **LUX-Lung 3**
  - Ph III, Stage IIIb/IV NSCLC, stratified by EGFR mutation (Exon 19 del, L858R, other)
  - afatinib vs chemo → prolonged PFS in afatinib group
- **LUX-Lung 6**
  - Ph III, first-line study in EGFR-mutant NSCLC (Asian population)
  - afatinib vs chemo (cis + gem)
  - 1st-line afatinib improves PFS

Yang et al, Lancet Oncology, 2012;
Sequist et al, JCO, 2013;
Wu et al, Lancet Oncology, 2014

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# Afatinib in uncommon EGFR mutations

**Largest analysis of prospectively identified pts with uncommon EGFR mutations**

**Uncommon EGFR Mutations**
- **de novo T790M**
- **exon 20 insertions**
- **other**

**Endpoints Assessed**
**ORR, DCR, PFS**

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Yang JC et al., *Proc IASLC* 2013;Abstract O03.05

# Afatinib exhibits activity in uncommon EGFR mutations

| Mutation | ORR % (n) | DCR % (n) | Median PFS | Median survival |
|---|---|---|---|---|
| De novo T790M (n=14) | 14.3 (2) | 64.2 (9) | 2.9 | 14.9 |
| Exon 20 insertions (n=23) | 8.7 (2) | 65.2 | 2.7 | 9.4 |
| Other (n=38) | 71.1 (27) | 84.2 (32) | 10.7 | 18.6 |

- RR low in T790M mutations and exon 20 insertions

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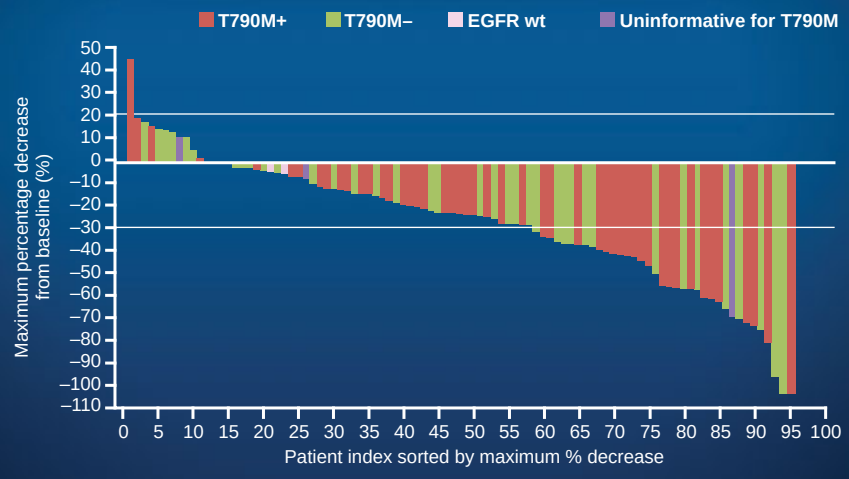
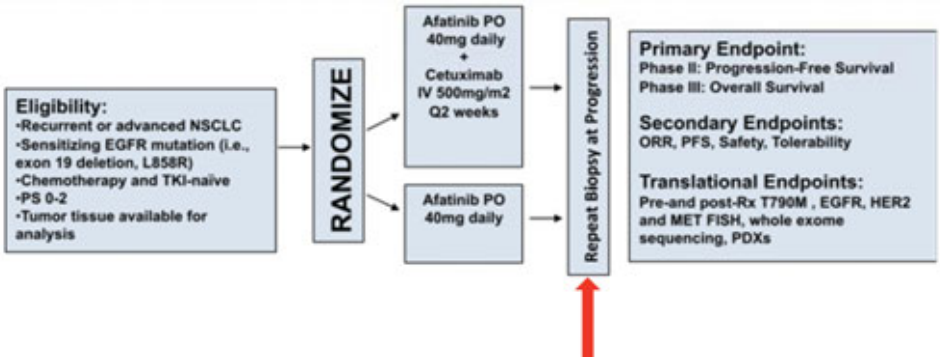
Yang JC et al., *Proc IASLC* 2013;Abstract O03.05

# Afatinib + cetuximab at MTD: Responses by T790M mutation




With permission from Janjigian YY et al. *Proc ESMO* 2012;Abstract 12007O.

## Proposed S1403: A Randomized Phase II/III Trial of Afatinib/Cetuximab versus Afatinib Alone in Treatment-Naïve, Advanced, *EGFR* Mutation-Positive NSCLC

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Hirsch F, SWOG Spring 2014 Group Meeting

## Bottom line

- Afatinib has modest activity in EGFR mutants refractory to EGFR TKI
- Atypical mutations do not respond as well as L858R or Del19, but afatinib has some activity in this group.
- Underpowered study but Chemo+erlotinib does not appear better than chemo in patients with EGFR-mutant disease who respond and then progress

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# Lung Cancer Tumor Board

## Clinical Investigators Provide Perspectives on Current Cases and Key Publications in Non-Small Cell Lung Cancer

**Friday, May 30, 2014**
**7:00 PM – 9:00 PM**
**Chicago, Illinois**

### Faculty


Roy S Herbst, MD, PhD
John V Heymach, MD, PhD
Alice Shaw, MD, PhD
Mark A Socinski, MD
Jean-Charles Soria, MD, PhD


### Moderator

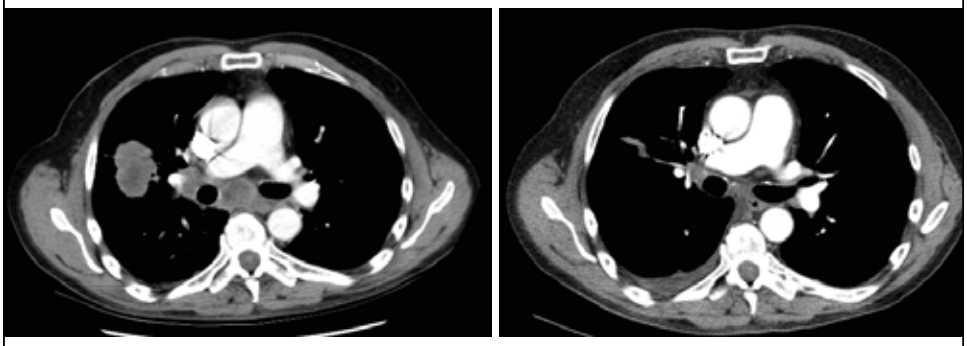

Neil Love, MD


Research To Practice®

## Case 1

- 66 yo M former smoker (10-15 py) diagnosed with metastatic NSCLC (squamous histology) in February 2011
- Genetic testing positive for ALK rearrangement
- He was treated with first-line crizotinib and achieved a PR lasting 10 months
- He had slow disease progression over a period of 4 months and was taken off crizotinib when he became symptomatic
- Once off crizotinib, he acutely worsened with RLL collapse and impending tamponade

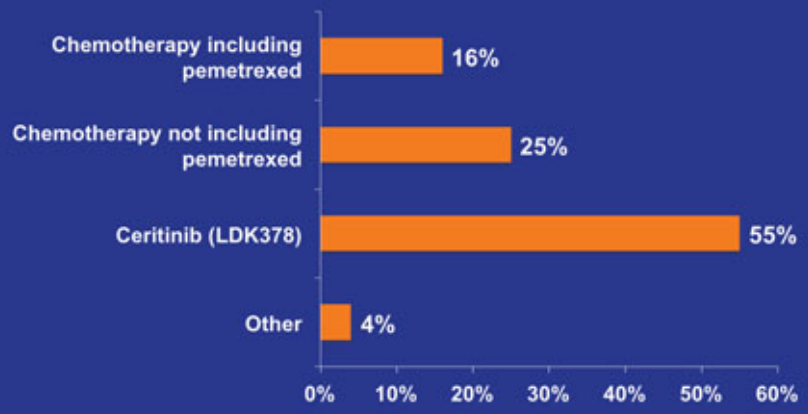
## Case 1



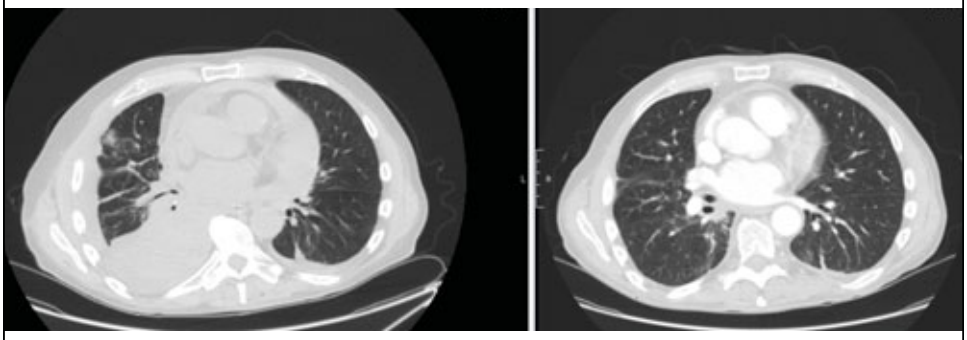
3-28-11 7-5-11

Start crizotinib 4-11-11

**A 66-year-old man with ALK-positive squamous cell cancer who has a partial response to crizotinib lasting 10 months presents with rapid disease progression that is compromising his performance status. What would your next therapy most likely be, assuming the patient is not eligible for a clinical trial?**




## Case 1



Baseline before LDK378

After 5 weeks of LDK378

# Management of ALK- and ROS1-Positive NSCLC

Alice T. Shaw, MD, PhD
Associate Professor of Medicine
Massachusetts General Hospital Cancer Center
Harvard Medical School
May 30, 2014

# Disclosures

| | |
|---|---|
| **Advisory Committee** | ARIAD Pharmaceuticals Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc |
| **Consulting Agreements** | ARIAD Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc |
| **Contracted Research** | Pfizer Inc |

## Clinical Features Associated with ALK vs ROS1 Rearrangements in Lung Cancer

| | ALK | ROS1 |
|---|---|---|
| Frequency in NSCLC | 3-7% | 1% |
| Average age | 50 yrs | 50 yrs |
| Gender (M:F) | Equal | Equal |
| Smoking history | Nonsmokers | Nonsmokers |
| Histology | Adenocarcinoma | Adenocarcinoma |
| Diagnosis | FISH, IHC, NGS | FISH, NGS |
| Other cancer types | ALCL, IMT, neuroblastoma, others | GBM, cholangiocarcinoma |
| Response rate to crizotinib (Ph 1 study) | 61% | 61%* |

*Updated as of ESMO 2013

## Activity of Crizotinib in ALK+ NSCLC

- 125 patients (94%) experienced some degree of tumor shrinkage during the study
- 87 of 143 patients had an objective response (60.8%), including 3 complete responses and 84 partial responses
- Median time to first documented objective response was 7.9 weeks
- Median duration of response was 49.1 weeks
- For all patients who received at least 1 dose of crizotinib, the median PFS was 9.7 months with a median follow-up of 16.3 months

Camidge DR et al. *Lancet Oncol* 2012;13(10):1011-9.

## Activity of Crizotinib in ROS1+ NSCLC

Ongoing Phase I Trial (N = 35)

- Objective response rate was 60%
  - CR = 2 (6%)
  - PR = 19 (54%)
- Stable disease: 10 (29%)
- Progressive disease: 1 (3%)
- 6-month PFS probability was 76%

Ou SH et al. *Proc ASCO* 2013;Abstract 8032.

## Responses to Crizotinib are Limited Due to Acquired Resistance

**What are the options for managing crizotinib relapses?**

## Option 1: Treatment Beyond PD (+/- Local Therapy)

- Of the 69 patients with investigator-documented disease progression, 39 continued to receive crizotinib for more than 2 weeks after disease progression
- In the opinion of the investigators, they were deriving ongoing clinical benefit from the drug
- 12 of these patients received crizotinib for at least 6 months from the time of their initial investigator-defined disease progression

Camidge DR et al. *Lancet Oncol* 2012;13(10):1011-9.

## Is There Clinical Benefit To Continuing Crizotinib Beyond Progression?

- Among 194 crizotinib-treated patients with RECIST-defined disease progression, 120 (62%) continued crizotinib beyond disease progression (CBPD)
- Patients who received CBPD had a significantly longer OS from the time of PD (median 16.4 versus 3.9 months) and from the time of initial crizotinib treatment (median 29.6 versus 10.8 months)

Ou SH et al. *Proc IASLC* 2013;Abstract MO07.01.
Ou SH et al. *Ann Oncol* 2014;25(2):415-22.

## Option 2: Switch to a Next Generation Inhibitor

- **Indicated for symptomatic or extensive progression**
- **Indicated for CNS progression if radiotherapy is not an option**
- **Becoming a standard approach in the US with the recent approval of ceritinib**
- **Likely superior to standard chemotherapy in terms of efficacy and tolerability**

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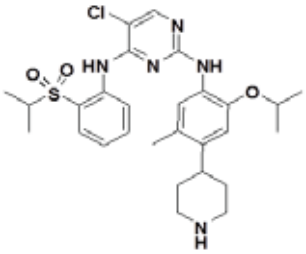
| ALK TKI | ROS1 Activity | Status | Ongoing Studies | Reference |
|---|---|---|---|---|
| Ceritinib (LDK378) | Yes | FDA approved (4-29-2014) | Phase 3 | Shaw et al., NEJM 2014 |
| Alectinib (CH5424802) | No | Investigational (Breakthrough Therapy Designation) | Phase 1/2 | Seto et al., Lancet Onc 2013; Ou et al., ESMO 2013 |
| AP26113 | Yes | Investigational | Phase 1/2 | Camidge et al., WCLC 2013 |
| ASP3026 | Yes | Investigational | Phase 1 | Patnaik et al., ASCO 2013 |
| X-396 | Yes | Investigational | Phase 1 | Lovly et al., CA Res 2011 |
| TSR-011 | Unk | Investigational | Phase 1/2 | Weiss et al., WCLC 2013 |
| NMS-E628 | Yes | Investigational | Phase 1 | Ardini et al., AACR 2013 |
| CEP-37440 | Unk | Investigational | Phase 1 | NCT01922752 |
| PF-06463922 | Yes | Investigational | Phase 1/2 | Zou et al., EORTC-AACR-NCI 2013 |

## Ceritinib (LDK378) is a Highly Potent ALK TKI

| $IC_{50}$ (nM) | Ceritinib | Crizotinib |
|---|---|---|
| ALK enzyme | **0.15** | **3** |
| BaF3-EML4-ALK | **1.7** | **16** |
| NCI-H2228 | **3.8** | **107** |
| NCI-H3122 | **6.3** | **245** |



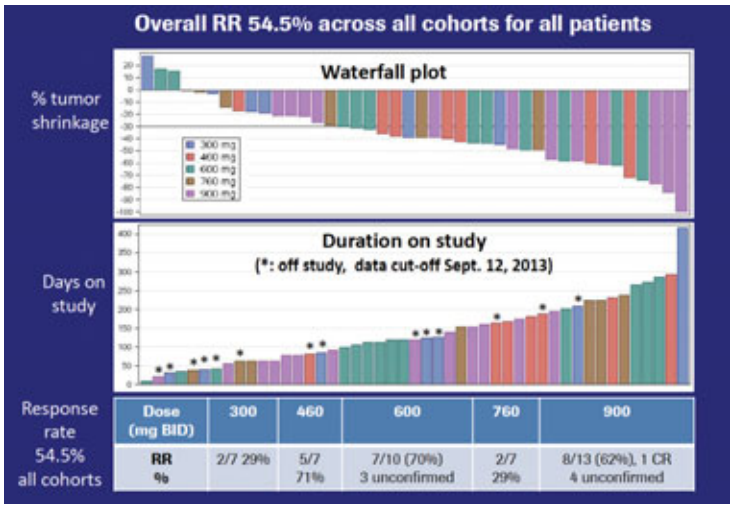

Ceritinib (LDK378)

## Clinical Activity of Ceritinib

- **ALK-rearranged NSCLC**
- **Ceritinib dose: 400-750 mg QD**
- **Confirmed ORR: 58% (95% CI, 45-67)**
- **Median PFS: 7.0 months**

Shaw AT et al. *N Engl J Med* 2014;370(13):1189-97.

# Preliminary Data with Alectinib (CH5424802) in Crizotinib Resistance

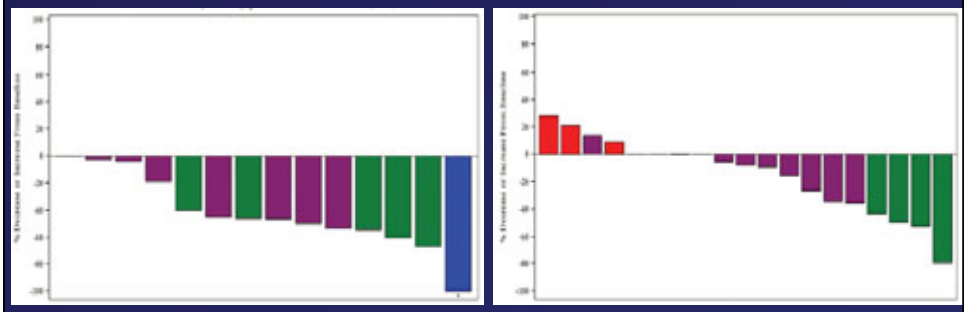



Gadgeel et al., WCLC 2013

# Intracranial Responses with Crizotinib

**Previously Treated for BM (N=14)**

**Previously Untreated for BM (N=19)**

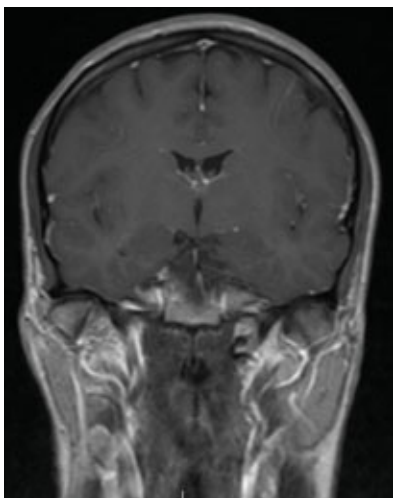


**ORR 18-33% within the CNS**
**DCR 56-62% within the CNS at 12 wks**

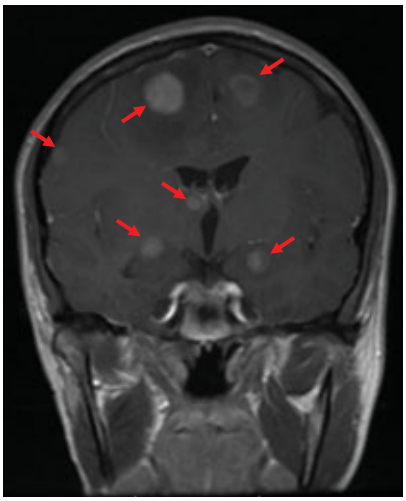
CR SD
PR PD

**Costa DB et al. *Proc IASLC* 2013;Abstract MO07.02.**

## The CNS is a Common Site of Relapse on Crizotinib



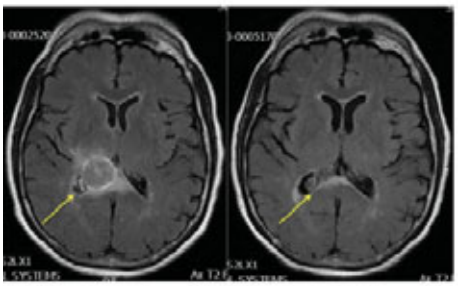
Baseline



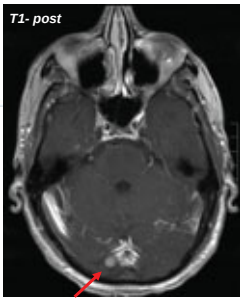
After 9 months of crizotinib

## CNS Responses to Next Generation TKIs

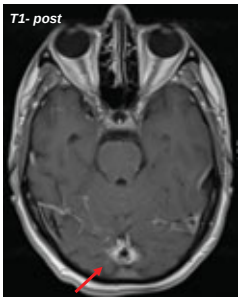
**Alectinib**




**Ceritinib**




Baseline




After 5 wks

# Lung Cancer Tumor Board
## Clinical Investigators Provide Perspectives on Current Cases and Key Publications in Non-Small Cell Lung Cancer

**Friday, May 30, 2014**
**7:00 PM – 9:00 PM**
**Chicago, Illinois**

**Faculty**

Roy S Herbst, MD, PhD
John V Heymach, MD, PhD
Alice Shaw, MD, PhD
Mark A Socinski, MD
Jean-Charles Soria, MD, PhD

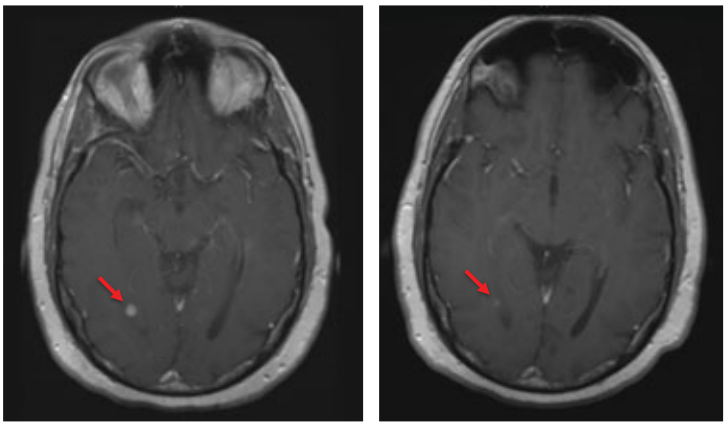
**Moderator**
Neil Love, MD

Research To Practice®

## Case 2

- 45 yo M neversmoker diagnosed with metastatic NSCLC in September 2009
- He was treated with 6 cycles of carbo/pem
- Genetic testing revealed an ALK rearrangement
- He was treated with crizotinib and achieved a PR
- In November 2012, after almost 2 years of crizotinib, he developed acute onset R hand numbness and twitching
- Brain MRI with numerous enhancing lesions, consistent with brain metastases
- Restaging CT scans with stable systemic disease

## Case 2



Baseline



After 3 months of LDK378


HEAT

## SELECT PUBLICATIONS


Borghaei H et al. **A phase III comparative study of nivolumab versus docetaxel in patients with previously treated advanced or metastatic squamous cell NSCLC.** *Proc ASCO* 2013;**Abstract TPS8122**.

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

Jänne PA et al. **Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial.** *J Clin Oncol* 2012;30(17):2063-9.

Kelly K et al. **A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results.** *Proc ASCO* 2014;**Abstract 7501**.

**Lung-MAP: S1400 biomarker-targeted second-line therapy in treating patients with recurrent stage IIIB-IV non-small cell lung cancer. NCT02154490**

Miller VA et al. **Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial.** *Lancet Oncol* 2012;13(5):528-38.

NSCLC Meta-analyses Collaborative Group; Arriagada R et al. **Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: Two meta-analyses of individual patient data.** *Lancet* 2010;375(9722):1267-77.

Ou SH et al. **Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC.** *Ann Oncol* 2014;25(2):415-22.

Patel JD et al. **PointBreak: A randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(34):4349-57.

Perol M et al. **REVEL: A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy.** *Proc ASCO* 2014;**Abstract LBA8006**.

Pignon JP et al. **Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group.** *J Clin Oncol* 2008;26(21):3552-9.

Rosell R et al. **Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial.** *Lancet Oncol* 2012;13(3):239-46.

Shaw AT et al. **Ceritinib in ALK-rearranged non-small-cell lung cancer.** *N Engl J Med* 2014;370(13):1189-97.

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

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

**Study of BMS-936558 (nivolumab) compared to docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC) (CheckMate 017). NCT01642004**

**Study of BMS-936558 (nivolumab) compared to docetaxel in previously treated metastatic non-squamous NSCLC (CheckMate 057). NCT01673867**

Thatcher N et al. **A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC).** *Proc ASCO* 2014;**Abstract 8008**.

Wislez M et al. **Customized adjuvant phase II trial in patients with non-small-cell lung cancer: IFCT-0801 TASTE.** *J Clin Oncol* 2014;32(12):1256-61.