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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reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

**FACULTY** — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Yale School of Medicine  
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**Contracted Research:** GlaxoSmithKline;  
**Data and Safety Monitoring Board:** Pfizer Inc.

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**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.

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This activity is supported by an educational grant from Lilly.

**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  
*This was an independent, accredited educational activity held adjunct to the ASCO Annual Meeting. This presentation is not sponsored or endorsed by ASCO.*
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Friday, May 30, 2014
7:00 PM – 9:00 PM
Chicago, Illinois

Faculty
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John V Heymach, MD, PhD
Alice Shaw, MD, PhD
Mark A Socinski, MD
Jean-Charles Soria, MD, PhD

Moderator
Neil Love, MD

Disclosures for Moderator Neil Love, MD

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# New Patients (Median)
# Patient Deaths (Median)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New Patients</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Lung Cancer</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>MM</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>NHL/CLL</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>60</td>
<td>7</td>
</tr>
</tbody>
</table>

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

**Within the past 12 months...**

**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

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

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

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

Patient n°1, 76 yo male patient

August 2010

- Chronic coughing
  - Diagnosis of Squamous cell carcinoma TTF1-pT2N1M0, stage IIA
  - Absence of EGFR, KRAS, BRAF, PI3K and HER2 mutations
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?

- None: 7%
- Cisplatin/vinorelbine: 37%
- Cisplatin/gemcitabine: 12%
- Cisplatin/docetaxel: 9%
- Carboplatin/vinorelbine: 7%
- Carboplatin/gemcitabine: 12%
- Carboplatin/docetaxel: 10%
- Other: 7%

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?

- None: 7%
- Cisplatin/vinorelbine: 17%
- Cisplatin/docetaxel: 1%
- Cisplatin/pemetrexed: 33%
- Carboplatin/vinorelbine: 7%
- Carboplatin/docetaxel: 2%
- Carboplatin/pemetrexed: 30%
- Other: 3%
Patient n°1, 76 yo male patient

ADJUVANT CHEMOTHERAPY
- Carboplatin AUC5
- Paclitaxel 175mg/m²
  Day1-Day21

4 cycles of chemotherapy
Absence of grade III or IV toxicities

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

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 |
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

**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 Carboplatin/ptaxel are the preferred regimens
- No role for adding induction or consolidation chemotherapy to concurrent chemoradiotherapy (incl unselected maintenance EGFR TKI)

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

Predictive markers for cytotoxic chemotherapy

Multiple compounds available in NSCLC

Search for surrogate biomarker

CYTOTOXICS
- Platin-salts
  - Cisplatin
  - Carboplatin
- Spindle poison
  - Vinorelbine
  - Docetaxel
  - Paclitaxel
  - Nab-paclitaxel
- Anti-metabolite
  - Gemcitabine
  - Pemetrexed
  - 5FU-DPD
- Topo-isomerase
  - Etoposide
  - Irinotecan
  - Topotecan

POTENTIAL BIOMARKER
- ERCC1
- MSH2
- P27
- GSTM1
- Bax
- ABC transporter expression
  - α- or β-tubulin expression
  - Tub mutations
- RRM1
- TS
- hENT1
- Drug efflux
  - Topoisomerase I
  - expression and mutations

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

Control arm
- CDDP-pemetrexed

Experimental arm customized
- EGFR mutated
  - Erlotinib
  - ERCC1+
  - Observation

EGFR wt
  - ERCC1−
  - CDDP-pemetrexed

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

**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

Stage IIB-IIIA NSCLC

Surgical Resection

Adjuvant Platinum-based Chemo or no Adjuvant Chemo

Randomization (2:1)
945 patients

Erlotinib 150 mg/day
Placebo

Primary Endpoint: Progression free survival

www.clinicaltrials.gov Identifier NCT00373425.

BR19: gefitinib vs placebo (OS)

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>Gefitinib versus Placebo: HR (95% CI)</th>
<th>Log rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type EGFR</td>
<td>1.21 (0.84-1.73)</td>
<td>0.30</td>
</tr>
<tr>
<td>Sensitizing EGFR mutation</td>
<td>1.58 (0.83-3.00)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

- Effect on normal tissue?
- Effect on preneoplastic tissue?
**ALChEMIST Adjuvant Lung Cancer Enrichment Marker Identification Sequencing Trial**

<table>
<thead>
<tr>
<th>ALCHEMIST SCREEN Component</th>
<th>ALK+ E4512</th>
<th>EGFR-mutant A081105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Registry</td>
<td>ALK+</td>
<td>EGFRmut</td>
</tr>
<tr>
<td>Prevalence All comers</td>
<td>~5%</td>
<td>~10%</td>
</tr>
<tr>
<td>n</td>
<td>6000-8000</td>
<td>336</td>
</tr>
<tr>
<td>Primary Endpt -- DFS-OS</td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td>Power</td>
<td>--</td>
<td>80%</td>
</tr>
<tr>
<td>One-sided α --</td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>HR</td>
<td>--</td>
<td>0.67</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Extended sequencing for additional targets (TCGA); correlation with local testing</td>
<td>Peripheral screening for ALK; RTPCR to identify fusion partners</td>
</tr>
</tbody>
</table>

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**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**

<table>
<thead>
<tr>
<th>R T Technique</th>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
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<tbody>
<tr>
<td>1. 3D-CRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. IMRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zubrod</td>
<td></td>
<td></td>
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<tr>
<td>1. 0</td>
<td></td>
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<tr>
<td>2. 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET Staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Non-Squamous</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Concurrent Treatment</strong></td>
<td><strong>Consolidation Treatment</strong></td>
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<tr>
<td></td>
<td>Arm A</td>
<td>Arm A</td>
</tr>
<tr>
<td></td>
<td>Concurrent chemotherapy*</td>
<td>Consolidation chemotherapy*</td>
</tr>
<tr>
<td></td>
<td>RT to 60 Gy, 5 x per wk for 6 wks</td>
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<tr>
<td></td>
<td>Arm B</td>
<td>Arm B</td>
</tr>
<tr>
<td></td>
<td>Concurrent chemotherapy*</td>
<td>Consolidation chemotherapy*</td>
</tr>
<tr>
<td></td>
<td>RT to 74 Gy, 5 x per wk for 7.5 wks</td>
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</tr>
<tr>
<td></td>
<td>Arm C</td>
<td>Arm C</td>
</tr>
<tr>
<td></td>
<td>Concurrent chemotherapy* and Cetuximab</td>
<td>Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td></td>
<td>RT to 60 Gy, 5 x per wk for 6 wks</td>
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</tr>
<tr>
<td></td>
<td>Arm D</td>
<td>Arm D</td>
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<td></td>
<td>Concurrent chemotherapy* and Cetuximab</td>
<td>Consolidation chemotherapy* and Cetuximab</td>
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<tr>
<td></td>
<td>RT to 74 Gy, 5 x per wk for 7.5 wks</td>
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</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Weight Loss (in prior 6 mos.)</th>
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<tbody>
<tr>
<td>1. EGFR</td>
<td>1. ≤ 5%</td>
</tr>
<tr>
<td>2. ALK</td>
<td>2. &gt; 5%</td>
</tr>
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</table>

EGFR TK Mutation Cohort

Arm 1: Erlotinib, 150 mg/day for 12 weeks

Arm 2: Concurrent chemotherapy and radiation, 64 Gy

Concurrent chemotherapy and radiation, 64 Gy

Courtesy E Vokes
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?

- Less than 5%: 30%
- 10%: 36%
- 25% 21%
- 45% 5%
- I don't know 8%

---

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Mark A Socinski, MD
Jean-Charles Soria, MD, PhD

Moderator
Neil Love, MD
Patient n°2, 75 yo male patient

- Never smoker
  No significant past medical history

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 IIIIB

- 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

- Lateral thoracotomy
- Invasion of the atrium
- No pneumonectomy possible

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

- Baseline

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

- 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
Patient n°2, 75 yo male patient

August 2011

September 7th, 2011

October 26th, December 7th, 2011

April 30th, 2014

Baseline

After 2 cycles

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 years and 4 months

Baseline

After 2 cycles

PS = 0
No sign of relapse at 2 years and 4 months after the adjuvant chemoradiotherapy
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?

![Bar chart showing treatment options]

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?

![Bar chart showing maintenance options]
Case 1

- Enrolled on SWOG-S0819 trial and received
  - Carboplatin AUC 6
  - Paclitaxel 200 mg/m²
  - 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

<table>
<thead>
<tr>
<th>Contracted Research</th>
<th>Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, Lilly, Merrimack Pharmaceuticals, Onyx Pharmaceuticals Inc, Pfizer Inc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data and Safety Monitoring Board</td>
<td>Millennium: The Takeda Oncology Company</td>
</tr>
<tr>
<td>Speakers Bureau</td>
<td>Celgene Corporation, Genentech BioOncology</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>CP</th>
<th>CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>10.3 months</td>
<td>10.3 months</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>0.94</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin/pemetrexed</th>
<th>Cisplatin/gemcitabine</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsquamous</td>
<td>11.8 mos</td>
<td>10.4 mos</td>
<td>0.81</td>
</tr>
<tr>
<td>Squamous</td>
<td>9.4 mos</td>
<td>10.8 mos</td>
<td>1.23</td>
</tr>
</tbody>
</table>


Bevacizumab—Response

Bevacizumab in Nonsquamous NSCLC: Key Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E4599¹</th>
<th>AVAiL²³</th>
<th>JO19907⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>PCB</td>
<td>PC</td>
<td>CGB (7.5)</td>
</tr>
<tr>
<td>P &lt; .001</td>
<td>35</td>
<td>15</td>
<td>34.1</td>
</tr>
<tr>
<td>P &lt; .0001</td>
<td>P = .0002</td>
<td>0.61 (P &lt; .009)</td>
<td></td>
</tr>
<tr>
<td>HR for PFS</td>
<td>0.66 (P &lt; .001)</td>
<td>0.75 (P = .003)</td>
<td>0.82 (P = .03)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>6.2 4.5</td>
<td>6.7 6.5 6.1</td>
<td>6.9 5.9</td>
</tr>
<tr>
<td>HR for OS</td>
<td>0.79 (P = .003)</td>
<td>0.93 (NS)</td>
<td>1.03 (NS)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>12.3 10.3</td>
<td>13.6 13.4 13.1</td>
<td>22.8 23.4</td>
</tr>
</tbody>
</table>


PointBreak: Study Design

- Randomized, open-label, phase III superiority study conducted in US
- Pemetrexed 500 mg/m²; Carboplatin AUC 6; Bevacizumab 15 mg/kg
- Paclitaxel 200 mg/m²; Carboplatin AUC 6; Bevacizumab 15 mg/kg
- Primary Endpoint: OS

Induction Phase
4 cycles, q21d

Pemetrexed + (folic acid & vitamin B₁₂) Carboplatin + Bevacizumab

Maintenance Phase
q21d until PD

Pemetrexed + (folic acid & vitamin B₁₂) Bevacizumab

Paclitaxel + Carboplatin + Bevacizumab

Bevacizumab

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

**PointBreak: PFS and OS (ITT Population)**

<table>
<thead>
<tr>
<th></th>
<th>Pem+ Cb+Bev</th>
<th>Pac+ Cb+Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS median (mo)</td>
<td>6.0</td>
<td>5.6</td>
</tr>
<tr>
<td>HR (95% CI); P value</td>
<td>0.83 (0.71, 0.96); P=0.012</td>
<td></td>
</tr>
<tr>
<td>ORR (%)</td>
<td>34.1</td>
<td>33.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pem+ Cb+Bev</th>
<th>Pac+ Cb+Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS median (mo)</td>
<td>12.6</td>
<td>13.4</td>
</tr>
<tr>
<td>HR (95% CI); P value</td>
<td>1.00 (0.86, 1.16); P=0.949</td>
<td></td>
</tr>
<tr>
<td>Survival rate (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>52.7</td>
<td>54.1</td>
</tr>
<tr>
<td>2-year</td>
<td>24.4</td>
<td>21.2</td>
</tr>
</tbody>
</table>


**PRONOUNCE: Study Design**

- Randomized, open-label, phase III superiority study conducted in US
- Pemetrexed 500 mg/m², Carboplatin AUC 6 (Pem+Cb)
- Paclitaxel 200 mg/m², Carboplatin AUC 6, Bevacizumab 15 mg/kg (Pac+Cb+Bev)

**Bev-Eligible Population**

- Chemo-naïve patients
- PS 0/1
- Stage IV, nonsquamous
- Stable treated CNS mets

**Exclusion:**

- Uncontrolled effusions

**Induction Phase**

- q21d, 4 cycles
- Pemetrexed (folic acid & vitamin B₁₂) + Carboplatin
- Paclitaxel + Carboplatin + Bevacizumab

**Maintenance Phase**

- q21d until PD
- Pemetrexed (folic acid & vitamin B₁₂)
- Bevacizumab

**R 1:1**

180 patients each

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)**

- **Pem+Cb:** median G4PFS = 3.9 (mo)
- **Pac+Cb+Bev:** median G4PFS = 2.9 (mo)

Log-rank p-value = 0.176

HR (90% CI) = 0.85 (0.70, 1.04)

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Pem+Cb</th>
<th>Pac+Cb+Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>182</td>
<td>179</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

- Binding with VEGF ligands: 18%
- Direct binding to VEGF receptor: 46%
- Interference with intracellular signaling: 5%
- None of the above: 0%
- I don't know: 31%
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...

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival (PFS)</td>
<td>39%</td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td>6%</td>
</tr>
<tr>
<td>Neither</td>
<td>4%</td>
</tr>
<tr>
<td>Both</td>
<td>17%</td>
</tr>
<tr>
<td>I don't know</td>
<td>35%</td>
</tr>
</tbody>
</table>

MOA of Anti-angiogenic Agents

Bevacizumab
- VEGF-A
- VEGF-B
- PIGF

Ligand Sequestration
- Bevacizumab

Ramucirumab
- VEGFR TK Inhibitor

Angiogenesis

Lymphangiogenesis
Stratified by histology (nonsquamous vs squamous):

- Nonsquamous: randomized 1:1 to 1 of 2 separate treatment arms: either Arm A or Arm B
- Squamous: randomized 1:1 to 1 of 2 separate treatment arms: either Arm C or Arm D (ongoing)

Patients are to receive the first-line therapy for a minimum of four 21-day cycles, up to 6 cycles, and then patients in Arms A, B, and D will enter a maintenance phase as detailed in the above schema.

*All patients treated with pemetrexed received dexamethasone, folic acid, and vitamin B12 supplementation.*

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

Randomize

N=1200
Stage IV 2nd line NSCLC pts
Prior platinum
All histologies
ECOG PS 0-2

1

Arm A:
Ramucirumab 10 mg/kg
Docetaxel 75 mg/m²

1

Arm B:
Placebo
Docetaxel 75 mg/m²

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

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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
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?

Carboplatin/paclitaxel 32%
Carboplatin/gemcitabine 42%
Carboplatin/nanoparticle albumin-bound (nab) paclitaxel 22%
Carboplatin/pemetrexed 5%
Other 0%
Objective tumor responses to nivolumab in patients with NSCLC...

- Often occur by the first evaluation at 8 weeks: 21%
- Usually slowly occur over 3 to 6 months: 31%
- Are rare: 5%
- I don’t know: 44%

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

- Auto-immune colitis: 5%
- Hypopituitarism: 1%
- Pseudoprogression (increase in size of tumor followed by response): 9%
- All of the above: 56%
- None of the above: 4%
- I don’t know: 24%
Necitumumab combined with gemcitabine/carboplatin as first-line treatment of metastatic squamous cell cancer resulted in a statistically significant improvement in...

Disclosures

<table>
<thead>
<tr>
<th>Consulting Agreements</th>
<th>Astellas, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Merck</th>
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</thead>
<tbody>
<tr>
<td>Contracted Research</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Data and Safety Monitoring Board</td>
<td>Pfizer Inc</td>
</tr>
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</table>
Efficacy of Nivolumab Monotherapy in Patients (N=129) with NSCLC

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

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

aTumors and responses were assessed after each cycle per modified RECIST v1.0.

bAll 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

- 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

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment-related Select AE, % (n)</th>
<th>Grade 3-4 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related select AE</td>
<td>41 (53)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Skin</td>
<td>16 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>6 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

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)

Phase 3 Trial
Stage IIIb/IV non-squamous NSCLC
N=574

Docetaxel
75 mg/m² IV Q3W

Nivolumab
3 mg/kg IV Q2W

Treat until progression or unacceptable toxicity or withdrawal of consent

Overall Survival (OS)

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
## Treatment-Related Adverse Events – NSCLC

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment-Related, n (%)</th>
<th>n = 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>Any Grade&lt;sup&gt;a&lt;/sup&gt;</td>
<td>56 (66%) 9 (11%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 3-4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17 (20%) 2 (2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>12 (14%) 1 (1%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>10 (12%) 0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>8 (9%) 1 (1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>7 (8%) 0</td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td>6 (7%) 0</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>6 (7%) 0</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>6 (7%) 0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td>5 (6%) 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>5 (6%) 1 (1%)</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td></td>
<td>4 (5%) 0</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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 pneumonits 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%)

<sup>a</sup> AEs occurring in ≥5% of patients.

<sup>b</sup> 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.

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

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>ORR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PD Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 3</td>
<td>83% (5/6)</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 2 and 3</td>
<td>46% (6/13)</td>
<td>23% (3/13)</td>
</tr>
<tr>
<td>(n = 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 1/2/3</td>
<td>31% (8/26)</td>
<td>38% (10/26)</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>23% (12/53)</td>
<td>40% (21/53)</td>
</tr>
<tr>
<td>(IHC 0/1/2/3 and 7 patients with diagnostic unknown; n = 53)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 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

Baseline Post C6 (Week 18) Post C12 (Week 36)

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
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.


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

<table>
<thead>
<tr>
<th>Squamous cell histology</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N/Events</td>
<td>Median PFS</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td><em>nab-P/C</em></td>
<td>229/137</td>
<td>5.6 mo</td>
<td>0.865 (0.245)</td>
<td>0.991 (0.944)</td>
<td></td>
</tr>
<tr>
<td><em>sb-P/C</em></td>
<td>221/134</td>
<td>5.7 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N/Events</td>
<td>Median PFS</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td><em>nab-P/C</em></td>
<td>254/137</td>
<td>6.9 mo</td>
<td>0.991 (0.944)</td>
<td>0.991 (0.944)</td>
<td></td>
</tr>
<tr>
<td><em>sb-P/C</em></td>
<td>264/151</td>
<td>6.9 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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


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
INSPIRE Phase III

947 Patients Stage IV Non-Squamous NSCLC
Randomized 1:1

- Necitumumab (IMC-11F8) - Days 1 and 8 of every 3-week cycle, max of 6 cycles
- Pemetrexed - Day 1 of every 3 week cycle, max of 6 cycles
- Cisplatin - Day 1 of every 3 week cycle, max of 6 cycles

Primary Outcome Measure – Overall Survival
Secondary Outcome Measures – PFS, ORR, TTF, AE, OS and PFS according to EGFR status

Enrollment stopped at 633 pts 02-02-11 following IDMC:
Primary analysis after 474 events.

Until Progressive Disease

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

SQUIRE Phase III

947 Patients Stage IV Squamous NSCLC
Randomized 1:1

- Necitumumab (IMC-11F8) - Days 1 and 8 of every 3-week cycle, max of 6 cycles
- Gemcitabine - Days 1 and 8 of every 3-week cycle, max of 6 cycles
- Pemetrexed - Days 1 and 8 of every 3-week cycle
- Cisplatin - Day 1 of every 3-week cycle, max of 6 cycles

Enrollment completed 02-22-12: 1093 pts with 98% tissue collection.
Press Release, August 2013: SURVIVAL BENEFIT!

Primary Outcome Measure – Overall Survival
Secondary Outcome Measures – PFS, ORR, TTF, AE, OS and PFS according to EGFR status

Various time points
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
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?

- **Radiate**: 26%
- **Start a TKI**: 73%
- **Other**: 1%

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?

- **Chemotherapy**: 18%
- **Chemotherapy, continue erlotinib**: 20%
- **Chemotherapy + afatinib**: 10%
- **Afatinib**: 39%
- **Afatinib + cetuximab**: 9%
- **Other**: 4%
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

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

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**

<table>
<thead>
<tr>
<th>Central Review</th>
<th>Investigator Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (median 1.1 months [95% CI 0.95-1.68])</td>
<td>Placebo (median 0.95 months [95% CI 0.95-0.99])</td>
</tr>
<tr>
<td>Afatinib (median 3.3 months [95% CI 2.79-4.40])</td>
<td>Afatinib (median 2.83 months [95% CI 2.73-4.01])</td>
</tr>
<tr>
<td>Hazard ratio 0.38 (95% CI 0.31-0.48)</td>
<td>Hazard ratio 0.37 (95% CI 0.30-0.44)</td>
</tr>
<tr>
<td>Log-rank test p value (one-sided) &lt;0.0001</td>
<td>Log-rank test p value (one-sided) &lt;0.0001</td>
</tr>
</tbody>
</table>

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.


<table>
<thead>
<tr>
<th>Kinases</th>
<th>Afatinib</th>
<th>Lapatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR wt</td>
<td>0.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>EGFR L858R</td>
<td>0.4</td>
<td>8</td>
<td>0.8</td>
</tr>
<tr>
<td>EGFR L858R/T790M</td>
<td>10</td>
<td>&gt;4000</td>
<td>1013</td>
</tr>
</tbody>
</table>

**In vitro** kinase assay

**Anchorage independent growth**

<table>
<thead>
<tr>
<th>EC50 [nM]</th>
<th>Target</th>
<th>Binding mode</th>
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</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>reversible</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>reversible</td>
</tr>
<tr>
<td>Afatinib</td>
<td>EGFR/HER2</td>
<td>irreversible</td>
</tr>
<tr>
<td>CP-724-714</td>
<td>HER2</td>
<td>reversible</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>EGFR/HER2</td>
<td>reversible</td>
</tr>
</tbody>
</table>
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

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

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

But what about chemo+EGFR TKI?

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

Janne et al, J Clin Oncol, 2012
Patients with stage IIIB/IV NSCLC
Progression after ≥12 wks of erlotinib
• Demonstrated benefit with CT scan after ≥4 wks erl. monotherapy

1° Endpoint: PFS
2° Obj: RR, OS

Pemetrexed or Docetaxel D1
Repeat Cycle

Pemetrexed or Docetaxel D1
AND
Erlotinib QD D2-19

CT PET scan (optional)
PD Off-study
SD PR CR
Continue on study 2 more cycles

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)

<table>
<thead>
<tr>
<th></th>
<th>Pem/doc (N = 24)</th>
<th>Erlotinib + pem/doc (N = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (m)</td>
<td>5.4</td>
<td>4.6</td>
<td>.569</td>
</tr>
<tr>
<td>Median OS (m)</td>
<td>18.7</td>
<td>14.7</td>
<td>.295</td>
</tr>
<tr>
<td>EGFR M+</td>
<td>17</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Yang et al., Lancet Oncology, 2012;
Sequist et al., JCO, 2013;
Wu et al., Lancet Oncology, 2014
Afatinib exhibits activity in uncommon EGFR mutations

- **RR low in T790M mutations and exon 20 insertions**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>ORR % (n)</th>
<th>DCR % (n)</th>
<th>Median PFS</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo T790M (n=14)</td>
<td>14.3 (2)</td>
<td>64.2 (9)</td>
<td>2.9</td>
<td>14.9</td>
</tr>
<tr>
<td>Exon 20 insertions (n=23)</td>
<td>8.7 (2)</td>
<td>65.2</td>
<td>2.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Other (n=38)</td>
<td>71.1 (27)</td>
<td>84.2 (32)</td>
<td>10.7</td>
<td>18.6</td>
</tr>
</tbody>
</table>

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

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
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
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
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?

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy including pemetrexed</td>
<td>16%</td>
</tr>
<tr>
<td>Chemotherapy not including pemetrexed</td>
<td>25%</td>
</tr>
<tr>
<td>Ceritinib (LDK378)</td>
<td>55%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Advisory Committee</th>
<th>ARIAD Pharmaceuticals Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc</th>
</tr>
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<tbody>
<tr>
<td>Consulting Agreements</td>
<td>ARIAD Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc</td>
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<tr>
<td>Contracted Research</td>
<td>Pfizer Inc</td>
</tr>
</tbody>
</table>

Clinical Features Associated with ALK vs ROS1 Rearrangements in Lung Cancer

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

*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

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

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)
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

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

<table>
<thead>
<tr>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>Ceritinib</th>
<th>Crizotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK enzyme</td>
<td>0.15</td>
<td>3</td>
</tr>
<tr>
<td>BaF3-EML4-ALK</td>
<td>1.7</td>
<td>16</td>
</tr>
<tr>
<td>NCI-H2228</td>
<td>3.8</td>
<td>107</td>
</tr>
<tr>
<td>NCI-H3122</td>
<td>6.3</td>
<td>245</td>
</tr>
</tbody>
</table>

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

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

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
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
**SELECT PUBLICATIONS**


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


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.


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
