The Practical Application of Research Advances and Emerging Data in the Management of 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 systemic treatment of localized NSCLC.
• Apply the results of emerging clinical research to the multimodality management of Stage III NSCLC.
• Use biomarkers, clinical characteristics and tumor histology to select individualized front-line and subsequent treatment approaches for patients with metastatic NSCLC.
• Compare and contrast the benefits and risks of combination chemobiologic, doublet and single-agent chemotherapy regimens when developing treatment plans for patients with advanced NSCLC.
• Recognize the effect of NSCLC tumor-specific mutations on relative response or resistance to treatment with EGFR tyrosine kinase inhibitors, ALK inhibitors and other emerging molecular-targeted agents.
• Identify patients with metastatic NSCLC who may experience clinical benefit from the addition of continuation or switch maintenance biologic therapy and/or chemotherapy.
• Recall the design of ongoing clinical trials evaluating novel investigational agents in NSCLC, and counsel appropriately selected patients about availability and participation.

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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 2013
**Expiration date:** August 2014

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Adjuvant Therapy for Localized NSCLC; Management of Locally Advanced Disease

Heather Wakelee, MD
Associate Professor of Medicine, Oncology
Stanford Cancer Institute
Stanford University
All patients with NSCLC for whom tissue has already been accessed, including those s/p surgical resection, should have their tumor specimens tested for EGFR and ALK.

**Case: Dr Lowenthal (Dr Wakelee)**

**How old is too old for cisplatin and/or bevacizumab?**

- 70 yo man, remote tobacco use (D/C 45 y ago)
- Routine pre-op (TURP) CXR abnormal
- CT and PET: 6-cm RLL mass (SUV 7), hilum 2.7 SUV
- VATS R lower lobectomy: 5.3-cm mod-poorly diff adeno, pan-WT, node-negative
- Patient is eligible for ECOG-E1505 (cis doublet with or without bevacizumab)

**Question:** Would you recommend participation, and if so, what doublet would you use?
A 70-year-old patient undergoes right lower lobectomy for a 5.3-cm pan-wild-type (PWT) adenocarcinoma (adeno) with negative nodes. What adjuvant systemic treatment would you recommend?
The same 70-year-old patient (5.3-cm PWT adeno, negative nodes) is eligible for the ECOG-E1505 study evaluating the addition of bevacizumab to cisplatin-based adjuvant chemotherapy. Would you recommend participation for this patient?
A 67-year-old remote smoker s/p surgery for stage IIIA adenocarcinoma with positive surgical margin and 7 out of 8 positive nodes. EGFR testing reveals an exon 19 deletion. In addition to other treatment, would you use an EGFR TKI?
The Questions

• What is your preferred non-protocol adjuvant chemotherapy doublet for younger patients with adenocarcinoma?

• What key clinical trial evidence has helped you shape your decision?

Which Chemotherapy in the Adjuvant Setting?

• All 3 positive adjuvant trials used cisplatin (2 with vinorelbine) for 4 cycles

• Cisplatin is THE standard (unless not tolerated)
  – but high use of carboplatin in NA in the elderly

• For the 2nd drug, can we extrapolate from the metastatic setting?
Which Chemotherapy in the Adjuvant Setting?

- Metastatic disease:
  - Carboplatin/paclitaxel = cisplatin/paclitaxel = cisplatin/docetaxel = cisplatin/gemcitabine
  - Cisplatin/docetaxel > cisplatin/vinorelbine
  - Cisplatin/pemetrexed > cisplatin/gemcitabine for non-squamous histology

Schiller NEJM 346:92, 2002; Fossela JCO 21:3016, 2003; Scagliotti JCO 26:3543, 2008
Wakelee ASCO 2011

A simple proof in adjuvant chemotherapy

- So IF in metastatic disease:
  - Cis/Vin < Cis/Doce
  - Cis/Doce = Cis/Gem
  - Cis/Gem < Cis/Pem (non-squam)

- Then: either cis/doce, cis/gem or cis/pem (non-squam) > cis/vin for adjuvant therapy
  - But this is BIOLOGY, not simple math

Wakelee ASCO 2011
However, NCCN Guidelines

- Adjuvant Chemotherapy, NSCLC-D
- Includes 5 published cisplatin regimens
  - Cis 50 d 1,8 + vin 25 d 1, 8, 15, 22 q 28
  - Cis 100 d 1 + vin 30 d 1,8,15, 22 q 28
  - Cis 75-80 d 1 + vin 25-30 day 1,8 q 21
  - Cis 100 d 1 + etop 100 day 1-3, q 28
  - Cis 80 d 1 + vinblastine 4 q wk - q 2 wk q 21
- Includes 3 other regimens – all cis 75 q 21
  - Gem 1250 d 1,8: Doce 75 d 1, Pem 500 d 1

Wakelee ASCO 2011

Phase II TREAT Trial

- 132 pts resected NSCLC
- 38% IB, 57% II : 43% Squamous
- Randomized to cis (50 D1,8)/vin (25 q wk) vs cis(75)/Pem (500) q 3 wk
- Delivery of total mean doses
  - 90% CP vs 66% CV

TREAT Trial Summary

- Study met the predefined primary endpoint of “feasibility”
- Mean cisplatin dose higher for the cisplatin/pemetrexed vs cisplatin/vinorelbine
- No survival data to date BUT
  - 45% squamous cell histology, 38% stage IB
- So unclear what survival data with adjuvant pemetrexed will mean in this setting


Which Adjuvant Chemotherapy?

- Strongest evidence for adjuvant chemotherapy in NSCLC is with cisplatin/vinorelbine
- TREAT trial gives some evidence to support common practice of substituting other cisplatin doublets
Chemotherapy on E1505

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Total</th>
<th>Arm A</th>
<th>Arm B (BEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin +</td>
<td>670</td>
<td>341</td>
<td>329</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>179(27%)</td>
<td>88(26%)</td>
<td>91(28%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>213(32%)</td>
<td>110(32%)</td>
<td>103(31%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>164(25%)</td>
<td>85(25%)</td>
<td>79(24%)</td>
</tr>
<tr>
<td>Pemetrexed* (non-sq only)</td>
<td>112(17%)</td>
<td>57(17%)</td>
<td>55(17%)</td>
</tr>
</tbody>
</table>

* Squamous (~30%) not eligible, option added 2009

Wakelee IASLC WCLC 2011: Abstract O42.03

The Questions

- Are any promising investigational agents or strategies in clinical testing for Stage IIIA/B disease, including the use of targeted therapy before chemoradiation?
Unresectable Stage III NSCLC: Truths we know
1: Chemotherapy adds to Radiation
2: Concurrent Chemo/Radiation Trumps Sequential

1: CALGB 8433

<table>
<thead>
<tr>
<th></th>
<th>Median Survival</th>
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</thead>
<tbody>
<tr>
<td>Radiation Alone</td>
<td>9.7 mo</td>
</tr>
<tr>
<td>Sequential Chemotherapy - Radiation</td>
<td>13.8 mo</td>
</tr>
</tbody>
</table>

2: RTOG 9410

<table>
<thead>
<tr>
<th></th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential Chemotherapy - Radiation</td>
<td>14.6 mo</td>
</tr>
<tr>
<td>Concurrent Chemotherapy/Radiation</td>
<td>17.1 mo</td>
</tr>
</tbody>
</table>

Dillman NEJM 1990
Curran JNCI 2011
Wakelee ASCO 2012

Unresectable Stage III NSCLC: What We Don’t Know:
Benefit of Induction or Consolidation Chemotherapy

- Induction chemotherapy –
  - CALGB 39801* negative
    - Weekly carboplatin/paclitaxel/XRT
      - +/- 2 cycles carboplatin AUC 6/Paclitaxel 200 mg/m2
- Consolidation chemotherapy –
  - Routinely included
  - Limited data from randomized trials…
- Benefit of additional agents not shown to date

Ongoing Phase III Trial: HD XRT +/- Cetuximab

Arm I/III
Concurrent chemotherapy
Paclitaxel/Carboplatin
Weekly x 7
RT to 60 Gy (2 Gy qd)
-/+ Cetuximab

Arm II/IV
closed 6/11
Concurrent chemotherapy
Paclitaxel/Carboplatin
Weekly x 7
RT to 74 Gy (2 Gy qd)
-/+ Cetuximab

All patients:
Consolidation
Chemotherapy x Q 3 weeks x 2 cycles
Paclitaxel (200 mg/m²) + Carboplatin (AUC = 6)

III A vs. IIIB
3DCRT vs. IMRT
Zubrod 0 vs 1

Randomize

Phase II RTOG 1306 NeoAdj
Targeted Therapy
Intergroup Stage III Proposal

EGFR +
Randomize

Erlotinib x 12 wks
Then chemo*/XRT (60 Gy)

Chemo/XRT (60 Gy)

ALK +
Randomize

Crizotinib x 12 wks
Then chemo*/XRT (60 Gy)

Chemo/XRT (60 Gy)

*Chemo is cis/etop OR weekly carbo/paclitaxel
Case: Dr Rupard (Dr Langer)

50 yo woman
- Auto accident → imaging: Large peripheral right lower lobe lung mass, bilateral hilar and mediastinal lymphadenopathy and diffuse left-sided lesions, likely from metastases
- PET scan: Bilateral hilar and lung lesions, no disease outside of the chest
- Percutaneous biopsy: Poorly differentiated pan-WT adenocarcinoma
- Patient is on multiple medications for difficult-to-control psychiatric disease (hypomania)

Question: What induction treatment would you use?
Which first-line chemotherapy and/or biologic therapy would you generally administer to an otherwise healthy 50-year-old patient with metastatic PWT adenocarcinoma of the lung?
Case: Dr Rupard (Dr Langer)

83 yo woman

- Several months of increasing cough and chest pain
- CT scan of chest: Large left pleural effusion and a 2.5-cm soft tissue mass in the left upper lobe of the lung abutting the mediastinum, with a satellite left lower lobe nodule
- Thoracentesis: Adenocarcinoma, pan-WT
- Talc pleurodesis: Initial good result but patient is PS 1-2

What is your usual first-line therapy for an older symptomatic patient (~80) with metastatic PWT adeno and PS 1-2 secondary to aging and the tumor?
What is your usual first-line therapy for an older symptomatic patient (~80) with metastatic PWT adeno and PS 1-2 secondary to aging and the tumor?

- Palliative care, no systemic therapy: 6%
- Single-agent chemotherapy: 37%
- Doublet chemotherapy: 37%
- Chemotherapy/bevacizumab: 3%
- Erlotinib: 15%
- Other: 2%

A 62-year-old patient receives cisplatin/pemetrexed as adjuvant therapy for PWT adeno and tolerates it well but experiences systemic disease relapse 2 years later. What is your next likely treatment?
A 62-year-old patient receives cisplatin/pemetrexed as adjuvant therapy for PWT adeno and tolerates it well but experiences systemic disease relapse 2 years later. What is your next likely treatment?

A 50-year-old patient underwent surgery 2 years ago for Stage I squamous cell carcinoma of the lung and received no adjuvant therapy. He now has histologically documented metastatic disease to bone and liver. What is your usual first-line systemic therapy?
A 50-year-old patient underwent surgery 2 years ago for Stage I squamous cell carcinoma of the lung and received no adjuvant therapy. He now has histologically documented metastatic disease to bone and liver. What is your usual first-line systemic therapy?

- Carboplatin/paclitaxel: 25%
- Carboplatin/gemcitabine: 29%
- Carboplatin/nab paclitaxel: 15%
- Chemotherapy/cetuximab: 1%
- Cisplatin doublet: 28%
- Other: 2%

For the same 50-year-old patient who underwent surgery 2 years ago for Stage I squamous cell carcinoma of the lung and received no adjuvant therapy and now has histologically documented metastatic disease to bone and liver. Would you likely use bevacizumab in addition to chemotherapy?
For the same 50-year-old patient who underwent surgery 2 years ago for Stage I squamous cell carcinoma of the lung and received no adjuvant therapy and now has histologically documented metastatic disease to bone and liver: Would you likely use bevacizumab in addition to chemotherapy?

Nonsmall Cell Lung cancer

- **Adenocarcinoma**
  - Glandular pattern
  - Mucin positivity (50%)
  - CK7+/CK20-
  - TTF-1+ (75%)

- **Squamous cell carcinoma**
  - Cellular keratinization
  - Intercellular bridges
  - Keratin “pearl” formation
  - CK7-/CK20-
  - TTF-1 neg
  - P63+ or p40+ CK5/6+
Emergence of Histology as Determinant of Therapy

Sandler: Paclitaxel-Carboplatin +/- Bevacizumab
Scagliotti: Gem-DDP vs. Pem-DDP
Socinski: nab-paclitaxel –Carbo vs Pac-Carbo

ECOG 4599: Phase III Trial of Bevacizumab in Non-Squamous NSCLC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PC</th>
<th>PCB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>15</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>4.5</td>
<td>6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>10.3</td>
<td>12.3</td>
<td>0.003</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>44</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>2-year survival (%)</td>
<td>15</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

PC = Paclitaxel 200 mg/m² Carboplatin AUC 6 mg/m² q3wk
PCB = Paclitaxel/carboplatin x 6 cycles + bevacizumab (15 mg/kg q3wk) to PD

Eligibility
• Non-squamous NSCLC
• No Hx of hemoptysis
• No CNS metastases

Stratification variables
• RT vs no RT
• Stage IIIB or IV vs recurrent
• Wt loss <5% vs ≥5%
• Measurable vs nonmeasurable

RT = radiotherapy; PD = progressive disease.
Study Design

- Stage IIIIB/IV NSCLC
- PS 0 - 1
- No prior chemo
- Randomization: gender, PS, stage, histo vs cyto dx, brain mets

Pemetrexed 500 mg/m² + Cisplatin 75 mg/m² day 1

Primary objective: Overall Survival
15% Non-inferiority margin (HR 1.17)
N = 1700 Patients, Power 80%

Gemcitabine 1250 mg/m² days 1 + 8
Cisplatin 75 mg/m² day 1;

B12, folate, and dexamethasone given in both arms

Scagliotti GV et al. JCO 2008; 26:3543

Overall Survival - All Patients: Cisplatin + Gemcitabine vs Cisplatin + Pemetrexed

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CP (n = 862)</th>
<th>CG (n = 863)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
<td>10.3 mo</td>
<td>10.3 mo</td>
<td>0.94 (0.84-1.05)</td>
</tr>
</tbody>
</table>

1.176 was non-inferiority margin

### Overall Survival in Patients with Nonsquamous Histology (N = 1,000)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CP (n = 512)</th>
<th>CG (n = 488)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
<td>11.8 mo</td>
<td>10.4 mo</td>
<td>0.81 (0.70-0.94)</td>
</tr>
</tbody>
</table>


### Pemetrexed Plus Cisplatin in 1st-line: Survival with Gemcitabine/Cisplatin for Patients with Squamous Cell Carcinoma (n = 473)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CP (n = 244)</th>
<th>CG (n = 229)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell (n = 473)</td>
<td>9.4 mo</td>
<td>10.8 mo</td>
<td>1.23 (1.00-1.51)</td>
</tr>
</tbody>
</table>

Phase III Trial of nab-paclitaxel-carbo vs carbo-paclitaxel

Chemo-naïve NSCLC
IIIB/IV
ECOG PS 0-1
Baseline peripheral neuropathy ≥ grade 2
N=1050

Stratification factors: stage IIIb vs IV, age <70 or ≥ 70, gender, histology (SCC vs non-SCC), geography
Primary endpoint: ORR
Secondary endpoint: PFS, OS, DCR, safety (NCI CTCAE v3)

Nab-paclitaxel 100 mg/m² d1, 8, 15
Carbo AUC 6 d1
No premeds

Paclitaxel 200 mg/m² d1
Carbo AUC 6 d1
Premeds: dex, antihistamines

Socinski MA et al. ASCO 2010;Abstract LBA7511

Objective Responses by Histology*

Interaction p-Value for Histology: 0.036

* Not a pre-specified subgroup analysis
## PFS – ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Ab-P/Carbo (n = 521)</th>
<th>Paclitaxel/ Carbo (n = 531)</th>
<th>HR</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/Events</td>
<td>521/297</td>
<td>531/312</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (mo)*</td>
<td>6.3</td>
<td>5.8</td>
<td>0.902</td>
<td>0.214</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.6-7.0</td>
<td>5.6-6.7</td>
<td>0.767-1.060</td>
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* PFS based on Independent assessment

## Secondary Endpoint: OS

<table>
<thead>
<tr>
<th></th>
<th>Events / N</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>744 / 1052</td>
<td>12.1</td>
</tr>
<tr>
<td>Japan</td>
<td>86 / 149</td>
<td>16.7</td>
</tr>
<tr>
<td>Russia/Ukraine</td>
<td>521 / 724</td>
<td>11.0</td>
</tr>
<tr>
<td>North America</td>
<td>127 / 165</td>
<td>12.7</td>
</tr>
<tr>
<td>Male</td>
<td>589 / 789</td>
<td>11.4</td>
</tr>
<tr>
<td>Female</td>
<td>155 / 263</td>
<td>16.8</td>
</tr>
<tr>
<td>&lt;70 yrs</td>
<td>639 / 896</td>
<td>11.4</td>
</tr>
<tr>
<td>≥70 yrs</td>
<td>105 / 156</td>
<td>19.9</td>
</tr>
<tr>
<td>Squamous</td>
<td>343 / 450</td>
<td>10.7</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>401 / 602</td>
<td>13.1</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>142 / 218</td>
<td>12.4</td>
</tr>
<tr>
<td>Stage IV</td>
<td>602 / 834</td>
<td>12.0</td>
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Secondary Endpoint: OS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arm A</th>
<th>Arm B</th>
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</thead>
<tbody>
<tr>
<td>Median OS, mon</td>
<td>10.4</td>
<td>6.2</td>
</tr>
<tr>
<td>Median PFS, mon</td>
<td>6.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Grade 3-4 hematologic tox</td>
<td>54.1%</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

Paclitaxel + Carboplatin Show Significant Benefits in Patients ≥70 yo with Advanced NSCLC

- Methods: Phase 3 study in 451 patients 70-89 yo
  - Arm A: Carboplatin AUC 6 every 4 weeks + paclitaxel 90 mg/m² (d1,8,15) Q 4wk vs
  - Arm B: Single-agent gemcitabine 1150 mg/m² or vinorelbine 30 mg/m², d1, d8

- Results

- Conclusions: Paclitaxel + carboplatin provides a significantly longer survival in elderly patients with advanced NSCLC than current standard single-agent therapy, with acceptable toxicity
Overall survival (ITT)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Monotherapy (n = 226)</th>
<th>Doublet chemotherapy (n = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>6.2 mo (95% CI 5.3-7.4)</td>
<td>10.3 mo (95% CI 8.3-13.3)</td>
</tr>
<tr>
<td>1-year survival</td>
<td>26.9% (95% CI 21-33.1)</td>
<td>45.1% (95% CI 38.2-51.8)</td>
</tr>
</tbody>
</table>

p = 0.00004

Exploratory Sub-group analysis

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>HR</th>
<th>95% LCL</th>
<th>95% UCL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (B:A)</td>
<td>451</td>
<td>0.639</td>
<td>0.515</td>
<td>0.792</td>
<td>0.000046</td>
</tr>
<tr>
<td>PS 0/1</td>
<td>329</td>
<td>0.622</td>
<td>0.479</td>
<td>0.806</td>
<td>0.0003</td>
</tr>
<tr>
<td>PS 2</td>
<td>122</td>
<td>0.646</td>
<td>0.439</td>
<td>0.951</td>
<td>0.0268</td>
</tr>
<tr>
<td>Age ≤ 80 yr</td>
<td>337</td>
<td>0.668</td>
<td>0.519</td>
<td>0.859</td>
<td>0.0016</td>
</tr>
<tr>
<td>Age &gt; 80 yr</td>
<td>114</td>
<td>0.559</td>
<td>0.368</td>
<td>0.851</td>
<td>0.0067</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>229</td>
<td>0.712</td>
<td>0.518</td>
<td>0.979</td>
<td>0.0365</td>
</tr>
<tr>
<td>Other histology</td>
<td>222</td>
<td>0.539</td>
<td>0.399</td>
<td>0.727</td>
<td>0.000053</td>
</tr>
<tr>
<td>Smokers</td>
<td>356</td>
<td>0.631</td>
<td>0.498</td>
<td>0.800</td>
<td>0.0001</td>
</tr>
<tr>
<td>Never smokers</td>
<td>94</td>
<td>0.625</td>
<td>0.368</td>
<td>1.060</td>
<td>0.0810</td>
</tr>
<tr>
<td>Weight loss &lt; 5 %</td>
<td>198</td>
<td>0.610</td>
<td>0.431</td>
<td>0.864</td>
<td>0.0053</td>
</tr>
<tr>
<td>Weight loss ≥ 5 %</td>
<td>246</td>
<td>0.732</td>
<td>0.553</td>
<td>0.968</td>
<td>0.0287</td>
</tr>
<tr>
<td>ADL = 6</td>
<td>351</td>
<td>0.593</td>
<td>0.462</td>
<td>0.761</td>
<td>0.000042</td>
</tr>
<tr>
<td>ADL &lt; 6</td>
<td>87</td>
<td>0.655</td>
<td>0.417</td>
<td>1.029</td>
<td>0.0665</td>
</tr>
<tr>
<td>MMS ≥ 24</td>
<td>372</td>
<td>0.601</td>
<td>0.473</td>
<td>0.764</td>
<td>0.000032</td>
</tr>
<tr>
<td>MMS &lt; 24</td>
<td>70</td>
<td>0.909</td>
<td>0.540</td>
<td>1.530</td>
<td>0.7188</td>
</tr>
</tbody>
</table>

OS – The univariate hazard ratio was derived from a Cox model with a single treatment covariate.
Phase III Trial Design: Tx-naïve PS 2 NSCLC

Eligibility:
• Stage IIIB/IV NSCLC (malignant effusion)
• ECOG PS 2
• No prior chemotherapy
• Stable CNS disease
• Measurable disease
• Adequate organ function (including GFR ≥ 45 ml/min)
• Signed informed consent

1:1 Randomization

Stratification factors:
• Stage: IIIB vs IV
• Age: ≥70 vs <70
• WT loss: ≥25% vs <5%

Arm A
Pemetrexed
500 mg/m² IV Q3W
X 4 cycles

Arm B
Pemetrexed
500 mg/m² IV Q3W
+ Carboplatin
AUC 5 IV Q3W

Primary endpoint:
Overall Survival

Secondary endpoints:
Progression-free survival
Overall response rate
Safety

Pre-medications:
• Vitamin B12: 1mg IM Injection
• Folic Acid: 350-1,000mcg po daily
• Dexamethasone 4mg po BID the day before, the day of, and the day after

Lilenbaum R et al. ASCO 2012;Abstract 7506

OVERALL SURVIVAL

HR=0.57 (0.41–0.79); p=0.001

With permission from Lilenbaum et al. ASCO 2012;Abstract 7506
Maintenance Therapy in the Management of NSCLC

John Heymach, M.D., Ph.D
Chair, Department of Thoracic/Head & Neck Medical Oncology
MD Anderson Cancer Center

Research To Practice Meeting

May 31, 2013

Case: Dr Morganstein (Dr Heymach)

57 yo woman, heavy smoker
- Presented with cough unresponsive to antibiotics
- Lung mass found, further workup revealed multiple masses in liver
- Biopsy confirmed pan-WT adenocarcinoma
- Carbo/pem/bev for 4 cycles resulting in a PR
- Treatment was tolerated with some difficulty (fatigue, GI symptoms), and patient required 3 antihypertensives (hydrochlorothiazide, amlodipine, lisinopril)
A 57-year-old patient is diagnosed with PWT adenocarcinoma in the lung and corresponding liver mets. The patient is treated with 4 cycles of carboplatin/pemetrexed/bevacizumab and achieves a PR. What type of maintenance treatment, if any, would you recommend?
An otherwise healthy 50-yo with PWT adeno experiences a partial response to your recommended first-line treatment. Which maintenance therapy, if any, would you likely use?

- No maintenance therapy: 8%
- Bevacizumab: 8%
- Pemetrexed: 26%
- Pemetrexed/bevacizumab: 50%
- Erlotinib: 8%
- Other: 0%
Do you use maintenance therapy for your patients with metastatic squamous cell lung cancer?

Do you use maintenance therapy for your patients with metastatic squamous cell carcinoma?

- Yes, almost always: 4%
- Yes, frequently: 7%
- Yes, occasionally: 17%
- Rarely: 20%
- No: 52%
Decisions, decisions: choices for maintenance therapy in lung adenocarcinoma

Induction chemo (4-6 cycles), +/- BV, with non-PD

CONTINUE

BV

Pem

BV+Pem

Pem

Erlo

Gem

SWITCH

ADD

Erlo to BV

Exploratory analysis of BV maintenance from E4599

Patients in ECOG 4599 n = 869

Received 6 cycles

Completed 6 cycles

Analysis population

<table>
<thead>
<tr>
<th>Survival</th>
<th>CP + bev induction followed by bev maintenance (n = 217)</th>
<th>CP induction + no maintenance (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
<td>4.4 mo</td>
<td>2.8 mo</td>
</tr>
<tr>
<td></td>
<td>HR = 0.75, ( p = 0.03 )</td>
<td></td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>12.4 mo</td>
<td>11.2 mo</td>
</tr>
<tr>
<td></td>
<td>HR = 0.64, ( p &lt; 0.001 )</td>
<td></td>
</tr>
</tbody>
</table>
PARAMOUNT: Phase III study of maintenance pem vs BSC after Pem/Cis induction

<table>
<thead>
<tr>
<th>Survival</th>
<th>Pemetrexed + BSC</th>
<th>Placebo + BSC</th>
<th>Log-rank p</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI)</td>
<td>4.1 mo (3.2-4.6)</td>
<td>2.8 mo (2.6-3.1)</td>
<td>&lt;0.0001</td>
<td>0.62 (0.49-0.79)</td>
</tr>
</tbody>
</table>

Paz-Ares et al, Lancet Oncology, 2012

JMEN Phase III trial of “switch” maintenance for NSCLC (non-squamous subset)

- Stage IIIb/IV NSCLC
- 4 cycles of gem, doc, or tax + cis/carb, w/ non-PD
- Primary endpoint: PFS

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Pemetrexed (n = 326)</th>
<th>Placebo (n = 156)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS Nonsquamous</td>
<td>4.5 mo</td>
<td>2.6 mo</td>
<td>0.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS Nonsquamous</td>
<td>15.5 mo</td>
<td>10.3 mo</td>
<td>0.70</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Ciuleanu et al, Lancet, 2009
Phase III IFCT-GFPC 0502 results: gem maintenance prolongs PFS

- Maintenance therapy with gemcitabine significantly delayed disease progression compared with the observation arm

PFS by independent review: gemcitabine versus observation

<table>
<thead>
<tr>
<th></th>
<th>Observation n=152</th>
<th>Gemcitabine n=149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>1.9</td>
<td>3.8</td>
</tr>
<tr>
<td>PFS at 3 months, %</td>
<td>30.3</td>
<td>55.0</td>
</tr>
<tr>
<td>PFS at 6 months, %</td>
<td>8.6</td>
<td>22.1</td>
</tr>
</tbody>
</table>

HR=0.55 (0.43–0.70)
Log-rank test, p<0.0001

ATLAS – maintenance erlotinib prolongs PFS in combination with BV

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab + placebo (n=373)</th>
<th>Bevacizumab + erlotinib (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at risk:</td>
<td>Bev + placebo</td>
<td>Bev + erlotinib</td>
</tr>
<tr>
<td></td>
<td>373</td>
<td>370</td>
</tr>
<tr>
<td></td>
<td>142</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

HR=0.722 (0.592–0.881)
Log-rank p=0.0012

PointBreak (JMHD): Phase III Study Design

Eligibility
- Stage III/IV NSCLC
- Nonsquamous
- No prior systemic therapy
- PS 0/1
- Treated brain metastases
- (N=939)

Stratified for:
- PS (0 vs 1)
- Sex (M vs F)
- Disease stage (IIIB vs IV)
- Measurable vs nonmeasurable disease

Superiority Trial
Primary endpoint: OS
Secondary endpoint: PFS

Eligibility - Stage III/IV NSCLC - Nonsquamous - No prior systemic therapy - PS 0/1 - Treated brain metastases - (N=939)

Stratified for:
- PS (0 vs 1)
- Sex (M vs F)
- Disease stage (IIIB vs IV)
- Measurable vs nonmeasurable disease

PointBreak: PFS from Randomization (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Pem + Cb + Bev</th>
<th>Pac + Cb + Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS median, months</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>0.79 (0.67, 0.94); P=0.006</td>
</tr>
<tr>
<td>TTPD, months</td>
<td>7.0</td>
<td>6.0</td>
</tr>
<tr>
<td>HR (95% CI); P value</td>
<td>0.74 (0.64, 0.86); P&lt;0.001</td>
<td>0.74 (0.64, 0.86); P&lt;0.001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>34.1</td>
<td>33.0</td>
</tr>
<tr>
<td>G4 PFS* median, months</td>
<td>4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>HR (95% CI); P value</td>
<td>0.74 (0.64, 0.86); P&lt;0.001</td>
<td>0.74 (0.64, 0.86); P&lt;0.001</td>
</tr>
</tbody>
</table>

*Exploratory analysis
Censoring rate for Pem + Cb + Bev was 26.8; for Pac + Cb + Bev was 23.3.
TTPD=time to progressive disease.
With permission from Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).
PointBreak: OS From Randomization (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Pem + Cb + Bev</th>
<th>Pac + Cb + Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS median, months</td>
<td>12.6</td>
<td>13.4</td>
</tr>
<tr>
<td>HR (95% CI); P</td>
<td>1.0 (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>

Survival rate, %

PointBreak Prespecified Analysis: PFS From Randomization (Maintenance Group)

<table>
<thead>
<tr>
<th></th>
<th>Pem + Cb + Bev (n=292)</th>
<th>Pac + Cb + Bev (n=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS median, months</td>
<td>8.6</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Time from Induction (Months)

Survival Probability

Censoring rate for Pem + Cb + Bev was 27.8; for Pac + Cb + Bev was 27.2

With permission from Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).
PointBreak Prespecified Analysis: OS From Randomization (Maintenance Group)

Prespecified exploratory noncomparative subgroup analyses. Censoring rate for Pem + Cb + Bev was 36.0; for Pac+ Cb + Bev was 30.2 With permission from Patel, et al. Presented at IASLC. 2012 (abstr LBPL1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pem + Cb + Bev</td>
<td>17.7</td>
</tr>
<tr>
<td>Pac + Cb + Bev</td>
<td>15.7</td>
</tr>
</tbody>
</table>

ECOG-E5508: Phase III trial of BV, Pem, or BV+Pem as maintenance therapy in advanced NSCLC

Eligibility
- BV eligible
- non-squam
- chemonaive
- no CNS mets

Induction
Carbo/pac/BV Q3w x 4 cycles

Non-PD
- BV
- Pem
- BV+Pem

Primary endpoint: OS
Secondary: PFS

PI: S. Ramilingam; clinicaltrials.gov; trial NCT01107626
Maintenance therapy for adenocarcinoma: my approach

• If using BV with induction without pem:
  – Continue BV
  – if EGFR M+ or suspicion high use BV/erlotinib

• If Pem/platinum/BV induction
  – Continue BV (consider adding pem if progression)
  – Consider Pem/BV in good PS pts tolerating rx well
  – if EGFR M+ or suspicion use BV/erlotinib

• If not using BV with induction:
  – Pem (cont. or switch) in good PS pts tolerating rx well
  – if EGFR M+ or suspicion use erlotinib
Case: Dr Ferris (Dr Camidge)

- 43 yo man, never smoker
- 2/2012:
  - Mental status change, right-sided weakness, visual changes, seizure
  - Brain MRI: Multiple lesions, some with hemorrhage
  - CT: RLL mass, extensive bone and thoracic mets
  - Bronchoscopy: Adenoca, EGFR mutant-negative
  - Whole-brain RT, ZDA, carbo/pem/bev → GI toxicity
- 4/2012:
  - ALK mutation assay returns as positive
  - Crizotinib 250 mg BID → neutropenia, dental infection → 200 mg BID
  - Excellent PR, PS 0, doing well
  - Still on treatment (14 mo)
Case: Dr Ferris (Dr Camidge), continued

- 5/30/13
  - Asymptomatic with controlled systemic disease
  - Surveillance brain MRI every 3 months noted all brain lesions stable except 1:
    - Right parietal lesion increased in size with associated hemorrhage and surrounding edema
    - Stereotactic radiosurgery and dex (crizotinib held during radiosurgery, then resumed)
Case: Dr Ferris (Dr Camidge)
Discussion points

- Nausea with crizotinib: ? taking with food
- Neutropenia and dose reduction: Patient is 130 pounds
- Continuing ZDA in the face of response → dental infection
- Assessment for androgen deprivation syndrome:
  - Free testosterone = 19.8 (normal 35-150)
  - Total testosterone = 65 (normal 250-1,100)
  - Asymptomatic for hypogonadism (true deficit or lab aberration?)
- What to do if the disease progresses systemically?

Should all patients with ALK or ROS1-positive disease be started on crizotinib, or should select patients receive first-line chemotherapy/biologic therapy?
1st line Facts

- **Crizotinib and ALK**
  - PROFILE 1001 – phase I any line (24/149 (16%)*)
  - PROFILE 1005 – phase II ≥2nd line (3/901**)
  - PROFILE 1007 – phase III 2nd line
  - [PROFILE 1014] – 1st line – ongoing

- **Crizotinib and ROS1**
  - PROFILE 1001 – phase I any line (2/15 (13%)***)

*Camidge et al, TLO 2012  
**protocol deviations, Kim et al, ASCO 2012  
***Shaw et al, ASCO 2012

### Table 2: Objective response rate according to patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n/N</th>
<th>Proportion with objective response (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>74/123</td>
<td>60.2% (50.9-68.9)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>13/20</td>
<td>65.0% (40.8-84.6)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>46/71</td>
<td>64.8% (52.5-75.8)</td>
</tr>
<tr>
<td>Women</td>
<td>41/72</td>
<td>56.9% (44.7-68.6)</td>
</tr>
<tr>
<td><strong>ECOG PS score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29/53</td>
<td>54.7% (40.4-68.4)</td>
</tr>
<tr>
<td>1</td>
<td>46/72</td>
<td>63.9% (51.7-74.9)</td>
</tr>
<tr>
<td>2</td>
<td>12/17</td>
<td>66.7% (44.0-89.7)</td>
</tr>
<tr>
<td>3</td>
<td>0/1</td>
<td>0.0% (0.0-97.5)</td>
</tr>
<tr>
<td><strong>Number of previous advanced or metastatic systemic treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14/22</td>
<td>63.6% (40.7-82.8)</td>
</tr>
<tr>
<td>1</td>
<td>26/44</td>
<td>59.1% (43.2-73.7)</td>
</tr>
<tr>
<td>2</td>
<td>20/31</td>
<td>64.5% (45.4-80.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>27/46</td>
<td>58.7% (43.2-73.0)</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>30/39</td>
<td>76.9% (60.7-88.9)</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>57/104</td>
<td>54.8% (44.7-64.6)</td>
</tr>
</tbody>
</table>

143 patients were evaluable for response. ECOG PS=Eastern Cooperative Oncology Group performance status. *Using the exact method based on the F distribution.

**ORR: Appears independent of line of therapy**

**Median PFS:**

1st line (n=24)  
18.3m (95% CI: 8.3-NR)  
>2nd line (n=125) 9.2m (95% CI: 7.3-12.7)
Main approaches

• Theoretical
  – ‘Best drug’ given first

• Legal
  – FDA ALK license is not line of therapy restricted
  – EMEA ALK license is line of therapy restricted
  – ROS1 not a licensed indication anywhere (yet)

• Pragmatic
  – Molecular test result back in time for 1st line therapy?

Randomized trials of crizotinib in ALK+ NSCLC: 1014

PROFILE 1014 (N=334)
- ALK-FISH positive, non-squamous NSCLC
- No prior treatment for advanced disease

Crizotinib 250 mg BID (n = 167) [continuous]

Crossover on PD

pemetrexed/cisplatin or pemetrexed/carboplatin (n = 167) infused on day 1 of a 21-day cycle
Are specific chemotherapeutic agents/regimens more effective than others in patients with known ALK rearrangements?

'Shaw et al, JCO 2009'

'EGFR TKI'
Median TTP
5 mo ALK+
13 mo EGFR+

10 ALK+, no PRs to erlotinib

'1st line platinum-based combination regimen'
Median TTP
8-10 mo all groups

13 ALK+, 3 PRs (25%) to platinum-based chemo (all non-pemetrexed containing*)

* Alice Shaw, Personal communication
### PFS by molecular status on pemetrexed-based therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% CI</th>
<th>P value (Chi squared)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular status (vs triple negative)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK+</td>
<td>0.36</td>
<td>0.17-0.73</td>
<td>0.0051*</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>1.0</td>
<td>0.49-2.04</td>
<td>0.9983</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>0.55</td>
<td>0.28-1.1</td>
<td>0.0952</td>
</tr>
</tbody>
</table>

* P values <0.05

**PROFILE 1007: PFS of Crizotinib vs Pemetrexed or Docetaxel**

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=172)</th>
<th>PEM (n=99)</th>
<th>DOC (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>72 (73)</td>
<td>54 (75)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.43 to 0.80)</td>
<td>0.30 (0.21 to 0.43)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

With permission from Shaw et al, ESMO 2012
PROFIE 1007: ORR\textsuperscript{a} by Independent Radiologic Review

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Graph showing ORR by treatment group.}
\end{figure}

\begin{itemize}
\item ORR\textsuperscript{a} by Independent Radiologic Review
\item ORR ratio: 3.4 (95\% CI: 2.5 to 4.7); P<0.0001
\end{itemize}

\begin{itemize}
\item Crizotinib (n=173\textsuperscript{b})
\item Chemotherapy (n=174\textsuperscript{b})
\item Crizotinib (n=172\textsuperscript{c})
\item Pemetrexed (n=99\textsuperscript{c})
\item Docetaxel (n=72\textsuperscript{c})
\end{itemize}

\begin{itemize}
\item LADC only
\end{itemize}

*RECIST v1.1; \textsuperscript{b}ITT population; \textsuperscript{c}as-treated population

Are other ALK inhibitors either available or under investigation?
Many new ALK inhibitors in development –

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Phase of testing</th>
<th>Status</th>
<th>Clinicaltrials.gov ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib (PF-023341066)</td>
<td>Pfizer</td>
<td>Phase II/III</td>
<td>Open</td>
<td>NCT00585195, NCT00932893, NCT01154140 and NCT00932451</td>
</tr>
<tr>
<td>ASP-3026</td>
<td>Astellas</td>
<td>Phase I</td>
<td>Open</td>
<td>NCT01284192</td>
</tr>
<tr>
<td>XL228</td>
<td>Eli Lilly</td>
<td>Phase I</td>
<td>Completed</td>
<td>NCT009525838</td>
</tr>
<tr>
<td>LDK378</td>
<td>Novartis</td>
<td>Phase I</td>
<td>With data in criz failures</td>
<td>NCT01283516</td>
</tr>
<tr>
<td>AP-26113</td>
<td>Ariad</td>
<td>Phase I</td>
<td>With data in criz naive</td>
<td></td>
</tr>
<tr>
<td>CH54248022</td>
<td>Chugai</td>
<td>Phase I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEP-37440</td>
<td>Cephalon</td>
<td>Predical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data taken from [101].

+HSP90 inhibitors e.g. from Astex, Infinity, Novartis, Synta
+ pemetrexed studies (SWOG1300)
+ immune stimulant studies (PD-1/PDL-1)

**LDK378 in advanced ALK+ NSCLC**

---

**Table 4. Anaplastic lymphoma kinase inhibitors currently in development.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Phase of testing</th>
<th>Status</th>
<th>Clinicaltrials.gov ID</th>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data taken from [101].

**LDK378 in advanced ALK+ NSCLC**

- **Best % change from baseline**
  - LDK378 400–750 mg PO qd; lung cancer patients only

<table>
<thead>
<tr>
<th></th>
<th>Prior crizotinib</th>
<th>Crizotinib-naive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSCLC with prior crizotinib, ≥400 mg/d</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>CR + PR (RECIST 1.0)</td>
<td>21 (47%)</td>
<td></td>
</tr>
<tr>
<td>CR + PR + uPR</td>
<td>36 (80%)</td>
<td></td>
</tr>
</tbody>
</table>

With permission from Shaw et al, ESMO 2012
Therapeutic Decision-Making for Patients with EGFR Mutations

Robert Pirker
Medical University of Vienna

The Practical Application of Research Advances and Emerging Data in the Management of Non-Small Cell Lung Cancer
Chicago, 31 May 2013

Case: Dr Hager (Dr Pirker)

- 56 yo woman, nonsmoker
- S/p RLL lobectomy for asymptomatic adenoca
- 27 mm, 1 node + → cis/vinorelbine (GI toxicity)
- Routine restaging: Mets to mediastinum, lung, liver, bone and brain (4 lesions)
- EGFR del(19) mutation
- Erlotinib 150 mg qd → near complete response
- No radiation therapy yet
A 56-year-old patient with adenocarcinoma of the lung and an EGFR exon 19 deletion presents with extensive systemic metastases and 4 small brain lesions. The patient is asymptomatic. Would you use local treatment to the brain (radiation therapy) or start an EGFR TKI?

- Local treatment: 35%
- EGFR TKI: 65%

A patient with an EGFR mutation receives erlotinib 150 mg PO daily and after responding for 1 year starts to show asymptomatic but definitive disease progression. What would you likely do outside of a trial setting?

- Stop erlotinib and start chemotherapy: 45%
- Escalate the dose of erlotinib: 10%
- Continue with erlotinib but start chemotherapy: 42%
- Other: 3%
EGFR-directed tyrosine kinase inhibitors (TKIs)

- Gefitinib
- Erlotinib
- Icotinib (EGFR)
- Afatinib (ErbB Family Blocker)
- Dacomitinib (pan-HER)
- AZD8931 (EGFR, HER2, HER3)
- Lapatinib (EGFR, HER2)
- Canertinib (EGFR, HER2)
- Neratinib (EGFR, HER2)
- Vandetanib (EGFR, VEGFR, RET)

Gefitinib & erlotinib in advanced NSCLC

- No improvement of 1st line chemotherapy
  INTACT-1, INTACT-2; TALENT, TRIBUTE
- Gefitinib in patients pre-treated with chemotherapy
  IDEAL-1, IDEAL-2
- Erlotinib established in patients pretreated with chemotherapy
  BR.21  *Shepherd FA et al. NEJM 2005,353,133*
- Erlotinib established as maintenance therapy in patients with stable disease after 1st line chemotherapy (European Union)
  SATURN  *Cappuzzo F et al. Lancet Oncol 2010,11,521*
Gefitinib & erlotinib in advanced NSCLC

- Initially studied in unselected patients (IDEAL, ISEL, BR.21)
- Preferential efficacy in selected patients
  - **Response rate**
    - Adenocarcinoma
    - Females
    - Never-smokers
    - South-East Asians
  - **Survival**
    - Never-smokers
    - South-East Asians
- Efficacy in patients with EGFR-activating mutations
  - Exon 19 deletions, exon 21 point mutations (L858R)
- Studies in selected patients
  - Clinical selection
  - EGFR-activating mutations

EGFR mutations and response to TKIs

Green = responsive
Red = non-responsive
Yellow-green = mixed response outcomes

http://www.somaticmutations-egfr.info
## Randomized studies of first-line EGFR TKIs in patients with EGFR mutation

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>N (EGFR mut+)</th>
<th>RR (%)</th>
<th>Median PFS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mok et al.</td>
<td>IPASS</td>
<td>261</td>
<td>71.2 vs. 47.3</td>
<td>9.8 vs. 6.4</td>
</tr>
<tr>
<td>Han et al.</td>
<td>First-SIGNAL</td>
<td>27</td>
<td>84.6 vs. 37.5</td>
<td>8.4 vs. 6.7</td>
</tr>
<tr>
<td>Mitsudomi et al.</td>
<td>WJTOG 3405</td>
<td>86</td>
<td>62.1 vs. 32.2</td>
<td>9.2 vs. 6.3</td>
</tr>
<tr>
<td>Maemondo et al.</td>
<td>NEJGSG002</td>
<td>114</td>
<td>73.7 vs. 30.7</td>
<td>10.8 vs. 5.4</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>OPTIMAL</td>
<td>154</td>
<td>83 vs. 36</td>
<td>13.1 vs. 4.6</td>
</tr>
<tr>
<td>Rosell et al.</td>
<td>EURTAC</td>
<td>174</td>
<td>58 vs. 15</td>
<td>9.7 vs. 5.2</td>
</tr>
<tr>
<td>Yang et al.</td>
<td>LUX LUNG-3</td>
<td>345</td>
<td>56 vs. 23</td>
<td>11.1 vs. 6.9</td>
</tr>
</tbody>
</table>


### IPASS: PFS by Mutation Status within Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin/paclitaxel</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events (intent-to-treat population, N = 609; 608)</td>
<td>74.4%</td>
<td>81.7%</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFS events (EGFR mutation-positive population, N = 132; 129)</td>
<td>73.5%</td>
<td>86.0%</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Gefitinib, HR=0.19, 95%CI (0.13, 0.26), p<0.001
No. events M+ = 97 (73.5%), No. events M- = 88 (96.7%)

*Carboplatin/paclitaxel, HR=0.78, 95%CI (0.57, 1.06), p=0.1103
No. events M+ = 111 (86.0%), No. events M- = 70 (82.4)*

*Mok T et al. ESMO 2008.
Mok T et al. N Engl J Med 2009;361:1 0.1056/NEJMoa0810699*
**Primary endpoint: PFS**

Independent review – all randomized patients

- **Afatinib**
  - Number at risk: 230
  - Progression-free survival (months): 11.1
  - PFS event, n (%): 152 (66)
  - Hazard ratio (95% confidence interval): 0.58 (0.43–0.78)
  - Median PFS (months): 11.1

- **Cis/pem**
  - Number at risk: 115
  - Progression-free survival (months): 6.9
  - PFS event, n (%): 69 (60)
  - Hazard ratio (95% confidence interval): 0.58 (0.43–0.78)
  - Median PFS (months): 6.9

With permission from Yang JC, et al.
EGFR-directed TKIs
Progress

• EGFR TKIs show preferential efficacy in tumors with EGFR-activating mutations.

• Gefitinib, erlotinib & afatinib administered until disease progression improve progression-free survival & quality of life compared to first-line chemotherapy in patients who harbor EGFR-activating mutations in their tumors.

• Mutation testing at the time of diagnosis has been established as a standard for patients with advanced NSCLC.

• Assessment as adjuvant therapy in patients with resected NSCLC
  – RADIANT

• Major impact on molecular research

EGFR-directed TKIs
Hurdles

• A survival benefit has not been proven.
  – Crossover ?
  – Acquired resistance to subsequent chemotherapy ?
  – Detrimental effect on survival in earlier stages ?

• TKIs versus 1st line chemo plus maintenance therapy ?

• Patients develop resistance against TKIs.
  – Primary versus acquired resistance

• Re-biopsy at time of resistance ?

• Reversal studies are ongoing.

• Response assessment
  – Are RECIST appropriate for these patients ?
  – Treatment beyond progression ?
EGFR TKI-resistant NSCLC
Ohashi K et al. JCO 2013, 31, 1070

Reversal of TKI resistance

- **MET inhibitors**
  - Phase III trial with erlotinib ± onartuzumab (MetMAb) is ongoing in patients with MET high tumors.
  - Tivantinib failed in a Phase III trial in unselected patients.

- **Second & third generation TKIs**
  - Afatinib did not improve survival but prolonged PFS (LUX-Lung 1).
    Miller VA et al. Lancet Oncol 2012,13,528

- **Afatinib plus cetuximab**: 30% response rate

- **Other approaches**
TKIs in advanced NSCLC
Treatment at time of progression

• Switch to chemotherapy (e.g. platinum-based doublet) and consider re-treatment with TKI after chemotherapy

• Experimental strategies
  – Continue with TKI
  – Add chemotherapy to TKI
  – Second or third generation TKIs
  – Afatinib plus cetuximab
  – Other approaches


Kabbinavar FF et al. Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). Proc ASCO 2010;Abstract 7526.


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


Patel J et al. A randomized, open-label, Phase 3, superiority study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (B) followed by maintenance Pem+B versus paclitaxel (Pac)+Cb+B followed by maintenance B in patients (pts) with Stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC). Proc IASLC 2012;Abstract LBPL1.


Randomized Phase III study of maintenance therapy with bevacizumab, pemetrexed, or a combination of bevacizumab and pemetrexed following carboplatin, paclitaxel and bevacizumab for advanced non-squamous NSCLC. NCT01107626


Socinski MA et al. Results of a randomized, phase III trial of nab-paclitaxel (nab-P) and carboplatin (C) compared with cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC). Proc ASCO 2013; Abstract LBA7511.


