Current Status of Advanced Lung Cancer Therapy
Paul A. Bunn, Jr, MD, Dudley Chair and Professor, Univ. of Colorado Cancer Center, Aurora, CO, USA

Consultant: Amgen, Astellas, AstraZeneca, Bayer, Biodesix, Boehringer-Ingelheim, BMS, Celgene, Daiichi-Sankyo, Eli Lilly, GSK, Merck, Novartis, Roche, Sanofi
### 2012 Treatment Algorithm

Determine Performance Status, Histology, and Presence of “Driver Mutations”

<table>
<thead>
<tr>
<th>PS 0-3</th>
<th>PS 0-1</th>
<th>PS 0-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EGFR Mutation Positive</strong> → erlotinib, gefitinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EML4/MK Fusion Mutation Positive</strong> → crizotinib trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Mutation Positive</strong> → specific inhibitor trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gemcitabine or taxane doublet²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>taxane doublet +/- bevacizumab⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pemetrexed doublet +/- bevacizumab⁴</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Line of Therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td><strong>CR, PR, SD</strong></td>
</tr>
<tr>
<td>Continue therapy until progression</td>
</tr>
<tr>
<td><strong>CR, PR, SD</strong></td>
</tr>
<tr>
<td>Switch maintenance -erlotinib³ or No maintenance</td>
</tr>
<tr>
<td><strong>CR, PR, SD</strong></td>
</tr>
<tr>
<td>Continue bevacizumab if given initially If no bevacizumab, switch maintenance -erlotinib⁵ or -pemetrexed⁵ or no maintenance</td>
</tr>
</tbody>
</table>

| **2nd Line** |
| **PD** |
| Chemotherapy¹ |
| **PD** |
| docetaxel or erlotinib³ |
| **PD** |
| docetaxel⁵ or erlotinib⁵ or pemetrexed |
The Present & Future-Tailored Therapy

- Sensitivity ( + )
  - Responders
    - Survival benefit
- Sensitivity ( - )
  - Non-Responder
    - Toxicity without survival benefit
    - Delay of effective treatment

Molecular profiling

Right therapy for right patient
Imatinib: Tyrosine Kinase Inhibitor

Gleevec: HOW IT WORKS
Most Lung Cancers Express EGFR, but Biomarkers were not incorporated into the initial trials.

Normal

Non-small cell carcinoma

Gene Copy by FISH

Protein Expression by IHC

EGFR, k-ras Mutation
Positions of Mutations Detected in EGFR Tyrosine Kinase Domain in NSCLC

EGF ligand binding          Tyrosine kinase          Autophosphorylation

<table>
<thead>
<tr>
<th>Exon</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
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<tbody>
<tr>
<td>718</td>
<td>745</td>
<td>776</td>
<td>835</td>
<td>858</td>
<td>861</td>
<td>869</td>
<td>964</td>
</tr>
</tbody>
</table>

GXGXXG  K  R  H  DFG  L  L  Y

Paez:  

Lynch:  

Pao:  

▲ Tumor with point mutation (amino acid substitution)
★ Tumor with in-frame deletion

EGF = endothelial growth factor; TM = transmembrane.

## Randomized Trials of EGFR TKI vs CT in 1st Line Rx

<table>
<thead>
<tr>
<th>Study</th>
<th>Response Rate</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURTAC</td>
<td>58.1% vs 14.9%</td>
<td>9.7 vs 5.2 mos (HR 0.37)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>83% vs 36%</td>
<td>13.1 vs 4.6 mos (HR 0.16)</td>
</tr>
<tr>
<td>NEJ 002</td>
<td>74% vs 31%</td>
<td>10.8 vs 5.4 mos (HR 0.30)</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>62% vs 31%</td>
<td>9.2 vs 6.3 mos (HR 0.49)</td>
</tr>
<tr>
<td>IPASS</td>
<td>71% vs 47%</td>
<td>9.5 vs 5.5 mos (HR 0.19)</td>
</tr>
</tbody>
</table>
Lux Lung 3 Study design

Stage IIIB (wet)/IV lung adenocarcinoma (AJCC version 6)

EGFR mutation in tumor
(central lab testing; Therascreen EGFR29* RGQ PCR)

Randomization 2:1
Stratified by:
EGFR mutation (Del19/L858R/other)
Race (Asian/non-Asian)

Afatinib 40 mg/day†

Cisplatin + Pemetrexed
75 mg/m² + 500 mg/m²
i.v. q21 days, up to 6 cycles

Primary endpoint: PFS (RECIST 1.1, independent review)‡
Secondary endpoints: ORR, DCR, DoR, tumor shrinkage, OS, PRO§, safety, PK

Yang JC, et al.
Time to deterioration in lung cancer-related symptoms

**Cough**
- Median time to deterioration (months): Atatinib n=230, NE; Cisplatin/ pebetrexed n=115, 8.0 months.
- Hazard ratio (95% confidence interval): 0.60 (0.41–0.87), P=0.007.

**Dyspnea**
- Median time to deterioration (months): Atatinib n=230, 10.3 months; Cisplatin/ pebetrexed n=115, 2.9 months.
- Hazard ratio (95% confidence interval): 0.69 (0.50–0.93), P=0.015.

**Pain**
- Median time to deterioration (months): Atatinib n=230, 4.2 months; Cisplatin/ pebetrexed n=115, 3.1 months.
- Hazard ratio (95% confidence interval): 0.83 (0.62–1.10), P=0.19.

Yang JC, et al., ASCO 2012
Randomized Trials of EGFR TKI vs CT in 1st Line Rx

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</tr>
<tr>
<td>LUX LUNG 3</td>
<td>56% vs 23%</td>
<td>11.1 vs 6.9 mo (HR 0.58)</td>
</tr>
</tbody>
</table>
Results of the BFR14 Imatinib in GIST Trial on Long-Term Survival

- **Results**
  - The rates of patients with relapse at 2 years post-randomization decreased with the duration of treatment: 38%, 20%, and 0% of patients randomized after 1, 3, and 5 years of imatinib treatment in the C-arm.

Comparison of PFS in interruption arm

Comparison of PFS in continuation arm

Le Cesne *et al.* Abstract #10015. Poster Discussion

American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 3 – 7, 2011
Randomized study on treatment-beyond-progression

Advance stage NSCLC with EGFR Mutation

EGFR TKI

PD By RECIST

EGFR TKI till PD By doctor Discretion*

Platinum-based Doublet Chemotherapy

Primary endpoint: OS

*Doctor Discretion: Symptomatic progression, multiple progression Threat to major organ...etc
Continuation of TKI + Local Rx for TKI PD on erlotinib or crizotinib

<table>
<thead>
<tr>
<th>study</th>
<th>N pts</th>
<th>PFS1</th>
<th>PFS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado</td>
<td>25</td>
<td>10</td>
<td>6.2</td>
</tr>
<tr>
<td>MSKCC</td>
<td>18</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

Weickhardt A et al, Proc ASCO 2012 # 7526
Yu A et al, Proc ASCO 2012 # 7527
**SELECT: Adjuvant Erlotinib**

- **2-Year DFS**: 94% (95% CI 79.5-98.5%)
- **Median duration of follow-up**: 2.5 years

**Graphs:**
- **Disease Free Probability**
- **Survival Probability**
- Median OS: Not reached

**Graph Details:**
- Time (years) range from 0 to 4
- Disease Free Probability range from 0 to 1
- Survival Probability range from 0 to 1

**Censored Data Points**
ALK Rearrangement and FISH

Mechanisms of Crizotinib Resistance

Doebele R et al, CCR 2012
LDK378 shows antitumor activity in ALK+ NSCLC

<table>
<thead>
<tr>
<th>Initial dose (mg)</th>
<th>Patients (n)</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400</td>
<td>8</td>
<td>2 (25)</td>
</tr>
<tr>
<td>≥400</td>
<td>33</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Other diseases</td>
<td>50 600</td>
<td>6</td>
</tr>
</tbody>
</table>

- Response rate **81% (21/26)** in NSCLC patients treated at ≥400 mg who progressed following crizotinib
  - Responses include confirmed + unconfirmed per RECIST 1.0 (6 patients with PR awaiting confirmatory scans)
Lung Cancer Mutation Consortium
Mutation found in 54% (280/516) of tumors completely tested. 97% of mutations mutually exclusive.
LCMC protocols linked to specific molecular lesions detected

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>LCMC Lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEK1</td>
<td>GSK1120212 Trametinib</td>
<td>P Jänne</td>
</tr>
<tr>
<td>BRAF (V600E)</td>
<td>GSK2118434 Dabrafenib</td>
<td>B Johnson</td>
</tr>
<tr>
<td>BRAF (not V600E)</td>
<td>GSK1120212</td>
<td>P Jänne</td>
</tr>
<tr>
<td>HER2</td>
<td>Dacomitinib</td>
<td>M Kris</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>BKM120</td>
<td>J Engelman</td>
</tr>
<tr>
<td>EGFR</td>
<td>Erlotinib + OSI 906</td>
<td>C Rudin</td>
</tr>
<tr>
<td></td>
<td>Erlotinib + MM 121</td>
<td>L Sequist</td>
</tr>
<tr>
<td>KRAS</td>
<td>Tivantinib + Erlotinib</td>
<td>J Schiller.P Jänne</td>
</tr>
<tr>
<td>NRAS</td>
<td>Trametinib</td>
<td>G Blumenschein</td>
</tr>
<tr>
<td>MET Amplification</td>
<td>Crizotinib</td>
<td>R Camidge</td>
</tr>
<tr>
<td>ALK</td>
<td>Crizotinib</td>
<td>R Camidge</td>
</tr>
<tr>
<td>ROS</td>
<td>Crizotinib</td>
<td>R. Camidge</td>
</tr>
</tbody>
</table>
### New Molecular Targets in Lung Cancers in the Last 6 Months

<table>
<thead>
<tr>
<th>Target</th>
<th>Author</th>
<th>Year</th>
<th>Sensitive to Kinase Inhibition?</th>
<th>Mutually Exclusive?</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROS1</strong></td>
<td>Bergethon</td>
<td>2012</td>
<td>Yes</td>
<td>Yes</td>
<td>2%-18/1073</td>
</tr>
<tr>
<td><strong>KIF5B-RET</strong></td>
<td>Seok, Kohno, Lipson, Takeuchi</td>
<td>2011-2012</td>
<td>Yes</td>
<td>Yes</td>
<td>14%-5/21 1-2% 2%</td>
</tr>
<tr>
<td><strong>HER2 Extracellular Domain Mutations</strong></td>
<td>Greulich</td>
<td>2012</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Rapid Responses to Crizotinib in Patients with ROS1-Positive NSCLC
Summary of Tumor Responses in Patients with Advanced ROS1+ NSCLC (N=14*)

*Response-evaluable population. †Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression. ‡Crizotinib held for >6 wks prior to first scans which showed PD. +, Treatment ongoing. For ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in weeks.

Data in the database as of April 19, 2012
Using Driver Mutations to Classify and Treat All Lung Cancers

- Adenocarcinoma: 62%
- Squamous Cell: 20%
- Small Cell: 13%
- Carcinoid
- Large Cell
- Large Cell Neuroendocrine: 5%

**DRIVER MUTATIONS**

- Unknown: 36%
- KRAS: 32%
- EGFR: 23%
- ALK: 3%
- HER2: 3%
- Double Mt: 1%
- BRAF: <1%
- PIK3CA: <1%
- MET: <1%
- MEK: <1%
- NRAS: <1%

- Unknown: 56%
- FGFR1 Amp: 20%
- PIK3CA: 10%
- PTEN: 10%
- DDR2: 4%

- Unknown: 90%
- PIK3CA: 10%
**Current:**
- Illumina HiSeq 2000
  - 300 – 600 Gigabases
  - 6 – 11 days

- Illumina MiSeq
  - 1.5 Gigabases
  - 1 day

- Ion Torrent PGM
  - 1 Gigabase
  - 6 hours

**Emerging:**
- Illumina HiSeq 2500
- Ion Torrent Proton

**Human Genome in a Day**
How to Select Therapy

- Molecular Features (eg. EGFR mt, EML4/ALK fusion)
- Clinical Features (eg. PS, wt loss, co-morbid conditions)
- Histologic Features (eg. Squamous vs Other)
2011 Treatment Algorithm

Determine Performance Status, Histology, and Presence of "Driver Mutations"

**PS 0-3**

1st Line
- EGFR Mutation Positive → erlotinib, gefitinib
- EML4/MK Fusion Mutation Positive → crizotinib trial
- Other Mutation Positive → specific inhibitor trial

**PS 0-1**

1st Line
- No mutation
- Squamous histology
  - gemcitabine or taxane doublet

**PS 0-1**

1st Line
- No mutation
- Non-squamous histology
  - taxane doublet +/- bevacizumab
  - pemetrexed doublet +/- bevacizumab

**Line of Therapy**

**1st Line**
- CR, PR, SD
  - Continue therapy until progression

**2nd Line**
- CR, PR, SD
  - Switch maintenance - erlotinib or
  - No maintenance

**2nd Line**
- PD
  - Chemotherapy

**2nd Line**
- PD
  - docetaxel or erlotinib

**2nd Line**
- PD
  - docetaxel or erlotinib or pemetrexed
Paclitaxel/Carbo +/- Bevacizumab in Adv. NSCLC: Survival by Treatment

12 mo. | 24 mo.
---|---
PC | 43.7% | 16.9%
PCB | 51.9% | 22.1%

HR: 0.77 (0.65, 0.93)
P = 0.007

Medians: 10.2, 12.5
Phase III Randomized Trial of Gem/Cis vs Pemetrexed/Cis

Overall Survival in Pts with Adenocarcinoma or Large Cell Ca.  

HR=0.81

Approved in US by FDA in 10/08 for non-squamous ca
Percentage of individual NSCLC histology by period

- Adenocarcinoma
- Squamous cell carcinoma
- Large cell carcinoma
- Bronchioloalveolar carcinoma
- Carcinoma NOS

- 1989-1994
- 1995-2000
- 2001-2006

Histology in NSCLC

- NSCLC characterized by various histologies
- NSCLC histologies include
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Large cell carcinoma
  - NOS, not otherwise specified
  - Bronchoalveolar carcinoma
- Predominant histologic type has shifted from squamous to adenocarcinoma in past 2 decades
- Increasing impact of histological typing in NSCLC

### Efficacy of Maintenance: PFS & OS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Maintenance drug</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switch Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Westeel et al.</td>
<td>181</td>
<td>Vinorelbine</td>
<td>0.77 (0.55-1.07)</td>
<td>1.08 (0.79-1.48)</td>
</tr>
<tr>
<td>Fidias et al.</td>
<td>309</td>
<td>Docetaxel</td>
<td>0.71 (0.55-0.92)</td>
<td>0.84 (0.65-1.08)</td>
</tr>
<tr>
<td>Cappuzzo et al.</td>
<td>889</td>
<td>Erlotinib</td>
<td>0.71 (0.62-0.82)</td>
<td>0.81 (0.70-0.95)</td>
</tr>
<tr>
<td>Ciuleanu et al.</td>
<td>663</td>
<td>Pemetrexed</td>
<td>0.60 (0.49-0.73)</td>
<td>0.79 (0.65-0.95)</td>
</tr>
<tr>
<td><strong>Continuation Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paz-Ares et al</td>
<td>539</td>
<td>Pemetrexed</td>
<td>0.62 (0.49-0.79)</td>
<td>13.9 vs 11.0</td>
</tr>
<tr>
<td>Brodowicz et al.</td>
<td>206</td>
<td>Gemcitabine</td>
<td>0.69 (0.56-0.86)</td>
<td>0.84 (0.52-1.30)</td>
</tr>
<tr>
<td>Belani et al.</td>
<td>255</td>
<td>Gemcitabine</td>
<td>1.09 (0.81-1.45)</td>
<td>0.97 (0.72-1.30)</td>
</tr>
<tr>
<td>Perol et al.</td>
<td>309</td>
<td>Gemcitabine</td>
<td>0.56 (0.44-0.72)</td>
<td>0.89 (0.67-1.15)</td>
</tr>
</tbody>
</table>
EGFR TKI-resistant aEGFRMT+ NSCLC: Afatinib (BIBW2992) + Cetuximab

*Horn et al: IASLC WCLC 2011*

**NOTE:** Preliminary Efficacy Appears Equivalent in T790M-cancers