EGFR-mutated advanced NSCLC: Who, Why and How in Selecting the Best Approach

Dr Tan Yew Oo
Singapore Oncology Consultants
Singapore
War Against CANCER
Outline of Talk

• Lung cancer therapy in 2014
• Who, why and how in personalized cancer therapy?
• EGFR-mutated advanced lung cancer
• Comparing the TKI landscape in making selection
• New drugs for resistant T790M
• Take home messages
Types of Lung Cancer Treatment 2002 - 2014

- Surgery
- Radiation Therapy
- Molecular Targeted Therapy
- Cytotoxic Chemotherapy
Is Chemotherapy Beneficial in NSCLC?

- “The survival benefit of combination chemotherapy to patients with advanced NSCLC is controversial.” (Rapp, JCO 6:633-641, 1988)
- “Previous controlled studies comparing chemotherapy and supportive care for treatment of this type of cancer [NSCLC] have not given consistent results.” (Cartei, JNCI, 85:794-800, 1993).
- “Chemotherapy for NSCLC remains controversial.” (Cullen, JCO, 17:3188-3194, 1999)
Systemic Therapy for NSCLC in 2014

Proposed Treatment Algorithm

- **EGFR mutation positive or ALK positive**
  - Good PS
    - **Nonsquamous**
      - Bevacizumab eligible
        - Platinum/pemetrexed (or other*) ± bevacizumab
      - Bevacizumab ineligible
        - End of first-line chemotherapy
          - Bevacizumab, erlotinib, pemetrexed or observation
          - Erlotinib or pemetrexed or observation
  - Squamous
    - Platinum/pemetrexed (or other*)
      - End of first-line chemotherapy
      - Based on prior therapy

- **Poor PS**
  - Single-agent or combination chemotherapy

**First line**

**Maintenance**

- Based on prior therapy

**Second line**

- Based on prior therapy

*With docetaxel, paclitaxel, gemcitabine, vinorelbine.

Paradigm Shift in Pathology . . .

Tissue sent to pathology

Morphologic analysis

IHC, special stains

Tumor genotyping

Tumor biomarkers
Outline of Talk

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Personalized Cancer Medicine

- **1960**: Estrogen Receptor
- **1970**: Tamoxifen in Breast Cancer
- **1980**: HER2/c-erbB2, Abl/bcr
- **1990**: Trastuzumab in Breast and Gastric Cancer
- **2000**: EGFR mutation in lung cancer, KRAS in colonic cancer
- **2010**: TKI in EGFR mutation positive adenocarcinoma of lung, Cetuximab in KRAS wild type in metastatic colorectal cancer
Why Personalized Medicine?

• “...when doctors can truly prescribe the right treatment, to the right person, at the right time,
• we will have a new level of precision and effectiveness that will provide the knowledge-driven power
• that is necessary to achieve our highest goals in healthcare reform –
• more effective disease prevention and early disease detection”

Quote: HHS Secretary Kathleen Sebelius 2009
THE FUTURE OF CANCER THERAPY

• Personalized or tailor-made treatment will enhance the likelihood of response to treatment
• Reduce the risks and toxicities
Predictive Diagnostic Tests: Concept

Responders ~40%
Non responders
Toxicity

Alternative Management

DRUG

Molecular analysis

100% response
Changing Paradigm of Lung Cancer Pathology

Types of Lung Cancer 1990
- Small Cell Lung Cancer
- Non-Small Cell Lung Cancer

Lung Cancer Subtypes 2000
- Small cell carcinoma
- Adenocarcinoma
- Squamous Cell Carcinoma
- Large Cell Carcinoma

The graph shows the change in the classification of lung cancer types from 1990 to 2000, with a focus on the shift from non-small cell to small cell lung cancer.
Refining the IHC Diagnosis of NSCLC-NOS

- NSCLC
  - Squamous: 87% accuracy
  - Adenoca: 80% accuracy
  - Occasional rare types
  - NSCLC-NOS
    *Immunohistochemistry to predict subtype*
    - TTF1, p63, CK5/6 & AB/PAS

- 60% to 75% of cases
- ~ 20% to 35% of cases overall

- NSCLC probably squamous: 83% accuracy
- NSCLC probably adeno
- NSCLC-NOS IHC not predictive
  - 50% Adenoca
  - 37% Large cell
  - 13% Squamous when resected

25% to 40% of cases

Changes in the Therapeutic Landscape of Stage IV Lung Cancer: 2002-2014

Adeno LCC-NOS SCC SCLC
EGFR mutants
ALK
ROS/RET
HER2
BRAF
KRAS

Changes in the Therapeutic Landscape of Stage IV Lung Cancer: 2002-2014

Adeno LCC-NOS SCC SCLC
Changes in the Therapeutic Landscape of Stage IV Lung Cancer: 2002-2014

Histology still guides the therapeutic choice for the vast majority of patients

- Adeno
- LCC-NOS
- SCC
Cisplatin/Pemetrexed vs Cisplatin/Gemcitabine in Advanced NSCLC: OS by Histology

**Nonsquamous**

- **Median Survival**
  - C/P: 11.8 mos
  - C/G: 10.4 mos
  - Adjusted HR: 0.81 (95% CI: 0.70-0.94)

**Squamous**

- **Median Survival**
  - C/P: 9.4 mos
  - C/G: 10.8 mos
  - Adjusted HR: 1.23 (95% CI: 1.00-1.51)

Changes in the Therapeutic Landscape of Stage IV Lung Cancer: 2002-2014

Histology still guides the therapeutic choice for the vast majority of patients.

NON-SQUAMOUS NSCLC

- Adeno
- LCC/NOS
- SCC
## Non Small Cell Lung Cancer

| Etiologies: |
|-----------------|-----------------|-----------------|
| % Smoker        | The East        | The West        |
| % Smoker in Female Patients | < 10            | 80              |
| % Objective Response to Chemotherapy | 40 – 70%        | 20 – 40%        |
| Median Survival for Patients with Advanced Disease – IIIB & IV | 12 – 24 months | 8 – 12 months |
| Response rate to EGFR-TKI in unselected patients | 20 – 40%        | < 10%           |
Racial Diversity
Outline of Talk

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• Who, why and how in personalized cancer therapy?

• **EGFR-mutated advanced lung cancer**
• Comparing the TKI landscape in making selection

• New drugs for resistant T790M
• Take home messages
NSCLC Adenocarcinoma: Beyond EGFR Mutations and ALK Translocation

MAPK
MEK
Gene transcription
Cell cycle progression
PI3-K
RAS
RAF
SOS
GRB2
PTEN
AKT
STAT
EGF
R
K
pY
R
pY
pY
K
P
DNA
myc
Myc
cyclin D1
Jun
Fos
p27
Ki67
Tunel
VEGF
survival/anti-apoptosis
angiogenesis
metastasis
chemotherapy/
radiotherapy resistance
Gene transcription
Cell cycle progression

Ki67
MAPK
MEK
Gene transcription
Cell cycle progression
PI3-K
RAS
RAF
SOS
GRB2
PTEN
AKT
STAT

DNA
myc
cyclin D1

p27
Ki67

chemotherapy/
radiotherapy resistance

Tunel
survival/anti-apoptosis

metastasis

VEGF
angiogenesis
Pathways successfully targeted in NSCLC (based on positive phase III trials)

Anti-EGFR MAb (cetuximab)

EGFR-TKI (gefitinib, erlotinib, afatinib)

Ligand binding and dimerisation

Other receptor tyrosine kinases (e.g. IGF-1R, c-Met)

Anti-VEGF therapy (bevacizumab)

HIF-1α

AMPK

TSC2

mTOR

Raf

Mek

Gene transcription, cellular effects

Proliferation

Invasion

Metastasis

Resistance to apoptosis

Angiogenesis

Herbst, et al. NEJM 2008
Lung Cancer Mutation Consortium: OS by Mutation and Treatment

Selection by clinical characteristics is not adequate for identifying *EGFR* mutations

- *EGFR* mutation status in Caucasians: ~90% wild-type

- Best clinical selection criteria only give 60% positivity (IPASS; Asian, adenocarcinoma, never/light ex-smoker, predominantly female\(^1\))

- *EGFR* mutation testing is essential to guide therapeutic decisions

## EGFR Mutation Status

<table>
<thead>
<tr>
<th>EGFR mutation status</th>
<th>Gefitinib (n=609)</th>
<th>Carboplatin/paclitaxel (n=608)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (% of all patients)</td>
<td>[% of patients with EGFR mutation positive]</td>
</tr>
<tr>
<td>Negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91 (14.9)</td>
<td>85 (14.0)</td>
</tr>
<tr>
<td>Positive&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletions</td>
<td>132 (21.7)</td>
<td>129 (21.2)</td>
</tr>
<tr>
<td>Exon 21 L858R</td>
<td>66 [50.0]</td>
<td>74 [57.4]</td>
</tr>
<tr>
<td>Exon 20 T790M</td>
<td>64 [48.8]</td>
<td>47 [36.4]</td>
</tr>
<tr>
<td>Other&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 [3.8]</td>
<td>6 [4.7]</td>
</tr>
<tr>
<td></td>
<td>3 [2.3]</td>
<td>7 [5.4]</td>
</tr>
<tr>
<td>Unknown&lt;sup&gt;d&lt;/sup&gt;</td>
<td>386 (63.4)</td>
<td>394 (64.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup> No mutation detected  
<sup>b</sup> Eleven patients had multiple mutations and are counted more than once  
<sup>c</sup> Includes 3 patients with exon 18 G719X, 5 with exon 20 S768I, and 2 with exon 21 L861Q  
<sup>d</sup> Patients without a tumour sample evaluable for EGFR mutation analysis, and samples which were not successfully analysed for EGFR mutation status were classified as unknown
Experts were asked how they would treat patients, with the following options:

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Platinum Chemotherapy</th>
<th>Nonplatinum Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>Cisplatin</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Carboplatin</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>None</td>
<td>Albumin-bound paclitaxel</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td>Etoposide</td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>Pemetrexed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vinorelbine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>
Gefitinib - Quinazoline EGFR-TKIs

ZD1839
Gefitinib
Iressa®

Small molecule inhibitors of EGFR TK
Reversible inhibitor of ATP binding site EGFR
IPASS: First-Line Treatment of Advanced Adenocarcinoma of Lung: Targeted Therapy vs Chemotherapy

**Patients**
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIIB / IV disease

**Endpoints**

*Primary*
- Progression-free survival (non-inferiority)

*Secondary*
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

*Exploratory*
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

**Gefitinib** (Iressa)

1:1 randomisation

**Paclitaxel + Carboplatin**

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Mok et al 2009, Fukuoka et al 2009
45 Year old Chinese Woman, Lifelong Non-Smoker

28/9/2009

19/10/2009
IPASS Pre-Planned Subgroup Analysis:
PFS in EGFR Mutation + vs Mutation - Patients

**EGFR mutation (+)**

- Gefitinib (n=132)
- Carboplatin / paclitaxel (n=129)

**HR (95% CI) = 0.48 (0.36, 0.64)**
**p<0.0001**

**mPFS = 9.5M (TKI) vs 6.3M (PC)**

**EGFR mutation (-)**

- Gefitinib (n=91)
- Carboplatin / paclitaxel (n=85)

**HR (95% CI) = 2.85 (2.05, 3.98)**
**p<0.0001**

**mPFS = 1.5M (TKI) vs 6.5M (PC)**

**Treatment by subgroup interaction test, p<0.0001**

ITT population
Cox analysis with covariates

Mok et al 2009, Fukuoka et al 2009
Clinical Presentation

- 90 year old Chinese lady with no past medical history of note presented with cough productive of greenish sputum and loss of consciousness in March 2013
- Seen by her son who is GP and given Avelox and referred to TTSH
- Chest X-ray showed multiple nodular opacities in both lungs
- CT thorax confirmed multifocal well circumscribed ground glass nodules with central consolidation and mild bronchiectasis in lower lobe airways
- CT brain showed age-appropriate involutional change and lacuna infarcts but no metastasis or intracranial bleed
Clinical Presentation

- PET-CT confirmed bilateral ground glass lung nodules of negligible to mildly increased activity raising possibility of multifocal adenocarcinomas of pulmonary origin
- C-reactive protein and CEA were elevated
- Seen on 17 April 2013 and recommended open lung biopsy and done on 19 April 2013
- Histopathology = invasive moderately differentiated adenocarcinoma with staining positive for CK7 and TTF-1 but negative for CK5/6, p63 and CK20 – compatible with primary from lung
- EGFR mutation positive in Exon 19 deletion but negative for Alk mutation
Clinical Presentation

- Started on oral gefitinib (Iressa) on 6 May 2013
- Developed transaminitis and leucopenia after 3 weeks.
- Changed to erlotinib (Tarceva) on 18 June 2013 but developed oral ulcers
- 16 July 2013 started back on Iressa and tolerated well
- Celebrated her 90th birthday on 3 October 2013
- Developed progression to gefitinib in April 2014 — Afatinib
Before and After 6 months on Gefitinib
Conclusions of Gefitinib in EGFR Mut.+ 

- Gefinitib is highly effective in the treatment of EGFR Mut+ advanced adenocarcinoma of the lung 
- EGFR Mutation testing should be performed whenever possible to dictate 1\textsuperscript{st} line therapy 
- Benefit of testing to treatment decision - example of “personalized medicine”
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Background: **EGFR M+ NSCLC**

- Presence of *EGFR* mutation (M+) defines a distinct subtype of NSCLC, sensitive to EGFR TKIs\(^1\):
  - Common sensitizing mutations (Del19, L858R) account for ~90% of cases
- Reversible EGFR TKIs are standard first-line treatment in *EGFR M+ NSCLC*, showing improved PFS and ORR in 7 randomized trials\(^2\)–\(^8\), but no difference in OS vs platinum-doublet chemotherapy\(^9\)–\(^15\).

<table>
<thead>
<tr>
<th>Trial</th>
<th>PFS HR</th>
<th>OS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURTAC</td>
<td>Erlotinib</td>
<td>0.47 (0.26, 0.78) ind</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>0.16 (0.10, 0.28) inv</td>
</tr>
<tr>
<td>ENSURE</td>
<td>Erlotinib</td>
<td>0.42 (0.27, 0.66) ind</td>
</tr>
<tr>
<td>IPASS</td>
<td>Gefitinib</td>
<td>0.48 (0.36, 0.64) inv</td>
</tr>
<tr>
<td>NEJ002</td>
<td>Gefitinib</td>
<td>0.30 (0.22, 0.41) ind</td>
</tr>
<tr>
<td>WJTOG3406</td>
<td>Gefitinib</td>
<td>0.49 (0.34, 0.71) inv</td>
</tr>
<tr>
<td>FIRST-SIGNAL</td>
<td>Gefitinib</td>
<td>0.54 (0.27, 1.1) inv</td>
</tr>
</tbody>
</table>


Presented by: James Chih-Hsin Yang
# First-line Treatment With EGFR TKIs vs Chemotherapy in EGFR-Mutated Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS, Mos (P Value)</th>
<th>Median OS, Mos (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEJ002[^1^,^2^]</td>
<td>Gefitinib vs carbo/pac</td>
<td>230</td>
<td>10.8 vs 5.4 (&lt; .001)</td>
<td>30.5 vs 23.6 (.31)</td>
</tr>
<tr>
<td>WJTOG3405[^3^,^4^]</td>
<td>Gefitinib vs cis/doc</td>
<td>177</td>
<td>9.2 vs 6.3 (&lt; .0001)</td>
<td>36 vs 39 (.443)</td>
</tr>
<tr>
<td>OPTIMAL[^5^,^6^]</td>
<td>Erlotinib vs carbo/gem</td>
<td>165</td>
<td>13.7 vs 4.6 (&lt; .0001)</td>
<td>22.7 vs 28.9 (.69)</td>
</tr>
<tr>
<td>EURTAC[^7^]</td>
<td>Erlotinib vs plt-based CT</td>
<td>174</td>
<td>9.7 vs 5.2 (&lt; .0001)</td>
<td>19.3 vs 19.5 (.87)</td>
</tr>
<tr>
<td>LUX-Lung 3[^8^]</td>
<td>Afatinib vs cis/pem</td>
<td>345</td>
<td>11.1 vs 6.9 (.001)</td>
<td>28.2 vs 28.2 (.385)</td>
</tr>
<tr>
<td>LUX-Lung 6[^9^]</td>
<td>Afatinib vs cis/gem</td>
<td>364</td>
<td>11.0 vs 5.6 (&lt; .0001)</td>
<td>23.1 vs 23.5 (.6137)</td>
</tr>
</tbody>
</table>

### Meta-analysis of Randomized First-line EGFR TKI Studies: Improved PFS

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFRmut (first-line therapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EURTAC</td>
<td>0.37 (0.25-0.54)</td>
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<tr>
<td>First-SIGNAL</td>
<td>0.54 (0.27-1.10)</td>
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<tr>
<td>GTOWG</td>
<td>1.08 (0.24-4.90)</td>
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<tr>
<td>INTACT1-2</td>
<td>0.55 (0.19-1.60)</td>
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</tr>
<tr>
<td>IPASS</td>
<td>0.48 (0.36-0.64)</td>
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<tr>
<td>LUX LUNG3</td>
<td>0.58 (0.43-0.78)</td>
<td></td>
</tr>
<tr>
<td>NEJ002</td>
<td>0.32 (0.24-0.44)</td>
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<tr>
<td>OPTIMAL</td>
<td>0.16 (0.11-0.26)</td>
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<tr>
<td>TALENT</td>
<td>0.59 (0.21-1.67)</td>
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<tr>
<td>TOPICAL</td>
<td>0.90 (0.39-2.06)</td>
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</tr>
<tr>
<td>TRIBUTE</td>
<td>0.49 (0.20-1.20)</td>
<td></td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>0.52 (0.38-0.72)</td>
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</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>0.43 (0.38-0.49)</strong></td>
<td><strong>0.43 (0.38-0.49)</strong></td>
</tr>
</tbody>
</table>

LUX Lung 3 and 6 Design

- Stage IIIIB/IV adenocarcinoma of the lung
- Presence of EGFR mutation in the tumor tissue*
- No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization

Stratification by EGFR mutation type: Del19/L858R/other and by race (LUX-Lung 3 only): Asian/non-Asian

- Afatinib
  40 mg orally once daily

- LUX-Lung 3¹:
  Cisplatin + pemetrexed up to 6 cycles

- LUX-Lung 6²:
  Cisplatin + gemcitabine up to 6 cycles

Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, OS, PRO, safety

*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
Median PFS in first-line phase III EGFR Mut+ studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>EURTAC</th>
<th>ENSURE</th>
<th>OPTIMAL</th>
<th>IPASS</th>
<th>First-SIGNAL</th>
<th>WITOG 3405</th>
<th>NEJSG 002</th>
<th>LUX-LUNG 3</th>
<th>LUX-LUNG 6</th>
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</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>10.4</td>
<td>11.0</td>
<td>13.7</td>
<td>9.5</td>
<td>8.0</td>
<td>8.4</td>
<td>10.8</td>
<td>11.1</td>
<td>11.0</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>11.0</td>
<td>11.0</td>
<td>11.0</td>
<td>5.1</td>
<td>5.5</td>
<td>6.3</td>
<td>5.3</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Afatinib</td>
<td>11.1</td>
<td>11.0</td>
<td>10.8</td>
<td>6.3</td>
<td>6.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum-doublet chem</td>
<td>5.3</td>
<td>5.4</td>
<td>5.6</td>
<td>5.3</td>
<td>5.4</td>
<td>6.9</td>
<td>6.9</td>
<td>6.9</td>
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</tr>
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</table>

References:
Selected AEs in phase III studies of firstline EGFR TKIs in \textit{EGFR Mut+ NSCLC}

<table>
<thead>
<tr>
<th>AEs</th>
<th>Grade 1–2</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Paronychia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erlotinib, Gefitinib, Afatinib

Distribution of EGFR mutations in lung cancer.

Sensitive Mutations

- G719X (3%)
- VAIKEL insertion (1%)
- LREA deletion (45%)
- L861X (2%)

Resistant Mutations

- L747S
- D761Y
- T790M
- T854A
- Exon 20 insertion (4%)

Ohashi K et al. JCO 2013;31:1070-1080
Combined OS Analysis: LUX-Lung 3, LUX-Lung 6: Key Findings

Combined OS analysis, common mutations only

OS by mutation subtype

Yang, A#8004

Presented by: H. Jack West

ASCO 50 Annual Meeting
Science & Society
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LUX-Lung 3 Patients</th>
<th>LUX-Lung 6 Patients</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>307</td>
<td>324</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>103</td>
<td>111</td>
<td>0.73</td>
</tr>
<tr>
<td>Female</td>
<td>204</td>
<td>213</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;65</td>
<td>189</td>
<td>246</td>
<td>0.82</td>
</tr>
<tr>
<td>≥65</td>
<td>118</td>
<td>78</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>EGFR mutation</strong></td>
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</tr>
<tr>
<td>Del19</td>
<td>169</td>
<td>186</td>
<td>0.54</td>
</tr>
<tr>
<td>L858R</td>
<td>138</td>
<td>138</td>
<td>1.30</td>
</tr>
<tr>
<td><strong>Baseline ECOG score</strong></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>115</td>
<td>78</td>
<td>0.96</td>
</tr>
<tr>
<td>1</td>
<td>191</td>
<td>246</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Never smoker</td>
<td>210</td>
<td>251</td>
<td>0.75</td>
</tr>
<tr>
<td>&lt;15 pack yrs, stopped &gt;1 yr ago</td>
<td>29</td>
<td>11</td>
<td>0.79</td>
</tr>
<tr>
<td>Other current/ex-smoker</td>
<td>68</td>
<td>62</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Asian</td>
<td>83</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Asian</td>
<td>224</td>
<td></td>
<td>0.82</td>
</tr>
</tbody>
</table>

Favors Afatinib  Favors Pem/Gis  Favors Gem/Gis
Relevant Comparison for Afatinib in 2014 is to other EGFR-TKIs

- Is timing of EGFR TKI critical re: crossover?
  - L858R population showed PFS benefit but reversal w/OS
  - Sequence of therapy may be relevant
- Would other EGFR TKIs show OS benefit if > 700 pts enrolled & results divided by mut’n subtype?

**LUX-Lung 7**

<table>
<thead>
<tr>
<th>EGFR Mut+</th>
<th>Gefitinib daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 316 (Asia)</td>
<td>Afatinib daily</td>
</tr>
</tbody>
</table>

Primary endpoint: OS

- Toxicity assessment will also be critical

Completed July, 2013
Outline of Talk

• Lung cancer therapy in 2014
• Who, why and how in personalized cancer therapy?
• EGFR-mutated advanced lung cancer
• Comparing the TKI landscape in making selection
• New drugs for resistant T790M
• Take home messages
Clinical activity of the mutant selective EGFR inhibitor AZD9291 in patients with EGFR inhibitor resistant non-small cell lung cancer (NSCLC)

Pasi A. Jänne,1 Suresh S. Ramalingam,2 James Chih-Hsin Yang,3 Myung-Ju Ahn,4 Dong-Wan Kim,5 Sang-We Kim,6 David Planchard,7 Yuichiro Ohe,8 Enriqueta Felip,9 Claire Watkins,10 Mireille Cantarini,10 Serban Ghiorghiu,10 Malcolm Ranson11

1Dana-Farber Cancer Institute, Boston, USA; 2Emory University, Winship Cancer Institute, Atlanta, USA; 3National Taiwan University Hospital, Taipei, Taiwan; 4Samsung Medical Center, Seoul, Republic of Korea; 5Seoul National University Hospital, Seoul, Republic of Korea; 6Asan Medical Center, Seoul, Republic of Korea; 7Gustave Roussy Institute, Villejuif, France; 8National Cancer Center Hospital East, Kashiwa-City, Japan; 9Vall d’Hebron University Hospital, Barcelona, Spain; 10AstraZeneca, Macclesfield, UK; 11University of Manchester, Christie Hospital, Manchester, UK

**Response Rate* in Overall Population**

Best percentage change from baseline in target lesion:
all evaluable patients, escalation and expansion (N=205)

- First patient dosed Mar 6, 2013
- Longest response >9 months ongoing at time of data cutoff
- ORR* = 53% (109/205; 95% CI 46%, 60%); no difference in ORR by race
- Overall disease control rate (CR+PR+SD) = 83% (171/205; 95% CI 78%, 88%)

<table>
<thead>
<tr>
<th></th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>240 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (205)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ORR</td>
<td>55%</td>
<td>44%</td>
<td>54%</td>
<td>58%</td>
<td>67%</td>
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</table>

*Includes confirmed responses and responses awaiting confirmation; *represents imputed values. Population: all dosed patients with a baseline RECIST assessment and an evaluable response (CR, PR, SD, or PD). N=205 (from 232 dosed patients, 27 patients with a current non-evaluable response are not included). CI, confidence interval; CR, confirmed complete response; ORR, overall response rate; PD, progressive disease; PR, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

Response Rate* in T790M + (central test)

Best percentage change from baseline in target lesion:
T790M+ evaluable patients, expansion cohorts only (N=107)

- ORR* = 64% (69/107; 95% CI 55%, 73%) in patients with EGFR T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>160</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (107)</td>
<td>10</td>
<td>29</td>
<td>34</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>ORR</td>
<td>50%</td>
<td>62%</td>
<td>68%</td>
<td>64%</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Includes confirmed responses and responses awaiting confirmation; #represents imputed values
Population: all dosed centrally confirmed T790M+ patients with a baseline RECIST assessment and an evaluable response (CR/PR, SD, or PD), N=107 (from 120 T790M+ patients; 13 patients with a current non-evaluable response are not included). D, discontinued; QD, once daily

Conclusions of AZD9291

- AZD9291 demonstrates promising efficacy (ORR 53%) in this global Phase I study in patients who have previously progressed on approved EGFR-TKI therapies
- Efficacy is greater in patients with T790M+ (ORR 64%) than in patients with T790M- (ORR 22%) EGFR-TKI-resistant NSCLC
- AZD9291 treatment is associated with no dose-limiting toxicities and a maximum tolerated dose was not defined
- The Phase II dose has been selected as 80 mg QD based on both the activity in patients with T790M+ NSCLC and the low incidence of toxicity
- US FDA breakthrough designation has been granted for AZD9291 for the treatment of patients with metastatic, EGFR T790M+ NSCLC whose disease has progressed during treatment with an FDA-approved EGFR-TKI
First-in-human evaluation of CO-1686

An irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M)

Best response in Phase 1 and early Phase 2 expansion cohort patients

Centrally confirmed T790M+ patients within therapeutic dose range (N=40)

ORR to date: 58%
Patient treated with CO-1686

- 3 previous treatment lines
- Erlotinib immediately before CO-1686
- 625 mg BID
- 82% target lesion reduction at C2
- CNS lesion response
Conclusions of CO-1686

- CO-1686 is an oral, selective, covalent inhibitor of mutant EGFR NSCLC (activating and T790M mutations)
  - Well-tolerated; only TKI to completely spare wild-type EGFR signaling
  - Most common toxicity is elevated glucose, which is well-managed with oral hypoglycemics
- Promising activity seen across all dose levels of Phase 1/2 trial
  - 58% ORR in biopsy-proven, heavily pretreated, centrally confirmed, T790M+ patients
  - CNS responses observed
- PFS is very encouraging
  - Current estimate exceeds 12 months
  - Median not yet reached
Personalized Medicine: New Definition

"Here's my sequence..."
New Yorker, 2007
EGFR-mutated advanced NSCLC – Take Home Messages

• **WHO**: Choosing the Right Patient and the Right Drug
• **WHY**: We have an increasing list of anti-cancer therapies requiring identification of genes, molecules or biomarkers to choose the appropriate drug
• **HOW**: Understanding of the pathophysiology and drug mechanism of action is a prerequisite for the development of a more individualized anti-cancer pharmacotherapy
• We are beginning to tailor our molecular targeted drugs according to specific EGFR mutation in advanced lung cancer
• In 2014, most oncologists must do companion molecular diagnostic tests to select the most appropriate drug for treating patients with EGFR-mutated advanced lung cancer
2014 World Cup Final 14 July 2014
Germany vs Argentina

THANK YOU FOR YOUR ATTENTION
ANY QUESTIONS?