State of the Art: Recent Therapeutic Advances in Lung Cancer 2016

Barbara Melosky
CONFLICT IN MY LIFE
Outline

• Discuss the Current Treatment Algorithms in NSCLC
• Provide an overview of Recent Advances in the treatment of NSCLC
• Review updates from ESMO ASIA 2015, ELCC GENEVA, and ASCO CHICAGO 2016
Current Treatment: Identify a Driver Mutation!

- EGFR
- ALK/ROS
- OTHER: BRAF, HER 2, RET, MET
Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

Non-Small Cell Lung Cancers – 2016

Non-Squamous Non-Small Cell Lung Cancers

- **Unknown mutation** 40%
- **KGAR** 30%
- **EGFR** 15%
- **MET** 4%
- **BRAF/PIK3CA** 2%
- **HER2/MEK** 2%
- **ROS1** 2%
- **RET** 1%

**EGFR**

Squamous

- **Unknown mutation** 60%
- **FGFR1 amp 20%
- **KRAS 6%
- **EGFR mut 5%
- **DDR2 4%
- **PIK3CA** 3%
- **BRAF** 2%

**MSKCC data**
Del19 and L858R: Most Common Mutations in the Tyrosine Kinase Domain of EGFR in NSCLC


Del19 = exon 19 deletions; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; L858R = exon 21 L858R point mutation; NSCLC = non-small cell lung cancer.
Median PFS in EGFR-M+ patients
- Gefitinib: 9.5 months
- Chemotherapy: 6.3 months
  - HR 0.48, 95% CI 0.36-0.64; \( P < 0.001 \)

EURTAC: PFS

- Median PFS$^1$
  - Erlotinib: 10.4 months
  - Chemotherapy: 5.2 months
    - HR 0.34, 95% CI 0.23, 0.49; $P<0.001$

Sub-group analyses of progression-free survival in the intention-to-treat population$^2$

IPASS: OS EGFR Mutation +

- Gefitinib (n=132)
- Carboplatin/paclitaxel (n=129)
- HR (95% CI)
  - 1.00; \( P=0.990 \)
- Median OS
  - G: 21.6 months
  - C/P: 21.9 months
- HR 1.00

EURTAC Overall Survival

- Erlotinib (n = 86)
- Chemo (n = 87)
- OS
  - 19.3
  - 19.5
  - 1.04 (0.65-1.68), \( P = 0.8702 \)
- HR 1.04

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Fukuoka M et al. JCO. 2011;29:2866-2874.
# EGFR TKI First- and Second-Generation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reversibility</th>
<th>Targets (IC&lt;sub&gt;50&lt;/sub&gt;, nM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Reversible</td>
<td>EGFR (3) HER2 (1830)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Reversible</td>
<td>EGFR (0.5) HER2 (512)</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>Irreversible</td>
<td>EGFR (6) HER2 (46) HER4 (74)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Irreversible</td>
<td>EGFR (0.5) HER2 (14) HER4 (1.0)</td>
</tr>
</tbody>
</table>

First-Generation

Second-Generation
Afatinib: LUX-Lung 3 and LUX-Lung 6

Stage IIIB (wet)/IV lung adenocarcinoma
EGFR mutation in tumour
(central lab testing; TheraScreen® EGFR29\textsuperscript{a} RGQ PCR)

Randomisation 2:1
Stratified by EGFR mutation
(Del19/L858R/other)

LUX-Lung 3\textsuperscript{1}
\( (n=345) \)
Cisplatin + Pemetrexed
75 mg/m\textsuperscript{2} + 500 mg/m\textsuperscript{2}
IV q21d, up to 6 cycles

LUX-Lung 6\textsuperscript{2}
\( (n=364; \text{Asian pts}) \)
Cisplatin + Gemcitabine
75 mg/m\textsuperscript{2} + 1000 mg/m\textsuperscript{2} D1, D8
IV q21d, up to 6 cycles

Cisplatin + Pemetrexed
75 mg/m\textsuperscript{2} + 500 mg/m\textsuperscript{2}
IV q21d, up to 6 cycles

Afatinib
40 mg/\textsuperscript{b}

Primary end point: PFS (RECIST 1.1, independent review)\textsuperscript{c}
Secondary end points: OS, PRO\textsuperscript{d}, ORR, DCR, DOR, tumour shrinkage, safety

\textsuperscript{a}EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.

\textsuperscript{b}Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10-mg decrements in case of related G3 or prolonged G2 AE.

\textsuperscript{c}Tumour assessments: q6 weeks until week 48 and q12 weeks thereafter until progression/start of new therapy.

\textsuperscript{d}Patient-reported outcomes: EQ-5D, EORTC QLQ-C30 and LC 13 at randomisation and q3 weeks until progression or new anticancer therapy.

Note: 15 patients in LUX-Lung 3 and 23 patients in LUX-Lung 6 were still on treatment as of May 2014.

EGFR = epidermal growth factor receptor; RGQ = rotor-gene Q; PCR = polymerase chain reaction; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; ORR = objective response rate; DCR = disease control rate; DOR = duration of response; OS = overall survival.

LUX-Lung 3 and LUX-Lung 6: Significant Improvement in PFS

Patients with common mutations

LUX-Lung 3\(^1\) (n=308)  
Afatinib vs Cis/Pem  
Median PFS 13.6 mo vs 6.9 mo  
HR for PFS 0.47, \(P<0.0001\)

LUX-Lung 6\(^{2,3}\) (n=324)  
Afatinib vs Cis/Gem  
Median PFS 11.0 mo vs 5.6 mo  
HR for PFS 0.25, \(P<0.0001\)

*Exon 19 deletions or exon 21 [L858R] substitutions.

PFS = progression-free survival.

LUX-Lung 3 and 6: OS in Common Mutations

**LUX-Lung 3**

- **Afatinib** (n=203)
  - Median, mo: 31.57
  - HR (95% CI): 0.78 (0.58-1.06)
  - P-value: 0.1099

- **Cis/Pem** (n=104)
  - Median, mo: 28.16

**LUX-Lung 6**

- **Afatinib** (n=216)
  - Median, mo: 23.6
  - HR (95% CI): 0.83 (0.62-1.09)
  - P-value: 0.1756

- **Cis/Gem** (n=108)
  - Median, mo: 23.5

**HR**

- **Afatinib** vs Cis/Pem: 0.78
- **Afatinib** vs Cis/Gem: 0.83

No. at risk:

- **Afatinib**
  - LUX-Lung 3: 203
  - LUX-Lung 6: 216
- **Cis/Pem**
  - LUX-Lung 3: 104
  - LUX-Lung 6: 108
- **Cis/Gem**
  - LUX-Lung 3: 104
  - LUX-Lung 6: 108

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PRESPECIFIED ENDPOINT

LUX-Lung 3 and LUX-Lung 6: OS in Del19 Subgroup

The Impact of 1st-line TKIs on OS: Meta-Analysis of Phase III Trials by Mutation Type – Del19

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>LUX-Lung 3</td>
<td>0.53 (0.36-0.79)</td>
</tr>
<tr>
<td></td>
<td>LUX-Lung 6</td>
<td>0.64 (0.44-0.94)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.59 (0.45-0.77)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>ENSURE</td>
<td>0.79 (0.48-1.30)</td>
</tr>
<tr>
<td></td>
<td>EURTAC</td>
<td>0.94 (0.57-1.54)</td>
</tr>
<tr>
<td></td>
<td>OPTIMAL</td>
<td>1.52 (0.91-2.52)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.04 (0.71-1.51)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>IPASS</td>
<td>0.86 (0.61-1.22)</td>
</tr>
<tr>
<td></td>
<td>NEJ002</td>
<td>0.83 (0.52-1.34)</td>
</tr>
<tr>
<td></td>
<td>WJTOG3405</td>
<td>1.19 (0.65-2.18)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.90 (0.70-1.17)</td>
</tr>
</tbody>
</table>
LUX-Lung 7

- Stage IIIb/IV adenocarcinoma of the lung
- EGFR mutation (Del19 and/or L858R) in the tumor tissue
- No prior treatment for advanced/metastatic disease
- ECOG PS 0/1

Afatinib 40 mg once daily

Stratified by:
- Mutation type (Del19/L858R)
- Brain metastases (present/absent)

Gefitinib 250 mg once daily

Primary endpoints:
- PFS (independent)
- TTF
- OS

Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Duration of disease control
- Tumor shrinkage
- HRQoL
- Safety

- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

*Central or local test.
†Dose modification to 50, 30, 20 mg permitted in line with prescribing information.

LUX-Lung 7: PFS

PFS by independent review

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>11.0</td>
<td>10.9</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.57–0.95)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0165</td>
<td></td>
</tr>
</tbody>
</table>

HR 0.73  P=0.0165
LUX-Lung 7: Response Rate

**Objective response and duration of response (independent review)**

- **ORR 70% vs 56%**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=112)</th>
<th>Gefitinib (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DoR (months)</td>
<td>10.1</td>
<td>8.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>(7.8–11.1)</td>
<td>(7.4–10.9)</td>
</tr>
</tbody>
</table>
LUX-Lung 7: Time to treatment failure (TTF)

- **Afatinib** (n=160)
  - Median TTF (months): 13.7
  - HR (95% CI): 0.73 (0.58–0.92)
  - p value: 0.0073

- **Gefitinib** (n=159)
  - Median TTF (months): 11.5
  - HR (95% CI): 0.73 (0.58–0.92)
  - p value: 0.0073

**No. of patients**

- Afatinib
  - 160
  - 148
  - 133
  - 113
  - 91
  - 68
  - 56
  - 48
  - 40
  - 25
  - 18
  - 9
  - 5
  - 0
  - 0

- Gefitinib
  - 159
  - 144
  - 120
  - 103
  - 74
  - 59
  - 43
  - 30
  - 21
  - 11
  - 6
  - 6
  - 2
  - 2
  - 0

### Not All TKIs Are Created Equal – LUX7

**Side Effects**

<table>
<thead>
<tr>
<th>AE category, %</th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>90.0</td>
<td>11.9†</td>
</tr>
<tr>
<td>Rash/acne*</td>
<td>88.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>64.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Paronychia*</td>
<td>55.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Dry skin</td>
<td>32.5</td>
<td>-</td>
</tr>
<tr>
<td>Pruritus</td>
<td>23.1</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>20.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>No case of ILD.</td>
<td>1.3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10.6</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.6</td>
<td>-</td>
</tr>
<tr>
<td>ALT increased</td>
<td>9.4</td>
<td>-</td>
</tr>
<tr>
<td>AST increased</td>
<td>6.3</td>
<td>-</td>
</tr>
</tbody>
</table>

*Grouped terms of AEs

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Park et al. ESMO Asia, 2015.
Overall Survival (IMMATURE)

Estimated overall survival probability

<table>
<thead>
<tr>
<th>Time to death (months)</th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>9</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>15</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>18</td>
<td></td>
<td></td>
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<tr>
<td>21</td>
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<td>24</td>
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<tr>
<td>27</td>
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<td>30</td>
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<td>33</td>
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<td>36</td>
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<td>39</td>
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<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td></td>
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</tr>
</tbody>
</table>

Median, mo: Afatinib 27.9, Gefitinib 25.0
HR (95% CI): Afatinib 0.87 (0.65-1.15), Gefitinib 0.33
P-value: Afatinib 0.33, Gefitinib 0.33

No. at risk:
- Afatinib: 160, 156, 153, 148, 139, 125, 111, 104, 91, 72, 56, 41, 21, 5, 0, 0
- Gefitinib: 159, 153, 148, 142, 133, 119, 105, 89, 79, 64, 55, 42, 20, 7, 1, 0

Data on file
Del19 and L858R: Most Common Mutations in the Tyrosine Kinase Domain of EGFR in NSCLC


Del19 = exon 19 deletions; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; L858R = exon 21 L858R point mutation; NSCLC = non-small cell lung cancer.
## Combined LUX-Lung 2, 3, & 6: Afatinib in Uncommon EGFR Mutations

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>ORR, n (%)</th>
<th>Median PFS, months (95% CI)</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exon 18:</strong> G719X (n=8)</td>
<td>14 (78)</td>
<td>13.8 (6.8–NE)</td>
<td>26.9 (16.4–NE)</td>
</tr>
<tr>
<td>G719X + T790M (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X + S768I (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X + L861Q (n=3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X + T790M + L858R (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exon 20:</strong> L861Q (n=12)</td>
<td>9 (56)</td>
<td>8.2 (4.5–16.6)</td>
<td>16.9 (15.3–21.6)</td>
</tr>
<tr>
<td>L861Q + G719X (n=3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L861Q + Del19 (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exon 21:</strong> S768I (n=1)</td>
<td>8 (100)</td>
<td>14.7 (2.6–NE)</td>
<td>NE (3.4–NE)</td>
</tr>
<tr>
<td>S768I + G719X (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S768I + L858R (n=2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

LUX-Lung 2, 3, & 6: AFATINIB
Tumour Shrinkage Uncommon Mutations\(^a\)

Clinical activity was observed in uncommon mutations (exon 18 [G719X], 20 [S768I], and 21 [L861Q]) that are known to be less responsive to first-generation EGFR TKIs.

\(^a\)N=67 (8 patients were not included due to insufficient data).

## First-, Second-, and Third-Generation EGFR TKIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reversibility</th>
<th>Targets (IC&lt;sub&gt;50&lt;/sub&gt;, nM)</th>
<th></th>
</tr>
</thead>
</table>
| Gefitinib      | First-Generation | Reversible | EGFR (3)  
                         |               | HER2 (1830)   |
| Erlotinib      | Reversible    | EGFR (0.5)  
                         |               | HER2 (512)   |
| Dacomitinib    | Irreversible  | EGFR (6)  
                         | HER2 (46)     | HER4 (74)   |
| Afatinib       | Irreversible  | EGFR (0.5)  
                         | HER2 (14)     | HER4 (1.0)  |
| Osimertinib    |               | EGFR (17)  
                         |               | TARGET T790 |
| Olmutinib      |               | EGFR (9)   |   |
PFS AURA Trial – 2nd-Line Aquired T790 M+

Yang JCH, et al. ELCC 2016; Abstract LBA2_PR.
## Causally Related AEs: AURA Ph I

<table>
<thead>
<tr>
<th>Causally-related AEs occurring in ≥15% of patients overall, n (%)</th>
<th>AURA Ph I (80 mg) N=63*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Paronychia (grouped terms)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Dry skin (grouped terms)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (14)</td>
</tr>
</tbody>
</table>

**Select AEs**

<table>
<thead>
<tr>
<th>ILD (grouped terms)²</th>
<th>0</th>
<th>0</th>
<th>1 (2)</th>
<th>1 (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*ILD 2.9 %
35/1200 pts

NO RASH or DIARRHEA
AURA3 Study Design

- A Phase III, open-label, randomised study of 410 patients

**POSITIVE TRIAL: PFS**

**World Lung Vienna 2016**

- NSCLC EGFR M+ Progression on EGFR TKI
- T790M+ (n=410)
- AZD9291 (80 mg po QD) (n=273)
- Platinum-based doublet chemotherapy q 3 w (n=137)
T790 Biopsy: Biopsy the tumor

A small piece of tissue is removed with a biopsy needle and looked at with a microscope.
Can We Find EGGR T790M From the Blood?
High ORR in Patients With Tumour or Plasma-Positive T790M Patients Treated With Osimertinib

Oxnard et al. ELCC 2016.
Investigator-assessed Confirmed Response Rate and PFS are Similar in T790M Patients by Plasma, Tissue, and Urine Test

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>n</th>
<th>Objective Response Rate* % (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>443</td>
<td>33.9 (29.5–38.5)</td>
</tr>
<tr>
<td>Plasma</td>
<td>374</td>
<td>32.1 (27.4–37.1)</td>
</tr>
<tr>
<td>Urine</td>
<td>169</td>
<td>36.7 (29.4–44.4)</td>
</tr>
</tbody>
</table>

**Progression-free survival**

- **Plasma**: Median (Months) 4.1, 95% CI 3.9–4.4, Range 0.1, 22.7
- **Tissue**: Median (Months) 5.0, 95% CI 4.2–6.0, Range 0.1, 22.7
- **Urine**: Median (Months) 4.3, 95% CI 4.0–6.2, Range 0.1, 22.2

Urine T790M: The Ultimate Liquid Biopsy!
Brain Metastases and Leptomeningeal disease

BLOOM Study Design - Overview

Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of AZD3759 or osimertinib in patients with EGFR mutation-positive advanced NSCLC

AZD3759

Dose escalation

- Cohort 1: 50 mg BID
- Cohort 2: 100 mg BID
- Cohort 3: 300 mg BID
- Cohort 4: 500 mg BID
- Cohort 5: 200 or 300 mg BID*

Dose expansion cohorts

- Leptomeningeal metastasis
  - EGFR-TKI naïve or pre-treated patients
- Brain metastasis
  - EGFR-TKI naïve patients

Leptomeningeal metastasis cohort, EGFR-TKI pre-treated patients

Extracranial stable, N=20 (current report)

T790M positive (extracranial tumor) and leptomeningeal metastasis cohort

No restriction on extracranial stable disease, N=20 (accrual ongoing)

*Both AZD3759 200 mg and 300 mg BID were explored to evaluate long-term tolerability and efficacy. BID, twice daily.
Osimertinib Activity Across LM Assessments

Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed radiological improvement
- Two patients had confirmed CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed improved neurological function

<table>
<thead>
<tr>
<th>Best MRI imaging intracranial response, n (%)</th>
<th>N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed*</td>
<td></td>
</tr>
<tr>
<td>Responding</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Unconfirmed</td>
<td></td>
</tr>
</tbody>
</table>

Population; efficacy, n=21. *Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination.

Best confirmed neurological status†

- Improved
- No change
- Worsened
- Early withdrawal
- Unconfirmed

Number of patients

- Normal (N=11)
  - 10

- Abnormal (N=10)
  - 5
  - 3
Summary: EGFR

• Current:
  – First line: Gefitinib/ Erlotinib/ Afatinib

• Recent Advances:
  – ESMO ASIA
    ▪ LUX Lung 7
  – ELCC:
    ▪ Aura Trial Second Line T790M+: PFS 11 months
    ▪ T790: Plasma may be as accurate as tumor
  – ASCO
    ▪ T790: Urine may be accurate
    ▪ New treatment for Leptomeningeal disease
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

Squamous

77%

Unknown mutation 40%

KRAS 30%

EGFR 15%

ALK 5%

MET 4%

BRAF/PIK3CA 2%

ROS1 2%

RET 1%

23%

FGFR1 amp 20%

KRAS 6%

EGFR mut 5%

DDR2 4%

PIK3CA 3%

BRAF 2%

Unknown mutation 60%

MSKCC data
PROFILE 1014:
First-line Crizotinib vs Pem/Cis PFS

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=172)</th>
<th>Chemotherapy (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>137 (80)</td>
</tr>
<tr>
<td>Median, months</td>
<td>10.9</td>
<td>7.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45 (0.35−0.60)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PFS Probability (%)

No. at risk
Crizotinib 172 120 65 38 19 7 1 0
Chemotherapy 171 105 36 12 2 1 0 0

Time (Months)
CNS Sanctuary

• Brain metastases

**MRI Detection of BMs**

- Solitary lesion
- Oligometastases
- Multiple BMs

Acquired Resistance in ALK+ NSCLC

- Most patients develop resistance to crizotinib
  - Usually within 1-2 years
  - CNS relapses are common
- Mechanisms of resistance are diverse
  - ALK resistance mutations
  - Alternative signaling pathways
    - EGFR activation/mutation
    - c-KIT amplification, KRAS mutation
Profile of Second-/Third-Generation ALK Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Activity Against L1196M</th>
<th>Other Kinases Inhibited</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>Pfizer</td>
<td>No</td>
<td>MET, ROS1</td>
<td>Approved</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Novartis</td>
<td>Yes</td>
<td>ROS1, IGFR1</td>
<td>Approved</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Chugai/Roche</td>
<td>Yes</td>
<td>RET</td>
<td>Phase III</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>Ariad</td>
<td>Yes</td>
<td>ROS1, EGFR</td>
<td>Phase II</td>
</tr>
<tr>
<td>ASP3026</td>
<td>Astellas</td>
<td>Yes</td>
<td>ROS1</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>Ignyta</td>
<td>Unknown</td>
<td>ROS1, TRK1/2/3</td>
<td>Phase II</td>
</tr>
<tr>
<td>X-396</td>
<td>Xcovery</td>
<td>Yes</td>
<td>ROS1</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>TSR-011</td>
<td>Tesaro</td>
<td>Yes</td>
<td>TRK1/2/3</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>PF-06463922</td>
<td>Pfizer</td>
<td>Yes</td>
<td>ROS1</td>
<td>Phase I/II</td>
</tr>
</tbody>
</table>
Best Percentage Change from Baseline (NSCLC)

- Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response.

Best percentage change from baseline (NSCLC)

- ALK inhibitor treated
- ALK inhibitor naive

RR 61.8%

N=228*

*Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response.
**ASCEND 1: PFS**

**Progression-free survival**
- ALK inhibitor treated (n=163)
- ALK inhibitor naïve (n=83)
- All (N=246)

**Key Results**
- Median: 9.03 (95% CI 6.93, 10.97)
- Median: 6.93 (95% CI 5.55, 8.67)
- RR 61.8%

**Number of patients still at risk**
- NSCLC with prior ALKi: 163, 108, 79, 52, 29, 13, 2, 1, 0, 0, 0, 0, 0
- NSCLC ALKi naïve: 83, 69, 55, 43, 32, 17, 6, 2, 0, 0, 0, 0, 0
- All NSCLC: 246, 177, 134, 95, 61, 30, 8, 3, 0, 0, 0, 0
CNS Exposure and BBB Transporters

- Lipid-soluble solutes passively cross the blood-brain barrier (BBB)
- BBB enforced by cross-membrane receptors such as P-gp
- P-gp actively transport molecules back out of the brain

- Crizotinib and ceritinib are P-gp substrates; alectinib is not
Alectinib in Patients with Crizotinib-resistant ALK+ NSCLC

Systemic BOR:
- PD (n=22)
- SD (n=35)
- PR (n=61)

RR 61%
Activity of Alectinib in Patients With Measurable CNS Metastases in ALK+ NSCLC

Updated analysis cut-off 8 Jan 2015.
CNS = central nervous system.
Adapted from: Ou et al. ASCO 2015.

Prior CNS radiation

- Yes (N=24)
- No (N=11)

RR 20/35 = 57%
# Reported Grade 3/4 Adverse Events With Alectinib

<table>
<thead>
<tr>
<th>AE of any cause in ≥10% patients, n (%)</th>
<th>All</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>45 (33)</td>
<td>39 (28)</td>
<td>6 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (26)</td>
<td>26 (19)</td>
<td>8 (6)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>34 (25)</td>
<td>27 (20)</td>
<td>6 (4)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>31 (23)</td>
<td>25 (18)</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>25 (18)</td>
<td>16 (12)</td>
<td>8 (6)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (16)</td>
<td>16 (12)</td>
<td>4 (3)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>19 (14)</td>
<td>15 (11)</td>
<td>4 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18 (13)</td>
<td>8 (6)</td>
<td>5 (4)</td>
<td>4 (3)</td>
<td>0*</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (12)</td>
<td>13 (9)</td>
<td>3 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST elevation</td>
<td>16 (12)</td>
<td>13 (9)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>16 (12)</td>
<td>15 (11)</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (11)</td>
<td>10 (7)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (10)</td>
<td>10 (7)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>14 (10)</td>
<td>7 (5)</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*One patient had a grade 5 event, unrelated to treatment.

AE = adverse event; ALT= serum glutamic-pyruvic transaminase (enzyme); AST = serum glutamic-oxaloacetic transaminase (enzyme).

Adapted from: Ou et al. ASCO 2015.
ALTA: Randomized Dose Evaluation of Brigatinib

A phase 2, open-label, multicenter, international study (NCT02094573)

- Locally advanced or metastatic ALK+ NSCLC
- PD on crizotinib
- No other ALK-directed therapy

Randomized 1:1

Brigatinib 90 mg qd
N = 112

Brigatinib 180 mg qd*
N = 110

Stratified by:
- Brain metastases at baseline
- Best response to prior crizotinib

- PD requiring an alternate therapy
- Intolerable toxicity
- Other reasons for discontinuation

Primary Endpoint: Confirmed ORR per RECIST v1.1 (assessed by investigator)

Key Secondary Endpoints: Confirmed ORR (assessed by an IRC), CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases†), duration of response, PFS, OS, safety, and tolerability

Randomized phase 2 design not intended for statistical comparisons between arms; however, post hoc comparisons were performed on PFS and OS to support dose selection

*Active brain metastases were defined as lesions with no prior radiotherapy or those with investigator-assessed progression after prior radiotherapy.
Brigatinib Antitumour Activity by Arm

90 mg qd

ORR 45%

180 mg qd†

ORR 54%

Progressive disease
Stable diseaseⅡ
Partial response
Complete response

Dotted line at –30% indicates threshold for partial response per RECIST v1.1
* Single response awaiting confirmation
† Patient had a lymph node target lesion which resolved to <10 mm shortest diameter (CR per RECIST v1.1)
‡ 180 mg qd with 7-day lead-in at 90 mg
ⅡCategory includes single responses that were not confirmed

Data as of February 29, 2016
Median PFS exceeds 1 year (12.9 months) with 180 mg brigatinib

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events / Total (%)</th>
<th>1-Year PFS Probability, % (95% CI)</th>
<th>Median PFS (95% CI)</th>
<th>Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 mg qd</td>
<td>50/112 (45)</td>
<td>39 (27–52)</td>
<td>9.2 months (7.4–15.6)</td>
<td>0.55 (0.35–0.86)</td>
</tr>
<tr>
<td>180 mg qd*</td>
<td>31/110 (28)</td>
<td>54 (37–68)</td>
<td>12.9 months (11.1–not reached)</td>
<td></td>
</tr>
</tbody>
</table>

*180 mg qd with 7-day lead-in at 90 mg
† Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Data as of February 29, 2016
## Second-Generation ALK Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib&lt;sup&gt;1&lt;/sup&gt; N = 163</th>
<th>Alectinib&lt;sup&gt;2&lt;/sup&gt; N = 138</th>
<th>Brigatinib&lt;sup&gt;3&lt;/sup&gt; N = 110</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design/Assessment</strong></td>
<td>Phase I/II Investigator/BIRC</td>
<td>Phase 2 BIRC</td>
<td>Phase 2 Investigator</td>
</tr>
<tr>
<td>PS 2</td>
<td>12%</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Brain Mets</td>
<td>60%</td>
<td>61%</td>
<td>67%</td>
</tr>
<tr>
<td>Previous Rx</td>
<td>56% (≥ 3 prior)</td>
<td>80% (≥ 2 prior)</td>
<td>74% (≥ 2 prior)</td>
</tr>
<tr>
<td>ORR</td>
<td>56% (49-64)</td>
<td>50% (41 – 59)</td>
<td>54% (43-65)</td>
</tr>
<tr>
<td>CNS Response</td>
<td>36%*&lt;br&gt;N = 28</td>
<td>57%&lt;br&gt;N = 35</td>
<td>67%&lt;br&gt;N = 12</td>
</tr>
<tr>
<td>Median PFS</td>
<td>6.9 m (5.6 – 8.7)</td>
<td>8.9 (5.6-11.3)</td>
<td>12.9 (11.1- NR)</td>
</tr>
</tbody>
</table>

*Retrospective Assessment
2. Ou, JCO 2016
TOKYO, February 10, 2016 - Chugai Pharmaceutical

JALEX Study

Alectinib vs Crizotinib
A phase III study Japan ALK positive NSCLC stopped early
PFS superior when treated with Alectinib

HOW SUPERIOR?
Primary Endpoint: PFS

First-Line

300 mg bid

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>25 (24.3%)</td>
<td>58 (55.8%)</td>
</tr>
<tr>
<td>Median, mo [95% CI]</td>
<td>NR [20.3 - NR]</td>
<td>10.2 [8.2 - 12.0]</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HR [99.6826% CI]</td>
<td>0.34 [0.17 - 0.71]</td>
<td></td>
</tr>
</tbody>
</table>

Progression-free survival rate (%) vs Time (months)

- Alectinib
  - No. of patients at risk:
    - At 0 months: 103
    - At 3 months: 93
    - At 6 months: 76
    - At 9 months: 49
    - At 12 months: 36
    - At 15 months: 27
    - At 18 months: 9
    - At 21 months: 1

- Crizotinib
  - No. of patients at risk:
    - At 0 months: 102
    - At 3 months: 86
    - At 6 months: 65
    - At 9 months: 40
    - At 12 months: 21
    - At 15 months: 14
    - At 18 months: 4

PFS NR!
HR .34
P<0.0001
Lorlatinib – a Next-Generation ALK/ROS1 Inhibitor

- Resistance to ALK TKIs can develop through secondary mutations in the ALK kinase domain\(^1\)\(^-\)\(^3\)
  - Secondary mutations have been observed in \(~25\%\) of patients with resistance to crizotinib\(^3\)\(^,\)\(^4\).

- Similarly, a subset of patients appear to develop acquired resistance to crizotinib through point mutations in the ROS1 kinase domain\(^4\)\(^-\)\(^6\).

- Using structure-based design, lorlatinib was identified as a novel macrocyclic ALK inhibitor with broad-spectrum ALK potency and CNS penetration\(^1\).

- Lorlatinib is also a potent inhibitor of ROS1\(^2\).

ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor

Clinical Activity: LORLATINIB ALK+ Patients

- ORR 46%
- PFS 11.4 months

Median PFS, months (95% CI): 11.4 (3.4–16.6)
12-month PFS, % (95% CI): 41.0 (23.2–58.0)
18-month PFS, % (95% CI): 23.4 (6.0–47.3)

ALK: anaplastic lymphoma kinase; CI: confidence interval; PFS: progression-free survival; ROS1: c-rearranged oncogene 1
Treatment-Related Adverse Events in ≥15% of Patients Treated at the RP2D

LORLATINIB

<table>
<thead>
<tr>
<th>Adverse event , n (%)</th>
<th>All Grades</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>16 (94)</td>
<td>2 (12)</td>
<td>9 (53)</td>
<td>5 (30)</td>
<td>0</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>14 (82)</td>
<td>5 (29)</td>
<td>7 (41)</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>9 (53)</td>
<td>6 (35)</td>
<td>3 (18)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia**</td>
<td>7 (41)</td>
<td>3 (18)</td>
<td>2 (12)</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Slow speech</td>
<td>3 (18)</td>
<td>3 (18)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Includes the preferred terms hypercholesterolemia and total cholesterol increased
**Includes the preferred terms hypertriglyceridemia and blood triglycerides increased
Other Grade 3 events included lipase increased and delirium

AE, adverse event; QD, once daily; RP2D, recommended phase II dose
• Current:
  ▪ First Line: Crizotinib
  ▪ Second Line: Ceritinib/ Alectinib

• Recent Advances:
  – ASCO
    ▪ First Line: Japan Alectinib
    ▪ Second Line: Brigatinib
    ▪ Third Line: Lorlatinib
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

- KRAS 30%
- EGFR 15%
- Unknown mutation 40%
- ALK 5%
- MET 4%
- BRAF/PIK3CA 2%
- HER2/MEK 2%
- ROS1 2%
- RET 1%

Unknown mutation 60%

- FGFR1 amp 20%
- KRAS 6%
- EGFR mut 5%
- DDR2 4%
- PIK3CA 3%
- BRAF 2%

Squamous

23%

RARE MUTATIONS

MSKCC data
Maximum Change in Target Lesion by Best Investigator-Assessed Confirmed Response

**BRAF V600: Dabrafenib and Trametinib**

**ORR 63% PFS 8.6 months**

Not Evaluable (NE) patients did not have a follow-up scan required for confirmation.

Overall response rate: 63% (95% CI, 49-76)

Presented by: David Planchard, MD, PhD
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

- KRAS: 30%
- EGFR: 15%
- Unknown mutation: 40%
- ALK: 5%
- MET: 4%
- BRAF/PIK3CA: 2%
- HER2/MEK: 2%
- ROS1: 2%
- RET: 1%

Squamous

- FGFR1 amp: 20%
- KRAS: 6%
- EGFR mut: 5%
- DDR2: 4%
- PIK3CA: 3%
- BRAF: 2%
- Unknown mutation: 60%

MSKCC data
AFATINIB: HER2 Lung Cancer

- HER2/neu mutations in 2 – 4% of lung adenocarcinomas
- More frequent in female, non-smokers and patients of Asian origin

Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu.
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

- KRAS: 30%
- EGFR: 15%
- Unknown mutation: 40%
- ALK: 5%
- MET: 4%
- BRAF/PIK3CA: 2%
- HER2/MEK: 2%
- ROS1: 2%
- RET: 1%

Squamous

- FGFR1 amp: 20%
- KRAS: 6%
- EGFR mut: 5%
- DDR2: 4%
- PIK3CA: 3%
- BRAF: 2%
- Unknown mutation: 60%

MSKCC data
Vandetanib 18 Patients
ORR 17% SD 28%
Se-Hoon Lee et al
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>30%</td>
</tr>
<tr>
<td>EGFR</td>
<td>15%</td>
</tr>
<tr>
<td>Unknown mutation</td>
<td>40%</td>
</tr>
<tr>
<td>ALK</td>
<td>5%</td>
</tr>
<tr>
<td>MET</td>
<td>4%</td>
</tr>
<tr>
<td>BRAF/PIK3CA</td>
<td>2%</td>
</tr>
<tr>
<td>HER2/MEK</td>
<td>2%</td>
</tr>
<tr>
<td>ROS1</td>
<td>2%</td>
</tr>
<tr>
<td>RET</td>
<td>1%</td>
</tr>
<tr>
<td>FGFR1 amp</td>
<td>20%</td>
</tr>
<tr>
<td>Unknown mutation</td>
<td>60%</td>
</tr>
</tbody>
</table>

Squamous

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>6%</td>
</tr>
<tr>
<td>EGFR mut</td>
<td>5%</td>
</tr>
<tr>
<td>DDR2</td>
<td>4%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>3%</td>
</tr>
<tr>
<td>BRAF</td>
<td>2%</td>
</tr>
<tr>
<td>MET</td>
<td>2%</td>
</tr>
<tr>
<td>KRAS 6%</td>
<td></td>
</tr>
<tr>
<td>EGFR mut 5%</td>
<td></td>
</tr>
<tr>
<td>DDR2 4%</td>
<td></td>
</tr>
<tr>
<td>PIK3CA 3%</td>
<td></td>
</tr>
<tr>
<td>BRAF 2%</td>
<td></td>
</tr>
</tbody>
</table>

MSKCC data
Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring MET Mutations Causing Exon 14 Skipping

Paul K. Paik\textsuperscript{1,2}, Alexander Drilon\textsuperscript{1,2}, Pang-Dian Fan\textsuperscript{3}, Helena Yu\textsuperscript{1,2}, Natasha Rekhtman\textsuperscript{3}, Michelle S. Ginsberg\textsuperscript{4}, Laetitia Borsu\textsuperscript{3}, Nikolaus Schultz\textsuperscript{5,6}, Michael F. Berger\textsuperscript{2,3,5}, Charles M. Rudin\textsuperscript{1,2}, and Marc Ladanyi\textsuperscript{3,5}
Wild-type MET

MET X14 Skipped
Exon 14
(regulatory domain)
A. Baseline and 4-week PET scan from patient 2 (MET c.3028G>C exon 14 splice variant) following treatment with cabozantinib.
E. Baseline and 8-week CT scan from patient 7 (MET c.3028G>T exon 14 splice variant) following treatment with crizotinib.
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

Squamous

CMET: EXON 14 Skipping 5% both Non-Squamous and Squamous

MSKCC data
Summary: RARE MUTATION

- **BRAF (2%)**
  - Dabrafenib and Trametinib
- **HER 2 (2%)**
  - Afatinib
- **RET (1%)**
  - Vandetinib
- **CMET EXON 14 Slice (5% and Squamous)**
  - Cabozatinib/Crizotinib
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

- KRAS 30%
- Unknown mutation 40%
- EGFR 15%
- ALK 5%
- MET 4%
- BRAF/PIK3CA 2%
- HER2/MEK 2%
- ROS1 2%
- RET 1%

Squamous

- FGFR1 amp 20%
- KRAS 6%
- EGFR mut 5%
- DDR2 4%
- PIK3CA 3%
- BRAF 2%
- Unknown mutation 60%

WILD TYPE
Overall Survival in Squamous Cell Carcinoma

Overall Survival Time (months) in Squamous Patients

OS Median (95% CI)
- Cis/Pem (N=244) 9.4 mos (8.4, 10.2)
- Cis/Gem (N=229) 10.8 mos (9.5, 12.1)
Overall Survival in Adenocarcinoma

- **Pemetrexed/Cisplatin** (n=436):
  - Median survival: 12.6 months (95% CI: 10.7-13.6)
  - Adjusted HR: 0.84 (95% CI: 0.71-0.99)
  - p-value: 0.033

- **Gemcitabine/Cisplatin** (n=411):
  - Median survival: 10.9 months (95% CI: 10.2-11.9)

ASCO 2012
PARAMOUNT: Overall Survival

HR: 0.78  (95% CI: 0.64–0.96)
Log-rank $P = 0.0195$

Survival Probability

Time from Randomization (Months)

PEM Maintenance
Immunotherapy
Targeting PD-1 Pathways

**Periphery**
- Dendritic cell
- T cell
- MHC
- TCR
- CD28
- B7

**Activation**
(cytokines, lysis, proliferation, migration to tumour)

**Tumour microenvironment**
- T cell
- T cell
- PD-L1

**CTLA-4 pathway**
- Anti-CTLA-4

**PD-1 pathway**
- PD-L1

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

<table>
<thead>
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<td>Merck</td>
<td>Phase I-III</td>
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<td>Durvalumab</td>
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<td>Atezolizumab</td>
<td>Engineered human IgG1 mAb</td>
<td>Roche</td>
<td>Phase I-II</td>
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</tbody>
</table>

Adapted from Dr. J. Brahmer ASCO 2013
Overall Survival

CheckMate 017
SQ NSCLC

HR=0.59 (95% CI: 0.44, 0.79),
P = 0.00025

1-yr OS rate=42%

CheckMate 057
Non-SQ NSCLC

HR=0.73 (96% CI: 0.59, 0.89);
P = 0.0015

1-yr OS rate=51%

Previously presented at ASCO 2015 (Abstracts 8009 and LBA109).
ORR CheckMate 017 & 057

**CheckMate 017**

Patients with Ongoing Response

- ORR 20%
  - 63% (17 of 27 patients with response)
- 33% (4 of 12 patients with response)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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</tbody>
</table>

**CheckMate 057**

- ORR 19%
  - 52% (29 of 55 patients with ongoing response)
- 14% (5 of 36 patients with ongoing response)

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</table>

**Table: CheckMate 017 (Squameuse) vs CheckMate 057 (Nonsquamous)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CheckMate 017</th>
<th>CheckMate 057</th>
</tr>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>NR</td>
<td>17.2 months</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.4 months</td>
<td>5.6 months</td>
</tr>
</tbody>
</table>

Horn et al. ECC 2015; Reckamp et al. World Lung Conference 2015.
## Clinical Development of Inhibitors of PD-1 Immune Checkpoint

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<td>Engineered human IgG1 mAb</td>
<td>Genentech</td>
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</table>
Association of PD-L1 Expression With Efficacy

- Assessed in purposefully collected tumor samples by a clinical-trial IHC assay (Dako) with the 22C3 antibody (Merck)

- Samples scored as the percentage of tumor cells with membranous PD-L1 staining—tumor proportion score, or TPS


- 35% <1%
- 40% 1-49%
- 25% >50%
Keynote 010

Patients
- Advanced NSCLC
- Confirmed PD after ≥2 cycles of platinum-doublet chemotherapy
- PD-L1 TPS ≥1%
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease
- No ILD or pneumonitis requiring systemic steroids

Stratification factors:
- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 statusb (TPS ≥50% vs 1%-49%)

Pembrolizumab
2 mg/kg IV Q3W for 24 months

Pembrolizumab
10 mg/kg IV Q3W for 24 months

Docetaxel
75 mg/m² Q3W per local guidelines

Screened 33% negative
Duration of Response
(RECIST v1.1, Central Review)

**PD-L1 TPS ≥1%**  
**ORR 18%**

**PD-L1 TPS ≥50%**  
**ORR 30%**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>NR (1+ to 20+)</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>NR (2+ to 18+)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>6 (1+ to 9+)</td>
</tr>
</tbody>
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<tr>
<th>Time, months</th>
<th>Response, %</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
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<td>60</td>
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Herbst et al. ESMO Asia 2015.
Keynote 010: Overall Survival

OS, PD-L1 TPS ≥1% (Total Population)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI)</th>
<th>Rate at 1y</th>
<th>HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 2 mg</td>
<td>10.4 (9.4-11.9)</td>
<td>43.2%</td>
<td>0.71 (0.58-0.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg</td>
<td>12.7 (10.0-17.3)</td>
<td>52.3%</td>
<td>0.61 (0.49-0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.5-9.8)</td>
<td>34.6%</td>
<td>-</td>
<td>-</td>
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</table>

OS, PD-L1 TPS ≥50% Stratum

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<th>Median (95% CI)</th>
<th>Rate at 1y</th>
<th>HR* (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Pembrolizumab 2 mg</td>
<td>14.9 (10.4-18.9)</td>
<td>43.2%</td>
<td>0.54 (0.38-0.77)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg</td>
<td>17.3 (11.8-18.0)</td>
<td>52.3%</td>
<td>0.50 (0.36-0.70)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
<td>34.6%</td>
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KEYNOTE-024: A Randomised Open-Label Phase III Trial of Pembrolizumab Versus Platinum Based Chemotherapy in 1L Subjects With PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (NCT02142738)

**FIRST-LINE PEMBROLIZUMAB**

Positive PFS
To be presented ESMO Copenhagen October 2016

Brahmer et al. WCLC 2015.
CHECKMATE-026: A Randomised Open-Label Phase III Trial of Nivolumab Versus Investigator’s Choice Chemotherapy in 1L Subjects With Stage IV or Recurrent PD-L1+ NSCLC (NCT02142738)

- Advanced NSCLC
- No prior systemic therapy
- No sensitizing EGFR or ALK mutations or brain mets
- ECOG PS 0 or 1
- PD-L1 ≥5%

**Primary objective:**
PFS in PD-L1+ patients (with strong expression)

**Secondary objective:**
ORR, PFS in all PD-L1+ patients

**BREAKING NEWS:** Trial did not meet primary endpoint
Summary: Immunotherapy

• Current
  – Second Line Nivolumab 3 mg/kg q 2 w
  – Second Line PDL1 >1% Pembrolizumab 2 mg/kg q 3 w

• Advances
  – First Line PDL1 > 50% Pembrolizumab 200 mg q 3 w
• **Look for a Driver Mutation**
  - **EGFR**
    - Gefitinib, erlotinib,
    - Afatinib, dacomitinib
    - 3rd generation osimertinib, olmutinib
  - **ALK**
    - Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
  - **Wildtype**
    - Chemotherapy Never Forget

• **New advances** in the treatment of NSCLC
  - Immune checkpoint inhibitors
  - Evolving PDL1 biomarker
State of the Art 2016:
Making Lung Cancer a Chronic Disease

Thank you