Systemic Treatment of Metastatic Lung Cancer: Times are changing

Barbara Melosky, MD
Objectives

• Review how targeted therapies are used
• Discuss when/what pathological testing should be done
• Explore the present and future role for immunotherapy
• Highlight toxicities: How do you treat
Conflict of Interest

• Advisory Board:
  – Lilly, Astra Zeneca, Boehringer Ingelheim, Merck, BMS, Novartis, Roche, Pfizer
Conflict in My Life
Current Treatment: First Thing We Do Identify a Driver Mutation!

- EGFR
- ALK
- RARE MUTATIONS:
  - ROS, 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

77%

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

23%

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

MSKCC data
Non-Small Cell Lung Cancers – 2016

Non-Squamous Non-Small Cell Lung Cancers

- EGFR 15%
- KRAS 30%
- 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

Presented at ASCO Annual Meeting
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.

**IPASS: PFS**

- Gefitinib: 9.5 months
- Chemotherapy: 6.3 months
  - HR 0.48, 95% CI 0.36–0.64; \( P < 0.001 \)

**EURTAC: PFS**

- 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\textsuperscript{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

EURTAC Overall Survival

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

Fukuoka M et al. JCO. 2011;29:2886-2874.

## EGFR TKI First- and Second-Generation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reversibility</th>
<th>Targets (IC$_{50}$, nM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Generation</strong></td>
<td></td>
<td></td>
</tr>
<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><strong>Second-Generation</strong></td>
<td></td>
<td></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>
Afatinib: LUX-Lung 3 and LUX-Lung 6

Stage IIIIB (wet)/IV lung adenocarcinoma
EGFR mutation in tumour

Stratified by EGFR mutation
Del19/L858R/other

LUX-Lung 3
(n=345)

- Cisplatin + Pemetrexed

LUX-Lung 6
(n=364; Asian pts)

- Afatinib 40 mg/d
- Cisplatin + Gemcitabine
LUX-Lung 3 and LUX-Lung 6: PFS

Patients with common mutations

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 3(^1) (n=308) Afatinib vs Cis/Pem</th>
<th>LUX-Lung 6(^2,3) (n=324) Afatinib vs Cis/Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>13.6 mo vs 6.9 mo</td>
<td>11.0 mo vs 5.6 mo</td>
</tr>
<tr>
<td>HR for PFS</td>
<td>0.47, (P&lt;0.0001)</td>
<td>0.25, (P&lt;0.0001)</td>
</tr>
</tbody>
</table>

PRESPECIFIED ENDPOINT

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

**LUX-Lung 3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at risk</th>
<th>Median, months</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>(n=112)</td>
<td>33.3</td>
<td>0.54 (0.36–0.79)</td>
<td>P=0.0015</td>
</tr>
<tr>
<td>Cis/Pem</td>
<td>(n=57)</td>
<td>21.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LUX-Lung 6**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at risk</th>
<th>Median, months</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>(n=124)</td>
<td>31.4</td>
<td>0.64 (0.44–0.94)</td>
<td>P=0.0229</td>
</tr>
<tr>
<td>Cis/Gem</td>
<td>(n=62)</td>
<td>18.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:
- Afatinib: 124 122 118 115 106 99 90 80 73 69 59 39 16 8 1 0
- Cis/Gem: 62 58 53 49 44 35 30 28 26 21 18 11 4 3 0 0

Estimated OS Probability

- **Afatinib:** 33.3 months
- **Cis/Pem:** 21.1 months
- **Afatinib:** 31.4 months
- **Cis/Gem:** 18.4 months

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

*Park et al. ESMO Asia. December 2015.*
LUX-Lung 7: PFS

Objective response and duration of response (independent review)

- ORR 70% vs 56%
- HR 0.73, p=0.0165

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>

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>-</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

No case of ILD.

4 case of ILD.

Park et al. ESMO Asia, 2015.
AFATINIB

Rash
Clindamycin 2%  Hydrocortisone 2% cream
Minocycline 100 mg bid for 4 weeks
Paronychia

- **Bethamethasone Valerate**
  - Apply bid to nail bed
  - M: 60g Rx 3

- **Liquid bandaid**

Mucositis

- **Kenalog Orobase 0.1%**
  - Apply bid to mouth
  - M: 1 bottle Rx 3
PROPHYLACTIC MINOCYCLINE

PanCanadian Rash Trial with EGFR Inhibitors

Optimal treatment of rash secondary to erlotinib

Barbara Melosky, Helen Anderson, Ron Burkes, Quincy Chu, Desiree Hao, Vincent Ho, Cheryl Ho, Wendy Lam, Christopher Lee, Natasha Leighl, Nevin Murray, Sophie Sun, Robert Winston, Janessa Laskin

JCO March 2016
## Incidence of Rash and Time to Severe Grade 3 Rash

<table>
<thead>
<tr>
<th></th>
<th>Incidence of any rash n (%)</th>
<th>Incidence of Grade 3 rash n (%)</th>
<th>P value</th>
<th>Mean (days) to Grade 3 rash onset</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1 (N=50)</td>
<td>84%</td>
<td>9.5%</td>
<td>P = 0.034 Arm 1 vs 3</td>
<td>17.4</td>
<td>P = 0.0147</td>
</tr>
<tr>
<td>Prophylactic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM 2 (N=50)</td>
<td>84%</td>
<td>14.3%</td>
<td>P = 0.065 Arm 2 vs 3</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Arm 3 (N=50)</td>
<td>82%</td>
<td>34.1%</td>
<td></td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

JCO March 2016
LUX-Lung 7: Impact of Afatinib Dose Modification on PFS

<table>
<thead>
<tr>
<th></th>
<th>&lt;40 mg</th>
<th>≥40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>12.8</td>
<td>11.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.34 (0.90–2.00)</td>
<td>0.1440</td>
</tr>
</tbody>
</table>

Estimated PFS probability

Time of progression-free survival (months)

- <40 mg
- ≥40 mg
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.

LUX-Lung 2, 3, & 6: AFATINIB
Uncommon Mutations

<table>
<thead>
<tr>
<th>Tumour Shrinkage in Uncommon Mutations (independent review)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum change from baseline (%)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>De novo T790M (n = 14)</strong></td>
</tr>
<tr>
<td><strong>Exon 20 insertions (n = 20)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Other point mutations or duplications in exons 18–21 (n = 33)</strong></td>
</tr>
<tr>
<td>L861Q, G719X, G719X+S768I, G719X+L861Q, E709G or V+L858R, S768I+L858R,</td>
</tr>
<tr>
<td>S768I, L861P, P848L, R776H+L858R, L861Q+Del19, K739_1744dup6</td>
</tr>
</tbody>
</table>

AFATINIB
Molecular Mechanisms of Acquired Resistance to EGFR TKI (N = 155)

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reversibility</th>
<th>Targets (IC₅₀, nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Reversible</td>
<td>EGFR (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 (1830)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Reversible</td>
<td>EGFR (0.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 (512)</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>Irreversible</td>
<td>EGFR (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 (46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER4 (74)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Irreversible</td>
<td>EGFR (0.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 (14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER4 (1.0)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td></td>
<td>EGFR (17)</td>
</tr>
<tr>
<td>Olmutinib</td>
<td></td>
<td>TARGET T790</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGFR (9)</td>
</tr>
</tbody>
</table>
**PFS AURA Trial – 2nd-Line Acquired T790 M+**

ELCC Geneva 2016

Yang JCH, et al. ELCC 2016; Abstract LBA2_PR.

**AURA pooled Ph II**

- **Probability of PFS**: 441 332 271 205 161 38 0
- **Number of patients at risk**: Osimertinib 80 mg
  - 0 3 6 9 12 15 18 21 24 27

**Best percentage change from baseline in target lesion size (%):**

- Complete response
- Partial response
- Stable disease
- Progressive disease
- Not evaluable

**PFS 11 months**

- **Osimertinib 80 mg**: 66%
## 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>
<tr>
<td>Select AEs</td>
<td></td>
</tr>
<tr>
<td>ILD (grouped terms)†</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>0</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>0</td>
</tr>
</tbody>
</table>

**NO RASH or DIARRHEA**

*ILD 2.9 % 35/1200 pts

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3,4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>6</td>
<td>16</td>
<td>4</td>
</tr>
</tbody>
</table>
January 20, 2016

Treatment:
Stop drug
High dose iv steroids
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 EGFR T790M From the Blood?
High ORR in Patients With Tumour or Plasma-Positive T790M Patients Treated With Osimertinib

**Tumour T790M positive (n=173)**

- ORR (95% CI): 62% (54, 70)
- Yellow: Plasma T790M positive
- Green: Plasma T790M negative
- Gray: Plasma T790M unknown

**Plasma T790M positive (n=164)**

- ORR (95% CI): 63% (55, 70)
- Blue: Tumour T790M positive
- Red: Tumour T790M negative
- Gray: Tumour unknown

Plasma 62%
Tumour 63%

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

<table>
<thead>
<tr>
<th></th>
<th>Median (Months)</th>
<th>95% CI</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>4.1</td>
<td>3.9–4.4</td>
<td>0.1, 22.7</td>
</tr>
<tr>
<td>Tissue</td>
<td>5.0</td>
<td>4.2–6.0</td>
<td>0.1, 22.7</td>
</tr>
<tr>
<td>Urine</td>
<td>4.3</td>
<td>4.0–6.2</td>
<td>0.1, 22.2</td>
</tr>
</tbody>
</table>

Urine T790M: The Ultimate Liquid Biopsy!
Summary: EGFR

• Current:
  – First line: Gefitinib/ Afatinib

• Recent Advances:
  ▪ LUX Lung 7 Afatinib
  ▪ Osimertinb Aura Trial 2nd Line T790M+: PFS 11 months
  ▪ T790: Plasma may be as accurate as tumor
  ▪ T790: Urine may be accurate
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%

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>

**Graph**: Kaplan-Meier plot of progression-free survival (PFS) probability.

- **Crizotinib** pathway shows a higher PFS probability compared to chemotherapy.
- **Table**: Summary of events and median PFS.
- **HR**: Hazard ratio with a 95% confidence interval.
# Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=172), n (%)</th>
<th>Chemotherapy (n=171), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td><strong>Vision disorder</strong></td>
<td>103 (60)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>103 (60)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>94 (55)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>80 (47)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>73 (42)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Elevated transaminases</strong></td>
<td>66 (38)</td>
<td>27 (16)</td>
</tr>
<tr>
<td><strong>Edema</strong></td>
<td>54 (31)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Upper respiratory infection</strong></td>
<td>44 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Dysgeusia</strong></td>
<td>44 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>37 (22)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>46 (27)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Alopecia</strong></td>
<td>14 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>23 (13)</td>
<td>7 (4)</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>15 (9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Characteristic Visual Effects with Crizotinib

- ‘Trails’ from lights in peripheral vision in low light conditions (e.g. dawn and dusk)¹
- Overlapping shadows or after-images²

- At edges of vision in low light conditions:
  - Image persistence
  - Flashes of light, which do not appear to be connected to a real light source
  - Flipped registration from high contrast images (e.g. stripes)

CNS Sanctuary

- Brain metastases

MRI Detection of BMs

Solitary lesion

Oligometastases

Multiple BMs

Should SRS Be Followed by WBRT?

Primary endpoints:

- Decline in Karnofsky performance score of WBRT 97.7 vs. 98.0 (p = 0.0007)
- Persistence of grade 2 or greater cognitive impairment at 3 months

**N0574 OS vs. ARM**

- Arm: SRS
- Arm: SRS + WBRT: HR = 1.02 (95% CI: 0.75, 1.38), p = 0.92

Presented by: Paul Brown, MD

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

*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*

#PFS event

Presented by: Dong-Wan Kim
STANDARD OF CARE SECOND LINE US
RR 61.8%

ESMO 2014
ASCEND 1: PFS

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

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 0 0
NSCLC ALKi naïve 83 69 55 43 32 17 6 2 0 0 0 0 0 0 0
All NSCLC 246 177 134 95 61 30 8 3 0 0 0 0 0 0 0
# Results: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>All Grades, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>114 (81.4)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>112 (80.0)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>88 (62.9)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>61 (43.6)</td>
<td>24 (17.1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>57 (40.7)</td>
<td>5 (3.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (36.4)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>48 (34.3)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>45 (32.1)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>44 (31.4)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>40 (28.6)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>30 (21.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29 (20.7)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>29 (20.7)</td>
<td>8 (5.7)</td>
</tr>
</tbody>
</table>

41.4% patients required dose adjustment or interruption
ASCEND-5

Stage IIIB/IV ALK+ NSCLC
PD at enrollment after prior crizotinib and chemotherapy
(1 platinum doublet)

236 patients
Stratified: PS; brain metastases

Randomize 1:1

Chemotherapy (INV choice):
PEM 500 mg/m^2
or
Docetaxel 75 mg/m^2

Ceritinib 750 mg/day
• Continuous oral dosing
• Once daily
• 21-day cycle

PEM maintenance
500 mg/m^2 q21d

Optional

PD (BIRC real time) → Ceritinib 750 mg

Optional

crossover

PD

Alectinib in Patients with Crizotinib-resistant ALK+ NSCLC Phase II

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

Sum of longest diameter, maximum decrease from baseline (%)

RR 61%
Alectinib in Patients With Measurable CNS Metastases

Crizotinib and ceritinib are P-gp substrates; alectinib is not

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

Primary Endpoint: PFS

FIRST-LINE

300 mg bid

Alectinib
(N=103)

Crizotinib
(N=104)

Events, n (%) 25 (24.3%) 58 (55.8%)
Median, mo [95% CI] NR [20.3 - NR] 10.2 [8.2 - 12.0]
P-value <0.0001
HR [99.6826% CI] 0.34 [0.17 - 0.71]

PFS NR!
HR .34
P<0.0001
**ALTA: Brigatinib Second Line**

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

**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

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

**Randomized 1:1**

- Brigatinib 90 mg qd  \(N = 112\)
  - Stratified by:
    - Brain metastases at baseline
    - Best response to prior crizotinib

- Brigatinib 180 mg qd*  \(N = 110\)
  - *With 7-day lead-in at 90 mg

- PD requiring an alternate therapy
- Intolerable toxicity
- Other reasons for discontinuation
Brigatinib Antitumour Activity by Arm

90 mg qd

ORR 45%

180 mg qd

ORR 54%

- Progressive disease
- Stable disease
- 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
|| Category includes single responses that were not confirmed

Data as of February 29, 2016
PFS by Arm

Median PFS exceeds 1 year (12.9 months) with 180 mg brigatinib

<table>
<thead>
<tr>
<th></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;sup&gt;1&lt;/sup&gt; N = 28</td>
<td>57% N = 35</td>
<td>67% 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
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)
## Treatment-Related Adverse Events in ≥15% of Patients Treated at the RP2D

**LORLATINIB**

<table>
<thead>
<tr>
<th>Adverse event</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
Summary: ALK

• Current:
  ▪ First Line: Crizotinib
  ▪ Second Line: Ceritinib/ Alectinib

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

RARE MUTATIONS

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

Presented at: ASCO Annual Meeting
Response in Patients with Advanced ROS1+ NSCLC

Crizotinib

Best overall response
- PD
- SD
- PR
- CR

Best change from baseline (%)

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>SD</th>
<th>PR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>43+</td>
<td>9</td>
<td>24</td>
<td>25+</td>
</tr>
<tr>
<td>8+</td>
<td>15+</td>
<td>28+</td>
<td>45+</td>
<td>44+</td>
</tr>
<tr>
<td>12</td>
<td>16+</td>
<td>44+</td>
<td>54+</td>
<td>80+</td>
</tr>
<tr>
<td>18</td>
<td>44+</td>
<td>54+</td>
<td>80+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†
Non-Small Cell Lung Cancers – 2015

RARE MUTATIONS

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%

BRAF 77%

Squamous

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

Unknown mutation 60%

MSKCC data

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual Meeting
Maximum Change in Target Lesion by Best Investigator-Assessed Confirmed Response

BRAF V600: Dabrafenib and Trametinib
ORR 63% PFS 8.6 months

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

Not Evaluable (NE) patients did not have a follow-up scan required for confirmation.
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

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

**HER2**

**Squamous**

- **FGFR1 amp** 20%
- **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
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%

23%

- 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

Vandetanib for 8 weeks
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

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

Squamous

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

MSKCC data

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual Meeting
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}
Exon 14 (regulatory domain)

MET X14 Skipped
CRIZOTINIB

Baseline

8-week follow-up crizotinib

Patient 7

CABOZATINIB

Baseline

4-week follow-up cabozantinib

Patient 2
Non-Small Cell Lung Cancers – 2015

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

MSKCC data
Summary: RARE MUTATION

• ROS (1%)
  – Crizotinib

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

WILD TYPE 77%

Squamous 23%

- FGFR1 amp 20%
- KRAS 6%
- EGFR mut 5%
- DDR2 4%
- PIK3CA 3%
- BRAF 2%
- Unknown mutation 60%
Overall Survival in Squamous Cell Carcinoma

**Overall Survival Probability**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Cis/Pem (N=244)</th>
<th>Cis/Gem (N=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>0.1</td>
<td>0.90</td>
<td>0.84</td>
</tr>
<tr>
<td>0.2</td>
<td>0.79</td>
<td>0.72</td>
</tr>
<tr>
<td>0.3</td>
<td>0.68</td>
<td>0.60</td>
</tr>
<tr>
<td>0.4</td>
<td>0.58</td>
<td>0.51</td>
</tr>
<tr>
<td>0.5</td>
<td>0.49</td>
<td>0.43</td>
</tr>
<tr>
<td>0.6</td>
<td>0.41</td>
<td>0.36</td>
</tr>
<tr>
<td>0.7</td>
<td>0.34</td>
<td>0.29</td>
</tr>
<tr>
<td>0.8</td>
<td>0.28</td>
<td>0.24</td>
</tr>
<tr>
<td>0.9</td>
<td>0.22</td>
<td>0.18</td>
</tr>
<tr>
<td>1.0</td>
<td>0.18</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**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 (95% CI): 12.6 mo (10.7-13.6)
- Adjusted HR (95% CI): 0.84 (0.71-0.99)
- p-value: 0.033*

Gemcitabine/Cisplatin (n=411)

- Median (95% CI): 10.9 mo (10.2-11.9)
- Adjusted HR (95% CI): 0.84 (0.71-0.99)
- p-value: 0.033*

ASCO 2012
PARAMOUNT: Overall Survival

HR: 0.78 (95% CI: 0.64–0.96)
Log-rank $P = 0.0195$
Immunotherapy
Targeting PD-1 Pathways

**Periphery**

- Dendritic cell
- T cell
- Anti-CTLA-4

**CTLA-4 pathway**

**Tumour microenvironment**

- T cell
- PD-L1

**PD-1 pathway**

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

- CTLA-4 pathway
- PD-1 pathway

# Clinical Development of Inhibitors of PD-1 Immune Checkpoint

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Molecule</th>
<th>Company</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Phase II, III multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab CT-011</td>
<td>Humanized IgG1 mAb</td>
<td>CureTech</td>
<td>Phase II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Humanized IgG4 mAb</td>
<td>Merck</td>
<td>Phase I-II</td>
</tr>
<tr>
<td></td>
<td>AMP-224</td>
<td>Recombinant PD-L2-Fc fusion protein</td>
<td>GlaxoSmithKline</td>
<td>Phase I</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Avelumab</td>
<td>Fully human IgG4 mAb</td>
<td>EMD Serono</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>Engineered human IgG1 mAb</td>
<td>Astra Zeneca</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>Engineered human IgG1 mAb</td>
<td>Roche</td>
<td>Phase I-II</td>
</tr>
</tbody>
</table>

Adapted from Dr. J. Brahmer ASCO 2013
Overall Survival

**CheckMate 017**
SQ NSCLC

- Nivolumab
- Docetaxel

1-yr OS rate = 51%

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

**CheckMate 057**
Non-SQ NSCLC

- Nivolumab
- Docetaxel

1-yr OS rate = 39%

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

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

CheckMate 017

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

CheckMate 057

- ORR 19%
  - 52% (29 of 56 patients with ongoing response)
  - 14% (5 of 36 patients with ongoing response)

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

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Molecule</th>
<th>Company</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab-BMS-936558</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Phase II, III multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Humanized IgG1 mAb</td>
<td>CureTech</td>
<td>Phase II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Keytruda</td>
<td>Humanized IgG4 mAb</td>
<td>Merck</td>
<td>Phase I-II</td>
</tr>
<tr>
<td></td>
<td>AMP-224</td>
<td>Recombinant PD-L2-Fc fusion protein</td>
<td>GlaxoSmithKline</td>
<td>Phase I</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Avelumab</td>
<td>Fully human IgG4 mAb</td>
<td>EMD Serono</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>Engineered human IgG1 mAb</td>
<td>MedImmune</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>Engineered human IgG1 mAb</td>
<td>Genentech</td>
<td>Phase I-II</td>
</tr>
</tbody>
</table>

Adapted from Dr. J. Brahmer ASCO 2013
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

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 status (TPS ≥50% vs 1%-49%)

Pembrolizumab
- 2 mg/kg IV Q3W for 24 months
- 10 mg/kg IV Q3W for 24 months

Docetaxel
- 75 mg/m² Q3W per local guidelines

End points in the total population and TPS ≥50% stratum
- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

Herbst et al. ESMO Asia. LBA3.
**Duration of Response**

**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>
<tr>
<td>Pembro 2 mg/kg</td>
<td>NR (1+ to 17+)</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>NR (2+ to 18+)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8 (2+ to 9+)</td>
</tr>
</tbody>
</table>

Herbst et al. ESMO Asia 2015.
Keynote 010: Overall Survival

OS, PD-L1 TPS ≥1% (Total Population)

- Treatment Arm: Pembrolizumab 2 mg/kg
  - Median OS: 10.4 (9.4-11.9) months
  - Rate at 1 year: 43.2%
  - HR: 0.71 (0.58-0.88), p < 0.0008
- Treatment Arm: Pembrolizumab 10 mg/kg
  - Median OS: 12.7 (10.0-17.3) months
  - Rate at 1 year: 52.3%
  - HR: 0.61 (0.49-0.75), p < 0.0001
- Treatment Arm: Docetaxel
  - Median OS: 8.5 (7.5-9.8) months
  - Rate at 1 year: 34.6%

OS, PD-L1 TPS ≥50% Stratum

- Treatment Arm: Pembrolizumab 2 mg/kg
  - Median OS: 14.9 (10.4-16.9) months
  - Rate at 1 year: 52.3%
  - HR: 0.54 (0.38-0.77), p < 0.0001
- Treatment Arm: Pembrolizumab 10 mg/kg
  - Median OS: 17.3 (11.8-22.8) months
  - Rate at 1 year: 62.3%
  - HR: 0.50 (0.36-0.70), p < 0.0001
- Treatment Arm: Docetaxel
  - Median OS: 8.2 (5.4-10.7) months
  - Rate at 1 year: 28.5%

Herbst et al. ESMO Asia. LBA3.
irAEs Immune Therapy

If not detected early, may result in more serious immune-mediated side effects.
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)

**Patients**
- Advanced or metastatic NSCLC
- No prior systemic therapy
- No *EGFR* sensitizing mutation or *ALK* translocation
- ECOG PS 0 to 1
- PD-L1 TPS ≥50%

**Stratification by:**
- ECOG PS (0 vs 1)
- Geographic region (East Asia vs non-East Asia)
- Histology (squamous vs nonsquamous)

**Randomize 1:1 N = 300**

**Pembrolizumab 200 mg IV Q3W**

**Optional Crossover**

**Positive OS**

**Given until progression, intolerable toxicity, investigator decision, or completion of 35 cycles**

**Follow-up for safety (≤90 days)**

**Follow-up for survival (every 2 months)**

**Investigator choice of chemotherapy for 4-6 cycles**

**Disease progression**

**Positive PFS**

To be presented ESMO Copenhagen October 2016

Brahmer et al. WCLC 2015.
FIRST-LINE NIVOLUMAB

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

Negative PFS
To be presented ESMO Copenhagen October 2016

Brahmer et al. WCLC 2015.
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
State of the Art NSCLC 2016

• **Look for a Driver Mutation**
  – EGFR
    ▪ Gefitinib, afatinib
    ▪ 3rd generation osimertinib
  – ALK
    ▪ Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib

• **Wildtype**
  ▪ Chemotherapy Never Forget

• **Immune checkpoint inhibitors**
  – Evolving PDL1 biomarker
Conclusion

Systemic Treatment of Metastatic Lung Cancer: Times are changing

Making Lung Cancer a Chronic Disease