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

Barbara Melosky
CONFLICT IN MY LIFE
• 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

Driver, NO TT = 2.4 ys

Driver, TT = 3.5 ys

NO driver = 2.1 ys
Non-Small Cell Lung Cancers – 2016

Non-Squamous Non-Small Cell Lung Cancers

Squamous

77%

EGFR

KRAS 30%

Unknown mutation 40%

EGFR 15%

ALK 5%

MET 4%

BRAF/PIK3CA 2%

HER2/MEK 2%

ROS1 2%

RET 1%

23%

FGFR1 amp 20%

EGFR mut 5%

KRAS 6%

DDR2 4%

PIK3CA 3%

BRAF 2%

Unknown mutation 60%

MSKCC data

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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.

• 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\textsuperscript{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\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 (0.65-1.68), \( P = 0.8702 \)
    - Median OS: 19.3 months vs 19.5 months


Fukuoka M et al. JCO. 2011;29:2866-2874.
<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>Afatinib</td>
<td>Irreversible</td>
<td>EGFR (0.5) HER2 (14) HER4 (1.0)</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>
</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® EGFR29a RGQ PCR)

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

**LUX-Lung 3**
(n=345)

- Cisplatin + Pemetrexed
  - 75 mg/m² + 500 mg/m²
  - IV q21d, up to 6 cycles

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

- Afatinib
  - 40 mg/d

- Cisplatin + Gemcitabine
  - 75 mg/m² + 1000 mg/m²
  - D1, D8
  - IV q21d, up to 6 cycles

**Primary end point:** PFS (RECIST 1.1, independent review)

**Secondary end points:** OS, PRO, ORR, DCR, DOR, tumour shrinkage, safety

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aEGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, L858R, G719S, G719A and G719C (or G719X), S768I.
bDose 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.
cTumour assessments: q6 weeks until week 48 and q12 weeks thereafter until progression/start of new therapy.
dPatient-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

*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) vs **Cis/Pem** (n=104)

- **Median, mo**: Afatinib 31.57, Cis/Pem 28.16
- **HR (95% CI)**: 0.78 (0.58-1.06)
- **P-value**: 0.1090

**HR .78**

<table>
<thead>
<tr>
<th>Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>203</td>
</tr>
<tr>
<td>104</td>
</tr>
</tbody>
</table>

LUX-Lung 6

**Afatinib** (n=216) vs **Cis/Gem** (n=108)

- **Median, mo**: Afatinib 23.6, Cis/Gem 23.5
- **HR (95% CI)**: 0.83 (0.62-1.09)
- **P-value**: 0.1756

**HR .83**

<table>
<thead>
<tr>
<th>Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>216</td>
</tr>
<tr>
<td>108</td>
</tr>
</tbody>
</table>

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>

Kato T et al. ISPOR 2015; PCN40.
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.

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

PFS by independent review

HR 0.73  P=0.0165

Median PFS (months)
Afatinib (n=160)  Gefitinib (n=159)
11.0           10.9

HR (95% CI)       0.73 (0.57–0.95)

p value
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)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTF (months)</td>
<td>13.7</td>
<td>11.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.58–0.92)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0073</td>
<td></td>
</tr>
</tbody>
</table>

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, 69, 56, 43, 30, 21, 11, 6, 6, 2, 2, 0

Probability of being on-treatment over time (months).
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

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

![Graph showing estimated overall survival probability over time for Afatinib and Gefitinib.]

- **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

- **Median, mo:**
  - Afatinib: 27.9
  - Gefitinib: 25.0

- **HR (95% CI):**
  - Afatinib: 0.87 (0.65-1.15)
  - Gefitinib: 0.33

- **P-value:**
  - 0.33

Data on file
SEPTEMBER 1ST 2016

Mature OS at ESMO
October 2016!
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&lt;sup&gt;a&lt;/sup&gt;</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=18)</td>
<td>14 (78)</td>
<td><strong>13.8 (6.8–NE)</strong></td>
<td><strong>26.9 (16.4–NE)</strong></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=16)</td>
<td>9 (56)</td>
<td><strong>8.2 (4.5–16.6)</strong></td>
<td><strong>16.9 (15.3–21.6)</strong></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=8)</td>
<td>8 (100)</td>
<td><strong>14.7 (2.6–NE)</strong></td>
<td><strong>NE (3.4–NE)</strong></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

Tumour Shrinkage in Uncommon Mutations (independent review)

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.

- De novo T790M (n = 14)
- Exon 20 insertions (n = 20)
- Other point mutations or duplications in exons 18–21 (n = 33)

* N=67 (8 patients were not included due to insufficient data).

<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>
</tbody>
</table>

Note: EGFR = Epidermal Growth Factor Receptor, HER = Human Epidermal Growth Factor Receptor, IC₅₀ = Inhibitory Concentration 50%
PFS AURA Trial – 2nd-Line Acquired T790 M+

PFS 11 months

Number of patients at risk:
- Osimertinib 80 mg

Probability of PFS

Best percentage change from baseline in target lesion size (%)
- Complete response
- Partial response
- Stable disease
- Progressive disease
- Not evaluable

Complete response

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><strong>ILD (grouped terms)</strong>^a</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
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

<table>
<thead>
<tr>
<th>Sample Type</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!
Brain Metastases and Leptomeningeal disease

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

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

Dose escalation

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

AZD3759

Osimertinib 160 mg QD

160 mg not 80 mg
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>
<th>Confirmed*</th>
<th>Unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responding</td>
<td>7 (33)</td>
<td>33%</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (43)</td>
<td>43%</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td>2 (10)</td>
<td></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

Neurological status at baseline

Normal (N=11) | Abnormal (N=10)

10 | 5
1 | 1
1 | 3

160 mg od
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

- 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%
**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>

No. at risk

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>172</td>
<td>171</td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td>105</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>36</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>20</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>25</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PFS Probability (%)

![Graph showing PFS probability over time for Crizotinib and Chemotherapy groups]
CNS Sanctuary

- Brain metastases

MRI Detection of BMs

Solitary lesion
Oligometastases
Multiple BMs

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.
ASCEND 1: PFS

Probability (%)

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

STANDARD OF CARE SECOND LINE US
Median: 9.03 (95% CI 6.93, 10.97)
(95% CI 11.10, non-estimable)

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 0

ESMO 2014
• 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%

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

*With 7-day lead-in at 90 mg

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

180 mg qd†

ORR 45%

ORR 54%

Best Change From Baseline in Target Lesions (%)

-100 -80 -60 -40 -20 0 20 40

Progressive disease Stable diseasePartial 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>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</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>0.35–0.86</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>Ceritinib¹ N= 163</th>
<th>Alectinib² N=138</th>
<th>Brigatinib³ N = 110</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design/A</strong></td>
<td><strong>Assessment</strong></td>
<td><strong>Phase I/II</strong></td>
<td><strong>Phase 2</strong></td>
</tr>
<tr>
<td><strong>Investigator/BIRC</strong></td>
<td></td>
<td><strong>BIRC</strong></td>
<td><strong>Investigator</strong></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%* 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
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></td>
<td>0.34 [0.17 - 0.71]</td>
</tr>
</tbody>
</table>

Progression-free survival rate (%)

- Alectinib
  - 103 patients at risk
  - Events: 25
  - Median PFS: NR
  - HR: 0.34 (0.17 - 0.71)

- Crizotinib
  - 104 patients at risk
  - Events: 58
  - Median PFS: 10.2 months
  - HR: NR

Time (months)

- No. of patients at risk:
  - Alectinib: 103, 93, 76, 49, 36, 27, 9, 1
  - Crizotinib: 104, 86, 65, 40, 21, 14, 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 \(\sim\)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**

**Graph:**
- **Ongoing treatment**
- **1 prior TKI**
- **≥2 prior TKI**

**Statistical Data:**
- 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)

**Patients:**
- ALK, anaplastic lymphoma kinase; CI, confidence interval; PFS, progression-free survival; ROS1, c-cnt 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
Summary: ALK

• 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%

Squamous

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

Unknown mutation 60%

RARE MUTATIONS

BRAF

MSKCC data
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

Non-Squamous

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

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
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

- Unknown mutation: 77%
  - RET 1%
  - KRAS 30%
  - EGFR 15%
  - ALK 5%
  - MET 4%
  - BRAF/PIK3CA 2%
  - HER2/MEK 2%
  - ROS1 2%

- Squamous
  - Unknown mutation: 23%
  - FGFR1 amp 20%
  - KRAS 6%
  - EGFR mut 5%
  - DDR2 4%
  - PIK3CA 3%
  - BRAF 2%

MSKCC data

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.
Vandetanib 18 Patients
ORR 17% SD 28%
Se-Hoon Lee et al

ASCO 2016
Non-Small Cell Lung Cancers – 2015

Non-Squamous Non-Small Cell Lung Cancers

- **Unknown mutation**: 40%
- **KRAS**: 30%
- **EGFR**: 15%
- **ALK**: 5%
- **MET**: 4%
- **BRAF/PIM3CA**: 2%
- **HER2/MEK**: 2%
- **ROS1**: 2%
- **RET**: 1%

Squamous

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

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

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

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

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

77% WILD TYPE

Squamous

23%

Unknown mutation 60%

Unknown mutation 60%

KRAS 30%

KRAS 6%

EGFR 15%

EGFR mut 5%

ALK 5%

BRAF 5%

MET 4%

MET 4%

BRAF/PIK3CA 2%

BRAF/PIK3CA 2%

HER2/MEK 2%

HER2/MEK 2%

ROS1 2%

ROS1 2%

RET 1%

RET 1%

FGFR1 amp 20%

FGFR1 amp 20%

MSKCC data
Overall Survival in Squamous Cell Carcinoma

Overall Survival Time (months) in Squamous Patients

Overall Survival Probability

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed/Cisplatin</td>
<td>12.6 mo (10.7-13.6)</td>
<td>0.84 (0.71-0.99)</td>
<td>0.033*</td>
</tr>
<tr>
<td>Gemcitabine/Cisplatin</td>
<td>10.9 mo (10.2-11.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)

PEMETREXED/CISPLATIN. PEM MAINTENANCE
Targeting PD-1 Pathways


Periphery

Dendritic cell

T cell

MHC

TCR

B7

CD28

CTLA-4

Anti-CTLA-4

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

Tumour microenvironment

T cell

PD-L1

CTLA-4 pathway

PD-1 pathway

Tumour cell

CTLA-4

CTLA-4 pathway

PD-1 pathway

PD-L1

### 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 (Opdivo)</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>
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</tbody>
</table>

Adapted from Dr. J. Brahmer ASCO 2013
Overall Survival

CheckMate 017
SQ NSCLC

CheckMate 057
Non-SQ NSCLC

1-yr OS rate=51%
1-yr OS rate=39%

1-yr OS rate=51%
1-yr OS rate=39%

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

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

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**

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

<table>
<thead>
<tr>
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<th>CheckMate 017 (Squameuse)</th>
<th>CheckMate 057 (Nonsquamous)</th>
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<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>
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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>Phase I-II</td>
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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

Screened 33% negative

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

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

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

R
1:1:1

Q3 w
Q3 w

Herbst et al. ESMO Asia. LBA3.
Duration of Response (RECIST v1.1, Central Review)

PD-L1 TPS ≥1%  ORR 18%

PD-L1 TPS ≥50%  ORR 30%

Treatment Arm | Median (range), mo
---|---
Pembro 2 mg/kg | NR (1+ to 20+)
Pembro 10 mg/kg | NR (2+ to 18+)
Docetaxel | 6 (1+ to 9+)

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), mo</th>
<th>Rate at 1y</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 2 mg/kg</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/kg</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>
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**OS, PD-L1 TPS ≥50% Stratum**

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<th>HR (95% CI)</th>
<th>P</th>
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<tr>
<td>Pembrolizumab 2 mg/kg</td>
<td>14.9 (13.0-19.6)</td>
<td>58.5%</td>
<td>0.56 (0.48-0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg/kg</td>
<td>17.3 (11.8-NR)</td>
<td>64.3%</td>
<td>0.50 (0.36-0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
<td>34.6%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Herbst et al. ESMO Asia. LBA3.
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%

Randomize 1:1
N = 300

Pembrolizumab 200 mg IV Q3W
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)

Optional Crossover
Positive OS

Investigator choice of chemotherapy for 4-8 cycles
Disease progression
Follow-up for safety (≤90 days)
Follow-up for survival (every 2 months)

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