Conversations in Oncology
November 12-13
Kerry Hotel
Pudong, Shanghai
China
State of the Art: Recent Therapeutic Advances in Lung Cancer 2016

Barbara Melosky, MD
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, ASCO Chicago 2016, and ESMO Copenhagen 2016**
Current Treatment: First Thing We Do Is 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

Driver, NO TT = 2.4 ys

Driver, TT = 3.5 ys

NO driver = 2.1 ys


Non-Squamous Non-Small Cell Lung Cancers

- KRAS 30%
- EGFR 15%
- Unknown mutation 40%
- ALK 5%
- MET 4%
- BRAF/PK3CA 2%
- HER2/MEK 2%
- ROS1 2%
- RET 1%

Squamous

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

• Gefitinib: 9.5 months
• Chemotherapy: 6.3 months
  - HR 0.48; 95% CI 0.36-0.64; P<0.001

• 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 population²
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

Overall Survival

EURTAC Overall Survival

OS
Erlotinib (n = 86)
Chemo (n = 87)

19.3
19.5
1.04 (0.65-1.68),
P = 0.8702

HR 1.04

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(_{50}), 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>
</tbody>
</table>
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

Afatinib
40 mg/db

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

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

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

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.


*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I; Dose escalated to 50 mg if limited AEs observed in cycle 1. Dose reduced by 10-mg decrements in case of related G3 or prolonged G2 AE; Tumour assessments: q6 weeks until week 48 and q12 weeks thereafter until progression/start of new therapy; 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.

**LUX-Lung 3**: n=345
**LUX-Lung 6**: n=364 (Asian pts)
LUX-Lung 3 and LUX-Lung 6: Significant Improvement in PFS

Patients with common mutations*

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 3 (n=308) Afatinib vs Cis/Pem</th>
<th>LUX-Lung 6 (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>

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

PFS = progression-free survival.


13.6 mo. in LL3
11.0 mo in LL6
LUX-Lung 3 and LUX-Lung 6: OS in Del19 Subgroup

**LUX-Lung 3**

- **Afatinib** (n=112)
  - Median, months: 33.3
  - HR (95% CI): 0.54 (0.36–0.79)
  - *P*-value: 0.0015

- **Cis/Pem** (n=57)
  - Median, months: 21.1

**LUX-Lung 6**

- **Afatinib** (n=124)
  - Median, months: 31.4
  - HR (95% CI): 0.64 (0.44–0.94)
  - *P*-value: 0.0229

- **Cis/Gem** (n=62)
  - Median, months: 18.4

---

**Estimated OS Probability**

- **Afatinib**
- **Cis/Pem**

**Time (Months)**: 0 3 6 9 12 18 21 24 27 30 33 36 39 42 45 48 51

**No. at risk:**

- **Afatinib**
  - 112 108 105 102 96 93 80 82 72 62 58 51 34 30 21 6 1 0
- **Cis/Pem**
  - 57 55 46 43 37 33 27 25 22 20 16 10 6 1 1 0 0

- **Afatinib**
  - 124 122 118 115 106 99 90 80 73 69 59 39 16 8 1 0 0
- **Cis/Gem**
  - 62 58 53 49 44 35 30 28 26 21 18 11 4 3 0 0

IMPRESSIVE

**Estimated OS Probability**

- **Afatinib**
- **Cis/Gem**

**Time (Months)**: 0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45

---

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>

Central or local test.

†Dose modification to 50, 30, 20 mg permitted in line with prescribing information.

LUX-Lung 7: PFS

Objective response and duration of response (independent review)

- ORR 70% vs 56%

<table>
<thead>
<tr>
<th></th>
<th>Axitinib (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>(7.4–10.5)</td>
</tr>
</tbody>
</table>

PFS by independent review

<table>
<thead>
<tr>
<th></th>
<th>Axitinib (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>

ORR 70% vs 56%

HR 0.73 P=0.0165
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

Not All TKIs Are Created Equal – LUX-Lung 7
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>1.3</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.

Four cases of ILD, three of them ≥ grade 3.
AFATINIB VERSUS GEFITINIB IN PATIENTS WITH EGFR MUTATION-POSITIVE NSCLC: OVERALL SURVIVAL DATA FROM THE PHASE IIB TRIAL LUX-LUNG 7

Luis Paz-Ares, Eng-Huat Tan, Li Zhang, Vera Hirsh, Kenneth O'Byrne, Michael Boyer, James Chih-Hsin Yang, Tony Mok, Ki Hyeong Lee, Shun Lu, Yuankai Shi, Sang-We Kim, Janessa Laskin, Dong-Wan Kim, Scott A. Laurie, Karl Kölbeck, Jean Fan, Nigel Dodd, Angela Märten, Keunchil Park
Updated Tumour Response

DoR = duration of response.

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>P=0.002</td>
<td>P=0.150</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>Del19</td>
<td>75</td>
<td>66</td>
</tr>
<tr>
<td>L858R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median DoR (months):
- Afatinib: 10.1
- Gefitinib: 8.3

95% CI:
- Afatinib: (8.2–11.1)
- Gefitinib: (7.3–10.2)
OS (Overall Population)

Estimated OS probability over time (months):

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median, months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27.9</td>
<td>24.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.86 (0.66–1.12)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.2580</td>
<td></td>
</tr>
</tbody>
</table>

Not significant
OS by EGFR Mutation Subtype

Del19

<table>
<thead>
<tr>
<th></th>
<th>Afatinib N=93</th>
<th>Gefitinib N=93</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>30.7</td>
<td>26.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.83 (0.58–1.17)</td>
<td>0.2841</td>
</tr>
</tbody>
</table>

L858R

<table>
<thead>
<tr>
<th></th>
<th>Afatinib N=67</th>
<th>Gefitinib N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>25.0</td>
<td>21.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.91 (0.62–1.36)</td>
<td>0.6585</td>
</tr>
</tbody>
</table>

No. at risk:

- Afatinib: 93 88 82 68 61 50 35 20 1
- Gefitinib: 93 86 79 66 52 39 29 17 0

No. at risk:

- Afatinib: 67 65 57 43 33 24 15 10 1
- Gefitinib: 66 62 54 39 28 23 19 10 0
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 (IC$_{50}$, 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+

OSIMERTINIB

AURA pooled Ph II

PFS 11 months

AURA pooled Ph II

Probability of PFS

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

Complete response
Partial response
Stable disease
Progressive disease
Not evaluable

66%

Number of patients at risk:

Osimertinib 80 mg

0 100 80 60 40 20 0

-20 -40 -60 -80 -100

0 3 6 9 12 15 18 21 24 27

Month

ELCC Geneva 2016

Yang 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>

NO RASH or DIARRHOEA

| ILD (grouped terms)                                           | 0        | 0       | 1 (2)    | 1 (2)     |
| Hyperglycaemia                                                | 0        | 0       | 0        | 0         |
| QT prolongation                                               | 0        | 0       | 1 (2)    | 1 (2)     |

ILD 2.9 %

35/1200 pts
MRS. W
Gefitinib for 1 year
AZ9291 November 24th

November 10, 2015
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)
T790M Biopsy: Tumor vs Plasma

A small piece of tissue is removed with a biopsy needle and analyzed with a microscope.
High ORR in Patients With Tumour or Plasma-Positive T790M: Patients Treated With Osimertinib

ELCC Geneva 2016

Oxnard et al. ELCC 2016.
Summary: EGFR

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

• Recent Advances:
  – ELCC
    ▪ Osimertinib Aura Trial 2nd Line T790M+: PFS 11m
  – ASCO 2016
    ▪ T790: Plasma may be as accurate as tumour
  – ESMO 2016:
    ▪ LUX-Lung 7 Afatinib OS 27.9 vs 24.5 months not significant

Non-Squamous Non-Small Cell Lung Cancers

- **Unknown mutation**: 40%
- **KRAS**: 30%
- **EGFR**: 15%
- **ALK**: 5%
- **MET**: 4%
- **BRAF/PK3CA**: 2%
- **HER2/MEK**: 2%
- **ROS1**: 2%
- **RET**: 1%

**ALK**

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

SMKCC 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>

CNS Sanctuary

- Brain is the issue in ALK

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 signalling 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.
ESMO 2014

ASCEND 1: PFS

STANDARD OF CARE SECOND LINE US
3.40 (95% CI 11.10, non-estimable)
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 0
ASCEND-5

ESMO 2016

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

236 patients
Randomize 1:1
Stratified: PS; brain metastases

Chemotherapy (INV choice):
PEM 500 mg/m²
or
Docetaxel 75 mg/m²

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

Optional

PEM maintenance
500 mg/m² q21d

PD (BIRC real time)

Optional

Ceritinib 750 mg
crossover

PD

ASCEND-5

Kaplan-Meier Plots of PFS (BIRC)

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib 750 mg (N=115)</th>
<th>Chemotherapy (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>83 (72.2)</td>
<td>89 (76.7)</td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td>5.4 (4.1, 6.9)</td>
<td>1.6 (1.4, 2.8)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.49 (0.36, 0.67)</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Scagliotti et al. ESMO 2016. LBA42_PR.
Secondary Survival Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib (N=115)</th>
<th>Chemotherapy (N=116)</th>
<th>HR (95% CI)</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS by investigator (95% CI), months</td>
<td>6.7 (4.4, 7.9)</td>
<td>1.6 (1.4, 2.6)</td>
<td>0.40 (0.29, 0.54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- OS data were immature (~50% of required events) and possibly confounded by the high number of patients who crossed over to ceritinib following PD with chemotherapy (n=75)
- At the data cut-off, there was no difference in median OS
  - HR (95% CI) = 1.0 (0.67, 1.49)
    - Log-rank p-value = 0.496
  - Median OS (95% CI)
    - Ceritinib = 18.1 months (13.4, 23.9)
    - Chemotherapy = 20.1 months (11.9, 25.1)

20 months third line!
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%
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>Dyspnoea</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>Diarrhoea</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.
JALEX Study

Alectinib vs Crizotinib first line ALK Positive
A phase III study in Japan;
PFS superior when treated with alectinib
Primary Endpoint: PFS

sodium lauryl sulphate (SLS)

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]

FIRST-LINE

Nokihara H et al. ASCO 2016. Abstract 9008

Approved FDA first line September 21, 2016

NR

PFS NR!  
HR .34  
P<0.0001

No. of patients at risk
Alectinib 103 103 93 76 49 36 27 9 1
Bcrizotinib 104 102 86 65 40 21 14 4 1

Time (months)
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
Brigatinib Antitumour Activity by Arm

90 mg qd

ORR 45%

180 mg qd†

ORR 54%

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

Gettinger SN et al. ASCO 2016. Abstract 9060
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>0.55 (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

Gettinger SN et al. ASCO 2016. Abstract 9060
### Second-Generation ALK Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib^1 N= 163</th>
<th>Alectinib^2 N=138</th>
<th>Brigatinib^3 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%* 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\(^2\)

\(^1\) Johnson TW, et al. *J Med Chem* 2014;57:4720-44
\(^3\) Doebele RC, et al. *Clin Cancer Res* 2012;18:1472-82
\(^4\) Zou HY, et al. *PNAS* 2015;112:3493-8

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, 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><strong>Hypercholesterolemia</strong></td>
<td><strong>14 (82)</strong></td>
<td><strong>5 (29)</strong></td>
<td><strong>7 (41)</strong></td>
<td><strong>2 (12)</strong></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><strong>Hypertriglyceridemia</strong></td>
<td><strong>7 (41)</strong></td>
<td><strong>3 (18)</strong></td>
<td><strong>2 (12)</strong></td>
<td><strong>2 (12)</strong></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

Solomon B et al. ASCO 2016. Abstract 9009
Summary: ALK

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

• Recent Advances:
  – ASCO 2016
    ▪ First Line: Japan Alectinib
    ▪ Second Line: Brigatinib
    ▪ Third Line: Lorlatinib
  – ESMO 2016
    ▪ Ceritinib Third Line
Non–Small Cell Lung Cancers: 2015

RARE MUTATIONS

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%

Squamous

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

MSKCC data
Response in Patients With Advanced ROS1+ NSCLC: Crizotinib

Non-Small Cell Lung Cancers: 2015

Non-Squamous Non-Small Cell Lung Cancers

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

**Total**: 77%

Squamous

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

**Total**: 23%

MSKCC data
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.

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%
- LBRAF 2%
- Unknown mutation 60%

MSKCC data
AFATINIB: HER2 Lung Cancer

- HER2/neu mutations in 2%–4% of lung adenocarcinomas
- More frequent in females, 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%

Squamous

- Unknown mutation 60%

MSKCC data

- FGFR1 amp 20%
- KRAS 6%
- EGFR mut 5%
- DDR2 4%
- PIK3CA 3%
- BRAF 2%
Vandetanib 18 Patients
ORR 17% SD 28%
Se-Hoon Lee et al

ASCO 2016

Vandetanib for 8 weeks
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%
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}
MET X14 Skipped

Exon 14 (regulatory domain)
CRIZOTINIB

Baseline 4-week follow-up cabozantinib

Patient 7

CABOZANTINIB

Baseline 4-week follow-up cabozantinib

Patient 2
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%

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

- **ROS (1%)**
  - Crizotinib

- **BRAF (2%)**
  - Dabrafenib and trametinib

- **HER 2 (2%)**
  - Afatinib

- **RET (1%)**
  - Vandetanib

- **CMET EXON 14 Slice (5% and Squamous)**
  - Cabozantinib/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: 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: 77%

FGFR1 amp: 20%

Unknown mutation: 60%
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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival (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

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

Survival Probability
Time from Randomisation (Months)
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
11.0 months
13.9 months
PEMETREXED/CISPLATIN...PEM MAINTENANCE

Immunotherapy

Science

Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack

AAAS
Targeting PD-1 Pathways

**Periphery**

- **Dendritic cell**
  - MHC
  - TCR
  - CD28
  - B7
  - Anti-CTLA-4

**Tumour microenvironment**

- **T cell**
  - Activation (cytokines, lysis, proliferation, migration to tumour)
  - PD-L1

**CTLA-4 pathway**

- B7
- CD28
- CTLA-4

**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</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
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\textsuperscript{1}

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

1-yr OS rate=42%

Number of Patients at Risk

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>135</th>
<th>113</th>
<th>86</th>
<th>69</th>
<th>52</th>
<th>31</th>
<th>15</th>
<th>7</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>137</td>
<td>103</td>
<td>68</td>
<td>45</td>
<td>30</td>
<td>14</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

CheckMate 057
Non-SQ NSCLC\textsuperscript{2}

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

1-yr OS rate=51%

Number of Patients at Risk

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>292</th>
<th>232</th>
<th>194</th>
<th>169</th>
<th>146</th>
<th>123</th>
<th>62</th>
<th>32</th>
<th>9</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>290</td>
<td>244</td>
<td>194</td>
<td>150</td>
<td>111</td>
<td>88</td>
<td>34</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Previously presented at ASCO 2015 (Abstracts 8009 and LBA109).
1. Spigel DR et al. ASCO 2015. Abstract 8009
2. Paz-Ares LG et al. ASCO 2015. LBA109
ORR CheckMate 017 & 057

CheckMate 017

- Nivolumab: ORR 20%
- 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>Pidilizumab CT-011</td>
<td>Humanized IgG1 mAb</td>
<td>CureTech</td>
<td>Phase II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Keytruda 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>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 tumour samples by a clinical-trial IHC assay (Dako) with the 22C3 antibody (Merck)
• Samples scored as the percentage of tumour cells with membranous PD-L1 staining—tumour proportion score or TPS

Keynote 010

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

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

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

**R 1:1:1**

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

**Docetaxel**
- 75 mg/m\(^2\) Q3W per local guidelines\(^c\)
Duration of Response

**PD-L1 TPS ≥1%**

<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>
</table>

**PD-L1 TPS ≥50%**

<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 17+)</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td></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)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 1 y (%)</th>
<th>HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>16.4 (9.4-11.9)</td>
<td>43.2%</td>
<td>0.71 (0.58-0.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pembro 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 (7.5-8.8)</td>
<td>34.6%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**2 mg:** 10.4 vs 8.5 HR .71 p<0.0008

### OS, PD-L1 TPS ≥50% Stratum

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>14.9 (10.4-NR)</td>
<td>0.54 (0.38-0.71)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>17.3 (11.8-NR)</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>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**2 mg:** 14.9 vs 8.2 HR .54 p<0.0002

---

Herbst et al. ESMO Asia. LBA3.
### 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>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>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>
<tr>
<td></td>
<td>Tecentriq</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
PHASE III OAK

Locally Advanced or Metastatic NSCLC
- 1-2 prior lines of chemo including at least 1 platinum based
- Any PD-L1 status

N = 1,225 enrolled

Stratification factors
- PD-L1 expression
- Histology
- Prior chemotherapy regimens

Primary Endpoints (first 850 enrolled patients):
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, Safety

Atezolizumab 1200 mg IV q3w

Docetaxel 75 mg/m² q3w

PD or loss of clinical benefit

1:1

PD

Q 3WEEK

A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression).

TC, tumor cells; IC, tumor-infiltrating immune cells.

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh
OVERALL SURVIVAL, ITT (N = 850)

HR, 0.73
(95% CI, 0.62, 0.87)
P = 0.0003
Minimum follow up = 19 months

**Median 9.6 mo**
(95% CI, 8.6, 11.2)

**Median 13.8 mo**
(95% CI, 11.8, 15.7)
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
Optional Crossover
Investigator choice of chemotherapy for 4-6 cycles
Disease progression

Follow-up for safety (≤90 days)
Follow-up for survival (every 2 months)

ENDPOINT PFS

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

Brahmer et al. WCLC 2015.
**Confirmed Objective Response Rate**

Δ17%  
\[ P = 0.0011 \]

**Pembrolizumab**  
- ORR, % (95% CI): 45%  
  - n = 63  
  - n = 6

**Chemotherapy**  
- ORR, % (95% CI): 28%  
  - n = 41  
  - n = 1

<table>
<thead>
<tr>
<th></th>
<th>Pembrol Responders</th>
<th>Chemo Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR, mo median (range)</td>
<td>2.2 (1.4-8.2)</td>
<td>2.2 (1.8-12.2)</td>
</tr>
<tr>
<td>DOR, mo median (range)</td>
<td>NR (1.9+ to 14.5+)</td>
<td>6.3 (2.1+ to 12.6+)</td>
</tr>
</tbody>
</table>

Assessed per RECIST v1.1 by blinded, independent central review.  
Data cut-off: May 9, 2016.
Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>73</td>
<td>10.3</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td>0.37-0.68</td>
<td></td>
</tr>
</tbody>
</table>

Assessed per RECIST v1.1 by blinded, independent central review. Data cut-off: May 9, 2016.

Reck M et al. ESMO 2016. Abstract LBA8_PR
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>NR</td>
<td>0.60</td>
<td>0.005</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td>(0.41-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

HR 0.6

Data cut-off: May 9, 2016.

Reck M et al. ESMO 2016. Abstract LBA8_PR
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC

Key eligibility criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No EGFR/ALK mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomisation

Nivolumab 3 mg/kg IV Q2W n = 271

Secondary endpoints:
- PFS (≥1% PD-L1+)\(^d\)
- OS
- ORR\(^d\)

Randomise 1:1

Chemotherapy Maximum of 6 cycles n = 270

Tumour scans Q6W until wk 48 then Q12W

Disease progression or unacceptable toxicity

Disease progression

Crossover nivolumab\(^c\) (optional)

Primary endpoint: PFS (≥5% PD-L1+)\(^d\)

\(^a\) Dako 28-8 validated; archival tumour samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralised.

\(^b\) Squamous: gemcitabine 1250 mg/m\(^2\) + cisplatin 75 mg/m\(^2\); gemcitabine 1000 mg/m\(^2\) + carboplatin AUC 5; paclitaxel 200 mg/m\(^2\) + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m\(^2\) + cisplatin 75 mg/m\(^2\); pemetrexed 500 mg/m\(^2\) + carboplatin AUC 6; option for pemetrexed maintenance therapy.

\(^c\) Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review.

\(^d\) Tumour response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review. Socinski M et al. ESMO 2016. Abstract LBA7.PR
### Summary of Response (≥5% PD-L1+)

**CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n=211)</th>
<th>Chemotherapy (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>26.1 (20.3, 32.5)</td>
<td>33.5 (27.2, 40.3)</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>24.2</td>
<td>33.0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.4</td>
<td>47.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>27.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>8.1</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Median time to response, months (range)</strong></td>
<td>2.8 (1.2, 13.2)</td>
<td>2.6 (1.2, 9.8)</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td>12.1 (8.8, NE)</td>
<td>5.7 (4.2, 8.5)</td>
</tr>
</tbody>
</table>

Socinski M et al. ESMO 2016. Abstract LBA7_PR
Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

- **Nivolumab**
  - No. of patients at risk: 211
  - Median PFS, months: 4.2 (95% CI: 3.0, 5.6)
  - 1-year PFS rate, %: 23.6
  - HR = 1.15 (95% CI: 0.91, 1.45), P = 0.2511

- **Chemotherapy**
  - No. of patients at risk: 212
  - Median PFS, months: 5.9 (95% CI: 5.4, 6.9)
  - 1-year PFS rate, %: 23.2

- **All randomised patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)**
OS (≥5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

Socinski M et al. ESMO 2016. Abstract LBA7_PR
Summary: Immunotherapy

• Current
  – Second-Line Nivolumab 3 mg/kg q 2 w
  – Second line Atezolizumab 200 mg IV q 3 w
  – Second-Line PDL1 >1% Pembrolizumab 2 mg/kg q 3 w

• Advances
  – First-Line PDL1 >50% Pembrolizumab 200 mg q 3 w
Advanced NSCLC: EGFR and ALK Negative

1st Line: Pembrolizumab 2 mg/kg q 3 week

2nd Line: Platinum doublet (Pem/gem based)

3rd Line: Afatinib/Erlotinib, Docetaxel +/- Nintendanib, Docetaxel +/- Ramicirumab,

4th Line: whatever has not been used previously

PDL-1 testing

PDL-1 > 50%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 50%
- Platinum doublet (Pem/gem based)

PDL-1 > 1-49%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 1%
- Atezolizumab 1200 mg IV q3week

Non Squamous/Squamous

PDL-1 testing

PDL-1 > 50%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 50%
- Platinum doublet (Pem/gem based)

Platinum doublet
- Pemexrexed
- Non squamous

PDL-1 testing

PDL-1 > 1-49%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 1%
- Atezolizumab 1200 mg IV q3week

Non squamous

PDL-1 testing

PDL-1 > 50%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 50%
- Platinum doublet (Pem/gem based)

Platinum doublet
- Pemexrexed
- Non squamous

PDL-1 testing

PDL-1 > 1-49%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 1%
- Atezolizumab 1200 mg IV q3week

Non squamous

PDL-1 testing

PDL-1 > 50%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 50%
- Platinum doublet (Pem/gem based)

Platinum doublet
- Pemexrexed
- Non squamous

PDL-1 testing

PDL-1 > 1-49%
- Pembrolizumab 2 mg/kg q 3 week

PDL-1 < 1%
- Atezolizumab 1200 mg IV q3week

Non squamous
Complicated
State of the Art: NSCLC 2016

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

• Wildtype
  ▪ Chemotherapy Never Forget

• Immune checkpoint inhibitors
  ▪ Moving into first line
  ▪ Evolving PDL1 biomarker
Conclusion

State of the Art 2016:
Making Lung Cancer a Chronic Disease

Thank you