INNOVATION IN LUNG CANCER MANAGEMENT

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FIRST-LINE THERAPY FOR METASTATIC NSCLC IN 2016

Stratification for *EGFR*, *ALK* and histology

- **EGFRm**
  - EGFR TKI

- **ALK+**
  - Crizotinib

- **EGFR WT/ALK-**
  - non-squamous
    - Platinum doublet + bevacizumab OR platinum + pemetrexed +/- bevacizumab

- **EGFR WT/ALK-**
  - squamous
    - Platinum-based doublet

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OPTIONS FOR METASTATIC NSCLC IN 2018

50%

- **EGFR WT/ALK-/ROS1-/PD-L1\(^{-}\)**
  - 1st: Platinum-based chemotherapy
  - 2nd: Immune checkpoint inhibitors
    - Nivolumab or atezolizumab

30%

- **EGFR WT/ALK-/ROS1-/PD-L1\(^{high}\)**
  - 1st: PD-1 inhibitor
    - Pembrolizumab
  - 2nd: Platinum-based chemotherapy
    - Osimertinib
    - Platinum-based Chemotherapy

- **EGFR\(^{+}\)**
  - 1st: EGFR TKIs
    - Erlotinib
    - Afatinib
    - Gefitinib
  - 2nd: EGFR TKIs
    - Osimertinib

20%

- **ALK\(^{+}\)**
  - 1st: ALK inhibitor
    - Alectinib
    - Crizotinib
    - Ceritinib

- **ROS1\(^{+}\)**
  - 1st: ALK/ROS1 inhibitor
    - Crizotinib

- **BRAF V600E**
  - Dabrafenib + trametinib

Systemic therapy
- Chemotherapy
- Immune checkpoint inhibitors*
- Clinical trials

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy.
IMMUNOTHERAPY SUPERIOR TO PLATINUM-BASED CHEMOTHERAPY

In patients with high levels of PD-L1 expression

Key eligibility criteria
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

Key endpoints
- Primary: PFS (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, and safety
- Exploratory: DOR

Overall survival

Events, n HR (95% CI)
Pembrolizumab 73 0.63 (0.47–0.86)
Chemotherapy 96

Median (95% CI)
Pembrolizumab 30.0 mo (18.3 mo–NR)
Chemotherapy 14.2 mo (9.8 mo–19.0 mo)

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

IMMUNOTHERAPY NOT SUPERIOR TO PLATINUM-BASED CHEMOTHERAPY

In patients with low levels of PD-L1 expression

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

Primary endpoint: PFS (≥5% PD-L1+)
Secondary endpoints:
• PFS (≥1% PD-L1+)
• OS
• ORR

Nivolumab
Randomize 1:1
Tumor scans Q6W until wk 48 then Q12W
Disease progression or unacceptable toxicity

Chemotherapy (histology dependent)
Maximum of 6 cycles
n = 270

Disease progression
Crossover nivolumab (optional)

Stratification factors at randomization:
• PD-L1 expression (<5% vs ≥5%)
• Histology (squamous vs non-squamous)

OS (≥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>Median OS, months (95% CI)</td>
<td>14.4 (11.7, 17.4)</td>
<td>13.2 (10.7, 17.1)</td>
</tr>
<tr>
<td>1-year OS rate, %</td>
<td>56.3</td>
<td>53.6</td>
</tr>
</tbody>
</table>

HR = 1.02 (95% CI: 0.80, 1.30)

• 60.4% in the chemotherapy arm had subsequent nivolumab therapy
• 43.6% in the nivolumab arm had subsequent systemic therapy

Socinski M, et al., Ann Oncol 2016;27 suppl_6, LBA7_PR. Courtesy of Dr Mark Socinski
## OVERVIEW OF PHASE III STUDIES OF ANTI-PD1/PDL1 THERAPY

In previously treated NSCLC

<table>
<thead>
<tr>
<th>Study arms</th>
<th>CheckMate 017&lt;sup&gt;1&lt;/sup&gt;</th>
<th>CheckMate 057&lt;sup&gt;1&lt;/sup&gt;</th>
<th>KEYNOTE-010&lt;sup&gt;2&lt;/sup&gt;</th>
<th>OAK&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab vs. docetaxel</td>
<td>Nivolumab vs. docetaxel</td>
<td>Pembrolizumab 2 or 10 mg/kg vs docetaxel</td>
<td>Atezolizumab vs. docetaxel</td>
</tr>
<tr>
<td>Phase of study</td>
<td>III</td>
<td>III</td>
<td>II/III</td>
<td>III</td>
</tr>
<tr>
<td>PD-L1 selected</td>
<td>No</td>
<td>No</td>
<td>Yes (TPS* ≥1%)</td>
<td>No</td>
</tr>
<tr>
<td>Study size, n</td>
<td>272 (135 vs. 137)</td>
<td>582 (292 vs. 290)</td>
<td>1033 (344 vs. 346 vs. 343)</td>
<td>850 in primary analysis&lt;sup&gt;§&lt;/sup&gt; (425 vs. 425)</td>
</tr>
<tr>
<td>Histology, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous</td>
<td>0</td>
<td>100</td>
<td>70</td>
<td>74</td>
</tr>
<tr>
<td>Squamous</td>
<td>100</td>
<td>0</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Line of therapy, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2L</td>
<td>100</td>
<td>88</td>
<td>69</td>
<td>75</td>
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<tr>
<td>3L</td>
<td>0</td>
<td>11</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>&gt;3L</td>
<td>0</td>
<td>&lt;1</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>0</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Minimum follow-up of latest data</td>
<td>~24 months</td>
<td>~24 months</td>
<td>~19 months</td>
<td>~19 months</td>
</tr>
</tbody>
</table>

*Tumour proportion score (TPS) is the proportion of viable tumour cells showing partial or complete membrane PD-L1 expression;<sup>*</sup> 1225 patients enrolled in total

PHASE III STUDIES OF NIVOLUMAB IN PREVIOUSLY TREATED NSCLC OS (3 YEARS’ MINIMUM FOLLOW-UP)

CheckMate 017 (SQ NSCLC)

CheckMate 057 (non-SQ NSCLC)

No. of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>135</td>
<td>137</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>137</td>
<td>137</td>
</tr>
</tbody>
</table>

HR (95% CI): 0.62 (0.48, 0.80)

HR (95% CI): 0.73 (0.62, 0.88)

Felip E, et al., Presented at ESMO 2017; poster 1301PD. With permission from Prof Enriqueta Felip
PEMBROLIZUMAB VERSUS DOCETAXEL

In pretreated NSCLC with PD-L1 expression: Survival results of the KEYNOTE 010 trial

PD-L1 score 50% or greater

Study population

ATEZOLIZUMAB VERSUS DOCETAXEL IN NSCLC: OAK TRIAL

Overall survival, ITT (n=850)

HR, 0.73\(^a\)
(95\% CI, 0.62, 0.87)
\(P = 0.0003\)

Minimum follow up = 19 months

Overall survival, ITT (n=850)

12-mo OS

55%

18-mo OS

40%

Median 13.8 mo
(95\% CI, 11.8, 15.7)

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

HR, 0.73\(^a\)
(95\% CI, 0.62, 0.87)
\(P = 0.0003\)

Minimum follow up = 19 months

No. at Risk
Atezolizumab 425 407 382 363 342 326 305 279 260 248 234 223 218 205 198 188 175 163 157 141 116 74 54 41 28 16 5 4 1
Docetaxel 425 390 365 336 311 286 263 236 219 195 179 168 151 140 132 123 116 104 98 90 70 51 37 28 16 6 3

\(^a\)Stratified HR.

HIGH LEVELS OF PD-L1 EXPRESSION PREDICTS HIGHER OS BENEFIT WITH IMMUNOTHERAPY

Atezolizumab in PD-L1+++ ¹

Pembrolizumab in PD-L1 score 50% or higher²


EVIDENCE OF SURVIVAL BENEFIT IN PD-L1 NEGATIVE: OAK TRIAL RESULTS

Significant benefit in PD-L1 negative with squamous and non-squamous histology

On-study Prevalence

- 16%
- 31%
- 55%
- 45%
- 100%

Subgroup
- TC3 or IC3: 0.41
- TC2/3 or IC2/3: 0.67
- TC1/2/3 or IC1/2/3: 0.74
- TC0 and IC0: 0.75

ITT
- 0.73

Median OS, mo
- Atezolizumab: n = 425, 20.5
- Docetaxel: n = 425, 8.9

TC, tumour cells; IC, tumour-infiltrating immune cells; OS, overall survival.

*Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups.

Barlesi F, et al., Presented at ESMO 2016; Abstract LBA44_PR
### 2-YEAR OS RATES OVERALL AND BY PD-L1 EXPRESSION LEVEL IN CHECKMATE 057 (NON-SQ NSCLC)

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>OS (%)</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>292</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>2-year OS</td>
<td>29</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Kaplan–Meier estimates</td>
<td>0.75</td>
<td>(0.63, 0.91)</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>108</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>2-year OS</td>
<td>25</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Kaplan–Meier estimates</td>
<td>0.91</td>
<td>(0.67, 1.22)</td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>123</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>2-year OS</td>
<td>37</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Kaplan–Meier estimates</td>
<td>0.62</td>
<td>(0.47, 0.83)</td>
<td></td>
</tr>
<tr>
<td>≥5%</td>
<td>95</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>2-year OS</td>
<td>44</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Kaplan–Meier estimates</td>
<td>0.48</td>
<td>(0.34, 0.68)</td>
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<tr>
<td>≥10%</td>
<td>86</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>2-year OS</td>
<td>45</td>
<td>13</td>
<td></td>
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<tr>
<td>Kaplan–Meier estimates</td>
<td>0.43</td>
<td>(0.30, 0.62)</td>
<td></td>
</tr>
</tbody>
</table>

- In CheckMate 057, consistent with the primary analysis, 2 PD-L1 expression level was associated with the magnitude of OS benefit at 2 years starting at the lowest level studied (1%).

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*a* Kaplan–Meier estimates, with error bars indicating 95% CIs  
*b* For the comparison of the full Kaplan–Meier survival curves for each treatment group

Borghaei H, et al., Presented at ASCO 2016; poster 9025. Courtesy of Dr Hossein Borghaei
NIVOLUMAB IMPROVES SURVIVAL OVER DOCETAXEL
Irrespective of PD-L1 expression in squamous-cell lung carcinoma

<table>
<thead>
<tr>
<th>Expression Level</th>
<th>Nivolumab (mOS)</th>
<th>Docetaxel (mOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% PD-L1 ≥1%</td>
<td>9.3</td>
<td>7.2</td>
</tr>
<tr>
<td>1% PD-L1 &lt;1%</td>
<td>8.7</td>
<td>5.9</td>
</tr>
<tr>
<td>5% PD-L1 ≥5%</td>
<td>10.0</td>
<td>6.4</td>
</tr>
<tr>
<td>5% PD-L1 &lt;5%</td>
<td>8.5</td>
<td>6.1</td>
</tr>
<tr>
<td>10% PD-L1 ≥10%</td>
<td>11.0</td>
<td>7.1</td>
</tr>
<tr>
<td>10% PD-L1 &lt;10%</td>
<td>8.2</td>
<td>6.1</td>
</tr>
</tbody>
</table>

WHICH PATIENTS ARE NOT CANDIDATE FOR SECOND-LINE IMMUNOTHERAPY?

Meta-analysis of trials with checkpoint inhibitors in patients with EGFR mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR wild-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 057</td>
<td>26.0%</td>
<td>0.66 (0.51, 0.86)</td>
</tr>
<tr>
<td>Keynote 010</td>
<td>52.0%</td>
<td>0.66 (0.55, 0.80)</td>
</tr>
<tr>
<td>POPLAR</td>
<td>11.0%</td>
<td>0.70 (0.47, 1.04)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>89.0%</td>
<td>0.66 (0.58, 0.76)</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 057</td>
<td>6.0%</td>
<td>1.18 (0.69, 2.00)</td>
</tr>
<tr>
<td>Keynote 010</td>
<td>3.8%</td>
<td>0.88 (0.45, 1.70)</td>
</tr>
<tr>
<td>POPLAR</td>
<td>1.1%</td>
<td>0.99 (0.29, 3.40)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>11.0%</td>
<td>1.05 (0.70, 1.55)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.70 (0.61, 0.80)</td>
</tr>
</tbody>
</table>

WHICH PATIENTS ARE NOT CANDIDATE FOR SECOND-LINE IMMUNOTHERAPY?

Combination of clinical factors and PD-L1 expression in Checkmate 057

Post-hoc, exploratory multivariate analysis suggested that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower or no tumour PD-L1 expression may be at higher risk of death within the first 3 months.

- These included the following known prognostic factors: <3 months since last treatment, PD as best response to prior treatment, and ECOG PS=1.

Peters S, et al., Presented at WCLC 2016. Abstract OA03. With permission from Dr Federico Cappuzzo
# EGFR TKIS VERSUS CHEMOTHERAPY IN EGFR\textsuperscript{mut}+ NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>Treatment</th>
<th>RR %</th>
<th>PFS</th>
<th>HR P-value</th>
<th>mOS (mos)</th>
<th>HR P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mPFS (mos)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IPASS *</td>
<td>97</td>
<td>Gefitinib</td>
<td>71.2</td>
<td>9.5</td>
<td>0.48</td>
<td>21.6</td>
<td>1.00</td>
</tr>
<tr>
<td>(Mok TS, et al. N Engl J Med 2009;361:947–57)</td>
<td>111</td>
<td>CBDCA + TXL</td>
<td>47.3</td>
<td>6.3</td>
<td>&lt;0.0001</td>
<td>21.9</td>
<td>0.99</td>
</tr>
<tr>
<td>First SIGNAL *</td>
<td>159</td>
<td>Gefitinib</td>
<td>84.6</td>
<td>8.0</td>
<td>0.54</td>
<td>27.2</td>
<td>1.04</td>
</tr>
<tr>
<td>(Lee JS, et al. J Thor Oncol 2009; 4(Suppl):PRS.4)</td>
<td>150</td>
<td>CDDP + GEM</td>
<td>37.5</td>
<td>6.3</td>
<td>0.008</td>
<td>25.6</td>
<td>NR</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>88</td>
<td>Gefitinib</td>
<td>62.1</td>
<td>9.2</td>
<td>0.48</td>
<td>36.0</td>
<td>1.18</td>
</tr>
<tr>
<td>(Mitsudomi T, et al. Lancet Oncol 2010;11:121–8)</td>
<td>89</td>
<td>CDDP + TXT</td>
<td>32.2</td>
<td>6.3</td>
<td>&lt;0.001</td>
<td>39.0</td>
<td>NR</td>
</tr>
<tr>
<td>NEJ 002</td>
<td>114</td>
<td>Gefitinib</td>
<td>73.7</td>
<td>10.4</td>
<td>0.36</td>
<td>27.7</td>
<td>0.89</td>
</tr>
<tr>
<td>(Maemondo M, et al. N Engl J Med 2010;362:2380–8)</td>
<td>114</td>
<td>CBDCA + TXL</td>
<td>30.7</td>
<td>5.5</td>
<td>&lt;0.001</td>
<td>26.6</td>
<td>0.48</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>82</td>
<td>Erlotinib</td>
<td>83.0</td>
<td>13.1</td>
<td>0.16</td>
<td>22.6</td>
<td>1.06</td>
</tr>
<tr>
<td>(Zhou C, et al. Lancet Oncol. 2011; 12:735–42)</td>
<td>72</td>
<td>CBDCA + GEM</td>
<td>36.0</td>
<td>4.6</td>
<td>&lt;0.0001</td>
<td>28.8</td>
<td>0.68</td>
</tr>
<tr>
<td>EURTAC</td>
<td>84</td>
<td>Erlotinib</td>
<td>54.5</td>
<td>9.4</td>
<td>0.34</td>
<td>19.3</td>
<td>1.04</td>
</tr>
<tr>
<td>(Rosell R, et al. Lancet Oncol 2012;13:239–46)</td>
<td>82</td>
<td>Platinum Doublet</td>
<td>10.5</td>
<td>5.2</td>
<td>&lt;0.0001</td>
<td>19.5</td>
<td>0.87</td>
</tr>
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<td>ENSURE</td>
<td>110</td>
<td>Erlotinib</td>
<td>68.2</td>
<td>11.1</td>
<td>0.43</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>(Wu Y-L, et al. J Thor Oncol 8:s603 Suppl. 2)</td>
<td>107</td>
<td>CDDP + GEM</td>
<td>39.3</td>
<td>5.7</td>
<td>&lt;0.0001</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>LUX Lung 3</td>
<td>230</td>
<td>Afatinib</td>
<td>56.0</td>
<td>11.1</td>
<td>0.58</td>
<td>16.6</td>
<td>1.12</td>
</tr>
<tr>
<td>(Sequist LV, et al. J Clin Oncol 2013;31:3327–34)</td>
<td>115</td>
<td>CDDP + PEM</td>
<td>23.0</td>
<td>6.9</td>
<td>0.0004</td>
<td>14.8</td>
<td>0.60</td>
</tr>
<tr>
<td>LUX Lung 6</td>
<td>242</td>
<td>Afatinib</td>
<td>66.9</td>
<td>11.0</td>
<td>0.28</td>
<td>22.1</td>
<td>0.95</td>
</tr>
<tr>
<td>(Wu Y-L, et al. Lancet Oncol 2014;15:213–22)</td>
<td>122</td>
<td>CDDP + GEM</td>
<td>23.0</td>
<td>5.6</td>
<td>&lt;0.0001</td>
<td>22.2</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Shown data are restricted to EGFR\textsuperscript{mut}+ population
ERLOTINIB VERSUS
ERLOTINIB+BEVACIZUMAB
As first-line therapy in EGFR^{mut+} NSCLC: Phase IIR study

Chemotherapy-naive
stage IIIB-IV or
postoperative recurrence
Non-squamous NSCLC
Activating EGFR mutations
❖ Exon 19 deletion
❖ Exon 21 L858R
Age ≥20 years
PS 0-1
No brain metastasis

Primary endpoint: PFS
Secondary endpoints: OS, ORR, QoL, symptoms improvement FACT-L scale and safety

ERLOTINIB VERSUS
ERLOTINIB+BEVACIZUMAB
As first-line therapy in EGFR\textsuperscript{mut+} NSCLC: PFS

OSIMERTINIB THE NEW STANDARD OF CARE IN PRETREATED EGFR<sup>T790M</sup>+

### AURA 3 trial design

**Key eligibility criteria**
- ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumour EGFR T790M mutation from a tissue biopsy taken after disease progression on first line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
- Stable* asymptomatic CNS metastases allowed

**Randomise**

<table>
<thead>
<tr>
<th>Osimertinib 80 mg orally (n=279)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum-pemetrexed (n=140)</td>
</tr>
<tr>
<td>Pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² q3w for up to 6 cycles + optional maintenance pemetrexed#</td>
</tr>
</tbody>
</table>

**Primary endpoint**
- PFS by investigator assessment (RECIST 1.1)

**Secondary and exploratory endpoints**
- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Tumour shrinkage
- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

**Optional crossover**
Protocol amendment allowed patients on chemotherapy to begin post-BICR confirmed progression open-label osimertinib treatment

### PFS in the study population

* Analysis of PFS by BICR was consistent with the investigator-based analysis: HR 0.28 (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

---

OSIMERTINIB THE NEW STANDARD OF CARE IN FIRST-LINE EGFRM+ NSCLC: FLAURA TRIAL DESIGN

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- ≥18 years*
- WHO performance status 0/1
- Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Primary endpoint: PFS based on investigator assessment (according to RECIST 1.1)
- The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%

Secondary endpoints: objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

Osimertinib 80 mg p.o. qd (n=279)

Randomised 1:1

EGFR-TKI SoC§;
Gefitinib 250 mg p.o. qd or Erlotinib 150 mg p.o. qd (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective progressive disease

Crossover was allowed for patients in the SoC arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

**FLAURA: PFS AND OS**

No. of Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>18.9 (15.2–21.4)</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>10.2 (9.6–11.1)</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57), P < 0.001

No. of Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>NC (NC–NC)</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>NC (NC–NC)</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88), P = 0.007

CNS progression events occurred in 17 (6%) vs. 42 (15%) patients receiving osimertinib vs. SoC (all patients).
CRIZOTINIB FIRST-LINE STANDARD OF CARE UP TO 2017 IN ALK+ NSCLC

PROFILE 1014 study design
Multicenter, randomised open-label Phase III study

Key entry criteria
- ALK-positive by central FISH testing
- Locally advanced, recurrent, or metastatic non-squamous NSCLC
- No prior systemic treatment for advanced disease
- ECOG PS 0–2
- Measurable disease
- Treated brain metastases allowed

Randomise

Crizotinib 250 mg bid po, continuous dosing (N=167)
Crizotinib continued after PD if ongoing clinical benefit
Pemetrexed 500 mg/m² + cisplatin 75 mg/m² OR carboplatin AUC 5–6 q3w for ≤6 cycles (N=167)
Crossover to crizotinib permitted after PD

PFS by independent radiologic review (all patients)

<table>
<thead>
<tr>
<th>All patients</th>
<th>Crizotinib (N=172)</th>
<th>Chem. (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>137 (80)</td>
</tr>
<tr>
<td>Median, mo</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>

At risk (ALL)

<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>19</td>
</tr>
<tr>
<td>20</td>
<td>12</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>


*ALK status determined using standard ALK break-apart FISH assay;

*Assessed by independent radiologic review.

*1-sided stratified log-rank test.
J-ALEX

Phase III study comparing alectinib versus crizotinib in ALK+ NSCLC

Key entry criteria
- Stage IIIB/IV or recurrent ALK+ NSCLC
- ALK centralised testing (IHC and FISH or RT-PCR)
- ECOG PS 0-2
- ≥1 measurable lesion assessed by investigator
- Treated/asymptomatic brain metastases allowed
- ≤1 prior chemotherapy

Alectinib 300 mg BID PO, 28-day cycle (N=100)

Crizotinib 250 mg BID PO, 28-day cycle (N=100)

Primary endpoint: PFS assessed by IFR*
Secondary endpoints: OS, ORR, PK, QoL, CNS PFS, and safety

Nokihara H, et al., J Clin Oncol 34, 2016 (suppl; abstr 9008) Presented at ASCO 2016
**J-ALEX PRIMARY ENDPOINT:**
**PFS BY IRF (ITT)**

- **Alectinib (n=103)**: HR=0.34 (0.17–0.71) p<0.0001
- **Crizotinib (n=104)**: NR (20.3–NR)

ALECTINIB IS SUPERIOR TO CRIZOTINIB IN ALK+ NSCLC

PFS in ALEX trial

Key eligibility
- Advanced or metastatic ALK+ NSCLC
- ALK+ by central IHC testing
- Treatment-naïve
- ECOG PS 0-2
- Measurable disease
- Asymptomatic brain metastases allowed

Randomise
N=286

Alectinib
- 600 mg bid po
- NO CROSSOVER per protocol

Crizotinib
- 250 mg bid po

Primary endpoint
- PFS (RECIST 1.1), by investigator review

Secondary endpoints
- PFS by IRC
- Time to CNS progression
- ORR, DOR
- OS
- Safety and tolerability
- Patient-reported outcomes

Stratification factors:
- ECOG PS (0/1 vs. 2)
- Race (Asian, non-Asian)
- Brain metastases (present vs. absent)

ASCEND 4 – CERITINIB VERSUS PLATIN-PEMETREXED
As first-line therapy in ALK+ NSCLC

Inclusion criteria
Stage IIIB/IV ALK+ NSCLC by Ventana IHC test (central)
Treatment-naive (no prior chemotherapy or ALK inhibitor)
WHO PS 0-2
Neurologically stable brain metastases (symptomatic or not)

Chemotherapy (Induction Investigator choice)*: Four cycles†
Pemetrexed 500 mg/m² + cisplatin 75 mg/m²
or Pemetrexed 500 mg/m² + carboplatin AUC 5–6

Ceritinib 750 mg/day†
Daily oral dosing in fasted state

PD (BIRC confirmed)
Optional
crossover to extension treatment

CR, PR, SD
Pemetrexed maintenance 500 mg/m² q21d
PD (BIRC confirmed)

Stratified randomisation:
WHO PS
Brain metastases
Prior neoadjuvant/adjuvant chemotherapy

*At the time when ASCEND-4 was designed and initiated, pemetrexed-platinum chemotherapy followed by pemetrexed maintenance was the standard of care in patients with non-squamous advanced NSCLC
†One cycle = 21 days
BIRC, Blinded Independent Review Committee; CR, complete response; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; WHO, World Health Organization.

Ceritinib demonstrated an estimated 45% risk reduction vs. chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib (N=189)</th>
<th>Chemotherapy (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>89 (47.1)</td>
<td>113 (60.4)</td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td>16.6 (12.6, 27.2)</td>
<td>8.1 (5.8, 11.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.55 (0.42, 0.73)</td>
<td></td>
</tr>
</tbody>
</table>

Stratified Log-rank p-value < 0.001
CNS INVOLVEMENT IN NSCLC

Higher incidence in EGFR\textsuperscript{mut+} or ALK+

All-comers incidence of BM\textsuperscript{1,2}

- BM 30% (25–40%)

EGFR+ patients treated with first-generation TKI\textsuperscript{3–5}

- BM 40% (30–60%)

ALK+ patients treated with crizotinib\textsuperscript{6,7}

- BM 50%

Incidence of BM is higher:
- Different tumour biology
- Lack of drug penetration
- Longer survival

ALK, anaplastic lymphoma kinase; BM, brain metastases; CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitor.

PROGNOSTIC IMPACT OF EGFR MUTATION AND/OR ALK REARRANGEMENTS IN BMS

Molecularly unselected NSCLC¹

- Overall Survival (proportion)
- Median survival in overall population: 7 mos
- Clinical factors: Age, KPS, extracranial disease, number of BMs

Molecularly selected lung ADC²

- Median survival in EGFRmut+/ALK+ NSCLC: 46 mos
- Clinical factors + EGFRmut+ and/or ALK+

CNS ACTIVITY OF 2\textsuperscript{ND}–3\textsuperscript{RD} GENERATION ALK-IS IN CRIZOTINIB-RESISTANT ALK+ NSCLCs

**Ceritinib, ASCEND 2\textsuperscript{1}**

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>No. (% of Patients With Target Brain Lesions at Study Entry (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>SD</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>UNK</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>OIRR*</td>
<td>9 (46.0)</td>
</tr>
<tr>
<td>IDCR*</td>
<td>16 (80.0)</td>
</tr>
</tbody>
</table>

**RR 45%**

**Alectinib, pooled analysis\textsuperscript{2} NP28761/NP28673**

**RR 64%**

**Brigatinib, ALTA trial\textsuperscript{3}**

- 90 mg once daily
- 180 mg once daily with 7-day lead-in at 90 mg

**RR 46%**

**RR 67%**

**Lorlatinib, Phase 1/2\textsuperscript{4}**

**RR 56%**

*Includes patients with active brain metastases at baseline (90 mg qd, n=16; 180 mg qd [with lead-in], n=14)

2. Gadgeel S, et al., J Clin Oncol 34(34), 2016: 4079–85; Reprinted with permission. © 2016. American Society of Clinical Oncology. All rights reserved.
NEW TARGETED THERAPIES ARE EFFECTIVE AGAINST BM

Alectinib more effective than crizotinib in preventing BM\(^1\)

Time to appearance of CNS disease in patients without CNS mets at baseline

Osimertinib more effective than chemotherapy in presence of BM\(^2\)

Median PFS, months (95\% CI)

8.5 (6.8, 12.3)

4.2 (4.1, 5.4)

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CONCLUSIONS

- Landscape of NSCLC therapy is rapidly evolving
- Immunotherapy is replacing chemotherapy in first-line setting in PD-L1 expressing NSCLC
- Immunotherapy is the new standard for EGFR\textsuperscript{wt}, ALK\textsuperscript{wt} NSCLC in second line irrespective of PD-L1 expression
- Gefitinib, erlotinib or afatinib seem equivalent in terms of efficacy irrespective of type of mutation
- Combination of erlotinib and bevacizumab is more effective than erlotinib alone
- Osimertinib is the best option in patients with EGFRT\textsuperscript{790M+} NSCLC
- Alectinib is replacing crizotinib in first-line therapy for ALK rearranged NSCLC
- New EGFR or ALK inhibitors cross blood brain barrier extending patient survival impacting on treatment of patients with brain metastases
THANK YOU!