Year in Review: Therapeutic Advances in Treating Advanced NSCLC

2017 Conversations in Oncology in Shanghai, China

Barbara Melosky
Outline

• Discuss the current treatment algorithms in non-squamous NSCLC

• Provide an overview of recent advances: review updates from
  – ELCC Geneva 2017
  – ASCO Chicago 2017
  – ESMO Madrid 2017
  – WCLC Japan 2017
Molecular Classification of NSCLC: 2017

Mutations in Adenocarcinoma

- KRAS 25.5%
- EGFR 16.1%
- Wild type 20.8%
- ALK 3.9%
- NRG1 3.2%
- DDR2 2.9%
- RIT1 2.2%
- ROS1 1.7%
- NTRK1 1.7%
- HER2 1.9%
- RET 0.7%
- MET exon 14 4.2%
- BRAF 6.9%
- NF1 8.1%
- Other 43.9%
Driver Mutations in Adenocarcinoma

France\textsuperscript{1}

NSCLC
(Biomarkers France [IFCT]; N = 17,664)

- EGFR (sensitizing) 10.1%
- EGFR (resistance) 0.9%
- HER2 1%
- KRAS 29%
- Unknown/wild type 50%
- ALK, 5%
- PI3K, 2%
- BRAF, 2% (V600E, 1.4%)

US\textsuperscript{2}

Adenocarcinoma
(Lung Cancer Mutation Consortium; N = 733)

- EGFR (sensitizing) 17%
- HER2, 3%
- KRAS, 25%
- No oncogenic driver detected 36%
- Mut > 1 gene, 3%
- MET, 1%
- NRAS, 1%
- MEK1, < 1%
- ALK, 8%
- PI3CA, 1%
- BRAF, 2% (V600E, 1.6%)

China\textsuperscript{3}

- EGFR 51%
- Unknown 27%
- KRAS 7%
- CTNNB1 4%
- PIK3CA 2%
- NRAS 1%
- FGFR13 1%
- RET 1%
- ROS1 1%
- ALK 4%

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

Del19 = exon 19 deletions; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; L858R = exon 21 L858R point mutation; NSCLC = non–small cell lung cancer.
IPASS: PFS

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

EURTAC: PFS

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

IPASS: PFS\(^1\)

**Exon 19 Del**

HR = 0.43

**L858R**

HR = 0.81

EURTAC: PFS\(^2\)

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

Overall Survival

**IPASS¹:** 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

**EURTAC² Overall Survival**

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

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

Patients with common mutations*

<table>
<thead>
<tr>
<th>Time of Progression Free Survival (Months)</th>
<th>Estimated PFS Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk:</td>
<td></td>
</tr>
<tr>
<td>LL3 Afatinib</td>
<td></td>
</tr>
<tr>
<td>204</td>
<td></td>
</tr>
<tr>
<td>169</td>
<td></td>
</tr>
<tr>
<td>143</td>
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<td>115</td>
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<td>75</td>
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<tr>
<td>49</td>
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<td>30</td>
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<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>LL3 Cis/Pem</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td></td>
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<tr>
<td>35</td>
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<td>17</td>
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<td>9</td>
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<tr>
<td>0</td>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>LL6 Afatinib</td>
<td></td>
</tr>
<tr>
<td>216</td>
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<tr>
<td>186</td>
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<td>152</td>
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<td>116</td>
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<td>55</td>
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<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>LL6 Cis/Gem</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td></td>
</tr>
<tr>
<td>21</td>
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</tr>
</tbody>
</table>

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

PFS = progression-free survival.

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

Prespecified Endpoint

**LUX-Lung 3**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=112)</th>
<th>Cis/Pem (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>33.3</td>
<td>21.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.54 (0.36–0.79)</td>
<td></td>
</tr>
<tr>
<td>( P )-value</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

**LUX-Lung 6**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=124)</th>
<th>Cis/Gem (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>31.4</td>
<td>18.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.64 (0.44–0.94)</td>
<td></td>
</tr>
<tr>
<td>( P )-value</td>
<td>0.0229</td>
<td></td>
</tr>
</tbody>
</table>

Estimated OS Probability

**Time (Months)**

**Afatinib**

- LUX-Lung 3: 33.3 months
- LUX-Lung 6: 31.4 months

**Cis/Pem**

**Cis/Gem**

No. at risk:

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Cis/Pem</th>
<th>Cis/Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUX-Lung 3</td>
<td>112</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>124</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

**IMPRESSIVE**

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

LUX-Lung 7

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

**Afatinib 40 mg QD†**

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

**Gefitinib 250 mg QD**

**Co-primary endpoints:**
- PFS (independent review)
- TTF
- OS

**Secondary endpoints:**
- ORR
- Time to response
- Duration of response
- Tumour shrinkage
- HRQoL

- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4 and 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.

Afatinib vs Gefitinib: Updated Outcomes – PFS

**Afatinib** vs **Gefitinib**: Updated Outcomes – PFS

Afatinib vs Gefitinib: Updated Outcomes – TTF

**Median, mo**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>13.7</strong></td>
<td><strong>13.7</strong></td>
<td><strong>11.5</strong></td>
</tr>
</tbody>
</table>

**HR (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.73</strong></td>
<td><strong>0.73</strong></td>
<td><strong>0.73</strong></td>
</tr>
</tbody>
</table>

**P-value**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.0073</strong></td>
<td><strong>0.0073</strong></td>
<td><strong>0.0073</strong></td>
</tr>
</tbody>
</table>

13.7 vs 11.5 months

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*P=0.0067; 1P=0.0029.

TTF = time from randomization to discontinuation for any reason.

Afatinib vs Gefitinib: Objective Response and Disease Control Rate by Independent Review


**Objective Response Rate (ORR)**

- **ITT**
  - Afatinib: 73%
  - Gefitinib: 56%
  - *P* = 0.002

- **Del19**
  - Afatinib: 75%
  - Gefitinib: 66%
  - *P* = 0.150

- **L858R**
  - Afatinib: 69%
  - Gefitinib: 42%
  - *P* = 0.003

**Median DoR, months**

- **ITT**
  - Afatinib: 10.1 (8.2, 11.1)
  - Gefitinib: 8.3 (7.3 – 10.2)

**Disease control rate (N)**

- Afatinib: 91.3% (146)
- Gefitinib: 87.4% (139)
Updated Overall Survival From LUX-Lung 7

No. at risk:

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>27.9</td>
<td>24.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.85 (0.66, 1.09)</td>
<td>0.1950</td>
</tr>
<tr>
<td>P-value</td>
<td>0.01950</td>
<td>0.1950</td>
</tr>
</tbody>
</table>

27.9 vs 24.5 months

Corral J et al. ELCC 2017; #93PD.
OS By \textit{EGFR} Mutation Subtype

\textbf{Del19}

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
& Afatinib & Gefitinib \\
\hline
Median, mo & 30.7 & 26.4 \\
HR (95\% CI) & 0.82 (0.58-1.15) & & \\
P-value & 0.242 & & \\
\hline
\end{tabular}
\end{center}

\textbf{L858R}

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
& Afatinib & Gefitinib \\
\hline
Median, mo & 25.0 & 21.2 \\
HR (95\% CI) & 0.89 (0.61-1.31) & & \\
P-value & 0.566 & & \\
\hline
\end{tabular}
\end{center}

No. at risk:

\begin{itemize}
\item Afatinib: 93, 88, 82, 68, 61, 50, 40, 27, 17, 1
\item Gefitinib: 67, 65, 57, 43, 33, 24, 19, 14, 6, 1
\end{itemize}

Corral J et al. ELCC 2017; #93PD.
# 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>-</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
OS Outcome With Afatinib Depending On Age Group

Long-term Responders (LTRs), Defined by Receiving Afatinib ≥3 Years

Post-hoc analysis identified 24 (LL3), 23 (LL6) and 19 (LL7) patients (LTRs) who received ≥3 years of afatinib

LTR = long-term responder.


### PFS in LL3/LL6 and TTF in LL7

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>LL3 PFS</th>
<th>LL6 PFS</th>
<th>LL7 TTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>39</td>
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<tr>
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<tr>
<td>48</td>
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</tr>
</tbody>
</table>

![PFS and TTF Graph](image)
Tumour Volume Change in LL3/6/7

Long term responder (n=66)*†

*Patients were ordered by maximum percentage decrease in tumour volume from baseline; †Tumour volume change not available for seven patients (two patients with NN in LL3, one patient with a CR and three patients with NN in LL6, and one patient with SD in LL7). CR = complete response; PR = partial response; SD = stable disease; NN = non-CR, non-progressive disease.

What about adding Bevacizumab?

Afatinib plus Bevacizumab (ABC Trial)

ORR 18.2%
SD 72%
**ARCHER 1050: Dacomitinib**

- Advanced NSCLC with *EGFR*-activating mutation(s)
- No prior systematic treatment of advanced NSCLC
- **No CNS metastasis**
- No prior *EGFR* TKI or other TKI
- ECOG PS 0, 1

**Primary endpoint**
PFS by blinded independent review

**Secondary endpoints**
PFS (investigator assessed), ORR, DOR, TTF, OS, safety, PROs

**Stratify**
Race (Asian vs non)
*EGFR* M+ (exon 19 vs 21)

Dacomitinib
45 mg PO QD (N=227)

Gefitinib
250 mg PO QD (N=225)
Shown are best responses in patients treated with dacomitinib or gefitinib. Each bar represents an individual patient’s maximum reduction in target lesion size.
**Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Daco (N=227)</th>
<th>Gef (N=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>136 (59.9%)</td>
<td>179 (79.6%)</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>14.7 (11.1, 16.6)</td>
<td>9.2 (9.1, 11.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.47–0.74)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

**PFS rate 30.6% vs 9.6%**

**14.7 mo vs 9.2 mo**

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>Dacomitinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>227</td>
<td>225</td>
</tr>
<tr>
<td>6</td>
<td>154</td>
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<td>12</td>
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<tr>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

++Censored.

Mok TS et al. ASCO 2017, abstract LBA9007.
Dose Modification

• Dacomitinib
  – First dose reduction: 30 mg/day
  – Second reduction: 15 mg/day

• Gefitinib
  – 250 mg every two days

<table>
<thead>
<tr>
<th></th>
<th>Median time to dose reduction</th>
<th>Median duration of dose reduction</th>
<th>Reduction to 30 mg daily</th>
<th>Reduction to 15 mg daily</th>
<th>Total number of patients with dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacomitinib (n=227)</td>
<td>2.8 months (range, 0.3 to 20.3)</td>
<td>11.3 months (range, 0.1 to 33.6)</td>
<td>87 (38.3%)</td>
<td>63 (27.8%)</td>
<td>150 (66.1%)</td>
</tr>
<tr>
<td>Gefitinib (n=224)</td>
<td>3.3 months (1.2 to 25.7)</td>
<td>5.2 months (0.3 to 17.8)</td>
<td>NA</td>
<td>NA</td>
<td>18 (8.0%)</td>
</tr>
</tbody>
</table>
Molecular Mechanisms of Acquired Resistance to First-/Second-Generation EGFR TKIs

AURA 3: PFS\textsuperscript{1}

10.1 months vs 4.4 months

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib (n=279)</th>
<th>Platinum-pemetrexed (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progressive-free survival, mo</td>
<td>10.1 (8.3-12.3)</td>
<td>4.4 (4.2-5.6)</td>
</tr>
<tr>
<td>HR for disease progression or death (95% CI)</td>
<td>0.82 (0.58-1.15)</td>
<td>0.242</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CNS PFS in AURA 3\textsuperscript{2}

Intracranial Response Rate: 70%

CNS PFS 11.7 months vs 5.6 months

FLAURA

Patients with locally advanced or metastatic NSCLC
- PS 0 / 1
- Exon 19 deletion / L858R
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS mets allowed

Endpoints
- Primary endpoint: PFS

Osimertinib (n=279)

Randomised 1:1

EGFR-TKI; Gefitinib or Erlotinib (n=277)

Crossover was allowed for patients in the SoC arm,

N = 556

Gefitinib, erlotinib not stratified
No afatinib or dacomitinib
No uncommon mutations
Brain mets not stratified
If no brain mets: followup in CNS not specified

FLAURA Primary Endpoint: PFS

- **Osimertinib** vs **Erlotinib/gefitinib**

**PFS Assessed by Investigator**

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib</th>
<th>Erlotinib/gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>18.9</td>
<td>10.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(15.2, 21.4)</td>
<td>(9.6, 11.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.46</td>
<td>(0.37-0.57)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**PFS Assessed by Independent Review**

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib</th>
<th>Erlotinib/gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>17.7</td>
<td>9.7</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(15.1, 21.4)</td>
<td>(8.5, 11.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45</td>
<td>(0.36-0.57)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*18.9 vs 10.2 months*

Does Sequence Matter?
OS in Patients Treated With 3rd-gen TKIs in LUX-Lung 7

Corral J et al. ELCC 2017; #93PD.

20% / 17% who discontinued afatinib/gefitinib received 3rd-generation TKIs (osimertinib, olmutinib, rociletinib)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (N=30)</th>
<th>Gefitinib (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>NE</td>
<td>48.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.20–1.19)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.107</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:

<table>
<thead>
<tr>
<th>Time to death (months)</th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>18</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>21</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>24</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>27</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>30</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>33</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>36</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>39</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>42</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>45</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>48</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>51</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>54</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>57</td>
<td>26</td>
<td>17</td>
</tr>
</tbody>
</table>

4 years+           4 years
EGFR: Advanced NSCLC

**EGFR mutation testing**
- L858R
  - EGFR TKI: afatinib, dacomitinib, gefitinib, erlotinib
- 19Del
  - EGFR TKI: afatinib preferred
- Uncommon mutations
  - EGFR TKI: afatinib preferred

**Plasma cfDNA testing**
- Tumour rebiopsy (T790M only)
- T790M-
  - Chemotherapy Doublet
- T790M+
  - Osimertinib
  - Chemotherapy Doublet

**1st Line**
- EGFR TKI: afatinib preferred

**2nd Line**
- Immunotherapy

**3rd Line**
- Immunotherapy

**4th Line**
- Immunotherapy

**Brain Mets**
- Osimertinib

* Dacomitinib will soon be included in the algorithm.

ALK Mutations
PROFILE 1014: First-line Crizotinib vs Pem/Cis PFS

Alectinib vs Crizotinib: Global ALEX Trial

**Randomize**
- Advanced or metastatic ALK+ NSCLC
- Treatment-naive
- ECOG PS 0–2
- Asymptomatic brain metastases allowed

**Alectinib**
- 600 mg BID PO

**Crizotinib**
- 250 mg BID PO

**Endpoints**
- Primary
  - PFS by investigator review
- Secondary
  - PFS by IRC
  - Time to CNS progression
  - ORR, DOR
  - OS
  - Safety and tolerability
  - Patient-reported outcomes

**Stratify**
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- Brain metastases (present vs absent)

Alectinib vs Crizotinib

PFS Independent Review

NR vs 11.1 months  HR .47

PFS Investigator

25.7 vs 10.4 months  HR .50

PFS 25.7 months
## CNS Prevention

### CNS metastases by IRC (%)

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>58 (38)</td>
<td>64 (42)</td>
</tr>
<tr>
<td>Absent</td>
<td>93 (62)</td>
<td>88 (58)</td>
</tr>
</tbody>
</table>

### CNS metastases treatment (%)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>None (62)</th>
<th>Whole brain RT (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>58</td>
<td>36 (62)</td>
<td>16 (28)</td>
</tr>
<tr>
<td>Alectinib</td>
<td>64</td>
<td>37 (58)</td>
<td>17 (27)</td>
</tr>
</tbody>
</table>

**38% vs 42%**

### 4 fold reduction

**CNS Prevention**

**38% vs 42%**

**Cumulative Incidence**

**Month 4**
**ASCEND 4: Phase 3 Randomized Global Open-label Study**

**Inclusion criteria**
- Stage III/IV ALK+ NSCLC
- Treatment-naive
- WHO PS 0-2
- Neurologically stable brain metastases (symptomatic or not)

**Chemotherapy**
- 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
ASCEND-4 Outcomes

PFS

- PFS 16.6 vs 8.1 months

OS

- Immature but favors ceritinib
ASCEND-4 Outcomes

ORR

72.5% (65.5, 78.7)

26.7% (20.5, 33.7)

△ 45.8%

CNS ORR

72.7% (16/22)

27.3% (6/22)

△ 45.4%

72.7 CNS Response
Efficacy and Updated Safety of Ceritinib (450 mg or 600 mg) With Low-Fat Meal vs 750 mg Fasted in ALK+ Metastatic NSCLC

Authors: Cho BC,1 Obermannova R,2 Bearz A,3 Kim DW,4 Orlov S,5 Borra G,6 Kim SW,7 Postmus P,8 Laurie S,9 Park K,10 Geater SL,11 Bettini A,12 Osborne K,13 Passos VQ,14 Chen Z,14 Dziadziszko R15
ASCEND-8: Phase 1, Randomized, Global, Open-label, Parallel Design Study

Inclusion criteria

- Stage IIIB/IV ALK+ NSCLC
- Treatment-naive* (efficacy analysis) or previously treated with ≥1 systemic therapy (PK analysis included both)
- ALK+ status was assessed by Ventana IHC (treatment-naive) or FDA approved FISH (previously treated)
- WHO PS 0-2
- Neurologically stable brain metastases (symptomatic or not)

R 1:1:1

- Ceritinib 450 mg/day with low-fat meal
- Ceritinib 600 mg/day with low-fat meal
- Ceritinib 750 mg/day under fasted conditions
**ASCEND-8 Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib 450 mg fed (N = 41)</th>
<th>Ceritinib 600 mg fed (N = 40)</th>
<th>Ceritinib 750 mg fasted (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (CR+PR), n (%) (95% CI)</td>
<td>32 (78.0) (62.4-89.4)</td>
<td>30 (75.0) (58.8-87.3)</td>
<td>28 (70.0) (53.5-83.4)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD+non-CR/non-PD), n (%) (95% CI)</td>
<td>38 (92.7) (80.1-98.5)</td>
<td>37 (92.5) (79.6-98.4)</td>
<td>36 (90.0) (76.3-97.2)</td>
</tr>
<tr>
<td>Median time to response, weeks (95% CI)</td>
<td>6.3 (6.0-6.9)</td>
<td>6.3 (6.1-12.1)</td>
<td>6.3 (6.0-12.3)</td>
</tr>
</tbody>
</table>

ORR and DCR are clinically relevant and consistent among the 3 treatment arms.
## Overview of GI Toxicities

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Ceritinib 450 mg fed (N = 89)</th>
<th>Ceritinib 600 mg fed (N = 86)</th>
<th>Ceritinib 750 mg fasted (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>41 (46.1)</td>
<td>8 (9.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>30 (33.7)</td>
<td>10 (11.2)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>27 (30.3)</td>
<td>4 (4.5)</td>
<td>0</td>
</tr>
</tbody>
</table>
ALTA: Randomized Dose Evaluation of Brigatinib

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

Randomized 1:1

Brigatinib 90 mg qd
- N = 112

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

Brigatinib 180 mg qd*
- N = 110

*With 7-day lead-in at 90 mg

Primary Endpoint: Confirmed ORR per RECIST v1.1 (assessed by investigator)
ALTA: Tumor Response and PFS

ORR 54%

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

Lorlatinib – Covers ALK Resistance Mutations

- Secondary mutations in the ALK domain can induce resistance to first- and second-generation ALK TKIs\(^1\)
- Lorlatinib is a selective inhibitor of ALK and ROS1 with broad-spectrum potency against most known ALK resistance mutations, including G1202R\(^1,2\)

Breakthrough Therapy designation from the FDA for use in patients with ALK-positive metastatic NSCLC previously treated with at least one ALK TKI

---

ALK, anaplastic lymphoma kinase; IC\(_{50}\), half-maximal inhibitory concentration; ND, not done; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.


Lorlatinib Can Cross the Blood–Brain Barrier

**Concentrations of Lorlatinib Achieved in CSF (Phase 1)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CSF Concentration Unbound (ng/mL)</th>
<th>Plasma Concentration Unbound (ng/mL)</th>
<th>CSF/Plasma Unbound Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.64</td>
<td>4.3</td>
<td>0.61</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>155</td>
<td>0.65</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>106</td>
<td>0.77</td>
</tr>
<tr>
<td>4</td>
<td>125</td>
<td>131</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Patients treated with lorlatinib 100 mg once daily.

Unbound refers to free drug not bound to plasma proteins.

**CNS Responses in Patients With Measurable Disease (Phase 1)**

- Off-treatment or progressive disease occurred
- No prior TKI
- 1 prior TKI
- ≥2 prior TKIs

R Indicates patients with ROS1 rearrangements

ALK, anaplastic lymphoma kinase; CNS, central nervous system; CSF, cerebrospinal fluid; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.

ALK+ Patients Previously Treated With ≥1 ALK TKI

EXP2 (Prior CRZ)

EXP3 (1 Prior TKI*)

EXP4 (2 Prior TKIs)

EXP5 (3 Prior TKIs)

Prior CRZ + chemotherapy or 1 other ALK TKI ± chemotherapy.
ALK, anaplastic lymphoma kinase; CRZ, crizotinib; TKI, tyrosine kinase inhibitor.

3 previous treatments
Treatment Algorithm for Advanced NSCLC

Non-Squamous: ALK Rearrangement

1st Line

Alectinib, Ceritinib, Crizotinib

2nd Line

Ceritinib, Alectinib, Brigatinib

3rd Line

Lorlatinib

4th Line

Chemotherapy doublet (pemetrexed based preferred)

4th Line

Immunootherapy
BRAF Mutations
BRAF Mutations

Pre-treated patients\(^1\)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>64 (58–71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (51%)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (49%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic origin</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>49 (86%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>0</th>
<th>17 (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>35 (61%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology at initial diagnosis</th>
<th>Adenocarcinoma</th>
<th>Large cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma (predominantly)</td>
<td>56 (98%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of tobacco use</th>
<th>Never smoker</th>
<th>Current smoker</th>
<th>Former smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 (28%)</td>
<td>6 (11%)</td>
<td>35 (61%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking history</th>
<th>Never</th>
<th>Current</th>
<th>Former</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30 pack-years</td>
<td>22 (54%)</td>
<td>6 (11%)</td>
<td>19 (46%)</td>
</tr>
<tr>
<td>≥30 pack-years</td>
<td>18 (35%)</td>
<td>8 (22%)</td>
<td>12 (26%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of previous systemic regimens for metastatic disease</th>
<th>1</th>
<th>38 (67%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥2</td>
<td>19 (33%)</td>
</tr>
</tbody>
</table>

Treatment-naive patients\(^2\)

<table>
<thead>
<tr>
<th>Age years</th>
<th>67 (62–74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (61%)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (39%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>30 (83%)</td>
</tr>
<tr>
<td>Native American or other Pacific Islander</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>0</th>
<th>13 (36%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>22 (61%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology at initial diagnosis</th>
<th>Adenocarcinoma</th>
<th>Adenosquamous Carcinoma (predominantly)</th>
<th>Large cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma (predominantly)</td>
<td>32 (89%)</td>
<td>1 (3%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking history</th>
<th>Never</th>
<th>Current</th>
<th>Former</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 (28%)</td>
<td>5 (14%)</td>
<td>23 (58%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pack-years</th>
<th>Median</th>
<th>18 (5–34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td>8 (22%)</td>
</tr>
<tr>
<td></td>
<td>10–30</td>
<td>9 (25%)</td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td>7 (19%)</td>
</tr>
</tbody>
</table>

Never Smokers 28%

Abrogation of Feedback Loop of Raf by Erk

Synergism to block both BRAF and MEK

Dabrafenib and Trametinib Second Line: BRAF V600E ASCO 2017


N=57

ORR 67%  
PFS 10.2 months

OS 18.2 months
Dabrafenib and Trametinib First Line: BRAF V600E

ORR 64%

PFS 10.9 months

OS 24.6 months

N=36

MET Mutations
Emibetuzumab (Anti-MET mAB)

PFS in Patients with the Highest MET Expression (≥90% cells MET 3+)

- Emi + Erl: 20.7 months median PFS (N=12; 90%CI: 5.4, NA)
- Erl: 5.4 months median PFS (N=12; 90%CI: 2.8, 17.2)

HR (90% CI): 0.39 (0.17, 0.91)

Scagliotti G et al. ASCO 2017, abstract 9019.
Mechanism of MET Exon 14 Skipping

MET X14 Skipped

Exon 14 (regulatory domain)
# c-Met Inhibitors in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>Ib</td>
<td>NCT00585195</td>
</tr>
<tr>
<td>Mersetinib</td>
<td>I</td>
<td>NCT02920996</td>
</tr>
<tr>
<td>Savolitinib</td>
<td>I</td>
<td>NCT02897479</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>II</td>
<td>NCT01639508</td>
</tr>
<tr>
<td>Capmantineib</td>
<td>II</td>
<td>NCT02750215</td>
</tr>
<tr>
<td>Tepotinib</td>
<td>II</td>
<td>NCT02864992</td>
</tr>
</tbody>
</table>
### Impact of MET Inhibitors on Survival Among Patients With MET Exon 14 Mutant Non-Small Cell Lung Cancer

#### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 148</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>72 (43-88)</td>
</tr>
<tr>
<td>Male</td>
<td>63 (43%)</td>
</tr>
<tr>
<td>Female</td>
<td>85 (57%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>54 (39%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>85 (61%)</td>
</tr>
<tr>
<td>&lt; 10 pack-years</td>
<td>17</td>
</tr>
<tr>
<td>≥ 10 pack-years</td>
<td>60</td>
</tr>
<tr>
<td>Pack-years unknown</td>
<td>8</td>
</tr>
<tr>
<td>Smoking status unknown</td>
<td>9</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>114 (77%)</td>
</tr>
<tr>
<td>Non-adenocarcinoma</td>
<td>34 (23%)</td>
</tr>
<tr>
<td>- Sarcomatoid/Pleomorphic</td>
<td>20</td>
</tr>
<tr>
<td>- Squamous</td>
<td>7</td>
</tr>
<tr>
<td>- Adenosquamous</td>
<td>5</td>
</tr>
<tr>
<td>- Poorly differentiated</td>
<td>2</td>
</tr>
<tr>
<td>Stage at diagnosis:</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>49 (36%)</td>
</tr>
<tr>
<td>II</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>III</td>
<td>31 (22%)</td>
</tr>
<tr>
<td>IV</td>
<td>41 (30%)</td>
</tr>
<tr>
<td>Initial stage unknown</td>
<td>10</td>
</tr>
<tr>
<td>Concurrent MET amplification</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>No</td>
<td>79 (79%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>48</td>
</tr>
</tbody>
</table>

Awad M et al. ASCO 2017 Abstract 8511.
Outcomes in Patients with MET Exon 14 Mutations

**Overall survival from date of stage IV diagnosis**

- **Never received a MET TKI**
  - N = 34
  - Median OS (95% CI) 8.1 months (5.3 – NR)

- **Received a MET TKI**
  - N = 27
  - Median OS (95% CI) 24.6 months (12.1 – NR)

**Outcomes on Crizotinib**

- **Progression-free survival on crizotinib**
  - (and no prior MET TKI)
  - N = 22
  - Median PFS (95% CI) 7.4 months (3.4 – NR)

- **Overall survival on crizotinib**
  - (and no other MET TKI)
  - Median OS (95% CI) 20.5 months (9.5 – NR)
PD-L1 Expression and Response to Immunotherapy in Patients With MET Exon 14 Altered Non-Small Cell Lung Cancer

Sebari J et al. ASCO 2017 Abstract 8512.
Sebani J et al. ASCO 2017 Abstract 8512.

Response to immunotherapy by irRECIST criteria

- ORR 6.7%
- 95% CI (0.32%)

ORR 1/15 = 6.7%

1 patient

PD-L1 and response to immunotherapy

- 6/15 had PD-L1 > 50%
- No partial responses among the 6 patients with PD-L1 ≥ 50

P = 0.0006

TMB is lower in patients with MET exon 14 altered NSCLCs

Sebani J et al. ASCO 2017 Abstract 8512.
PD-1/L1 mAB
Pacific Trial
Practice Changing
Targeting PD-1 Pathway

Tumour microenvironment

Durvalumab

T cell

PD-1

PD-L1

Tumour cell

PD-L1
Stage III NSCLC
> concurrent CTRT is better than sequential CTRT

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer
Anne Auperin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyohiko Furuse, Pierre Fournel, Jose Bideros, Gerald Clamon, Hakki Caneyi Ulutan, Rebecca Plauta, Takehara Yamazaki, Marie-Cécile Bezannier, Apollonia Uiterhove, Xiaofei Wang, Lesley Stewart, Rodrigo Artigada, Sarah Burdess, and Jean-Pierre Pignon

6 RCTs – 1,205 patients
- Absolute benefit 4.5% at 5 years
- Improved local control
- Increased acute oesophageal toxicity
- No increase in pulmonary toxicity

Median OS 18 months
15% alive 5 years

Auperin et al, J Clin Oncol 28:2181-2190, 2010
Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)

- PS score 0, 1
- PD-L1 not necessary

Durvalumab 10 mg/kg q2w for up to 12 months
N=476

Placebo 10 mg/kg q2w for up to 12 months
N=237

Planned sample size: N=702 patients

Co-primary endpoints: PFS and OS

1–42 days post-cCRT

2:1, stratified by age, sex, and smoking history

ESMO 2017
# PACIFIC: Antitumor Activity

## Objective Response

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab (N=443)*</th>
<th>Placebo (N=213)*</th>
<th>Treatment effect (HR [95% CI])‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response, n (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>6 (1.4)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>120 (27.1)</td>
<td>33 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>233 (52.6)</td>
<td>119 (55.9)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>73 (16.5)</td>
<td>59 (27.7)</td>
<td></td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>10 (2.3)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

## Duration of response, months

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab (N=443)*</th>
<th>Placebo (N=213)*</th>
<th>Treatment effect (HR [95% CI])‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>13.8 (6.0–NR)</td>
<td>0.43 (0.22–0.84)</td>
</tr>
</tbody>
</table>

Paz-Ares et al. ESMO 2017, abstract LBA_PR.
PACIFIC: PFS

**ESMO 2017**

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab (N=476)</th>
<th>Placebo (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI), months</td>
<td>16.8 (13.0–18.1)</td>
<td>5.6 (4.6–7.8)</td>
</tr>
</tbody>
</table>

**HR 0.52**

*P<0.0001*

16.8 vs 5.6 months
11 month difference!

HR 0.52

50%

25%

Paz-Ares et al. ESMO 2017, abstract LBA_PR.
PACIFIC: Time to Distant Metastasis or Death

HR 0.52
*P* < 0.0001

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of death or distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from randomization (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>Durvalumab</td>
<td>Placebo</td>
</tr>
<tr>
<td>1</td>
<td>476</td>
<td>237</td>
</tr>
<tr>
<td>3</td>
<td>407</td>
<td>184</td>
</tr>
<tr>
<td>6</td>
<td>336</td>
<td>129</td>
</tr>
<tr>
<td>9</td>
<td>288</td>
<td>106</td>
</tr>
<tr>
<td>12</td>
<td>173</td>
<td>63</td>
</tr>
<tr>
<td>15</td>
<td>91</td>
<td>32</td>
</tr>
<tr>
<td>18</td>
<td>46</td>
<td>16</td>
</tr>
<tr>
<td>21</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

9 month difference

Paz-Ares et al. ESMO 2017, abstract LBA_PR.
Pneumonitis (grouped terms) or radiation pneumonitis, n (%)*

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab (N=475)</th>
<th>Placebo (N=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>161 (33.9)</td>
<td>58 (24.8)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>16 (3.4)</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>5 (1.1)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>30 (6.3)</td>
<td>10 (4.3)</td>
</tr>
</tbody>
</table>
Practice Changing

Surgery vs Durvalumab

OAK: Treatment Beyond Progression

Atezolizumab

T cell

PD-L1

Tumour cell

PD-L1

PD-1

ASCO 2017

OAK: Overall Survival, ITT (N=850)

HR, 0.73\textsuperscript{a}  
(95% CI, 0.62, 0.87)  
P=0.0003

168/332 = 50\% Treated Beyond Progression

Median 9.6 mo  
(95% CI, 8.6, 11.2)  
Median 13.8 mo  
(95% CI, 11.8, 15.7)
OS Post-PD in Atezolizumab Arm: By Post-PD Treatment

Atezolizumab
n = 425

No PD per RECIST v1.1
n = 53, 22%

PD per RECIST v1.1
n = 332, 78%

Continued Atezo Post-PD
n = 168, 51%

Other anti-cancer NPT Post-PD
n = 94, 28%

No anti-cancer NPT Post-PD
n = 70, 21%

mOS
95% CI
12.7 mo
(9.3, 14.9)
8.8 mo
(6.0, 12.1)
2.2 mo
(1.9, 3.4)

12.7 months

Best Change in Target Lesions with Atezolizumab TBP

Relative to new (reset) baseline at PD

N= 168

7% (12/168) had subsequent response in target lesions (≥ 30% reduction post-PD)
49% (83/168) had stable target lesions (best change between +20% and ~30%)
Post-PD tumor reduction or stability was observed across all PD-L1 expression subgroup(s)

49% Stable
7% ORR
3.6% 12/332

Presented by David Gandara at 2017 ASCO Annual Meeting.
Non-randomized Comparisons Introduce Biases for OS Analysis

### Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab-arm Patients Post-PD (n = 332)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuing atezolizumab</td>
</tr>
<tr>
<td></td>
<td>n = 168</td>
</tr>
<tr>
<td>Worsening of ECOG PS</td>
<td>18%</td>
</tr>
<tr>
<td>% Increase in target lesion SLD, median (range)</td>
<td>16.5 (-100.0 – +175.0)</td>
</tr>
<tr>
<td></td>
<td>Other anti-cancer treatment</td>
</tr>
<tr>
<td></td>
<td>n = 94</td>
</tr>
<tr>
<td>Worsening of ECOG PS</td>
<td>29%</td>
</tr>
<tr>
<td>% Increase in target lesion SLD, median (range)</td>
<td>21.6 (-100.0 – +110.5)</td>
</tr>
<tr>
<td></td>
<td>No anti-cancer treatment</td>
</tr>
<tr>
<td></td>
<td>n = 70</td>
</tr>
<tr>
<td>Worsening of ECOG PS</td>
<td>33%</td>
</tr>
<tr>
<td>% Increase in target lesion SLD, median (range)</td>
<td>22.6 (-76.6 – +89.5)</td>
</tr>
</tbody>
</table>

### Survival Analysis

- **Overall Survival (OS)**:
  - 18-mo OS: 37%
  - 20-mo OS: 20%
  - 12-mo OS: 9%

- **Median OS (mOS)**:
  - Atezolizumab: 12.7 mo
  - Other anti-cancer NPT Post-PD: 8.8 mo
  - No anti-cancer NPT Post-PD: 2.2 mo

- **95% CI**:
  - Atezolizumab: (9.3, 14.9)
  - Other anti-cancer NPT Post-PD: (6.0, 12.1)
  - No anti-cancer NPT Post-PD: (1.9, 3.4)

### Selection Bias and not randomized

- Discussant Dr. Solange Peters

---

Presented by Solange Peters at 2017 ASCO Annual Meeting.
KEYNOTE-024: Updated Analysis Pembrolizumab Versus Platinum-based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%

Julie R. Brahmer,1 Delvys Rodríguez-Abreu,2 Andrew G. Robinson,3 Rina Hui,4 Tibor Csőszi,5 Andrea Fülöp,6 Maya Gottfried,7 Nir Peled,8 Ali Tafreshi,9 Sinead Cuffe,10 Mary O’Brien,11 Suman Rao,12 Katsuyuki Hotta,13 Antonio Riccio,14 Jing Yang,14 M. Catherine Pietanza,14 Martin Reck15
Targeting PD-1 Pathway


Tumour Microenvironment

Pembrolizumab

T cell

PD-L1

Tumour cell

PD-1

PD-L1
PD-L1 Expression and Pembrolizumab

- PD-L1 TPS cutoff point of 50% was identified in KEYNOTE-001 using independent training and validation sets¹
- FDA-approved and CE-marked companion diagnostic: PD-L1 IHC 22C3 pharmDx (Dako)

**Key Eligibility Criteria**
- Untreated stage IV NSCLC
- PD-L1 TPS $\geq$ 50%
- ECOG PS 0-1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

**Pembrolizumab**
200 mg IV Q3W
(2 years)

**Platinum-Doublet Chemotherapy**
(4-6 cycles)

**PD**

**Both Non Squamous and Squamous**

**Key End Points**

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

---

*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.*
KEYNOTE-024: Tumor Response and PFS

Reck M et al. ESMO 2016. Abstract 437O

Progression-Free Survival

- **ORR, % (95% CI)**
  - Pembrolizumab: 45% (n=63)
  - Chemotherapy: 28% (n=41)
  - \( \Delta 17\% \)
  - \( P = 0.0011 \)

- **HR (95% CI)**
  - Pembrolizumab: 0.50 (0.37-0.68)
  - Chemotherapy: 10.3 vs 6.0 months

- **Median, mo**
  - Pembrolizumab: 10.3
  - Chemotherapy: 6.0

- **Events, n**
  - Pembrolizumab: 73
  - Chemotherapy: 116
KEYNOTE-024: Overall Survival

50% Crossover

<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></td>
<td></td>
</tr>
</tbody>
</table>

HR 0.60

Data cut-off: May 9, 2016.

Reck M et al. ESMO 2016. Abstract 437O
Overall Survival: Updated Analysis

**Pembrolizumab**
- Median OS: 30.0 months (18.3 months–NR)
- 1-year OS: 70.3%
- 2-year OS: 54.8%
- HR: 0.63 (0.47–0.86)
- P = 0.002

**Chemotherapy**
- Median OS: 14.2 months (9.8 months–19.0 months)
- 1-year OS: 51.5%
- 2-year OS: 34.5%

**HR 0.63**
- 30 months vs 14.2 months

**62% Crossover**

Brahmer JR et al. WCLC 2017. Abstract OA 17.06
## KEYNOTE-024: Tumor Responses

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (N = 154)</th>
<th>Chemotherapy (N = 151)</th>
<th>Crossover to Pembrolizumab (N = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response, n</td>
<td>70</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>45.5 (45% 7)</td>
<td>29.8 (22.6–37.8)</td>
<td>20.7 (12.6–31.1)</td>
</tr>
<tr>
<td><strong>Second Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response, n</td>
<td>17</td>
<td>45</td>
<td>20%</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>2.0 (2.0–4.1)</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Median Time to Response, mo (range)</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Censored duration of response, n</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
KEYNOTE-021 COHORT G: Updated Analysis Pemetrexed/Carboplatin +/- Pembrolizumab for Advanced NSCLC Non Squamous

Hossein Borghaei,1 Corey J. Langer,2 Shirish Gadgeel,3 Vassiliki A. Papadimitrakopoulou,4 Amita Patnaik,5 Steven F. Powell,6 Ryan D. Gentzler,7 Renato G. Martins,8 James P. Stevenson,9 Shadia I. Jalal,10 Amit Panwalkar,11 James Chih-Hsin Yang,12 Matthew Gubens,13 Lecia V. Sequist,14 Mark M. Awad,15 Joseph Fiore,16 Sanatan Saraf,16 Harry Raftopoulos,16† Leena Gandhi15
Phase II

KEYNOTE-021 Cohort G

Study Population
- Untreated stage IIIb or IV nonsquamous NSCLC
- No activating EGFR mutation or ALK translocation
- Provision of a sample for PD-L1 assessment
- ECOG PS 0 or 1
- No untreated brain metastases
- No ILD or pneumonitis requiring systemic steroids

End Points
- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Key secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS
- No alpha allocated for updated analysis; all P values are nominal (one-sided P < 0.025)

Pembrolizumab 200 mg Q3W for 2 years
Pemetrexed 500 mg/m²
+ Carboplatin AUC
5 mg/mL/min Q3W for 4 cycles

Pemetrexed 500 mg/m²
+ Carboplatin AUC
5 mg/mL/min Q3W for 4 cycles

PD, progressive disease.

a Randomization was stratified by PD-L1 TPS <1% vs ≥1%. 

b Indefinite maintenance therapy with pemetrexed 500 mg/m² Q3W permitted.
KEYNOTE-021: Tumor Responses

Approved by the FDA!
April 2017  First line
Pem/Carbo + Pembrolizumab

ESMO 2017¹
Δ26.4%
(95% CI, 8.9%–42.3%)
\( P = 0.0016^a \)

WCLC 2017²
Δ24.8%
(95% CI, 7.2%–40.9%)
\( P = 0.0029^a \)

KEYNOTE-021: PFS

ESMO 2017

WCLC 2017

Progression-Free Survival
(RECIST v1.1 by Blinded, Independent Central Review)

HR .54

Median (95% CI)
19.0 (8.5–NR)
8.9 (6.2–11.8)

Events, n/N
Pembro + PC 26/60
PC alone 40/63

HR (95% CI)
0.54
(0.33–0.88)

P = 0.0067

No. at risk

60 51 43 35 26 18 13 8 5 1

Time, months

0 3 6 9 12 15 18 21 24 27

*P value is descriptive (one-sided P < 0.05).
Data cut-off: May 31, 2017

2. Borghaei H et al. WCLC 2017. Abstract OA 17.01
KEYNOTE-021: OS

Data Cut-off: August 8, 2016¹

Median Follow-up: 10.6 mo
HR: 0.90 (0.42–1.91); P = 0.39

Data Cut-off: December 31, 2016²

Median Follow-up: 14.5 mo
HR: 0.69 (0.36–1.31); P = 0.13a

Data Cut-off: May 31, 2017

Median Follow-Up: 18.7 mo

- Median (95% CI)
  - NR (22.8–NR)
  - 20.9 (14.9–NR)

- Events, n/N
  - Pembro + PC: 20/60b
    - HR (95% CI): 0.59 (0.34–1.05)
    - P = 0.03a
  - PC alone: 31/63b

¹P value is descriptive (one sided P < 0.025). ²24 additional deaths since primary analysis (pembro + PC, n=7; PC alone, n=17)

IFCT-1502 CLINIVO: Real-life experience with nivolumab in patients with advanced NSCLC

Olivier MOLINIER, Clarisse AUDIGIER-VALETTE, Jacques CADRANEL, Isabelle MONNET, José HUREAUX, Werner HILGERS, Eric FAUCHON, Elisabeth FABRE, Benjamin BESSE, Philippe BRUN, Daniel COËTMEUR, Elisabeth QUOIX, Pierre MOURLANETTE, Fabrice BARLESI, Stéphanie BORDENAVE-CAFFRE, Thomas EGENOD, Pascale MISSY, Franck MORIN, Denis MORO-SIBILOT, Nicolas GIRARD
Efficacy of Nivolumab: PS ≥2 Patients

<table>
<thead>
<tr>
<th>Best response</th>
<th>Total (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>12% [6.5%-18.3%]</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>31% [23.1%-39.7%]</td>
</tr>
<tr>
<td>Disease Control</td>
<td>44% [35.0%-52.6%]</td>
</tr>
<tr>
<td>Progression</td>
<td>56% [47.4%-65.0%]</td>
</tr>
</tbody>
</table>

PS = 2
Median OS, IC95%: 3.4 [2.7-4.5] (n=170, 136 events)

Median PFS, IC95%: 1.7 [1.5-1.8] (n=170, 160 events)
Advanced NSCLC: Wild Type

PD-L1 Testing

1st Line
- PD-L1 ≥ 50%
  - Pembrolizumab Q3 w
- PD-L1 < 50%
  - Pemetrexed/Platinum doublet
  - Pemetrexed (Non-squamous)

2nd Line
- PD-L1 ≥ 1%
  - Pembrolizumab Q3 w
- PD-L1 ≥ 0%
  - Nivolumab Q2 w
  - Atezolizumab Q3 w

3rd Line
- Platinum doublet
- Afatinib (squamous), Erlotinib (non-squamous), Docetaxel +/- Ramicirumab

Based on results of initial testing

Year in Review 2017

• EGFR:
  – Dacomitinib, Osimertinib, T790 testing

• ALK:
  – Alectinib first line, Ceritinib, Brigatinib, Lorlatinib

• BRAF:
  – Dabrafenib and Trametinib

• cMET Exon 14 Skip:
  – Crizotinib

• Immunotherapy:
  – PACIFIC, KN 024, KN 21G
  – PD-L1, TMB and Microenvironment
For more information about other BI events and collaborations, please visit www.inOncology.com