T790M INHIBITOR AS FIRST LINE THERAPY: PROMISES AND PITFALLS

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DISCLOSURE SLIDE

AstraZeneca, BMS, Clovis, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Boehringer Ingelheim,
EGFR mutated lung cancer patient

1\textsuperscript{st}/2\textsuperscript{nd} generation TKI

Progression T790m-

Chemotherapy

Death

EGFR mutated lung cancer patient

1\textsuperscript{st}/2\textsuperscript{nd} generation TKI

Progression T790M+

Third generation TKI

Chemotherapy

Death

Third generation (anilino-pyrimidines)

WZ4002

CO-1686

AZD9291
## EGFR-TKI in 1st ligne treatment increase PFS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N (EGFRmut)</th>
<th>RR</th>
<th>Median PFS(months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURTAC³</td>
<td>Erlotinib vs cddp/doc</td>
<td>173</td>
<td>58.1% vs 14.9%</td>
</tr>
<tr>
<td>OPTIMAL⁴</td>
<td>Erlotinib vs carbo/gem</td>
<td>154</td>
<td>83% vs 36%</td>
</tr>
<tr>
<td>IPASS⁵</td>
<td>Gefitinib vs carbo/pacli</td>
<td>261</td>
<td>71.2% vs 47.3%</td>
</tr>
<tr>
<td>NEJ002⁶</td>
<td>Gefitinib vs carbo/pacli</td>
<td>224</td>
<td>73.7% vs 30.7%</td>
</tr>
<tr>
<td>WJTOG3405⁷</td>
<td>Gefitinib vs cddp/doc</td>
<td>172</td>
<td>62.1% vs 32.2%</td>
</tr>
<tr>
<td>LL3¹</td>
<td>Afatinib vs cddp/pem</td>
<td>345</td>
<td>56% vs 23%</td>
</tr>
<tr>
<td>LL6²</td>
<td>Afatinib vs cddp/gem</td>
<td>364</td>
<td>66.9% vs 23%</td>
</tr>
</tbody>
</table>

9.2-13.7 months

T790M positive – Progression free survival

mPFS: 13.5 months

Osimertinib 80mg

Rocelitinib 500mg or 625mg

mPFS: 8.0 months

Pasi A Janne et al, ELCC 2015; LV Sequist et al, ASCO 2015
Benefit of T790M inhibitor

EGFR mut → 1st/2nd generation TKI → Progression T790m- → Chemotherapy → Death

EGFR mut → 1st /2nd generation TKI → Progression T790M+ → Third generation TKI → Chemotherapy → Death

PFS1: 9.2-13.7 months
PFS2 Osimertinib: 13.5 months
PFS2 Rocelitinib: 8.0 months
PFS1 + PFS2: 17.2 to 27.5 months

OS
What is the Best Sequence?

Today

EGFR mut → 1st generation TKI → Progression T790m- → Chemotherapy → Death

EGFR mut → 1st generation TKI → Progression T790M+ → Third generation TKI → Chemotherapy → Death

PFS1 + PFS2 : 17.2 to 27.5 months

Tomorrow

EGFR mut → Third generation TKI → Progression → Chemotherapy

PFS = PFS1 + PFS2
• ‘Hitting harder’ the EGFRm target
  – Inhibits mutant EGFR with sensitising mutation (ex19 or L858R) and dual mutant EGFR with de novo/secondary T790M resistance mutation

![Relative IC50 diagram with T790M inhibitor as first line]
Tumour shrinkage in EGFRm+ NSCLC tumour xenografts (Osimertinib)

- AZD9291 induces sustained tumour shrinkage in PC9 and H3255 tumour xenografts

Suresh Ramalingam et al, ESMO 2014

AZD9291 at 25 mg/kg in mouse approximates to clinical exposure of 80 mg once daily, gefitinib at 6.25 mg/kg in mouse approximates to clinical exposure of 250 mg once daily; afatinib at 7.5 mg/kg in mouse approximates to clinical exposure of 40 mg once daily

QD, once daily
Expect a prolonged control of the disease compared to currently available TKIs

- *In vitro* in EGFRm+ (exon 19 deletion) PC9 cells, resistance to AZD9291 took significantly longer to emerge compared with other TKIs\(^1\)
  - Resistance to 10 nM AZD9291 took on average 43 days longer to develop than with 0.8 nM afatinib, 30 nM WZ4002, or 20 nM gefitinib

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IC50, half-maximal inhibitory concentration
1. Eberlein et al. Proceedings of the 105th Annual Meeting of the American Association for Cancer Res
    Diego, CA, abstract 1722.

Presented by Suresh Ramalingam at the 34th Congress of the European Society for Medical Oncology, ESMO 2014
Detection of T790M resistance in EGFR-TKI-treated PC9 cell lines

- In contrast to gefitinib and afatinib, AZD9291 acquired resistance *in vitro* in PC9 cell lines was not dependent on T790M$^1$

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Tumors resistant to EGFR inhibitors can arise via different mechanisms

• Acquired resistance caused by
  – pre-existing EGFR T790M positive clones
  – or via genetic evolution of initially EGFR T790M negative drug-tolerant cells

Aaron N Hata et al, nature 2016
# Wide variation in frequency of de novo EGFR T790M mutations

<table>
<thead>
<tr>
<th>Ref</th>
<th>Method</th>
<th>Baseline T790M mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maheswaran et al</td>
<td>Scorpion ARMS</td>
<td>38%</td>
</tr>
<tr>
<td>Sequist et al</td>
<td>Direct seq</td>
<td>5,9%</td>
</tr>
<tr>
<td>Nakamura et al</td>
<td>MBQ-PQ</td>
<td>9,4%</td>
</tr>
<tr>
<td>Rosell et al</td>
<td>TaqMan assay + PNA</td>
<td>34,9%</td>
</tr>
<tr>
<td>Wu et al</td>
<td>Direct sequencing</td>
<td>1%</td>
</tr>
<tr>
<td>Fujita et al</td>
<td>Colony hydridization</td>
<td>78,9%</td>
</tr>
<tr>
<td>Su et al</td>
<td>MALDI-TOF</td>
<td>25%</td>
</tr>
<tr>
<td>Sakai et al</td>
<td>SABER</td>
<td>7%</td>
</tr>
<tr>
<td>Costa et al</td>
<td>Taqman probe+PNA</td>
<td>65,3%</td>
</tr>
<tr>
<td>Yu et al</td>
<td>MALDI-TOF MS</td>
<td>2%</td>
</tr>
</tbody>
</table>

ARMS, amplification refractory mutation system; MBQ-QP, mutation-biased polymerase chain reaction — quenching probe; PNA, peptide-nucleic acid; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; SABER, single allele base extension reaction.

Erlotinib and bevacizumab in pts with advanced NSCLC with activating EGFR mutations with and without T790M mutation.

**BELIEF trial**

*T790M at diagnosis was documented in 34% of patients*

<table>
<thead>
<tr>
<th>Events/N</th>
<th>Median PFS, months (95%CI)</th>
<th>12-month PFS, % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>57/109</td>
<td>13.8 (10.3, 21.3)</td>
</tr>
<tr>
<td>T790M+</td>
<td>15/37</td>
<td>16.0 (13.1, NE)</td>
</tr>
<tr>
<td>T790M-</td>
<td>42/72</td>
<td>10.5 (9.2, 16.2)</td>
</tr>
</tbody>
</table>

**Progression-free survival (%)**

- **All patients**
- **T790M+**
- **T790M-**

**No at risk**

<table>
<thead>
<tr>
<th>All pts</th>
<th>109</th>
<th>102</th>
<th>95</th>
<th>86</th>
<th>75</th>
<th>54</th>
<th>43</th>
<th>35</th>
<th>25</th>
<th>21</th>
<th>18</th>
<th>12</th>
<th>11</th>
<th>7</th>
<th>5</th>
<th>4</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td>T790M+</td>
<td>37</td>
<td>36</td>
<td>32</td>
<td>29</td>
<td>25</td>
<td>21</td>
<td>19</td>
<td>16</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>T790M-</td>
<td>72</td>
<td>66</td>
<td>63</td>
<td>57</td>
<td>50</td>
<td>33</td>
<td>24</td>
<td>19</td>
<td>16</td>
<td>13</td>
<td>11</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Pretreatment EGFR T790M Mutation Predicts Shorter EGFR Tyrosine Kinase Inhibitor Response Duration

25.2% EGFR- T790M+

matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) and next-generation sequencing (NGS)

Kang-Yi Su et al, JCO 2012
**LUX-Lung 7 PFS by independent review**

Estimated PFS probability

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>36</th>
<th>39</th>
<th>42</th>
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</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>160</td>
<td>142</td>
<td>112</td>
<td>94</td>
<td>67</td>
<td>47</td>
<td>34</td>
<td>27</td>
<td>21</td>
<td>13</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median PFS**

- **Afatinib (n=160):** 11.0 months
- **Gefitinib (n=159):** 10.9 months

**HR (95% CI):**

- **Afatinib:** 0.73 (0.57–0.95)
- **Gefitinib:**

**p value:**

- **Afatinib vs Gefitinib:** 0.0165

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**Keunchil Park et al, ESMO Asia 2015**

**Effect of Afatinib on T790M... ??**
Efficacy in patients with Del19 or L858R mutation

**Del 19**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>12.7</td>
<td>11.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.55–1.06)</td>
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</tr>
<tr>
<td>p value</td>
<td>0.1071</td>
<td></td>
</tr>
</tbody>
</table>

**L858R**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>10.9</td>
<td>10.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.71 (0.47–1.06)</td>
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</tr>
<tr>
<td>p value</td>
<td>0.0856</td>
<td></td>
</tr>
</tbody>
</table>

Keunchil Park et al, ESMO Asia 2015
## Drug-related AEs (>10%)

<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>16.3</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

†Plus 1 case of grade 4 diarrhea
‡Plus 1 case of grade 4 increased ALT
ALT, alanine aminotransferase; AST, aspartate aminotransferase
T790M inhibitor as first line

• ‘Hitting harder’ the EGFRm target

• Better tolerability profile versus available EGFR TKIs
higher level of selectivity towards mutant EGFR vs. wild type

- allowing a wider therapeutic margin
- and also a better tolerability profile versus available EGFR TKIs

Wild Type EGFR

EGFRm

T790M+

3rd generation

Effective inhibition of EGFR Ex19 del, L858R, T790M while avoiding wild-type EGFR related toxicities

Wild Type EGFR

EGFRm

T790M+

Early generation EGFR-TKIs preferentially bind the activated EGFR mutant kinase and the wild type EGFR kinase

AZD9291

1st and 2nd generation EGFR-TKI

Rash

Diarrhoea

Paronychia

Erlotinib, Gefitinib, Afatinib

~80% (5-15% Grd ¾)

~60% (3-10% Grd ¾)

Patients (%)

Grade 1–2

Grade 3–4

Erlotinib, Gefitinib, Afatinib

NR

NR

NR

~80% (5-15% Grd ¾)

~60% (3-10% Grd ¾)

0 20 40 60 80 100

EORTC OPTIMAL WJOG 3405 NEJSG 002 LUX-Lung 3 LUX-Lung 6

EORTC OPTIMAL WJOG 3405 NEJSG 002 LUX-Lung 3 LUX-Lung 6

EORTC OPTIMAL WJOG 3405 NEJSG 002 LUX-Lung 3 LUX-Lung 6

# Osimertinib Phase I/II: All-causality adverse events

<table>
<thead>
<tr>
<th>Patients with an AE, %</th>
<th>20 mg (N=21)</th>
<th>40 mg (N=58)</th>
<th>80 mg (N=103)</th>
<th>160 mg (N=80)</th>
<th>240 mg (N=21)</th>
<th>Total (N=283)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Gr</td>
<td>Gr ≥3</td>
<td>Any Gr</td>
<td>Gr ≥3</td>
<td>Any Gr</td>
<td>Gr ≥3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>29 0</td>
<td>47 2</td>
<td>36 1</td>
<td>68 3</td>
<td>76 5</td>
<td>50 2</td>
</tr>
<tr>
<td>Rash, grouped terms</td>
<td>24 0</td>
<td>33 0</td>
<td>38 0</td>
<td>63 3</td>
<td>76 5</td>
<td>46 1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>38 10</td>
<td>19 0</td>
<td>26 3</td>
<td>24 0</td>
<td>33 0</td>
<td>25 2</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 5</td>
<td>17 0</td>
<td>18 1</td>
<td>34 1</td>
<td>43 0</td>
<td>24 1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14 0</td>
<td>16 0</td>
<td>15 0</td>
<td>36 0</td>
<td>24 0</td>
<td>22 0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>14 0</td>
<td>9 0</td>
<td>21 2</td>
<td>29 4</td>
<td>38 5</td>
<td>22 2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14 0</td>
<td>21 0</td>
<td>19 0</td>
<td>20 0</td>
<td>38 0</td>
<td>21 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 5</td>
<td>26 0</td>
<td>16 0</td>
<td>19 0</td>
<td>19 5</td>
<td>19 1</td>
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<tr>
<td>Constipation</td>
<td>5 0</td>
<td>26 0</td>
<td>21 0</td>
<td>18 0</td>
<td>14 0</td>
<td>19 0</td>
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<tr>
<td>Cough</td>
<td>19 0</td>
<td>17 0</td>
<td>13 0</td>
<td>21 0</td>
<td>0 0</td>
<td>16 0</td>
</tr>
</tbody>
</table>

Select AEs of interest

<table>
<thead>
<tr>
<th>Hyperglycaemia (n=8)</th>
<th>0 0</th>
<th>3 0</th>
<th>4 0</th>
<th>2 0</th>
<th>2 0</th>
<th>0 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT prolongation (n=10)</td>
<td>0 0</td>
<td>2 0</td>
<td>4 1</td>
<td>1 0</td>
<td>5 0</td>
<td>0 0</td>
</tr>
<tr>
<td>ILD-like events (n=8)</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>3 2</td>
<td>6 4</td>
<td>3 2</td>
</tr>
</tbody>
</table>

LBA2_PR - Osimertinib (AZD9291) in pre-treated pts with T790M-positive advanced NSCLC: updated Phase 1 (P1) and pooled Phase 2 (P2) results

J. Yang¹, S. Ramalingam², P. Jänne³, M. Cantarini⁴, T. Mitsudomi⁵; ¹TW, ²GA/US, ³MA/US, ⁴GB, ⁵JP

Rocelitinib
Common Treatment-related Adverse Events

<table>
<thead>
<tr>
<th>AE</th>
<th>Rocelitinib dose</th>
<th>500mg BID (N=119)</th>
<th>625mg BID (N=236)</th>
<th>750mg BID (N=95)</th>
<th>1000mg BID (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td>42 (35)</td>
<td>107 (45)</td>
<td>56 (59)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>39 (33)</td>
<td>94 (40)</td>
<td>28 (30)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>23 (19)</td>
<td>79 (34)</td>
<td>35 (37)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>15 (29)</td>
<td>37 (30)</td>
<td>21 (27)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td></td>
<td>16 (13)</td>
<td>53 (23)</td>
<td>25 (26)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>18 (15)</td>
<td>38 (16)</td>
<td>24 (25)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
<td>17 (14)</td>
<td>30 (13)</td>
<td>20 (21)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>10 (8)</td>
<td>38 (16)</td>
<td>13 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td>12 (10)</td>
<td>21 (9)</td>
<td>16 (17)</td>
<td>1 (17)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>AE</th>
<th>Rocelitinib dose</th>
<th>500mg BID (N=119)</th>
<th>625mg BID (N=236)</th>
<th>750mg BID (N=95)</th>
<th>1000mg BID (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td>20 (17)</td>
<td>56 (24)</td>
<td>34 (36)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>

- No ILD observed in 500mg BID dose group
  - 7/456 cases overall (1.5%)
  - Rocelitinib continuation possible with steroid cover
  - No fatal ILD in program

- No paronychia or stomatitis observed; trivial rash
- Grade 3 QTc prolongation at 500mg BID = 2.5%
- Treatment-related AEs leading to drug discontinuation seen in 2.5% of cases at 500mg BID (4% overall)
- Hyperglycemia readily managed with oral agents
  - No contraindication for pre-existing diabetic patients

ILD=interstitial lung disease.

Lecia V. Sequist et al, ASCO2015
T790M inhibitor as first line

• ‘Hitting harder’ the EGFRm target
• Better tolerability profile versus available EGFR TKIs
• Optimising brain penetration
Optimising brain penetration

All comers incidence of BM
- BM 40% (40-50%)

EGFR + patients treated with 1st generation TKI
- BM 40% (30-60%)

ALK+ patients treated with crizotinib
- BM 50%

CNS involvement in NSCLC

Sorensen JB et al, J Clin Oncol.1988;6: 1474

Homuro et al, Cancer.2005: 3, 2344
Hoen S et al, Clin Cancer Res 2010: 16, 5873
Lee YJ et al, Cancer 2010: 116, 1336

**Figure 1.** The actuarial incidence of isolated central nervous system failure, measured by the Kaplan-Meier method, in patients with clinical benefit from epidermal growth factor tyrosine kinase inhibitors.
Osimertinib is distributed to mouse brain to a greater extent than gefitinib, CO-1686, or afatinib.

At clinically relevant doses, AZD9291 distribution to the brain is ~10-fold higher than gefitinib.

[\textsuperscript{11}C]AZD9291 is distributed to cynomolgus monkey brain

Brain metastases – Case Study 2

- Sixty-year-old Taiwanese female diagnosed with advanced NSCLC (L858R) in January 2011
- AZD9291 80 mg daily started 2 September 2013 in expansion cohort, best response PR. A single brain met target lesion decreased from 13 mm at baseline to 12 mm at Week 6, 8 mm at Week 12–18 (38% shrinkage). NTLs including brain mets had non-CR/non-PD reported for 4 months between 8 October 2013 to 2 January 2014, but progressed in the brain met NTLs on 13 February 2014

Brain MRI
A) Baseline on 9 August 2013. B) 8 October 2013

NE, not evaluable
### ORR by medical history of brain metastases

#### AZD9291 data from phase II studies

<table>
<thead>
<tr>
<th></th>
<th>ORR in pooled dataset (evaluable for response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BICR evaluable set</td>
<td>66.1% (263/398) 95% CI 61.2, 70.7%</td>
</tr>
<tr>
<td>With brain metastases</td>
<td>62.0% (98/158) 95% CI 54.0, 69.6%</td>
</tr>
<tr>
<td>Without brain metastases</td>
<td>68.8% (165/240) 95% CI 62.5, 74.6%</td>
</tr>
</tbody>
</table>

**Median PFS, months (95% CI)**
- Full analysis set: 9.7 (9.7, NC)
- With brain metastases: 8.0 (6.9, 8.5)
- Without brain metastases: 9.7 (9.7, NC)

---

BICR, blinded independent central review; CI, confidence interval; ORR, objective response rate

---

Myung-ju Ahn et al, ECCO 2015
T790M inhibitor as first line

- ‘Hitting harder’ the EGFRm target
- Better tolerability profile versus available EGFR TKIs
- Optimising brain penetration
- Exposure of the entire EGFR-mut population (T790M false -)
Rate in T790M negative cohorts (central test)

DCR (CR+PR+SD) in patients with centrally tested T790M negative tumours was 64% (44 / 69; 95% CI 51, 75)

<table>
<thead>
<tr>
<th></th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (69)</td>
<td>3</td>
<td>17</td>
<td>29</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>67% (9, 99)</td>
<td>12% (2, 36)</td>
<td>21% (8, 40)</td>
<td>30% (12, 54)</td>
<td>23% (14, 35)</td>
</tr>
</tbody>
</table>

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014

Striking Activity in T790M-negative Patients

Best Response for Target Lesions
Centrally Confirmed T790M Negative 1686-008 Pts at 500 or 625mg BID (Clinical Dose Group)

- RECIST ORR = 42% overall
- mPFS = 7.5mo

- False negative?
- Real tumor heterogeneity?
- Specific mechanism of action of the compound?

JC. Soria et al
Phase I dose escalation/expansion study design (NCT01802632)

- For the first-line cohorts, patients with a documented EGFR-TKI-sensitising mutation and who have received no prior therapy for advanced stage NSCLC were enrolled.
- Patients received AZD9291 once daily as an 80 mg or 160 mg capsule.

**Escalation**
Not preselected by T790M status

**Expansion**
Enrollment by local testing followed by central laboratory confirmation (cobas EGFR Mutation Test) of T790M status or by central laboratory testing alone.

*Prior therapy not permissible in this cohort. #Paired biopsy cohort patients with T790M+ tumours. ##Not selected by mutation status, US only.

Suresh S. Ramalingam et al, IASLC 2015
Tumor response in AZD9291 first-line cohorts by dose

Population: evaluable for response, data cut-off August 1, 2015; RECIST 1.1, programatically calculated from investigator-recorded tumor measurement
CI, confidence interval; D, discontinued

<table>
<thead>
<tr>
<th></th>
<th>80 mg N=30</th>
<th>160 mg N=30</th>
<th>Total N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed objective response rate</td>
<td>67%</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>(95% CI 47, 83)</td>
<td>(95% CI 65, 94)</td>
<td>(95% CI 62, 85)</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>93%</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>(95% CI, 78, 99)</td>
<td>(95% CI 88, 100)</td>
<td>(95% CI 89, 100)</td>
</tr>
<tr>
<td>Best objective response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>2*</td>
<td>2*</td>
</tr>
<tr>
<td>Partial response</td>
<td>20</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Best percentage change in target lesion size – all patients

Population: evaluable for response, data cut-off August 1, 2015; RECIST 1.1, programatically calculated from investigator-recorded tumor measurement
CI, confidence interval; D, discontinued

Suresh S. Ramalingam et al, IASLC 2015
DoR and PFS in AZD9291 first-line cohorts (investigator assessed)

### Duration of response

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median DoR, months (95% CI)</th>
<th>Maximum DoR, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>13.6 (11.1, NC) Maturity: 35%</td>
<td>18.0+</td>
</tr>
<tr>
<td>160 mg</td>
<td>NC (9.7, NC) Maturity: 28%</td>
<td>12.6+</td>
</tr>
<tr>
<td>Total</td>
<td>NC (12.3, NC) Maturity: 31%</td>
<td>18.0+</td>
</tr>
</tbody>
</table>

### Progression-free survival

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median PFS, months (95% CI)</th>
<th>Maximum PFS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>NC (12.3, NC) Maturity: 40%</td>
<td>19.2+</td>
</tr>
<tr>
<td>160 mg</td>
<td>NC (11.1, NC) Maturity: 30%</td>
<td>13.8+</td>
</tr>
<tr>
<td>Total</td>
<td>NC (13.7, NC) Maturity: 35%</td>
<td>19.2+</td>
</tr>
</tbody>
</table>

---

LBA1_PR - Osimertinib as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts


Population: all dosed patients, data cut-off August 1, 2015

Progression events that do not occur within 14 weeks of the last evaluable assessment (of first dose) are censored

*Duration of response is the time from first documentation of response until date of progression or death or last evaluable RECIST assessment for patients who do not progress; †Calculated using the Kaplan-Meier technique; ‡Progression-free survival is the time from date of first dosing until the date of objective disease progression or death

DoR, duration of response; NC, not calculable; PFS, progression-free survival

Suresh S. Ramalingam et al, IASLC 2015
## Adverse events (all causality) in AZD9291 first-line cohorts

### AEs by preferred term (all grade) occurring in ≥25% of patients overall

<table>
<thead>
<tr>
<th>AEs by preferred term (grouped terms)</th>
<th>All patients</th>
<th>80 mg N=30 n (%)</th>
<th>160 mg N=30 n (%)</th>
<th>Total N=60 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Gr ≥3</td>
<td>Any grade</td>
<td>Gr ≥3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td>21 (70)</td>
<td>0</td>
<td>25 (83)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (60)</td>
<td>0</td>
<td>26 (87)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>12 (40)</td>
<td>0</td>
<td>12 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>9 (30)</td>
<td>0</td>
<td>15 (50)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>10 (33)</td>
<td>0</td>
<td>13 (43)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (27)</td>
<td>0</td>
<td>8 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (27)</td>
<td>0</td>
<td>7 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (23)</td>
<td>1 (3)</td>
<td>8 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (27)</td>
<td>0</td>
<td>7 (23)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Select AEs of interest

<table>
<thead>
<tr>
<th>AEs by preferred term (all grade)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 mg N=30 n (%)</td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
</tr>
<tr>
<td>ILD (grouped terms)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*Six grade 4, 16 grade ≥5, two currently ungraded. Of these, a total of four patients are reported to have died due to ILD (grade 5).
Population: all dosed patients, data cut-off August 1, 2015
AE, adverse event*
**FLAURA Study Design**

**Enrollment by local* or central# EGFR mutation testing of biopsy sample**

**Stratified by:**
- Asian / non-Asian
- Ex19del / L858R

Randomize patients 1:1

**AZD9291 (80 mg p.o. qd)**

**RECIST 1.1 assessment every 6 weeks until objective progressive disease**

Patients randomized to standard of care may receive AZD9291 after progression§

**Primary objective: efficacy by PFS**

EGFR-TKI standard of care##: gefitinib (250 mg p.o. qd) or erlotinib (150 mg p.o. qd)

*With central laboratory assessment performed for sensitivity
#cobas™ EGFR Mutation Test (Roche Molecular Systems)
##Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation
§Patients randomized to the standard of care treatment arm may receive open-label treatment with AZD9291 on central confirmation of both objective disease progression and T790M positive tumor
OS, overall survival; PFS2, second progression-free survival (time from randomization to second progression); p.o., orally
**Study Design:**
- Open label, randomized phase 3 study of ASP8273 vs erlotinib or gefitinib in first-line treatment of patients with Stage IIIB or IV EGFR+ NSCLC (N=540)
- Primary endpoint: PFS per independent radiology review (IRR)
- Key secondary endpoints: OS, ORR per IRR, PFS (inv), DCR
What will be the magnitude of the PFS T790M inhibitor 1\textsuperscript{st} line and resistance?

EGFR mut \rightarrow 1\textsuperscript{st} generation TKI \rightarrow Progression T790m- \rightarrow Chemotherapy \rightarrow Death

EGFR mut \rightarrow 1\textsuperscript{st} generation TKI \rightarrow Progression T790M+ \rightarrow Third generation TKI \rightarrow Chemotherapy \rightarrow Death

PFS1 + PFS2 : 17.2 to 27.5 months

Resistance mechanism?

EGFR mut \rightarrow Third generation TKI \rightarrow Progression \rightarrow Chemotherapy

OS
Tumor heterogeneity has important clinical implications.

**EGFR activating mutation**
- EGFR T790M
- EGFR C797S

**EGFR activating mutation**
- EGFR T790M
- **+ Unknown resistance**

**EGFR activating mutation**
- Loss of T790M

HER2, MET, BRAF...

Kenneth S Thress et al, nature 2015
Allelic Context of C797S Mutation Acquired Impacts Sensitivity to Subsequent Treatment Strategies

Matthew J. Niederst et al, CCR 2015
Phase I of AZD9291 in combination or alternating with gefitinib in EGFR inhibitor naive EGFR mutant lung cancer

**Patients**
- ECOG PS 0-2
- Histologically confirmed Stage IV NSCLC with activating *EGFR* mutation (L858R or exon 19 del)
- EGFR TKI naïve
- No untreated or uncontrolled CNS disease
- Any lines of prior systemic therapy
- Eligible for repeat biopsy at resistance

**Objectives**

**Primary**
- Feasibility of combination or alternating therapy for 6 cycles

**Secondary**
- Rate of grade 3/4 events
- ORR
- PFS
- Rate of change of plasma EGFR mutation(s) over time
- Proportion of patients who become plasma “negative” for EGFR activation mutation
- Tumor cfDNA burden resistance over time and correlation with PFS
- Evaluation of resistance mechanisms

Amanda Redig - DFCI
Inhibitor of anti-apoptotic factors BCL-xL and BCL-2 enhances apoptotic response of late-resistant EGFRT790M cells

% Tumor response

% Apoptosis

Aaron N Hata et al, nature 2016
Cotargeting EGFR and MEK prolongs effective treatment duration in EGFR L858R/T790M genetically engineered mice

Erin M. Tricker et al, cancer discovery 2015
**Osimertinib + Durvalumab: Toxicity (TATTON study)**

- AZD9291 + durvalumab combination regimens have demonstrated a comparable safety profile with AZD9291 and durvalumab in patients with advanced NSCLC.

<table>
<thead>
<tr>
<th>AEs*</th>
<th>3 mg/kg (Asia) n=6</th>
<th>3 mg/kg (ROW) n=7</th>
<th>10 mg/kg (Asia) n=4</th>
<th>10 mg/kg (ROW) n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events, n</td>
<td>Any Grade</td>
<td>Grade ≥3</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>WBC count decreased</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

3 cases of pneumonitis reported at ASCO in 23 patients

---

136O - Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: Results from the TATTON phase Ib trial


*Occurring in ≥3 instances at any dose

Rociletinib Clinical Development Program

**TIGER-1 (Phase 2)**
- Randomized rociletinib vs erlotinib
- Includes front-line, treatment-naïve patients
- Enrollment complete

**NCT02630186 (Phase 1b/2)**
- Rociletinib in combination with MPDL3280A (atezolizumab)
- First and later line patients
- Enrollment open in USA; enrollment in France opens soon

**TIGER-2 (Phase 2)**
- Single-arm, single-agent rociletinib
- 2nd-line EGFR mutant NSCLC
- Enrollment complete

**TIGER-X (Phase 1/2)**
- Single-arm, single-agent rociletinib
- ≥2nd-line patients who have received ≥1 prior EGFR-directed therapy
- Enrollment complete

**TIGER-3 (Phase 3)**
- Randomized rociletinib vs single-agent chemotherapy
- >2nd-line EGFR mutant NSCLC; T790M-positive and negative patients
- Enrollment open

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.
Conclusion

- **Drug resistance** limits the long term success of even the most effective targeted therapies
- **Prevention** may be a better strategy than treatment of resistance
- Best treatment strategy needs to be both effective and tolerable

- In treatment-naïve patients with EGFRm positive advanced NSCLC, Osimertinib demonstrates encouraging clinical activity and a manageable tolerability profile

- **Role of tumor heterogeneity** with EGFR T790M + and - cancer cells can both pre-exist and evolve from drug-tolerant cells
- To further improve outcomes, combination regimens that prevent or overcome resistance might be needed in first line
THANK YOU!

Acknowledgments

Jean-Charles SORIA
Benjamin BESSE
Thierry Le Chevalier

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