Best of ASCO 2014
Lung

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Stanford Cancer Institute
Stanford, California USA

Outline

• ALK:
  – 8002: 1st line crizotinib Profile 1014
  – 8003: ASCEND – ceritinib
• EGFR:
  – 8004: Lux lung 3+6 OS analysis
  – 8000: onartuzumab- Met lung
  – 8005: Bevacizumab + erlotinib
  – 8009: AZD9291 : 8010: CO-1686
  – 7501: RADIANT
• OTHER ANTIBODIES:
  – 8006: ramucirumab-REVEL
  – 8007: PD-L1 MK3475
  – 8008: Necitumumab-Squire
• SCLC:
  – 7502: SCLC Thoracic XRT
  – 7503: SCLC PCI
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Results: Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Patients N=273</th>
<th>Comorbidities and Disease Characteristics</th>
<th>Patients N=273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at NSCLC diagnosis (years), mean ± SD</td>
<td>65.1 ± 12.2</td>
<td>Comorbidity index≥2, N (%)</td>
<td>198 (73%)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>142 (52%)</td>
<td>CI 0-2</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td>162 (59%)</td>
<td>CI 3-5</td>
<td>65 (24%)</td>
</tr>
<tr>
<td>White</td>
<td>162 (59%)</td>
<td>CI &gt;5</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>49 (18%)</td>
<td>Disease characteristics</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>36 (13%)</td>
<td>Cancer histology, N (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>22 (8%)</td>
<td>Adenocarcinoma</td>
<td>222 (81%)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>3 (1%)</td>
<td>Large cell carcinoma</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>1 (0%)</td>
<td>Squamous cell carcinoma</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Smoking history, N (%)</td>
<td></td>
<td>Mixed</td>
<td>30 (11%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>90 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light smoker</td>
<td>91 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>89 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PROFILE 1014 Study Design – Mok abstr 8002

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
- Stable treated brain metastases allowed

Endpoints
- Primary:
PFS (RECIST 1.1, independent radiologic review [IRR])
- Secondary:
  ORR
  OS
  Safety
  Patient-reported outcomes (EORTC QLQ-C30, LC13)

CROSSOVER TO CRIZOTINIB PERMITTED AFTER PROGRESSION:

\[ ^a \text{ALK status determined using standard ALK break-apart FISH assay} \]
\[ ^b \text{Stratification factors: ECOG PS (0/1 vs. 2), Asian vs. non-Asian race, and} \]
\[ ^c \text{Brain metastases (present vs. absent)} \]
\[ ^d \text{Assessed by IRR} \]

Primary Endpoint Met: Crizotinib Superior to Pemetrexed-based Chemotherapy in Prolonging PFS\[ ^a \]

- Events, n (%)
  - Crizotinib (N=172): 100 (58)
  - Chemotherapy (N=171): 137 (80)
- Median, months
  - Crizotinib: 10.9
  - Chemotherapy: 7.0
- HR (95% CI)
  - Crizotinib: 0.45 (0.35–0.60)
  - Chemotherapy: <0.0001
- ORR 74% vs 45%

Data cutoff: November 30, 2013

\[ ^a \text{Assessed by IRR} \]
\[ ^b \text{1-sided stratified log-rank test} \]

Mok abstr 8002
Waterfall Plot: Best Percent Change from Baseline in Target Lesion Size

- **Complete response**
- **Partial response**
- **Stable disease**
- **Progressive disease**

**Patients with early death, indeterminate response, or non-measurable disease not shown**

**Per RECIST v1.1, a complete response can occur with <100% change from baseline when lymph nodes are included as target lesion.**

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**ASCEND-1 Study Design- Kim abstr 8003**

Global pivotal phase 1 trial including 20 centers across 11 countries

**Expansion Phase**
- Evaluate 750 mg RD
- N=255 patients with ALK+ tumors*

- N=246 patients with ALK+ NSCLC tumors

**ALK inhibitor treated**
- N=163

**ALK inhibitor naïve**
- N=83

**Recruitment closed July 2013**
- 31 October 2013 data cut-off used for current analysis
- Study ongoing

*9 ALK+ patients had cancers other than NSCLC

**All received crizotinib and 5 also received alectinib**

**Key Objectives:** to determine anti-tumor efficacy and safety of ceritinib

- Dose escalation phase (n=59) closed May 2012 with RD of 750 mg/day
- Shaw A et al. NEJM 2014;370(13):1189–1197
- ALKi: ALK inhibitor; RD: recommended dose

**Presented by: Dong-Wan Kim**
Best Percentage Change from Baseline (NSCLC)

*Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response

Progression-Free Survival in Patients with ALK+ NSCLC

Number of patients still at risk:

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>ALK inhibitor treated (N=163)</th>
<th>ALK inhibitor naïve (N=83)</th>
<th>All (N=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>163</td>
<td>83</td>
<td>246</td>
</tr>
<tr>
<td>3</td>
<td>153</td>
<td>63</td>
<td>216</td>
</tr>
<tr>
<td>6</td>
<td>103</td>
<td>38</td>
<td>141</td>
</tr>
<tr>
<td>12</td>
<td>51</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

Median: non-estimable (95% CI 8.31, non-estimable) PFS rate at 12 months: 61.3%
Median: 8.21 months (95% CI 6.70, 10.12) PFS rate at 12 months: 39.1%
Median: 6.90 months (95% CI 5.39, 8.41) PFS rate at 12 months: 28.4%
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Treatment Naïve EGFR\textsuperscript{mut} Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maemondo</td>
<td>Gefitinib vs Carboplatin / Paclitaxel</td>
<td>230</td>
<td>10.8 vs 5.4 (P &lt; .001)</td>
<td>30.5 vs 23.6 (P = .31)</td>
</tr>
<tr>
<td>Mitsudomi</td>
<td>Gefitinib vs Cisplatin / Docetaxel</td>
<td>177</td>
<td>9.2 vs 6.3 (P &lt; .0001)</td>
<td>36 vs 39 (HR: 1.19)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs Carboplatin / Gemcitabine</td>
<td>165</td>
<td>13.1 vs 4.6 (P &lt; .0001)</td>
<td>HR: 1.065 (P = .65)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs plat-based chemotherapy</td>
<td>174</td>
<td>9.7 vs 5.2 (P &lt; .0001)</td>
<td>19.3 vs 19.5 (P = .87)</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>Afatinib vs Cisplatin/pemetrexed</td>
<td>345</td>
<td>11.1 vs 6.9 (P = .001)</td>
<td>ASCO 2014</td>
</tr>
</tbody>
</table>

LUX 3+6: Combined OS analysis: common mutations (n=631) - Neither trial alone reach significance

**Afatinib**
- Median, months: 27.3
- HR (95%CI), p-value: 0.81 (0.66–0.99), p=0.0374

**Chemo**
- Median, months: 24.3

No of patients
- Afatinib: 419
- Chemo: 212

Estimated OS probability

Combined OS analysis: mutation categories

**Del19**
- Median, months:
  - Afatinib: 31.7
  - Chemo: 20.7
- HR (95%CI), p-value:
  - Afatinib: 0.59 (0.45–0.77), p=0.0051

**L858R**
- Median, months:
  - Afatinib: 22.1
  - Chemo: 26.9
- HR (95%CI), p-value:
  - Afatinib: 1.25 (0.92–1.71), p=0.1600
Resistance

- Despite impressive results in first line trials, RESISTANCE almost always develops.
- Strategies looking at addition of drugs to delay resistance:
  - Promise with chemotherapy or bevacizumab, but limited with other agents.
- Strategies to overcome resistance once it has developed:
  - Exciting data with afatinib/cetuximab, CO-1686, AZD9291.

Global Phase 3 Trial (METLung)* of Onartuzumab plus Erlotinib in NSCLC: Trial Design

Patients with stage IIIB/IV 2L/3L NSCLC (N=490)

- Erlotinib + onartuzumab
- Erlotinib + placebo

Treatments:
- Erlotinib 150mg PO QD
- Onartuzumab/placebo 15mg/kg i.v. q3w

Primary endpoint:
- OS

Secondary endpoints:
- PFS
- ORR
- QoL
- Safety
- PK

Stratification criteria:
- EGFR mut vs wt
- MET 2+ vs 3+
- Number of prior treatments
- Histology

No crossover tx

Survival follow-up

1:1

Presented by: David R. Spigel, M.D., PASCO 2014 8000

*METLung (OAM4971g, NCT01456325)
**OAM4971g: Overall Survival Results**

*EGFR mutation* placebo N=29 Med OS:NE Onartuzumab N=28, Med OS 12.6 mo

- HR 4.68: (0.97–22.63)
- Median 9.1 months (95% CI 7.7–10.2)
- HR 1.27 (95% CI: 0.98–1.65)
- p=0.07

**Placebo + erlotinib (n=249)**

**Onartuzumab + erlotinib (n=250)**

Censored

**Number of patients at risk:**

<table>
<thead>
<tr>
<th></th>
<th>Placebo + erlotinib</th>
<th>Onartuzumab + erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>249</td>
<td>250</td>
</tr>
<tr>
<td>Censored</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Observed</td>
<td>226</td>
<td>246</td>
</tr>
<tr>
<td>Observed + censored</td>
<td>229</td>
<td>250</td>
</tr>
</tbody>
</table>

**Probability of overall survival**

- Median 6.8 months (95% CI 6.1 – 7.5)
- Median 9.1 months (95% CI 7.7–10.2)

Presented by: David R. Spigel, M.D abstr 8000.

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**Erlotinib+Bevacizumab Study**

**design**

- **Chemotherapy-naïve**
- **Non-squamous NSCLC**
- **Activating EGFR mutations***
  - Exon 19 deletion
  - Exon 21 L858R
- **No brain metastasis**

**EB combination**

- Erlotinib 150mg qd + bevacizumab 15mg/kg q3w *(n = 75)*

**E monotherapy**

- Erlotinib 150mg qd *(n = 75)*

**Primary endpoint:**
- PFS (RECIST v1.1, independent review)

**Secondary endpoints:**
- OS, tumor response, QoL, safety

Presented by: Terufumi Kato, ABSTR 8005, ASCO 2014
**Primary endpoint: PFS by independent review**

<table>
<thead>
<tr>
<th></th>
<th>EB</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>16.0</td>
<td>9.7</td>
</tr>
<tr>
<td>HR</td>
<td>0.54 (95% CI: 0.36–0.79)</td>
<td></td>
</tr>
<tr>
<td>P value*</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

*log-rank test, two-sided

**EGFR-TKIs: Secondary Resistance**

- 37 patients rebiopsied at the time of progression
- 6/18 patients with T790M had other molecular abnormalities
- 5 patients had SCLC phenotype

Two Trials to Compare Ongoing EGFR TKI for Acquired Resistance

**Primary endpoint:** progression-free survival

**Pl: Tony Mok & Jean-Charles Soria**

- Activating EGFR TKI
- Response to EGFR TKI > 4 mo
- No prior chemotherapy
- N = 250

**Randomized**

- Cisplatin/Pemetrexed
- Cisplatin/Pemetrexed + ongoing gefitinib

**Pl: Leora Horn (Vanderbilt)**

- Advanced NSCLC
- Activating EGFR TKI
- Response to EGFR TKI > 4 mo
- No prior chemotherapy
- PS 0/1
- N = 120

**Randomized**

- Cis/CARBO + Pemetrexed
- Cis/CARBO + ongoing erlotinib
- Cis/CARBO +Pemetrexed

Erlotinib re-treatment

Afatinib + Cetuximab at MTD: Responses by T790M Mutation

CO1686: Best response in Ph1 + early Phase 2 expansion cohort patients

Centrally confirmed T790M+ patients within therapeutic dose range (N=40)

ORR to date: 58%

CO-1686 Adverse events

Treatment-related adverse events* occurring in >10% of CO-1686 patients (N=72) treated at efficacious doses, n (%)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14 (19)</td>
<td>10 (14)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14 (19)</td>
<td>8 (11)</td>
<td>16 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (19)</td>
<td>3 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (13)</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (10)</td>
<td>7 (10)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (10)</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QTc prolonged</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td>5 (7)</td>
<td>0</td>
</tr>
</tbody>
</table>

*excluding malignancy-related adverse events (eg. disease progression)

3 (4%) patients with any form of rash, all Grade 1
**AZD9291: ORR* in overall population**

Best percentage change from baseline in target lesion: all evaluable patients, escalation and expansion (N=205)

- First patient dosed Mar 6, 2013
- Longest response >9 months ongoing at time of data cutoff
- ORR* = 53% (95% CI 46%, 60%): ORR 64% in T790M+
- Overall disease control rate (CR+PR+SD) = 83% (95% CI 78%, 88%)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N (205)</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>240 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>55%</td>
<td>55%</td>
<td>44%</td>
<td>54%</td>
<td>58%</td>
<td>67%</td>
</tr>
</tbody>
</table>

*Includes confirmed responses and responses awaiting confirmation; # represents imputed values. Population: all dosed patients with a baseline RECIST assessment and an evaluable response (CR, PR, SD or PD), N=205 (from 232 dosed patients, 27 patients with a current non-evaluable response are not included). CI, confidence interval; CR, confirmed complete response; ORR, overall response rate; PR, confirmed partial response; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Presented by: Pasi A. Jänne, ASCO 2014

**AZD9291 Adverse events**

<table>
<thead>
<tr>
<th>Patients with an AE, %</th>
<th>20 mg (N=21)</th>
<th>40 mg (N=57)</th>
<th>80 mg (N=74)</th>
<th>160 mg (N=80)</th>
<th>240 mg (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Gr</td>
<td>Any Gr</td>
<td>Any Gr</td>
<td>Any Gr</td>
<td>Any Gr</td>
<td>Any Gr</td>
</tr>
<tr>
<td>Gr ≥3</td>
<td>Gr ≥3</td>
<td>Gr ≥3</td>
<td>Gr ≥3</td>
<td>Gr ≥3</td>
<td>Gr ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Paronychia</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

Select AEs of interest

- Hyperglycemia: 0 0 0 0 0
- QT prolongation: 0 0 0 0 0
- ILD-like event*: 0 0 0 0 0

*All seven patients responded well to treatment with no fatal events. Review of these events is ongoing. Population: all dosed patients, N=232; does not include first-line or tablet cohorts.

Presented by: Pasi A. Jänne
Preliminary Comparison

<table>
<thead>
<tr>
<th></th>
<th>RR T790M +</th>
<th>RR T790M -</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib/Cetux</td>
<td>32%</td>
<td>28%</td>
<td>4.66</td>
</tr>
<tr>
<td>HM 61713</td>
<td>29%</td>
<td>12%</td>
<td>4.34*</td>
</tr>
<tr>
<td>CO-1686</td>
<td>58%</td>
<td>Inc.</td>
<td>↑</td>
</tr>
<tr>
<td>AZD 9291</td>
<td>65%</td>
<td>22%</td>
<td>↑</td>
</tr>
</tbody>
</table>

Any Grade (Gr3) | Diarrhea | Rash | ILD/SOB* | Inc BS | QTc |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib/Cetux</td>
<td>71%</td>
<td>97%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CO-1686</td>
<td>23%</td>
<td>4%</td>
<td>NR</td>
<td>55% (22%)</td>
<td>15% (7%)</td>
</tr>
<tr>
<td>AZD 9291 80mg</td>
<td>20%</td>
<td>27%</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>HM 61713</td>
<td>21%</td>
<td>24%</td>
<td>10%*</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

RADIANT
Adjuvant NSCLC +/-Erlotinib

ELIGIBLE:
- Resected I-IIIA
- ≥Lobectomy
- Required IHC/FISH for EGFR
- Chemo optional

RANDOMIZE
- Erlotinib 150 mg po qd X 2 yrs
- Placebo x 2 yrs

2:1

DFS as primary endpoint
Median follow-up duration = 47 months.

Placebo (32 events): Median = 28.5 months
Erlotinib (39 events): Median = 46.4 months

Log-rank test: p = 0.0391

HR: 0.61 (95% CI: 0.384, 0.981)

Placebo
Erlotinib

Placebo (32 events)
Erlotinib (39 events)

Disease-free Survival (Months)
**RADIANT OS– EGFR M+**

- Overall Survival (Months)
- Overall Survival Probability
- Erlotinib (22 events)
- Median: not reached
- Log-rank test: p=0.8153
- HR: 1.09 (95% CI: 0.545, 2.161)

**Number at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56</td>
<td>102</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>91</td>
</tr>
<tr>
<td>18</td>
<td>53</td>
<td>88</td>
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<td>24</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>30</td>
<td>41</td>
<td>75</td>
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<tr>
<td>36</td>
<td>30</td>
<td>43</td>
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<tr>
<td>42</td>
<td>24</td>
<td>26</td>
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<tr>
<td>48</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>54</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Placebo (13 events)
- Median: not reached

---

**US ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial**

- Stage I-III NSCLC
- <6 mo post-op
- N=6000-8000
- For ~300-400
- EGFR mut (Sequencing)
- ALK+ (FISH)
- Erlotinib x 2 yrs
- Placebo x 2 yrs
- Crizotinib x 2 yrs
- Placebo x 2 yrs
Outline

• ALK:
  – 8002: 1st line crizotinib Profile 1014
  – 8003: ASCEND – ceritinib

• EGFR:
  – 8004: Lux lung 3+6 OS analysis
  – 8005: onartuzumab- Met lung
  – 8006: Bevacizumab + erlotinib
  – 8007: AZD9291 : 8010: CO-1686
  – 7501: RADIANT

• OTHER ANTIBODIES:
  – 8006: ramucirumab-REVEL
  – 8007: PD-L1 MK3475
  – 8008: Necitumumab-Squire

• SCLC:
  – 7502: SCLC Thoracic XRT
  – 7503: SCLC PCI

REVEL: Study Design – Perol abstr 8006

- Stage IV NSCLC after one platinum-based chemo +/- maintenance
- Prior Bev allowed
- All histologies
- PS 0 or 1

Stratification factors:
• ECOG PS 0 vs 1
• Gender
• Prior maintenance
• East-Asia vs. ROW

Primary endpoint: Overall Survival

Secondary endpoints:
PFS, ORR, safety, patient-reported outcomes

Randomize

Ramucirumab 10 mg/kg + Docetaxel 75 mg/m² q3wks N=628

Placebo + Docetaxel 75 mg/m² q3wks N=625

Treatment until disease progression or unacceptable toxicity

Abbreviations: Bev=bevacizumab; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=objective response; PFS=progression-free survival; ROW=rest of the world; q3wks=every 3 weeks.
REVEL Progression-Free Survival =
ITT Population, Investigator Assessment

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI)</th>
<th>Censoring Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM+DOC</td>
<td>4.5 (4.2-5.4)</td>
<td>11.1%</td>
</tr>
<tr>
<td>PL+DOC</td>
<td>3.0 (2.8-3.9)</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

RAM+DOC vs PL+DOC:
Stratified HR (95% CI) = 0.762 (0.677-0.859)
Stratified log-rank P < .0001

No diff by histology or prior therapy

REVEL: Overall Survival
ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI)</th>
<th>Censoring Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM+DOC</td>
<td>10.5 (9.5-11.2)</td>
<td>31.8%</td>
</tr>
<tr>
<td>PL+DOC</td>
<td>9.1 (8.4-10.0)</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

RAM+DOC vs PL+DOC:
Stratified HR (95% CI) = 0.857 (0.759-0.979)
Stratified log-rank P = .0235
Clinical Development of PD-1 Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab-BMS-936558</td>
<td>Fully human IgG4</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab CT-011</td>
<td>Humanized IgG1</td>
<td>Phase II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab MK-3475</td>
<td>Humanized IgG4</td>
<td>Phase III</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559 (no longer in development in NSCLC)</td>
<td>Fully human IgG4</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Medl-4736</td>
<td>Engineered human IgG1</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>MPDL-3280A</td>
<td>Engineered human IgG1</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>MSB0010718C</td>
<td>Human IgG1</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Slide courtesy Julie Brahmer, ASCO discussant

KEYNOTE-001: PD-L1 Expression in Previously Untreated NSCLC

Previously Untreated Patients With Advanced NSCLC Screened for PD-L1
N = 84

Tumor Biopsy Evaluable for PD-L1
n = 73

PD-L1+ Tumors (Proportion Score ≥ 1)
N = 57

Patients Eligible for Treatment with Evaluable Imaging at Baseline by irRC
N = 45

Patients with Evaluable Imaging at Baseline by RECIST 1.1
N = 42

Presented by: Naiyer A. Rizvi, abstr 8007

Analysis cut-off date: March 3, 2014.
### Antitumor Activity by MK-3475 Dose

<table>
<thead>
<tr>
<th>MK-3475 Dose</th>
<th>RECIST v1.1, Central Review</th>
<th>irRC, Investigator Review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 mg/kg Q 3W</td>
<td>n</td>
<td>n (%)</td>
</tr>
<tr>
<td>6</td>
<td>2 (33) [4 - 78]</td>
<td>3 (50%) [12%, 88%]</td>
</tr>
<tr>
<td>10 mg/kg Q 3W</td>
<td>20</td>
<td>4 (20) [6 - 44]</td>
</tr>
<tr>
<td>10 mg/kg Q 2W</td>
<td>16</td>
<td>5 (31) [11 - 59]</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>11 (26) [14 - 42]</td>
</tr>
</tbody>
</table>

- Interim median PFS<sup>c</sup>:
  - 27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review
  - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review

#### Study Design

**Screening**
- Entry criteria: Stage IV squamous NSCLC<sup>1,2</sup>
- ECOG PS 0-2

**Randomization (R)** stratified by:
- ECOG PS (0-1 vs. 2)
- Geographic region (North America, Europe and Australia vs. South America, South Africa and India vs. Eastern Asia)

**Gem-Cis + Neci q3w (N = 545)**
- Necitumumab (800 mg D1, D8)
- Gemcitabine (1250 mg/m², D1, D8)
- Cisplatin (75 mg/m², D1)

**Gem-Cis q3w (N = 548)**
- Gemcitabine (1250 mg/m², D1, D8)
- Cisplatin (75 mg/m², D1)

**Maximum of 6 cycles**

- PR
- CR
- SD

- **PD**

Radiographic tumor assessment (investigator read): at baseline and every 6 weeks until PD

Mandatory tissue collection<sup>3</sup>

1. AJCC TNM Classification, 7th edition, 2009
2. UICC TNM Classification of Malignant Tumors, 7th edition, 2009
3. Minimum 4 slides archived paraffin-embedded tumor tissue
OVERALL SURVIVAL: SQUIRE vs FLEX

H score NS in Squire

<table>
<thead>
<tr>
<th>Chemo</th>
<th>ORR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31.2%</td>
<td>5.7mo</td>
</tr>
<tr>
<td>Chemo</td>
<td>28.8%</td>
<td>5.5 mo (HR 0.85 p=0.02)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemo + Ab</th>
<th>ORR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Ab</td>
<td>36%</td>
<td>4.8 mo</td>
</tr>
<tr>
<td>Chemo</td>
<td>29%</td>
<td>4.8 mo (p=0.39)</td>
</tr>
</tbody>
</table>

Outline

- ALK:
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- SCLC:
  - 7502: SCLC Thoracic XRT
  - 7503: SCLC PCI
CREST Trial Design

ES-SCLC, WHO 0-2 → 4-6 platinum-based chemotherapy

RANDOMIZE

TRT (10 x 3Gy) Start 2-7 wks post chemo

PCI

Any response No brain mets No pleural mets

PCI

Primary Endpoint: Overall Survival

Presented by: Ben Slotman ABSTR 7502

CREST results

- N= 498, Median age 63, 55% male, 76% distant mets
- Randomized to thoracic radiotherapy (30 Gy in 10 fx)
- Minimal Toxicity Noted

- OS HR = 0.84 (95%CI 0.69-1.01), p=0.066
- 24 month OS +/- TRT (95% CI)
  - 13% vs 3%

- PFS HR = 0.73 (95%CI 0.61-0.87), p=0.001
- Thoracic radiotherapy could be offered in addition to PCI to patients responding to initial chemotherapy – ongoing RTOG study

Presented by: Ben Slotman ,ABSTR 7502
Prophylactic cranial irradiation in Extensive stage SCLC: OS

1 year: 27.1% vs. 13.3%
HR: 0.68 (0.52-0.88)   p=0.003

Design of current PCI study

Primary endpoint: Overall Survival
N= 163; median age 69; >80% men
### Time to Brain Metastasis

<table>
<thead>
<tr>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=84</td>
<td>n=79</td>
</tr>
<tr>
<td>BM at 12 months</td>
<td>32.4%</td>
</tr>
</tbody>
</table>

Gray's test: P < 0.001 (2-sided)

### Overall Survival

<table>
<thead>
<tr>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=84</td>
<td>n=79</td>
</tr>
<tr>
<td>No. of OS Events</td>
<td>61</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.38 (0.95-2.02)</td>
</tr>
<tr>
<td>Median OS (95%CI), mo</td>
<td>10.1 (8.5-13.2)</td>
</tr>
</tbody>
</table>

PFS HR 1.12, NS

Slightly more 2\textsuperscript{nd}, 3\textsuperscript{rd} line chemo in No PCI arm

Seto PASCO 2014, 7502
Conclusions

• ALK:
  – 8002: 1st line crizotinib Profile 1014 – 1st line crizotinib now SOC
  – 8003: ASCEND – ceritinib – Ceritinib now approved after crizotinib failure
• EGFR:
  – 8004: Lux lung 3+6 OS analysis – OS benefit in combined analysis, Del19 different
  – 8000: onartuzumab- Met lung - Negative
  – 8005: Bevacizumab + erlotinib – Could consider as 1st line in EGFRmut NSCLC
  – 8009: AZD9291 : 8010: CO-1686 – Both very promising with ongoing trials
  – 7501: RADIANT – Negative trial. No OS benefit even in EGFRmut, ongoing studies
• OTHER ANTIBODIES:
  – 8006: ramucirumab-REVEL – positive, but unclear how much impact
  – 8007: PD-L1 MK3475 – positive, PD-1 and PD-L1 coming soon
  – 8008: Necitumumab - Squire – positive, but unclear how much impact
• SCLC:
  – 7502: SCLC Thoracic XRT – positive, could consider
  – 7503: SCLC PCI – negative, PCI not for everyone