Lung Cancer: State of the Art

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I do intend to discuss an off-label use of a product during this activity. The following products will be discussed,
1) Dabrafenib and Trametenib for BRAF mutated NSCLC
2) Cabozantanib and Vandetanib for RET mutated NSCLC
3) Brigatanib and Lorlatanib for ALK+/ROS-1 + NSCLC
4) Crizotinib and Cabozantanib for MET mutated NSCLC
Financial Disclosure(s)

I currently have or have had the following relevant financial relations to disclose:

- Merck and BMS
- Provided Grant support for research for investigator initiated trials
First line Therapy

- Squamous cell:
  - Carboplatin + Taxane
  - Carboplatin + Gemcitabine +/- Necitumumab
  - Immunotherapy (not yet, but probably soon)

- Non-squamous cell:
  - Chemotherapy +/- Bevacizumab
  - Molecularly targeted therapy
  - Immunotherapy (not yet, but probably soon)
Cisplatin + Gemcitabine +/- Necitumumab
1st line stage IV squamous cell lung cancer

HR (95%CI): 0.84 (0.74, 0.96); P = 0.012

Median OS (95%CI), months:
- Gem-Cis + Neci: 11.5 (10.4, 12.6)
- Gem-Cis: 9.9 (8.9, 11.1)

Overall survival (%)

Patients / events:
- Gem-Cis + Neci: 545 / 418
- Gem-Cis: 548 / 442

Time since randomization (months)

Non-Squamous NSCLC

• Induction therapy X 4-6 cycles
  – Carboplatin + Pemetrexed +/- Bevacizumab
  – Carboplatin + Paclitaxel + Bevacizumab

• Maintenance therapy:
  – Switch maintenance
  – Continuation maintenance
Continuation maintenance: Pemetrexed

Paz Ares et al, Lancet Oncology 2012 (13); 247-55

- Cisplatin + Pemetrexed X 4
- Pemetrexed
- Placebo
Continuation maintenance: Pemetrexed OS

<table>
<thead>
<tr>
<th>Time from Randomization (Months)</th>
<th>Pem</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
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<tr>
<td>6</td>
<td>0.8</td>
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<tr>
<td>9</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>12</td>
<td>0.6</td>
<td>0.6</td>
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<tr>
<td>15</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
<td>0.4</td>
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<tr>
<td>21</td>
<td>0.3</td>
<td>0.3</td>
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<td>24</td>
<td>0.2</td>
<td>0.2</td>
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<tr>
<td>27</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Survival Probability

- **OS Median (mo)**
  - Pem: 13.9 (95% CI: 12.8-16.0)
  - Placebo: 11.0 (95% CI: 10.0-12.5)

- **Censoring (%)**
  - Pem: 28.7
  - Placebo: 21.7

- **Survival Rate (%) (95% CI)**
  - 1-year:
    - Pem: 58 (53-63)
    - Placebo: 45 (38-53)
  - 2-year:
    - Pem: 32 (27-37)
    - Placebo: 21 (15-28)

Patients at Risk

- **Pem + BSC**
  - 359
  - 333
  - 272
  - 235
  - 200
  - 166
  - 138
  - 105
  - 79
  - 43
  - 15
  - 2
  - 0

- **Placebo + BSC**
  - 180
  - 169
  - 131
  - 103
  - 78
  - 65
  - 49
  - 35
  - 23
  - 12
  - 8
  - 3
  - 0
Which regimen is preferred for non-squamous NSCLC?

Carboplatin/Paclitaxel/BEV → BEV

Carboplatin/Pemetrexed → Pemetrexed
Similar Overall Survival

Pem+Cb: median OS = 10.5 (mo)
Pac+Cb+Bev: median OS = 11.7 (mo)

Log-rank p-value = 0.615
HR (95% CI) = 1.07 (0.83, 1.36)

Patients at Risk
Pem+Cb 182 156 125 102 72 48 33 20 11 11 5 5 5 5 5
Pac+Cb+Bev 179 151 121 96 73 59 38 28 10 3 1 1 0 0 0
Maintenance BEV vs. PEM/BEV: AVAPERL

Barlesi et al, JCO 2013;31:3004-3011

- Bevacizumab + Pemetrexed
- Bevacizumab + Pemetrexed + Cisplatin
- Bevacizumab
- CR/PR/SD

R
Improved PFS but not OS with Pemetrexed/Bev maintenance
Maintenance BEV vs. PEM/BEV using different induction regimens: U.S.

Patel et al, JCO 2013;31:4349-4357

- Pemetrexed + Carboplatin + Bevacizumab
- Paclitaxel + Carboplatin + Bevacizumab
- Pemetrexed + Bevacizumab
- Bevacizumab
Point Break: overall survival

HR = 1.0 (95% CI: 0.86–1.16)
Log-rank $P = 0.949$

- **Pem Arm**
  - Median OS = 12.55 mo (95% CI: 11.30–14.03)
- **Pac Arm**
  - Median OS = 13.4 mo (95% CI: 11.86–14.91)
Looking at this data together

<table>
<thead>
<tr>
<th>Trial</th>
<th>Induction</th>
<th>Maint.</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 4599</td>
<td>Cb/Pac/Bev</td>
<td>Bev</td>
<td>12.3</td>
</tr>
<tr>
<td>Point Break</td>
<td>Cb/Pac/Bev</td>
<td>Bev</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>Cb/Pem/Bev</td>
<td>Pem/Bev</td>
<td>12.5</td>
</tr>
<tr>
<td>PARAMOUNT</td>
<td>Cis/Pem</td>
<td>Pem</td>
<td>13.9</td>
</tr>
<tr>
<td>AVAPERL</td>
<td>Cis/Pem/Bev</td>
<td>Pem/Bev</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bev</td>
<td>15.7</td>
</tr>
</tbody>
</table>

- Sandler et al NEJM 2006;355; Patel et al, JCO 2013; Luis Paz-Ares, Lancet 2012; Barlesi et al, JCO 2013
So, with a variety of options, is there a single standard?
So, with a variety of options, is there a single standard?

NO
Mutational burden of lung cancer is enormous

- 20,687 genes in the human genome
  - Comprised of > 3 billion base pairs

- Tobacco-related: 8-10 mutations per 1 million base pairs
  - Multiple chromosomal re-arrangements are common

- Non-smokers: 0.8-1 mutations per 1 million base pairs
## Recurrent Molecular Alterations


<table>
<thead>
<tr>
<th>Alteration</th>
<th>Adenocarcinoma</th>
<th>Squamous</th>
<th>Small Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 mutation</td>
<td>46%</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>RB mutation</td>
<td></td>
<td>7%</td>
<td>75%</td>
</tr>
<tr>
<td>Kras mutation</td>
<td>33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAF mutation</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET mutation</td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1 mutation</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI3KCA mutation</td>
<td>7%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>STK11 mutation</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN mutation</td>
<td></td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>ALK translocation</td>
<td>3-8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROS-1 translocation</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET translocation</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYC amplification</td>
<td></td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>CDKN2A amplification</td>
<td>20%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>
Molecularly targeted therapy

• EGFR activating mutation [exon 19 or 21]:
  – Erlotinib, Afatinib and Gefitinib are FDA approved

• ALK gene-rearrangement:
  – Crizotinib, Ceritinib, Alectinib

• ROS-1 gene re-arrangement:
  – Crizotinib
First line EGFR TKI vs. chemotherapy in EGFR mut + NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR (%)</th>
<th>Median PFS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TKI</td>
<td>Chemo</td>
</tr>
<tr>
<td>IPASS</td>
<td>71</td>
<td>47</td>
</tr>
<tr>
<td>First-SIGNAL</td>
<td>84</td>
<td>37</td>
</tr>
<tr>
<td>WJTOG</td>
<td>62</td>
<td>32</td>
</tr>
<tr>
<td>NEJ002</td>
<td>73</td>
<td>30</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>83</td>
<td>36</td>
</tr>
<tr>
<td>Erlotinib (EURTAC)</td>
<td>58</td>
<td>15</td>
</tr>
<tr>
<td>Afatinib (LUX-Lung 3)</td>
<td>56</td>
<td>22</td>
</tr>
<tr>
<td>Afatinib (LUX-Lung 6)</td>
<td>67</td>
<td>23</td>
</tr>
</tbody>
</table>
Is there a preferred EGFR Tki?

- Stage IIIB/IV adenocarcinoma of the lung
- EGFR mutation (Del19 and/or L858R) in the tumor tissue
- No prior treatment for advanced/metastatic disease

Afatinib 40 mg

Gefitinib 250 mg

PFS by independent review

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Estimated PFS probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>9</td>
<td>0.4</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>27%*</td>
</tr>
<tr>
<td>21</td>
<td>18%†</td>
</tr>
<tr>
<td>24</td>
<td>15%</td>
</tr>
<tr>
<td>27</td>
<td>8%</td>
</tr>
<tr>
<td>30</td>
<td>3%</td>
</tr>
<tr>
<td>33</td>
<td>1%</td>
</tr>
<tr>
<td>36</td>
<td>0%</td>
</tr>
<tr>
<td>39</td>
<td>0%</td>
</tr>
<tr>
<td>42</td>
<td>0%</td>
</tr>
</tbody>
</table>

Median PFS (months) Afatinib (n=160) 11.0 Gefitinib (n=159) 10.9
HR (95% CI) 0.73 (0.57–0.95)
p value 0.0165

ORR and DCR by independent review

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del19, %</td>
<td>73.1</td>
<td>65.6</td>
</tr>
<tr>
<td>L858R, %</td>
<td>65.7</td>
<td>42.4</td>
</tr>
<tr>
<td>Median DoR, months (95% CI)</td>
<td>10.1 (7.8–11.1)</td>
<td>8.4 (7.4–10.9)</td>
</tr>
<tr>
<td>DCR, % (n)</td>
<td>91.3% (146)</td>
<td>87.4% (139)</td>
</tr>
</tbody>
</table>

Better OS with Exon 19 mutation vs. L858R when choosing Tki 1st line

Is there a preferred Tki?

- Afatinib is more active than Gefitinib in patients with EGFR mutated tumors.
- Afatinib is slightly more effective than Erlotinib in patients with squamous cell cancer.
- Possible survival advantage for Afatinib over chemotherapy in patients with Exon 19 mutations:
  - Gefitinib and Erlotinib have not demonstrated.
  - LOTS of caveats (caution)!!
- Afatinib is associated with higher frequency of side effects, including rash.
ALK + NSCLC: Crizotinib is standard

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Crizotinib (N=172)</th>
<th>Chemotherapy (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 (58)</td>
<td>137 (80)</td>
</tr>
<tr>
<td>Median, months</td>
<td>10.9</td>
<td>7.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45 (0.35−0.60)</td>
<td></td>
</tr>
</tbody>
</table>
ROS1+ NSCLC: Crizotinib is standard


ORR 72%
Second line therapy: Chemo, Targeted therapy, and Immunotherapy

- FDA approved agents are:
  - Docetaxel
  - Docetaxel + Ramucirumab
  - Pemetrexed (non-squamous only)
  - EGFR Tki’s:
    - Erlotinib in 2nd or 3rd line (regardless of EGFR status)
    - Afatinib (squamous cell)
    - Osimertinib (T790M only)
  - ALK Tki’s:
    - Crizotinib, Ceritinib and Alectinib
  - ROS-1, RAF, RET, MET agents (not FDA approved)
  - Nivolumab and Pembrolizumab
• 1253 patients randomized

• Improved RR, PFS, and OS favoring RAM

• More neutropenia/FN and HTN with RAM
### Ramucirumab + Docetaxel vs. Placebo + Docetaxel: PFS and OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (95% CI)</th>
<th>Censoring rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab + docetaxel</td>
<td>10.5 months (9.5-11.2)</td>
<td>31.8%</td>
</tr>
<tr>
<td>Placebo + docetaxel</td>
<td>9.1 months (8.4-10.0)</td>
<td>27.0%</td>
</tr>
<tr>
<td>Ramucirumab vs placebo</td>
<td>Stratified HR 0.86 (95% CI 0.75-0.98); p=0.023</td>
<td></td>
</tr>
</tbody>
</table>

**Progression-free survival**

- **Ramucirumab plus docetaxel**
- **Placebo plus docetaxel**
- Censored

**Overall survival**

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Ramucirumab plus docetaxel</th>
<th>Placebo plus docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab</td>
<td>628</td>
<td>527</td>
</tr>
<tr>
<td>Placebo</td>
<td>625</td>
<td>501</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>628</td>
</tr>
<tr>
<td>3</td>
<td>527</td>
</tr>
<tr>
<td>6</td>
<td>425</td>
</tr>
<tr>
<td>9</td>
<td>329</td>
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<tr>
<td>12</td>
<td>231</td>
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<td>15</td>
<td>156</td>
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<td>18</td>
<td>103</td>
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<td>70</td>
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<td>33</td>
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<tr>
<td>36</td>
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</table>

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>625</td>
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<tr>
<td>3</td>
<td>383</td>
</tr>
<tr>
<td>6</td>
<td>204</td>
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<td>9</td>
<td>120</td>
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<td>27</td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>
Osimertinib is standard 2\textsuperscript{nd} line therapy in EGFR T790M disease

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\textsuperscript{1}Li et al, Oncogene, 2008; \textsuperscript{2}Ranson et al, WCLC, 2013
Osimertinib in T790M+ NSCLC

ORR 66%
ALK inhibitors: 2\textsuperscript{nd} line and beyond

- Ceritinib FDA approved in ALK + patients previously treated with Crizotinib
  - Response Rate: 56%

- Alectinib FDA approved in ALK + patients previously treated with Crizotinib
  - Response Rate: 50%; brain met RR: 57%

Shaw et al, NEJM 2013;368:2385-94
Shaw et al, NEJM 2014;370:1189-97
Abstract 8008, ASCO 2015
Alectinib vs. Crizotinib (n=207)
Nokihara et al, ASCO 2016, Abstract 9008

• No prior ALK inhibitors allowed
• >40% prior tobacco use
• Alectinib 300 mg bid (FDA approved dose 600mg)
• Crizotinib 250 mg bid
• PFS favored Alectinib (HR 0.34), p<0.0001
• Alectinib better tolerated
Primary Endpoint: PFS by IRF (ITT Population)

- **Alectinib** (N=103)
  - Events, n (%): 25 (24.3%)
  - Median, mo [95% CI]: NR [20.3 - NR]
  - P-value: <0.0001
  - HR [99.6826% CI]: 0.34 [0.17 - 0.71]

- **Crizotinib** (N=104)
  - Events, n (%): 58 (55.8%)
  - Median, mo [95% CI]: 10.2 [8.2 - 12.0]

**Graph Details:**
- Progression-free survival rate
- No. of patients at risk:
  - Alectinib: 103, 103, 93, 76, 49, 36, 27, 9, 1
  - Crizotinib: 104, 102, 86, 65, 40, 21, 14, 4
- Time (months): 0, 1, 3, 6, 9, 12, 15, 18, 21, 24, 27
- Median PFS: 10.2 months
Brigatinib in ALK + NSCLC
Kim et al, ASCO 2016, Abstract 9007

• Active against ALK re-arranged, Crizotinib-resistant mutants
• All patients had progressed on Crizotinib
• 222 patients randomized to receive one of two doses (90 mg qd or 180 mg qd)
• RR: 46-54%
Lorlatinib in patients with ALK or ROS-1 + NSCLC
Solomon et al, ASCO 2016, Abst 9009

- Active against ALK and ROS-1 mutant lines
  - Appears to be the most potent agent against a variety of ALK mutants
  - More potent ROS-1 inhibitor than Crizotinib or Ceritinib

- 54 patients treated; ¾ had brain mets
- Can elevate lipids
- 57% RR in 2nd line ALK setting
- 42% in 3rd line ALK setting
- 9 of 11 patients with ROS-1 responded
My Thoughts

• Crizotinib is NOT our best **ALK inhibitor**

• Alectinib is my preferred 1\(^{st}\) line agent in ALK + NSCLC for now

• Brigatinib and Lorlatinib may be even better

• In my opinion, these agents will all supplant the use of Crizotinib in ALK + NSCLC
# Overcoming Crizotinib Resistance in Advanced ROS1+ NSCLC

<table>
<thead>
<tr>
<th></th>
<th>WT ROS1</th>
<th>G2032R</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtinib1</td>
<td>3,700 nM</td>
<td>---</td>
<td>None – not active</td>
</tr>
<tr>
<td>Ceritinib2</td>
<td>10.9 nM</td>
<td>277 nM</td>
<td>Phase 2 (SIGNATURE)</td>
</tr>
<tr>
<td>Brigatinib2</td>
<td>2.7 nM</td>
<td>322 nM</td>
<td>Investigator initiated trials</td>
</tr>
<tr>
<td>Lorlatinib3</td>
<td>0.16 nM</td>
<td>167 nM</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Cabozantinib2</td>
<td>2 nM</td>
<td>13.5 nM</td>
<td>Phase 2 (MSKCC)</td>
</tr>
<tr>
<td>Foretinib4</td>
<td>~3 nM</td>
<td>50 nM</td>
<td>None</td>
</tr>
<tr>
<td>Crizotinib2</td>
<td>2.1 nM</td>
<td>254 nM</td>
<td>Phase 1 (PROFILE 1001)</td>
</tr>
</tbody>
</table>

Newest Targetable Mutations in Lung Cancer

- HER-2
- BRAF
- RET
- MET
HER-2 is a member of the EGFR family

• Prior attempts to target HER-2 in lung cancer have yielded modest results

• HER-2 amplification or over-expression by IHC does not correlate with response to HER-2 inhibitors in lung cancer

• HER-2 mutations have been previously unstudied
  ▪ Case reports of responses to Afatanib or Lapatanib
Her-2 exon 20 insertion mutations
Abstract 11076 and e12649, ASCO 2015

• Approximately 2% NSCLC
• Adenocarcinomas
• More commonly in non-smokers
• Concomitant EGFR, ALK, ROS-1 aberrations are infrequent (1-5%)
• If WT for EGFR, ALK, and ROS-1, incidence is as high as 7%
• Response rate higher with Afatanib compared with 1st generation EGFR Tki (18% vs 7%)
Dabrafenib + Trametinib in BRAF V600e

Abstract 8006, ASCO 2015; Abstract 107, ASCO 2016

- BRAF mutations occur in 2% of lung cancers
- Dabrafenib monotherapy: 32% RR and 56% DCR
- Combination of RAF and MEK inhibitors effective in melanoma
- Heavily pretreated population, most were smokers
- Combination (n=57) RR 63%; DCR 79%
- Median duration of response: 9 months
RET rearranged NSCLC
Abstract 8007, ASCO 2015; Abstract 9013 and 9012, ASCO 2016

• RET fusions are similar to ALK/ROS-1
• Usually adenocarcinoma, never/former/light smokers
• Cabozantinib inhibits ROS-1, RET, MET, KIT, VEGFR2
  – 60 mg daily tested (140 mg FDA approved dose)
  – 38% RR and 56% SD in 16 patients treated
• Vandetanib
  – 17% PR and 44% SD in 18 patients treated in 1 study
  – 53% PR and 35% SD in 19 patients in another study
MET oncogene
Abstracts 8020, 8021; Frampton et al, Cancer Discovery 2015

• Can be amplified or mutated in extra-cellular domain, non-kinase transmembrane domain, or intra-cellular TK domain

• Exon 14 splice mutation in non-kinase transmembrane domain results in loss of Exon 14 and activation of MET

• Mutually exclusive of other oncogenic drivers

• NOT smoking related
Crizotinib in MET Exon 14 altered NSCLC
Drilon et al, ASCO 2016, Abstract 108

• 21 patients treated

• 2/3 former smokers

• 76% adenocarcinoma, 14% sarcomatoid carcinoma

• 86% treated as 2\textsuperscript{nd} line or beyond
Antitumor Activity

Maximum Response to Crizotinib in Patients with MET Exon 14-Altered Lung Cancers
(n=16 with measurable disease at baseline and ≥1 response assessment scan)

- Partial response (PR), confirmed
- Stable disease (SD): includes 4 unconfirmed PRs
- * Stable disease and 0% change from baseline

Presented at: ASCO ANNUAL MEETING ‘16
Presented by: Alexander Drilon MD
## Summary of Targeted Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>ALK</th>
<th>ROS-1</th>
<th>MET</th>
<th>RET</th>
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<tbody>
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<td>Crizotinib</td>
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<tr>
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<td>Translocation</td>
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<td>N/A</td>
<td>N/A</td>
<td>??</td>
</tr>
</tbody>
</table>

*Tumor mutational burden

*I prefer NGS in most of my patients, rather than individual gene testing.*
Immunotherapy

• Nivolumab

• Pembrolizumab
Squamous Cell Carcinoma
Nivolumab vs. Docetaxel 2nd line

Non-Squamous NSCLCs
Nivolumab vs. Docetaxel 2\textsuperscript{nd} line

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
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<tbody>
<tr>
<td>mOS, mo</td>
<td>12.2</td>
<td>9.4</td>
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<tr>
<td>HR</td>
<td>0.73 (96% CI: 0.59, 0.89)</td>
<td>(P = 0.0015)</td>
</tr>
</tbody>
</table>

1-yr OS rate = 51\%
1-yr OS rate = 39\%
**Pembrolizumab vs. Docetaxel**

**Median Overall Survival**

Patients with 50% tumor proportion score:
- 14.9 months for pembro 2 mg/kg
- 17.3 months for pembro 10 mg/kg
- 8.2 months for docetaxel

Overall Population:
- 10.4 months for pembro 2 mg/kg
- 12.7 months for pembro 10 mg/kg
- 8.5 months for docetaxel

**Updated Data on OS based TPS**

1-24%  HR 0.74
25-49%  HR 0.86
50-74%  HR 0.58
≥ 75%  HR 0.51

ASCO 2016, Abstract 9015

Herbst R et al The Lancet. 2015.
Assessment of Immune Cells in NSCLC Tumor Tissues – IHC Markers

- CD45RO
- CD8
- CD4
- CD3
- CD57
- Granzyme B
- FOXP3
- PD-1
- CD68
- PD-L1 High
- PD-L1 Moderate
- PD-L1 Negative

Edwin Parra et al, MD Anderson Cancer Center, 2015
Immuno-profiling Multiplex IF Vectra™ Panels

E. Parra and J. Rodriguez, MD Anderson Cancer Center, 2015
Summary

• Major advances are taking place in the treatment of patients with advanced NSCLC

• There is reason for renewed hope and optimism that some patients can live significantly longer with a high quality of life

• Will these advances translate into more cures in the early stage/locally advanced setting?