NON-SMALL CELL LUNG CANCER – 2014

NEWER APPROACHES:
GENETIC ALTERATIONS AND IMMUNE CHECKPOINT STRATEGIES

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SYSTEMIC APPROACHES TO ADVANCED CANCER

2014

CHEMOTHERAPY

BOTH

MOLECULARLY TARGETED APPROACHES
HALLMARKS OF CANCER

- Evading apoptosis
- Sustained angiogenesis
- Limitless replicative potential
- Insensitivity to anti-growth signals
- Tissue invasion and metastasis
- Self-sufficiency in growth signals

Positions of Mutations Detected in HER1/EGFR Tyrosine Kinase Domain in NSCLC


A Couple of Targets

▲ Tumor with point mutation (amino acid substitution)
★ Tumor with in-frame deletion

TM = transmembrane
Survival by Smoking Status

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Erlotinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never Smokers</strong></td>
<td>24.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Response Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Survival</td>
<td>12.3 mos</td>
<td>5.6 mos</td>
</tr>
<tr>
<td>HR=0.42</td>
<td></td>
<td>(95% CI 0.28 to 0.64)</td>
</tr>
<tr>
<td><strong>Current/Ex-Smokers</strong></td>
<td>3.9%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Response Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Survival</td>
<td>5.5 mos</td>
<td>4.6 mos</td>
</tr>
<tr>
<td>HR=0.87</td>
<td></td>
<td>(95% CI 0.71 to 1.05)</td>
</tr>
</tbody>
</table>

META-ANALYSIS 2014:
Impact of EGFR-TKIs on Survival and PFS in NSCLC based in Mutation + Patients Only: Clinical and Genetic Correlations

• Publications from 2004 to 2014
• Randomized comparisons of 1st Line treatment of Chemotherapy versus EGFR TKIs
• 7 Trials which included 1649 patients
• Exon 19 deletions & Exon 21 L858 substitutions were >90% of the mutations
• Analyzed for differences among subgroups, including:
  – Exon 19 versus Exon 21 mutations
  – Smoking History
  – Gender
  – Also: Performance Status, Age, Tumor Histology, Ethnic origin

## META-ANALYSIS 2014: Impact of EGFR-TKIs on PFS in NSCLC based on EGFR Mutational Status: Results

<table>
<thead>
<tr>
<th>EGFR TKI versus CHEMOTHERAPY:</th>
<th>HR: 0.37 (95% CI: .33 - .43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXON 19 versus EXON 21</td>
<td></td>
</tr>
<tr>
<td>EXON 19 - HR: 0.25</td>
<td>EXON 21 - HR: 0.48 (P &lt; 0.001)</td>
</tr>
<tr>
<td>SMOKING HISTORY</td>
<td></td>
</tr>
<tr>
<td>NEVER SMOKERS - HR: 0.32</td>
<td>SMOKERS - HR: 0.51 (P &lt; 0.0008)</td>
</tr>
<tr>
<td>GENDER</td>
<td></td>
</tr>
<tr>
<td>WOMEN - HR: 0.33</td>
<td>MEN - HR: 0.45 (P &lt; 0.03)</td>
</tr>
<tr>
<td>AGE, ETHNIC ORIGIN, HISTOLOGY*, PS*</td>
<td>No Significant Differences *</td>
</tr>
</tbody>
</table>

* But > 94% of pts PS 0,1 and adenocarcinoma
META-ANALYSIS 2013 and 2014: Impact of EGFR-TKIs on Survival and PFS in NSCLC based on EGFR Mutations: Conclusions

- These are the largest meta-analyses in these settings
- The results establish for the first time that the impact of EGFR-TKIs is the same in either First- or Second-line settings
- Nearly all of the benefit of EGFR-TKI is in patients who harbor activating EGFR mutations (mutation positive status)
  - Valid for First-Line, Second-Line, and Maintenance settings
- EGFR-TKIs plus Chemo is not better than EFGR-TKIs alone

**For EGFR mutation + patients:**
- Large PFS benefits are seen; survival benefit not found since BR.21
  - With > 90% of patients ‘crossing-over,’ this result is not surprising
- Among patients with mutations, major differences are found depending on the mutation and on common clinical factors

EGFR-TKI Resistance Pathways

Reference: Yu et al, CCR 2013
<table>
<thead>
<tr>
<th>EGFR TKIs AND TARGET AFFINITY</th>
<th>ERLOTINIB</th>
<th>AFATINIB</th>
<th>CO 1686</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR wt</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>EGFR mutated</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Resistance Mechanism T790M</td>
<td>--</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Phase I – II: CO-1686 in *EGFR* mutant NSCLC

Best response in Phase 1 and early Phase 2 expansion cohort patients

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

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>ORR to date: 58%</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 mg BID FB / 500 mg HBr</td>
<td><em>Ongoing</em></td>
</tr>
<tr>
<td>750 mg BID HBr</td>
<td></td>
</tr>
<tr>
<td>625 mg BID HBr</td>
<td></td>
</tr>
<tr>
<td>1000 mg BID HBr</td>
<td></td>
</tr>
</tbody>
</table>

Reference: Sequist *Proc ASCO* 2014, Abstract #8010
### EGFR TKIs: Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Any Grade 3</th>
<th>Diarrhea</th>
<th>Rash</th>
<th>Lung (ILD)</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>57%</td>
<td>80%</td>
<td>1%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Afatinib / Cetuximab</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>22%</td>
<td></td>
</tr>
<tr>
<td>AZD9291</td>
<td>20%</td>
<td>27%</td>
<td>3%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>HM61713</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

*NR* indicates not reported.
NON-SMALL CELL LUNG CANCER
- Incidence and Smoking Status -

Smoking Status and Lung Cancer

- Smokers
- Non-Smokers
NON-SMALL CELL LUNG CANCER
- Identified Mutations in Non-Smokers with Adenocarcinoma -

Mutations

- EGFr: 44%
- EML4-ALK: 24%
- Kras: 10%
- Other: 8%
- Unknown: 14%

MG Kris. Targeted Therapy in Lung Cancer Meeting. February 2010
**EML4-ALK** Fusion Oncogene

“Echinoderm Microtubule-Associated Protein-Like 4 / Anaplastic Lymphoma Kinase”

Frequency in NSCLC:
- 1% - 7% of Asians
- 13% of unselected
- 22% of never / light smokers
- 33% of never / light smokers with wild-type *EGFR*

Rapid progress in targeting *ALK*

Identification of *ALK* rearrangements in lung cancers\(^1\)

Accelerated approval for *crizotinib*\(^2,3\)

05/2014: Accelerated approval for *ceritinib* in acquired resistance\(^4\)

07/2014: Approval in Japan for *alectinib*\(^5,6\)

1) Soda *et al*, Nature 2007
2) Kwak *et al*, NEJM 2010
3) Shaw *et al*, NEJM 2013
4) Shaw *et al*, NEJM 2014
5) Seto *et al*, Lancet 2013
6) Nakagawa, *et al* ASCO 2014, #8103
Clinical Activity of Crizotinib in ALK-Positive NSCLC

- N = 82, mean age 51
- 52% male
- 56% Caucasian,
- 35% Asian
- 76% never smokers
- 23% former smokers
- Adenocarcinoma 96%

Response Rate = 57%
PFS at 6 mo = 72%

Treatment-related Adverse Events:

- Grade 1 events in 40%-52% of patients: nausea, diarrhea, vomiting, vision disturbance (light accommodation)
- Grade 3/4 ALT elevation in 6%
- Rarer (all trials): Pulmonary Toxicity

Kwak, et al. NEJM 2010
Crizotinib Phase III – Second Line - versus Docetaxel / Pemetrexed (PFS)

Shaw et al, *NEJM* 2013

Crizotinib 250 mg bid orally

Hazard ratio for progression or death in the crizotinib group, 0.49 (95% CI, 0.37–0.64)
P<0.001

Crizotinib median PFS = 7 months
Evaluation of Crizotinib as First-line Therapy

**Crizotinib (N = 172)**
- Events, n: 100 (58%)
- Median PFS: 10.9 mos
- HR (95% CI): 0.45 (0.35–0.60)
- *p* < 0.0001

**Pemetrexed + Cis or Carbo (N = 172)**
- Events, n: 137 (80%)
- Median PFS: 7.0 mos

Mok et al, *Proc ASCO* 2014
HALLMARKS OF CANCER

- Evading apoptosis
- Sustained angiogenesis
- Self-sufficiency in growth signals
- Limitless replicative potential
- Insensitivity to anti-growth signals
- Tissue invasion and metastasis

NON-SMALL CELL LUNG CANCER
- Identified Mutations in Non-Smokers with Adenocarcinoma -

HER2  BRAF  AKT1  PIK3CA

Mutations

- 14% EGFr
- 44% Other
- 24% EML4-ALK
- 10% Unknown
- 8% Kras
- PD-1 not favoring Adeno or Non-Smokers

Programmed Cell Death protein 1, PD-1, cell surface protein encoded by PDCD1 gene

Targeting immunosuppression by blocking the PD-L1 / PD-1 pathway

Adaptive Tumor Expression of PD-L1

IFNγ-mediated up-regulation of tumor PD-L1

PD-1/ PD-L1 - mediated *Inhibition* of tumor cell killing

The PD-1/PD-L1 Immune Checkpoints

Tumor cell

T-cell

Dendritic cell

PD-L1
MHC
Peptide
T-cell receptor

PD-1

CD28
B7.1/2
MHC
Peptide
T-cell receptor

CTLA-4
B7.1/2

TARGETS
T-cell checkpoint inhibitors in NSCLC: PD-1 / PD-L1 Targeted Monoclonal Antibodies - Preliminary Efficacy Data -

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>N *</th>
<th>Response Rate</th>
<th>PFS &gt; 24wks</th>
<th>1 year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab¹</td>
<td>PD-1</td>
<td>129</td>
<td>17-24%</td>
<td>27-35%</td>
<td>32-56%</td>
</tr>
<tr>
<td>Pembrolizumab²</td>
<td>PD-1</td>
<td>217</td>
<td>18-20%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MEDI 4736³⁴</td>
<td>PD-L1</td>
<td>58</td>
<td>16%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MPDL 3280A⁶</td>
<td>PD-L1</td>
<td>41</td>
<td>22%</td>
<td>46%</td>
<td>NR</td>
</tr>
</tbody>
</table>

¹ Brahmer ASCO 2014, #8112  
² Garon, ASCO 2014, #8020  
³ Segal, ASCO 2014, #3002  
⁴ Brahmer, ASCO 2014, #8021  
⁵ Spigel, ASCO 2013, #8008

* All as Second-Line Treatment
## Pembrolizumab Treatment-Related Adverse Events

### Adverse Events of Any Grade, Incidence >5%

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event, n (%)</th>
<th>N = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>36 (80%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (22%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (7%)</td>
</tr>
</tbody>
</table>

### Grade 3-4 Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event, n (%)</th>
<th>N = 45</th>
<th>Resulted in Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood creatine phosphokinase increased (Gr 4)</td>
<td>1 (2%)</td>
<td>No</td>
</tr>
<tr>
<td>Pericardial effusion (Gr 3)</td>
<td>1 (2%)</td>
<td>No</td>
</tr>
<tr>
<td>Pneumonitis (Gr 3)</td>
<td>1 (2%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute kidney injury (Gr 2)</td>
<td>1 (2%)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Reference: Rizvi et al *Proc ASCO* 2014
Is PD-L1 a useful biomarker in NSCLC?

<table>
<thead>
<tr>
<th>Drug/ Sponsor</th>
<th>Nivolumab BMS</th>
<th>Pembrolizumab Merck</th>
<th>MPDL3280A Genentech</th>
<th>MEDI4736 MedImmune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>28-8</td>
<td>22C3</td>
<td>???</td>
<td>SP263</td>
</tr>
<tr>
<td>Cells scored</td>
<td>Tumor cell membrane</td>
<td>Tumor cell and stroma</td>
<td>Infiltrating immune cells [recently changed]</td>
<td>???</td>
</tr>
<tr>
<td>Tissue</td>
<td>Archival</td>
<td>Recent</td>
<td>Arch./Recent</td>
<td>Arch./Recent</td>
</tr>
<tr>
<td>Setting</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Line</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Line</td>
</tr>
<tr>
<td>Cut-point</td>
<td>1%</td>
<td>1%</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

For NVO
- Topalian, NEJM 2012
- Grosso, ASCO 2013, #3016ne
- Brahmer, ASCO 2014, #8112
- Gettinger, ASCO 2014, #8024

For Pembrol
- Daud, AACR 2014
- Ghandi, AACR 2014
- Rizvi, ASCO 2014, #8009
- Garon, ASCO 2014, #8020

For MPDL3280A
- Hamid, ASCO 2013, #9010
- Herbst, ASCO 2013, #3000
- Powderly, ASCO 2013, #3001
- Spigel, ASCO 2013, #8008

For MEDI4736
- Segal, ASCO 2014, #3002
- Brahmer, ASCO 2014, #8021
T-cell checkpoint inhibitors in NSCLC: PD-1 / PD-L1 Targeted Monoclonal Antibodies - Observations -

• Several agents targeting this pathway are under investigation
• Responses have been reported, in 15% - 25% of patients given these agents as monotherapy
• Activity does not favor only patients who are non-smokers or have adenocarcinoma
• It is not yet clear if tumor PD-L1 over-expression is a predictor of antitumor activity
• It is not yet clear whether targeting PD-1 or PD-L1 is a better approach in terms of efficacy or toxicity
The effect of Chemotherapy and novel agents in Non-small Cell Lung Cancer

The Magnitude of Various Interventions on Survival

- Relative Reduction in the Risk of Death: **25% to 50%:**
  - Combination Chemotherapy vs Supportive Care (17 trials)*
  - Chemotherapy vs Supportive Care - 2nd Line (4 trials)**

- Relative Reduction in the Risk of Death: **10% to 25%:**
  - Two agents vs One (65 Trials)**
  - Cisplatin vs Carboplatin (5 Trials)*
  - Cisplatin regimens vs non-platinum regimens (14 Trials)*
  - Adjuvant chemotherapy vs no further treatment (12 Trials)*

- Relative Reduction in the Risk of Death: **5% to 10%:**
  - Bevacizumab + Chemotherapy vs Chemotherapy (1 of 2 Trials)
  - Cetuximab + Chemotherapy vs Chemotherapy (1 of 2 Trials)

* Also 2 or more meta-analyses ** Also 1 meta-analysis
NON-SMALL CELL LUNG CANCER
Treatment Considerations in 2014

• We now have at least three distinct treatment strategies:
  - Chemotherapy
  - Genetic abnormalities: Mutations / Rearrangements
  - Immune Checkpoint Inhibition

• Newer pathways have the potential to identify individual patients likely to respond to treatment

• Chemotherapy remains the largest contributor to survival benefit for the whole population

• Much research focuses on resistance pathways

• Toxicity profiles vary, but much work needs to be done

• Is there reason to expect that only 3 distinct pathways or strategies are possible?