Personalized Treatment Approaches for Lung Cancer

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Chair, Thoracic Oncology Site Committee
UCSF Helen Diller Family Comprehensive Cancer Center
Disclosures

- **Consulting**
  - AbbVie, ARIAD, AstraZeneca, Bristol-Myers Squibb, Genentech/Roche, Mersana, Novartis, Pfizer

- **Research Funding (to institution)**
  - Celgene, Merck, Novartis, OncoMed, Roche

- I will discussing non-FDA approved treatment/indications during my presentation today (research findings)
Two themes

- Targeted therapies
- Immunotherapy
Two themes

- **Targeted therapies**
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations

- **Immunotherapy**
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage
Two themes

- Targeted therapies
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations

- Immunotherapy
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage
Targets

NSCLC as one disease
Targets

NSCLC as one disease

Histology-Based Subtyping

- Adenoca 55%
- Squamous 34%
- Others 11%

Histology??
Targets

NSCLC as one disease

Histology-Based Subtyping

- Others 11%
- Squamous 34%
- Adenoca 55%

Targets

Two themes

- **Targeted therapies**
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations

- **Immunotherapy**
  - Where we’re at: PD-1 inhibition in the 1st and 2nd line
  - Where we’re going: combos and early stage
EGFR – Epidermal growth factor receptor

- 10-30% of NSCLC patients
- Higher prevalence among:
  - Asians
  - Younger patients
  - Females
  - Never-smokers
  - Adenocarcinoma
EGFR

- 3 approved first line drugs: erlotinib, gefitinib, afatinib
- 2009 IPASS study (Mok et al in NEJM)
### EGFR

- 1\textsuperscript{st} line use established since 2009...
- ...but resistance inevitably develops.

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**Diagram:**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Adeno</th>
<th>Adeno</th>
<th>Adeno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR TKI status</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Treatment</td>
<td>Chemo</td>
<td>Erlotinib</td>
<td>Chemo</td>
</tr>
<tr>
<td>Timeline</td>
<td>2007</td>
<td>2008</td>
<td>2009</td>
</tr>
</tbody>
</table>

EGFR

- 1st line use established since 2009...
- ...but resistance inevitably develops.

**EGFR resistance: T790M, the “gatekeeper”**
EGFR resistance: T790M, the “gatekeeper”

- Osimertinib

- Engineered to inhibit EGFR exon 19/L858R AND T790M, but less inhibitory of normal (“wild-type”) EGFR
  - Effectiveness when erlotinib (or others) fail
  - Fewer toxicities

Janne, NEJM 2015.
EGFR resistance: T790M, the “gatekeeper”

- AURA3: osimertinib vs platinum-pemetrexed in T790M+
  - PFS 10.1 vs 4.4 mo, HR 0.3, p<0.001

Mok, NEJM 2017.
Osimertinib first line

- FLAURA: osimertinib vs erlotinib/gefitinib (not selected for T790M)

Soria, NEJM 2017.
EGFR take-home points

- Cancers evolve
- Biopsy at the beginning to figure out the driver mutation
  - ...and consider biopsy at progression to figure out the resistance mechanism
  - Osimertinib should follow 1st line 1st/2nd gen EGFR agent if T790M found
  - ...and should now be 1st line in most patients (pending approval)
- Future directions:
  - Study resistance to osimertinib?
  - 3rd/4th generation drugs?
EGFR—epidermal growth factor receptor

- 10-30% of NSCLC patients
- Higher prevalence among:
  - Asians
  - Younger patients
  - Females
  - Never-smokers
  - Adenocarcinoma

ALK—anaplastic lymphoma kinase

- 4-7% of NSCLC patients
- Higher prevalence among:
  - Younger patients
  - Never-smokers
  - Adenocarcinoma
ALK

- 2007 detected as an alteration in NSCLC
- 2011 crizotinib approved
  - Single-arm ORR 50, 61%
  - Vs docetaxel in the 2nd line, PFS 7.7 vs 3.0 mos
  - Vs platinum combo in the 1st line, PFS 10.9 vs 7.0 mos
ALK

- …but resistance inevitably develops.
- Why?
  - Crizotinib good, not great as an ALK inhibitor, so cancer can overcome it
  - Poor brain penetration, so cancer can thrive there
  - Other mutations develop
- 2nd generation ALK inhibitors—better ALK activity, better CNS activity
  - Ceritinib approved 2014 (duration 7.1 mos post-crizotinib)
  - Alectinib approved 2015 (duration 7.5 mos post-crizotinib)
ALK resistance

- But what about 2\textsuperscript{nd} generation first line?
- ALEX (ASCO 2017, NEJM 2017), alectinib vs crizotinib
  - RR 83 vs 76%

FDA approved 11/17
ALK take-home points

- Cancers evolve
- Biopsy at the beginning to figure out the driver mutation
  - And biopsy at progression to determine next drug?
  - Lorlatinib
    - RR 31% after 3 prior TKIs

Gainor, Cancer Discovery, 2016
Two themes

- **Targeted therapies**
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations

- **Immunotherapy**
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage
Targets other than EGFR and ALK

Targets other than EGFR and ALK

Targets other than EGFR and ALK

- **ASCO 2015**
  - BRAF V600E (more often seen in melanoma), 1-2%
    - Dabrafenib + trametinib ORR 63%, PFS 9.7mo
    - Now FDA approved for NSCLC

- **ASCO 2016**
  - MET exon 14 skipping, 3-4%
    - (often older patients, current/former smokers, sarcomatoid)
    - Crizotinib ORR 44%, PFS not yet reached
  - RET rearrangement, 1-2%
    - Cabozantinib ORR 38%
    - Vandetinib ORR 53%
Take-home points on other targets

- You can’t treat a mutation you don’t know
The NCCN NSCLC Guidelines panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Take-home points on other targets

- You can’t treat a mutation you don’t know
- Beyond EGFR and ALK, drugs may not be FDA-approved
  - Should we treat?
EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

<table>
<thead>
<tr>
<th>Genetic Alteration (ie, Driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-level <em>MET</em> amplification or <em>MET</em> exon 14 skipping mutation</td>
<td>crizotinib&lt;sup&gt;1-5&lt;/sup&gt;</td>
</tr>
<tr>
<td>RET rearrangements</td>
<td>cabozantinib&lt;sup&gt;6,7&lt;/sup&gt;, vandetanib&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>HER2 mutations</td>
<td>trastuzumab&lt;sup&gt;9&lt;/sup&gt; (category 2B), afatinib&lt;sup&gt;10&lt;/sup&gt; (category 2B)</td>
</tr>
</tbody>
</table>
Take-home points on other targets

- You can’t treat a mutation you don’t know
- Beyond EGFR and ALK, drugs may not be FDA-approved
  - Should we treat?
  - Consider clinical trials! Access to new drugs, data for everyone.
Two themes

- **Targeted therapies**
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations

- **Immunotherapy**
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage
Immunotherapy: Not a new idea

**FIRST USE OF COLEY’S MIXED BACTERIAL TOXINS**

William B. Coley creates a filtered mixture of bacteria and bacterial lysates, composed of *Streptococcus pyogenes* and *Bacillus prodigiosus*, called “Coley’s Toxins,” to treat tumors. His first patient is a 21-year old man named John Ficken with a large inoperable tumor (likely a malignant sarcoma). After treatment with the toxins, Ficken had a complete remission, lasting until his death 26 years later of a heart attack.

Immunotherapy: PD1/PD-L1 (and CTLA4)

Ribas A. NEJM 2012
The Food and Drug Administration on Thursday approved the first of an eagerly awaited new class of cancer drugs that unleashes the body’s immune system to fight tumors.

The drug, which will sell under the name was approved for patients with advanced melanoma who have exhausted other therapies.

Cancer researchers have been almost giddy in the last couple of years about the potential of drugs like which seem to solve a century-old mystery of how cancerous cells manage to evade the body’s immune system.
Immunotherapy- PD1/PD-L1

- High rates of somatic mutations in lung cancer may contribute to increased immunogenicity
- Therapies targeting the PD-L1/PD-1 pathway will alter the treatment of NSCLC

Lung Cancer Treatment Using Immune System Wins F.D.A. Approval

By ANDREW POLLACK    MARCH 4, 2015

The first immune-based treatment for lung cancer won approval from the Food and Drug Administration on Wednesday, and it could displace more conventional chemotherapy for certain patients, at least.

The drug, from is one of a class of medicines that have electrified oncologists in recent years because they free the body’s own immune system to attack tumors.

also known as nivolumab, was approved last year to treat advanced cases of the skin cancer melanoma, but the approval for lung cancer is in some ways more significant.
Checkmate 017: Nivolumab vs docetaxel in squamous cell NSCLC

Nivolumab prescribing instructions
Checkmate 017/057: Nivolumab vs docetaxel

Squamous

- Response rate
  - Nivo 20% vs docetaxel 9%
- Median duration of response
  - Nivo NR vs docetaxel 8.4mo

Non-squamous

- Response rate on 057
  - Nivo 19% vs docetaxel 12%
- Median duration of response
  - Nivo 17.2mo vs docetaxel 5.6mo

Nivolumab PI, Paz-Ares, ASCO 2015
Checkmate 057: Nivo vs doce in non-squam NSCLC

OS by PD-L1 Expression

1. ≥1% PD-L1 expression level
   - Nivo: 17.2 mo
   - Doc: 9.0 mo
   - HR (95% CI) = 0.59 (0.43, 0.82)

2. ≥5% PD-L1 expression level
   - Nivo: 18.2 mo
   - Doc: 8.1 mo
   - HR (95% CI) = 0.43 (0.30, 0.63)

3. ≥10% PD-L1 expression level
   - Nivo: 19.4 mo
   - Doc: 8.0 mo
   - HR (95% CI) = 0.40 (0.26, 0.59)

Paz-Ares, ASCO 2015
Checkmate 057: Nivo vs doce in non-squam NSCLC

OS by PD-L1 Expression

- ≥1% PD-L1 expression level
  - Nivo: 17.2 months
  - Doc: 9.0 months
  - HR (95% CI): 0.59 (0.43, 0.82)

- ≥5% PD-L1 expression level
  - Nivo: 18.2 months
  - Doc: 8.1 months
  - HR (95% CI): 0.43 (0.30, 0.63)

- ≥10% PD-L1 expression level
  - Nivo: 19.4 months
  - Doc: 8.0 months
  - HR (95% CI): 0.40 (0.26, 0.59)

- <1% PD-L1 expression level
  - Nivo: 10.4 months
  - Doc: 10.1 months
  - HR (95% CI): 0.90 (0.66, 1.24)

- <5% PD-L1 expression level
  - Nivo: 9.7 months
  - Doc: 10.1 months
  - HR (95% CI): 1.01 (0.77, 1.34)

- <10% PD-L1 expression level
  - Nivo: 9.9 months
  - Doc: 10.3 months
  - HR (95% CI): 1.00 (0.76, 1.31)

Paz-Ares, ASCO 2015
KEYNOTE-010: Pembrolizumab vs docetaxel in PD-L1+ NSCLC

- Overall survival
- PD-L1>50% pts
  - Pembro 14.9 vs 17.3 vs docetaxel 8.2 mo

- All pts PD-L1>1%
  - Pembro 10.2 vs 12.7 vs docetaxel 8.5 mo

Herbst, Lancet 2016
OAK: Atezolizumab vs docetaxel, 2nd or 3rd line (PD-L1 inhibitor)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Atezolizumab n = 425</th>
<th>Docetaxel n = 425</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>≥65 y</td>
<td>45%</td>
<td>49%</td>
</tr>
<tr>
<td>Male</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>Squamous</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>ECOG PS, 0/1</td>
<td>37%/64%</td>
<td>38%/62%</td>
</tr>
<tr>
<td>No. of prior therapies, 1/2</td>
<td>75%/25%</td>
<td>75%/25%</td>
</tr>
<tr>
<td>History of tobacco use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Current/previous</td>
<td>14% / 66%</td>
<td>16% / 67%</td>
</tr>
<tr>
<td>Known EGFR status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant/WT</td>
<td>10% / 75%</td>
<td>10% / 73%</td>
</tr>
</tbody>
</table>

Overall survival, ITT (n = 850)

- **HR, 0.73** (95% CI, 0.62, 0.87)
- **P=0.0003**
- Minimum follow-up = 19 months

Median 13.8 mo (95% CI, 11.8, 15.7)
Median 9.6 mo (95% CI, 8.6, 11.2)

No. at risk
Atezolizumab
425 407 382 361 342 326 305 279 160 248 234 223 218 205 198 188 175 163 157 141 116
Docetaxel
425 390 365 336 311 286 263 236 219 195 179 168 151 140 132 113 116 104 98 90 70 51 37 28 16 6 3

Barlesi, ESMO 2016
Safety of PD-1 inhibitors

Herbst, Lancet 2016

Superior tolerability compared to chemo

---

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab 2 mg/kg (n=339)</th>
<th>Pembrolizumab 10 mg/kg (n=343)</th>
<th>Docetaxel (n=309)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-5</td>
<td>Any grade</td>
</tr>
<tr>
<td>Occurring in ≥10% of patients in any group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>46 (14%)</td>
<td>3 (1%)</td>
<td>43 (13%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45 (14%)</td>
<td>4 (1%)</td>
<td>49 (14%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (11%)</td>
<td>1 (&lt;1%)</td>
<td>31 (9%)</td>
</tr>
<tr>
<td>Rash</td>
<td>29 (9%)</td>
<td>1 (&lt;1%)</td>
<td>44 (13%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>24 (7%)</td>
<td>2 (1%)</td>
<td>22 (6%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20 (6%)</td>
<td>1 (&lt;1%)</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13 (4%)</td>
<td>0 (0%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>10 (3%)</td>
<td>3 (1%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Of special interest occurring in ≥2 patients in the pembrolizumab groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>28 (8%)</td>
<td>0 (0%)</td>
<td>28 (8%)</td>
</tr>
<tr>
<td>Pneumonitis†</td>
<td>16 (5%)</td>
<td>7 (2%)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12 (4%)</td>
<td>0 (0%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Severe skin reactions</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Pancreatitis§</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Myositis</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

*Decided by the investigator. Events are listed in descending frequency in the pembrolizumab 2 mg/kg group. †Respective of attribution to study drug. Events are listed in descending order of frequency in the pembrolizumab 2 mg/kg group. ‡Includes patients with interstitial lung disease (one in the pembrolizumab 2 mg/kg group, two in the pembrolizumab 10 mg/kg group, and two in the docetaxel group). §Includes one patient with acute pancreatitis.

Table 2: Adverse events in the safety population
PD-1 inhibitor 2nd line take-home messages

- Nivolumab, pembrolizumab and atezolizumab with similar benefit and toxicity, ~20% in all comers
  - Nivo and atezo approved for all comers 2nd line
  - Pembro approved for PD-L1+ >1% 2nd line
    - Nivo q2w, atezo and pembro q3w
- Toxicities DIFFERENT than chemo
  - Majority find it better tolerated…
  - ...but any organ can be inflamed
  - Low threshold to evaluate CT chest (pneumonitis), thyroid function tests (hypo or hyperthyroiditis), etc
  - Consider use of steroid, other immune modulators
PD-1 inhibitor 1\textsuperscript{st} line?

- 1\textsuperscript{st} line trials presented at ESMO 2016
  - Pembro vs chemo in PD-L1≥50%
  - Nivo vs chemo in PD-L1≥5%
PD-1 inhibitor 1\textsuperscript{st} line?

- 1\textsuperscript{st} line trials presented at ESMO 2016
  - Pembrolizumab vs chemo in PD-L1≥50% \textbf{POSITIVE}
  - Nivolumab vs chemo in PD-L1≥5%  \textbf{NEGATIVE}
Pembrolizumab 1\textsuperscript{st} line (PD-L1\geq 50\%)

**KEYNOTE-024 Study Design** (NCT02142738)

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

**Key End Points**
- Primary: PFS (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, safety
- Exploratory: DOR

\textsuperscript{a}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.

Recht, ESMO 2016
Pembrolizumab 1st line (PD-L1 ≥50%)
Pembrolizumab 1st line (PD-L1≥50%)

Progression-Free Survival

<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>73</td>
<td>10.3</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td>0.37-0.68</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:

- Pembro: 154, 104, 89, 44, 22, 3, 1
- Chemo: 151, 99, 70, 18, 9, 1, 0

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.
Pembrolizumab 1st line (PD-L1 ≥ 50%)

Overall Survival

<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>0.60 (0.41-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab

Crossover from chemo to pembro: 66/151 (44%)
Pembrolizumab 1st line (PD-L1 ≥50%)

Confirmed Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Pembro Responders n = 69</th>
<th>Chemo Responders n = 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR, mo median (range)</td>
<td>2.2 (1.4-8.2)</td>
<td>2.2 (1.8-12.2)</td>
</tr>
<tr>
<td>DOR, mo median (range)</td>
<td>NR (1.9+ to 14.5+)</td>
<td>6.3 (2.1+ to 12.6+)</td>
</tr>
</tbody>
</table>

Assessed per RECIST v1.1 by blinded, independent central review. Data cut-off: May 9, 2016.

Recht, ESMO 2016
Nivolumab 1st line (PD-L1 ≥ 5%)

Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 211)</th>
<th>Chemotherapy (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>4.2 (3.0, 5.6)</td>
<td>5.9 (5.4, 6.9)</td>
</tr>
<tr>
<td>1-year PFS rate, %</td>
<td>23.6</td>
<td>23.2</td>
</tr>
</tbody>
</table>

HR = 1.15 (95% CI: 0.91, 1.45), P = 0.2511

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

Socinski, ESMO 2016
Nivolumab 1st line (PD-L1 ≥ 5%)

OS (≥ 5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab n = 211</th>
<th>Chemotherapy n = 212</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>14.4 (11.7, 17.4)</td>
<td>13.2 (10.7, 17.1)</td>
</tr>
<tr>
<td>1-year OS rate, %</td>
<td>56.3</td>
<td>53.6</td>
</tr>
<tr>
<td>HR</td>
<td>1.02 (0.80, 1.30)</td>
<td></td>
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</tbody>
</table>

- 60.4% in the chemotherapy arm had subsequent nivolumab therapy
- 43.6% in the nivolumab arm had subsequent systemic therapy

No. of patients at risk:
- Nivolumab: 211, 186, 156, 133, 118, 98, 49, 14, 4, 0, 0
- Chemotherapy: 212, 186, 153, 137, 112, 91, 50, 15, 3, 1, 0

All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)
Take-home points: 1st line

- Nivolumab
- Pembrolizumab (PD-L1>1%)
- Atezolizumab

And 2nd line (if chemo 1st line):
- Nivolumab
- Pembrolizumab (PD-L1>1%)
- Atezolizumab

---

See Principles of Pathologic Review (NSCL-A).

Two themes

- Targeted therapies
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations

- Immunotherapy
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage
Future of immunotherapy in NSCLC

- Use PD1 inhibitors with chemo?
  - Motivation: Cancer cell death → release cancer cell antigens → improved priming and activation might let PD1 inhibitors work better
  - Caveats:
    - Steroids with some chemos
    - General immunosuppressive state post-chemo
    - Compound toxicity

- Awaiting phase 3 studies of chemo +/- PD1 inhibitors
  - Early data: Langer et al (Lancet Oncol and ESMO 2016), n=123 carboplatin/pemetrexed +/- pembrolizumab
    - RR 55 vs 29%, PFS 13.0 vs 8.9 mo

- APPROVED by FDA 5/10/17, before phase 3 data released
Future of immunotherapy in NSCLC

- Use PD1 inhibitors with other immunotherapy?
  - Motivation: PD1 inhibition alone only works in 20% of tumors—what about the rest? Can we prime for response to PD1 inhibition?
  - Caveats:
    - Hard to anticipate results based on pre-clinical models
    - Additive (even synergistic) efficacy possible, but so is additional toxicity

- Awaiting studies of chemo vs PD1 vs PD1/CTLA4
  - CTLA4 inhibitor already approved in melanoma (ipilimumab)
  - Early data: Hellman et al (ASCO 2016) nivolumab vs nivolumab/ipilimumab
Early data: 1st line nivo/ipi

Await data from adequately powered phase 3 trials... next year?

Hellman, ASCO 2016
Case of Pathological CR in One Patient Treated With Nivo 3 Q2W + Ipi 1 Q6W

* 54-yr-old male (former smoker, 52 pack-yr) with metastatic large-cell lung cancer (PD-L1 <1%)
  * 53% total tumor size reduction by RECIST
  * Radiographic residual lesions in the lung and mediastinal lymph nodes, without distant disease

![Graph showing change from baseline with dates for treatment initiation and discontinuation.]

**Before nivo + ipi therapy**

**Following nivo + ipi therapy**

![Images of CT scans before and after therapy with red arrows indicating tumor reduction.]

*No viable tumor in resected residual lesion*

Right upper lobe wedge resection (nodule #1) Mar 2016

Courtesy of Dr. William Travis, MSKCC

*Patient was included as having partial response and PD-L1 expression unknown in analysis at time of database lock*
Future of immunotherapy in NSCLC

- Use PD1 inhibitors in early stage disease?
  - Motivation: Potential downstaging, research platform for evaluating treatment effect in vivo
  - Caveats:
    - Toxicity
    - Upstaging if not effective, esp in aggressive tumors
- Awaiting early studies
Early data: Neoadjuvant nivo

Neoadjuvant anti-PD1, nivolumab, in early stage, resectable NSCLC

- Day -28 and -14 nivolumab followed by surgery at Day 0
  - Primary: safety
  - Exploratory endpoints: correlates in blood and tumor, % pathologic response, RFS, OS
- 18 pts enrolled: ~1/3 at stage IIIA
- Only one grade 3/4 toxicity, no delay in surgery
- Radiographic response: 4 pts (3 were PD-L1+)
- Pathologic response (<10% residual viable tumor at resection\(^1\)): 7/18 pts (39%)
- Pathologic downstaging: 7/18

\(^1\) Pataer et al. JTO 2012
P. Forde, et al. ESMO 2016. Abstract LBA41_PR
UCSF efforts: Neoadjuvant pembrolizumab

- 2 approved investigator-initiated studies
  - PembroX (Yom, Fong, Gubens, Jablons)
    - Neoadjuvant pembro +/- XRT
  - “IO-SPY Lung” (Gubens, Fong, Jablons)
    - Neoadjuvant pembro combinations
UCSF efforts: Neoadjuvant pembrolizumab

- "IO-SPY Lung" (Gubens, Fong, Jablons)

<table>
<thead>
<tr>
<th>WEEK</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td>Cohort A:</td>
<td>Pembro</td>
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<td>Cohort B:</td>
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<td>Pembro Varilimumab</td>
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<td>Cohort C:</td>
<td>Pembro Daily epacadostat</td>
<td>Pembro</td>
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<td>Cohort D:</td>
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<td>Pembro Cisplatin/pemetrexed</td>
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</table>

varilimumab = CD27 agonist, epacadostat = IDO inhibitor
Future of immunotherapy in NSCLC

Chen and Mellman, Immunity 2013
Future of immunotherapy in NSCLC

Chen and Mellman, Immunity 2013
Future of immunotherapy key points

- Stay tuned…
  - for data on chemo combos
  - for data on immunotherapy combos
  - for data on immunotherapy in earlier stage disease
- Clinical trials are the way forward
  - Special role for immunoREFRACTORY patients
- Value in medicine
Lung Cancer Treatment Using Immune System Wins F.D.A. Approval

By ANDREW POLLACK       MARCH 4, 2015

The first immune-based treatment for lung cancer won approval from the Food and Drug Administration on Wednesday, and it could displace more conventional chemotherapy for certain patients, at least.

The drug, [REDACTED] from [REDACTED] is one of a class of medicines that have electrified oncologists in recent years because they free the body’s own immune system to attack tumors.

[REDACTED] also known as nivolumab, was approved last year to treat advanced cases of the skin cancer melanoma, but the approval for lung cancer is in some ways more significant.
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Lung cancer is the leading cause of cancer deaths by far, with 224,000 new diagnoses and nearly 160,000 deaths last year. That means approval to treat lung cancer could help more patients and also result in much larger sales for Bristol-Myers. The drug sells for about $12,500 a month.
Future of immunotherapy key points

- Stay tuned…
  - for data on chemo combos
  - for data on immunotherapy combos
  - for data on immunotherapy in earlier stage disease

- Clinical trials are the way forward
  - Special role for immunorefractory patients

- Value in medicine
  - These are expensive drugs…
  - ...but optimizing them (better combos, better patient selection) may yield superior value by meaningfully improving survival in our patients
Thank you!