IMMUNOTHERAPY
STATE OF THE ART IN LUNG CANCER

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Lung cancer facts

- Lung cancer is characterized by a strongly immunosuppressive environment
- We have been enrolling thousands of patients in strictly negative vaccine trials
- Lung tumors display ~200 nonsynonymous mutations per tumor. Lung cancers from smokers have 10 times as many somatic mutations as those from non-smokers.
Physicochemical properties of the mutagen determine which adduct is formed, what repair mechanism is induced and which mispairing is permissible.

Fingerprint mutation due to tobacco exposure is a C → A transversion, which is predominantly found in smokers.
The PD-1 Pathway Inhibits T Cell Activation

Dephosphorylation

Reduced TCR signaling
Reduced cytokine production
Reduced target cell lysis
Altered lymphocyte motility
Metabolic programming

ITSM - SHP-2
ITIM - P
CD3
TCR
MHC
CD8
CTLA4
B7-1
PD-1
PD-1 ligand
PD-L1 (B7-H1)
PD-L2 (B7-DC)
APC

Freeman, ESMO IO 2015
Several PD-1/PD-L1 inhibitors are being evaluated in NSCLC

<table>
<thead>
<tr>
<th>PD-1</th>
<th>Nivolumab BMS-936558</th>
<th>Fully human IgG4 mAb</th>
<th>Bristol-Myers Squibb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>MK-3475</td>
<td>Humanized IgG4 mAb</td>
<td>Merck</td>
<td>Phase III</td>
</tr>
<tr>
<td>Pidilizumab</td>
<td>CT-011</td>
<td>Humanized IgG1 mAb</td>
<td>CureTech</td>
<td>Phase II</td>
</tr>
<tr>
<td>PDR001</td>
<td></td>
<td>Humanized IgG4 mAb</td>
<td>Novartis</td>
<td>Phase II</td>
</tr>
<tr>
<td>AMP-224</td>
<td></td>
<td>Recombinant PD-L2-Fc fusion protein</td>
<td>GlaxoSmithKline</td>
<td>Phase I</td>
</tr>
<tr>
<td>MEDI-0680</td>
<td></td>
<td>Humanized IgG4 mAb</td>
<td>Medimmune - AZ</td>
<td>Phase I</td>
</tr>
<tr>
<td>REGN2810</td>
<td></td>
<td>Humanized IgG4 mAb</td>
<td>Regeneron/Sanofi</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>Durvalumab MedI-4736</th>
<th>Engineered human IgG1 mAb</th>
<th>MedImmune - AZ</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>MPDL-3280A</td>
<td>Engineered human IgG1 mAb</td>
<td>Genentech</td>
<td>Phase III</td>
</tr>
<tr>
<td>Avelumab</td>
<td>MSB0010718C</td>
<td>Engineered human IgG1 mAb</td>
<td>EMD Serono</td>
<td>Phase III</td>
</tr>
<tr>
<td>BMS-936559</td>
<td></td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
Checkpoint Inhibitors for lung cancer

Advanced NSCLC

– The quest for a biomarker
– Evidence-based data for late lines
– Learnings from late line trial
– Frontline immunotherapy
Checkpoint Inhibitors for lung cancer

Advanced NSCLC

– **The quest for a biomarker**
– Evidence-based data for late lines
– Learnings from late line trial
– Frontline immunotherapy
High mutation load in NSCLC

Huge variation across cancer types

1000-fold!

Lawrence M et al. Nature 2013
Mutation frequency varied markedly across patients within a cancer type.
Highly significant correlation between non-synonymous mutation burden and durable pembrolizumab benefit

91% durable benefit (partial or stable response lasting >6 months) in high mutation burden and any level of PD-L1 expression

Some highly mutated tumors do not respond...
• Survival is related to clonal neoantigen burden
• CD8+ TILs react to clonal neoantigens

Cytotoxic chemotherapy (& targeted therapies) induce only subclonal neoantigens

McGranahan, Science 2016; Jamal CCR 2015
<table>
<thead>
<tr>
<th></th>
<th>Nivolumab: BMS</th>
<th>Pembrolizumab: Merck</th>
<th>Atezolizumab: Roche</th>
<th>Durvalumab: AstraZeneca</th>
<th>Avelumab: Pfizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab Clone</td>
<td>28-8</td>
<td>22C3</td>
<td>SP142</td>
<td>SP263</td>
<td>73-10</td>
</tr>
<tr>
<td>Diagnostic Partner</td>
<td>Dako</td>
<td>Dako</td>
<td>Ventana</td>
<td>Ventana</td>
<td>Dako</td>
</tr>
<tr>
<td>Scoring Method</td>
<td>% of PD-L1–expressing tumour cells</td>
<td>% of PD-L1–expressing tumour cells</td>
<td>% of PD-L1–expressing tumour cells or immune cells</td>
<td>% of PD-L1–expressing tumour cells</td>
<td>% of PD-L1–expressing tumour cells</td>
</tr>
<tr>
<td>Diagnostic Status</td>
<td>Complementary: testing not required</td>
<td>Companion: testing required</td>
<td>Dx not approved for NSCLC setting</td>
<td>Dx not approved for durvalumab in any setting</td>
<td>Dx not approved for avellumab in any setting</td>
</tr>
<tr>
<td>Approved IVD</td>
<td>US/EU: All patients eligible</td>
<td>EU: All patients eligible</td>
<td>US: ≥50%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PD-L1 Threshold</td>
<td>≥1% (pos), ≥5% (strong), or ≥10%</td>
<td>≥1% (pos)</td>
<td>≥50% (strong)</td>
<td>TC / IC 3(+)</td>
<td>TBC, TC between all &gt;1% and 25% with moderate or high intensity</td>
</tr>
</tbody>
</table>

* PD-L1 Thresholds

- TC / IC 3(+)
- TC / IC 2(+)
- TC / IC 1(+)
- TC / IC 0(−)
Three methods results in similar staining of NSCLC tumour cells

Analytical comparison of tumour staining for 39 NSCLC cases using all four PD-L1 assays, and clinical diagnostic comparison.

### Can Clinical Scoring Algorithm be Interchanged?

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Assay</th>
<th>Platform</th>
<th>Scoring algorithm</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous NSCLC</td>
<td>28-8</td>
<td>DAKO</td>
<td>TC 1%</td>
<td>Nivo</td>
</tr>
<tr>
<td>NSCLC</td>
<td>22C3</td>
<td>DAKO</td>
<td>TC 50%</td>
<td>Pembro</td>
</tr>
<tr>
<td>NSCLC</td>
<td>SP142</td>
<td>VENTANA</td>
<td>TC1%/50% (?)</td>
<td>Atezo</td>
</tr>
<tr>
<td>NSCLC</td>
<td>SP268</td>
<td>VENTANA</td>
<td>TC 25% (?)</td>
<td>Durva</td>
</tr>
</tbody>
</table>

36.9% of the cases with discrepant results between the assays
The Cancer Immunogram

- Tumor foreignness
  - Mutational load

- General immune status
  - Lymphocyte count

- Absence of Checkpoints
  - PD-L1

- Immune cell infiltration
  - Intratumoral T cells

- Absence of soluble inhibitors
  - IL6->CRP/ESR

- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization

- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN-g sensitivity
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– Learnings from late line trial
– Frontline immunotherapy
Second line single agent chemotherapy improves survival

The database for a survival advantage of 2nd line chemotherapy is based on only one study of docetaxel vs BSC

Shepherd, J Clin Oncol 2000
Anti-PD1 vs docetaxel in pretreated advanced NSCLC

Borghaei, ASCO 2016

Any PD-L1
mOS: 9.2 vs 6 mos

PD-L1>1%
mOS: 10.4 vs 8.5 mos

Borghaei, ASCO 2016 & Herbst NEJM 2015

Any PD-L1
mOS: 12.2 vs 9.6 mos

PD-L1>50%
mOS: 14.9 vs 8.2 mos
Anti-PDL1 vs docetaxel in pretreated advanced NSCLC

12-mo OS: 55% vs 41%
18-mo OS: 40% vs 27%
mOS: 13.8 vs 6 mos 9.6

Any PD-L1
TC3 or IC3: 0.41
TC2/3 or IC2/3: 0.67
TC1/2/3 or IC1/2/3*: 0.74
TC0 and IC0: 0.75
ITT*: 0.73

Median OS, mo
Atezolizumab: n = 425
Docetaxel: n = 425
TC3 or IC3: 20.5 vs 8.9
TC2/3 or IC2/3: 16.3 vs 10.8
TC1/2/3 or IC1/2/3*: 15.7 vs 10.3
TC0 and IC0: 12.6 vs 8.9
ITT*: 13.8 vs 9.6

Hazard Ratio*
In favor of atezolizumab
In favor of docetaxel
0.41*
(95% CI, 0.27, 0.64)
P < 0.0001*
Minimum follow up = 19 months

Barlesi, ESMO 2016
Checkpoint Inhibitors for lung cancer

Advanced NSCLC

– The quest for a biomarker
– Evidence-based data for late lines
– Learnings from late line trial
– Frontline immunotherapy
Lesson 1: PD-L1 enrichment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Events/patients (n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>332/634</td>
<td>0.65 (0.52-0.81)</td>
</tr>
<tr>
<td>Female</td>
<td>189/399</td>
<td>0.69 (0.51-0.94)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>317/604</td>
<td>0.63 (0.50-0.79)</td>
</tr>
<tr>
<td>≥65</td>
<td>204/429</td>
<td>0.76 (0.57-1.02)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>149/348</td>
<td>0.73 (0.52-1.02)</td>
</tr>
<tr>
<td>1</td>
<td>367/678</td>
<td>0.63 (0.51-0.78)</td>
</tr>
<tr>
<td><strong>PD-L1 tumour proportion score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>204/442</td>
<td>0.53 (0.40-0.70)</td>
</tr>
<tr>
<td>1-49%</td>
<td>317/591</td>
<td>0.76 (0.60-0.96)</td>
</tr>
<tr>
<td><strong>Tumour sample</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archival</td>
<td>266/455</td>
<td>0.70 (0.54-0.89)</td>
</tr>
<tr>
<td>New</td>
<td>255/578</td>
<td>0.64 (0.50-0.83)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>128/222</td>
<td>0.74 (0.50-1.09)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>333/708</td>
<td>0.63 (0.50-0.79)</td>
</tr>
<tr>
<td><strong>EGFR status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>46/86</td>
<td>0.88 (0.45-1.70)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>447/875</td>
<td>0.66 (0.55-0.80)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>521/1033</td>
<td>0.67 (0.56-0.80)</td>
</tr>
</tbody>
</table>
Lesson 2: Observed OS effect is **stronger** than PFS effect

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS (HR)</th>
<th>OS (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate-057 (ITT)</td>
<td>0.92</td>
<td>0.73</td>
</tr>
<tr>
<td>CheckMate-057 (≥ 1% PD-L1 +ve)</td>
<td>0.70</td>
<td>0.59</td>
</tr>
<tr>
<td>CheckMate-057 (&lt; 1% PD-L1 +ve)</td>
<td>1.19</td>
<td>0.90</td>
</tr>
<tr>
<td>CheckMate-017 (ITT)</td>
<td>0.62</td>
<td>0.59</td>
</tr>
<tr>
<td>POPLAR (ITT)</td>
<td>0.98</td>
<td>0.77</td>
</tr>
<tr>
<td>POPLAR (TC or IC 1/2/3)</td>
<td>0.87</td>
<td>0.63</td>
</tr>
<tr>
<td>POPLAR (TC or IC0)</td>
<td>1.17</td>
<td>1.12</td>
</tr>
<tr>
<td>KEYNOTE 010 (≥ 1% PD-L1 +ve)</td>
<td>0.88</td>
<td>0.71</td>
</tr>
<tr>
<td>KEYNOTE 010 (≥ 50% PD-L1 +ve)</td>
<td>0.59</td>
<td>0.54</td>
</tr>
<tr>
<td>OAK (ITT)</td>
<td>0.63</td>
<td>0.73</td>
</tr>
<tr>
<td>OAK (TC3 or IC3)</td>
<td>0.95</td>
<td>0.41</td>
</tr>
</tbody>
</table>
Lesson 3: Plateau and long term survival

Herbst, WCLC 2016
### Lesson 4: Adverse event profile of I-O therapies compared with chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Checkmate 017¹</th>
<th>Checkmate 057¹</th>
<th>KEYNOTE 010²</th>
<th>POPLAR³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo (n=113)</td>
<td>DTX (n=129)</td>
<td>Nivo (n=287)</td>
<td>DTX (n=268)</td>
</tr>
<tr>
<td>TRAEs, %</td>
<td>61</td>
<td>87</td>
<td>71</td>
<td>88</td>
</tr>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>8</td>
<td>56</td>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
<td>2</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

- Learning curve in detecting lung infiltrates & treating lung symptoms (pneumonitis 3%)

Lesson 5: stabilization or improvement of patient related outcomes

Lung Cancer Norm (UK-based): 0.67

Table: Mean EQ-5D Utility Index Score

<table>
<thead>
<tr>
<th>Week</th>
<th>Nivolumab (n=97)</th>
<th>Docetaxel (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>36</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>42</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>54</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Nivolumab for SQ NSCLC: EQ-5D Utility Index

Population Norm:

Lung Cancer Norm (UK-based): 0.67

Reck, ESMO 2015
Checkpoint Inhibitors for lung cancer

Advanced NSCLC

– The quest for a biomarker
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– Learnings from late line trial
– **Frontline immunotherapy**
First line platinum doublet chemotherapy is a more challenging competitor than docetaxel

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>PD-L1+ %</th>
<th>RR %</th>
<th>PFS (median) months</th>
<th>OS (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAMOUNT (NSCC)</td>
<td>359</td>
<td>?</td>
<td>30</td>
<td>6.9</td>
<td>16.9</td>
</tr>
<tr>
<td>E4599 (NSCC)</td>
<td>434</td>
<td>?</td>
<td>35</td>
<td>6.2</td>
<td>12.3</td>
</tr>
<tr>
<td>Squire (SCC)</td>
<td>545</td>
<td>?</td>
<td>31</td>
<td>5.7</td>
<td>11.5</td>
</tr>
</tbody>
</table>
ORR by PD-L1 expression levels in 1L NSCLC

- **CheckMate 012**
  - All patients (N=52)
  - PD-L1 Cutoffs: 50% (n=12), 25% (n=18), ≥25% (n=32), <1% (n=14)
  - ORR (%): 50, 44

- **KN-001**
  - All patients (N=65)
  - PD-L1 Cutoffs: ≥50% (n=24), 1% - 49% (n=46), <1% (n=10)
  - ORR (%): 17.4

- **BIRCH**
  - All patients (N=59)
  - PD-L1 Cutoffs: ≥25% (n=49), <25% (n=9)
  - ORR (%): 26, 19

- **Durva (NCT01693562)**
  - All patients (N=59)
  - PD-L1 Cutoffs: ≥25% (n=49), <25% (n=9), ≥1% (n=35), <1% (n=10)
  - ORR (%): 29, 27

- **JAVELIN Solid Tumor**
  - All patients (N=75)
  - PD-L1 Cutoffs: ≥25% (n=28), ≥1% (n=35), <1% (n=10), TILs ≥10% (n=4)
  - ORR (%): 15.4, 21.4, 20, 18.7

- **PD-L1 Cutoffs:** 25%
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC

**Key eligibility criteria:**
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No EGFR/ALK mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression\(^a\)
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

**Stratification factors at randomization:**
- PD-L1 expression (<5% vs ≥5%)\(^a\)
- Histology (squamous vs non-squamous)

**Study Design:**

**Nivolumab**
- 3 mg/kg IV Q2W
- n = 271

**Chemotherapy (histology dependent)\(^b\)**
- Maximum of 6 cycles
- n = 270

**Primary endpoint:** PFS (≥5% PD-L1+)\(^d\)

**Secondary endpoints:**
- PFS (≥1% PD-L1+)\(^d\)
- OS
- ORR\(^d\)

**Randomize 1:1**

- Disease progression or unacceptable toxicity
- Tumor scans Q6W until wk 48 then Q12W
- Disease progression
- Crossover nivolumab\(^c\) (optional)

\(^a\)Dako 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized

\(^b\)Squamous: gemcitabine 1250 mg/m\(^2\) + cisplatin 75 mg/m\(^2\); gemcitabine 1000 mg/m\(^2\) + carboplatin AUC 5; paclitaxel 200 mg/m\(^2\) + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m\(^2\) + cisplatin 75 mg/m\(^2\); pemetrexed 500 mg/m\(^2\) + carboplatin AUC 6; option for pemetrexed maintenance therapy

\(^c\)Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review

\(^d\)Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review
PD-L1 >5% CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

No. of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 211</td>
<td>211</td>
<td>212</td>
</tr>
<tr>
<td>Nivolumab n = 211</td>
<td>211</td>
<td>212</td>
</tr>
<tr>
<td>Med PFS, months</td>
<td>4.2</td>
<td>5.9</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.0, 5.6)</td>
<td>(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)

Socinsky, ESMO 2016
### PFS and OS Subgroup Analyses (All Randomized Patients)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients, n</th>
<th>Unstratified HR</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nivolumab</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>271</td>
<td>270</td>
</tr>
<tr>
<td>≥65 years</td>
<td></td>
<td>123</td>
<td>137</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td></td>
<td>148</td>
<td>133</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>184</td>
<td>148</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>87</td>
<td>122</td>
</tr>
<tr>
<td>ECOG PS = 0</td>
<td></td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>ECOG PS ≥1</td>
<td></td>
<td>185</td>
<td>177</td>
</tr>
<tr>
<td>Squamous</td>
<td></td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Non-squamous</td>
<td></td>
<td>206</td>
<td>206</td>
</tr>
<tr>
<td>Never smoker</td>
<td></td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
<td>186</td>
<td>182</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>≥50% PD-L1+</td>
<td></td>
<td>88</td>
<td>126</td>
</tr>
</tbody>
</table>

Socinsky, ESMO 2016
KEYNOTE-024 Study Design (NCT02142738)

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

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

Pembrolizumab 200 mg IV Q3W (2 years)
Platinum-Doublt Chemotherapy (4-6 cycles)

R (1:1) N = 305

Pembrolizumab 200 mg Q3W for 2 years

Platinum-Doublt Chemotherapy (4-6 cycles)
PD-L1 >50%: Keynote 024
Pembrolizumab vs Chemotherapy in First-line NSCLC

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

Pembrolizumab (Pembro) vs Chemotherapy (Chemo)

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td>(0.37-0.68)</td>
</tr>
</tbody>
</table>

PFS, %

No. at risk

<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>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>154</td>
<td>104</td>
<td>89</td>
<td>44</td>
<td>22</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>151</td>
<td>99</td>
<td>70</td>
<td>18</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Reck, ESMO 2016
PD-L1 >50%: Keynote 024
Pembrolizumab vs Chemotherapy in First-line NSCLC

- 50% in the chemotherapy arm had subsequent pembrolizumab therapy

Data cut-off: May 9, 2016.
PD-L1 >50%: Keynote 024

Assessed per RECIST v1.1 by blinded, independent central review.
Pembro better than nivo?

Overall Survival in the Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>210</td>
<td>208</td>
</tr>
<tr>
<td>186</td>
<td>179</td>
</tr>
<tr>
<td>171</td>
<td>146</td>
</tr>
<tr>
<td>154</td>
<td>122</td>
</tr>
<tr>
<td>143</td>
<td>92</td>
</tr>
<tr>
<td>135</td>
<td>76</td>
</tr>
<tr>
<td>111</td>
<td>60</td>
</tr>
<tr>
<td>81</td>
<td>38</td>
</tr>
<tr>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median OS: niv (23.1-NR) vs dacarbazine (11.2 [9.6-13.0])
HR (95% CI): 0.43 (0.33-0.57), P<0.001

Overall Survival
Combination strategies might be necessary frontline
Nivolumab ± Ipilimumab ORR by Tumor PD-L1 Expression

CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC

- 5 CRs (10%) were achieved in the nivolumab monotherapy cohort (1 in a patient with tumor PD-L1 expression <1%)
- 6 CRs (8%) were achieved in the nivolumab + ipilimumab cohorts\(^a\) (3 in patients with tumor PD-L1 expression <1%)

Based on a September 2016 database lock; \(^a\)3 determined radiographically per RECIST v1.1 and 3 identified by pathologic evaluation
OS by Tumor PD-L1 Expression

CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC

- Data are based on median follow-up durations of 16 months (combination cohorts) and 22 months (monotherapy)

Based on a September 2016 database lock
### Key Eligibility Criteria
- Untreated stage IIIB or IV nonsquamous NSCLC
- No activating EGFR mutation or ALK translocation
- Provision of a sample for PD-L1 assessment
- ECOG PS 0-1
- No untreated brain metastases
- No ILD or pneumonitis requiring systemic steroids

### R (1:1) N=123

#### Chemo/IO combination: the first NSCLC phase 2 trial

- **Pembrolizumab 200 mg Q3W for 2 years**
  + Carboplatin AUC 5 mg/mL/min + Pemetrexed 500 mg/m² Q3W for 4 cycles

- **Carboplatin AUC 5 mg/mL/min + Pemetrexed 500 mg/m² Q3W for 4 cycles**

### End Points
- **Primary:** ORR (RECIST v1.1 per blinded, independent central review)
- **Key secondary:** PFS
- **Other secondary:** OS, safety
- **Exploratory:** Relationship between antitumor activity and PD-L1 TPS

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*Langer, ESMO 2016*
Keynote 021: cumulative vs synergistic effect?

Assessed per RECIST v1.1 by blinded, independent central review.
Projected read-out of many phase 3 anti PD1/PD-L1 combination Trials in First-Line Advanced NSCLC (>15’000 patients)

**Legend**

- **PD1/PDL1 Monotherapy**
- **PD1 or PDL1 CT Combo**
- **CTLA4 + PD1**

**2016**
- **Pembrolizumab monotherapy**
  - >50% PDL1+
  - Keynote 024 Q2 2016

**2017**
- **Pembrolizumab monotherapy**
  - >1% PDL1+
  - Keynote 042 Q2 2018

**2018**
- **Pembrolizumab + platinium / pemetrexed (non-squamous)**
  - Keynote 189 Q3 2017

**2019**
- **Atezolizumab monotherapy**
  - all histologies
  - PD1+ Impower 110 Q2 2018

**2020**
- **Avelumab mono vs Pt doublet PD-L1+**
  - JAVELIN lung 100 Q1 2018

**Soria, ESMO 2016**
Advanced Small Cell Lung Cancer: evolution of therapy

1970s: Alkylating Based Chemotherapy (CMV)
1980s: Anthracycline Based Chemotherapy (CAV)
1990s: Platinum Based Chemotherapy (EP/IP)
2000s: Targeted Therapy and Sequencing
2010s: Immunotherapy and ADCs?
A highly mutated SCLC genome with complex signatures of tobacco exposure

- 180-240 mutations per tumour
Variable levels of tumour-infiltrating lymphocytes (TILs) in 48% cases, most frequently located at the interface between carcinoma cells and stroma.
## PD-L1 expression in SCLC

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Current or former smoker</th>
<th>Never smoked</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current or former smoker</td>
<td>95 (97%)</td>
<td>57 (93%)</td>
<td>48 (89%)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>3 (3%)</td>
<td>4 (7%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

### PD-L1 expression level:

- **≥1%**:
  - Current or former smoker: 10 (14%)
  - Never smoked: 9 (24%)
  - Unknown: 5 (13%)

- **<1%**:
  - Current or former smoker: 59 (86%)
  - Never smoked: 28 (76%)
  - Unknown: 35 (88%)

- **≥5%**:
  - Current or former smoker: 4 (6%)
  - Never smoked: 2 (5%)
  - Unknown: 1 (3%)

- **<5%**:
  - Current or former smoker: 65 (94%)
  - Never smoked: 35 (95%)
  - Unknown: 39 (98%)

- Indeterminate, not evaluable, or missing: 29 (30%), 24 (39%), 14 (26%)

*Antonia, ASCO and Lancet Oncol 2016*
Addition of ipilimumab to chemotherapy did not prolong OS in patients with newly diagnosed extensive-stage disease SCLC
Beyond frontline chemotherapy: Current standard of care...

Response rate 7-10%
Pembrolizumab in >1% PD-L1 SCLC

Objective response rate: 33.3% (95% CI, 15.6–55.3)
Clinical benefit rate (CR + PR + SD ≥6 months): 33.3% (95% CI, 15.6–55.3)

OS (months)  
N = 24
Events, n (%)  15 (62.5%)
Median OS (95% CI)  9.7 (4.1 – NR)

Bar length are best target lesion change, bar shading are best overall response.
Data cutoff date: June 20, 2016.
Ipilimumab and nivolumab in ED SCLC

CheckMate 032 (NCT01928394) study design

Patients with SCLC with progressive disease after ≥1 prior line of therapy, including a platinum-based regimen in first line (unselected by PD-L1 expression) (N = 183)

First-line platinum-treated patients*
- Platinum-sensitive: 55 (56%)
- Platinum-resistant†: 30 (31%)
- Unknown: 10 (10%)

Nivolumab 3 mg/kg IV Q2W (n = 80)

- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W for 4 cycles (n = 47)
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 53)
- Nivolumab 1 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 3)

Primary objective: ORR per RECIST v1.1
Secondary objective: safety
Exploratory objectives: PFS, OS, biomarker analysis

Antonia, ASCO and Lancet Oncol 2016
CheckMate 032: Nivolumab ± ipilimumab in Recurrent SCLC

<table>
<thead>
<tr>
<th>Events/number at risk</th>
<th>Median OS, Months (95% CI)</th>
<th>Median follow-up time, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab-3</td>
<td>71/98</td>
<td>4.1 (3.0, 9.1)</td>
</tr>
<tr>
<td>Nivolumab-1 + ipilimumab-3</td>
<td>40/61</td>
<td>7.9 (3.6, 14.2)</td>
</tr>
</tbody>
</table>

1-yr OS = 42%

1-yr OS = 30%

2-yr OS = 30%\(^b\)

2-yr OS = 17%\(^c\)

Hellmann, WCLC 2016
Immune-Related AEs With Immunotherapy

- **Skin**
  - Dermatitis exfoliative
  - Erythema multiforme
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Vitiligo
  - Alopecia

- **Eye**
  - Uveitis
  - Iritis

- **Endocrine**
  - Hypothyroidism
  - Hyperthyroidism
  - Adrenal insufficiency
  - Hypophysitis

- **Pulmonary**
  - Pneumonitis
  - Interstitial lung disease
  - Acute interstitial pneumonitis

- **Gastrointestinal**
  - Colitis
  - Enterocolitis
  - Necrotizing colitis
  - GI perforation

- **Renal**
  - Nephritis, autoimmune
  - Renal failure

- **Neurologic**
  - Autoimmune neuropathy
  - Demyelinating polyneuropathy
  - Guillain-Barré
  - Myasthenia gravis–like syndrome

- **Hepatic**
  - Hepatitis, autoimmune

- **Eye**
  - Uveitis
  - Iritis

Adapted from clinicaloptions.com
A 64-year-old caucasian woman diagnosed with stage IV SCLC on October 2013, underwent treatment with palliative chemotherapy followed by thoracic radiation therapy and PCI.

In February 2014, local pulmonary SCLC recurrence treated by right middle lobectomy.

In November 2014 the patient developed biopsy-confirmed liver metastatic SCLC.

Subsequent disease progression on several lines of therapy (carboplatin/etoposide, AC, topotecan).
Clinical Case: SCLC, safety of combination therapy?

- June 2016 she received IV nivolumab 3 mg/kg + IV ipilimumab 1 mg/kg

- Four days after she developed a subacute memory and psychomotor impairment, space & temporal disorientation.

- CSF showed positive anti-GABA-B, anti-Hu and anti-Purkinje cells antibody

- High dose of steroids. Two weeks later, temporal disorientation and memory troubles persisted. The spatial disorientation disappeared.
Six weeks later

16 weeks later

22 weeks later

Seven months off-treatment
Ongoing SCLC clinical trials

Keynote 068 / EORTC 1416

IMpower 133

N=400

Key Eligibility Criteria
- Patients with ES-SCLC
- No prior treatment for ES-SCLC
- ECOG performance status 0 - 1

Primary endpoint OS/PFS

N=400

Atezolizumab + Carboplatin + Etoposide

Atezolizumab maintenance

Placebo + Carboplatin + Etoposide

Placebo maintenance

Primary endpoint OS/PFS
Ongoing ipi/nivo SCLC clinical trials

### Anti-PD1

**Nivolumab**

**CA209-451 (Ph 3)**
- **ED-SCLC (maintenance after platinum-based chemotherapy)**
  - N=810
  - Primary endpoint: OS/PFS

**CheckMate 331 (Ph 3)**
- **Relapsed SCLC**
  - N=480
  - Primary endpoint: OS

**CA209-032 (Ph 1/2)**
- **SCLC, TNBC, GC, BC or PC**
  - N=410
  - Primary endpoint: ORR

### Anti-CTLA-4

**Ipilimumab**

**ETOP/STIMULI (Ph 2)**
- **Limited-stage SCLC (after chemo-radiation)**
  - N=260
  - Primary endpoint: OS

**ICE (Ph 2)**
- **ED-SCLC**
  - N=42
  - Primary endpoint: PFS
How to overcome resistance to immunotherapy?
Thanks for your attention