IMMUNOTHERAPY
STATE OF THE ART IN LUNG CANCER

Solange Peters MD-PhD
Head Medical Oncology and Thoracic Clinic
Oncology Department & Ludwig Institute
Manchester ESMO Preceptorship
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I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations:

Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp and Dohme, and Merck Serono, Pfizer, Regeneron and Takeda.

I declare no conflict of interest.
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.

Vogelstein, Science 2013
Lawrence, Nature 2013
Mutational smoking signature

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.

Jia et al. BMC Medical Genomics 2014
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, ITIM, CD3, TCR, PD-1, PD-L1 (B7-H1), PD-L2 (B7-DC), MHC, CD8, CTLA4, B7-1, APC

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

<table>
<thead>
<tr>
<th>PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab</strong>&lt;br&gt;BMS-936558</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong>&lt;br&gt;MK-3475</td>
</tr>
<tr>
<td>Pidilizumab&lt;br&gt;CT-011</td>
</tr>
<tr>
<td>PDR001</td>
</tr>
<tr>
<td>AMP-224</td>
</tr>
<tr>
<td>MEDI-0680</td>
</tr>
<tr>
<td>REGN2810</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Durvalumab</strong>&lt;br&gt;Medi-4736</td>
</tr>
<tr>
<td><strong>Atezolizumab</strong>&lt;br&gt;MPDL-3280A</td>
</tr>
<tr>
<td>Avelumab&lt;br&gt;MSB0010718C</td>
</tr>
<tr>
<td>BMS-936559</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

Lawrence M et al. Nature 2013

1000-fold!
Mutation frequency varied markedly across patients within a cancer type.

Lawrence M et al. Nature 2013
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

High nonsynonymous burden (n=17) vs. Low nonsynonymous burden (n=17)

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
## Some complexity in PD-L1 Diagnostics for NSCLC

<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><strong>Ab Clone</strong></td>
<td>28-8</td>
<td>SP263</td>
<td>SP142</td>
<td>SP263</td>
<td>73-10</td>
</tr>
<tr>
<td><strong>Diagnostic Partner</strong></td>
<td>Dako</td>
<td>Ventana</td>
<td>Dako</td>
<td>Ventana</td>
<td>Ventana</td>
</tr>
<tr>
<td><strong>Scoring Method</strong></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><strong>Diagnostic Status</strong></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><strong>Approved IVD PD-L1 Threshold</strong></td>
<td>US/EU: All patients eligible</td>
<td>EU: All patients eligible</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>PD-L1 Thresholds</strong></td>
<td>≥1% (pos), ≥5% (strong), or ≥10% Validated</td>
<td>≥1% (pos), ≥50% (strong) Validated</td>
<td>TC / IC 3(+)</td>
<td>TC / IC 2(+)</td>
<td>TBC, TC between all &gt;1% and 25% with moderate or high intensity</td>
</tr>
</tbody>
</table>
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


- Various tests perform equally
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% (?) IC 1%/10% (?)</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
- Immune cell infiltration
  - Intratumoral T cells
- Absence of Checkpoints
  - PD-L1
- 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

Blank et al., Science 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
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

Any PD-L1
mOS: 9.2 vs 6 mos

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

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

Barlesi, ESMO 2016

Any PD-L1 mOS: 13.8 vs 6 mos 9.6

Median OS, mo
Atezolizumab Docetaxel
TC3 or IC3 n = 425 n = 425
0.41 0.67 0.74
20.5 16.3 15.7
9.6 10.8 10.3

TC2/3 or IC2/3
0.75
12.6 8.9

TC1/2/3 or IC1/2/3
13.8

TC0 and IC0

ITT*

0.2
1
2
Hazard Ratio*
In favor of atezolizumab
In favor of docetaxel

HR, 0.41*
(95% CI, 0.27, 0.64)
P < 0.0001b
Minimum follow up = 19 months

PDL-1 ≥ 50% TC Or ≥ 10% IC

Median 8.9 mo
(95% CI, 5.6, 11.6)

Median 20.5 mo
(95% CI, 17.5, NE)
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>Sex</th>
<th>Events/patients (n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<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>Age (years)</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>ECOG performance status</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>PD-L1 tumour proportion score</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>Tumour sample</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>Histology</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></td>
<td>0.63 (0.50-0.79)</td>
</tr>
<tr>
<td>EGFR status</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>Overall</td>
<td>521/1033</td>
<td>0.67 (0.56-0.80)</td>
</tr>
</tbody>
</table>

Favours pembrolizumab | Favours docetaxel
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 017&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Checkmate 057&lt;sup&gt;1&lt;/sup&gt;</th>
<th>KEYNOTE 010&lt;sup&gt;2&lt;/sup&gt;</th>
<th>POPLAR&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo (n=113)</td>
<td>Nivo (n=287)</td>
<td>Pembro 2 mg/kg (n=339)</td>
<td>Pembro 10 mg/kg (n=343)</td>
</tr>
<tr>
<td></td>
<td>DTX (n=129)</td>
<td>DTX (n=268)</td>
<td>DTX (n=309)</td>
<td>DTX (n=309)</td>
</tr>
<tr>
<td>TRAEs, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>61</td>
<td>71</td>
<td>63</td>
<td>81</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>8</td>
<td>11</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
<td>&lt;1</td>
<td>1</td>
<td>2</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

Mean EQ-5D Utility Index Score

Nivolumab (n = 97)

<table>
<thead>
<tr>
<th>Week</th>
<th>EQ-5D Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>60</td>
<td>1</td>
</tr>
</tbody>
</table>

Docetaxel (n = 89)

<table>
<thead>
<tr>
<th>Week</th>
<th>EQ-5D Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>48</td>
<td>21</td>
</tr>
<tr>
<td>54</td>
<td>18</td>
</tr>
<tr>
<td>60</td>
<td>13</td>
</tr>
</tbody>
</table>

Population Norm

Lung Cancer Norm (UK-based): 0.67

Nivolumab for SQ NSCLC: EQ-5D Utility Index

Reck, ESMO 2015
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**
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

<table>
<thead>
<tr>
<th>Study</th>
<th>ORR (%)</th>
<th>Cutoffs</th>
<th>PD-L1 L1 expression level</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 012</td>
<td>50</td>
<td>≥50% (n=12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>≥25% (n=18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>&gt;1% (n=32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>&lt;1% (n=14)</td>
<td></td>
</tr>
<tr>
<td>KN-001</td>
<td>58.3</td>
<td>≥50% (n=24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>1%–49% (n=46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>&lt;1% (n=10)</td>
<td></td>
</tr>
<tr>
<td>BIRCH</td>
<td>26</td>
<td>≥25% (n=49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>&lt;25% (n=9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>&lt;1% (n=9)</td>
<td></td>
</tr>
<tr>
<td>Durva</td>
<td>29</td>
<td>≥25% (n=49)</td>
<td></td>
</tr>
<tr>
<td>(NCT01693562)</td>
<td>27</td>
<td>&lt;25% (n=9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.4</td>
<td>&lt;1% (n=10)</td>
<td></td>
</tr>
<tr>
<td>JAVELIN Solid Tumor</td>
<td>21.4</td>
<td>≥10% (n=75)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>TILs &lt;10% (n=41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 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
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

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

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

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

- **Randomize 1:1**
- Disease progression or unacceptable toxicity
- Tumor scans Q6W until wk 48 then Q12W
- Disease progression
- Crossover nivolumab (optional)

**Primary endpoint:** PFS (≥5% PD-L1+)
**Secondary endpoints:**
- PFS (≥1% PD-L1+)
- OS
- ORR

---

*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/m² + cisplatin 75 mg/m²; gemcitabine 1000 mg/m² + carboplatin AUC 5; paclitaxel 200 mg/m² + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m² + cisplatin 75 mg/m²; pemetrexed 500 mg/m² + 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</td>
<td>211</td>
<td>212</td>
</tr>
</tbody>
</table>

Table of median PFS, months (95% CI) and 1-year PFS rate, %:

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Chemotherapy</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>

Overall survival results:

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

Socinsky, ESMO 2016

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)
## PFS and OS Subgroup Analyses (All Randomized Patients)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients, n</th>
<th>Nivolumab</th>
<th>Chemotherapy</th>
<th>Unstratified HR</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>OS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>271</td>
<td>270</td>
<td>1.19</td>
<td>1.08</td>
</tr>
<tr>
<td>≥65 years</td>
<td></td>
<td>123</td>
<td>137</td>
<td>1.21</td>
<td>1.04</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td></td>
<td>148</td>
<td>133</td>
<td>1.17</td>
<td>1.13</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>184</td>
<td>148</td>
<td>1.05</td>
<td>0.97</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>87</td>
<td>122</td>
<td>1.36</td>
<td>1.15</td>
</tr>
<tr>
<td>ECOG PS = 0</td>
<td></td>
<td>85</td>
<td>93</td>
<td>1.69</td>
<td>1.11</td>
</tr>
<tr>
<td>ECOG PS ≥1</td>
<td></td>
<td>185</td>
<td>177</td>
<td>1.01</td>
<td>1.02</td>
</tr>
<tr>
<td>Squamous</td>
<td></td>
<td>65</td>
<td>64</td>
<td>0.83</td>
<td>0.82</td>
</tr>
<tr>
<td>Non-squamous</td>
<td></td>
<td>206</td>
<td>206</td>
<td>1.29</td>
<td>1.17</td>
</tr>
<tr>
<td>Never smoker</td>
<td></td>
<td>30</td>
<td>29</td>
<td>2.51</td>
<td>1.02</td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
<td>186</td>
<td>182</td>
<td>1.14</td>
<td>1.09</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>52</td>
<td>55</td>
<td>1.03</td>
<td>1.05</td>
</tr>
<tr>
<td>≥50% PD-L1+</td>
<td></td>
<td>88</td>
<td>126</td>
<td>1.07</td>
<td>0.90</td>
</tr>
</tbody>
</table>

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

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

R (1:1)
N = 305

Pembrolizumab
200 mg IV Q3W (2 years)

Platinum-Doublet Chemotherapy
(4-6 cycles)

Pembrolizumab
200 mg Q3W for 2 years

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

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

- 50% in the chemotherapy arm had subsequent pembrolizumab therapy

<table>
<thead>
<tr>
<th>Time, months</th>
<th>No. at risk</th>
<th>Events, n (Median, mo, HR (95% CI), P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>154</td>
<td>151</td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>123</td>
</tr>
<tr>
<td>6</td>
<td>121</td>
<td>106</td>
</tr>
<tr>
<td>9</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cut-off: May 9, 2016.

Reck, ESMO 2016
PD-L1 >50%: Keynote 024

ORR, % (95% CI)

45% \( \Delta 17\% \) \( P = 0.0011 \)

- Pembrolizumab: n = 6
- Chemotherapy: n = 1

Reck, ESMO 2016
Pembro better than nivo?

**Overall Survival in the Intent-to-Treat Population**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n=220)</th>
<th>Dacarbazine (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (23.1–NR)</td>
<td>11.2 (9.6–13.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.43 (0.33–0.57); P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival**

- **1-yr OS**: 70.7% for Nivolumab, 46.3% for Dacarbazine
- **2-yr OS**: 57.7% for Nivolumab, 26.7% for Dacarbazine

**Overall Survival (Months)**

<table>
<thead>
<tr>
<th>Number of Subjects at Risk</th>
<th>Overall Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>210 186 171 154 143 135 111 81 30 4 0</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>208 179 146 122 92 76 60 38 16 1 0</td>
</tr>
</tbody>
</table>
Combination strategies might be necessary frontline

DEFICIT

Insufficient priming/activation naïve T cells

THERAPEUTIC APPROACH

- Block multiple checkpoints (CTLA-4, PD-1, LAG-3, TIM-3)
- Activate stimulatory pathways (CD137, OX-40, CD27, ICOS, GITR)
- Administer stimulatory cytokines (IL-2, IL-12)

Freeman, ESMO IO 2015
Nivolumab ± Ipilimumab ORR by Tumor PD-L1 Expression

CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC

Based on a September 2016 database lock; *3 determined radiographically per RECIST v1.1 and 3 identified by pathologic evaluation

- 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 (3 in patients with tumor PD-L1 expression <1%)
OS by Tumor PD-L1 Expression

CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC

- All treated patients (n = 77)
  - 1-year OS rate: 76%

- ≥1% PD-L1 (n = 46)
  - 1-year OS rate: 87%

- ≥50% PD-L1 (n = 13)
  - 1-year OS rate: 100%

- All treated patients (n = 52)
  - 1-year OS rate: 73%

- ≥1% PD-L1 (n = 32)
  - 1-year OS rate: 69%

- ≥50% PD-L1 (n = 12)
  - 1-year OS rate: 83%

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

Based on a September 2016 database lock
Chemo/IO combination: the first NSCLC phase 2 trial

Key Eligibility Criteria

• Untreated stage IIIIB 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

Pembrolizumab 200 mg Q3W for 2 years
+ Carboplatin AUC 5 mg/mL/min + Pemetrexed 500 mg/m\(^2\) 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

**Randomization** was stratified by PD-L1 TPS <1% vs ≥1%.

Indefinite maintenance therapy with pemetrexed 500 mg/m\(^2\) Q3W permitted.

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

Assessed per RECIST v1.1 by blinded, independent central review.

Langer, ESMO 2016
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
- Nivolumab monotherapy
  - PDL1+
  - CheckMate-026 Q3 2016

**2017**
- Pembrolizumab + platinium / pemetrexed (non-squamous)
  - Keynote 189 Q3 2017
- Avelumab mono vs Pt doublet
  - PD-L1+
  - JAVELIN lung 100 Q1 2018

**2018**
- Pembrolizumab monotherapy
  - >1% PDL1+
  - Keynote 042 Q2 2018
- Atezolizumab monotherapy
  - all histologies
  - PD1+
  - Impower 110 Q2 2018
- Nivolumab mono vs Niv + Ipi vs Niv + Pt doublet vs Pt doublet
  - IMpower 150 (Q1 2017)
  - CheckMate-227 Q3 2018

**2019**
- Atezolizumab monotherapy
  - all histologies
  - PD1+
  - Impower 130 (non-SCC) Impower 131 (SCC) Q3 2018

**2020**
- Pembrolizumab monotherapy
  - >1% PDL1+
  - Keynote 042 Q2 2018
- Atezolizumab monotherapy
  - all histologies
  - PD1+
  - Impower 110 Q2 2018
- Pembrolizumab monotherapy
  - >50% PDL1+
  - Keynote 024 Q2 2016

**Legend**

PD1/PDL1 Monotherapy

PD1 or PDL1 CT Combo

CTLA4 + PD1

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

1970s
Alkylation 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>Group 1 (97%)</th>
<th>Group 2 (93%)</th>
<th>Group 3 (89%)</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>

<table>
<thead>
<tr>
<th>PD-L1 expression level‡</th>
<th>Group 1 (97%)</th>
<th>Group 2 (93%)</th>
<th>Group 3 (89%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1%</td>
<td>10 (14%)</td>
<td>9 (24%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>59 (86%)</td>
<td>28 (76%)</td>
<td>35 (88%)</td>
</tr>
<tr>
<td>≥5%</td>
<td>4 (6%)</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>65 (94%)</td>
<td>35 (95%)</td>
<td>39 (98%)</td>
</tr>
<tr>
<td>Indeterminate, not evaluable, or missing</td>
<td>29 (30%)</td>
<td>24 (39%)</td>
<td>14 (26%)</td>
</tr>
</tbody>
</table>

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)

Bar length are best target lesion change, bar shading are best overall response.
Data cutoff date: June 20, 2016.

PA Ott et al., WCLC 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*

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum-sensitive</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Platinum-resistant†</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Nivolumab 3 mg/kg IV Q2W

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

**Graph:**
- **OS (%)** vs **Months**
- **Nivolumab-3**
  - 1-yr OS = 42%
  - 1-yr OS = 30%
- **Nivolumab-1 + ipilimumab-3**
  - 2-yr OS = 30%
  - 2-yr OS = 17%

**Table:**

<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>40/61</td>
<td>7.9 (3.6, 14.2)</td>
<td>21.0</td>
</tr>
<tr>
<td>71/98</td>
<td>4.1 (3.0, 9.1)</td>
<td>15.7</td>
</tr>
</tbody>
</table>
Immune-Related AEs With Immunotherapy

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

Eye
- Uveitis
- Iritis

Hepatic
- Hepatitis, autoimmune

Gastrointestinal
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

Renal
- Nephritis, autoimmune
- Renal failure

Endocrine
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

Pulmonary
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

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

Hepatitis, autoimmune

Eye
- Uveitis
- Iritis

Pulmonary
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

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

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

Gastrointestinal
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

Renal
- Nephritis, autoimmune
- Renal failure

Adapted from clinicaloptions.com
SCLC, safety of combination therapy?

• 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
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
  - Nivolumab
  - Nivolumab + ipilimumab
  - Placebo
- CheckMate 331 (Ph 3)
  - Relapsed SCLC N=480
  - Primary endpoint: OS
  - Nivolumab
  - Topotecan + amrubcin
- CA209-032 (Ph 1/2)
  - SCLC, TNBC, GC, BC or PC N=410
  - Primary endpoint: ORR
  - Nivolumab
  - Nivolumab + ipilimumab

**Anti-CTLA-4**

**Ipilimumab**
- ETOP/STIMULI (Ph 2)
  - Limited-stage SCLC (after chemo-radiation) N=260
  - Primary endpoint: OS
  - Ipilimumab + nivolumab
  - Observation
- ICE (Ph 2)
  - ED-SCLC N=42
  - Primary endpoint: PFS
  - Ipilimumab + etoposide + carboplatin
Response to cancer immunotherapy

Kalbasi et al., J Clin Invest 2013
How to overcome resistance to immunotherapy?

1. Strong PD-L1 & high mutational load
   - Are suppressive myeloid cells present?
     - Yes: Anti-PDL1/PD1
     - No: Anti-PDL1/PD1 plus Anti-CSF1R
2. Weak PD-L1
   - IDO/lymphocestin expressed?
     - Yes: Anti-PDL1/PD1 plus IDO inhibitor
     - No: Anti-PDL1/PD1
3. No PD-L1
   - No identifiable immune targets
4. Are T cells at tumor periphery?
   - Yes: Anti-PDL1/PD1 plus Chemo Radiotherapy Targeted therapy
   - No: Anti-PDL1/PD1
5. MHC loss?
   - Yes: Tumor antigen expression?
     - Yes: Anti-PDL1/PD1 plus Anti-angiogenics Anti-stroma agents
     - No: Anti-PDL1/PD1 plus T cell bispecifics CAR-T
   - No: No T cells?
     - Yes: Antigen experienced?
       - Yes: Anti-PDL1/PD1 plus Anti-OX40 Anti-GTLA4 Anti-CD40 Targeted IL2
       - No: No identifiable immune targets
Thanks for your attention