Immune checkpoint inhibitors in thoracic malignancies

Rolf Stahel
University Hospital
Zürich Switzerland
2 Immune checkpoint inhibitors in thoracic malignancies

- Advanced NSCLC
  - Activity in pretreated patients
  - PD-L1 and other potential biomarkers
  - Activity in first line
- Earlier stages NSCLC
  - Consolidation after chemoradiotherapy
  - Adjuvant after section
- Small cell lung cancer
- Mesothelioma
- Thymic carcinoma
Evolution of second line therapy for NSCLC: Key studies

Docetaxel > BSC

Non-inferiority of pemetrexed to docetaxel

Erlotinib > placebo (2\textsuperscript{nd} or 3\textsuperscript{rd} line)

Shepherd, JCO 2000

Hanna, JCO 2004

Shepherd, NEJM 2005
4. Docetaxel plus nintedanib (LUME-Lung-1) or docetaxel plus ramucirumab (REVEL) versus docetaxel plus placebo for second-line treatment of stage IV NSCLC: Overall survival benefit

**LUME-Lung 1:**
Adenocarcinoma

**OS 12.6 vs 10.3 ms**

**REVEL:** 25% squamous cell carcinoma

**OS 10.5 vs 9.1 ms**

*Reck, Lancet Oncol 2014; Garon, Lancet Oncol 2014*
Activity of immune checkpoint inhibitors in pretreated patients with advanced NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Atezolizumab</th>
<th>Durvalumab</th>
<th>Avelumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>129</td>
<td>475</td>
<td>175</td>
<td>228</td>
<td>184</td>
</tr>
<tr>
<td>RR SCC Non-SCC</td>
<td>17%</td>
<td>23.5%</td>
<td>27%</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Drug rel AE All grades</td>
<td>41%</td>
<td>71%</td>
<td>66%</td>
<td>50%</td>
<td>77%</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>4.7%</td>
<td>9.5%</td>
<td>11%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>RR PDL-1 + PDL-1 -</td>
<td>16%</td>
<td>42% (&gt;50%)</td>
<td>34% IC2/3 or TC 2/3</td>
<td>13%</td>
<td>10% (&lt;1%)</td>
</tr>
</tbody>
</table>

Monotherapy with anti-PD1 nivolumab in second or later line NSCLC (phase I data)

- 54% pretreated with 3-5 therapies
- 17% confirmed responses, 5% unconventional iR

Gettinger, Chicago 2014
Monotherapy with anti-PD1 pembrolizumab in second or later lane (phase 1 data)

- Pretreated pts. Same efficacy 2mg or 10mg/kg
- Lower ORR in patients with liver metastases: 13.6% vs 21.2%

Hellman, WCLC 2015
Randomized phase II study comparing atezolizumab (vs docetaxel) in 2L/3L NSCLC (POPLAR)

- Median survival: Atezolizumab 12.6 months (9.7, 16.4) vs Docetaxel 9.7 months (8.6, 12.0)
- HR = 0.73 (0.53, 0.99)
- P value = 0.040

Vansteenkiste, ECCO-ESMO 2015
POPLAR: OS by PD-L1 Expression

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>47 (16%)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>105 (37%)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>198 (68%)</td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>92 (32%)</td>
</tr>
<tr>
<td>ITT</td>
<td>N = 287</td>
</tr>
</tbody>
</table>

Hazard Ratio

- In favor of atezolizumab: 0.49
- In favor of docetaxel: 0.73

Vansteenkiste, ECCO-ESMO 2015
Effect of second line nivolumab on lung term survival: Confirmation of CheckMate 63

CheckMate 63: all histologies, 56% > 3rd line: 18-months OS rate 27%

CheckMate 17: SCC, 2nd line: 18-months OS rate 28%

CheckMate 57: Non-SCC, 2nd line: 18-months OS rate 38%

Horn, WCLC 2015
Second line therapy of squamous cell lung cancer: Comparisons across recent studies

Nivolumab vs Doc:
9.2 vs 6.0 months; HR 0.62 (0.48-0.81)

Pemetrexed vs Doc
6.2 vs 7.4 months; HR 1.56 (0.8-2.26)

Docetaxel Ramucirumab vs Doc
9.5 vs 8.2 months; HR 0.88 (0.69–1.13)

Docetaxel Nintedanib vs Doc
8.6 vs 8.7 months; HR 1.01 (0.85-1.21)

Afatinib vs Erlotinib
7.9 vs 6.8 months; HR 0.81 (0.69-0.95)

Second line therapy of non-squamous cell lung cancer: Comparisons across recent studies

Nivolumab vs Doc:
12.2 vs 9.4 months; HR 0.73 (0.59-0.89)

Pemetrexed vs Doc
9.3 vs 8.0 months; HR 0.78 (0.61-1.00)

Docetaxel Ramucirumab vs Doc
11.1 vs 9.7 months; HR 0.83 (0.71–0.97)

Docetaxel Nintedanib vs Doc
12.6 vs 10.3 months, HR 0.83 (0.7-0.99)

Horn, ECC0-ESMO 2015: Scaglotti Clin Lung Cancer 2010; Garon, Lancet Oncol 2014; Reck, Lancet Oncology 2014
Treatment effect on overall survival in predefined subsets

<table>
<thead>
<tr>
<th>EGFR Mutation Status</th>
<th>N</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69, 2.00)</td>
</tr>
<tr>
<td>Not Detected</td>
<td>340</td>
<td>0.66 (0.51, 0.86)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>160</td>
<td>0.74 (0.51, 1.06)</td>
</tr>
<tr>
<td>ALK Translocation Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Detected</td>
<td>243</td>
<td>0.71 (0.52, 0.96)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>318</td>
<td>0.80 (0.62, 1.04)</td>
</tr>
<tr>
<td>KRAS Mutation Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>62</td>
<td>0.52 (0.29, 0.95)</td>
</tr>
<tr>
<td>Not Detected</td>
<td>123</td>
<td>0.98 (0.66, 1.48)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>397</td>
<td>0.74 (0.58, 0.94)</td>
</tr>
<tr>
<td>MET Receptor Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Reported</td>
<td>566</td>
<td>0.73 (0.60, 0.89)</td>
</tr>
<tr>
<td>Cell Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>541</td>
<td>0.78 (0.64, 0.96)</td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
<td>0.42 (0.20, 0.91)</td>
</tr>
<tr>
<td>Time from Diagnosis to Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 Year</td>
<td>350</td>
<td>0.79 (0.62, 1.01)</td>
</tr>
<tr>
<td>Other</td>
<td>232</td>
<td>0.69 (0.49, 0.96)</td>
</tr>
<tr>
<td>Time from Completion of Most Recent Regimen to Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 Months</td>
<td>364</td>
<td>0.85 (0.67, 1.08)</td>
</tr>
<tr>
<td>3–6 Months</td>
<td>115</td>
<td>0.69 (0.44, 1.08)</td>
</tr>
<tr>
<td>&gt;6 Months</td>
<td>103</td>
<td>0.46 (0.27, 0.79)</td>
</tr>
<tr>
<td>Prior Neo-adjuvant vs. Adjuvant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>42</td>
<td>0.89 (0.41, 1.91)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>524</td>
<td>0.74 (0.60, 0.91)</td>
</tr>
<tr>
<td>CNS Metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68</td>
<td>1.04 (0.62, 1.76)</td>
</tr>
<tr>
<td>No</td>
<td>514</td>
<td>0.71 (0.58, 0.88)</td>
</tr>
</tbody>
</table>
Phase III study of nivolumab versus docetaxel in second line non-squamous cell lung cancer (CheckMate-57): Overall survival

<table>
<thead>
<tr>
<th>PD-L1 expression level</th>
<th>Nivolumab n</th>
<th>Docetaxel n</th>
<th>Unstratified HR (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>123</td>
<td>123</td>
<td>0.59 (0.43, 0.82)</td>
<td>0.0646</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>108</td>
<td>101</td>
<td>0.90 (0.66, 1.24)</td>
<td></td>
</tr>
<tr>
<td>≥5%</td>
<td>95</td>
<td>86</td>
<td>0.43 (0.30, 0.63)</td>
<td>0.0004</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>136</td>
<td>138</td>
<td>1.01 (0.77, 1.34)</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>86</td>
<td>79</td>
<td>0.40 (0.26, 0.59)</td>
<td>0.0002</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>145</td>
<td>145</td>
<td>1.00 (0.76, 1.31)</td>
<td></td>
</tr>
<tr>
<td>Not quantifiable at baseline</td>
<td>61</td>
<td>66</td>
<td>0.91 (0.61, 1.35)</td>
<td></td>
</tr>
</tbody>
</table>

| PFS                    |             |             |                          |                     |
| ≥1%                    | 123         | 123         | 0.70 (0.53, 0.94)        | 0.0227              |
| <1%                    | 108         | 101         | 1.19 (0.88, 1.61)        |                     |
| ≥5%                    | 95          | 86          | 0.54 (0.39, 0.76)        | <0.0001             |
| <5%                    | 136         | 138         | 1.31 (1.01, 1.71)        |                     |
| ≥10%                   | 86          | 79          | 0.52 (0.37, 0.75)        | 0.0002              |
| <10%                   | 145         | 145         | 1.24 (0.96, 1.61)        |                     |
| Not quantifiable at baseline | 61          | 66          | 1.06 (0.73, 1.56)        |                     |

* Interaction P-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.

Paz-Ares, ASCO 2015;
PD-L1 expression

CheckMate 17

CheckMate 57

KEYNOTE 1
**Pembrolizumab for the treatment of NSCLC: Prevalence of PD-L1 positivity and response according to PD-L1 positivity**

<table>
<thead>
<tr>
<th>PS 0%</th>
<th>PS 1-24%</th>
<th>PS 25-49%</th>
<th>PS 50-74%</th>
<th>PS 75-100%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence, all screened patients, n (%)</strong></td>
<td>323 (39.2)</td>
<td>255 (31.0)</td>
<td>55 (6.7)</td>
<td>71 (8.6)</td>
</tr>
<tr>
<td><strong>ORR in CTA-evaluable patients, n (%) [95% CI]</strong></td>
<td>7 (8.1) [3.3-15.9]</td>
<td>19 (12.9) [8.0-19.4]</td>
<td>6 (19.4) [7.5-37.5]</td>
<td>13 (29.6) [16.8-45.2]</td>
</tr>
</tbody>
</table>

*Prevalence and ORR (RECIST v1.1 by central review) assessed in patients whose samples were evaluable by the CTA, regardless of the interval between tumour and
PD-L1 as a biomarker

Differential effects depend upon the Dose-response relationship

PD-L1 IHC score

Response?

‘Negative’

‘Positive’

0 10 20 30 40 50 60 70 80 90 100

Courtesy Keith Kerr
Mutational landscape determines sensitivity of PD-1 blockade in NSCLC: Candidate neoantigens, response and PFS

Rizvi, Science 2015
15LBA: High tumoral IFNγ mRNA, PD-L1 protein, and combined IFNγ mRNA/PD-L1 protein expression associates with response to durvalumab (anti-PD-L1) monotherapy in NSCLC patients – Higgs B et al

- **Key results**
  - The ORR was 16% [32/300] (95%CI 11, 22) and pre-treatment PD-L1 status influenced response: patients who were PD-L1 positive had an ORR of 27% [23/84] (95%CI 18, 38) compared with 5% [5/92] (95%CI 2, 12) for patients who were PD-L1 negative
  - ORR by PD-L1 and IFNγ status is shown in the figure
Less toxicity with immune checkpoint inhibitors in comparative studies

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Nivolumab squamous %</th>
<th>Docetaxel squamous %</th>
<th>Afatinib squamous %</th>
<th>Docetaxel / Ramucirumab %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>59</td>
<td>87</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>8</td>
<td>58</td>
<td>57</td>
<td>79</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Peters, WCLC 2015
CheckMate 57: Treatment-related adverse events

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 287)</th>
<th></th>
<th>Docetaxel (n = 268)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade, %</td>
<td>Grade 3–4, a %</td>
<td>Any Grade, %</td>
<td>Grade 3–4, a %</td>
</tr>
<tr>
<td><strong>Total patients with an event</strong></td>
<td>69</td>
<td>10</td>
<td>88</td>
<td>54</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>1</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>1</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>&lt;1</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10</td>
<td>&lt;1</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>1</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>&lt;1</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>&lt;1</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>&lt;1</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>0</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>
EQ-5D Utility Index:
Mean Scores Over Time While on Treatment

Higher scores indicate better health status.
Only time points that had PRO data available for ≥5 patients in either treatment arm are plotted on the graph.

Population Norm

Lung Cancer Norm (UK-based): 0.67

Nivolumab (n = 97)
Docetaxel (n = 89)

Reck, ECCO-ESMO 2015
Pembrolizumab for the treatment of NSCLC: PD-L1 staining of tumor cells
Pembrolizumab first line date (Keynote 001)

Median PFS was 6.1 months in all treated patients and 12.5 months with >50% PD-L1 staining.

OS was not reached in all treated patients or in patients with ≥50% staining, and was 16.2 months and 10.4 months in patients with staining in 1%–49% and <1% of cells, respectively.
BIRCH met its primary endpoint in all predefined subgroups per protocol-specified criteria

- Majority of responses were ongoing (> 61% in TC3 or IC3)
- Median DOR was 7 mo in 3L+, NR in 1L/2L in TC3 or IC3, although follow-up is limited
- IRF- and INV-assessed ORRs (per RECIST v1.1) were similar. In TC3 or IC3, eg, 27% vs 29% in 3L+; 24% vs 25% in 2L; and 26% vs 31% in 1L, respectively

Besse, ECCO-ESMO 2015
## Chemotherapy combination trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>n</th>
<th>ORR (%)</th>
<th>Grade 3–4 AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP28328</td>
<td>PhII solid tumours (incl. 1L NSCLC)</td>
<td>atezo + chemo</td>
<td>(n=58)</td>
<td>Atezo + carbo/pac</td>
<td>8*</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atezo + carbo/pem</td>
<td>17*</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atezo + carbo/abrax</td>
<td>16*</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pembro + carbo/pac</td>
<td>Pembro + carbo/pem</td>
<td>25</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-021</td>
<td>PhI/II 1L NSCLC</td>
<td>pembro + chemo</td>
<td>(n=49)</td>
<td>N10 + gem/cis</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N10 + pem/cis</td>
<td>15</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N10 + carbo/pac</td>
<td>15</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N5 + carbo/pac</td>
<td>15</td>
<td>29%</td>
</tr>
<tr>
<td>CheckMate 012</td>
<td>PhI 1L NSCLC</td>
<td>nivo (N) + chemo</td>
<td>(n=56)</td>
<td>N1 q3w + I1 q3w</td>
<td>31</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N1 q2w + I1 q6w</td>
<td>40</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N3 q2w + I1 q12w</td>
<td>38</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N3 q2w + I1 q6w</td>
<td>39</td>
<td>28%</td>
</tr>
</tbody>
</table>

Immunotherapy combination trial: CheckMate-12 ipilimumab and nivolumab. Treatment-related AEs

<table>
<thead>
<tr>
<th></th>
<th>Nivo 1 + Ipi 1 Q3W (n = 31)</th>
<th>Nivo 1 Q2W + Ipi 1 Q6W (n = 40)</th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade</strong></td>
<td>77</td>
<td>73</td>
<td>74</td>
<td>69</td>
<td>71</td>
</tr>
<tr>
<td><strong>Any Grade 3–4</strong></td>
<td>29</td>
<td>35</td>
<td>29</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td><strong>Treatment-related AEs leading to discontinuation, %</strong></td>
<td>13</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>Nivolumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median number of doses (range)</td>
<td>4 (1–42)</td>
<td>7 (1–26)</td>
<td>13 (1–26)</td>
<td>8 (1–25)</td>
<td>8 (1–62)</td>
</tr>
<tr>
<td>Median duration of therapy, wks (range)</td>
<td>12.0 (3.0–92.0)</td>
<td>16.0 (2.0–59.0)</td>
<td>28.7 (2.0–52.0)</td>
<td>18.0 (2.0–53.0)</td>
<td>16.0 (2.0–129.6)</td>
</tr>
<tr>
<td><strong>Ipilimumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median number of doses (range)</td>
<td>NC 1–4g</td>
<td>3 (1–9)</td>
<td>3 (1–5)</td>
<td>2 (1–9)</td>
<td>NA</td>
</tr>
<tr>
<td>Median duration of therapy, wks (range)</td>
<td>11.6 (3.0–24.0)</td>
<td>17.6 (6.0–59.0)</td>
<td>35.7 (12.0–60.0)</td>
<td>15.0 (6.0–54.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* There were no treatment-related deaths. Toxicities mainly GI, hepatic, endocrine, skin, lung
Immunotherapy combination trial: CheckMate-12
ipilimumab and nivolumab: Efficacy by PD-L1 expression

<table>
<thead>
<tr>
<th></th>
<th>≥1% PD-L1 expression</th>
<th>&lt;1% PD-L1 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo 1 + Ipi 1 Q3W  (n = 12)</td>
<td>Nivo 1 Q2W + Ipi 1 Q6W (n = 21)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>mPFS, wks (95% CI)</td>
<td>11.5 (7.1, )</td>
<td>21.1 (11.4, )</td>
</tr>
<tr>
<td>PFS rate at 24 wks, % (95% CI)</td>
<td>42 (15, 67)</td>
<td>40 (18, 61)</td>
</tr>
</tbody>
</table>

- All patients had available pretreatment tumor samples; 76% (113/148) had samples evaluable for PD-L1 expression
- Median DOR was not reached in any arm, regardless of PD-L1 expression
Phase 3 anti PD1/PD-L1 Combination Trials in First-Line Advanced NSCLC

### Nivolumab

**CHECKMATE 227**
- Treatment-naïve or recurrent NSCLC
  - N=1980
- Primary endpoints: OS, PFS

**CHECKMATE 026**
- Treatment-naïve non-squamous NSCLC
  - PD-L1+ NSCLC
  - N=495
- Primary endpoint: PFS

**KEYNOTE-110**
- Advanced NSCLC
  - N=675
- Primary endpoint: OS

**KEYNOTE-130**
- Stage IV non-squamous NSCLC
  - N=1240
- Primary endpoint: OS

**KEYNOTE-150**
- Pembrolizumab
  - Stage IV non-squamous NSCLC
  - N=580
  - Pembrolizumab + pemetrexed/platinum
  - Primary endpoint: PFS

**KEYNOTE-042**
- Pembrolizumab
  - Treatment-naïve non-squamous NSCLC
  - PD-L1+ NSCLC
  - N=1240
  - Pembrolizumab 200 mg IV Q3W
  - SOC chemotherapy
  - Primary endpoint: OS

### Pembrolizumab

**KEYNOTE-189**
- Treatment-naïve non-squamous NSCLC
  - N=400
- Primary endpoint: PFS

**KEYNOTE-189**
- Pembrolizumab + pemetrexed/platinum
  - Treatment-naïve non-squamous NSCLC
  - PD-L1+ NSCLC
  - N=495
  - Pembrolizumab + pemetrexed/platinum
  - Primary endpoint: PFS

**KEYNOTE-042**
- Pembrolizumab
  - Stage IV squamous NSCLC
  - N=1200
  - Pembrolizumab + paclitaxel + carboplatin
  - Primary endpoint: PFS

### Atezolizumab

**IMPOWER 111**
- Stage IV non-squamous NSCLC
  - PD-L1+ NSCLC
  - N=400
  - Atezolizumab + carboplatin + nab-paclitaxel
  - Primary endpoint: PFS

**IMPower 130**
- Stage IV non-squamous NSCLC
  - N=550
  - Atezolizumab + carboplatin + nab-paclitaxel
  - Primary endpoint: PFS

**IMPower 131**
- Stage IV squamous NSCLC
  - N=1200
  - Atezolizumab + carboplatin + paclitaxel + carboplatin
  - Primary endpoint: PFS

**IMPower 150**
- Stage IV non-squamous NSCLC
  - N=1200
  - Atezolizumab + carboplatin + paclitaxel + carboplatin
  - Primary endpoint: PFS

### Durvalumab

**MYSTIC**
- Advanced NSCLC
  - N=675
- Primary endpoint: PFS

**NEPTUNE**
- First-line metastatic NSCLC
  - N=800
- Primary endpoint: OS

**IMPower 110**
- Stage IV non-squamous NSCLC
  - N=400
  - Atezolizumab
  - Carboplatin or carboplatin + pemetrexed
  - Primary endpoint: PFS

**IMPower 111**
- Stage IV squamous NSCLC
  - N=400
  - Atezolizumab
  - Gemcitabine + cisplatin or carboplatin
  - Primary endpoint: PFS

**IMPower 130**
- Stage IV non-squamous NSCLC
  - N=550
  - Atezolizumab + carboplatin + nab-paclitaxel
  - Primary endpoint: PFS

**IMPower 131**
- Stage IV squamous NSCLC
  - N=1200
  - Atezolizumab + carboplatin + paclitaxel + carboplatin
  - Primary endpoint: PFS

**IMPower 150**
- Stage IV non-squamous NSCLC
  - N=1200
  - Atezolizumab + bevacizumab + paclitaxel + carboplatin
  - Primary endpoint: PFS
Immune checkpoint inhibitors in earlier stages of NSCLC treated with chemoradiotherapy

Consolidation after chemoradiotherapy

• NICOAS: A Feasibility Trial Evaluating Anti-PD1 Nivolumab Consolidation After Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B NSCLC

• PACIFIC: A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy
Immune checkpoint inhibitors after complete resection of NSCLC: PEARLS
SCLC: Nivolumab and nivolumab – ipilimumab combinations

SCLC (n = 128) with progressive disease after ≥1 prior line of therapy, including a platinum-based regimen in first line (unselected by PD-L1 expression)

Nivolumab 3 mg/kg IV Q2W (n = 40)

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

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

A Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 38)

Nivolumab 3 mg/kg IV Q2W

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

Database lock: February 16, 2015

Antonia, ASCO 2015
SCLC: Nivolumab and nivolumab – ipilimumab combinations: Tumor responses and PD-L1 expression

Antonia, ASCO 2015

<table>
<thead>
<tr>
<th>PD-L1 expression level, n (%)</th>
<th>Nivolumab (n = 22)</th>
<th>Nivolumab + Ipilimumab (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>15 (68)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>≥1%</td>
<td>7 (32)</td>
<td>6 (33)</td>
</tr>
</tbody>
</table>

\(^a\)Combined data for nivolumab 1 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 cohorts. \(^b\)Not evaluable due to specimens that are not quantifiable, indeterminate, or not yet obtained; 10 nonevaluable samples and 8 not yet obtained in the nivolumab arm, 6 nonevaluable samples and 26 not yet obtained in the nivolumab 1 + ipilimumab 3 arm. Only pts with target lesion at baseline and ≥1 on-treatment tumor assessment are included (nivolumab, n = 34, nivolumab + ipilimumab, n = 40).
**SCLC: Pembrolizumab**

### Antitumor Activity

(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0.0-14.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>29.2</td>
<td>12.6-51.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>4.2</td>
<td>0.1-21.1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10</td>
<td>41.7</td>
<td>22.1-63.4</td>
</tr>
<tr>
<td>No assessment(^b)</td>
<td>6</td>
<td>25.0</td>
<td>9.8-46.7</td>
</tr>
</tbody>
</table>

**Objective response rate:** 29.2% (95% CI, 12.6–51.1)

**Disease control rate\(^c\):** 33.3% (95% CI, 15.6–55.3)

---

\(^a\) Both confirmed and unconfirmed responses are included. Response was assessed by RECIST v1.1 per investigator review.

\(^b\) Includes patients who died or discontinued for clinical progression before the first imaging assessment (n = 3) or who had not reached the first imaging assessment at data cutoff (n = 3). Patients with CR, PR, or SD of any duration. Data cutoff date: June 24, 2015.

\(^c\) Patients with CR, PR, or SD of any duration. Data cutoff date: September 7, 2015.
SCLC: Pembrolizumab (Keynote-28): PD-L1 expression

- Samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: performed at a central laboratory using a prototype assay and the 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma
- SCLC cohort: of 147 evaluable samples, 42 PD-L1 positive (28.6%)

Examples of PD-L1 Staining in SCLC Specimens from KEYNOTE-028
SCLC: Pembrolizumab (Keynote-28): Antitumor activity

(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0.0-14.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>29.2</td>
<td>12.6-51.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>4.2</td>
<td>0.1-21.1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10</td>
<td>41.7</td>
<td>22.1-63.4</td>
</tr>
<tr>
<td>No assessment(b)</td>
<td>6</td>
<td>25.0</td>
<td>9.8-46.7</td>
</tr>
</tbody>
</table>

Objective response rate: 29.2% (95% CI, 12.6–51.1)
Disease control rate\(c\): 33.3% (95% CI, 15.6–55.3)

\(a\)Both confirmed and unconfirmed responses are included. Response was assessed by RECIST v1.1 per investigator review.
\(b\)Includes patients who died or discontinued for clinical progression before the first imaging assessment (n = 3) or who had not reached the first imaging assessment at data cutoff (n = 3).
\(c\)Patients with CR, PR, or SD of any duration. Data cutoff date: June 24, 2015.

Ott, WCLC 2015
SCLC: Pembrolizumab (Keynote-28): Change from baseline over time

- Median DOR: 29.1 weeks (0.1+ to 29.1)
- 6 of 7 responses\(^b\) are ongoing with patients still on treatment
STIMULI protocol amendment 1

• **Treatment arm**
  - **induction phase**: nivolumab (1mg/kg i.v.) plus ipilimumab (3mg/kg i.v.), Q3W, 4 doses
  - **maintenance phase**: nivolumab (240mg i.v.), Q2W, until PD for max 1 year

• **Observation arm**: best supportive care

---

**Diagram:**

- **Screening:**
  - LD SCLC
  - FDG-PET-CT or CT
  - Brain MRI or CT

- **Chemo-Radiotherapy:**
  - cis-carboplatin + etoposide
  - 4 cycles

- **Tumour evaluation:**
  - PD no
  - RT → RT

- **Consolidation vs observation:**
  - induction
    - combination nivolumab/ipilimumab
  - maintenance
    - nivolumab

- **Biomaterial for translational research:**
  - Serum
  - Whole blood
  - Biopsy: FFPE block or slides

- **CT scans for tumour assessment:**
  - up to 18 months: every 9 weeks
  - up to 2 years: every 12 weeks
  - years 3 & 4: every 6 months
  - at 5 years

- **At progression:**
  - Serum
  - Whole blood
  - Voluntary re-biopsy: → FFPE block
Pleural plaques

Pleural mesothelioma

Asbestosis
Mesothelioma: Pembrolizumab (Keynote-28): PD-L1 screening

Patients Screened
n = 84

Samples Evaluable for PD-L1
n = 80

PD-L1–Positive Tumors
n = 38

Patients Enrolled
N = 25

Nonevaluable
- Insufficient sample (n = 3)
- Uninterpretable PD-L1 staining (n = 1)

Reasons for exclusion
- ECOG PS ineligible (n = 6)
- No measurable disease (n = 1)
- Declined study participation (n = 1)
- Other (n = 5)

45.2% PD-L1+
Mesothelioma: Pembrolizumab (Keynote-28): Antitumor activity

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0.0–13.7</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>28.0</td>
<td>12.1–49.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12</td>
<td>48.0</td>
<td>27.8–68.7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
<td>16.0</td>
<td>4.5–36.1</td>
</tr>
<tr>
<td>No assessment</td>
<td>2</td>
<td>8.0</td>
<td>1.0–26.0</td>
</tr>
</tbody>
</table>

Objective response rate: 28.0% (95% CI, 12.1–49.4)
Disease control rate: 76.0% (95% CI, 54.9–90.6)

Alley, WCLC 2015
Mesothelioma: Pembrolizumab (Keynote-28): Antitumor activity

Alley, WCLC 2015
Intensitiy and duration of therapy?
A case of a 70-year old man with stage IV adenocarcinoma of the lung treated with two doses of atezolizumab

April 2014: Pretreatment
September 2014: After 2 doses of therapy in June 2014
March 2015: Hilar progression
T cell immune checkpoints as targets for immunotherapy

- Agonistic antibodies directed towards activating co-stimulatory molecules
- Blocking antibodies against co-inhibitory molecules may enhance T-cell stimulation to promote tumor destruction