Immune checkpoint inhibitors in NSCLC

Rolf Stahel
University Hospital of Zürich

Madrid, 2.2. 2017
Several PD-1/PD-L1 inhibitors are being evaluated in NSCLC

<table>
<thead>
<tr>
<th>PD-1</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab BMS-936558</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Phase III</td>
</tr>
<tr>
<td>Pembrolizumab MK-3475</td>
<td>Humanized IgG4 mAb</td>
<td>Merck</td>
<td>Phase III</td>
</tr>
<tr>
<td>Pidilizumab CT-011</td>
<td>Humanized IgG1 mAb</td>
<td>CureTech</td>
<td>Phase II</td>
</tr>
<tr>
<td>PDR001</td>
<td>Humanized IgG4 mAb</td>
<td>Novartis</td>
<td>Phase II</td>
</tr>
<tr>
<td>AMP-224</td>
<td>Recombinant PD-L2-Fc fusion protein</td>
<td>GlaxoSmithKline</td>
<td>Phase I</td>
</tr>
<tr>
<td>MEDI-0680</td>
<td>Humanized IgG4 mAb</td>
<td>Medimmune - AZ</td>
<td>Phase I</td>
</tr>
<tr>
<td>REGN2810</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></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab MedI-4736</td>
<td>Engineered human IgG1 mAb</td>
<td>Medimmune - AZ</td>
<td>Phase III</td>
</tr>
<tr>
<td>Atezolizumab MPDL-3280A</td>
<td>Engineered human IgG1 mAb</td>
<td>Genentech</td>
<td>Phase III</td>
</tr>
<tr>
<td>Avelumab MSB0010718C</td>
<td>Engineered human IgG1 mAb</td>
<td>EMD Serono</td>
<td>Phase III</td>
</tr>
<tr>
<td>BMS-936559</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
The complexity of the LD-L1 diagnostics of NSCLC

<table>
<thead>
<tr>
<th>Ab Clone</th>
<th>Diagnostic Partner</th>
<th>Scoring Method†</th>
<th>Diagnostic Status</th>
<th>Approved IVD PD-L1 Threshold</th>
<th>PD-L1 Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab: BMS</td>
<td>Dako</td>
<td>% of PD-L1–expressing tumour cells</td>
<td>Complementary: testing not required</td>
<td>US/EU: All patients eligible</td>
<td>≥1% (pos), ≥5% (strong), or ≥10% validated</td>
</tr>
<tr>
<td>Pembrolizumab: Merck</td>
<td>Dako</td>
<td>% of PD-L1–expressing tumour cells</td>
<td>Companion: testing required</td>
<td>EU: All patients eligible</td>
<td>≥1% (pos), ≥5% (strong), or ≥10% validated</td>
</tr>
<tr>
<td>Atezolizumab: Roche</td>
<td>Dako</td>
<td>% of PD-L1–expressing tumour cells or immune cells</td>
<td>US/EU: SQ and NSQ NSCLC</td>
<td>US: ≥50%</td>
<td>TC / IC 3(+)</td>
</tr>
<tr>
<td>Durvalumab: AstraZeneca</td>
<td>Dako</td>
<td>% of PD-L1–expressing tumour cells</td>
<td>Dx not approved for NSCLC setting</td>
<td>EU: ≥1%</td>
<td>TC / IC 2(+)</td>
</tr>
<tr>
<td>Avelumab: Pfizer</td>
<td>Dako</td>
<td>% of PD-L1–expressing tumour cells</td>
<td>Dx not approved for durvalumab in any setting</td>
<td>NA</td>
<td>TC / IC 1(+)</td>
</tr>
</tbody>
</table>

*TC / IC 0(−)*

Validated

TBC, TC between all >1% and 25% with moderate or high intensity

NA

NA

NA

NA

NA
Example of PD-L1 tumor expression

Not only technical validation, also clinical validation required
Not all animals are created equal

Hirsch, AACR 2016
Analytical evaluation results: Mean TPS per case based on 3 readers: Tumor cells

- Analytical comparison of TPS by case for each assay
- Data points represent the mean score from 3 pathologists for each assay on each case
- No clinical diagnostic cutoff applied
- Conclusion: 3 of 4 assays are analytically similar for tumor cell staining
German ring trial: Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas

<table>
<thead>
<tr>
<th>Threshold</th>
<th>28.8</th>
<th>22C3</th>
<th>sp142</th>
<th>sp263</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 vs 1+%</td>
<td>2.8%</td>
<td>7.4%</td>
<td>9.6%</td>
<td>6.3%</td>
</tr>
<tr>
<td>49 vs 50+%</td>
<td>5.2%</td>
<td>8.3%</td>
<td>8.5%</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

Interobserver concordance for the scoring of PD-L1-positive carcinoma cells. Pairwise comparisons of each sample and each combination of the nine observers. Each field indicates the absolute number of the respective score-pairing. Concordant scores (diagonal) are highlighted gray.

Scheel. Mod Pathol 2016
Mutational load and outcome of immune checkpoint inhibitor therapies in NSCLC

Rizvi, Science 2015

Roziak, BMJ Med 2016
Treatment effect on overall survival in Checkmate 57 and KEYNOTE 10

Borghaei. NEJM 2015; Herbst Lancet 2015
Checkmate 017 and 057: 2-years update of OAS (no biomarker selection),

* No biomarker selection

Borghael, ASCO 2016
Checkmate 017 and 057: 2-years update PFS (no biomarker selection)

Borghael, ASCO 2016
Checkmate 057: OS by PD-L1 Expression

Based on a July 2, 2015 DBL. Symbols represent censored observations.

EMA Opdivo Product Characteristics
KEYNOTE 10: Pembrolizumab versus doxetaxel in 2nd line NSCLC (\(\geq 1\%\) of tumor cells PD-L1 positive)

**OS, PD-L1 TPS \(\geq 1\%\) (Total Population)**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 1 y</th>
<th>HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrol 2 mg/kg</td>
<td>10.4 (9.4-11.9)</td>
<td>43.2%</td>
<td>0.71 (0.58-0.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pembrol 10 mg/kg</td>
<td>12.7 (10.0-17.3)</td>
<td>52.3%</td>
<td>0.61 (0.49-0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.5-9.8)</td>
<td>34.6%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**OS, PD-L1 TPS \(\geq 50\%\) Stratum**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrol 2 mg/kg</td>
<td>14.9 (10.4-NR)</td>
<td>0.54 (0.38-0.77)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pembrol 10 mg/kg</td>
<td>17.3 (11.8-NR)</td>
<td>0.50 (0.36-0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Herbst, ESMO Asia 2015, Lancet*
Relationship between level of PD-L1 expression and outcomes in the KEYNOTE-010 trial

P values are nominal only given the post-hoc nature of the analyses.
Horizontal dotted lines represent the ORR for pembrolizumab and docetaxel in the TPS ≥1% population.

Baas, ASCO 2016
OAK: A randomized phase III study comparing atezolizumab with docetaxel in advanced NSCLC

PHASE III OAK STUDY DESIGN

PrimaryEndpoints (first 850 enrolled patients):
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

SecondaryEndpoints: ORR, PFS, DoR, Safety

OVERALL SURVIVAL, ITT (N = 850)

HR, 0.73\(^{a}\) (95% CI, 0.62, 0.87) \(P = 0.0003\) Minimum follow up = 19 months

OS BY PD-L1 EXPRESSION

Barlesi, ESMO 2016
Less toxicity with immune checkpoint inhibitors in second line comparative studies

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Check-mate 17</th>
<th>Checkmate 57</th>
<th>KEYNOTE 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of patients</td>
<td>% of patients</td>
<td>% of patients</td>
</tr>
<tr>
<td>N</td>
<td>59</td>
<td>69</td>
<td>63</td>
</tr>
<tr>
<td>Doc</td>
<td>87</td>
<td>88</td>
<td>66</td>
</tr>
<tr>
<td>All</td>
<td>59</td>
<td>69</td>
<td>63</td>
</tr>
<tr>
<td>3-5</td>
<td>8</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>79</td>
</tr>
</tbody>
</table>
Case study, R.M. 1952

• 06/15 Diagnosis: Pleomorphic carcinoma RUL, clinical state stage T3N1M1 (bone)
• 07/15 – 08/15 3 cycles of cisplatin and gemcitabine
• 28.08.2015 Re-Staging: progression in bone
Case study, R.M. 1952

- 29.09.2015  Right upper lobe resection ypT3 ypN1 (1/8)
- 06.11.2015  Re-Staging: progression bone, LN

Nov 2015  RT Sacrum, paravertebral, Os
Case study, R.M. 1952

Emergency hospitalisation 05.01.2016

- PiO2 67%; no fever, ECOG 3-4
- CRP 115, LDH 680; Leucocytes 11 G/l

- Methylprednisolon 250mg iv (1d)
- Prednison 200mg (2d), 100mg (2d), 50mg (3d), 25mg (3d), 20mg (3d), 10mg (2d), 5mg (2d)
- Tazobac + Bactrim
Case study, R.M. 1952

11/2015

Durable clinical benefit in patients PD-L1–Expressing NSCLC who completed pembrolizumab (from KEYNOTE-010)

Pleateau above 30% emerging

Clinical benefit of pembrolizumab is durable after 2 years of treatment

Herbst, WCLC 2016
Are we ready to use biomarkers for selection of patients for treatment with immune checkpoint inhibitors in NSCLC?

- PD-L1 expression is a – albeit imperfect - biomarker. It needs further prospective clinical validation in addition to laboratory validation. However, evolving data on the first line use of immune checkpoint inhibitors suggests its use as biomarker to become routine practice.

- Other evolving biomarkers not yet suitable for clinical routine include:
  - Co-localization with tumor infiltrating lymphocytes
  - Immunologic signatures
  - Neoantigen load

- In the presence of oncogenic driver mutations (and in non-smokers) the use of second line chemotherapy is preferable.
Immune checkpoint inhibitors in second line NSCLC

• Immune checkpoint inhibition provides a survival benefit as compared to second line chemotherapy
• The safety profile is superior to the safety profile of chemotherapy
• Patient-reported outcomes suggest a stable or improved health status while on treatment
• The optimal duration of therapy is an important issue in need to be addressed
• Biomarker selection also in second line?
ORR by PD-L1 expression levels in first line NSCLC with single agent PD-1 or PD-L1 directed antibody

<table>
<thead>
<tr>
<th>Study</th>
<th>PD-L1 Cutoffs</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 012</td>
<td>&gt;50% (n=12)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>25% (n=18)</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>1% (n=32)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>TC3 or IC3</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>TC2/8 or IC2/8</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>&gt;25% (n=49)</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>&gt;1% (n=10)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>All patients</td>
<td>17.4</td>
</tr>
</tbody>
</table>

| KN-001                 | >50% (n=24)   | 58.3    |
|                        | 25% (n=46)    |         |
|                        | 1% (n=10)     |         |
|                       | >25% (n=49)   | 29      |
|                       | >1% (n=9)     | 11      |
|                       | All patients  | 10.4    |

| BIRCH                  | >50% (n=13)   | 15.4    |
|                        | 25% (n=28)    |         |
|                        | 1% (n=10)     |         |
|                       | >25% (n=75)   | 21.4    |
|                       | >1% (n=4)     | 7.0     |
|                       | All patients  | 20      |

| Durva                  | >50% (n=13)   | 18.7    |
|                        | 25% (n=28)    |         |
|                        | 1% (n=10)     |         |
|                       | >25% (n=75)   | 12.2    |
|                       | >1% (n=4)     |         |
|                       | All patients  | 10.4    |

| JAVELIN Solid Tumor    | >50% (n=12)   | 50      |
|                        | 25% (n=18)    |         |
|                        | 1% (n=32)     |         |
|                       | TC3 or IC3    |         |
|                       | TC2/8 or IC2/8|         |
|                       | >25% (n=49)   |         |
|                       | >1% (n=10)    |         |
|                       | All patients  |         |

PD-L1 Cutoffs:
- >50%
- >25%
- >1%
- TC3 or IC3
- TC2/8 or IC2/8
- >25%
- >1%
- All patients
- TILs >10%
- TILs <10%
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: 2 doses of therapy in June 2014

March 2015: Hilar progression
Nivolumab for first line treatment of advanced NSCLC

Response rate:
- All: 23%  
- PD-L1 ≥ 50%: 50%  
- PD-L1 ≥ 5%: 31%  
- PD-L1 < 5%: 15%  
- PD-L1 < 1%: 14%  

Gettinger, JCO 2016
Results in treatment naïve patients with advanced NSCLC enrolled in KEYNOTE-001

<table>
<thead>
<tr>
<th>TPS</th>
<th>Median, mo (95% CI)</th>
<th>18-mo Rate, %</th>
<th>24-mo Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>NR (22.1-NR)</td>
<td>72.7</td>
<td>60.6</td>
</tr>
<tr>
<td>1%-49%</td>
<td>19.5 (10.7-22.2)</td>
<td>50.1</td>
<td>32.5</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>14.7 (3.4-NR)</td>
<td>50.0</td>
<td>37.5</td>
</tr>
</tbody>
</table>

Hui, ASCO 2016
Phase 3 PD1/PD-L1 combination in 1L 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+ (N=400). Primary endpoint: PFS.

**Pembrolizumab**
- **KEYNOTE-189**: Treatment-naïve non-squamous NSCLC (N=1240). Primary endpoint: OS.
- **KEYNOTE-042**: PD-L1+ NSCLC (N=1180). Primary endpoint: OS.
- **KEYNOTE-024**: PD-L1+ NSCLC (N=300). Primary endpoint: OS.

**Durvalumab**
- **MYSTIC**: Advanced NSCLC (N=675). Primary endpoint: PFS.
- **NEPTUNE**: First-line metastatic NSCLC (N=400). Primary endpoint: OS.

**Atezolizumab**
- **Impower 110**: Stage IV non-squamous PD-L1+ NSCLC (N=400). Primary endpoint: PFS.
- **Impower 111**: Stage IV squamous NSCLC (N=400). Primary endpoint: PFS.
- **Impower 130**: Stage IV non-squamous NSCLC (N=330). Primary endpoint: PFS.
- **Impower 131**: Stage IV squamous NSCLC (N=1200). Primary endpoint: PFS.
- **Impower 150**: Stage IV non-squamous NSCLC (N=1200). Primary endpoint: PFS.

**Pembrolizumab + Nivolumab**
- **Impower 111**: Stage IV squamous NSCLC (N=1200). Primary endpoint: PFS.

**Pembrolizumab + Atezolizumab**
- **Impower 131**: Stage IV squamous NSCLC (N=1200). Primary endpoint: PFS.

**Pembrolizumab + Durvalumab**
- **KEYNOTE-042**: PD-L1+ NSCLC (N=1180). Primary endpoint: OS.

**Pembrolizumab + Nivolumab + Ipilimumab**
- **IMPRESS**: Treatment-naïve non-squamous NSCLC PD-L1+ (N=400). Primary endpoint: PFS.

**Pembrolizumab + Atezolizumab + Bevacizumab**
- **Impower 150**: Stage IV non-squamous NSCLC (N=1200). Primary endpoint: PFS.
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%

**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

  ![Key Eligibility Criteria Diagram](Image)

- **R (1:1) N = 365**

- **Platinum-Doublt Chemotherapy (4-6 cycles)**

- **Pembrolizumab 200 mg IV Q3W (2 years)**

  ![Pembrolizumab Treatment Diagram](Image)

**PD-L1 Screening**

- 1934 patients entered screening
- 1729 submitted samples for PD-L1 assessment
- 1653 samples evaluable for PD-L1
- 500 TPS ≥50% (30%)
- 1153 TPS <50%

**Key End Points**

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

*Reck, ESMO 2016*
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%

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

**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>

Reck, ESMO
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%

Reck, ESMO 2016
KEYNOTE-024: Treatment related side effects with incidence >10%

Data cut-off: May 9, 2016.
KEYNOTE-024: Immune-mediated adverse events

Overall incidence
- 29.2% any grade
- 9.7% grade 3-4
- No grade 5 events
CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice of platinum-based doublet chemotherapy as first-line therapy for stage IV/recurrent PD-L1 positive NSCLC

Baseline Characteristics (All Randomized Patients)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 271)</th>
<th>Chemotherapy (n = 271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time from diagnosis to randomization (range), months</td>
<td>1.9 (0.3, 214.9)</td>
<td>2.0 (0.5, 197.3)</td>
</tr>
<tr>
<td>&lt;3 months, %</td>
<td>75.6</td>
<td>71.9</td>
</tr>
<tr>
<td>Tumor histology, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>24.4</td>
<td>23.7</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>75.6</td>
<td>76.3</td>
</tr>
<tr>
<td>Selected sites of metastases (lesions), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>12.2</td>
<td>13.3</td>
</tr>
<tr>
<td>Liver</td>
<td>19.9</td>
<td>13.3</td>
</tr>
<tr>
<td>Median sum of target lesion diameters, mm (range)</td>
<td>82.5 (14, 218)</td>
<td>68.0 (15, 272)</td>
</tr>
<tr>
<td>PD-L1 expression, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5%</td>
<td>76.8</td>
<td>77.8</td>
</tr>
<tr>
<td>≥25%</td>
<td>48.7</td>
<td>60.7</td>
</tr>
<tr>
<td>≥50%</td>
<td>32.5</td>
<td>46.7</td>
</tr>
<tr>
<td>≥75%</td>
<td>20.7</td>
<td>27.4</td>
</tr>
</tbody>
</table>
CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice of platinum-based doublet chemotherapy as first-line therapy for stage IV/recurrent PD-L1–positive NSCLC

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

No. of patients at risk:
Nivolumab 211 104 71 49 35 24 6 3 1 0
Chemotherapy 212 144 74 47 28 21 8 1 0 0

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

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 (95% CI)</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>
</tbody>
</table>

HR = 1.02 (95% CI: 0.80, 1.30)

No. of patients at risk:
Nivolumab 211 186 156 133 118 86 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)

Sosinski, ESMO 2016
EC Approves Frontline Pembrolizumab for PD-L1+ Metastatic NSCLC

Silas Inman @silasinman
Published Online: Tuesday, Jan 31, 2017

The European Commission has expanded the indication for pembrolizumab (Keytruda) to include the frontline treatment of patients with metastatic non–small cell lung cancer (NSCLC) that expresses PD-L1 on ≥50% of cells and does not harbor an EGFR or ALK mutation.

The approval was based on data from phase III KEYNOTE-024 trial, and
Nivolumab in combination with platinum-based doublet chemotherapy for first line treatment of advanced NSCLC

RR 33%  47%  47%  43%

Rizvi, JCO 2016
Pembrolizumab plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C

Carboplatin/Paclitaxel

Carboplatin/Paclitaxel + Bev

Carboplatin/Pemetrexed

Gadgeel, ASCO 2016
Pembrolizumab plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C

Gadgeel, ASCO 2016
Randomized phase-2 study of carboplatin and pemetrexed with or without pembrolizumab as first line therapy of advanced NSCLC: Keynote-21 Cohort G

**KEYNOTE-021 Cohort G**

**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

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

Langer, ESMO 2016
Randomized phase-2 study of carboplatin and pemetrexed with or without pembrolizumab as first line therapy of advanced NSCLC: Keynote-21 Cohort G

**Progression-Free Survival**
(RECIST v1.1 by Blinded, Independent Central Review)

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>23</td>
<td>0.53 (0.31-0.91)</td>
</tr>
<tr>
<td>Chemo alone</td>
<td>33</td>
<td>0.0102 (0.004-0.23)</td>
</tr>
</tbody>
</table>

**ORR, % (95% CI)**

- Pembro + Chemo: 55% (43-77%)
- Chemo Alone: 29% (13-63%)

*Delta 26% P = 0.0016*

Data cut-off: August 2, 2016.

Langer, ESMO 2016
Phase 1 CheckMate 012 study design: First-line nivolumab ± ipilimumab in NSCLC

Stage IIIB/IV NSCLC (any histology), no prior chemotherapy for advanced disease, ECOG PS 0 or 1

- Nivolumab 3 mg/kg IV Q2W<sup>a</sup>
- Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q12W<sup>b</sup>
- Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W<sup>b</sup>

Until disease progression<sup>c</sup> or unacceptable toxicity

**Primary endpoint:** safety and tolerability

**Secondary endpoints:** ORR (RECIST v1.1) and PFS rate at 24 weeks assessed by investigators

**Exploratory endpoints:** OS, efficacy by PD-L1 expression

- Updated data<sup>d</sup> presented here are based on median follow-up durations of 22 months (monotherapy) and 16 months (combination cohorts)
  - Overall additional follow-up relative to previous reports: monotherapy, +~18 months; combination cohorts, +6 months<sup>2</sup>

ClinicalTrials.gov number NCT01454102; <sup>a</sup>Treatment allocation not randomized; <sup>b</sup>Treatment allocation randomized; earlier cohorts evaluated other dosing schedules/regimens<sup>2</sup>

<sup>c</sup>Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit

<sup>d</sup>Based on a September 2016 database lock


*Gettinger, WCLC 2016*
Phase 1 CheckMate 012 response rate by tumor PD-L1 expression:

Hellmann, Lancet Oncol 2016
Phase 1 CheckMate 012 OAS by tumor PD-L1 expression:

All treated patients (n = 77)

- Nivo 3 Q2W + ipi 1 Q6/12W
- 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)

- Nivo 3 Q2W
- 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

Gettinger, WCLC 2016
Phase 1 CheckMate 012 treatment related adverse events:

- The safety profile of nivolumab plus ipilimumab with longer follow-up was similar to that reported previously.\(^1\)

Based on a September 2016 database lock; select AEs are those with potential immunologic etiology; *All treatment-related pulmonary events were pneumonitis; rxn = reaction


*Getttinger, WCLC 2016*
Projected read-out of many phase 3 anti PD1/PD-L1 combination Trials in First-Line Advanced NSCLC (>15’000 patients)

- **2016**
  - Pembrolizumab monotherapy >50% PD-L1+ Keynote 024 Q2 2016
  - Nivolumab monotherapy PD-L1+ 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% PD-L1+ Keynote 042 Q2 2018
  - Atezolizumab monotherapy all histologies PD-L1+ Impower 110 Q2 2018
  - Nivolumab mono vs Niv + Ipi vs Niv + Pt doublet vs Pt doublet CheckMate-227 Q1 2018

- **2019**
  - Atezolizumab + chemo IMpower 130 (non-SCC) Impower 131 (SCC) Q3 2018
  - Atezolizumab + chemo vs SoC SoC NEPTUNE Q4 2018

- **2020**
  - Durvalumab + tremelimumab vs SoC MYSTIC Q1 2017
  - Durvalumab ± tremelimumab vs SoC NEPTUNE Q4 2018

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

Soria, ESMO 2016