Session 6: Future development

Immunotherapy of Lung Cancer

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Integrated Centers of Oncology R Gauducheau
University of Nantes
France
Evidence of possible immune reaction to tumors
- Ehrlich (1909), Burnet & Thomas 1950
- TAA

Tumor immunology extensively studied since the 1970

Disappointing results until recently
- Non-specific immune stimulation
  - PolyA-PolyU, BCG, C Parvum, γIFN, αIFN, Interleukine 2,

- Specific, Antigen mediated immune stimulation with vaccine:
  - Mage3, MUC 1, BEC 1, 1E10, Anti EGF…
  - Tumor cell vaccine + TGFβ (Lucanix)
  - All failed in large randomized trials despite promising earlier results and documented immune response
FIGURE 2. Cancer immunoediting. The proposed process of cancer immunoediting consists of three distinct phases: elimination, equilibrium, and escape. In the elimination phase, innate and adaptive immune responses recognize and destroy cancer cells (immunosurveillance), suppressing tumor development. In the equilibrium phase, tumor clones that escape the elimination phase remain dormant, during which tumor growth does not occur but the immunogenicity of the tumor cells continues to be shaped by selective immune pressure. In the escape phase, tumor cell clones that are resistant to the immune system proliferate unchecked. Adapted with permission from Annu Rev Immunol 2011;29:235–271.
**Figure 1.** T cells are an important component of the antitumor immune response.

Abbreviation: APC, antigen-presenting cell.
FIGURE 1. Adaptive anticancer immunity. The adaptive anticancer immune response is initiated by immature DCs, which capture and process tumor antigens. DCs subsequently undergo maturation and migrate to tumor-draining lymph nodes, where they present tumor antigens within MHC molecules to naive T cells, triggering a protective T-cell response. T-cell activation requires interaction not only between the antigen–MHC complex on DCs and TCRs but also among an array of co-stimulatory molecules, including CD80/86 on DCs and the CD28 receptor on T cells. The adaptive anticancer immune response culminates with the infiltration of activated cytotoxic T cells into the tumor, killing cancer cells. DC, dendritic cell; MHC, major histocompatibility; TCR, T-cell receptor.
Incorporating Immune-Checkpoint Inhibitors into Systemic Therapy of NSCLC

Stéphane Champiat, MD, Ecaterina Ileana, MD, Giuseppe Giaccone, MD, PhD, Benjamin Besse, MD, PhD, Giannis Mountzios, MD, PhD, Alexander Eggermont, MD, PhD, and Jean-Charles Soria, MD, PhD
Tumor immunology and the PD-L1/PD-1 pathway.

CTLA-4 versus PD-1

Ribas, NEJM 2012
T cell immune checkpoints as targets for immunotherapy

- Agonistic antibodies directed towards activating co-stimulatory molecules

- Blocking antibodies against co-inhibitory molecules to enhance T-cell stimulation to promote tumor destruction
High rates of somatic mutations in lung cancer may contribute to increased immunogenicity.

Therapies targeting the PD-L1/PD-1 pathway will alter the treatment of NSCLC.

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Programmed Death-Ligand1 IHC in Lung cancer: in what state is this art?

FIGURE 1. Programmed death receptor-1 with its ligand (PDL-1) immunostaining performed using the E1LN3N clone anti-PD-L1 from Cell Signaling Technology (Boston) with standard detection techniques. A, Squamous cell carcinoma showing a strong, uniform positive reaction in tumor cells. B, Despite being negative in tumor cells in the center of the image, there is a positive reaction in macrophages and other immune cells in the tumor stroma. C, Most alveolar macrophages are positive for PD-L1. D, This adenocarcinoma is negative for PD-L1.

### TABLE 1. Immunotherapeutic Agents in Clinical Development for the Treatment of Advanced Non–Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkpoint inhibitors</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Fully human IgG4 monoclonal antibody directed against PD-1 on T cells</td>
</tr>
<tr>
<td>Pembrolizumab (MK-3475)</td>
<td>Humanized IgG4 monoclonal antibody directed against PD-1 on T cells</td>
</tr>
<tr>
<td>BMS-936559</td>
<td>Fully human IgG4 monoclonal antibody directed against PD-L1 on tumor cells</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>Human IgG1 monoclonal antibody directed against PD-L1 on tumor cells</td>
</tr>
<tr>
<td>MEDI4736</td>
<td>Fully human IgG1 monoclonal antibody directed against PD-L1 on tumor cells</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Fully human IgG1 monoclonal antibody directed against CTLA-4 on T cells</td>
</tr>
<tr>
<td>Liblumab (IPH2102)</td>
<td>Fully human monoclonal antibody directed against the killer-cell immunoglobulin-like receptor on NK cells</td>
</tr>
<tr>
<td>BMS-98016</td>
<td>Monoclonal antibody directed against the lymphocyte-activation gene 3 on tumor infiltrating lymphocytes</td>
</tr>
<tr>
<td>Vaccines</td>
<td></td>
</tr>
<tr>
<td>Tecemotide (liposomal BLP25)</td>
<td>Vaccine composed of the exposed core peptide of MUC-1</td>
</tr>
<tr>
<td>Racotumomab</td>
<td>Patient idiotype-specific vaccine against NGg GM3</td>
</tr>
<tr>
<td>TG4010</td>
<td>Vaccine that uses a recombinant vaccinia virus (modified virus of Ankara) that encodes for human MUC-1 and IL-2</td>
</tr>
<tr>
<td>Nonspecific immune stimulator</td>
<td></td>
</tr>
<tr>
<td>Talactoferrin alfa</td>
<td>Recombinant human lactoferrin</td>
</tr>
</tbody>
</table>

CTLA-4, cytotoxic T lymphocyte antigen-4; IgG, immunoglobulin G; IL-2, interleukin-2; MUC-1, mucin 1; NGg, N-glycolyl; NK, natural killer; NSCLC, non–small-cell lung cancer; PD-1, programmed death 1; PD-L1, programmed death ligand-1.

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Carbone, David P.; Gandara, David R.; Antonia, Scott J.; Zielinski, Christoph; Paz-Ares, Luis

Journal of Thoracic Oncology. 10(7):974-984, July 2015.1
Immunotherapy of Lung Cancer

TARGETING IMMUNE CHECK-POINT INHIBITORS

CTLA 4
PD1
PD-L1
CTLA 4 as Immune check-point inhibitor

- **CTLA 4**: Cytotoxic T-Lymphocyte-Associated Antigen 4
- Is acting the early phase of immune response
- Mostly in tumor draining lymph nodes
- At the Priming phase of Cytotoxic T cells
- Ipilimumab and Tremelimumab are 2 anti CTLA4 MoAbs
Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non–Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study

Thomas J. Lynch, Igor Bondarenko, Alexander Luft, Piotr Serwatowski, Fabrice Barlesi, Raju Chacko, Martin Sebastian, Joel Neal, Haolan Lu, Jean-Marie Cuillerot, and Martin Reck
Progression-free survival per immune-related response criteria (irPFS) and WHO criteria.
Kaplan-Meier plots for overall survival (OS).

A

B

Deaths/patients
Control 51/66
Phased Ipi 51/68

Median (95% CI), months
Control 8.28 (6.80 to 12.39)
Phased Ipi 12.22 (9.26 to 14.39)

HR (95% CI)
Control 0.87 (0.59 to 1.28)
Phased Ipi 0.23

No. at risk
Control 66 62 60 54 52 49 47 38 33 30 29 26 24 22 18 16 14 13 9 8 7 5 4 1 0 0
Phased Ipi 68 67 65 61 58 52 47 46 44 42 38 34 32 29 26 22 20 18 16 13 10 9 7 4 3 1 1 0

Deaths/patients
Control 51/66
Concurrent Ipi 51/70

Median (95% CI), months
Control 8.28 (6.80 to 12.39)
Concurrent Ipi 9.69 (7.59 to 12.48)

HR (95% CI)
Control 0.99 (0.67 to 1.46)
Concurrent Ipi 0.48

No. at risk
Control 66 62 60 54 52 49 47 38 33 30 29 26 24 22 18 16 14 13 9 8 7 5 4 1 0 0
Concurrent Ipi 70 66 61 56 51 47 45 42 39 35 32 31 27 22 21 19 18 16 14 8 7 5 4 1 0 0

Thomas J. Lynch et al. JCO 2012;30:2046-2054
Ipilimumab in Lung Cancer

- Ipilimumab (YERVOY®) is not approved in NSCLC
- Presently being evaluated also in SCLC
Targeting immune check-point inhibitors

<table>
<thead>
<tr>
<th>PD1-PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD1:</strong></td>
</tr>
<tr>
<td>Nivolumab (Opdivo®) <em>EMA approved</em></td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda®)</td>
</tr>
<tr>
<td><strong>PD-L1:</strong></td>
</tr>
<tr>
<td>MPDL3280A (Atezolizumab)</td>
</tr>
<tr>
<td>MEDI4736</td>
</tr>
</tbody>
</table>
Phase III, Randomized Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous (non-SQ) Cell Non-small Cell Lung Cancer (NSCLC)

Luis Paz-Ares,1 Leora Horn,2 Hossein Borghaei,3 David R. Spigel,4 Martin Steins,5 Neal E. Ready,6 Laura Q. Chow,7 Everett E. Vokes,8 Enriqueta Felip,9 Esther Holgado,10 Fabrice Barlesi,11 Martin Kohlhäufl,12 Óscar Arrieta,13 Marco Angelo Burgio,14 Jérôme Fayette,15 Scott N. Gettinger,16 Christopher T. Harbison,17 Cécile Dorange,17 Friedrich Graf Finckenstein,17 Julie R. Brahmer18

1Hospital Universitario Virgen Del Rocio, Sevilla, Spain; 2Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; 3Fox Chase Cancer Center, Philadelphia, PA, USA; 4Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; 5Thoraxklinik, Heidelberg University Hospital, Heidelberg, Germany; 6Duke University Medical Center, Durham, NC, USA; 7University of Washington, Seattle, WA, USA; 8University of Chicago Medicine & Biological Sciences, Chicago, IL, USA; 9Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; 10Hospital De Madrid, Norte Sanchinarro, Spain; 11Aix Marseille University; Assistance Publique Hôpitaux de Marseille, Marseille, France; 12Robert-Bosch-Krankenhaus, Gerlingen, Germany; 13Instituto Nacional De Cancerologia, Mexico City, Mexico; 14IRST IRCCS Meldola (Forlì - Cesena) Italy; 15Centre Léon Bérard, Lyon, France; 16Yale Comprehensive Cancer Center, New Haven, CT, USA; 17Bristol-Myers Squibb, Princeton, NJ, USA; 18The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Courtesy of L Paz-Ares ASCO 2015
CheckMate 057 (NCT01673867) Study Design

- Stage III/IV non-SQ NSCLC
- Pre-treatment (archival or recent) tumor samples required for PD-L1
- ECOG PS 0–1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed
  - Prior TKI therapy allowed for known ALK translocation or EGFR mutation
  - N = 582

Randomize 1:1

Nivolumab
3 mg/kg IV Q2W until PD or unacceptable toxicity
n = 292

• Primary Endpoint
  - OS
• Additional Endpoints
  - ORR
  - PFS
  - Safety
  - Efficacy by tumor PD-L1 expression
  - Quality of life (LCSS)

Docetaxel
75 mg/m² IV Q3W until PD or unacceptable toxicity
n = 290

• Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

PD-L1 expression measured using the Dako/BMS automated IHC assay
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

a Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); b Per RECIST v1.1 criteria as determined by the investigator.
**Progression-free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, mo</td>
<td>2.3</td>
<td>4.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.92 (95% CI: 0.77, 1.11); P = 0.3932</td>
<td></td>
</tr>
</tbody>
</table>

1-yr PFS rate = 19%

1-yr PFS rate = 8%

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>292</td>
<td>290</td>
</tr>
<tr>
<td>1-yr PFS rate</td>
<td>19%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Symbols represent censored observations.
Key results

- 18-month update showed median survival was unchanged (12.2 months with nivolumab vs. 9.4 months with docetaxel)
- OS rate at 18 months was higher with nivolumab than docetaxel (39% vs. 23%, HR 0.72 [95%CI 0.60, 0.88]; p=0.0009)
OS by PD-L1 Expression

≥1% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivo</th>
<th>Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (mo)</td>
<td>17.2</td>
<td>9.0</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.59 (0.43, 0.82)

<1% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivo</th>
<th>Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (mo)</td>
<td>10.4</td>
<td>10.1</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.90 (0.66, 1.24)

≥5% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivo</th>
<th>Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (mo)</td>
<td>18.2</td>
<td>8.1</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.43 (0.30, 0.63)

<5% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivo</th>
<th>Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (mo)</td>
<td>9.7</td>
<td>10.1</td>
</tr>
</tbody>
</table>

HR (95% CI) = 1.01 (0.77, 1.34)

≥10% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivo</th>
<th>Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (mo)</td>
<td>19.4</td>
<td>8.0</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.40 (0.26, 0.59)

<10% PD-L1 expression level

<table>
<thead>
<tr>
<th></th>
<th>Nivo</th>
<th>Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (mo)</td>
<td>9.9</td>
<td>10.3</td>
</tr>
</tbody>
</table>

HR (95% CI) = 1.00 (0.76, 1.31)

Symbols represent censored observations.
Summary

- Nivolumab is the first PD-1 inhibitor to significantly improve OS vs docetaxel in previously treated patients with advanced non-SQ NSCLC
  - 27% reduction in risk of death (HR = 0.73; \( P = 0.0015 \))
- Nivolumab significantly improved ORR vs docetaxel (\( P = 0.0246 \))
- PD-L1 expression is predictive of benefit with nivolumab, starting at the lowest expression level (1%)
  - Median OS nearly doubled with nivolumab vs docetaxel across PD-L1 expression continuum
  - No difference in OS seen when PD-L1 was not expressed in the tumor
  - ORR nearly tripled in PD-L1 expressors
- Safety profile of nivolumab was favorable vs docetaxel and consistent with prior studies
- CheckMate 057 is the second phase III trial to demonstrate superior survival of nivolumab over docetaxel in advanced NSCLC
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.
Kaplan–Meier Curves for Overall Survival.

Efficacy of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non–Small-Cell Lung Cancer.

Summary

- Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit versus standard-of-care docetaxel in previously-treated patients with advanced SQ NSCLC
  - 41% reduction in risk of death (HR 0.59; $P = 0.00025$)
  - 1-yr OS: 42% vs 24%
  - mOS: 9.2 vs 6.0 mo
- Nivolumab demonstrated superiority over docetaxel across all secondary efficacy endpoints
  - ORR: 20% vs 9% ($P = 0.0083$)
  - 1-yr PFS: 21% vs 6.4%; mPFS: 3.5 vs 2.8 mo (HR 0.62; $P = 0.0004$)
- Nivolumab benefit was independent of PD-L1 expression
- The safety profile of nivolumab was favorable versus docetaxel and consistent with prior studies
- Nivolumab received FDA approval in the US on March 4, 2015 for metastatic SQ-NSCLC with progression on or after platinum-based chemotherapy
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S.
PD-L1 Expression in Non–Small-Cell Lung Cancers.

< 1%

1-49%

> 50%

Progression-free Survival.

Overall Survival.

Table 1. Adverse Events in 495 Patients in the Treated Population.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Grade 3–5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>96 (19.4)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>53 (10.7)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>52 (10.5)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>48 (9.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>45 (9.1)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40 (8.1)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (7.5)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>34 (6.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>24 (4.8)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>21 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21 (4.2)</td>
<td>19 (3.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 (4.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>19 (3.8)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>18 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis†</td>
<td>18 (3.6)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Elevation in aspartate aminotransferase</td>
<td>15 (3.0)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (2.8)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Dermatitis acniform</td>
<td>13 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Elevation in alanine aminotransferase</td>
<td>11 (2.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Chills</td>
<td>10 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (2.0)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>15 (3.0)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

* Listed are events that were considered to be related to treatment by the investigator and were reported in at least 2% of patients.
† Included among patients with pneumonitis is one patient with grade 5 interstitial lung disease.
33LBA: Efficacy and Safety of Pembrolizumab (Pembro; MK-3475) for Patients (Pts) With Previously Treated Advanced Non-Small Cell Lung Cancer (NSCLC) Enrolled in KEYNOTE-001 – Soria JC et al

Study objective

- To evaluate the efficacy and safety of pembrolizumab in patients with previously treated NSCLC enrolled in KEYNOTE-001 study

Key patient inclusion criteria

- Previously treated NSCLC (n=449)

Pembrolizumab 10 mg/kg q3w

PD-L1+ & ≥1 previous therapy (n=280)

PD-L1- & ≥1 previous therapy (n=43)

PD-L1+ or PD

PD-L1+ & ≥2 previous therapies (n=33)

PD-L1+ & ≥1 previous therapy (n=55)

PD-L1- & ≥2 previous therapies (n=38)

33LBA: Efficacy and Safety of Pembrolizumab (Pembro; MK-3475) for Patients (Pts) With Previously Treated Advanced Non-Small Cell Lung Cancer (NSCLC) Enrolled in KEYNOTE-001 – Soria JC et al

Key results
- Survival outcomes in patients treated with pembrolizumab 10 mg/kg are shown below

<table>
<thead>
<tr>
<th>TPS Score</th>
<th>OS Median (95%CI)</th>
<th>OS 6-month rate, %</th>
<th>PFS Median (95%CI)</th>
<th>PFS 6-month rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS ≥50% (n=99)</td>
<td>15.5 (10.0, NR)</td>
<td>71.6</td>
<td>5.8 (2.1, 10.3)</td>
<td>49.9</td>
</tr>
<tr>
<td>TPS 1–49% (n=127)</td>
<td>7.8 (5.8, 12.4)</td>
<td>57.3</td>
<td>2.3 (2.1, 3.4)</td>
<td>25.5</td>
</tr>
<tr>
<td>TPS &lt;1% (n=68)</td>
<td>8.6 (5.5, 12.0)</td>
<td>57.1</td>
<td>2.1 (2.0, 4.0)</td>
<td>23.2</td>
</tr>
<tr>
<td>Total (n=394)</td>
<td>11.3 (8.8, 14.0)</td>
<td>63.0</td>
<td>3.0 (2.2, 4.0)</td>
<td>34.0</td>
</tr>
</tbody>
</table>

Among patients treated at 10 mg/kg, median duration of response was greatest for those who had TPS score ≥50% (23.3 months; range 2.1–23.3) compared with TPS 1–49% (12.5; 9.9–12.5) and TPS <1% (NR; 1.0, 15.6)

Conclusions
- Treatment with pembrolizumab was associated with a robust, durable antitumour response in patients with previously treated advanced NSCLC
  - Patients with PD-L1 TPS ≥50% had the greatest response and faster time to response
  - As a result of similar safety and efficacy outcomes for doses 2–10 mg/kg, the dose of 2 mg/kg q3w appears to be the optimal dose in NSCLC

Conclusions

- Pembrolizumab had an acceptable side-effect profile and showed antitumor activity in patients with advanced non–small-cell lung cancer.

- PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab.
Anti PD-L1 Antibodies
Atezolizumab and MEDI4736

- **Less advanced in their development**

- **POPLART Trial** *(ASCO 2015? ESMO/ECCO 2015)*
  - 2nd-3rd line Atezolizumab vs. Docetaxel n=287 patients
  - Predictive score on PD-L1 expression on IC or TC
  - Good correlation between score OS, PFS and RR

- **MEDI4736**
  - Ongoing trial vs. Placebo late line
  - Preliminary results only in early phase trials
    - No correlation with PD-L1 expression.
14LBA: Atezolizumab monotherapy vs docetaxel in 2L/3L non-small cell lung cancer: Primary analyses for efficacy, safety and predictive biomarkers from a randomized phase II study (POPLAR) – Vansteenkiste J et al

Study objective
A phase 2 study to examine the efficacy and safety of atezolizumab in patients with advanced NSCLC

Key patient inclusion criteria
- Metastatic or locally advanced NSCLC
- Second- or third-line
- Disease progression on a prior platinum therapy
(n=287)

Primary endpoint
- OS in ITT and PD-L1 expression subgroups

Secondary endpoints
- PFS, ORR and DOR in ITT and PD-L1 expression subgroups
- Safety

Stratification
- PD-L1 IC expression (0 vs. 1 vs. 2 vs. 3)
- Histology (squamous vs. non-squamous)
- Prior chemotherapy regimens (1 vs. 2)

Randomization
1:1

Atezolizumab
1200 mg IV q3w
(n=144)

Until loss of clinical benefit

Docetaxel
75 mg/m² IV q3w
(n=143)

PD
PD-L1 Expression on TC and IC is a Potential Predictive Biomarker for Atezolizumab in NSCLC

- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC
- Distinct TC and IC sub-populations exist at each of four cutoff levels (Gettinger et al., ASCO 2015)
- PD-L1 expression on TC and IC was independently predictive of response (Horn et al. and Spigel et al., ASCO 2015)

TC0 and IC0
TC1/2/3 and IC1/2/3
TC2/3 and IC2/3
TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+, respectively.

Spira I.A. et al J Clin Oncol 33, 2015 (suppl; abstr 8010)
Key results
- Atezolizumab was associated with significant improvements in OS in the ITT population
  - Median OS for atezolizumab was 12.6 months compared with 9.7 months for docetaxel (HR 0.73 [95%CI 0.53, 0.99], p=0.040)
  - OS was greater in patients with higher PD-L1 expression
16LBA: Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1-selected non-small cell lung cancer (NSCLC) – Besse B et al

Study objective

- To assess the efficacy and safety of atezolizumab in cohorts of patients with locally advanced or metastatic NSCLC who had or had not received prior treatment

Key patient inclusion criteria

- Locally advanced or metastatic NSCLC
- Tumor PD-L1 expression by IHC (TC2/3 and/or IC2/3)
- ECOG PS 0–1
- No brain mets (n=667)

Cohort 1 (first-line)
No prior chemotherapy (n=142)

Cohort 2 (second-line)
1 prior platinum chemotherapy (n=271)

Cohort 3 (≥third-line)
≥2 prior chemotherapies (incl. 1 platinum) (n=39)

Primary endpoint
- ORR

Secondary endpoints
- PFS, DOR, OS, safety

16LBA: Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1-selected non-small cell lung cancer (NSCLC) – Besse B et al

- **Key results**
  - The majority of responses are ongoing
  - Median DOR was 7 months for ≥third-line and not reached for both first- and second-line in TC3 or IC3

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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
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
  - Change in tumour size from baseline by pre-treatment IFNγ mRNA/PD-L1 status is shown below

n=all patients with baseline and ≥1 follow-up scan; n-=number of patients with tumour shrinkage

Immunotherapy of Lung Cancer

- After years of failure, immunotherapy resuscitated in lung cancer
- Immune check-point inhibition with confirmed data
- More to come in early metastatic lines or stage and combination

- Just the beginning of it...
- May as well explain why vaccines have failed