NON-SMALL CELL LUNG CANCER
ESMO PRECEPTORSHIP SINGAPORE 15-16/11/2017

Immunotherapy in NSCLC

Name
Jean-Yves DOUILLARD MD, PhD
ESMO Chief Medical Officer
IMMUNOTHERAPY FOR NSCLC

- Immunotherapy in the treatment has been developed for the past 50 years...without success
  - Lots of it were non-specific immuno-stimulation, vaccines
  - Documented immune response occurred
  - ...but without clinical impact

- For the past 15 years, better understanding of anti-tumour immunology and immune-escape have allowed manipulation of the immune response and of the tumour micro-environment leading to an improve efficacy of cancer immunotherapy, dominated the use of Immune Check Point Inhibitors.

- Its application in several solid tumour has been successful and has been practice changing, including in NSCLC
Fig 1. The cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitory checkpoint pathway is important in regulating early T-cell activation. It competes with the costimulatory receptor CD28 for their common ligands, CD80 and CD86. CTLA-4 receptor is only expressed on T cells. CD80 and CD86 are expressed on antigen-presenting cells (APCs). The programmed cell death-1 (PD-1) inhibitory pathway is important in regulating T-cell responses to inflammation or infection. The PD-1 receptor, which can be expressed on T cells, B cells, or natural killer (NK) cells, binds to its ligands, either PD-L1 or PD-L2. PD-L1 can be expressed both on APCs or tumor cells. The major histocompatibility complex binds to the T-cell receptor (MHC-TCR complex) to deliver the first signal, antigen recognition, to stimulate T-cell activation.
Figure 1 Ligand–receptor interactions between tumour cells and immune cells in the tumour microenvironment

Table 1. Pathways that tumors may exploit to escape the immune system

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Role of the tumor and immune effects[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Interaction of CD80/86 on APCs with CTLA-4 on T cells, inhibits T-cell costimulation, suppressing T-cell activation [18, 21]</td>
</tr>
<tr>
<td>PD-1</td>
<td>Expression of PD-1 ligands (PD-L1/PD-L2) by tumor cells binds to PD-1 on T cells and other immune cells, inhibiting their activity [19]</td>
</tr>
<tr>
<td>Other T-cell checkpoint and activation pathways</td>
<td>Tumors may act through a range of direct and indirect mechanisms to dysregulate other checkpoint and activating pathways involved in T-cell regulation (e.g., LAG-3, TIM-3 [inhibitory]; CD137, OX-40, CD40 [activating]) [18]</td>
</tr>
<tr>
<td>KIRs</td>
<td>NK cells have inhibitory and activating receptors that engage MHC I molecules; tumor cells that maintain MHC I expression may escape NK cell detection and killing [20]</td>
</tr>
<tr>
<td>FAS/FAS ligand</td>
<td>Expression of FAS ligand by tumor cells can kill activated T cells expressing FAS (induction of FAS-mediated cell death; similar role observed for TRAIL/TRAIL ligand) [22]</td>
</tr>
</tbody>
</table>

Figure 3. Checkpoint and activating receptors on T cells are targets for immunotherapy. From [17] with permission from Macmillan Publishers Ltd.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>1st line treatment</th>
<th>2nd and later lines treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVOLUMAB (Nivolumab®) Anti PD-1 IgG4</td>
<td>Not approved (FDA/EMA)</td>
<td>APPROVED (FDA/EMA)</td>
</tr>
<tr>
<td></td>
<td>No testing required 3mg/kg Q 2w</td>
<td></td>
</tr>
<tr>
<td>PEMBROLIZUMAB (Keytruda®) Anti PD-1 IgG4</td>
<td>APPROVED All histologies (FDA/EMA) PD-L1 TPS&gt;50% 200mg Q3w Testing: Pharma DX 22C3 As single agent</td>
<td>APPROVED All histologies (FDA/EMA) PD-L1 TPS&gt;1% PD-L1 TPS&gt;1% 200mg Q3w (FDA) 2mg/kg q 3w (EMA)</td>
</tr>
<tr>
<td></td>
<td>In combination with Chemotherapy (Pem-Carbo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AND (by FDA only)</td>
<td>As single agent</td>
</tr>
<tr>
<td>ATEZOLIZUMAB (Tecentriq®) Anti PD-L1 IgG1</td>
<td>Not approved (FDA/EMA)</td>
<td>APPROVED All histologies (FDA/EMA)</td>
</tr>
<tr>
<td></td>
<td>No testing required 1200mg Q 3w</td>
<td></td>
</tr>
</tbody>
</table>
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

The checkmate studies 017 (Squamous) and 027 (Non-squamous)

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

BRAHMERJ ET AL. N ENGL J MED 2015;373:123-135

BORGHAEI H ET AL. N ENGL J MED 2015;373:1627-1639
Nivolumab vs. Docetaxel: OS according to PD-L1 staining

A

B

C

Published in: Leora Horn; David R. Spigel; Everett E. Vokes; Esther Holgado; Neal Ready; Martin Steins; Elena Poddubskaya; Hossein Borghaei; Enriqueta Felip; Luis Paz-Ares; Adam Pluzanski; Karen L. Reckamp; Marco A. Burgio; Martin Kohlhäufel; David Waterhouse; Fabrice Barlesi; Scott Antonia; Oscar Arrieta; Jérôme Fayette; Lucio Crinò; Naiyer Rizvi; Martin Reck; Matthew D. Hellmann; William J. Geese; Ang Li; Anne Blackwood-Chirchir; Diane Healey; Julie Brahmer; Wilfried E.E. Eberhardt; JCO Ahead of Print DOI: 10.1200/JCO.2017.74.3062 Copyright © 2017 American Society of Clinical Oncology

Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057)

Leora Horn, David R. Spigel, Everett E. Vokes, Esther Holgado, Neal Ready, Martin Steins, Elena Poddubskaya,
PEMBROLIZUMAB IN 1ST LINE NSCLC: KEYNOTE 024

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

- All histologies (18% SQ)
- TPS ≥ 50%
- Brain met 9%
- Never smoker 6%

44% crossed over to Pembrolizumab at PD

PEMBROLIZUMAB + CARBO-PEMETREXED IN 1ST LINE NSCLC: KEYNOTE 021

**KEYNOTE-021 Cohort G**

**Study Population**
- Untreated stage IIIB or IV nonsquamous NSCLC
- No activating EGFR mutation or ALK translocation
- Provision of a sample for PD-L1 assessment
- ECOG PS 0 or 1
- No untreated brain metastases
- No IILD or pneumonitis requiring systemic steroids

**End Points**
- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS
- No alpha allocated for updated analysis; all P values are nominal (one-sided P < 0.025)

### Objective response

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab plus chemotherapy (N=60)</th>
<th>Chemotherapy (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%) (95% CI)</td>
<td>33 (55%; 42–68)</td>
<td>18 (29%; 18–41)</td>
</tr>
<tr>
<td>Estimated % difference (95% CI)</td>
<td>26% (9–42)</td>
<td>..</td>
</tr>
<tr>
<td>p value</td>
<td>0.0016</td>
<td>..</td>
</tr>
</tbody>
</table>

### Smoking status

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Pembrolizumab plus chemotherapy (N=60)</th>
<th>Chemotherapy (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current or former smoker</td>
<td>45 (75%)</td>
<td>54 (86%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>15 (25%)</td>
<td>9 (14%)</td>
</tr>
</tbody>
</table>

### Stable brain metastases

<table>
<thead>
<tr>
<th>Stable brain metastases</th>
<th>Pembrolizumab plus chemotherapy (N=60)</th>
<th>Chemotherapy (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (15%)</td>
<td>6 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

### PD-L1 TPS

<table>
<thead>
<tr>
<th>PD-L1 TPS</th>
<th>Pembrolizumab plus chemotherapy (N=60)</th>
<th>Chemotherapy (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>21 (35%)</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>1-49%</td>
<td>19 (32%)</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>≥50%</td>
<td>20 (33%)</td>
<td>17 (27%)</td>
</tr>
</tbody>
</table>

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

- Median (95% CI): 19.3 (8.5–NR) vs 8.9 (2.2–11.6)

### Overall Survival

- Pembrolizumab + PC: 20/60 (0.59; 0.34–1.05) with P = 0.03
- PC alone: 31/63 (0.77; 0.49–1.30)

Corey C Langer et al The Lancet Oncol 2016, 17: 11 1497
Hossein Borghaei updated ESMO Madrid 09/2017
Pembrolizumab versus docetaxel, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Primary End-Point OS and PFS

- All histologies (20% SQ)
- TPS > 50% = 43%
- TPS 1-49% = 57%
- Brain met 15%
- Never smoker 18%

Herbst R et al  
ATEZOLIZUMAB IN 2ND LINE NSCLC: THE OAK STUDY

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3 open-label, multicentre randomised controlled trial

Co Primary End-Point OS and PD-L1 expression by T/C score

- All histologies (26% S)
- Never smoker 18%

### PD-L1 subgroups

<table>
<thead>
<tr>
<th>T/C or I/C</th>
<th>Count</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>72 (17%)</td>
<td>89</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>129 (30%)</td>
<td>103</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>241 (57%)</td>
<td>103</td>
</tr>
<tr>
<td>TC0 and ICO</td>
<td>180 (42%)</td>
<td>89</td>
</tr>
<tr>
<td>ITT</td>
<td>850 (100%)</td>
<td>96</td>
</tr>
</tbody>
</table>

Study Flowchart
Eleven randomized clinical trials were added to the original analysis of 14 trials.
IMMUNOTHERAPY OF LUNG CANCER

More Immune Check Point in evaluation

❖ Atezolizumab + Paclitaxel-Carbo + Bevacizumab vs. Paclitaxel-Carbo + Bev: the Impower 150 trial
  ❖ Phase III in Non-squamous NSCLC 1st line (to be presented at ESMO IO meeting Dec 2017)

❖ Avelumab: Human IgG1 MoAb anti PD-L1 (Merck KGA/Pfizer)
  ❖ JAVELIN Lung 100 in 1st line NSCLC (PD-L1+ NSCLC) vs. Chemo

❖ Durvalumab: Human IgG1 MoAb anti PD-L1 (AstraZeneca)
  ❖ PACIFIC trial in unresectable stage III NSCLC
  ❖ MYSTIC trial Durvalumab, Durvalumab-Tremelimumab* vs SOC 1st line
  ❖ NEPTUNE trial Durvalumab-Tremelimumab vs Chemo 1st-line
  ❖ ARCTIC trial Durvalumab (PD-L1+), Durvalumab-Tremelimumab (PD-L1-) vs SOC 3rd line
  ❖ ADJUVANT Durvalumab vs Placebo in resected NSCLC

* Tremelimumab: Anti-CTLA-4 MoAb
PACIFIC TRIAL
A breakthrough in local advanced stage III NSCLC

- Patients with stage III, locally advanced, unresectable NSCLC, no PD after cCRT
- All-comers population

1–42 days post-cCRT
2:1 randomization, stratified by age, sex, and smoking
N=713

Co-primary endpoints
- PFS by BICR using RECIST
- OS

Key secondary endpoints
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

2:1 randomization,
stratified by age,
sex, and smoking
N=713

PFS HR, 0.52
Two-sided P<0.0001

Median PFS months
Durvalumab (N=476) 16.8
Placebo (N=237) 5.6
12-month PFS
55.9%
35.3%
18-month PFS
44.2%
27.0%

HR, 0.52
Two-sided P<0.0001

Median,months
Durvalumab 23.2 (23.2–NR)
Placebo 14.6 (10.6–18.6)

L. Paz-Ares ESMO Madrid 2017 and SJ. Antonia et al NEJM on line Sept 8th 2017
First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer

**Checkmate 026**

**MYSTIC Trial**

Durvalumab vs Durvalumab+Tremelimumab vs. SOC 1st line

1st Primary end-point of PFS > SOC for Durva+Treme not met in PD-L1 > 25%

2nd Primary end-point of Durva > SOC not met

The trial continues to assess OS

IMMUNOTHERAPY OF NSCLC: THE FAILURES

Ipilimumab

Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non–Small-Cell Lung Cancer
2016

SOC replacements: elimination of chemotherapy for SOC regimens

Immune profiling: patient selection to predict benefit

New technologies: expansion of the therapeutic toolbox

Future

Substantial survival improvements across wide populations

Improved end points: accelerate development

Complex combinations: maximise efficacy

Cure
IMMUNOTHERAPY OF NSCLC

Points to be considered

❖ Patients selection
❖ Duration of treatment
❖ Tolerance and toxicity management
❖ Cost and sustainability
PD-L1 expression on tumour cells is evaluated by IHC

The antibody used for testing varies according to the antibody used for treatment

Other predictive biomarkers are not readily evaluable (immune gene profile, TILs, Tumour Mutation Burden…)

<table>
<thead>
<tr>
<th>Antibody clone</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Atezolizumab</th>
<th>Durvalumab</th>
<th>Avelumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay developer</td>
<td>Dako&lt;sup&gt;5,25&lt;/sup&gt;</td>
<td>Ventana&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Dako&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>Ventana&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Dako&lt;sup&gt;95&lt;/sup&gt;</td>
</tr>
<tr>
<td>PD-L1 immunohistochemistry scoring&lt;sup&gt;*&lt;/sup&gt;</td>
<td>TC</td>
<td>TC</td>
<td>TC</td>
<td>TC and/or tumor-infiltrating IC</td>
<td>TC</td>
</tr>
<tr>
<td>PD-L1 levels evaluated in clinical trials</td>
<td>TC: ≥ 1%, ≥ 5%, ≥ 10%&lt;sup&gt;5&lt;/sup&gt;</td>
<td>TC: ≥ 1%, ≥ 5%, ≥ 10%&lt;sup&gt;5&lt;/sup&gt;</td>
<td>TC: ≥ 1%, ≥ 50%&lt;sup&gt;22&lt;/sup&gt;</td>
<td>TC: ≥ 1%, ≥ 50%&lt;sup&gt;22&lt;/sup&gt;</td>
<td>TC: ≥ 60% (TC3)† IC: ≥ 10% (IC3)†&lt;sup&gt;6,16&lt;/sup&gt;</td>
</tr>
<tr>
<td>PD-L1 level in first-line therapy</td>
<td>NA</td>
<td>NA</td>
<td>TC ≥ 50%</td>
<td>TC ≥ 60%</td>
<td>NA</td>
</tr>
<tr>
<td>PD-L1 level in second-line therapy</td>
<td>None</td>
<td>None</td>
<td>TC ≥ 1%</td>
<td>TC ≥ 1%</td>
<td>None</td>
</tr>
<tr>
<td>Approved IVD PD-L1 expression levels</td>
<td>US/EU/Japan: all patients eligible</td>
<td>EU: all patients eligible</td>
<td>US/EU/Japan: ≥ 50% (previously untreated); ≥ 1% (previously treated)</td>
<td>US/EU: all patients eligible</td>
<td>Not available for NSCLC</td>
</tr>
</tbody>
</table>

Abbreviations: IC, immune cells; IVD, in vitro diagnostic; NA, not applicable; NSCLC, non-small-cell lung cancer; NSO, non-squamous; PD-L1, programmed death-ligand 1; SQ, squamous; TC, tumor cells.

*All assays score cells at any intensity.
†TC0 < 1%, TC1 1% to < 5%, TC2 5% to < 50%, TC3 ≥ 50%, IC0 < 1%, IC1 1% to < 5%, IC2 5% to < 10%, IC3 ≥ 10%.
Multicenter Comparison of 22C3 PharmDx (Agilent) and SP263 (Ventana) Assays to Test PD-L1 Expression for NSCLC Patients to Be Treated with Immune Checkpoint Inhibitors

Antonio Marchetti, MD, PhD, a,b Massimo Barberis, MD, b Renato Franco, MD, c

Figure 3. Scatter diagrams illustrating the correlation between the programmed death ligand 1 immunohistochemical 22C3 pharmDx test (22C3) and in vitro diagnostics Ventana programmed death ligand 1 (SP263) expression levels in each of the four centers. See the text for details.
IMMUNOTHERAPY OF NSCLC: RESPONSE EVALUATION

- Conventional Response Evaluation Criteria may not be adapted to immunotherapy
  - WHO, RECIST
- Mechanisms of action of CPI include local interaction between Immune cells and Tumour cells
- Increase in target size may not always reflect Progressive disease
- Pseudo-Progression is a new terminology, reflecting the increase in target size due to local infiltration of the tumour with Activated T cells as a result of immune reaction

Images from Nishino M et al. Nat Rev Clin Oncol Nov 2017
Table 1 | Summary of the response assessment strategy using different criteria

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Bidimensional approach</th>
<th>Unidimensional approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement</td>
<td>LD x SD (cm²)</td>
<td>LD x SD (cm²)</td>
</tr>
<tr>
<td>Criteria for PR *</td>
<td>≥50% decrease</td>
<td>≥50% decrease</td>
</tr>
<tr>
<td>Criteria for PD *</td>
<td>≥25% increase, new lesion, or non-target PD</td>
<td>≥25% increase</td>
</tr>
<tr>
<td>New lesions</td>
<td>Define PD</td>
<td>Do not define PD</td>
</tr>
<tr>
<td>Confirmation of PD</td>
<td>Not needed</td>
<td>Required on a consecutive scan (at least 4 weeks later)</td>
</tr>
</tbody>
</table>

*The percent change is calculated in comparison with the measurements at baseline. **The percent change is calculated in comparison with the measurements at the nadir (smallest tumour burden since baseline). LD, longest diameter; PD, progressive disease; PR, partial response; SD, short-axis diameter (longest perpendicular diameter).

IMMUNOTHERAPY OF NSCLC: DURATION OF TREATMENT

CHECKMATE 153: RANDOMIZED RESULTS OF CONTINUOUS VS 1-YEAR FIXED-DURATION NIVOLUMAB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

David R. Spigel, MPH1, Michael McCleod, MD2, Maen A. Hussein, MD3, David M. Waterhouse, MD4

- 220 patients on treatment at 1 year
- 1,245 patients treated

Efficacy analyses:
- Continuous nivolumab: 76 had response or SD at randomization
- Stop nivolumab: 87 had response or SD at randomization

Graphs showing PFS and OS over time with continuous and 1-year nivolumab treatment, including HR values and 95% CIs.
The tolerance profile on Immune check points inhibitors is quite different from conventional chemotherapy.

- Acute, during infusion side effects are rare but infusion reaction may occur (1-3%).
- Most of the side effect are immune mediated and are reversible.
- Immune mediated reaction are not dose-related.
IMMUNOTHERAPY OF NSCLC: TOLERANCE AND MANAGEMENT OF TOXICITIES

Figure 2: The most common adverse events in patients treated with ipilimumab, pembrolizumab, nivolumab, or ipilimumab plus nivolumab.

Figure 3: Adverse events of special interest noted with immune-checkpoint inhibitors.
Main toxicities occurrence with immune check-points inhibitors

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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**Adverse Events**

**Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057)**

Leora Horn, David R. Spigel, Everett E. Vokes, Esther Holgado, Neal Ready, Martin Steins, Elena Poddubskaya, Hossein Borghaei, Enriqueta Felip, Luis Paz-Ares, Adam Pluzanski; Karen L. Reckamp; Marco A. Burgio; Martin Kohlhäufel; David Waterhouse; Fabrice Barlesi; Scott Antonia; Oscar Arrieta; Jérôme Fayette; Lucio Crinò; Naiyer Rizvi; Martin Reck; Matthew D. Hellmann; William J. Geese; Ang Li; Anne Blackwood-Church; Diane Healey; Julie Brahmer; Wilfried E.E. Eberhardt; JCO Ahead of Print

DOI: 10.1200/JCO.2017.74.3062

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CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen¹, F. Carbonnel², C. Robert³, K. M. Kerr⁴, S. Peters⁵, J. Larkin⁶ & K. Jordan⁷, on behalf of the ESMO Guidelines Committee*
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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IMMUNOTHERAPY OF LUNG CANCER

Unanswered Questions

- Is this treatment sustainable?
  - Ever increasing costs put the Health Care Systems at risk
  - Equal access to best treatment is compromised

- What is the real long term benefit?
  - In metastatic lung cancer
  - In locally advanced stage III
  - In adjuvant setting
Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057)

Lunin Horn, David R. Spigel, Everett E. Vokes, Esther Holgado, Neal Ready, Martin Steins, Elena Poddubskaya,

Published in: Leora Horn; David R. Spigel; Everett E. Vokes; Esther Holgado; Neal Ready; Martin Steins; Elena Poddubskaya; Hossein Borghaei; Enriqueta Felip; Luis Paz-Ares; Adam Pluzanski; Karen L. Reckamp; Marco A. Burgio; Martin Kohlhäeufl; David Waterhouse; Fabrice Barlesi; Scott Antonia; Oscar Arrieta; Jérôme Fayette; Lucio Crinò; Naiyer Rizvi; Martin Reck; Matthew D. Hellmann; William J. Geese; Ang Li; Anne Blackwood-Chirchir; Diane Healey; Julie Brahmer; Wilfried E.E. Eberhardt; JCO Ahead of Print
DOI: 10.1200/JCO.2017.74.3062
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ARE IMMUNE CHECK POINT INHIBITORS SUSTAINABLE?

- Expensive drugs:
  - Nivolumab (3mg/kg Q 2w) \(\approx 30$/mg \) Adult 70kg, cost 6300$ Q 2w 3m tt: 37 800$, 12m tt: 151 200$
  - Pembrolizumab (200mg fixed dose Q 3w) cost 8632$ Q 3w 3m tt: 34 528$, 12m tt: 138 112$

- Long treatment duration:
  - \(\approx 50\%\) without progression at 18 months (Pembro 1\textsuperscript{st}-line)
  - \(\approx 12\text{-}16\%\) without progression at 24 months (Nivo 2\textsuperscript{nd} line)
  - Treatment continuation after 1 year is of proven benefit

- Cost evaluation in France
  - 45 000 cases (year 2015), estimated 28 000 stage IV mNSLC eligible to treatment
  - PD-L1 TPS > 50% 9000 pts
  - If all of them receive at least 7m of Pembro 1\textsuperscript{st} line: cost \(\approx 726\ M\$\)
ARE IMMUNE CHECK POINT INHIBITORS SUSTAINABLE?

- Expensive drugs:
  - Nivolumab per month
  - Pertuzumab per month

- Long treatment duration:
  - \( \approx 50\% \) without progression at 18 months (Pembro 1st line)
  - \( \approx 12-16\% \) without progression at 24 months (Nivo 2nd line)
  - Treatment continuation is of proven benefit
IMMUNOTHERAPY IN NSCLC

Conclusion

- Immunotherapy is now established in the treatment of mNSCLC independent of histology
- Tolerance profile is better than with conventional chemotherapy
- Objective Responses have to be properly evaluated
  - Patient selection remains unclear
- Long-lasting disease control may be observed
- Accessibility and sustainability of ICI treatment are remaining issues
- Other promising immune pathway are presently explored.