G Bootsma
Immunotherapie
Immunotherapie:

18:00 – 18:25 uur
Immunotherapie
Dr. Gerben Bootsma, longarts, Zuyderland MC

18:25 – 18:50 uur
SCLC / mesothelioom
Dr. Ben van den Borne, longarts, Catharina ziekenhuis

18:50 – 19:15 uur
RT en combinatie immunotherapie
Prof. dr. Dirk de Ruysscher, radiotherapeut-oncoloog
MAASTRO Clinic
Immunotherapie:

18:00 – 18:25 uur

Immunotherapie
Dr. Gerben Beek

18:25 – 18:50 uur

RT en combinatie immunotherapie
Prof. dr. Dirk de Ruysscher, radiotherapeut-oncoloog
MAASTRO Clinic
Immunotherapie in vroege stadia
Waiting for IMMUNOTHERAPY in EARLY STAGE

**ADJUVANT setting**

- **PEARLS**
  - NCT02564372
  - N=1040
  - Pembrolizumab: 100 mg Q3W for 1 year
  - Placebo
  - End Point: DFS

- **BR31**
  - NCT02273373
  - N=1340
  - Durvalumab: 10 mg/kg Q2W for 1 year
  - Placebo
  - End Point: DFS in PD-L1+ and DFS overall

- **AIIWIL**
  - NCT02595944
  - N=923
  - Nivolumab: 240 mg Q2W for 1 year
  - Observation
  - End Point: DFS & OS

- **IMPower 010**
  - NCT0436718
  - N=1280
  - Atezolizumab: 1200 mg Q3W for 1 year
  - Observation
  - End Point: DFS in II-IIIA, DFS in PD-L1+ in II-IIIA, DFS in ITT

**Neo-ADJUVANT setting**

- Top trials:
  - TOP 1501 (NCT02813820)
  - PRINCEPS (NCT02994576)
  - KN617 (NCT03425643)
  - CM1815 (NCT02998528)
  - IMPower 130 (NCT03456063)
  - AEgEAN (NCT03800134)
Stadium III NSCLC adjuvant IT

Dirk..
Figure 3. Updated OS in the ITT population

<table>
<thead>
<tr>
<th></th>
<th>No. of events/total no. of patients (%)</th>
<th>Median OS (95% CI) months</th>
<th>12-month OS rate (95% CI) %</th>
<th>24-month OS rate (95% CI) %</th>
<th>36-month OS rate (95% CI) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab</td>
<td>210/476 (44,1)</td>
<td>NR (38,4–NR)</td>
<td>83,1 (79,4–86,2)</td>
<td>66,3 (61,8–70,4)</td>
<td>57,0 (52,3–61,6)</td>
</tr>
<tr>
<td>Placebo</td>
<td>194/237 (56,5)</td>
<td>29,1 (22,1–35,1)</td>
<td>74,5 (69,5–79,7)</td>
<td>55,3 (49,6–61,4)</td>
<td>45,5 (37,0–49,0)</td>
</tr>
</tbody>
</table>

Stratified hazard ratio for death, 0,69 (95% CI, 0,55–0,86)
Stratified hazard ratio for death from the primary analysis, 0,68 (95% CI, 0,53–0,87)

*Updated subgroup analysis of OS is presented in Figure 4 and was consistent with that reported at the time of the primary OS.*
1457PD: Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – Results from the European Thoracic Oncology Platform (ETOP 6-14) NICOLAS phase II trial – Peters S, et al

- **Study objective**
  - To evaluate the efficacy of nivolumab combined with 1L concurrent chemoradiotherapy in patients with unresectable locally advanced NSCLC

**Key patient inclusion criteria**
- Unresectable locally advanced stage IIIA/B NSCLC
- Nodal status N2 or N3
- ECOG PS 0–1 (n=79)

**Primary endpoints**
- Grade ≥3 pneumonitis-free rate, 1-year PFS rate

**Secondary endpoints**
- Time to first grade ≥3 pneumonitis, ORR, OS, time-to-treatment failure, safety

**Platinum-based chemotherapy** + radiotherapy
- 66 GY/33 fractions for 3 cycles + 4 doses nivolumab 360 mg q3w

**Nivolumab** 480 mg q4w up to 1 year

*Cisplatin + vinorelbine/etoposide/pemetrexed

**Key results**

### PFS: Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>PFS events, n (%)</th>
<th>12-mo PFS, % (95%CI)</th>
<th>Median, months (95%CI)</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>13 (46.4)</td>
<td>66.3 (45.2, 88.9)</td>
<td>27.4 (7.3, NE)</td>
<td>0.11</td>
</tr>
<tr>
<td>IIIB</td>
<td>33 (66.0)</td>
<td>50.0 (35.6, 62.8)</td>
<td>12.1 (8.9, 17.8)</td>
<td></td>
</tr>
</tbody>
</table>

### PFS: Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>PFS events, n (%)</th>
<th>12-mo PFS, % (95%CI)</th>
<th>Median, months (95%CI)</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQ</td>
<td>19 (67.9)</td>
<td>56.3 (35.9, 72.3)</td>
<td>13.5 (10.1, 22.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>NSQ</td>
<td>26 (55.3)</td>
<td>54.5 (39.1, 67.5)</td>
<td>12.9 (7.2, NE)</td>
<td></td>
</tr>
</tbody>
</table>

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1457PD: Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – Results from the European Thoracic Oncology Platform (ETOP 6-14) NICOLAS phase II trial – Peters S, et al

• Key results (cont.)
  – Overall, pneumonitis was reported by 34 patients (7 grade 3, 1 grade 5), oesophagitis by 24 patients (5 grade 3) and dyspnoea by 27 patients (2 grade 3)
  – In total, 240 nivolumab TRAEs were reported; 26 grade 3, 5 grade 4 and 4 grade 5 (colitis, pulmonary fibrosis, autoimmune disorder, pneumonitis). Of these, 7% (17/240 TRAEs) led to permanent discontinuation

• Conclusions
  – In patients with unresectable locally advanced NSCLC combining nivolumab with concurrent chemoradiation is feasible, without any unexpected safety signal
  – The PFS observed for combining nivolumab with concomitant definitive chemoradiation as 1L therapy compares favourably to other studies in the same patient population
Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – NICOLAS phase II trial.

S. Peters et al, ESMO 1457PD

Primary endpoints:
- Pneumonitis-free rate of grade ≥ 3 (CTCAE V4.0) any time during 6 months post radiotherapy.
- Hierarchically tested: 1-year progression-free survival (PFS) (from chemotherapy start)

Hierarchical design: IF safety proven → Efficacy evaluation:
- 1-year PFS, sample size n=74
- \( H_0: \text{PFS}_0 \leq 45\% \) vs \( H_1: \text{PFS}_1 > 60\% \) (1-sided alpha=5%, power=83%)
- Success rule: at least 41 patients reach 1-year without PFS event (i.e., maximum 33 PFS events)

Authors Conclusions
- Based on the formal hierarchical efficacy analysis, we cannot reject the null hypothesis of 1-year PFS rate ≤45% versus 60% (p=0.23).
- Overall (N=79 patients), the estimate of 1-year survival rate is 50.1% (95% CI: 38.3, 60.7%).
- NICOLAS PFS with a median of 12.7 months, compares favourably to studies in the same population, all reporting less than 12 months median.
Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC—NICOLAS phase II trial.

Primary endpoints:
- Pneumonitis-free rate of grade ≥ 3 (CTCAE V4.0) any time during 6 months post radiotherapy.
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Hierarchical design: If safety proven → Efficacy evaluation:
- 1-year PFS, sample size n=74
- H₀: PFSₐ ≤ 45% vs H₁: PFSₐ > 60% (1-sided alpha=5%, power=83%)
- Success rule: at least 41 patients reach 1-year without PFS event (i.e., maximum 33 PFS events)

Discussant Conclusions
- The study failed the formal planned hierarchical efficacy analysis and not exciting efficacy data
- Pneumonitis: 7/79 had grade 3 and 1 grade 5 AND overall toxicity was however not negligible
- In the future we need to strictly enforce exact T and N staging in all CT/RT trials this includes not only PET-CT but also EBUS mediastinal staging
St IV NSCLC
IMpower110: Interim OS Analysis of a Phase III Study of Atezolizumab (atezo) vs Platinum-Based Chemotherapy (chemo) as 1L Treatment (tx) in PD-L1–selected NSCLC


¹Sarah Cannon Research Institute, Nashville, TN, USA; ²European Institute of Oncology, Milan, Italy; ³Weill Cornell Medical Center, New York, NY, USA; ⁴Asklepios Lung Clinic, Munich-Gauting, Germany; ⁵Centro de Pesquisa Clínica, Hospital São Lucas, Porto Alegre, Brazil; ⁶PUCRS School of Medicine, Porto Alegre, Brazil; ⁷Nagoya University Graduate School of Medicine, Aichi, Japan; ⁸Vall d’Hebron University Hospital, Barcelona, Spain; ⁹Clinical Hospital Center Bezanijska Kosa, Belgrade, Serbia; ¹⁰Prince of Songkla University – Hat Yai, Songkhla, Thailand; ¹¹Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; ¹²Genentech, Inc., South San Francisco, CA, USA; ¹³Medical University of Gdansk, Gdansk, Poland; ¹⁴Yale School of Medicine, New Haven, CT

esmo.org
Background

- Anti–PD-1 monotherapy or PD-L1/PD-1 inhibitors in combination with platinum-based doublet chemotherapy, with or without bevacizumab, are 1L standards of care in metastatic NSCLC\(^1,2\)
  - Tumour PD-L1 expression level and histology are used to determine treatment regimens
- In the Phase II BIRCH study, atezolizumab monotherapy demonstrated tolerability and efficacy in PD-L1–selected patients with advanced NSCLC across lines of therapy\(^3\)
- The Phase III IMpower110 study (NCT02409342) evaluates atezolizumab monotherapy as 1L treatment in PD-L1–selected patients, independent of tumour histology
  - We report results of the interim OS analysis in IMpower110

---

1L, first-line.
IMpower110 Study Design

- Primary endpoint: OS in WT population
- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; nsq, non-squamous; PD, progressive disease; q3w, every 3 weeks; R, randomised; sq, squamous; TC, tumour cells; WT, wild-type.  

- PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC.  
- PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC.  
- 554 patients in the WT population.  
- Cisplatin 75 mg/m² or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m² IV q3w.  
- Cisplatin 75 mg/m² + gemcitabine 1250 mg/m² or carboplatin AUC 5 + gemcitabine 1000 mg/m² IV q3w.  

Survival follow-up
using both tumor cell (TC) and tumor-infiltrating immune cell (IC)
POPLAR: Both TC and IC are independent predictors of survival improvement

Using both tumor cell (TC) and tumor-infiltrating immune cell (IC)
The primary OS endpoint was tested hierarchically in the following order: TC3 or IC3 WT → TC2/3 or IC2/3 WT → TC1/2/3 or IC1/2/3 WT.

The secondary endpoint of PFS can be formally tested only when the primary endpoint is positive among all 3 populations.
OS: TC3 or IC3 WT

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Arm A (atezo) n = 107</th>
<th>Arm B (chemo) n = 98</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo OS (95% CI), %</td>
<td>76.3 (68.2, 84.4)</td>
<td>70.1 (60.8, 79.4)</td>
</tr>
<tr>
<td>12-mo OS (95% CI), %</td>
<td>64.9 (55.4, 74.4)</td>
<td>50.6 (40.0, 61.3)</td>
</tr>
</tbody>
</table>

HR\(^a\) 0.59 (95% CI: 0.40, 0.89); \(P = 0.0106\)\(^b\)

Median OS, 13.1 mo (95% CI: 7.4, 18.5)
Median OS, 20.2 mo (95% CI: 16.5, NE)

Median follow-up, 15.7 mo (range, 0-35)

No. at risk
- Atezolizumab: 107 94 85 80 66 61 48 40 34 25 18 16 11 7 6 5 2
- Chemotherapy: 98 89 75 65 50 40 33 28 19 12 9 7 6 4 3 3 3 1

NE, not estimable. \(^2\) Stratified. \(^3\) Stratified log-rank.
Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis
TC3 or IC3 WT: OS in Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>OS HR (95% CI)</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 65 years</strong></td>
<td>102 (49.8)</td>
<td>0.59 (0.34, 1.04)</td>
<td>NE 13.1</td>
</tr>
<tr>
<td>65-74 years</td>
<td>80 (39.0)</td>
<td>0.63 (0.34, 1.19)</td>
<td>17.8 10.4</td>
</tr>
<tr>
<td>75-84 years</td>
<td>22 (10.7)</td>
<td>1.04 (0.19, 5.70)</td>
<td>NE 16.2</td>
</tr>
<tr>
<td>Male</td>
<td>143 (69.8)</td>
<td>0.57 (0.35, 0.93)</td>
<td>23.1 13.1</td>
</tr>
<tr>
<td>Female</td>
<td>62 (30.2)</td>
<td>0.69 (0.34, 1.39)</td>
<td>17.8 14.1</td>
</tr>
<tr>
<td>White</td>
<td>169 (82.4)</td>
<td>0.67 (0.44, 1.03)</td>
<td>17.8 13.1</td>
</tr>
<tr>
<td>Asian</td>
<td>35 (17.1)</td>
<td>0.38 (0.13, 1.13)</td>
<td>NE 14.1</td>
</tr>
<tr>
<td>Never used tobacco</td>
<td>24 (11.7)</td>
<td>1.83 (0.63, 5.31)</td>
<td>8.0 15.9</td>
</tr>
<tr>
<td>Current tobacco user</td>
<td>49 (23.9)</td>
<td>0.35 (0.14, 0.88)</td>
<td>NE 10.2</td>
</tr>
<tr>
<td>Previous tobacco user</td>
<td>132 (64.4)</td>
<td>0.60 (0.36, 1.00)</td>
<td>23.1 13.1</td>
</tr>
<tr>
<td>Non-squamous histology</td>
<td>155 (75.6)</td>
<td>0.62 (0.40, 0.96)</td>
<td>20.2 10.5</td>
</tr>
<tr>
<td>Squamous histology</td>
<td>50 (24.4)</td>
<td>0.56 (0.23, 1.37)</td>
<td>NE 15.3</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>73 (35.6)</td>
<td>0.42 (0.20, 0.92)</td>
<td>NE 15.7</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>132 (64.4)</td>
<td>0.69 (0.43, 1.10)</td>
<td>16.5 13.1</td>
</tr>
<tr>
<td><strong>All TC3 or IC3 WT patients</strong></td>
<td><strong>205 (100)</strong></td>
<td><strong>0.59 (0.40, 0.89)</strong></td>
<td><strong>20.2 13.1</strong></td>
</tr>
</tbody>
</table>

* The 1 patient in the ≥ 85 years subgroup is not included; 1 patient’s race was unknown. ° Unstratified. ° Stratified. 
Data cutoff: 10 September 2018.
OS: TC2/3 or IC2/3 WT

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Arm A (atezo)</th>
<th>Arm B (chemo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo OS</td>
<td>79.3 (73.1, 85.5)</td>
<td>76.1 (69.3, 82.8)</td>
</tr>
<tr>
<td>(95% CI), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-mo OS</td>
<td>60.7 (52.6, 68.7)</td>
<td>56.0 (47.7, 64.3)</td>
</tr>
<tr>
<td>(95% CI), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR,(^a) 0.72 (95% CI: 0.52, 0.99); P = 0.0416(^b,c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS, 14.9 mo  (95% CI: 10.8, 16.6)</td>
<td></td>
<td>Median OS, 18.2 mo  (95% CI: 13.3, NE)</td>
</tr>
<tr>
<td>Median follow-up, 15.2 mo (range, 0-35)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>Atezolizumab</th>
<th>166</th>
<th>151</th>
<th>139</th>
<th>128</th>
<th>108</th>
<th>92</th>
<th>66</th>
<th>54</th>
<th>42</th>
<th>30</th>
<th>19</th>
<th>17</th>
<th>11</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>162</td>
<td>150</td>
<td>131</td>
<td>117</td>
<td>95</td>
<td>75</td>
<td>57</td>
<td>46</td>
<td>32</td>
<td>17</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\) Stratified. \(^b\) Stratified log-rank. \(^c\) Not crossing the pre-specified alpha boundary. Data cutoff: 10 September 2018.

Spigel et al. IMPower110 Interim OS Analysis
OS: TC1/2/3 or IC1/2/3 WT

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Arm A (atezo)</th>
<th>Arm B (chemo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo OS (95% CI), %</td>
<td>76.2 (71.1, 81.3)</td>
<td>75.7 (70.5, 80.9)</td>
</tr>
<tr>
<td>12-mo OS (95% CI), %</td>
<td>57.6 (51.2, 64.0)</td>
<td>54.3 (47.7, 60.8)</td>
</tr>
</tbody>
</table>

HR,\(^a\) 0.83 (95% CI: 0.65, 1.07); \(P = 0.1481^{b,c}\)

Median OS, 14.1 mo (95% CI: 11.0, 16.6)
Median OS, 17.5 mo (95% CI: 12.8, 23.1)

Median follow-up, 13.4 mo (range, 0-35)

No. at risk
Atezolizumab 277 252 226 204 170 134 93 74 58 37 22 17 11 7 6 5 2
Chemotherapy 277 254 223 199 153 108 79 63 43 24 10 7 6 4 3 3 1

\(^a\) Stratified. \(^b\) Stratified log-rank. \(^c\) For descriptive purposes only.
Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis
ALL-CAUSE AEs
> 5% difference between arms

Arm A (atezo) n = 286
Arm B (chemo) n = 263

- Anaemia
- Nausea
- Neutropenia
- Constipation
- Thrombocytopenia
- Vomiting
- Increased blood creatinine
- Decreased platelet count
- Leukopenia
- Decreased neutrophil count
- Increased AST
- Pruritus
- Hypothyroidism

AST, aspartate aminotransferase.
Atezolizumab monotherapy showed statistically significant and clinically meaningful OS improvement in the TC3 or IC3 WT population vs platinum-based chemotherapy (HR, 0.59 [95% CI: 0.40, 0.89]; \( P = 0.0106 \))

The OS testing boundary was not crossed in the TC2/3 or IC2/3 WT population. Therefore, the TC1/2/3 or IC1/2/3 WT population was not formally tested

- IMpower110 will continue to the OS final analysis

In the TC3 or IC3 WT population, atezolizumab showed meaningful improvement in PFS, ORR and DOR vs chemotherapy

The safety profile of atezolizumab was consistent with prior observations; no new or unexpected safety signals were identified

Additional biomarker analyses will be presented at a future congress

- PD-L1 IHC by SP263 and 22C3, and bTMB

Atezolizumab represents a promising 1L treatment option in patients with PD-L1–high NSCLC
Conclusions (authors and discussant Dr. Naiyer Rizvi)

- The safety profile of atezolizumab was consistent with prior observations; no new or unexpected safety signals were identified.
- Atezolizumab represents a promising 1L treatment option in patients with PD-L1-high NSCLC.
- Outcomes with other PD-L1 diagnostic antibodies than SP142; 22C3 IHC? TC3 vs. IC3? TC2/IC2?
Tumor Mutational Burden (TMB)

The elephant in the room

Dead or Will it get you to the right place?

R.I.P. TMB

Transports Metropolitans de Barcelona
Immunotherapy - who to give?

SELECT THE RIGHT PATIENT FOR EFFICACY

**Biomarkers for IO**

**CANCER CELL - TISSUE**
- PD-L1 IHC
  - Neo-antigens
  - Driver mutations
- MSI
- TMB

**MICROENVIRONMENT**
- Immune phenotype
- TCR sequencing
- Cytokines signature

**IMMUNE INFILTRATING CELLS**
- TILs
- Immuno score

**BLOOD**
- sPD-L1
- CTCs
- ctDNA
  1. bTMB
  2. AF dynamic
- Leukocytes ratio

Courtesy of A.Marabelle, adapted

TMB and relevance in immunotherapy treatment
TMB is independent of PD-L1 expression level

CM 26 - WES

MSK - IMPACT

Peters AACR 2017 * Rizvi JCO 2018
Association Between Tissue TMB and Clinical Outcomes with Pembrolizumab Monotherapy in PD-L1-Positive Advanced NSCLC in the KEYNOTE-010 and 042 Trials

Roy S. Herbst¹, Gilberto Lopes², Dariusz M. Kowalski³, Makoto Nishio⁴, Yi-long Wu⁵, Gilberto de Castro Jr⁶, Paul Baas⁷, Dong-Wan Kim⁸, Matthew A. Gubens⁹, Razvan Cristescu¹⁰, Deepti Aurora-Garg¹⁰, Andrew Albright¹⁰, Mark Ayers¹⁰, Andrey Loboda¹⁰, Jared Lunceford¹⁰, Julie Kobie¹⁰, Gregory Lubiniecki¹⁰, M. Catherine Pietanza¹⁰, Bilal Piperdi¹⁰, Tony SK Mok¹¹

¹Yale University School of Medicine, Yale Cancer Center, New Haven, CT, USA; ²Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; ³The Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; ⁴Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; ⁵Guandong Lung Cancer Institute, Guangdong General Hospital, and Guangdong Academy of Medical Sciences, Guangdong, China; ⁶Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; ⁷Netherlands Cancer Institute, Amsterdam, Netherlands; ⁸Seoul National University Hospital, Seoul, Republic of Korea; ⁹University of California, San Francisco, CA, USA; ¹⁰Merck &Co., Inc, Kenilworth, NJ, USA; ¹¹State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Shatin, Hong Kong, China
Background

- Pembrolizumab improved OS vs chemotherapy in patients with previously treated (KEYNOTE-010) and treatment-naive (KEYNOTE-042) PD-L1+ (TPS ≥1%), advanced NSCLC.1,2

Methods: Clinical Utility of TMB

**Rationale for WES TMB cutpoint**

- Exploratory TMB cutpoint was identified as a biologically optimal threshold across multiple tumor types in pembrolizumab studies using WES platform\(^1,2\)
- WES platform:
  - Comprehensive, gold standard method of sequencing cancer genetics including somatic alterations\(^3\)
  - Benchmark method in ongoing TMB assessment harmonization efforts\(^3,4\)
  - Consistent analytical pipeline across the pembrolizumab translational program

**Clinical Utility of tTMB**

- Assessed using prespecified exploratory cutpoint of 175 mut/exome
- Derived using GEP and WES TMB data from multiple tumor cohorts across the pembrolizumab clinical program\(^1,2,5\)
- Yields most statistically significant difference in distribution of an 18-gene GEP in a mixed-tumor dataset\(^1,2,5\)
- Most closely approximates 13 mut/Mb by FoundationOne CDx (legacy F1CDx, Foundation Medicine proprietary pipeline QSR_F1Dx_v1.03) and 10 mut/Mb (updated pipeline F1Dx_v3.2)

---

**Association of tTMB ($\log_{10}$) With Efficacy (KEYNOTE-010$^a$)**

<table>
<thead>
<tr>
<th>Nominal $P$ Value$^b$</th>
<th>Pembro (n = 164)</th>
<th>Chemo (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>0.006 (one-sided)</td>
<td>0.410 (two-sided)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.001 (one-sided)</td>
<td>0.579 (two-sided)</td>
</tr>
<tr>
<td>ORR</td>
<td>0.009 (one-sided)</td>
<td>0.330 (two-sided)</td>
</tr>
</tbody>
</table>

**tTMB was associated with outcomes for pembro as a continuous variable but not with chemo based on $\alpha = 0.05$ significance level and AUROC analysis.**

---

$^a$All patients were PD-L1-positive (TPS >1%). Wilcoxon test. $P$ values are one-sided for pembro as the a priori hypothesis was that tTMB was positively associated with improved outcomes of pembro. $P$ values are two-sided for placebo because there was no a priori hypothesis regarding the direction of the association between tTMB and outcomes of chemo. TMB was assessed as a continuous, $\log_{10}$-transformed variable.

Data cutoff date: Mar 16, 2018.
Clinical Utility for OS (KEYNOTE-010\textsuperscript{a}): tTMB Cutpoint of 175 mut/exome

<table>
<thead>
<tr>
<th>tTMB ≥175 mut/exome</th>
<th>tTMB &lt;175 mut/exome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 0.56 (95% CI 0.38-0.83)</td>
<td>HR 0.85 (95% CI 0.56-1.30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI)</th>
<th>Pembro (n=81)</th>
<th>Chemod (n=51)</th>
<th>Pembro (n=83)</th>
<th>Chemod (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>14.1 mo (10.0-19.2)</td>
<td>7.6 mo (5.0-10.7)</td>
<td>9.3 mo (8.3-12.5)</td>
<td>7.2 mo (4.5-14.3)</td>
</tr>
</tbody>
</table>

*All patients were PD-L1-positive (TPS ≥1%). Data cutoff date: Mar 16, 2018.*
Association of tTMB (log_{10}) With Efficacy (KEYNOTE-042)

<table>
<thead>
<tr>
<th>Nominal P Value</th>
<th>Pembro (n = 414)</th>
<th>Chemo (n = 379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>&lt;0.001 (one-sided)</td>
<td>0.060 (two-sided)</td>
</tr>
<tr>
<td>PFS</td>
<td>&lt;0.001 (one-sided)</td>
<td>0.174 (two-sided)</td>
</tr>
<tr>
<td>ORR</td>
<td>&lt;0.001 (one-sided)</td>
<td>0.035 (two-sided)</td>
</tr>
</tbody>
</table>

ROC Curves of ORR for tTMB

- **Pembro**: 0.67 (0.61-0.73)
- **Chemo**: 0.57 (0.50-0.63)

tTMB was associated with outcomes for pembro as a continuous variable but not chemo in general, based on α = 0.05 significance level and AUROC.

---

*a All patients were PD-L1-positive (TPS ≥1%). *b Wald test. *c P values are one-sided for pembro as the a priori hypothesis was that tTMB was positively associated with improved outcomes of pembro. P values are two-sided for placebo as there was no a priori hypothesis regarding the direction of association between tTMB and outcomes of chemo. TMB was assessed as a continuous, log_{10}-transformed variable. tTMB showed negative directions of association with OS and PFS in the chemo arm.

Data cutoff date: Sep 4, 2018.
Clinical Utility for OS (KEYNOTE-042\textsuperscript{a}):
tTMB Cutpoint of 175 mut/exome

\[
\begin{align*}
tTMB \geq 175 \text{ mut/exome} \\
\text{HR 0.62 (95\% CI 0.48-0.80)} \\
\end{align*}
\]

\[
\begin{array}{c|c|c}
\text{Pembro} & 21.9 \text{ mo (17.0-26.7)} \\
(n=180) & \\
\text{Chemo (n=165)} & 11.6 \text{ mo (9.9-14.2)} \\
\end{array}
\]

\[
\begin{align*}
tTMB < 175 \text{ mut/exome} \\
\text{HR 1.09 (95\% CI 0.88-1.36)} \\
\end{align*}
\]

\[
\begin{array}{c|c|c}
\text{Pembro (n=234)} & 12.0 \text{ mo (9.2-14.8)} \\
\text{Chemo (n=214)} & 12.3 \text{ mo (11.3-16.2)} \\
\end{array}
\]

*All patients were PD-L1-positive (TPS ≥1\%). Data cutoff date: Sep 4, 2018.*
Pembrolizumab Plus Platinum-Based Chemotherapy for Metastatic NSCLC: Tissue TMB (tTMB) and Outcomes in KEYNOTE-021, 189, and 407

Luis Paz-Ares, Corey J. Langer, Silvia Novello, Balazs Halmos, Ying Cheng, Shirish M. Gadgeel, Rina Hui, Shunichi Sugawara, Hossein Borghaei, Razvan Cristescu, Deepti Aurora-Garg, Andrew Albright, Andrey Loboda, Julie Kobie, Jared Lunceford, Mark Ayers, Gregory M. Lubiniecki, M. Catherine Pietanza, Bilal Piperdi, Marina C. Garassino

1Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center, Universidad Complutense and Ciberonc, Madrid, Spain; 2Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; 3University of Turin, Orbassano, Italy; 4Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA; 5Jilin Cancer Hospital, Changchun, China; 6Karmanos Cancer Institute, Detroit, MI, USA (currently at University of Michigan, Ann Arbor, MI, USA); 7Westmead Hospital and University of Sydney, Sydney, NSW, Australia; 8Sendai Kousei Hospital, Miyagi, Japan; 9Fox Chase Cancer Center, Philadelphia, PA, USA; 10Merck & Co., Inc., Kenilworth, NJ, USA; 11Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Study Designs

KEYNOTE-021 Cohort C (N = 24)\textsuperscript{1}

- Key Eligibility Criteria
  - Untreated stage IIIb or IV nonsquamous NSCLC
  - No activating EGFR mutation or ALK translocation
  - ECOG PS 0-1

- Pembrolizumab 2 mg/kg Q3W for 2 years
  - Carboplatin and Pemetrexed 500 mg/m\textsuperscript{2} Q3W for 4 cycles

- Pembrolizumab 10 mg/kg Q3W for 2 years
  - Carboplatin and Pemetrexed 500 mg/m\textsuperscript{2} Q3W for 4 cycles

KEYNOTE-021 Cohort G (N = 123)\textsuperscript{2,3}

- Key Eligibility Criteria
  - Untreated stage IIIb or IV nonsquamous NSCLC
  - No activating EGFR mutation or ALK translocation
  - ECOG PS 0-1

- Pembrolizumab 200 mg Q3W for 2 years
  - Carboplatin and Pemetrexed 500 mg/m\textsuperscript{2} Q3W for 4 cycles

KEYNOTE-189 (N = 616)\textsuperscript{4}

- Key Eligibility Criteria
  - Untreated stage IV nonsquamous NSCLC
  - No activating EGFR mutation or ALK translocation
  - ECOG PS 0-1

- Pembrolizumab 200 mg Q3W for 2 years
  - Carboplatin or Cisplatin and Pemetrexed 500 mg/m\textsuperscript{2} Q3W for 4 cycles

- Placebo for 2 years
  - Carboplatin or Cisplatin and Pemetrexed 500 mg/m\textsuperscript{2} Q3W for 4 cycles

KEYNOTE-407 (N = 559)\textsuperscript{5}

- Key Eligibility Criteria
  - Untreated stage IV squamous NSCLC
  - ECOG PS 0-1

- Pembrolizumab 200 mg Q3W for 2 years
  - Carboplatin + Paclitaxel or nab-Paclitaxel Q3W for 4 cycles

- Placebo for 2 years
  - Carboplatin and Paclitaxel or nab-Paclitaxel Q3W for 4 cycles

### Association of tTMB ($\log_{10}$) With Efficacy

<table>
<thead>
<tr>
<th>Nominal $P$ Value$^a$</th>
<th>KEYNOTE-021 C and G</th>
<th>KEYNOTE-189</th>
<th>KEYNOTE-407</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembro + Chemo (n = 44)</td>
<td>Chemo Alone (n = 26)</td>
<td>Pembro + Chemo (n = 207)</td>
</tr>
<tr>
<td>ORR</td>
<td>0.180</td>
<td>0.279</td>
<td>0.072</td>
</tr>
<tr>
<td>PFS</td>
<td>0.187</td>
<td>0.409</td>
<td>0.075</td>
</tr>
<tr>
<td>OS</td>
<td>0.081</td>
<td>0.475</td>
<td>0.174</td>
</tr>
</tbody>
</table>

$^a$P were values calculated using the Wald test and are one-sided for pembro + chemo (a priori hypothesis that tTMB was positively associated with improved outcomes for pembro + chemo) and two-sided for chemo alone and placebo + chemo (no a priori hypothesis regarding direction of the association between tTMB and outcomes).

Data cutoff dates: Dec 1, 2017 (KEYNOTE-021); Sep 21, 2018 (KEYNOTE-189); May 9, 2019 (KEYNOTE-407).

No association between tTMB (continuous, $\log_{10}$-transformed) and efficacy for pembrolizumab + chemotherapy or chemotherapy ± placebo in any study based on $\alpha = 0.05$ significance level.
Conclusions

• Higher tTMB levels as assessed by WES were associated with **improved clinical outcomes** for **pembrolizumab monotherapy** in patients with PD-L1-positive advanced NSCLC
• PD-L1 1-49% and TMB high may be appropriate for pembrolizumab monotherapy
• **Pembrolizumab/chemotherapy** combinations active in **both TMB high and low tumors**
• Limitations:
  o Exploratory analysis
  o Analysis in subsets of patients with available tTMB in these trials

• TMB high and PD-L1 <1% ?
• Different methods and definitions of TMB testing – harmonization needed
Next-generation sequencing and assessment of tumour mutational burden: are these tools ready for clinical routine use?

L. Hendriks, pulmonologist, MD, PhD
Maastricht UMC+, The Netherlands
Impact of TMB on anti-PD-1

UPDATE ESMO 2019:
SIMILAR RESULTS FOR KEYNOTE 010 & 042
BUT NOT FOR KEYNOTE 021, 189 & 407

TMB definition

Number of mutations in genome......

The black box
TMB pitfalls

Genes covered

Exome (coding region - approx. 1-2% of genome) -
1MB = 1 million nucleotides

Variability regarding definition

Missense vs “all” mutations

Chang mol diagnosis and therapy 2019 * Chan ann oncol 2018
TMB pitfalls

Heterogeneity primary – LN - metastasis

Intratumor heterogeneity
30%, up to 14 mut/Mb difference!
TMB pitfalls

TMB does not equal neoantigen
And neoantigens do not equal T-cell reactivity....
TMB pitfalls
tumor microenvironment matters

Brain mets often high TMB

But less T-cell clonality in brain mets

Stein JCO precision oncology 2019 * Mansfield Sci Rep 2018
TMB summary

✓ Why?
  ✓ Biological rationale
  ✓ High TMB associated with long term outcome across tumor types

✓ Pitfalls - drawbacks
  ✓ Heterogeneity++
  ✓ Be aware of type of test (definition, coverage, genes sequenced, race)
  ✓ TAT 2 weeks for tissue, < 1 week for blood

✓ Implement?
  ✓ Interesting but not ready for clinical use yet
KEEP CALM
EQUIPMENT
NOT READY
FOR USE, YET
IO-IO combinations: more is better?
Nivolumab + Low-Dose Ipilimumab Versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: CheckMate 227 Part 1 Final Analysis

Solange Peters,1 Suresh Ramalingam,2 Luis Paz-Ares,3 Reyes Bernabe Caro,4 Bogdan Zurawski,5 Sang-We Kim,6 Aurelia Alexandru,7 Lorena Lupinacci,8 Emmanuel de la Mora Jimenez,9 Hiroshi Sakai,10 István Albert,11 Alain Vergnenegre,12 Martin Reck,13 Hossein Borghaei,14 Julie R. Brahmer,15 Kenneth O'Byrne,16 William J. Geese,17 Prabhu Bhagavatheeswaran,17 Faith E. Nathan,17 Matthew D. Hellmann18

1Centre hospitalier universitaire Vaudois (CHUV), Lausanne University, Lausanne, Switzerland; 2Winship Cancer Institute, Emory University, Atlanta, GA, USA; 3Hospital Universitario Doce de Octubre, CNIO, Universidad Complutense & Ciberonc, Madrid, Spain; 4Hospital Universitario Virgen Del Rocio, Seville, Spain; 5Ambulatorium Chemoterapi, Bydgoszcz, Poland; 6Asan Medical Center, Seoul, Republic of Korea; 7Institute Of Oncology “Prof. Dr. Alexandru Trestioreanu” Bucha, Bucharest, Romania; 8Hospital Italiano De Buenos Aires, Buenos Aires, Argentina; 9Instituto Jilinsenio De Oncologia, Guadalajara, Jalisco, Mexico; 10Saitama Cancer Center, Saitama, Japan; 11Matra Gyogyintezet, Matrahaza, Hungary; 12Limoges University Hospital, Limoges, France; 13Lung Clinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; 14Fox Chase Cancer Center, Philadelphia, PA, USA; 15Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 16Princess Alexandra Hospital, Brisbane, Queensland, Australia; 17Bristol-Myers Squibb, Princeton, NJ, USA; 18Memorial Sloan-Kettering Cancer Center, New York, NY, USA
CheckMate 227 Part 1 Study Design

Key Eligibility Criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing EGFR mutations or known ALK alterations
- No untreated CNS metastases
- ECOG PS 0–1

Stratified by SQ vs NSQ

Part 1a
- PD-L1 expression ≥ 1%
  - R 1:1:1
  - N = 1189

Part 1b
- PD-L1 expression < 1%
  - R 1:1:1
  - N = 560

NIVO + (low-dose) IPI
- n = 396

NIVO
- n = 396

NIVO + (low-dose) IPI
- n = 187

NIVO + chemo
- n = 186

PD-L1 dual-primary endpoint

Dual-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB populations
- OS in PD-L1 ≥ 1% populations

Secondary endpoints (PD-L1 hierarchy):
- PFS: NIVO + chemo vs chemo in PD-L1 < 1%
- OS: NIVO + chemo vs chemo in PD-L1 < 1%
- OS: NIVO vs chemo in PD-L1 ≥ 50%

Database lock: July 2, 2019; minimum follow-up for primary endpoint: 29.3 months
Study treatments continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy.

* NCT02477826; **NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W); ***NIVO (240 mg Q2W); ^NIVO (360 mg Q3W); $TMB dual-primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; ^Alpha allocated was 0.025 overall (0.023 for final analysis)
OS and PFS With NIVO + IPI vs NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

**OS**
- **NIVO + IPI (n = 396)**: Median OS, mo 17.1, HR (vs chemo) 0.79 (97.7% CI, 0.65–0.96)
- **NIVO (n = 396)**: Median OS, mo 15.7, HR (vs chemo) 0.88 (95% CI, 0.75–1.04)
- **Chemo (n = 397)**: Median OS, mo 14.9

**PFS by BICR**
- **NIVO + IPI (n = 396)**: Median PFS, mo 5.1, HR (vs chemo) 0.82 (95% CI, 0.69–0.97)
- **NIVO (n = 396)**: Median PFS, mo 4.2, HR (vs chemo) 0.99 (95% CI, 0.84–1.17)
- **Chemo (n = 397)**: Median PFS, mo 5.6

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm, 44% in the NIVO arm, and 54% in the chemo arm; subsequent immunotherapy was received by 8%, 8%, and 43%, respectively.

*HR (95% CI) for NIVO + IPI vs NIVO, 0.90 (0.76–1.07); HR (95% CI) for NIVO + IPI vs NIVO, 0.83 (0.71–0.97).*
OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%

- PFS for NIVO + chemo vs chemo (secondary endpoint) in PD-L1 < 1% was met (HR, 0.73; P = 0.0070)
- OS for NIVO + chemo vs chemo was not met; subsequent secondary endpoints in the hierarchy are descriptive

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively. Among patients with PD-L1 <1%, patients were randomized 1:1:1 across treatment arms.
### OS for NIVO + IPI vs Chemo By Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

<table>
<thead>
<tr>
<th>Randomized groups</th>
<th>Median OS, months</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIVO + IPI</strong> n = 583</td>
<td>Chemo n = 583</td>
<td>Stratified</td>
<td>Stratified</td>
</tr>
<tr>
<td>All randomized (N = 1166)</td>
<td>17.1</td>
<td>13.9</td>
<td>0.73</td>
</tr>
<tr>
<td>PD-L1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 &lt; 1% (n = 373)</td>
<td>17.2</td>
<td>12.2</td>
<td>0.62</td>
</tr>
<tr>
<td>PD-L1 ≥ 1% (n = 793)</td>
<td>17.1</td>
<td>14.9</td>
<td>0.79^a</td>
</tr>
<tr>
<td><strong>Additional exploratory subgroups analyses not controlled by randomization</strong></td>
<td></td>
<td>Unstratified</td>
<td>Unstratified</td>
</tr>
<tr>
<td>PD-L1</td>
<td>1–49% (n = 396)</td>
<td>15.1</td>
<td>15.1</td>
</tr>
<tr>
<td>≥ 50% (n = 397)</td>
<td>21.2</td>
<td>14.0</td>
<td>0.70</td>
</tr>
<tr>
<td>TMB^b (mut/Mb)</td>
<td>low, &lt; 10 (n = 380)</td>
<td>16.2</td>
<td>12.6</td>
</tr>
<tr>
<td>high, ≥ 10 (n = 299)</td>
<td>23.0</td>
<td>16.4</td>
<td>0.68</td>
</tr>
</tbody>
</table>

(modified from Peters ESMO 2019)

^aStratified HR (97.72% CI); ^bUnstratified HR for NIVO + IPI vs chemo in TMB evaluable (n = 679) and non evaluable (n = 487) patients was 0.74 (95% CI, 0.61–0.88) and 0.74 (95% CI, 0.60–0.92), respectively.
Safety Summary of Treatment-Related AEs in All Randomized Patients Treated with NIVO + IPI, NIVO, or Chemo

<table>
<thead>
<tr>
<th>TRAE, a %</th>
<th>NIVO + IPI (n = 576)</th>
<th>NIVO (n = 391)</th>
<th>Chemo (n = 570)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>77</td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td>TRAE leading to discontinuation</td>
<td>18</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Most frequent TRAEs (≥ 15%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>&lt; 1</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt; 1</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

- With 18 months more follow-up, safety was consistent.
- Median duration of therapy (range) was 4.2 mo (0.03–2.6 mo (0.03–37.6+) with chemo.

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W).

Includes events reported between first dose and 30 days after last dose of study drug; *Study treatment-related death event occurred in 3% of patients; †Treatment-related deaths in the NIVO + IPI arm were pneumonia, sepsis, and respiratory, and in the NIVO arm were pneumonitis, and critical neutropenia and sepsis; deaths in the chemo arm were disease, and thrombocytopenia.


### Event KN-189

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3, 4, or 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>404 (99.8)</td>
<td>272 (67.2)</td>
</tr>
<tr>
<td>Event leading to discontinuation of all treatment</td>
<td>55 (13.8)</td>
<td>48 (11.9)</td>
</tr>
</tbody>
</table>
Conclusions Authors

- CheckMate 227 is the first phase 3 randomized trial to show NIVO + IPI vs chemo is effective in NSCLC
- NIVO + IPI represents a first-line treatment option for patients with NSCLC with the potential to provide a long-term OS benefit, and preserve chemo treatment options in the second-line setting  

**However** (Discussant Dr Sanjay Popat):

- In PDL1+ OS benefit driven by \( \geq 50\% \) group, beware the trAEs & discontinuation rate for similar OS benefit with IO mono & less toxicity.
- A potential role in PDL1-negatives, but not seemingly better than chemo-pembro and with notable toxicities.
- Is nivo-ippi the preferred clinical option? This depends on other treatment options and balance of efficacy and safety (patient individualization).
- **Comment** (also pointed out by Dr. Popat): will nivo-ippi improve the “tail” of the OS curve due to an ipi effect maintaining long term survivors?
OUDEREN ?
Doctors want to give their cancer patients every chance. But are they pushing off hard talks too long?

The Problem With Miracle Cancer Cures
By Robert M. Wachter

Widespread Hype Gives False Hope To Many Cancer Patients

The Challenge of Prognostication in the Era of Immunotherapy

Immunotherapy: hype and hope
The Lancet Oncology
Published: July, 2018 • DOI: https://doi.org/10.1016/S1470-2045(18)30317-6
Verouderd immuunsysteem en kanker ontwikkeling

Cancer Immunoediting

Immun-elimination → Immu-no-equilibrium → Immu-no-escape

Oxidative stress
SASP
Inflamm-aging

? IMMUNE SYSTEM AGING
Innate immune response hyperactivation

T cell aging

Innate immune cell aging

Functions of NK, PMN, MØ, DC

Naive T cells
Memory T cells: exhaustion senescence

Zijn er data bij oudere NSCLC patiënten en immunotherapie?

Safety and Efficacy of Pembrolizumab Monotherapy in Elderly Patients With PD-L1 Positive Advanced NSCLC: Pooled Analysis From KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042

264/2612 = 10% ouderen
Overleven oudereen versus jongeren

Kaplan-Meier Estimate of OS
PD-L1 TPS ≥1% (KN010, KN024, KN042)

Geen relevante verschillen in bijwerkingen

Geldt voor iedere PD-L1 subgroep
Waar letten we bij ouderen nu op bij immunotherapie?
Wat heeft naast leeftijd en conditie invloed?

- Sarcopenie
  - Prognostisch en predictief
  - Primair vs secundair
  - Meer inflammatoire markers

Age ➔ PS ➔ Body Composition ➔ Immunotherapy Efficacy/Toxicity
Immunotherapy & Body Composition: Efficacy

- 251 Patients on Phase-1 Trials
- Prognostic Score: PS3-CT
  - PS3-CT:
    - High Tumor Burden (> 9 cm)
    - Low Skeletal Muscle Index (< 53 cm² m⁻²)
    - Non-Pulmonary Visceral Metastases

Ook meer toxiciteit!
Stelling I

• Ouderen moeten in aanmerking komen voor immunotherapie voor longkanker
  • Ip JA maar...

Stelling II

• Immunotherapie is niet zo effectief bij ouderen als bij jongeren
  • Ip NEE maar..
Vragen ?
MPM
**ETOP 9-15 PROMISE-meso – Study Design & Objectives**

**Key eligibility criteria**
- Malignant pleural mesothelioma (all histologies)
- Progression after previous platinum-based chemotherapy
- ECOG PS 0-1
- Measurable or evaluable disease according to RECIST 1.1 criteria
- Adequate haematological, renal, and liver function
- Availability of tumour tissue for translational research

**Pembrolizumab**
- 200 mg fixed dose i.v. day 1 of each 3 week cycle (q3w)

**Institutional choice Chemotherapy**
- Gemcitabine 1000 mg/m² q1/8 q3w i.v. or
- Vinorelbine 30 mg/m² q1/8 q3w i.v. or
- Vinorelbine 60/80 mg/m² q1/8 q3w p.o.

**Treatment until progression by RECIST 1.1, max 2 years**
* *beyond PD allowed in case of clinical benefit

**RECIST 1.1 Assessment:**
- Every 9 weeks for the first 6 months and 12 weeks thereafter

**Cross-over to pembrolizumab allowed at progression**

**Primary endpoint:**
- Progression-free survival (PFS) assessed by independent radiology review (IRR)

**Secondary endpoints:**
- Objective response rate (ORR)
- Time to treatment failure (TTF)
- Overall survival (OS)
- Investigator assessed (IA) PFS
- Adverse events

**Correlative endpoints:**
- Outcome by PD-L1 status

---

*Stratification factor*
- Histological subtype: Epithelioid vs. Non-epithelioid

---

Popat S et al, Abstract 1665, Prefered Paper 30 Sep
Progression Free Survival by IRR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/N</th>
<th>Median PFS (95%CI)</th>
<th>6m PFS% (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>56/71</td>
<td>3.4 m (2.2, 4.3)</td>
<td>27.4% (17.1, 38.7)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>62/73</td>
<td>2.5 m (2.1, 4.2)</td>
<td>25.0% (15.5, 35.6)</td>
</tr>
</tbody>
</table>

HR* (95%CI): 1.06 (0.73, 1.53)  p* = 0.76

*Stratified by histological subtype

92% (91/99) IRR PDs were identified also by IA

Popat S et al, Abstract 1665
PFS (IRR) by PD-L1 status

<table>
<thead>
<tr>
<th>Events/N</th>
<th>Median PFS (95%CI)</th>
<th>6m PFS (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo.</td>
<td>11/17</td>
<td>4.4 m (1.4, 7.4)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>16/19</td>
<td>4.2 m (2.1, 7.5)</td>
</tr>
</tbody>
</table>

HR* (95%CI):
1.25 (0.56, 2.83)  
*p*= 0.67

TPS <1%

No at Risk
Chemotherapy: 17 13 8 6 3 2 0  
Pembrolizumab: 19 16 12 6 4 1 1

ETOP 9-15 PROMISE-meso | 2019 ESMO Congress, Barcelona

ETOP 9-15 PROMISE-meso | 2019 ESMO Congress, Barcelona

TPS ≥1%

No at Risk
Chemotherapy: 34 27 13 7 4 2 0  
Pembrolizumab: 32 21 15 6 4 2 2

ETOP 9-15 PROMISE-meso | 2019 ESMO Congress, Barcelona

HR* (95%CI):
1.06 (0.63, 1.80)  
*p*= 0.82

*Stratified by histological subtype

Popat S et al, Abstract 1665
Overall Survival

Deaths/N Median OS (95%CI) 6m OS% (95%CI)
Chemotherapy 34/71 11.7 m (7.4, NE) 72.9% (60.8, 81.7)
Pembrolizumab 37/73 10.7 m (7.6, NE) 68.5% (56.5, 77.8)

NE: Not estimable

HR* (95%CI): 1.04 (0.66, 1.67) p*= 0.85

No at Risk
Chemotherapy
Pembrolizumab

Analysis HR* (95% CI) p*
Censored 1.44 (0.77, 2.67) 0.25
Inverse probability weighting (IPW) 1.07 (0.67, 1.71) 0.79

*Stratified by histological subtype

Popat S et al, Abstract 1665
Best Overall Response – Duration of Response (DOR) by IRR

<table>
<thead>
<tr>
<th>Pembrolizumab N (%)</th>
<th>Chemotherapy N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>22% (13%, 33%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>16 (21.9)</td>
</tr>
<tr>
<td>Progression of Disease (PD)</td>
<td>17 (23.3)</td>
</tr>
<tr>
<td>Not Evaluable (NE)</td>
<td>33 (45.2)</td>
</tr>
<tr>
<td>Median DOR* (95% CI)</td>
<td>7 (9.6)</td>
</tr>
</tbody>
</table>

* Updated as of August 2010

16 responders  → 7 PD and 4 deaths
4 responders   → 3 PD

Pembrolizumab

Chemotherapy

N=66, excluding 7 NE patients and 2 with missing (%) change

Stratified p=0.004
IMpower133: Primary PFS, OS, and safety in a Ph1/3 study of 1L atezolizumab + carboplatin + etoposide in extensive-stage SCLC


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IMPOWER133: UPDATED OVERALL SURVIVAL (OS) ANALYSIS OF FIRST-LINE (1L) ATEZOLIZUMAB (ATEZO) + CARBOPLATIN + ETOPOSIDE IN EXTENSIVE-_STAGE SCLC (ES-SCLC)

Martin Reck,1 Stephen V. Liu2, Aaron S. Mansfield3, Tony Mok4, Arnaud Scherpereel5, Niels Reinmuth6, Marina Chiara Garassino7, Javier De Castro Carpeno8, Raffaele Califano9, Makoto Nishio10, Francisco Orlandi11, Jorge Arturo Alatorre Alexander12, Ticiana Leal13, Ying Cheng14, Jong-Seok Lee15, Sivuonthan Lam16, Mark McCleland16, Yu Deng16, See Phan16, Leora Horn17

1Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; 2Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; 3Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA; 4State Key Laboratory of South China, The Chinese University of Hong Kong, China; 5University of Lille, CHU Lille, Inserm, U1189 - ONCO-THAI - F-59000 Lille, France; 6Thoracic Oncology, Asklepios Clinics Munich-Gauting, Gauting, Germany; 7Thoracic Oncology Unit, Instituto Nazionale dei Tumori, Milan, Italy; 8Hospital Universitario La Paz, Madrid, Spain; 9Department of Medical Oncology, Christie NHS Foundation Trust, Manchester, UK; 10The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; 11Instituto Nacional del Tórax, Prosalud Oncología, Santiago, Chile; 12Health Pharma Professional Research, Mexico City, Mexico; 13University of Wisconsin Carbone Cancer Center, Madison, WI; 14Jilin Cancer Hospital, Jilin, China; 15Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; 16Genentech, Inc., South San Francisco, CA, USA; 17Vanderbilt University Medical Center, Nashville, TN, USA
**IMpower133 study design**

**Patients with (N = 403)**
- Measurable ES-SCLC (RECIST version 1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

**Stratification**
- Sex (male vs female)
- ECOG PS (0 vs 1)
- Brain metastases (yes vs no)\(^a\)

---

**Induction**
- **Atezolizumab + carboplatin + etoposide**
  - Four 21-day cycles

**Maintenance**
- **Atezolizumab**
- **Placebo + carboplatin + etoposide**
  - Four 21-day cycles

**Survival follow-up**
- Treat until PD or loss of clinical benefit

**Co-primary end points**
- Overall survival
- Investigator-assessed PFS

**Key secondary end points**
- Objective response rate
- Duration of response
- Safety

- Updated OS in ITT and by PD-L1 subgroups
- Updated DOR/ORR in ITT
- Updated Safety

---

*Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m\(^2\) IV, Days 1–3.*

\(^a\) Only patients with treated brain metastases were eligible.
Overall survival

12-month OS
51.7%

38.2%

Atezolizumab + CP/ET (N = 201)
Placebo + CP/ET (N = 202)

OS events, n (%) 104 (51.7) 134 (66.3)
Median OS, months (95% CI) 12.3 (10.8, 15.0) 10.3 (9.3, 11.3)
HR (95% CI) 0.70 (0.54, 0.91) **p = 0.0069**
Median follow-up, months 13.9

No. at risk
Atezolizumab Placebo
201 202
191 194
187 189
182 186
180 183
174 171
159 160
142 131
130 114
121 96
108 81
92 59
74 36
58 27
46 21
33 13
21 8
11 3
5
3
2
2

*Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.
Updated OS in ITT

<table>
<thead>
<tr>
<th></th>
<th>Atezo + CP/ET (n = 201)</th>
<th>Placebo + CP/ET (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>12.3 (10.8, 15.8)</td>
<td>10.3 (9.3, 11.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.60, 0.95)</td>
<td>p = 0.0154*</td>
</tr>
</tbody>
</table>

*P-value is provided for descriptive purpose.

CCOD 24 January 2019

Median follow-up, 22.9 months

IMpower133 Updated OS Analysis: presented by Dr Martin Reck

Commissie BOM:

PASKWIL 2016 superioriteit

**Palliatief, effectiviteit**
- winst totale overleving: > 12 weken of HR < 0,7
- winst progressievrij overleving: > 12 weken of HR < 0,7

**Gradering volgens ESMO-MCBS (inclusief bijdrage door QoL-analyse)**

**Bijwerkingen (verschil tussen de behandelarmen)**
- lethal (absoluut): < 5%
- acuut, ernstig: < 25%
- chronisch beperkend

**Conclusie**
De toevoeging van atezolizumab aan standaard eerstelijns chemotherapie met carboplatine en etoposide bij patiënten met SCLC-ES leidt tot een 2,0 maanden langere OS (12,3 versus 10,3 maanden; HR: 0,70 [95%-BI: 0,54-0,90]; P = 0,007) en een verlenging van de PFS van 0,9 maanden (5,2 versus 4,3 maanden; HR: 0,77 [95%-BI: 0,62-0,96]; P = 0,02). Deze resultaten voldoen niet aan de criteria voor een positief advies volgens de PASKWIL-criteria voor palliatieve behandeling. ←
CASPIAN Study Design

Phase 3, global, randomised, open-label, sponsor-blind multicentre study

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1 N=805 (randomised)

Primary endpoint
- OS

Secondary endpoints
- PFS
- ORR
- Safety & tolerability
- Health-related QoL

Following preplanned interim analysis by the IDMC, the durvalumab + tremelimumab + EP versus EP comparison continues to final analysis.
CASPIAN Study

**Progression-free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + EP</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>226 (84.3)</td>
<td>233 (66.8)</td>
</tr>
<tr>
<td>mPFS* months (95% CI)</td>
<td>5.1 (4.7–6.2)</td>
<td>5.4 (4.8–6.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.645–0.938)</td>
<td></td>
</tr>
</tbody>
</table>

**ORR***

OR 1.56
(95% CI 1.095–2.218)

Patients with response, %

- Durvalumab + EP (n=268): 67.9%
- EP (n=269): 57.6%

*Investigator assessed per RECIST v1.1
Overall Survival (Primary Endpoint)

- **Durvalumab + EP**
  - Events: 155 (57.6%)
  - mOS: 13.0 (95% CI: 11.5–14.8)
  - HR: 0.73 (0.591–0.909)
  - p-value: 0.0047

- **EP**
  - Events: 181 (67.3%)
  - mOS: 10.3 (9.3–11.2)
  - HR: 0.73 (0.591–0.909)
  - p-value: 0.0047

2.7 mnd. = 11.7 wkn

→ 1.8 dag tekort = 43 uur
## CASPIAN vs IMpower 133

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab+EP (n=268)</th>
<th>EP (n=269)</th>
<th>Atezolizumab +EC (n=201)</th>
<th>EC + placebo (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>62</td>
<td>63</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>Male,%</strong></td>
<td>70.9</td>
<td>68.4</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td><strong>White/Asian,%</strong></td>
<td>85.4/13.4</td>
<td>82.2/15.6</td>
<td>81/16</td>
<td>79/18</td>
</tr>
<tr>
<td><strong>PS 0/1,%</strong></td>
<td>36.9/63.1</td>
<td>33.5/66.5</td>
<td>36/64</td>
<td>33/67</td>
</tr>
<tr>
<td><strong>Smoker,%</strong></td>
<td>91.8</td>
<td>94.4</td>
<td>95.5</td>
<td>98.5</td>
</tr>
<tr>
<td><strong>Brain meta,%</strong></td>
<td>10.4</td>
<td>10.0</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><strong>Liver meta,%</strong></td>
<td>40.3</td>
<td>38.7</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Open label</td>
<td>Open label</td>
<td>Placebo control</td>
<td>Placebo control</td>
</tr>
<tr>
<td><strong>Carbo/cisplatin</strong></td>
<td>78.5/24.5</td>
<td>78.2/25.2</td>
<td>100/-</td>
<td>100/-</td>
</tr>
<tr>
<td><strong>No.chemo (med)</strong></td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>PCI,%</strong></td>
<td>-</td>
<td>8</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>
## CASPIAN vs IMpower 133

<table>
<thead>
<tr>
<th></th>
<th>CASPIAN Durvalumab+EP (n=268)</th>
<th>EP (n=269)</th>
<th>IMpower 133 Atezolizumab +EC (n= 201)</th>
<th>EC + placebo (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, m</td>
<td>13.0</td>
<td>10.3</td>
<td>12.3</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>HR=0.73</td>
<td></td>
<td>HR=0.7</td>
<td></td>
</tr>
<tr>
<td>OS at 12m, %</td>
<td>53.7</td>
<td>39.8</td>
<td>51.7</td>
<td>38.2</td>
</tr>
<tr>
<td>PFS, m</td>
<td>5.1</td>
<td>5.4</td>
<td>5.2</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>HR=0.78</td>
<td></td>
<td>HR=0.77</td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>67.9</td>
<td>57.6</td>
<td>60.2</td>
<td>64.4</td>
</tr>
<tr>
<td>DOR, m</td>
<td>5.1</td>
<td>5.1</td>
<td>4.2</td>
<td>3.9</td>
</tr>
<tr>
<td>G 3/4 AEs</td>
<td>61.5</td>
<td>62.4</td>
<td>67.2</td>
<td>63.8</td>
</tr>
<tr>
<td>irAE</td>
<td>19.6</td>
<td>2.6</td>
<td>39.9</td>
<td>24.5</td>
</tr>
<tr>
<td>Biomarker</td>
<td>NA</td>
<td>NA</td>
<td>Only bTMB available</td>
<td></td>
</tr>
<tr>
<td>Poststudy Tx</td>
<td>42</td>
<td>44</td>
<td>50/14/1/5</td>
<td>57/18/7</td>
</tr>
</tbody>
</table>
Predictive Biomarker to Select Patients Benefit from IO?

**CASPIAN**

- **OS**
  - Durablemab + EP
    - (n=265)
  - EP (n=265)
  - Events, n (%): 155 (58.8) vs 162 (61.5)
  - mOS, months (95% CI): 13.0 (11.5–14.5) vs 10.3 (9.3–11.2)
  - HR (95% CI): 0.73 (0.59–0.90)
  - p = 0.0047
  - 53.7% of patients remain OS at 2 years
  - 39.8% at 3 years
  - 24.7% at 4 years

- **PFS**
  - Durablemab + EP
    - (n=265)
  - EP (n=265)
  - Events, n (%): 220 (84.3) vs 230 (88.6)
  - mPFS, months (95% CI): 5.1 (4.7–5.2) vs 5.4 (5.0–5.5)
  - HR (95% CI): 0.78 (0.64–0.96)

---

**IMpower133**

- **OS**
  - Atezolizumab + CPET (n=269)
  - Pazopanib (n=269)
  - mOS, months (95% CI): 12.3 (8.9–15.6) vs 9.3 (9.0–11.3)
  - HR (95% CI): 0.78 (0.54–1.11)
  - p = 0.3089
  - 51.7% of patients remain OS at 2 years
  - 38.2% at 3 years

- **PFS**
  - Atezolizumab + CPET (n=269)
  - Pazopanib (n=269)
  - mPFS, months (95% CI): 5.2 (4.4–5.4) vs 4.2 (4.1–5.4)
  - HR (95% CI): 0.77 (0.52–1.16)
  - p = 0.2017
  - 50.9% of patients remain PFS at 6 months
  - 22.4% at 12 months

 Median follow-up months:
 - CASPIAN: 13.0
 - IMpower133: 13.3
CASPION - EXPLORATORY PD-L1 ANALYSIS

- 94.9% and 77.6% of patients had PD-L1 expression <1% on TCs and ICs, respectively
- Due to low PD-L1 expression, a 1% cut-off was used in post-hoc analyses

- Durvalumab + EP was associated with improved OS vs EP, regardless of PD-L1 expression with a 1% cut-off
- No significant interaction was observed with OS based on PD-L1 expression as a continuous variable (TC, p=0.54; IC, p=0.23); similar results were observed with PFS and ORR

Paz Ares L et al, ESMO Proferred Paper 28Sep
IMpower 133-Update on biomarkers

- PD-L1 and bTMB biomarkers identify distinct patient populations in ES-SCLC
- Post-hoc exploratory analysis conducted for OS by PD-L1 expression
  - The PD-L1 IHC biomarker evaluable population (BEP) comprised 34% of the ITT population
  - VENTANA SP263 assay was used to determine PD-L1 status on slide sections ≤ 1 year old
  - PD-L1 expression was observed mostly on immune cells (IC), with limited expression on tumour cells (TC)
  - Efficacy analyses were conducted using PD-L1 expression cut-offs of 1% and 5%

**PD-L1 IHC expression in ES-SCLC (n = 137)**

<table>
<thead>
<tr>
<th>IC</th>
<th>% BEP (n)</th>
<th>TC</th>
<th>% BEP (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1%</td>
<td>49.6% (68)</td>
<td>&lt; 1%</td>
<td>94.2% (129)</td>
</tr>
<tr>
<td>≥ 1%</td>
<td>50.4% (69)</td>
<td>≥ 1%</td>
<td>5.8% (8)</td>
</tr>
<tr>
<td>≥ 5%</td>
<td>20.4% (28)</td>
<td>≥ 5%</td>
<td>1.5% (2)</td>
</tr>
</tbody>
</table>

- PD-L1 analysis was based on a limited data set (34% of the ITT)

**PD-L1 Expression ≥ 1% TC or IC**

**PD-L1 Expression < 1% TC or IC**

**Overall Survival (%)**

- **Atteo + CP/ET (n = 38)**
  - Median OS, mo (95% CI): 9.7 (7.8, 17.4)
  - HR (95% CI): 0.87 (0.51, 1.49)
- **Placebo + CP/ET (n = 38)**
  - Median OS, mo (95% CI): 10.6 (8.3, 14.7)

- **Atteo + CP/ET (n = 28)**
  - Median OS, mo (95% CI): 10.2 (7.5, 15.7)
  - HR (95% CI): 0.51 (0.30, 0.89)
- **Placebo + CP/ET (n = 57)**
  - Median OS, mo (95% CI): 3.3 (6.9, 9.1)

Median follow-up, 22.9 months
bTMB did not differentiate benefit of atezolizumab in IMpower133

<table>
<thead>
<tr>
<th>Population</th>
<th>Atezolizumab + CP/ET</th>
<th>Placebo + CP/ET</th>
<th>OS hazard ratioa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n = 261)</td>
<td>12.3</td>
<td>10.9</td>
<td>0.74 (0.54, 1.02)</td>
</tr>
<tr>
<td>Female (n = 142)</td>
<td>12.5</td>
<td>9.5</td>
<td>0.65 (0.42, 1.00)</td>
</tr>
<tr>
<td>&lt; 65 years (n = 217)</td>
<td>12.1</td>
<td>11.5</td>
<td>0.92 (0.64, 1.32)</td>
</tr>
<tr>
<td>≥ 65 years (n = 186)</td>
<td>12.5</td>
<td>9.6</td>
<td>0.53 (0.36, 0.77)</td>
</tr>
<tr>
<td>ECOG PS 0 (n = 140)</td>
<td>16.6</td>
<td>12.4</td>
<td>0.79 (0.49, 1.27)</td>
</tr>
</tbody>
</table>

Biomarker study is not available in CASPIAN study!

No brain metastases (n = 368) 12.6 10.4 0.69 (0.52, 0.99)
Liver metastases (n = 149) 9.3 7.8 0.81 (0.55, 1.20)
No liver metastases (n = 254) 16.8 11.2 0.64 (0.45, 0.90)

| bTMB < 10 mut/mb (n = 139) 11.8 9.2 0.70 (0.45, 1.07) |
| bTMB ≥ 10 mut/mb (n = 212) 14.6 11.2 0.68 (0.47, 0.97) |

bTMB < 16 mut/mb (n = 271) 12.5 9.9 0.71 (0.52, 0.98)
bTMB ≥ 16 mut/mb (n = 80) 17.8 11.9 0.63 (0.35, 1.15)

ITT (N = 403) 12.3 10.3 0.70 (0.54, 0.91)


a Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
### CASPIAN - PATTERNS OF FIRST PROGRESSION

#### Types of progression

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + EP (N=268)</th>
<th>EP (N=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total progression events, n (%)</strong></td>
<td>226 (84.3)</td>
<td>233 (86.6)</td>
</tr>
<tr>
<td><strong>RECIST-defined progression, n (%)</strong></td>
<td>192 (71.6)</td>
<td>194 (72.1)</td>
</tr>
<tr>
<td>Target lesions</td>
<td>115 (42.9)</td>
<td>106 (39.4)</td>
</tr>
<tr>
<td>Non-target lesions</td>
<td>66 (24.6)</td>
<td>61 (22.7)</td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
<td>111 (41.4)</td>
<td>127 (47.2)</td>
</tr>
<tr>
<td><strong>Death in absence of progression, n (%)</strong></td>
<td>34 (12.7)</td>
<td>39 (14.5)</td>
</tr>
</tbody>
</table>

**Sites of new lesions (>5% patients)**

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + EP (N=268)</th>
<th>EP (N=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New lesions, n (%)</strong></td>
<td>111 (41.4)</td>
<td>127 (47.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>23 (8.6)</td>
<td>41 (15.2)</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>31 (11.6)</td>
<td>31 (11.5)</td>
</tr>
<tr>
<td>Liver</td>
<td>15 (5.6)</td>
<td>24 (8.9)</td>
</tr>
<tr>
<td>Bone</td>
<td>12 (4.5)</td>
<td>19 (7.1)</td>
</tr>
<tr>
<td>Regional lymph nodes</td>
<td>15 (5.6)</td>
<td>12 (4.5)</td>
</tr>
</tbody>
</table>

- Numerically fewer patients developed new lesions at first progression with durvalumab + EP versus EP
- No difference in the incidence of new brain/CNS lesions between arms

*CNS, central nervous system*
CASPION – TIME TO DETERIORATION

- Durvalumab + EP was favoured across all symptoms

**QLQ-C30**
- Appetite loss (n=454)
  - HR (95% CI): 0.70 (0.542-0.899)
- Constipation (n=468)
  - HR: 0.65 (0.489-0.855)
- Diarrhoea (n=477)
  - HR: 0.59 (0.442-0.774)
- Fatigue (n=476)
  - HR: 0.75 (0.574-0.989)
- Nausea/Vomiting (n=488)
  - HR: 0.82 (0.653-1.027)
- Pain (n=472)
  - HR: 0.80 (0.626-1.027)
- Insomnia (n=435)
  - HR: 0.79 (0.615-1.021)
- Hiccough (n=458)
  - HR: 0.75 (0.583-0.980)
- Dyspnoea (n=481)
  - HR: 0.76 (0.630-1.026)
- Haemoptysis (n=487)
  - HR: 0.79 (0.623-1.030)
- Pain in arm/shoulder (n=478)
  - HR: 0.64 (0.459-0.876)
- Pain in chest (n=478)
  - HR: 0.70 (0.535-0.915)
- Pain in other parts (n=468)
  - HR: 0.70 (0.575-0.900)

**QLQ-C13**
- Dyspnoea (n=481)
  - HR: 0.64 (0.459-0.876)
- Fatigue (n=476)
  - HR: 0.70 (0.535-0.915)
- Cough (QLQ-C13)*
  - HR: 0.70 (0.535-0.915)

Paz Ares L et al, ESMO Proferred Paper 28Sep
Vragen voor checkpoint inhibitie bij SCLC

• Caspian studie: immature data. Worden deze beter?
• Data arm: durva/tremilumumab + chemo?
• Identificeren van een subgroep die op immuuntherapie respondeert?
• Is een biomarker wel haalbaar in de dagelijkse praktijk?
• Wat zijn gevolgen als we in Nederland geen immuuntherapie geven bij SCLC?