THE VALUE OF PD-L1 EXPRESSION AS PREDICTOR OF BENEFIT WITH IMMUNE CHECKPOINT INHIBITORS

Systematic review across solid tumours

Ahmad Awada, Luis Castelo-Branco, Emiliano Calvo, Irene Moreno, Karima Oualla, Ines Pires da Silva, Francesco Sclafani
METHODOLOGY:

- Systematic review from Phase III clinical trials with Immune Checkpoint Inhibitors on different solid tumour settings and data available by PDL1 stratification
- Publications until July 2019
TOPICS

- Introduction
- Untreated NSCLC (Luis Castelo-Branco L; Ahmad Awada)
- Melanoma (Ines Pires da Silva)
- Head and Neck (Karima Oualla)
- Genito-Urinary (Irene Moreno; Emiliano Calvo)
- Gastro-Intestinal (Francesco Sclafani)
PD-L1 IS AN IMPORTANT INHIBITOR OF T-CELLS CITOTOXICITY

Tumour cell

T-cell

THERE ARE DIFFERENT REGULATORY MECHANISMS OF PD-L1 EXPRESSION AND IT IS VARIABLE OVER TIME

### PD-L1 ASSESSMENT BY DIFFERENT TECHNIQUES

Summary of PD-L1 monoclonal antibodies and technical aspects for evaluation and agencies’ approvals in NSCLC

<table>
<thead>
<tr>
<th>PD-L1 mAb clone</th>
<th>Ab host species</th>
<th>Automated platform</th>
<th>Checkpoint inhibitor (target)</th>
<th>PD-L1 scoring</th>
<th>Definition of positivity (cutoffs)</th>
<th>FDA status</th>
<th>EMA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>22C3</td>
<td>Mouse</td>
<td>Dako (Autostainer Link 48)</td>
<td>Pembrolizumab (PD-1)</td>
<td>TC</td>
<td>TC ≥1% (minimum of 100 TC)</td>
<td>Companion</td>
<td>CE mark</td>
</tr>
<tr>
<td>28-8</td>
<td>Rabbit</td>
<td>Dako (Autostainer Link 48)</td>
<td>Nivolumab (PD-L1)</td>
<td>TC</td>
<td>TC ≥1% (minimum of 100 TC)</td>
<td>Complementary</td>
<td>CE mark</td>
</tr>
<tr>
<td>SP142</td>
<td>Rabbit</td>
<td>Ventana (BenchMark ULTRA)</td>
<td>Atezolizumab (PD-L1)</td>
<td>TC, IC</td>
<td>TC ≥50% or IC ≥10% (minimum of 50 TC with associated stroma)</td>
<td>Complementary</td>
<td>CE mark</td>
</tr>
<tr>
<td>SP263</td>
<td>Rabbit</td>
<td>Ventana (BenchMark ULTRA)</td>
<td>Durvalumab (PD-L1)</td>
<td>TC</td>
<td>TC ≥25% (minimum of 100 TC)</td>
<td>FDA approval only for urothelial carcinoma</td>
<td>CE mark for nivolumab and pembrolizumab in NSCLC and durvalumab in urothelial carcinoma</td>
</tr>
<tr>
<td>73-10</td>
<td>Rabbit</td>
<td>Dako</td>
<td>Avelumab (PD-L1)</td>
<td>TC</td>
<td>TC ≥1% (minimum cells not defined)</td>
<td>FDA approval</td>
<td>NA</td>
</tr>
</tbody>
</table>

THE EXPRESSION OF PDL1 IN TUMOUR CELLS COULD BE ASSOCIATED WITH THE EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN SOLID TUMOURS?
PREVIOUSLY UNTREATED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)
UNTREATED STAGE IV NSCLC

Immune Checkpoint Inhibitors (ICIs) Phase III clinical trials with results

ICIs only

- KEYNOTE-024
- KEYNOTE-042
- CHECKMATE-026
- CHECKMATE-227*

ICIs + Chemotherapy

- KEYNOTE-189
- KEYNOTE-407
- IMpower-150
- IMpower-130
- IMpower-131
- IMpower-132

*Includes also combination Nivo+IPI and Nivolumab + chemo
Histology agnostic – Pembrolizumab trials

### UNTREATED STAGE IV NSCLC

- **PD-L1 TPS ≥ 50%**
  - No EGFR/ALK
  - **KEYNOTE-024**
    - Pembro vs Platinum-doublet
    - Hazard ratio (OS)
      - 0.60 (0.41-0.89)

- **PD-L1 TPS ≥ 1%**
  - No EGFR/ALK
  - **KEYNOTE-042**
    - Pembro vs carbo + paclitaxel or pemetrexed
    - Hazard ratio (OS)
      - PD-L1 ≥ 1%: 0.81 (0.71-0.93)
      - PD-L1 ≥ 20%: 0.77 (0.64-0.92)
      - PD-L1 ≥ 50%: 0.69 (0.56-0.85)

---

G Lopez ASCO 2018; M. Reck ESMO 2016.
PEMBRO VS CHEMO
UNTREATED NSCLC (KEYNOTE-042)

PD-L1 $\geq 50\%$

**Benefit**

PD-L1 1-49%

**Non-Benefit**

Overall survival (%)

Reprinted from The Lancet, 393 (10183), Mok TSK, et al, Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial, 1819-1830, Copyright 2019, with permission from Elsevier.
Histology agnostic – CheckMate 227 Trial – Results by PD-L1

- **PD-L1 < 1%**
  - TMB ≥10 mut/Mb
  - Nivo + Ipi vs chemo
  - HR (PFS) 0.48 (0.27–0.87)

- **PD-L1 ≥ 1%**
  - TMB ≥10 mut/Mb
  - Nivo + Ipi vs chemo
  - HR (PFS) 0.62 (0.44–0.88)

H. Borghaei ASCO 2018. M.D. Hellmann NEJM 2018
UNTREATED STAGE IV NSCLC SQUAMOUS

**KEYNOTE-407**
Carbo + paclitaxel/Nab + pembrolizumab vs Carbo + paclitaxel/Nab + placebo

- HR (PFS): 0.56 (0.45-0.70)
  - TPS < 1%: 0.68 (0.47-0.98)
  - TPS 1-49%: 0.56 (0.39-0.80)
  - TPS ≥ 50%: 0.37 (0.24-0.58)

**Impower 131**
Carbo + paclitaxel + atezolizumab (A) vs Carbo + Nabpaclitaxel + atezolizumab (B) vs Carbo + Nabpaclitaxel (C)

- Arm B vs Arm C
  - HR (PFS): 0.71 (0.60-0.85)
  - TC 0 and IC 0: 0.81 (0.64-1.03)
  - TC 1/2 or IC 1/2: 0.70 (0.53-0.92)
  - TC 3 or IC 3: 0.44 (0.27-0.71)

L Parez-Ares ASCO 2018; R Jotte ASCO 20185
Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial, 924-937, Copyright 2019, with permission from Elsevier.
Chemotherapy-naïve patients with Stage IV non-squamous NSCLC without EGFR or ALK genetic alteration

**Stratification factors:**
- Sex
- Smoking status
- ECOG PS
- Chemotherapy regimen

**N=578**

**Induction therapy**
- **Arm APP**
  - Atezolizumab + carboplatin or cisplatin + pemetrexed
  - 4 or 6 cycles
- **Arm Ppa**
  - Carboplatin or cisplatin + pemetrexed
  - 4 or 6 cycles

**Maintenance therapy**
- Atezolizumab + pemetrexed
- Pemetrexed

**Maintenance treatment until PD by RECIST v1.1 or loss of clinical benefit**

Co-primary endpoints: INV-assessed PFS and OS
Secondary endpoints: INV-assessed ORR and DOR, patient-reported outcomes and safety measures
Exploratory analyses: Clinical and biomarker subgroup analyses
- Biomarker-evaluable tissue not mandatory for enrolment (was available from 60% of patients)


^Atezolizumab: 1200 mg IV q3w; Carboplatin: AUC 6 mg/mL/min IV q3w; Cisplatin: 75 mg/m^2^ IV q3w; Pemetrexed: 500 mg/m^2^ IV q3w. NCT02657434. Data cutoff: May 22, 2018.
IMPOWER-132
PFS BY PD-L1 STATUS

**PD-L1 High**
TC3 or IC3

**PD-L1 Low**
TC1/2 or IC1/2

**PD-L1 Negative**
TC0 and IC0

<table>
<thead>
<tr>
<th></th>
<th>APP (n = 63)</th>
<th>PP (n = 73)</th>
<th>APP (n = 68)</th>
<th>PP (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, %</strong></td>
<td>72%</td>
<td>55%</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>**CR</td>
<td>PR, %**</td>
<td>0</td>
<td>72%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Median DOR, mo</strong></td>
<td>NE</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>12-month PFS</strong></td>
<td>46%</td>
<td>25%</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Median PFS, mo</strong></td>
<td>10.8</td>
<td>6.5</td>
<td>6.2</td>
<td>5.7</td>
</tr>
<tr>
<td><em><em>HR</em> (95% CI)</em>*</td>
<td>0.46 (0.22, 0.96)</td>
<td>0.80 (0.56, 1.16)</td>
<td>0.45 (0.31, 0.64)</td>
<td></td>
</tr>
</tbody>
</table>

APP, avelozilumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.  
* Overall HR 0.57 (0.45, 0.73) in biomarker-evaluable patients (60% of ITT).  
* Unstratified HR. Data cutoff: May 22, 2018.
### SUMMARY OF RESULTS BY PDL1 SUBGROUPS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumour type</th>
<th>Interventions</th>
<th>Nº of patients</th>
<th>Main outcomes - results</th>
<th>Hazard Ratio (HR) by pdl1 stratification groups*</th>
<th>Trend for increased benefit with higher PDL1?</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-024</td>
<td>Advanced NSCLC and PD-L1 ≥ 50%</td>
<td>1 - Pembrolizumab 2 - Chemotherapy</td>
<td>305 (1:1)</td>
<td>mPFS 1 - 10.3 months 2 - 6.0 months</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>KEYNOTE-189</td>
<td>Metastatic non-squamous NSCLC without sensitising EGFR or ALK mutations</td>
<td>1 - Chemo 2 - Chemo + Pembro</td>
<td>616 (2:1)</td>
<td>mOS at 12 months 1 - 69.2% 2 - 49.4% HR for death, 0.49 (0.38 to 0.64)</td>
<td>PDL1 &lt; 1%: 0.59  PDL1 1-49%: 0.55  PDL1 ≥ 50 %: 0.42</td>
<td>Yes</td>
</tr>
<tr>
<td>IMPOWER-150</td>
<td>Nonsquamous NSCLC</td>
<td>1 - Atezo + Chemo 2 - Beva + Chemo 3 - Atezolizumab + Beva + Chemo</td>
<td>2 – 336 pts 3 – 356 pts</td>
<td>mPFS 1 - 8.3 months 2 - 8.3 months HR 0.59 (0.50–0.70)</td>
<td>TC0 and ICO: 0.77  TC0/1/2 and ICO1/2: 0.68  TC1/2 or IC1/2: 0.56  TC1/2/3 or IC1/2/3: 0.50  TC3 or IC3: 0.39</td>
<td>Yes</td>
</tr>
<tr>
<td>KEYNOTE-042</td>
<td>Advanced NSCLC PD-L1 ≥ 50%</td>
<td>1 - Pembrolizumab 2 - Platinum based chemotherapy</td>
<td>1274 (1:1)</td>
<td>OS PDL1 ≥ 50% 20.0 vs 12.2 months  PDL1 ≥ 20% 17.7 vs 13.0 months  PDL1 ≥ 1% 16.7 vs 12.1 months</td>
<td>PDL1 ≥1%: 0.81  PDL1 ≥20%: 0.77  PDL1 ≥ 50%: 0.69</td>
<td>Yes</td>
</tr>
<tr>
<td>Impower-130</td>
<td>Non-squamous NSCLC</td>
<td>1 - Atezo + Carbo + Nab-paclitaxel 2 - Carbo + Nab-paclitaxel</td>
<td>724 (2:1)</td>
<td>mOS 1 - 18.6mo; 2 – 13.9 mo mPFS 1 -7.0 mo vs 2 - 5.5 mo</td>
<td>PDL1 negative: 0.72 (0.56–0.91)  PDL1 low: 0.61 (0.43–0.85)  PDL1 High: 0.51 (0.34–0.77)</td>
<td>Yes</td>
</tr>
<tr>
<td>Impower-131</td>
<td>Stage IV squamous NSCLC</td>
<td>A - Atezo + Carbo + paclitaxel  B - Atezo + Carbo + Nabpaclitaxel  C - Carbo + Nabpaclitaxel</td>
<td>1021 (1:1:1)</td>
<td>mPFS B - 6.3mo C - 5.6 (HR, 0.715; P = 0.0001)</td>
<td>PDL1 neg: 0.81 (0.64-1.03)  PDL1 low: 0.70 (0.53-0.92)  Pdl1 high: 0.44 (0.27-0.71)</td>
<td>Yes</td>
</tr>
<tr>
<td>CHECKMATE-026</td>
<td>Untreated stage IV or recurrent NSCLC and PD-L1 ≥ 1%</td>
<td>1 - Nivolumab 2 - Platinum based chemotherapy</td>
<td>423 (1:1)</td>
<td>mPFS 1 - 4.2 months 2 - 5.9 months</td>
<td>Pdl1 ≥ 5%: 1.18  Pdl1 ≥ 50%: 1.07</td>
<td>NO</td>
</tr>
<tr>
<td>KEYNOTE-047</td>
<td>Metastatic squamous NSCLC</td>
<td>1 - Chemo + Pembro 2 - Chemo + placebo</td>
<td>559 (1:1)</td>
<td>mOS 1 - 15.9 months 2 - 11.3 months, HR 0.64 (0.49-0.85)</td>
<td>PDL1 &lt; 1%: 0.61  PDL1 1-49%: 0.57  PDL1 &gt; 50%: 0.64</td>
<td>NO</td>
</tr>
<tr>
<td>CHECKMATE-227</td>
<td>Stage IV or recurrent NSCLC that was not previously treated with chemotherapy</td>
<td>Nivo Nivo + IPI Nivo + chem Chemo</td>
<td>2220 (1:1:1)</td>
<td>1-year PFS (patients with high TMB) nivolumab+ipilimumab 42.6% chemotherapy 13.2%</td>
<td>PD-L1 &lt; 1%; TMB ≥ 10 mut/Mb: 0.48  PD-L1 ≥ 1%; TMB ≥ 10 mut/Mb  HR 0.82</td>
<td>NO</td>
</tr>
<tr>
<td>Impower-132</td>
<td>Stage IV non-squamous NSCLC without EGFR or ALK genetic alteration</td>
<td>1 - Atezo + platin + pemetrexed 2 - Platin + pemetrexed</td>
<td>578 (1:1)</td>
<td>12-mo PFS 1 – 33.7% 2 – 17%</td>
<td>PDL1 neg – HR 0.45 (0.31, 0.64)  PDL1 low – HR 0.80 (0.56, 1.16)  PDL1 high – HR 0.46 (0.22, 0.96)</td>
<td>NO</td>
</tr>
</tbody>
</table>

* HR from main outcome results
NSCLC AND PD-L1 EXPRESSION
IMPLICATION FOR CLINICAL
PRACTICE AND RESEARCH

Trend for increased benefit with ICIs alone on enriched PD-L1 NSCLC
On Combination ICI + chemo less importance of PD-L1 expression
Many uncertainties on the real value of PD-L1 for clinical practice with ICIs in untreated NSCLC

Important questions to be answered

- Why PD-L1 expression has a high value in some studies and low in others?
- PD-L1 expression combined with other biomarkers (eg. TMB; specific neo-antigens) for a score predictor of response in NSCLC?
- Are checkpoint inhibitors monotherapy better than combination with chemotherapy in PD-L1≥ 50% NSCLC untreated tumours?
- Chemo + ICI 1st line vs sequence of treatment, regardless PD-L1 expression?
MELANOMA
### PHASE III ICI TRIALS IN MELANOMA STRATIFIED BY PD-L1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Drugs</th>
<th>Clinical outcome</th>
<th>Definition and % of PD-L1+ melanomas</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 1325</td>
<td>Stage III resected melanoma No in-transit mets IIA (N1a &gt;1 mm )</td>
<td>(1) Pembrolizumab 200mg Q3W (n=514) (2) Placebo 200mg Q3W (n=505)</td>
<td>1-year RFS</td>
<td>Pembro: 75.4% Placebo: 61.0% HR 0.57; 98.4% CI, 0.43-0.74; p&lt;0.001</td>
<td>≥1% of PD-L1+ tumour and adjacent immune cells</td>
</tr>
<tr>
<td>CM-066</td>
<td>Metastatic melanoma BRAF WT Treatment naïve</td>
<td>(1) Nivolumab 3mg/Kg Q2W + Placebo 1000mg/m² Q3W (n=210) (2) DTIC 1000mg/m² Q3W + Placebo 3mg/Kg Q2W (n=208)</td>
<td>mPFS</td>
<td>Nivolumab + placebo: 5.1 months DTIC + placebo: 2.2 months HR 0.43; 95% CI, 0.34-0.56; p&lt;0.001</td>
<td>≥5% of PD-L1+ tumour cells</td>
</tr>
<tr>
<td>CM-067</td>
<td>Metastatic melanoma Treatment naïve</td>
<td>(1) Ipilimumab 3mg/Kg Q3W + Nivolumab 1mg/Kg Q3W (n=314) (2) Nivolumab 3mg/Kg Q2W (n=316) (3) Ipilimumab 3mg/Kg Q3W (n=315)</td>
<td>mPFS</td>
<td>Ipilimumab + Nivolumab: 11.5 months* Nivolumab: 6.9 months* Ipilimumab: 2.9 months* HR 0.42; 95% CI 0.31-0.57; p&lt;0.001</td>
<td>≥5% of PD-L1+ tumour cells</td>
</tr>
<tr>
<td>KN-006</td>
<td>Metastatic melanoma One prior line of treatment was allowed (except anti-PD(L)1 or anti-CTLA-4)</td>
<td>(1) Pembrolizumab 10mg/Kg Q2W (n=279) (2) Pembrolizumab 10mg/Kg Q3W (n=277) (3) Ipilimumab 3mg/Kg Q3W (n=278)</td>
<td>mPFS</td>
<td>Pembrolizumab Q2W: 5.6 months Pembrolizumab Q3W: 4.1 months Ipilimumab: 2.8 months HR 0.61; 95% CI 0.50-0.75; p&lt;0.001</td>
<td>≥1% of PD-L1+ tumour and adjacent immune cells</td>
</tr>
</tbody>
</table>

RFS = recurrence-free survival. mPFS = median progression-free survival
PHASE III ICI TRIALS IN MELANOMA STRATIFIED BY PD-L1

**Adjuvant**

EORTC 1325 trial
Pembro vs Placebo

HR (RFS) with pembro
PD-L1+ 0.54; 95% CI, 0.42-0.69; p<0.001
PD-L1- 0.47; 95% CI, 0.26-0.85; p=0.01

**Metastatic**

Checkmate-066
Keynote-006

Checkmate-067


HR = Hazard ratio; RFS = recurrence-free survival.

HR = Hazard ratio; RFS = recurrence-free survival.
Patients with PDL1-positive melanoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total No.</th>
<th>No. with Event</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>428</td>
<td>102</td>
<td>0.54 (0.42–0.69)</td>
</tr>
<tr>
<td>Placebo</td>
<td>425</td>
<td>176</td>
<td>1.00</td>
</tr>
</tbody>
</table>

P < 0.001 by stratified log-rank test

No. at Risk
- Pembrolizumab: 428, 370, 350, 333, 317, 281, 266, 156, 61, 13, 0
- Placebo: 425, 353, 317, 281, 233, 141, 55, 13, 0

Patients with PDL1-negative melanoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total No.</th>
<th>No. with Event</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>59</td>
<td>20</td>
<td>0.47 (0.26–0.85)</td>
</tr>
<tr>
<td>Placebo</td>
<td>57</td>
<td>27</td>
<td>1.00</td>
</tr>
</tbody>
</table>

P = 0.01 by stratified log-rank test

No. at Risk
- Pembrolizumab: 59, 51, 47, 44, 37, 20, 10, 2, 0
- Placebo: 57, 46, 34, 30, 23, 12, 5, 2, 0

PHASE III ICI TRIALS IN MELANOMA STRATIFIED BY PD-L1

**Checkmate-066**
1. Nivolumab + Placebo
2. DTIC + Placebo

**Checkmate-067**
1. Ipilimumab + Nivolumab
2. Nivolumab
3. Ipilimumab

**Keynote-006**
1. Pembro 10 mg/kg Q2W
2. Pembro 10 mg/kg Q3W
3. IPI 3 mg/Kg Q3W

**Metastatic**

- **ORR with Nivo + Placebo**
  - PD-L1+: 52.7%
  - PD-L1-: 33.1%

- **mPFS in PD-L1+**
  - IPI + NIVO = NIVO (14m)

- **mPFS in PD-L1-**
  - IPI + NIVO (11.2m) > NIVO (5.3m)

ORR = objective response rate; mPFS = median progression-free survival.
CHECKMATE-067
METASTATIC: IPI VS NIVO VS IPI+NIVO

PD-L1+ melanoma

PD-L1- melanoma

Reprinted from The Lancet, 390 (10105), Schachter J. et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006), 1853-1862, Copyright 2017, with permission from Elsevier.
MELANOMA AND PD-L1 EXPRESSION

Implication for clinical practice and research

In melanoma, PD-L1 is not a good biomarker of response to immune checkpoint inhibitors

Challenges:
- Different antibodies and thresholds
- Intra & intertumour heterogeneity

The greatest benefit with the combination of nivolumab and ipilimumab versus nivolumab alone seems to occur in PD-L1- melanomas
HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)
CHECKMATE 141

HNSCC progression after platinum based therapy – Nivo vs Chemo

**PD-L1 expressors (≥1%)**
(57% of the tested patients)

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo</td>
<td>8.2 (6.7, 9.5)</td>
<td>0.55 (0.39, 0.78)</td>
</tr>
<tr>
<td>IC</td>
<td>4.7 (3.8, 6.2)</td>
<td></td>
</tr>
</tbody>
</table>

**PD-L1 non-expressors (<1%)**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo</td>
<td>6.5 (4.4, 11.7)</td>
<td>0.73 (0.49, 1.09)</td>
</tr>
<tr>
<td>IC</td>
<td>5.5 (3.7, 8.5)</td>
<td></td>
</tr>
</tbody>
</table>

Reprinted from Oral Oncology, 81, Ferris RL, et al. Nivolumab vs investigator’s choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumour PD-L1 expression, 45-51, Copyright 2018, with permission from Elsevier.
PHASE III KEYNOTE-040 STUDY

Key eligibility criteria
- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 months of multimodal therapy using platinum\(^a\)
- ECOG PS 0 or 1
- Known p16 status (oropharynx)\(^b\)
- Tissue sample\(^c\) for PD-L1 assessment\(^d\)

Stratification factors
- ECOG PS (0 vs 1)
- p16 status (positive vs negative)
- PD-L1 TPS\(^d\) (\(\geq 50\%\) vs <50\%)

Clinical trials:
- Pembrolizumab 200 mg IV q3w for 2 y
- Methotrexate 40 mg/m\(^2\) qw\(^e\)
  OR
- Docetaxel 75 mg/m\(^2\) q3w
  OR
- Cetuximab 250 mg/m\(^2\) qw\(^f\)

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

\(^a\)Limit of 2 prior therapies for R/M HNSCC.
\(^b\)Assessed using the CINtec p 16 Histology assay (Ventana); cutpoint for positivity = 70%.
\(^c\)Newly collected preferred.
\(^d\)Assessed using the PD-L1 IHC 22C3 pharmDx assay. TPS, tumour proportion score = % of tumour cells with membranous PD-L1 expression.
\(^e\)Could be increased to 60 mg/m\(^2\) qw in the absence of toxicity.
\(^f\)Following a loading dose of 400 mg/m\(^2\).

Overall survival in the intention-to-treat populations according to PD-L1 expression category

Reprinted from The Lancet, 393 (10167), Cohen EW, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study, 156-167. Copyright 2019, with permission from Elsevier.
**KEYNOTE-048 STUDY DESIGN (NCT02358031)**

### Key eligibility criteria
- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment\(^a\)
- Known p16 status in the oropharynx\(^b\)

### Stratification factors
- PD-L1 expression\(^a\) (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

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\(^a\)Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS, tumour proportion score = % of tumour cells with membranous PD-L1 expression. 
\(^b\)Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. 
\(^c\)Following a loading dose of 400 mg/m\(^2\). Burtness et al. Abstract #LBA8 PR. ESMO 2018.
Overall survival: P vs E, CPS ≥20 population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>62%</td>
<td>0.61 (0.45-0.83)</td>
</tr>
<tr>
<td>EXTREME</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate 56.9% 44.9%
24-mo rate 36.3% 22.1%
Median (95% CI) 14.9 mo (11.6-21.5) 10.7 mo (8.8-12.8)

Overall survival: P vs E, CPS ≥1 population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>69%</td>
<td>0.78 (0.64-0.96)</td>
</tr>
<tr>
<td>EXTREME</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate 51.0% 43.6%
24-mo rate 30.2% 18.6%
Median (95% CI) 12.3 mo (10.8-14.9) 10.3 mo (9.0-11.5)

OVERALL SURVIVAL: P+C VS E, TOTAL POPULATION

## PHASE III TRIALS TESTING ICIS IN RECURRENT/METASTATIC HNSCC BY PD-L1 STATUS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumour type</th>
<th>Interventions</th>
<th>Nº of patients</th>
<th>PD-L1 Expression location</th>
<th>Cut-off</th>
<th>HR for OS Overall</th>
<th>HR for OS PD-L1+</th>
<th>HR for OS PD-L1-</th>
<th>PDL-1 a relevant biomarker?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkmate-141</td>
<td>Metastatic HNSCC in 2nd line</td>
<td>Nivolumab vs chemotherapy</td>
<td>240</td>
<td>TCs</td>
<td>&gt;1%</td>
<td>0.68</td>
<td>0.55</td>
<td>0.73</td>
<td>Yes</td>
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</tr>
<tr>
<td>KEYNOTE-040</td>
<td>Metastatic HNSCC in 2nd line</td>
<td>Pembrolozumab vs chemotherapy</td>
<td>247</td>
<td>TCs + Ics (CPS) TCs (TPS)</td>
<td>CPS &gt;1</td>
<td>0.80 (P 0.016)</td>
<td>CPS ≥1</td>
<td>CPS &lt;1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>TPS &gt;50%</td>
<td>0.74</td>
<td>CPS ≥50%</td>
<td>CPS &lt;1</td>
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<td></td>
<td></td>
<td>0.53</td>
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<td>1.28</td>
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<td></td>
<td></td>
<td>0.93</td>
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</tr>
<tr>
<td>KEYNOTE-048</td>
<td>Metastatic HNSCC in 1st line</td>
<td>1. Pembro vs chemo</td>
<td>882</td>
<td>TCs + Ics (CPS)</td>
<td>CPS &gt;1%</td>
<td>0.77 (P 0.0086)</td>
<td>0.78</td>
<td>0.61</td>
<td>Ø</td>
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<td></td>
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<td></td>
<td>CPS &gt;20%</td>
<td></td>
<td>Ø</td>
<td>0.61</td>
<td>Ø</td>
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<tr>
<td></td>
<td></td>
<td>2. Pembro + chemo vs chemo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.71</td>
<td>0.93</td>
<td>No for combination with chemo</td>
</tr>
</tbody>
</table>

OS: overall survival; HR: hazard ratio; TCs: tumour cells; Ics: immune cells; CPS: number of PD-L1-positive cells divided by total number of tumour cells 100; TPS: percentage of tumour cells with membranous PD-L1 expression Ø, data no available
IMPLICATION OF PD-L1 EXPRESSION AND CHALLENGES IN CLINICAL PRACTICE FOR HNSCC

- **KEYNOTE-048** – Better OS with pembrolizumab monotherapy in first line HNSCC and trend for more benefit with higher PD-L1 expression (CPS ≥20% vs ≥1%)
- Benefit on combination pembrolizumab + chemo regardless PDL-1 expression
- **KEYNOTE-040** – Improved OS with higher pd-L1 expression
- **CHECKMATE-141** – Trend for more benefit with higher PD-L1 expression
- No firm conclusion on the value of pd-L1 for clinical practice with ICIs in HNSCC
  - Trend for relevance on ICI monotherapy but lower importance on combination ICI+ chemo
- Other different biomarkers under investigation: HPV status, tumour immune infiltration, TMB, etc.
RENAL CARCINOMA
## POSITIVE PHASE III TRIALS WITH CPI IN METASTATIC RENAL CANCER

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Interventions</th>
<th>No. pts</th>
<th>Main outcomes results</th>
<th>Adverse events</th>
<th>PDL1 stratification</th>
</tr>
</thead>
</table>
| CHECKMATE-214       | Ph III, 1st line                             | A. Nivo (3 mg/kg)-Ipi (1 mg/kg)        | 1096 (1:1) | **OS.** N-I: Not Reached (NR)/S: 26 m  
**PFS.** N-I: 11,6 m/S: 8,4 m  
**ORR.** N-I: 42%./S: 27% | Any grades: N-I: 93%; S: 97%  
G3/G4: N-I: 46%; S: 63% | No (regardless PDL1 status) |
|                      | Intermediate-bad prognostic (Including sarcomatoid) | B. Sunitinib                           |         |                                          |                |                     |
| IMMOTION 151        | Ph III, 1st line                             | A. Atezo + Beva B. Sunitinib           | 915 (1:1) | **OS.** PDL1+: All: A-B 34 m vs S: 32,7 m  
A-B 33,6 m vs S: 34,9 m  
**PFS.** PDL1+: All: A-B 11,2 m vs S: 7,7 m. A-B 11,2 m vs S: 8,4 m  
**ORR.** PDL1+: All: A-B 43% vs S: 35%. A-B 37% vs S: 33% | Any grades: A-B: 93%/S: 97%  
G3/G4: A-B: 46%/S: 63%  
AEs-Discontinuation: 5% (A-B) vs 8% (S) | Yes <1% vs ≥1%, assessed by ICH- VENTANA PD-L1 SP142 assay |
|                      | (Including sarcomatoids)                      |                                        |         |                                          |                |                     |
| JAVELIN RENAL 101   | Ph III 1st line                              | A. Avelumab + Axitinib B. Sunitinib    | 886 (1:1) | **OS.** PDL1+: All: A-A NR vs S: NR  
A-A NR vs S: NR  
**PFS.** PDL1+: All: A-A 13,8 m vs S: 7,2 m. A-A 13,8 m vs S: 8,4 m  
**ORR.** PDL1+: All: A-A 55,2% vs S: 25,5%. A-A 51,4% vs S: 25,7% | Any grades: A-A: 99,5%  
S: 99,3%  
G3/G4: A-A: 71,2%  
S: 71,5% | Yes <1% vs ≥1%, assessed by ICH- VENTANA PD-L1 (SP263) assay |
<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Interventions</th>
<th>No pts</th>
<th>Main outcomes results</th>
<th>Adverse events</th>
<th>Pdl1 stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-426</td>
<td>Ph III, 1st line</td>
<td>1. Pembro + Axitinib 2. Sunitinib</td>
<td>1062 (1:1)</td>
<td>OS: P-A: NR S: NR PFS: P-A 15,1 m S: 10,1 m ORR: P-A 59,3% S: 35,7%</td>
<td>Any grades:</td>
<td>• No results so far</td>
</tr>
<tr>
<td></td>
<td>(including sarcomatoid</td>
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<td>-P-A: 98,4%</td>
<td>• Assessed by IHC 22C3 pharmDx assay (CPS)</td>
</tr>
<tr>
<td></td>
<td>features)</td>
<td></td>
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<td>-S: 99,5%</td>
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<td>G3/G4:</td>
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<td>-P-A: 75,8%</td>
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<td>-S: 70,6%</td>
<td></td>
</tr>
<tr>
<td>CHECKMATE-025</td>
<td>Ph III, 2nd/3rd line</td>
<td>1. Nivo 2. Everolimus</td>
<td>821 (1:1)</td>
<td>OS: PDL1+: N 21,8 m vs E: 18,8 m All: N 25 m vs E: 19 m -&gt; PDL1 &lt;1%: N 27,4 m vs E 21,2 m</td>
<td>Any grades:</td>
<td>• Yes, but just OS</td>
</tr>
<tr>
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<td>-N: 79%</td>
<td>• Assessed by Dako PD-L1 ICH staining</td>
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<td>-E: 88%</td>
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<td>G3/G4:</td>
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<td></td>
<td></td>
<td></td>
<td>-N: 19%</td>
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<td></td>
<td>-E: 39%</td>
<td></td>
</tr>
</tbody>
</table>
**1ST LINE: CHECKMATE 214**

Intermediate/Poor risk prognostic group

1ST LINE: IMMOTION 151: ATEZO+BEVA

PFS in PDL1+ cohort

OS in ITT cohort

Reprinted from The Lancet, 393 (10189), Rini BI, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial, 2404-2415, Copyright 2019, with permission from Elsevier
• PD-L1 expression (≥1% immune cells) associated with the longest PFS in the A+Ax arm and the shortest in the S arm (HR: 0.63)
• High-CD8+ cells extended PFS in the A+Ax arm and the reduced in the S arm

1ST LINE: KEYNOTE 426: PEMBRO + AXI

PFS in ITT population

OS in ITT population

Exploratory analysis of OS by subgroups

RENAL CELL CARCINOMA AND PD-L1 EXPRESSION

Learned lessons for clinical practice

CPI has been rapidly adopted into the routine care of patients

CPI: opportunity of long term survival

CPI: treatment-free survival – QoL (against TKIs)

New approaches needed: Subsequent treatments, perioperative strategy, new combinations

Better understanding of the immunological effects of TKIs and mTOR inhibitors (sequence)

Clinical trials with IO agents need to use IO endpoints

Selecting patients: Searching for new biomarkers
UROTHELIAL CARCINOMA
POSITIVE PHASE III TRIALS WITH CPI IN METASTATIC UROTHELIAL CANCER

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Interventions</th>
<th>No patients</th>
<th>Main outcomes results</th>
<th>Adverse events</th>
<th>PDL1 stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMVIGOR-210</td>
<td>Ph II</td>
<td>Atezolizumab</td>
<td>119</td>
<td>OS: 15,9 m</td>
<td>Any: 66%</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Cohort 1: 1st line, cisplatin-ineligible *PDL1&gt;5%</td>
<td></td>
<td>(cohort 1)</td>
<td>PFS: 2,7 m</td>
<td>G3/G4: 16%</td>
<td>- Assessed by SP142 assay (Ventana, AZ, USA).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR: IC2/3: 23% (9% CR)</td>
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<td></td>
<td></td>
<td></td>
<td>- IC0 (&lt;1%), IC1 (≥1% but &lt;5%), and IC2/3 (≥5%).</td>
</tr>
<tr>
<td>KEYNOTE-052</td>
<td>Ph II</td>
<td>Pembrolizumab</td>
<td>370</td>
<td>OS: 11,95 m</td>
<td>Any: 62%</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1st line, cisplatin-ineligible * CPS &gt; 10%</td>
<td></td>
<td></td>
<td>PFS: 2,3 m</td>
<td>G3/G4: 19%</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td>ORR: 28,9 (8,1% CR)</td>
<td></td>
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</tr>
<tr>
<td>IMVIGOR-211</td>
<td>Ph III</td>
<td>1. Atezolizumab 2. Chemotherapy-CT (investigator choice): - Vinflunine - Paclitaxel - Docetaxel</td>
<td>467 (931 in total)</td>
<td>OS: Atezo: 8,9 m; IC2/3: 11,1 m</td>
<td>Any: -Atezo: 69%; IC2/3: 75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd line (after platinum)</td>
<td></td>
<td></td>
<td>CT: IC2/3: 10,6 m</td>
<td>-Chemo: 89%; IC 2/3: 88%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>PFS: Atezo: 2,4 m; CT: 4,2 m</td>
<td></td>
<td>- Assessed by VENTANA SP142 PD-L1 IHC assay.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR: Atezo:13,4%; IC2/3: 23% (7% CR)</td>
<td></td>
<td>- IC0 (&lt;1%), IC1 (≥1% but &lt;5%), and IC2/3 (≥5%)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>CT: 13,4%; IC2/3: 21,6%</td>
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<tr>
<td>CHECKMATE-275</td>
<td>Ph II</td>
<td>Nivolumab</td>
<td>265</td>
<td>OS: 8,7 m</td>
<td>Any: 64%</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2nd line (after platinum)</td>
<td></td>
<td></td>
<td>PDL1&lt; 1%: 5,95 m; PDL1 &gt;1%: 11,3 m</td>
<td>G3/G4: 18%</td>
<td></td>
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<td></td>
<td>PFS: 2 m</td>
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<td></td>
<td>ORR: 19,6%</td>
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<td></td>
<td>PDL1 &lt;1%: 16,1%; PDL1 &gt;1%: 23,8%; PDL1 &gt;5%: 28,4%</td>
<td></td>
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</tr>
</tbody>
</table>

- Assessed by Dako 22C3 assay, CPS.
- PD-L1 cut-off to define a positive level at which responses were most enriched.

- Assessed by VENTANA SP142 PD-L1 IHC assay.
- ≥1% or ≥5% tumour cell membrane staining
## POSITIVE PHASE III TRIALS WITH CPI IN METASTATIC UROTHELIAL CANCER

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Interventions</th>
<th>No patients</th>
<th>Main outcomes results</th>
<th>Adverse events</th>
<th>PDL1 stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY 1108</td>
<td>Ph I/II</td>
<td>Durvalumab</td>
<td>191</td>
<td>OS 18,2 m</td>
<td>Any: 60,7%</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2nd line (after platinum)</td>
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<td></td>
<td>PDL1 high: 20 m</td>
<td>G3/G4: 6,8%</td>
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<td>PDL1 low/negative: 8,1 m</td>
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<td></td>
<td>PFS 1,5 m</td>
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<td>PDL1 high: 2,1 m</td>
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<td>PDL1 low/negative: 1,4 m</td>
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<td></td>
<td>ORR 17,8%</td>
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<td></td>
<td>PDL1 high: 27,6%</td>
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<td></td>
<td>PDL1 low/negative: 5,1%</td>
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<tr>
<td>JAVELIN SOLID TUMOURS</td>
<td>Ph Ib</td>
<td>Avelumab</td>
<td>249</td>
<td>OS 6,5 m</td>
<td>Any: 67%</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2nd line (after platinum)</td>
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<td></td>
<td></td>
<td></td>
<td>PDL1 &gt;5%: 8,2 m</td>
<td>G3/G4/G5: 10,8%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PDL1 &lt;5%: 6,2 m</td>
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<td></td>
<td>PFS 6,3 m (by inmune-related response), 1,5 m</td>
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<td></td>
<td></td>
<td>PDL1 &gt;5%: 11,9 m</td>
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<td></td>
<td></td>
<td>PDL1 &lt;5%: 6,1 m</td>
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<td></td>
<td>ORR 17%</td>
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<tr>
<td>KEYNOTE-045</td>
<td>Ph III</td>
<td>1. Pembrolizumab-P</td>
<td>542 (748)</td>
<td>OS (CPS&gt;10%) P: 10,3 m; CT: 7,4 m</td>
<td>Any: 60,9% P: 60,9%</td>
<td>Yes,</td>
</tr>
<tr>
<td></td>
<td>2nd line (after platinum)</td>
<td>2. Chemotherapy-CT: - Vinflunine - Paclitaxel - Docetaxel</td>
<td></td>
<td></td>
<td>C: 90,2%</td>
<td>- Assessed by PD-L1 IHC 22C3 pharmDx assay (Dako North America)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS (CPS&gt;10%) P: 2,1 m; CT: 3,3 m</td>
<td>G3/G4/G5: 15% P: 15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR (CPS&gt;10%) P: 21,1% ; CT: 11,4%</td>
<td>C: 49,4%</td>
<td></td>
</tr>
</tbody>
</table>

- **OS**: Overall Survival
- **PFS**: Progression-Free Survival
- **ORR**: Objective Response Rate
- **PDL1** stratification refers to the percentage of PD-L1 positivity in tumor samples.
ADVANCED UC: TREATMENT ALGORITHM

1st LINE

Cisplatin eligible
- Gemcitabine-Cisplatin
- ddMVAC

PD <12mo
- Atezo
- Pembro
- Nivolumab
  (+/- Ipi)
- Durvalumab
- Avelumab

PD >12mo
- Platinum-based rechallenge

2nd LINE

PD <12mo
- Pembro/Atezo?
- CPI

PD >12mo
- CPI
- Vinflunine/Taxanes

3rd LINE

Ineligible for

Any platinum
- Low
- Carboplatin-based
- Pembro/Atezo?

Cisplatin
- High
- Vinflunine/Taxanes
- Other CPI/Clinical trials
- Taxanes?/Other CPI/Clinical trials
1ST LINE - INELIGIBLE PD-L1 >5%
ATEZOLIZUMAB: IMVIGOR 210

Restriction by PDL1 status in previously untreated patients: Decreased survival in patients with low PDL-1 expression

ORR IC2/3 28% (23% all groups)
Median OS: 15.9 months (95% CI 6.6-9.3) for the entire cohort of pts

Updated results:
OS: 11.95 m
PFS: 2.3 m
ORR: 28.9 (8.1% CR)

Reprinted from The Lancet Oncol, 18 (11), Balar AV, et al, First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study, 1483-1492, copyright 2017, with permission from Elsevier.
By permission of Dr Vuky J, J Clin Oncol 2018;36(suppl).; Presented at ASCO 2018; Abstract 4524.
2ND LINE
ATEZOLIZUMAB: IMVIGOR 211

**Negative results:**
- PD-L1+: More favourable outcome with both CT and atezolizumab
- PD-L1 assay disparities

Reprinted from The Lancet, 391 (10122), Powles T, et al, Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial, 748-757, copyright 2018, with permission from Elsevier.
5% of CR in second-line setting!

Open-label, single-arm, Phase 2 study

- Metastatic or locally advanced mUC
- Disease progression on prior platinum-based therapy
- Evaluable PD-L1 tumour tissue sample

Nivolumab 3 mg/kg IV every 2 wk

Treat until progression or unacceptable toxicity

N=270

Binded independent review committee (BIRC) assessment of response using RECIST v1.1

Reprinted from The Lancet Oncol, 18 (3), Sharma P, et al, Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial, 312-322, copyright 2017, with permission from Elsevier.
Overall Survival in PD-L1 Combined Positive Score (CPS) ≥10 population

- Median OS: Pembrolizumab 10.3 m vs CT 7.4 m
- ORR: Pembrolizumab 21.1% vs CT 11.4%

2ND LINE
AVELUMAB: JAVELIN SOLID TUMOUR

Phase 1b, UC cohort (n=249)
Single-arm, multicenter trial

## 2ND LINE
DURVALUMAB: STUDY 1108

<table>
<thead>
<tr>
<th></th>
<th>PD-L1 high</th>
<th>PD-L1 low/negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>98(30)</td>
<td>79(35)</td>
<td>191(68)</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>20(11.6-NE)</td>
<td>8.1(3.1-NE)</td>
<td>18.2(8.1-NE)</td>
</tr>
<tr>
<td>OS rate, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>72(62-80)</td>
<td>51(38-63)</td>
<td>64(56-71)</td>
</tr>
<tr>
<td>9 mo</td>
<td>66(53-77)</td>
<td>41(21-60)</td>
<td>57(47-66)</td>
</tr>
<tr>
<td>12 mo</td>
<td>63(49-74)</td>
<td>41(21-60)</td>
<td>55(44-65)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>2.1(1.4-2.8)</td>
<td>1.4(1.3-1.5)</td>
<td>1.5(1.4-1.9)</td>
</tr>
<tr>
<td>PFS rate, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>31(22-41%)</td>
<td>8(3-16%)</td>
<td>22(16-28)</td>
</tr>
<tr>
<td>9 mo</td>
<td>25(16-35%)</td>
<td>8(3-16%)</td>
<td>18(12-25)</td>
</tr>
<tr>
<td>12 mo</td>
<td>21(13-31%)</td>
<td>8(3-16%)</td>
<td>16(10-23)</td>
</tr>
</tbody>
</table>

- Median time to response: 1.41 mo (range 1.2-7.2)
- Median duration of response (DOR) in as-treated population: Not reached (17/34 responders -50%- had a response lasting at least 6 mo and 26 -76.5%- had an ongoing response at data cut off
- Tumour shrinkage and Deep durable changes were seen in both PD-L1 subgroups
- Median PFS 1.5 mo (95% CI, 1.4-1.9), median OS 18.2 mo (95% CI, 8.1-Not estimable - NE-)

Data retrieved from Powles, JAMA Oncol, 2017
CPIs have shown long-term durable response and tolerable safety profiles.

However, ORR with CPI just around 25-30%.

Combination of different agents (antiPD1/PD-L1 + chemotherapy, antiangiogenics, etc.) / New drugs: M7824 (TGFβ, Sanjeev Mariathasan, Nature 2018) are needed.

There is controversy between PD-L1 expression and ORR.

New biomarkers to guide therapy and develop novel combination therapies.
PREVIOUSLY UNTREATED OESOPHAGO-GASTRIC CANCER
Pembrolizumab trials

**KEYNOTE-062**
- Pembro vs chemotherapy
  - Gastric or OGJ ADC
    - Hazard ratio (PFS)
      - PD-L1 CPS ≥1: 1.66 (1.37-2.01)
      - PD-L1 CPS ≥10: 1.10 (0.79-1.51)
    - Hazard ratio (OS)
      - PD-L1 CPS ≥1: 0.91 (0.69-1.18)
      - PD-L1 CPS ≥10: 0.69 (0.49-0.97)

**KEYNOTE-062**
- Pembro + chemo vs chemotherapy
  - Gastric or OGJ ADC
    - Hazard ratio (PFS)
      - PD-L1 CPS ≥1: 0.84 (0.70-1.02)
      - PD-L1 CPS ≥10: 0.73 (0.53-1.00)
    - Hazard ratio (OS)
      - PD-L1 CPS ≥1: 0.85 (0.70-1.03)
      - PD-L1 CPS ≥10: 0.85 (0.62-1.17)

Overall survival: P vs C (CPS ≥1)

- 12-mo rate: Pembro 47%, Chemo 46%
- 24-mo rate: Pembro 19%, Chemo 19%
- Median (95% CI): Pembro 10.6 mo (7.7-12.8) vs Chemo 11.1 mo (9.2-12.8)

Overall survival: P vs C (CPS ≥10)

- 12-mo rate: Pembro 57%, Chemo 47%
- 24-mo rate: Pembro 22%, Chemo 26%
- Median (95% CI): Pembro 17.4 mo (9.1-23.1) vs Chemo 10.8 mo (8.5-13.8)

*NI, non-inferiority margin; HR (95% CI) = 0.91 (0.74-1.13); P = 0.162 for superiority of P vs C; Data cutoff: March 26, 2019.

Progression-free survival: P vs C

**CPS ≥1**
- Events HR (95% CI)
  - Pembro 88% 1.66
  - Chemo 89% (1.37-2.01)
- Median (95% CI)
  - Pembro: 2.0 mo (1.5-2.8)
  - Chemo: 6.4 mo (5.7-7.0)
- 12-mo rate
  - Pembro: 14%
  - Chemo: 19%

**CPS ≥10**
- Events HR (95% CI)
  - Pembro 80% 1.10
  - Chemo 89% (0.79-1.51)
- Median (95% CI)
  - Pembro: 2.9 mo (1.6-5.4)
  - Chemo: 6.1 mo (5.3-6.9)
- 12-mo rate
  - Pembro: 21%
  - Chemo: 16%

PFS assessed per RECIST v1.1 by blinded independent central review (final analysis of PFS occurred at IA2); Data cutoff: Sept 28, 2018.

PEMBRO + CHEMO VS CHEMO
1ST LINE GASTRIC/OGJ (KEYNOTE-062)

Overall survival: P+C vs C (CPS ≥1)

Overall survival: P+C vs C (CPS ≥10)

PEMBRO + CHEMO VS CHEMO
1ST LINE GASTRIC/OGJ (KEYNOTE-062)

Progression-free survival: P+C vs C

CPS ≥1

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>83%</td>
<td>0.84</td>
<td>0.039</td>
</tr>
<tr>
<td>Chemo</td>
<td>89%</td>
<td>(0.70-1.02)</td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate
26% (19%)

Median (95% CI)
6.9 mo (5.7-7.3)
6.4 mo (5.7-7.0)

CPS ≥10

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>79%</td>
<td>0.73</td>
</tr>
<tr>
<td>Chemo</td>
<td>89%</td>
<td>(0.53-1.00)</td>
</tr>
</tbody>
</table>

12-mo rate
31% (16%)

Median (95% CI)
5.7 mo (5.5-8.2)
6.1 mo (6.3-6.9)

PFS assessed per RECIST v1.1 by blinded independent central review (final analysis of PFS occurred at IA2); Data cutoff: Sept 28, 2018.

## Trials with ICI and PD-L1

### Subgroups untreated oesophago-gastric cancer patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumour type</th>
<th>Interventions</th>
<th>Nº of patients</th>
<th>Main outcomes results</th>
<th>Pdl1 stratification Results (HR)*</th>
<th>Pdl1 good predictor of response?</th>
</tr>
</thead>
</table>
| KEYNOTE-062   | Advanced/metastatic gastric or gastro-oesophageal adenocarcinoma | 1- Pembrolizumab  
2- Pembrolizumab + chemotherapy  
3- Chemotherapy | 763 (1:1:1)             | mOS (CPS ≥ 1)  
1 – 10.6 months  
3 – 11.1 months  
HR (1 vs 3): 0,91 (0,69-1,18) p=na | 1 vs 3 CPS ≥ 10:  
HR OS 0,69 (0.49-0.97)  
1 vs 3 CPS ≥ 10:  
HR PFS 1,10 (0.79-1.51) | Yes? |
|               |                                                  |                                                                                |                | mPFS (CPS ≥ 1)  
1 – 2.0 months  
3 – 6.4 months  
HR (1 vs 3): 1,66 (1,37-2,01) p=na | 2 vs 3 CPS ≥ 10:  
HR OS 0,85 (0.62-1.17) |        |
|               |                                                  |                                                                                |                | mOS (CPS ≥ 1)  
2 – 12.5 months  
3– 11.1 months  
HR (2 vs 3): 0,85 (0,70-1,03) p=0.046 | 2 vs 3 CPS ≥ 10:  
HR PFS 0.73 (0.53-1.00) |        |
|               |                                                  |                                                                                |                | mPFS (CPS ≥ 1)  
2 – 6.9 months  
3 – 6.4 months  
HR (2 vs 3): 0,84 (0,70-1,02) p=0.039 |        |
PREVIOUSLY TREATED OESOPHAGO-GASTRIC CANCER
SECOND LINE ADVANCED OR METASTATIC OESOPHAGO-GASTRIC CANCERS

Pembrolizumab trials

**KEYNOTE-181**
Pembro vs chemotherapy

- Oesophageal or OGJ SCC and ADC
- **Hazard ratio (OS)**
  - PD-L1 CPS any: 0.85 (0.72-1.01)
  - PD-L1 CPS ≥ 10: 0.67 (0.50-0.89)

**KEYNOTE-061**
Pembro vs paclitaxel

- Gastric or OGJ ADC
- **Hazard ratio (OS)**
  - PD-L1 CPS < 1: 1.20 (0.89-1.63)
  - PD-L1 CPS ≥ 1: 0.82 (0.66-1.03)
  - PD-L1 CPS ≥ 10: 0.64 (0.41-1.02)

Shah M et al, ASCO 2019; Shitara K et al, Lancet 2018
PD-L1 CPS ≥ 1
No benefit

PD-L1 CPS ≥ 10
Benefit?

Reprinted from The Lancet, 392 (10142), Shitara K, et al, Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial, 123-133, copyright 2018, with permission from Elsevier.
THIRD LINE ADVANCED OR METASTATIC OESOPHAGO-GASTRIC CANCERS

Nivolumab trials

ATTRACTION-2
Nivo vs placebo

Gastric or OGJ ADC

Hazard ratio (OS)
PD-L1 any: 0.63 (0.51-0.78)
PD-L1 < 1%: 0.72 (0.49-1.05)
PD-L1 ≥ 1%: 0.51 (0.21-1.25)

Kang YK et al, Lancet 2017
NIVOLUMAB VS PLACEBO 3RD LINE GASTRIC/OGJ (ATTRACTION-2)

PD-L1 ≥ 1%

PD-L1 < 1%

Reprinted from The Lancet, 390 (10111), Kang YK et al, Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial, 2461-2471, copyright 2017, with permission from Elsevier.
THIRD LINE ADVANCED OR METASTATIC OESOPHAGO-GASTRIC CANCERS

Avelumab trials

JAVELIN Gastric 300
Avelumab vs chemotherapy

Gastric or OGJ ADC

Hazard ratio (OS)

- PD-L1 any: 1.1 (0.9-1.4)
- PD-L1 < 1%: 1.22 (0.91-1.64)
- PD-L1 ≥ 1%: 0.94 (0.57-1.55)

AVELUMAB VS CHEMO 3\textsuperscript{RD} LINE GASTRIC/OGJ (JAVELIN GASTRIC 300)

PD-L1 ≥ 1% versus PD-L1 < 1%

## TRIALS WITH ICI AND PD-L1 SUBGROUPS PRE-TREATED OESOPHAGO-GASTRIC CANCER PATIENTS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumour type</th>
<th>Interventions</th>
<th>Nº of patients</th>
<th>Main outcomes results</th>
<th>Pd1 stratification Results (HR)*</th>
<th>Pd1 good predictor of response?</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-061</td>
<td>Advanced/metastatic gastric or gastro-oesophageal adenocarcinoma</td>
<td>1 – Pembrolizumab 2- Paclitaxel</td>
<td>592 (1:1)</td>
<td>mOS (PD-L1 CPS ≥ 1)</td>
<td>1 - 9.1 months 2 - 8.3 months</td>
<td>PD-L1 CPS ≤ 1: 1.20 (0.89-1.63) PD-L1 CPS ≥ 1: 0.82 (0.66-1.03) PD-L1 CPS ≥ 10: 0.64 (0.41-1.02) Yes?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.82 (0.66-1.03) p=0.0421</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-181</td>
<td>Advanced/metastatic oesophageal or gastro-oesophageal junction squamous cell carcinoma or adenocarcinoma</td>
<td>1 – Pembrolizumab 2- Investigator-choice (Paclitaxel, Docetaxel, or Irinotecan)</td>
<td>628 (1:1)</td>
<td>mOS (PD-L1 CPS ≥ 10)</td>
<td>1 - 9.3 months 2 - 6.7 months</td>
<td>PD-L1 CPS any: 0.85 (0.72-1.01) PD-L1 CPS ≥ 10: 0.67 (0.50-0.89) Yes?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.67, (0.50-0.89), p=0.0029</td>
<td></td>
</tr>
<tr>
<td>ATTRACTION-2</td>
<td>Advanced/metastatic gastric or gastro-oesophageal junction adenocarcinoma</td>
<td>1 – Nivolumab 2 – Placebo</td>
<td>493 (2:1)</td>
<td>mOS (PD-L1 unselected)</td>
<td>1 - 5.26 months 2 - 4.14 months</td>
<td>PD-L1 ≥ 1%: 0.51 (0.21-1.25) PD-L1 &lt; 1%: 0.72 (0.49-1.05) See comments</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.63, (0.51-0.78), p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>JAVELIN GASTRIC 300</td>
<td>Advanced/metastatic gastric or gastro-oesophageal junction adenocarcinoma</td>
<td>1 – Avelumab 2- Investigator-choice (Paclitaxel, Irinotecan, or Best supportive care)</td>
<td>371 (1:1)</td>
<td>mOS (PD-L1 unselected)</td>
<td>1 - 4.6 months 2 - 5.0 months</td>
<td>PD-L1 ≥ 1%: 0.94 (0.57-1.55) PD-L1 &lt; 1%: 1.22 (0.91-1.64) See comments</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>HR 1.1 (0.9-1.4), p=0.81</td>
<td></td>
</tr>
</tbody>
</table>
Main findings or subgroup analyses of all randomised phase III trials completed so far (KEYNOTE-061, KEYNOTE-062, KEYNOTE-181, ATTRACTION-2 and JAVELIN Gastro 300) suggest some consistent association between PD-L1 expression and increased benefit from immune checkpoint inhibitors.

Heterogeneity, however, exists between these trials in terms of assay for PD-L1 expression, PD-L1 scoring system, definition of PD-L1 positivity, timing of PD-L1 testing (retrospective vs prospective). Furthermore the small numbers of subgroup analyses and the lack of interaction tests do not allow drawing final conclusions.

Important questions to be answered

- Which are the optimal PD-L1 scoring system and cut-off value for PD-L1 positivity?
- What is the impact of the site/timing of PD-L1 testing on PD-L1 status and its prediction of treatment benefit?
- What is, if any, the added value of PD-L1 testing in patients with MSI-H tumours or tumours with high TMB?
- Does the potential predictive power of PD-L1 expression change if immune checkpoint inhibitors are given in combination with chemotherapy or other agents?
- What are the most appropriate outcome measures/endpoints to assess the clinical benefit from immune checkpoint inhibitors?
PREVIOUSLY TREATED COLORECTAL CANCER
THIRD LINE ADVANCED OR METASTATIC COLORECTAL CANCER

Atezolizumab + Cobimetinib vs Regorafenib

Hazard ratio (OS)
PD-L1 high: 0.80
PD-L1 low: 1.26

Hazard ratio (OS)
PD-L1 high: 0.80
PD-L1 low: 1.81

Atezolizumab +/- Cobimetinib vs Regorafenib in PD-L1 high

Atezolizumab +/- Cobimetinib vs Regorafenib in PD-L1 low

Reprinted from The Lancet Oncol, 20(6), Eng C, et al, Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial, 849-861, Copyright 2019, with permission from Elsevier.
# TRIALS WITH ICI AND PD-L1 SUBGROUPS

Pre-treated colorectal cancer patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumour type</th>
<th>Interventions</th>
<th>Nº of patients</th>
<th>Main outcomes results</th>
<th>PdL1 stratification Results (HR)*</th>
<th>PDL1 good predictor of response?</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMblaze370</td>
<td>Advanced/metastatic colorectal adenocarcinoma</td>
<td>1 – Atezolizumab + cobimetinib 2- Atezolizumab 3 - Regorafenib</td>
<td>363 (2:1:1)</td>
<td>mOS (PD-L1 any) 1 – 8.87 months 2 – 7.10 months 3 – 8.51 months</td>
<td>1 vs 3 PD-L1 &lt; 1%: 1.26 PD-L1 ≥ 1%: 0.80</td>
<td>Yes?</td>
</tr>
</tbody>
</table>

HR (1 vs 3): 1.00 (0.73-1.38) p=0.99
HR (2 vs 3): 1.19 (0.83-1.71) p=0.34
The impact of PD-L1 expression on the clinical benefit from immune checkpoint inhibitors in colorectal cancer is difficult to assess. Only one randomised phase III study has been completed so far (IMblaze370) and the results appear to suggest a possible association between PD-L1 expression and increased benefit from immune checkpoint inhibitors.

Important questions to be answered

- Can PD-L1 (high) expression identify a subgroup of MSS colorectal cancer patients who might be sensitive to immune checkpoint inhibitors? More data are needed.
- Is PD-L1 testing of any value in patients with MSI-H tumours or tumours with high TMB?
- Which are the optimal PD-L1 scoring system and cut-off value for PD-L1 positivity?
- What is the impact of the site/timing of PD-L1 testing on PD-L1 status and its prediction of treatment benefit?
FINAL CONCLUSIONS

Implication for clinical practice and research

Although not a perfect biomarker, there is a trend for increased benefit with ICIs on enriched PDL1 solid tumours.

But on Combination ICI + chemo pdl1 expression seems to be less relevant.

There are still many uncertainties on the real value of PDL1 for clinical practice with ICIs in solid tumours.

Important questions to be answered:

- Why PDL1 expression has a high value in some studies and low in others?
- More data on cut-off value for PDL1 expression and how it changes over time?
- Combine PDL1 expression with other biomarkers (eg. TMB; specific neo-antigens, etc)?
- To identify best strategies with ICIs in low/negative PDL1 tumours?
- Are ICIs alone a better strategy for enriched PDL1 subgroups and combo ICI+chemo better on lower/negative PDL1 expression subgroups?
THANK YOU!
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Inês Pires da Silva has reported no conflict of interest

Karima Oualla has reported no conflict of interest

Irene Moreno has reported Speaker’s fees: BMS

Francesco Sclafani has reported no conflict of interest
Emiliano Calvo has reported
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2. Leadership role: Director, Clinical Research, START Madrid, Director, Clinical Research, HM Hospitals Group, Madrid
3. Stocks or ownership: START, Oncoart Associated, International Cancer Consultants
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