Immune checkpoint inhibitors in NSCLC

Jordi Remon Masip
CIOCC Barcelona – HM Delfos
@JordiRemon
Background

• Where we come from...?

• Where we are...?

• Where we go ahead...?

• Conclusions
Background

- Where we come from...?
- Where we are...?
- Where we go ahead...?
- Conclusions
Just 3 years ago...CT the SoC

Stage IV SCC

- Age
  - PS
    - <70 years and PS 0-1
    - ≥70 years and PS 0-1

4-6 cycles:
- Cisplatin – gemcitabine (I, A)
- Cisplatin – docetaxel (I, A)
- Cisplatin – metsimide (I, A)
- Carboplatin – paclitaxel (I, A)
- Carboplatin – nedaplatin (I, B)
- Cisplatin – gemcitabine – nectumumab (EGF expression by HS)(I, B, NCI5)

Stage IV NSCC

- <70 years and PS 0-1
  - 4-6 cycles:
    - Cisplatin – paclitaxel (I, A)
    - Cisplatin – gemcitabine (I, B)
    - Carboplatin – paclitaxel (I, B)
    - Carboplatin – nab-paclitaxel (I, B)

- ≥70 years and PS 0-1
  - 4-6 cycles:
    - Carboplatin-based doublets (I, B)
    - Single-agent chemotherapy (gemcitabine, vinorelbine or docetaxel) (I, A)

PS 0-1

Partial response or stable disease

Maintenance treatment:
- Pembrolizumab (switch) (I, B)
- Pembrolizumab (continuation) (I, A)
- Erlotinib (EGFR-activating mutations) (I, B)
- I+ bevacizumab (I, B, NCI5)

PS 0-2

≥70 years and PS 0-2

≥70 years and PS 0-1

<70 years and PS 2

≤3 years ago...CT the SoC

Novello – Ann Oncol 2016
Anti-PD(L)1 and anti-CTLA4 mAb

Hendriks – Nature 2018 (modified)
Know your Immune Checkpoint Antibodies

**Anti-CTLA-4**
- Ipilimumab*
- Tremelimumab*

**Anti-PD-1**
- Nivolumab
- Pembrolizumab

**Anti-PD-L1**
- Atezolizumab
- Durvalumab
- Avelumab*

*Not approved in NSCLC in 2019

Courtesy of Prof. Besse
We have already 5-y OS data with ICI

5-y OS with nivolumab / pembrolizumab in previously treated NSCLC ~ 15%
(In PD-L1 ≥ 50%, 5-y OS: ~23%)

5-y OS with pembrolizumab in 1st line NSCLC ~ 23%
(In PD-L1 ≥ 50%, 5-y OS: ~30%)

NIVOLUMAB PEMBROLIZUMAB

Gettinger – WCLC 2019 * Garon – JCO 2019
Long term NSCLC survivors

5-y OS pooled analysis CM 017&057 (nivolumab)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 427)</th>
<th>Docetaxel (n = 427)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>11.1</td>
<td>8.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(9.2–13.1)</td>
<td>(7.2–9.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.68 (0.59–0.78)</td>
<td></td>
</tr>
</tbody>
</table>

PD-L1 expression < 1%

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 163)</th>
<th>Docetaxel (n = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI), mo</td>
<td>9.7 (7.6–10.7)</td>
<td>7.8 (6.7–8.9)</td>
</tr>
</tbody>
</table>

PD-L1 expression ≥ 1%

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 185)</th>
<th>Docetaxel (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI), mo</td>
<td>13.4 (10.0–17.7)</td>
<td>8.5 (7.0–9.3)</td>
</tr>
</tbody>
</table>

Gettinger – WCLC 2019 * Brahmer – AACR 2019
ICI SoC in 2\textsuperscript{nd} Line NSCLC 2016

ESMO guidelines

- 4-6 cycles
  - Platinum-based ChT:
    - Cisplatin/gemcitabine [I, A]
    - Cisplatin/docetaxel [I, A]
    - Cisplatin/paclitaxel [I, A]
    - Carboplatin/gemcitabine [I, A]
    - Carboplatin/docetaxel [I, A]
    - Carboplatin/paclitaxel [I, A]
    - Carboplatin/vinorelbine [I, A]
    - nab-PC [I, B]

- PS 0-2

- Nivolumab [I, A, MCBS 5]
- Atezolizumab [I, A; MCBS 5]
- Pembrolizumab if PD-L1 \(>1\) [I, A; MCBS 5]
- Docetaxel [I, B]
- Ramucirumab/docetaxel [I, B; MCBS 1]
- Erlotinib [I, C]
- Atezolizumab [I, C; MCBS 2]

Nivo - All comers

Pemb - PD-L1 \(\geq 1\%\)

PDL1 \(\geq 50\%\):

- 14.9 vs. 17.3 vs. 8.2
- HR 0.54, HR 0.50

Atezo - All comers

TC3/IC3: 20.5 vs. 8.9


Do not duplicate or distribute without permission of ESO and the author.
Jumping from 2\textsuperscript{nd} to 1\textsuperscript{st} line strategy

- KEYNOTE 024
- KEYNOTE 042
- KEYNOTE 189
- KEYNOTE 407
- IMpower 110
- IMpower 150
- IMpower 132
- IMpower 130
- IMpower 131
- CheckMate 026
- CheckMate 227
- CheckMate 9LA
- B-F1RST (ph II)
- MYSTIC
- POSEIDON

Do not duplicate or distribute without permission of ESO and the author.
Multiple trials with ICI 1st Line

<table>
<thead>
<tr>
<th>Trial</th>
<th>PD-L1 TPS</th>
<th>Treatment</th>
<th>PFS / OS (months)</th>
<th>AEs, Grade 3-5 (* All toxicities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-024</td>
<td>≥50%</td>
<td>Pembrolizumab</td>
<td>10.3 / 14.2</td>
<td>FDA 31% vs 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem or Paclitaxel</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>CheckMate 026</td>
<td>≥5%</td>
<td>Nivolumab</td>
<td>4.2 / 4.3</td>
<td>FDA 18% vs 52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem or Paclitaxel</td>
<td>5.9 / 13.2</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-042</td>
<td>≥1%</td>
<td>Pembrolizumab</td>
<td>6.5 / 12.1</td>
<td>FDA 18% vs 41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem or Paclitaxel</td>
<td>5.4 / 16.7</td>
<td></td>
</tr>
<tr>
<td>IMpower150</td>
<td>Nonsquamous</td>
<td>Atezolizumab + Bev + Plat/Paclitaxel</td>
<td>8.3 / 14.7</td>
<td>EMA 59% vs 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bev + Plat/Paclitaxel</td>
<td>6.8 / 14.7</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-189</td>
<td>Nonsquamous</td>
<td>Pembrolizumab + Plat/Pem</td>
<td>4.2 / 8.8</td>
<td>FDA 67% vs 66%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + Plat/Pem</td>
<td>19.2/19.3</td>
<td></td>
</tr>
<tr>
<td>IMpower132</td>
<td>Nonsquamous</td>
<td>Atezolizumab + Plat/Pem</td>
<td>5.2 / 13.6</td>
<td>EMA 57% vs 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem</td>
<td>7.6 / 16.1</td>
<td>FDA 75% vs 61%</td>
</tr>
<tr>
<td>IMpower130</td>
<td>Nonsquamous</td>
<td>Atezolizumab + Carb/Carb/or Paclitaxel</td>
<td>7.0 / 13.0</td>
<td>EMA 70% vs 66%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carb/Carb/or Paclitaxel</td>
<td>5.6 / 18.5</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-407</td>
<td>Squamous</td>
<td>Pembrolizumab + Plat/Tax</td>
<td>6.4 / 11.3</td>
<td>EMA 69% vs 58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + Plat/Tax</td>
<td>15.0 / 15.0</td>
<td></td>
</tr>
<tr>
<td>IMpower131</td>
<td>Squamous</td>
<td>Atezolizumab + Carb/Carb/or Paclitaxel</td>
<td>6.3 / 14.0</td>
<td>FDA 54% vs 38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carb/Carb/or Paclitaxel</td>
<td>5.8 / 15.6</td>
<td></td>
</tr>
<tr>
<td>CheckMate 227</td>
<td>PD-L1 neg (only PFS)</td>
<td>Nivolumab + Plat/Pem or Gem</td>
<td>5.6 / 15.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>CheckMate 227</td>
<td>TMB ≤10 mut/Mb</td>
<td>Nivolumab + Ipilimumab</td>
<td>7.2 / 16.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>MYSTIC</td>
<td>PD-L1 25%</td>
<td>Durvalumab</td>
<td>4.7 / 16.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem or Paclitaxel</td>
<td>5.4 / 12.9</td>
<td></td>
</tr>
<tr>
<td>MYSTIC</td>
<td>PD-L1 25%</td>
<td>Durvalumab + Tremelimumab</td>
<td>3.3 / 11.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem or Paclitaxel</td>
<td>5.4 / 12.9</td>
<td></td>
</tr>
<tr>
<td>MYSTIC</td>
<td>TMB ≥16 mut/Mb (only OS)</td>
<td>Durvalumab + Tremelimumab</td>
<td>10.5 / 16.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plat/Pem or Gem or Paclitaxel</td>
<td>5.4 / 12.9</td>
<td></td>
</tr>
</tbody>
</table>

* Permission required to duplicate or distribute.
Background

• Where we come from...?

• Where we are...?

• Where we go ahead...?

• Conclusions
# PD-L1 as a biomarker in NSCLC

Meta-analysis. N=6664 from phase I-III trials

<table>
<thead>
<tr>
<th>Study and Cancer Type</th>
<th>PD-L1 Positive</th>
<th>PD-L1 Negative</th>
<th>Weight (%)</th>
<th>Odds Ratio IV, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>Total No. of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antonia et al\textsuperscript{15}</td>
<td>14</td>
<td>49</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Borghaei et al\textsuperscript{16}</td>
<td>34</td>
<td>95</td>
<td>14</td>
<td>136</td>
</tr>
<tr>
<td>Brahmer et al\textsuperscript{14}</td>
<td>9</td>
<td>42</td>
<td>11</td>
<td>75</td>
</tr>
<tr>
<td>Fehrenbacher et al\textsuperscript{60}</td>
<td>11</td>
<td>50</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>Garon et al\textsuperscript{12}</td>
<td>60</td>
<td>176</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>Gettinger et al\textsuperscript{11}</td>
<td>5</td>
<td>33</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Gettinger et al\textsuperscript{30}</td>
<td>8</td>
<td>26</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Herbst et al\textsuperscript{13}</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Herbst et al\textsuperscript{19}</td>
<td>86</td>
<td>290</td>
<td>40</td>
<td>400</td>
</tr>
<tr>
<td>Rittmeier et al\textsuperscript{49}</td>
<td>29</td>
<td>129</td>
<td>28</td>
<td>292</td>
</tr>
<tr>
<td>Rizvi et al\textsuperscript{17}</td>
<td>6</td>
<td>25</td>
<td>7</td>
<td>51</td>
</tr>
<tr>
<td>Spigel 2015</td>
<td>14</td>
<td>43</td>
<td>28</td>
<td>136</td>
</tr>
<tr>
<td>Verschraegen et al\textsuperscript{16}</td>
<td>6</td>
<td>28</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Wakerley et al\textsuperscript{48}</td>
<td>86</td>
<td>302</td>
<td>122</td>
<td>659</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>359</strong></td>
<td><strong>1,295</strong></td>
<td><strong>1,984</strong></td>
<td><strong>39.5</strong></td>
</tr>
</tbody>
</table>

Total events: 359, 277

Heterogeneity: $I^2 = 0.03; \\chi^2 = 15.46, df = 13 (P = .28); I^2 = 16%$

Test for overall effect: $Z = 7.72 (P < .001)$
Interchangeability of the 22C3, 28-8, and SP263 assays and lower sensitivity of the SP142, greater sensitivity of the 73-10 assay compared with that of the other assays

Tsao – JTO 2019
ICI in PD-L1 positive tumors: OS

**Negative**

- CHECKMATE 026
  - PD-L1 ≥5% (28-4)
  - 14.4 mo. vs. 13.2 mo.
  - HR = 1.02 (0.80 to 1.30)

**Positive**

- KEYNOTE 042
  - PD-L1 ≥1% (22C3)
  - 16.7 mo. vs. 12.1 mo.
  - HR = 0.81 (0.71 to 0.93)

Subgroup PD-L1 ≥ 50% HR 0.90 (0.59-1.28)

- 60% crossover

Subgroup PD-L1 ≥ 50% HR 0.90 (0.59-1.28)

- 60% crossover

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

**Negative**

- IMPOWER 110
  - PD-L1 ≥1% (SP147)
  - HR = 0.83 (95% CI: 0.65, 1.07); P = 0.1481
  - Subgroup TC3/IC3 HR 0.59 (0.40-0.89)

- Median OS, 14.1 mo.
  - (95% CI: 10.0, 16.5)

- Median OS, 17.5 mo.
  - (95% CI: 12.8, 23.1)

**Positive**

- KEYNOTE 024
  - PD-L1 ≥50% (22C3)
  - 16.7 mo. vs. 13.2 mo.
  - HR= 0.65 (0.50-0.86), p=0.001

- Median (95% CI)
  - 26.3 mo (18.3–40.4 mo)
  - 14.2 mo (9.8–18.3 mo)

**Not allowed (29%)**

- 65% crossover

**Not allowed (20%)**

- 60% crossover

**Do not duplicate or distribute without permission of ESO and the author**
ICI in High PD-L1 positive NSCLC

**KEYNOTE 024, PD-L1 ≥50% (22C3)**
Follow-up: 3-year

**KEYNOTE 042, PD-L1 ≥50% (22C3)**
Follow-up: 13 months

**IMPOWER 110, PD-L1 TC3/IC3 (SP142)**
Follow-up: 16 months

In PD-L1 ≥50% (~30% of NSCLC), we could say: BYE, BYE chemotherapy at least in 1st L

However PD-L1 level is relevant

N=187 aNSCLC PD-L1 ≥ 50% receiving commercial Pembrolizumab in 1st Line

Aguilar – Ann Oncol 2019 * Edahiro – PLoSOne 2019
Adding anti-CTLA4 in PD-L1 positive tumors

**MYSTIC: PD-L1 ≥25%** (SP26.3)

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + tremelimumab (n=163)</th>
<th>Chemotherapy (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>113 (69.3)</td>
<td>128 (79.0)</td>
</tr>
<tr>
<td>mOS, months (95% CI)</td>
<td>11.9 (9.0–17.7)</td>
<td>12.9 (10.5–15.0)</td>
</tr>
<tr>
<td>HR (90.7% CI)</td>
<td>0.63 (0.41–1.02)</td>
<td>0.202</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

~25%

PD-L1 ≥ 50%  HR 0.76 (0.55–1.07)

Not allowed (40%)

**CHECKMATE 227: PD-L1 ≥1%** (28.8)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 396)</th>
<th>Chemo (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>17.1</td>
<td>14.9</td>
</tr>
<tr>
<td>HR</td>
<td>0.79</td>
<td>0.65–0.96</td>
</tr>
<tr>
<td>97.72% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

~25%

PD-L1 ≥ 50%  HR 0.70 (0.55–0.90)

Not allowed (36%)

Rizvi – ESMO Asia 2018 * Reinmuth – ELCC 2019

Peters – ESMO 2019 * Hellman – NEJM 2019

Do not duplicate or distribute without permission of ESO and the author
Rationale of Chemo-IO combination

- Chemotherapy induces immunogenic cell death and modulate immunogenicity of tumor cells
  - enhancing tumor antigen presentation, upregulating of co-stimulatory molecule but down-regulation of co-inhibitory molecule, T cell activation, and reducing MDSC/Tregs in TME
- PD-1/PD-L1 inhibition restores tumor specific T cell immunity and reversal of immune suppression leads to deeper and more durable antitumor response

Slide courtesy of Prof. Ahn – WCLC 2019
KEYNOTE 021G, phase II

**PFS**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Number of events (%)</th>
<th>Median PFS, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab plus PC</td>
<td>60</td>
<td>29 (49.7)</td>
<td>24.8 (8.5–NR)</td>
<td>0.53 (0.33–0.86)</td>
<td>0.0040</td>
</tr>
<tr>
<td>PC alone</td>
<td>53</td>
<td>43 (63.3)</td>
<td>9.3 (6.2–14.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Number of events (%)</th>
<th>Median OS, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab plus PC</td>
<td>60</td>
<td>22 (56.7)</td>
<td>NR (24.5–NR)</td>
<td>0.56 (0.32–0.95)</td>
<td>0.0151</td>
</tr>
<tr>
<td>PC alone</td>
<td>63</td>
<td>35 (55.6)</td>
<td>21.1 (14.9–NR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RR: 56.7% vs. 30.2%, p=0.0016**

Crossover: 73.2%

FDA approval
On 10th May 2017

Borghaei – JTO 2018
**KEYNOTE 189**

**POSITIVE PFS & OS**

- Untreated stage IV non-squamous NSCLC
- No sensitizing EGFR or ALK alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

**Stratification Factors**
- PD-L1 expression (TPS < 1% vs ≥ 5%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

17% stable BM

- ~30% PD-L1 ≥ 50%
- ~70% CBDCA ≥ 50%
- ~88% smokers

**Primary endpoint:** OS / PFS

Gandhi – NEJM 2018

**IMPOWER 132**

**POSITIVE PFS, not OS**

- Chemotherapy-naive patients with Stage IV non-squamous NSCLC without EGFR or ALK genetic alteration
- Stratification factors:
  - Sex
  - Smoking status
  - ECOG PS
  - Chemotherapy regimen

**N = 578**

- Co-primary endpoints: INV-assessed PFS and OS

**Induction therapy**

- **Arm APP**
  - Atezolizumab + carboplatin or cisplatin + pemetrexed
  - 4 or 6 cycles

- **Arm PP**
  - Carboplatin or cisplatin + pemetrexed
  - 4 or 6 cycles

**Maintenance therapy**

- Atezolizumab + pemetrexed

**Maintenance Treatment**

- Until PD by RECIST v1.1 or loss of clinical benefit

Papadimitakoupolou – WCLC 2018

**Crossover not allowed**

- But 37.1% in control arm received ICI
**IMPOWER 150**

### POSITIVE PFS & OS

**Arm B vs. C**

- **Stage IV or recurrent metastatic nonsquamous NSCLC**
- **Chemotherapy-naïve**
- **Tumor tissue available for biomarker testing**
- **Any PD-L1 IHC status**
- **Stratification factors:**
  - Sex
  - PD-L1 IHC expression
  - Liver metastases
  - \( N = 1202 \)

**End-Point:** Investigator-PFS / OS in ITT-WT
- 17% IC3/TC3.
- 47% IC0/TC0.
- 11% EGFR-mut., 2% ALK-positive

**Arm A**
- Atezolizumab\(^b\) + Carboplatin\(^c\) + Paclitaxel\(^d\)
- 4 or 6 cycles

**Arm B**
- Atezolizumab\(^b\) + Carboplatin\(^c\) + Paclitaxel\(^d\) + Bevacizumab\(^e\)
- 4 or 6 cycles

**Arm C (control)**
- Carboplatin\(^c\) + Paclitaxel\(^d\) + Bevacizumab\(^e\)
- 4 or 6 cycles

**Maintenance therapy (no crossover permitted)**
- Treated with atezolizumab until PD per RECIST v1.1 or loss of clinical benefit
- AND/OR
  - Treated with bevacizumab until PD per RECIST v1.1

**Crossover not allowed!**

But ~31.7% in arm C received ICI

---

**IMPOWER 130**

### POSITIVE PFS & OS

- **Patients with chemotherapy-naïve stage IV non-squamous NSCLC**
- **Stratification:**
  - Sex
  - Baseline liver metastases
  - PD-L1 tumour expression

- \( (ITT: N = 723^b; \ ITT-WT: n = 679) \)

**Induction treatment (4 or 6 21-day cycles)**
- Atezo + carboplatin + nab paclitaxel (CnP)

**Maintenance treatment**
- Atezo + carboplatin + nab paclitaxel (CnP)
- Best supportive care or pemetrexed q3w

**Crossover allowed 41% (ICI 59.2%)**

**Co-primary endpoints:** investigator-assessed PFS and OS (ITT-WT population)
- ITT-WT population: randomised patients excluding those with EGFR or ALK genomic alterations
IO + CT in Non-Squamous: PFS, ITT

KEYNOTE 189  Platinum/Pem +/- Pembrolizumab

- Hazard ratio for disease progression or death: 0.52 (95% CI: 0.43–0.64)
  - RR: 47.6% vs. 18.9%, p<0.001

- Median PFS: 8.8 mo. vs. 4.9 mo.

IMPOWER 150  CBDCA/Taxol/BVZ +/- Atezolizumab (B vs. C)

- Median follow-up: ~20 mo

- RR: 63.5% vs. 48%

- HR: 0.59 (95% CI: 0.50, 0.70)
  - P < 0.0001

- Median, 8.3 mo (95% CI: 7.7, 9.8)

IMPOWER 132  Platinum/Pem +/- Atezolizumab

- RR: 47% vs. 32%

- Median follow-up: 14.8 mo
  - HR: 0.60 (95% CI: 0.49, 0.72)
    - P = 0.0001

- Median PFS: 7.6 mo vs. 5.2 mo (95% CI: 3.3, 5.6)

IMPOWER 130  CBDCA/nab-Paclitaxel +/- Atezolizumab

- RR: 49.2% vs. 32%

- Median follow-up: ~20 mo

- HR: 0.64 (95% CI: 0.54–0.77)
  - P<0.0001

- Median PFS: 7.8 mo vs. 5.8 mo (95% CI: 6.2–7.5)

Gandhi – NEJM 2018 * Papadimitakoupoulo – WCLC 2018

IO + CT in Non-Squamous: OS, ITT

**KEYNOTE 189**
Platinum/Pem +/- Pembrolizumab

**IMPOWER 150**
CBDCA/Taxol/BVZ +/- Atezolizumab (B vs C)

**IMPOWER 132**
Platinum/Pem +/- Atezolizumab

**IMPOWER 130**
CBDCA/nab-Paclitaxel +/- Atezolizumab

11.3 mo.

FDA approval on 21st August 2018
EMA approval on 10th September 2018

FDA approval (wt) on 7th December 2018
EMA approval (EGFR/ALK) on 1st February 2019

FDA approval on 4th December 2019

Platinum/Pem +/− Pembrolizumab

Platinum/Pem +/− Atezolizumab

Gandhi – NEJM 2018 * Papadimitakoupolou – WCLC 2018

OS in **EGFR/ALK-positive subgroup**

- IMpower 130
  - Nab-Paclitaxel, Carboplatin +/- Atezo

- IMpower 150
  - Paclitaxel, Carboplatin, Bevacizumab +/- Atezo

**Cappuzzo - ESMO 2018**

**West – Lancet Oncol 2019**

**Socinski - ASCO 2018**


**Positive role of Atezo + Beva in this population?**

HR, 0.98
(95% CI: 0.41–2.31)

OS (%)
Median, 14.4 mo
I. Median, 14.4 mo

HR, 0.54
(95% CI: 0.29, 1.03)

Overall Survival (%)

17.5 mo
NE
### IMPOWER 150 – OS subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1–High (TC3 or IC3) WT</td>
<td>136 (20%)</td>
<td>Arm B: 25.2, Arm C: 15.0</td>
</tr>
<tr>
<td>PD-L1–Low (TC1/2 or IC1/2) WT</td>
<td>226 (32%)</td>
<td>Arm B: 20.3, Arm C: 16.4</td>
</tr>
<tr>
<td>PD-L1–Negative (TC0 and IC0) WT</td>
<td>339 (49%)</td>
<td>Arm B: 17.1, Arm C: 14.1</td>
</tr>
<tr>
<td>Liver Metastases WT</td>
<td>94 (14%)</td>
<td>Arm B: 13.2, Arm C: 9.1</td>
</tr>
<tr>
<td>No Liver Metastases WT</td>
<td>602 (86%)</td>
<td>Arm B: 19.8, Arm C: 16.7</td>
</tr>
<tr>
<td>ITT (including EGFR/ALK+)</td>
<td>800 (100%)</td>
<td>Arm B: 19.8, Arm C: 14.9</td>
</tr>
<tr>
<td>EGFR/ALK+ only</td>
<td>104 (13%)</td>
<td>Arm B: NE, Arm C: 17.5</td>
</tr>
<tr>
<td>ITT-WT</td>
<td>696 (87%)</td>
<td>Arm B: 19.2, Arm C: 14.7</td>
</tr>
</tbody>
</table>

**Hazard Ratio**

- In favor of Arm B: atezo + bev + CP
- In favor of Arm C: bev + CP

Socinski – ASCO 2018 * Socinski – NEJM 2018
IO + CT in Squamous

KEYNOTE 407

- Key eligibility criteria:
  - Untreated stage IV N1L1C1 with squamous histology
  - ECOG PS 0 or 1
  - Provision of a sample for PD-L1 assessment
  - No symptomatic brain metastases
  - No pneumonitis requiring systemic steroids

- Stratification factors:
  - PD-L1 expression (TPS >1% vs. ≤1%)
  - Choice of taxane (paclitaxel vs. nab-paclitaxel)
  - Geographic region (east vs. west of the world)

- End points:
  - Primary: PFS (RECIST v1.1, BICR) and OS
  - Secondary: ORR and DOR (RECIST v1.1, BICR), safety

- Optimal Crossover:
  - Pembrolizumab 200 mg Q2W for up to 36 cycles

- PFS

- OS

IMPOWER 131

- Stage IV squamous NSCLC
  - Chemotherapy naïve
  - ECOG PS 0 or 1
  - Any PD-L1 IHC status

- Stratification factors:
  - Sex
  - PS and IHC expression
  - Prior chemotherapy

- Co-primary endpoints:
  - Investigator-assessed PFS per RECIST v1.1 (ITT)
  - OS (ITT)

- Secondary endpoints:
  - PFS and OS in PD-L1 subgroups
  - ORR, DOR, safety

- 43% Crossover ICI

NEGATIVE
Pembrolizumab in PD-L1 < 1%: KN 021G, KN189, KN407

N=243 patients CT+ ICI (38% received 2ND line), N=185 CT alone (42% of crossover)

**PFS**
- Pembrolizumab + Chemotherapy: 172 events, HR (95% CI) 0.67 (0.54–0.84)
- Chemotherapy: 145 events

**OS**
- Pembrolizumab + Chemotherapy: 112 events, HR (95% CI) 0.56 (0.43–0.73)
- Chemotherapy: 110 events

**RR**
- 47% vs. 29%

Borghaei – WCLC 2019
Pembrolizumab in PD-L1 < 1%: KN 021G, KN189, KN407

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of Events/Pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>222/428</td>
<td>0.56 (0.43–0.73)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>109/220</td>
<td>0.41 (0.28–0.60)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>113/208</td>
<td>0.74 (0.51–1.08)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>143/291</td>
<td>0.62 (0.45–0.87)</td>
</tr>
<tr>
<td>Female</td>
<td>79/137</td>
<td>0.46 (0.30–0.72)</td>
</tr>
<tr>
<td>Region of enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>18/49</td>
<td>0.42 (0.15–1.18)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>204/373</td>
<td>0.57 (0.44–0.77)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>71/158</td>
<td>0.49 (0.31–0.76)</td>
</tr>
<tr>
<td>1</td>
<td>151/368</td>
<td>0.60 (0.43–0.83)</td>
</tr>
</tbody>
</table>

Subgroup

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number of Events/Pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>73/194</td>
<td>0.61 (0.38–0.93)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>140/223</td>
<td>0.52 (0.37–0.73)</td>
</tr>
</tbody>
</table>

Smoking status

<table>
<thead>
<tr>
<th>Current/former</th>
<th>Number of Events/Pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>203/386</td>
<td></td>
<td>0.59 (0.44–0.78)</td>
</tr>
<tr>
<td>Never</td>
<td>22/42</td>
<td>0.34 (0.14–0.81)</td>
</tr>
</tbody>
</table>

Brain metastases

<table>
<thead>
<tr>
<th>Yes</th>
<th>Number of Events/Pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46/65</td>
<td></td>
<td>0.41 (0.22–0.74)</td>
</tr>
<tr>
<td>No</td>
<td>176/363</td>
<td>0.57 (0.43–0.77)</td>
</tr>
</tbody>
</table>

Liver metastases

<table>
<thead>
<tr>
<th>Yes</th>
<th>Number of Events/Pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55/80</td>
<td></td>
<td>0.79 (0.46–1.35)</td>
</tr>
<tr>
<td>No</td>
<td>165/346</td>
<td>0.53 (0.35–0.73)</td>
</tr>
</tbody>
</table>

Borghaei – WCLC 2019
Improving OS overtime

- Importance of histology
- Role of maintenance therapy
- Role of immuno + chemo

New SoC, so, the new Comparator arm in trials

Chemotherapy by histology, and chemo plus bevacizumab.

New maintenance therapy

- Chemo-IO

Treatment evolution without biomarker

- Best soport care
  - 2-4 months
- Platinum doublet chemo
  - 6-8 months
- Platinum base chemo and 3er generations
  - 8-10 months
- 12 months
- 16,9 months
- 22 months


Slide courtesy of Dr Delvys Rodriguez (modified)
## In PD-L1 ≥ 50% ICI vs. ICI+CT

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>G≥ 3 AE’s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KN024</td>
<td>45%</td>
<td>0.50 (0.37-0.68)</td>
<td>0.65 (0.50-0.86)</td>
<td>31%</td>
</tr>
<tr>
<td>KN042</td>
<td>39%</td>
<td>0.81 (0.67-0.99)</td>
<td>0.69 (0.56-0.85)</td>
<td>18%</td>
</tr>
<tr>
<td>IM110</td>
<td>38%</td>
<td>0.63 (0.45-0.88)</td>
<td>0.59 (0.40-0.89)</td>
<td>32%</td>
</tr>
<tr>
<td>CM227 N+I</td>
<td>53%</td>
<td>0.62 (0.49-0.79)</td>
<td>0.70 (0.55-0.90)</td>
<td>33%</td>
</tr>
<tr>
<td><strong>ICI CT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KN189</td>
<td>62%</td>
<td>0.36 (0.26-0.51)</td>
<td>0.59 (0.39-0.88)</td>
<td>72%</td>
</tr>
<tr>
<td>KN407</td>
<td>58%</td>
<td>0.37 (0.24-0.58)</td>
<td>0.64 (0.37-1.10)</td>
<td>70%</td>
</tr>
<tr>
<td>IM130</td>
<td>69%</td>
<td>0.51 (0.34-0.77)</td>
<td>0.84 (0.51-1.39)</td>
<td>75%</td>
</tr>
<tr>
<td>IM150</td>
<td>69%</td>
<td>0.39 (0.25-0.80)</td>
<td>0.70 (0.43-1.13)</td>
<td>45%</td>
</tr>
</tbody>
</table>

**More is better?**

Do we really need to chose?

They are probably similar.....
In PD-L1 ≥ 50% ICI vs. ICI+CT

**KN024**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>154</td>
<td>97 (63)</td>
<td>0.65 (0.50–0.86)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>151</td>
<td>113 (75)</td>
<td>( P = 0.001^a )</td>
</tr>
</tbody>
</table>

**KN189**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab/Pemb/Plat</td>
<td>52.0%</td>
<td>0.56 (0.45–0.70)</td>
</tr>
<tr>
<td>Placebo/Pemb/Plat</td>
<td>69.9%</td>
<td></td>
</tr>
</tbody>
</table>

Reck – WCLC 2019 * Gdgeel – ASCO 2019
Tumor Mutational Burden (TMB)

Schumacher – Nature 2015
Is there any role for ICI+ICI?

CheckMate 227

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%
N = 1189

NIVO + (low-dose) IPI
n = 396

Chemo
n = 397

Part 1b
PD-L1 expression < 1%
N = 550

NIVO + (low-dose) IPI
n = 187

Chemo
n = 186

NIVO + chemo
n = 177

R 1:1:1

Treatment until disease progression, unacceptable toxicity, or for 2 years for immunotherapy

Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population
- OS in PD-L1 ≥ 1% population

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%

Hellmann – NEJM 2019 * Peters – ESMO 2019
CHECKMATE 227 high TMB

**Press release Oct 19th**

*Updated analysis, TMB ≥10 mut/Mb*

**HR for OS =0.77**

(95% CI: 0.56 to 1.06).

Median OS 23.03 mo. vs. 16.72 mo.

on the chemotherapy arm

**ORR (TMB ≥10 mut/Mb)**

Press release Oct 19th

**Updated analysis, TMB ≥10 mut/Mb**

**HR for OS =0.77**

(95% CI: 0.56 to 1.06).

Median OS 23.03 mo. vs. 16.72 mo.

on the chemotherapy arm

**ORR (TMB ≥10 mut/Mb)**

- **Nivo + ipl**
  - CR: 3.6
  - PR: 45.3
  - 63/139

- **Chemo**
  - CR: 0.6
  - PR: 26.9
  - 43/160

Hellmann – NEJM 2018
CM227: Primary Endpoint: OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

- **Part 1a**
  - NIVO + IPI (n = 396)
  - Chemo (n = 397)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 396)</th>
<th>Chemo (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>17.1</td>
<td>14.9</td>
</tr>
<tr>
<td>HR</td>
<td>0.79</td>
<td>0.65 – 0.96</td>
</tr>
<tr>
<td>97.72% CI</td>
<td></td>
<td>P = 0.007</td>
</tr>
<tr>
<td>No. at risk</td>
<td>396</td>
<td>341</td>
</tr>
<tr>
<td></td>
<td></td>
<td>295</td>
</tr>
<tr>
<td></td>
<td></td>
<td>264</td>
</tr>
<tr>
<td></td>
<td></td>
<td>244</td>
</tr>
<tr>
<td></td>
<td></td>
<td>212</td>
</tr>
<tr>
<td></td>
<td></td>
<td>190</td>
</tr>
<tr>
<td></td>
<td></td>
<td>165</td>
</tr>
</tbody>
</table>

**Control arm should not be considered the SoC**

Crossover not allowed (~40% received ICI)

**Hellmann – NEJM 2019 * Peters – ESMO 2019**
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></td>
<td>NIVO + IPI n = 583</td>
<td>Chemo n = 583</td>
<td>Stratified</td>
</tr>
<tr>
<td>All randomized (N = 1166)</td>
<td>17.1</td>
<td>13.9</td>
<td>≥1%</td>
</tr>
<tr>
<td>PD-L1 &lt; 1% (n = 373)</td>
<td>17.2</td>
<td>12.2</td>
<td>≥20%</td>
</tr>
<tr>
<td>PD-L1 ≥ 1% (n = 793)</td>
<td>17.1</td>
<td>14.9</td>
<td></td>
</tr>
</tbody>
</table>

Additional exploratory subgroups analyses\(^b,c\)

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>Median OS, months</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–49% (n = 396)</td>
<td>16.1</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>≥ 50% (n = 397)</td>
<td>21.2</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TMB(^d) (mut/Mb)</th>
<th>Median OS, months</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>low, &lt; 10 (n = 380)</td>
<td>16.2</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>high, ≥ 10 (n = 299)</td>
<td>23.0</td>
<td>16.4</td>
<td></td>
</tr>
</tbody>
</table>

No consistent correlation was observed between survival outcomes with NIVO + IPI vs chemo and PD-L1 or TMB alone or in combination.

---

Hellmann – NEJM 2019 * Peters – ESMO 2019

---

Do not duplicate or distribute without permission of ESO and the author.
Coming trials with positive results

**NEPTUNE** Negative trial

**CheckMate 9LA Study** Positive trial

**Press Release**

*CheckMate -9LA, a Phase 3 Trial Evaluating Opdivo (nivolumab) Plus Low-Dose Yervoy (ipilimumab) Combined with Chemotherapy, Meets Primary Endpoint Demonstrating Superior Overall Survival Compared to Chemotherapy Alone in First-Line Lung Cancer*

Study evaluated Opdivo plus low-dose Yervoy given concomitantly with two cycles of chemotherapy vs. chemotherapy alone for the first-line treatment of advanced non-small cell lung cancer.

Crossover to immunotherapy from the chemotherapy arm was not permitted per study protocol.*
TMB

PD-L1 IHC

Is still the king

Slide courtesy of Prof Besse (modified)
Background

• Where we come from...?

• Where we are...?

• Where we go ahead...?

• Conclusions
VARGADO Study: nintedanib after ICI

- RR 58%. DCR 83%
- PFS 5.5 mo. OS: not mature
- 62% had PD as the best RR to ICI

Grohé – Future Oncol 2019
SEOM guidelines

Stage IV NSCLC (no targetable alterations)

PS 0-1

1st line

PD-L1 < 50%

SCC

Platinum based-CT (I,A)
Platinum+Taxane+Pembrolizumab (I,A)
Platinum+Taxane+Atezolizumab (III,B)

non-SCC

Platinum+Pemetrexed (II,A)
Taxol+CBDCA+Bevercizumab (I,A)
Paclitaxel+CBDCA+Bevacizumab (II,A)
Platinum+Pemetrexed+Pembrolizumab (I,A)
Platinum+Pemetrexed+Atazoluzumab (II,B)

PS 2

PD-L1 ≥ 50%

SCC and non-SCC

Single agent CT (I,B)
Carboplatin-based CT (II,A)

PS 3-4

BSC (II,B)

2nd line

If no prior IO:
- Nivolumab (I,A)
- Atezolizumab (I,A)
- Pembrolizumab (PD-L1 >1%) (I,A)
- Docetaxel (IB)

3rd line

Docetaxel (if not previously given)

If no prior IO:
- Nivolumab (IA)
- Atezolizumab (IA)
- Pembrolizumab (PD-L1 >1%) (I,A)
- Docetaxel (IB) +/- Nintedanib (II,B)
- Pemetrexed (I,B) (if not previously given)

Docetaxel +/- Nintedanib
Pemetrexed (if not previously given)

Docetaxel + Nintedanib (non-SCC)
Pemetrexed (non-SCC)
Docetaxel

CT: chemotherapy; SCC: squamous; BSC: best supportive care
(*) combination of Immunotherapy + CT may be considered
# Not EMA approved

Majem – Clin Transl Oncol 2018
Post-ICI: Different scenarios

---

KEYNOTE 024

- Primary resistance/hyperprogression
- Resistance Mechanisms Role of combinations
- Acquired resistance after PR/SD
- Stop for toxicity
- Rechallenge
- Durable benefit
- Free-interval? Monotherapy vs. combination?

Reck – NEJM 2016 (Slide courtesy of Dr Pérol, modified)
ICI after ICI: hyperprogression

ICI in HyperPD

Change From Baseline (%) vs. Time Since First Dose (months)

14% HPD with IO vs. 5% with CT

Resistance and treatments at PD

Figure 1: Mechanisms operating in the establishment of immuno-resistant niches

Syn – Lancet Oncol 2017
Is rechallenge optimal?

KEYNOTE 010
N=14. 70% Clinical benefit

KEYNOTE 024
N=10. 70% Clinical benefit

Herbst – ESMO 2018
Reck – WCLC 2019
Treatment duration?: Check Mate 153

Key eligibility criteria:
- Advanced/metastatic NSCLC
- ≥1 prior systemic therapy
- ECOG PS 0–2
- Treated CNS metastases allowed

N=163 w/o PD

Continuous nivolumab

Nivolumab
3 mg/kg IV Q2W
Treatment for 1 year

Re

Stop nivolumab

Nivolumab retreatment allowed at PD

N=1.245

CR / PR: HR 0.45 [0.24-0.85]
SD: HR 0.44 [0.17-1.09]

PFS

OS

Median, months
(95% CI)
6-month 1-year
Continuous tx
NR (NR) 80 85
1-year tx
10.3 (5.4, 15.2) 69 40
HR: 0.42 (95% CI: 0.25, 0.71)

Median, months
(95% CI)
6-month 1-year
Continuous tx
NR (NR) 97 88
1-year tx
23.2 (23.2, NA) 95 81
HR: 0.63 (95% CI: 0.33, 1.20)
Adjuvant vs. NEO-adjuvant

PEARLS
NCT02504372
N=1080
Post Surgery RO IB (≥ 4 cm)-IIIA ACT as indicated PS 0-1

BR31
NCT02273375
N=1360
Durvalumab: 10 mg/Kg Q2W 1 y.
End Point: DFS
Placebo

ANVIL
NCT02595944
N=903
Nivolumab: 240 mg Q2W 1 y.
End Point: DFS & OS
Observation

IMpower 010
NCT02486718
N=1260
Atezolizumab 1200 mg Q3W 1 y.
End Point: DFS in II-IIIA
DFS in PD-L1+ in II-IIIA
DFS in ITT
Observation

KEYNOTE 617
NCT03425643
N=786
CT + Pembrolizumab: 200 mg
End Point: DFS
Placebo

CHECKMATE 816
NCT02998528
N=300
CT + Nivolumab: 360 mg
End Point: DFS overall
CT Q3W x 3

IMPOWER 030
NCT03456063
N=374
CT + Atezolizumab: 1200 mg
End Point: DFS in II-IIIA
CT + Placebo Q3W x 4
Atezolizumab 1 y.

AELEAN
NCT03800134
N=300
CT + Durvalumab: 1500 mg
End Point: DFS in II-IIIA
CT + Placebo Q3W x 4
Durvalumab 1 y.

End Point: EFS/OS
End Point: EFS/pCR
End Point: MPR

Slide by Jordi Remon
New treatment paradigm in NSCLC 2020?

Oncogene addiction

- **EGFR**
- **ALK**
- **ROS1**
- **BRAF**
- **RET**
- **V600E**
- **ex14**
- **MET**
- **NTRK**
- **T790M**
- **T790M – or 1st L. Osim.**
- **Crizotinib**
- **Ceritinib**
- **Alectinib**
- **Larotrectinib**
- **Entrectinib**
- **Pemetrexed**
- **Platinum**
- **Lorlatinib**

**1st L**
- Crizotinib*,# Entrectinib*
- Dabrafenib + Trametinib*#
- Crizotinib*,# Ceritinib *# Alectinib# Gefitinib + ChT

**2nd L**
- T790M +
- Osimertinib**
- Pem / Platinum ABCP#

**PD-L1**
- **Non-Squamous**
  - PD-L1 ≤ 1%
  - PD-L1 1-49%
  - PD-L1 ≥ 50%
- **Squamous**
  - PD-L1 ≤ 1%
  - PD-L1 1-49%

**ICI contraindication**

- Pembrolizumab*,# Atezol.,@
- Pembrol. + Cb + Pem*,#
- Atezolizumab. + Cb + NabP*,
- ABCP*,# Nivo + Ipi@
- Platinum-based CT +/- BVZ

- Pembrolizumab + Cb + Taxanes*
- Pembrolizumab + Cb + Taxanes*

- Platinum-based CT
- Docetaxel + Nintedanib#
- Docetaxel + Ramucirumab*
- Docetaxel + Ramucirumab*

- Platinum-douplet
- Afatinib*#

- NabP:
- ABCP: Atezolizumab, BVZ, carboplatin,paclitaxel

*FDA approved *#: FDA breakthrough; #EMA approved; @Not yet approved

Algorithm by Jordi Remon
Conclusions

- Standard in 1\textsuperscript{st} line NSCLC:
  - Pembrolizumab if PDL1 strong + (>50%), also with CT.
  - Pembrolizumab + CT in others, including PD-L1 negative
  - Atezolizumab + CT +/- bev.: approved, define subgroups

- IO + IO combo not clear the best place in the therapeutic strategy and the predictive role of TMB remains uncertain.

- Challenges: Duration, new combinations and biomarkers.