Immune checkpoint inhibition in early stage NSCLC, SCLC and mesothelioma

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University Hospital of Zürich

Zürich, May 11, 2019
Consultant or Advisory Role in the last two years
I have received honoraria as a consultant at advisory boards from Abbvie, Astra Zeneca, Boehringer Ingelheim, MSD, Pfizer, Roche and Takeda.

Speaker Honoraria in the last two years
I have received honoraria as a speaker from Astra Zeneca, Boehringer Ingelheim, Lilly, MSD and Roche.

DMC in the last two years
Roche and Takeda

Financial Support of ETOP trials (president and scientific chair)
Astra Zeneca, BMS, Boehringer Ingelheim, MSD, Roche, and Pfizer
Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs.
Update systemic therapy of NSCLC

- Immune checkpoint inhibition for earlier stages of NSCLC
- Immune checkpoint inhibition SCLC
- Immune checkpoint inhibition in mesothelioma
Randomized phase III comparison of standard-dose versus high-dose chemo-radiotherapy ± cetuximab for stage III NSCLC

<table>
<thead>
<tr>
<th>Stratify</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT Technique</td>
<td>Concurrent chemotherapy* RT to 60 Gy, 5 x per wk for 6 wks</td>
<td>Concurrent chemotherapy* RT to 74 Gy, 5 x per wk for 7.5 wks</td>
<td>Concurrent chemotherapy* and Cetuximab RT to 60 Gy, 5 x per wk for 6 wks</td>
<td>Concurrent chemotherapy* and Cetuximab RT to 74 Gy, 5 x per wk for 7.5 wks</td>
</tr>
<tr>
<td>Consolidation Treatment</td>
<td>Consolidation chemotherapy*</td>
<td>Consolidation chemotherapy*</td>
<td>Consolidation chemotherapy* and Cetuximab</td>
<td>Consolidation chemotherapy* and Cetuximab</td>
</tr>
</tbody>
</table>

*Carboplatin and paclitaxel

One-sided log-rank p=0.0042

Median PFS 11 months

One-sided log-rank, p=0.2938

Bradley, Lancet Oncology 2015
PACIFIC: Consolidation durvalumab for 1 year after chemoradiotherapy of stage III NSCLC: Progression-free survival

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (28 countries)\(^1\)\(^-\)\(^3\)
- Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting (N=702)
- Absence of progression following at least 2 cycles of platinum-based chemotherapy concomitant with radiation therapy
- Primary endpoints\(^1\)
  - PFS, OS
- Secondary endpoints\(^1\)
  - ORR, DoR, DSR
  - Safety/tolerability
  - PK, immunogenicity, QoL
- Arm 1 (n=468): Durvalumab i.v. 10 mg/kg q2w for up to 12 months
- Arm 2 (n=234): Placebo i.v. q2w

Median PFS from start of therapy @ 20 months

Paz-Ares, ESMO 2017; Antonia, NEJM 2017
Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC

<table>
<thead>
<tr>
<th></th>
<th>No. of Events/Total No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
<th>12-Mo Overall Survival Rate (95% CI)</th>
<th>24-Mo Overall Survival Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab</td>
<td>183/476</td>
<td>NR (34.7–NR)</td>
<td>83.1 (79.4–86.2)</td>
<td>66.3 (61.7–70.4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>116/237</td>
<td>28.7 (22.9–NR)</td>
<td>75.3 (69.2–80.4)</td>
<td>55.6 (48.9–61.8)</td>
</tr>
</tbody>
</table>

Stratified hazard ratio for death, \( 0.68 \) (99.73% CI, 0.47–0.997)
Two-sided \( P = 0.0025 \)

Antonia, NEJM 2018
Exploratory analyses of overall survival in PACIFIC

Faivre-Finn, ESMO 2018
Exploratory analyses of overall survival in PACIFIC

<table>
<thead>
<tr>
<th></th>
<th>PFS (BICR)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>No. of events / No. of patients (%)</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>Durvalumab / Placebo</td>
</tr>
<tr>
<td>ITT&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;14 days</td>
<td>≥14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50/120 (41.7) / 164/356 (46.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46/62 (74.2) / 111/175 (63.4)</td>
</tr>
</tbody>
</table>

Faivre-Finn, ESMO 2018
Neoadjuvant PD-1 blockade in resectable lung cancer with two infusions of nivolumab 2 weeks apart: Major pathological response

63yo M, ex-smoker, adeno, PD-L1 2%+, <10% viable tumor at resection

% pathological regression:

MPR 9/21 (45%)

Forde, ESMO 2016 and NEJM 2018
Neoadjuvant atezolizumab

MPR in 10 out of 45 patients (22% [95% CI: 11%, 37%]) without an EGFR or ALK genetic alteration

No observable correlation between pathologic and radiographic responses
## Adjuvant phase III clinical trials in NSCLC

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Phase</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer (ANVIL)</td>
<td>Phase III</td>
<td>IB-IIIA</td>
<td>DFS OS</td>
</tr>
<tr>
<td>Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS)</td>
<td>Phase III</td>
<td>IB-IIIA</td>
<td>DFS</td>
</tr>
<tr>
<td>A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer (IMpower 010)</td>
<td>Phase III</td>
<td>IB-III</td>
<td>DFS</td>
</tr>
<tr>
<td>Double Blind Placebo Controlled Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC</td>
<td>Phase III</td>
<td>IB-III</td>
<td>DFS in PD-L1 positive</td>
</tr>
</tbody>
</table>
Systemic therapy for patients with early stage NSCLC without oncogenic driver mutation – integrating immunotherapy

• Durvalumab consolidation after chemoradiotherapy for stage III NSCLC is a new standard of care
• Integrating immune checkpoint inhibition into neoadjuvant therapy of operable stages of NSCLC is being investigated
• Four large randomized trials are testing the role of adjuvant therapy with immune checkpoint inhibitors
Update systemic therapy of NSCLC

- Immune checkpoint inhibition for earlier stages of NSCLC
- Immune checkpoint inhibition SCLC
- Immune checkpoint inhibition in mesothelioma
KEYNOTE-028 pembrolizumab in patients with extensive-stage PD-L1 positive SCLC: Results from the phase Ib KEYNOTE-028 study

Ott, JCO 2016
KEYNOTE-158 Phase II study of pembrolizumab in second line ED SCLC

PD-L1 positive by combined positive score (CPS)

Chung, ASCO 2018
Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in SCLC

Hellmann, Cancer Cell 2018
Phase 3 studies of immune checkpoint inhibitors in second line treatment or as maintenance in extensive disease SCLC

**Nivolumab**
- **Checkmate-331**
  - SCLC second line
  - N=798
  - Primary endpoints: OS
  - Nivolumab or placebo
    - Nivolumab
    - Topotecan or Amrubicine
  - OS negative

**Atezolizumab**
- **IFCT-1603**
  - SCLC second line
  - N=79
  - Primary endpoints: OS
  - Atezolizumab
    - Topotecan or platin/eto
  - OS negative

**Nivolumab**
- **Checkmate-451**
  - SCLC ED after EP (SD or OR)
  - N=940
  - Primary endpoints: PFS and OS
  - Nivolumab or placebo
    - Nivolumab
    - Nivolumab/Iplimimab
    - Placebo
  - OS negative
Randomized phase 3 study of nivolumab monotherapy versus chemotherapy in relapsed SCLC: Results from CheckMate 331
A randomized non-comparative phase 2 study of anti-PD-L1 atezolizumab or chemotherapy as second-line therapy in patients with SCLC: Results from the IFCT-1603 Trial

Unrelated to PD-L1 expression

\[
\text{HR (adjusted)}_{\text{Arm Atezolizumab}} = 0.84 [0.45-1.58] ; \ p=0.60
\]

\[
\text{HR (adjusted)}_{\text{Arm Atezolizumab}} = 2.26 [1.30-3.93] ; \ p=0.004
\]
Nivolumab plus ipilimumab, nivolumab, or placebo as maintenance therapy in patients with ED SCLC after first-Line platinum-based chemotherapy: Results from CheckMate 451

Key eligibility criteria
- ED-SCLC at diagnosis
- No symptomatic CNS metastases
- ECOG PS 0 or 1
- Ongoing response of CR, PR or SD following 4 cycles of platinum-based 1L chemotherapy

Stratified by ECOG PS (0 vs 1), prior PCI (yes vs no), sex

- Primary endpoint:
  - OS: nivolumab + ipilimumab vs placebo
- Secondary endpoints:
  - OS: nivolumab vs placebo
  - PFS: nivolumab + ipilimumab vs placebo
  - PFS: nivolumab vs placebo
- Exploratory endpoints:
  - ORR and DOR
  - Safety and tolerability

Treat until disease progression or unacceptable toxicity, for a maximum of 2 years

Owonikoko, ELCC 2019
Nivolumab plus ipilimumab, nivolumab, or placebo as maintenance therapy in patients with ED SCLC after first-Line platinum-based chemotherapy: Results from CheckMate 451

Owonikoko, ELCC 2019
Nivolumab plus ipilimumab, nivolumab, or placebo as maintenance therapy in patients with ED SCLC after first-Line platinum-based chemotherapy: Results from CheckMate 451

### Treatment-Related AEs

<table>
<thead>
<tr>
<th>TRAE, n (%)</th>
<th>Nivolumab + ipilimumab (n = 276)</th>
<th>Nivolumab (n = 279)</th>
<th>Placebo (n = 273)</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>238 (86)</td>
<td>145 (52)</td>
<td>170 (61)</td>
</tr>
<tr>
<td>Serious TRAEs</td>
<td>104 (37)</td>
<td>87 (31)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>TRAE leading to discontinuation</td>
<td>80 (29)</td>
<td>69 (25)</td>
<td>22 (8)</td>
</tr>
</tbody>
</table>

**Most frequent TRAEs (≥15%)**

- **Diarrhea**: 67 (24) | 15 (5) | 40 (14) | 3 (1) | 19 (7) | 0
- **Pruritus**: 66 (24) | 3 (1) | 31 (11) | 0 | 22 (8) | 0
- **Rash**: 65 (23) | 5 (2) | 17 (6) | 1 (< 1) | 11 (4) | 1 (< 1)
- **Fatigue**: 59 (21) | 8 (3) | 55 (20) | 6 (2) | 40 (15) | 1 (< 1)
- **Decreased appetite**: 54 (19) | 6 (2) | 27 (10) | 1 (< 1) | 22 (8) | 1 (< 1)

**Treatment-related deaths**

- 7 (2) | 1 (< 1) | 1 (< 1)

- Patients received a median of 2 nivolumab doses and 2 ipilimumab doses in the nivolumab plus ipilimumab arm and 5 doses in the nivolumab arm.

*Owonikoko, ELCC 2019*
Phase 3 studies of immune checkpoint inhibitors as first line therapy of extensive disease SCLC

**Atecolizumab**
*IMpower-133*
- SCLC ED
  - N=500
  - Atecolizumab + EP
  - EP
  - Primary endpoints: PFS and OS

**Pembrolizumab**
*KEYNOTE-604*
- SCLC ED
  - N=430
  - Pembrolizumab + EP
  - EP
  - Primary endpoints: PFS and OS

**Durvalumab**
*CASPION*
- SCLC ED
  - N=984
  - EP
  - Durvalumab/Tremelimumab
  - Durvalumab + EP
  - Primary endpoint: PFS and OS
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: Trial design

Patients with (N = 403):
- Measurable ES-SCLC (RECIST v1.1)
- 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)\textsuperscript{a}

Induction (4 x 21-day cycles)
- Atezolizumab (1200 mg IV, Day 1)
  + carboplatin
  + etoposide
- Placebo
  + carboplatin
  + etoposide

Carboplatin: AUC 5 mg/mL/min IV, Day 1
Etoposide: 100 mg/m\textsuperscript{2} IV, Days 1–3

Maintenance
- Atezolizumab
  Treat until PD or loss of clinical benefit
- Placebo
  PCI per local standard of care

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

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

Liu, WCLC 2018; Horn, NEJM 2018
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: OS

- 12-month OS
  - Atezolizumab: 51.7%
  - Placebo: 38.2%

- Median OS, months (95% CI):
  - Atezolizumab + CP/ET: 12.3 (10.8, 15.9)
  - Placebo + CP/ET: 10.3 (9.3, 11.3)

- HR (95% CI):
  - Atezolizumab: 0.70 (0.54, 0.91)
  - Placebo: 0.70 (0.54, 0.91)
  - p = 0.0089

- Median follow-up, months:
  - Atezolizumab: 13.9
  - Placebo: 13.9

Liu, WCLC 2018; Horn, NEJM 2018
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: Response

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Atezolizumab + CP/ET</th>
<th>Placebo + CP/ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2.5</td>
<td>1.0</td>
</tr>
<tr>
<td>CR/PR</td>
<td>60.2</td>
<td>64.4</td>
</tr>
<tr>
<td>SD</td>
<td>20.9</td>
<td>21.3</td>
</tr>
<tr>
<td>PD</td>
<td>10.9</td>
<td>6.9</td>
</tr>
</tbody>
</table>

### Duration of Response


<table>
<thead>
<tr>
<th>Duration of response</th>
<th>Atezolizumab + CP/ET (N = 121)</th>
<th>Placebo + CP/ET (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration, months (range)</td>
<td>4.2 (1.4⁸ to 19.5)</td>
<td>3.9 (2.0 to 16.1⁹)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.70 (0.53, 0.92)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event-Free Rate</th>
<th>Atezolizumab + CP/ET</th>
<th>Placebo + CP/ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month event-free rate (%)</td>
<td>32.2</td>
<td>17.1</td>
</tr>
<tr>
<td>12-month event-free rate (%)</td>
<td>14.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Patients with ongoing response — no. (%)³

| patients with ongoing response — no. (%)³ | 18 (14.9) | 7 (5.4) |

*Liu, WCLC 2018; Horn, NEJM 2018*
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: PFS

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab + CP/ET (N = 201)</th>
<th>Placebo + CP/ET (N = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>171 (85.1)</td>
<td>189 (93.6)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.2 (4.4, 5.6)</td>
<td>4.3 (4.2, 4.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.77 (0.62, 0.96)</td>
<td>p = 0.017</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>13.9</td>
<td></td>
</tr>
</tbody>
</table>

Liu, WCLC 2018; Horn, NEJM 2018
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: PFS

Clinical data cutoff date: April 24, 2018.

Liu, WCLC 2018; Horn, NEJM 2018
Study design:
Multicentre, open label, randomized phase II trial, ETOP sponsored, collaboration with IFCT and other trial groups

Primary objectives:
PFS and OS

Sample size:
260 randomized patients
• The addition of atezolizumab to carboplatin and etoposide improves the survival of extensive disease SCLC
• Randomized trials of maintenance or second line immune checkpoint inhibition in SCLC have been negative
• The potential of immune checkpoint inhibition of increasing the cure rate of SCLC is under investigation
Update systemic therapy of NSCLC

- Immune checkpoint inhibition for earlier stages of NSCLC
- Immune checkpoint inhibition SCLC
- Immune checkpoint inhibition in mesothelioma
Summarizing available results on single agent immune checkpoint inhibitors in mesothelioma second or later line

<table>
<thead>
<tr>
<th>Study</th>
<th>Keynote-028+ Pembrolizumab</th>
<th>NivoMes Nivolumab</th>
<th>MERIT Nivolumab</th>
<th>“Chicago” Pembrolizumab</th>
<th>Avelumab Unselected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Number</td>
<td>25</td>
<td>34</td>
<td>34</td>
<td>64</td>
<td>53</td>
</tr>
<tr>
<td>PR</td>
<td>5 (20%)</td>
<td>8 (24%)</td>
<td>10 (29.4)</td>
<td>14 (22%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (52%)</td>
<td>8 (24%)</td>
<td>13</td>
<td>26 (41%)</td>
<td>27 (47%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.5 months</td>
<td>2.6 months</td>
<td>6.1 months</td>
<td>4.1 months</td>
<td>4.1 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>18 months</td>
<td>11.8 months</td>
<td>17.3 months</td>
<td>11.5 months</td>
<td>10.7 months</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Safety</td>
<td>DCR12w 40%: 48%</td>
<td>PFS</td>
<td>RR &gt;25%</td>
<td>NR</td>
</tr>
</tbody>
</table>

+ PD-L1 positive only
1 Levels of PD-L1 expression did not correlate with response
2 Higher responses in PD-L1 positive tumors
3 Higher responses in sarcomatous mesothelioma
Summarizing available results on combined agent immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>MAPS-2</th>
<th>INITIATE</th>
<th>NIBIT</th>
<th>DREAM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo</td>
<td>Ipi/Nivo</td>
<td>Ipi/Nvo</td>
<td>Tremi/Durva*</td>
</tr>
<tr>
<td>Patient Number</td>
<td>54</td>
<td>54</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>PR</td>
<td>18.5%</td>
<td>25.9%</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>SD</td>
<td>25.9%</td>
<td>24.1%</td>
<td>38%</td>
<td>35%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4 months</td>
<td>5.6 months</td>
<td>6.2 months</td>
<td>5.7 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>11.9 months</td>
<td>15.9 months</td>
<td>&gt;12.7 months</td>
<td>16.6 months</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>DCR12w 40%: 44%</td>
<td>DCR12w 40%: 52%</td>
<td>irR</td>
<td>PFS6m: 65% 57% (ns)</td>
</tr>
</tbody>
</table>

* first line therapy
Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial

**RR 19%**  
**RR 28%**

**Median PFS**  
4.0 months  
5.6 months

**Median OS**  
11.9 months  
15.9 months

*Scherpereel, Lancet Oncol 2019*
DREAM: Final results of a phase 2 trial of durvalumab with first line chemotherapy in mesothelioma

**Trial design – Single-arm, multicentre phase II trial with a safety run-in, N=96**

- Population
  - 1st line MPM
  - Non-surgical
  - No prior RT to measurable disease
  - ECOG PS 0-1
  - No PD-L1 selection

- Induction
  - Cisplatin 75mg/m² + Pembrolizumab 500mg/m² + Durvalumab 1125mg q3w

- Maintenance
  - Durvalumab 1125mg q3w x 52 w

- Outcomes
  - PFS6*
  - ORR (CR + PR)*
  - Toxicity
  - OS
  - mRECIST for MPM, mREC

- 6 cycles

- To total 17 cycles durvalumab

**Progression Free Survival (mRECIST)**

<table>
<thead>
<tr>
<th>Median PFS, mo (95% CI)</th>
<th>PFS6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy + Durvalumab</td>
<td>6.2 (5.5-9.0)</td>
</tr>
<tr>
<td>PFS6</td>
<td>31/54 (57%)</td>
</tr>
</tbody>
</table>

**Statistical considerations**

- 2-stage Simon’s design: 31 in stage 1, additional 23 in stage 2, for total n=54

- 6 patients in an initial safety run-in using a 3+3 design

- The hypothesis was that the regimen would be worthy of pursuit if the true PFS6 rate was 65% or higher, but not if it was 45% or lower

- 90% power with a one-sided type 1 error rate of 5%

* mRECIST for MPM, mREC

Nowak, WCLC 2017
DREAM: Final results of a phase 2 trial of durvalumab with first line chemotherapy in mesothelioma

**Progression-Free Survival (mRECIST)**

<table>
<thead>
<tr>
<th>Median PFS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy + Durvalumab</td>
</tr>
<tr>
<td>PFS6</td>
</tr>
</tbody>
</table>

**Objective tumour response**

<table>
<thead>
<tr>
<th>Response</th>
<th>Confirmed response mRECIST (%)</th>
<th>Confirmed response iRECIST (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 (48)</td>
<td>27 (50)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (37)</td>
<td>20 (37)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (15)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

Nowak, WCLC 2017
PROMISE-meso: Pembrolizumab in advanced pretreated malignant pleural mesothelioma

**Study design:**
- Multicentre, randomised, phase III trial, ETOP sponsored

**Primary objectives:**
- To assess safety and efficacy of pembrolizumab versus standard chemotherapy in MPM

**Primary endpoint:**
- Progression-free survival (based on independent radiological review)

**Sample size:**
- 142 randomized patients
CA209-743: A phase III, randomized, open label trial of nivolumab in combination with ipilimumab versus pemetrexed with cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma

Study design:

Key eligibility criteria:
- Unresectable untreated pleural mesothelioma
- Available tumor sample
- PS 0-1
- No prior Chemotherapy for pleural mesothelioma

Ipiilimumab 1 mg/kg Q6 weeks + Nivolumab 3 mg/kg Q2 weeks (up to progression/toxicity*)

Stratification Factors:
- Histology (epithelioid vs. sarcomatoid or mixed histology subtypes)
- Gender

Cisplatin 75mg/m2 or Carboplatin AUC 5 + Pemetrexed 500 mg/m2 in 21 day cycles for up to six cycles

* Treatment beyond initial investigator assessed progression according to mRECIST specific to mesothelioma, will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

ClinicalTrials.gov Identifier: NCT02899299

- Primary Outcome Measures:
  - OS / PFS
- Secondary/exploratory Outcome Measures:
  - ORR, DCR, PRO, association between PD-L1 expression and efficacy measures, safety, PK/immunogenicity
Study design:
- Randomised multicentre phase III
- ETOP sponsored

Co-primary endpoints:
- Progression-free survival
- Overall survival

Secondary endpoints:
- Overall response
- Disease control
- Time to treatment failure
- Duration of response
- Safety and tolerability
- Patient reported outcome / QoL

Sample size:
320 randomized patients
• Several phase II studies indicate activity of immune checkpoint inhibition in malignant pleural mesothelioma

• Comparative studies in second and first line are ongoing and hopefully will lead to regulatory approval