Immune checkpoint inhibitors in other thoracic malignancies

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A highly mutated SCLC genome with complex signatures of tobacco exposure

Smoking signature (G>T transversions):
In H209 cell-line, 23’000 somatic substitutions identified, including 134 in coding exons.

Pleasance Nature 2010
A highly mutated SCLC genome with complex signatures of tobacco exposure

3 comprehensive genomics papers define important aspects of the genomic landscape of SCLC

- *Rudin et al.* 35 primary tumors and 28 cell lines
- *Peifer et al.* 29 primary tumors
- *George et al.* 110 primary tumors

- Non-synonymous mutation rate 5.5-7.4/Mb (melanoma 6-6.5)
- 180-240 mutations per tumour
CTLA-4: Ipilimumab combined with paclitaxel and carboplatin in extensive disease SCLC, double-blind randomized phase II trial (concurrent versus phased ipilimumab)
Phase I/II Study (CheckMate 032) of Nivolumab With or Without Ipilimumab for Treatment of Recurrent Small Cell Lung Cancer (SCLC)

Scott J. Antonia,1 Johanna Bendell,2 Matthew Taylor,3 Emiliano Calvo,4 Dirk Jäger,5 Filippo de Braud,6 Patrick A. Ott,7 M. Catherine Pietanza,8 Leora Horn,9 Dung T. Le,10 Michael A. Morse,11 José A. López-Martin,12 Paolo A. Ascierto,13 Olaf Christensen,14 Joseph F. Grosso,14 Jason Simon,14 Chen-Sheng Lin,14 Joseph Paul Eder15

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PRESENTED AT: ASCO ANNUAL MEETING
Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

Patients with SCLC with progressive disease after ≥1 prior line of therapy, including a platinum-based regimen in first line (unselected by PD-L1 expression) (N = 183)

- Nivolumab 3 mg/kg IV Q2W (n = 80)
- Nivolumab 1 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 3)
- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W for 4 cycles (n = 47)
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 53)

Primary objective: ORR per RECIST v1.1
Secondary objective: safety
Exploratory objectives: PFS, OS, biomarker analysis

Antonia, Lancet Oncol 2016
Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

RR 10%

RR 23%

RR 19%
Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial
Pembrolizumab (MK-3475) in Patients With Extensive-Stage Small Cell Lung Cancer: Preliminary Safety and Efficacy Results from KEYNOTE-028

Patrick A. Ott,1 Elena Elez,2 Sandrine Hiret,3 Dong-Wan Kim,4 Rebecca A. Moss,5 Tammy Winser,6 Shuai Sammy Yuan,6 Jonathan Cheng,6 Bilal Piperdi,6 Janice Mehnert5

1Dana-Farber Cancer Institute, Boston, MA; 2Vall d’Hebron Institute of Oncology, Barcelona, Spain; 3ICO René Gauducheau, Nantes, France; 4Seoul National University Hospital, Seoul, South Korea; 5Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; 6Merck & Co., Inc., Kenilworth, NJ
Immunotherapy for SCLC
PDL1+

PD-L1 Screening: SCLC Cohort

Patients Screened for PD-L1
n = 157

Samples Evaluable for PD-L1
n = 147

PD-L1–Positive Tumors
n = 42

Patients Treated as of March 13, 2015
N = 20

*Patients with CNS metastases that were stable for 24 weeks could enroll.
*1 additional patient was misenrolled and never treated. An additional 4 patients were enrolled and treated after the March 13, 2015, data cutoff date of this analysis.
# Immunotherapy for SCLC PDL1+

## Antitumor Activity (RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>35</td>
<td>15-59</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0-17</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>35</td>
<td>15-59</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>5</td>
<td>0-25</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9</td>
<td>45</td>
<td>23-69</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>15</td>
<td>3-38</td>
</tr>
</tbody>
</table>

<sup>a</sup>Both confirmed and unconfirmed responses are included. Includes patients who died or discontinued for clinical progression before the first imaging assessment (n = 1 each) or who have not reached the first imaging assessment (n = 1).

<sup>b</sup>Data cutoff date: March 13, 2015.
Immunotherapy for SCLC
PDL1+
SCLC: ongoing trials

**Anti-PD1**

- **Nivolumab**
  - CA209-451 (Ph 3): ED-SCLC (maintenance after platinum-based chemotherapy) N=810
  - Primary endpoint: OS/PFS
  - Nivolumab
  - Nivolumab + ipilimumab
  - Placebo

- CheckMate 331 (Ph 3): Relapsed SCLC N=480
  - Primary endpoint: OS
  - Nivolumab
  - Topotecan + amrubicin

- CA209-032 (Ph 1/2): SCLC, TNBC, GC, BC or PC N=410
  - Primary endpoint: ORR
  - Nivolumab
  - Nivolumab + ipilimumab

**Anti-CTLA-4**

- **Ipilimumab**
  - ETOP/STIMULI (Ph 2): Limited-stage SCLC (after chemo-radiation) N=260
    - Primary endpoint: OS
    - Ipilimumab + nivolumab
    - Observation

  - ICE (Ph 2): ED-SCLC N=42
    - Primary endpoint: PFS
    - Ipilimumab + etoposide + carboplatin

- Carboplatin/etoposide +/- Atezolizumab (concurrent and maintenance) in ED SCLC (NCT02763579, IMPower 133)
STIMULI: Immunotherapy after chemoradiotherapy in LD SCLC (amendment 1)

**Chemo-Radiotherapy:**
- **cis-/carboplatin + etoposide**
- 4 cycles

**Screening:**
- LD SCLC

**Consolidation vs observation:**
- **induction**
  - combination nivolumab/ipilimumab
- **maintenance**
  - nivolumab

**Tumour evaluation:**
- PD: no → RT
- PD: yes → off

**RT (Thoracic Radiotherapy):**
- start: day 1 of chemo cycle 1 or day 1 of chemo cycle 2
- accelerated schedule preferred

**CT scans for tumour assessment:**
- up to 18 months: every 9 weeks
- up to 2 years: every 12 weeks
- years 3 & 4: every 6 months
- at 5 years

**Biomaterial for translational research:**
- Serum
- Whole blood
- Biopsy: FFPE block or slides

**At progression:**
- Voluntary re-biopsy: → FFPE block

**Co-primary endpoints:** PFS & OS

**Sample Size:** 260 randomized patients
Metastatic SCLC (n = 152)
- First line metastatic
- Measurable disease
- ECOG PS 0-1
- PD-L1 status

Keynote-068/EORTC 1416

Primary endpoint: Progression-free survival @ 6 months
Mesothelioma – mutational load

- Mesotheliomas contain an average of 24 protein coding alterations per sample, a considerably lower rate than other types of malignancies.

*Bueno, Nat Gen 2016*
Tremelimumab in second or third line versus placebo in malignant mesothelioma

**DETERMINE Study Design**
Global, Randomized, Double-Blind, Placebo-Controlled, Phase 2b Trial

- **N=571**
  - Pleural/peritoneal MM
  - ECOG PS 0–1
  - 1–2 prior regimens (including a platinum)
  - Measurable disease

- **2:1 randomization**

- **Stratification:**
  - Pleural vs. peritoneal
  - 2nd vs. 3rd line
  - EORTC low vs. high risk

- Tremelimumab i.v.
  - 10 mg/kg q4w x 7 doses, then q12w
  - n=382

- Placebo i.v.
  - n=189

**Primary endpoint: Overall survival (OS)**

- Key secondary endpoints: 18-month OS, PFS, overall response, disease control rate (DCR), durable DCR, safety

- Statistics: 90% power to detect an overall HR of 0.71 (increase in 2-sided 0.05 level test)

**DETERMINE: Overall Survival (ITT Population)**

<table>
<thead>
<tr>
<th></th>
<th>Tremelimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>382</td>
<td>189</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>307 (80.4%)</td>
<td>154 (81.5%)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>7.7</td>
<td>7.3</td>
</tr>
<tr>
<td>18-mo survival</td>
<td>17.4%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

Analysis with 2 stratification factors (EORTC status and line of therapy)

- **OS HR = 0.92**
- 95% 2-sided CI = 0.76, 1.12
- 2-sided p-value = 0.408

Kindler ASCO 2016
Pembrolizumab (Anti-PD1) für Mesothelioma
KeyNOTE-028

Pembrolizumab 10 mg/kg IV Q2W

Response Assessment*

Complete or partial response or stable disease

Confirmed progressive disease or unacceptable toxicity

Treat for 24 months or until progression or intolerable toxicity

Discontinue pembrolizumab

Alley_AACR 2015
Pembrolizumab (Anti-PD1) für Mesothelioma
KeyNOTE-028

Patients Screened
n = 84

Samples Evaluable for PD-L1
n = 80

PD-L1-Positive Tumors
n = 38

45.2% PD-L1+

Patients Enrolled
N = 25

Nonevaluable
- Insufficient sample (n = 3)
- Uninterpretable PD-L1 staining (n = 1)

Reasons for exclusion
- ECOG PS ineligible (n = 6)
- No measurable disease (n = 1)
- Declined study participation (n = 1)
- Other (n = 5)

Alley_AACR 2015
## KeyNOTE-028 Responses

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

**N = 25**

**Objective response rate:** 28% (95% CI, 12-49)

**Disease control rate:** 76% (95% CI, 55-91)
KeyNOTE-028 Responses

Change From Baseline in Sum of Longest Diameter of Target Lesion, %

-100
-80
-60
-40
-20
0
20
40
60
80
100

20%
-30%

Epithelioid
Sarcomatoid
Biphasic
Not specified/reported

Alley_AACR 2015
Avelumab (PD-L1) in mesothelioma cohort pretreated with platin/pemetrexed

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>66 (32-84)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (60.4)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (39.6)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (26.4)</td>
</tr>
<tr>
<td>1</td>
<td>39 (73.6)</td>
</tr>
<tr>
<td>Tumor histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>43 (81.1)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (11.3)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time since first diagnosis, years (range)</td>
<td>1.8 (0.4-31.3)</td>
</tr>
<tr>
<td>Number of prior anticancer therapy lines, n (%)*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (32.1)</td>
</tr>
<tr>
<td>2</td>
<td>14 (26.4)</td>
</tr>
<tr>
<td>3</td>
<td>11 (20.8)</td>
</tr>
<tr>
<td>≥4</td>
<td>10 (18.9)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.0 (1-9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Staining cut-off level n=39 evaluable</th>
<th>PD-L1+ n (%)</th>
<th>PD-L1- n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1% tumor cells, any intensity</td>
<td>20 (51.3)</td>
<td>19 (48.7)</td>
</tr>
<tr>
<td>≥5% tumor cells, any intensity</td>
<td>14 (35.9)</td>
<td>25 (64.1)</td>
</tr>
<tr>
<td>≥25% tumor cells, moderate-to-high intensity</td>
<td>7 (17.9)</td>
<td>32 (82.1)</td>
</tr>
<tr>
<td>≥10% tumor-infiltrating immune cells</td>
<td>6 (15.4)</td>
<td>33 (84.6)</td>
</tr>
</tbody>
</table>

Hassan, ASCO 2016
Avelumab (PD-L1) in mesothelioma cohort pretreated with platin/pemetrexed

<table>
<thead>
<tr>
<th>Best overall response by RECIST v1.1</th>
<th>n=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>5 (9.4)*</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>25 (47.2)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>18 (34.0)</td>
</tr>
<tr>
<td>Non-evaluable, n (%)</td>
<td>5 (9.4)</td>
</tr>
<tr>
<td>Overall response rate, % (95% CI)</td>
<td>9.4 (3.1, 20.7)</td>
</tr>
<tr>
<td>Disease control rate, % (95% CI)</td>
<td>56.6 (42.3, 70.2)</td>
</tr>
</tbody>
</table>

[Hassan, ASCO 2016]
A multicentre randomised phase III trial comparing pembrolizumab versus standard chemotherapy for advanced pre-treated malignant pleural mesothelioma

**PROMISE-meso:** PembROlizuMab Immunotherapy versus Standard chemotherapy for advanced prE-treated malignant pleural mesothelioma
Malignant pleural mesothelioma after/on one previous line of chemotherapy

Progression of disease

R 1:1
Malignant pleural mesothelioma after/on one previous line of chemotherapy

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

Chemotherapy by institutional choice
- Gemcitabine 1000 mg/m² *d1/d8, q3w i.v.* or
- Vinorelbin 30 mg/m² *d1/d8, q3w i.v.* or
- Vinorelbin 60 mg/m² *d1/d8 q3w p.o.*

Progression of disease

Week ≤ 4 0 3 6 9 18 27 39

... until PD by irRECIST, for max 2 years
Malignant pleural mesothelioma after/on one previous line of chemotherapy

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

Chemotherapy by institutional choice
- Gemcitabine 1000 mg/m² d1/d8, q3w i.v. or
- Vinorelbine 30 mg/m² d1/d8, q3w i.v. or
- Vinorelbine 60 mg/m² d1/d8 q3w p.o.

Progression of disease

Cross-over

Week ≤4 0 3 6 9 18 27 39

... until PD by irRECIST, for max 2 years
PROMISE-meso: PembROlizuMab Immunotherapy versus Standard chemotherapy for advanced pre-treated malignant pleural mesothelioma

Sample size: 142 randomised patients

Randomisation: stratified by PS 0-1 vs 2 sarcomatoid histological subtype vs not

Primary endpoint: Progression-free survival

Secondary endpoints: Objective response
Overall survival
Time to treatment failure
Immune-related PFS
Tolerability assessed by adverse events graded acc. CTCAE v4.0
NIVOTHYM

Study design: Multicentre, single arm, phase II trial, EORT sponsored
Primary objectives: To assess the PFS rate of nivolumab a 6 months
Patient selection: Relapsed/advanced thymic carcinoma and type B3 thymoma
Sample size: Two stage design, with safety assessment after 10 pts randomized patients

Eligible patients → Nivolumab 240 mg IV q2 weeks until PD, unacceptable toxicity, pts refusal or death

- CT scan of thorax and superior abdomen every 9 weeks
- Required at 6 months