IMMUNOTHERAPY FOR SMALL CELL LUNG CARCINOMA & MESOTHELIOMA

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DISCLOSURE SLIDE

I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations:

Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp and Dohme, and Merck Serono, Pfizer, Regeneron and Takeda.

I declare no conflict of interest.
Incidence of NSCLC, SCLC, and Mesothelioma

Non-small cell lung cancer\(^1\)-\(^3\)

80%-85% of all lung cancers
- Incidence in US: 176,960 - 188,020
- Incidence in EU: 328,160 - 348,670
- Incidence in Japan: 52,813 - 56,114

Small cell lung cancer\(^3\),\(^4\)

~15% of all lung cancers
- Incidence in North America and Europe: 55,001
- Incidence in Japan: 17,044

Mesothelioma\(^5\),\(^6\)

- Incidence in US: ~3,000
- Incidence in European countries:
  - Germany: 1,673
  - France: 675
- Incidence in East Asia:
  - South Korea: 479

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The PD-1 Pathway Inhibits T Cell Activation

Dephosphorylation

Reduced TCR signaling
Reduced cytokine production
Reduced target cell lysis
Altered lymphocyte motility
Metabolic programming

ITSM
SHP-2
Proximal signaling kinases

PD-1
PD-1 ligand

PD-L1 (B7-H1)
PD-L2 (B7-DC)

MHC

CD3
TCR

CD8

ITIM

CTLA4

B7-1

Nivolumab
Pembrolizumab
Atezolizumab
Avelumab
Durvalumab

Ipilimumab
Tremelimumab

APC

Freeman, ESMO IO 2015
LOOKING FOR A PREDICTIVE BIOMARKER
PD-L1 predictive ability across cancer types

Yang, Oncotarget 2016, Chen, Nature 2017
SMALL CELL LUNG CANCER
ES Small Cell Lung Cancer: Evolution of Therapy

1970s
Alkylation Based Chemotherapy (CMV)

1980s
Anthracycline Based Chemotherapy (CAV)

1990s
Platinum Based Chemotherapy (EP/IP)

2000s
Targeted Therapy and Sequencing

2010s
Immunotherapy and ADCs?

Horn, WCLC 2016
SCLC has been forgotten for a while

AACR 2014: 15%

ASCO 2014: <3%
• SCLC sequencing on 110 whole genomes found evidence for a nearly universal and biallelic loss of TP53 and RB1
• Rare tumors lacking RB1 mutations showed alternative mechanisms of RB1 inactivation
• No actionable targets: Many suppressor genes mutations and MYC amplification

George J, Nature 2015
Peters, ASCO 2016
What do we know about SCLC?

PD-L1 expression in SCLC

CheckMate 032:
Tumor PD-L1 expression in non-randomized cohort (n = 159)

- Immunohistochemistry with the 22C3 antibody
- Positivity: membrane cells or positive stroma
- SCLC cohort: of

82%

18%

≥1%

<1%

Ott, WCLC 2016
What do we know about SCLC?

TILs

Variable levels of tumour-infiltrating lymphocytes (TILs) in 48% cases, most frequently located at the interface between carcinoma cells and stroma.

Schultheis, European Journal of Cancer 2015
A highly mutated SCLC genome with complex signatures of tobacco exposure

Smoking signature:
In H209 cell-line, 23’000 somatic substitutions identified, including 134 in coding exons.

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
SCLC is almost exclusively found in patients with history of smoking and is characterized by high TMB\textsuperscript{1,2}

MARKEDLY DECREASED EXPRESSION OF CLASS I
HISTOCOMPATIBILITY ANTIGENS, PROTEIN, AND mRNA
IN HUMAN SMALL-CELL LUNG CANCER

BY AUSTIN DOYLE, W. JOHN MARTIN, KEIKO FUNA, ADI GAZDAR,
DESMOND CARNEY, SUE ELLEN MARTIN, ILONA LINNOILA,
FRANK CUTTITTA, JAMES MULSHINE, PAUL BUNN, AND JOHN MINNA

From the NCI-Navy Medical Oncology Branch and the Division of Cancer Treatment, National
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20814; and the Department of Pathology, National Institutes of Health,
Bethesda, Maryland 20814

J Exp Med 1985

- SCLC cells have decreased expression of class I (human leukocyte antigen [HLA]-
  A, -B, or -C) and class II (HLA-DR) antigens due to reduced gene transcription
The Cancer Immunogram for SCLC

- Tumor foreignness
  - Mutational load
- General immune status
  - Lymphocyte count
- Immune cell infiltration
  - Intratumoral T cells
- Absence of Checkpoints
  - PD-L1
- Absence of soluble inhibitors
  - IL6->CRP/ESR
- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization
- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN-g sensitivity

Blank et al., Science 2016
Patients with limited-stage SCLC who achieved an objective response to chemoradiotherapy treated with rIFNα-2a (3 million units [MU]/m² subcutaneously three times per week escalated to 9 MU/m² as tolerated) or observation for 2 years.

**Figure 2.** Overall survival curve from the second randomization for patients randomized to receive rIFNα-2a or observation only.

<table>
<thead>
<tr>
<th></th>
<th>At Risk</th>
<th>Deaths</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon maintenance</td>
<td>65</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>No maintenance</td>
<td>68</td>
<td>51</td>
<td>16</td>
</tr>
</tbody>
</table>

*p = .77*
Recombinant interferon-gamma given every other day as maintenance therapy in SCLC patients who achieved a complete or nearly-complete response to induction therapy.

Median OS 8.9 vs 9.9
Addition of ipilimumab to chemotherapy did not prolong OS in patients with newly diagnosed extensive SCLC.
Beyond frontline chemotherapy: Current standard of care...

Response rate 7-10%

- Hazard ratio (95% CI): 0.64 (0.45, 0.90)
- Log-rank $P = .0104$
- 24 v 14 weeks
KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–Positive Advanced Solid Tumors

**Patients**
- Small cell lung cancer

**Previous lines of therapy**
- 1: 3 (12.5%)
- 2: 12 (50.0%)
- ≥3: 9 (37.5%)

**Response Assessment**

- Complete or partial response or stable disease
- Treat for 24 months or until progression or intolerable toxicity
- Confirmed progressive disease or unacceptable toxicity
- Discontinue pembrolizumab

*aResponse assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 (investigator assessed) and safety

Secondary end points: PFS, OS, duration of response

If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later.
Pembrolizumab in >1% PD-L1 SCLC

Objective response rate: 33.3% (95% CI, 15.6–55.3)
Clinical benefit rate (CR + PR + SD ≥6 months): 33.3% (95% CI, 15.6–55.3)
Nivolumab ± Ipilimumab in Recurrent SCLC: Phase 1/2 CheckMate 032 Study Design

- Patients with SCLC (N = 217)\(^a\)
- ≥1 prior line of therapy
- PD-L1 unselected

- Nivolumab 3 mg/kg IV Q2W (n = 98)\(^b\)
- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W for 4 cycles (n = 61)\(^c\)
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 55)

Until disease progression or unacceptable toxicity

- Nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity

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

Database lock: August 09, 2016

- Based on data from the previous database lock, the nivolumab-3 and nivolumab-1 + ipilimumab-3 arms were selected for further development in SCLC; updated data from these arms are presented here

\(^a\)Includes 3 patients from nivolumab-1 + ipilimumab-1 arm; \(^b\)Median follow-up of 15.7 months; \(^c\)Median follow-up of 21.0 months
DOR = duration of response; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival
Tumor Responses (PD-L1 expression)

CheckMate 032
Nivolumab Monotherapy

CheckMate 032
Nivolumab-1 + Ipilimumab-3

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab-3 (n = 98)</th>
<th>Nivolumab-1 + Ipilimumab-3 (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, % (95% CI)</td>
<td>11 (6, 18)</td>
<td>25 (15, 37)</td>
</tr>
<tr>
<td>Platinum-sensitive, % (n/N)</td>
<td>13 (7/56)</td>
<td>25 (7/28)</td>
</tr>
<tr>
<td>Platinum-resistant, % (n/N)</td>
<td>8 (3/37)</td>
<td>24 (6/25)</td>
</tr>
<tr>
<td>Patients with 1 prior regimen, % (n/N)</td>
<td>10 (4/40)</td>
<td>28 (9/32)</td>
</tr>
<tr>
<td>Patients with ≥2 prior regimens, % (n/N)</td>
<td>12 (7/58)</td>
<td>21 (6/29)</td>
</tr>
</tbody>
</table>

Rizvi, WCLC 2017
CheckMate 032: Nivolumab ± Ipilimumab in Recurrent SCLC
1-Year OS Rates\(^a\) by PD-L1 Expression

- Across cohorts, 73% evaluable for PD-L1 expression at baseline; 17% (of PD-L1 evaluable samples) with ≥1% tumor PD-L1 expression

\(^a\)Kaplan–Meier estimates, with error bars indicating 95% CIs
CheckMate 032: Nivolumab ± ipilimumab in Recurrent SCLC

<table>
<thead>
<tr>
<th></th>
<th>Events/number at risk</th>
<th>Median OS, Months (95% CI)</th>
<th>Median follow-up time, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab-3</td>
<td>71/98</td>
<td>4.1 (3.0, 9.1)</td>
<td>15.7</td>
</tr>
<tr>
<td>Nivolumab-1 + ipilimumab-3</td>
<td>40/61</td>
<td>7.9 (3.6, 14.2)</td>
<td>21.0</td>
</tr>
</tbody>
</table>

1-yr OS = 42%

1-yr OS = 30%

2-yr OS = 30%

2-yr OS = 17%

Hellmann, WCLC 2016
Tumor Mutation Burden Distribution

CheckMate 032 Exploratory TMB Analysis Nivo ± Ipi in Previously Treated SCLC

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Total missense mutations, no.</th>
<th>CheckMate 032</th>
<th>CheckMate 026 (NSCLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low TMB</td>
<td>0 to &lt;143</td>
<td>Nivolumab</td>
<td>Nivolumab + ipilimumab</td>
</tr>
<tr>
<td>Medium TMB</td>
<td>143 to 247</td>
<td>100 to 242</td>
<td>100 to 242</td>
</tr>
<tr>
<td>High TMB</td>
<td>≥248</td>
<td>≥243</td>
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</tbody>
</table>
ORR by Tumor Mutation Burden Subgroup

CheckMate 032 Exploratory TMB Analysis Nivo ± Ipi in Previously Treated SCLC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Nivolumab</th>
<th>Nivolumab + ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMB-evaluable</td>
<td>11.3</td>
<td>28.2</td>
</tr>
<tr>
<td>Low TMB</td>
<td>4.8</td>
<td>22.2</td>
</tr>
<tr>
<td>Medium TMB</td>
<td>6.8</td>
<td>16.0</td>
</tr>
<tr>
<td>High TMB</td>
<td>21.3</td>
<td>46.2</td>
</tr>
</tbody>
</table>
**OS by Tumor Mutation Burden Subgroup**

CheckMate 032 Exploratory TMB Analysis Nivo ± Ipi in Previously Treated SCLC

### Nivolumab

<table>
<thead>
<tr>
<th>TMB Subgroup</th>
<th>Low TMB</th>
<th>Med TMB</th>
<th>High TMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), mo</td>
<td>3.1 (2.4, 6.8)</td>
<td>3.9 (2.4, 9.9)</td>
<td>5.4 (2.8, 8.0)</td>
</tr>
</tbody>
</table>

1-y OS = 35.2%

1-y OS = 26.0%

1-y OS = 22.1%

### Nivolumab + ipilimumab

<table>
<thead>
<tr>
<th>TMB Subgroup</th>
<th>Low TMB</th>
<th>Med TMB</th>
<th>High TMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), mo</td>
<td>3.4 (2.8, 7.3)</td>
<td>3.6 (1.8, 7.7)</td>
<td>22.0 (8.2, NR)</td>
</tr>
</tbody>
</table>

1-y OS = 62.4%

1-y OS = 23.4%

1-y OS = 19.6%

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Median (95% CI) OS, overall TMB-evaluable population: 3.9 (2.8, 6.1) months for nivolumab and 7.0 (3.2, 8.8) months for nivolumab + ipilimumab

NR = not reached
CheckMate 032: Nivolumab ± Ipilimumamab in Recurrent SCLC
Treatment-Related AEs in ≥10% of Patients

- No additional treatment-related deaths were reported; at prior disclosure, 2 treatment-related deaths occurred with nivolumab-1 + ipilimumamab-3: one due to myasthenia gravis and one due to worsening of renal failure
- Grade 3–4 treatment-related limbic encephalitis occurred in 1 patient in the nivolumab-3 arm
- Treatment-related pneumonitis occurred in 4 patients in the nivolumab-3 arm (2 grade 3–4 events) and 2 patients in the nivolumab-1 + ipilimumamab-3 arm (1 grade 3–4 event)

DC = discontinuation
Immune-Related AEs are a concern in SCLC

- **Skin**
  - Dermatitis exfoliative
  - Erythema multiforme
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Vitiligo
  - Alopecia

- **Eye**
  - Uveitis
  - Iritis

- **Endocrine**
  - Hypothyroidism
  - Hyperthyroidism
  - Adrenal insufficiency
  - Hypophysitis

- **Pulmonary**
  - Pneumonitis
  - Interstitial lung disease
  - Acute interstitial pneumonitis

- **Gastrointestinal**
  - Colitis
  - Enterocolitis
  - Necrotizing colitis
  - GI perforation

- **Renal**
  - Nephritis, autoimmune
  - Renal failure

- **Neurologic**
  - Autoimmune neuropathy
  - Demyelinating polyneuropathy
  - Guillain-Barré
  - Myasthenia gravis–like syndrome

- **Hepatic**
  - Hepatitis, autoimmune

- **Eye**
  - Uveitis
  - Iritis

Adapted of clinicaloptions.com
• June 2016 she received IV nivolumab 1 mg/kg + IV ipilimumab 3 mg/kg

• Four days after she developed a subacute memory and psychomotor impairment, space & temporal disorientation.

• CSF showed positive anti-GABA-B, anti-Hu and anti-Purkinje cells antibody
10 months off-treatment
Select Ongoing Trials with I-O in SCLC$^{1,2}$

**Monotherapy**

- **Nivo**
  - Checkmate 331 (2L, LD/ED)

- **Pembro**
  - KEYNOTE-028 (2L, ED)$^2$
  - KEYNOTE-158 (2L+, ED)

- **Atezo**
  - NCT01375842 (1L+, ED)$^3$

- **Rova-T ± dexamethasone**
  - SCRX001-007 (ED)
  - TRINITY (3L+, ED)
  - TAHOE (2L, ED)
  - MERU (2L, ED)

**Combination therapy**

- **Nivo + ipi**
  - Checkmate 032 (2L+, LD/ED)$^4$
  - STIMULI (1L, LD)
  - Checkmate 451 (1L, ED)

- **Durva + treme**
  - NCT02937818 (2L, ED)

- **Pembro + MK-1308**
  - NCT03179436 (2L, ED)

- **CT ± durva ± treme**
  - NCT02658214 (1L, LD/ED)
  - CASPIAN (1L, ED)

- **Durva + olaparib**
  - MEDIOLA (2L, ED)

- **Nivo ± ipi + Rova-T**
  - M16-300 (2L+, ED)

- **Pembro + Pt + etoposide**
  - KEYNOTE-604 (1L, ED)

- **Atezo + Pt + etoposide**
  - IMpower 133 (1L, ED)

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MESOTHELIOMA
Challenges and Unmet Needs in Treating Mesothelioma

- 80%–85% of cases are pleural (MPM)\(^1\)
- Long-term OS is poor for patients with MPM, with <5% of patients surviving for 5 years\(^2\)
- 1L treatment for unresectable MPM is often Pt-doublet chemotherapy, with no 2L SOC\(^3\)
- The immune system is capable of mounting a tumor-specific response to mesothelioma\(^4\)
  - Lymphocytic infiltration of mesotheliomas has been associated with improved survival

Mesothelioma Mutation load

- Whole-exome sequencing on DNA from 22 MPMs and matched blood samples. Identification of 517 somatic mutations across 490 mutated genes
- Mean of 23 somatic mutations per tumor (range 2-51; 0.79/Mb), a considerably lower than other types of malignant tumors

Guo, Cancer Res, 2015
## TILs

<table>
<thead>
<tr>
<th>Marker</th>
<th>N (%)</th>
<th>Median OS</th>
<th>95%CI</th>
<th>P-value*</th>
</tr>
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<tbody>
<tr>
<td>CD3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>54 (25)</td>
<td>14.3</td>
<td>(9.4, 24.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>High</td>
<td>162 (75)</td>
<td>16.8</td>
<td>(15.0, 19.8)</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>113 (52)</td>
<td>15.2</td>
<td>(10.6, 19.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>High</td>
<td>105 (48)</td>
<td>17.0</td>
<td>(14.5, 24.8)</td>
<td></td>
</tr>
<tr>
<td>CD8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>86 (40)</td>
<td>14.7</td>
<td>(12.0, 19.8)</td>
<td>0.061</td>
</tr>
<tr>
<td>High</td>
<td>131 (60)</td>
<td>17.0</td>
<td>(14.5, 21.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marker</th>
<th>N (%)</th>
<th>Median OS</th>
<th>95%CI</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td>143 (67)</td>
<td>16.2</td>
<td>(13.8, 19.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>CD4</td>
<td>72 (33)</td>
<td>17.4</td>
<td>(15.0, 23.3)</td>
<td></td>
</tr>
<tr>
<td>CD8</td>
<td>28 (13)</td>
<td>15.0</td>
<td>(7.4, 21.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Stroma</td>
<td>188 (87)</td>
<td>17.0</td>
<td>(14.9, 20.1)</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival

- **Low (n=86)**: 14.7
- **High (n=131)**: 17.0

\[ P = .061 \]

Ujiie, OncoImmunology 2015
• PD-L1 expression by immunohistochemistry ranges between 20% and 70%.
• PD-L1 expression was significantly associated with a worse survival and overexpression was more common in non-epitheloid histology.
DETERMINE: study design

Phase 2b global, randomised, double-blind, placebo-controlled study

Patients with unresectable malignant mesothelioma who have progressed after 1 or 2 systemic treatments N=564

Randomise 2:1

Tremelimumab
10 mg/kg IV q4w for 6 doses then q12w (N=376)

Placebo
IV q4w for 6 doses then q12w (N=188)

- Primary endpoint:
  - OS
- Secondary endpoints:
  - 18-month OS
  - Durable DCR
  - Duration of response
  - PFS
  - ORR
  - QoL
  - Safety and tolerability
  - Immunogenicity
  - PK
DETERMINE: study design

Kindler and al, ASCO 2016; Alley Lancet Oncol 2017
## Single-Arm monotherapy trials Data With I-O in Mesothelioma

<table>
<thead>
<tr>
<th></th>
<th>NivoMes</th>
<th>MERIT</th>
<th>KEYNOTE-028</th>
<th>JAVELIN Solid Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>2</td>
<td>2</td>
<td>1B</td>
<td>1</td>
</tr>
<tr>
<td><strong>Estimated Enrollment</strong></td>
<td>34</td>
<td>34</td>
<td>25</td>
<td>53</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Nivolumab 3 mg/kg q2w</td>
<td>Nivolumab 240 mg flat dose q2w</td>
<td>Pembrolizumab 10 mg/kg q2w</td>
<td>Avelumab 10 mg/kg q2w</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td>MPM, ≥1 prior lines of chemotherapy</td>
<td>Recurrent MPM, ≥1 prior lines of Pt-based chemotherapy</td>
<td>MPM, failure/inability to receive standard therapy, ≥1% PD-L1+ (46% of screened samples)</td>
<td>Unresectable pleural/peritoneal mesothelioma; prior platinum/pemetrexed</td>
</tr>
<tr>
<td><strong>Primary Endpoint(s)</strong></td>
<td>DCR at 12 weeks</td>
<td>ORR</td>
<td>ORR, safety</td>
<td>DLT, BOR</td>
</tr>
</tbody>
</table>
| **Key Findings**         | • Nivolumab met primary endpoint of ≥40% DCR  
  • Responses were seen regardless of PD-L1 levels | • Nivolumab met endpoint 30% ORR  
  • Epithelioid and sarcomatoid | • Pembrolizumab was well tolerated and may confer anti-tumor activity in PD-L1+ MPM (20% ORR) | • Avelumab had antitumor activity in patients with PD-L1± tumors (9.4% ORR)  
  • Acceptable safety profile |
IFCT-1501 MAPS2: Nivolumab ± Ipilimumab in 2–3L MPM

Phase 2, randomized, non-comparative study evaluating efficacy and safety of 2–3L treatment with nivolumab ± ipilimumab for unresectable MPM

N=125

- Unresectable MPM
- PD after 1 or 2 previous lines of chemotherapy including a platinum doublet
- ECOG PS 0–1

R 1:1

CT scan every 12 weeks

For ≤2 years or until PD or unacceptable toxicity

Nivolumab 3 mg/kg IV q2w

Nivolumab 3 mg/kg IV q2w + Ipilimumab 1 mg/kg IV q6w

Primary Outcome Measures: 12-week DCR
Secondary Outcome Measures: Safety, PFS, OS, QoL, predictive value of PD-L1, prognostic value of various biomarkers

Zalcman et al., 2017, ESMO.
IFCT-1501 MAPS2: Overall Survival

<table>
<thead>
<tr>
<th>Tumor assessment % (95% CI)</th>
<th>Nivolumab (n=54)</th>
<th>Nivolumab + ipilimumab (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response</td>
<td>18.5 (8.2, 28.9)</td>
<td>27.8 (15.8, 39.7)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>25.9 (14.2, 37.6)</td>
<td>22.2 (11.1, 33.3)</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>44.4 (31.2, 57.7)</td>
<td>50.0 (36.7, 63.3)</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>51.9 (38.5, 65.2)</td>
<td>42.6 (29.4, 55.8)</td>
</tr>
<tr>
<td>Not Evaluable/Not Done/Not Done/Missing</td>
<td>3.7 (0.0, 8.7)</td>
<td>7.4 (0.4, 14.4)</td>
</tr>
</tbody>
</table>

Tumor Response at 12 Weeks (First 108 Eligible Patients)

Zalcman et al., 2017, ESMO.
### INITIATE

<table>
<thead>
<tr>
<th>Dose/schedule of ipilimumab nivolumab</th>
<th>1 mg/kg IV q6 wks 240 mg flat dose q2wks* (until progression or toxicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of CT scans</td>
<td>Q 6 weeks</td>
</tr>
<tr>
<td>Failure to start (various reasons)</td>
<td>3 of 38</td>
</tr>
<tr>
<td>Paired biopsies</td>
<td>29</td>
</tr>
</tbody>
</table>

- Single arm Simon’s 2-stage design
- Disease Control Rate (SD+PR+CR) of 50% at 12 week
- Disease progression on or after 1 (71%) or 2 lines incl pemetrexed + a platinum
- Single arm Simon’s 2-stage design
- Disease Control Rate (SD+PR+CR) of 50% at 12 week
- Disease progression on or after 1 (71%) or 2 lines incl pemetrexed + a platinum

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>7 (27%)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>DCR</td>
<td>20 (74%)</td>
</tr>
<tr>
<td>PFS</td>
<td>144 days</td>
</tr>
<tr>
<td>Ongoing</td>
<td>15/27</td>
</tr>
</tbody>
</table>

Baas, WCLC 2017
WCLC MA 19.02: Tremelimumab plus Durvalumab in First- or Second-Line Mesothelioma Patients: Final Analysis of the NIBIT-MESO-1 Study – Calabro L, et al

• Tremelimumab 1 mg/kg q4w for 4 doses + durvalumab 20 mg/kg q4w for 13 doses

<table>
<thead>
<tr>
<th>Patients (n=40)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ir-ORR, % (95%CI)</td>
<td>27.5 (14.6, 43.9)</td>
</tr>
<tr>
<td>ir-CR, %</td>
<td>0</td>
</tr>
<tr>
<td>ir-PR, %</td>
<td>27.5</td>
</tr>
<tr>
<td>ir-SD, %</td>
<td>37.5</td>
</tr>
<tr>
<td>ir-PD, %</td>
<td>35.0</td>
</tr>
<tr>
<td>ir-DCR, % (95%CI)</td>
<td>65.0 (48.3, 79.4)</td>
</tr>
<tr>
<td>Median duration ir-OR</td>
<td>NR</td>
</tr>
<tr>
<td>Median duration DC, months (95%CI)</td>
<td>14.1 (12.1, 16.1)</td>
</tr>
</tbody>
</table>

• Conclusions
  – NIBIT-MESO-1 met its primary endpoint, irAEs of any grade occurred in 75% of patients and TRAEs were generally manageable
  – The combination of tremelimumab and durvalumab in malignant mesothelioma warrants further exploration

Trials of I-O in Mesothelioma

**Monotherapy**

- **Treme**
  - DETERMINE (2-3L)
- **Pembro**
  - KEYNOTE-028 (2L)
  - KEYNOTE-158 (≥2L)
  - NCT02399371 (2L)
  - PROMISE-MESO (2L)
- **Avel**
  - JAVELIN Solid Tumor (≥2L)

- **Nivo**
  - NivoMes (≥2L)
  - CONFIRM (≥3L)
  - MERIT(2L+)

- **Atezo**
  - NCT02458638 (≥2L)

**Combination Therapies**

- **Ipi + nivo**
  - MAPS2 (2L-3L)
  - INITIATE (≥2L)
  - Checkmate 743 (1L)
- **Durva + treme**
  - NIBIT-MESO-1 (2L)
- **Durva + cis/pem**
  - PrE0505 (1L)
- **Atezo + cis/pem**
  - SWOG 1619 (neoadj)
- **Pembro + FAKi**
  - NCT02758587 (2L)
- **Pembro + anet**
  - NCT03126630 (2L)
- **Pembro + cis/pem**
  - NCT02784171 (1L)

- **Completed or has efficacy results**
- **Negative findings**
- **Ongoing phase 1 trial**
- **Ongoing phase 2 or 3 trial**
FDA has required a protracted dose escalation in currently accruing phase 1 clinical trials testing the safety and efficacy of mesothelin-specific CARs.

Recently, interim results from one mesothelin-specific CAR phase 1 study were presented in which as many as $3 \times 10^7$ cells were infused.

Although no on-target toxicities were observed, neither was radiographic evidence of anti-tumor activity...
Climical trials with CART directed to mesothelin and fibroblast activation protein

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Phase</th>
<th>Line</th>
<th>Primary Endpoint</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of Relapsed and/or Chemotherapy Refractory Advanced Malignancies by CART-meso</td>
<td>Phase I</td>
<td>2nd and later line</td>
<td>Safety</td>
<td>20</td>
</tr>
<tr>
<td>Malignant Pleural Disease Treated With Autologous T Cells Genetically Engineered to Target the Cancer-Cell Surface Antigen Mesothelin</td>
<td>Phase I</td>
<td>2nd line</td>
<td>Safety</td>
<td>24</td>
</tr>
<tr>
<td>CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer</td>
<td>Phase I/II</td>
<td>1st and later line</td>
<td>Safety and Dose Finding</td>
<td>136</td>
</tr>
<tr>
<td>Re-directed T Cells for the Treatment (FAP)-Positive Malignant Pleural Mesothelioma</td>
<td>Phase I</td>
<td>1st and later line</td>
<td>Safety</td>
<td>6</td>
</tr>
</tbody>
</table>

Stahel, ESMO IO 2016
THYMIC EPITHELIAL TUMOURS
TT: multimodal therapy

- Surgery for resectable disease
- Postoperative RT for R1-2 and stages III-IV
- Chemotherapy: preoperative or palliative
- Backbone: platin +/- anthracycline
- Frequently used: PAC, EP
- Further lines: gemcitabine, taxanes, sunitinib, corticosteroids
PD-L1

<table>
<thead>
<tr>
<th>Reference</th>
<th>PD-L1 positive TC</th>
<th>PD-L1 positive Thymoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCH, Tokyo [Katsuya, Lung Cancer 2015]</td>
<td>70% (n=37)</td>
<td>23% (n=101)</td>
</tr>
<tr>
<td>Stanford University [Padda, JTO 2015]</td>
<td>75% (n=4)</td>
<td>82% (n=65)</td>
</tr>
</tbody>
</table>

- No relation between PD-L1 and chemotherapy activity
- Not a prognostic factor in thymic epithelial tumours but higher PD-L1 expression related to adverse pathological features, including WHO classification type and Masaoka–Koga stage
TILs

Tissue specimens from 32 patients who underwent surgical resection for thymic carcinoma between 1994 and 2008

<table>
<thead>
<tr>
<th>Marker expression</th>
<th>Patients, n (%)</th>
<th>5-y survival (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>CD4</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>26(18.8)</td>
<td>70.6</td>
<td>0.402</td>
</tr>
<tr>
<td>High</td>
<td>6(81.3)</td>
<td>83.3</td>
<td></td>
</tr>
<tr>
<td>Stroma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>17(53.1)</td>
<td>55.8</td>
<td>0.037</td>
</tr>
<tr>
<td>High</td>
<td>15(46.9)</td>
<td>93.3</td>
<td></td>
</tr>
<tr>
<td><em>CD8</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>21(65.6)</td>
<td>58.7</td>
<td>0.186</td>
</tr>
<tr>
<td>High</td>
<td>11(34.4)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Stroma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22(68.8)</td>
<td>66.7</td>
<td>0.909</td>
</tr>
<tr>
<td>High</td>
<td>10(31.3)</td>
<td>90.0</td>
<td></td>
</tr>
</tbody>
</table>

Concurrent low levels of CD4+, CD8+, and CD20+ (p = 0.025) in tumor stroma were significantly associated with poor prognosis.

Shim, Lung Cancer 2011
Paraneoplastic syndromes

• Myasthenia gravis (up to 65%)
• Hypogammaglobulinemia (up to 10%)
• Pure red cell aplasia (up to 5%)
• Polymyositis, arthritis
• Systemic lupus erythematosus SLE
• Ulcerative colitis
# Pembrolizumab Trials in TET

<table>
<thead>
<tr>
<th></th>
<th>Cho, South Korea</th>
<th>Giaccone, USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (all pretreated)</td>
<td>33 (26 TC and 7 T)</td>
<td>41 TC</td>
</tr>
<tr>
<td>Trial treatment</td>
<td>Pembrolizumab 200 mg q3w</td>
<td></td>
</tr>
<tr>
<td>Median number of cycles</td>
<td>8 (1-13)</td>
<td>6 (1-31)</td>
</tr>
<tr>
<td>ORR</td>
<td>24%</td>
<td>22% (6 of 9 responders had PDL1 = 50% or higher)</td>
</tr>
<tr>
<td>irAE grade 3-4</td>
<td>4 hepatic, 3 cardiac, 3 neurologic, 1 thyroid</td>
<td>5 hepatic, 2 cardiac, 1 diabetes, 1 pemphigoid</td>
</tr>
<tr>
<td>Conclusions</td>
<td>High incidence in irAE, management is essential</td>
<td>irAE are more frequent than in other tumors</td>
</tr>
</tbody>
</table>
Pembro

**Adverse Events**

- Median 6 cycles (1-35)
- Mostly mild AEs
- 6 patients had severe irAEs
- Female gender more commonly associated with autoimmune disorders (4/6, P= 0.026)
- 3 patients interrupted treatment because of irAEs (all responders) and 3 because of progression around the time of the irAE
- 5 patients developed hypothyroidism and 1 hyperthyroidism

**Side Effects of Special Interest (irAEs)**

**Polymyositis/myocarditis**
Developed after 2 cycles with severe asthenia, dyspnea and muscle aches. Required hospitalization, complete A-V block, pace-maker placement and steroids. Patient recovered completely. No response.

**Hepatitis/pancreatitis/Diabetes mellitus type 1**
Developed hyperglycemia grade 4, after 4 cycles. Associated with severe increase of lipase (grade 3) and amylase (grade 1) and grade 3 transaminitis. Required insulin. Did not reverse. Patient on insulin, doing well. No response.

**Bullous pemphigoid**

**Polymyositis/hepatitis/myocarditis/MG**
Developed after 2 cycles with severe asthenia, and severe muscle and joint pains. Transaminase elevation grade 4. Required hospitalization and iv steroids. Complete A-V block, pace-maker placement and steroids. Recovered; recurrence of liver enzyme elevation and vague signs of MG (achR positive); steroids again, mestinon. Reactivation of Hepatitis B. Almost complete response after only 2 cycles, ongoing at 10+ months.

**Polymyositis/hepatitis**

**Grade 3 transaminitis**
Developed after 20 cycles, recovered on steroids. Taken off-treatment. Then relapsed and placed on steroids again. Almost complete response. Recurred after 24 months. Rechallenged.
ETOP/EORTC Nivothym phase II

Documented PD during or after completion of first line platinum-based chemotherapy

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

Tumor assessment (imaging)
First tumor assessment during screening
Key messages

• SCLC (mutations, TILs 50%, PD-L1 low)
  – Interesting data with ipi/nivo and in high TMB
• Mesothelioma (low mutations, TILS and PD-L1 high)
  – Interesting results with PD(L1) blockade
  ➢ For both CTLA4 alone not satisfactory
• Thymoma (mutations? TILs? PD-L1 high)
• Thymic carcinoma (mutations? TILS 30%, PD-L1 high)

Many trials ongoing in these rare entities
Thank you for your attention