Post IASLC: updates da Sidney
November 28, 2013 Lucca

Targeting CTLA4, PD1/PDL1: effetti e tossicità

Luana Calabrò
Medical Oncology and Immunotherapy, Department of Oncology
University Hospital of Siena, Istituto Toscano Tumori
SIENA, ITALY
Evolving Therapeutic Options for Cancer Treatment

- Surgery
- Chemotherapy
- Radiotherapy
- Immunotherapy
Response Patterns

**Response in baseline lesions**

- **PD:** Progressive Disease
- **PR:** Partial Response
- **CR:** Complete Response

'**Stable disease**' with slow, steady decline in total tumor volume

- **SPD** = Sum of the Product of the perpendicular Diameters (a measure of tumor volume)

**Response after initial increase in total tumor volume**

- **6 months**

**Response in index and new lesions**

- **At or after the appearance of new lesions**

Harmankaya et al. Poster presentation ESMO 2008 #784P
T-cell costimulatory receptors
Anti-CTLA4 antibodies

- **Tremelimumab (CP675,206)**
  - Pfizer/MedImmune
  - IgG2 isotype antibody
  - Half-life time: 22 days

- **Ipilimumab (MDX-010)**
  - BMS/Medarex
  - IgG\textsubscript{1} isotype antibody
  - Half-life time: 12.5 days
Immunomodulating mAb in solid tumors

Calabrò L. Semin. Oncol 2010
CA184041 – irPFS Results

Phased Schedule (NSCLC)
- Study met primary end-point
  - Phased schedule significantly improved irPFS
  - No significant improvement for concurrent schedule

Phased Schedule (SCLC)

Lynch T, JCO 2012
Reck M, Ann Oncol 2013
CA184-104 Study Design (Phase III)

NSCLC Squamous Stage IV

Arm A
Induction C C C C C C
+ + + + I I I I
CR PR SD

Maintenance I I I I

Toxicity Progression Follow-up

Arm B
Induction C C C C C C
+ + + + P P P P
CR PR SD

Maintenance P P P P

Overall Survival

PD or AE leading to DC

Randomize

Screening

920 pts

I = ipilimumab
P = placebo
C = chemotherapy

Primary end-point: OS
Primary end-point: OS
Study population:
• ED SCLC
• Brain mets allowed if stable
• Measurable disease not required

Approximately 210 sites
33 countries
1100 subjects
Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial

Luana Calabrò, Aldo Morra, Ester Fonsatti, Ornella Cotaia, Giovanni Amato, Diano Giannarelli, Anna Maria Di Giacomo, Riccardo Danielli, Maresa Alhornante, Luciano Mutti, Michele Maio
## Best Tumor Response and Disease Control
(MESOT-TREM-2008)

<table>
<thead>
<tr>
<th>Patients (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>Progressive disease</td>
</tr>
<tr>
<td>Disease control</td>
</tr>
</tbody>
</table>

Data are n (%) or n (%), 95% CI. Tumours were assessed at 70–90 days (RECIST 1.0 for peritoneal or modified RECIST for pleural malignant mesothelioma).^{19} RECIST=Response Evaluation Criteria in Solid Tumors.
Patient # 11

Patient alive (+38 months), received 8 cycles

Baseline  | **PD** after 2\textsuperscript{nd} dose  | **PR** after 4\textsuperscript{th} dose  | **PR** after 7\textsuperscript{th} dose
Kaplan-Meier curve of overall survival (MESOT-TREM-2008)

Median OS was 10.7 months
(95% C.I.: 0-24.4)

24 months OS: 36.7%

As of October 2013: 5 pts still alive
5 patients alive at 30 months
2 patients alive at 36 months

Calabrò et al, Lancet Oncology 2013
Kaplan Meyer curves of overall survival according to the circulating CD4+ICOS+ at day 30 Cycle 1 in MM pts

Calabrò et al, Lancet Oncology 2013
Trial design MESOT-TRENTREM-2012

Enrollment started on 31 July 2012 and completed on 16 July 2013

University Hospital of Siena, Italy
Phase II Multicenter, International, Randomized Trial of Tremelimumab in Patients With Unresectable Mesothelioma (Trial D4880C00003 Sponsored by MedImmune)

- **Relapsed/Refractory Malignant Mesothelioma (2nd/3rd line)**
  - Total recruitment = 180 patients (OS events)

  - Randomized **TREME: PLACEBO 2:1** (120/60)

  - **Stratification Factors**
    - European Organization for Research and Treatment of Cancer (EORTC) status (low-risk vs high-risk)
    - Line of therapy (second vs third)
    - Anatomical site (pleural vs peritoneal)

  - Dosing schedules:
    - **Treme 10mg/kg**
      - Q4Wk (Non Dosing visits: V9, 11, 13)
    - **Treme 10mg/kg**
      - Q12Wk
    - **Placebo**
      - Q4Wk (Non Dosing visits: V9, 11, 13)
      - Q12Wk

  - Total recruitment = 180 patients (OS events)
Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFN\(\gamma\) release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

Tumor cell

IFN\(\gamma\)R

T-cell receptor

MHC

PD-L1

PD-L2

PD-1

Nivolumab

PD-1 Receptor Blocking Ab

Dendritic cell

MHC

CD28

B7

PD-1

PD-L1

PD-L2

Shp-2

PI3K

NF\(\kappa\)B

Other

T-cell receptor

Presented By Mario Sznol, MD at 2013 ASCO Annual Meeting
# PD1/PD-L1 Inhibitors in Clinical Development

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab (MDX 1106, BMS-936558, BMS-ONO)</td>
<td>IgG4 fully human antibody</td>
</tr>
<tr>
<td></td>
<td>Lambrolizumab (MK-3475, Merck)</td>
<td>IgG4 engineered humanized antibody</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab (CT-11, CureTech-Teva)</td>
<td>IgG1 humanized antibody</td>
</tr>
<tr>
<td></td>
<td>AMP-224 (Apilimmune-GSK)</td>
<td>Fc-PD-L2 fusion protein</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-935559 (MDX 1105, BMS-ONO)</td>
<td>IgG4 fully human antibody</td>
</tr>
<tr>
<td></td>
<td>MPDL3280A (Genetech/Roche)</td>
<td>IgG1 fully human antibody</td>
</tr>
<tr>
<td></td>
<td>MEDI4776 (MedImmune)</td>
<td>IgG1-k fully human antibody</td>
</tr>
</tbody>
</table>
CA209-003: Study Design for NSCLC Cohort

Eligible NSCLC patients randomized between 3 nivolumab dose levels
(n=129)

- Nivolumab 1 mg/kg IV Q2W (n=33)
- Nivolumab 3 mg kg IV Q2W (n=37)
- Nivolumab 10 mg/kg IV Q2W (n=59)

Q2W = every 2 weeks

*Randomization did not include the first 19 patients (treated mostly at 10 mg/kg) enrolled in initial part of the study

(1-5 previous line CT, median >3)
Duration of Response and Overall Survival

NSCLC Responders\(^a,b\) by Histology

- **Squamous**
- **Non-squamous**

- Durable responses were observed; responses are ongoing in 45% of patients (10/22)
- Higher ORRs observed at 3 and 10 mg/kg nivolumab doses relative to 1 mg/kg dose
- Rapid responses; 50% of patients (11/22) demonstrating response at first assessment (8 weeks)

Duration of response up to discontinuation of therapy
Ongoing response
Time to response
Response duration followin discontinuation of therapy

**All Treated Subjects with NSCLC**

<table>
<thead>
<tr>
<th>Died/Treated</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>94/129</td>
<td>9.90 (7.80,12.40)</td>
</tr>
</tbody>
</table>

Median OS: 9.9 Months (7.8, 12.4)
Median OS=14.9% (7.3-NE) at 3mg

1 year OS Rate 42% (48 pts at risk)
2 year OS Rate 24% (20 pts at risk)

*Responses were assessed by modified RECIST v1.0
All efficacy analyses based on data collected as of September 2013

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

WCLC 2013 Brahamer J, M018-03
Drug-Related Select Adverse Events (≥1%) Occurring in NSCLC Patients (N=129) Treated with Nivolumab

- No new safety signals emerging, with all patients now having ≥1 year of follow-up
- Select AE definition: AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention
- Drug-related pneumonitis (any grade) occurred in 8 NSCLC patients (6%); 3 patients (2%) with NSCLC had grade 3-4 pneumonitis of which 2 cases were fatal

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment-related Select AE, % (n)</th>
<th>Any Grade % (n)</th>
<th>Grade 3-4 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related select AE</td>
<td>41 (53)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>16 (20)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12 (15)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7 (9)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>6 (8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (6)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>4 (5)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>3 (4)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Safety data based on a March 2013 analysis

WCLC 2013  Brahamer J, M018-03  Mercury ID: ONCHQ13NP10127; Approved 5Nov2013; Expires 5 Nov2015
Overview of ORR from NSCLC exploratory analysis (5% cutoff)

Total NSCLC Patient Cohort Population
(N = 129)
ORR 17%

Unknown PD-L1 status
(n = 66)
ORR 20%

Known PD-L1 status
(n = 63)
ORR 14%

PD-L1+
(n = 31)
ORR 16%

PD-L1–
(n = 32)
ORR 13%
Ongoing phase 3 trials of nivolumab in NSCLC: PD-L1 expression analysis

**CA209-017**
NCT01642004  
(Phase 3; N = 264)

Patients with stage IIIb/IV squamous cell NSCLC

- **Primary Objectives**
  - ORR and OS
- **Secondary Objectives**
  - PFS
  - ORR and OS by PD-L1 status
  - Duration of OR
  - Time to OR
  - Proportion of patients exhibiting disease-related symptom progression (Lung Cancer Symptom Scale)

**CA209-057**
NCT01673867  
(Phase 3; N = 574)

Patients with stage IIIb/IV non-squamous cell NSCLC

- **Primary Objective**
  - OS
- **Secondary Objectives**
  - ORR
  - PFS
  - ORR and OS by PD-L1 status
  - Duration of OR
  - Time to OR
  - Proportion of patients exhibiting disease-related symptom progression (Lung Cancer Symptom Scale)

**PFS = progression-free survival**
MEDI-4736 anti-PDL1-MedImmune

Khleif S.et al, ESMO 2013
MEDI-4736 anti-PDL1-MedImmune

Change in Tumor Size Over Time

*Tumor growth exceeding 100% is truncated.

Note: Posttreatment CT scans not available for 2 patients (1 NSCLC patient each at 0.1 and 0.3 mg/kg).

CT, computed tomography; NSCLC, non-small cell lung cancer.
Data as of 18 August 2013.

Khleif S et al, ESMO 2013
### Treatment-Related AEs

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>By Dose Level, n</th>
<th>Total, n (%)</th>
<th></th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 mg/kg (n=4)</td>
<td>0.3 mg/kg (n=4)</td>
<td>1.0 mg/kg (n=3)</td>
<td>Any Grade (N=11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (9.1)</td>
</tr>
</tbody>
</table>

No treatment-related grade 3/4 AEs or deaths

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Khleif S et al., ESMO 2013
In the last few years we have witnessed a real revolution. The anti-CTLA4 mAb can be considered a milestone of a new era of cancer treatment, demonstrating for the first time that the immunotherapy alone or in combination with other therapeutic modalities, is a key strategy to improve the outcome of cancer patients, and it will play an increasingly important role in the new cancer management also in other cancer histotypes.

**Next steps:**
- Which patients
- When start treatment
- Combination/sequencing
- Identification of biomarkers
Back-up slides
# Immune-Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Arm A Concurrent IPI + Chemo (N=71)</th>
<th>Arm B Phased IPI + Chemo (N=67)</th>
<th>Arm C Placebo Chemo Only (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Gr 3</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Any irAE</td>
<td>46 (64.8)</td>
<td>13 (18.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>40 (56.3)</td>
<td>3 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (16.9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>20 (28.2)</td>
<td>2 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>21 (29.6)</td>
<td>5 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (29.6)</td>
<td>5 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>4 (5.6)</td>
<td>2 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>ALT</td>
<td>4 (5.6)</td>
<td>2 (2.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Lynch T, JCO 2012
Kinetics of appearance of immune-related adverse event.

Activity by Baseline Histology (CA184041, NSCLC)

<table>
<thead>
<tr>
<th>Response</th>
<th>Patient group</th>
<th>Phased-Ipi vs Control</th>
<th>Concurrent-Ipi vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>irPFS</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mWHO-PFS</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Best change in tumor burden according to EGFR and KRAS mutation status

Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for progressive disease per RECIST v1.0
PD-L1 expression in NSCLC samples stained with 28-8 (anti-PD-L1) antibody

<table>
<thead>
<tr>
<th>% Staining</th>
<th>1%</th>
<th>5%</th>
<th>20%</th>
<th>65%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Negative Control Antibody</strong></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
</tbody>
</table>
### ORRs by PD-L1 expression in patients with NSCLC

<table>
<thead>
<tr>
<th>PD-L1 Cutoff</th>
<th>PD-L1 Status</th>
<th>Number of Patients, n/N (%)</th>
<th>ORR&lt;sup&gt;a&lt;/sup&gt;, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>Positive</td>
<td>35/129 (27)</td>
<td>5/35 (14)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>28/129 (22)</td>
<td>4/28 (14)</td>
</tr>
<tr>
<td></td>
<td>Unknown&lt;sup&gt;b&lt;/sup&gt;</td>
<td>66/129 (51)</td>
<td>13/66 (20)</td>
</tr>
<tr>
<td>5%</td>
<td>Positive</td>
<td>31/129 (24)</td>
<td>5/31 (16)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>32/129 (25)</td>
<td>4/32 (13)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>66/129 (51)</td>
<td>13/66 (20)</td>
</tr>
</tbody>
</table>

<sup>a</sup>ORR of patients evaluable for PD-L1; ORR includes complete or partial responders determined by RECIST

<sup>b</sup>Unknown represents patients for which no sample was obtained or whose sample quality did not allow determination of PD-L1 status.
Best change in tumor burden and response kinetics according to histology

Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for PD per RECIST v1.0

Scott G et al, P2.11-038
Conclusions

- In this heavily pretreated population of patients with NSCLC, nivolumab
  - Produces durable responses
  - Demonstrates an encouraging survival profile
  - Demonstrates a manageable safety profile
- Higher ORRs are noted at the 3- and 10-mg/kg nivolumab doses relative to the 1-mg/kg dose
- In some patients, tumor response continued following discontinuation of therapy
- Nivolumab demonstrates responses across a broad array of NSCLC patient populations regardless of histology, including populations of more heavily pretreated patients (≥3 prior approximately), older patients (age ≥70 years old) and patients with and without tumors driven by KRAS or EGFR mutations
Response According to PD-L1 Expression (cont)

- There is no apparent association between PD-L1 expression and NSCLC histology (Table 3)
- There was no clear association of ORR in patients with PD-L1+ tumors and tumor histology or nivolumab dose (Table 3)
- Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation-positive tumors appear to have higher PD-L1 expression at both the 1% and 5% cutoff (Table 4)
Conclusions

- In this cohort of patients with advanced NSCLC receiving nivolumab therapy
  - Nivolumab activity was numerically higher in the PD-L1$^+$ patients (Table 2 and Figure 4)
  - PD-L1$^-$ patients exhibited ORs
- Nivolumab monotherapy does not increase ALC, and ALC does not appear to be associated with response to nivolumab
- Activated CD4$^+$ and CD8$^+$ T cells may not represent a pharmacodynamic marker for response to nivolumab treatment
Results (cont)

Genes overexpressed in PD-L1+ tumors
Results (cont)

Genes overexpressed in PD-L1+ tumors

- The PD-L1 gene is differentially expressed in PD-L1 protein-positive compared with protein-negative samples (as evaluated by IHC), however:
  - Association between PD-L1 gene and PD-L1 protein expression was only seen at the highest expression levels (>80% positive staining)
  - At lower expression levels, no apparent correlation was seen between PD-L1 gene and protein expression (Figure 4)
Results (cont)

PD-L1 and PTEN/PI3K Protein Expression

- No apparent association was found between PD-L1 protein expression by IHC and PTEN or EGFR-protein expression as measured by IHC (Figure 5)
Conclusions

- The PD-L1 gene is differentially expressed in PD-L1 protein-positive compared with protein-negative samples (as evaluated by IHC); association was observed only above 80% PD-L1+ staining
  - Identification of patients based solely on gene expression will likely omit a population of IHC-positive patients
- No apparent association was noted between tumor PD-L1 expression and lung cancer histology, PTEN, or EGFR status
- Preliminary results, while limited by sample size and the lack of associated clinical results, demonstrate that KRAS mutation-positive tumors tend to have higher PD-L1 expression; a majority of NSCLC tumors with KRAS mutations are PD-L1+
Conclusions (cont)

- PD-L1 expression correlated with:
  - Several immune-related genes, including CD274, KLRC1, and IFNG
  - Several genes associated with tumor cell proliferation, including MET, AREG, and EREG
- Analysis for the other mutations (eg, PIK3CA, TP53) showed no association with PD-L1 status
- Preliminary results suggest an association of PD-L1 expression with key pathways involved in tumor immune suppression and tumor proliferation/inhibition of apoptosis. Further studies are required to better understand the direct link between PD-L1 expression and tumor progression.
ALC as a pharmacodynamic or predictive marker of nivolumumab monotherapy

Patients With NSCLC

Individual Responder  Individual Nonresponder  Responder Mean  Nonresponder Mean

WCLC 2013  Mercury ID: ONCHQ13NP10127; Approved 5Nov2013; Expires 5 Nov2015
Levels of activated T cells and Treg cells in patients treated with nivolumab
Conclusions (cont)

● The current retrospective biomarker analysis has limitations
  – Use of archived samples from heavily pretreated patients
  – Low rate of ascertainment of tissue samples
  – Potential effects of prior treatment on PD-L1 expression
  – Because of the unique efficacy profile of immune-based therapies, ORR may not be the optimal endpoint to assess the predictive role of biomarkers