Updates on treatment advances in small cell lung cancer, mesothelioma, thymoma and thymic carcinoma

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Washington, DC
2 cases
SCLC and MESOTHELIOMA

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Lombardi Comprehensive Cancer Center
Georgetown University

Ft. Lauderdale February 14, 2016
Small cell lung cancer

- 63 yo with 42 year history of smoking
- Hemoptysis and intense cough in July 2014
- Chest X-ray, pneumonia, antibiotics
- CT scan: large (7cm) primary tumor right hemithorax, mediastinal adenopathy, liver metastasis
- Biopsy of liver metastasis: small cell lung carcinoma
- Carboplatin-etoposide 6 cycles, with disappearance of thoracic disease (Aug-Dec 2014)
- 5/26/15 progression of liver metastasis
- Experimental treatment vs standard treatment
  - Experimental treatment with doxorubicin and ganetespib: good response, severe mucositis and diarrhea
  - Tumor shrinkage continues after 6 doxorubicin cycles and ganetespib alone
Small cell lung cancer

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• Experimental treatment vs standard treatment
  • Experimental treatment with doxorubicin and ganetespib: good response, severe mucositis and diarrhea
  • Tumor shrinkage continues after 6 doxorubicin cycles and ganetespib alone
Multiple pleural lesions right hemithorax
Malignant pleural mesothelioma

• 76 yo Caucasian man
• Abnormal routine chest X-ray end of 2013
• CT scan Jan 2014 shows multiple pleural-based masses right hemithorax
• CT guided biopsy: epithelioid mesothelioma
• Treatment of “early stage” mesothelioma
• Carbo-pemetrexed x6 with minor response
  • Right VATS pleurectomy and decortication on 11/6/14: surgeon says that there was more tumor than expected based on the CT scan; likely non-radical resection; radiotherapy felt too extensive
• Jan 2015 progression
• April 2015 doxorubicin + ganetespib, stable disease after 6 cycles
• September 2015 progression, pembrolizumab
Minor response to “neoadjuvant chemotherapy”

Baseline

2 months
Malignant pleural mesothelioma

- 76 yo Caucasian man
- Abnormal routine chest X-ray end of 2013
- CT scan Jan 2014 shows multiple pleural based masses right hemithorax
- CT guided biopsy: epithelioid mesothelioma
- Treatment of “early stage” mesothelioma
- Carbo-pemetrexed x6 with minor response
- Right VATS pleurectomy and decortication on 11/6/14: surgeon says that there was more tumor than expected based on the CT scan; likely non-radical resection; radiotherapy felt too extensive
- Jan 2015 progression
- April 2015 doxorubicin + ganetespib, stable disease after 6 cycles
- September 2015 progression, pembrolizumab
Recurrent pleural mesothelioma: before and after 6 cycles of pembrolizumab
Updates on treatment advances in small cell lung cancer, mesothelioma, thymoma and thymic carcinoma

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## Disclosures

<table>
<thead>
<tr>
<th>Advisory Committee</th>
<th>Celgene Corporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contracted Research</td>
<td>AstraZeneca Pharmaceuticals LP, Karyopharm Therapeutics</td>
</tr>
</tbody>
</table>
SMALL CELL LUNG CANCER
CheckMate 032 Study Design

SCLC (n = 128) with progressive disease after ≥1 prior line of therapy, including a platinum-based regimen in first line (unselected by PD-L1 expression)

Nivolumab 3 mg/kg IV Q2W (n = 40)

Nivolumab 1 mg/kg + Ipiplimumab 1 mg/kg IV Q3W for 4 cycles (n = 3)

Nivolumab 1 mg/kg + Ipiplimumab 3 mg/kg IV Q3W for 4 cycles (n = 47)

Nivolumab 3 mg/kg IV Q2W

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

Database lock: February 16, 2015

*Data from this cohort will be presented at a later time.

Presented By Scott Antonia at 2015 ASCO Annual Meeting
KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors

**Patients**
- Small cell lung cancer
- Failure of or inability to receive standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion
- PD-L1 positivity
- No autoimmune disease or interstitial lung disease

**Pembrolizumab 10 mg/kg IV Q2W**

**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

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

**Primary end points**: ORR per RECIST v1.1 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 24 weeks later.*

Presented By Patrick Ott at 2015 ASCO Annual Meeting
DLL3

- Notch pathway implicated in regulating neuroendocrine vs epithelial cell fate decision in developing lung
- Ligands DLL1 (delta-like), DLL4, JAG1 and JAG2 activate Notch receptor in trans
- DLL3 predominantly in Golgi and unable to activate Notch. It inhibits both trans- and cis-activation by interacting with Notch and DLL1
- High expression of DLL3 in SCLC and LC NEC; low expression in normal tissues
Activity of SC16LD6.5 on PDX of neuroendocrine carcinomas of the lung

Lu64 SCLC

Lu86 SCLC

Lu37 LCNEC

Rovalpituzumab tesirine (SC16LD6.5) – phase I in SCLC

- A DLL3 antibody-drug conjugate
- 0.05 – 0.8 mg/kg q3w or q6w
- 52 SCLC patients in second and third line
- Thrombocytopenia and capillary leak syndrome
- 44% of 16 DLL3 high expressors (H score ≥ 120) had PR
- 22% response rate in all patients (32) treated at MTD

Rudin CM et al. World Conference on Lung Cancer 2015
MESOTHELIOMA
Malignant Pleural Mesothelioma (MPM)
- Histologically proven
- PS = 0-2
- No cardiovascular comorbidity
- Chemonaïve

IFCT-GFPC-0701 trial: MAPS

IFCT-sponsored, open-label, multi-centre randomized phase II-III trial

A
Pemetrexed 500 mg/m² D1
Cisplatin 75mg/m² D1
6 cycles, Q21D

R 1:1

B
Pemetrexed 500 mg/m² D1
Cisplatin 75mg/m² D1
Bevacizumab 15 mg/kg D1
6 cycles, Q21D

Surveillance
No cross-over allowed

Maintenance Bevacizumab
15 mg/kg D1, Q21D until progression

CT-scan Q 3 cycles in both arms.
Response assessed with modified RECIST criteria for mesothelioma

Stratification: center, histology (epithelioid vs. sarcomatoid/mixed), PS (0-1 vs. 2), smoking status (ever smoker vs. never-smoker)

Presented By Gerard Zalcman at 2015 ASCO Annual Meeting
## Focus on bevacizumab-related toxicities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arm A (n=224)</th>
<th>Arm B (n=222)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Embolism &amp; Venous Thrombosis</td>
<td>3 (1.3%)</td>
<td>12 (5.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>3 (1.4%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.4%)</td>
<td>3 (1.4%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (0.4%)</td>
<td>6 (2.7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Arterial Thrombosis</td>
<td>0</td>
<td>5 (2.3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>3 (1.4%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>2 (0.9%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>14 (6.3%)</td>
<td>63 (37.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>14 (6.3%)</td>
<td>79 (35.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0 (0.0%)</td>
<td>4 (1.8%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (1.3%)</td>
<td>125 (56.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (0.9%)</td>
<td>21 (9.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (0.4%)</td>
<td>53 (23.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>51 (23.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 (0.4%)</td>
<td>37 (16.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>11 (5.0%)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (0.4%)</td>
<td>19 (8.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>7 (3.2%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage (without epistaxis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>2 (0.9%)</td>
<td>20 (9.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>0</td>
<td>2 (0.9%)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*1 brain hemorrhage leading to death (grade 5), 10 days later.

Presented By Gerard Zalcman at 2015 ASCO Annual Meeting
Efficacy: ITT Progression-free Survival (PFS)

median follow-up = 39.4 mo [11.0-83.0]

- Median PFS: 7.48 mo, 95%CI: [6.79-8.13]
- Median PFS: 9.59 mo, 95%CI: [8.49-10.59]

Stratified HR = 0.61; 95%CI [0.50-0.75]

\( p < 0.0001 \)

IFCT 0701 ‘MAPS’ randomized phase 3 trial

Presented By Gerard Zalcman at 2015 ASCO Annual Meeting
Efficacy: ITT Overall Survival (OS)

median follow-up = 39.4 mo [11.0-83.0]

- Median Overall Survival: 16.07 mo, 95%CI: [14.00-17.93]
- Median Overall Survival: 18.82 mo, 95%CI: [15.90-22.62]

Stratified HR=0.76; 95%CI [0.61-0.94]

\[ p=0.0127 \]

IFCT0701 ‘MAPS’ randomized phase 3 trial

Presented By Gerard Zalcman at 2015 ASCO Annual Meeting
KEYNOTE-028 (NCT02054806): Phase 1b Multi-Cohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors

**Pembrolizumab 10 mg/kg IV Q2W**

**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.

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

**Primary end points:** ORR per RECIST v1.1 and safety

**Secondary end points:** PFS, OS, duration of response

**Power:** With ~22 subjects enrolled, this study provides 80% power to demonstrate that the ORR exceeds 10%

*If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy is received.

Alley AACR 2015_19Apr15
Analysis of PD-L1 Expression

- Samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: performed at a central laboratory using a prototype assay and the 22C3 antibody clone
- Positivity: membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma
- MPM cohort: of 80 evaluable samples, 38 PD-L1 positive (45.2%)

Examples of PD-L1 Staining in MPM Specimens from KEYNOTE-028

PD-L1 Negative  PD-L1 Positive
## Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Total N = 25</th>
<th>Resulted in Interruption</th>
<th>Resulted in Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash(^a) (all grade 1)</td>
<td>4 (16)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ALT/AST increased (grade 3)</td>
<td>1 (4)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypersensitivity (grade 2)</td>
<td>1 (4)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Iridocyclitis (uveitis) (grade 2)</td>
<td>1 (4)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^a\)Includes maculopapular rash.
Analysis cut-off date: January 20, 2015.
Antitumor Activity  
(RECIST v1.1, Investigator Review)  

<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(^a)</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(^b)</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Objective response rate: 28% (95% CI, 12-49)  
Disease control rate: 76% (95% CI, 55-91)  

\(^a\)Includes confirmed and unconfirmed responses.  
\(^b\)Patients who discontinued therapy before the first post-treatment scan due to progressive disease.  
Analysis cut-off date: January 20, 2015.
Maximum Percentage Change From Baseline in Target Lesions\textsuperscript{a} (RECIST v1.1, Investigator Review)

\textsuperscript{a}Includes patients with $\geq$1 postbaseline tumor assessment ($n = 23$). Analysis cut-off date: January 20, 2015.
Level of PD-L1 Expression and Response

- Using prototype IHC assay, no relationship between level of PD-L1 expression on tumor and immune cells within tumor nests and frequency of response
  - One-sided $P = 0.284$ by logistic regression

Patients were eligible for enrollment if they had PD-L1 expression in $\geq 1\%$ of tumor or immune cells in tumor nests or staining in the stroma.
Data cutoff date: June 24, 2015.
THYMIC EPITHELIAL TUMORS
# Phase II studies in pretreated patients with TETs

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Total #</th>
<th>Thymomas</th>
<th>RR (%)</th>
<th>mPFS (m)</th>
<th>mOS (m)</th>
<th>Thymic carcinoma</th>
<th>RR (%)</th>
<th>mPFS (m)</th>
<th>mOS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loehrerr ASCO 2006</td>
<td>Pemetrexed</td>
<td>27</td>
<td>16</td>
<td>17</td>
<td>10.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmieri Future Oncol 2014</td>
<td>Capecitabine + gemcitabine</td>
<td>30</td>
<td>22</td>
<td>40 (combined)</td>
<td>11 (combined)</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wakelee ASCO 2015</td>
<td>Amrubin</td>
<td>33</td>
<td>14</td>
<td>29</td>
<td>8.7</td>
<td>NR</td>
<td></td>
<td>19</td>
<td>11</td>
<td>8.5</td>
</tr>
<tr>
<td>Loehrerr JCO 2004</td>
<td>Octreotide + prednisone</td>
<td>38</td>
<td>32</td>
<td>38</td>
<td>8.8</td>
<td>NR</td>
<td>5 + 1 carcinoid</td>
<td>0</td>
<td>4.5</td>
<td>23.4</td>
</tr>
<tr>
<td>Palmieri Cancer 2002</td>
<td>Octreotide + prednisone</td>
<td>16</td>
<td>13</td>
<td>38</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
<td>33</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Kurup ASCO 2005</td>
<td>Gefitinib</td>
<td>26*</td>
<td>19</td>
<td>5</td>
<td>ND</td>
<td>ND</td>
<td>7</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Bedano ASCO 2008</td>
<td>Erlotinib + Bevacizumab</td>
<td>18</td>
<td>11</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>7</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Salter ASCO 2008</td>
<td>Imatinib</td>
<td>11</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Giaccone JTO 2009</td>
<td>Imatinib</td>
<td>7**</td>
<td>2B3</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>5</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Palmieri CPP 2012</td>
<td>Imatinib</td>
<td>15***</td>
<td>12</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Giaccone JCO 2011</td>
<td>Belinostat</td>
<td>41</td>
<td>25</td>
<td>8</td>
<td>11.4 TTP</td>
<td>NR (&gt;29.3)</td>
<td>16</td>
<td>0</td>
<td>2.7 TTP</td>
<td>12.4</td>
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<tr>
<td>Gubens Lung Cancer 2015</td>
<td>Saracatinib</td>
<td>21</td>
<td>12</td>
<td>0</td>
<td>5.7</td>
<td>37.5</td>
<td>9</td>
<td>0</td>
<td>3.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Thomas Lancet Oncol 2015</td>
<td>Sunitinib</td>
<td>41</td>
<td>16</td>
<td>6</td>
<td>8.5</td>
<td>15.5</td>
<td>25</td>
<td>26</td>
<td>7.2</td>
<td>NR (&gt;17)</td>
</tr>
<tr>
<td>Zucale ASCO 2014</td>
<td>Everolimus</td>
<td>50</td>
<td>30</td>
<td>20</td>
<td>NR (&gt;12.4)</td>
<td>NR</td>
<td>19</td>
<td>21</td>
<td>5.5</td>
<td>18.6</td>
</tr>
<tr>
<td>CDK-125-006</td>
<td>Milciclib</td>
<td>58</td>
<td>14 B3</td>
<td>0</td>
<td>8.9</td>
<td>53.6</td>
<td>44</td>
<td>6.8</td>
<td>4.8</td>
<td>24.2</td>
</tr>
</tbody>
</table>
Thymic carcinoma
Response Rate: 26% (6/23)

Thymoma
Response Rate: 6% (1/16)

Thomas A. et al. Lancet Oncol. 2015
Sunitinib in TETs: progression-free and overall survival
# PD-L1 immunohistochemistry in TETs

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibody</th>
<th>Definition of Positive</th>
<th>Positive thymomas</th>
<th>Positive thymic carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 2003</td>
<td>Ab 29E.5A9 or 29E.2A3</td>
<td>Not stated</td>
<td>81% (21/26)</td>
<td>88% (7/8)</td>
</tr>
<tr>
<td>Padda 2015</td>
<td>rabbit MoAb clone 15</td>
<td>High intensity</td>
<td>68% (44/65)</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>Naidoo ASCO 2015</td>
<td>rabbit MoAb E1L3N</td>
<td>≥ 25% tumor cells positive</td>
<td>94% (11/12)</td>
<td>34% (4/12)</td>
</tr>
<tr>
<td>Katsuya ASCO 2015</td>
<td>rabbit MoAb E1L3N</td>
<td>H-score ≥3</td>
<td>67% (6/9)</td>
<td>41% (7/17)</td>
</tr>
<tr>
<td>Katsuya 2015</td>
<td>rabbit MoAb E1L3N</td>
<td>H-score ≥3</td>
<td>23% (22/101)</td>
<td>70% (26/38)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>49% (104/213)</td>
<td>59% (47/79)</td>
</tr>
</tbody>
</table>
Pembrolizumab in Thymic Carcinoma (NCT02364076)

- **Main eligibility:**
  - failure on prior chemotherapy
  - no autoimmune disorders
- **Therapy:** 2mg/kg q3w
- **Correlative studies:**
  - NGS
  - CRC
  - PD-L1 expression
- **Accrual:**
  - started in March 2015
  - 23 patients
Patient #4 before and after 2 cycles