Multidisciplinary management of thoracic malignancies

Thursday, 04/14/2016, 04:45 PM - 06:15 PM
Room A
Discussant abstracts 98O and 208O_PR

David Carbone, MD PhD
Director, The James Thoracic Center
The Ohio State University
Columbus, Ohio
Disclosures

• Consulting/honoraria from:
  – Genentech/Roche
  – Pfizer
  – Novartis
  – BioDesix
  – Merck
  – EMD Serono
  – GSK
  – Boehringer Ingelheim
  – Amgen
Response to crizotinib (Xalkori) in ALK+ patient

4/26/2011

9/27/2011
Nivolumab in second line squamous - OS

Brahmer, NEJM 2015
CHARACTERIZATION OF TUMOR INFILTRATING LYMPHOCYTES IN RESECTABLE EARLY-STAGE NON-SMALL CELL LUNG CANCER

Sean Hall
Division of Thoracic Surgery, University Hospital of Bern
The immunology of early vs. late stage tumors

- Resection of lung cancer results in only about 50% cures
- Immunotherapy has the potential to increase the number of cures
- The host response observable in tumors presenting as early stage and those presenting as late stage may be different and even perhaps cause and effect
  - A 4 cm stage I tumor may have an ongoing immune response that has kept it from metastasizing
  - A 5 mm tumor that presents with bone, liver and brain metastases may not have the same responses
- Most of the data to date are on overtly metastatic patients
- Understanding responses in early stage tumors is important for optimizing immunotherapy of early stage disease
Lymphocyte infiltration correlates with good outcome

But only a small subset has intense lymphocytic infiltration

What are the characteristics of these cells??

Brambilla, JCO 2016
> Increased infiltration of CD4+ T cells in Adenocarcinoma

> Subpopulations of TILs are not altered in Squamous cell carcinoma
TIL subpopulations: Evidence of exhaustion in Adenocarcinoma

Adenocarcinoma, N=33, paired t-test, two sided

- % CD107a-PD-1+ (CD4+ gate)
  - N vs T: p<0.0001

- % CD107a-PD-1+ (CD8+ gate)
  - N vs T: p<0.0001

- MFI CD127 (CD4+ cells)
  - N vs T: p=0.77

- MFI CD127 (CD8+ cells)
  - N vs T: p=0.048
TILS in early stage NSCLC

- T-cell subsets seem different in adenocarcinoma and squamous
- Exhaustion markers present in both
- Implications for adjuvant/neoadjuvant PD-1 pathway intervention is unclear
- Implications for intervention with other immune modulators, informed by these analyses, is an exciting potential of these studies.
If no progression is seen at D20 CT, an additional 2 cycles are given before surgery.
CRS-207 with Chemotherapy in Malignant Pleural Mesothelioma (MPM): Results from a Phase 1b Trial

Thierry Jahan¹, Raffit Hassan², Evan Alley³, Hedy Kindler⁴, Scott Antonia⁵, Chan Whiting⁶, Lisa M. Coussens⁷, Aimee Luck Murphy⁶, Anish Thomas², Dirk G. Brockstedt⁶

¹Department of Medicine, Division of Hematology Oncology, University of California, San Francisco, San Francisco, CA; ²Thoracic and GI Oncology Branch, National Cancer Institute, Bethesda, MD; ³Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA; ⁴Gastrointestinal Oncology and Mesothelioma Programs, Section of Hematology/Oncology, University of Chicago, Chicago, IL; ⁵Thoracic Oncology Department, Moffitt Cancer Center, Tampa, FL; ⁶Aduro Biotech, Inc., Berkeley, CA; ⁷Oregon Health & Science University, Portland, OR
CRS-207

- Live-attenuated *Listeria monocytogenes*—expressing mesothelin
- Induces innate and adaptive immunity
- Tested prime/boost vaccination with GVAX and CRS-207 in pancreatic adenocarcinoma (Le et al, JCO 2015).
  - Randomized 2:1 to two doses of Cy/GVAX followed by four doses of CRS-207 (arm A) or six doses of Cy/GVAX (arm B) every 3 weeks.
  - OS was 6.1 months in arm A versus 3.9 months in arm B (hazard ratio [HR], 0.59; *P* .02).
Key points on cancer vaccines

- Prevention vs. therapy
  - Treatment is more challenging
- Active vs. passive immunity
- Cellular vs. humoral immunity
  - T-cells vs. antibodies
- Antigens
  - TSA, TAA, whole cell vaccines
- Antigen is necessary but not sufficient
  - Adjuvants (chemical or cellular), viral/bacterial vectors
- Tumors suppress immunity
  - Overcoming immunosuppression (e.g. PD1)
## Lung cancer vaccination > phase 3 trials (ca. 8000 R patients)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Phase 3</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely resected IB-IIIA</td>
<td>MAGE-A3 ASCI MAGRIT target 2270</td>
<td>Recruited (reported ESMO 14)</td>
</tr>
<tr>
<td>Stage IIIA-B treated by radiochemotherapy</td>
<td>Tecemotide (L-BLP25) START target 1300</td>
<td>Recruited (reported ASCO 13)</td>
</tr>
<tr>
<td>III (not amenable to radical treatment) and IV</td>
<td>Belagenpumatucel-L STOP target 700</td>
<td>Recruited (reported ECCO/ESMO 13)</td>
</tr>
<tr>
<td>Strategies with chemotherapy</td>
<td>rEGF target 1000</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>TG4010 TIME target 1000</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Racotumomab (1E10) target 1082</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Due to the absence of treatment effect no assessment of Gene signature feasible.

Vansteenkiste J et al, ESMO 2014
Study Design
Phase 1B study to evaluate the safety and induction of immune response of CRS-207 in combination with pemetrexed and cisplatin in front-line therapy of adults with MPM

Up to 60 Subjects with MPM and no prior treatment

2 PRIME Doses
CRS-207 every 2 weeks

Up to 6 CYCLES Standard Chemotherapy
PEMETREXED/CISPLATIN every 3 weeks

2 BOOST Doses*
CRS-207 every 2 weeks

* Currently enrolling in Cohort 2 of study which administers low-dose Cy (200 mg/m2) 1 day prior to CRS-207

* Subjects may continue with maintenance CRS-207 every 8 weeks if clinically stable
Best Overall Response (BOR): N=34 Evaluable Subjects*

- PR: 20/34 (59%)
- SD: 12/34 (35%)
- PD*: 2/34 (6%)

85% of subjects exhibited tumor shrinkage

*34/38 subjects evaluable for response; 4 subjects did not have post-baseline tumor measurements

*1 subject had clinical progression and did not have post-baseline tumor measurements
CRS-207 Induced Immune Cell Recruitment and Activation in the Tumor Microenvironment

- **CD45^+Lin^-**
- Mast cells
- Neut/Eos
- DC mature
- DC immature
- CD163^+ Macrophage
- CD163^- Macrophage
- B cells
- NK
- CTL
- TH1
- TH2
- TH17
- TREG (FoxP3)
- TH0

**Graphs:**
- **CTL/Treg ratio**
- **Cytotoxic T cells**

**Patient ID:**
- 009-018
- 004-004
- 004-001
Conclusions:

- Response rate, waterfall plot, PFS, remarkable
- No data on mesothelin-specific CTL
- BUT – single arm trial, so caution is in order.
  - Untreated, good PS patients
  - Sarcomatoid-predominant histology excluded
- Randomized study planned
16TH WORLD CONFERENCE ON LUNG CANCER

Save the Date!

Abstract Submission Open: January 2015
Registration Open: January 2015
Abstract Submission Deadline: April 24, 2015
Abstract Notifications: June 22, 2015
Early Registration Deadline: June 26, 2015
Late Breaking Abstract Submission Deadline: July 10, 2015
Regular Registration Deadline: July 24, 2015

SEPTEMBER 6–10, 2015
→ DENVER, COLORADO, USA

CURE FOR LUNG CANCER