Disclosure Information

Suzanne L. Topalian, MD

I have the following financial relationships to disclose:

- **Consultant for:** Bristol-Myers Squibb (uncompensated), Jounce Therapeutics, Sanofi, and Amplimmune (spouse)
- **Research grant support from** Bristol-Myers Squibb
- **Royalties through institution:** Amplimmune (spouse), Bristol-Myers Squibb (spouse)
“Cancer is a genetic disease”
- rationale for personalized medicine
- limitation: rapid resistance

Cancer is an immunological disorder
- immunotherapy is a common denominator that can activate immune responses against mutant proteins
- the adaptable immune system can keep pace with tumor evolution
The adaptive immune system: an “ideal” anti-cancer agent

**Diversity**
- T cells - $10^{18}$
- Antibodies - $10^{22}$

**Specificity**
Can distinguish minute chemical alterations

**Memory**
After effective antigen priming, immunity can last for decades
Immune tolerance: Multiple barriers to tumor elimination

Regulatory immune cells
- T reg cells
- MDSCs

Immunosuppressive cytokines
- IL-6, IL-10, TGF-β, VEGF

T-cell inhibitory receptors
- CTLA-4, PD-1, LAG-3, etc.

Solution: adoptive transfer of T cells optimized/engineered ex vivo

Solution: systemic blockade of suppressive cytokines or inhibitory receptors/ligands ("immune checkpoints")
Anti-CTLA-4 (ipilimumab) was approved for treating metastatic melanoma based on improved overall survival in a randomized study.

However, the grade 3-4 drug-related toxicity rate approximated the clinical benefit rate.
The PD-1/PD-L1 pathway: New strategies for immune checkpoint blockade

PD-L1 is expressed by many human tumors and may play a pivotal role in local cancer immunosuppression
Role of PD-1 in suppressing antitumor immunity

Activation (cytokines, lysis, prolif., migration)

Inhibition (anergy, exhaustion, death)

TCR Signal 1

(+) Signal 2

PD-1

PD-L1

Tumor

T cell

MHC-Ag

B7.1

CD28

TCR Signal 1

APC

Tumor
Role of PD-1 in suppressing antitumor immunity

**Activation**
(cytokines, lysis, prolif., migration)

**Inhibition**
(Anergy, exhaustion, death)

**TCR Signal 1**

**TCR Signal 2**

**MHC-Ag**

**B7.1**

**CD28**

**APC**

**T cell**

**PD-L1**

**PD-1**

**Anti-PD-1**

**Tumor**
CTLA-4 vs. PD-1: Distinct immune checkpoints

**Naïve/Resting T Cell**

- APC
  - B7.1/2
  - CD28
  - CTLA-4

**T Cell Priming**

- APC
  - Costim. ligand
  - Costim. receptor

**Traffic to Periphery**

- Tissue
  - PD-L1
  - PD-1

**Experienced T Cell**

- APC
  - Costim. ligand
  - Costim. receptor

**CTLA-4 vs. PD-1**

- Topalian et al., Curr Opin Immunol 2012
Nivolumab (anti-PD-1)
(BMS-936558, MDX-1106, ONO-4538)

- Fully human IgG4 anti-human PD-1 blocking mAb
- High affinity for PD-1 ($K_D \sim 3$ nM), blocks binding to both known ligands: PD-L1 (B7-H1, broadly inducible) and PD-L2 (B7-DC, selective for APCs)
- Favorable safety profile and preliminary evidence of clinical activity in patients with treatment-refractory solid tumors in a first-in-human study (Brahmer et al., J Clin Oncol 2010)
Two early phase clinical trials of anti-PD-1 (nivolumab) in patients with advanced solid tumors
(Brahmer et al., JCO 2010; Topalian et al., NEJM 2012)

1st Treatment Cycle

Day 1
Dose 0.3-10 mg/kg

Day 57
Scans

Follow Up or Additional Treatment Cycle(s)

Day 85
Scans

2 years
or until CR/PR or PD

1st Treatment Cycle

Days 1, 15, 29, 43
Dose 0.1-10 mg/kg

Day 57
Scans

Follow Up or Additional Treatment Cycle(s)

2 years
or until CR or PD

Eligible patients: treatment-refractory metastatic lung cancer, melanoma, kidney, colon, or prostate cancer
Durable anti-PD-1 responses **OFF THERAPY:**

**immune memory**

*(Lipson et al., CCR 2013)*

- **CRC**
  - CR Stop Rx
  - Latest eval.: CR

- **RCC**
  - Stop Rx Best resp.(PR)
  - Latest eval.: CR

- **MEL**
  - Stop Rx Best resp.(PR)
  - New LN met
  - Resume Rx PR
  - Latest eval.: PR
Clinical activity of anti-PD-1 (nivolumab)

- 294 patients started therapy between 2008-2012 and had ≥6 mo. follow-up. No ORs in CRC (n=19) or CRPC (n=17)
- 28/54 responses lasted ≥1 yr in patients with ≥1 yr follow-up
- Toxicity: grade 3-4 drug-related AEs15%, mortality 1%

Topalian et al., ESMO 2012

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dose (mg/kg)</th>
<th>No. pts</th>
<th>ORR (CR/PR) No. pts (%)</th>
<th>SD ≥24 wk No. pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>1-10</td>
<td>122</td>
<td>20 (16)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>MEL</td>
<td>0.1-10</td>
<td>106</td>
<td>33 (31)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>RCC</td>
<td>1 or 10</td>
<td>34</td>
<td>10 (29)</td>
<td>9 (27)</td>
</tr>
</tbody>
</table>
Anti-PD-1 response kinetics and durable tumor control off therapy

Change in Target Lesions from Baseline (%)

Weeks Since Treatment Initiation

Melanoma 1 mg/kg

Maximum duration of therapy

First occurrence of new lesion

On study

Off study
35-year-old patient had disease progression after surgery and IL-2.
Response to anti-PD-1 ongoing at 23 months.
Partial regression of metastatic kidney cancer in response to anti-PD-1

- 57-year-old patient developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib
- Currently in cycle 12 anti-PD-1 therapy (~23 months) with ongoing PR
Response of a “non-immunogenic” tumor to anti-PD-1: Squamous cell lung cancer

History:
61-year-old patient with stage IV NSCLC refractory to multiple surgeries, RT, 2 multidrug chemotherapy regimens, and epigenetic therapy (5-AZA and entinostat).

Recently completed 2 yrs anti-PD-1 therapy.
Drug-related AEs of special interest in ≥ 3% of 304 patients receiving anti-PD-1

<table>
<thead>
<tr>
<th>AEOSI (&quot;irAE&quot;)</th>
<th>All grades (n, %)</th>
<th>Grade 3-4 (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>138 (45)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Rash</td>
<td>41 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (12)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>31 (10)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>ALT ↑</td>
<td>13 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>AST ↑</td>
<td>11 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>TSH ↑</td>
<td>11 (4)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pneumonitis*</td>
<td>10 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>9 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>8 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*There were 3 (1%) deaths in patients with pneumonitis (2 NSCLC, 1 CRC). AEOSIs in ≤1% of pts included colitis, hepatitis, hypophysitis, nephritis and thyroiditis. Analysis as of July 2012. Topalian et al, ESMO 2012
Prior therapies included multiple surgeries, RT and temozolomide.

Nephritis developed after 8 months of anti-PD-1 therapy, associated with administration of radiographic contrast dye.

Partial response of metastatic mucosal melanoma to anti-PD-1, associated with nephritis.
Nephritis associated with anti-PD-1 therapy: serologic and cellular immune components

H&E, 400 X

CD3

plasma cell

glomerulus

tubule

intraepithelial T cell
Signal anti-apoptotic signal in tumor cells

APC/Target cell

? anti-apoptotic signal in tumor cells

PD-L1

Anti-PD-1

PD-L2

B7.1

T CELL

(-) signal

APC/Target cell

? anti-apoptotic signal in tumor cells

PD-L1

Anti-PD-L1

PD-L2

B7.1

T CELL

(-) signal
If PD-1 pathway blockade acts locally in the tumor immune microenvironment........

Then it follows that the tumor site may hold the key to optimizing anti-PD-1/PD-L1 therapy:
- Biomarkers to select patients most likely to respond to therapy
- Early indicators of treatment outcomes
- Identification of resistance pathways and development of synergistic combinatorial therapies
Preliminary molecular marker studies: Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical response to anti-PD-1

49 patients include 20 with melanoma, 13 NSCLC, 7 colon, 6 kidney, and 3 prostate cancer.

* Normal renal glomerulus
Correlation of PD-L1 expression with tumor type in 49 patients treated with anti-PD-1

Responders/total: 8/20 3/13 2/6 0/7 0/3

Patients were “PD-L1+” if ≥5% of tumor cells in any tumor biopsy expressed cell surface PD-L1, using mAb 5H1 (L. Chen) and manual staining technique.
2 Mechanisms for PD-L1 up-regulation in tumors

**Innate Resistance**

Constitutive tumor signaling induces PD-L1 on tumor cells

**Adaptive Resistance**

PD-L1 expression reflects immune reaction

Oncogenic Pathway

- MHC-pep
- TCR
- PD-L1
- PD-1

TUMOR → T Cell

- TUMOR
- Stats
- IFN-g

T Cell → TUMOR

- T Cell
- TUMOR
Focal PD-L1 expression in melanoma: geographic co-localization with TILs creates a “shield” against immune attack
PD-L1 expression in melanoma correlates with the presence of TILs and increased overall survival in patients with metastatic disease.

TILs are necessary but not sufficient for PD-L1 expression.

(Taube et al., Science Transl Med 2012)
PD-L1 expression on tumor cells and TAMs in oropharyngeal SCCHN: association with CD8+ TILs, IFN-γ and HPV+ tumors

Lyford-Pike, Pai, et al., Cancer Res 2013
PD-L1 expression on tumor cells and TAMs in Merkel cell Ca: association with CD8+ TILs, MCV, and overall survival

Lipson, Taube, et al., Cancer Immunol Res 2013
PD-1 pathway in virus-associated cancers: at the crossroads of cancer immunology and microbial immunology

- Principles of PD-1/PD-L1 mechanism-of-action first demonstrated in preclinical models of infectious disease
- PD-1 pathway restrains host immune responses against chronic infection
- Virus-associated cancers account for a large proportion of cancer deaths worldwide
- PD-1 blockade now in the clinic for virus-associated hepatocellular cancer, in planning for HIV
Potential PD-1 pathway interactions in chronic HIV infection

- Increased PD-L1 expression on APCs in HIV infection
- PD-1 and other co-inhibitory molecules are expressed on HIV specific CD8 T cells
- PD-1+ CD4 T cells might be an important latent viral reservoir

Diagram:
- APC
- PD-L1/2
- PD-1
- CD4 T cell HIV+
- CD8 T cell
- (?)
- (-)
Dissecting mechanisms and resistance pathways: Immune infiltrates at the boundary of PD-L1+ melanoma cells

- IFN-γ mRNA is overexpressed in PD-L1(+) vs. PD-L1(-) melanomas (Taube et al., Science Transl Med 2012)
- Gene expression profiling reveals inflammatory signature in PD-L1(+) tumors
Gene expression profile of TILs from PD-L1(+) vs. (-) melanomas reveals functional groups of differentially expressed genes and potential bypass pathways.

- log₁₀ p value vs. log₂ fold change

- Th1, CD8 T, Check-point

multiplex qRT-PCR, CD45 normalization
Association of lymphocyte activation gene-3 (LAG-3)+ lymphocytes with PD-L1+ melanoma cells

Young, Taube et al., AACR 2013 abstr. #465

Meeker, Taube, Advanced Cell Diagnostics
Synergistic anti-tumor effects of dual checkpoint blockade: anti-PD-1 and anti-LAG-3 in a murine tumor model

(Shown: MC38 colon cancer)

Drake, Vignali, Korman, Pardoll et al., Cancer Res 2012
Therapeutic implications for PD-1 pathway blockade in adaptive resistance model

**Strong** endogenous anti-tumor immune response

- PD-L1 up-regulation in tumor
- RESPONSE

**Weak** endogenous anti-tumor immune response

- No PD-L1 up-regulation in tumor

1. Inducer of anti-tumor immunity (vaccine, TKIs, “immunogenic” chemo, RT)

2. Anti-PD-1 monotherapy

**Inducer of anti-tumor immunity**

- Endogenous anti-tumor immune response
- PD-L1 expression in tumor
- RESPONSE
## PD-1 pathway blocking agents in clinical testing

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

<table>
<thead>
<tr>
<th>Company</th>
<th>PD-1</th>
<th>PD-L1 (B7-H1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplimmune/GSK</td>
<td>AMP-224 (PD-L2/Fc fusion protein)</td>
<td>N/A</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>Nivolumab/BMS-936558/MDX-1106/Ono-4538 (fully human IgG4 mAb)</td>
<td>BMS-936559/MDX-1105 (fully human IgG4 mAb)</td>
</tr>
<tr>
<td>CureTech</td>
<td>Pidilizumab/CT-011 (humanized IgG1 mAb)</td>
<td>N/A</td>
</tr>
<tr>
<td>Genentech</td>
<td>N/A</td>
<td>MPDL3280A (Fc-modified IgG1 mAb)</td>
</tr>
<tr>
<td>MedImmune</td>
<td>N/A</td>
<td>Medi4736 (mAb)</td>
</tr>
<tr>
<td>Merck</td>
<td>Lambrolizumab/MK-3475 (humanized IgG4 mAb)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
How can the path to clinical approval be accelerated?

Regulatory challenges for targeted immunotherapies:
- Defining appropriate endpoints for clinical efficacy
- Understanding unique side-effects and developing effective monitoring and management guidelines
- Identifying biomarkers predicting response, which may be dynamic and tissue-specific
ACKNOWLEDGEMENTS

Thanks to collaborating clinical trial centers.
Sponsored by BMS, NIH, Barney Fdn., and Melanoma Research Alliance