Immuno-oncology: an introduction.

P. Pauwels
(UZA, UA)
Dendritic cell

Cytotoxic T cell

MHC class I

proteasome

extracellular antigens
A | Lymphatic tissue: CTLA-4 checkpoint

1. Antigen-presenting complex primes T-cell by presenting antigen

2. T-cell activation
   - CD28 ↔ CD80/86
   - T-cell deactivation
   - CTLA-4 ↔ CD80/86

3. Anti-CTLA-4 restores T-cell activation by inhibiting CTLA-4 ↔ CD80/86

B | Peripheral tissue: PD-1/PD-L1 checkpoint

4. T-cell recognizes and kills tumor through antigen recognition

5. T-cell deactivation
   - PD-L1/PD-L2 ↔ PD-1

6. Anti-PD-1/PD-L1 inhibits PD-1 ↔ PD-L1 and restores T-cell activation
Loss of CTLA-4 Leads to Massive Lymphoproliferation and Fatal Multiorgan Tissue Destruction, Revealing a Critical Negative Regulatory Role of CTLA-4
1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation in lymph nodes
4. T cell trafficking to tumors
5. T cell infiltration into tumors
6. T cell recognition of cancer cells
7. Cancer cell killing

BRAFi
poly I:C
expansion
maturation
anti-PD-L1
block immunosuppression
b

Immunological ignorance

Non-functional immune response

Excluded infiltrate

Pre-treatment

Pre-treatment

Pre-treatment

On treatment (week 9)

On treatment (week 6)

On treatment (week 6)
METABOLIC COMPETITION
between T cells and tumors...

TUMOR

Highly Antigenic Regressive Tumor

Enhance glycolysis/glucose acquisition

Tumor outcompetes T cells for nutrients

Tumor Progresses

REGRESSION

T cells nutrient sufficient

↑ Glycolysis

● IFN-γ production intact

PROGRESSION

T cells nutrient restricted

↓ Glycolysis

● IFN-γ production defective
Innate (tumor cell intrinsic) resistance

Constitutive tumor signaling induces PD-L1 on tumor cells

Adaptive resistance

T cell induced PD-L1 up-regulation

Cross-presentation of tumor antigen?
A Threshold Level of Intratumor CD8$^+$ T-cell PD1 Expression Dictates Therapeutic Response to Anti-PD1

Shin Foong Ngiow$^{1,2}$, Arabella Young$^{1,2}$, Nicolas Jacquenot$^{3,4,5,6}$, Takahiro Yamazaki$^{3,4,5,6}$, David Enot$^{3,4,5,6,7}$, Laurence Zitvogel$^{3,4,5,6}$, and Mark J. Smyth$^{1,2}$
T-cell PD1 Levels Set a Threshold for Response

Cancer Res; 75(18) September 15, 2015
Classifying Cancers Based on T-cell Infiltration and PD-L1

Michele W.L. Teng¹,², Shin Foong Ngiow³, Antoni Ribas⁴,⁵, and Mark J. Smyth²,³
Letter

Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens

Matthew M. Gubin¹, Xiuli Zhang², Heiko Schuster³, Etienne Caron⁴, Jeffrey P. Ward¹,⁵, Takuro Noguchi⁶, Yulia Ivanova¹, Jasreet Hundal⁶, Cora D. Arthur¹, Willem-Jan Krebber⁷, Gwenn E. Mulder⁷, Mireille Toebes⁸, Matthew D. Vesely¹, Samuel S. K. Lam¹, Alan J. Korman⁹, James P. Allison¹⁰, Gordon J. Freeman¹¹, Arlene H. Sharpe¹², Erika L. Pearce¹, Ton N. Schumacher⁸, Ruedi Aebersold⁴,¹³, Hans-Georg Rammensee⁵, Cornelis J. M. Melief⁷,¹⁴, Elaine R. Mardis⁶,¹⁵, William E. Gillanders², Maxim N. Artyomov¹ & Robert D. Schreiber¹
Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (50). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.
State of the Art: Concise Review

Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer

In what state is this art?

Keith M. Kerr, MBChB, FRCPath,* Ming-Sound Tsao, MD, PhD,† Andrew G. Nicholson, DM, FRCPath,‡ Yasushi Yatabe, MD, PhD,§ Ignacio I. Wistuba, MD, PhD,∥ and Fred R. Hirsch, MD, PhD,¶

On behalf of the IASLC Pathology Committee

(J Thorac Oncol. 2015;10: 985–989)
Table 4. Immunohistochemical Methods for Evaluating Tumor PD-L1 Expression

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>JHU</th>
<th>Bristol-Myers Squibb</th>
<th>Merck</th>
<th>Roche/Genentech</th>
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<tbody>
<tr>
<td>mAb clone</td>
<td>SH1</td>
<td>2B8</td>
<td>22C3</td>
<td>SP142</td>
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<tr>
<td>Automated</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Staining location scored</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Membranous</td>
<td>Membranous</td>
</tr>
<tr>
<td>Cell type scored</td>
<td>Tumor</td>
<td>Tumor</td>
<td>Tumor and/or infiltrating immune cells</td>
<td>Infiltrating immune cells</td>
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</tbody>
</table>

"Positive" cutoff

- 

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>MEL, NSCLC, Renal, Colorectal, Prostate</th>
<th>MEL</th>
<th>MEL</th>
<th>NSCLC</th>
<th>NSCLC</th>
<th>RCC</th>
<th>HNSCC</th>
<th>MEL</th>
<th>NSCLC</th>
<th>Bladder</th>
<th>MEL</th>
<th>NSCLC</th>
<th>Solid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1-positive patients/total patients (%)</td>
<td>25/42</td>
<td>12/44</td>
<td>17/58</td>
<td>74/210</td>
<td>9/15</td>
<td>33/68</td>
<td>29/107</td>
<td>81/104</td>
<td>89/125</td>
<td>159/194</td>
<td>55/205</td>
<td>15/30</td>
<td>48/184</td>
</tr>
<tr>
<td>Reference</td>
<td>(60)</td>
<td>(27)</td>
<td>(45)</td>
<td>(35)</td>
<td>(60)</td>
<td>(49)</td>
<td>(27)</td>
<td>(78)</td>
<td>(71)</td>
<td>(82)</td>
<td>(27)</td>
<td>(50)</td>
<td>(26)</td>
</tr>
</tbody>
</table>

NOTE. PD-L1 expression in formalin-fixed, paraffin embedded (FFPE) tumor specimens was evaluated using distinct immunohistochemical assays and scoring methods. Some references report results from different cut-offs for positive scoring in the same cohorts. Final methods and cut-off values are likely to be determined after additional clinical follow-up and analysis of ongoing studies.

a Positive cutoff, definition of PD-L1⁺ specimen according to threshold percent of cells staining with PD-L1-specific mAb.

b Updated scoring system for NSCLC defines a PD-L1⁺ specimen as having ≥1% tumor cells expressing cell surface PD-L1, and subdivides "strong" positives (≥50% staining) in "weak" positives (<50% staining).

c PD-L1⁺ defined as IHC 2 and IHC 3.

d PD-L1⁺ defined as ≥5% infiltrating cells or tumor cells expressing PD-L1.

e PD-L1⁺ defined as "tumors with infiltrating immune cells that stain for PD-L1 using Genentech/Roche Ex IHC".

JHU, Johns Hopkins University; MEL, melanoma.