Cancer immunotherapy by PD-1 blockade

Keynote Lecture
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ESMO Asia Congress 2015
Disclosure of Conflict of Interest

Honjo Tasuku

Matters requiring disclosure of COI with regard to our presentation are as follows;

Research founding: ONO PHARMACEUTICAL CO., LTD.
Cancer Immunotherapy

1. cancer antigen vaccination

2. activation of immune cell *in vitro*

3. cytokine

4. blockade of negative immune regulators
Two step regulation of immune cell activation

**Activation phase**
- naive T cell
  - TCR
  - CD28
  - CD80/86
  - CTLA-4

**Effector phase**
- activated T cells
  - TCR
  - PD-1
  - PD-L1, PD-L2
  - ICOS

**APC (or tumor)**
- Ag peptide on MHC
- CD80/86
- CTLA-4

**Car driving**
- get out of a parking lot

**Drive on a road**
Discovery of PD-1 (programmed cell death-1) cDNA


cDNA subtraction between apoptotic and normal cells
PD-1 is expressed on T cells and centrocytes in the light zone of GC in human tonsil

**Images:**
- **PD-1 / Ki67**
- **PD-1 / CD3**
- **PD-1 / CD20**
PD-1 is required for self-tolerance

**C57BL/6 PD-1KO**
Nephritis
Arthritis
*Nishimura H et al, Immunity (1999)*

**BALB/c PD-1KO**
Dilated cardiomyopathy
Gastritis
*Nishimura H et al, Science (2001)*

**NOD Diabetes**
WT
PD-1 KO
*Wang J et al, PNAS (2005)*

**MRL**
Myocarditis

**WT**
**PD-1 KO**
Since PD1 is a negative immune regulator, its blockade may help treatment of cancer and infectious diseases.
Identification of PD-1 ligands PD-L1 and PD-L2

• By 1998, PD-1, a negative immune receptor. To isolate a PD-1 ligand, screening cells by binding with PD-1-Ig.

• Sept. 1998, I proposed collaboration on this project to Steve Clark in Genetic Institute (GI) by using his Biacore machine.

I sent to GI all the reagents for the assay.

• Clive Wood (GI) obtained several B7 related cDNA with unknown function from Gordan Freeman. One of them turned out to be PD-L1.


Then, similarly PD-L2

Positive and negative regulators of immune response

Expression  | APC | APC(ind), B(ind) other tissues(ind) | APC(ind), B(ind) other tissues
--- | --- | --- | ---
Ligand  | CD80 B7.1 | CD86 B7.2 | ICOS-L B7h B7RP-1 | PD-L1 B7H1 | PD-L2
Receptor  | CD28 | CTLA4 | ICOS | PD-1
Function  | positive | negative | positive | negative
Expression  | T | T (ind) | T (ind) | T(ind), B(ind),
Molecular mechanism of immune inhibition by PD-1

Antigen receptor

Coreceptor

Kinase

Activation signal

ZAP70

PD-1

ITSM

SHP-2 (phosphatase)

negative signal

Okazaki et al. PNAS (2001)
Inhibition of tumorigenesis of J558L in PD-1−/− mice

Iwai et al. PNAS 2002

J558L
→ BALB/c
PD-1+/+

J558L
→ BALB/c
PD-1−/−

Tumor volume (mm³)

Days after inoculation

N=4

N=4
Inhibition of tumorigenesis of P815/PD-L1 by anti-PD-L1

Iwai et al. PNAS 2002
PD-1 blockade inhibits metastasis of melanoma (mouse model)

Humanized anti-PD-1 antibody

Established by Human immunoglobulin Tg mice (Xenogenic mice: patent by Ono pharm. And Medarex: May 9, 2005)

Subclass: IgG4S228P
mutant IgG4 (S228P) stabilizes the protein and reduces ADCC.
KD = 2.6 nmol/L

Approved as Investigation New Drug by FDA (USA; Aug 1, 2006)
Clinical trials in Japan and US

BMS (US)

2006 - present
phase I, II, III

recurrent·refractory tumor
(NSCLC, colon cancer, melanoma, RCC, prostate cancer)

Collaboration

Ono (JPN)

2009 - present
phase I, II, III

recurrent·refractory tumor

(2011/9/11 BMS press release)
Data summary

296 patients involved

CR or PR on NSCLC, melanoma and RCC

Cumulative response rates of:

18% (14 of 76 patients) among NSCLC,
28% (26 of 94 patients) among Melanoma
27% (9 of 33 patients) among RCC

Grade 3 or 4 drug related adverse events in 14% patients (including 3 death by immune-related pulmonary toxicity)

Topalian et al. NEJM 2012
Durable response by PD-1 blockade

“Responses were durable; 20 of 31 responses lasted 1 year or more in patients with long follow-up.”

From Topalian et al. NEJM 2012
Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant ovarian cancer

Junzo Hamanishi, MD, PhD
Kyoto University, Japan

Junzo Hamanishi, Masaki Mandai*, Takafumi Ikeda, Manabu Minami, Atsushi Kawaguchi, , Masashi Kanai, Yukiko Mori, Shigemi Matsumoto, Toshinori Murayama, Shunsuke Chikuma, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Akihiko Ueda, Satoshi Morita, Masayuki Yokode, Akira Shimizu, Tasuku Honjo, Ikuo Konishi
Kyoto University, Japan , *Kinki University, Japan

Hamanishi et al. J Clin Oncol. 2015
Negative correlation between PD-1 ligand expression with prognosis

Hamanishi et al. PNAS (2006)
# Clinical Effect: Best Overall Response

<table>
<thead>
<tr>
<th>Dose</th>
<th>total (n)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>RR</th>
<th>DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1/10 (10%)</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>2/10 (20%)</td>
<td>4/10 (40%)</td>
</tr>
</tbody>
</table>

Response rate is 20% in 3 mg/kg cohort.

(Hamanishi et al. JCO. 2015)
Follow-up Study (on going)

Change in target lesions from baseline (%)

Nivolumab q2wks div. One Year-Treatment

No Treatment

Durable response without treatment

(Hamanishi et al. ASCO. 2015)
Response Changes in Tumor Burden in Patients with Hodgkin's Lymphoma Receiving Nivolumab

Rumdomized Study on Untreated Melanoma Patients with Nivolumab and Dacarbazine (Alkylating Agent)

Overall Survival

Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73)
P<0.001

Patients Who Died

<table>
<thead>
<tr>
<th>Patients Who Died</th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>no./total no.</td>
<td>50/210</td>
<td>96/208</td>
</tr>
</tbody>
</table>

Median Survival

<table>
<thead>
<tr>
<th>Median Survival</th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>mo (95% CI)</td>
<td>Not reached</td>
<td>10.8 (9.3–12.1)</td>
</tr>
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No. at Risk

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>210</td>
<td>185</td>
<td>150</td>
</tr>
<tr>
<td>150</td>
<td>105</td>
<td>82</td>
</tr>
<tr>
<td>105</td>
<td>45</td>
<td>22</td>
</tr>
<tr>
<td>45</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Why can anti PD-1 cure cancer?

• Tumor cells continuously mutate and produce non-self antigens. A large immune repertoire can recognize and attack almost all cancer antigens.

• In most cases the immune surveillance can eliminate tumor cells. However, tumor cells may induce immune tolerance and grow.

• Anti-PD-1 breaks immune tolerance.
Cancer cells accumulate mutations

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Mutations per megabase</th>
<th>Coding mutations per tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
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<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower grade glioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate (adenocarcinoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney (papillary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney (clear cell)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas (adenocarcinoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head-Neck (squamous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach (adenocarcinoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (adenocarcinoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (squamous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Iñigo M. et al. Science 2015
The reason why immunotherapy but not chemotherapy has durable effects

<table>
<thead>
<tr>
<th>Cancer cells</th>
<th>selection by drug A</th>
<th>resistsants by drug A</th>
<th>mutagenesis by drug B</th>
<th>more resistsants</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>A1</td>
<td></td>
<td>A2</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>B1</td>
<td></td>
<td>B2</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>C1</td>
<td></td>
<td>C2</td>
</tr>
</tbody>
</table>

Lymphocytes can recognize and attack all of them
Colon cancers with mutation-prone genetic alterations respond better to PD-1 antibody

Phase 2 study with 41 patients with progressive metastatic carcinoma

Le, D et al. NEJM May 30, 2015
Advantages of anti-PD-1 therapy

1. Less adverse effects
   → Probably because of rheostatic regulation

2. Effective for a wide range of tumors
   (about 100 clinical trials)

3. Sustained effects to responders
   → 2 and 3 are probably due to huge repertoire of the Ag receptor

4. Possible combination with other anti-cancer treatments
Future challenge of PD-1 Ab cancer immunotherapy

1. Although milder the side-effect autoimmune symptoms inevitably develop and must be carefully watched.

2. Important to understand why there are non-responder patients (30% in melanoma).

3. Important to identify markers for responders or non-responders.
Why some patients do not respond to anti PD-1?

Host immune system may not be activated?

a. Tumors are not highly mutagenic
   → Testable

b. Patients’ immune system may be defective either genetically or environmentally
   → Testable and combination therapy

c. Other mechanisms of immune suppression
Many cancer patients are waiting for αPD-1 treatment.

What should be done for the best benefit for cancer patients?

I. Academic studies
   a. responder marker identification
   b. improvement of efficacy

II. Pharmaceutical industry
   a. acceleration of αPD-1 approval to many types of cancers
   b. many companies should coordinate for this goal.
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Research group

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Hamanishi et al. J Clin Oncol. 2015
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