Immunotherapy for gynecological cancers: Challenges and opportunities

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ESMO Asia 2015
Precision medicine and developmental therapeutics in gynaecologic oncology
Special Symposium
Disclosure

• I am principal investigator of clinical trial with nivolumab sponsored by Ono Pharmaceutical company, Japan.

• I receive a research fund from Daiichisankyo, Japan (outside the presenting work)
Cancer Immune Escape

Tumor microenvironment

Escape

Immune cells

Cancer

antigen↓, MHC↓, TGFβ, IDO, PD-L1↑, Treg • iDC

PD-L1/PD-L2 expression
COX1 /COX2 expression
NKG2D-Ligands deletion
Immune-gene therapy for ovca model
Immunological clustering in ovca patients

(Hamanishi, et al. PNAS 2007)
(Liu/Hamanishi, et al. Mod Pathol 2009)
(Li/Hamanishi, et al. Can Imm Imm 2009)
(Hamanishi et al. Stem Cells 2010)
(Hamanishi et al. Clin Immunol 2011)
T cell inactivation

Cancer cell

PD-L1 (PD-1 ligand 1)
- Negative co-signaling protein; B7 family
- Is expressed on dendritic cells, heart, placenta and cancer cells

PD-1 (Programmed cell death -1)
- Negative co-signaling receptor
- Is discovered by Honjo. T (1992)
- Is expressed on active T cells and myeloid cells
- Induces peripheral immuno-tolerance

PD-1 signal induces cancer immune escape
PD-1 signal blocking is a target for OvCa?

Cancer Cell

**PD-L1** (PD-1 ligand 1)

- **PD-L1 low**
- **PD-L1 high**

48/70 (68%)

( Hamaishi et al. PNAS 2007)

**anti-PD-1 antibody** (Nivolumab)

PD-1 signal blocking may be a new treatment for OvCa
Nivolumab (ONO-4538/BMS-936558)

- Fully human IgG4 PD-1 blocking antibody
- Binding to PD-1 and inhibiting PD-1/PD-L1 pathway
- Clinical anti-tumor effect on melanoma, kidney cancer and lung cancer

Drugs and safety data were provided by Ono.Japan and BMY in USA.
Platinum-resistant OvCa, n=20

**Endpoints**

- **primary**: Response rate (best response rate)
- **secondary**: Safety, PFS, OS, DCR

**Nivolumab**
1mg/kg n=10
3mg/kg n=10

**CT**

1 course

2~ 6 courses

- **Disease progression**
- **CR, PR, SD**
- **Off study**
- **Follow up**

**Anti-tumor response**: RECIST v1.1.
**Adverse effect**: CTCAE v4.0.
## 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>
<tr>
<td>Total</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>10</td>
<td>1</td>
<td>3/20 (15%)</td>
<td>9/20 (45%)</td>
</tr>
</tbody>
</table>

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

Hamanishi et al. JCO 2015
Two patients with Complete response

① 59yo. Serous adenoca. Multi-Pelvic LN recurrence (Nivo. 3mg/kg)

Baseline 4 months

② 60yo. Clear cell. Peritoneal dissemination recurrence (Nivo. 3mg/kg)
Survival Analysis

1mg/kg

3.5 months

PFS (%)

(month)

3mg/kg

3.0 months

(month)

Total

3.5 months

(month)

cf. 2nd line Chemo: PFS=3.5Ms, OS=12Ms

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

Change in target lesions from baseline (%)

Nivolumab One Year-Treatment

No Treatment >12 months

Durable response after Nivolumab-treatment

Hamanishi et al. ASCO 2015
PD-L1 expression and anti-tumor response

PD-L1 is not correlated to anti-tumor response??

(Hamanishi et al. JCO 2015)
Nivolumab is well tolerated for OvCa patients

- Total RR was 15%
- 3 mg/kg (RR=20%*) is favorable than 1 mg/kg

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>Melanoma</th>
<th>Renal cancer</th>
<th>Lung cancer</th>
<th>Ovarian cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>19-41 % (28 %)</td>
<td>24-37% (27%)</td>
<td>6-32 % (18 %)</td>
<td>10-20%* (15%)</td>
</tr>
</tbody>
</table>

(Topalian NEJM 2012)
Our Next Goal

- Additional indication of Nivolumab for OvCa

Phase IIa (Kyoto Univ.)
Phase IIb (Multi-institute)

larger-scaled
• Additional indication of Nivolumab for OvCa

⇒ Next larger-scale clinical trial for OvCa starts.

• Biomarker exploration for efficacy and safety

  • Anti-tumor effect
  • Side effect
  • Minimal treatment period

OMICS (DNA, RNA, Protein)

Clinical samples from 20 Patients (tumor, blood)
Our Next Goal

• Additional indication of Nivolumab for OvCa

⇒ Next larger-scale clinical trial for OvCa starts.

• Biomarker exploration for efficacy and safety

⇒ PD-L1 is a biomarker of Nivolumab for OvCa...?
⇒ Other reverse translational research is needed

• Overcome Nivolumab-resistance cases

⇒ Combination: vaccine, molecular target or chemotherapy?
⇒ New immuno-suppressive factors?
**Chemo-immunotherapy with aPD-1 Ab in mouse ovarian cancer model**

**Mouse ovarian cancer cell line ID8 model**

In the experiment, C57/Bl6 mice were injected subcutaneously with ID8 cells on day 0. Treatment with PBS (Paclitaxel) + IgG or aPD-1 Ab or aPD-L1 Ab started on day 14 and continued every 4 days until day 150.

The survival rate of the mice was evaluated, showing a significant improvement in survival for the mice treated with PTX + aPD-1 Ab compared to the control group.

*Peng, Hamanishi et al. Cancer Res. in press*
New B7-Hx expression on gynecologic malignancies

Murat, Hamanishi et al. submitted
PD-1 signal and Gynecologic Cancers

**Ovarian Cancer**
- PD-L1\(\alpha\)poor prognosis (Hamnishi PNAS2007)
- PD-1+TIL\(\alpha\)poor prognosis (Matsuzaki PNAS 2010)
- BRACA-/- \(\alpha\)PD-L1exp. (Strickland ASCO2015) etc.
- Nivo, Pembro, Avel and Durav

**Endometrial Cancer**
- PD-L1exp. (Vanderstraeten CCI 2014)
- MSI\(\alpha\)PD-L1exp. (Howitt ASCO 2015)
- Pembrolizumab (pII) (NCT02549209)

**Cervical Cancer**
- PD-1+TIL\(\alpha\)poor prognosis (Karim CCR 2009)
- Nivoluamb (pII) by NCI (NCT02257528)

**Vulval/Vaginal Cancer (melanoma)**
- Nivoluamb or Pembrolizumab
The view of PD-1 inhibitors for gynecologic cancer

Vulva/Vaginal Cancer (Melanoma) → Nivo and/or Pembro

Cervical Cancer → Nivolumab (pII)

Nivolumab (pII)
Kyoto Univ. JPN

Pembrolizumab (pII)

Pembro + TC (pII)
Pembro + ddT (pII)
Pembro + TKI (pII)

Endometrial Cancer → Pembro + TC (pII)

RR=12%(3/26)

2012 2014 2015 2016 ?

BMS-936559(pI)

Averumab (pI)

RR=11%(8/75)

Atezolizumab + Ipi (pl)
Durvalumab + Treme (pl)
Durvalumab + PARPi (pl/II)

Averumab + PLD (pIII)

Anti-PD-L1 antibody

Anti-PD-1 antibody

Hamanishi et al. in submission

2012

2014

2015

2016 ?
The role of PD-1 inhibitors

Operation/Biopsy

Diagnosis

Sampling

Medication

Chemotherapy

Molecular Target

Radiation

Immunotherapy

Biomarker

Diagnosis/Classification

Mutanome

Immune Monitoring

Biomarker

Medical Expense

Side effect

Gender? Onco-fertility?

Value = \frac{Benefit}{Cost + Toxicity}

*TR: translational research

**rTR: reverse translational research

§ Saltz et al. ASCO2015

Hamanishi et al. in submission
New types of cancer immunotherapies are attractive and some ones are hopeful as next anti-tumor strategy for gynecologic malignancies.

PD-1 inhibitors have potential benefit not only for ovarian cancer, but also for other gynecologic tumors.

The key to further development of PD-1 inhibitors is - to find predictive biomarkers for antitumor effects, - to investigate good combination treatments and - to consider the benefit, cost and toxicity.
Research group

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