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

Immunotherapy for gynecological cancers: Challenges and opportunities

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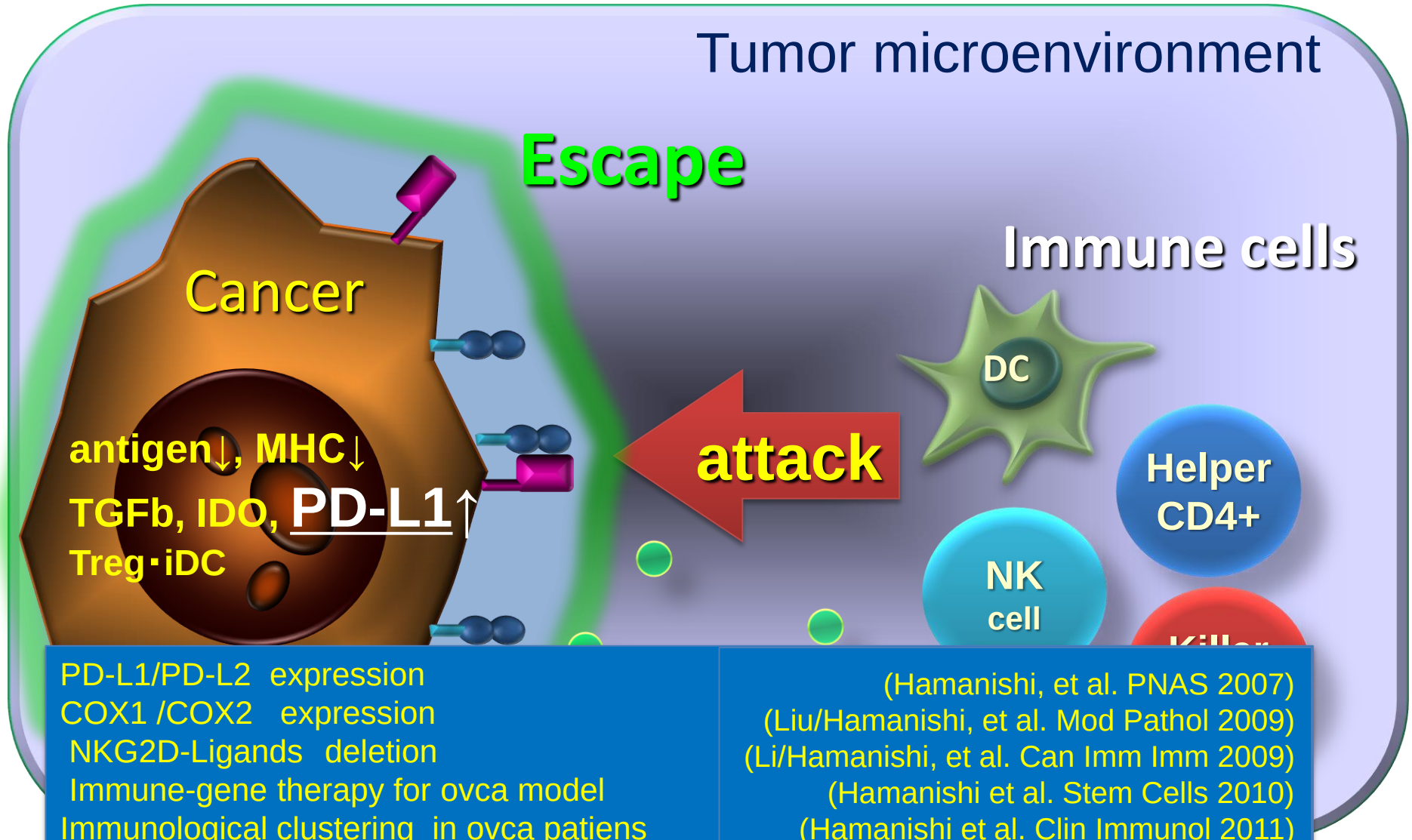
December 18, 2015

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)

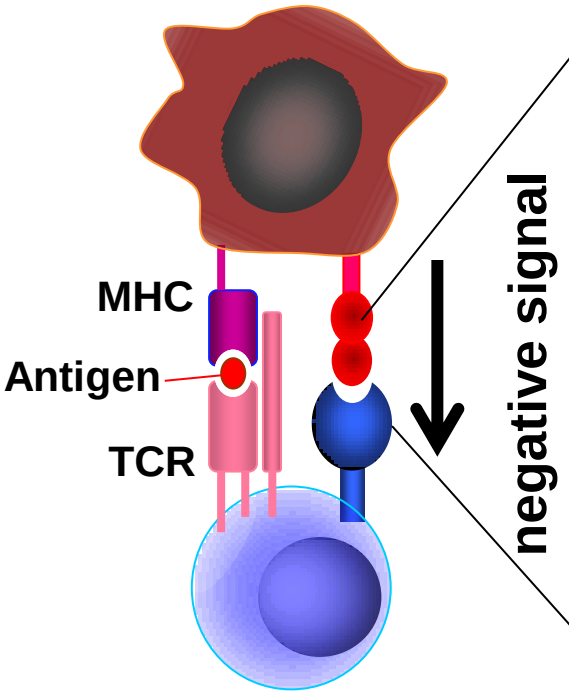
Cancer Immune Escape



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

(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)

Immune checkpoint PD-1 signal



negative signal

PD-L1 (PD-1 ligand 1)

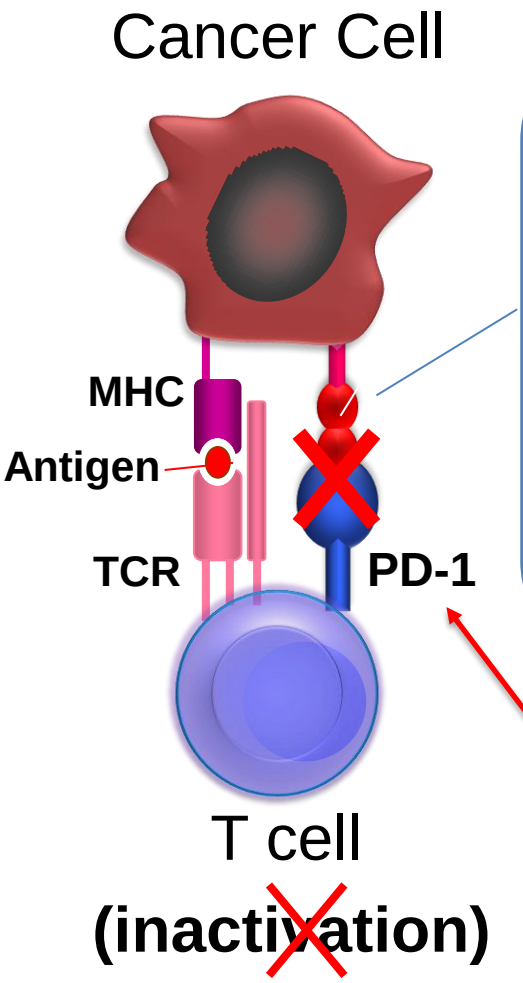
- Negative co-signal protein; B7 family
- is expressed on dendritic cells, heart, placenta and **Cancer cells**

PD-1 (Programmed cell death -1)

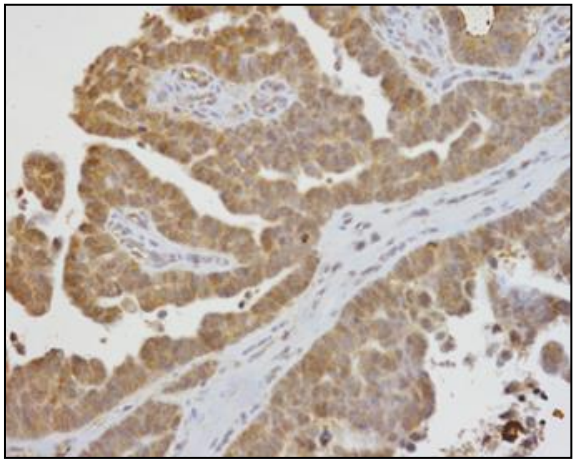
- Negative co-signal receptor
- is discovered by Honjo. T (1992)
- is expressed on active T cells and myeloid cells
- induces **peripheral immuno-tolerance**

PD-1 signal induces cancer immune escape

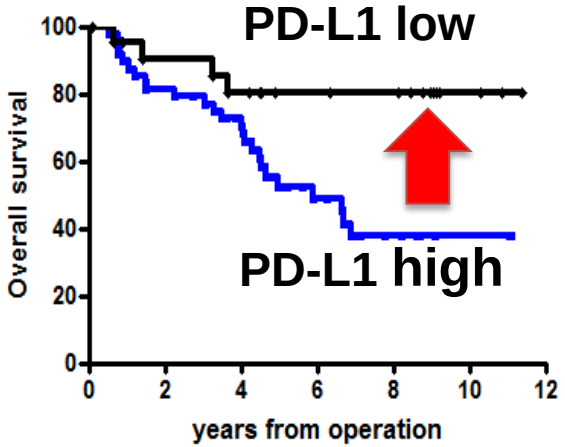
PD-1 signal blocking is a target for OvCa ?



PD-L1 (PD-1 ligand 1)



48/70（68%）



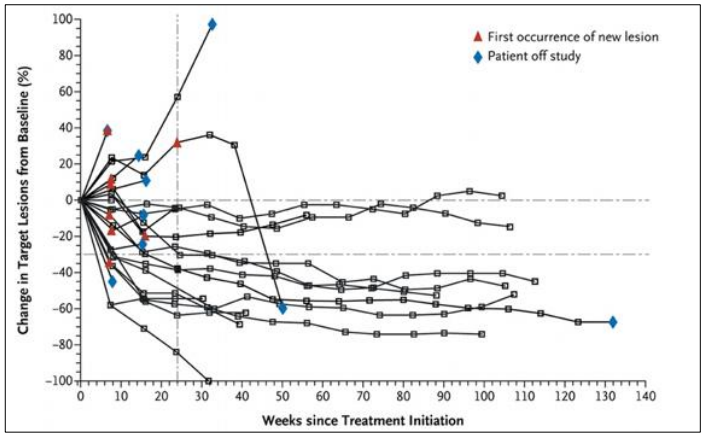
(Hamanishi et al. PNAS 2007)

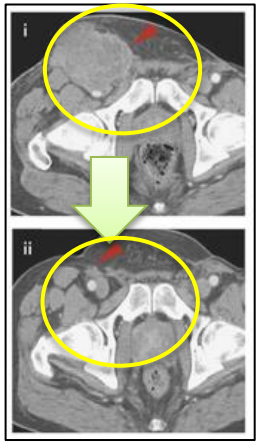
anti-PD-1 antibody (Nivolumab)

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





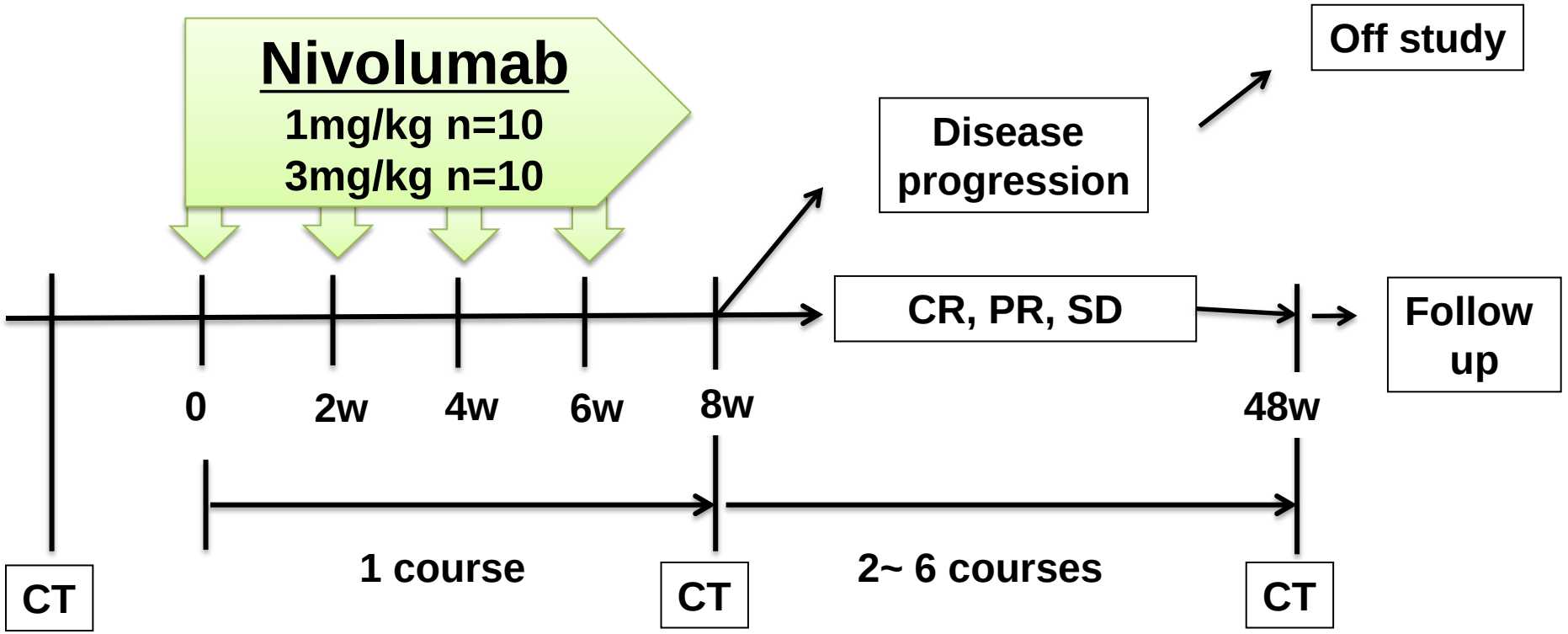
(Topalian et al. NEJM 2012)

Drugs and safety data were provided by Ono.Japan and BMY in USA.

Study schedule

JPRN-UMIN000005714

Platinum-resistant OvCa, n=20



Anti-tumor response: RECIST v1.1.
Adverse effect: CTCAE v4.0.

Endpoints

primary : Response rate (best response rate)

secondary: Safety, PFS, OS, DCR

Clinical Effect : Best Overall Response

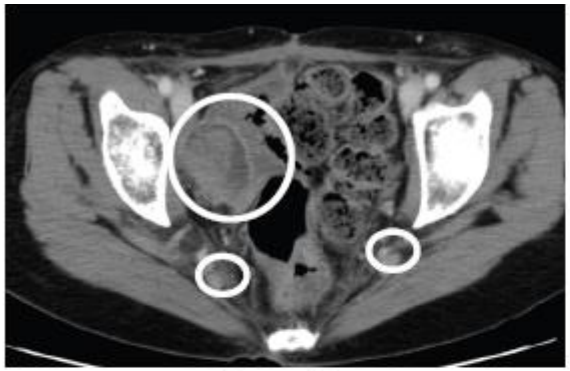
Dose	total (n)	CR	PR	SD	PD	NE	RR	DCR
1 mg/kg	10	0	1	4	4	1	1/10 (10%)	5/10 (50%)
3 mg/kg	10	2	0	2	6	0	2/10 (20%)	4/10 (40%)
Total	20	2	1	6	10	1	3/20 (15%)	9/20 (45%)

Response rate is 20 % in 3 mg/kg cohort

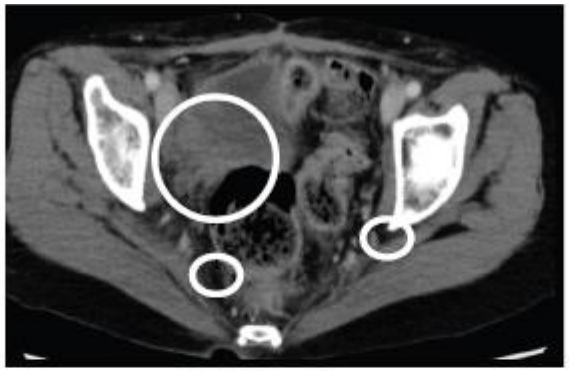
Hamanishi et al. *JCO* 2015

Two patients with Complete response

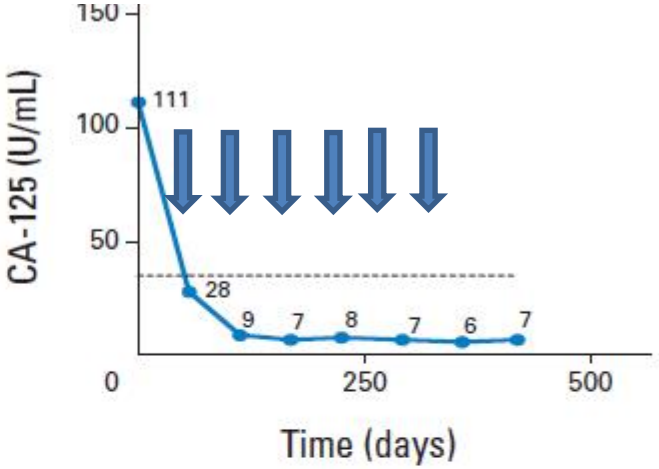
① 59yo. Serous adenoca. Multi-Pelvic LN recurrence（Nivo. 3mg/kg）



Baseline

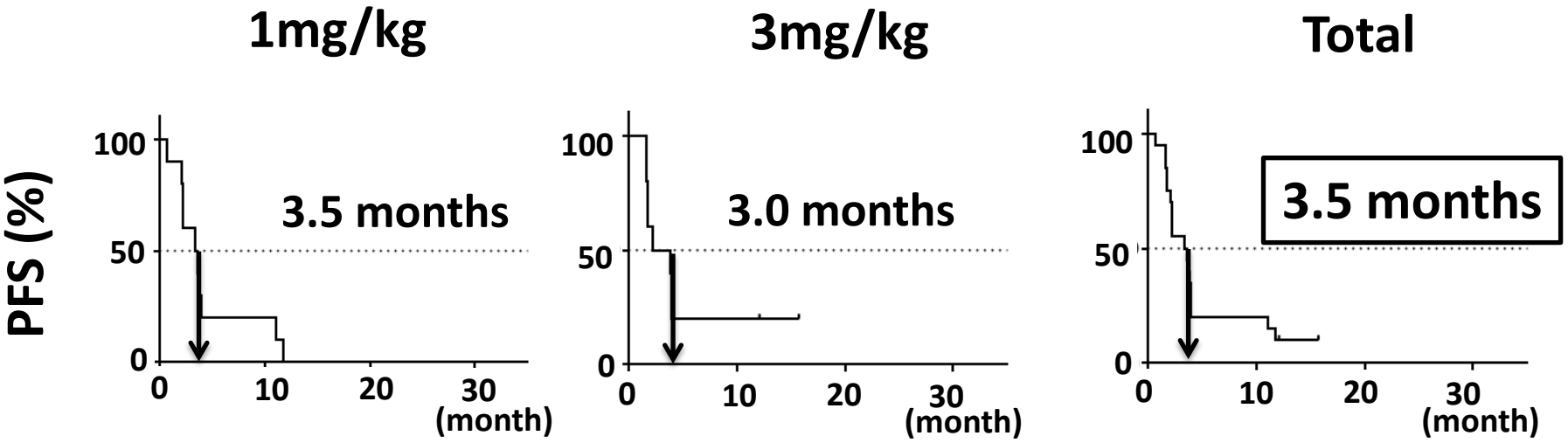


4 months



Hamanishi et al. *JCO*. 2015.

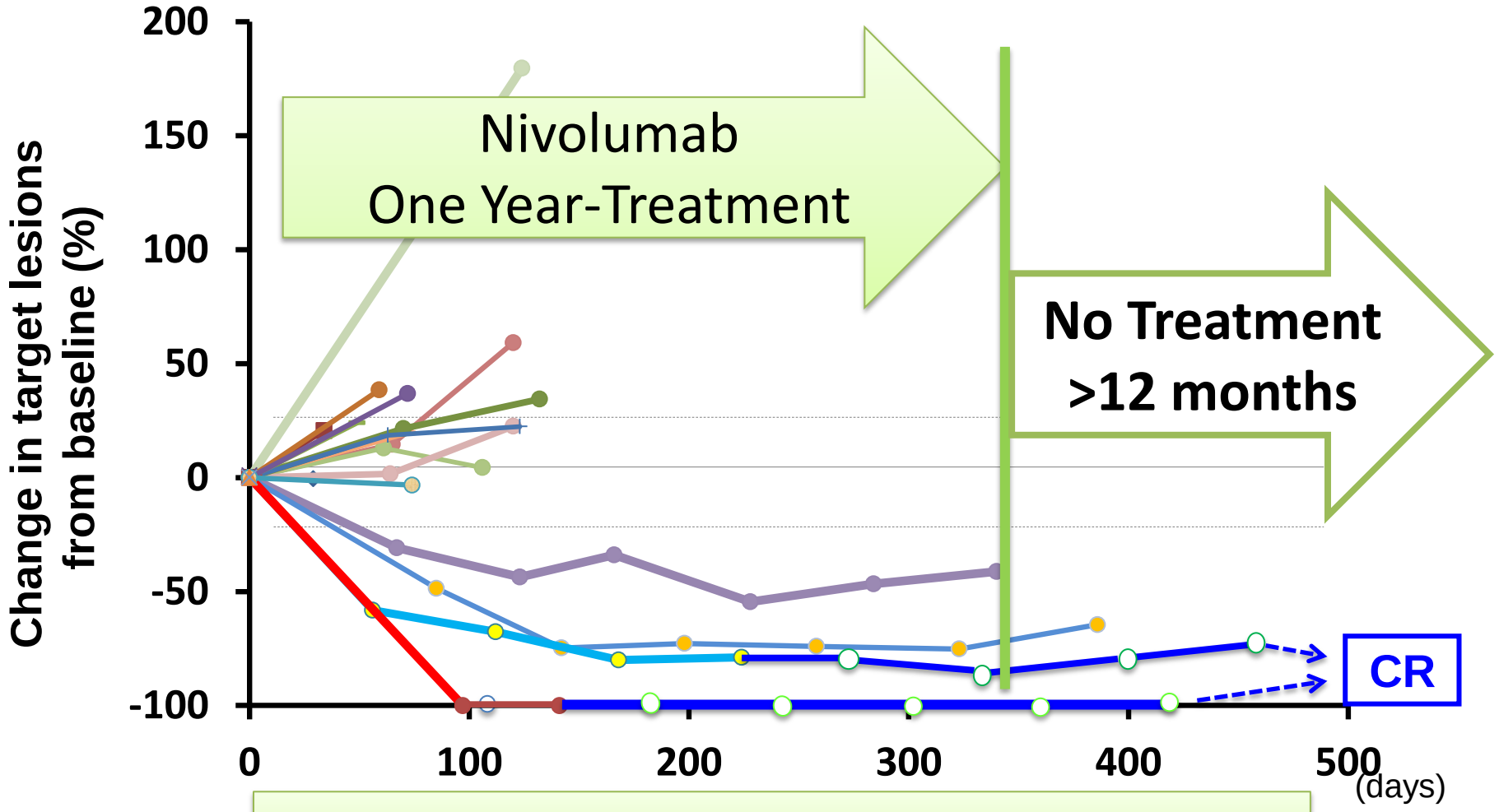
Survival Analysis



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

Hamanishi et al. *JCO* 2015

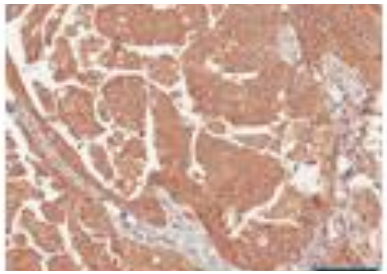
Follow-up Study (on going)

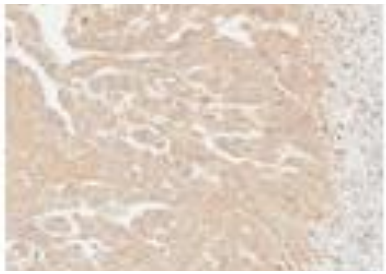


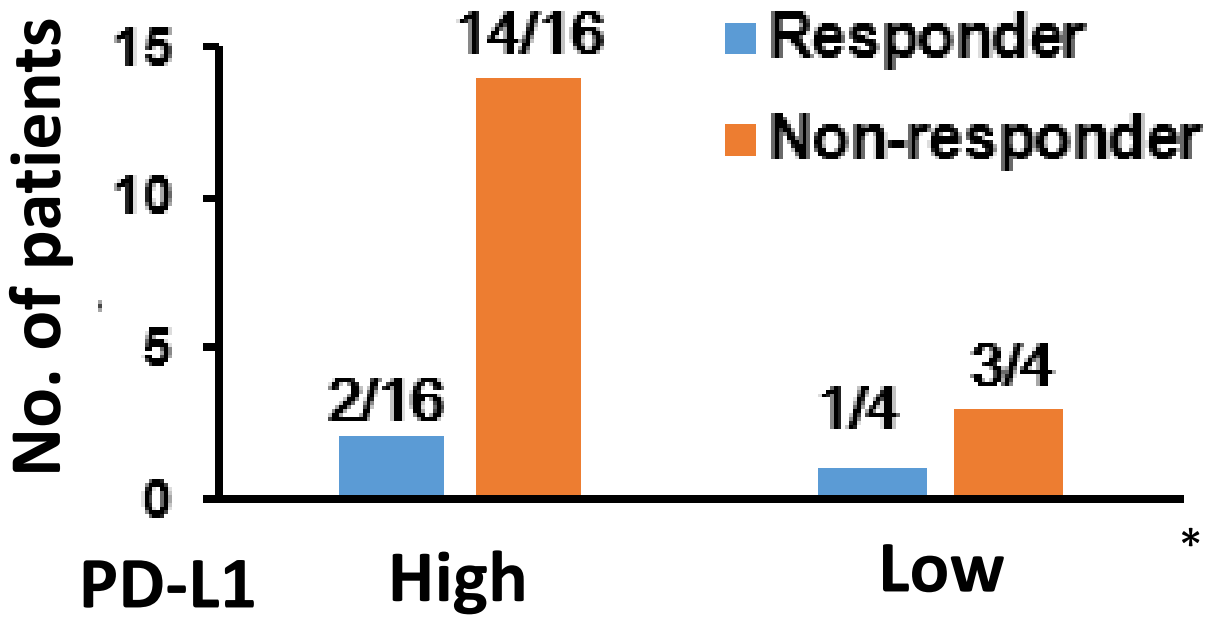
Durable response after Nivolumab-treatment

Hamanishi et al. ASCO 2015

PD-L1 expression and anti-tumor response







p= 0.509

*Responder: CR+PR

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

(Hamanishi et al. *JCO* 2015)

Short summary

- Nivolumab is well tolerated for OvCa patients
- Total RR was 15%
- 3 mg/kg (RR=20%*) is favorable than 1 mg/kg

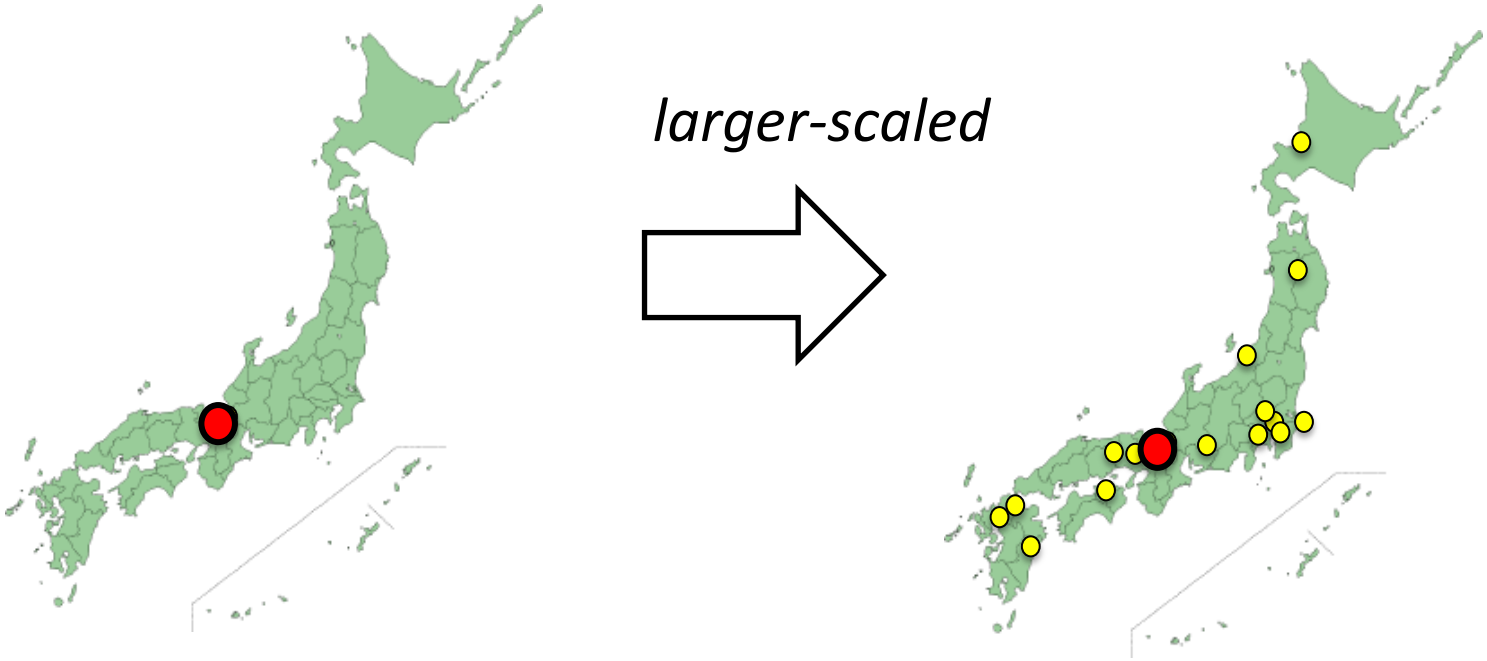
Nivolumb	Melanoma	Renal cancer	Lung cancer	Ovarian cancer*
Response Rate	19-41 % **(28 %)**	24-37% **(27%)**	6-32 % **(18 %)**	**10-20%*** **(15%)**

(Topalian NEJM 2012)

Our Next Goal

- Additional indication of Nivolumab for OvCa

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



Our Next Goal

- 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*

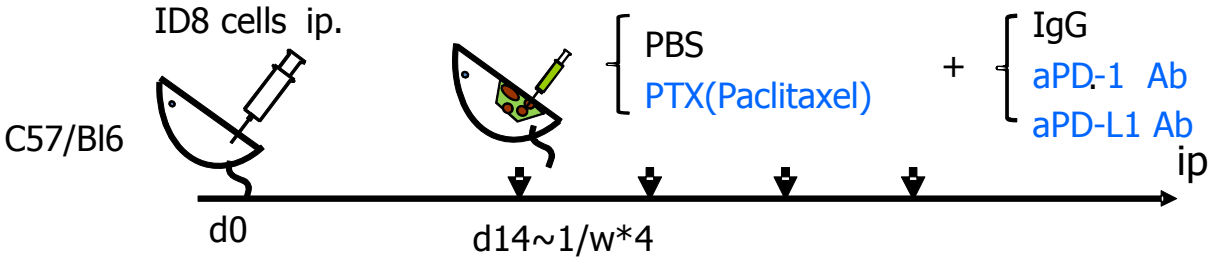
- Overcome Nivolumab-resistance cases

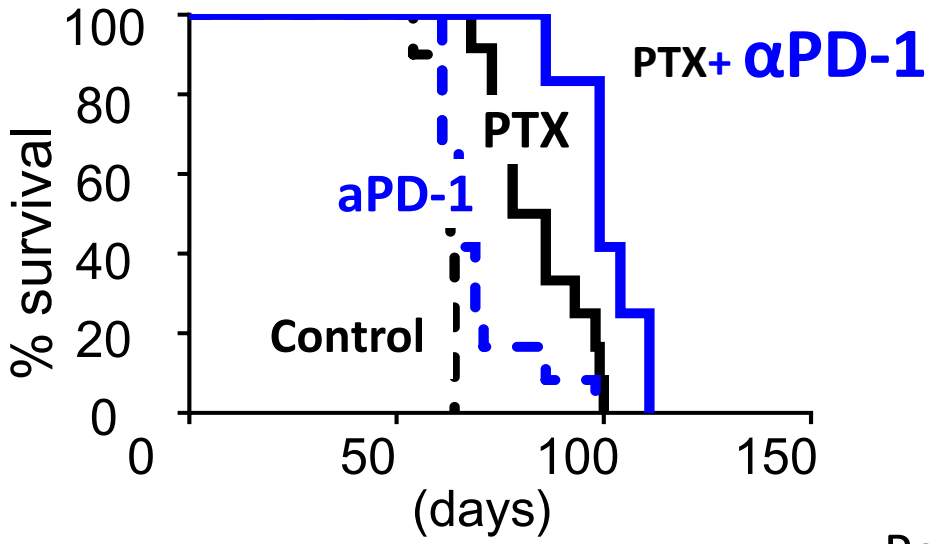
  ⇒ *Combination :vaccine, molecular target or chemotherapy ?*

  ⇒ *New immuno-suppressive factors ?*

Chemo-immunotherapy with aPD-1 Ab in mouse ovarian cancer model

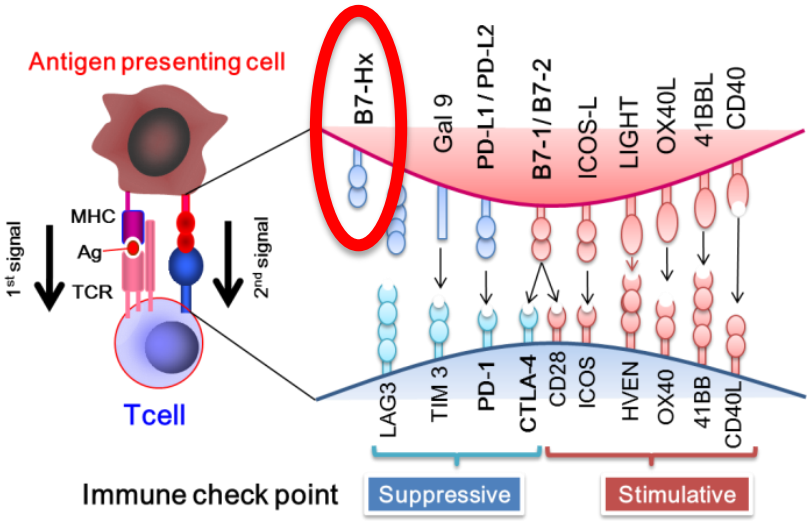
Mouse ovarian cancer cell line ID8 model

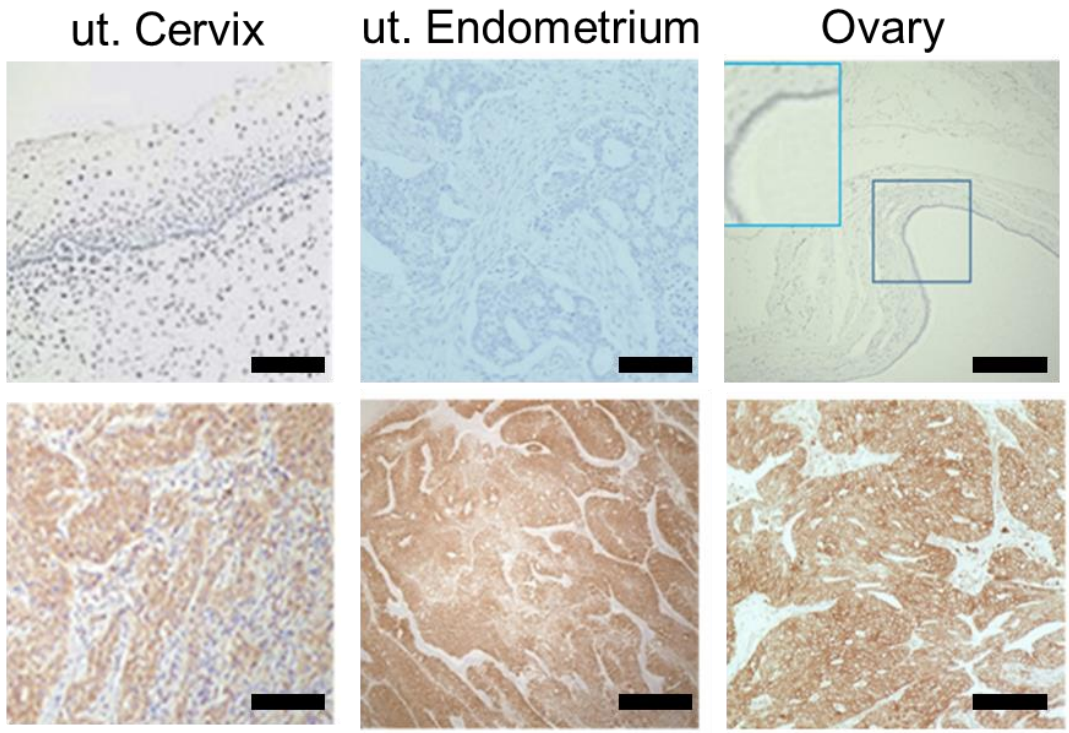




Peng, Hamanishi et al. *Cancer Res.* in press

New B7-Hx expression on gynecologic malignancies

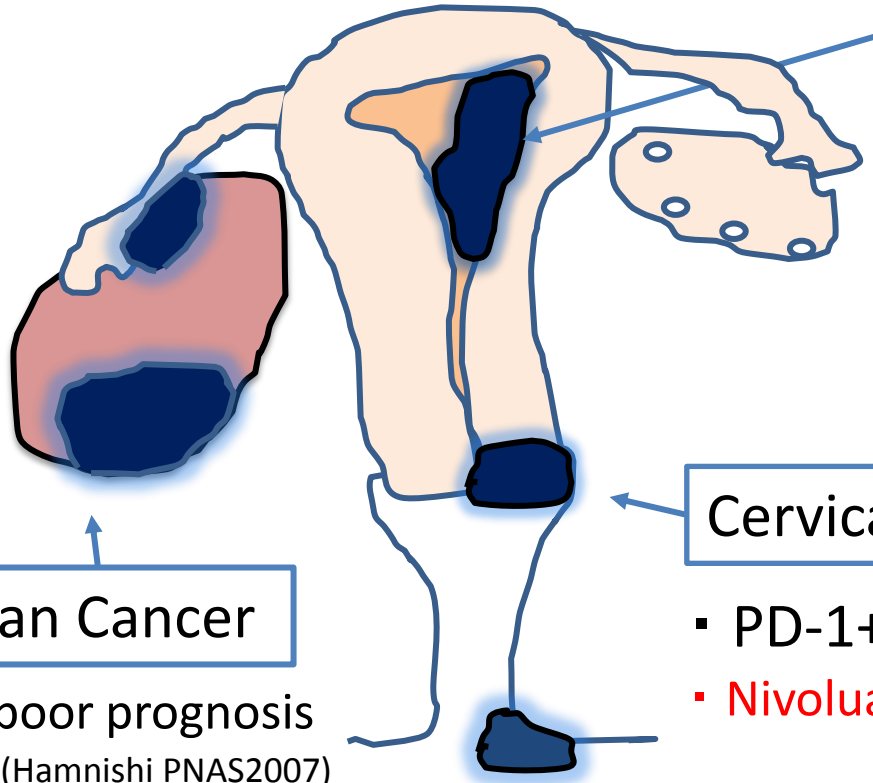




Murat, Hamanishi et al. *submitted*

Next target ?

PD-1 signal and Gynecologic Cancers



Endometrial Cancer

- PD-L1exp. (Vanderstraeten CCI 2014)
- MSI∝PD-L1exp.(Howitt ASCO 2015)
- Pembrolizumab (pII) (NCT02549209)

Cervical Cancer

- PD-1+TIL∝poor prognosis (Karim CCR 2009)
- Nivoluamb (pII) by NCI (NCT02257528)

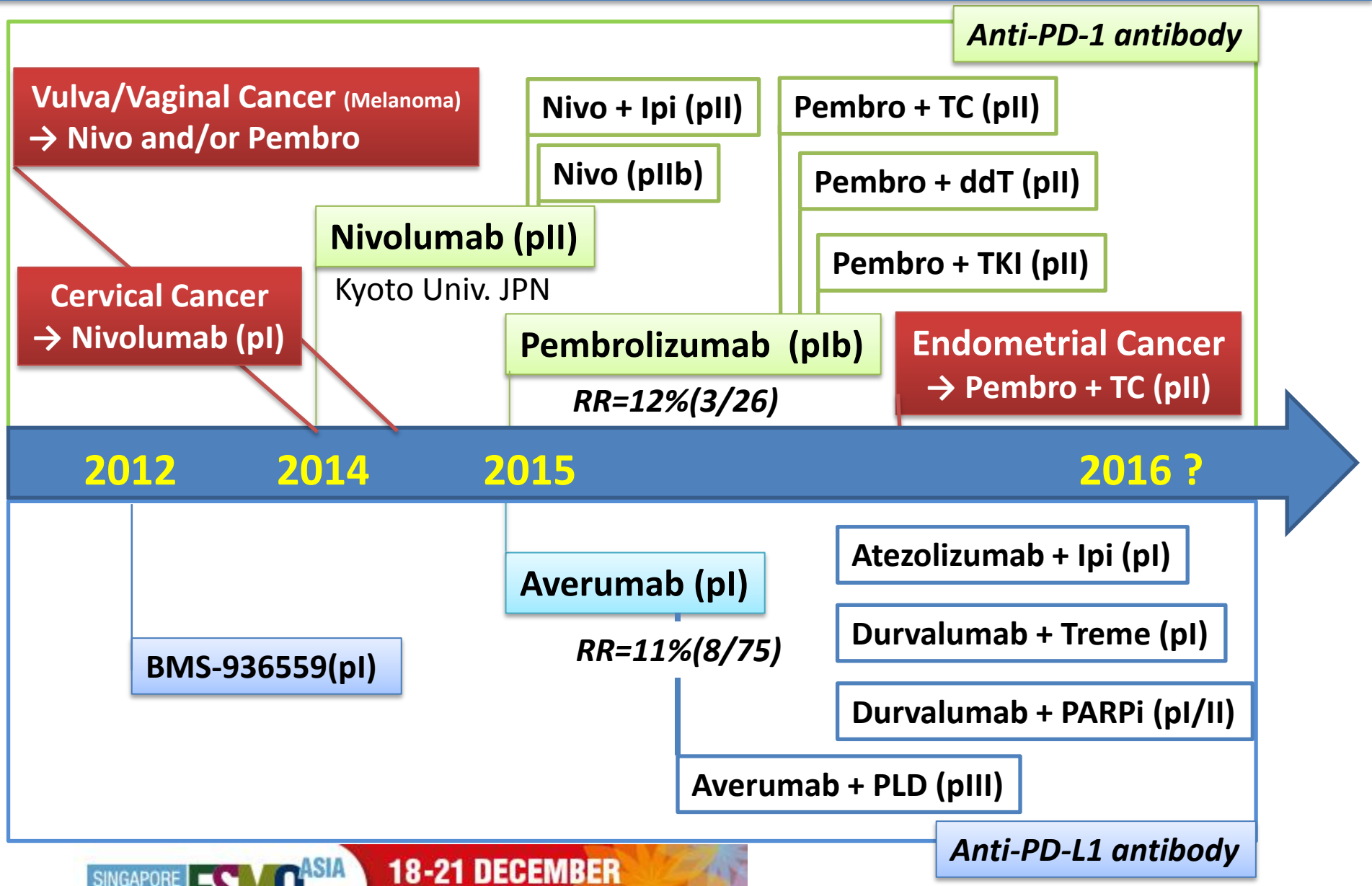
Ovarian Cancer

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

Vulval/Vaginal Cancer (melanoma)

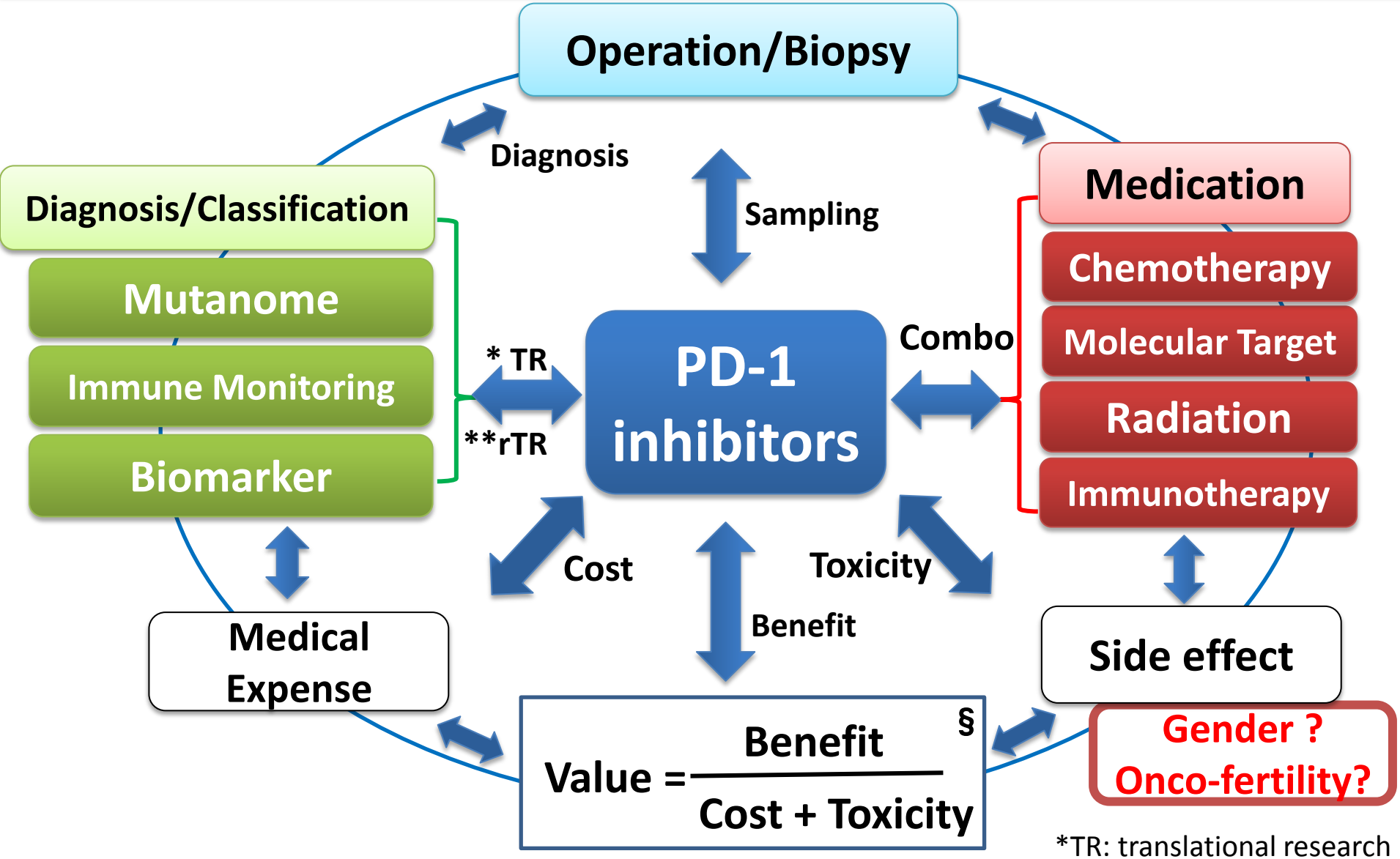
- Nivoluamb or Pembrolizumab

The view of PD-1 inhibitors for gynecologic cancer



Hamanishi et al. in submission

The role of PD-1 inhibitors



*TR: translational research

**rTR: reverse translational research

§ Saltz et al. ASCO2015
Hamanishi et al. in submission

Summary

- 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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