Cancer immunotherapy by PD-1 blockade

Smalley Keynote
SITC 2015

2015. 11. 6

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Kyoto University Graduate School of Medicine

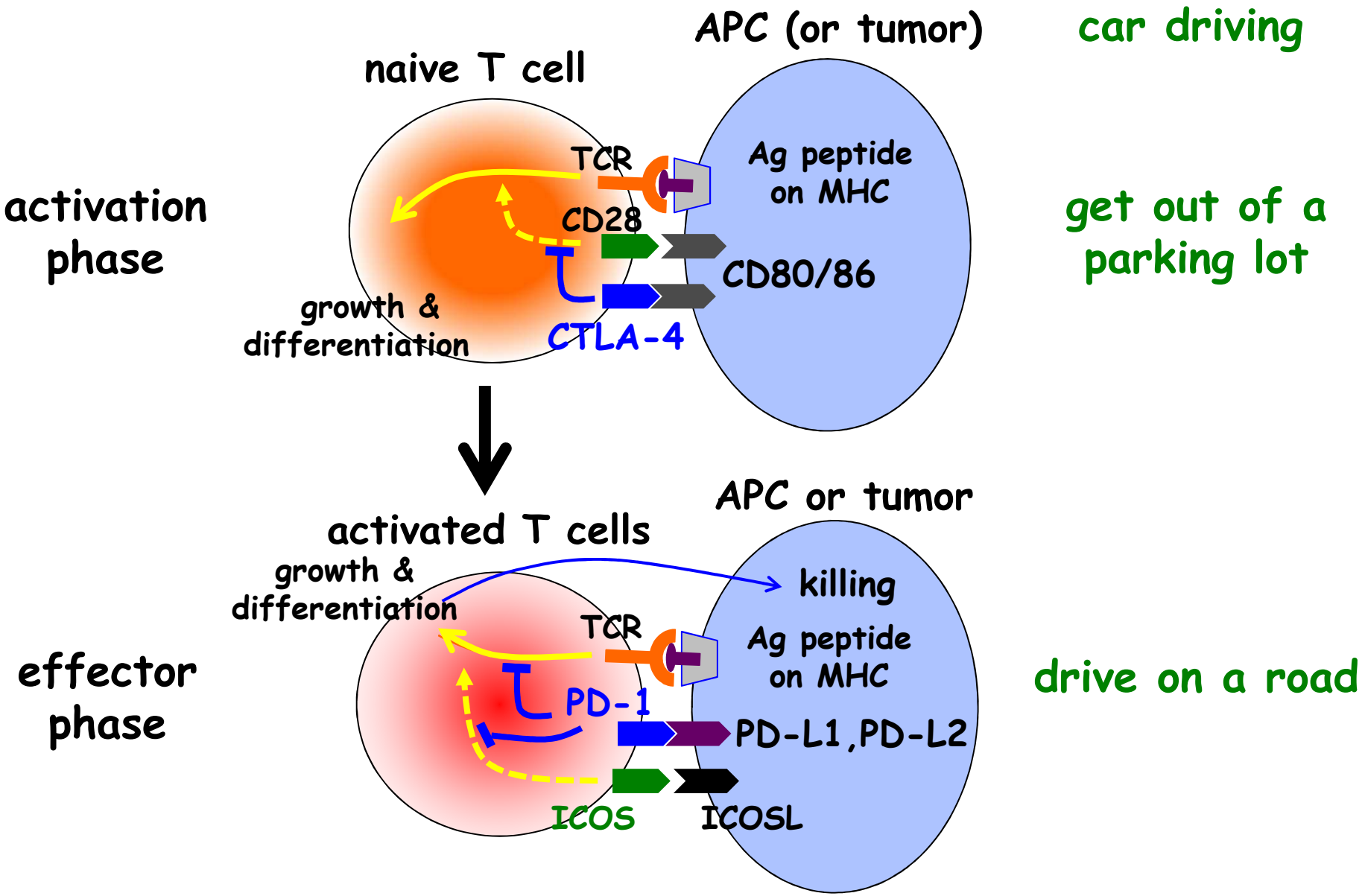
Cancer patients and death

	New patients	death
World (2012)	$14\times10^{6/y}$	8.2×10^{6}
Japan (2013)	$0.64\times10^{6/y}$ (3.00×10^{6})	0.36×10^{6}

Cancer Immunotherapy

1. cancer antigen vaccination
2. activation of immune cell *in vitro*
3. cytokine
4. blockade of negative immune regulators

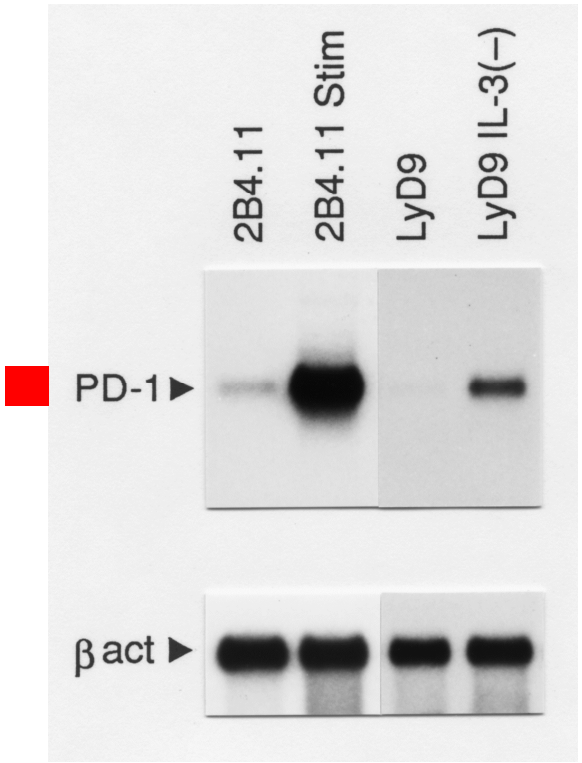
Two step regulation of immune cell activation

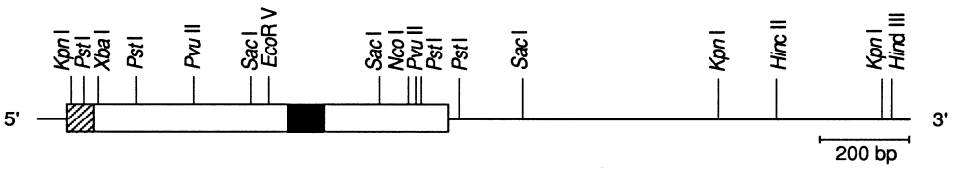


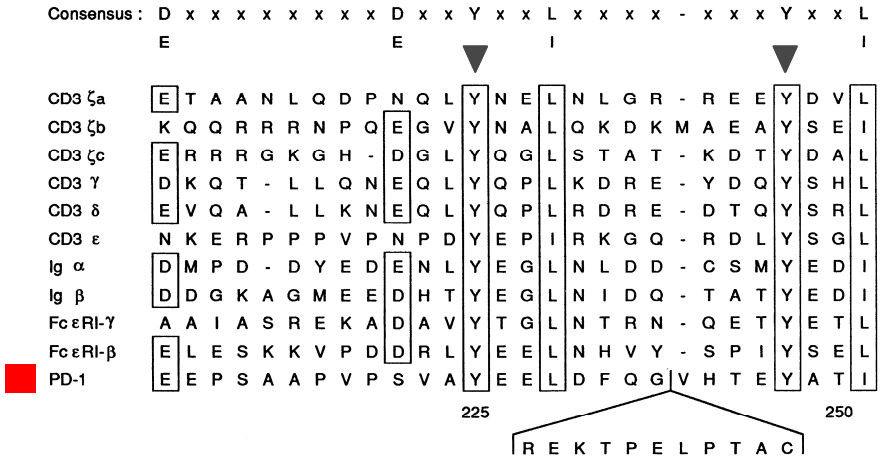
Discovery of PD-1 (programmed cell death-1) cDNA

Ishida, Y. et al. (1992). *EMBO J.* 11, 3887-3895.

cDNA substraction between apoptotic and normal cells

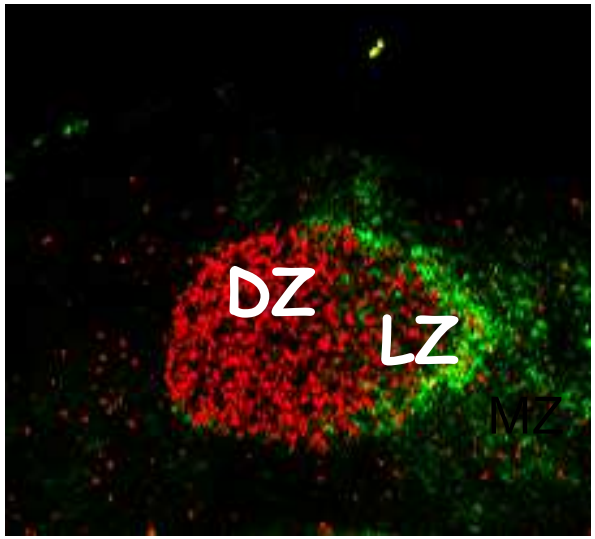




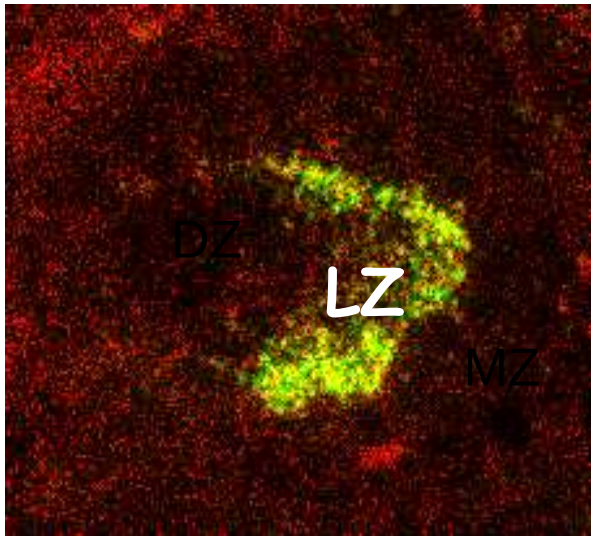


PD-1 is expressed on T cells and centrocytes in the light zone of GC in human tonsil

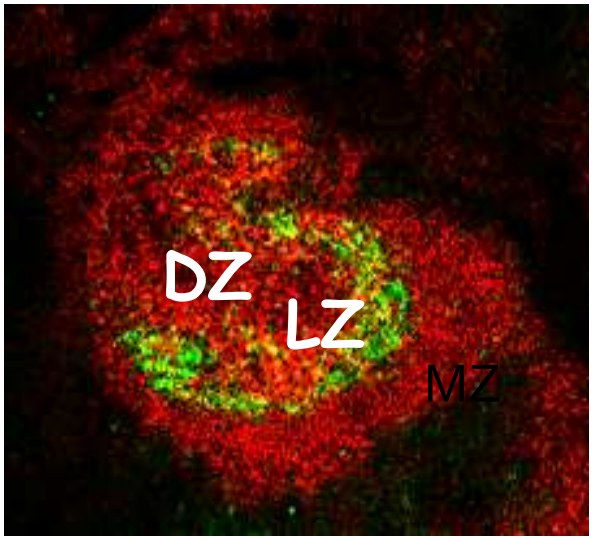
PD-1 / Ki67



PD-1 / CD3



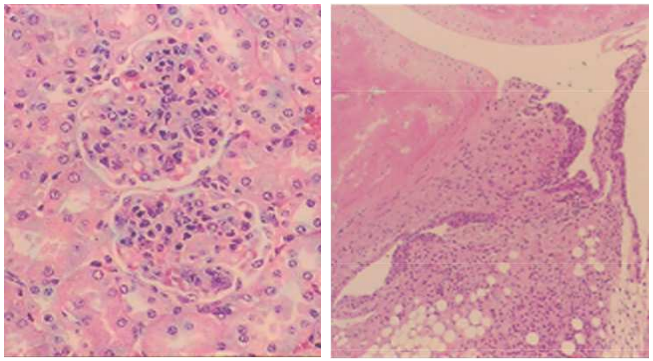
PD-1 / CD20



PD-1 is required for self-tolerance

Nephritis Arthritis

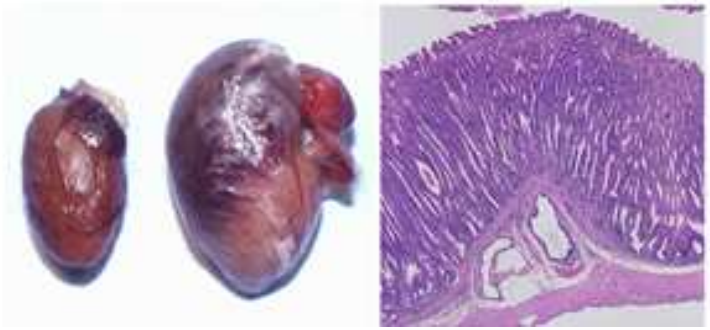
C57BL/6
PD-1KO



Nishimura H et al, Immunity (1999)

Dilated cardiomyopathy Gastritis

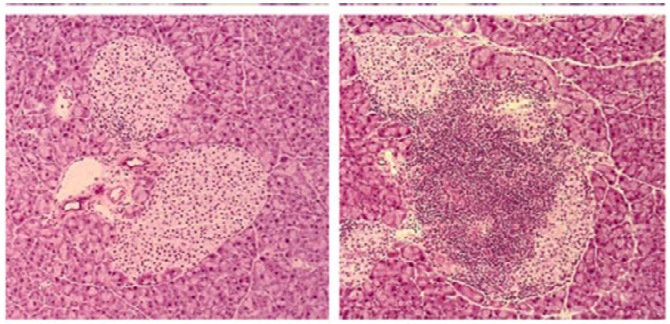
BALB/c
PD-1KO



Nishimura H et al, Science (2001)

WT PD-1 KO

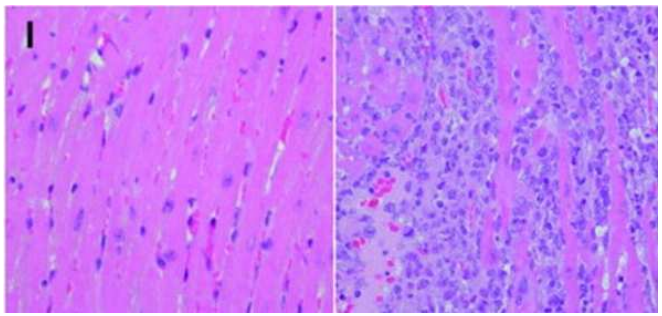
NOD
Diabetes



Wang J et al, PNAS (2005)

WT PD-1 KO

MRL
Myocarditis



Wang J et al, Int Immunol (2010)

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.

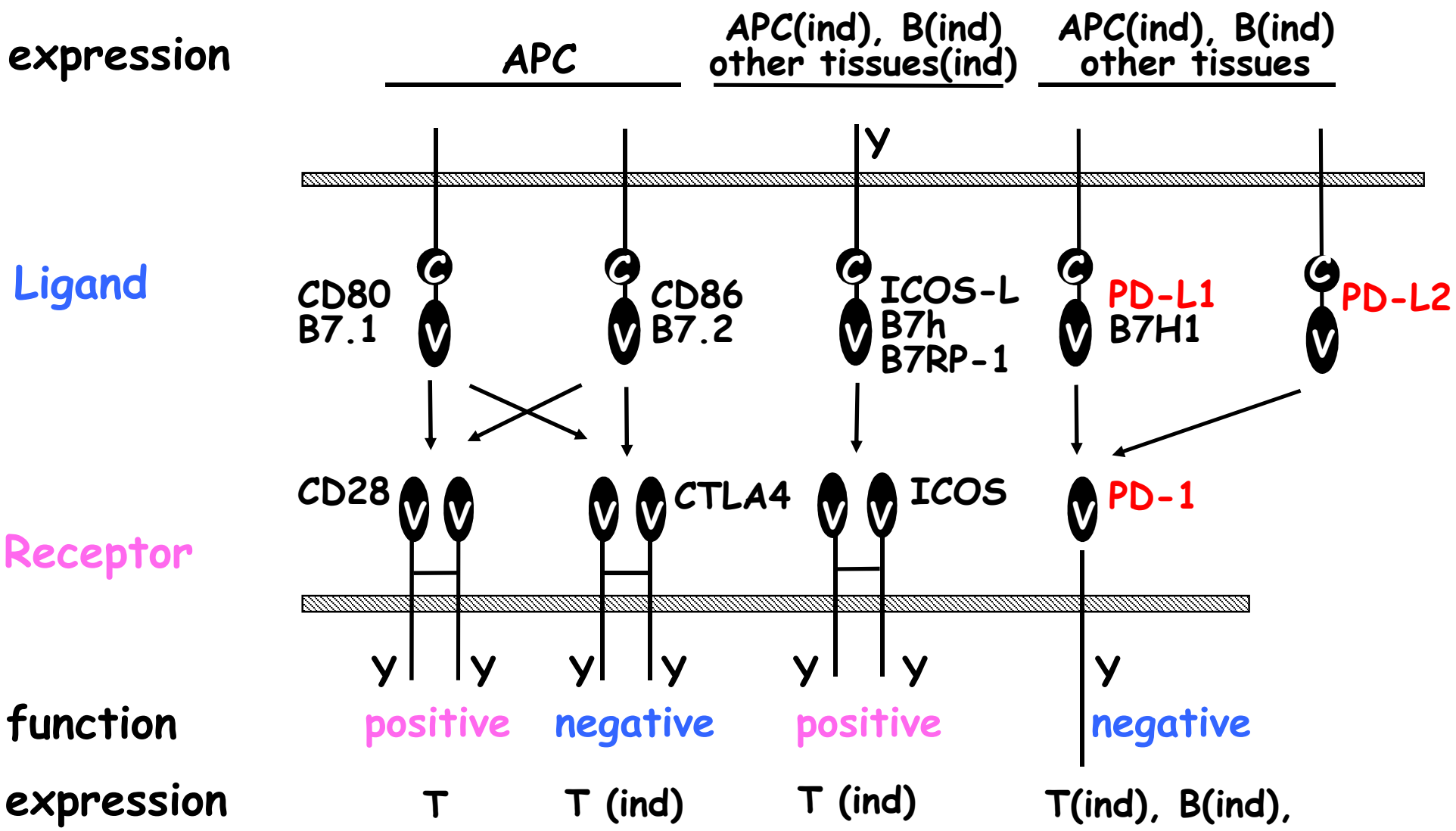
- **Clive Wood (GI) obtained several B7 related cDNA with unknown function from Gordan Freeman. One of them turned out to be PD-L1.**

  Freeman, G. J., Long, A. J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., Fitz, L. J., Malenkovich, N., Okazaki, T., Byrne, M. C., Horton, H. F., Fouser, L., Carter, L., Ling, V., Bowman, M. R., Carreno, B. M., Collins, M., Wood, C. R. and Honjo J. Exp. Med. 192 1027-1034 (2000)

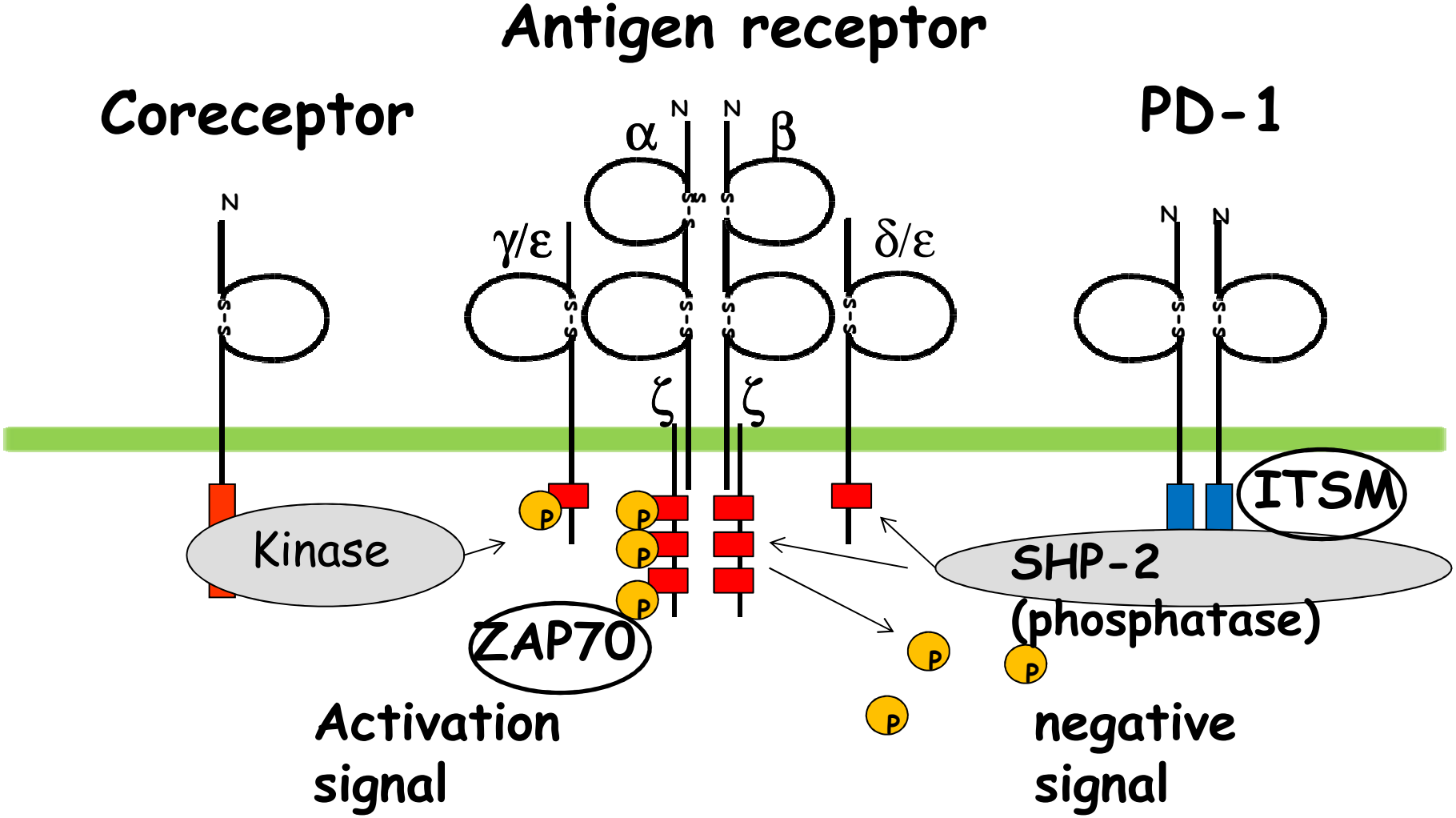
  Then, similarly PD-L2

  Latchman, Y., Wood, C. R., Chernova, T., Chaudhary, D., Borde, M., Chernova, I., Iwai, Y., Long, A. J., Brown, J. A., Nunes, R., Greenfield, E. A., Bourque, K., Boussiotis, V. A., Carter, L. L., Carreno, B. M., Malenkovich, N., Nishimura, H., Okazaki, T., Honjo, T., Sharpe, A. H. and Freeman, G. J. Nature Immunol. 2 261-268 (2001)

Positive and negative regulators of immune response



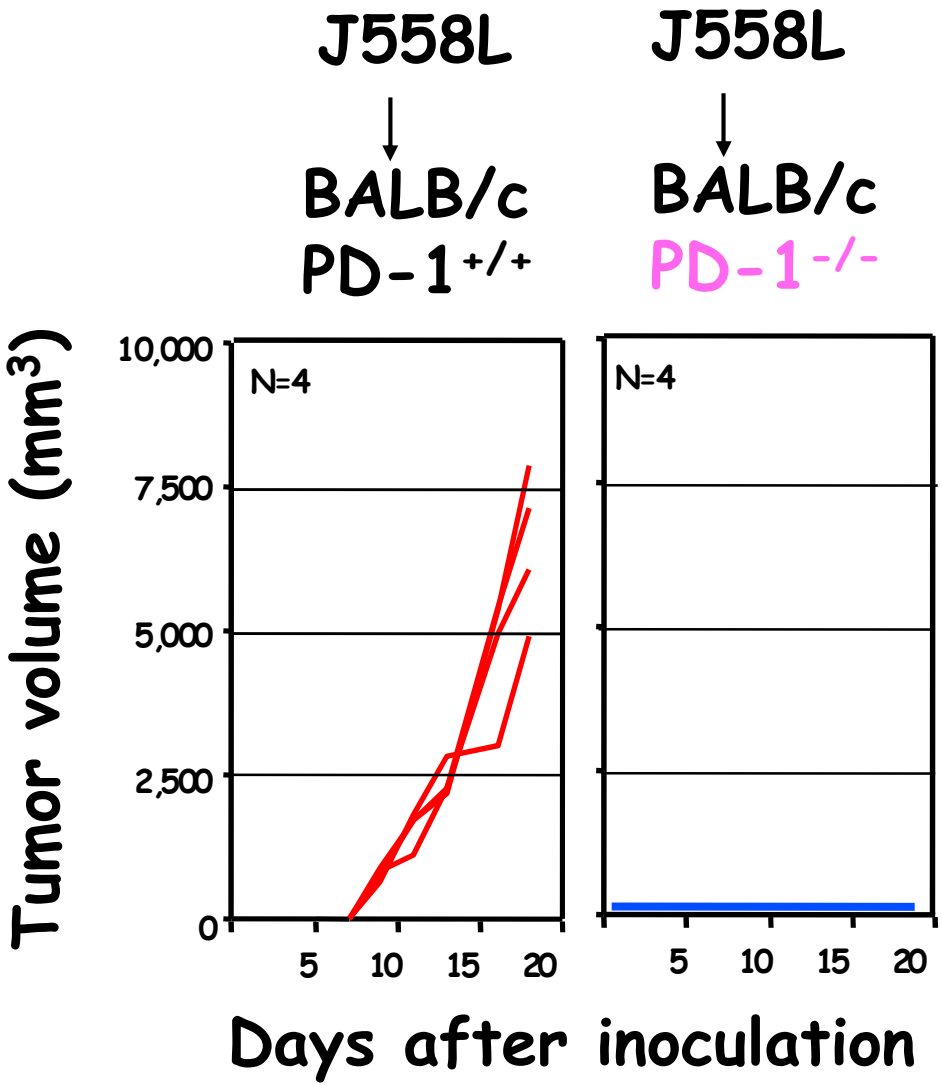
Molecular mechanism of immune inhibition by PD-1



Okazaki et al. PNAS (2001)

Inhibition of tumorigenesis of J558L in PD-1$^{-/-}$ mice

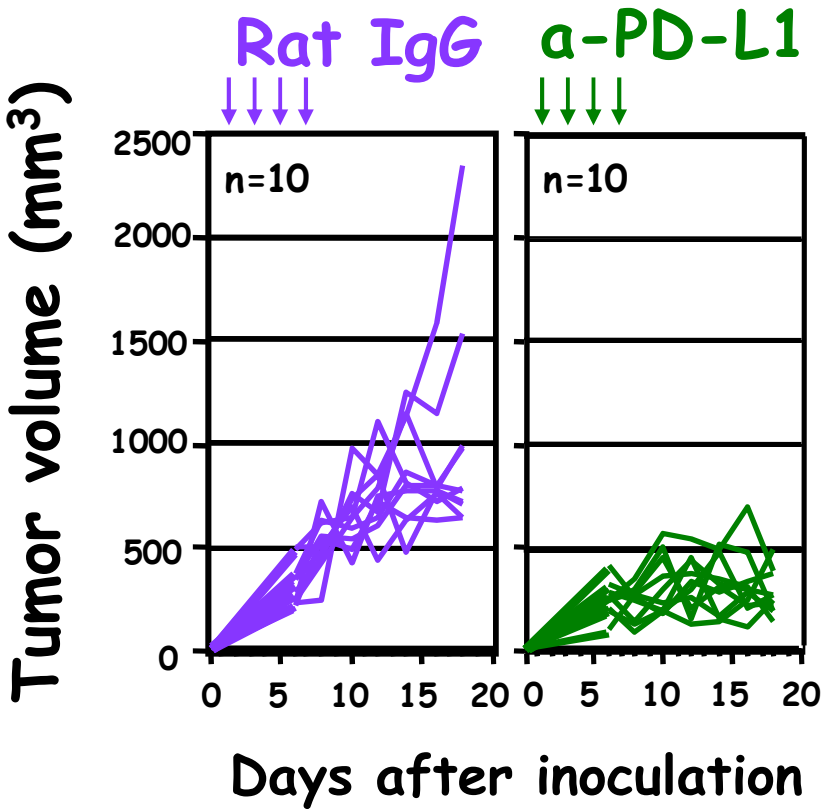
Iwai et al. PNAS 2002

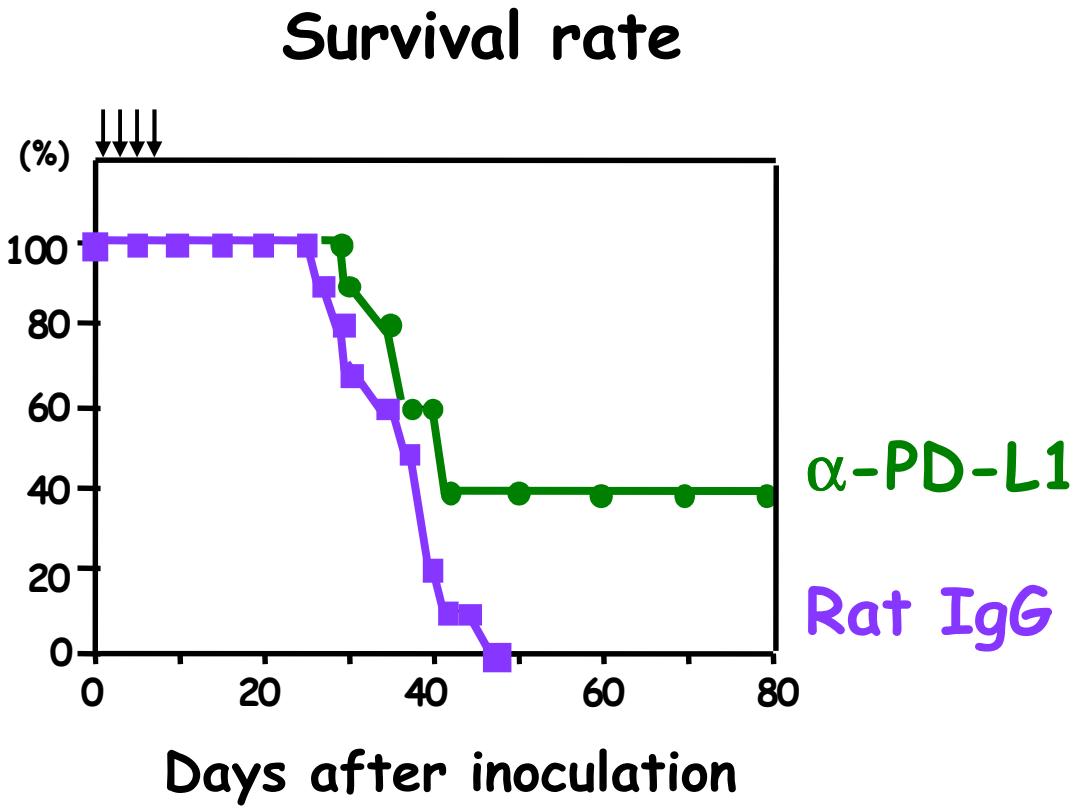


Inhibition of tumorigenesis of P815/PD-L1 by anti-PD-L1

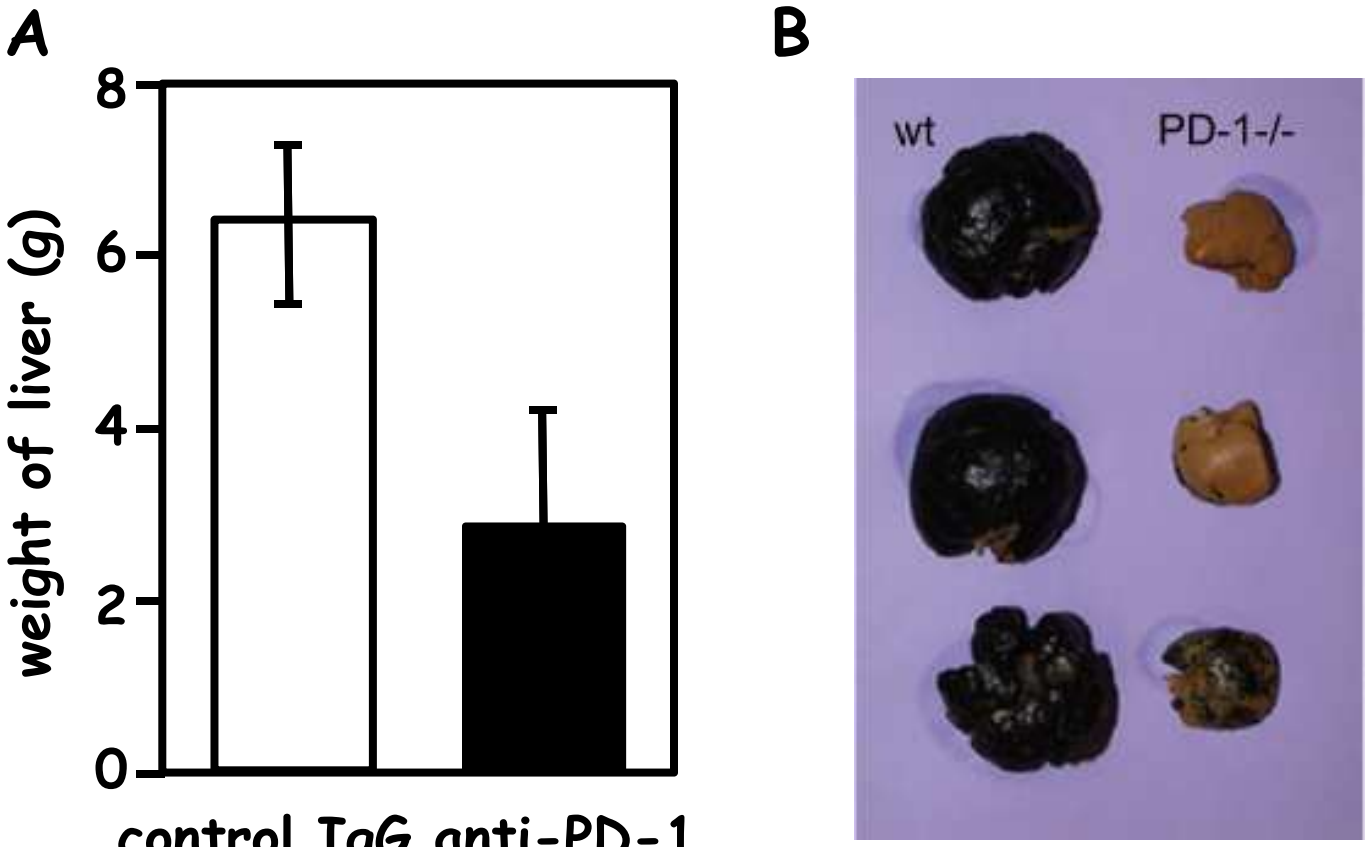
Iwai et al. PNAS 2002

P815/PD-L1→ DBA/2





PD-1 blockade inhibits metastasis of melanoma (mouse model)



Iwai et al. Int. Immunol. (2005)

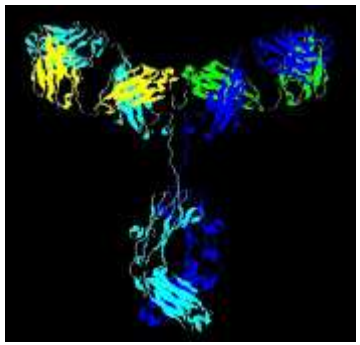
Humanized anti-PD-1 antibody

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



一般的な抗体の構造
（イメージ図）

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:

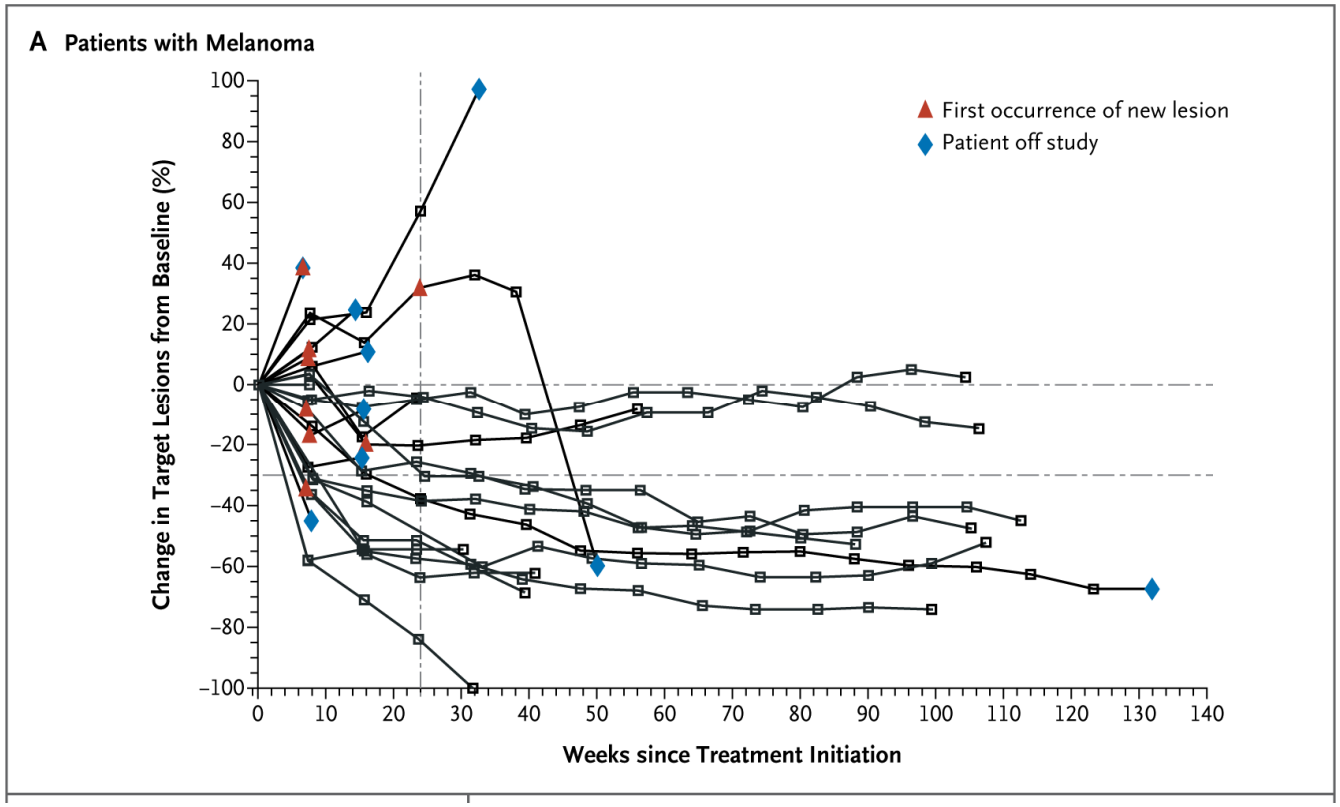
18% (14 of 76 patients) among NSCLC,
28% (26 of 94 patients)among Melanoma
27% (9 of 33 patients) among RCC

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

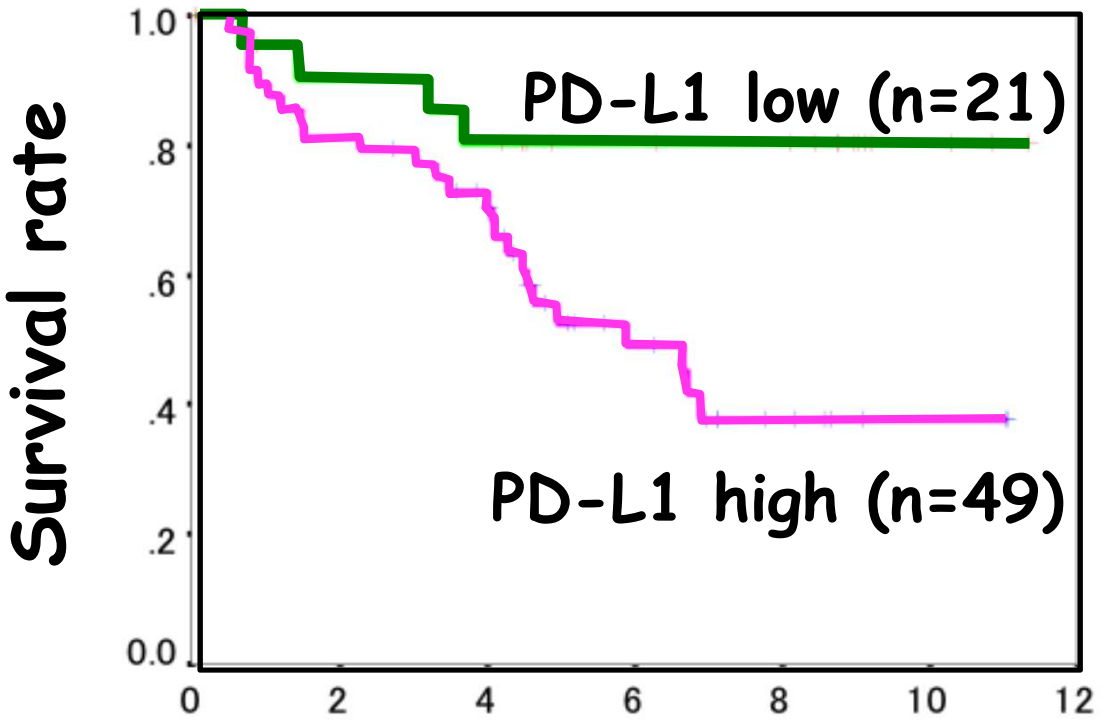
Junzo Hamanishi, MD, PhD
Kyoto University, Japan

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



P=0.0164

Hamanishi et al. PNAS (2006)

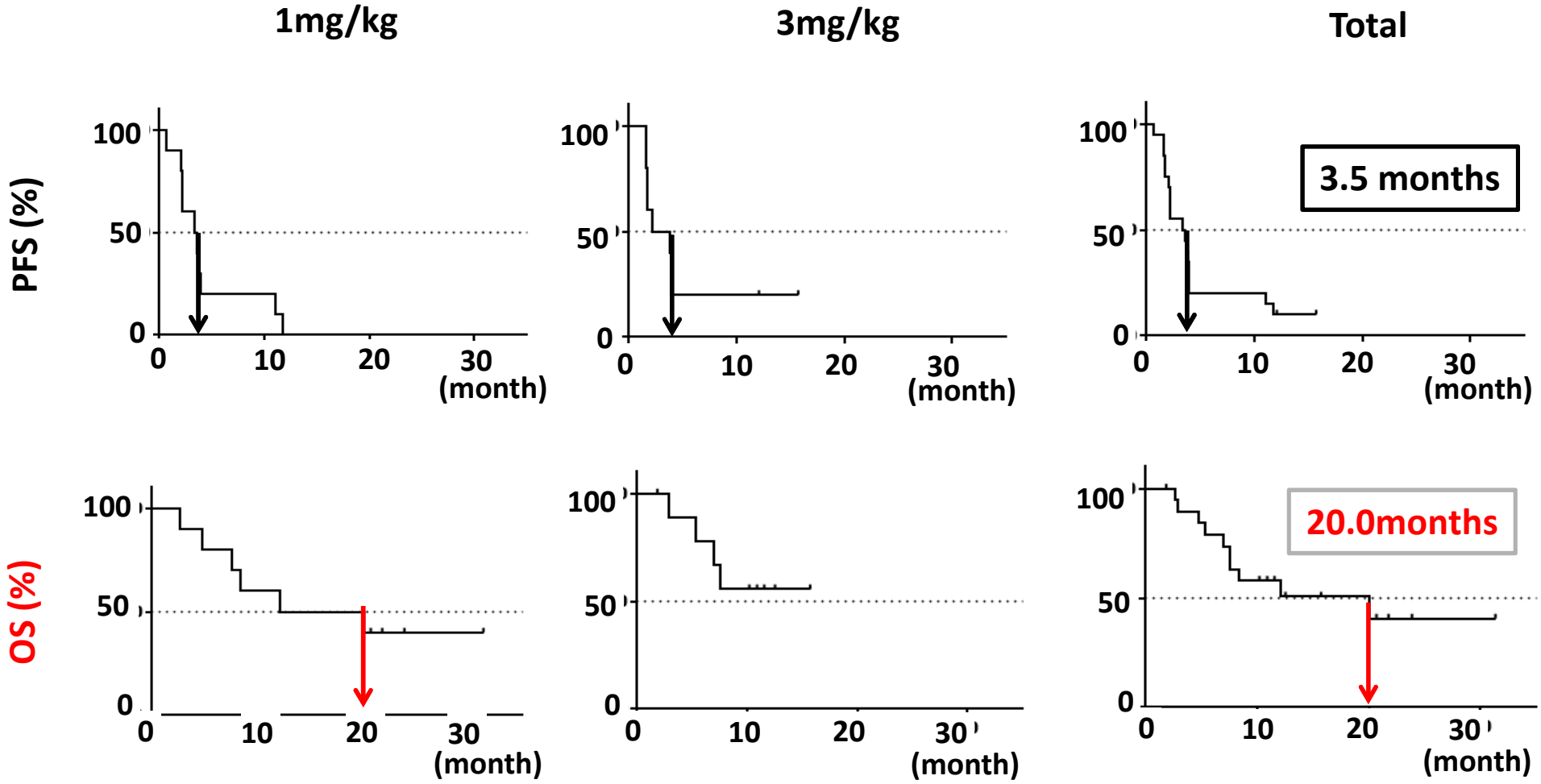
Clinical Effect : Best Overall Response

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)

Survival Analyses



Conventional Chemo: PFS=3.5M, OS=12M

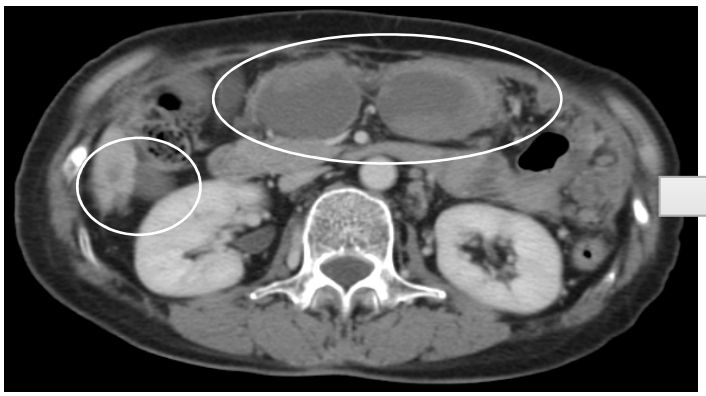
(Hamanishi et al. *JCO.* 2015)

Overall survival prolonged to 20.0 months

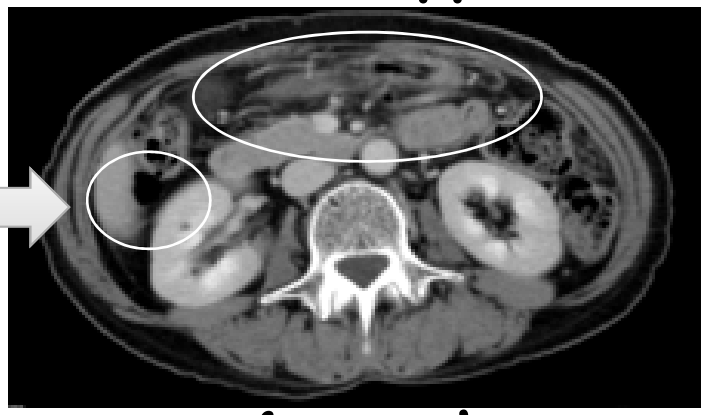
A Responder with Ovarian Cancer (clear cell):Nivolumab 3mg/kg

History: 60 yr. Stage Ic with progressive disease after RSO, MMC/CPT11*3, SCH+BSO, CPT/CDDP*5, TC*2

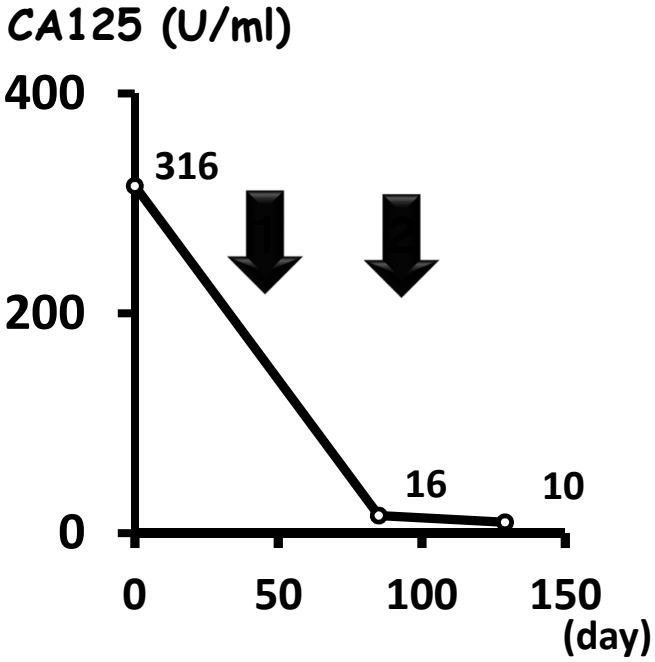
Peritoneal dissemination ⇒ disappeared



Baseline

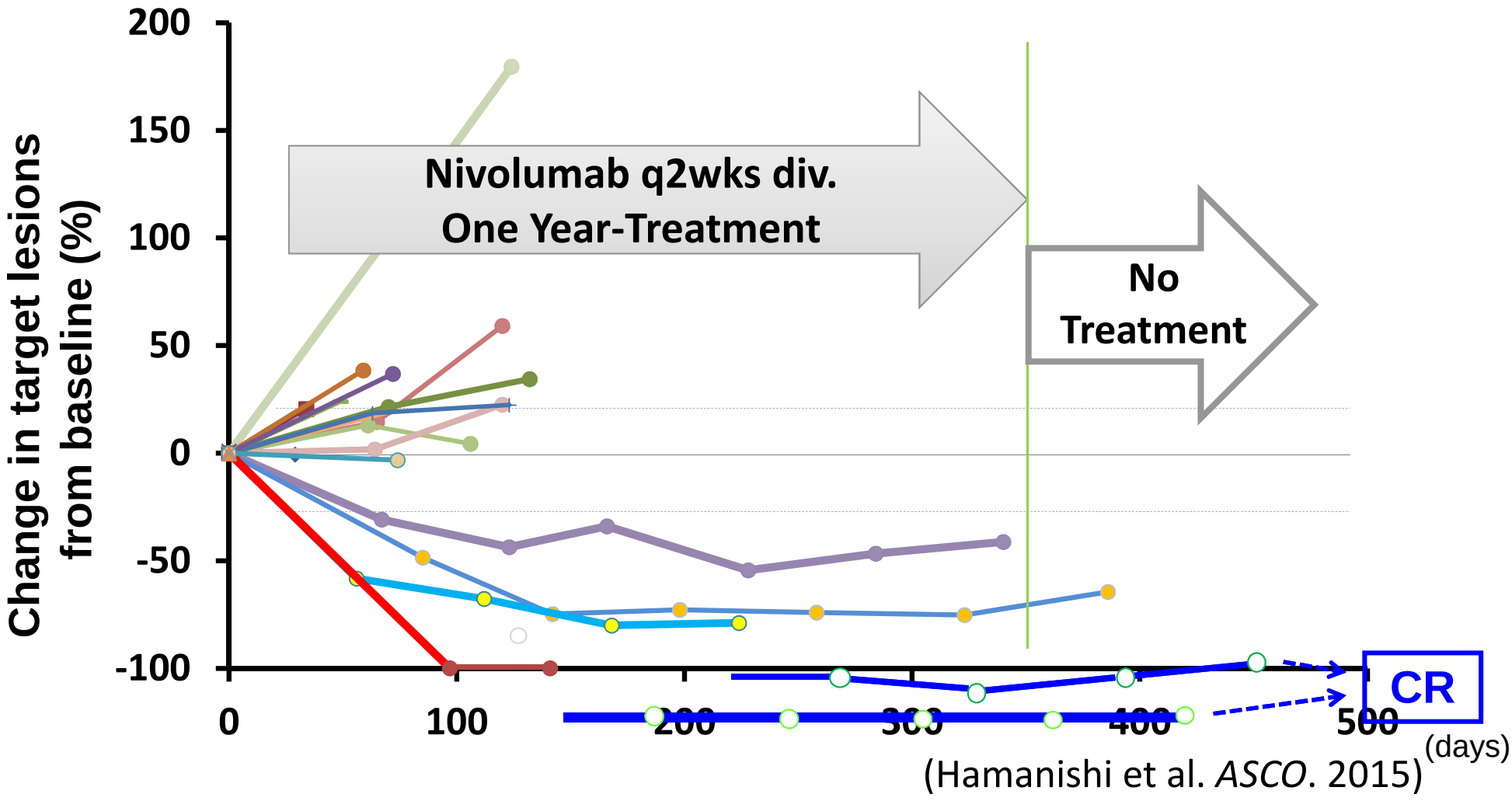


4 months



Hamanishi et al. J Clin Oncol. 2015

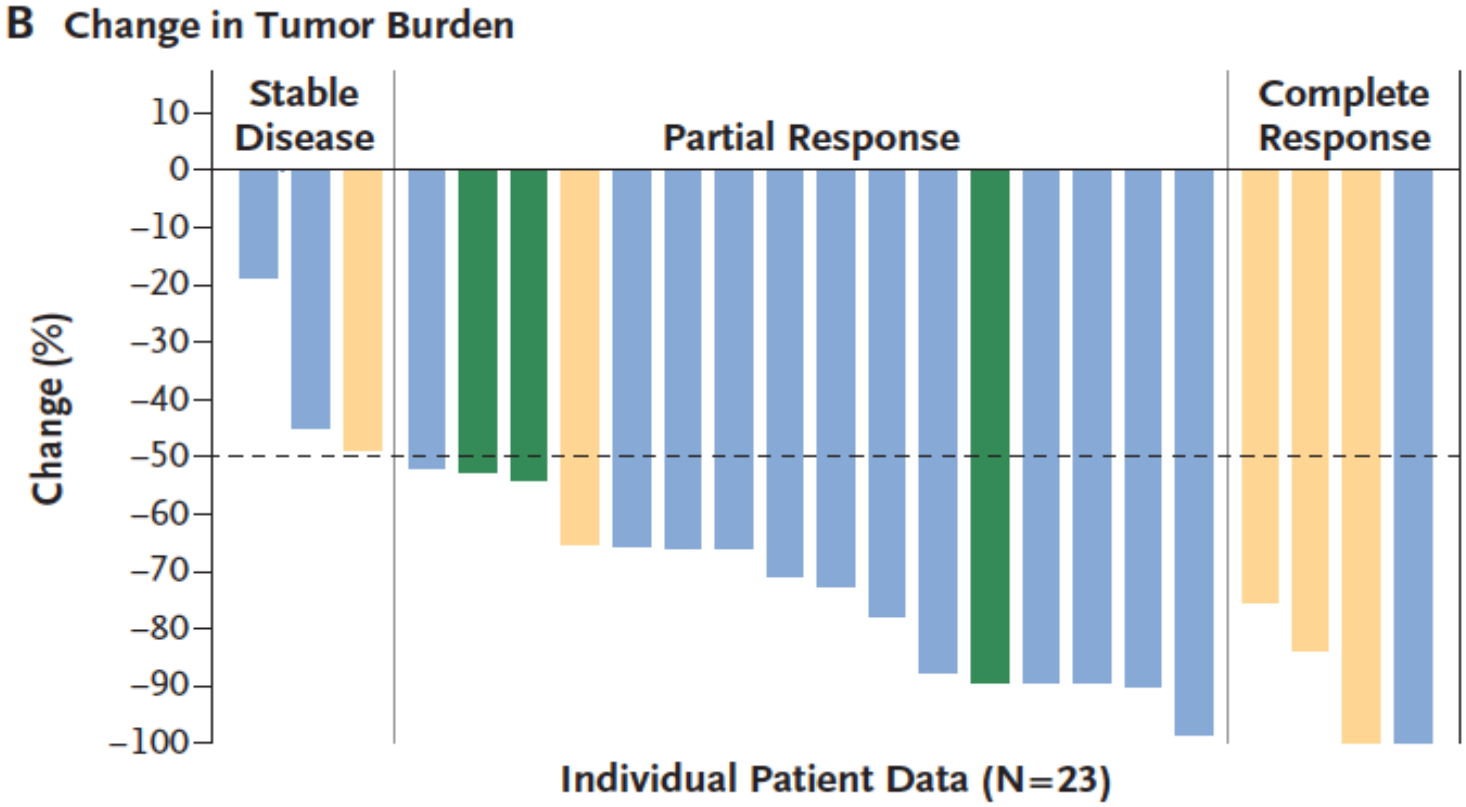
Follow-up Study (on going)



(Hamanishi et al. *ASCO*. 2015)

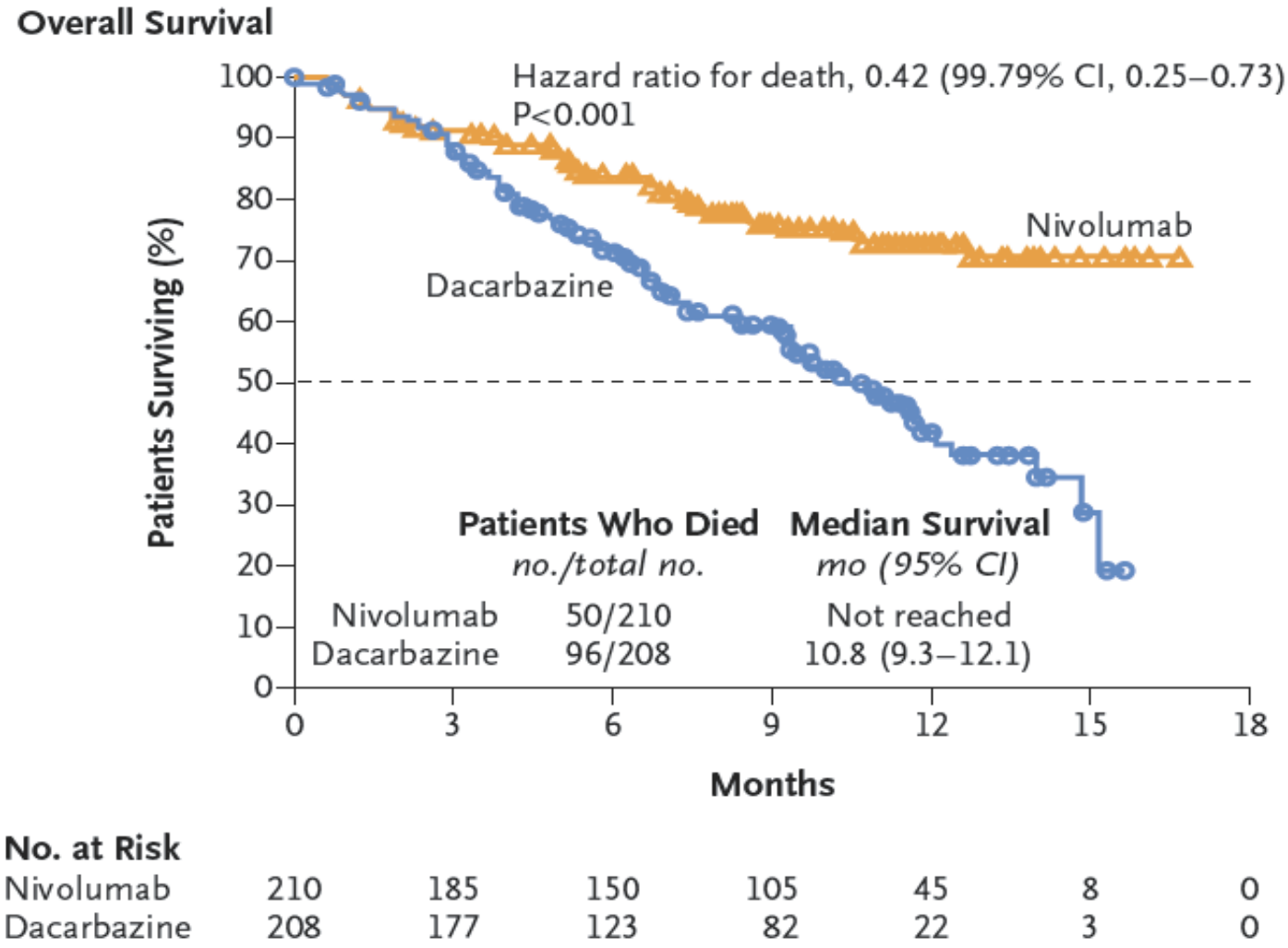
Durable response without treatment

Response Changes in Tumor Burden in Patients with Hodgkin's Lymphoma Receiving Nivolumab



Ansell SM et al. N Engl J Med 2014. December 6

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

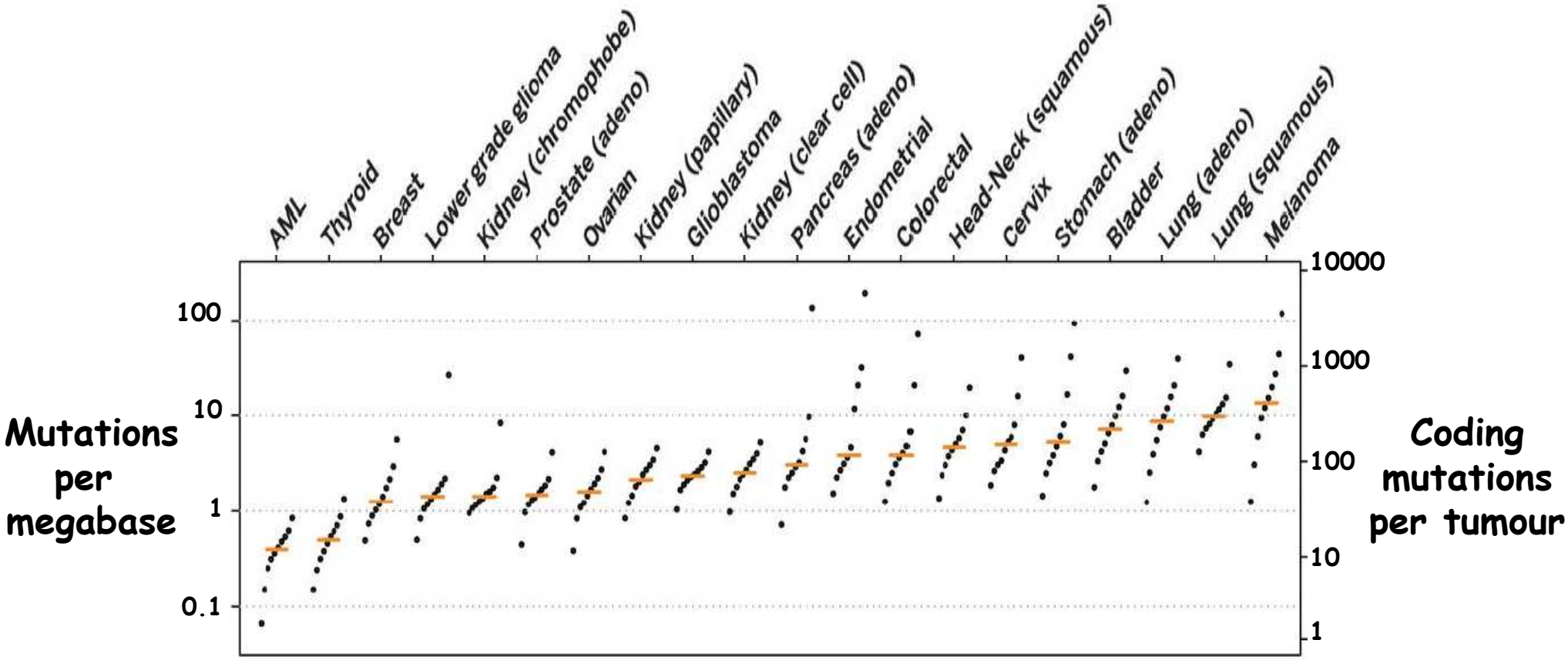


Robert C et al. N Engl J Med 2014. November 16

Why does anti PD-1 work?

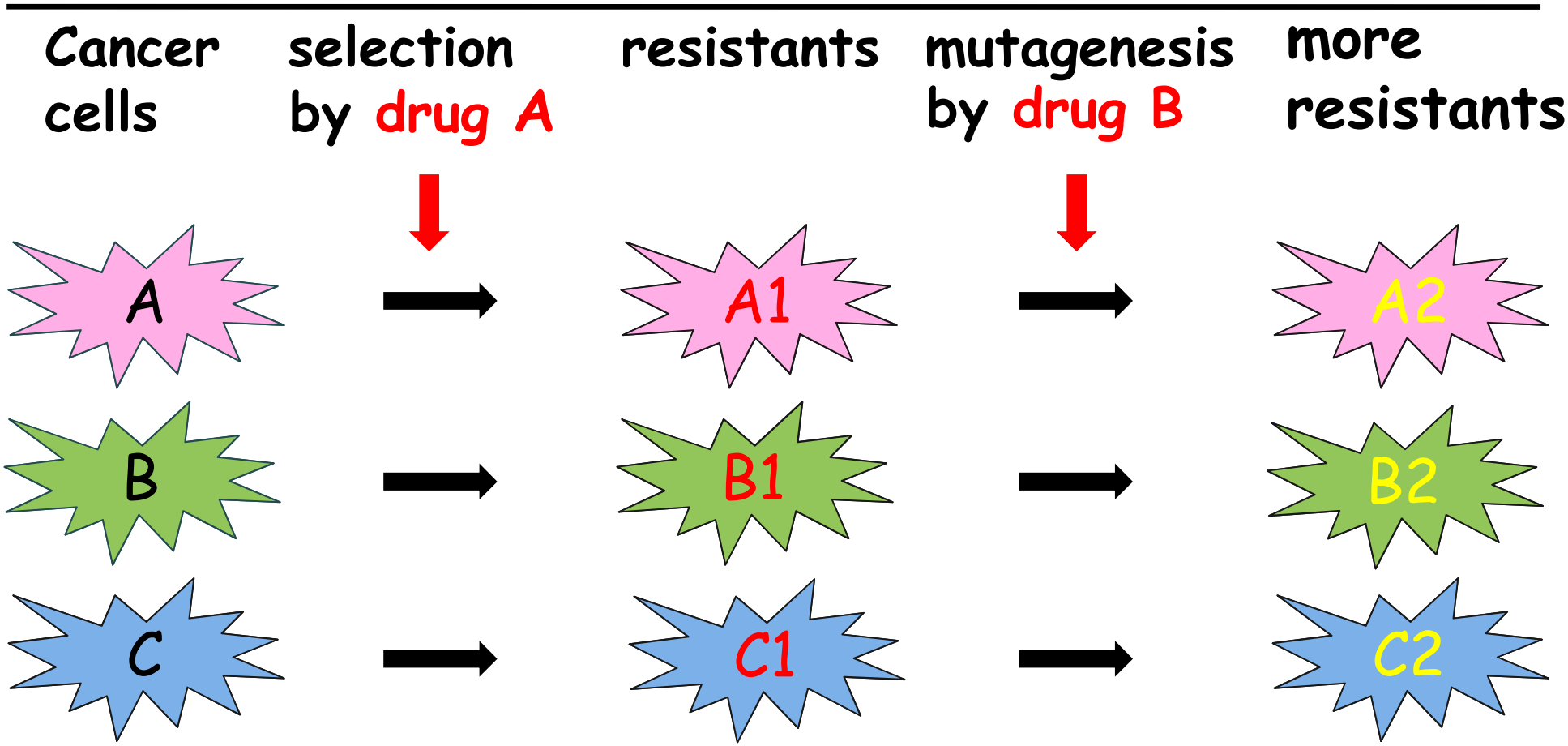
- Tumor cells continuously mutate and produce non-self antigens.
  A large immune repertoire can recognize and attack almost all cancer antigens.
- In most cases the immune surveillance can eliminate tumor cells.
  However, tumor cells may induce immune tolerance and grow.
- Anti-PD-1 breaks immune tolerance.

Cancer cells accumulate mutations



Iñigo M. et al. Science 2015

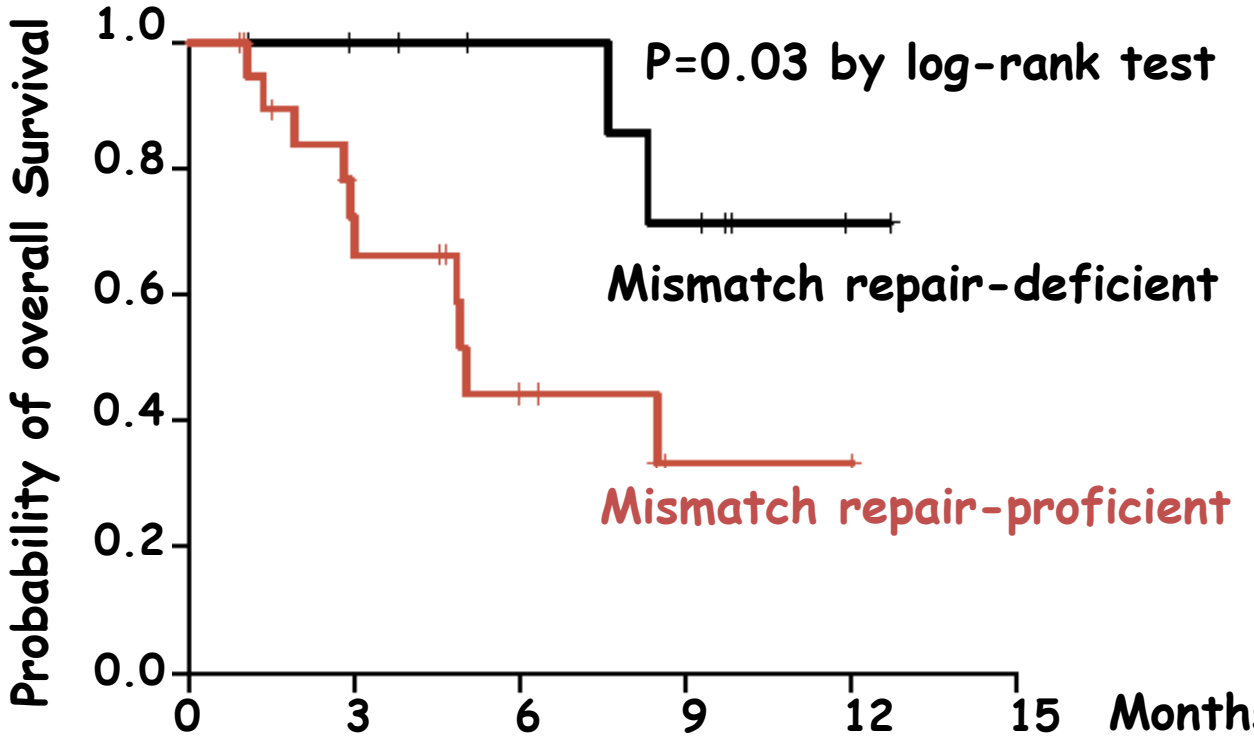
The reason why immunotherapy but not chemotherapy has durable effects



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



No. at Risk						
Mismatch repair-deficient	11	9	7	5	1	0
Mismatch repair-proficient	21	12	5	1	1	0

Le, D et al. NEJM May 30,2015

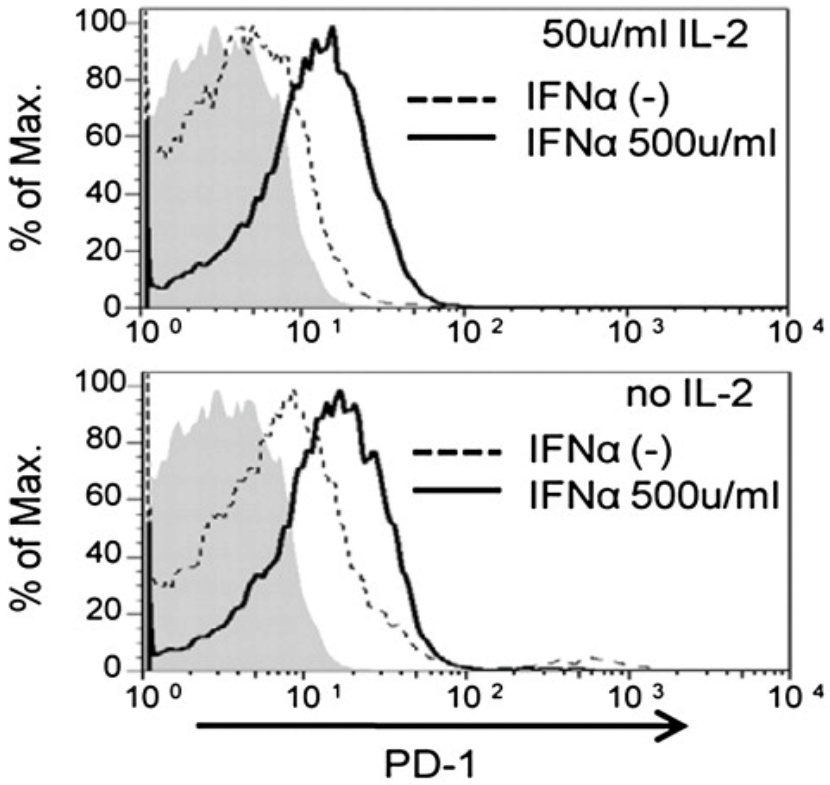
What is the mechanism for the immune tolerance by tumors?

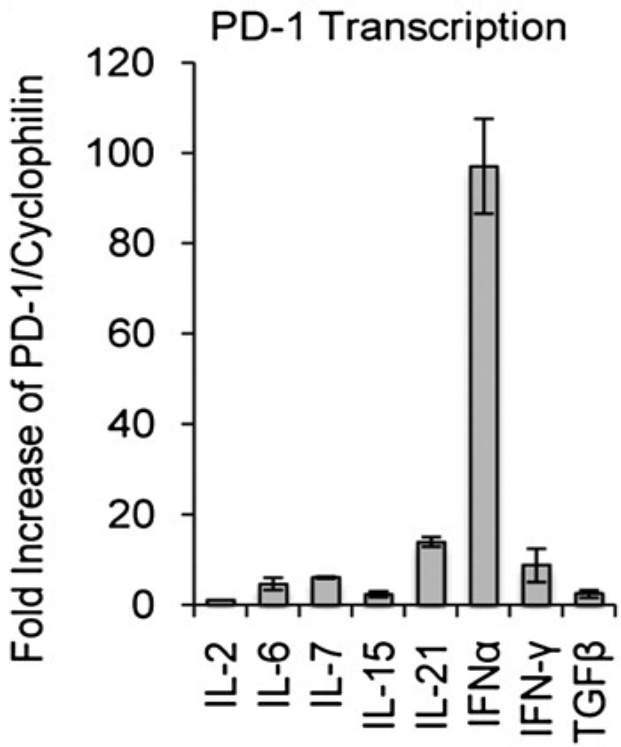
1) PD-L1/2 expression on tumors
   - many tumors express PD-L1/2
   - However, no clear association between tumor PD-L1/2 expression and efficacy of anti PD-1 treatment

2) Tumor inflammation can induce PD-1 expression on lymphocytes
   - IFNa stimulates and prolongs PD-1 expression on T cells and PD-L1 on tumor cells (Terawaki et al J. I. 2011).

3) Other unknown mechanisms
   negative coreceptors, inhibitory cytokines/chemokines

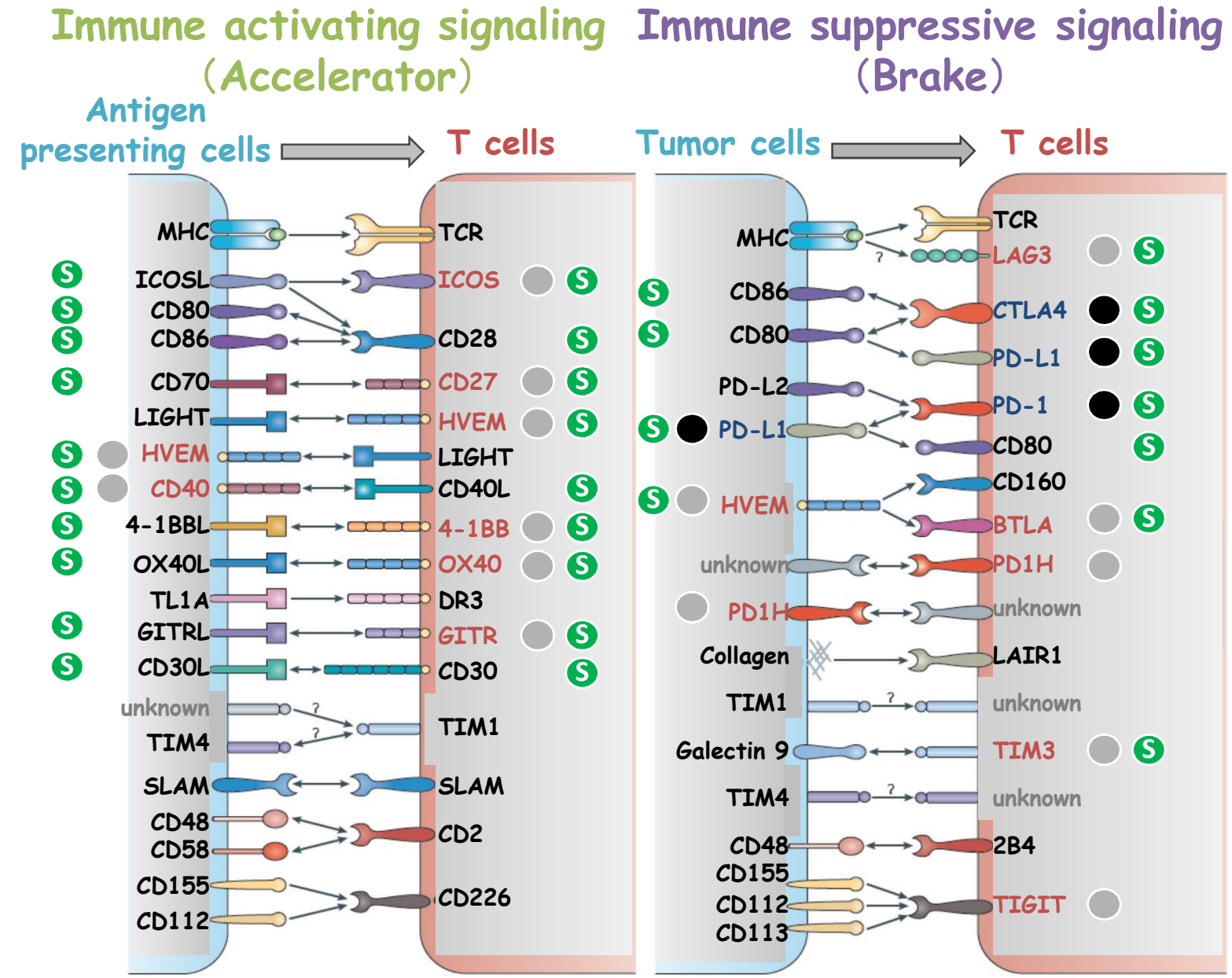
IFNa induces PD-1 on Do11.10 T cells





Terawaki et al. J. Immunol. (2011)

Candidates of soluble biomarker for cancer immunotherapy



Antibody drugs

- Approved
- Under development or clinical trial

S Molecules that can be soluble form

Based on Nat Rev Immunology 13, 227-242 (2013)

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 .

Acknowledgements

Research group

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Hamanishi et al. J Clin Oncol. 2015

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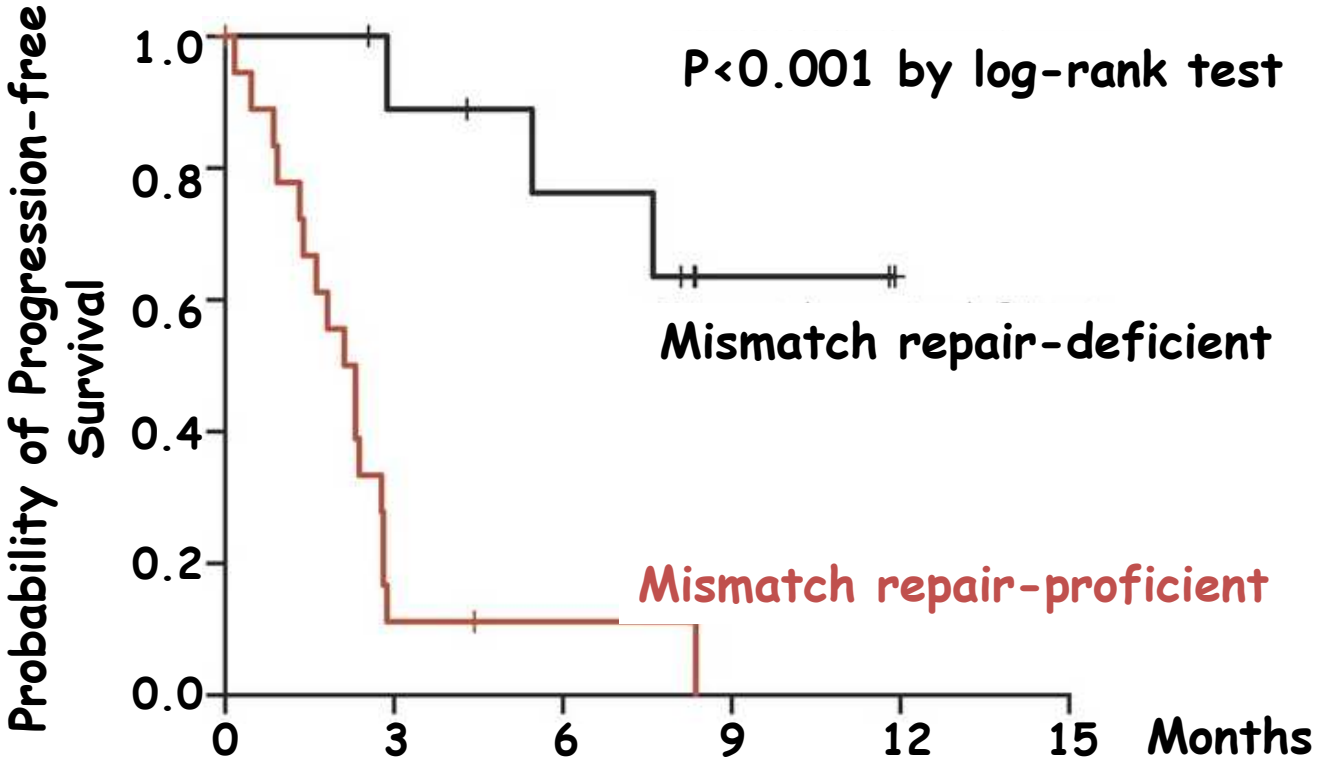
Colon cancers with mutation-prone genetic alterations respond better to PD-1 antibody

Phase 2 study with 41 patients with progressive metastatic carcinoma



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Le, D et al. NEJM May 30,2015