CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON

Inserm
Institut national
de la santé et de la recherche médicale

Centre Léon Bérard

Cours du Groupe d'Oncologie de la
Société de Pneumologie de Langue Francaise
(GOLF)

20 Septembre 2016

Immunothérapie en Cancérologie: checkpoints immunologiques et voies de recherche

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Team N°11 « Therapeutic targeting of tumor cells and their immune environment »
Christophe Caux DR Inserm

CONTRE LE CANCER LA LIGUE 101 comités

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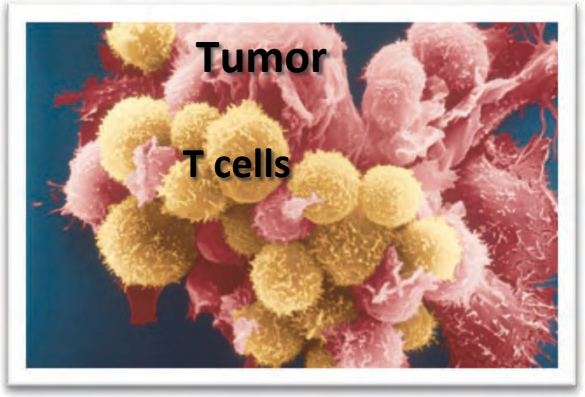
INSTITUT NATIONAL DU CANCER

The Breast Cancer Research Foundation

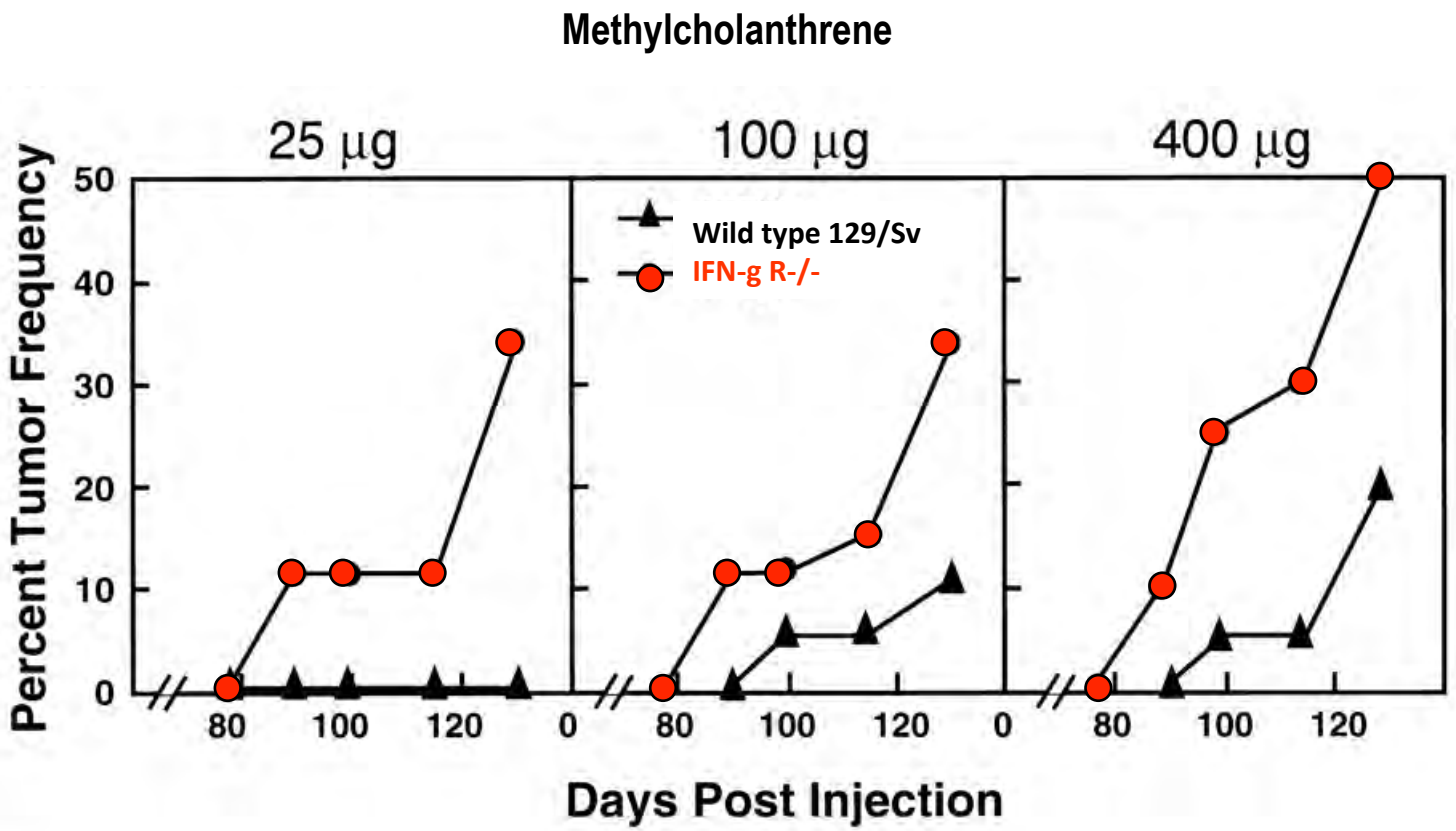
Association pour la Recherche sur le Cancer

Immuno-surveillance and escape mechanisms

- **Evidences of tumor immuno-surveillance**
- The immune system as a barrier to tumor formation and progression
- Cancer cells: How they avoid immune surveillance and destruction
- Immune Checkpoints



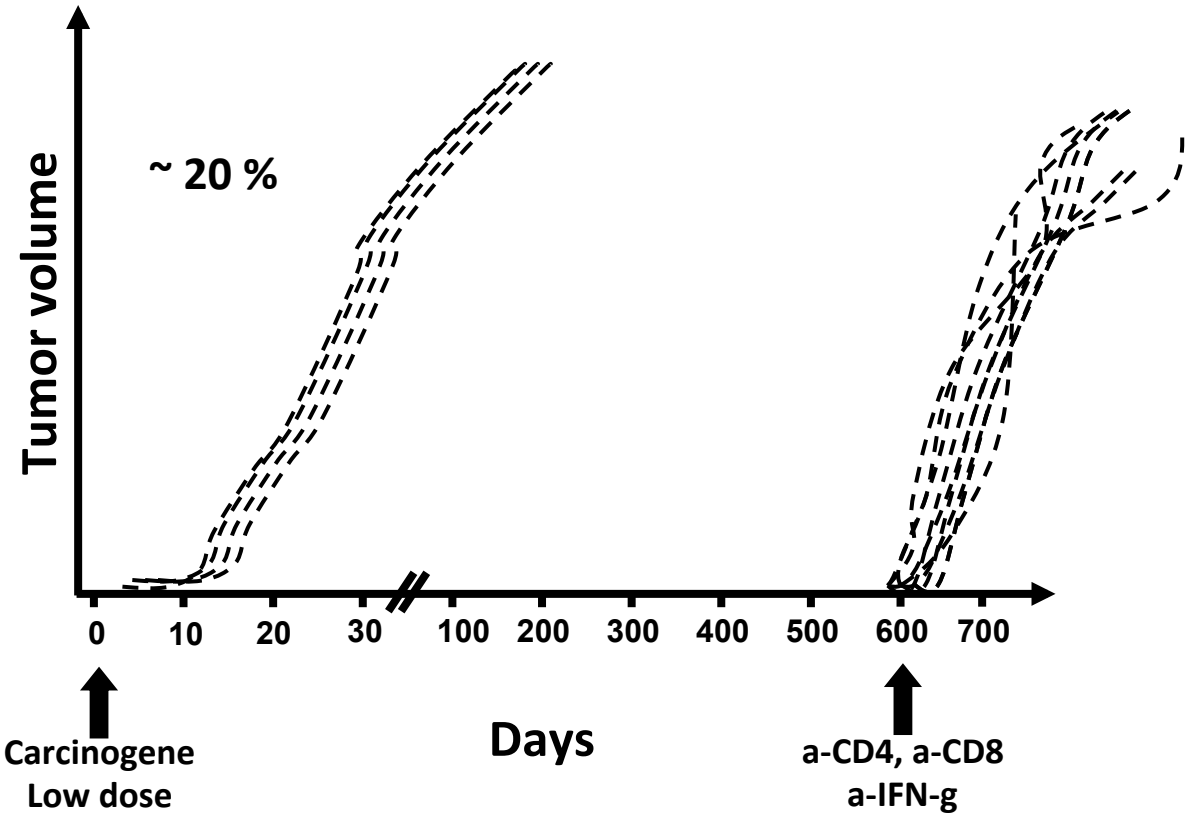
Evidences of Tumor Immuno-Surveillance in Immunocompetent Mice: Example of IFNg[1]



Methylcholanthrene-induced tumors in IFN-g R K.O.mice.[1]

1. Kaplan DH et al. *PNAS.* 1998; 95:7556-7560

Evidences of Tumor Immuno-Surveillance in Immunocompetent Mice: Role of T cells[1]



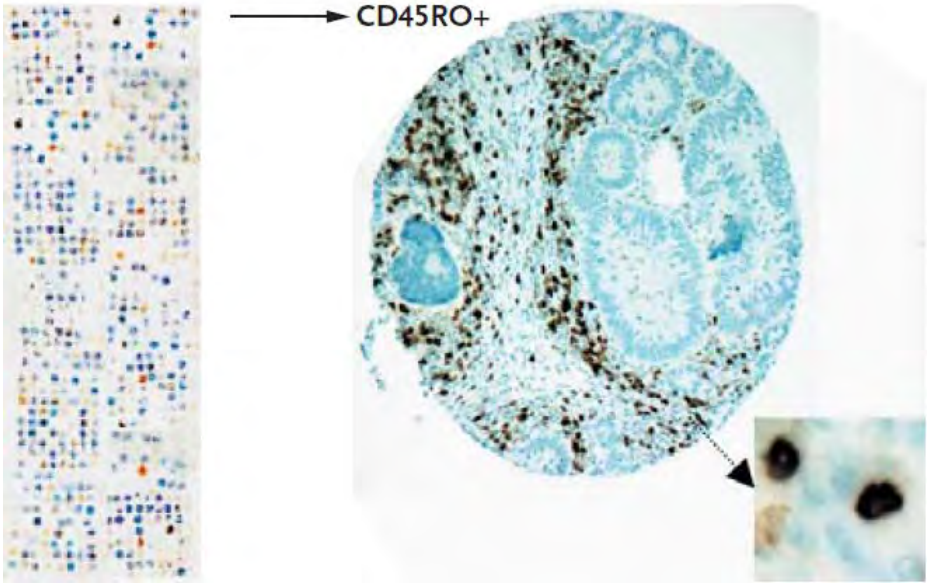
1. Koebel CM, LJ Old, M Smyth & Schreiber RD, *Nature* 2007, 450(7171):903-7.

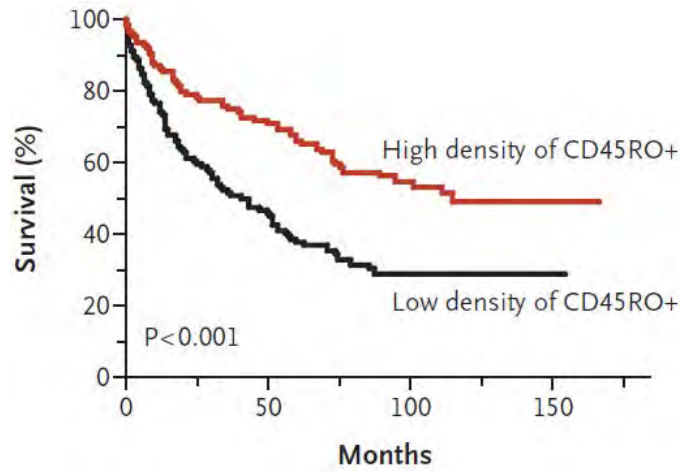
Evidences of Tumor Immuno-Surveillance in Human: Increased Cancer Incidence in Immuno-Depressed Transplanted Patients[1]

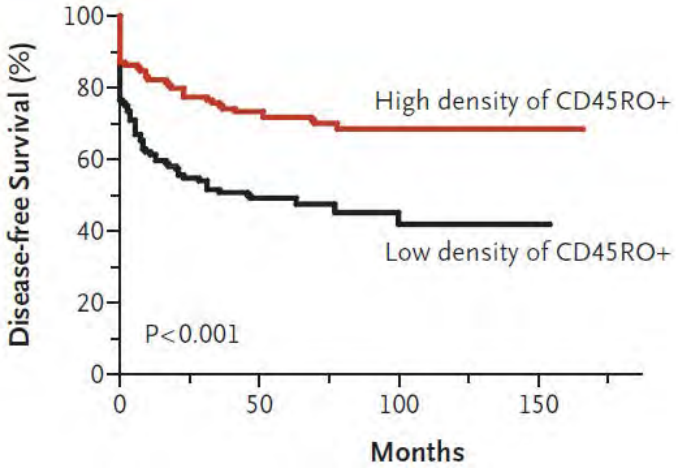
Tumor Site	Ratio
Skin (non-melanoma)	24.7
Thyroid	14.3
Endocrine system	13.8
ORL	10.8
Vulva, vagina	10.3
Non-Hodgkin Lymphoma	9.1
Kidney	5.5
Colorectal	3.6
Lung	2.4
Brain	2.4
Prostate	2.1
Melanoma	1.7

1. Birkeland, *Int J Cancer* 1995 30: 183-9.

Effector Memory T Cells Infiltration Predict Survival in Colorectal Cancer[1]

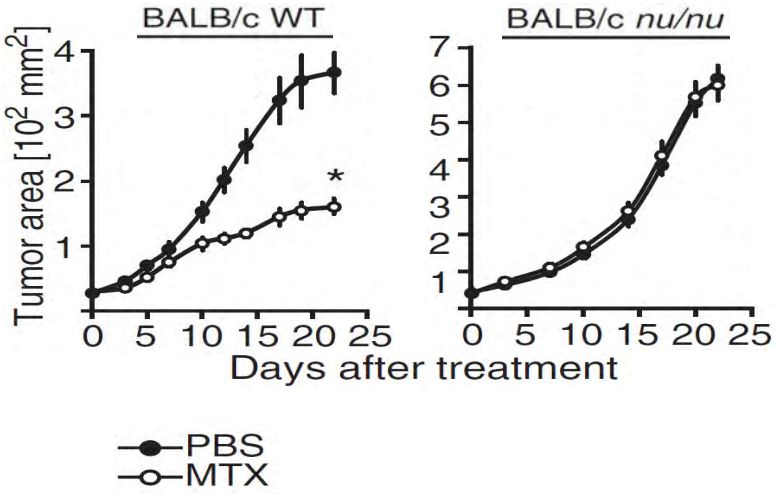


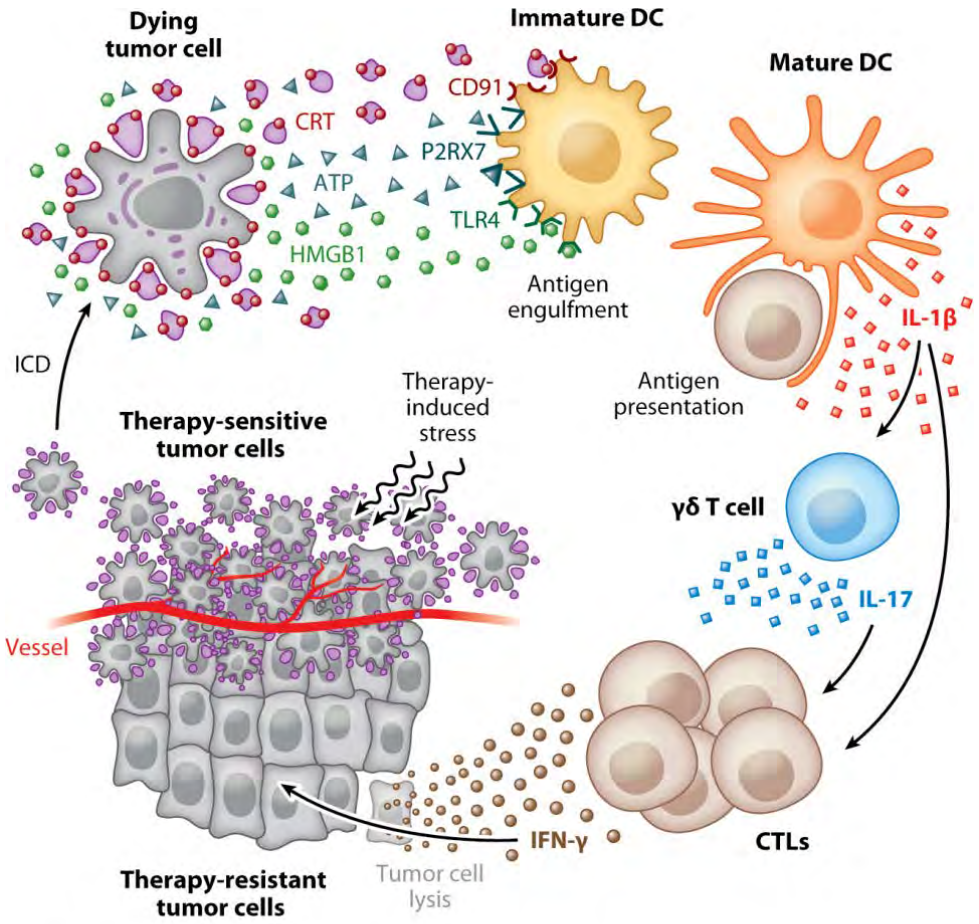




1. Pages F et al. *N Engl J Med.* 2005;353:2654–2666.
2. Galon J et al. *Science* 2006;313:1960–64.

Immunogenic Cell Death in Cancer Therapy





Michaud M, Kroemer G. *Science.* 2011; 334:1573-7.
Kroemer G, Zitvogel L. *Annu Rev Immunol*. 2013; 31:51-72.

Immuno-surveillance and escape mechanisms

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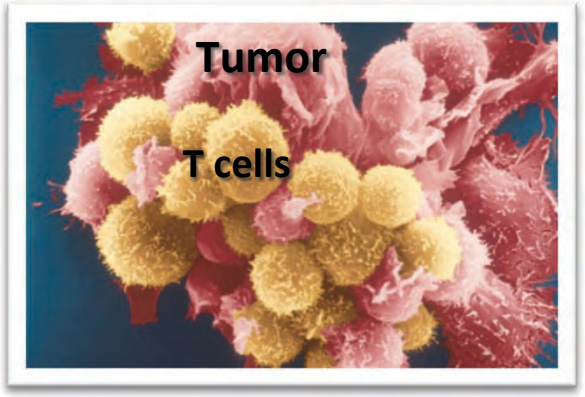
- **The immune system as a barrier to tumor formation and progression**
- Cancer cells: How they avoid immune surveillance and destruction
- Immune Checkpoints

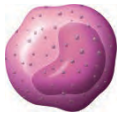


Both Innate and Adaptive Arms of The Immune System Can Fight Tumors

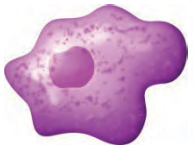
Innate Immunity

Can recognize native structures through somatic encoded receptors from pathogens and nascent tumor cells and destroy them

NK cells

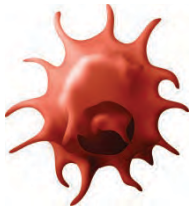


Macrophages



Hematopoietic Stem cell

Dendritic cells



T cells

B cells

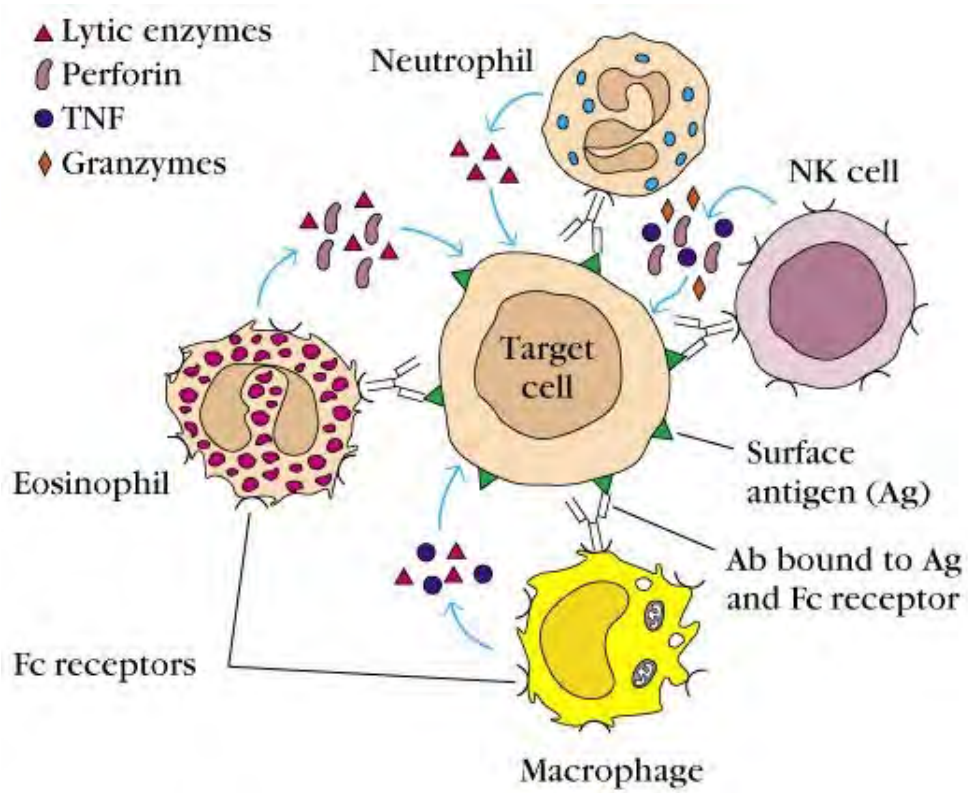
Adaptive Immunity

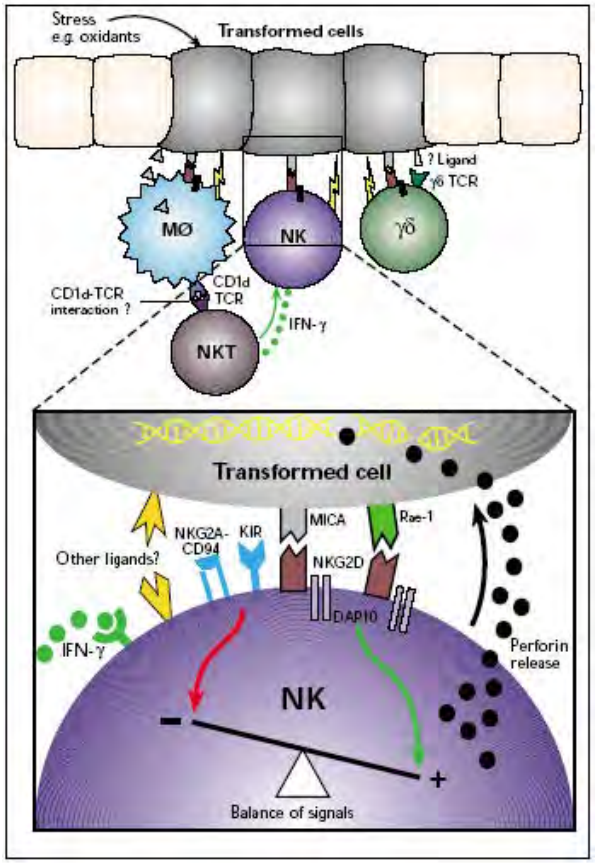
Recognize and eradicate pathogens and nascent tumor cells through their antigen receptor TCR & BCR (high diversity due to genetic recombination)

NK = natural killer.

1. Norvell A. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:11–24.

The Innate Immune System Fight Tumors Via a Variety of Functionally Specialized Cells[1]





Destruction of Infected cells by Cytotoxicity, Phagocytosis or Antibody Dependent Cell Cytotoxicity

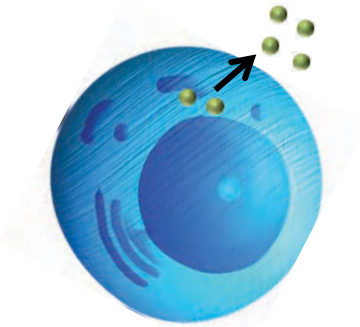
NK = natural killer.

1. Norvell A. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:11–24.

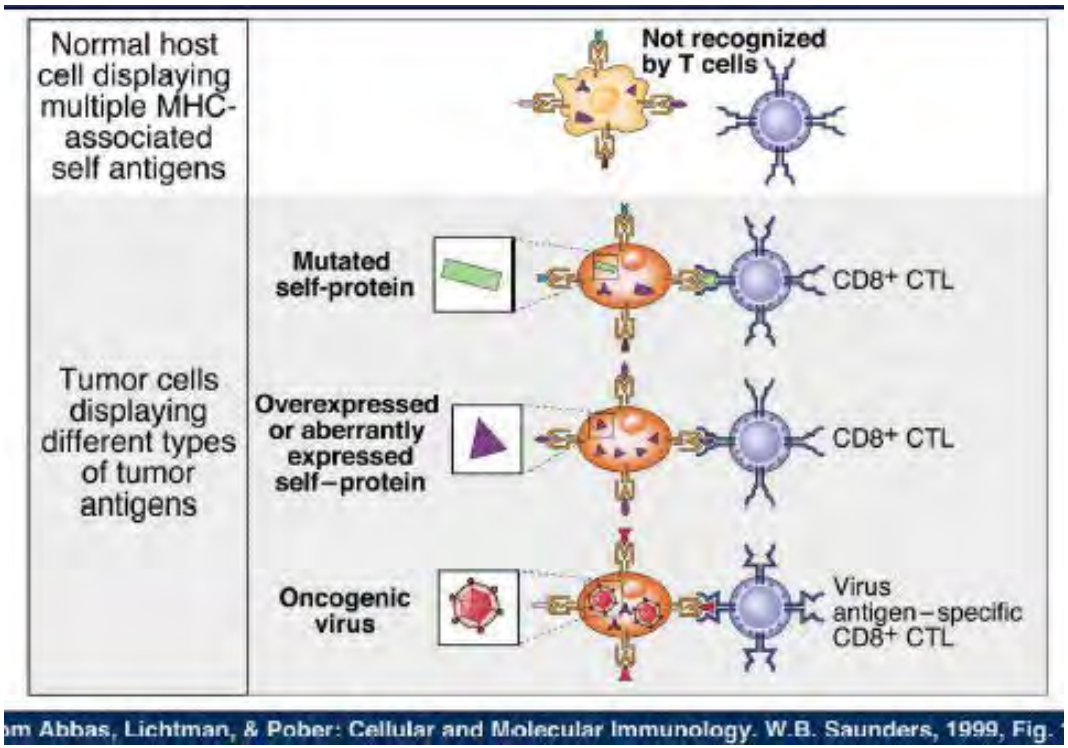
Some Tumor Cells Express Multiple Antigens That Are Not Expressed by Normal Cells[1]

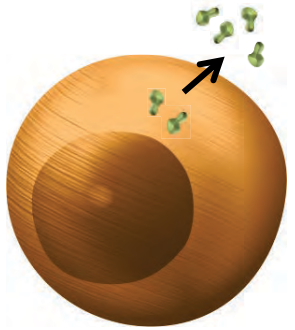
Normal cells express/release molecules that don't elicit an immune response (tolerance to normal self).

Tumor cells express/release abnormal self antigens that cause them to be recognized as foreign entities and therefore elicit an immune response.



NORMAL CELL

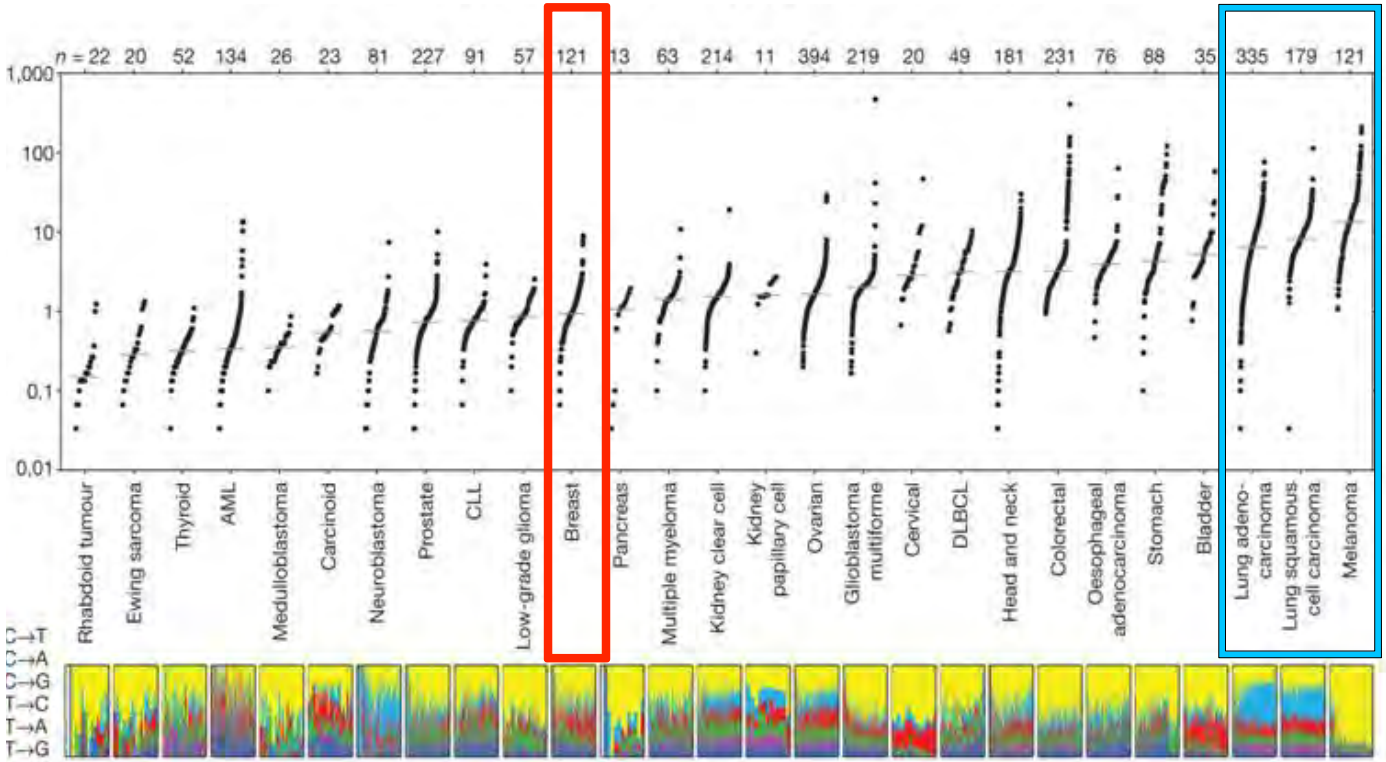




TUMOR CELL

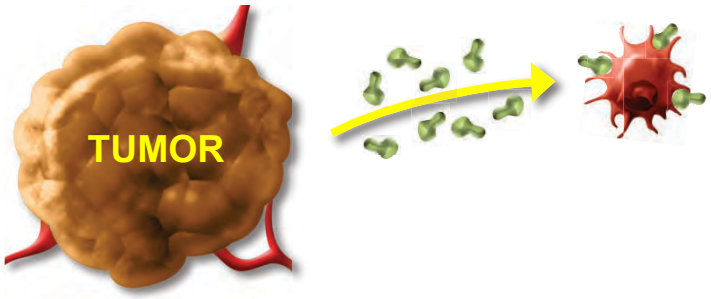
1. Finn OJ. *N Engl J Med*. 2008;358:2704–2715.

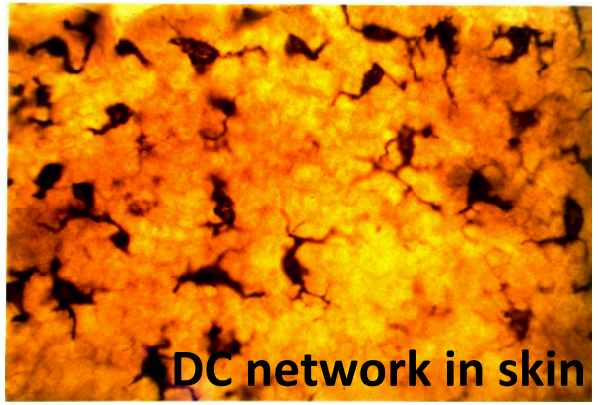
Mutational Heterogeneity in Cancer Creates Therapeutic Challenges and Opportunities



Altered proteins contain new epitopes for immune recognition, providing a common denomination for immunotherapy

T cells Are Important in the Ability of the Immune System to Detect and Destroy Tumor Cells[1]





1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

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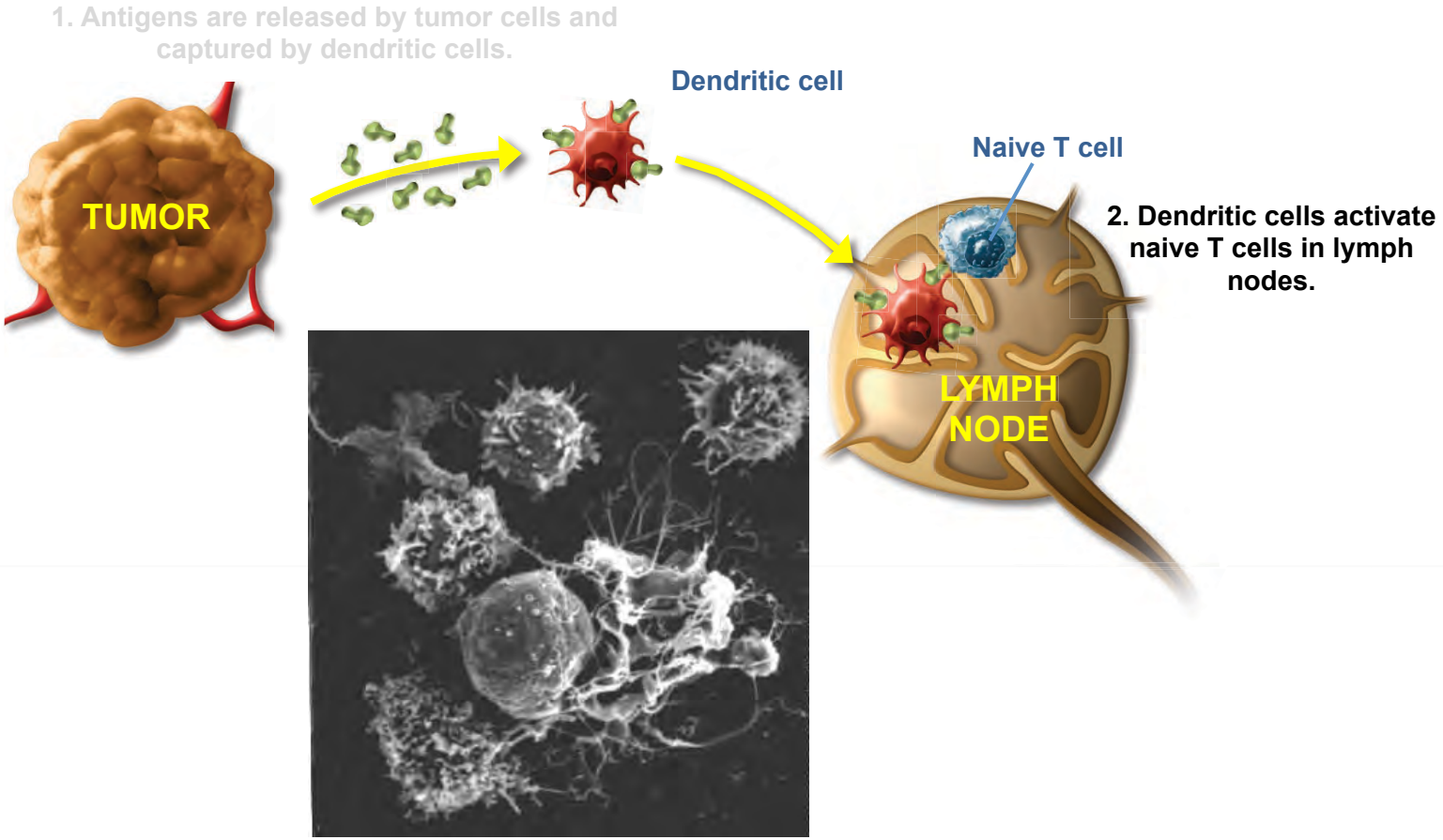

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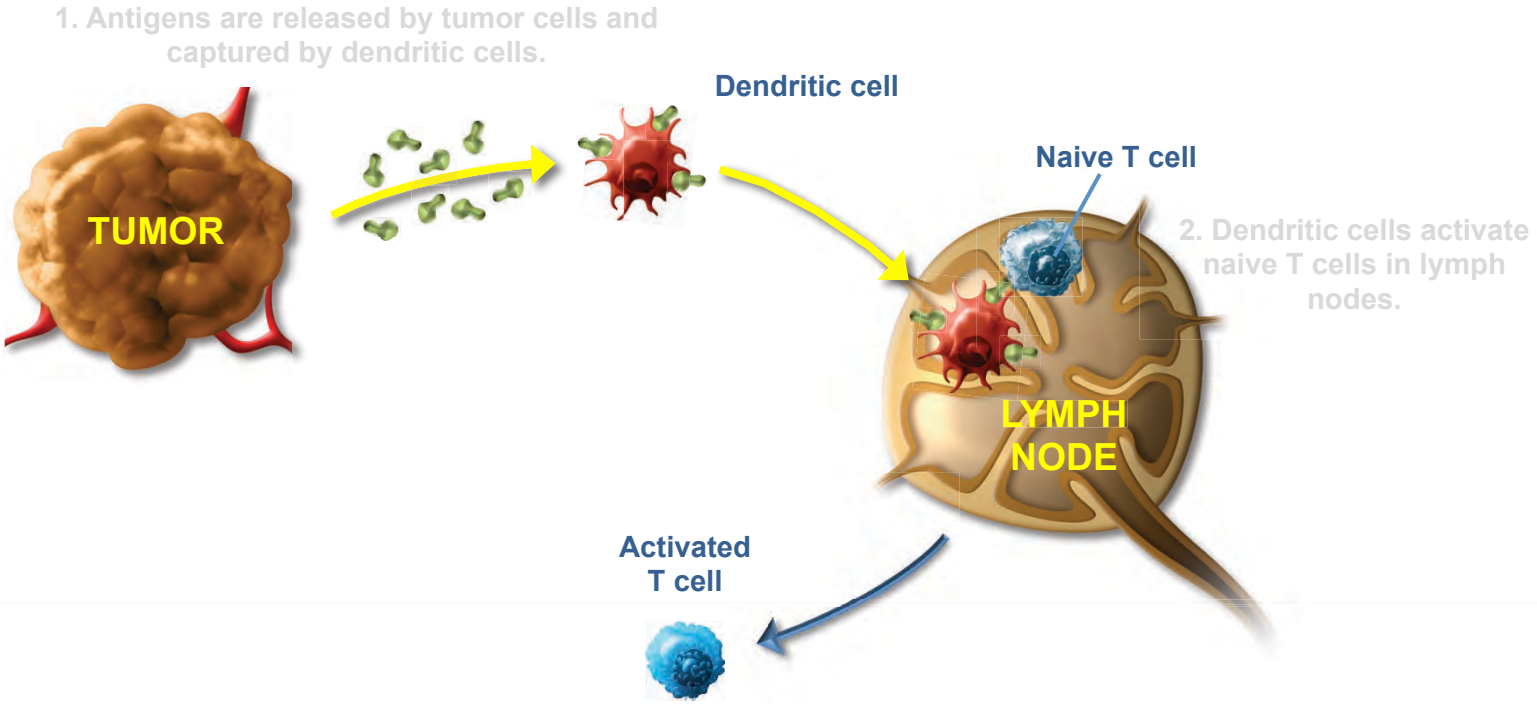

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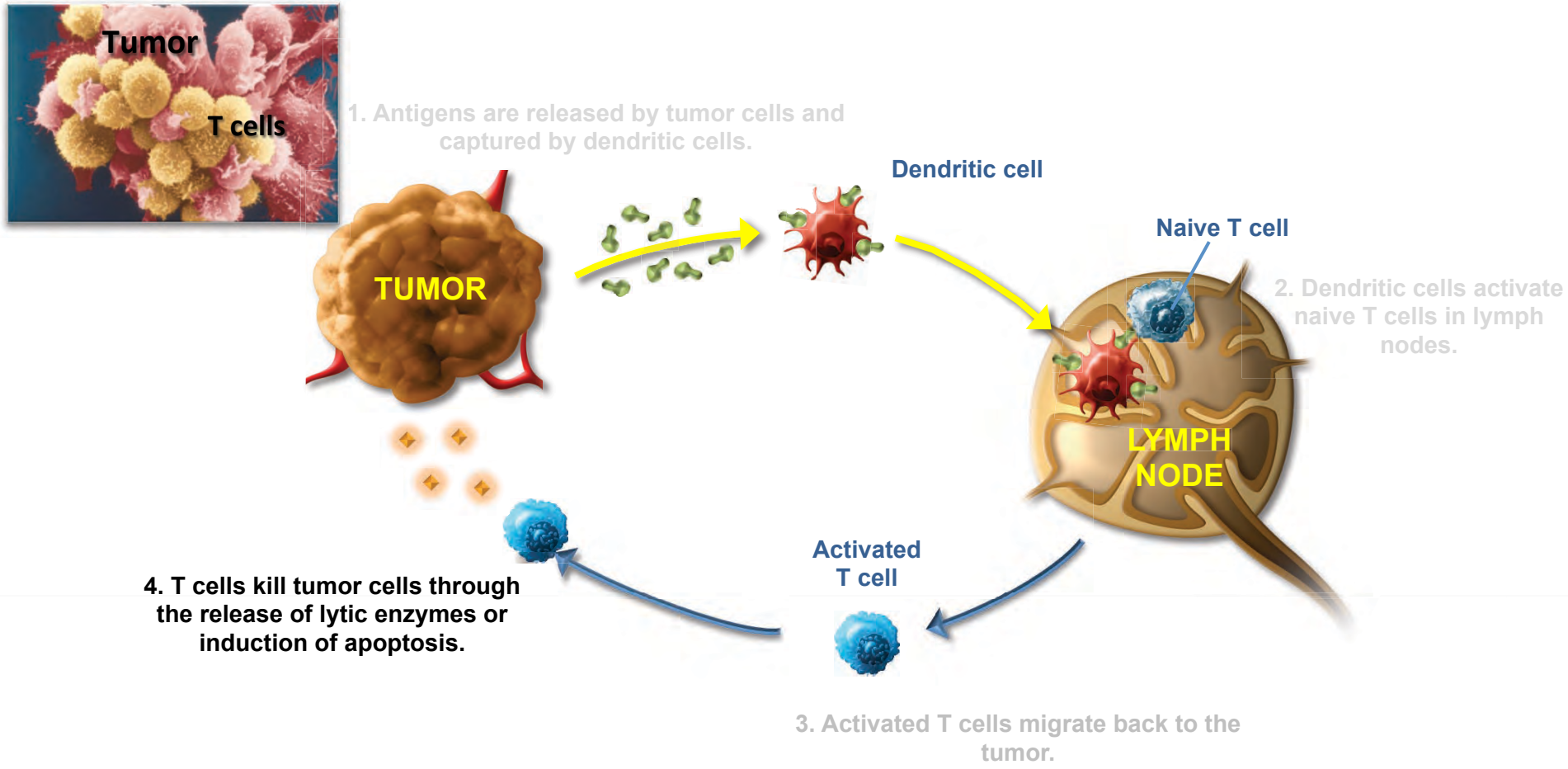
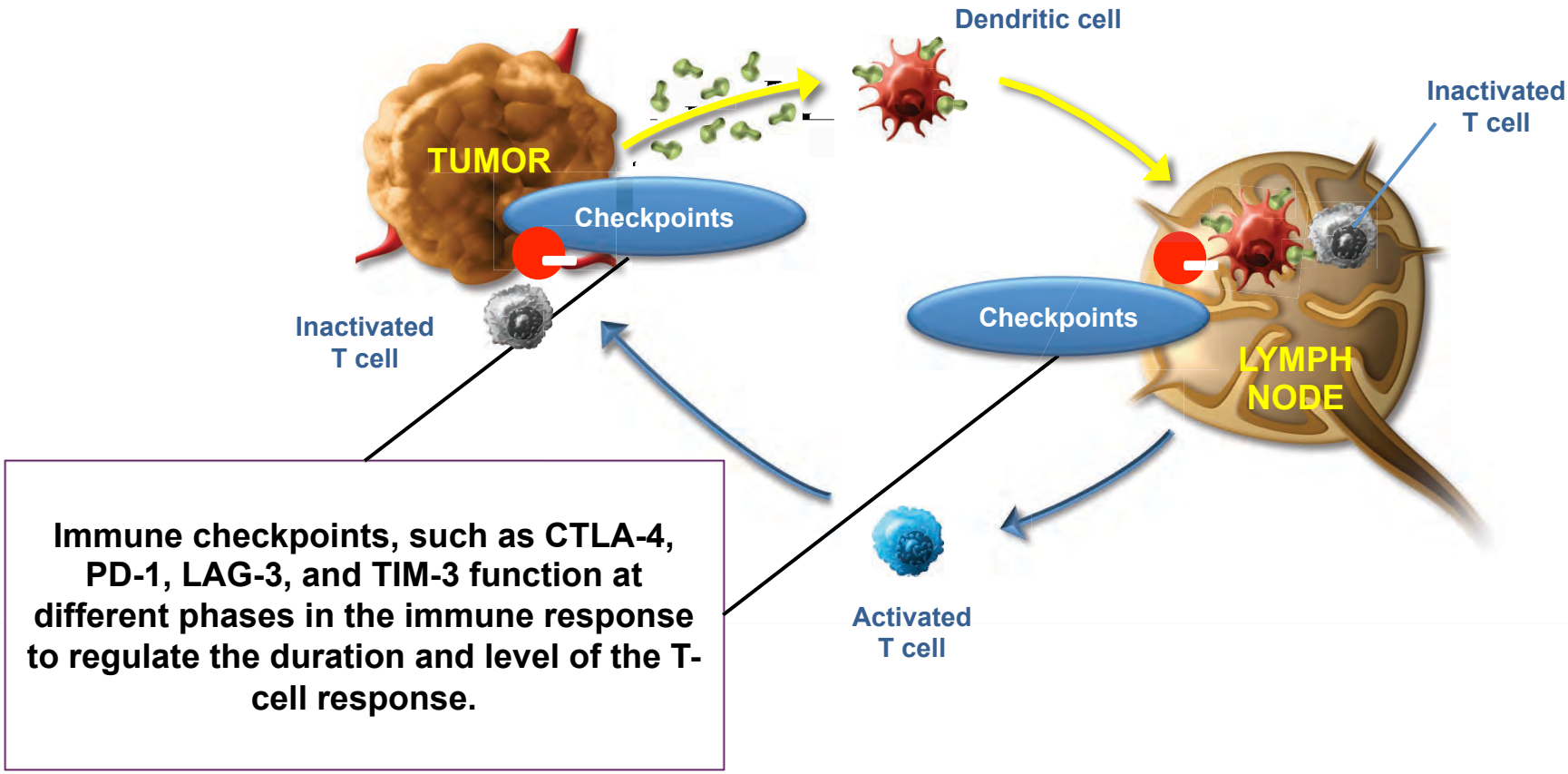


1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity[1]



Immune checkpoints, such as CTLA-4, PD-1, LAG-3, and TIM-3 function at different phases in the immune response to regulate the duration and level of the T-cell response.

CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1; LAG-3 = lymphocyte activation gene 3; TIM-3 = T-cell immunoglobulin and mucin protein 3.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264.

Immuno-surveillance and escape mechanisms

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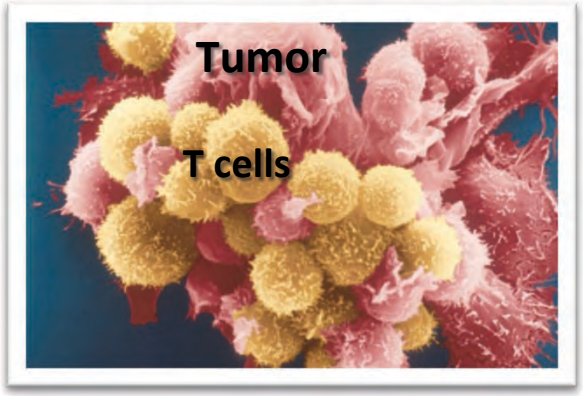
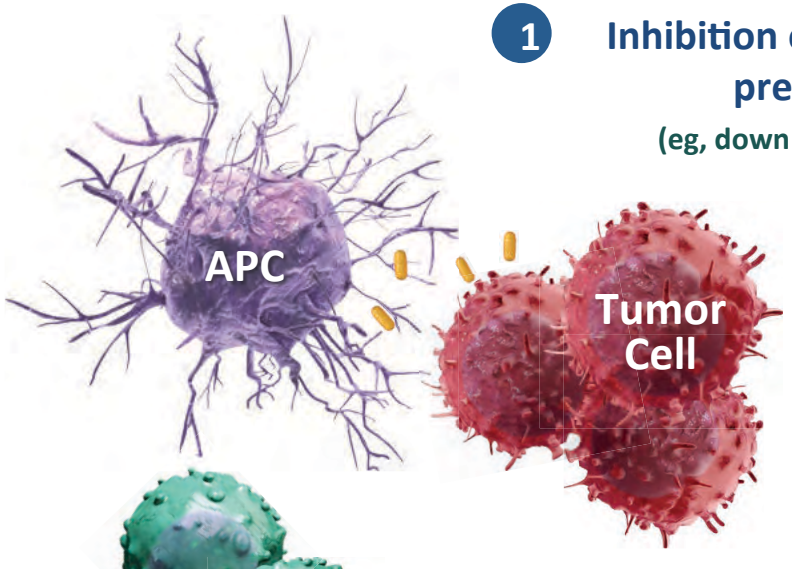


- **Cancer cells: How they avoid immune surveillance and destruction**
- Immune Checkpoints

Tumor escape mechanisms



1 **Inhibition of tumor antigen presentation**

(eg, down regulation of MHC I)

2 **Secretion of immunosuppressive factors**

(eg, TGF-B)

3 **Recruitment of immunosuppressive cell types**

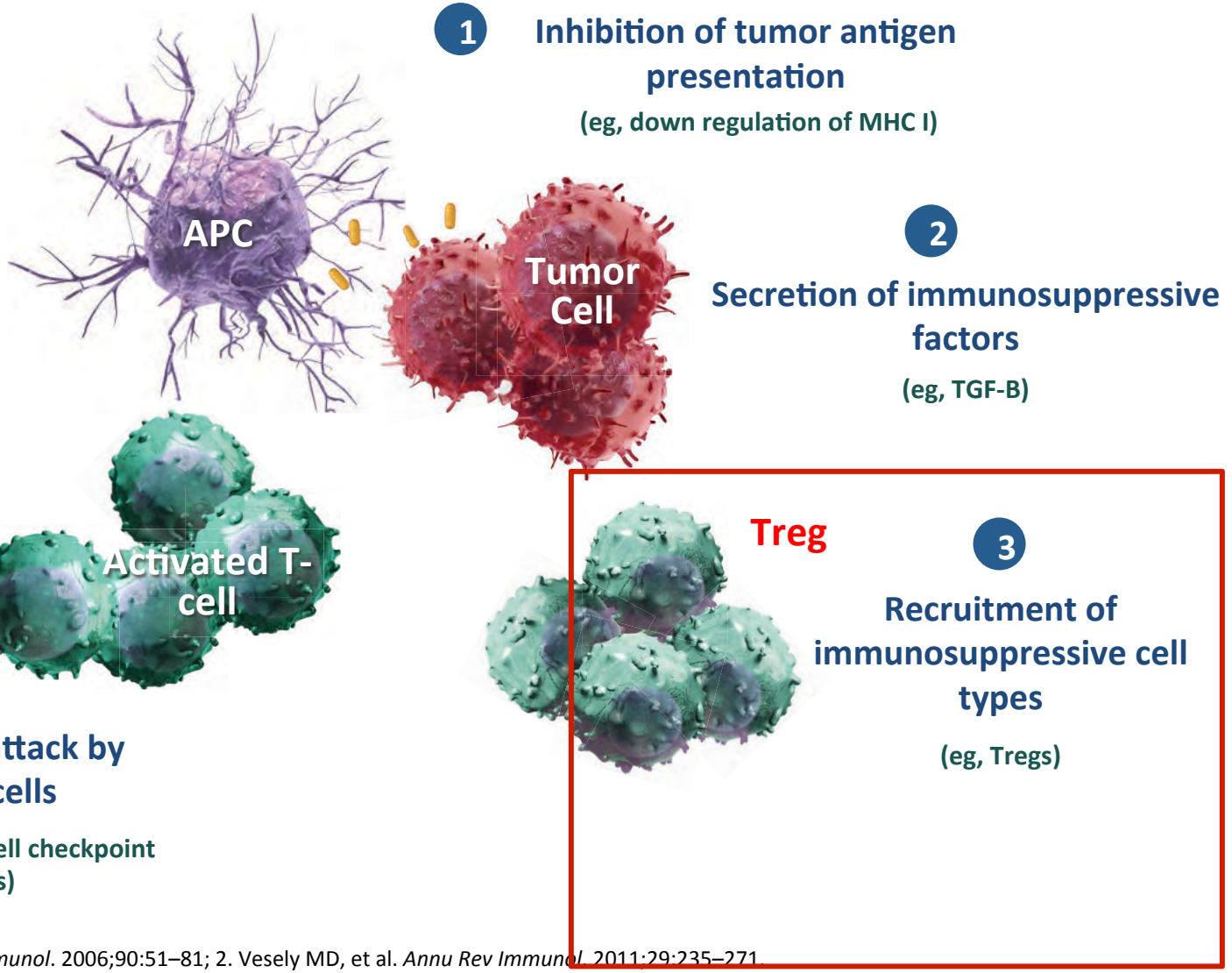
(eg, Tregs)

4 **Inhibition of attack by immune cells**

(eg, disruption of T-cell checkpoint pathways)

1. Drake CG, et al. *Adv Immunol*. 2006;90:51–81; 2. Vesely MD, et al. *Annu Rev Immunol*. 2011;29:235–271.

Tumor escape mechanisms



1. Drake CG, et al. *Adv Immunol*. 2006;90:51–81; 2. Vesely MD, et al. *Annu Rev Immunol*. 2011;29:235–271.

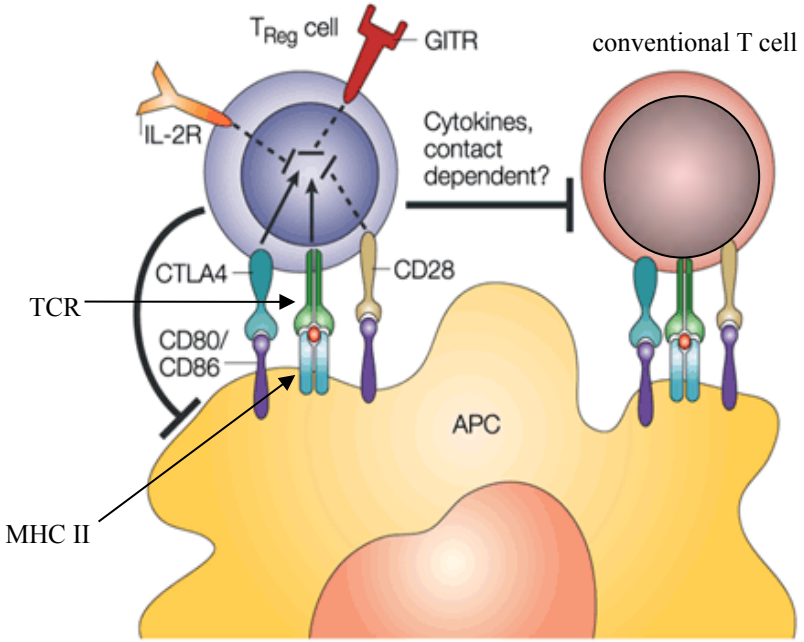
3. Recruiting Immunosuppressive Cells : ie Treg
Exploiting Immune Tolerance Pathways

Regulatory T lymphocytes (Treg) inhibit conventional T cell activation

- Involved in auto-immunity
- Contributing to tumor development

- Increase Treg frequency in blood of patients suffering from different cancer types (Udaya 2002, Wolf 2003)

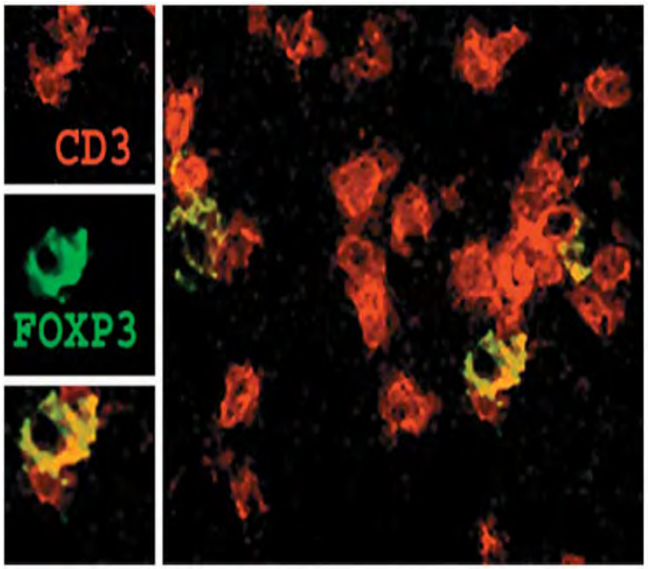
- Negative Impact on patients survival in ovarian cancer (Curiel 2004)



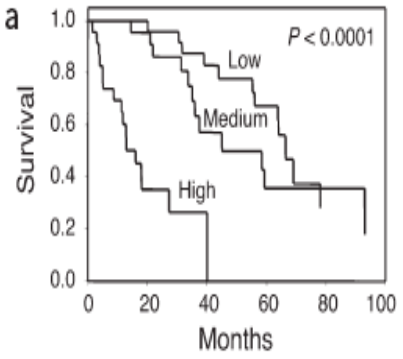
Nature Reviews | Immunology

Adapté de : Wood, K.J. and Sakaguchi, S. (2003) *Nat Rev Immunol* **3**, 199-210

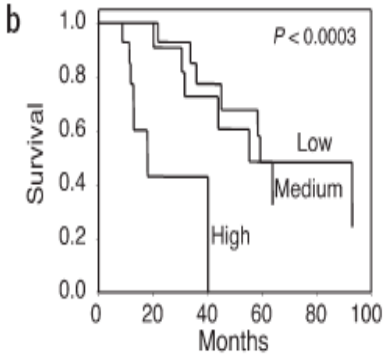
Regulatory T cell (Treg) Infiltration Is a Bad Prognosis Factor in Ovarian Tumor



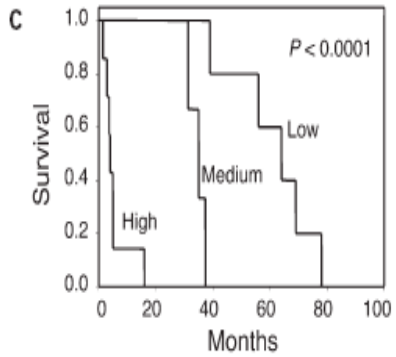
All stages



Stages III

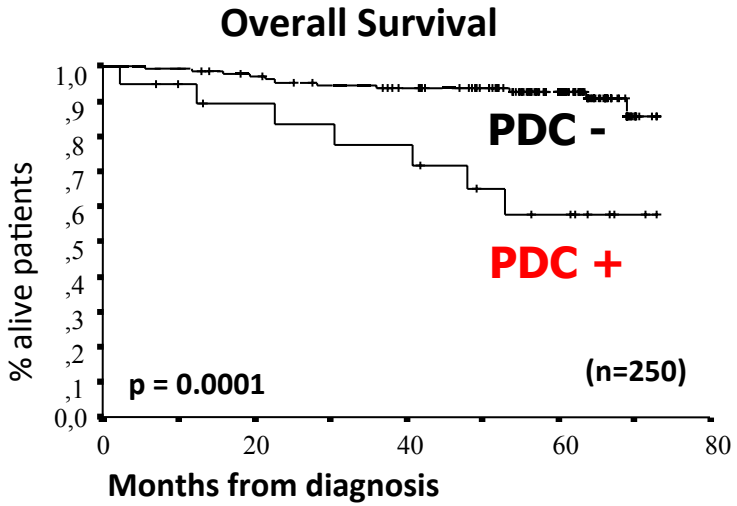


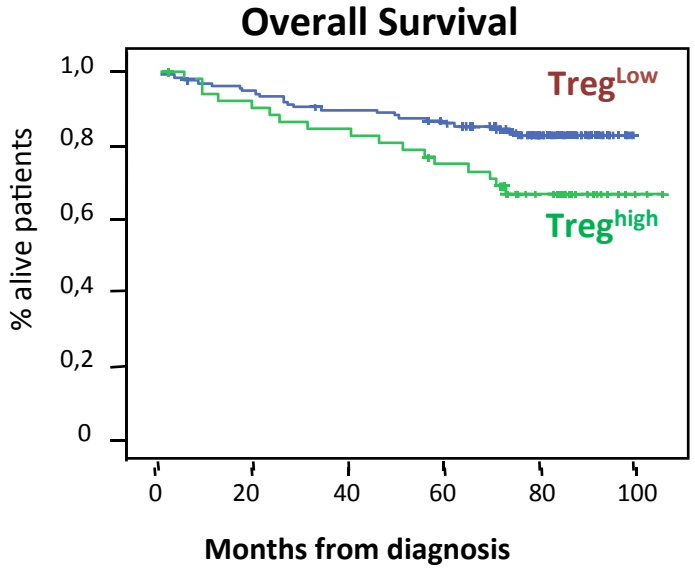
Stages IV

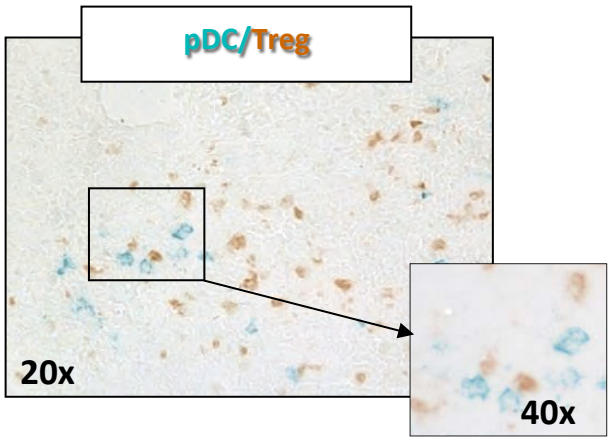


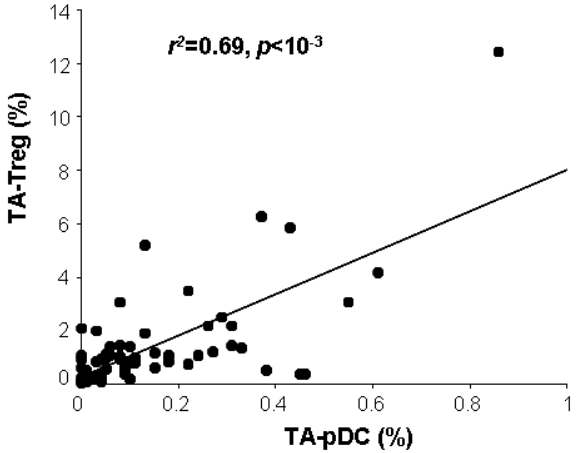
Curiel. *Nat Med*. 2004;10:942.

Plasmacytoid Dendritic Cells (pDC) and Treg at the Center of Immunosuppressive Networks in Breast Tumors









1. Gobert M, *Cancer Res,* 2009; **2**. Ménétrier-Caux C, *Cancer Res,* 2009; **3**. Faget J, Ménétrier-Caux C*, Cancer Res,* 2011; **4**. Labidi-Galy Bendriss-Vermare N*, Cancer Res* 2011; **5**. Faget J, Ménétrier-Caux, *Cancer Res,* 2012; **6**. Sisirak V, Bendriss-Vermare N*, Cancer Res* 2012; **7**. Sisirak V, Bendriss-Vermare N, *Int J Cancer* 2013; **8**. Le Mercier I, Puisieux I, Goutagny N*, Cancer Res* 2013

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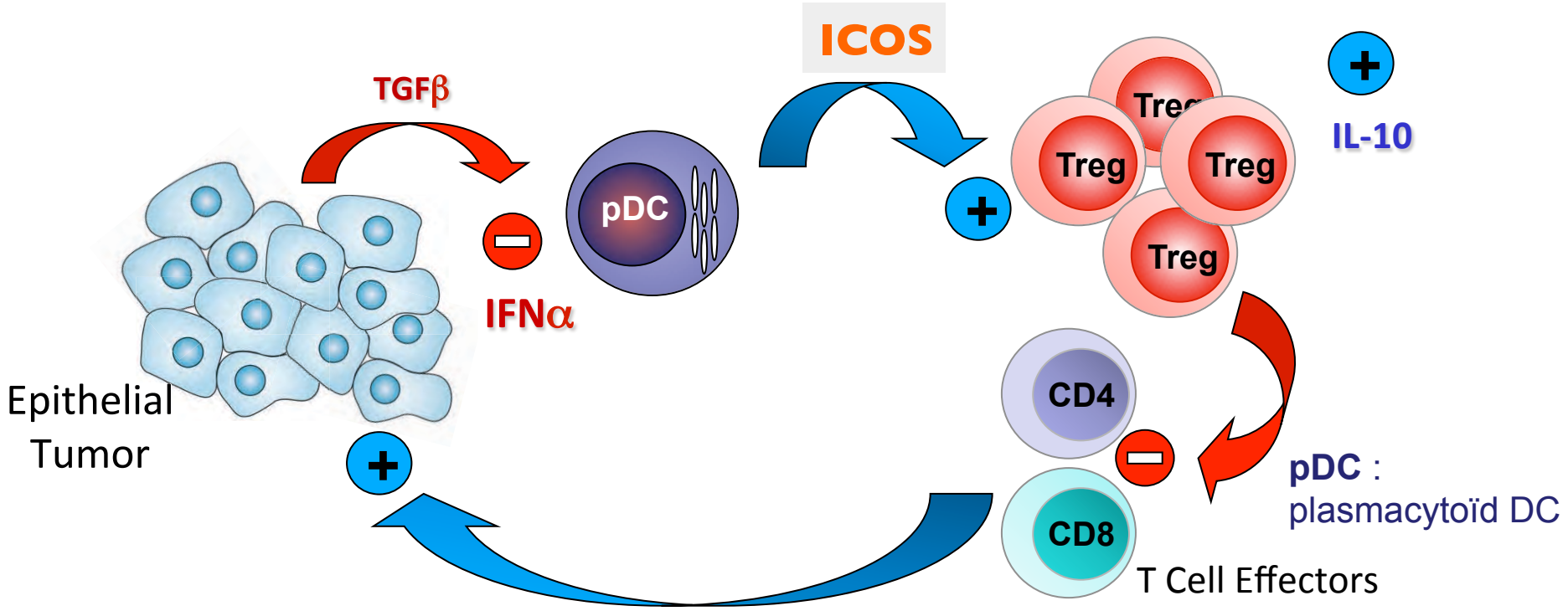

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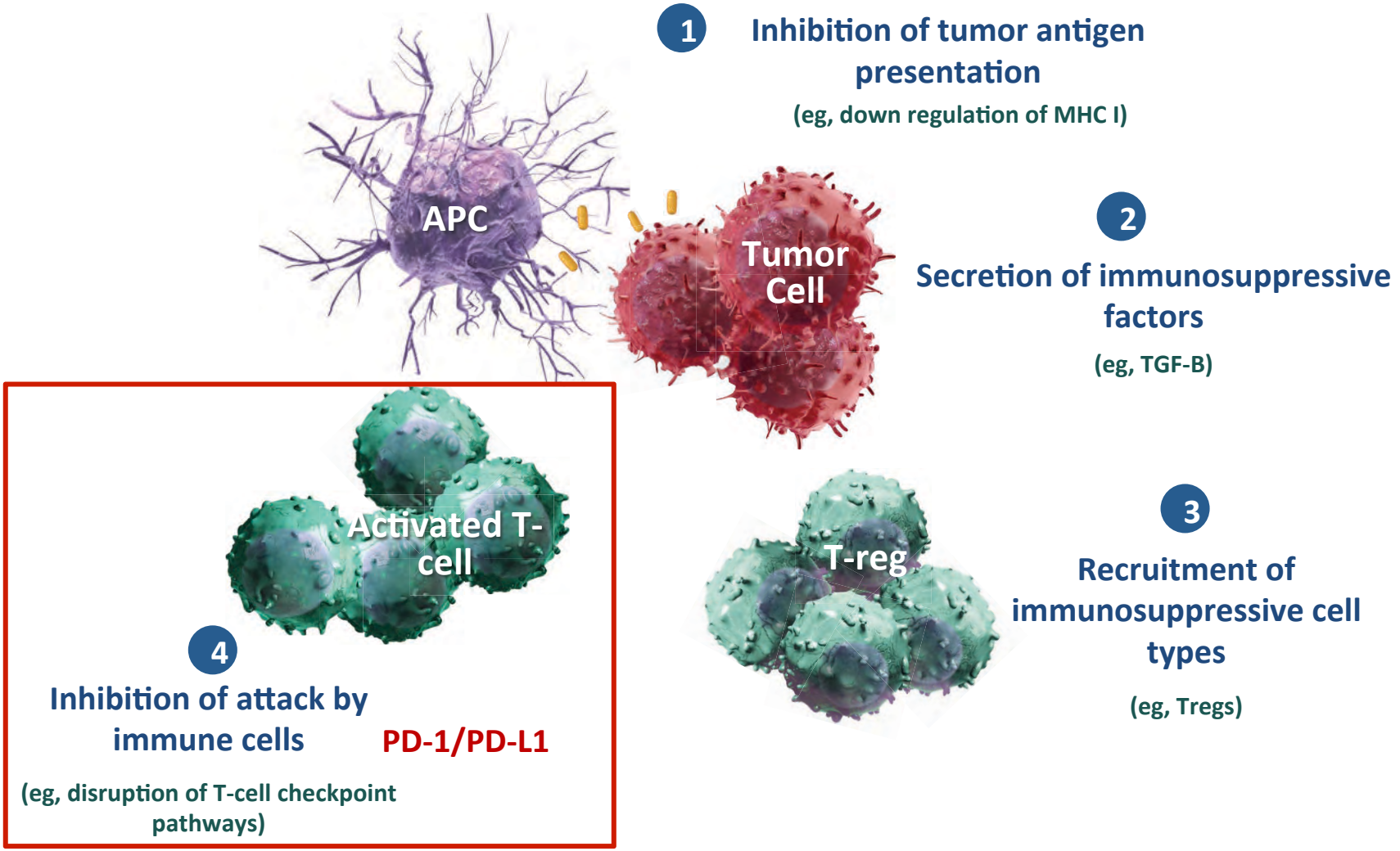
Tumor escape mechanisms



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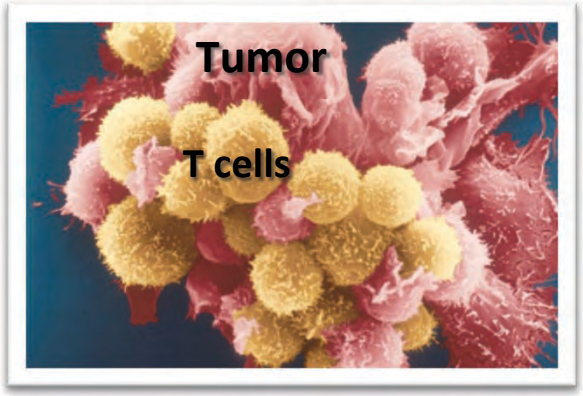
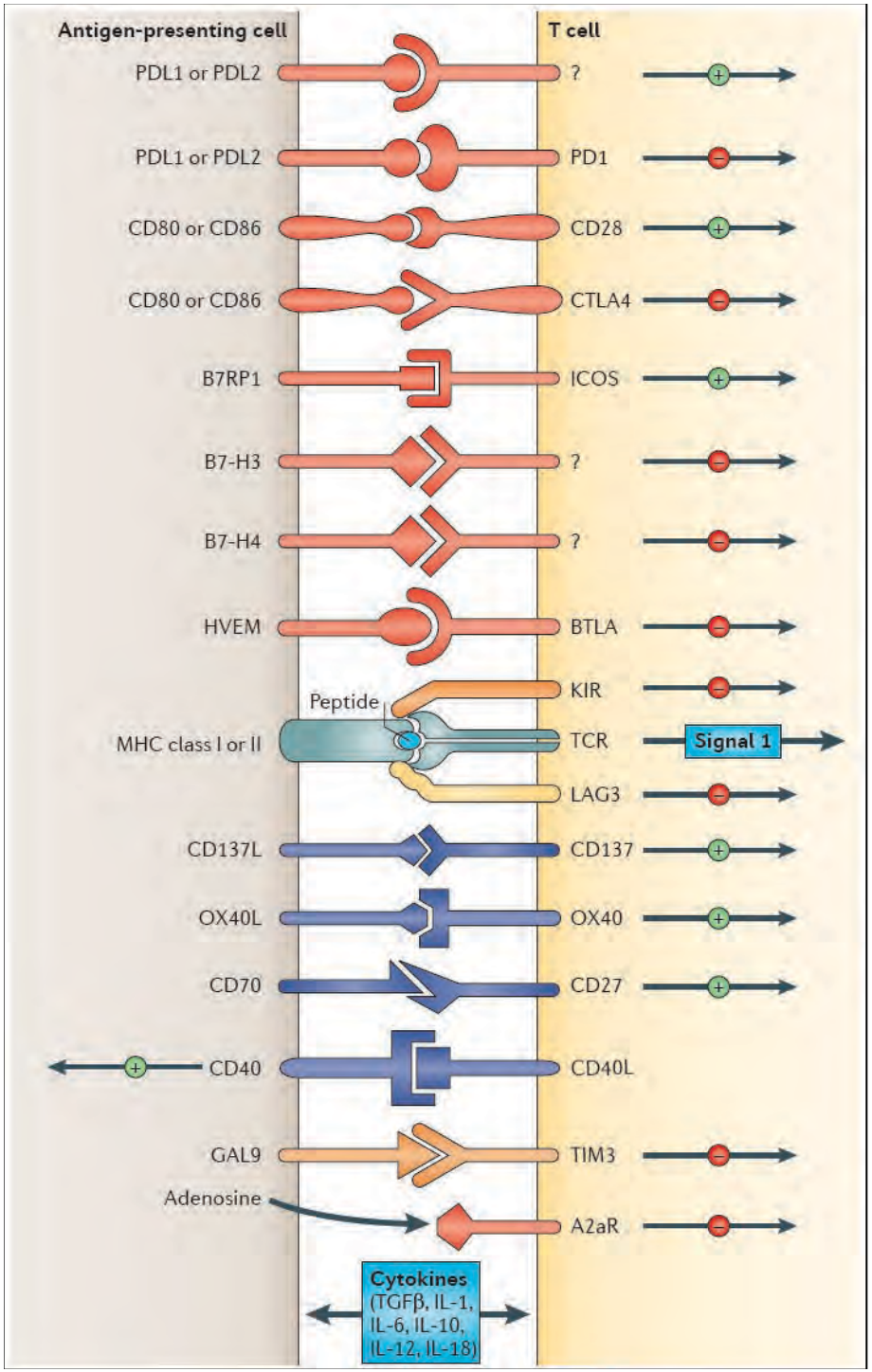


- Cancer cells: How they avoid immune surveillance and destruction
- **Immune Checkpoints**

Immune Checkpoints

- Checkpoint pathways
  - **CTLA-4 and PD-1**
- Other Checkpoints: B7 family and others
- Beyond Checkpoints: Costimulators
- Beyond T cells: NK, DC, Macrophage
- Markers for checkpoint pathway inhibition

Immune Checkpoints



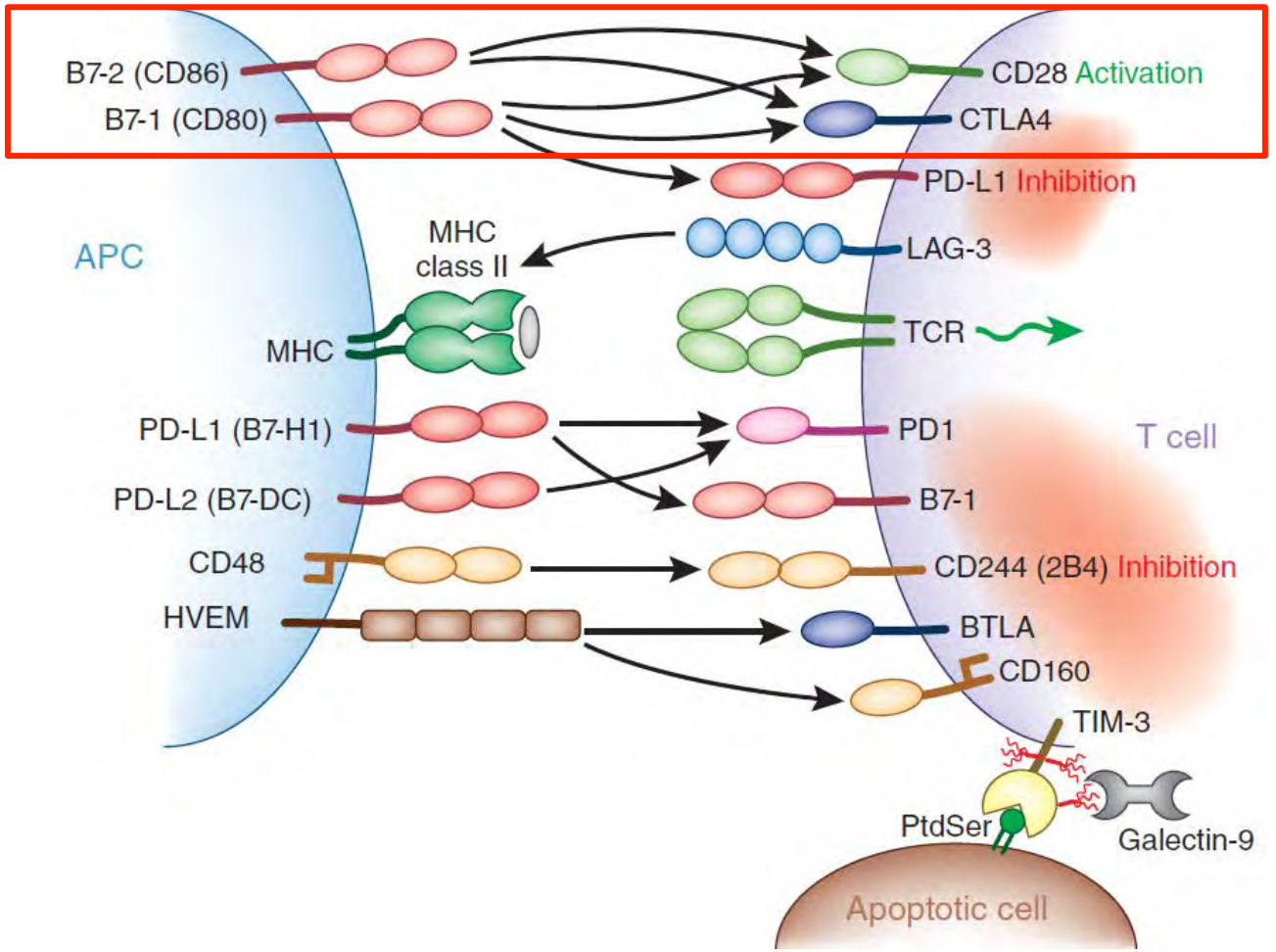
Famille B7

Famille TNF

Pardoll. *Nat Rev Cancer.* 2012.

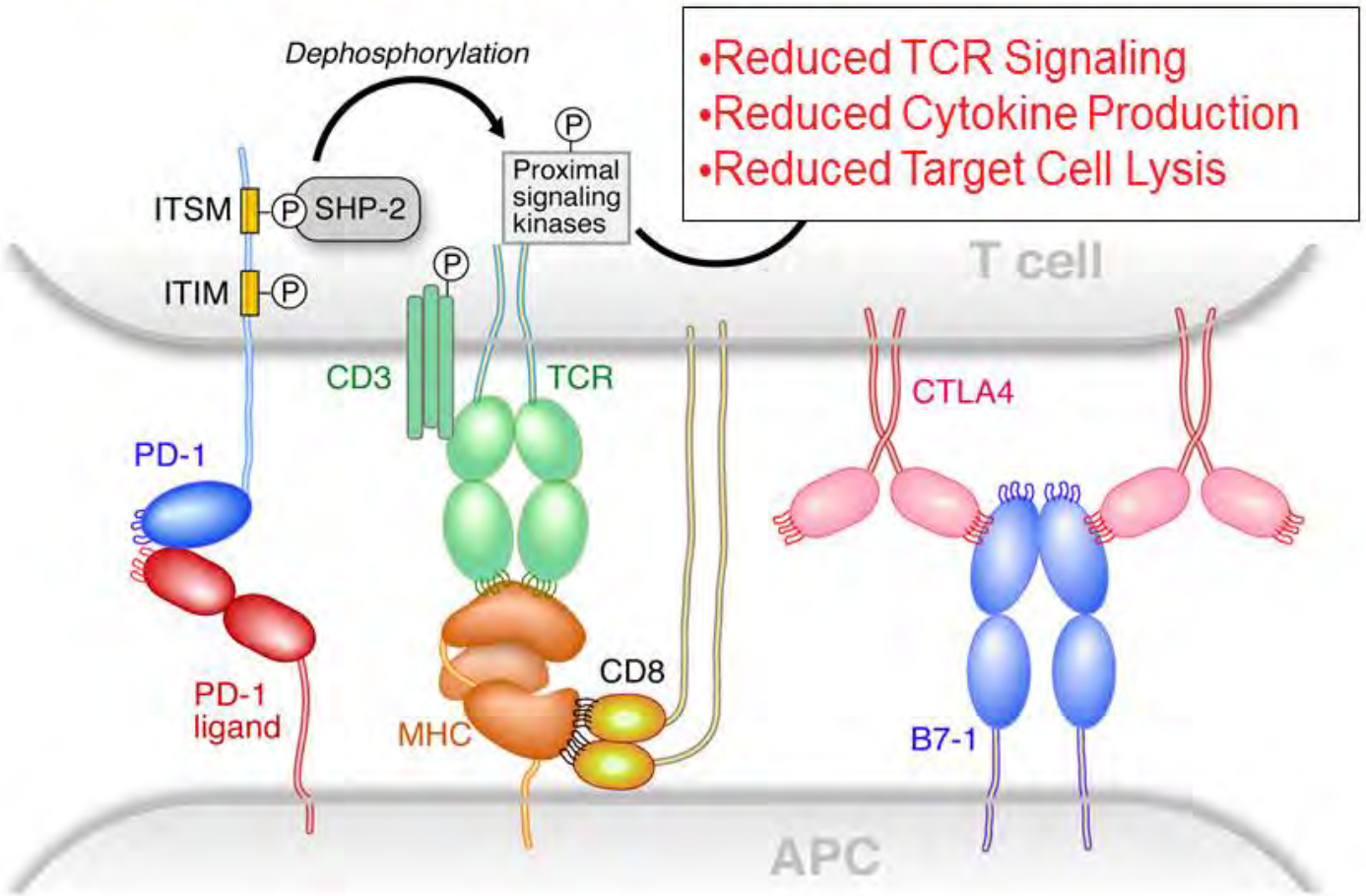
Tumor Infiltrating Lymphocytes Express Multiple Immunoinhibitory Receptors

These are druggable targets for tumor immunotherapy



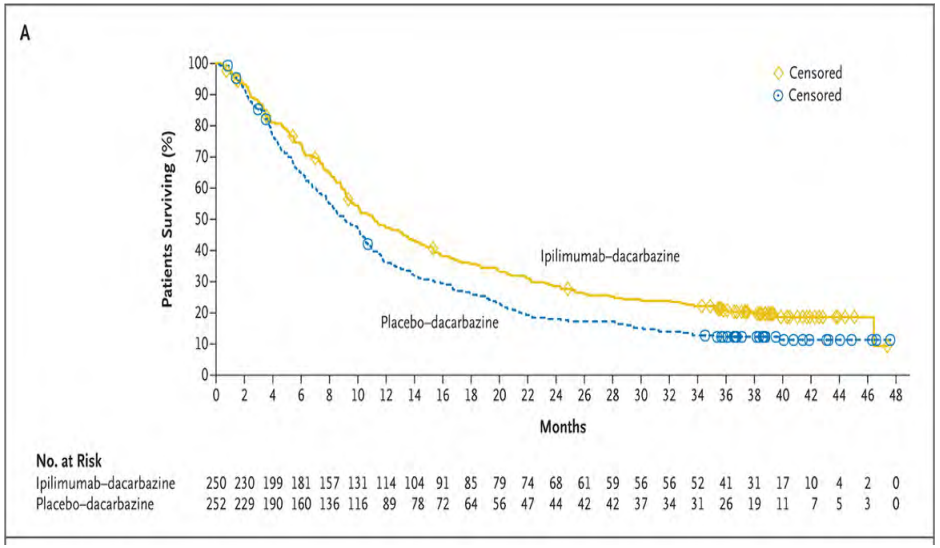
GJ Freeman & AH Sharpe. *Nat Immunol.* 2012.

CTLA-4 and PD-1 Pathway Inhibits T Cell Responses

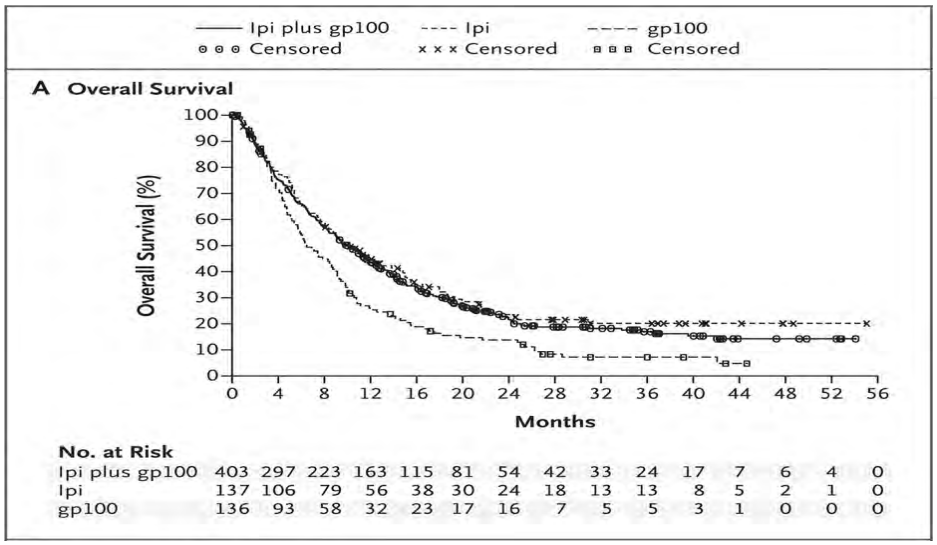


G Freeman 2008; PNAS 105:10275

Ipilimumab (Anti- CTLA4) Improve Long Term Survival in Metastatic Melanoma



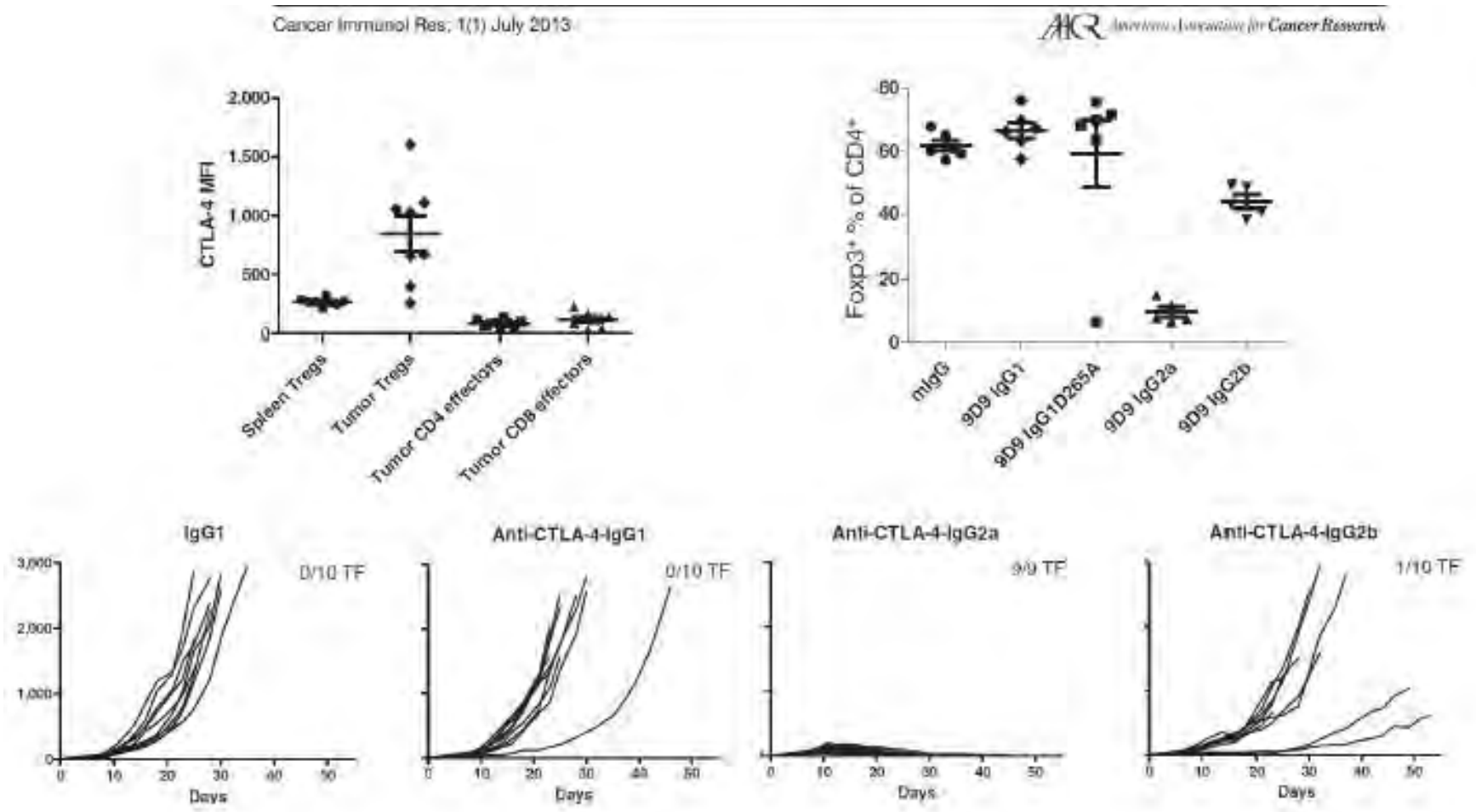
Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.[1]



Improved survival with ipilimumab in patients with metastatic melanoma. [2]

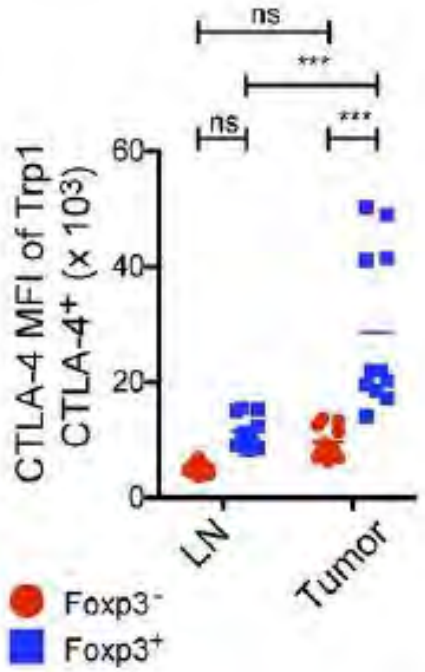
1. Robert C, Thomas L, et al. *N Engl J Med*. 2011; 364:2517-26.
2. Hodi FS, O'Day SJ, et al. *N Engl J Med.* 2010; 363:711-23

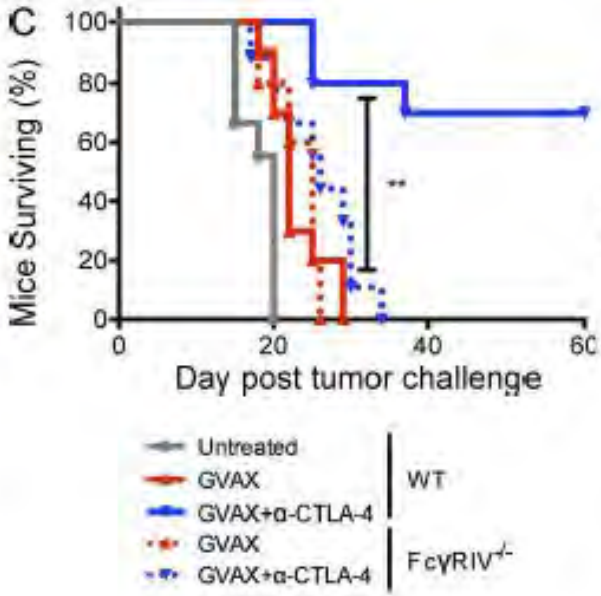
Anti-CTLA4 of IgG2a isotype Enhance Antitumor Activity Through Depletion of Intratumoral Tregs

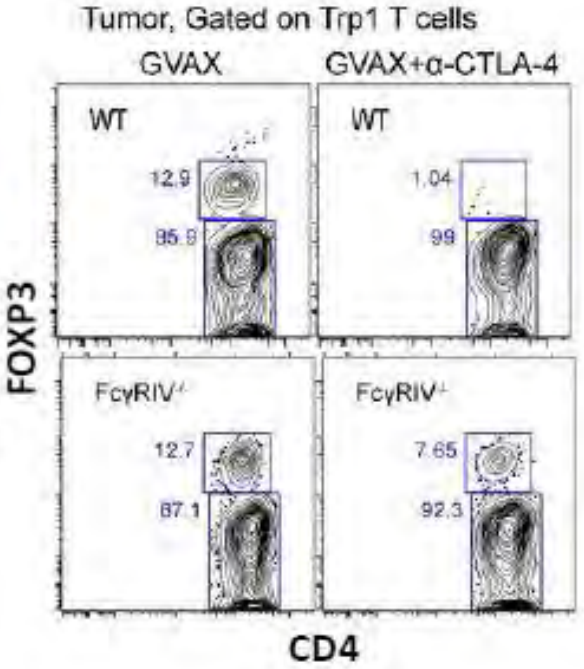


Selby MJ & Korman AJ. *Cancer Immunol Res.* 2013;1:32-42.

Fc-Dependent Depletion of Tumor Infiltrating Treg co-Defines the Efficacy of anti-CTLA4 Therapy







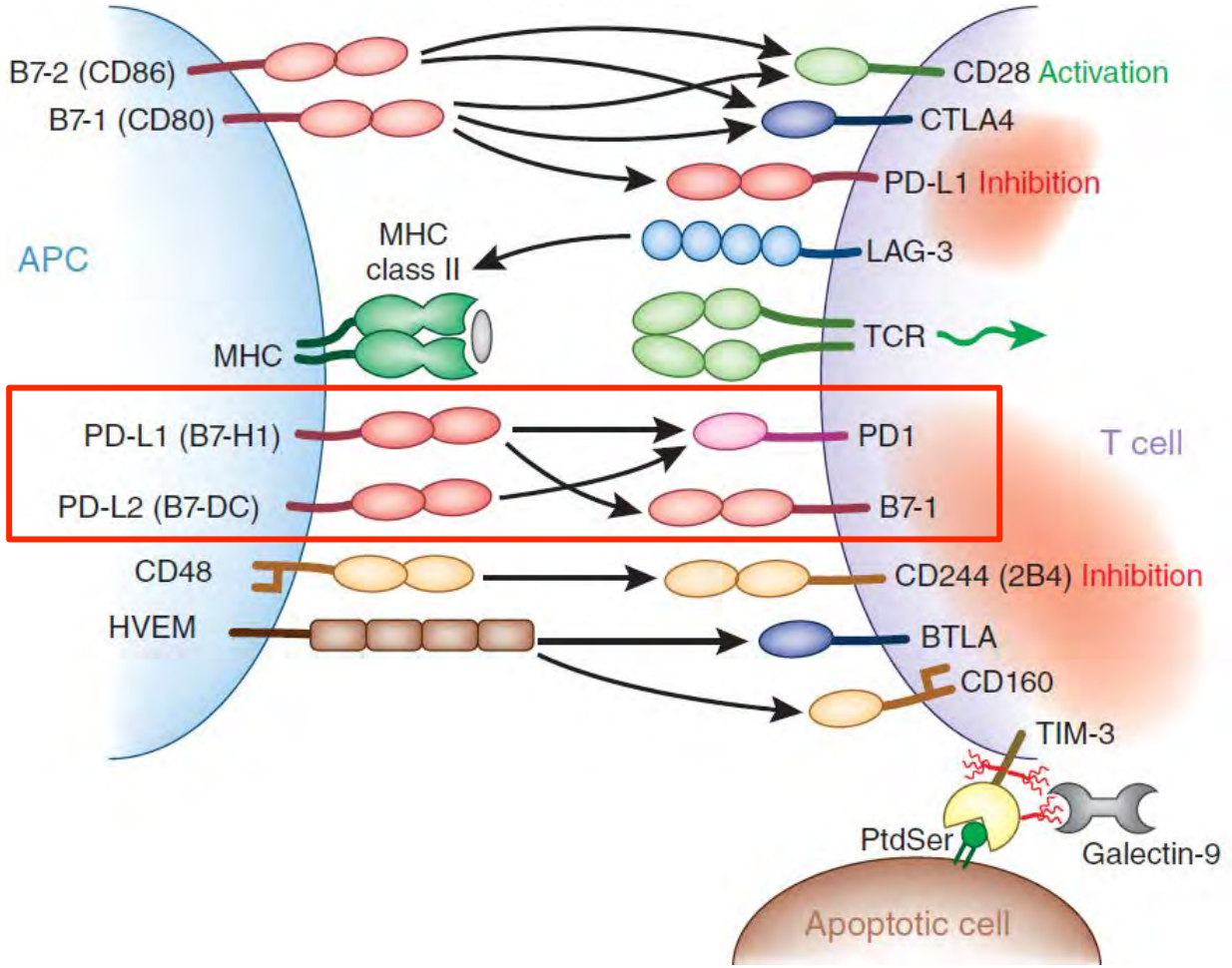
T-infiltrating Tregs express high levels of surface CTLA-4

Intra-Tumoral T-specific Tregs are depleted by α–CTLA-4 therapy via FcgRIV+ Cells

Simpson TR & Quezada A. *J Exp Med.* 2013; 210:1695-710.

Tumor Infiltrating Lymphocytes Express Multiple Immunoinhibitory Receptors

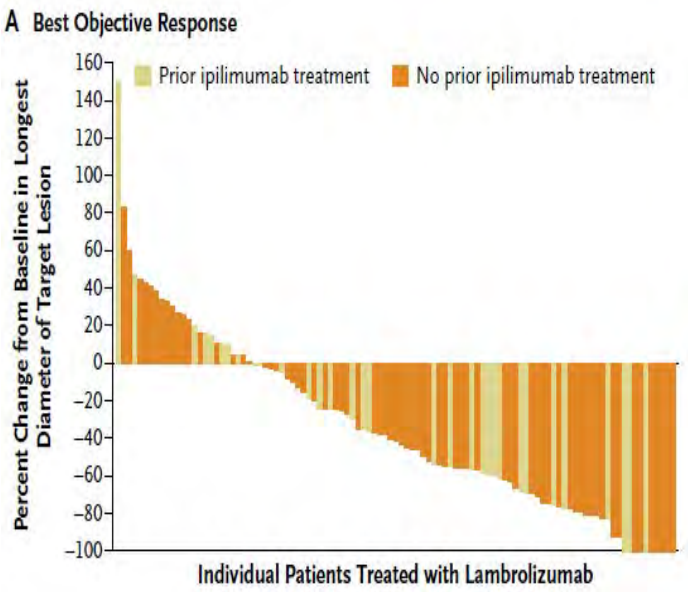
These are druggable targets for tumor immunotherapy

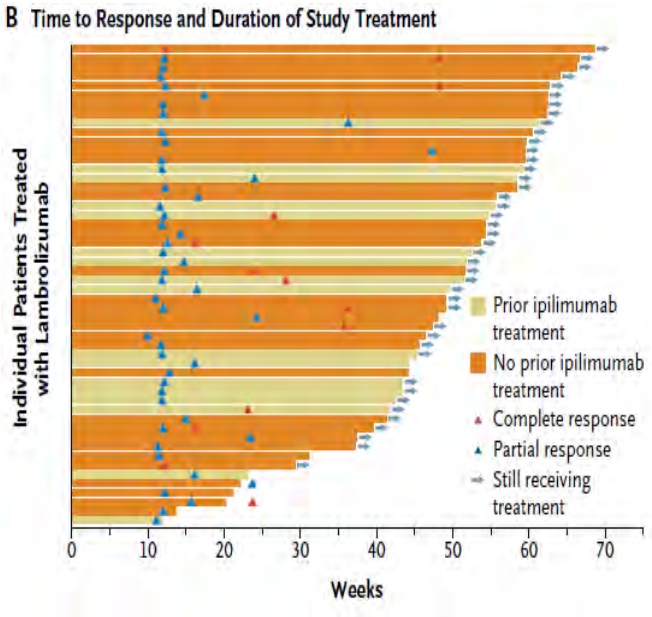


GJ Freeman & AH Sharpe. *Nat Immunol.* 2012.

Potent Therapeutic Efficacy of Pembrolizumab (anti-PD1 MSD) in Melanoma

53% objective Responses



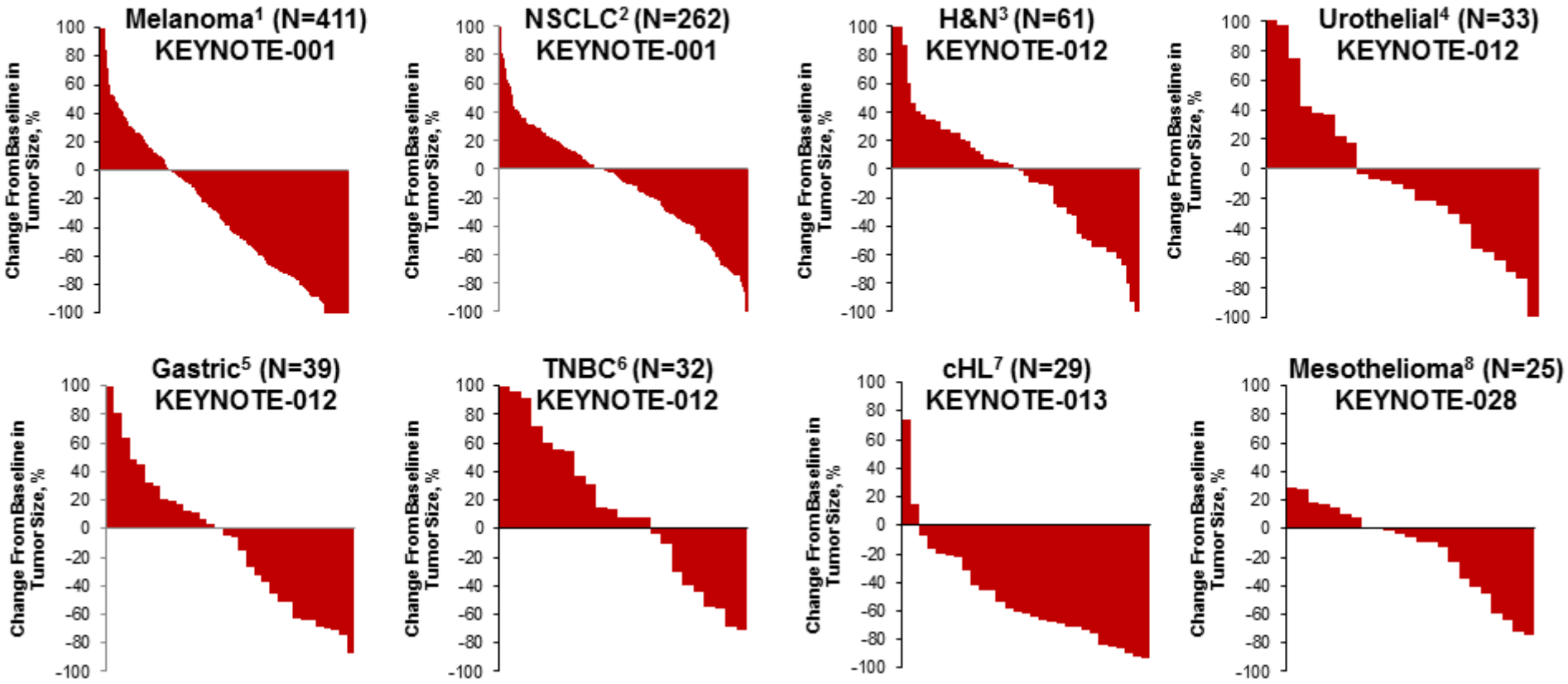


N=135, 13% grade 3/4 toxicity

Hamid O. *NEJM.* 2013.

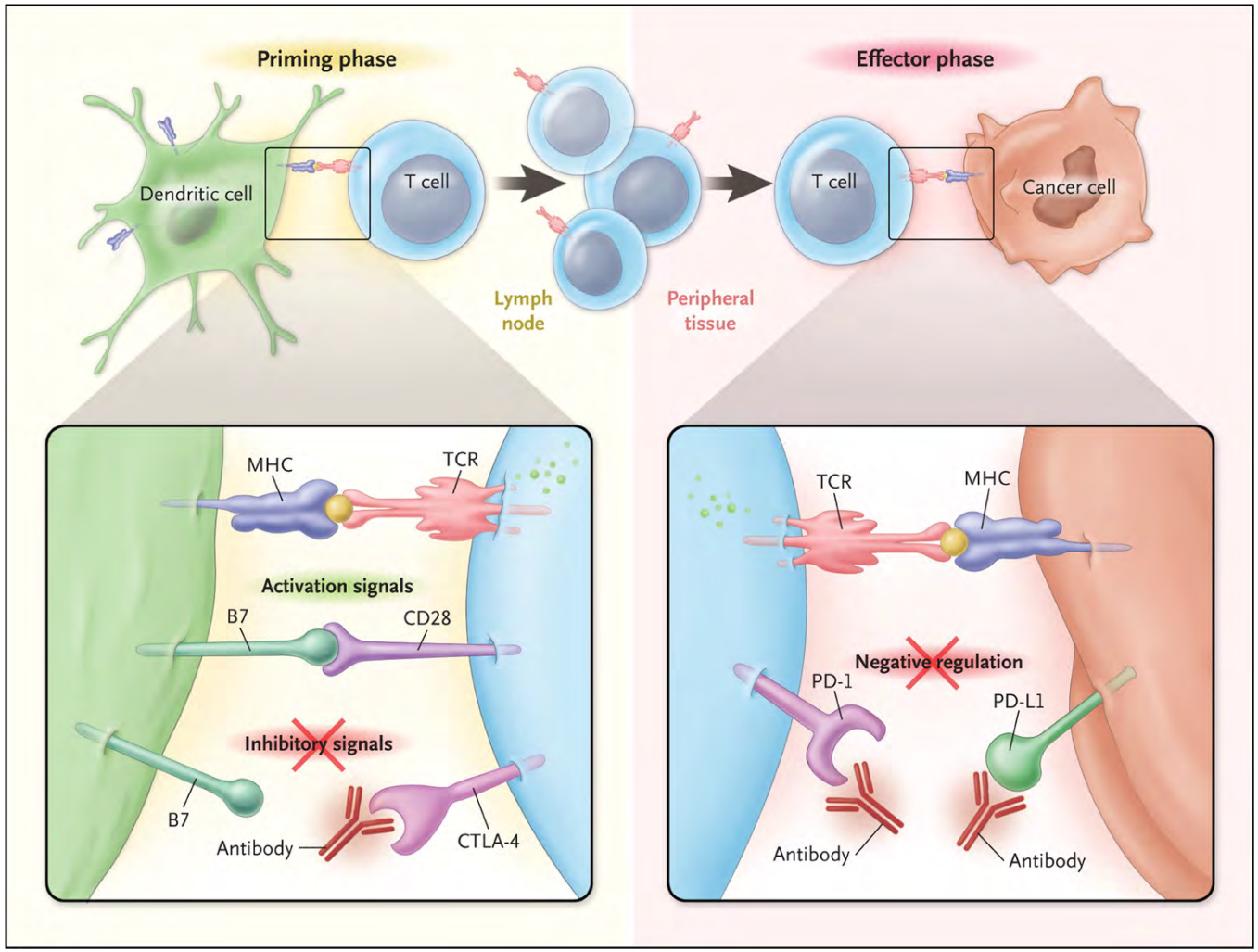
A. Varga, June 1, 2015

Pembrolizumab Antitumor Activity



1. Daud A et al. 2014 SMR; 2. Garon EB et al. ESMO 2014; 3. Chow LQ et al. ESMO 2014; 4. O'Donnell P et al. 2015 Genitourinary Cancers Symposium; 5. Muro K et al. 2015 Gastrointestinal Cancers Symposium; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. 2014 ASH Annual Meeting; 8. Alley EA et al. 2015 AACR.

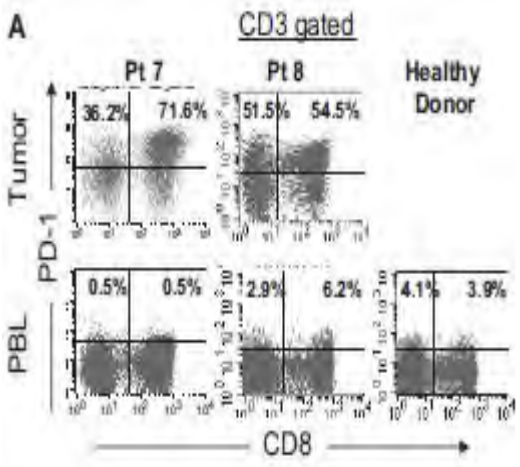
Differences Between Blocking CTLA4/B7 and Blocking PD-1/PD-L1

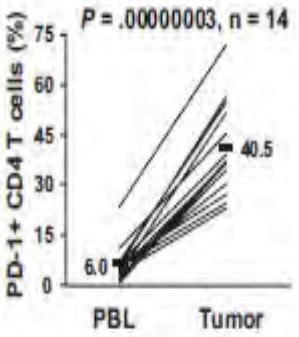


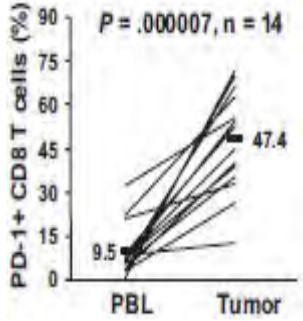
Ribas A. *N Engl J Med.* 2012;366:2517-2519.

Tumor Antigen–Specific CD8 T cells Infiltrating the Tumor Express High Levels of PD-1 and Are Functionally Impaired

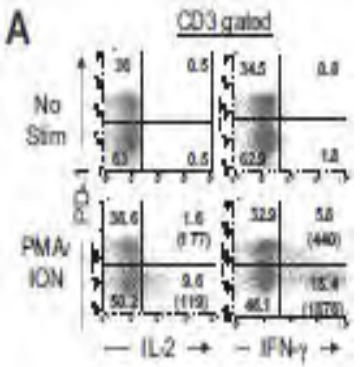
Tumor infiltrating T cells upregulate PD1

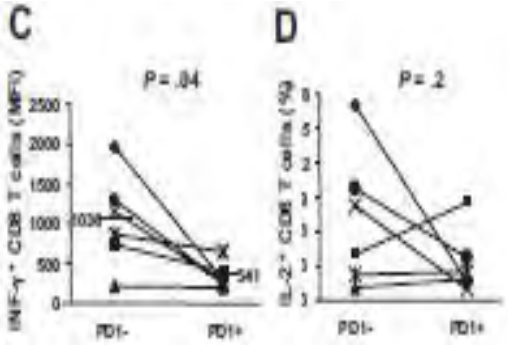






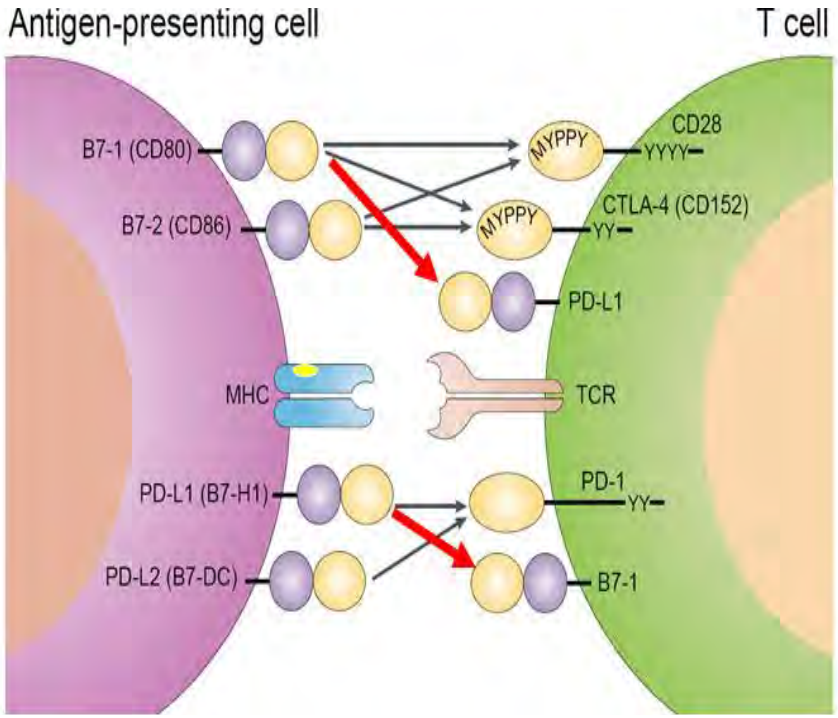
PD1 expressing T cells are dysfunctional





Ahmadzadeh M & Rosenberg SA. *Blood*. 2009; 114:1537-44

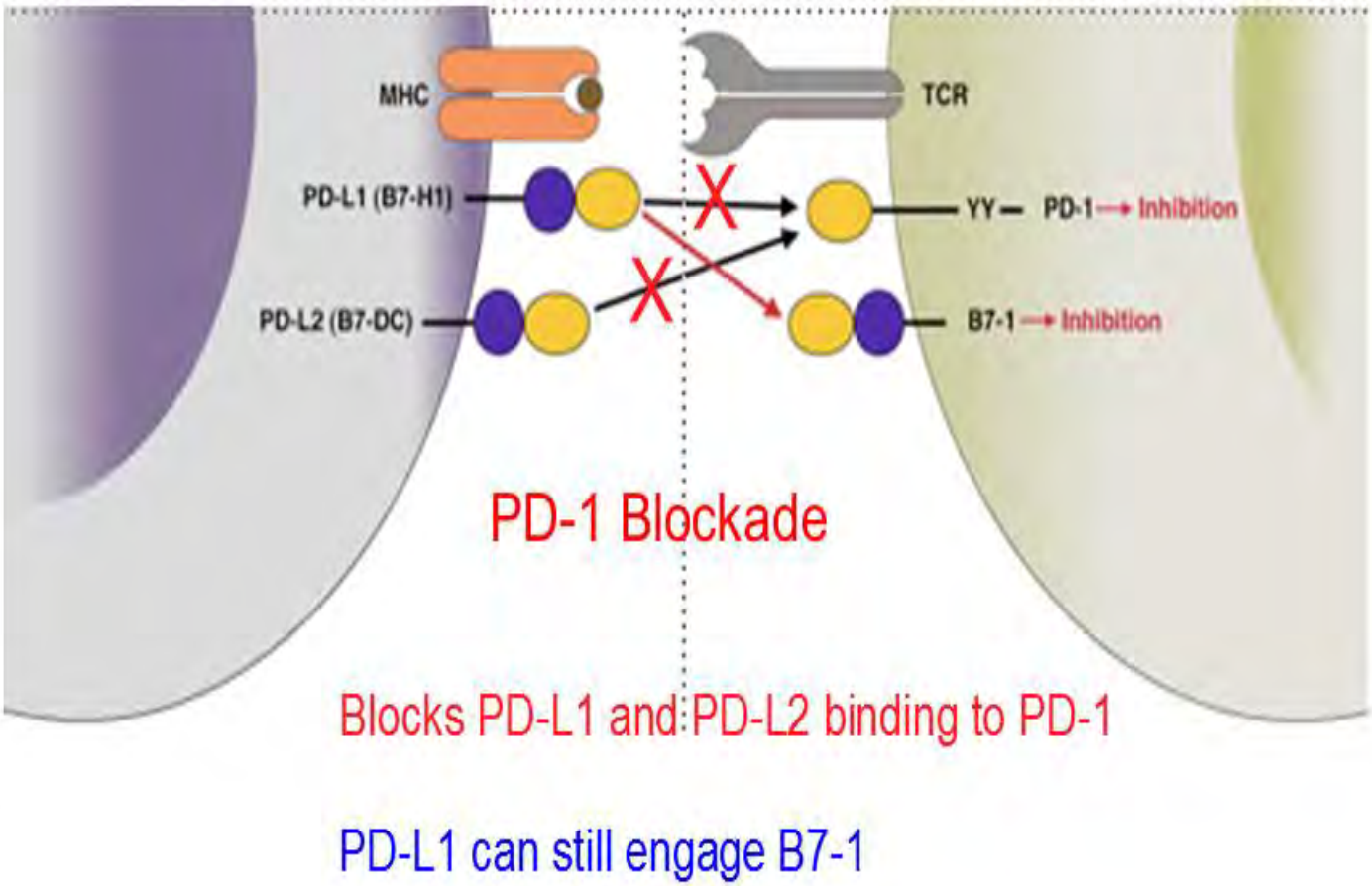
PD-L1: B7-1 Pathway Also Inhibits T Cell Responses



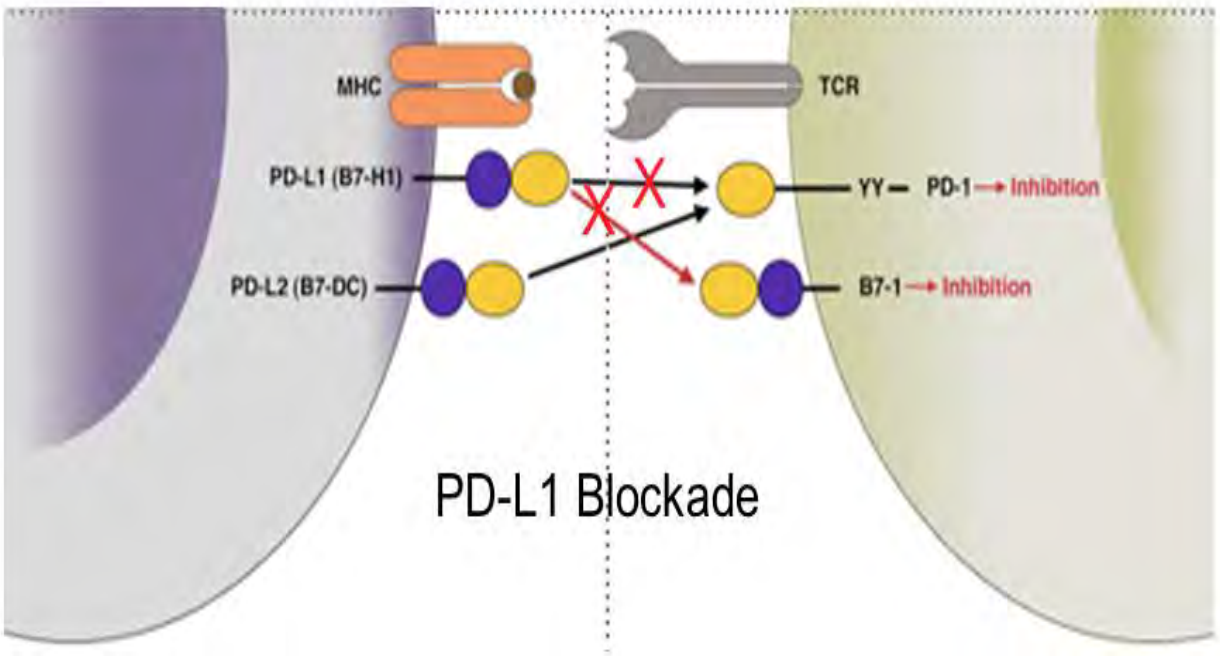
- B7-1 interacts more strongly with PD-L1 (1.7µM) than with CD28 (4µM) but less strongly than with CTLA-4 (0.2 µM)
- All therapeutic PD-L1 Abs are dual blockers
- B7-1: PD-L1 interaction inhibits T cell responses predominant role in controlling effector T cell responses

Butte, et al. *Immunity.* 2007.
Paterson, et al. *JI.* 2011.

Anti-PD-1 and Anti-PD-L1 mAbs Block Distinct Interactions



Anti-PD-1 and Anti-PD-L1 mAbs Block Distinct Interactions



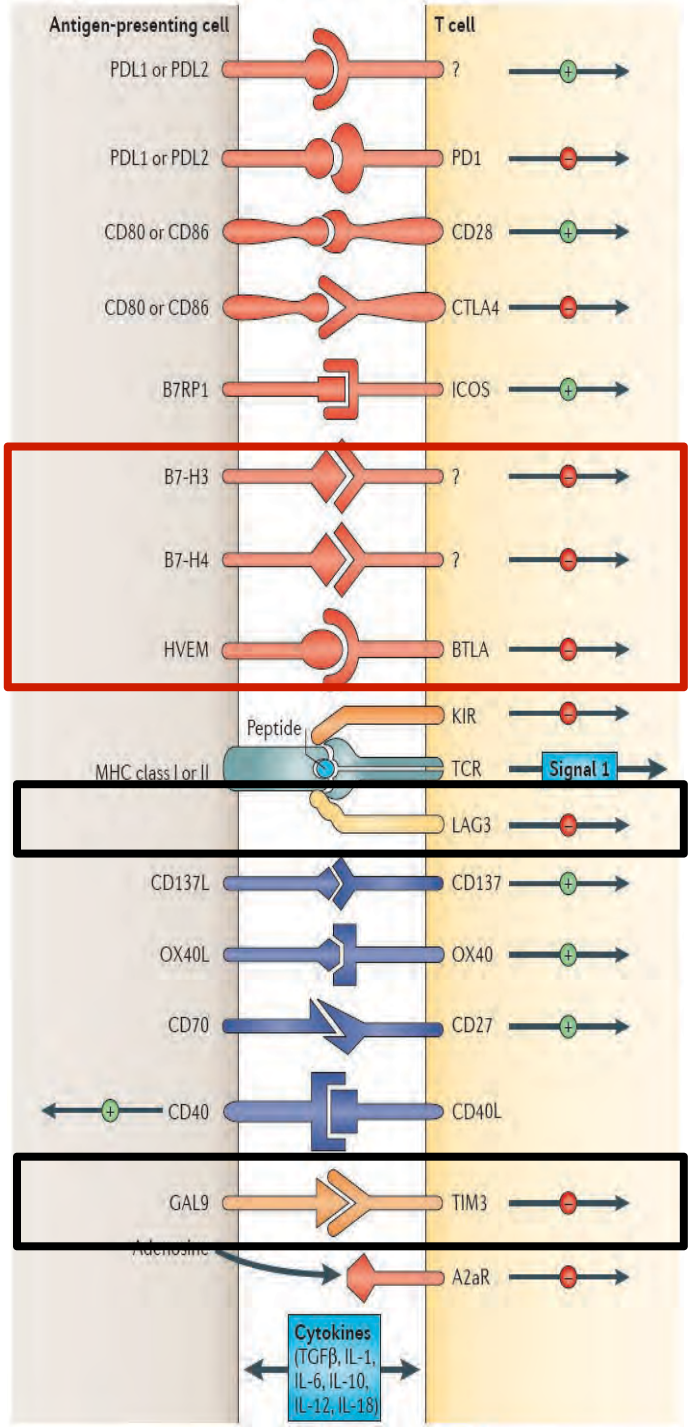
Blocks PD-L1 binding to PD-1 and B7-1

PD-L2 can still engage PD-1

Immune Checkpoints

- Checkpoint pathways
  - CTLA-4 and PD-1
- **Other Checkpoints: B7 family and others**
- Beyond Checkpoints: Costimulators
- Beyond T cells: NK, DC, Macrophage
- Markers for checkpoint pathway inhibition

Other Immune Checkpoints



B7 familly

LAG3, TIM3, …

Pardoll. *Nat Rev Cancer.* 2012.

LAG-3 (lymphocyte activation gene-3)

- Ig superfamily member
- Binds MHC class II (like CD4)
- Expressed by activated T cells
- LAG-3 ligation inhibits TCR signaling
- Also expressed by Tregs. Blocking of LAG-3 results in inhibition of suppressive capacity
- Activation of CD8+ T cells leads to LAG-3 upregulation
- LAG-3 may render CD8+ T cells in a tolerogenic state
- Combined anti-PD1 and anti-LAG-3 may have better anti-tumor effects

TIM-3 (T cell immunoglobulin-3)

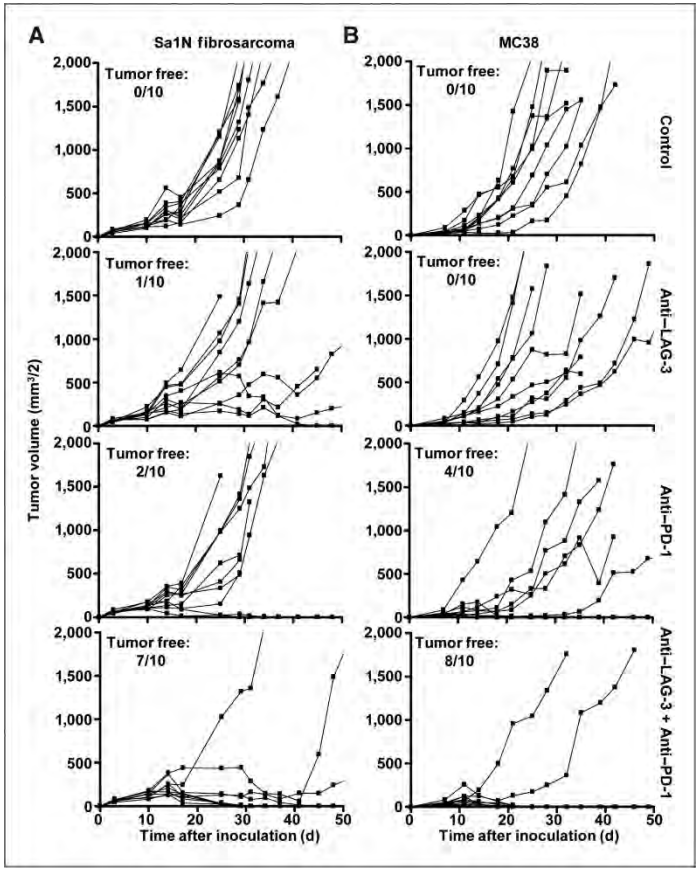
- Ig superfamily member consists of an N-terminal IgV domain and a mucin domain
- Tim-3 ligand: S-type lectin galectin-9 (Gal-9), soluble molecule widely expressed, upregulated by IFN-γ
- Tim-3 as a negative regulatory molecule: negative regulator of IFN-g-secreting $CD4^+$ T helper 1 and $CD8^+$ T cytotoxic 1 cells
- Promote development of CD8+ T cell exhaustion
- In vivo blockade results in exacerbated autoimmunity and abrogation of tolerance in experimental models,
- Induce expansion of myeloid-derived suppressor cells (MDSC), expressing high levels of Gla-9
- Tumor infiltrating lymphocytes co-expressed PD-1 and TIM-3

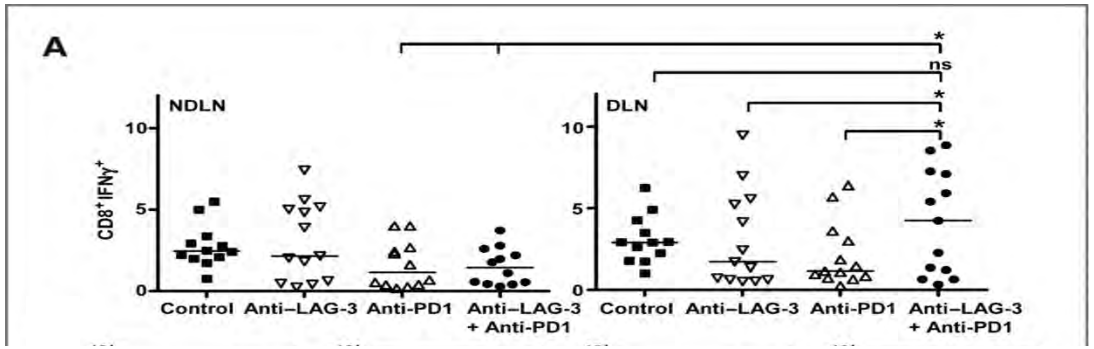
Sakuishi K, *Trends Immunol*. 2011; 32:345-9
Anderson AC. *Curr Opin Immunol*. 2012; 24:213-6

New Combination Immunotherapies:

- Anti-PD1/PDL1 + anti-LAG3
- Anti-PD1/PDL1 + anti-TIM-3
- Anti-PD1 + agonistic anti-GITR
- Anti-PD1 + other agonistic antibodies
- Triple combinations?
  (anti-CTLA4 + anti-PD1 + 3rd new drug)

Combinatorial anti–LAG-3/anti–PD-1 Treatment Inhibits Tumor Growth

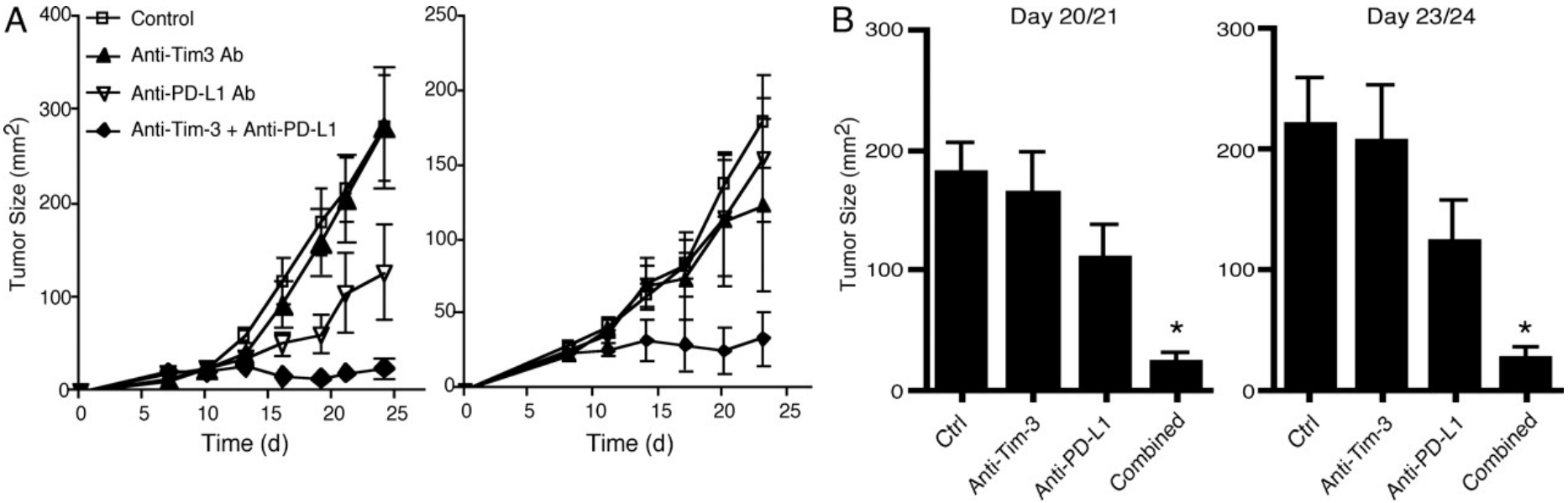




Anti-LAG-3 + Anti-PD-1

Woo S et al. *Cancer Res.* 2012;72:917-927.

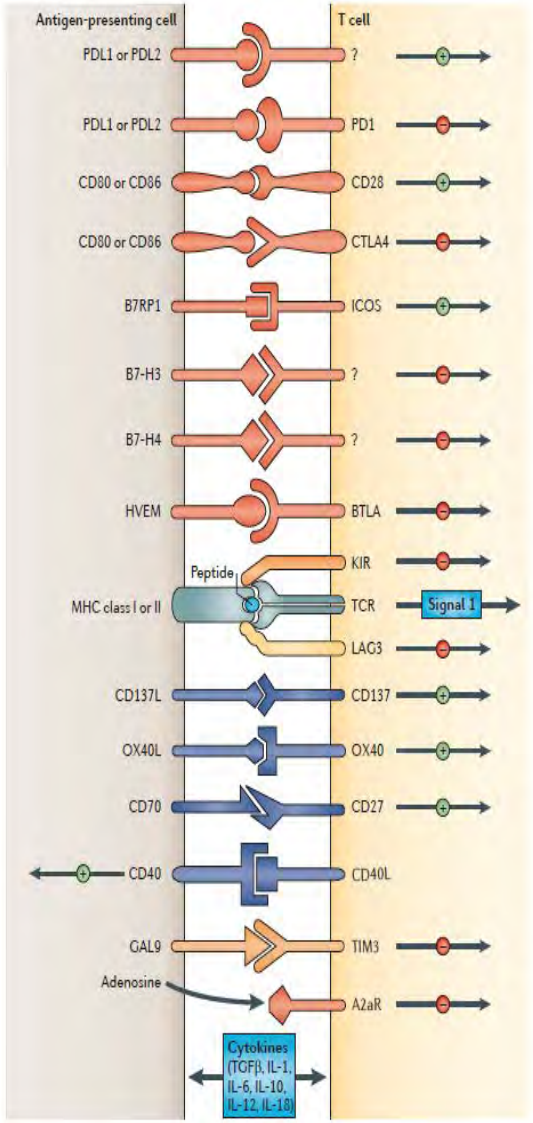
Effect of Targeting the Tim-3 and PD-1 Signaling Pathways on Tumor Growth.



CT26 tumor cells implanted into wild-type BALB/c mice.

Sakuishi K et al. *J Exp Med* 2010;207:2187-2194

Immune Checkpoint Pathways in clinical trials



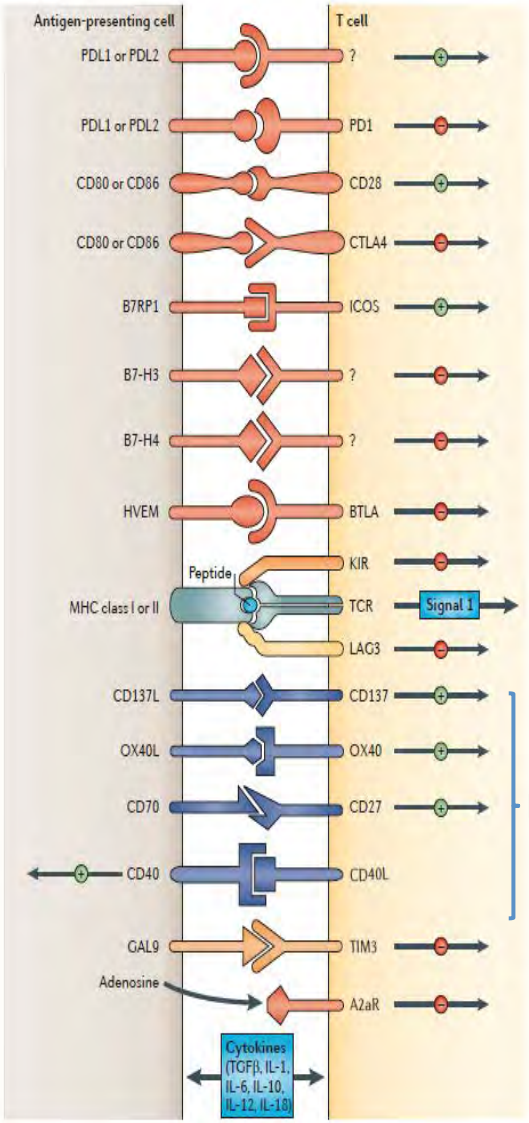
Target	Biological function	Antibody or fusion protein	State of clinical development
B7/Ig family			
CTLA-4	inhibitory receptor	ipilimumab, fully human IgG4	EMA and FDA approved for melanoma, phase II and III trials in RCC, SCLC/NSCLC, prostate, pancreatic, ovarian, and Merkel cell carcinoma
		tremelimumab, fully human IgG2	failed in phase III for melanoma, phase II in mesothelioma
PD-1	inhibitory receptor	nivolumab, fully human IgG4	phase III for melanoma and NSCLC recruiting, phase II in RCC
		lambrolizumab (MK-3475), humanized IgG4	phase III for melanoma and NSCLC recruiting, phase II in CRC
		CT-011, humanized IgG	phase II in follicular lymphoma, DLBCL, multiple myeloma, AML, RCC, CRC, pancreatic cancer
		AMP-224 PD-L1 and human IgG1 fusion protein	no active study
PD-L1	inhibitory ligand	BMS-936559 (MDX-1105), human IgG4	no recruiting study
		MEDI4736, engineered human IgG1	phase 1 recruiting
		MPDL3280A, engineered human IgG1	phase 2 in melanoma, NSCLC
ICOS	co-stimulatory receptor	MEDI570, fully human IgG1	phase 1 terminated
		AMG557, fully human IgG2	phase 1b in SLE and psoriasis
B7-H3	inhibitory ligand	MGA271, humanized IgG1	phase 1b in melanoma
B7-H4	inhibitory ligand		preclinical development
LAG3	inhibitory receptor	IMP321, recombinant soluble LAG-3Ig fusion protein	phase 2 in melanoma
TIM3	inhibitory receptor		preclinical development

Blank CU, *Current Op Oncol. 2014.*

Immune Checkpoints

- Checkpoint pathways
  - CTLA-4 and PD-1
- Other Checkpoints: B7 family and others
- **Beyond Checkpoints: Costimulators**
- Beyond T cells: NK, DC, Macrophage
- Markers for checkpoint pathway inhibition

Immune Costimulation Pathways in Clinical Trials



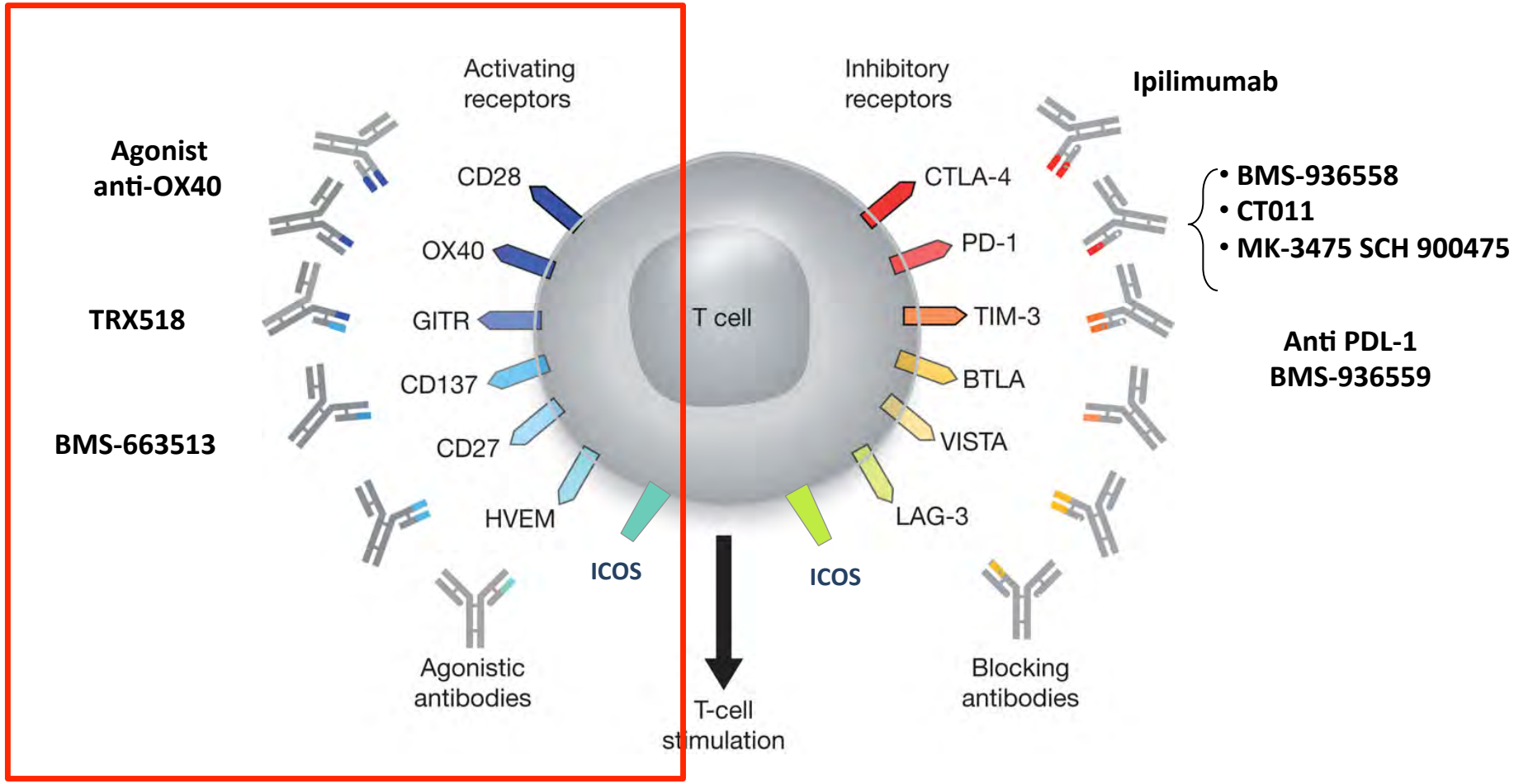
Famille TNF

Positive Costimulation Pathways

TNF(R) family			
CD40	co-stimulatory receptor	CP-870,893, fully human IgG2	phase 1b in melanoma (+tremelimumab) and pancreatic cancer (+gemcitabine)
		lucatumumab, fully human IgG1	phase 2 in lymphoma
		Dacetuzumab (SGN040), humanized IgG1	
CD137	co-stimulatory receptor	Urelumab (BMS-663513), fully human IgG4	phase 2 in melanoma, phase 1b in NSCLC and B-NHL
		PF-05082566, fully human IgG2	phase 1b in NHL (+rituximab)
CD27	co-stimulatory receptor	CDX-1127, fully human IgG1	phase 1
OX40	co-stimulatory receptor	anti-CD40 mouse IgG	phase 1
OX40L	co-stimulatory ligand	RO4989991, fully human IgG1	phase 2 in allergic asthma
GITR	co-stimulation	TRX518, engineered human IgG1	Phase 1b in melanoma

Blank CU. *Current Op Oncol.* 2014.

T cell Targets for Immunoregulatory Antibody Therapy



Mellman *et al. Nature.* 2011;480,480-489.

Beyond Checkpoints: GITR Co-stimulation

- GITR (Glucocorticoid-Induced Tumor necrosis factor-related Receptor) is constitutively expressed at high levels on Tregs and at low on resting CD4+ and CD8+ T cells, and NK cellss[1,2]
- GITR expression is highly upregulated on activated CD4+ and CD8+ T cells and NK cells, including tumor infiltrating lymphocytes
- GITR modulation has been indicated as one of the top 25 most promising research areas by the American National Cancer Institute, and clinical trials started[2]
- GITR ligation by GITRL (or anti-GITR agonist antibodies) provides a costimulatory signal that enhances both CD4+ and CD8+ T cell proliferation and effector functions leading to enhanced cellular and humoral immunity
- In addition, costimulation through GITR has been shown to render naive or effector T cells (Teffs) resistant to the suppressive effects of Tregs
- In contrast, blocking GITR-GITRL signaling with antagonist anti-GITRL antibodies inhibits T lymphocyte activation

1. Mouse glucocorticoid-induced tumor necrosis factor receptor ligand is costimulatory for T cells. Tone, M., Tone, Y., Adams, E., Yates, S. F., Frewin, M. R., Cobbold, S. P. & Waldmann, H. (2003) *Proc. Natl. Acad. Sci. USA* 100, 15059–15064
2. Pharmacological modulation of GITRL/GITR system: therapeutic perspectives. Giuseppe Nocentini, Simona Ronchetti, Maria Grazia Petrillo and Carlo RiccardiBritish *Journal of Pharmacology* (2012) 165 2089–2099 2089

Beyond Checkpoints: CD137/4-1BB Co-stimulation

- CD137/4-1BB, member of the TNF receptor superfamily T cell costimulatory receptor, is induced, when T cells receive antigen-specific signals
- Signals via CD137/4-1BB are costimulatory in nature
- CD137/4-1BB signaling by anti-4-1BB activates various immune competent cells , including T and NK cells, and APCs, leading to activation, cytokine induction, upregulation of CTL activity, and increased survival
- Signals through 4-1BB are more biased toward CD8+ T cells and NK cells, both *in vitro*, and *in vivo*
- *In vivo* administration of agonistic anti-CD137/4-1BB into mice promote CD8+ T cell expansion, and protect against several pathological conditions, including autoimmunity, cancer, and transplantation. The reasons underlying the *in vitro* vs. *in vivo* functions of anti-4-1BB are currently unclear.
- Targeting CD137/4-1BB either by anti- 4-1BB alone, or in combination with other agents, has powerful anticancer properties.
- A fully human IgG4 anti-CD137 antibody is under development with signs of clinical activity and dose-dependent effects.

Vinay DS, Kwon BS. 4-1BB (**CD137**), an inducible costimulatory receptor, as a specific target for **cancer** therapy. *BMB Rep*. 2014 Mar;47(3):122-9.
Ascierto PA, Simeone E, Sznol M, Fu YX, Melero I. Clinical experiences with anti-**CD137** and anti-PD1 therapeutic antibodies. *Semin Oncol*. 2010 Oct;37(5):508-16.

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  - CTLA-4 and PD-1
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- Beyond Checkpoints: Costimulators
- **Beyond T cells: NK, DC, Macrophage**
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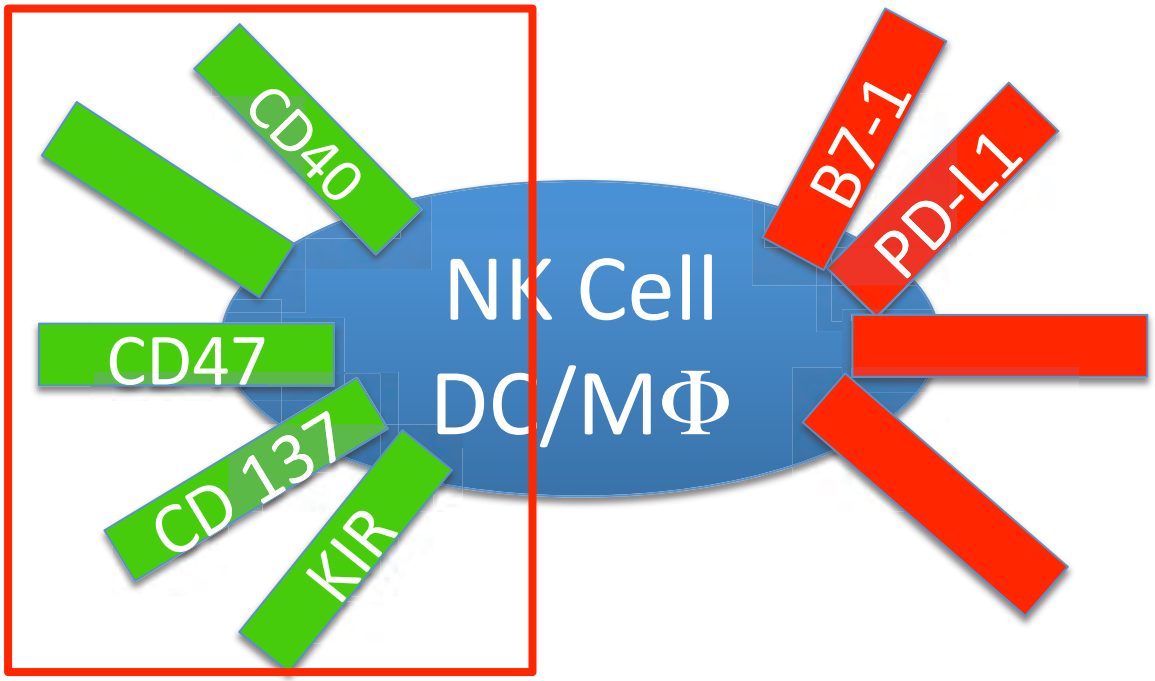
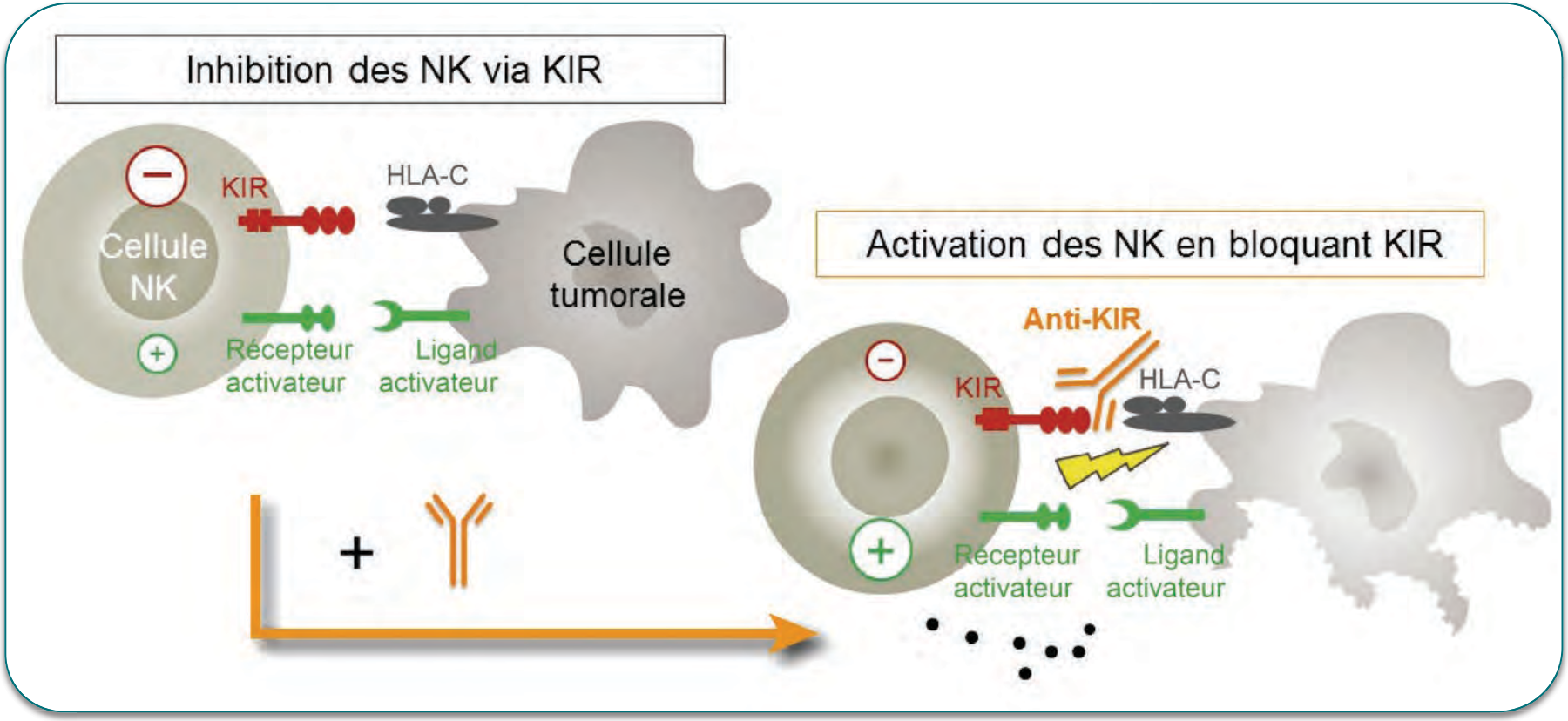
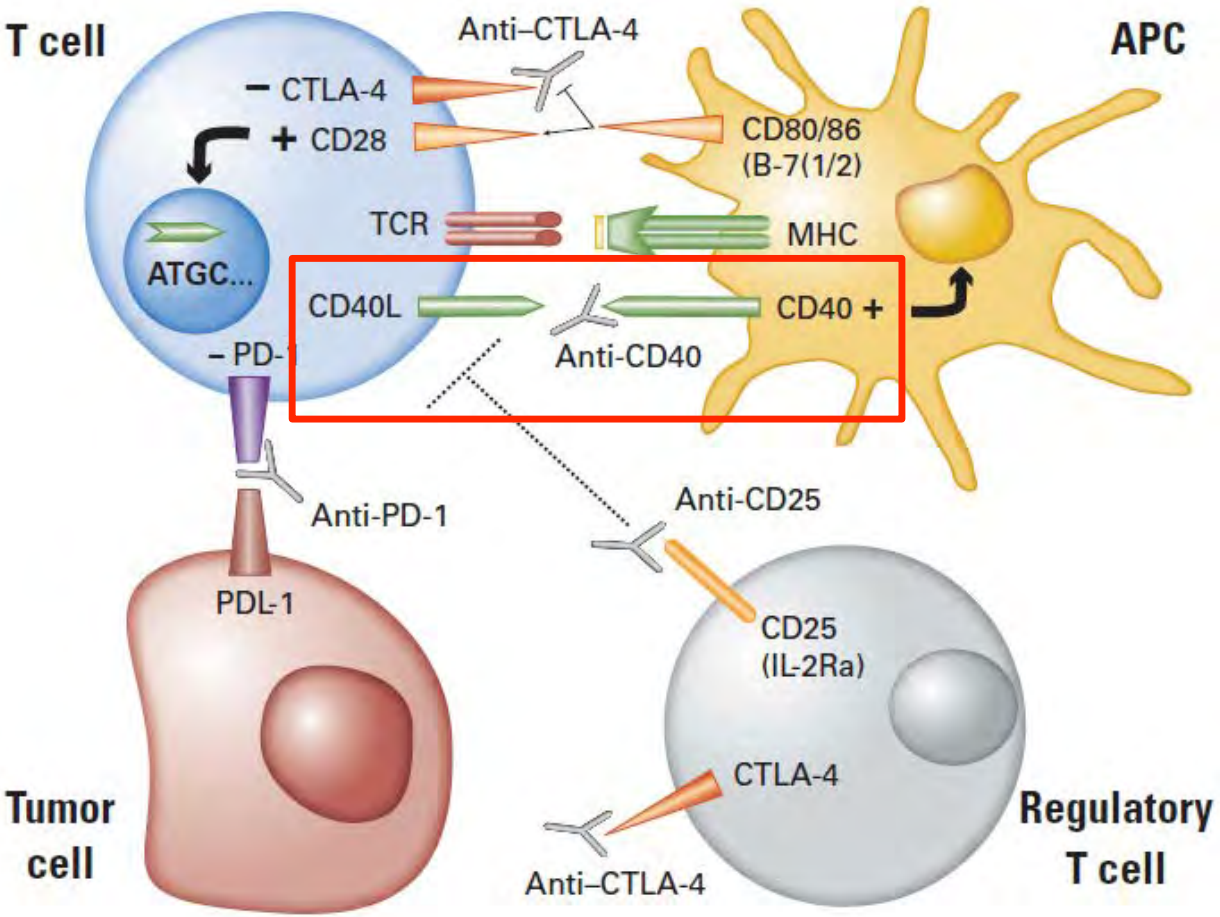
Beyond T Cells: NK, DC, Macrophage



Immuno-modulation des lymphocytes NK



Anti-CD40 to Stimulate DC and Induced Anti-Tumor Immunity



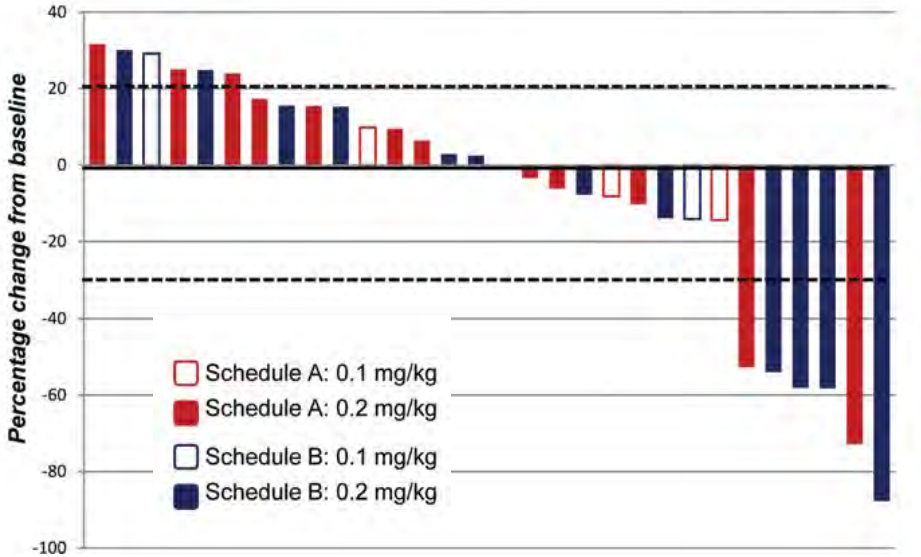
Kandalaft. *J Clin Oncol.* 2011.

Anti-CD40 mAb induce objective responses (20%) in pancreatic and ovarian cancers

Pancreatic cancer

PR, N=5 (20%)

Ovarian cancers

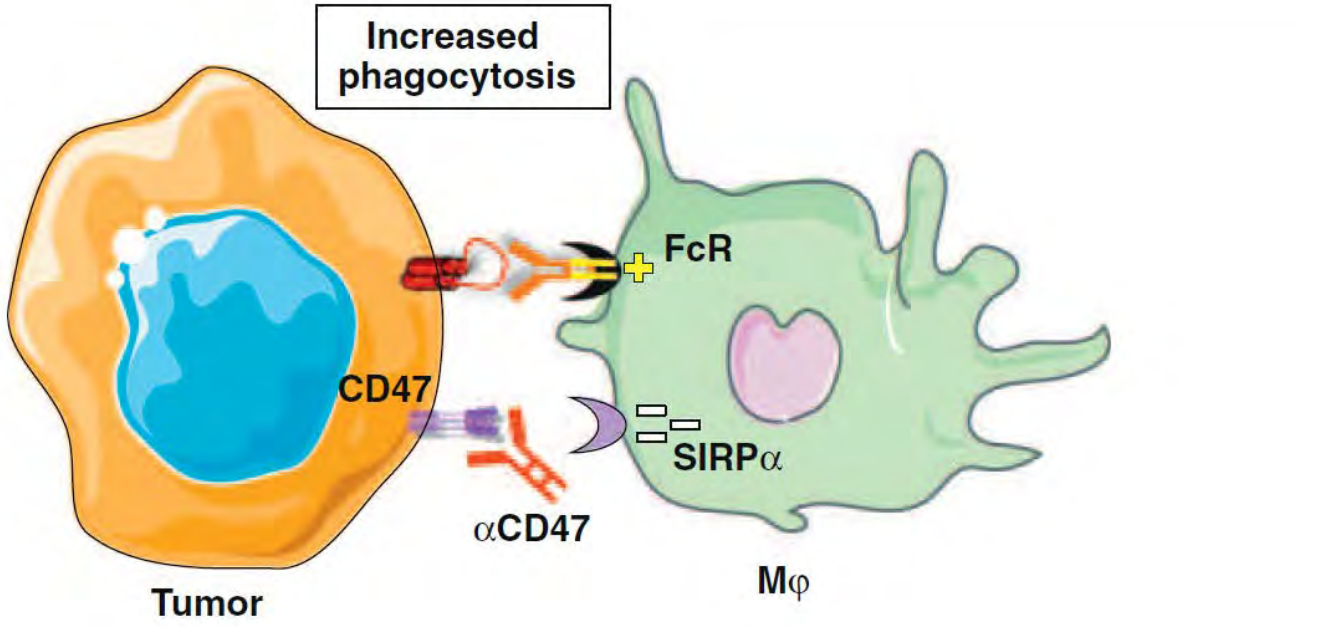


PR, N=6 (20%)
1 Ovarian cancer

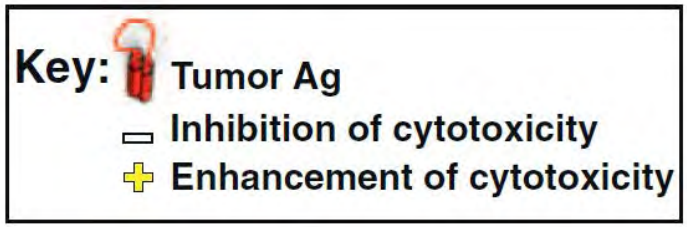
Beatty GL, *Science* 2011

Vonderheide RH, *Oncoimmunology* 2013

Anti-tumor mAb + anti-CD47: Boost Macrophages Antibody Dependent Cell Phagocytosis (ADCP)

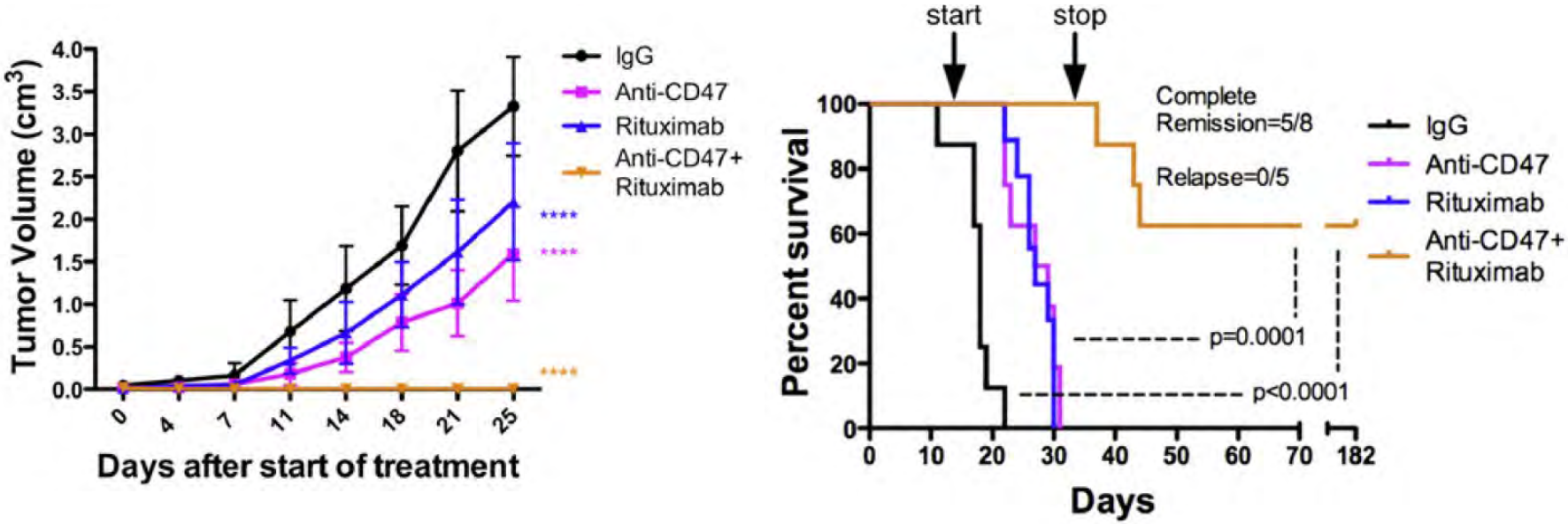


Block the "Don't Eat Me" Signal



Houot R, Kohrt HE, Marabelle A, Levy R. Targeting immune effector cells to promote antibody-induced cytotoxicity in cancer immunotherapy. *Trends Immunol*. 2011;32:510-6.

Anti-CD47 mAb Synergizes with Rituximab to Promote Phagocytosis and Eradicate Non-Hodgkin Lymphoma.



Chao MP, &, Levy R, Weissman IL, Majeti R. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell. 2010 Sep 3;142(5):699-713.

Immune Checkpoints

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- Beyond Checkpoints: Costimulators
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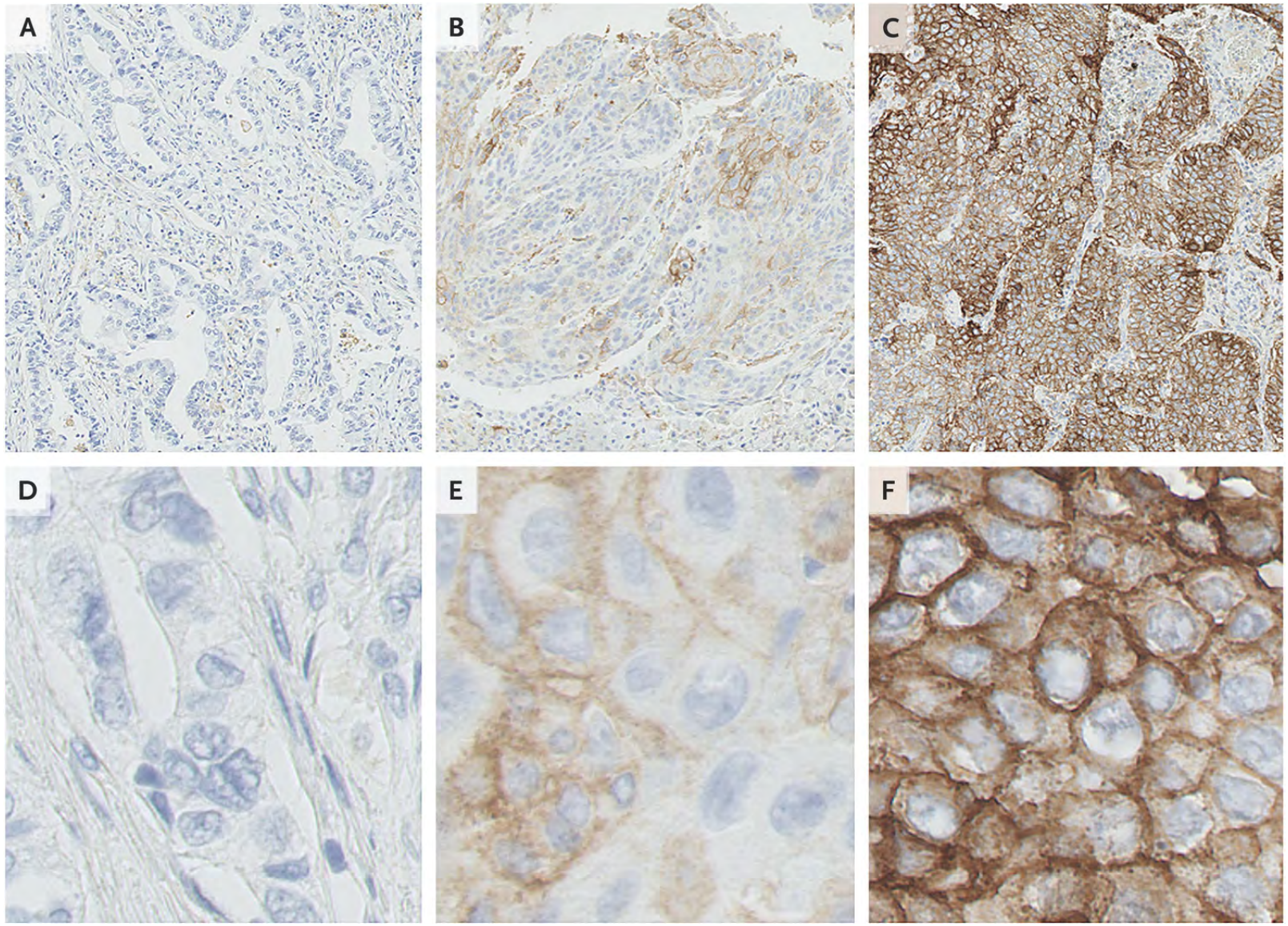
- **Markers for checkpoint pathway inhibition**

Markers for Checkpoint Pathway Inhibition

- **Issues in clinical trials**
  - **Predict the patients that will benefit from the treatment (to limit unbeneficial tox)**
  - **Define alternative therapeutic approaches for non-responding patients**
  - **Determine best potential association with tumor targeted therapies**
  - **Define biomarker for immunotherapy treatment suspension**

PD-L1 Expression in Non–Small-Cell Lung Cancers.



Garon EB et al. N Engl J Med 2015

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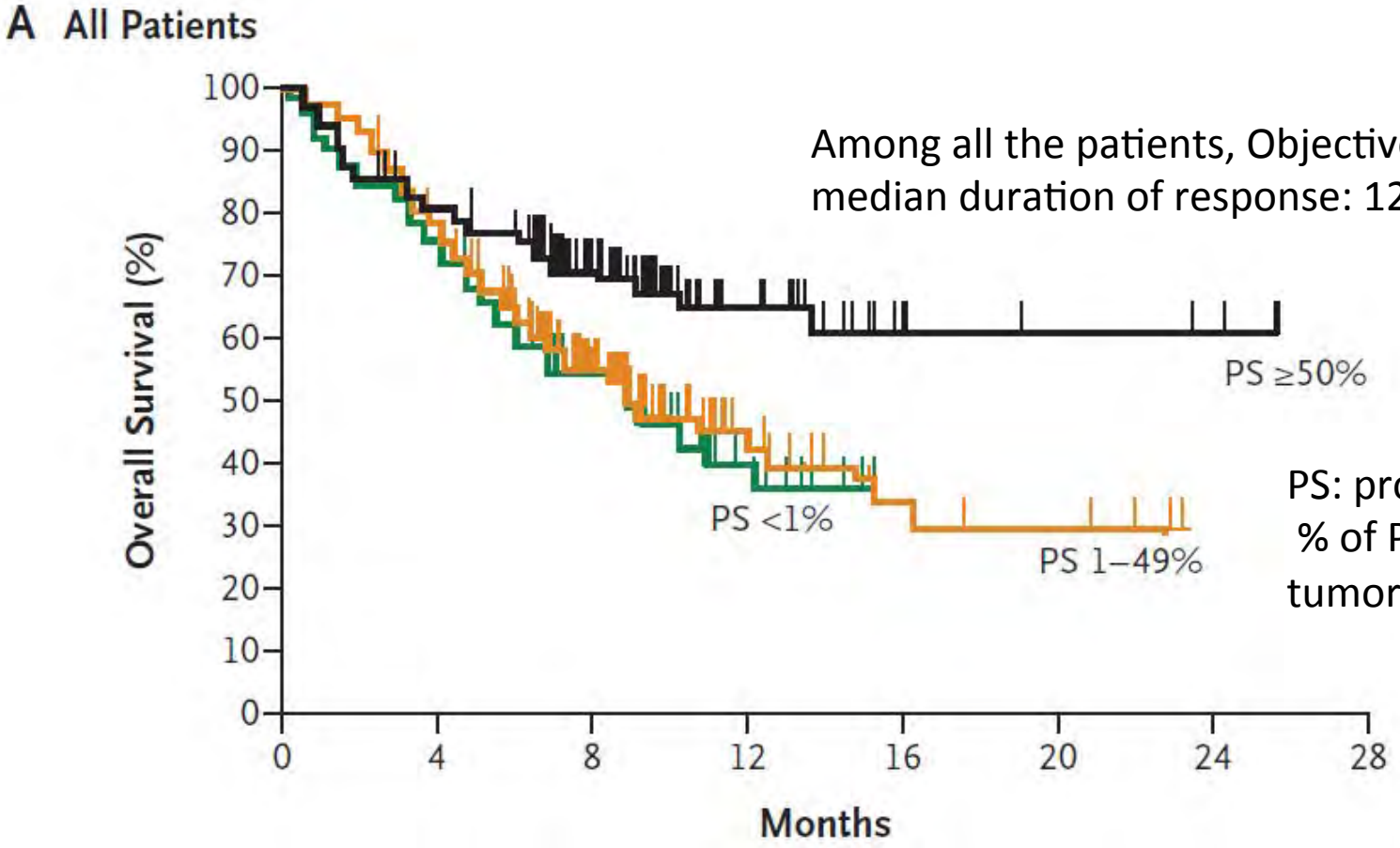
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer



Among all the patients, Objective Response: 19.4%
median duration of response: 12.5 months.

PS: proportion score =
% of PD-L1 expressing
tumor cells

No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

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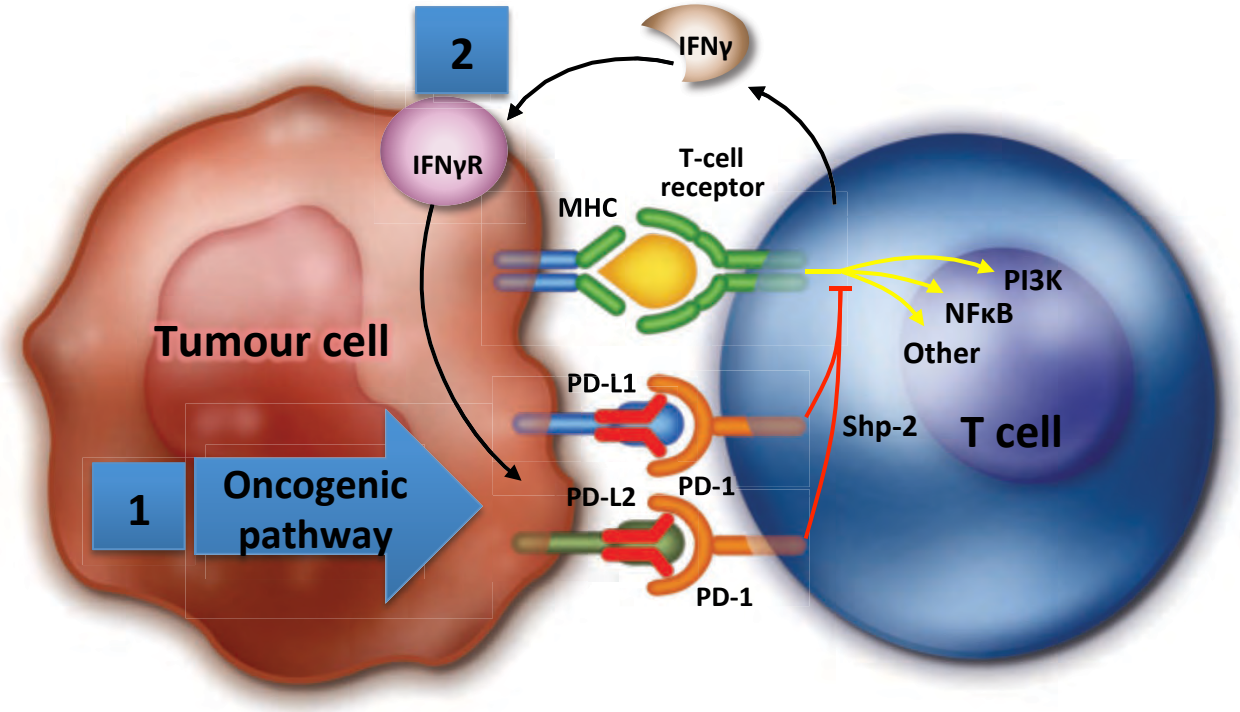
ORR according to PD-L1 Expression in Patients with Solid Tumors

Rx Antibody	Testing Method	N	PD-L1 + RR	PD-L1 - RR
Nivolumab[1]	Manual staining – 5H1 5% cutoff Tumor staining	49	13/31 42%	0/18 0%
Nivolumab[2]	Dako automated 5% cutoff Tumor staining	38	7/17 41%	3/21 14%
MPDL3280A[3]	Automated Roche Dx IHC 1% cutoff Tumor immune cell staining	103	13/36 36%	9/67 13%
Ipi/Nivo[4]	Dako automated 5% cutoff Tumor staining	56	8/14 57%	17/42 40%
MPDL3280A (anti-PD-L1)[5]		130	26/60 43%	8/70 11%

From: Immuntherapy in Cancer: From Principles to Practice

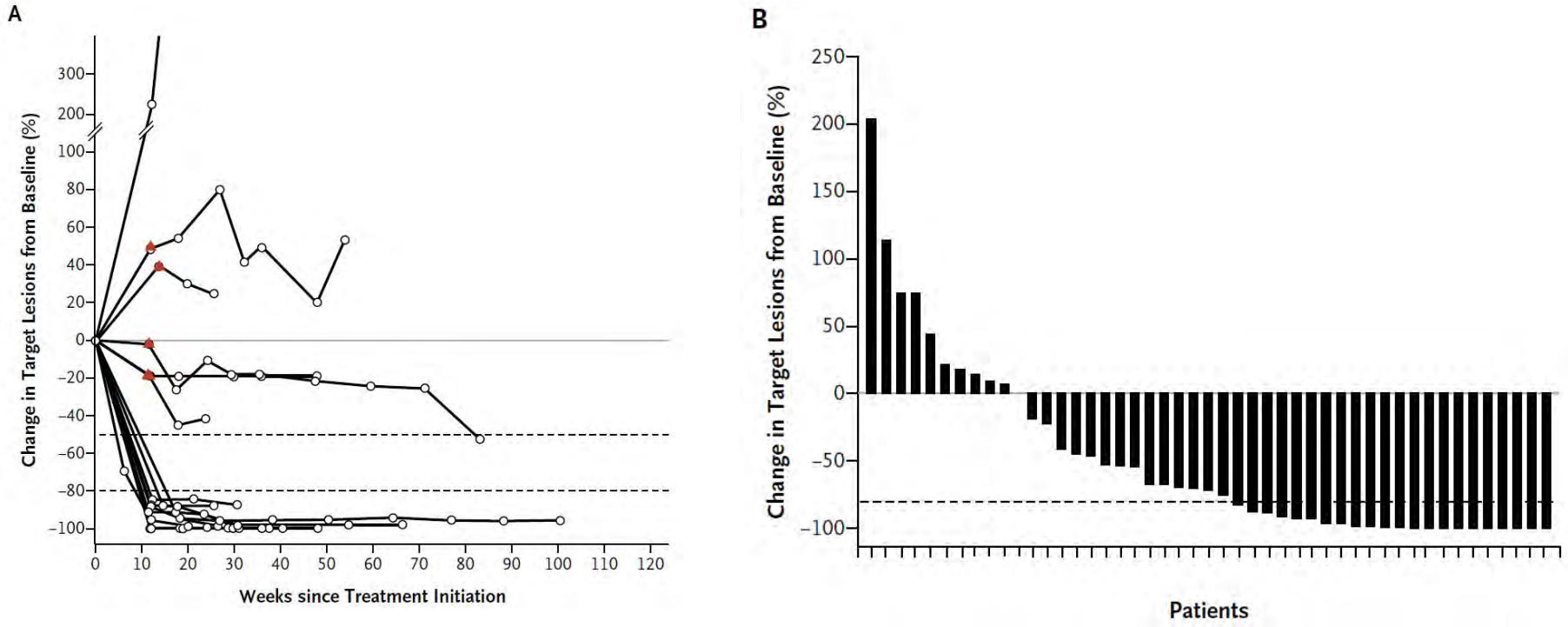
1. Topalian SL, et al. *N Engl J Med*. 2012;366:2443-54. 2. Grosso J, et al. ASCO 2013. Abstract 3016. 3. Herbst RS, et al. ASCO 2013. Abstract 3000. 4. Sznol M, et al. ASCO 2014. LBA9003. 5. Powles T, *Nature* 2014; 515:558-562

Oncogene versus T cell–Driven PD-L1 Expression Up-Regulation



Sznol M et al. ASCO 2013. Abstract CRA9006.

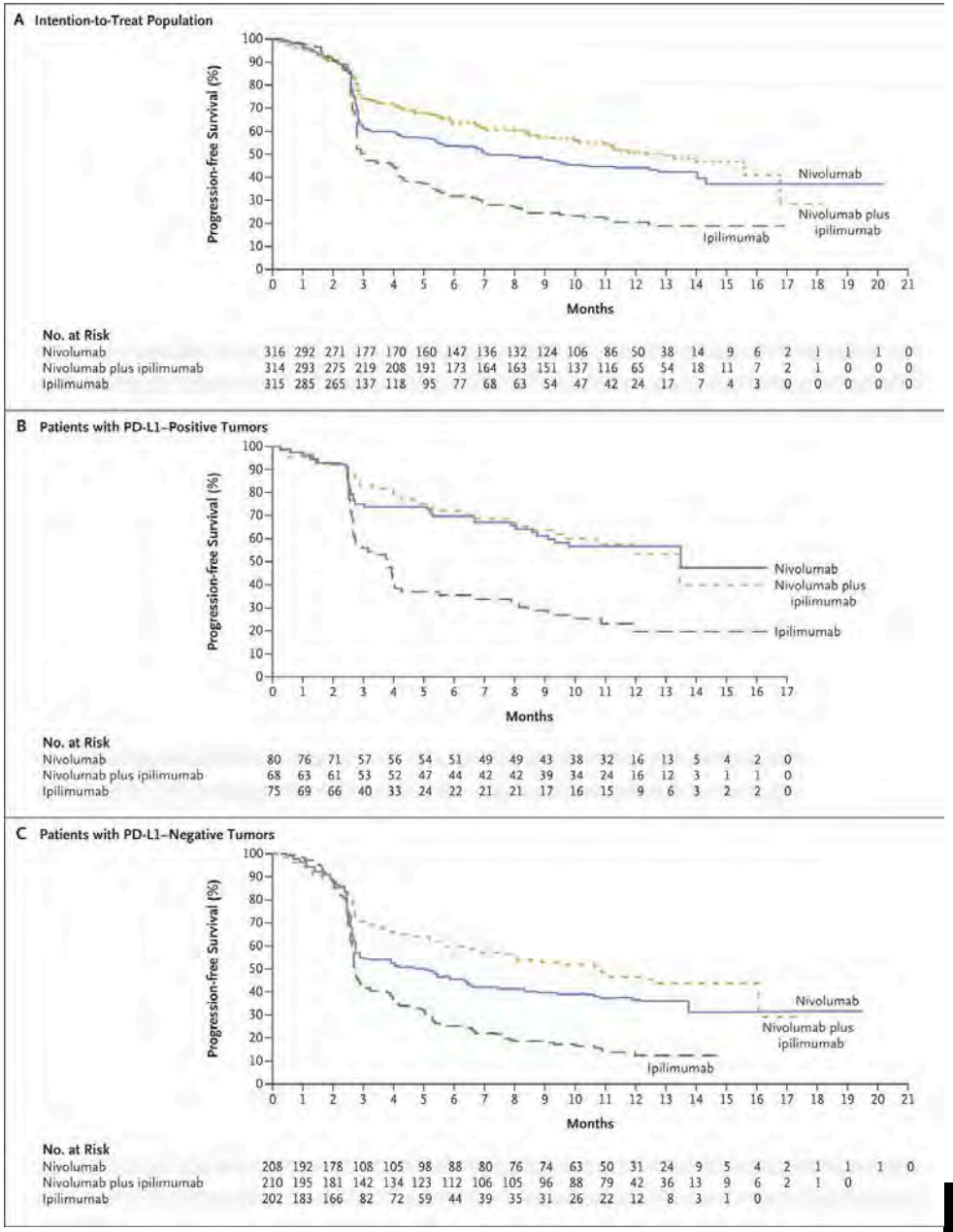
Nivolumab (Anti-PD1) + Ipilimumab (anti-CTLA4) in advanced melanoma



53 patients included,
40% objective clinical responses,
65% with either immune or clinical response
At the highest dose, 53% clinical response with 80% tumor regression

Nivolumab + Ipilimumab in advanced melanoma.
Wolchok SL, et al., N Engl J Med. 2013

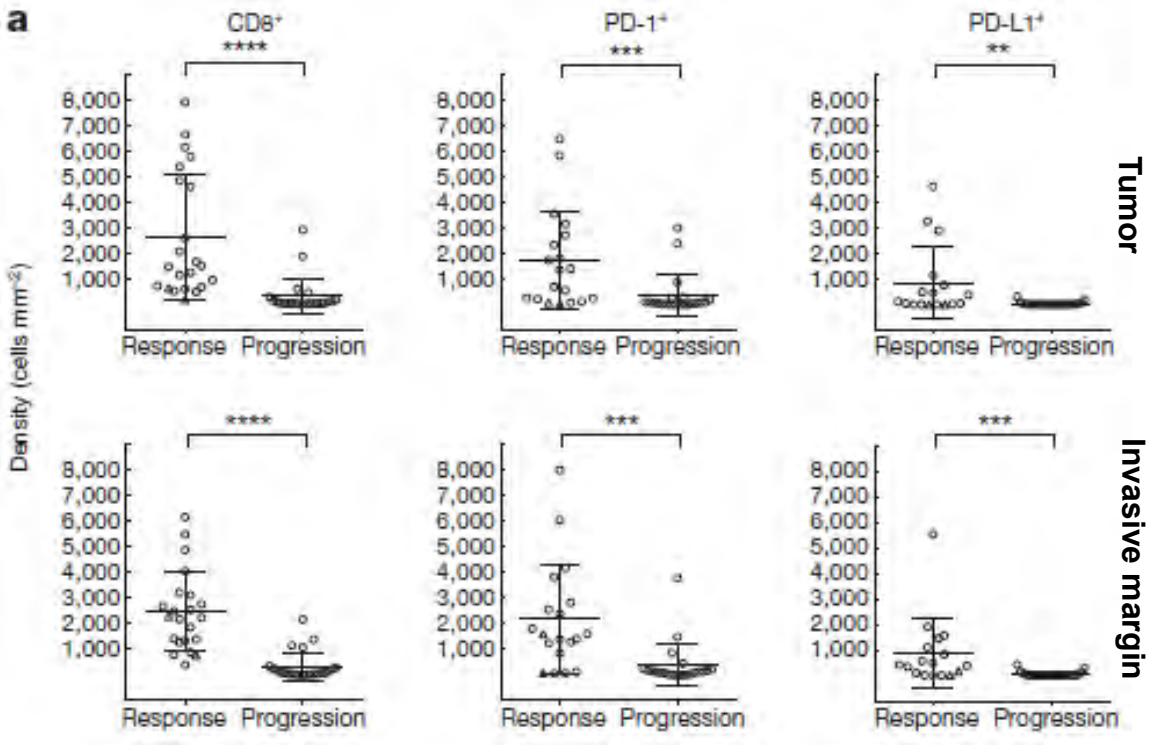
Progression-free Survival.

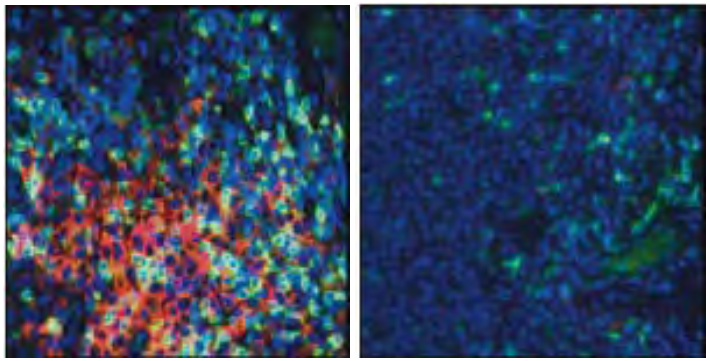


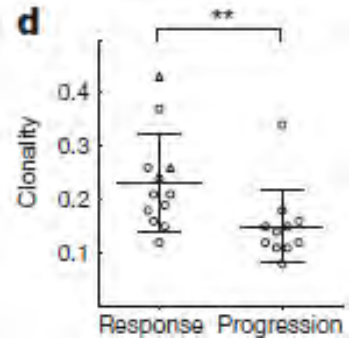
The NEW ENGLAND JOURNAL of MEDICINE

Larkin J et al. N Engl J Med 2015;373:23-34

Baseline Density, Location and Proximity of CD8+, PD-1+, PD-L1+ and T-cell Repertoire Predict Anti-PD1 Treatment Outcome.



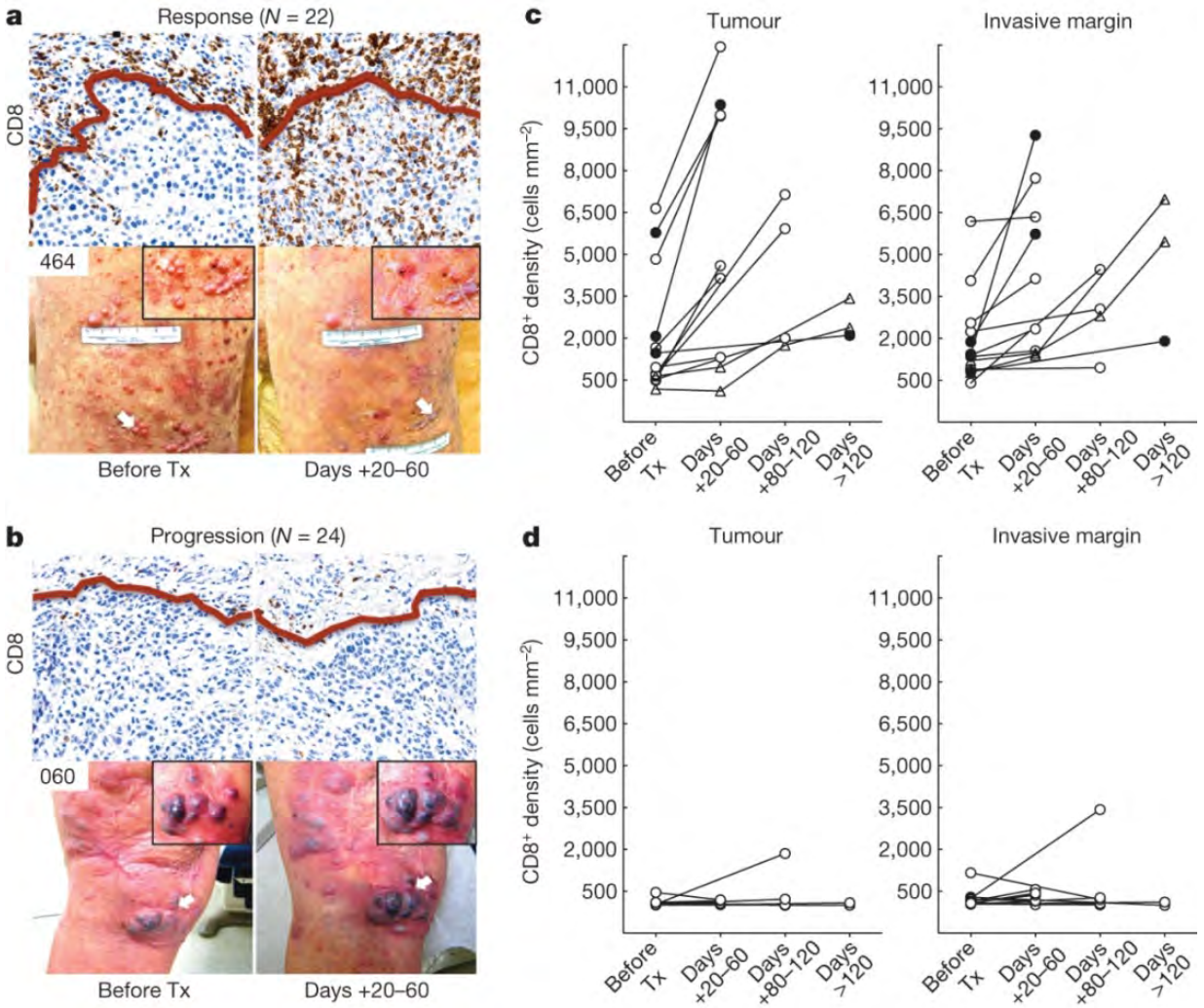




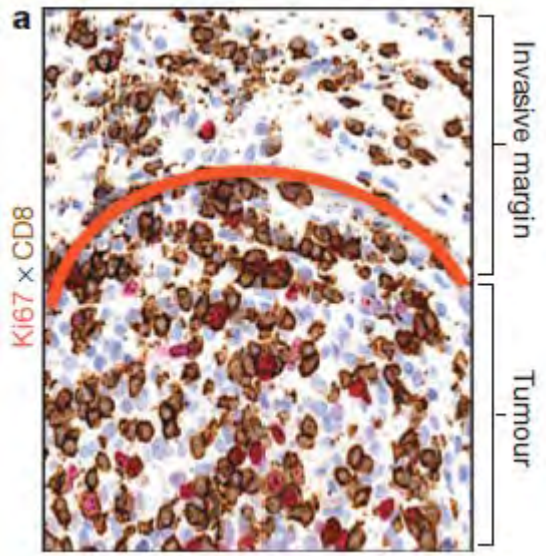
PC Tumeh *et al. Nature* **515**, 568-571 (2014)

nature

CD8 T Cell Infiltration Increases Following Anti-PD1 Treatment



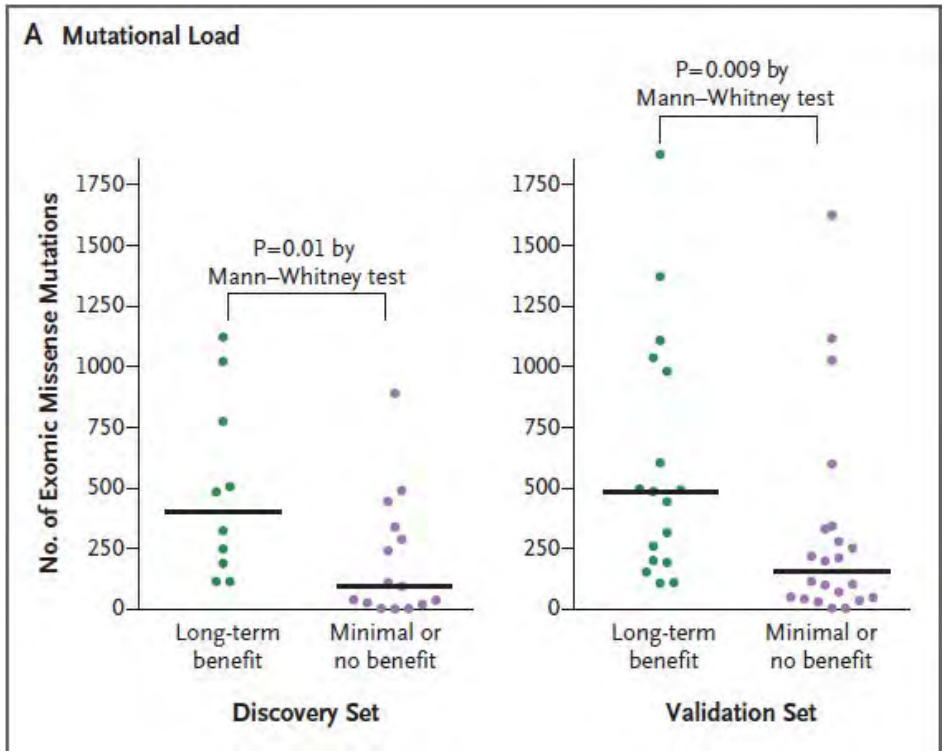
CD8 T cells proliferate following anti-PD1 treatment

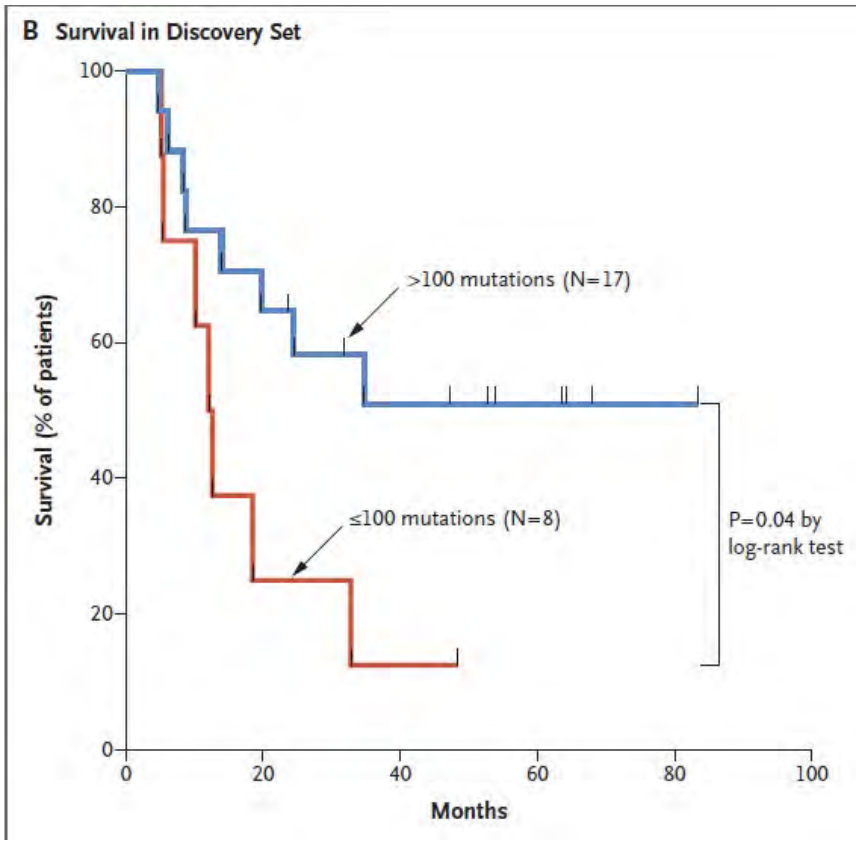


nature

PC Tumeh *et al. Nature* **515**, 568-571 (2014)

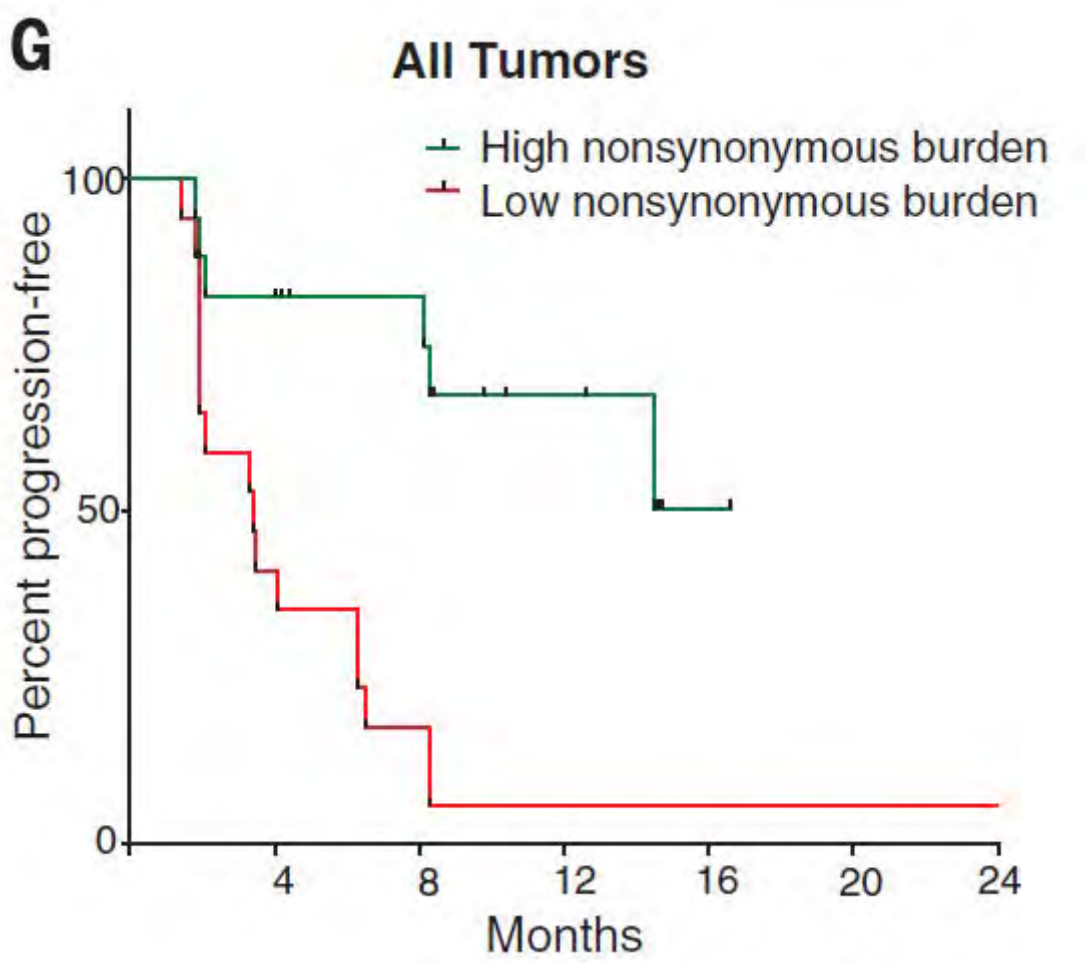
Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment (melanoma).





Snyder A et al. N Engl J Med 2014.

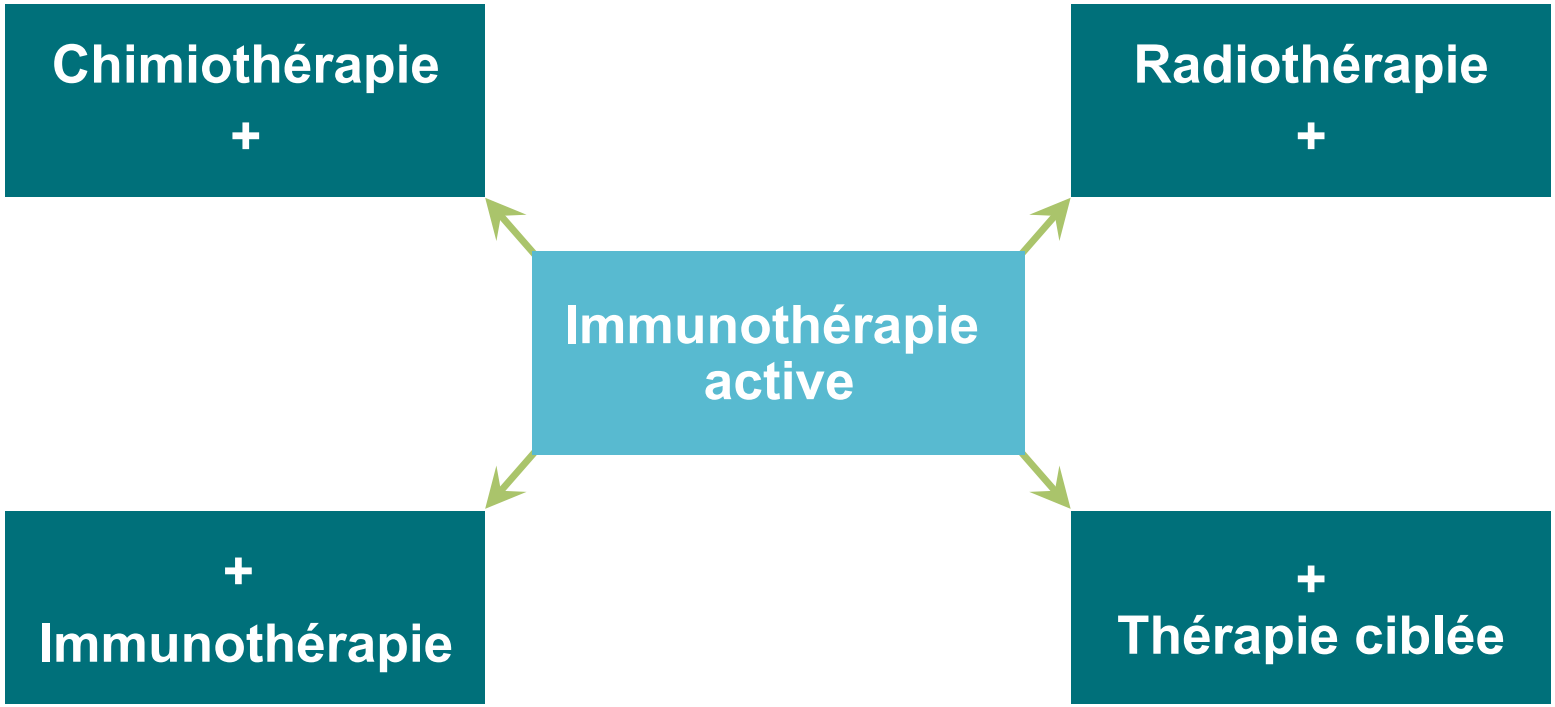
Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer



Rizvi NA et al. Science 2015

Combinaisons thérapeutiques

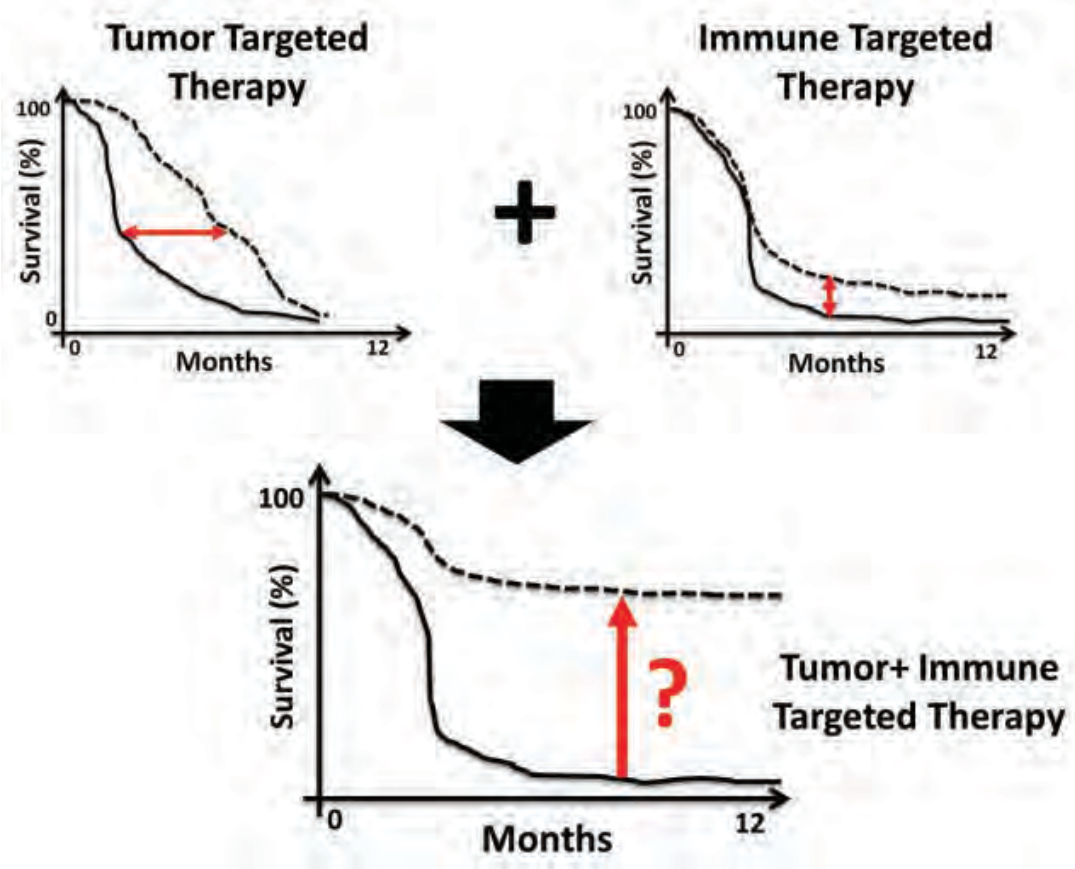
Approches explorées[1-4]



- **Rationnel, stratégie, séquence ?**

1. Drake CG. Ann Oncol 2012;23(suppl 8):viii41-viii46. 2. Hannani D, et al. Cancer J 2011;17:351-8.
3. Ménard C, et al. Cancer Immunol Immunother 2008;57:1579-87. 4. Ribas A, et al. Curr Opin Immunol 2013:25:291-6.

Combined Targeted and Immunotherapy: The Future of Personalized Medicine



Marabelle A, Caux C. *Blood*. 2012; 120:4454-5.