Oncology

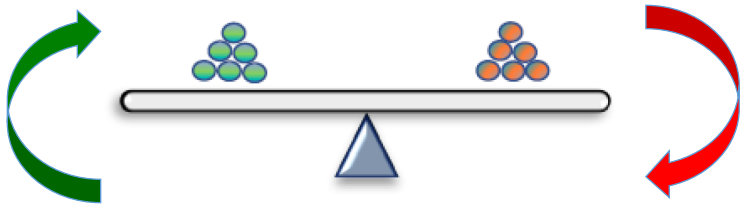
Anti-cancer therapies II: Immunotherapies

The role of the immune system in cancer

Some immune cells *support* the growth of the tumor

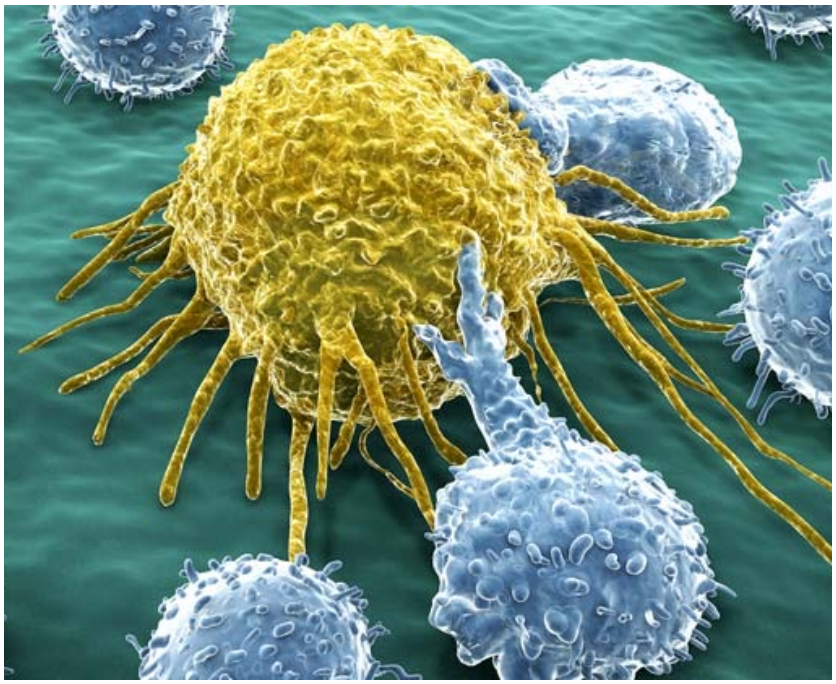
Some immune cells *limit* the growth of the tumor

Tumor progression



Tumor regression

Cancer immunotherapy



Immune checkpoint blockade (PD1, CTLA4)

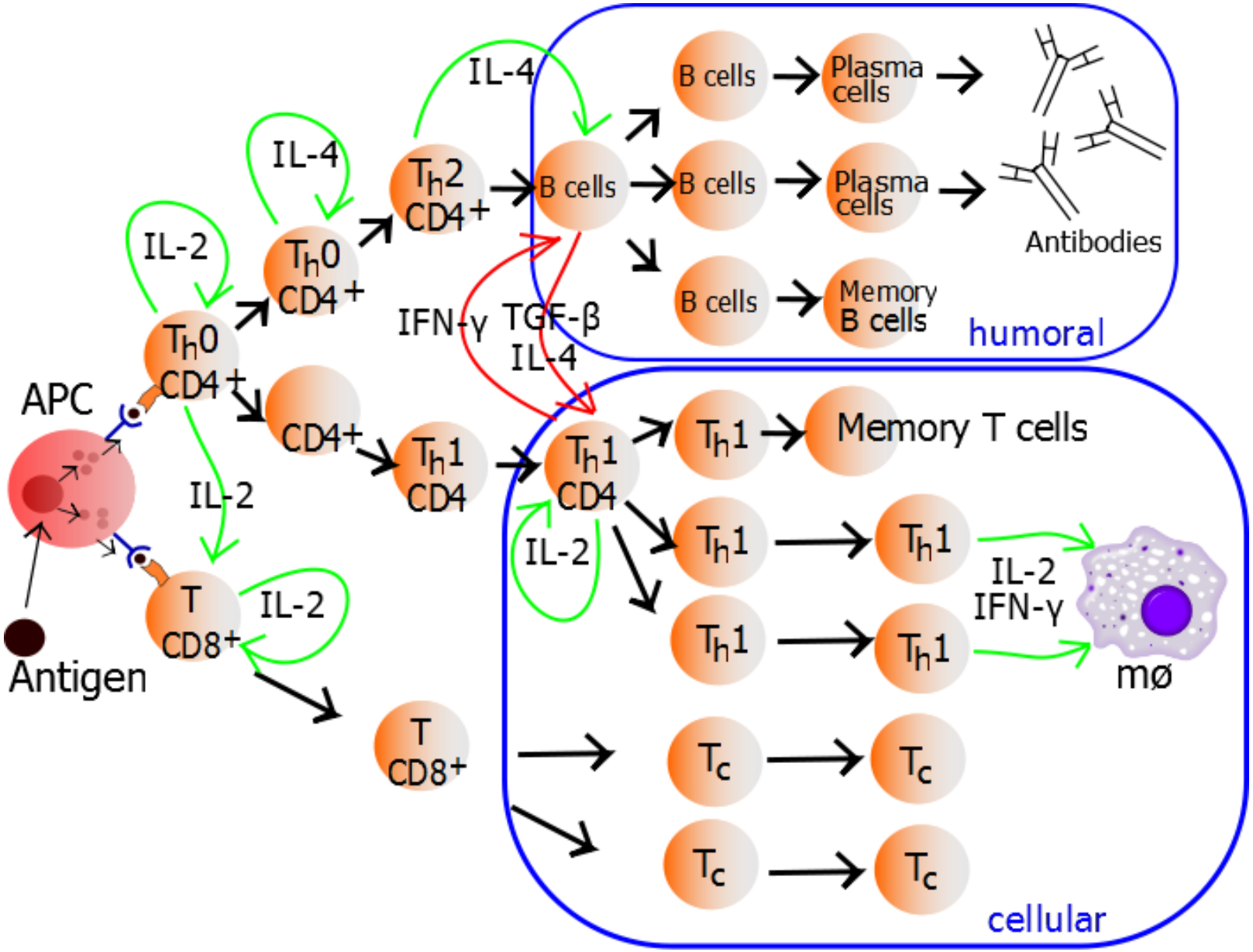
Adoptive T cell therapies

Tumor vaccines

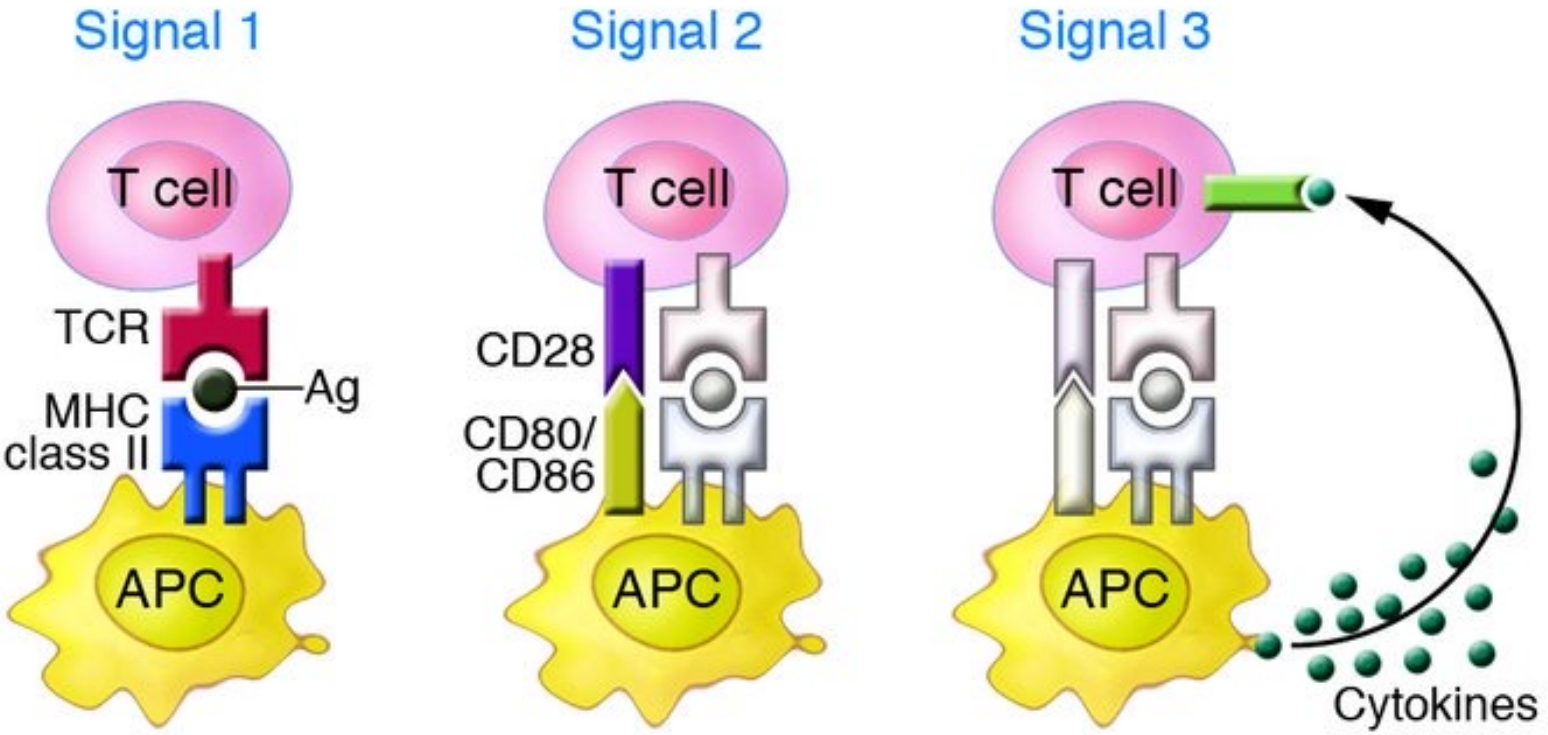
Dendritic cell vaccines

Immune cytokines

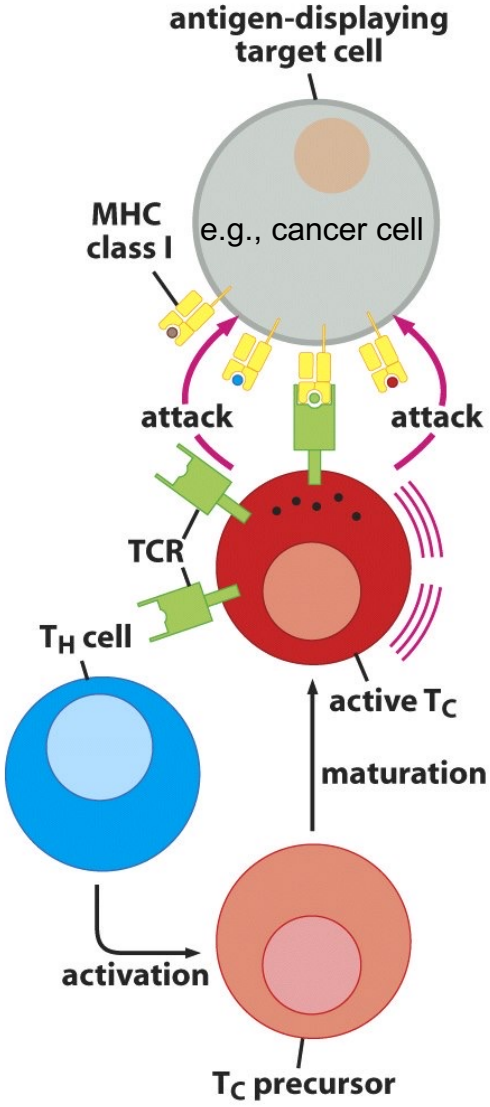
T cells


IL-4
IL-4
IL-2
IL-2
IL-2
IL-2
IL-2
IL-4
IFN-γ
TGF-β
IL-4
APC
Antigen
T_h0 CD4+
T_h0 CD4+
CD4+
T_h2 CD4+
T_h1 CD4
T_h1 CD4
T CD8+
T CD8+
B cells
B cells
B cells
Plasma cells
Plasma cells
Antibodies
Memory B cells
humoral
T_h1
T_h1
T_h1
T_h1
T_h1
Memory T cells
IL-2
IFN-γ
mø
T_c
T_c
T_c
T_c
cellular

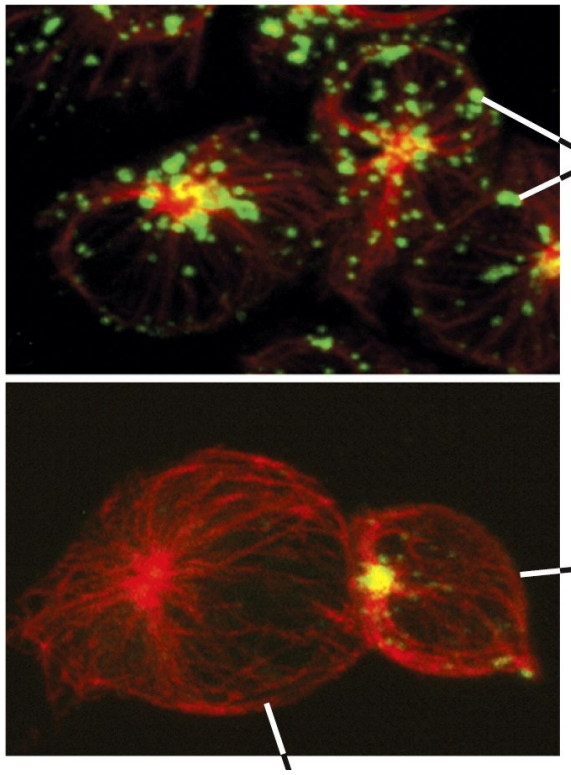
The 3 signals for T cell activation



Adaptive cytotoxic responses



ALL CELLS can present antigens via MHCI



Lytic granules (perforin, granzymes) are scattered in the T_C cell cytoplasm

Upon contact with the target cell, the lytic granules localize at the cells' contact, are released and kill the target cell

Figure 15.11 *The Biology of Cancer* (© Garland Science 2007)

Are tumors *immunogenic*?

Does the immune system mount anti-tumor immune responses?

Immunization of mice by exposure to killed cancer cells

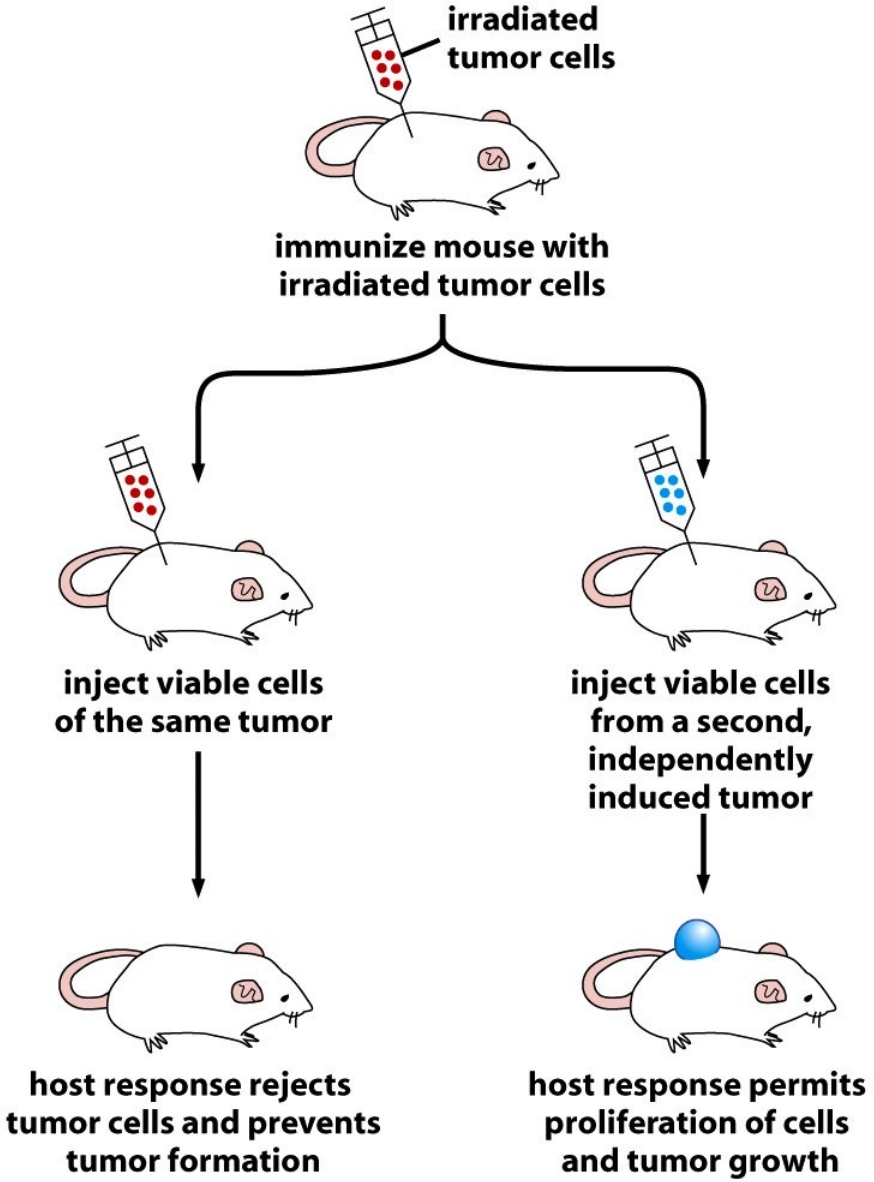
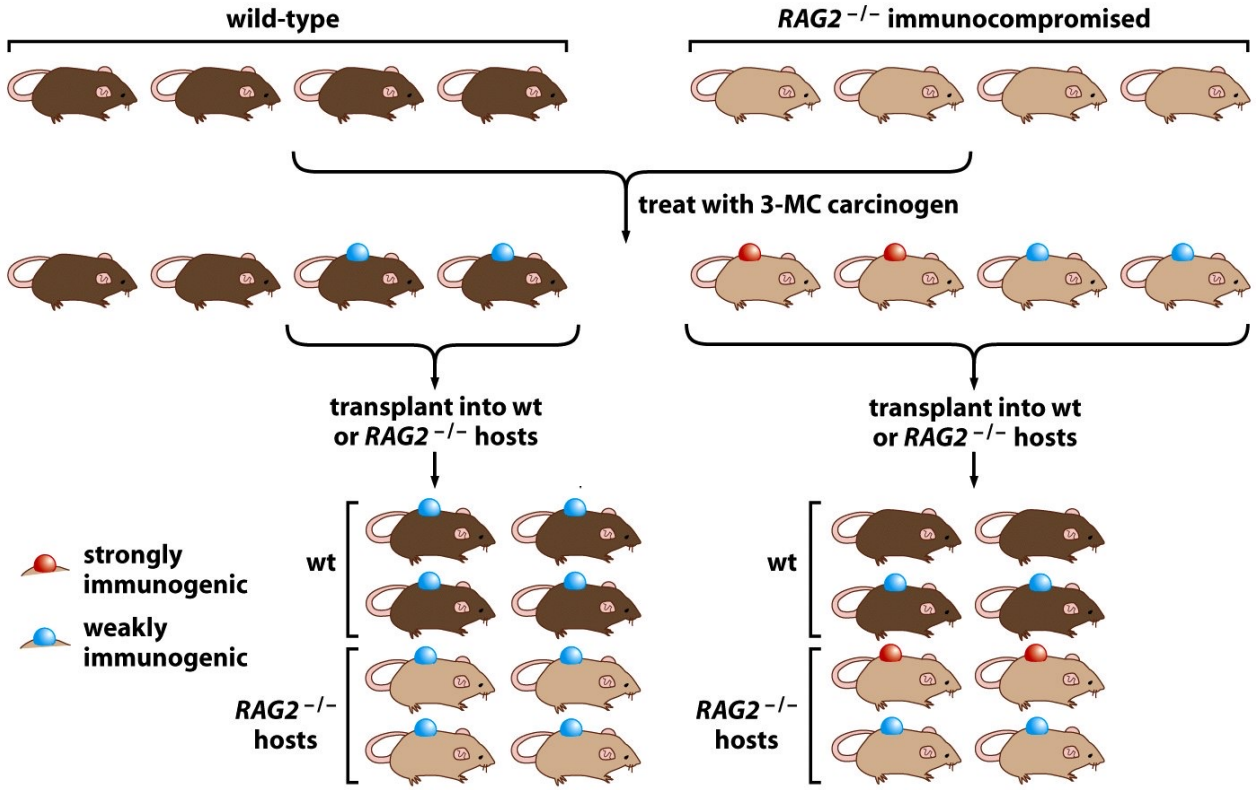


Figure 15.17 *The Biology of Cancer* (© Garland Science 2007)

Evidence for immunogenicity of carcinogen-induced tumors in mice



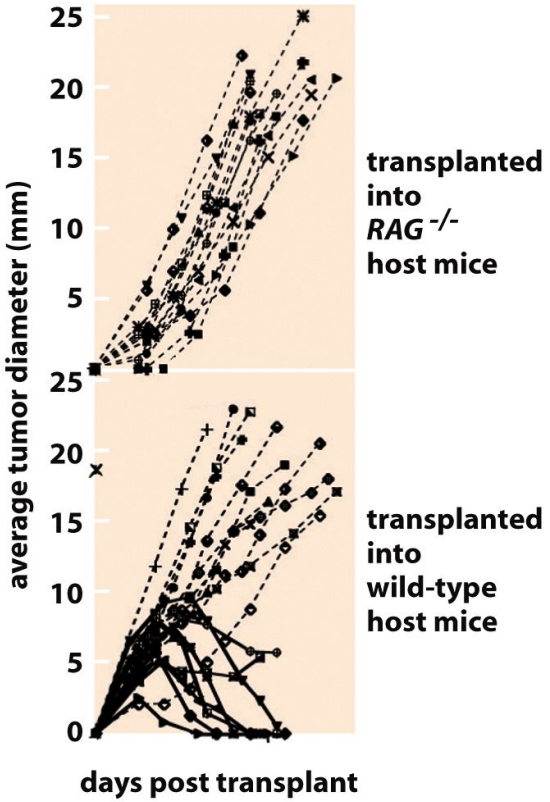
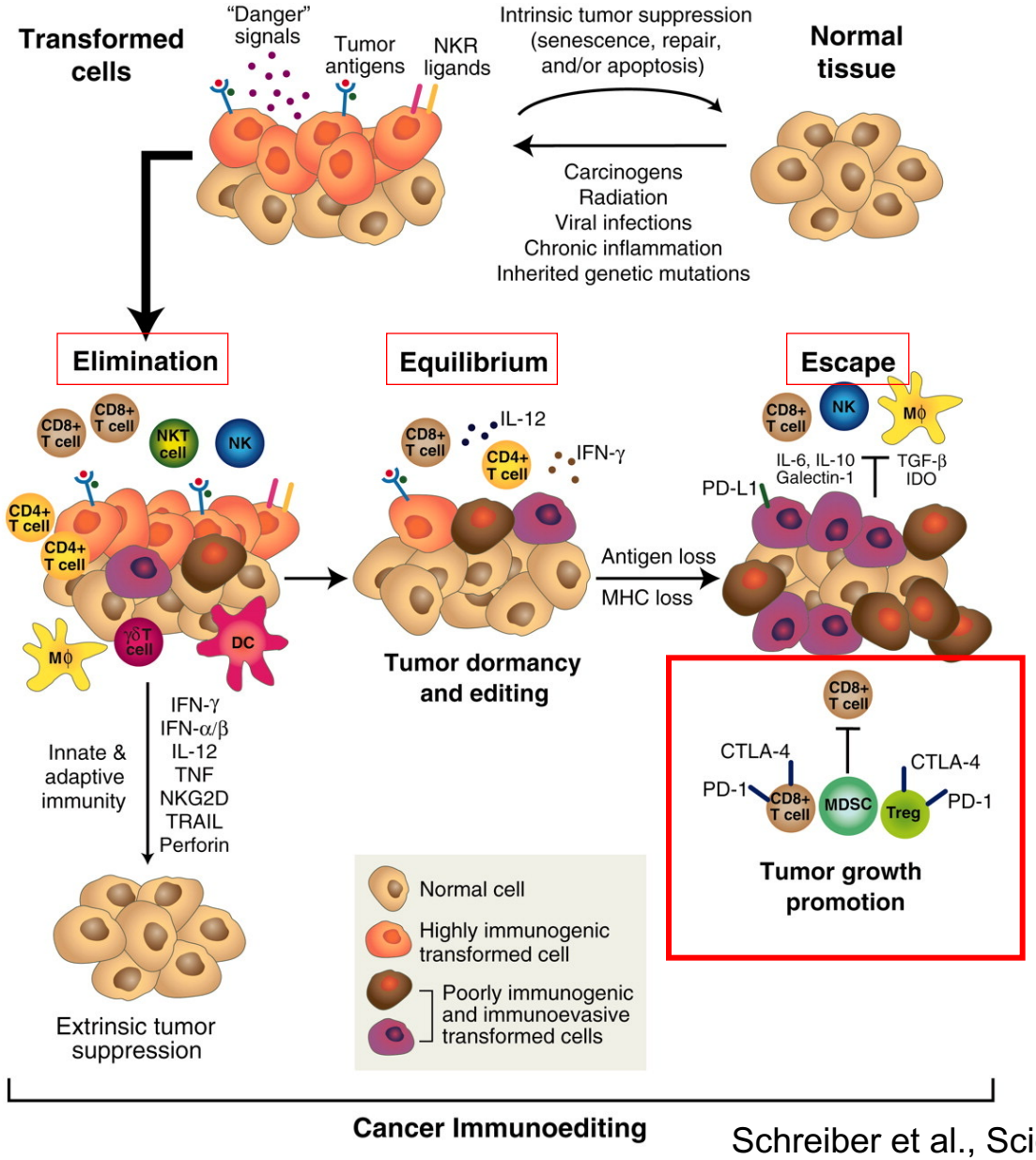


Figure 15.19a *The Biology of Cancer* (© Garland Science 2007)

Immunoediting



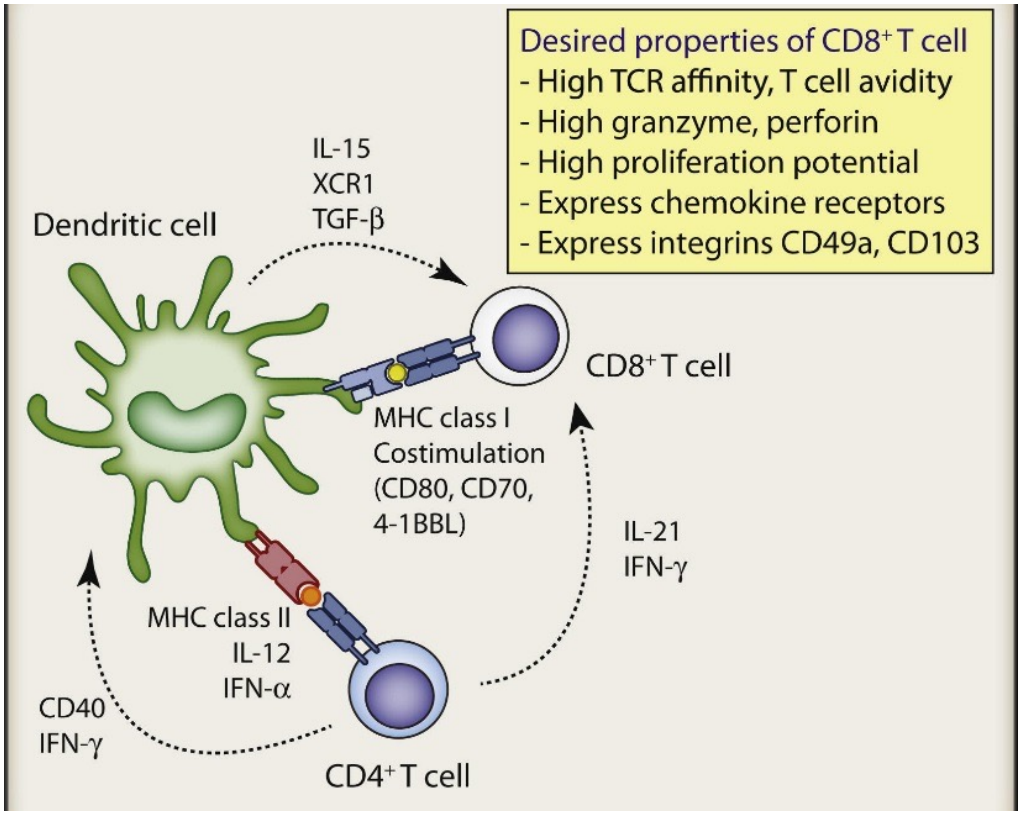
Immuno-suppression

Schreiber et al., Science **331**, 1565 (2011)

Eliciting immune attacks on tumors: Cancer immunotherapies

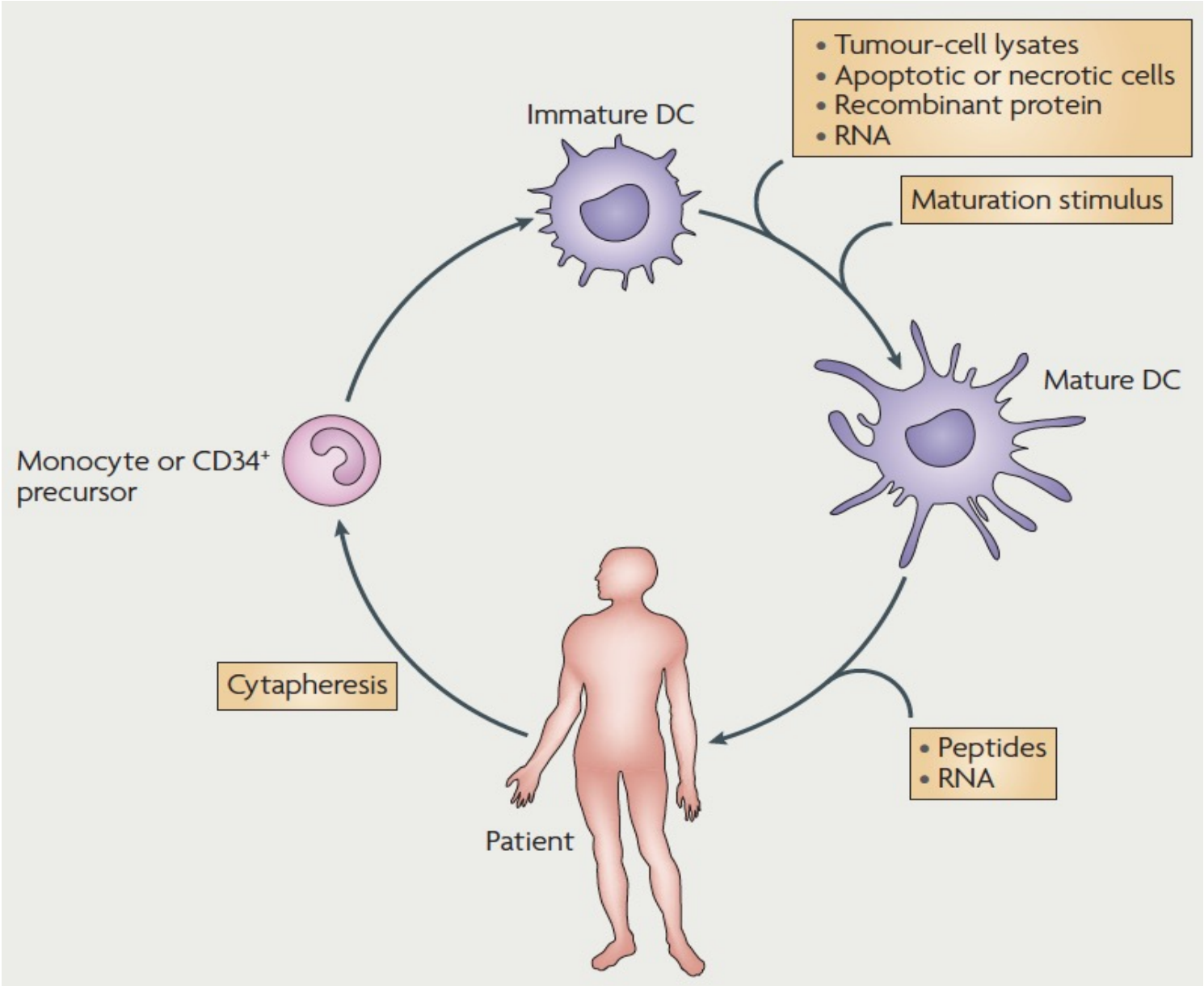
Therapeutic cancer vaccines

1) Nontargeted vaccines (peptide vaccines)
   - Short or long peptides – long peptides with the advantage of inducing broad immunity with both $CD8^+$ and $CD4^+$ cells through endogenous dendritic cells (DCs).
2) Vaccination with ex-vivo-generated dendritic cells (DCs) pulsed with tumor antigens
   - Extensively tested, FDA approved the treatment of metastatic prostate cancer with Sipuleucel-T (4-month-prolonged median survival)
3) In vivo DC targeting



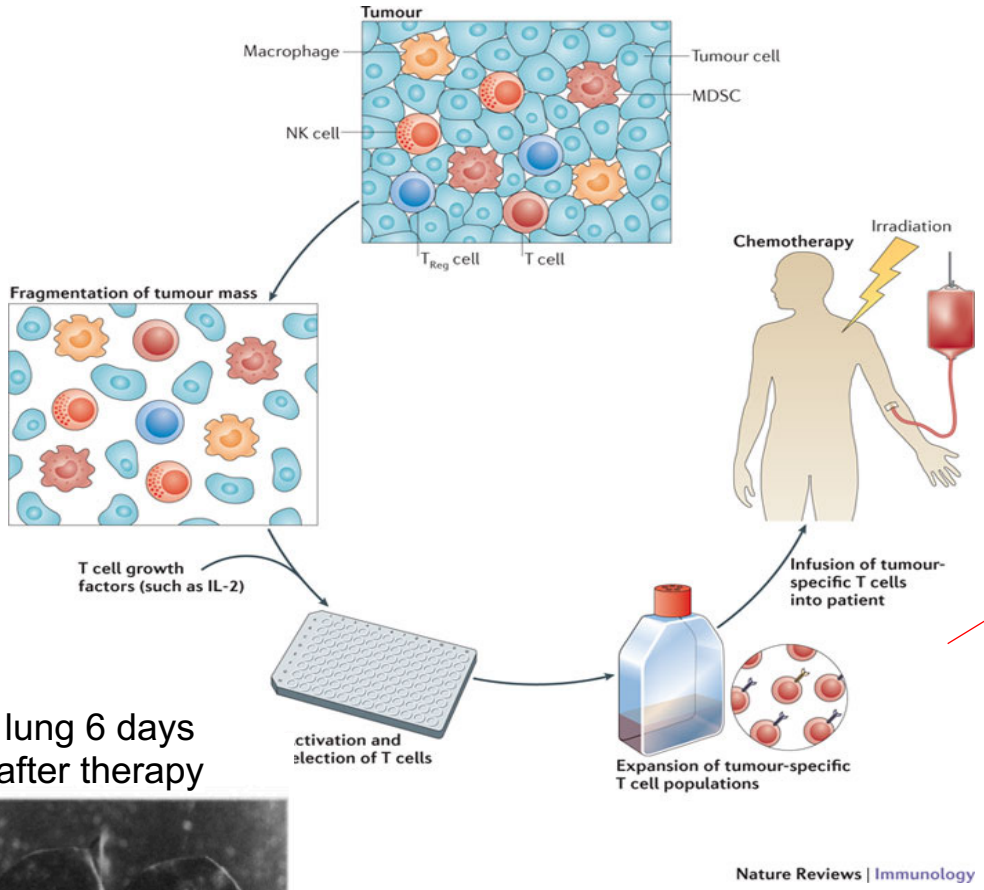
Palucka K & Banchereau J., *Immunity* **39**, 38 (2013)

Dendritic cell (DC) vaccines



Tacken et al., *Nat Rev Immunol* 2007

Adoptive T cell transfer



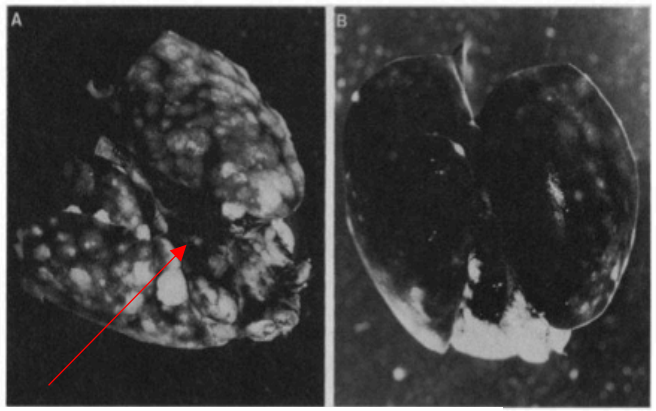
Either:

- Whole tumor T cells (all)
- Tumor-antigen specific T cells (after selection)

Restifo et al., *Nat Rev Immun* **12**, 269 (2012)

lung before therapy

lung 6 days after therapy

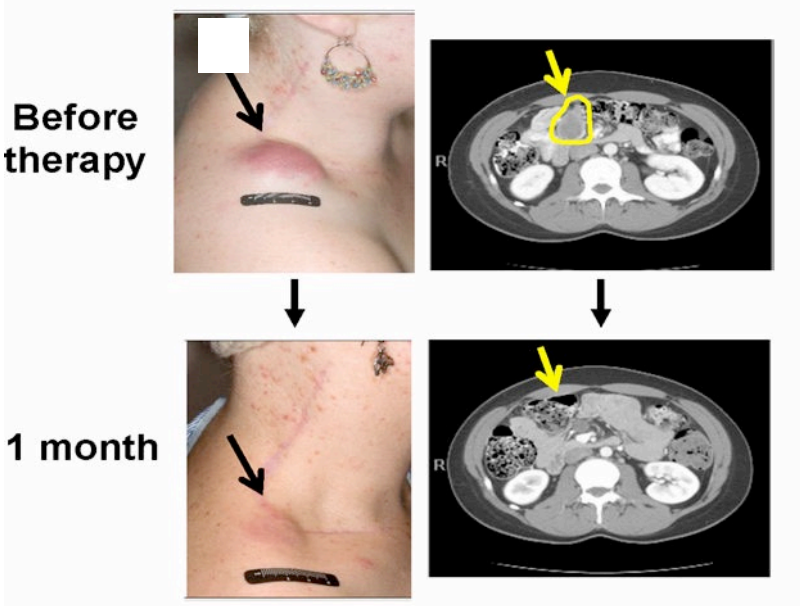


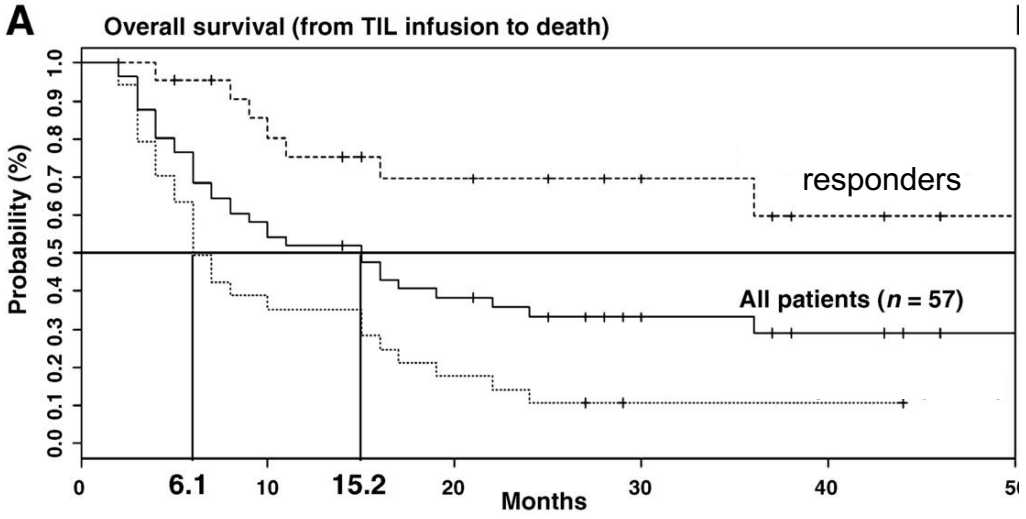
Lung mets of MC38 mouse cancer cells

First study showing that tumor-infiltrating lymphocytes (TILs) that were expanded with IL-2 in vitro can lead to tumor regression in mice with sarcoma and colon adenocarcinoma.

Rosenberg et al., *Science*, **233**, 1318 (1986)

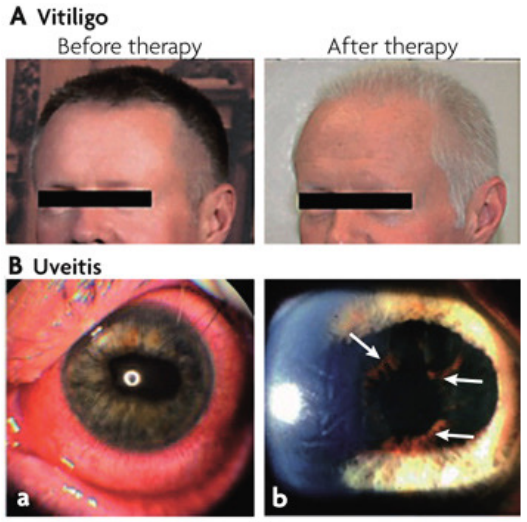
Adoptive T cell transfer – clinical data





TILs mediate durable responses in patients with metastatic melanoma irrespective of prior treatment

- TILs were obtained from metastatic melanoma lesions
- Transiently lymphodepleted patients were treated with their expanded TILs, followed by two cycles of high-dose interleukin (IL)-2 therapy.

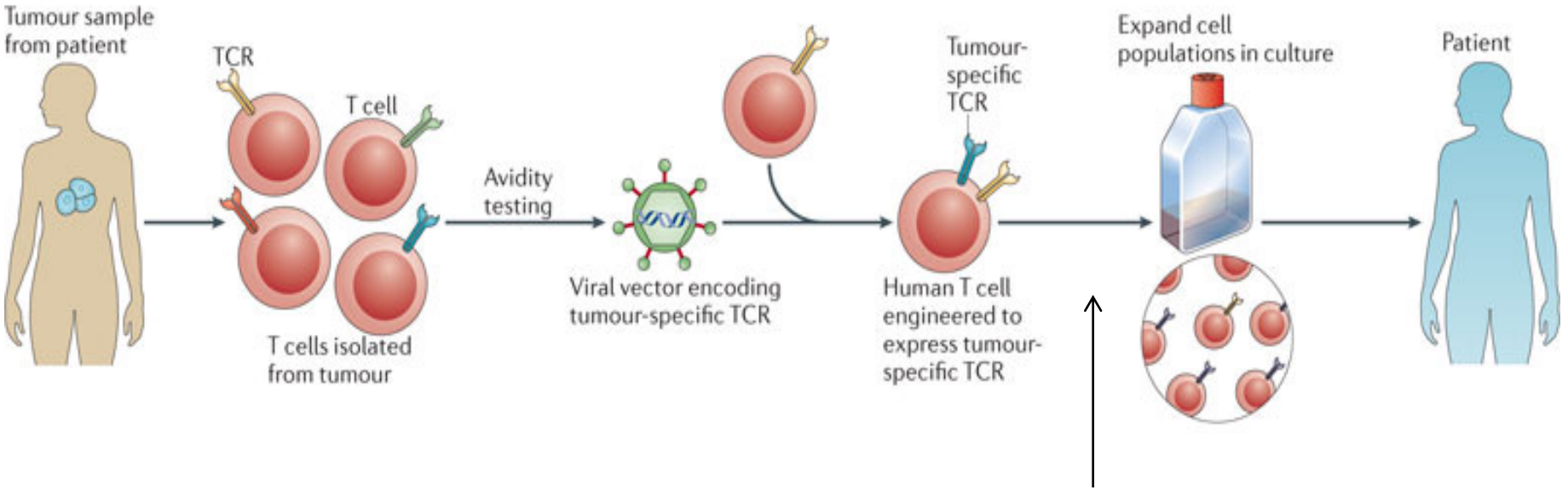


Challenges:

- Target specificity of transferred T cells
- T-cell exhaustion
- The immunosuppressive nature of tumor microenvironment
- Autoimmunity (e.g. uveitis)
- Clear benefits only in melanoma (mutation load?)

Caspi R., *Nat Rev Immun* **8**, 970 (2008)
Radvanyi et al., *Clin Cancer Res* **18**, 6758 (2012)
Besser et al., *Clin Cancer Res* **19**, 4792 (2013)

Genetic engineering of T cells: TCR transfer



Restifo et al., *Nat Rev Immun* **12**, 269 (2012)

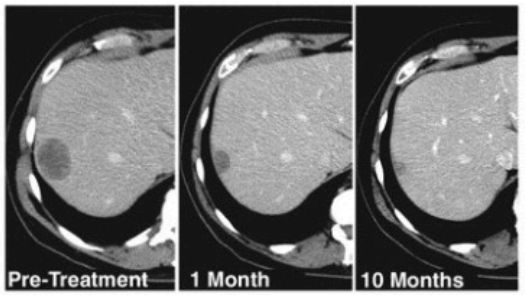
TCR transfer: clinical data

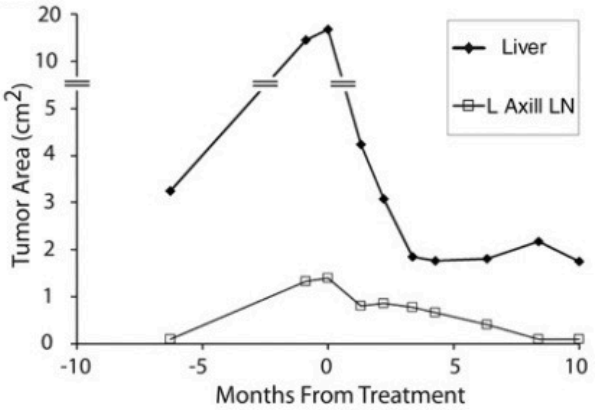
Genes encoding TCRs that are specific to a variety of tumor antigens have now been cloned:

- MART-1 (melanoma)
- Gp100 (melanoma)
- NY-ESO-1 cancer-testis antigen

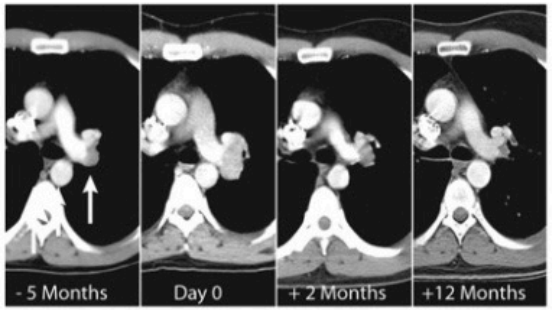
Melanoma patients, who received MART-1-specific engineered T cells:

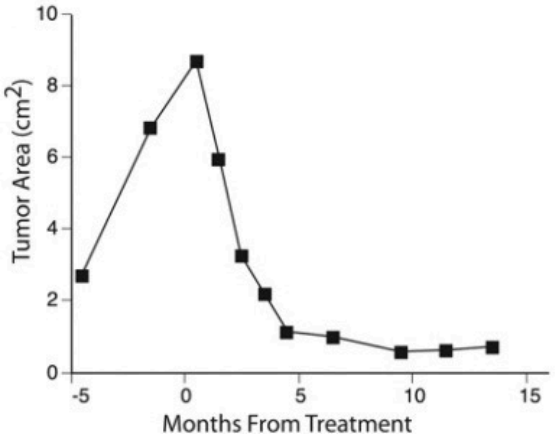
liver metastasis





lymph node metastasis



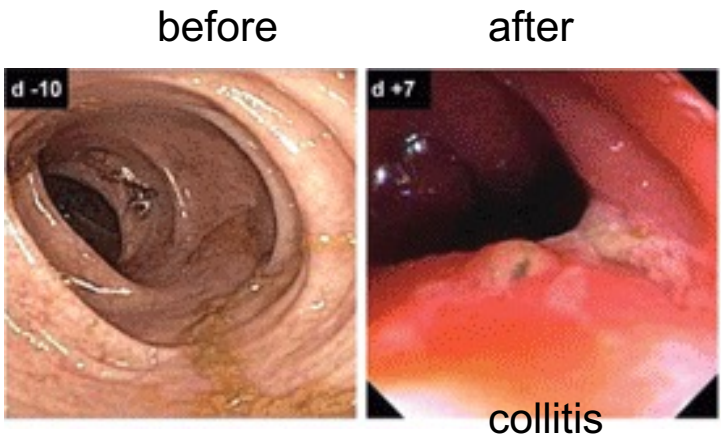


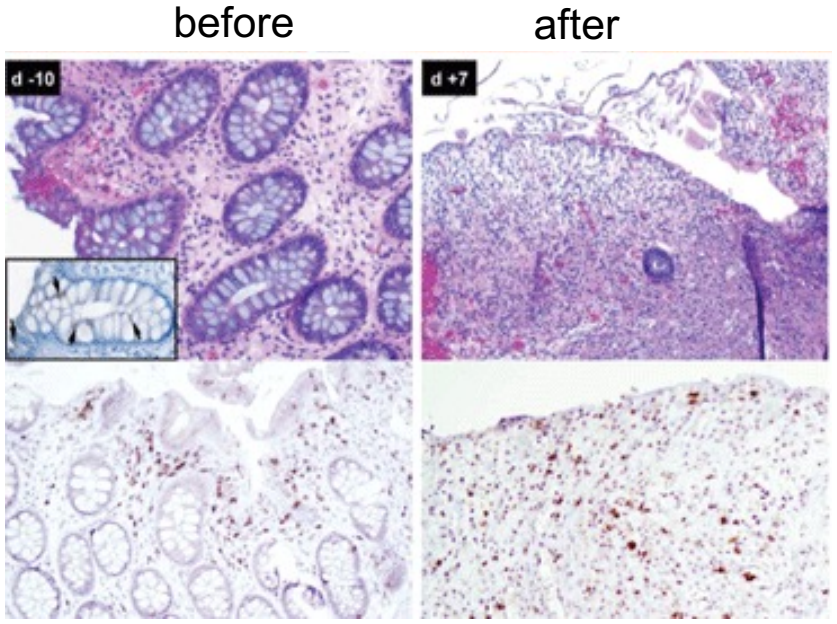
Morgan et al., *Science* **314**, 126 (2006)

TCR transfer: challenges

The affinity of engineered receptors can be increased by:
- changes to the complementarity-determining regions
- directed evolution (selection of best performing TCR)

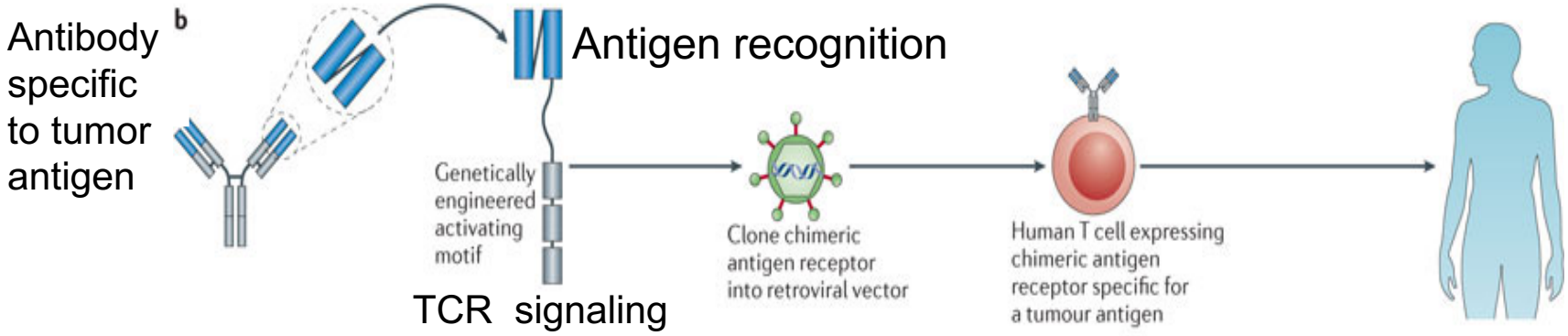
Challenges:
- Matching HLA restriction elements (TCR is specific to a given HLA/peptide)
- Possibility of «on target» toxicities
    - Targeting carcinoembryonic antigen (CEA) in colon cancer ➡ lymphocyte recognition of the normal levels of CEA present in colonic mucosa





Parkhurst et al., *Mol Ther* **19**, 620 (2011)

Genetic engineering of T cells: Chimeric antigen receptors (CARs)



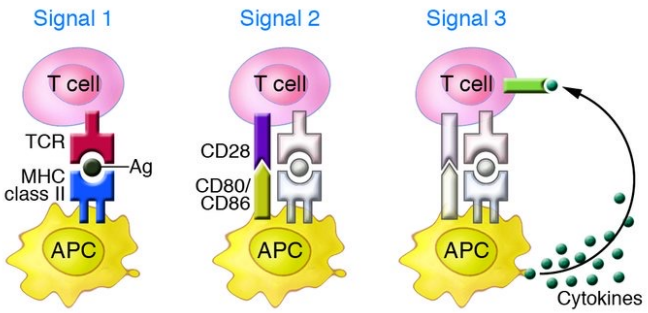
Restifo et al., Nat Rev Immun **12**, 269 (2012)

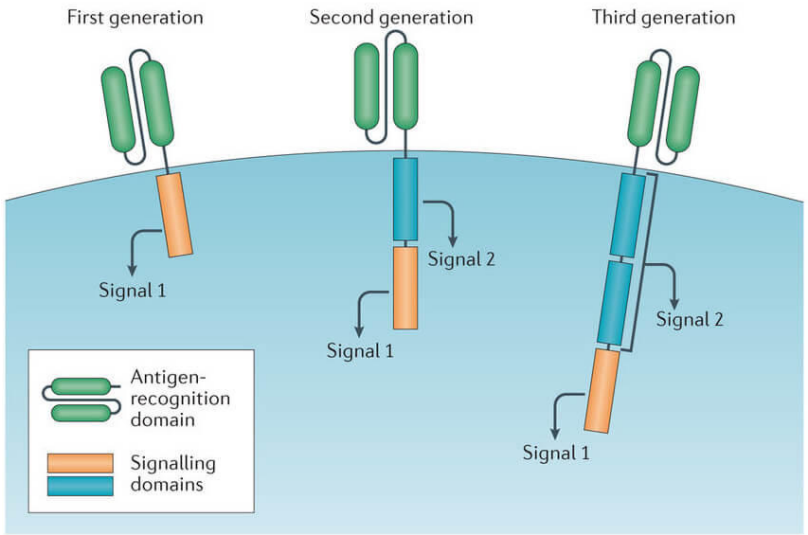
Chimeric antigen receptors (CARs) vs TCRs:

- CARs recognize MHC/HLA-nonrestricted structures on the surface of target cancer cells
- TCRs recognize mainly intracellular antigens that have been processed and presented as peptide complexes with MHC/HLA molecules

Challenges:

- Possibility of «on target - off tumor» toxicities





Approved CAR-T therapies

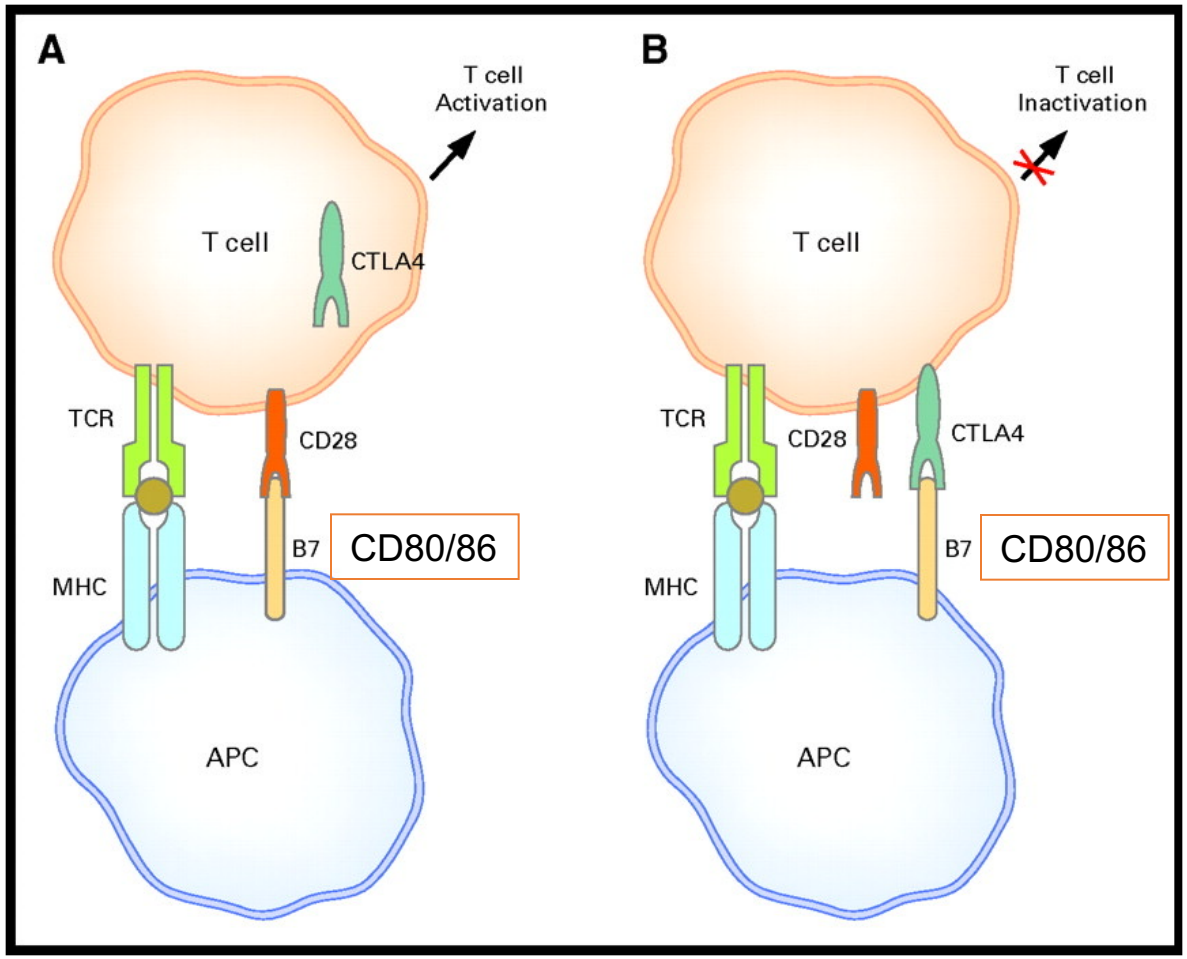
Name	Target Antigen	Brand	FDA Approval	Indications
Tisagenlecleucel	CD19	Kymriah	August 2017 May 2018	r/r B-cell precursor ALL, r/r large B-cell lymphoma
Axicabtagene ciloleucel	CD19	Yescarta	October 2017 March 2021	r/r large B-cell lymphoma r/r follicular lymphoma
Brexucabtagene autoleucel	CD19	Tecartus	July 2020 October 2021	r/r MCL (July 2020) r/r B-cell precursor ALL (Oct 2021)
Lisocabtagene maraleucel	CD19	Breyanzi	February 2021	r/r large B-cell lymphoma
Idecabtagene vicleucel	BCMA	Abecma	March 2021	r/r MM
Ciltacabtagene autoleucel	BCMA	Carvykti	February 2022	r/r MM

MM: multiple myeloma (B cell malignancy)

Chimeric antigen receptors (CARs) are being actively investigated in solid tumors, with promising results in glioblastoma. However, it seems that the spectacular responses observed in leukemia/lymphoma do not recapitulate in solid cancers because of tumor-induced immunosuppression and other barriers to T-cell killing.

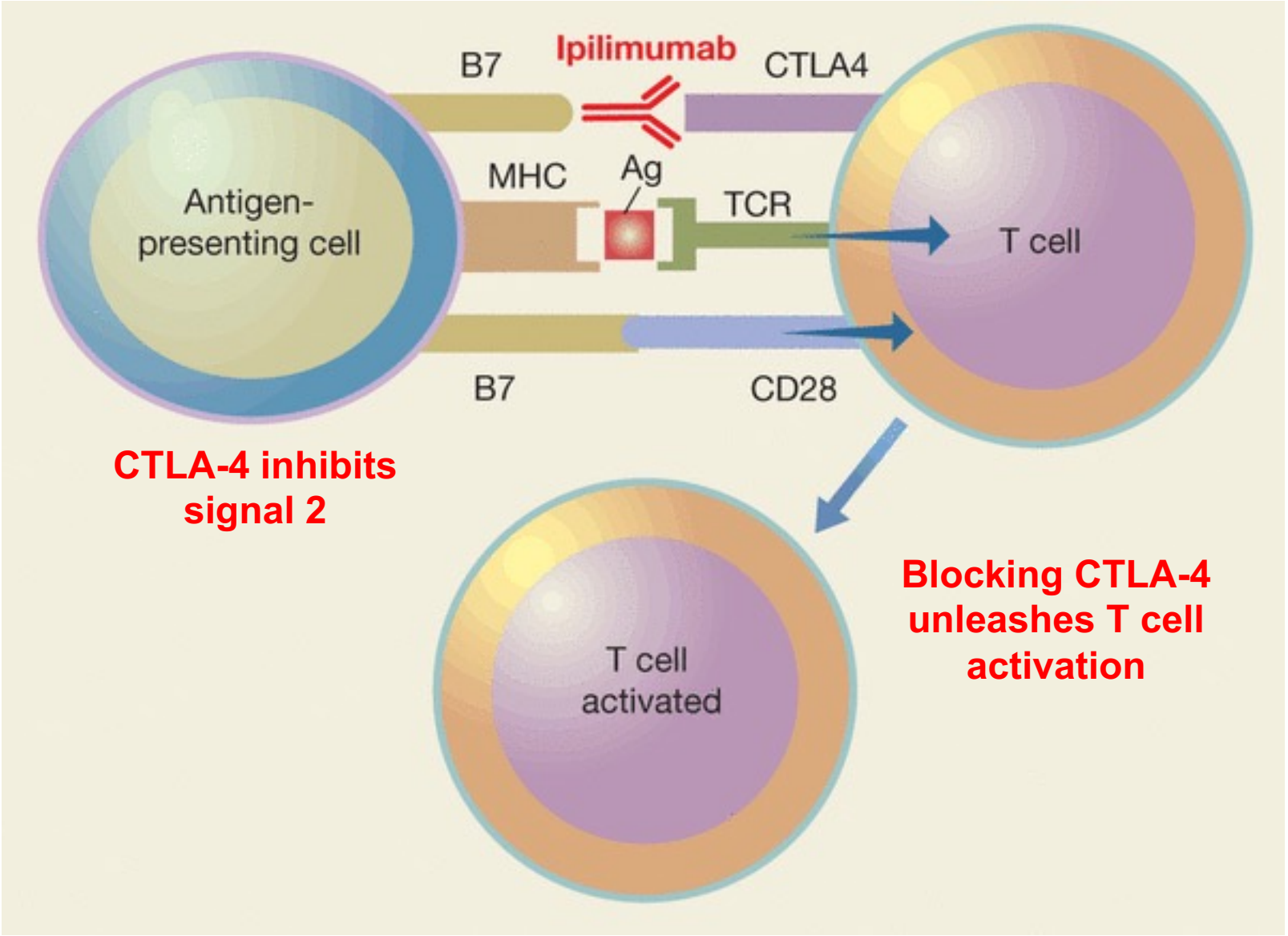
Targeting cancer-associated immunosuppression

Immunosuppression in the tumor microenvironment: inhibitory signals I

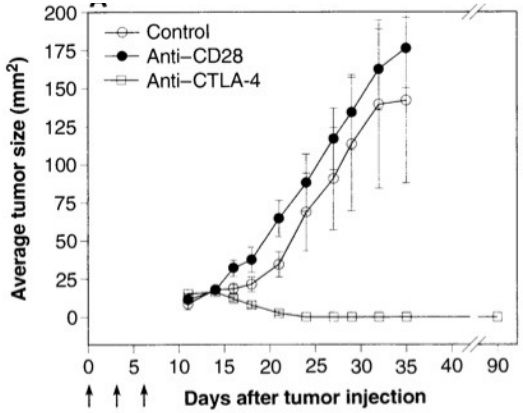


Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) dominantly binds to CD80/86 (co-stimulatory molecules) on antigen-presenting cells (APC) and thus blocks the costimulatory activity of CD28 on effector T cells. Blocking CTLA-4 by moAb unleashes T-cell activation.

Immunosuppression in the tumor microenvironment: inhibitory signals I

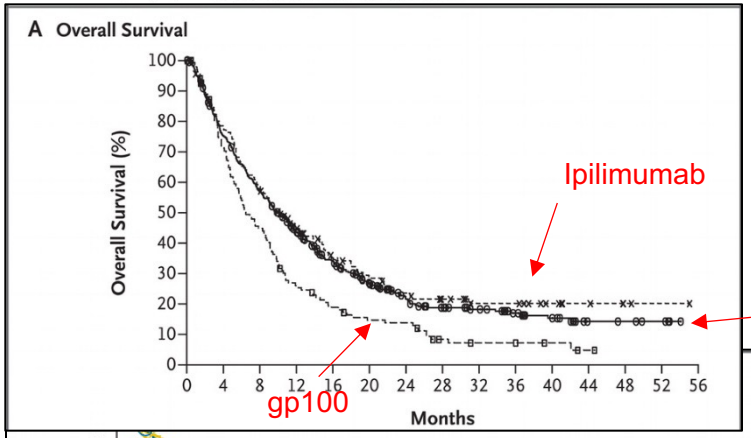


Immune checkpoint blockade: CTLA-4



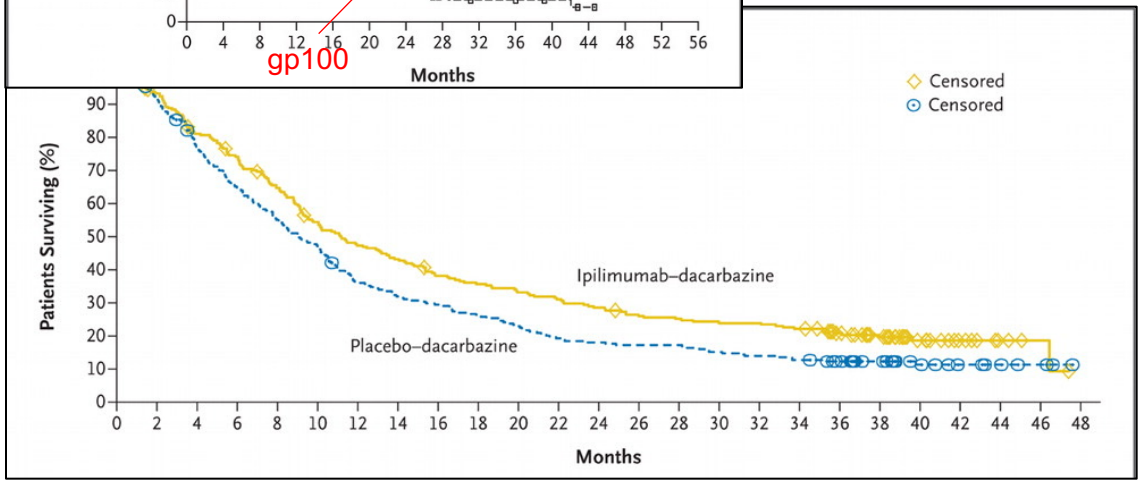
Anti-CTLA-4 antibody treatment hyperactivates T lymphocytes followed by the elimination of the tumors.

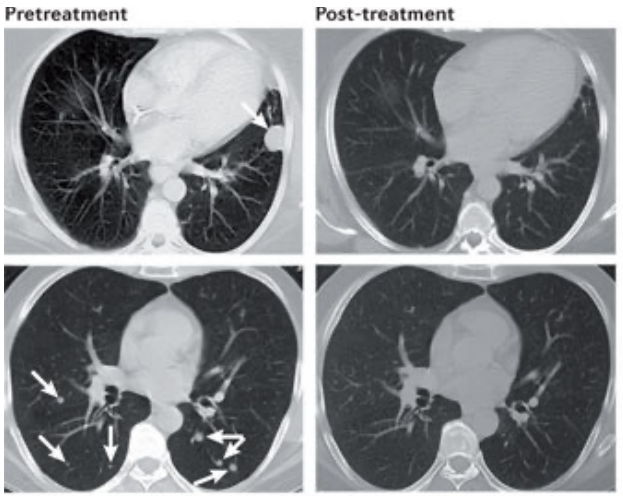
Leach et al., Science, **271**, 1734 (1996)



Ipilimumab: anti-CTLA-4 IgG1 antibody approved in 2011 in the US and Europe as therapy for advanced/metastatic melanoma. (Only modest anti-tumor effects in kidney, lung and prostate cancers.)

Ipilimumab + gp100



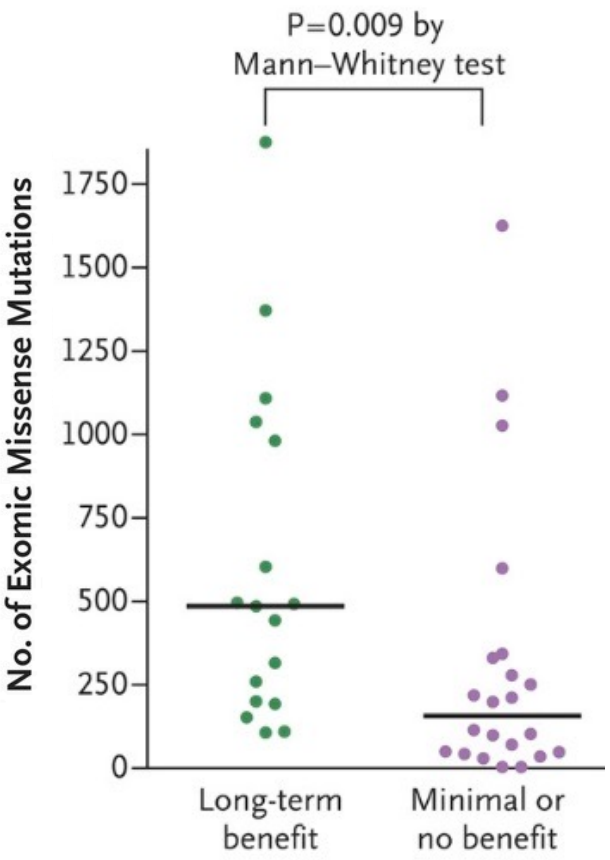


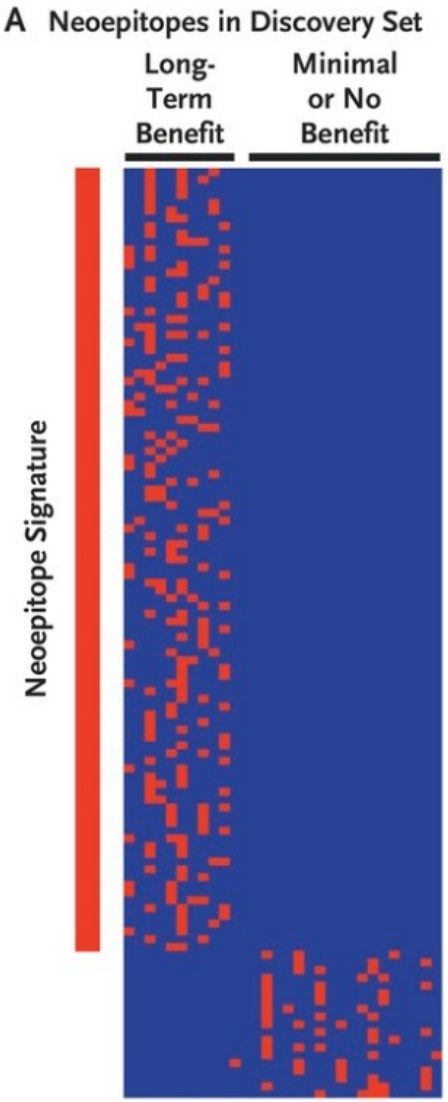
Hodi et al., *N. Engl. J. Med.*, **363**, 711 (2010)

Robert et al., *N. Engl. J. Med.*, **364**, 2517 (2011)

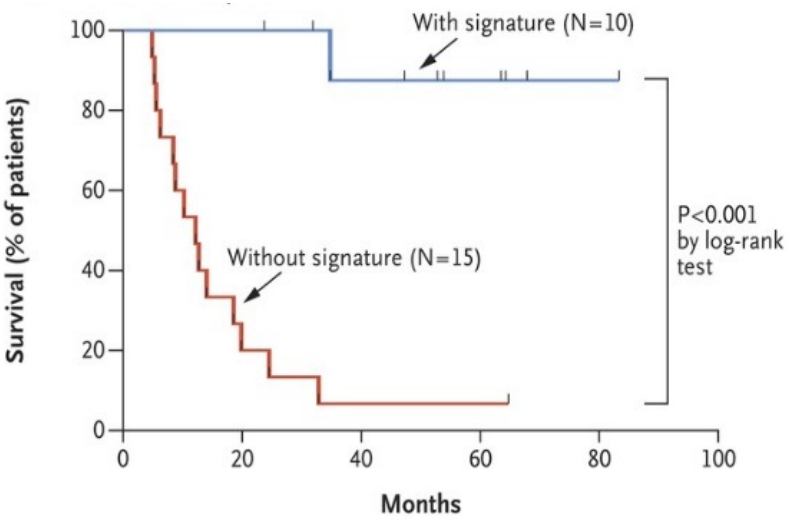
Predictive biomarkers of response to CTLA-4 blockade

Mutational load (melanoma)



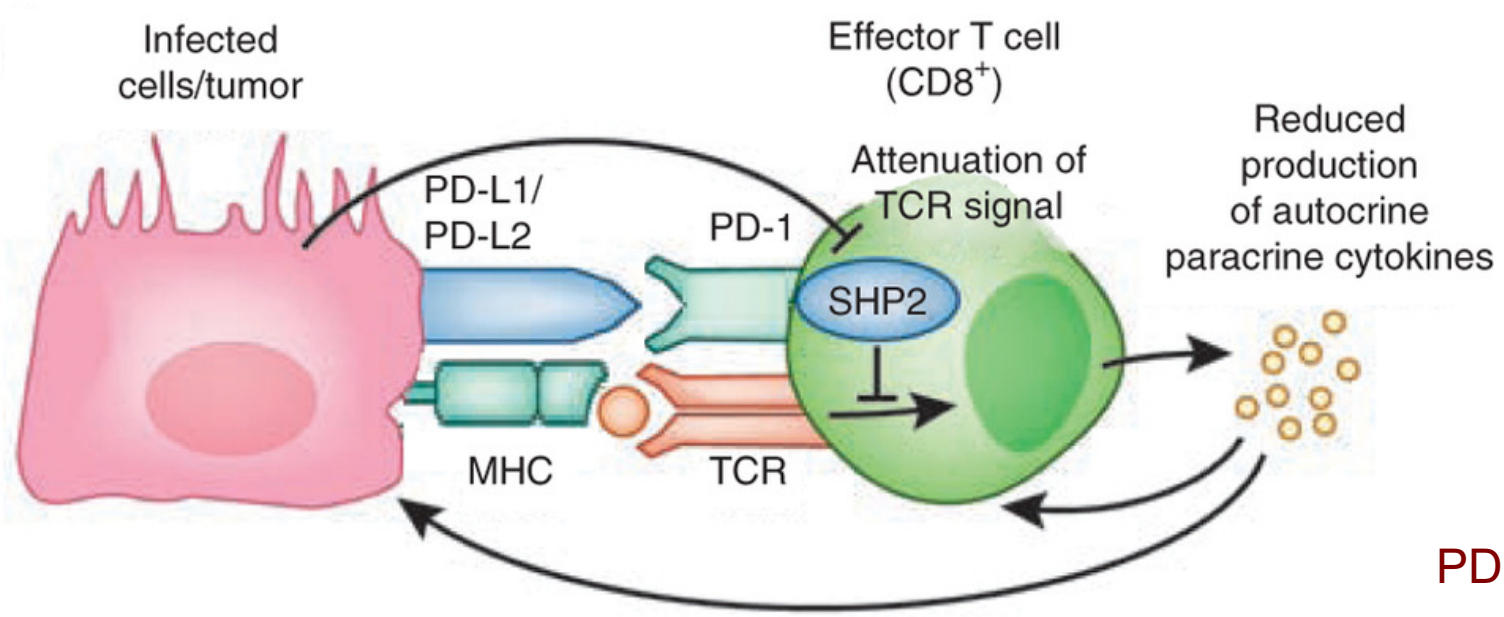


Specific tumor neoantigens



Snyder et al., *N Engl J Med* **371**, 2189 (2014)

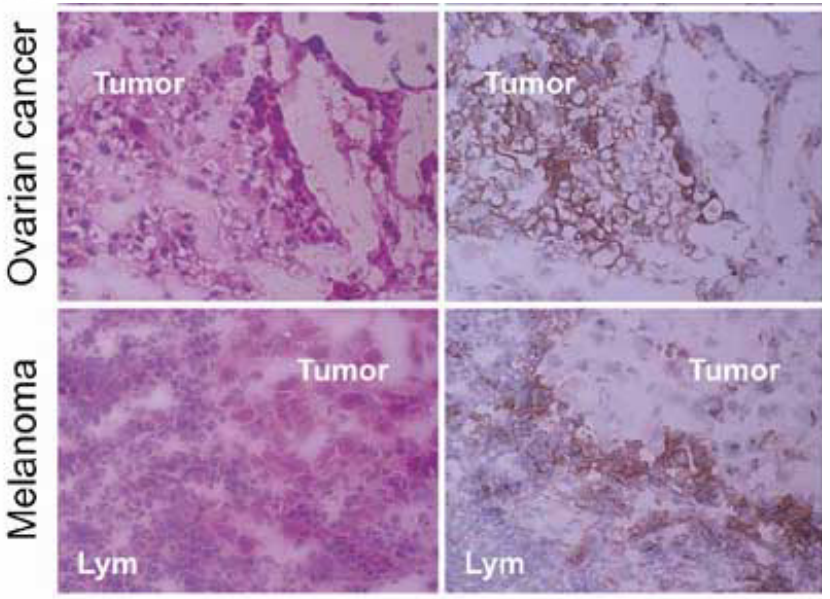
Immunosuppression in the tumor microenvironment: inhibitory signals II



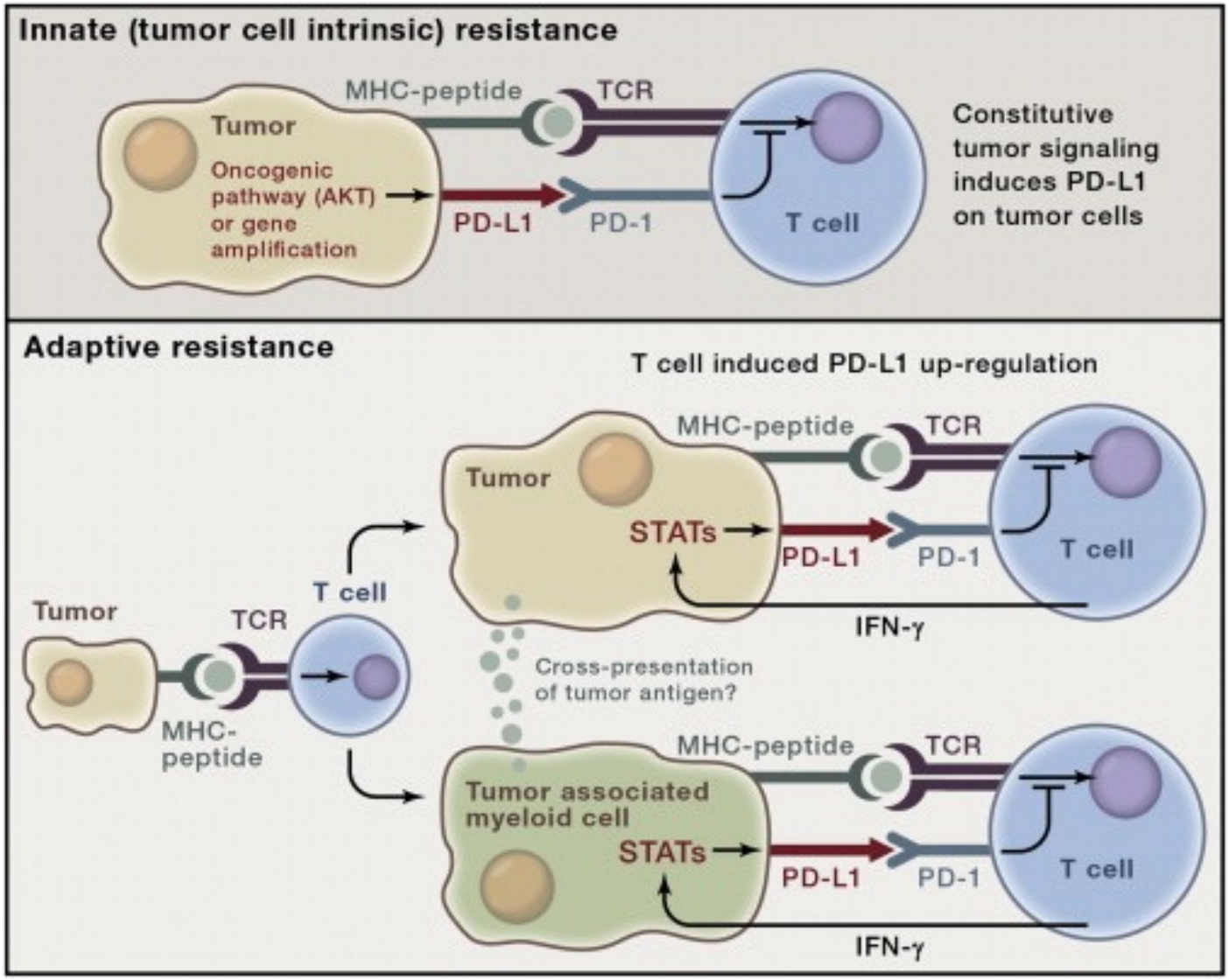
PDL1

Okazaki et al., Nature Immunology **14**, 1212 (2013)

Programmed cell death protein 1 (PD-1) induces unresponsiveness through attenuating antigen-specific signals. It binds to **PD-L1** and L2 ligands expressed on cancer cells as well as macrophages and other stromal cells. **PD-L1 is upregulated in many human cancers**, such as lung, ovary, colon carcinomas and melanomas



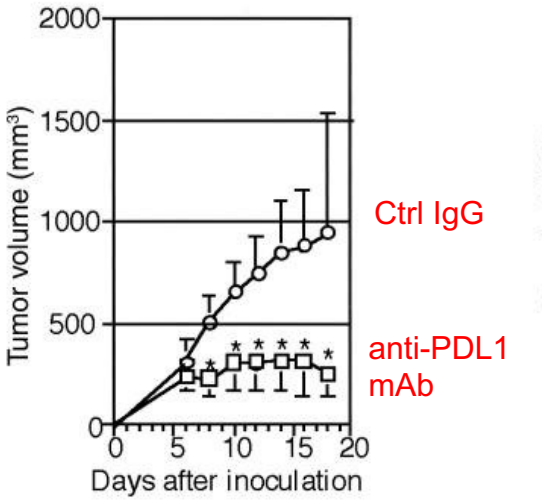
Regulation of PD1 ligands (PDL1 and 2)

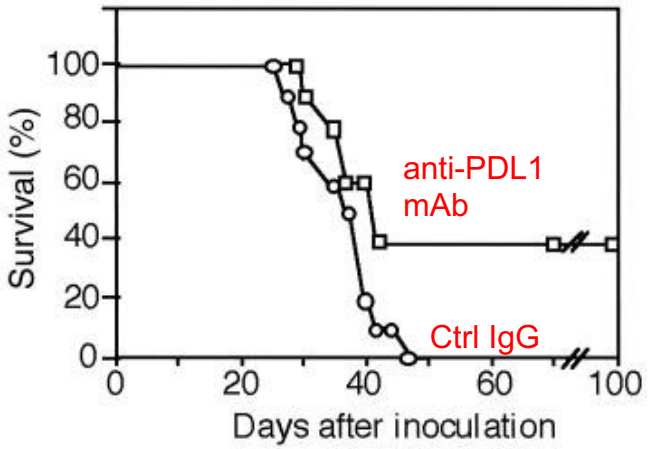


Dong et al., *Nat Med*, **8**, 793 (2002)

Ahmadzadeh et al., *Blood*, **8**, 1537 (2009

Immune checkpoint blockade: PD1-PDL1

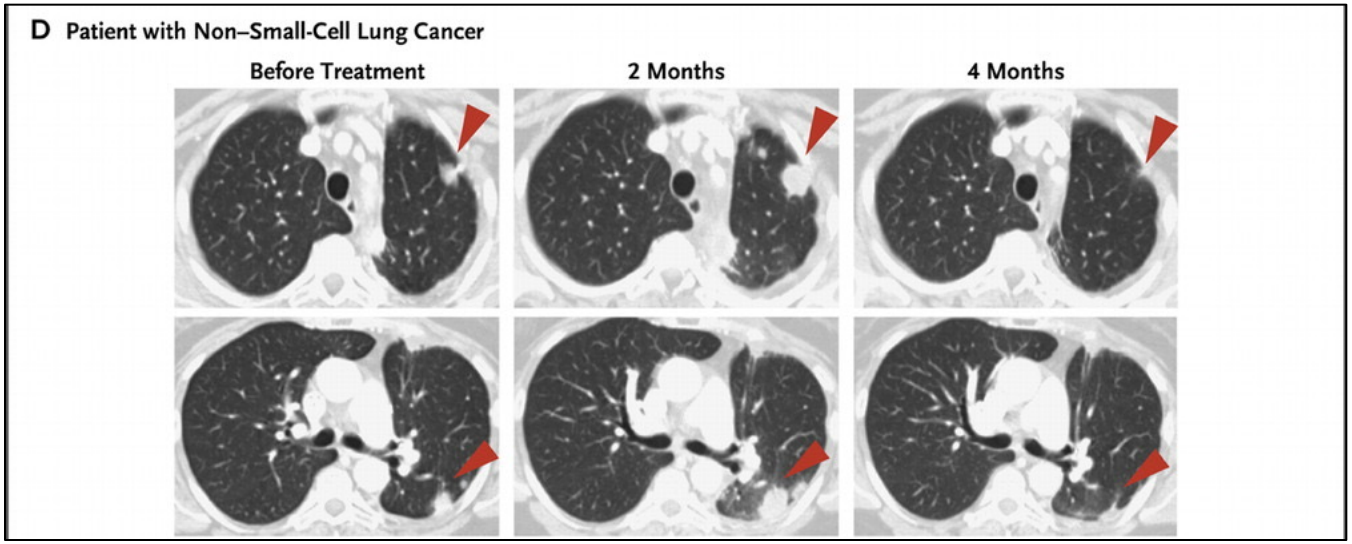




Myeloma cells injected in BALB/c mice showed decreased tumor growth and increased survival after anti-PD-L1 antibody treatment.

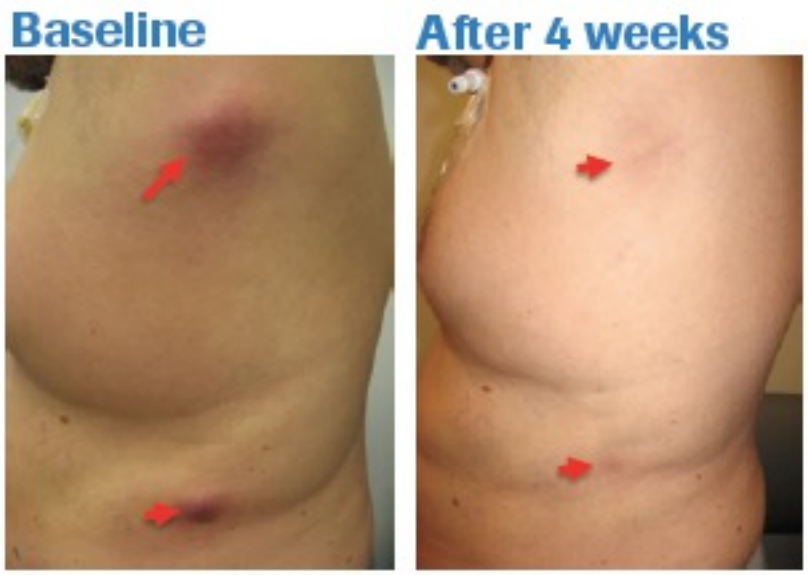
Iwai et al., PNAS, **99**, 12293 (2002)

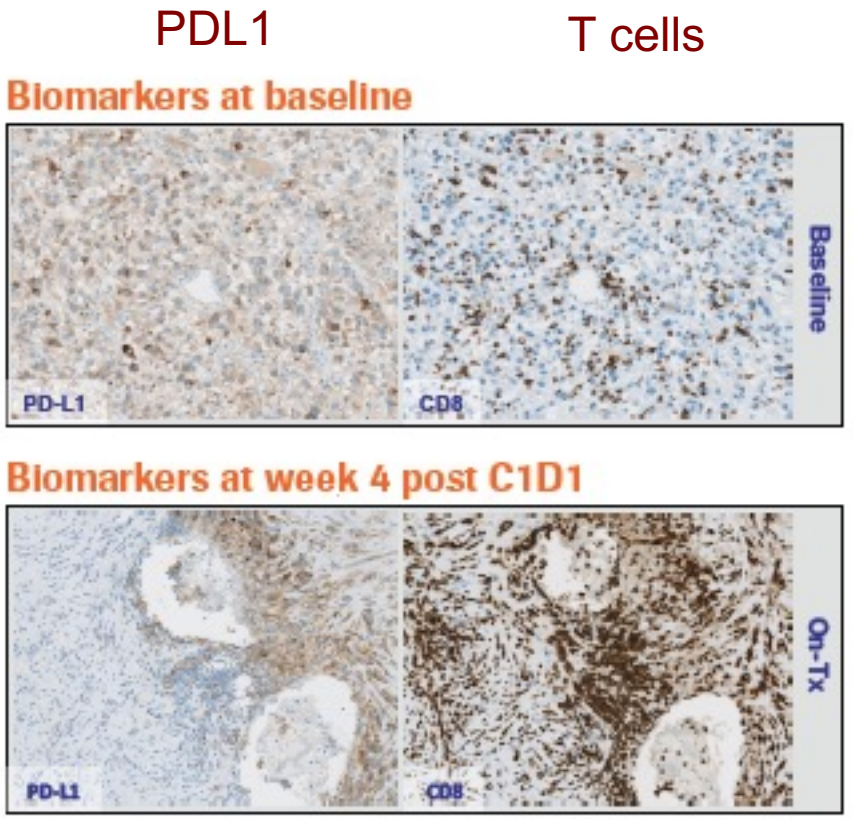
Nivolumab: anti-PD1 antibody, which showed durable responses in advanced treatment-refractory NSCLC, bladder carcinoma and melanoma (approved).



Topalian et al., *N Engl J Med*, **366**, 2443 (2012)

Immune checkpoint blockade: PD1-PDL1
Determinants of tumor response





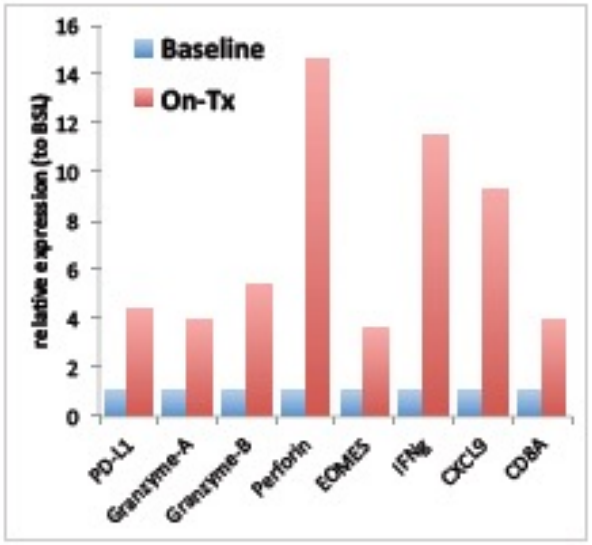
51-year-old male with RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus

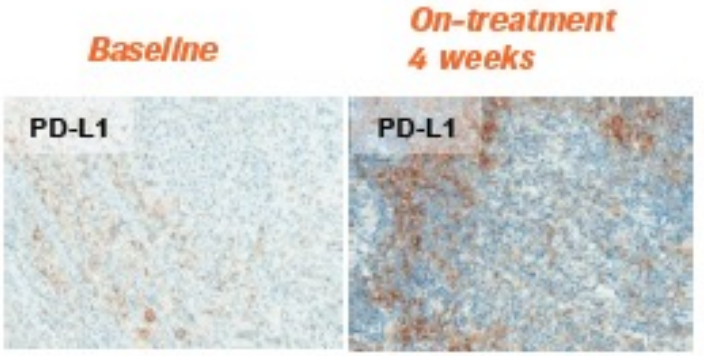
Immune checkpoint blockade: PD1-PDL1
Determinants of tumor response

T cell genes

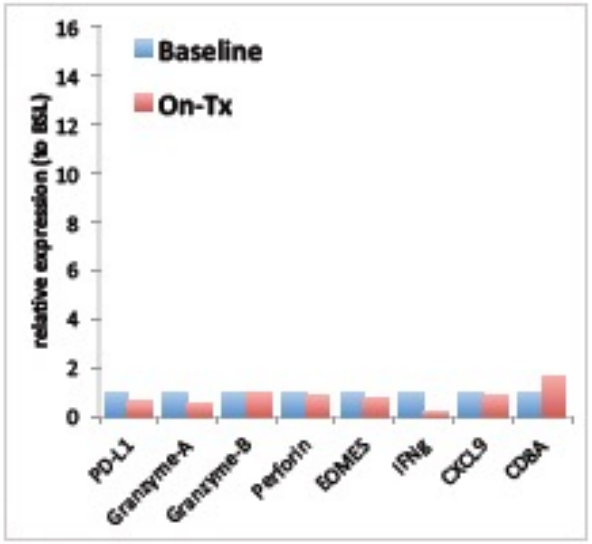
T cells

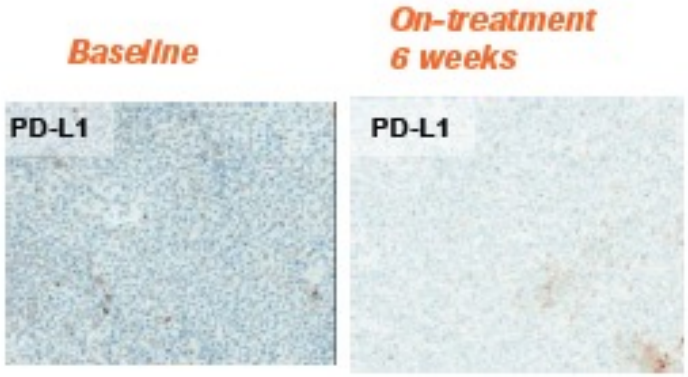
Responder





Non-responder

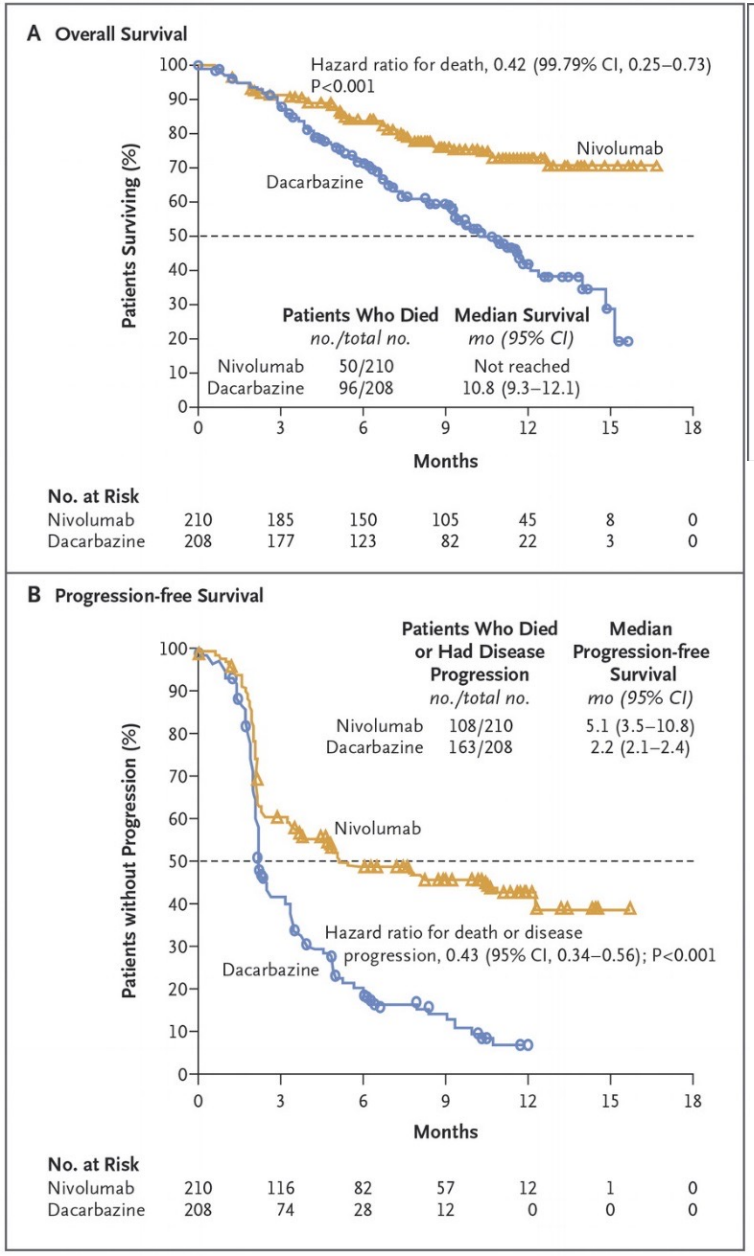




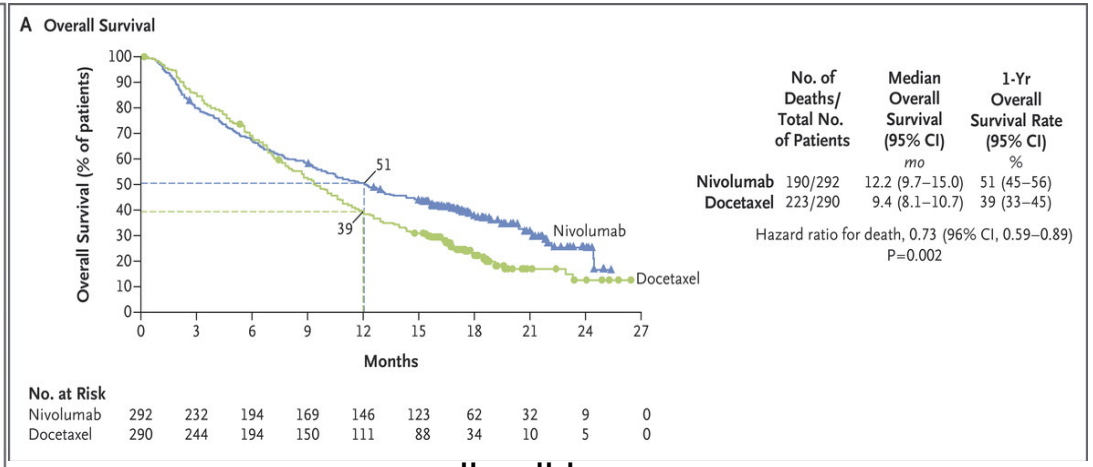
Herbst et al (2014) *Nature* Nov 27;515(7528):563-7

CancerImmu
Genente

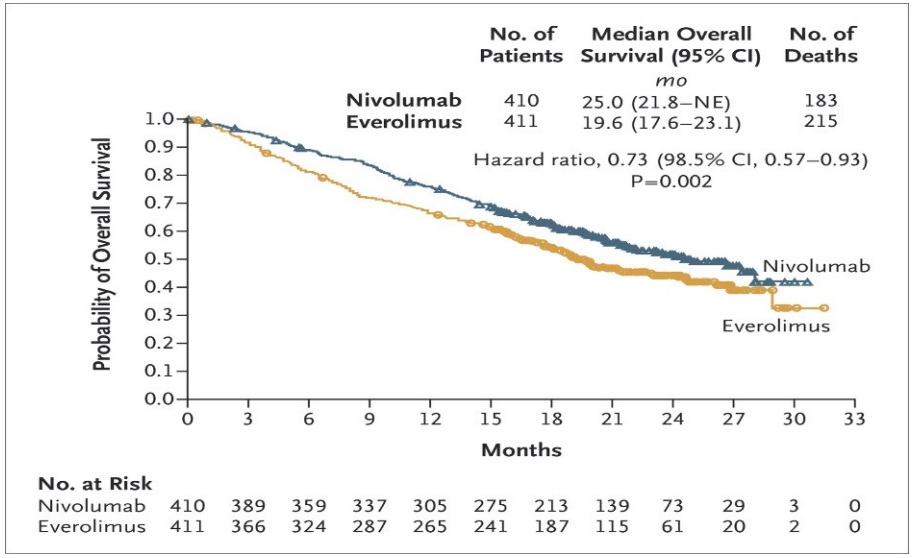
PD1/PDL1 blockade: Initial clinical results



melanoma



nonsquamous non-small cell lung cancer



renal cell carcinoma

Robert C et al. *N Engl J Med* 2015;372:320-330.

Borghaei H et al. *N Engl J Med* 2015;373:1627-1639.

Motzer RJ et al. *N Engl J Med* 2015;373:1803-1813.

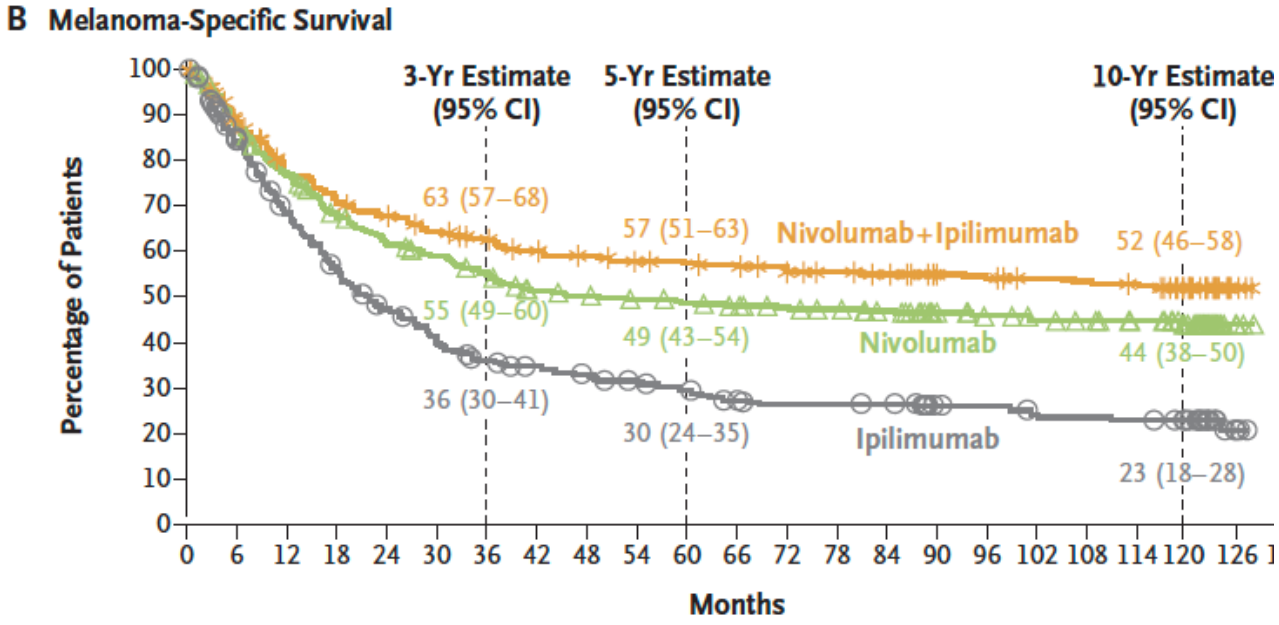
PD1 blockade: 2025 clinical results in melanoma

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 2, 2025 VOL. 392 NO. 1

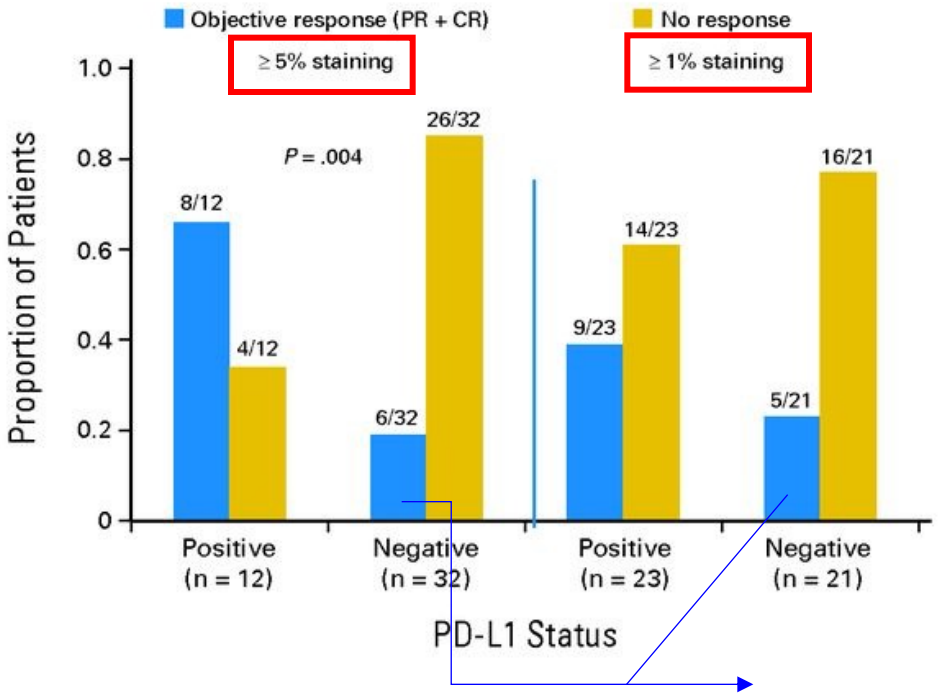
Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, P. Rutkowski, C.L. Cowey, D. Schadendorf, J. Wagstaff, P. Queirolo, R. Dummer, M.O. Butler, A.G. Hill, M.A. Postow, C. Gaudy-Marqueste, T. Medina, C.D. Lao, J. Walker, I. Márquez-Rodas, J.B.A.G. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, S. Sandhu, C. Lebbé, P.A. Ascierto, G.V. Long, C. Ritchings, A. Nassar, M. Askelson, M.P. Benito, W. Wang, F.S. Hodi, and J. Larkin, for the CheckMate 067 Investigators*



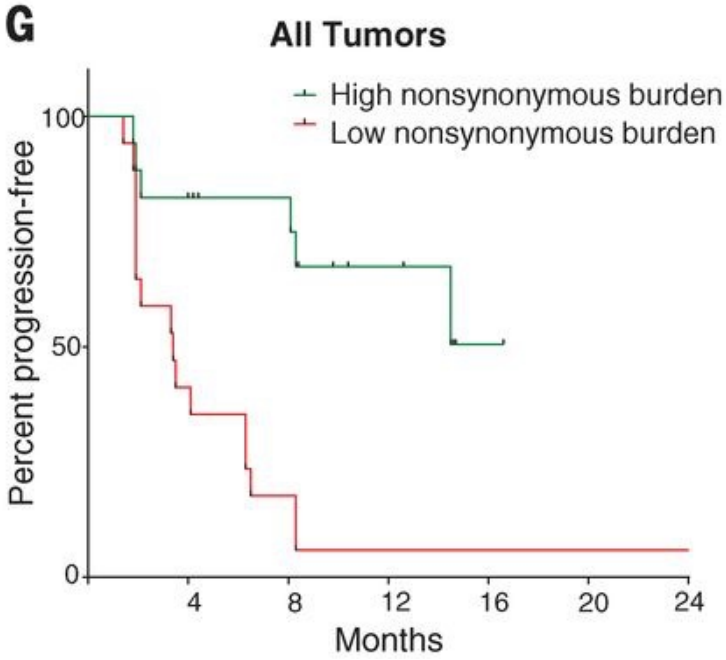
Predictive biomarkers of response to PDL1-PD1 blockade

PD-L1 expression



responsive
although negative
for PD-L1

Mutational load

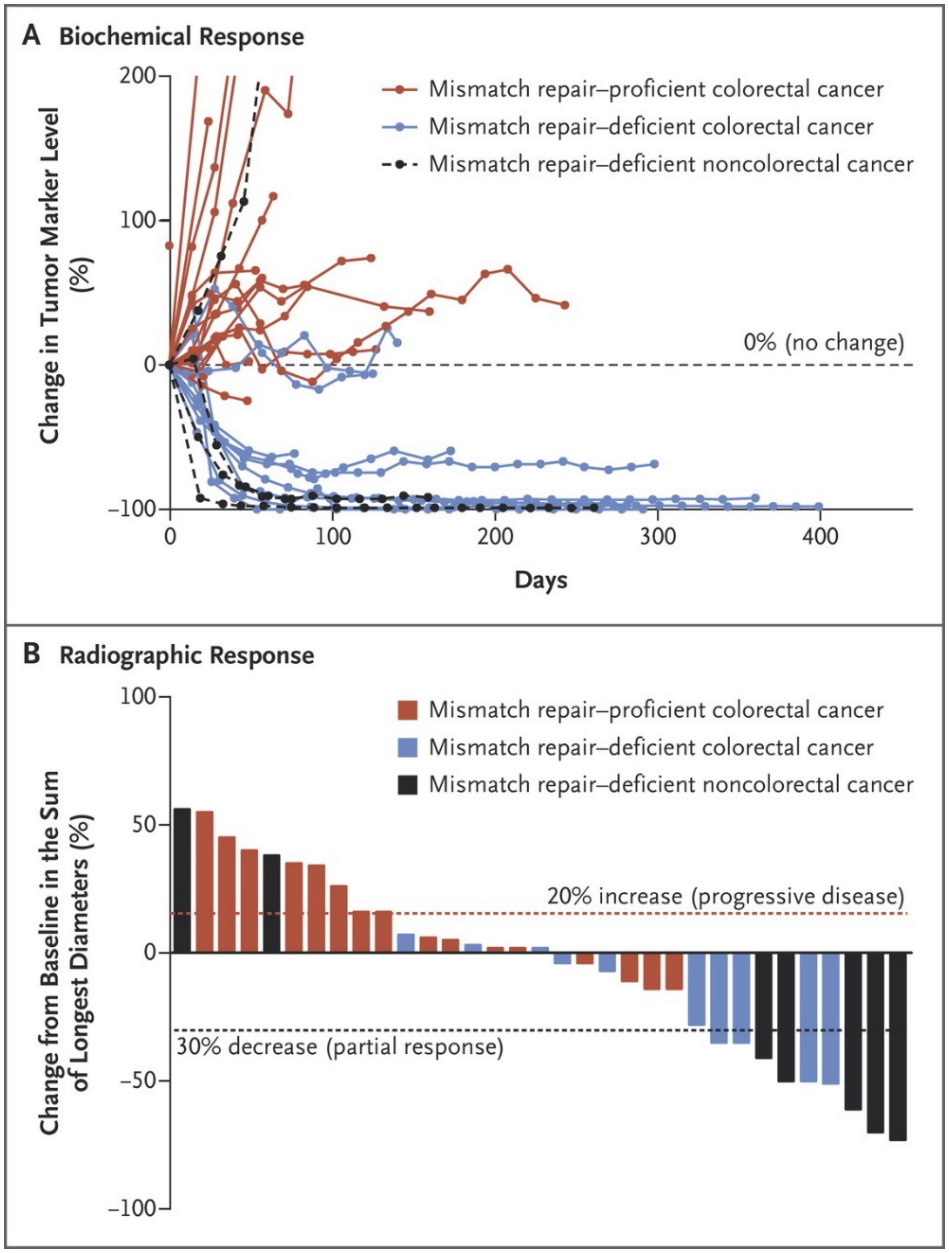


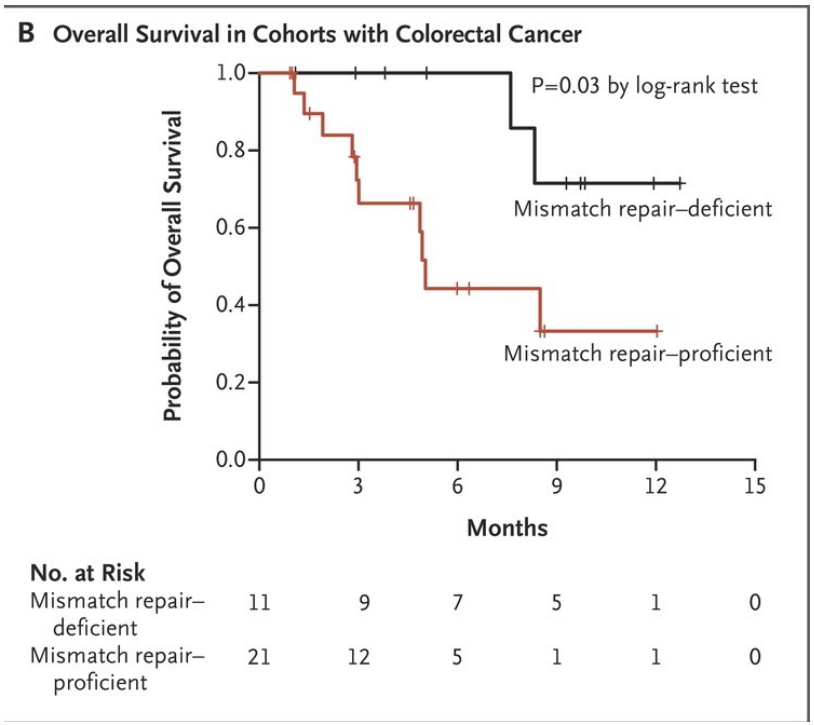
NSCLC patients with higher nonsynonymous mutations have a longer PFS after anti-PD1 treatment.

Weber et al., *J Clin Oncol* **31**, 4311 (2013)

Naiyer A. Rizvi et al. Science;348:124-128 (2015)

PD-1 blockade in tumors with mismatch-repair deficiency





Mismatch-repair deficiency increases the number of somatic mutations. Increase in mutation-associated neoantigens in the tumor enhances endogenous T cell infiltration (>diversity), but these T cells are non-functional. Anti-PD1 treatment reactivates these exhausted tumor-infiltrating T cells.

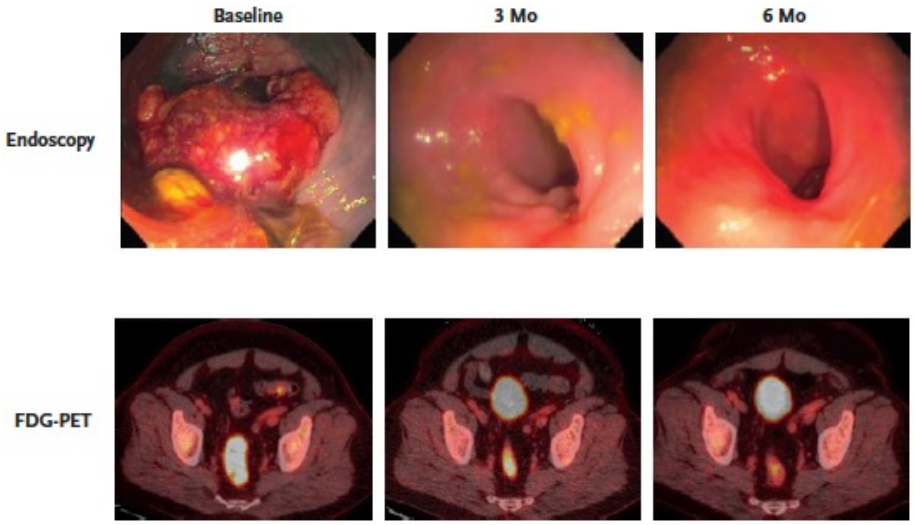
Le et al. *N Engl J Med* 2015;372:2509-2520.

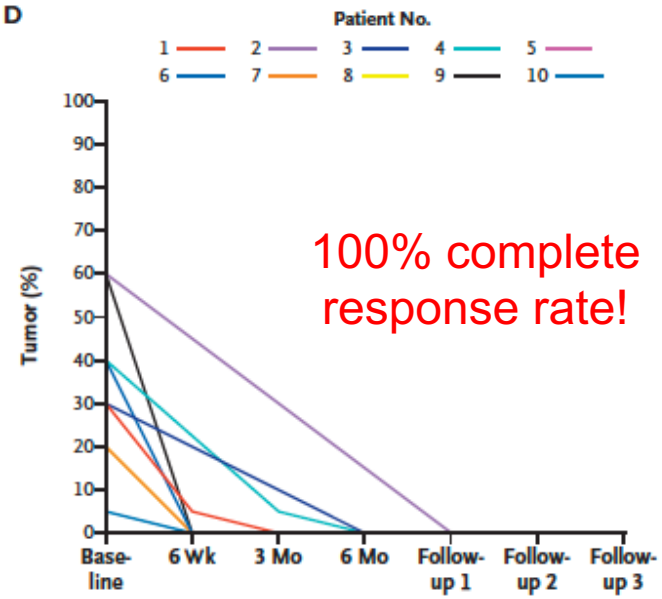
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.





100% complete response rate!

N Engl J Med 2022;386:2363-76.
DOI: 10.1056/NEJMoa2201445

Immune checkpoint blockade: PD1-PDL1 Challenges

Table 1. Drugs in Clinical Development that Block PD-1 or PD-L1

Target	Drug Name	Other Names	Source	Isotype and Characteristics	Clinical Testing Phase
PD-1	MEDI0680	AMP-514	MedImmune/ AstraZeneca	information not available	phase I
	nivolumab	Opdivo, BMS-936558, MDX-1106, ONO-4538	Bristol-Myers Squibb, Ono Pharmaceuticals	fully human IgG4[a]	approved, treatment-refractory unresectable melanoma (Japan, United States) and squamous NSCLC (United States)
	pembrolizumab	Keytruda, MK-3475, lambrolizumab	Merck	humanized IgG4	approved, treatment-refractory unresectable melanoma (United States)
	pidilizumab	CT-011	CureTech	humanized IgG1	phase I-II
PD-L1	BMS-936559	MDX-1105	Bristol-Myers Squibb	fully human IgG4[a]	phase I
	MEDI4736	none	MedImmune/ AstraZeneca	Fc-modified human IgG1[b]	phase I-III
	MPDL3280A	RG7446	Genentech/ Roche	Fc-modified human IgG1[b]	phase I-III Atezolizumab (approved)
	MSB0010718C	none	EMD Serono	fully human IgG1[a]	phase I-II

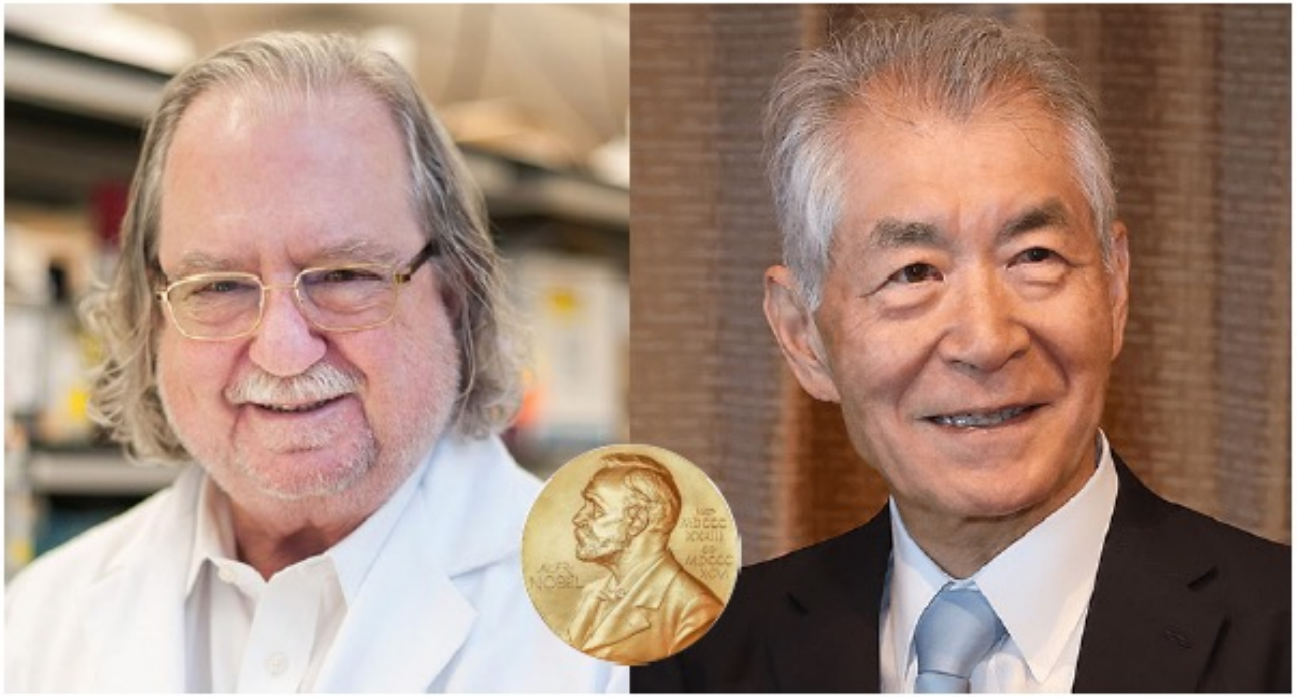
[a]Fully human mAbs were produced in genetically engineered mice.
[b]Fc-modified mAbs were engineered to abrogate ADCC and complement-dependent cytotoxicity (CDC).

Challenges of targeting PD1-PDL1 pathway:

- PD-L1 expression in the tumor is not always a biomarker of potential response to treatment
- Immune-related adverse events (less than anti-CTLA4 blockade)
- «pseudo-progression» or even «iper-progression»

2018 Nobel Prize for Medicine

CTLA4



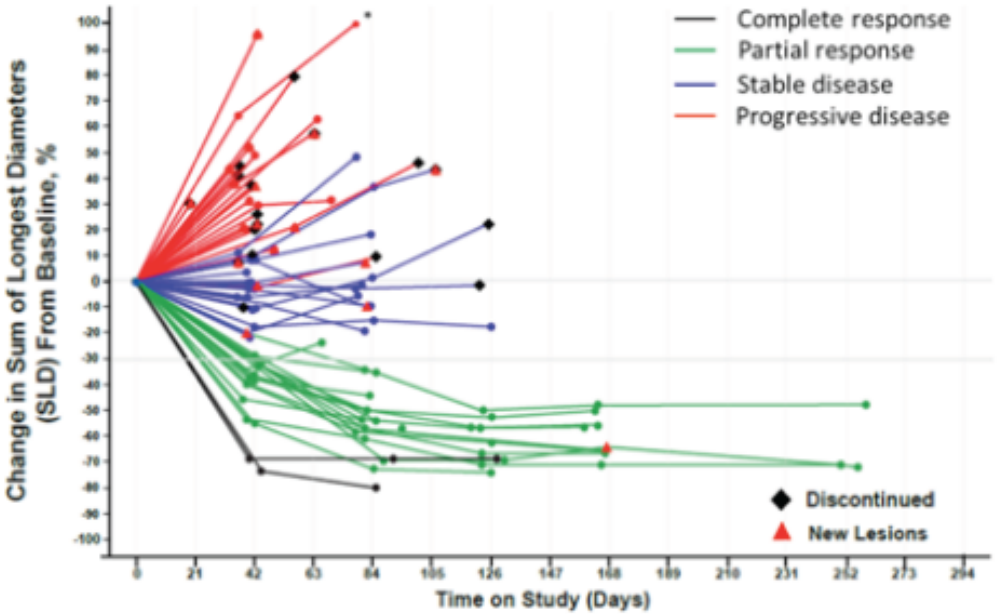
James P. Allison

Tasuko Honjo

PDL1

Immunotherapies:
Heterogeneity of tumor responses

MPDL3280A Phase 1 Data: Urothelial Bladder Cancer Patients



Progressive Disease (PD)

Why do many patients not respond?

- *No pre-existing immunity?*

Stable disease (SD)

What combinations will promote PRs & CRs?

- *Insufficient T cell immunity?*
- *Multiple negative regulators?*

Monotherapy durable responses (PR/CR)

What are the drivers of single agent response?

How can PRs be enhanced to CRs?

- *Insufficient T cell immunity?*
- *Multiple negative regulators?*

PR, partial response
CR, complete response

Challenges of anti-cancer immunotherapy

Response

No response

Tumor phenotype by T cell staining

20-30% patients

- T cells present in tumor
- Chemokines present (attract leukocytes)

↓

Responsive to single agent immunotherapies

How to increase magnitude and duration of response?

70-80% patients

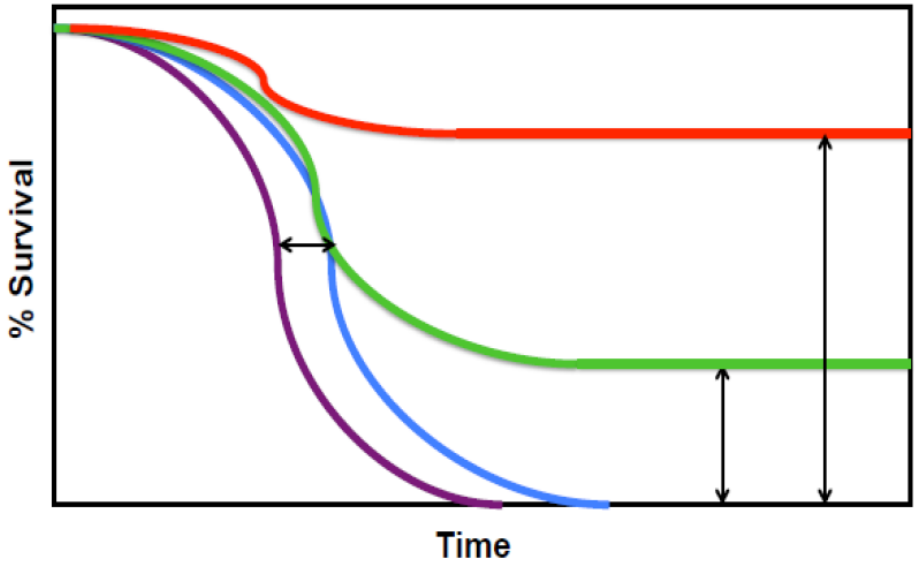
- Lack lymphocytic infiltrates

↓

Non-responsive to single agent immunotherapies

How to increase response rates and/or extend indications?

State-of-the-art and prospects of anti-cancer immunotherapies



Targeted therapies (cancer cells): incremental improvements of time-related endpoints

Immune checkpoint blockade: long-lasting clinical benefit in a subset of treated patients, in some cancer types

Goal: identification of treatment combinations that enhance the fraction of responders and/or expand indications

Summary: strategies for anti-cancer immunotherapy

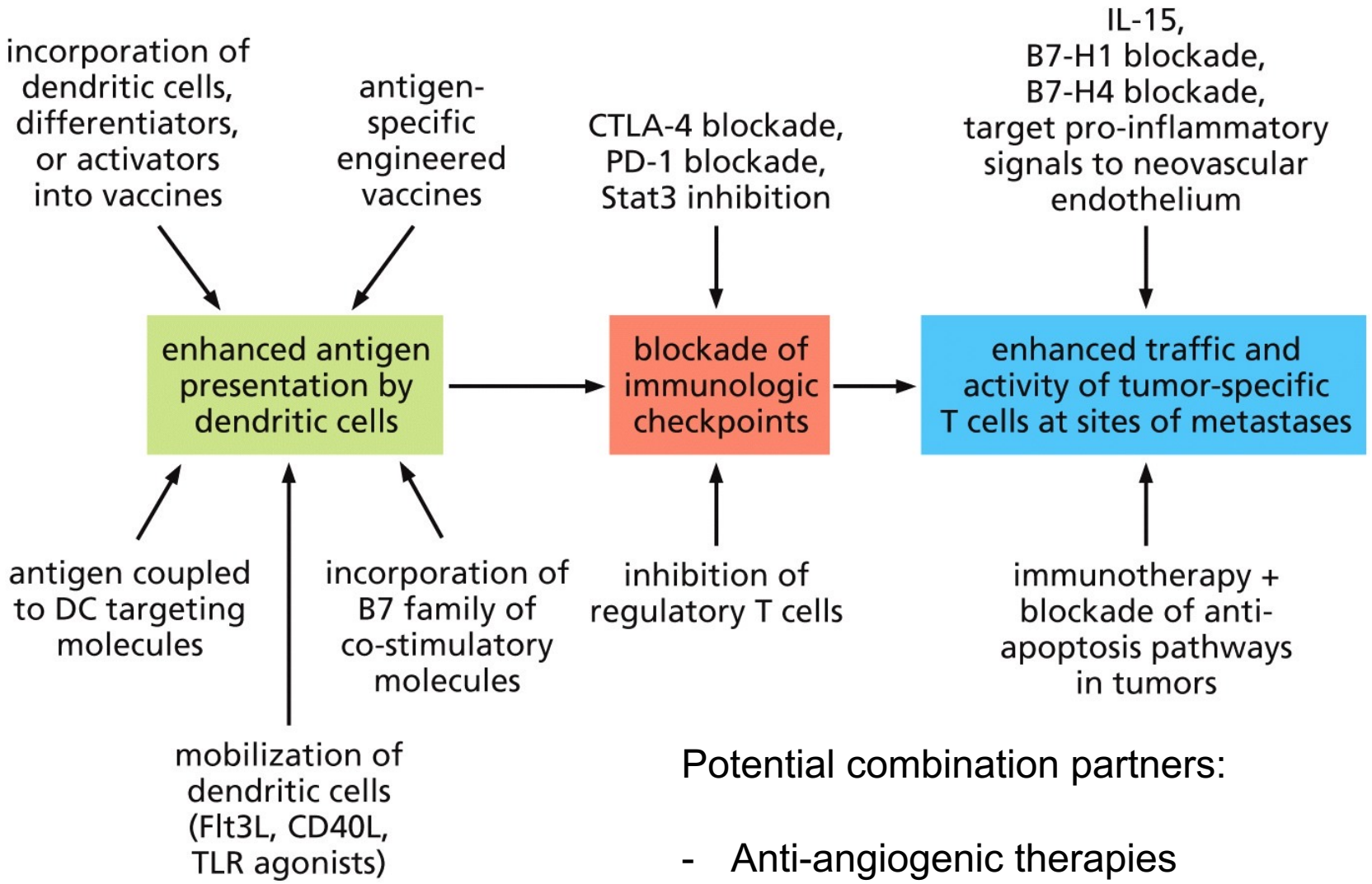


Figure 15.44 The Biology of Cancer (© Garland Science 2014)

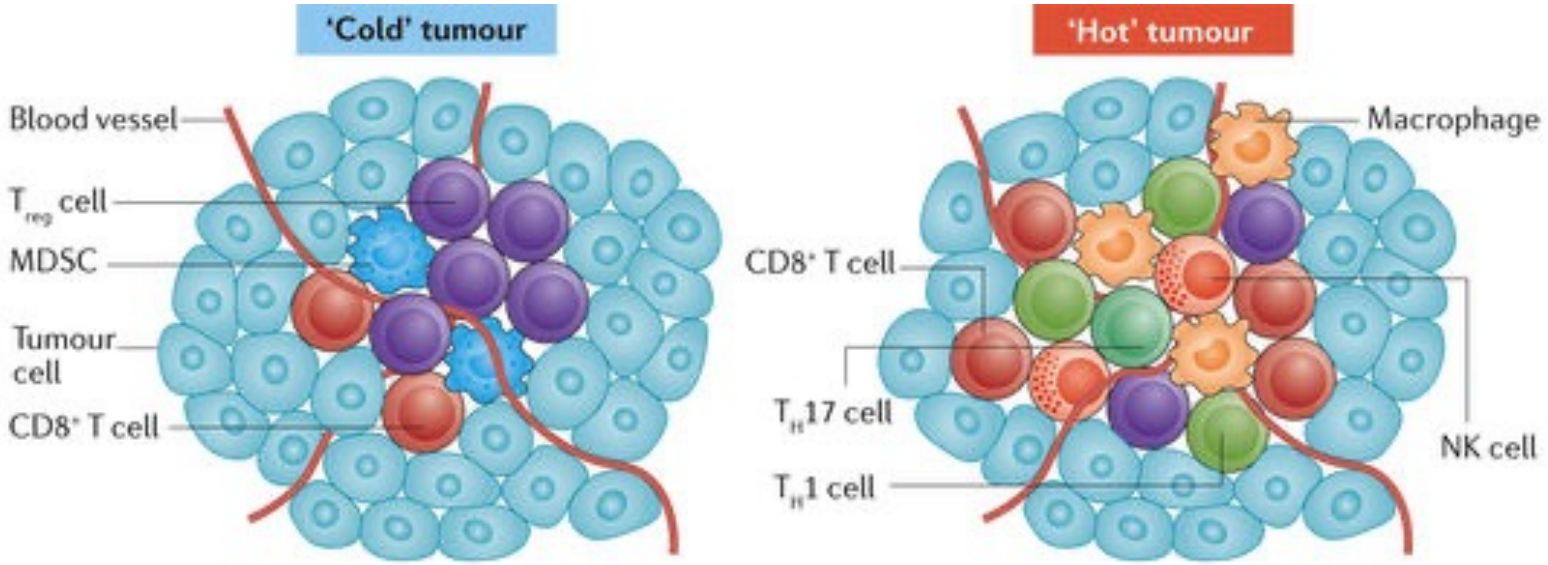
Potential combination partners:

- Anti-angiogenic therapies
- Immunogenic chemotherapies

Cancer immunotherapies: Immunoscore predicts response

Poor response

Good response

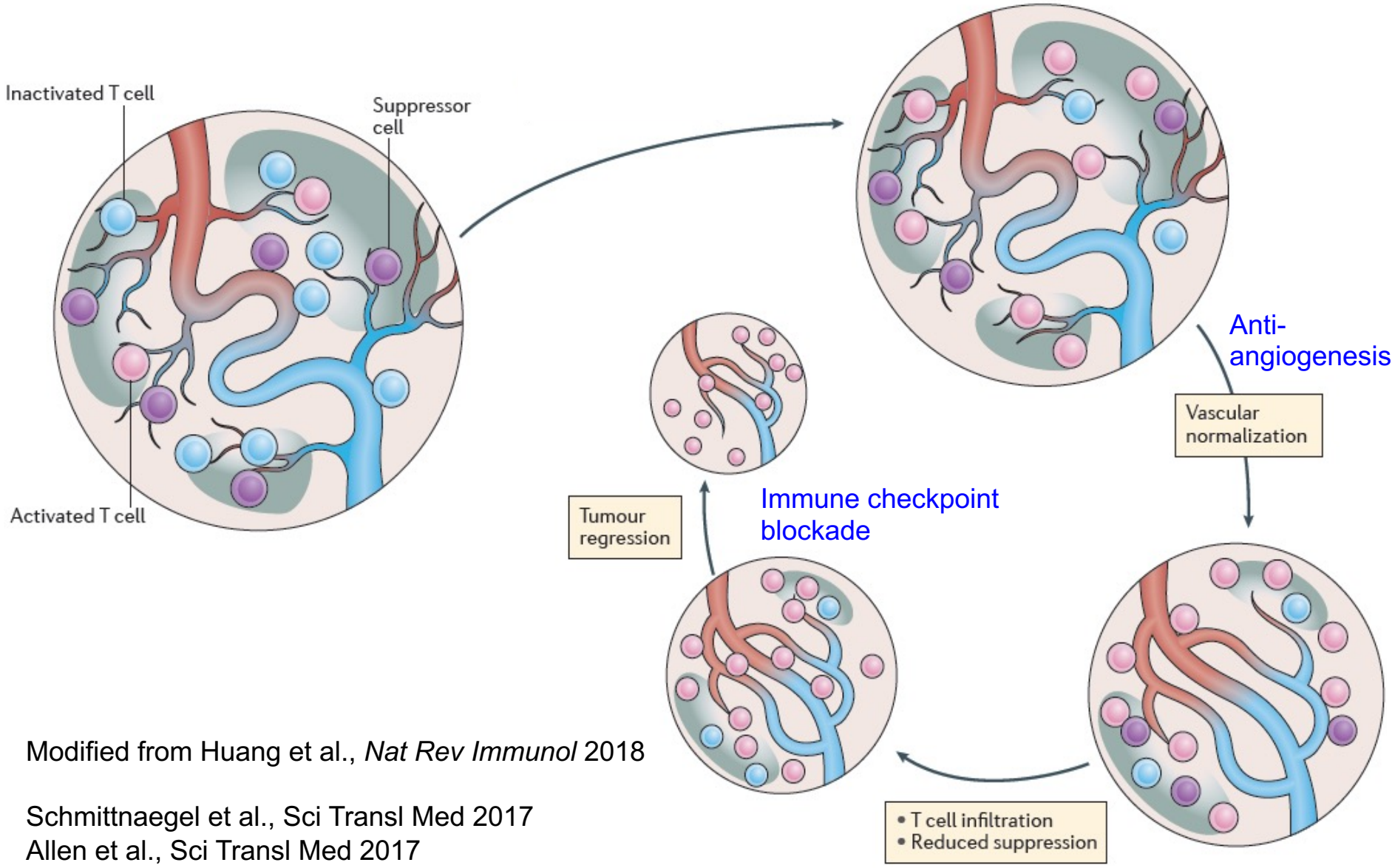


Immunological characteristics	• Enriched in immunosuppressive cytokines • High numbers of T_{reg} cells and MDSCs • Few T_H1 cells, NK cells and CD8⁺ T cells • Few functional APCs	• Enriched in T_H1-type chemokines • High numbers of effector immune cells (T_H1 cells, NK cells and CD8⁺ T cells) • High numbers of functional APCs

Nature Reviews | Immunology

Nagarsheth et al., *Nat Rev Immunol* 2017

Anti-angiogenic immunotherapy



Modified from Huang et al., *Nat Rev Immunol* 2018

Schmittnaegel et al., Sci Transl Med 2017
Allen et al., Sci Transl Med 2017
Kashyap et al., PNAS, in press
Ragusa et al., JCI, in press

Clinical benefits of anti-angiogenic immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

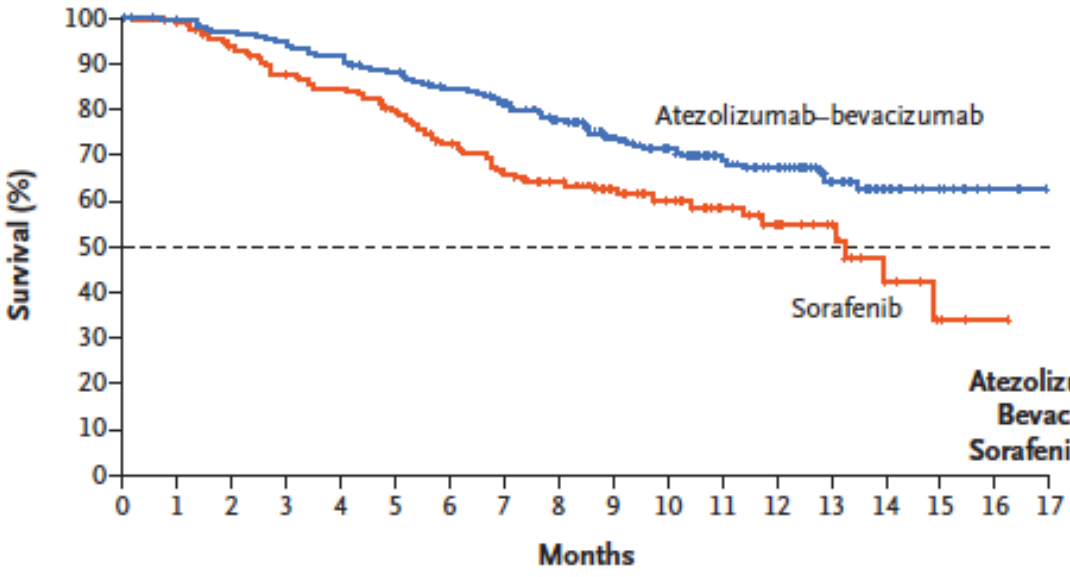
ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*

Clinical benefits of anti-angiogenic immunotherapy

A Overall Survival



	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

No. at Risk

Atezolizumab–bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE