Basic Principles of Tumor Immunotherapy

Ryan J. Sullivan, M.D.

Massachusetts General Hospital Cancer Center

Boston, MA

Disclosures

- Consulting Fees: Biodesix, Novartis Pharmaceuticals
- Other: Boehringer Ingelheim
- *I **WILL** be discussing non-FDA approved treatments during my presentation*.

Fundamental Truth

Every cancer that has been diagnosed has figured out how to defend it-“self” against the immune system

sitc

NIH NATIONAL CANCER INSTITUTE

Guiding Principle of Immunotherapy

An individual's cancer can be eradicated if the immune system can be instructed to do so

sitc

NIH NATIONAL CANCER INSTITUTE

A not-so recent Proof of Principle

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

sitc

NIH NATIONAL CANCER INSTITUTE

Proof of Principle #1:
Why did this work?

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

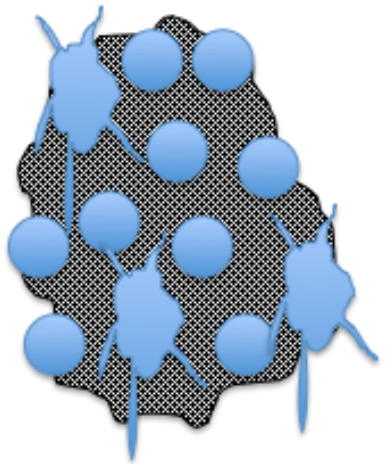
Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

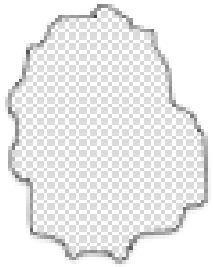
MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

Triggers release of soluble factors (cytokines)

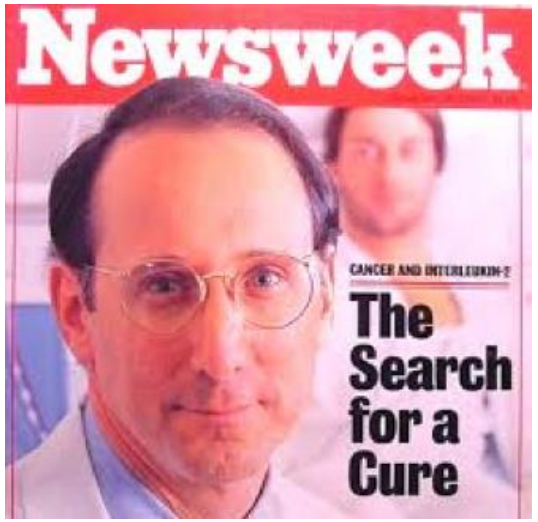


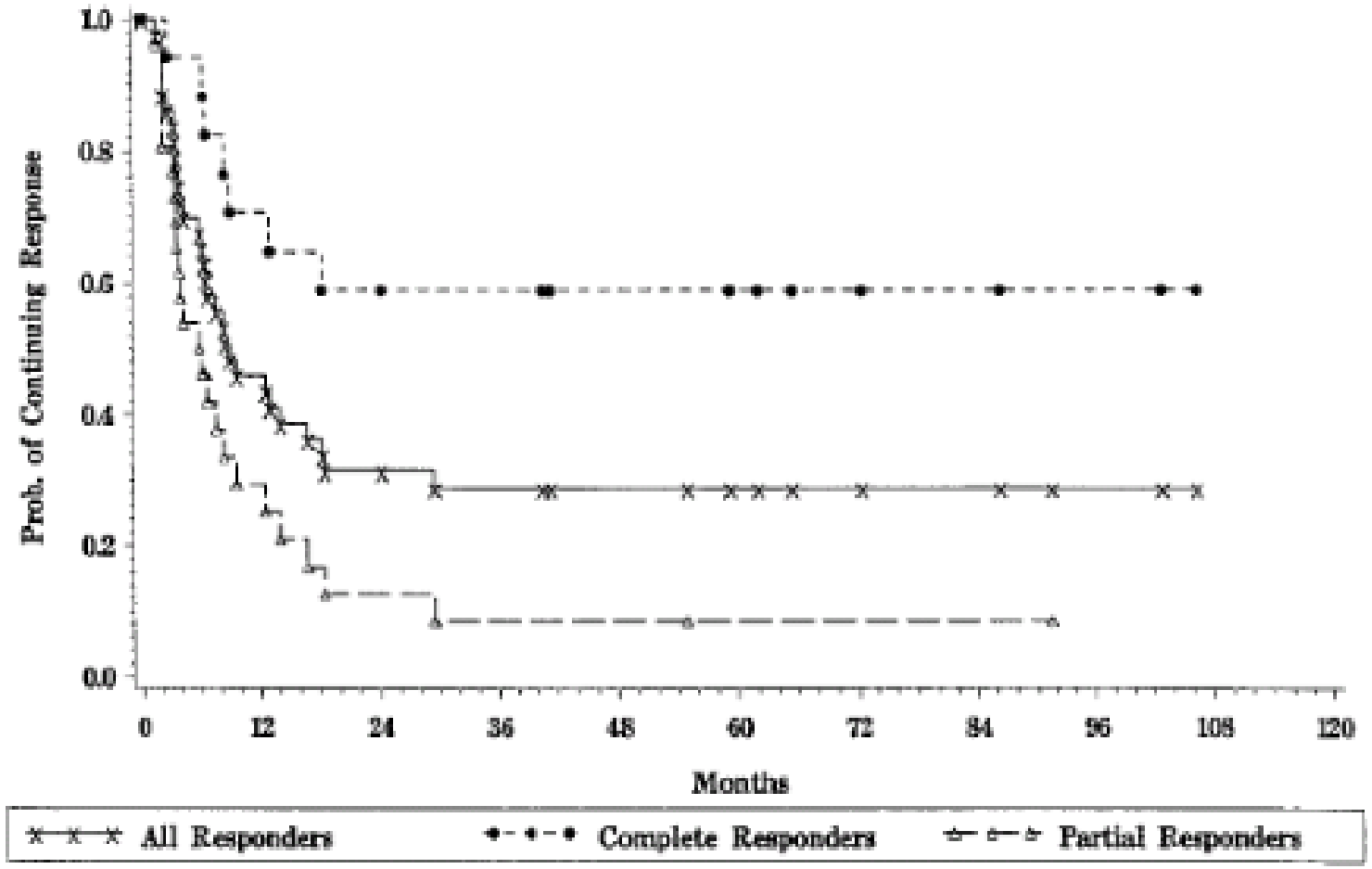


sitc

NIH NATIONAL CANCER INSTITUTE

A semi-recent Proof of Principle



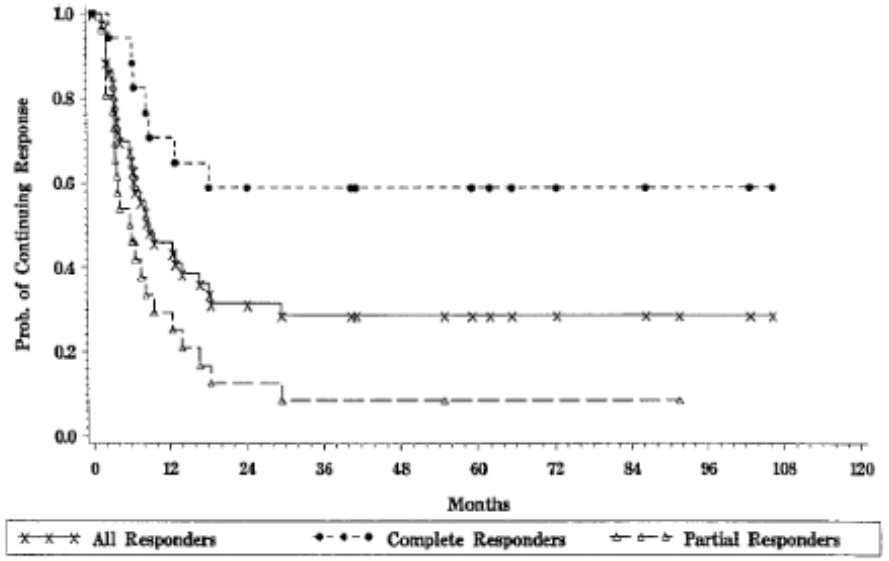


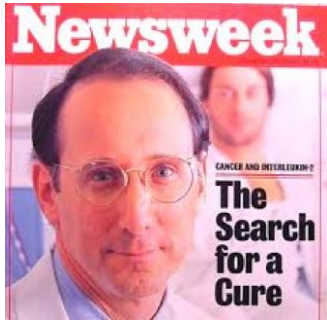
Atkins et al. J Clin Oncol. 1999

sitc

NIH NATIONAL CANCER INSTITUTE

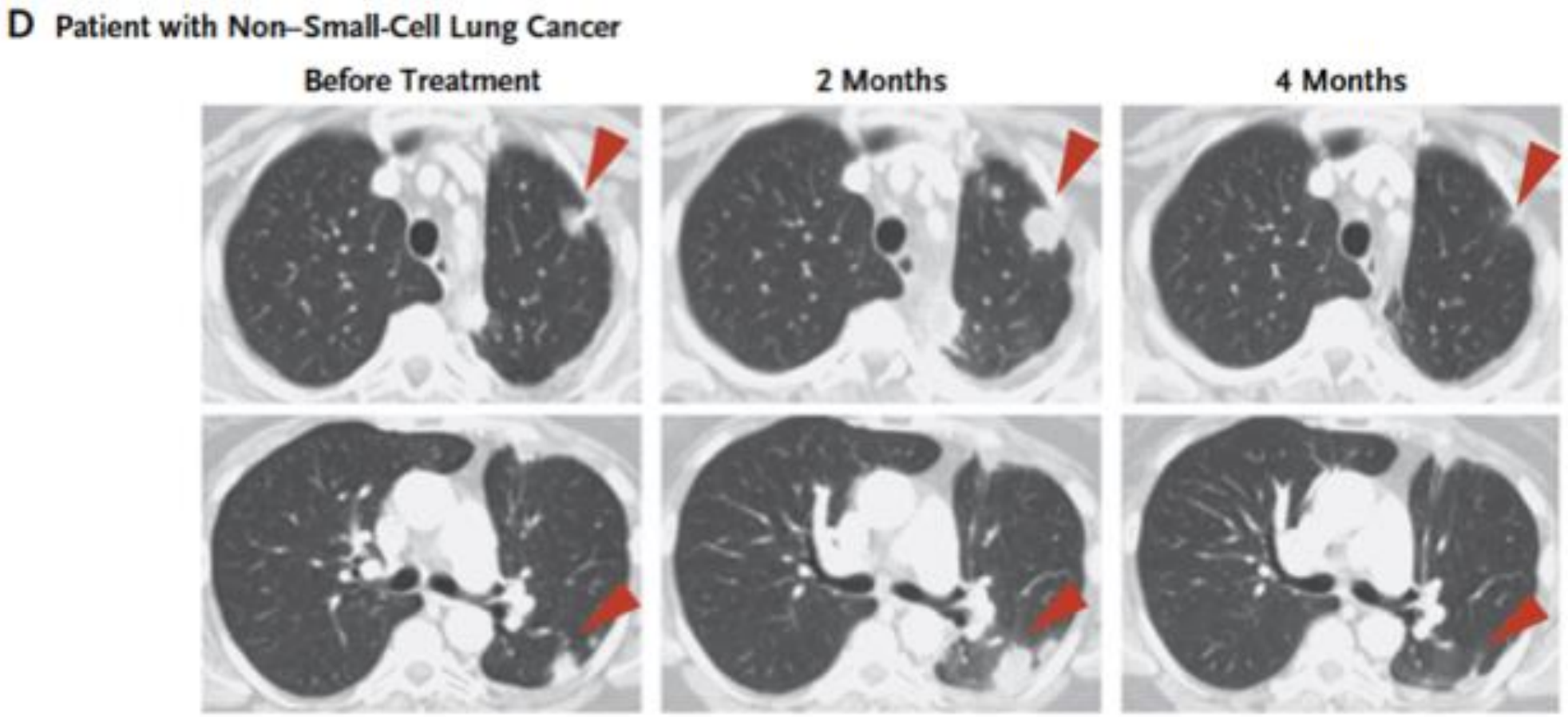
Proof of Principle #2:
Why did this work?





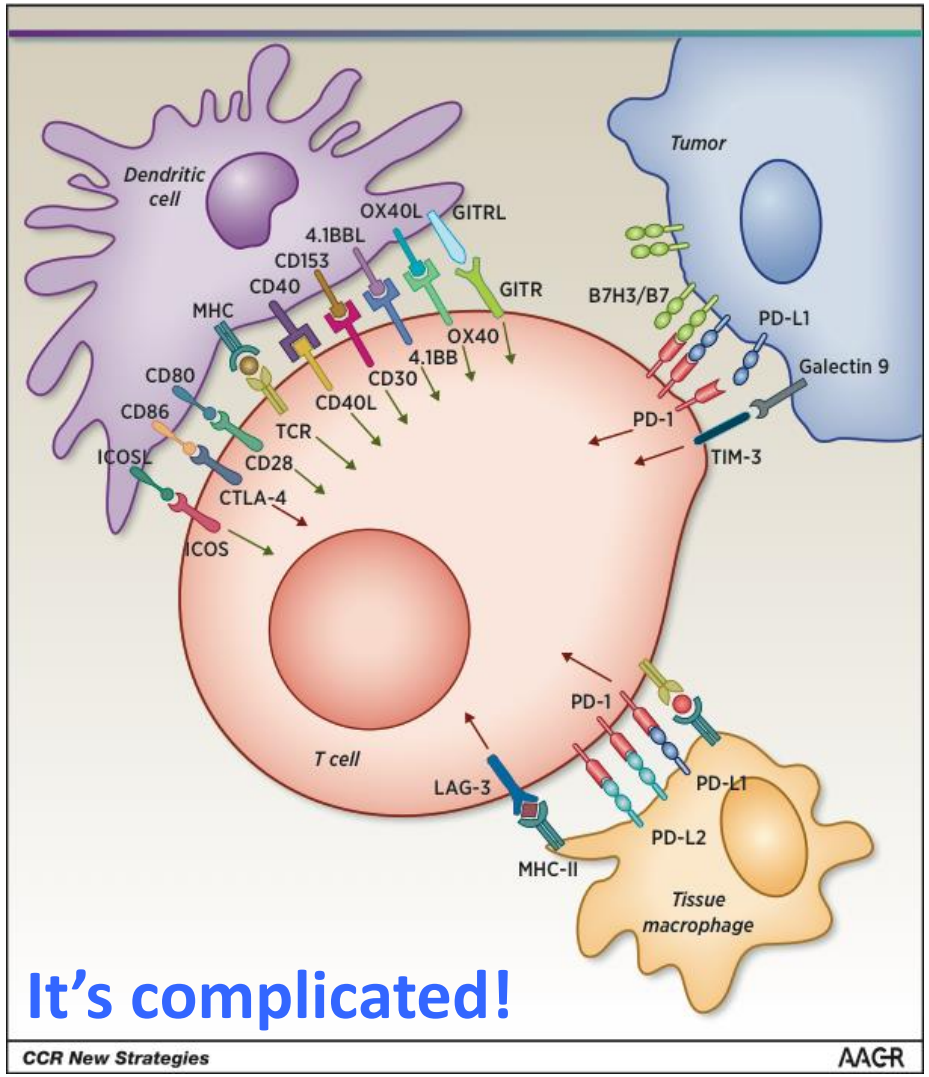
NATIONAL CANCER INSTITUTE

A recent Proof of Principle



Topalian et al. NEJM 2012

Proof of Principle #3:
Why did this work?



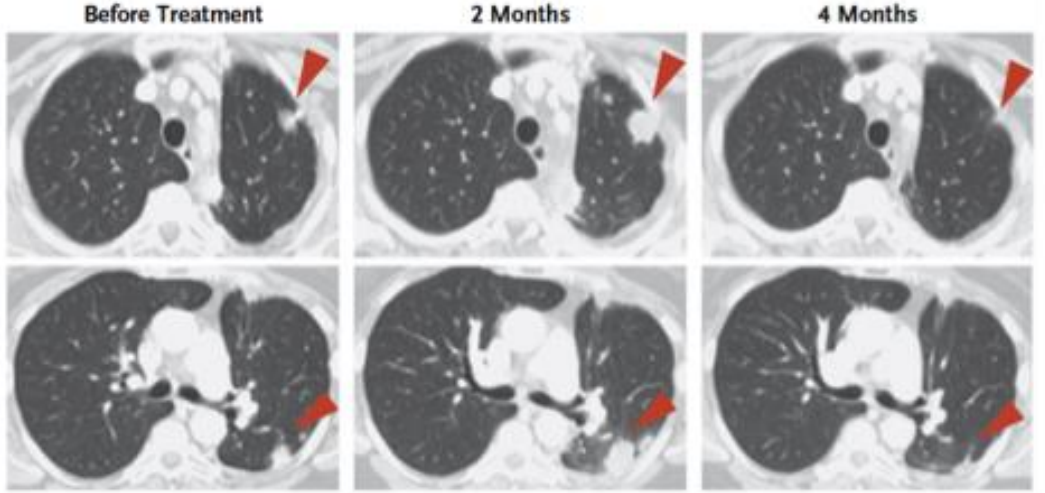
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

D Patient with Non–Small-Cell Lung Cancer



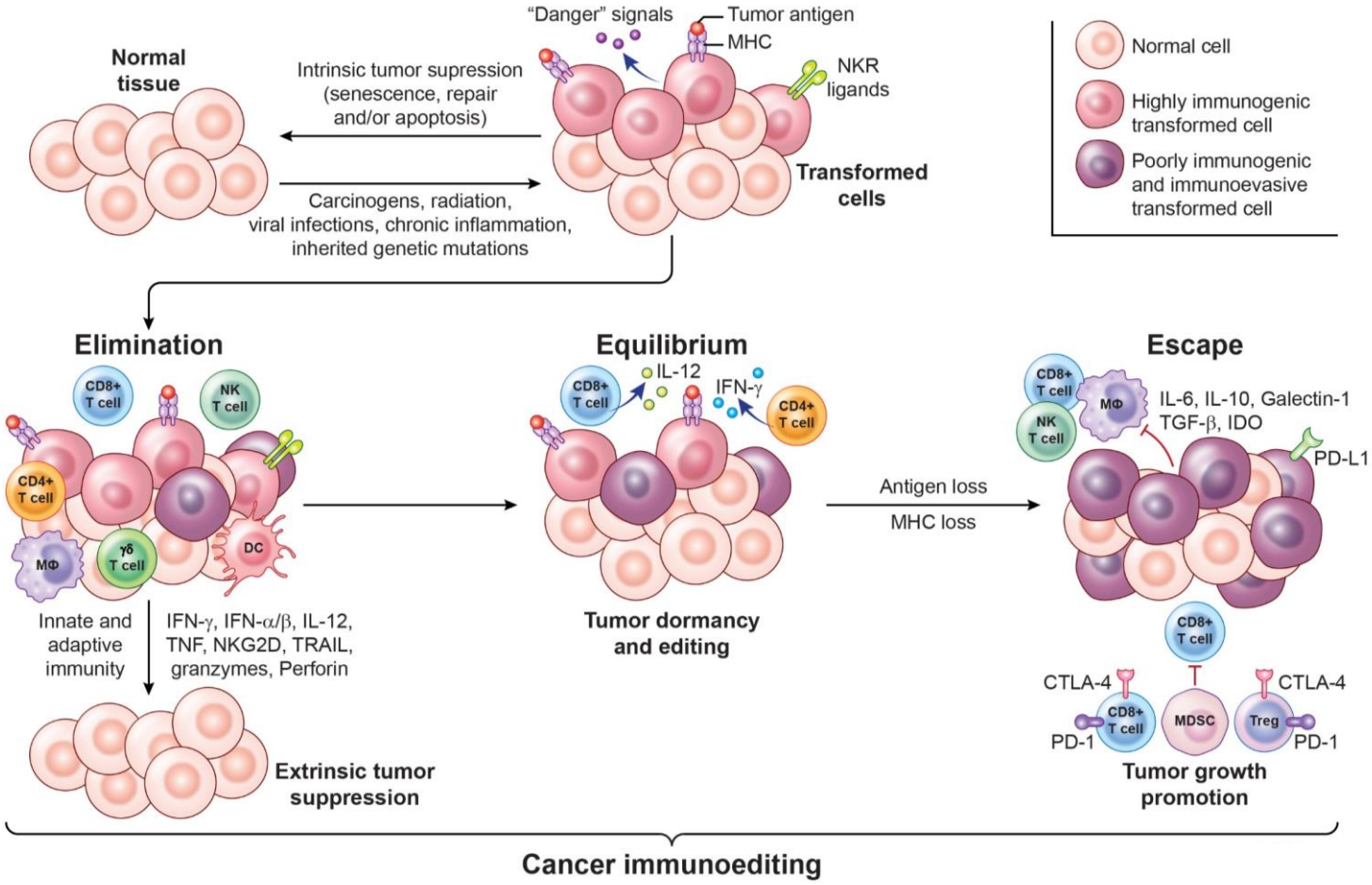
sitc

NIH NATIONAL CANCER INSTITUTE

Learning Objectives

- Define the interaction between the tumor and the immune system
  - Mechanisms of tumor immunosuppression
  - Basics of the tumor microenvironment
  - Mechanisms of overcoming immunosuppression
- Describe approaches to Tumor Immunotherapy
  - Improving immunogenicity: Vaccines, XRT, chemotherapy, TLR
  - Cellular therapy
  - Checkpoint inhibitors
  - Targeting the microenvironment
- Describe present state of biomarkers

Basics of the Tumor Microenvironment



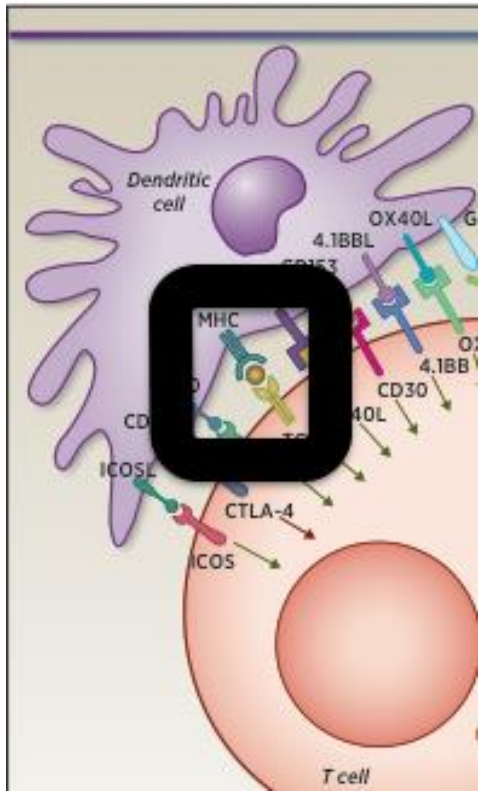
How does the immune system kill cancer?

It is all about the T-cell!!!

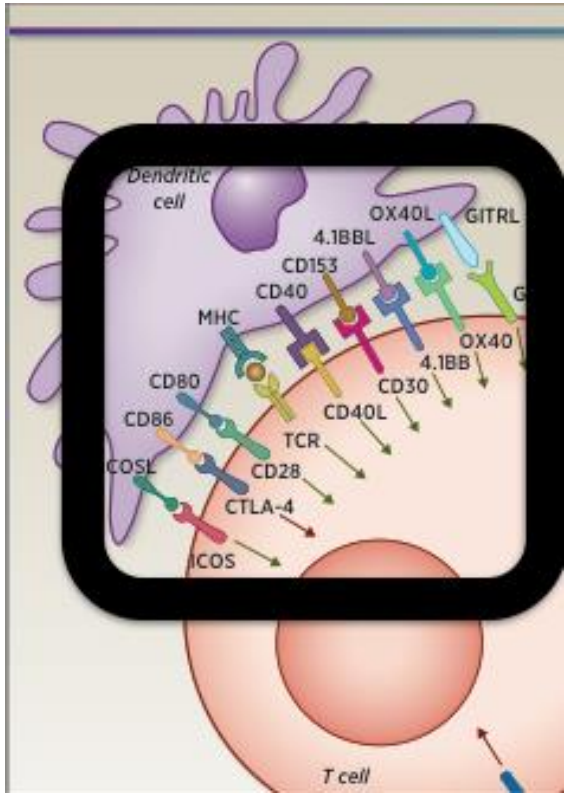
sitc

NIH NATIONAL CANCER INSTITUTE

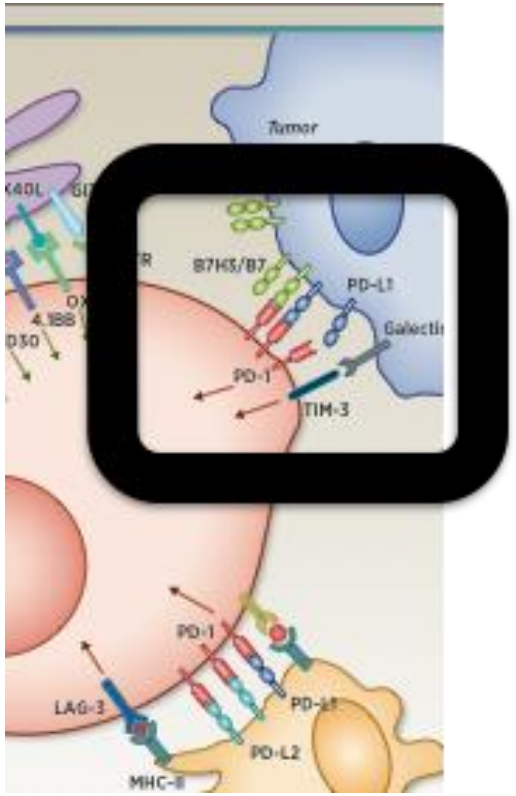
It is all (mostly) about the T-cell



1. Tumor recognition



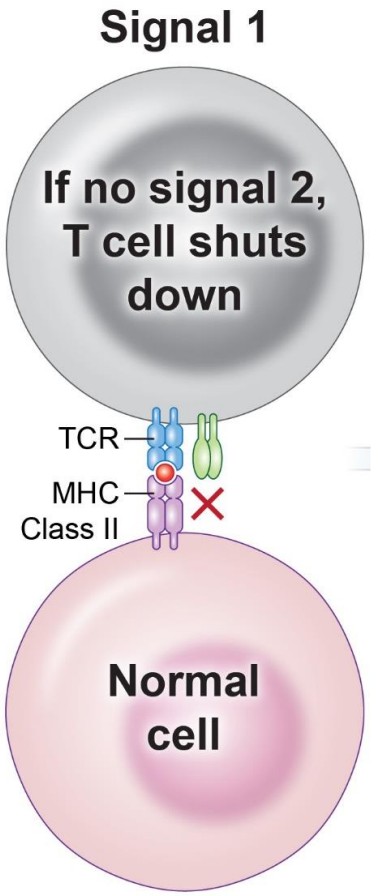
2. Immune cell Activation



3. Tumor infiltration

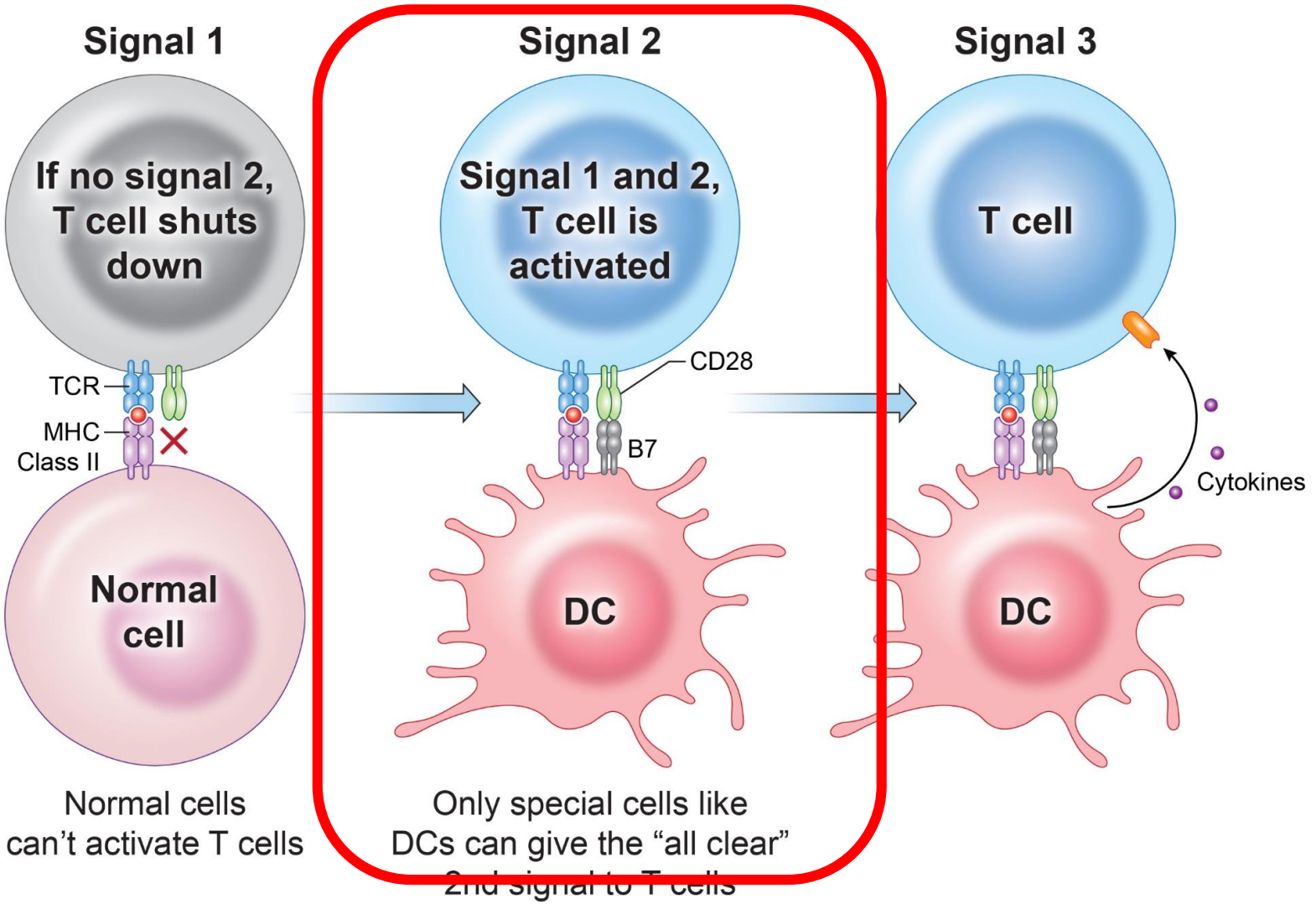
Sullivan and Flaherty. Clin Cancer Res 2015.

T cell activation is antigen-specific

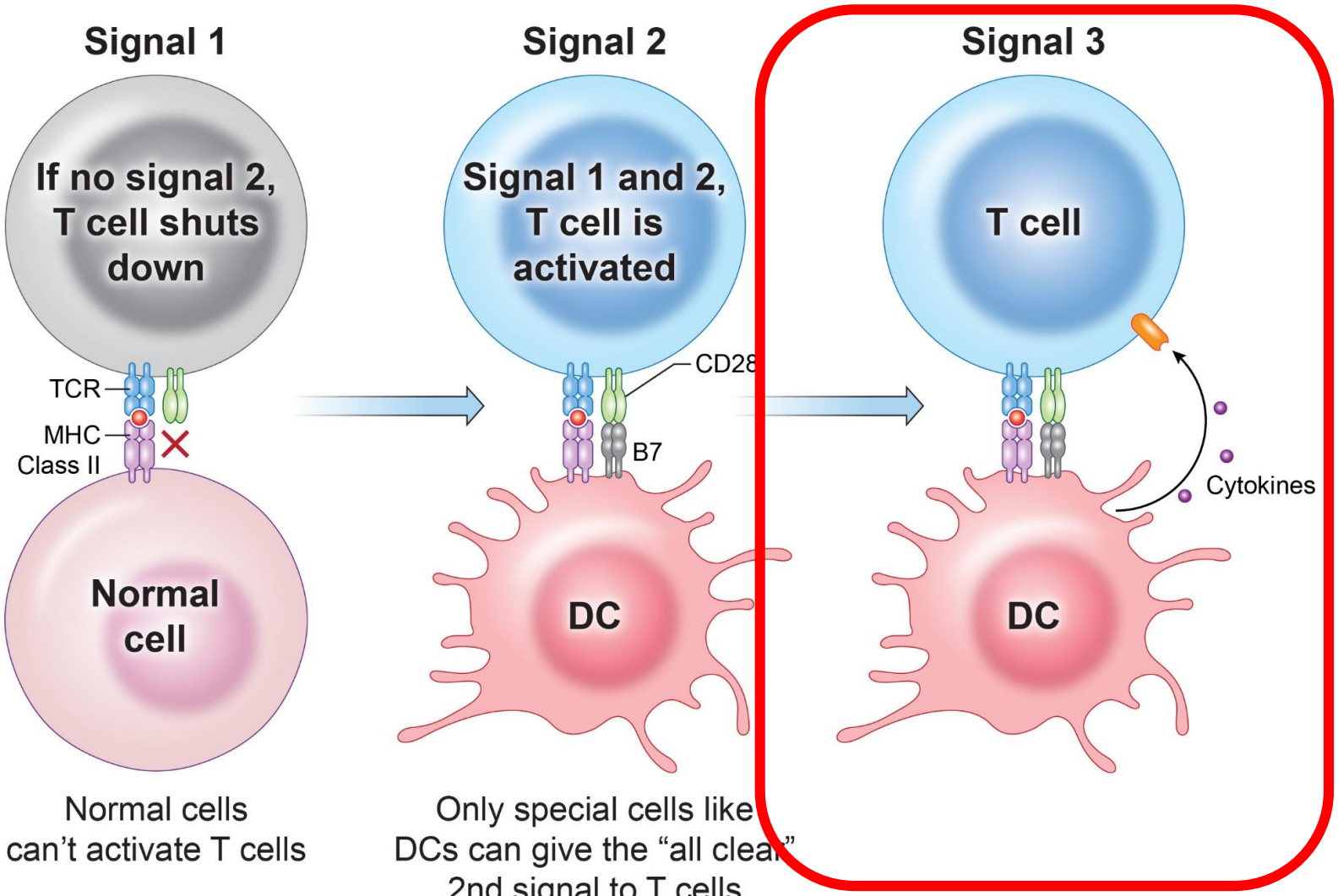


Normal cells can't activate T cells

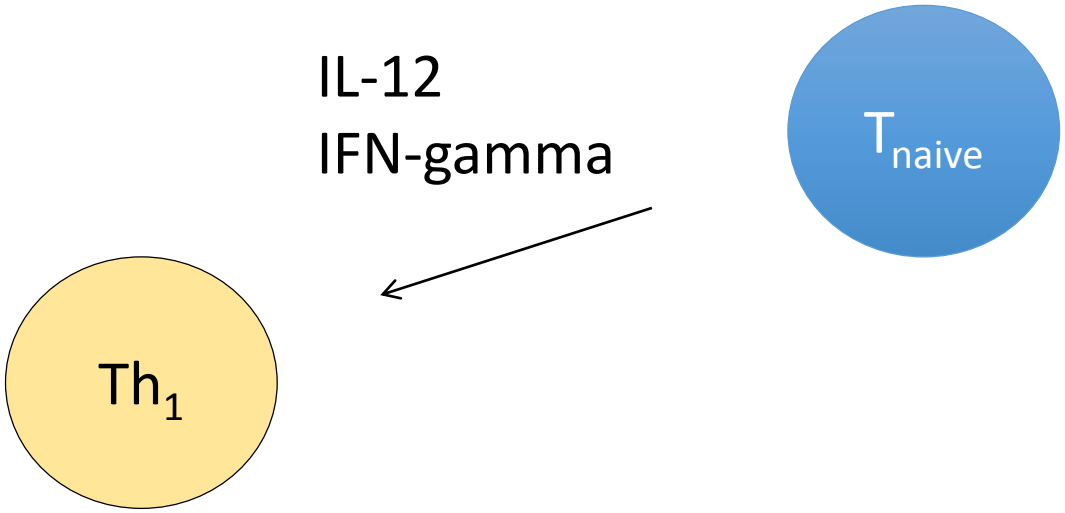
Signal #2 is tightly regulated



Signal #3 Provides the T-cell direction



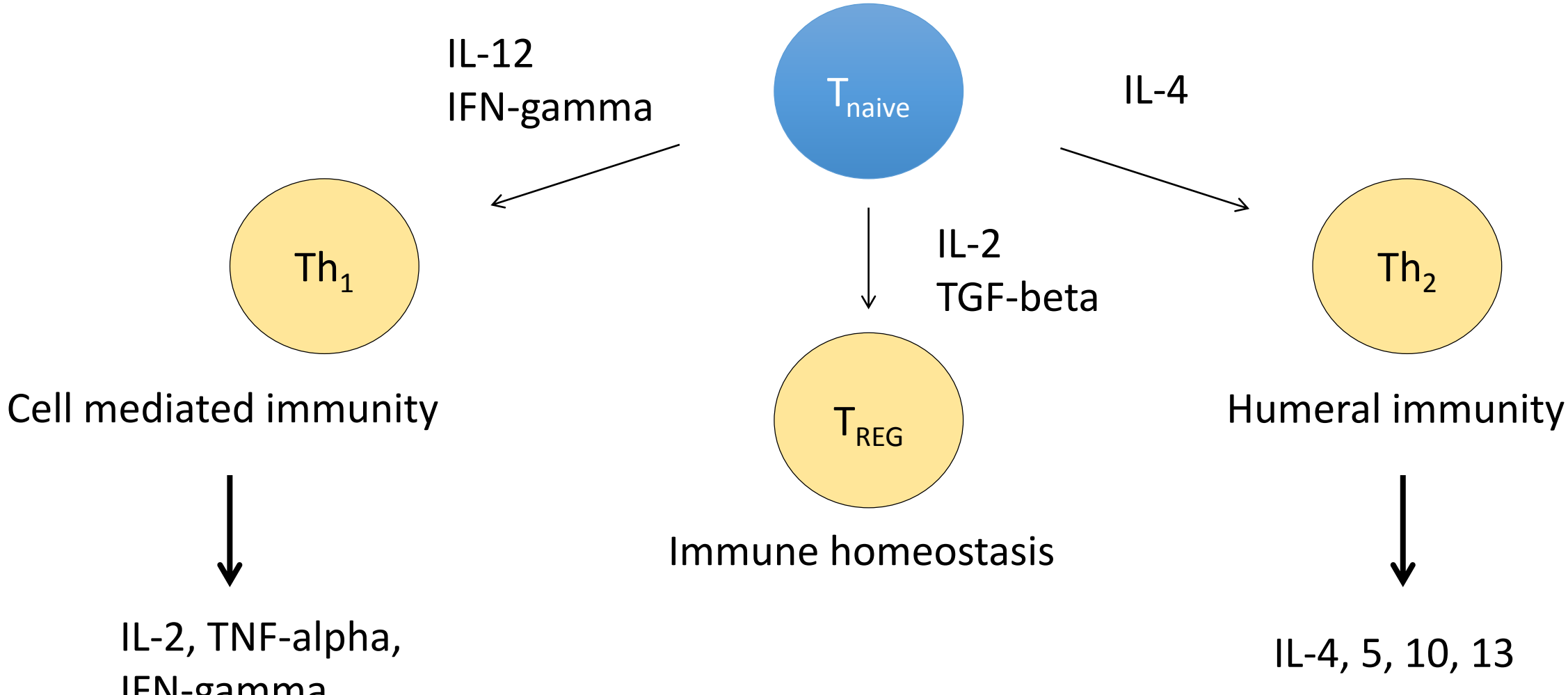
Roles of Cytokines in T-cell Polarization



Cell mediated immunity

IL-2, TNF-alpha,
IFN-gamma

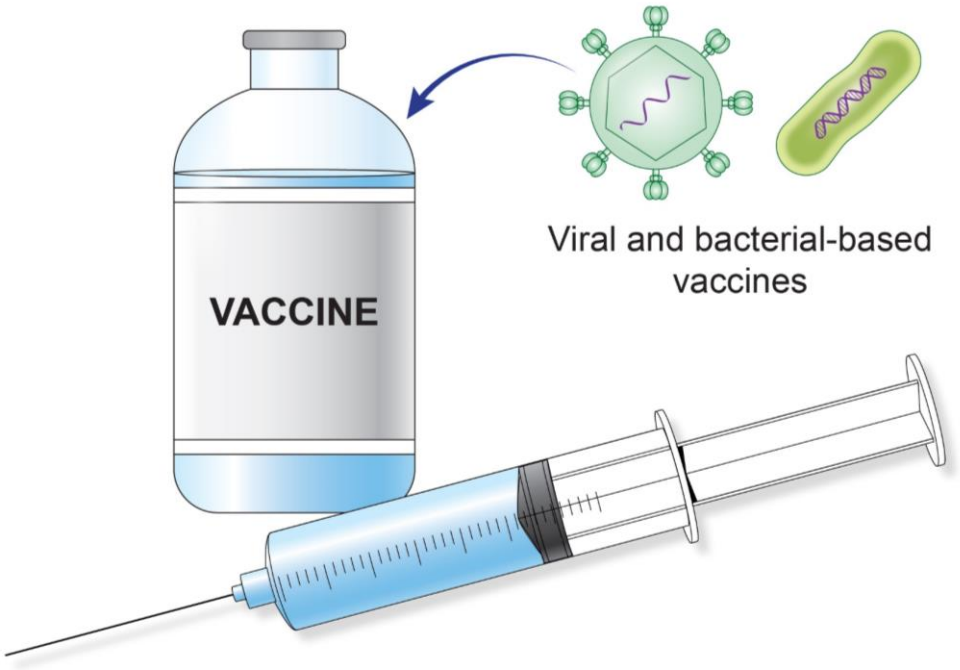
Roles of Cytokines in T-cell Polarization

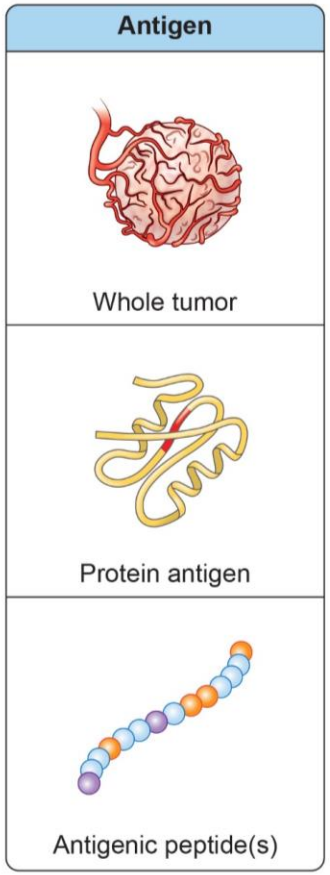


sitc

NIH NATIONAL CANCER INSTITUTE

Enhancing Tumor Recognition: Vaccines

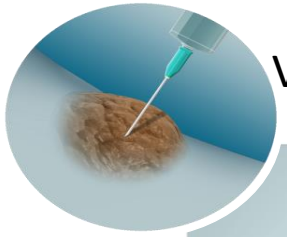




sitc

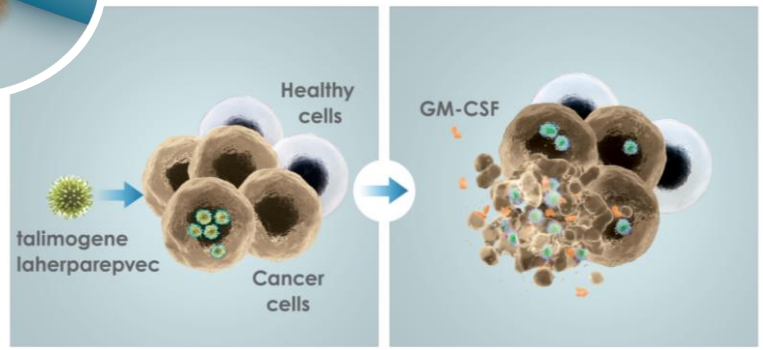
NIH NATIONAL CANCER INSTITUTE

Enhancing Tumor Recognition: Vaccines



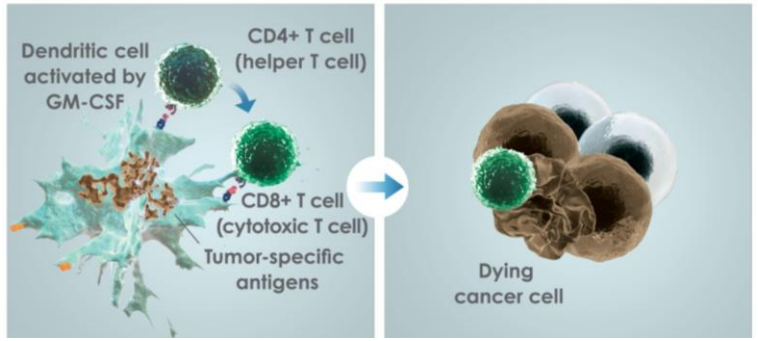
Local Effect:
Virally-Induced Tumor Cell Lysis

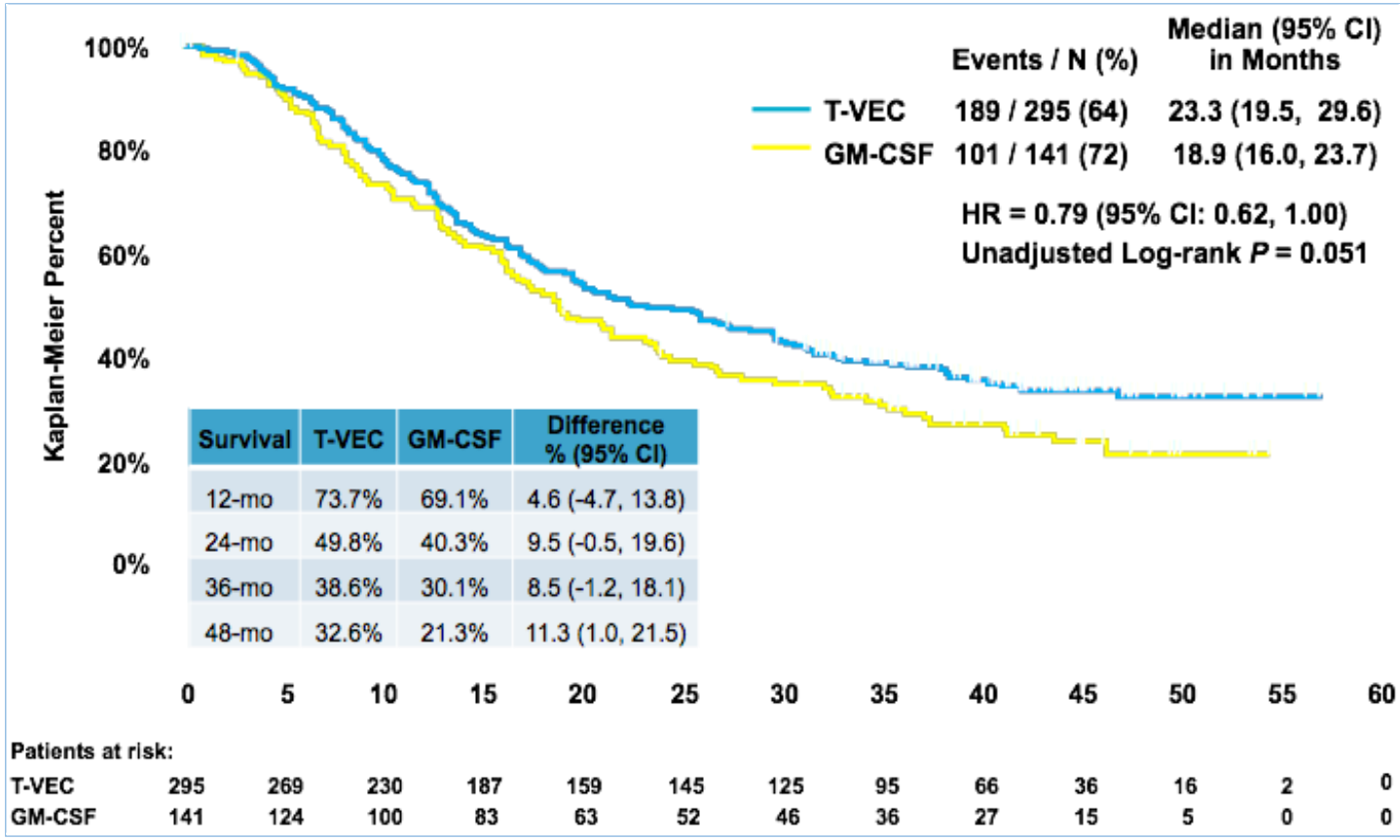
Selective viral replication in tumor tissue



Systemic Effect:
Tumor-Specific Immune Response

Systemic tumor-specific immune response

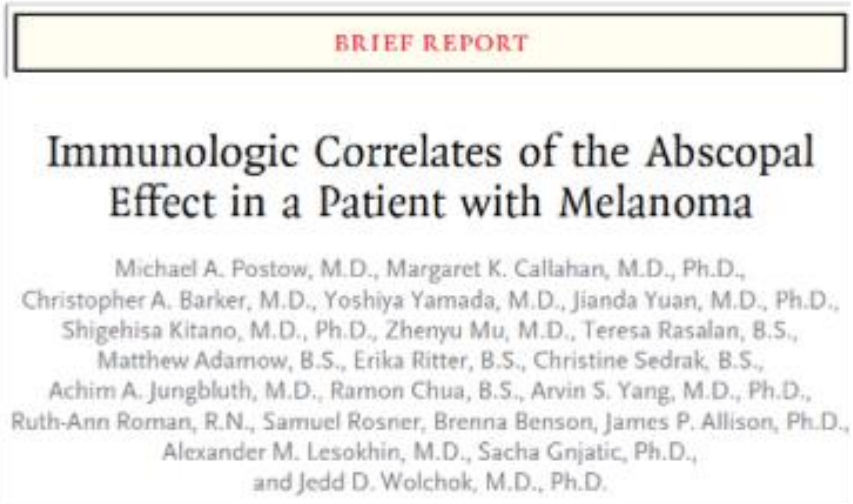




Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-mo	73.7%	69.1%	4.6 (-4.7, 13.8)
24-mo	49.8%	40.3%	9.5 (-0.5, 19.6)
36-mo	38.6%	30.1%	8.5 (-1.2, 18.1)
48-mo	32.6%	21.3%	11.3 (1.0, 21.5)

Kaufman et al. ASCO 2015

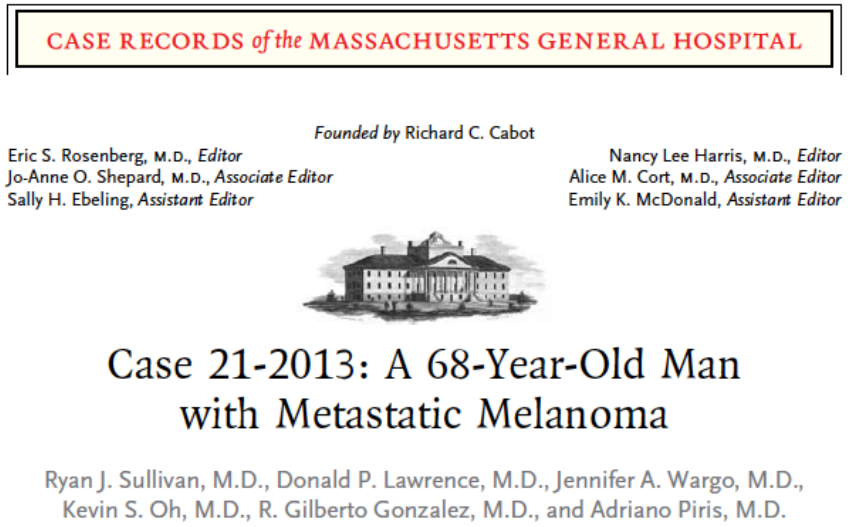
Enhancing Tumor Recognition: Radiation as Vaccine



BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.



CASE RECORDS *of the* MASSACHUSETTS GENERAL HOSPITAL

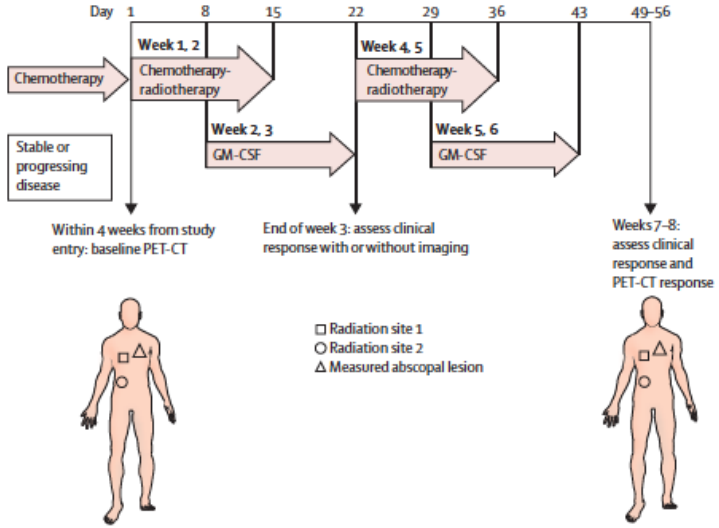
Founded by Richard C. Cabot

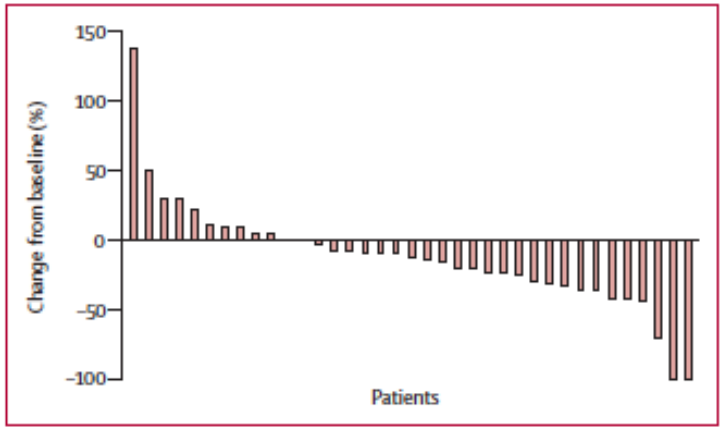
Eric S. Rosenberg, M.D., *Editor*
Jo-Anne O. Shepard, M.D., *Associate Editor*
Sally H. Ebeling, *Assistant Editor*

Nancy Lee Harris, M.D., *Editor*
Alice M. Cort, M.D., *Associate Editor*
Emily K. McDonald, *Assistant Editor*

Case 21-2013: A 68-Year-Old Man with Metastatic Melanoma

Ryan J. Sullivan, M.D., Donald P. Lawrence, M.D., Jennifer A. Wargo, M.D., Kevin S. Oh, M.D., R. Gilberto Gonzalez, M.D., and Adriano Piris, M.D.



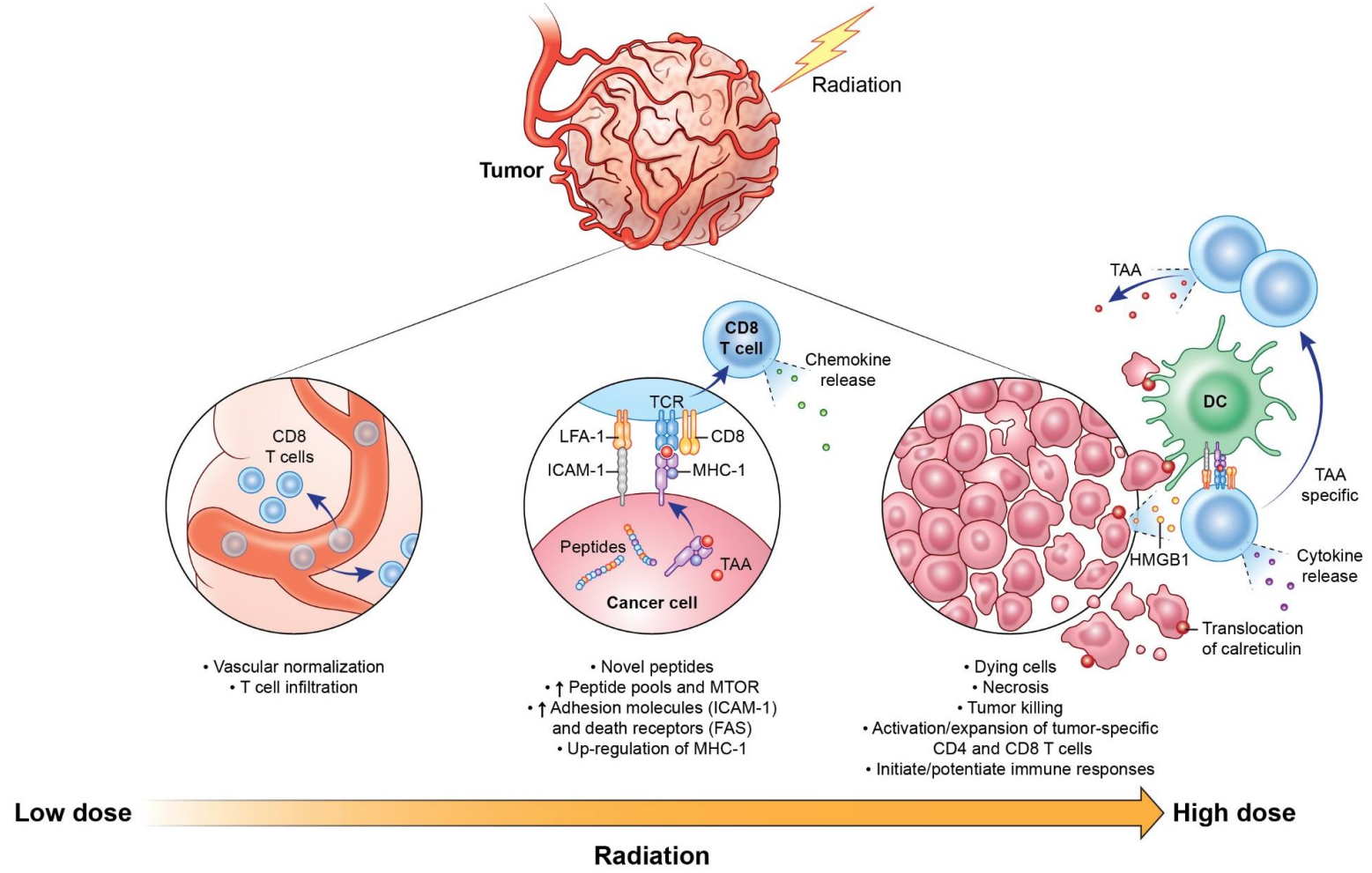


Abscopal Effect

- 50 years worth of case reports/series
- First trial to test hypothesis
- 41 patients, 9 PRs, 2 CRs

Golden et al. Lancet Oncol. 2015

Enhancing Tumor Recognition: Radiation as Vaccine



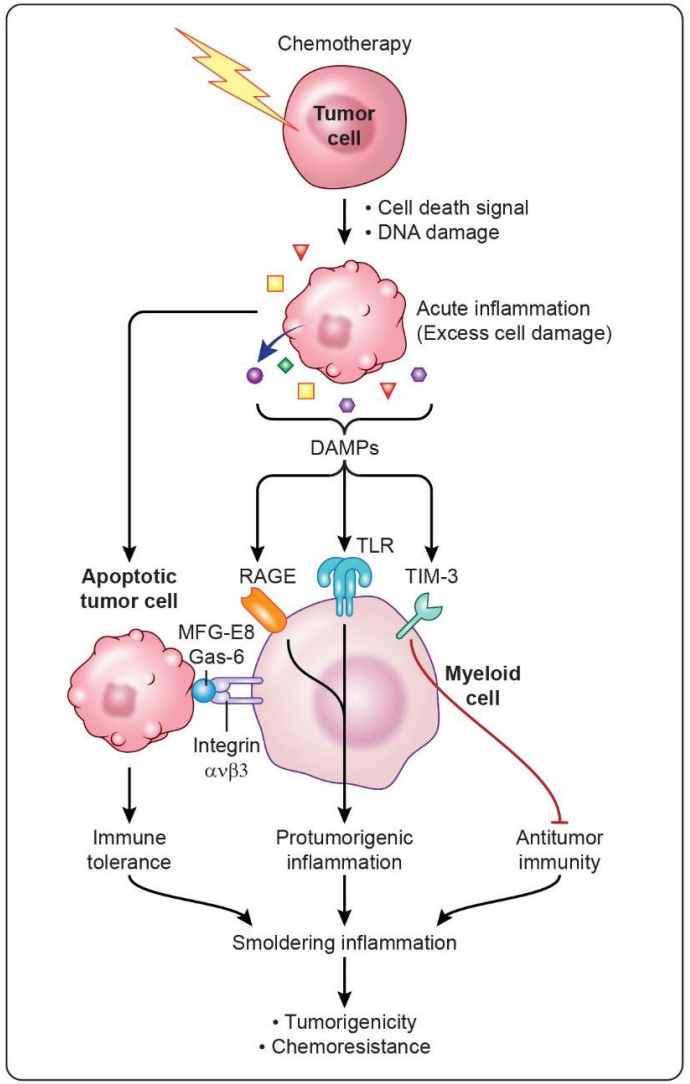
Exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer

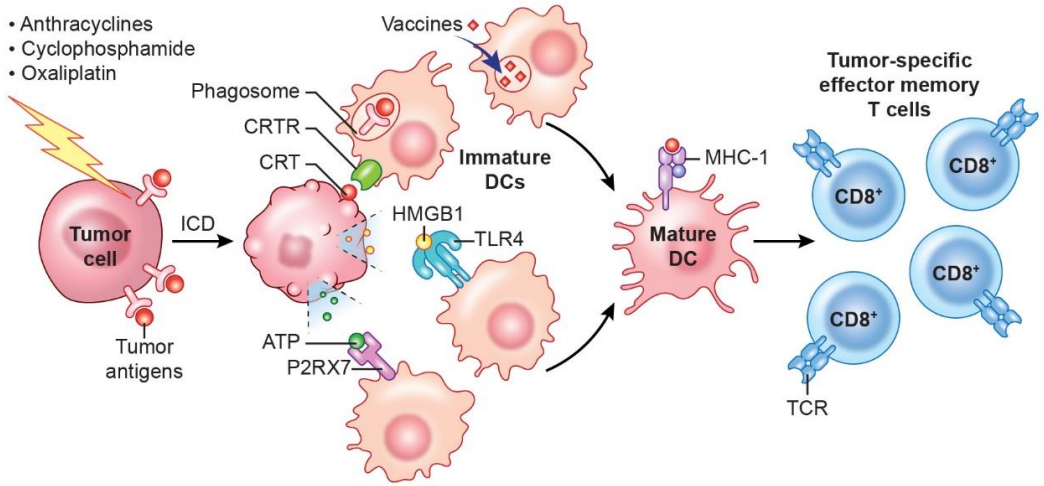
http://www.ncbi.nlm.nih.gov/pubmed/18777956

sitc

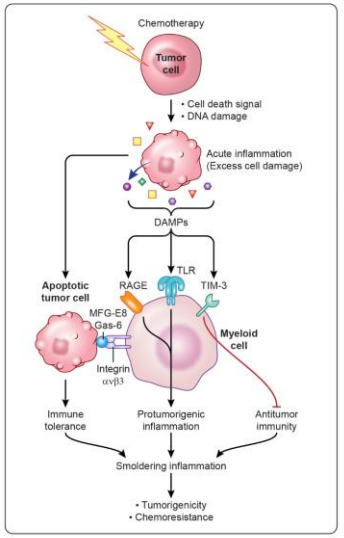
NIH NATIONAL CANCER INSTITUTE

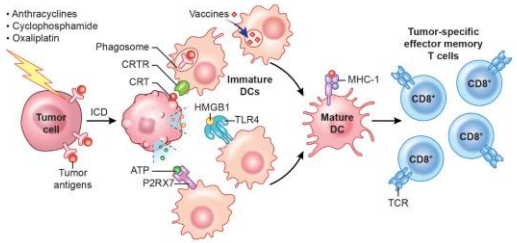
Enhancing Tumor Recognition: Chemotherapy as Vaccine





Enhancing Tumor Recognition: Chemotherapy as Vaccine

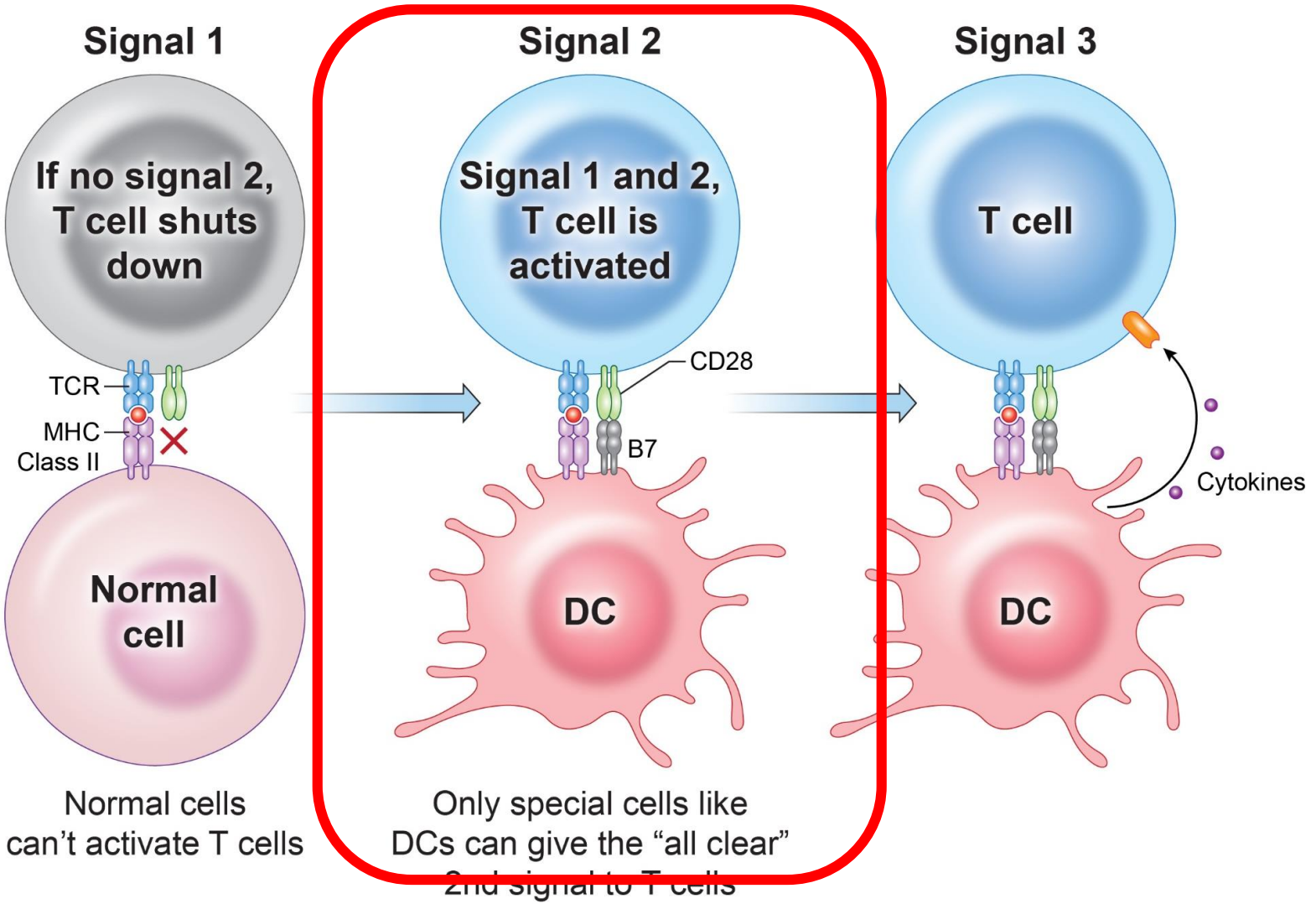




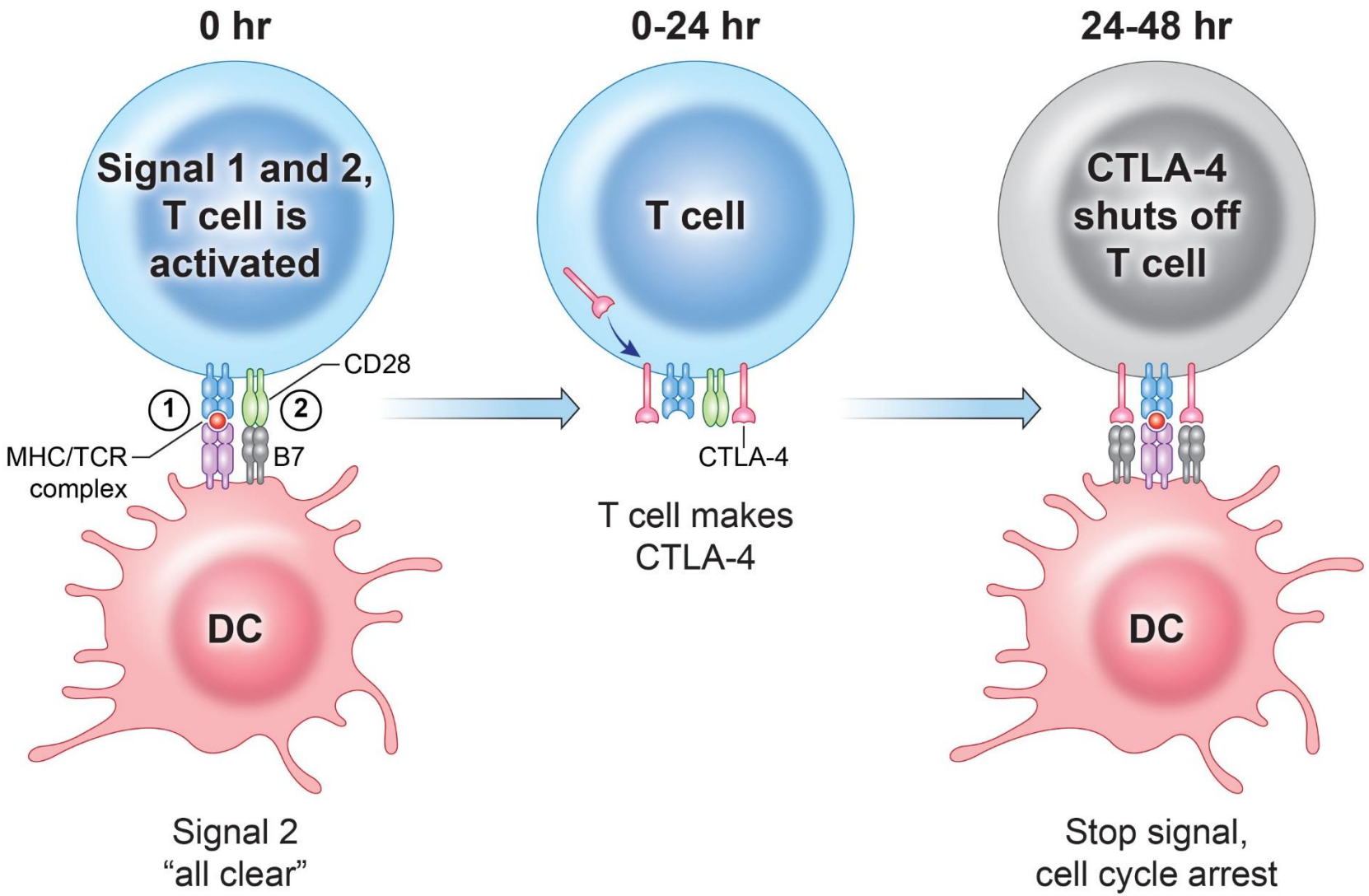
Agent	Indications	Notes
Cyclophosphamide	Lymphoma, leukemia, solid tumors	• Immunosuppressive at high doses • Increases class I HLA expression on cancer cells • Selectively inhibits Treg cells and MDSCs, perhaps with a preferential activity on intratumoral populations • Favors the differentiation of IL-17-producing CD4+ cells • Stimulates the expansion of CD8α+ DCs • Restores T cell and NK cell functions • InhibitsIL-4, IL-10 and IL-13 production • Induces immunogenic cell death
Doxorubicin	Several solid and haematopoietic tumors	• Favors the proliferation of tumor-specific CD8+ T cells • Promotes tumor infiltration by IL-17-secreting γδ T cells and activated IFNγ-secreting CD8+ T cells • Induces immunogenic cell death • Stimulates antigen presentation by DCs • Increases the permeability of tumor cells to granzyme B • Induces MCP1 expression on tumor cells, in turn driving the establishment of an immunosuppressive stroma
Gemcitabine	NSCLC, pancreatic cancer, bladder cancer, breast cancer	• Increases class I HLA expression • Enhances tumor antigen cross-presentation • Selectively kills MDSCs
Oxaliplatin	Colorectal cancer	• Increases class I HLA expression • Inhibits PDL2 expression • Induces immunogenic cell death

Galluzzi et al. Nat Reviews Drug Discov. 2011

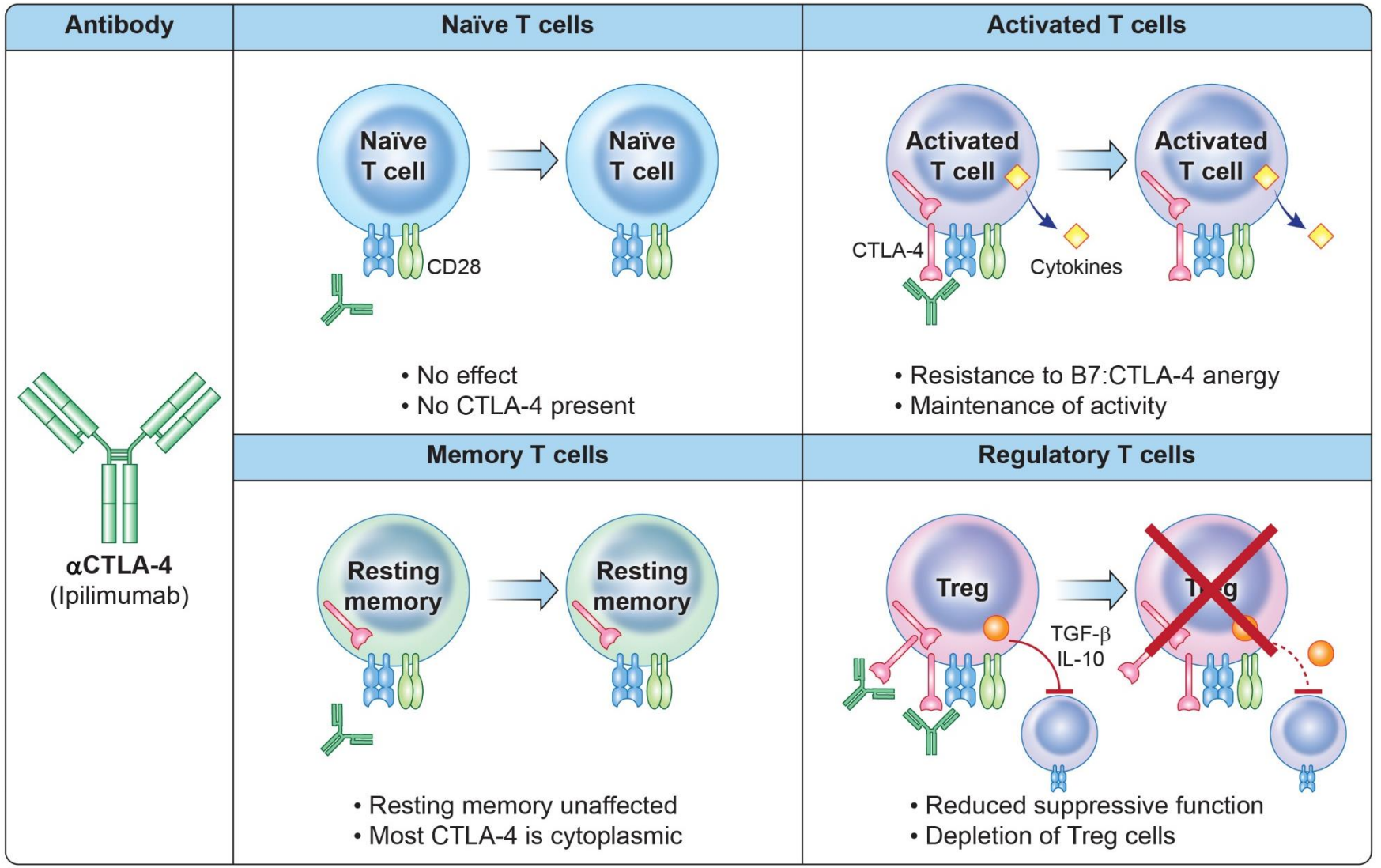
Signal #2 is tightly regulated



CTLA4 limits the responsiveness of activated T cells

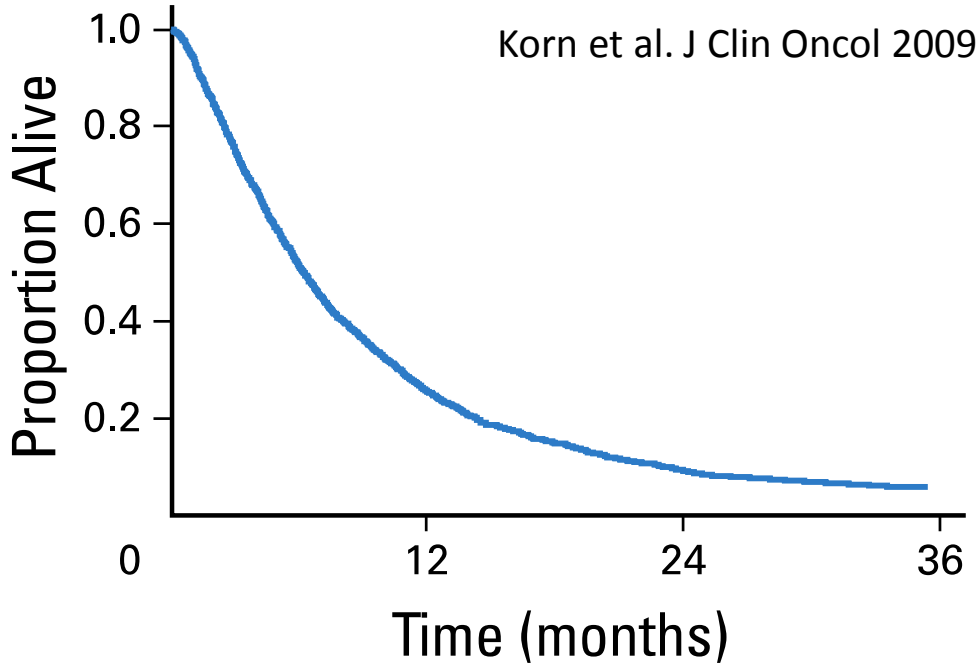


Improving immune activation

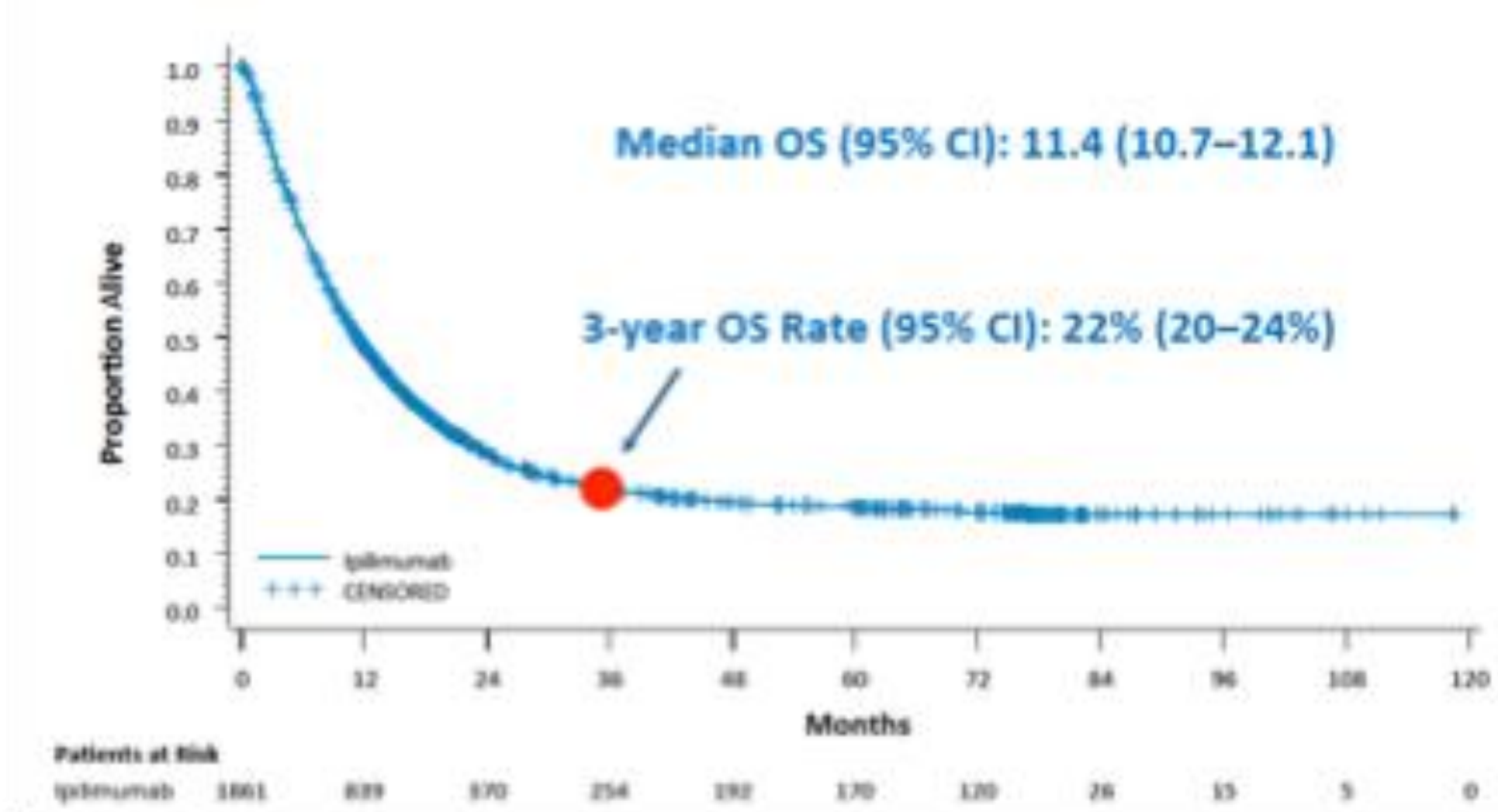


Where we came from in melanoma…

An Era of Futility:
1975-2005



Ipilimumab (ipi) is associated with prolonged survival

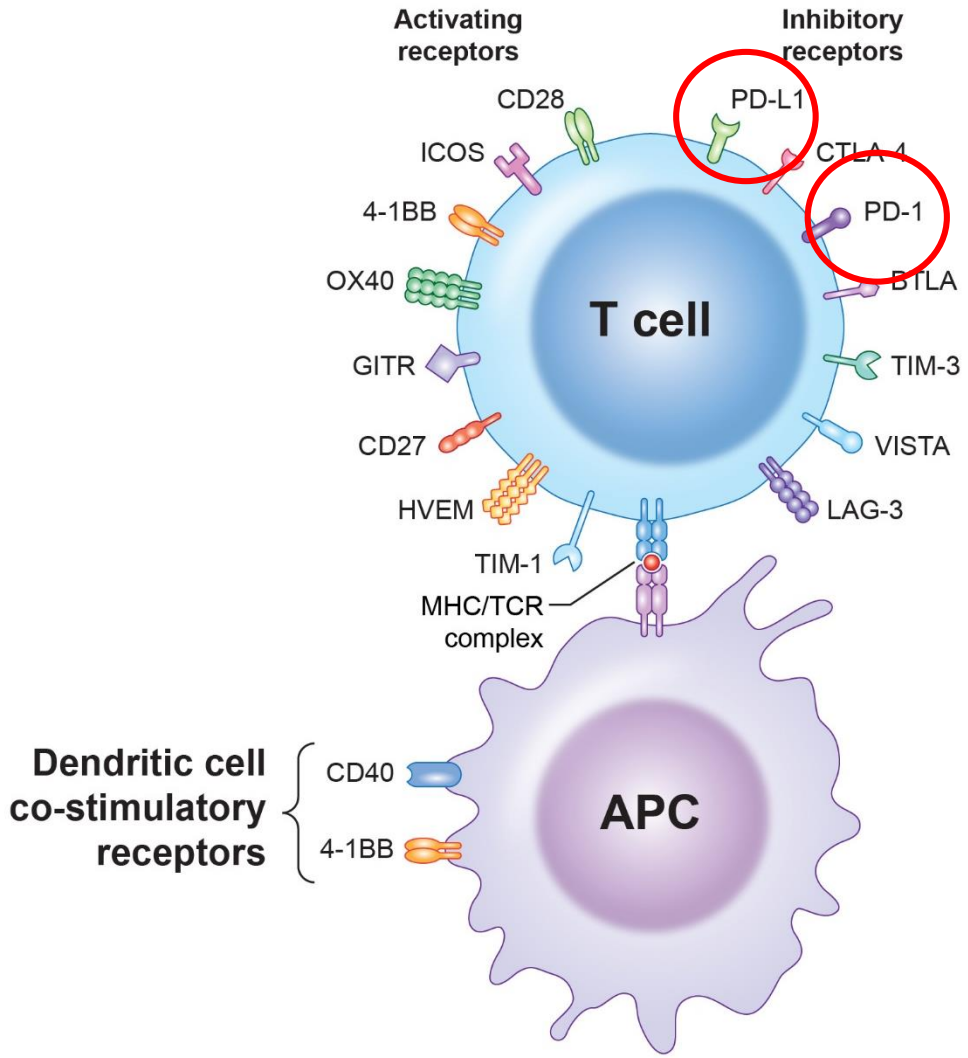


Hodi et al. ECCO 2014; Schadendorf et al. 2015

sitc

NIH NATIONAL CANCER INSTITUTE

Beyond CTLA4 inhibition



T cell immune checkpoint-modulating antibodies in the clinic

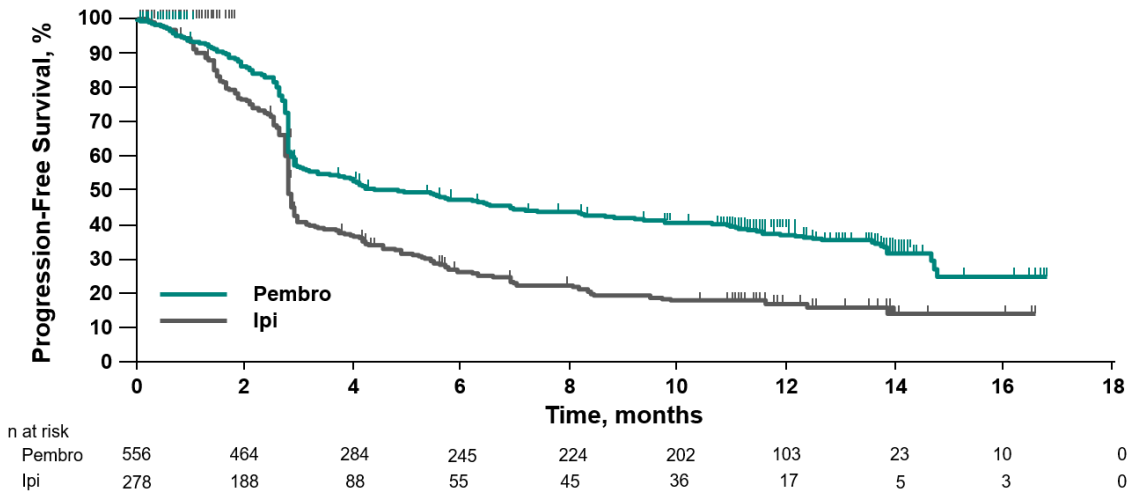
Target molecule	Drug	Development stage
CTLA-4	Ipilimumab	FDA approved
	Tremelimumab	Phase III trial
PD-1	Pembrolizumab	FDA approved
	Nivolumab	FDA approved
	AMP-514/MEDI0680	Phase I trial
PD-L1	Atezolizumab	FDA approved
	Durvalumab	Phase III trial
	Avelumab	Phase III trial
	BMS-936559	Phase I trial
4-1BB	Urelumab	Phase I trial
	PF-05082566	Phase I trial
OX-40	MEDI6469	Phase I trial
	MEDI6383 (rOX40L)	Phase I trial
	MOXR0916	Phase I trial
GITR	TRX518	Phase I trial
CD27	CDX-1127	Phase I trial
CD40	CP-870, 893	Phase I trial
LAG3	BMS-986016	Phase I trial

sitc

NIH NATIONAL CANCER INSTITUTE

The reason we are here:
Targeting anti-PD1/PDL1

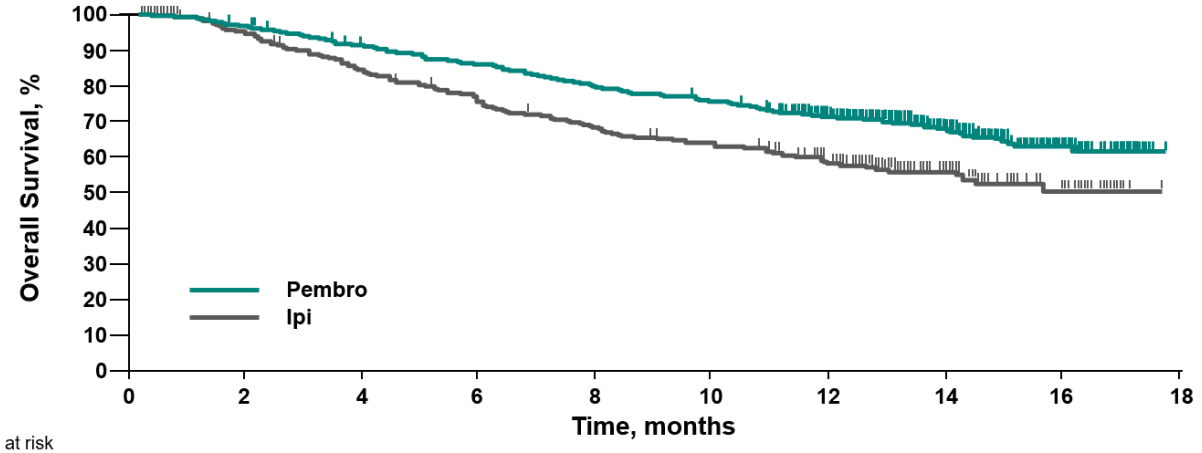
Melanoma: Front-line anti-PD1 therapy is better ipi



n at risk

Pembro	556	464	284	245	224	202	103	23	10	0
Ipi	278	188	88	55	45	36	17	5	3	0

	N	No. events	Median PFS, mo (95% CI)	12-month PFS rate, %	HR[a] (95% CI)	*P* value
Pembro	556	343	4.8 (3.7-6.5)	37	0.60 (0.50-0.72)	<0.00001
Ipi	278	198	2.8 (2.8-2.9)	17	---	---



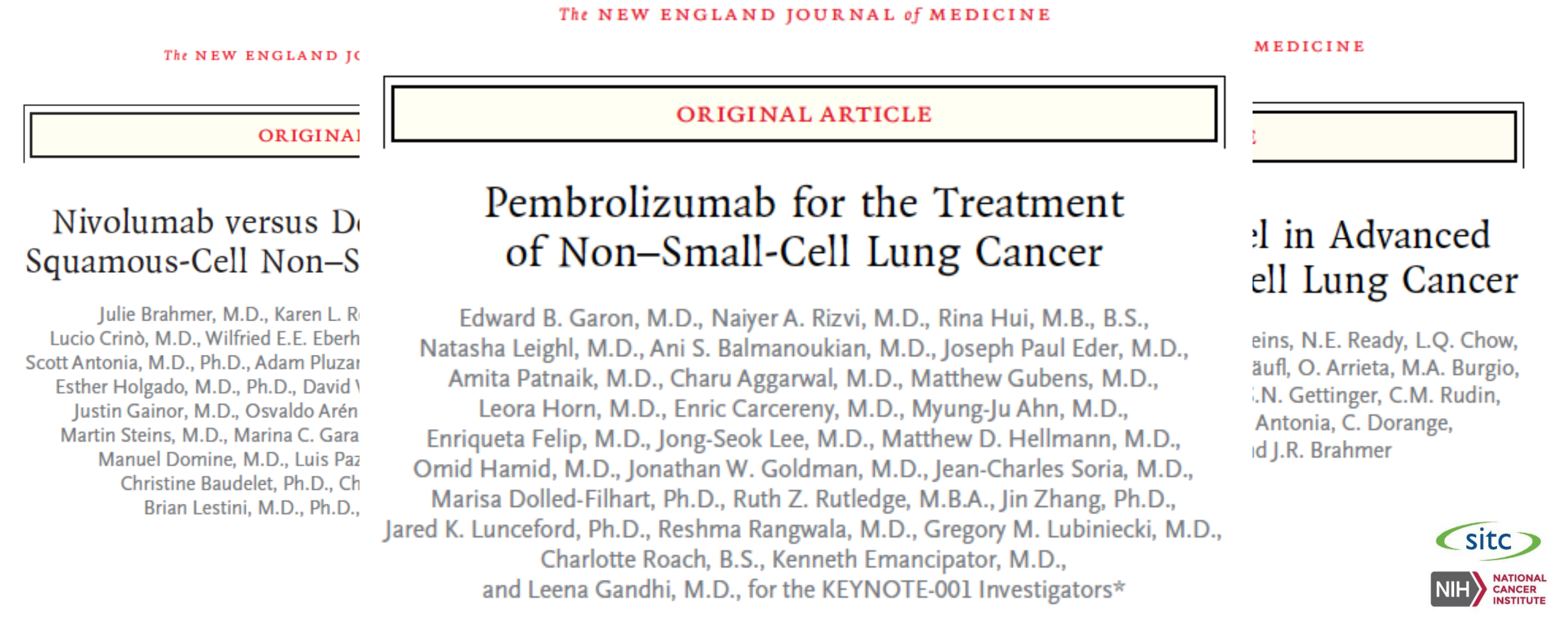
n at risk

Pembro	556	532	499	471	434	414	335	138	37	0
Ipi	278	242	212	188	169	157	117	51	17	0

	N	No. events	Median OS, mo (95% CI)	12-month OS rate, %	HR[a] (95% CI)	*P* value
Pembro	556	177	NR (NR-NR)	71	0.65 (0.52-0.83)	0.00020
Ipi	278	112	NR (12.7-NR)	58	---	---

Ribas et al AACR 2015; Robert et al. NEJM 2015; Carlino et al AACR 2016.

Anti-PD1 therapy in lung cancer



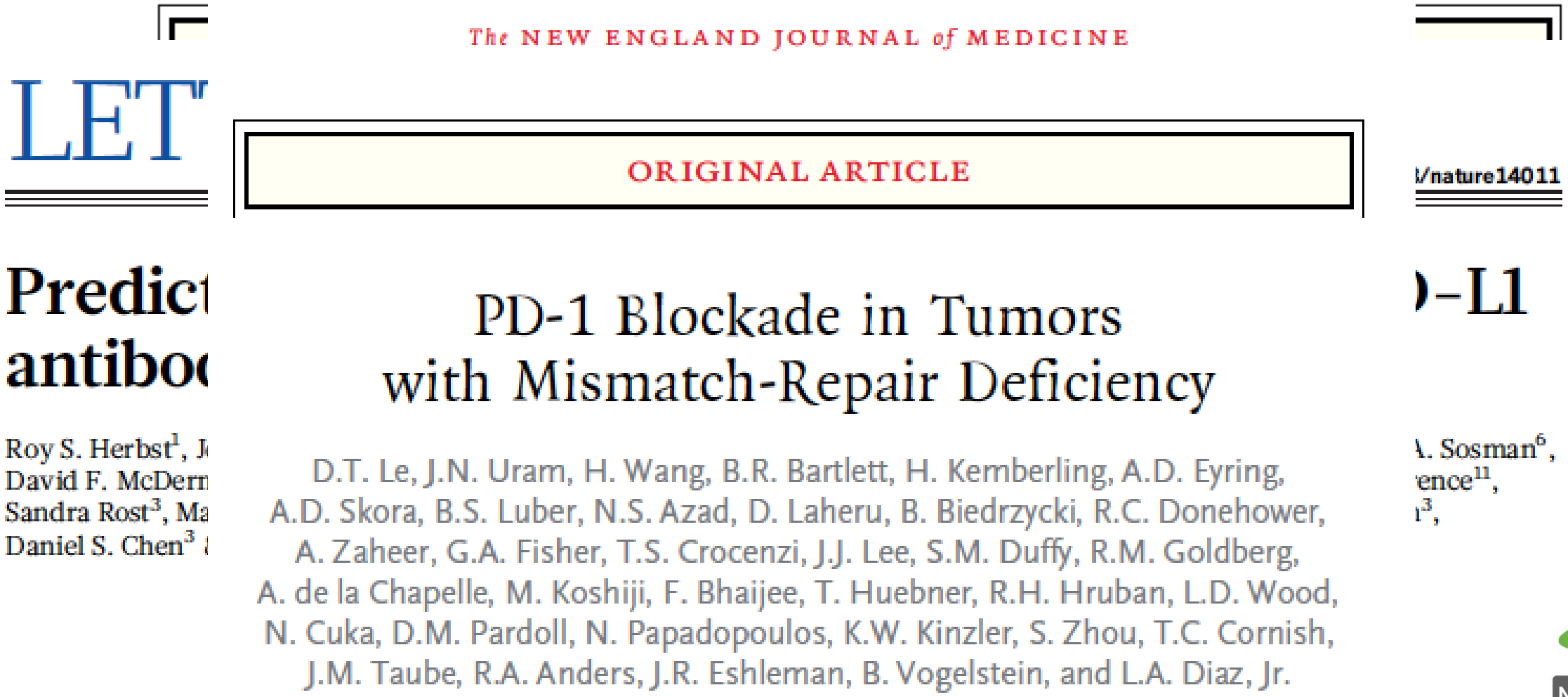
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

Anti-PD1 therapy: Immunotherapy for the masses



The NEW ENGLAND JOURNAL of MEDICINE

LET

ORIGINAL ARTICLE

l/nature14011

Predict

antibo

)-L1

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Roy S. Herbst[1], J
David F. McDerr
Sandra Rost[3], Ma
Daniel S. Chen[3]

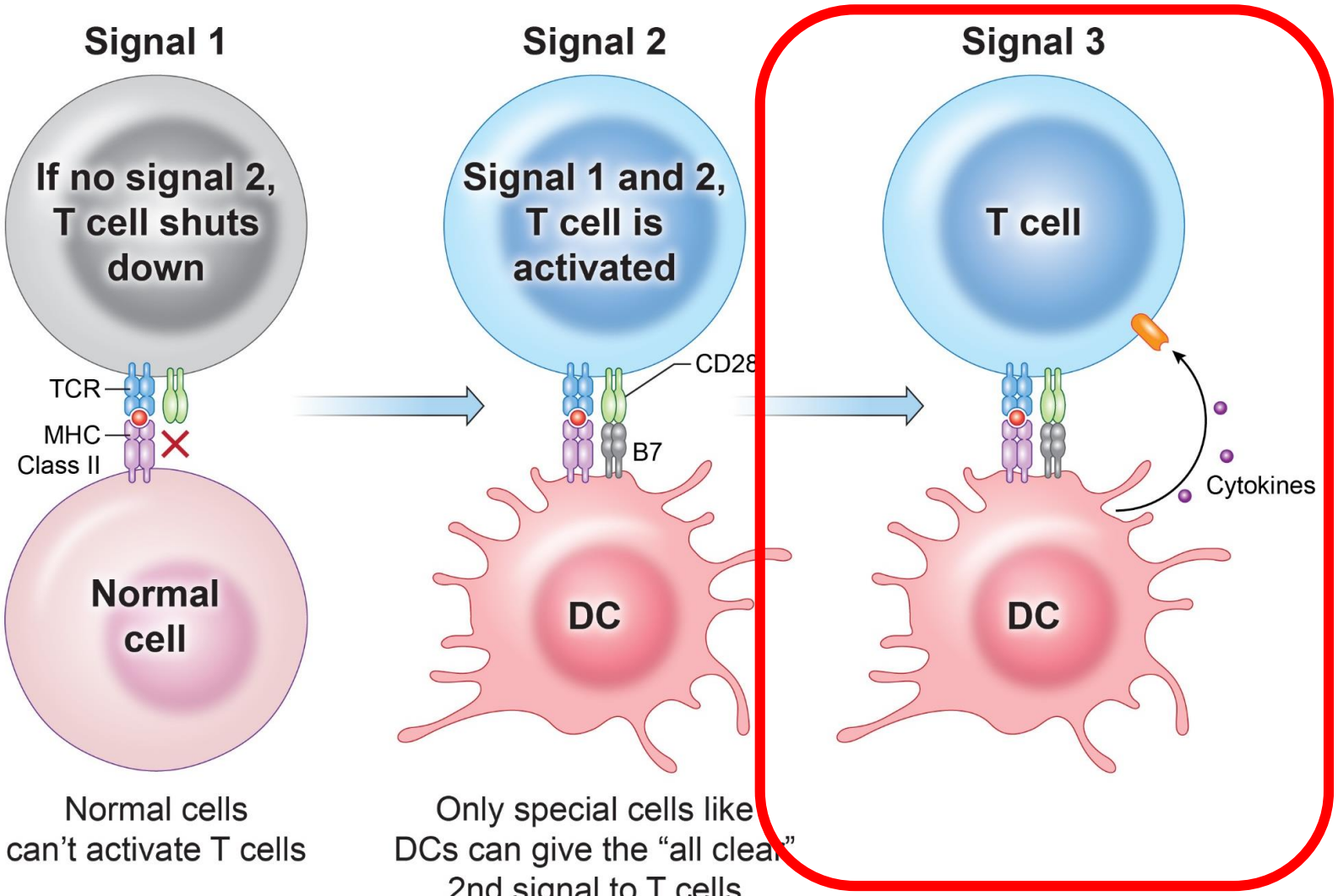
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

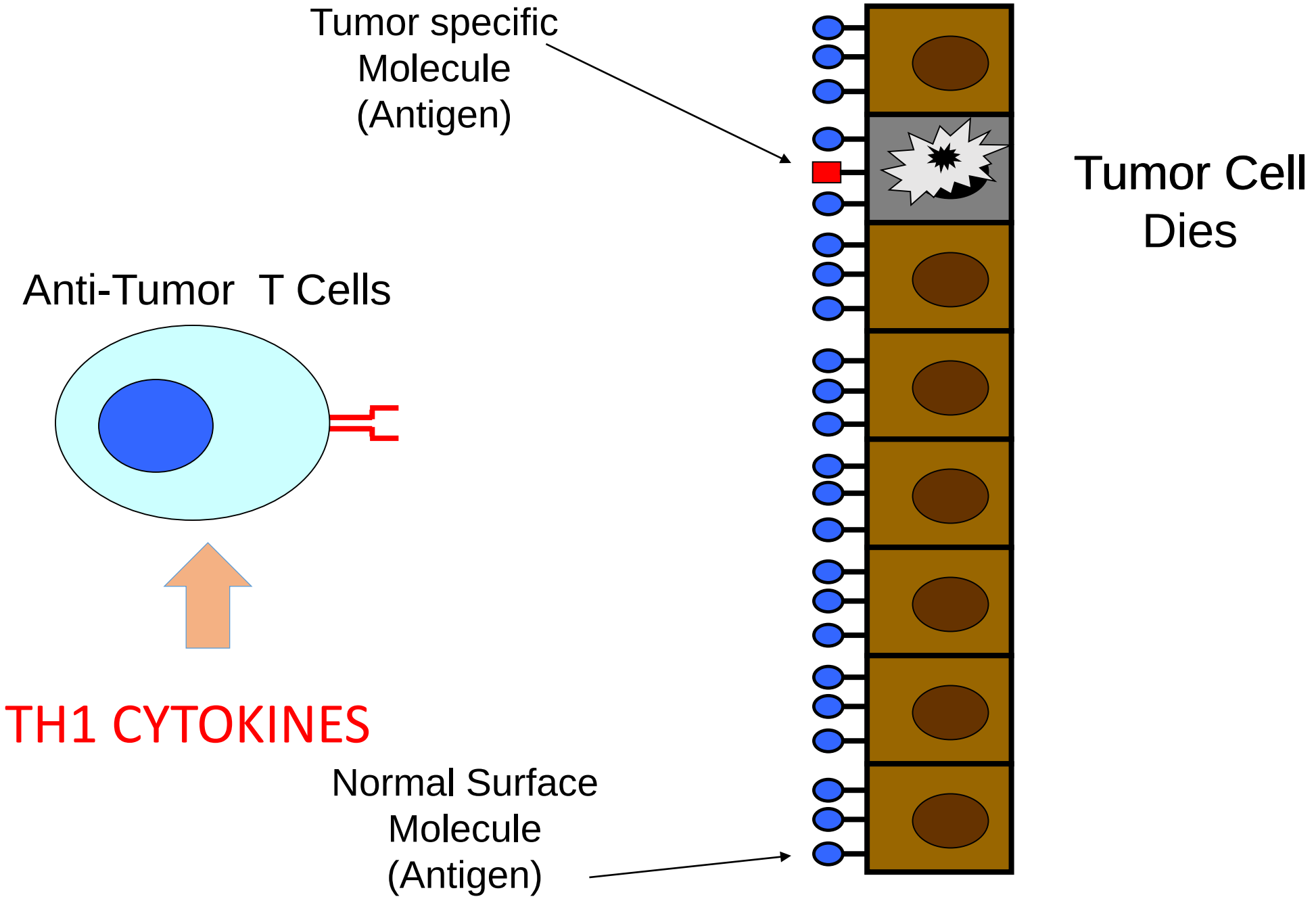
A. Sosman[6],
ence[11],
i[3],

sitc

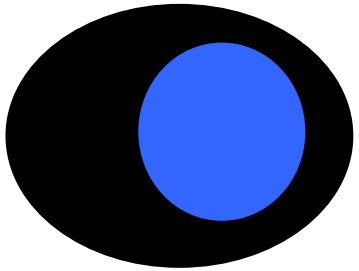
NIH NATIONAL CANCER INSTITUTE

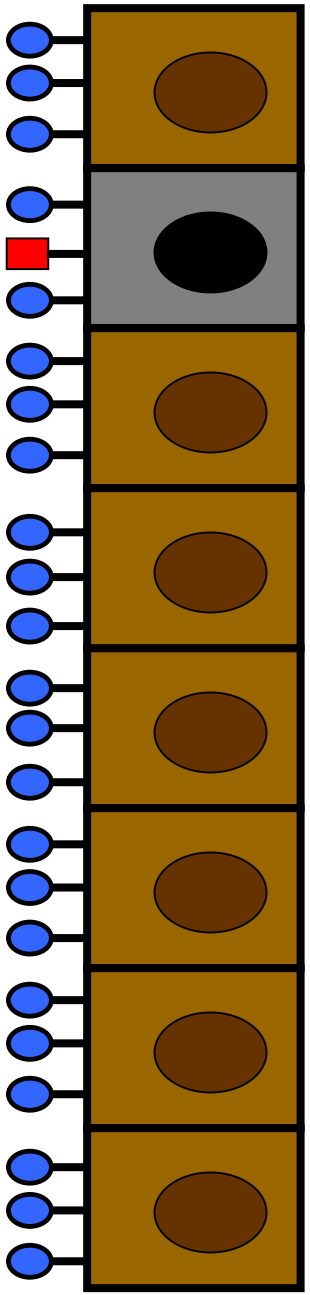
Signal #3 Provides the T-cell direction




Tumor specific
Molecule
(Antigen)
Tumor Cell
Dies
Anti-Tumor T Cells
TH1 CYTOKINES
Normal Surface
Molecule
(Antigen)

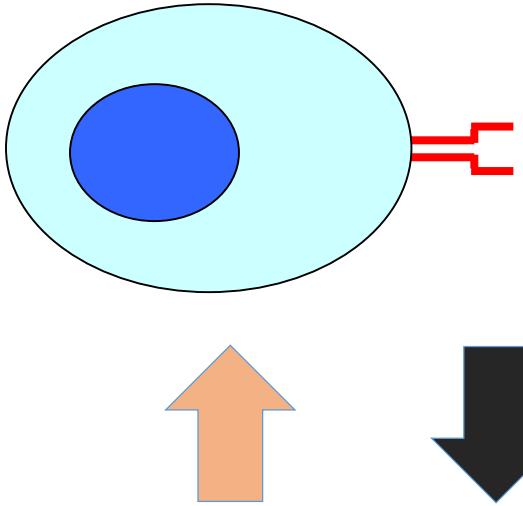
T Reg





Tumor Cell

Anti-Tumor T Cells

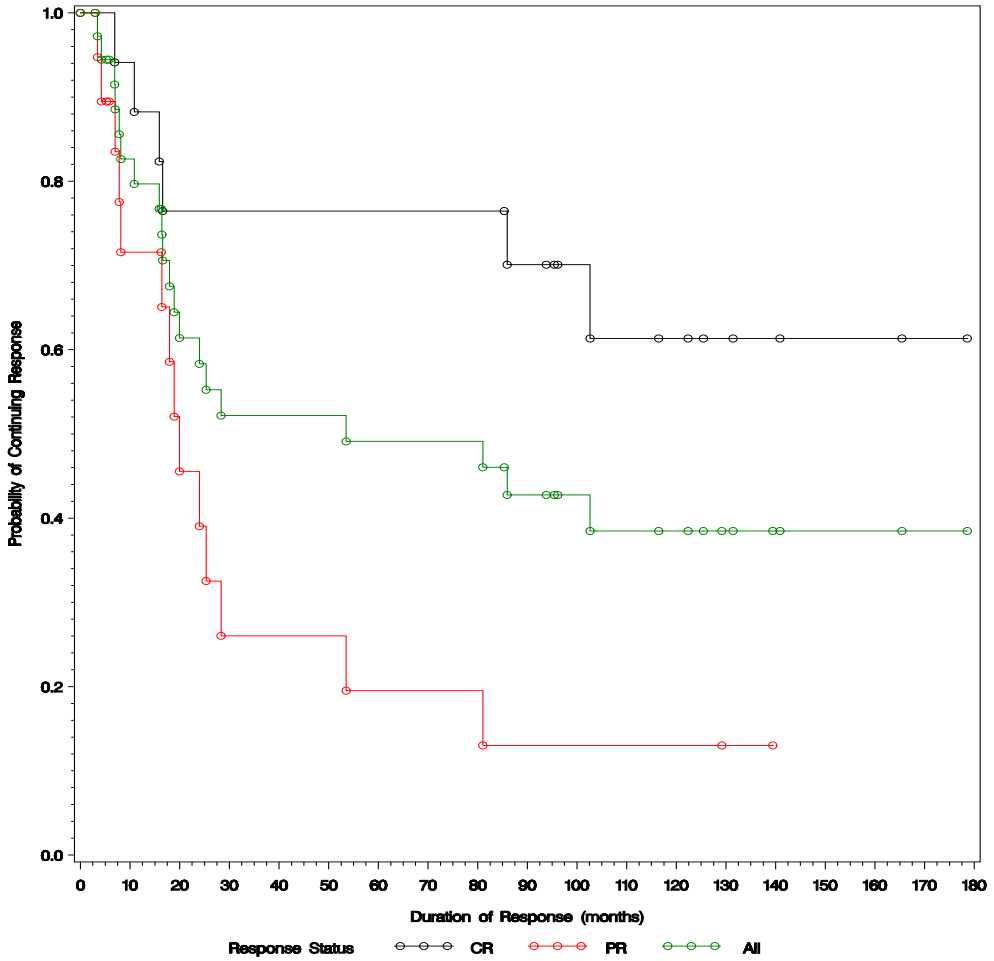


TH1 CYTOKINES

TH2 CYTOKINES

Interleukin 2 in RCC

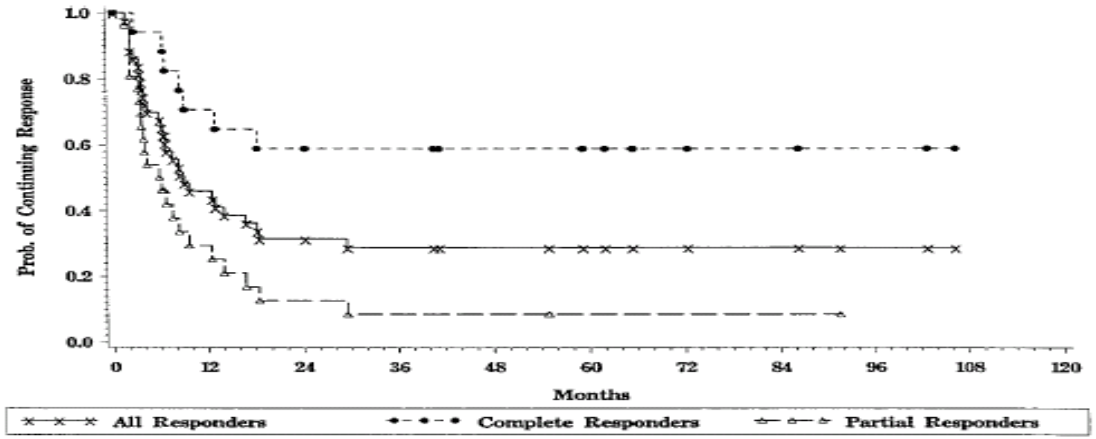
- Cohorts of 156 and 95 patients with RCC treated with HD IL-2
- RR: 21 and 23% respectively
  - Improved compared to LD IL-2 (13 and 10%)
- Durable complete responses
  - ~5-10%
- FDA approved in 1992

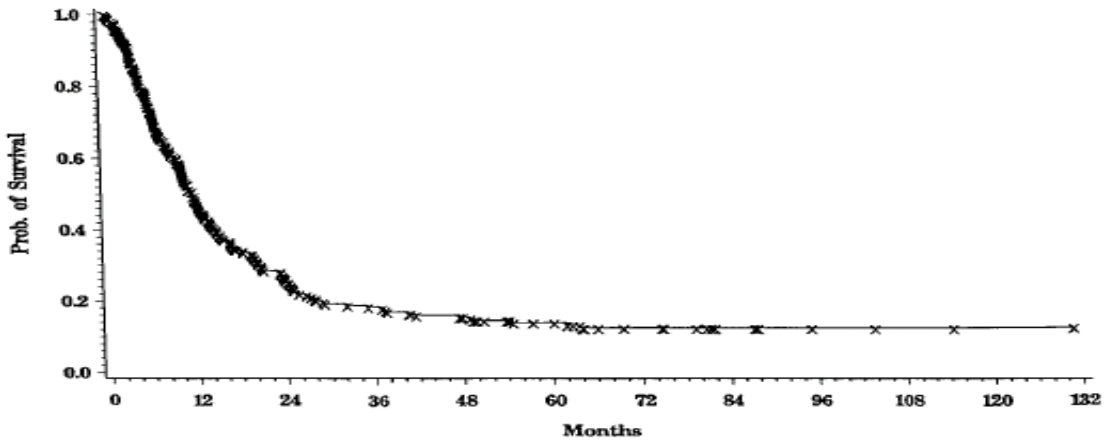


Fyfe et al J Clin Oncol. 1995
Yang et al. J Clini Oncol. 2003
McDermott et al. J Clin Oncol. 2005

Interleukin 2 in melanoma

- 270 melanoma pts treated between 1985-1993
- RR: 16% (43 / 270)
  - Some large volume and visceral
  - Most soft tissue and lung
- Durable responses
  - Median 8.9 mos
  - CR: not reached
- Survival
  - Median 11.4 mos
  - 11% @ 5yrs
- FDA approved 1996





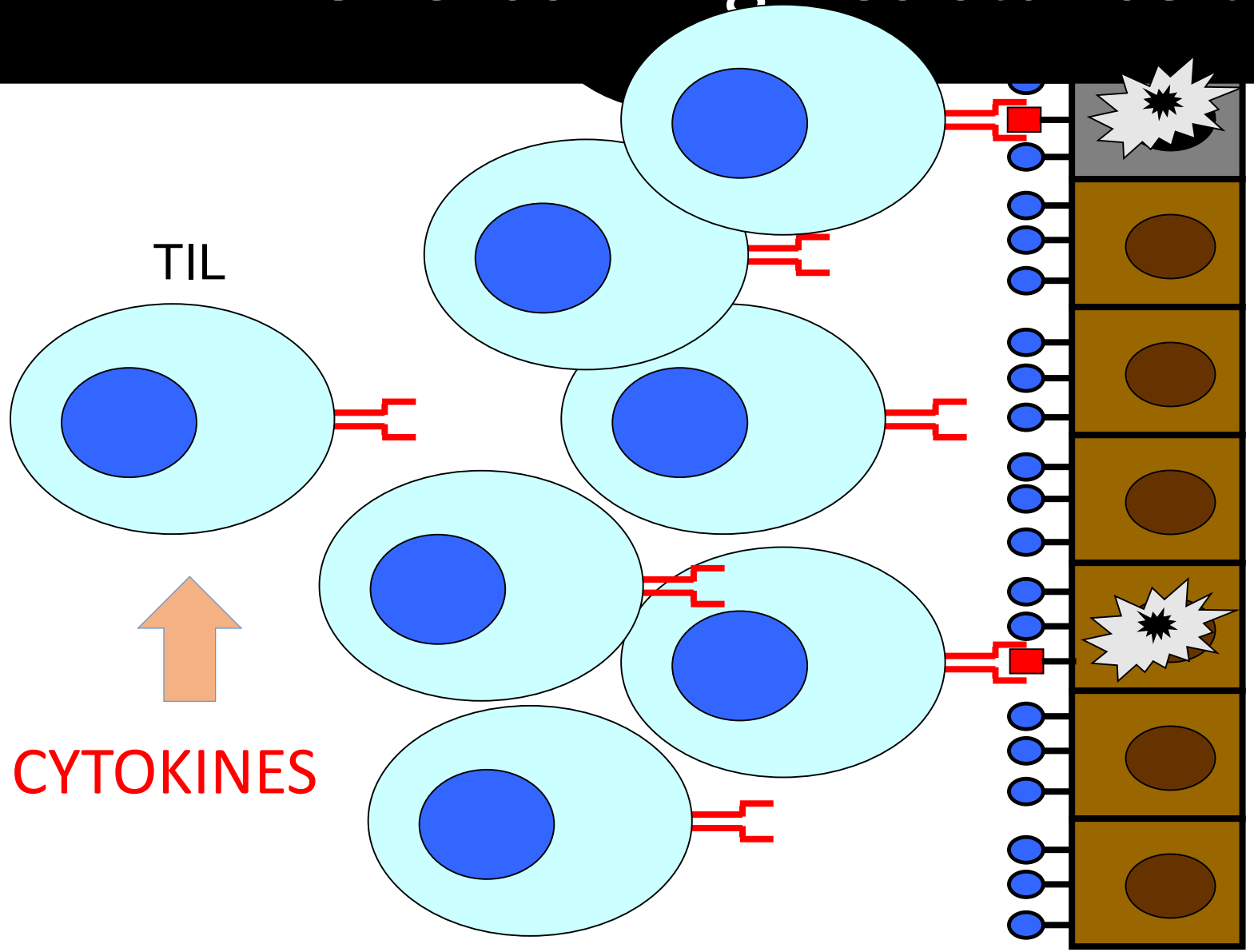
Atkins et al J Clin Oncol, 1999

Interleukin 2 Summary

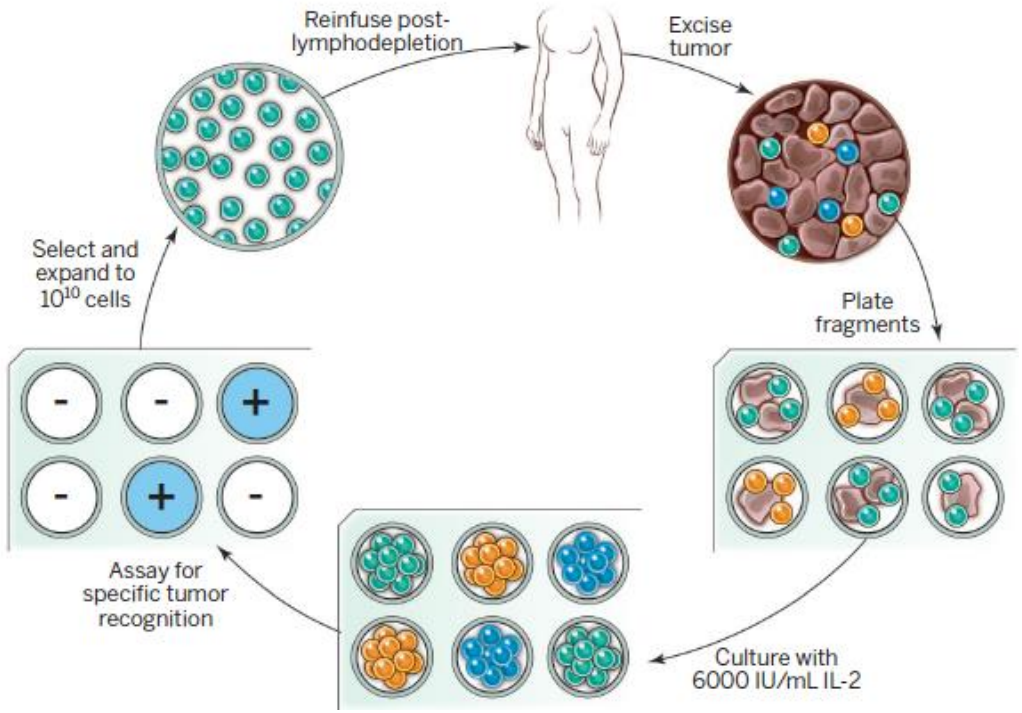
- Advantages
  - Complete and durable responses
  - Defined, brief treatment period
  - Limited long-term adverse effects

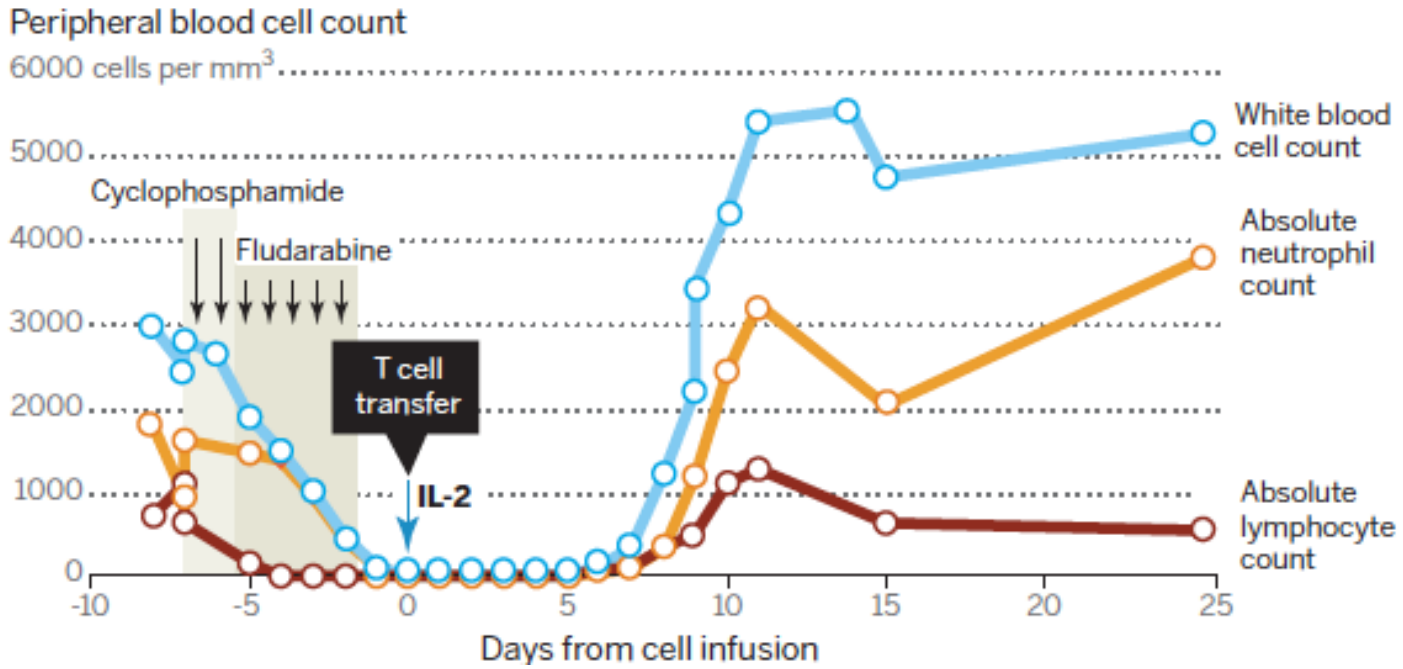
- Disadvantages
  - Low response rate
  - High acute toxicity limits the eligible cohort
  - Requires inpatient hospitalization
  - Rare fatalities reported (<2%)

Overcoming Resistance to IL-2



Adoptive Cell Therapy



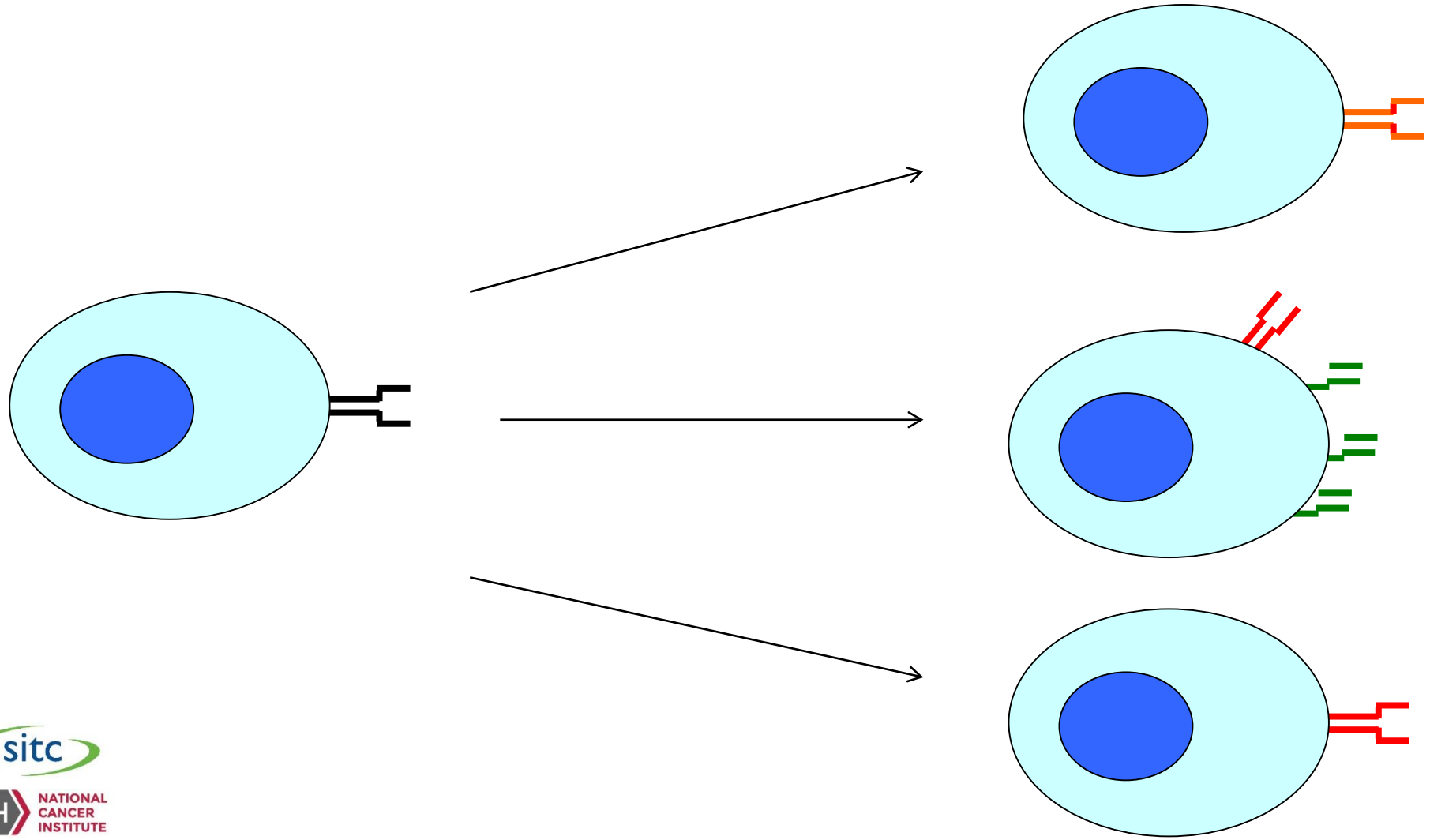


Rosenberg and Restifo. Science. 2015

Adoptive Cell Therapy: (Selected) Clinical Trial Results

Disease	# patients	Response rate	Ref
Melanoma	20	55%	Rosenberg et al. NEJM 1988
Melanoma	86	34%	Rosenberg et al. JNCI 1994
Melanoma	93	56%	Rosenberg et al. CCR 2011
Melanoma	57	40% (29% on intention to treat)	Besser et al. CCR 2013
Cervical cancer	9	33%	Hinrich et al. ASCO 2014

Overcoming Resistance to ACT



Engineer more specific TCRs

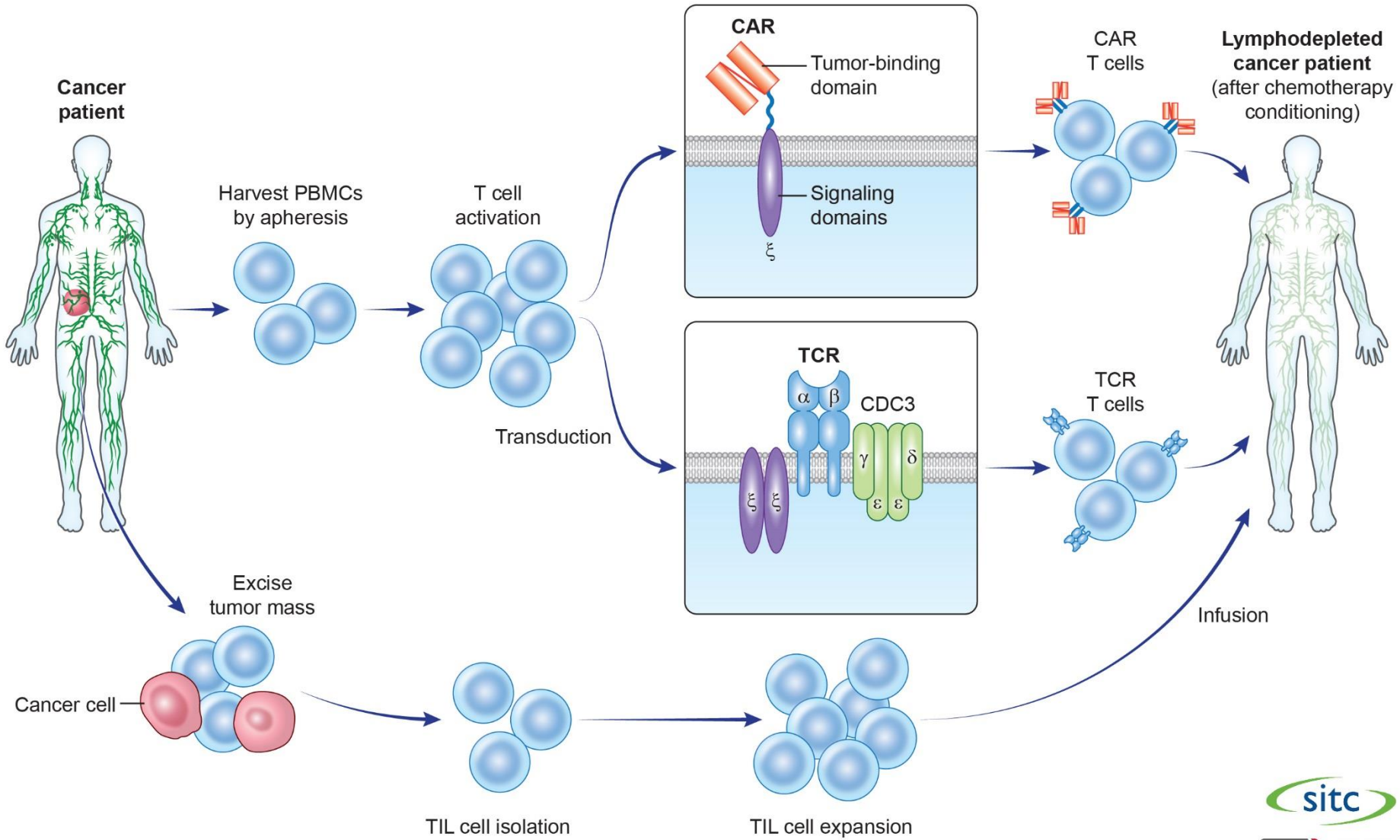
Engineer more specific receptors

Pick more specific TIL

sitc

NIH NATIONAL CANCER INSTITUTE

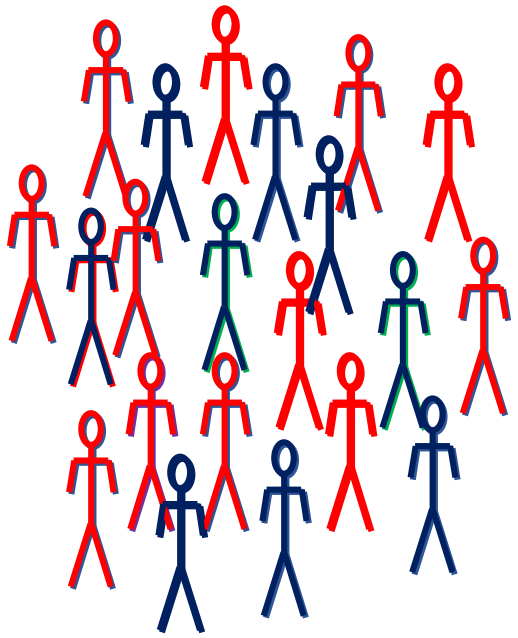
Adoptive T cell therapy can involve engineered (CAR, TCR) or patient-derived (TIL, PBMC) T cells



sitc

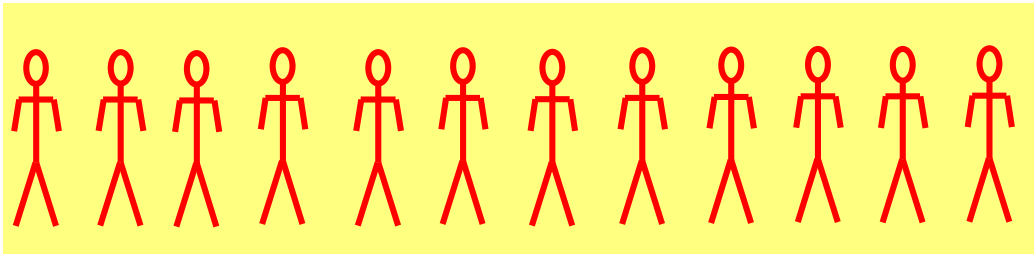
NIH NATIONAL CANCER INSTITUTE

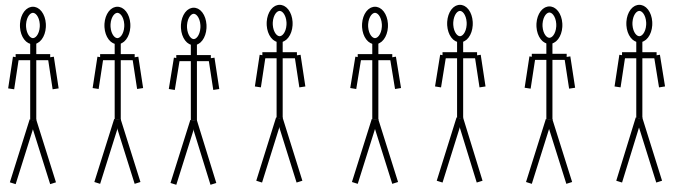
Optimizing Selection Strategy: Identifying immunotherapy responders



Blood or Tissue Assay

Immunotherapy responsive



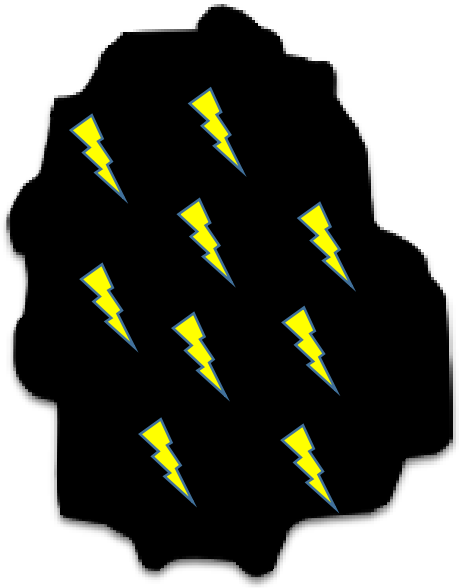


Immunotherapy non-responsive

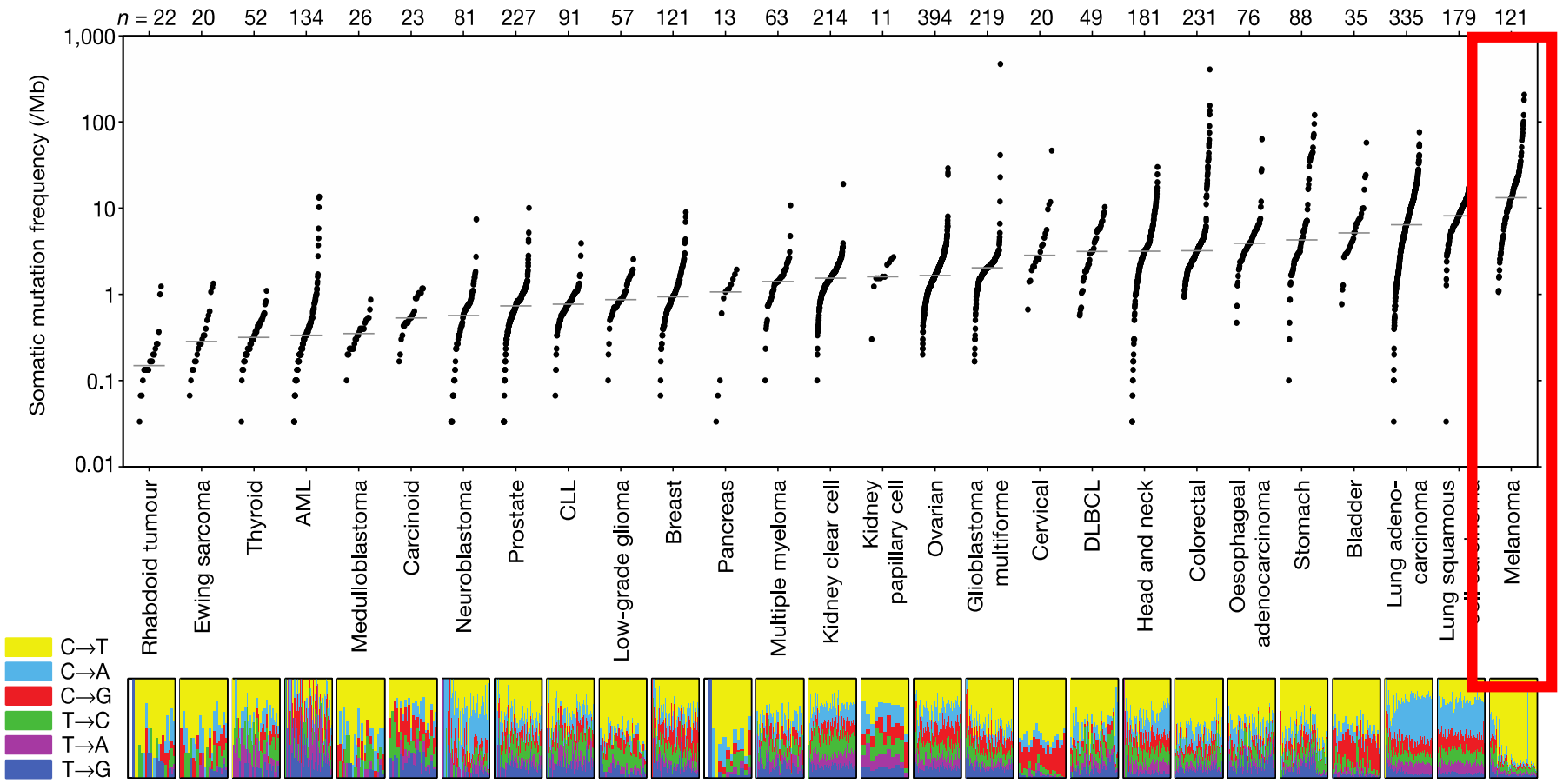
sitc

NIH NATIONAL CANCER INSTITUTE

Emerging Predictive Model of PD1 responsiveness

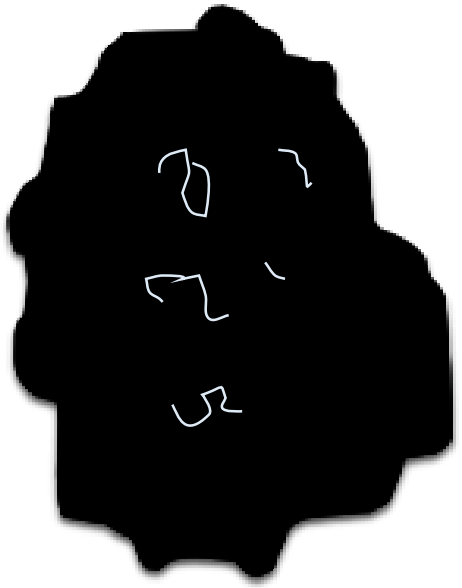


Mutational Load



Lawrence et al. Nature 2013

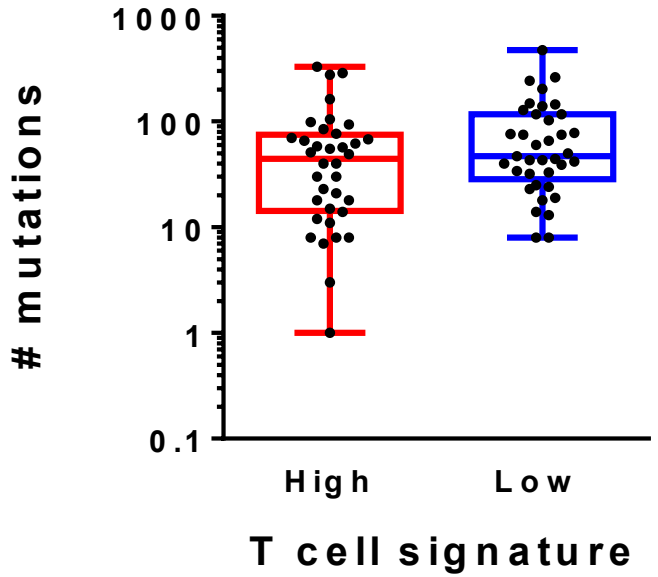
Emerging Predictive Model of PD1 responsiveness



Mutational Load

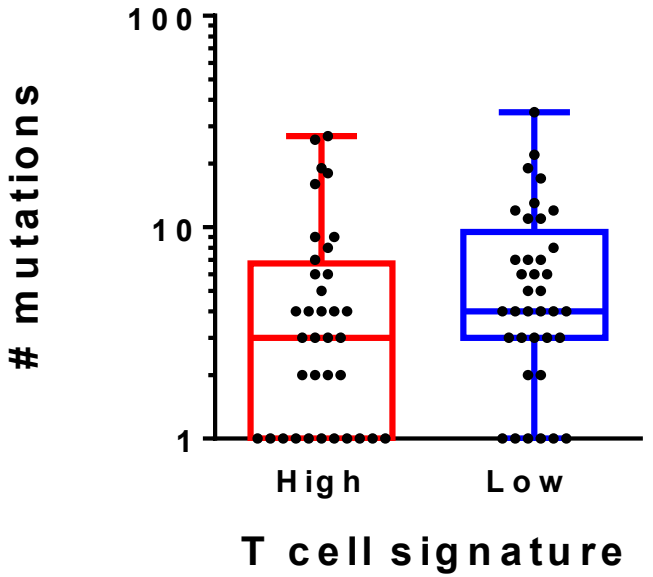
Neoantigen load

All neoantigens



p=0.36

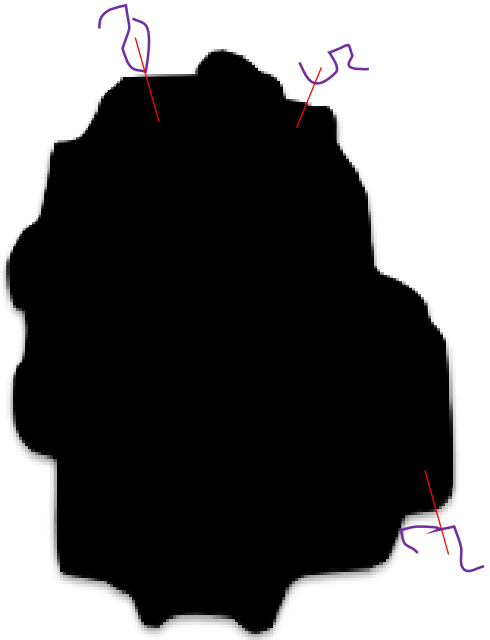
Selected highly binding neoantigens



p=0.44

Gajewski et al. ASCO 2015

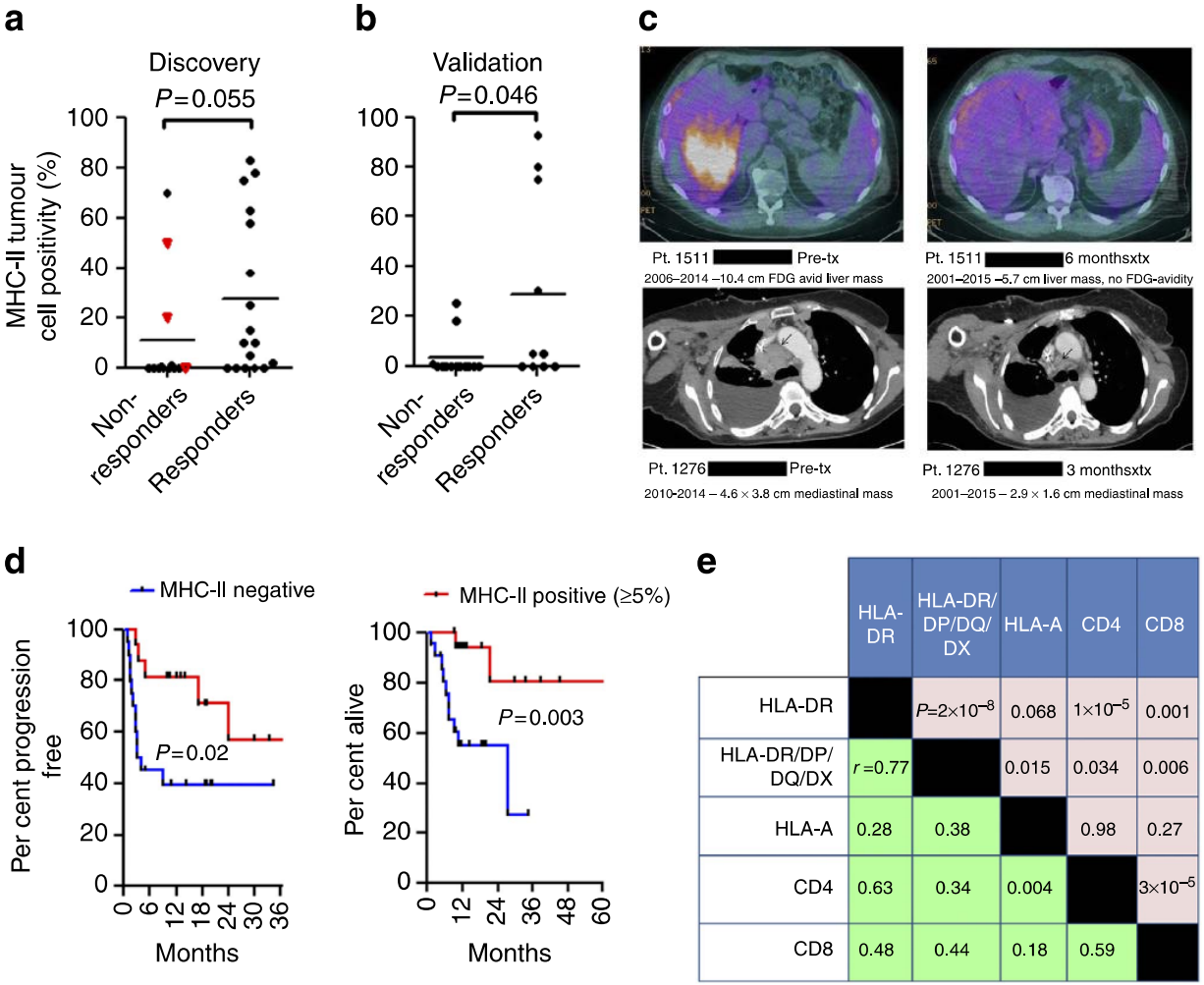
Emerging Predictive Model of PD1 responsiveness



Mutational Load

Neoantigen load

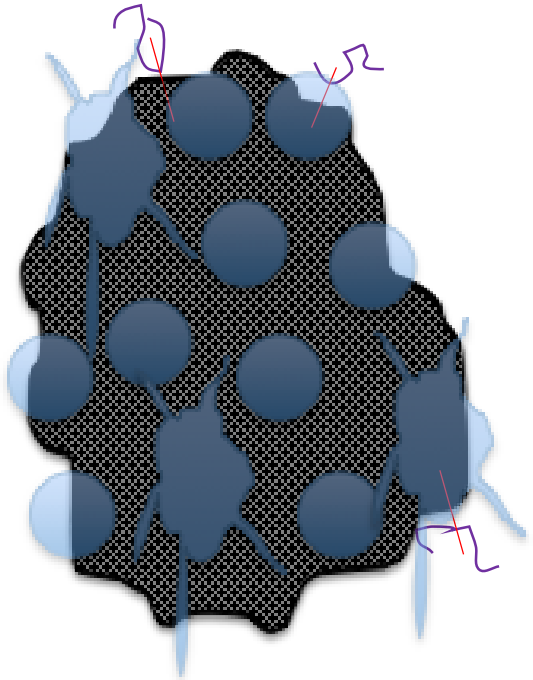
Antigen expression machinery



	HLA-DR	HLA-DR/DP/DQ/DX	HLA-A	CD4	CD8
HLA-DR		$P=2\times10^{-8}$	0.068	1×10^{-5}	0.001
HLA-DR/DP/DQ/DX	$r=0.77$		0.015	0.034	0.006
HLA-A	0.28	0.38		0.98	0.27
CD4	0.63	0.34	0.004		3×10^{-5}
CD8	0.48	0.44	0.18	0.59	

Johnson et al. Nature Commun. 2016

Emerging Predictive Model of PD1 responsiveness

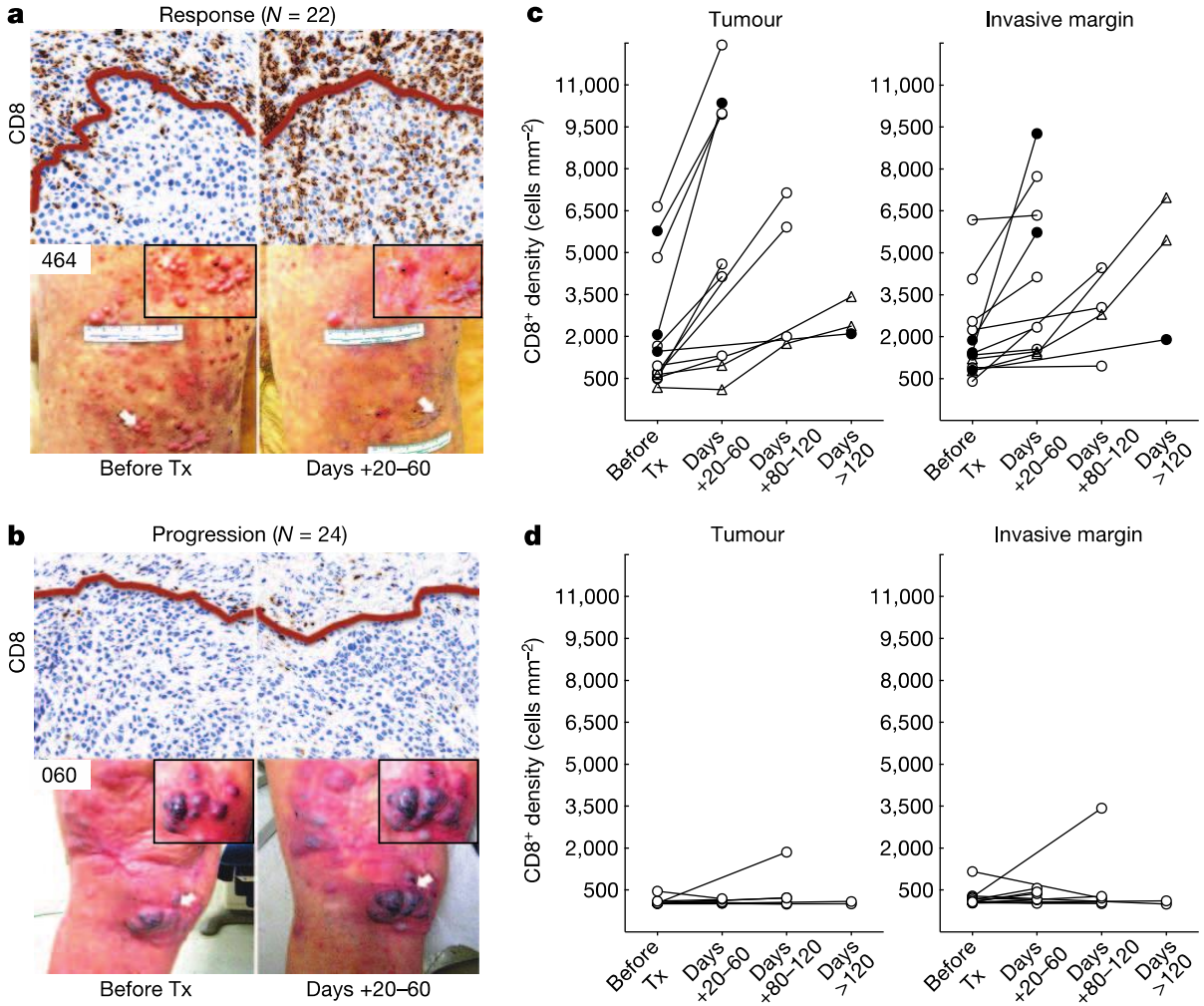


Mutational Load

Neoantigen load

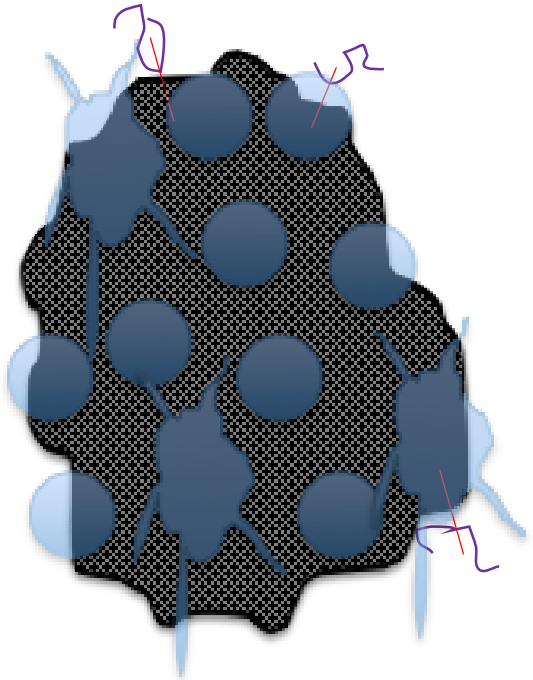
Antigen expression machinery

T-cell infiltration



Tumeh et al. Nature 2015

Emerging Predictive Model of PD1 responsiveness

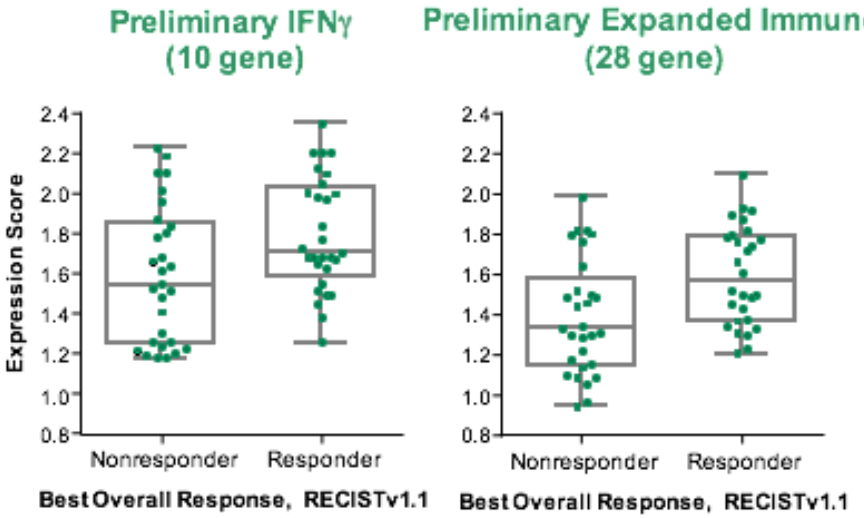


Mutational Load

Neoantigen load

Antigen expression machinery

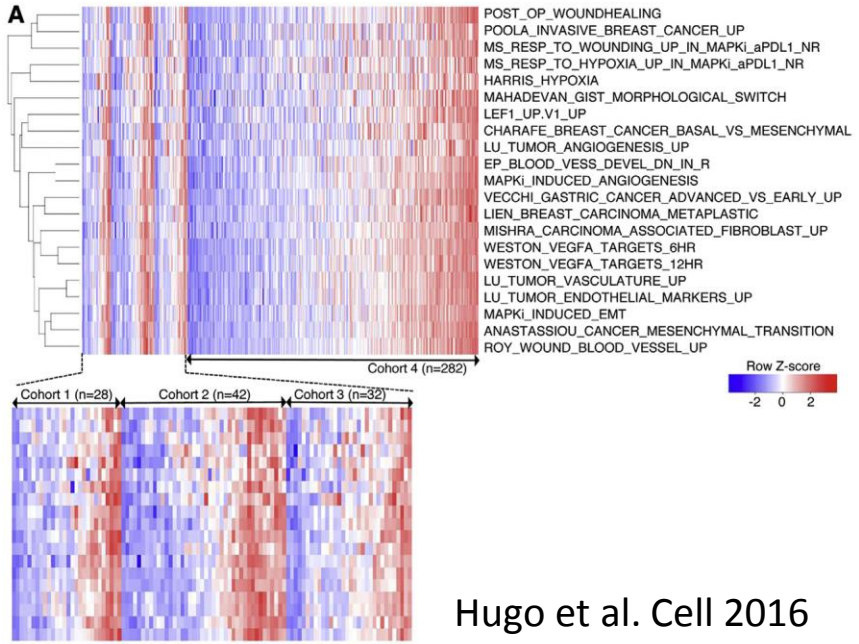
T-cell infiltration



Correlation With Response in the Validation Set[a]

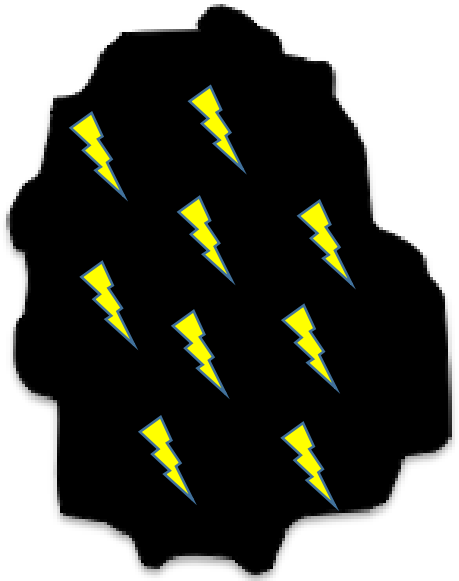
Signature	BOR by RECIST N = 51	PFS by RECIST N = 62	OS N = 62
Preliminary IFNγ	*P* = 0.047	*P* = 0.016	*P* = 0.090
Preliminary expanded immune	*P* = 0.027	*P* = 0.015	*P* = 0.105

Ribas et al. ASCO 2015

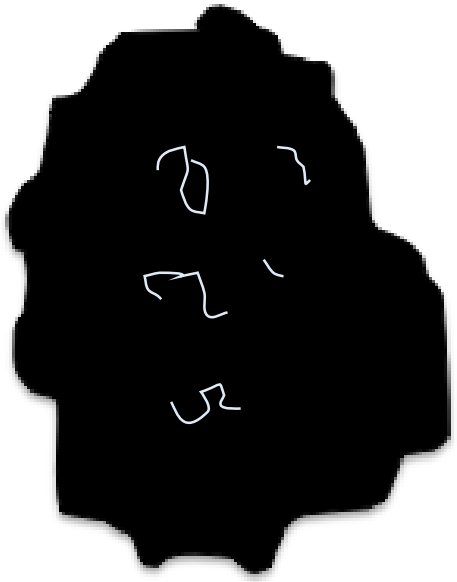


Hugo et al. Cell 2016

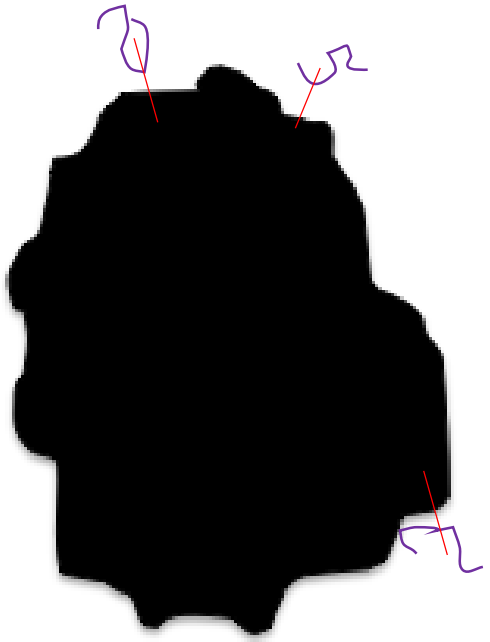
Emerging Predictive Model of PD1 responsiveness



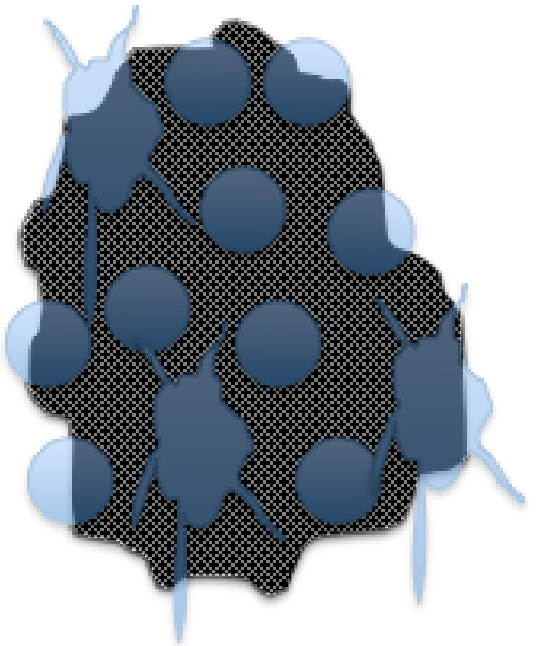
Mutational Load



Neoantigen load



Antigen expression machinery

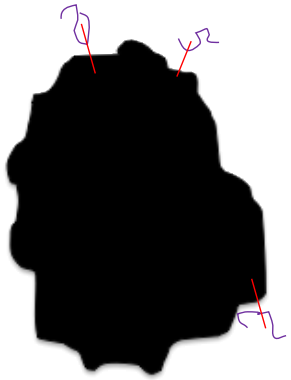


T-cell infiltration

Tissue/Tumor response is PDL1 expression

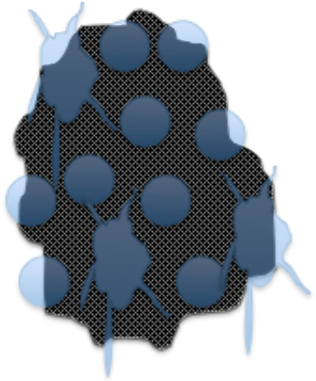
Neoantigen load

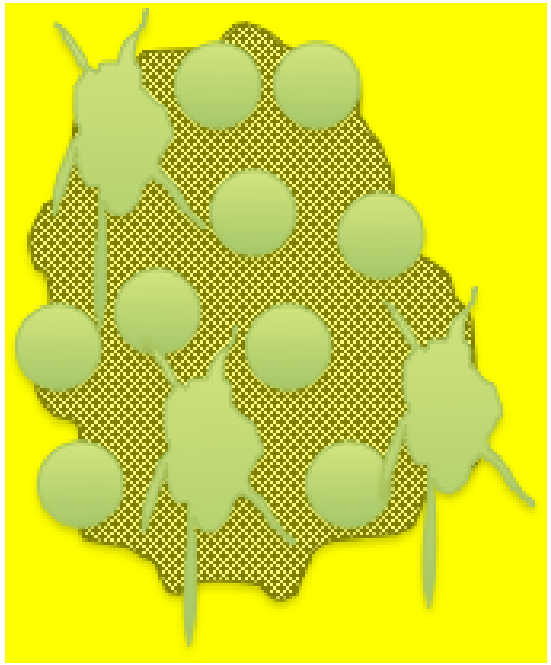
Mutational Load



Antigen expression machinery

T-cell infiltration

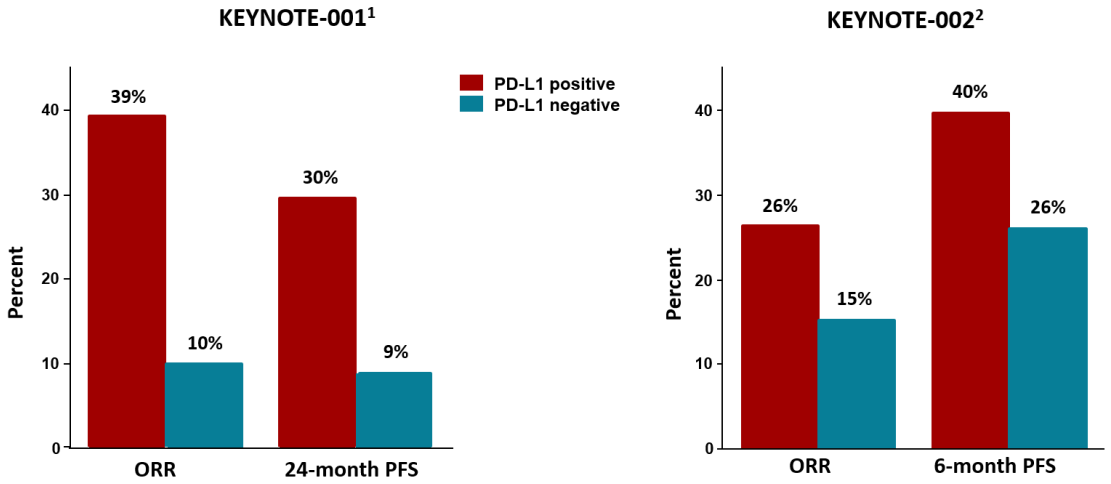




PD-L1 expression

PDL1 expression is associated with better outcomes

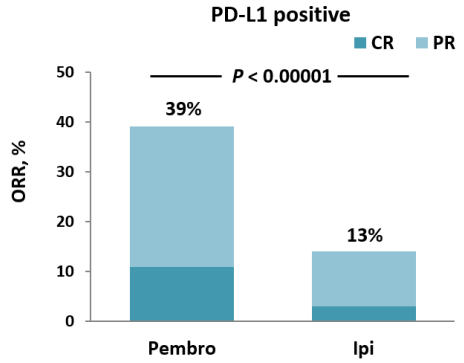
PD-L1 Expression Correlates with Improved Response



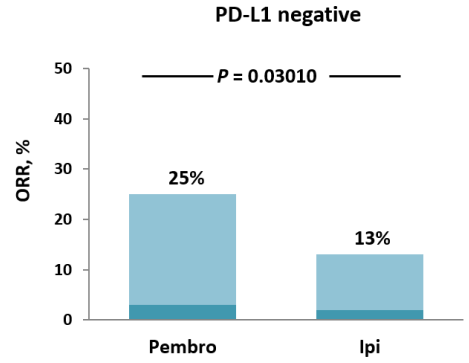
- PD-L1 positive[a]: 76%
- PD-L1 positive[a]: 69%

PD-L1 expression was assessed in pretreatment tumor biopsies by immunohistochemistry (IHC) using the 22C3 antibody (Merck);
PD-L1 positivity was defined as PD-L1 expression in ≥1% of tumor and associated immune cells.
[a]Among patients with samples evaluable for PD-L1 expression.
1. Daud A, et al. Presented at: SMR 2015 Congress; November 18-21, 2015; San Francisco, CA.
2. Puzanov I, et al. Presented at: 2015 ASCO Annual Meeting: May 29-June 2, 2015; Chicago, IL.

Best Overall Response by PD-L1 Expression



	PD-L1 positive	
	Pembro	Ipi
Median duration of response[a], days (range)	NR (42+ – 429+)	337 (41 – 412+)



	PD-L1 negative	
	Pembro	Ipi
Median duration of response[a], days (range)	NR (33+ – 418+)	NR (127+ – 295+)

[a]Based on patients with best overall response of confirmed complete or partial response.
Analysis cut-off date: March 3, 2015.

Carlino et al. AACR 2016

Summary:
The state of predictive biomarker development

Analysis of the tumor:

- Total mutation burden
- Types of mutations (neoantigens)
- Capability of being recognized by the immune system

Analysis of immune cells in the tumor

- Presence or absence of cells
- Location of immune cells (periphery versus central)
- Types of immune cells (killers vs suppressors)
- Activity of the cells (gene expression analysis)

Response of the tumor against the immune cells

- PD-L1 expression
- Other “immune checkpoint” molecule expression

Analysis of blood…

Thank you!