Advances in Cancer Immunotherapy- San Francisco
SITC-SMR Session,
3:05 p.m. – 3:30 p.m.

Checkpoint Inhibitor Therapy

Antoni Ribas, M.D., Ph.D.
Professor of Medicine
Professor of Surgery
Professor of Molecular and Medical Pharmacology
Director, Tumor Immunology Program, Jonsson Comprehensive Cancer Center (JCCC)
University of California Los Angeles (UCLA)
Chair, Melanoma Committee at SWOG

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Antoni Ribas, MD, PhD

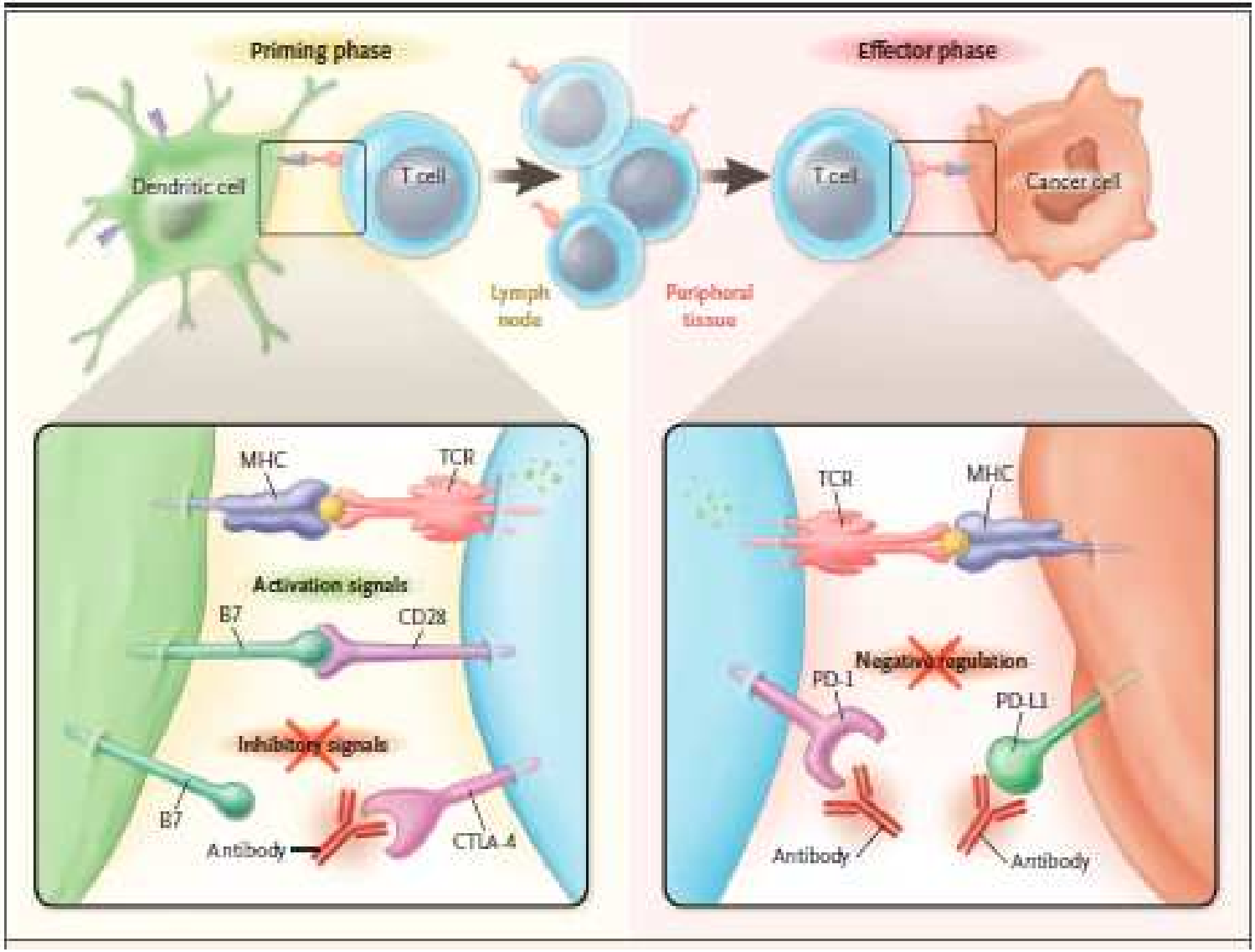
DISCLOSURES

Amgen, Merck:

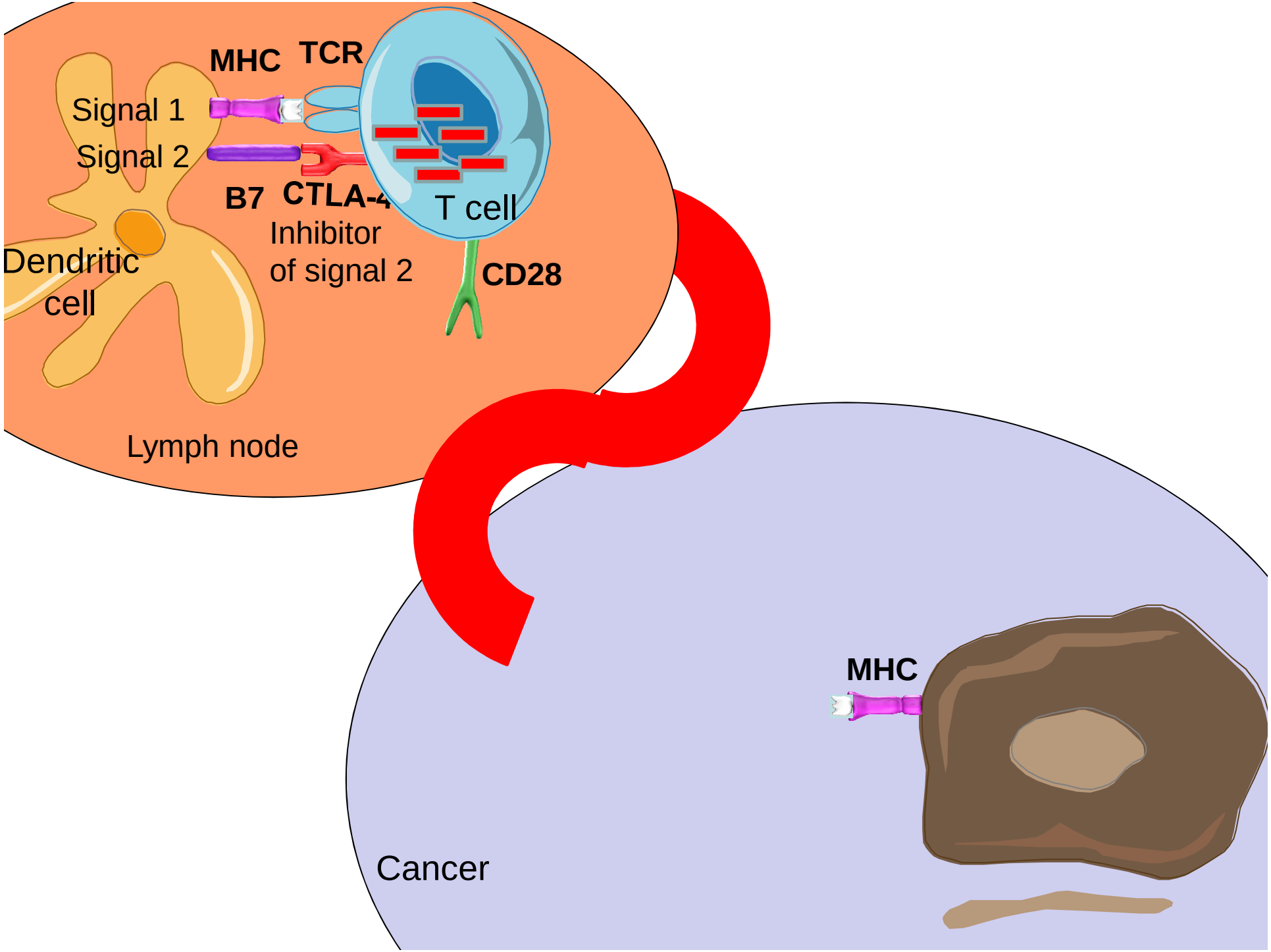
Consultant – Honoraria to UCLA

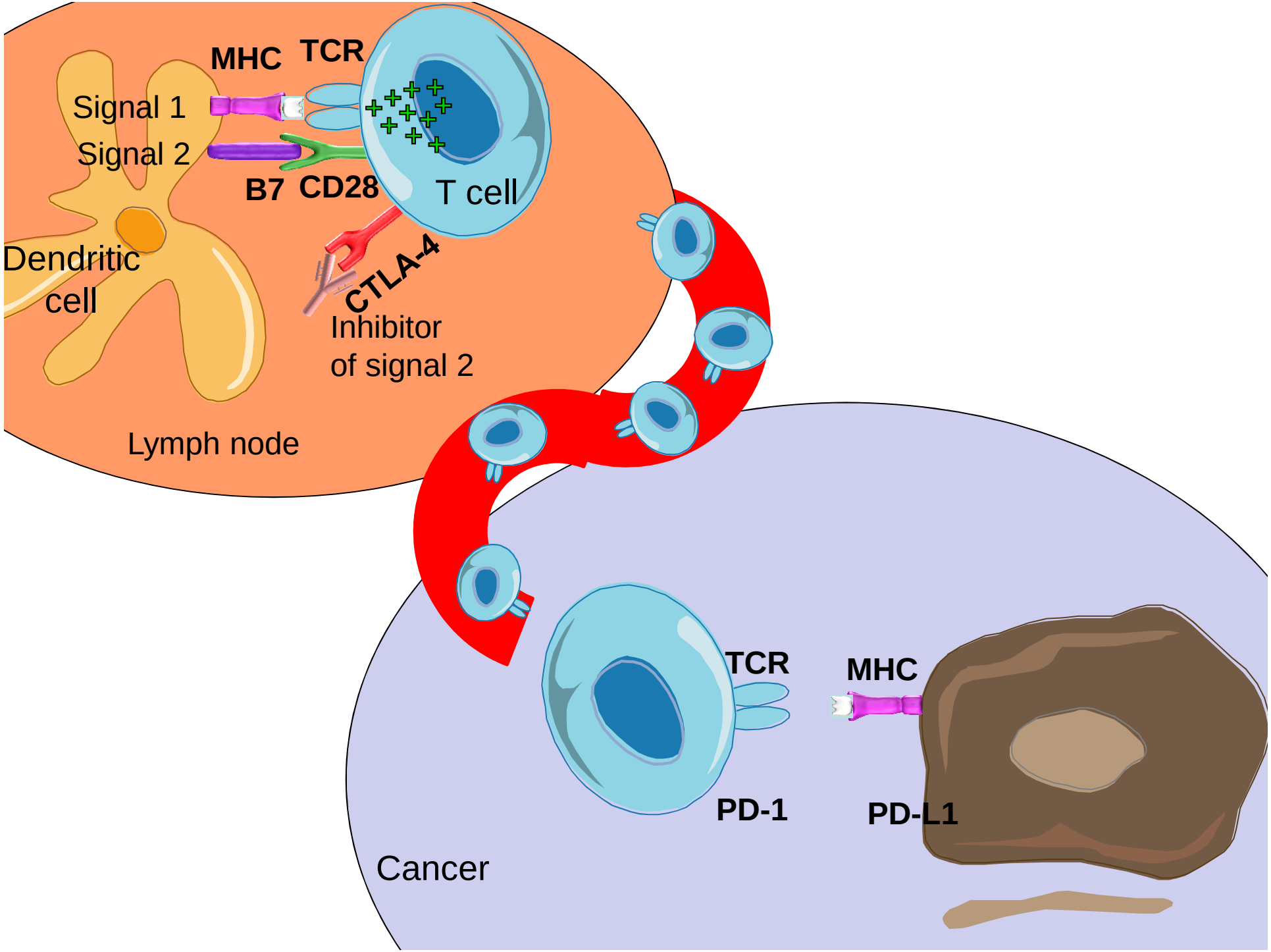
Kite Pharma, Compugen, FLX Bio, CytomX, Arcus:

Scientific Advisory Board – Stock



Ribas, NEJM 2012; Jun 28; 366 (26): 2517-9


MHC
TCR
Signal 1
Signal 2
B7
CTLA-4
Inhibitor
of signal 2
T cell
CD28
Dendritic
cell
Lymph node
MHC
Cancer


MHC
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Lymph node
TCR
MHC
PD-1
PD-L1
Cancer

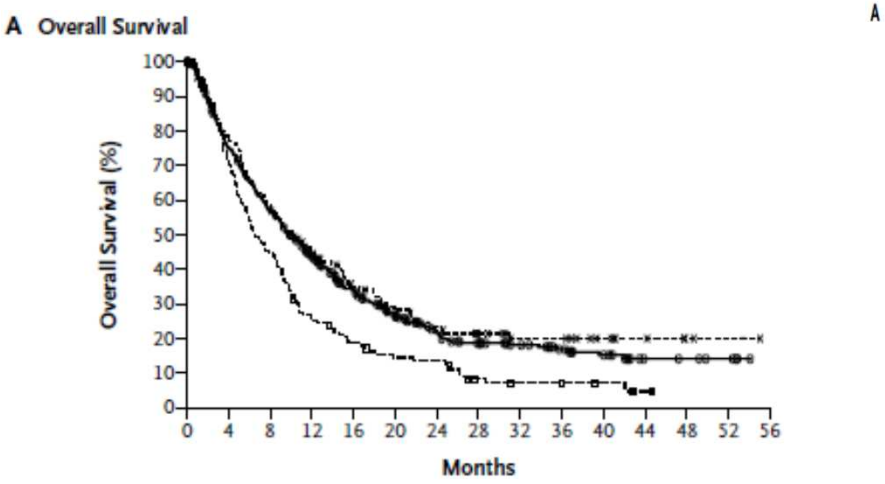
Ipilimumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



3 mg/kg x 4 doses q3w

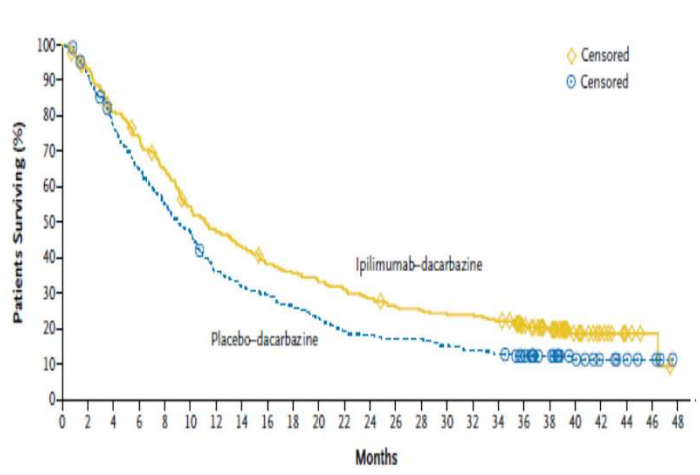
N Engl J Med. 2010 Aug 19;363(8):711-23.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

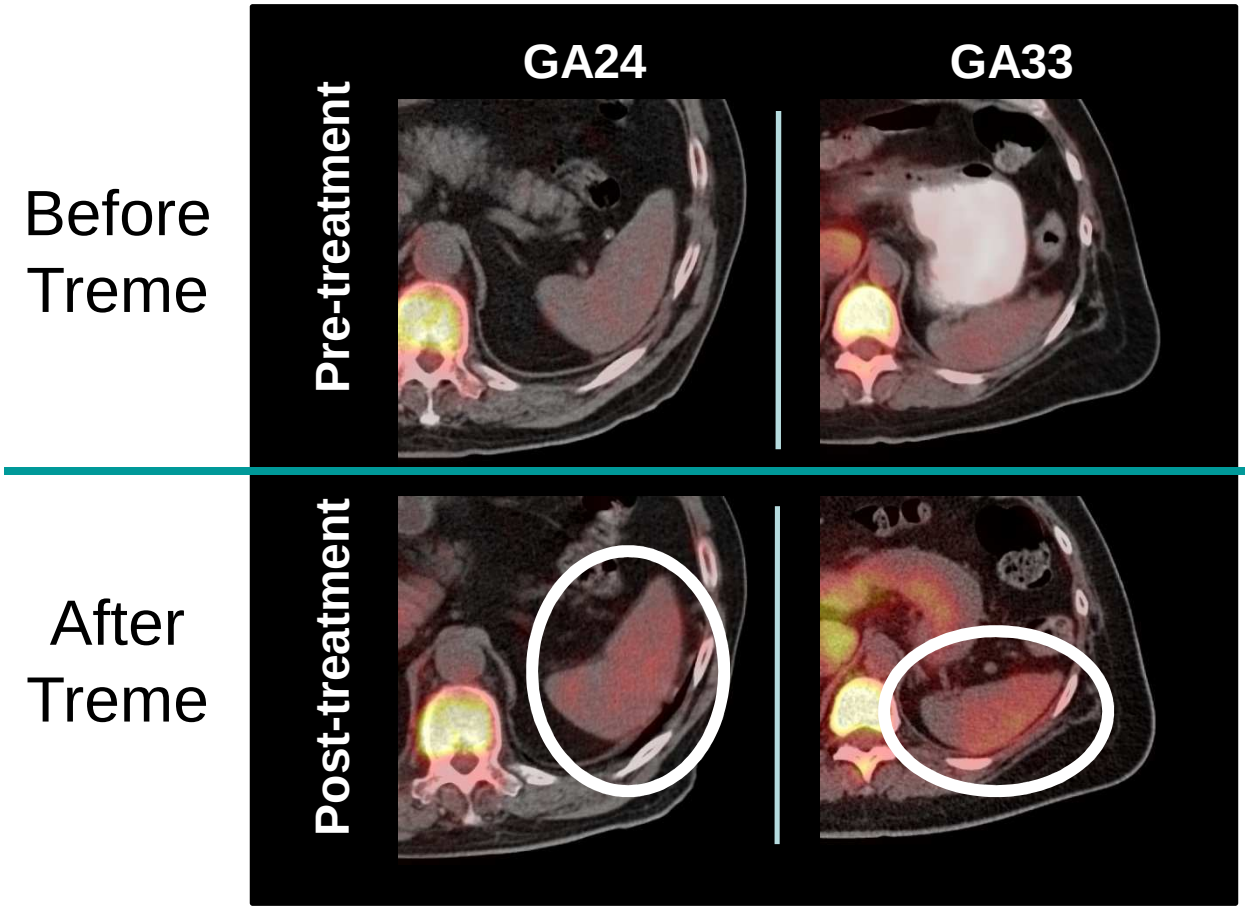
Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

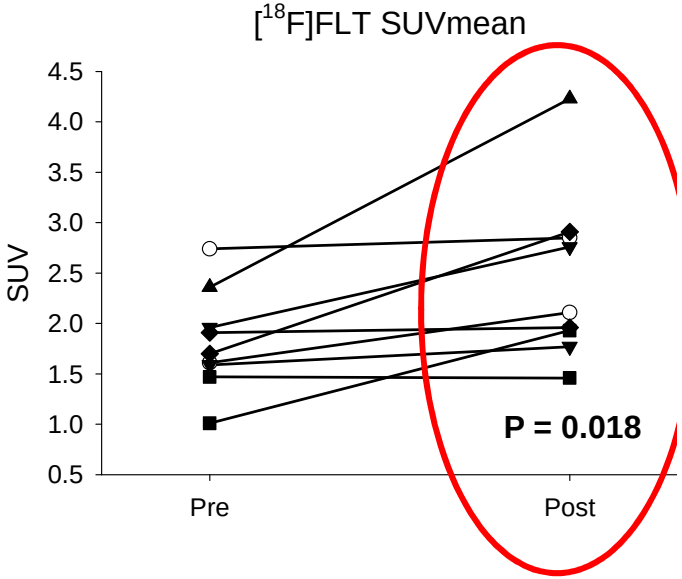


10 mg/kg x 4 doses q3w, then q3mo + dacarbazine

N Engl J Med. 2011 Jun 30;364(26):2517-26.

[^{18}F]FLT PET tracer uptake in the spleen before and after tremelimumab





Molecular imaging with the PET probe [^{18}F]FLT (radiolabeled thymidine) allows mapping and non-invasive imaging of cell proliferation in spleen after CTLA4 blockade in patients with metastatic melanoma.

Ribas… McCarthy, Czernin *et al*. JNM 2010

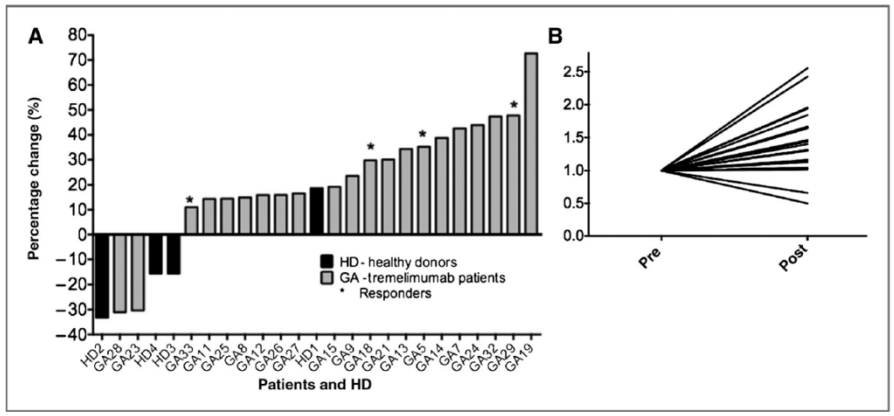
CTLA4 blockade diversifies peripheral T cell responses

Cancer Therapy: Clinical

Clinical Cancer Research

CTLA4 Blockade Broadens the Peripheral T-Cell Receptor Repertoire

Lidia Robert[1], Jennifer Tsoi[2], Xiaoyan Wang[1,3], Ryan Emerson[7,8], Blanca Homet[1,9], Thinle Chodon[1], Stephen Mok[1,2], Rong Rong Huang[4], Alistair J. Cochran[4], Begoña Comin-Anduix[5,6], Richard C. Koya[5,6], Thomas G. Graeber[2,6], Harlan Robins[7,8], and Antoni Ribas[1,2,5,6]



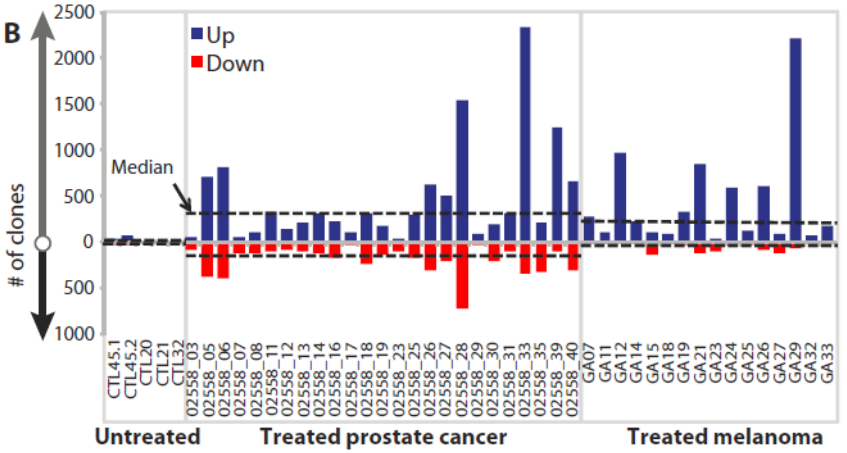
Clin Cancer Res; 20(9) May 1, 2014

RESEARCH ARTICLE

CANCER

Improved Survival with T Cell Clonotype Stability After Anti–CTLA-4 Treatment in Cancer Patients

Edward Cha,[1] Mark Klinger,[2] Yafei Hou,[1] Craig Cummings,[2] Antoni Ribas,[3] Malek Faham,[2] Lawrence Fong[1]*



www.ScienceTranslationalMedicine.org 28 May 2014 Vol 6 Issue 238 238ra70

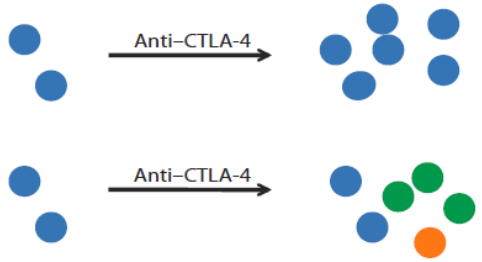
CTLA4 blockade diversifies peripheral T cell responses without expanding pre-existing ones

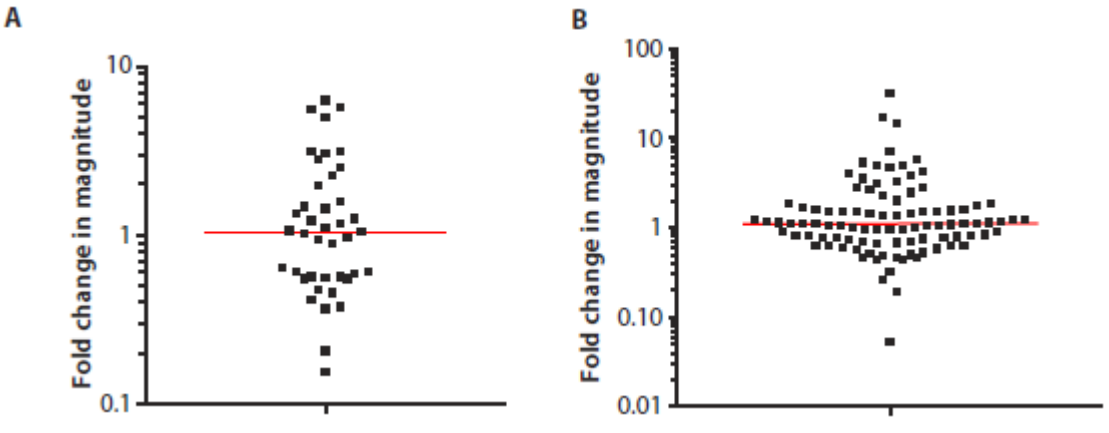
RESEARCH ARTICLE

IMMUNOTHERAPY

Anti–CTLA-4 therapy broadens the melanoma-reactive CD8$^+$ T cell response

Pia Kvistborg,[1]* Daisy Philips,[1] Sander Kelderman,[1] Lois Hageman,[1] Christian Ottensmeier,[2] Deborah Joseph-Pietras,[2] Marij J. P. Welters,[3] Sjoerd van der Burg,[3] Ellen Kapiteijn,[3] Olivier Michielin,[4] Emanuela Romano,[4] Carsten Linnemann,[1] Daniel Speiser,[4] Christian Blank,[1] John B. Haanen,[1†] Ton N. Schumacher[1*†]



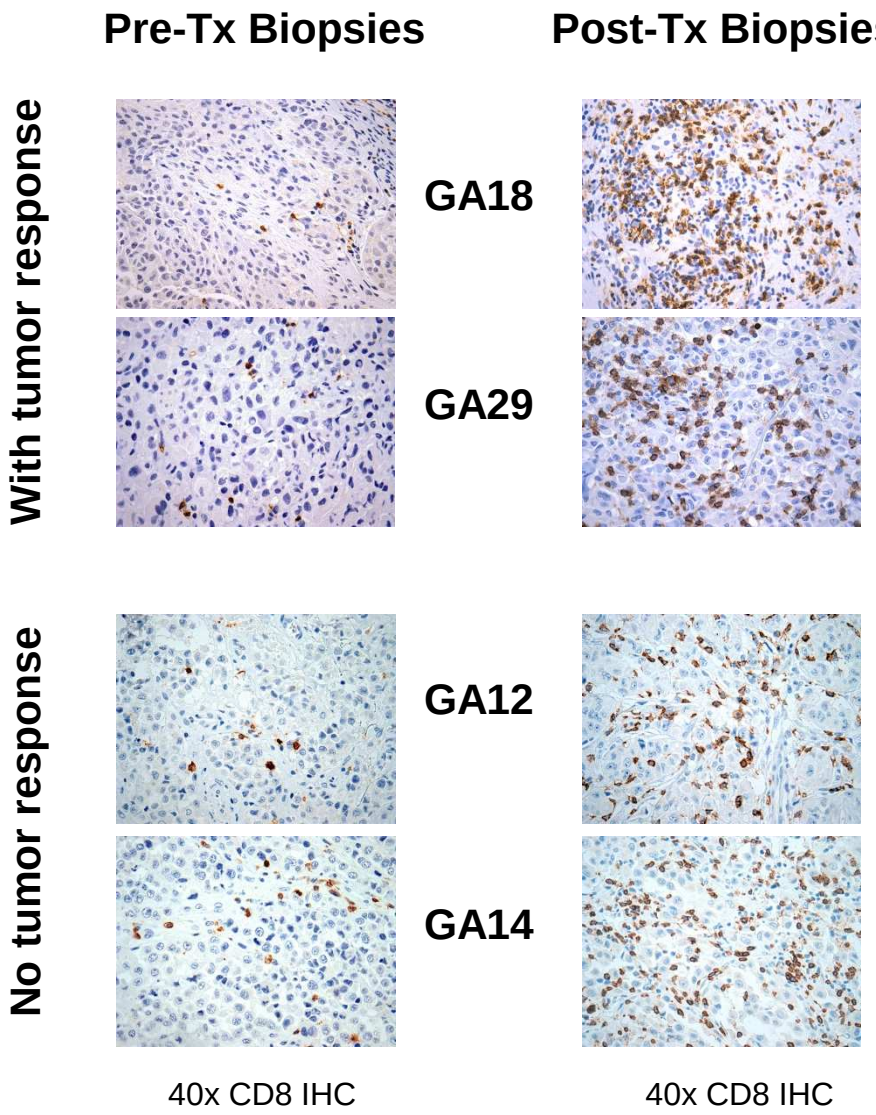


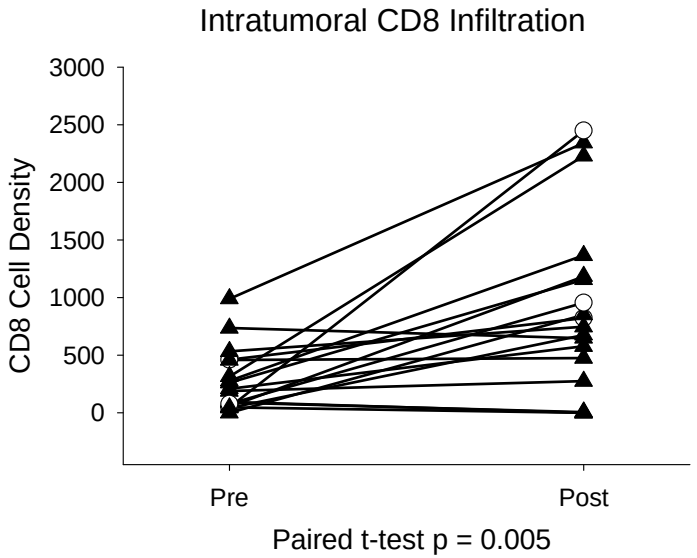
Changes in 40 melanoma antigens

Changes in 96 virus antigens

Change in antigen recognition/mo

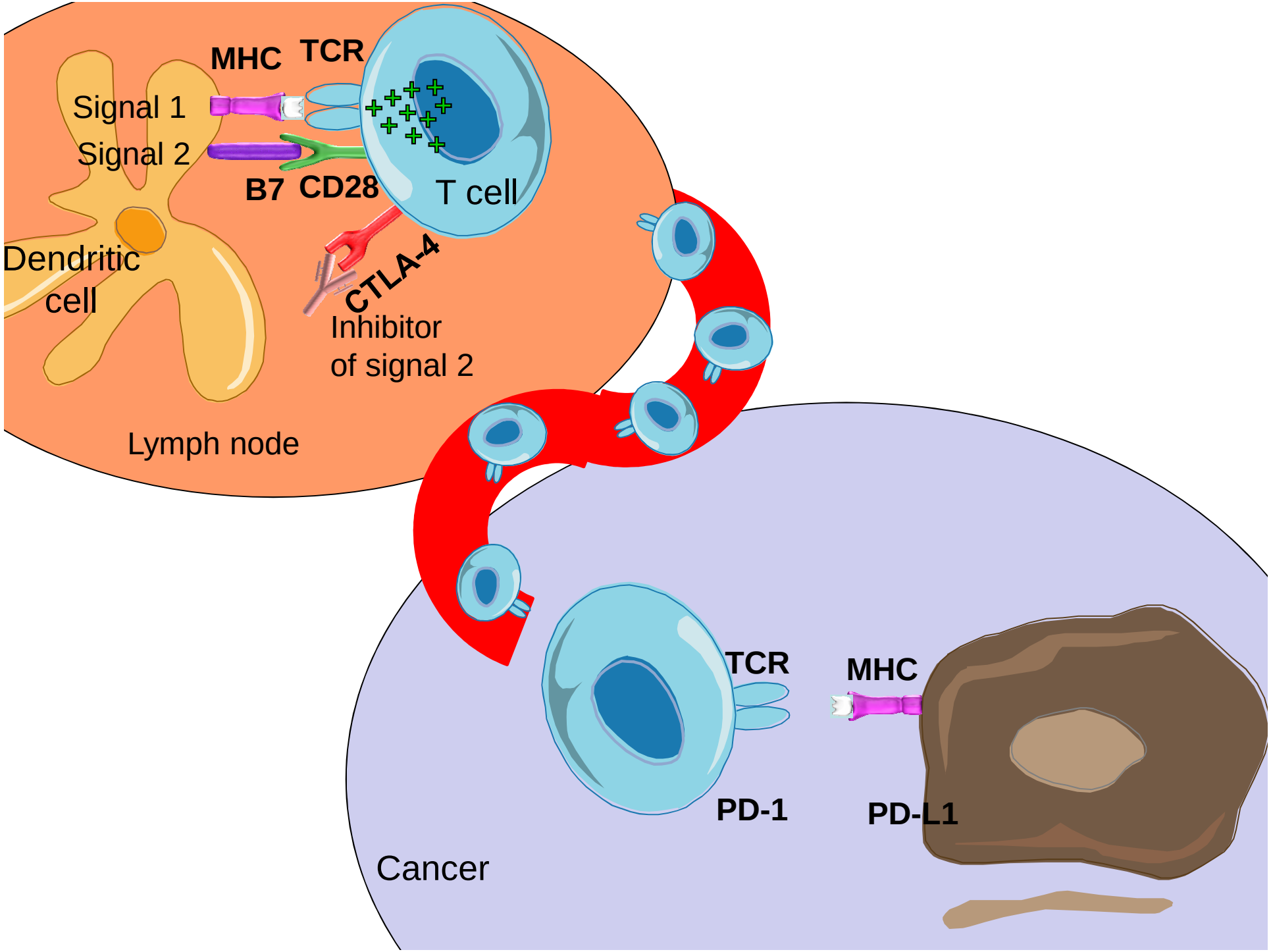
Increase in TIL in most patients treated with anti-CTLA4 (tremelimumab) regardless of tumor response





CTLA4 blockade brings T cells into tumors

Huang… Cochran, Ribas Clinical Cancer Research 2011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Dendritic cell
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Inhibitor of signal 2
Lymph node
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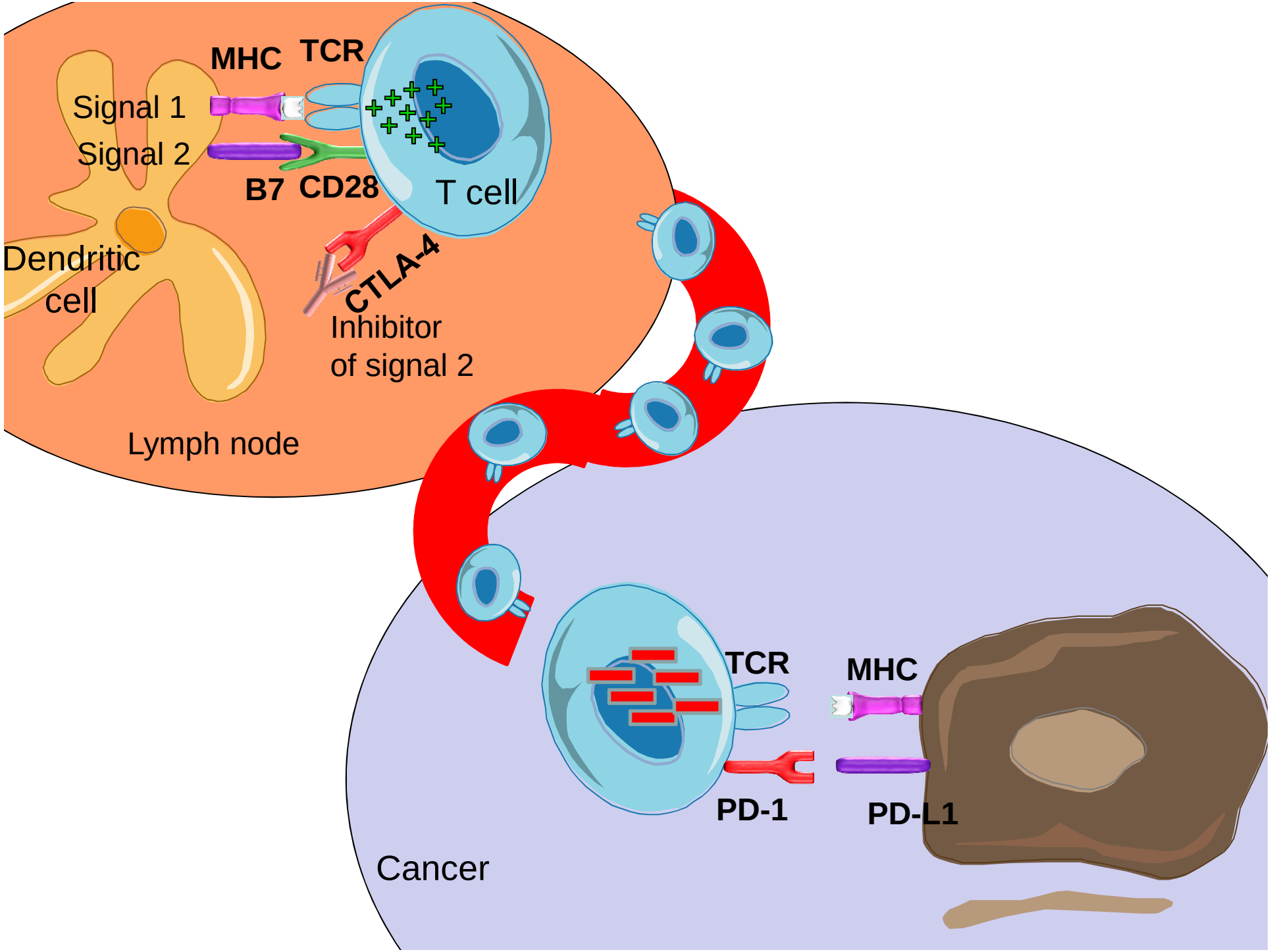
MHC
PD-1
PD-L1
Cancer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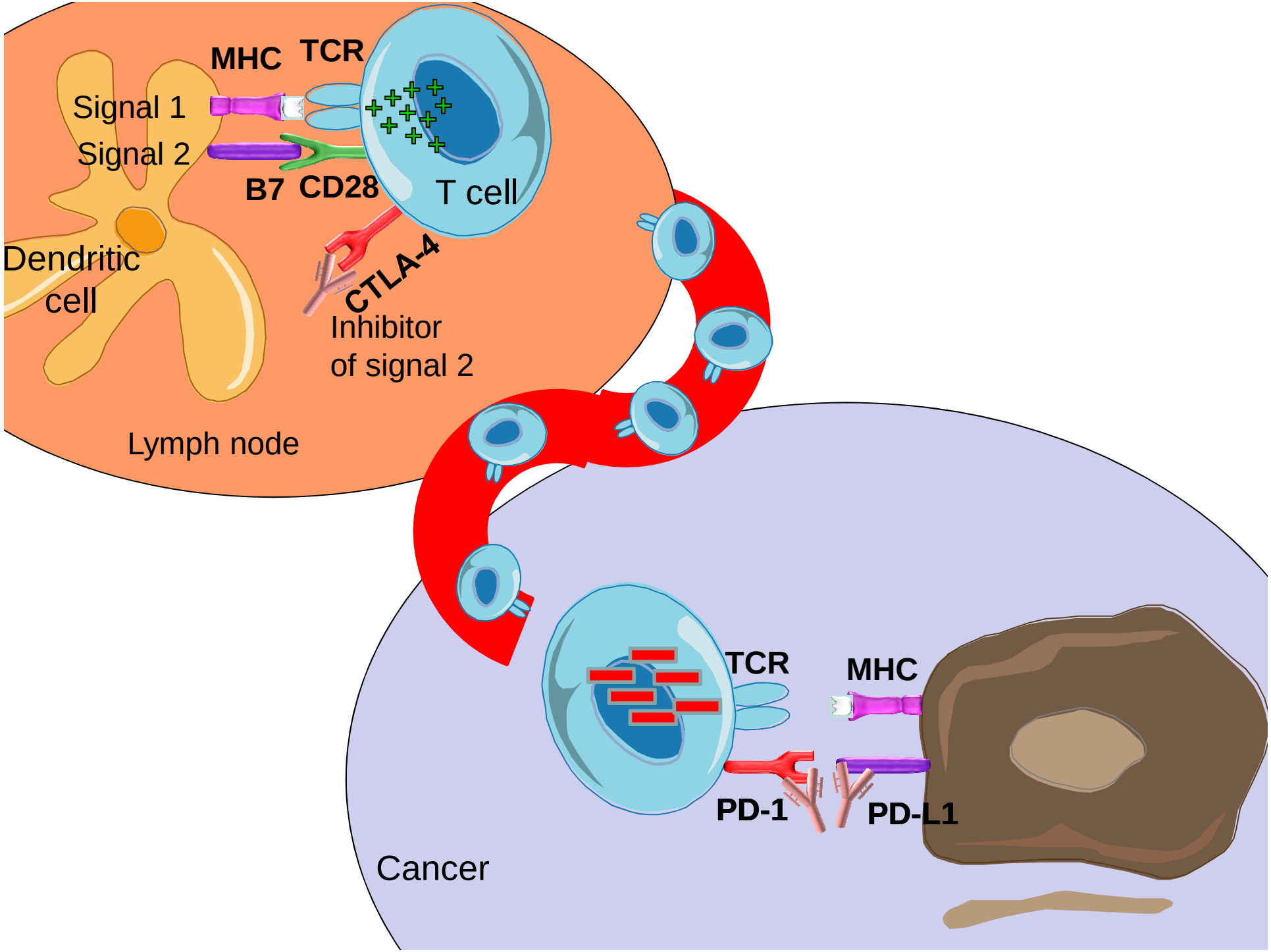
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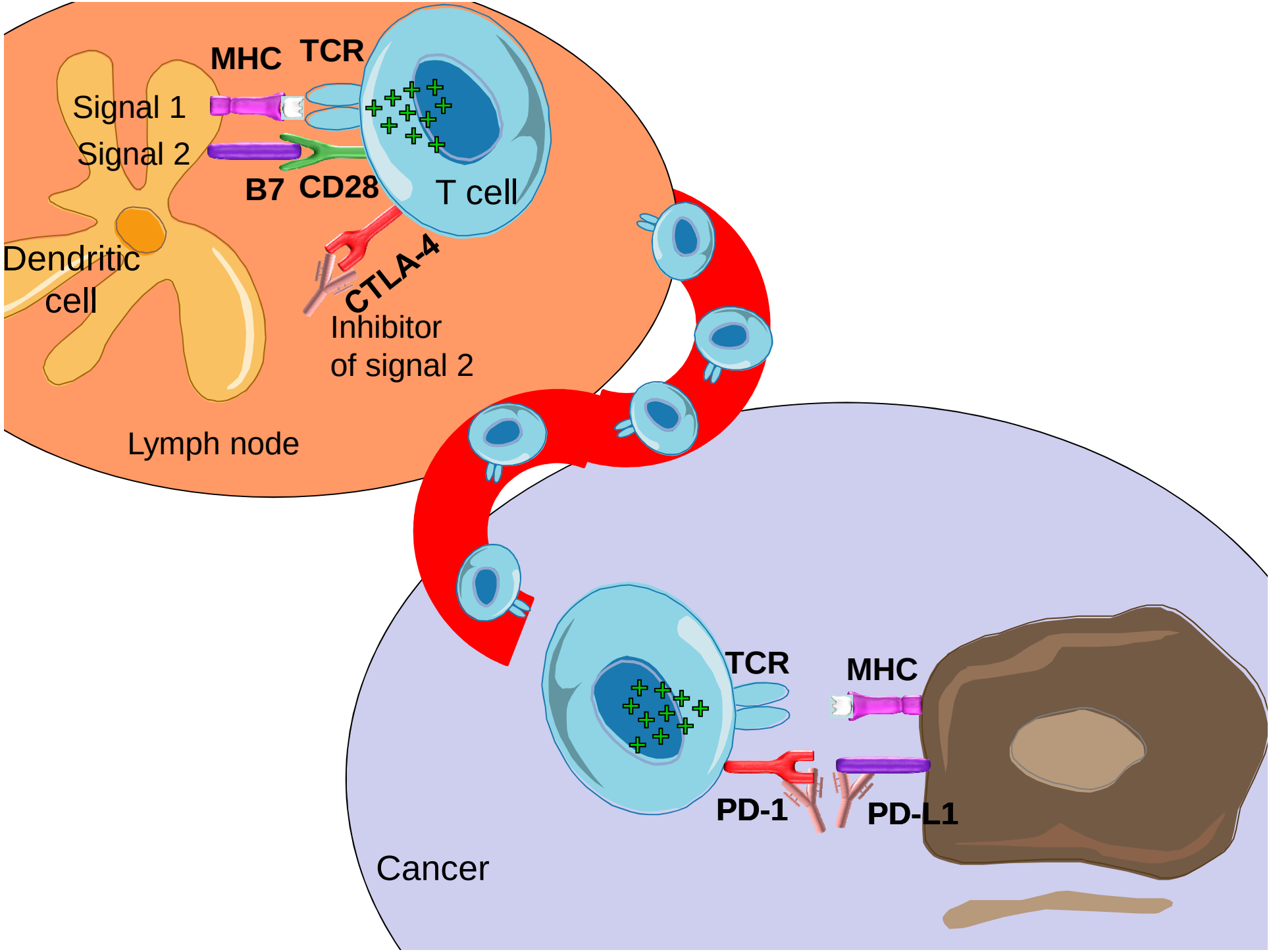
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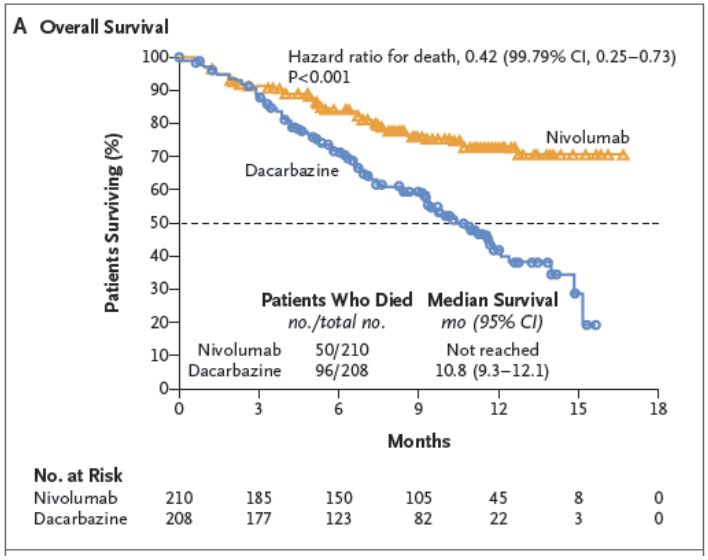
PD-1
PD-L1
Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.



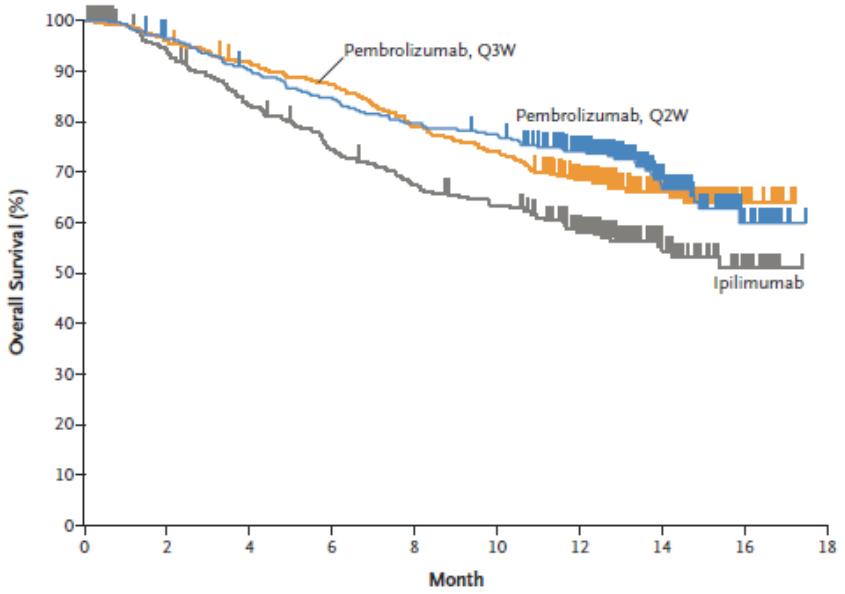
NEJM 2015 Jan 22; 372: 320-30.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*



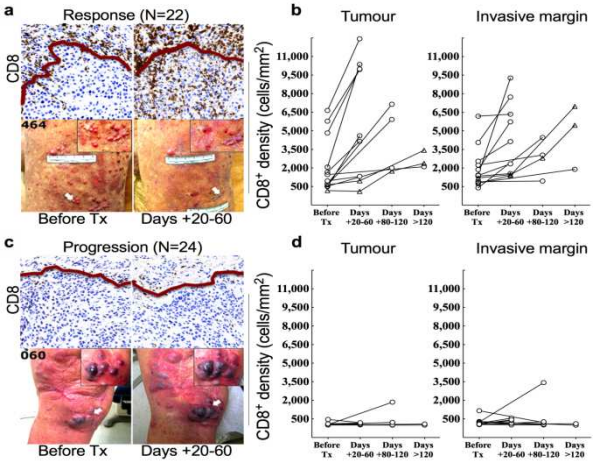
NEJM 2015, Jun 25; 372: 2521-2532

PD-1/L1 blockade early clinical data

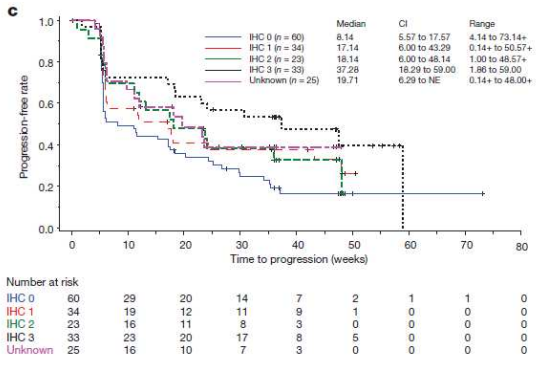
- Long lasting responses in patients with:
  - Melanoma (30-35%)
  - NSCLC (20-25%)
  - Bladder (25%)
  - Hodgkin's (65-85%)
  - Merkel cell carcinoma (71%)
  - Head and neck
  - Gastric
  - Ovarian
  - Colorectal
  - Liver

How can we select patients poised to respond to PD-1/L1 blockade?

1. Pre-existing T cell infiltration triggering adaptive PD-L1 expression

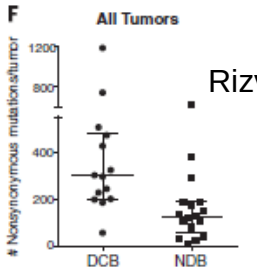


Tumeh, Nature 2014

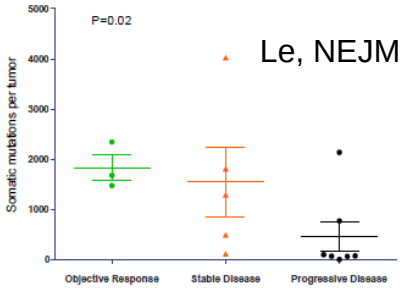


Herbst, Nature 2014

2. Mutational load

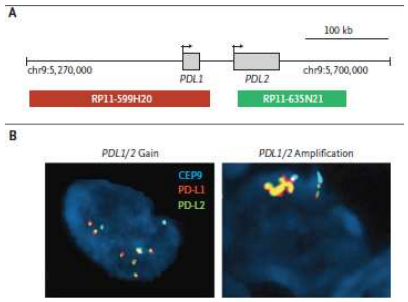


Rizvi, Science 2015



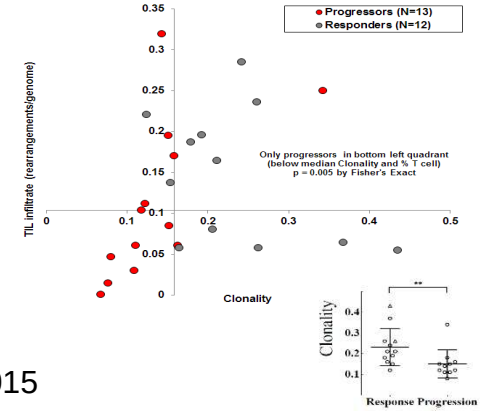
Le, NEJM 2015

3. PDJ amplicon



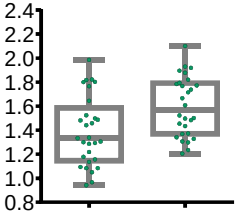
Ansell, NEJM 2015

4. TCR clonality



Tumeh, Nature 2014

5. IFN signature by expression profiling



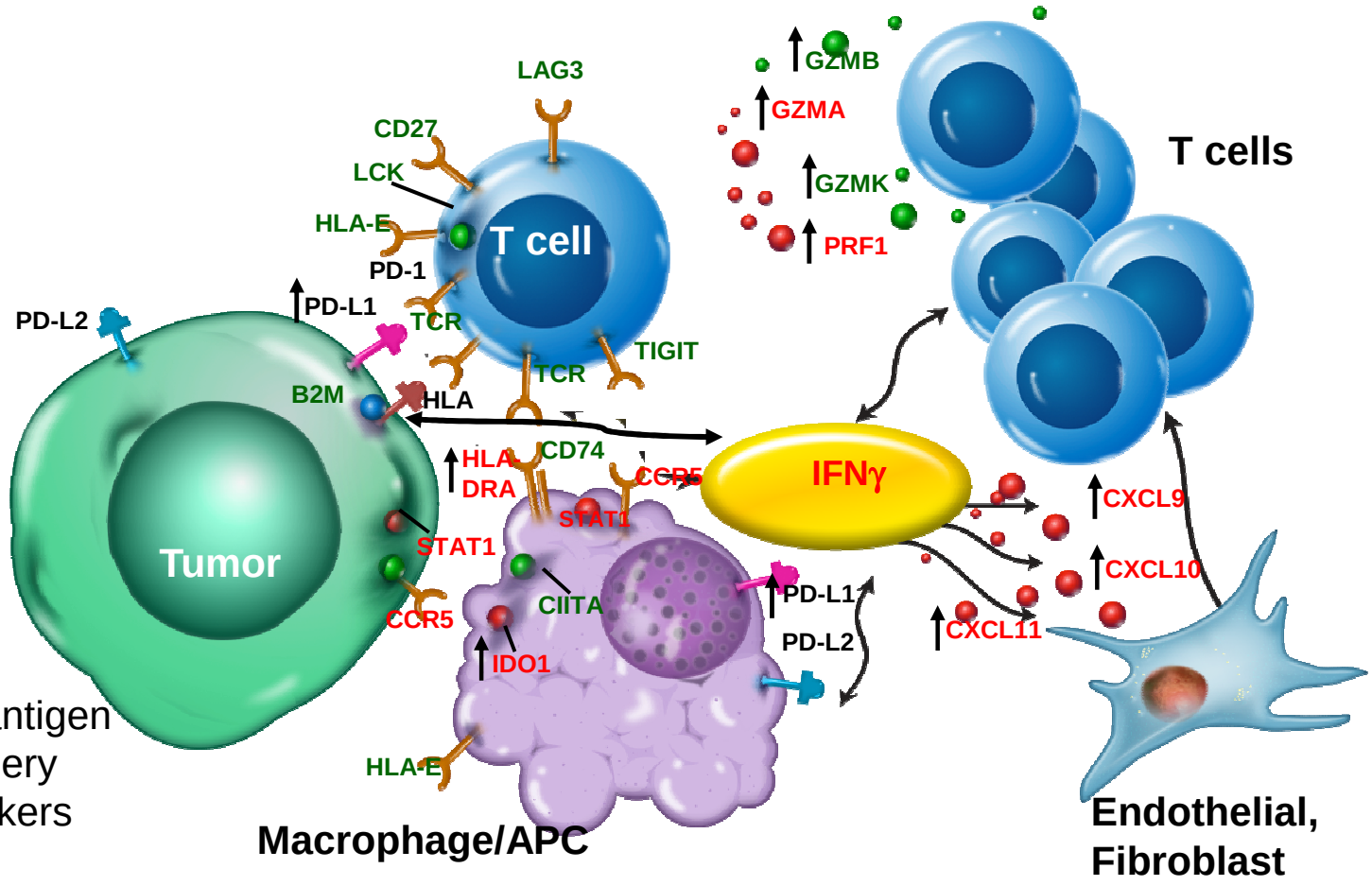
Ribas, ASCO 2015

Best Overall Response, RECISTv1.1

Expanded Gene Signatures Identified During Discovery Analysis Reveal Biology of Complex Immune Synapse

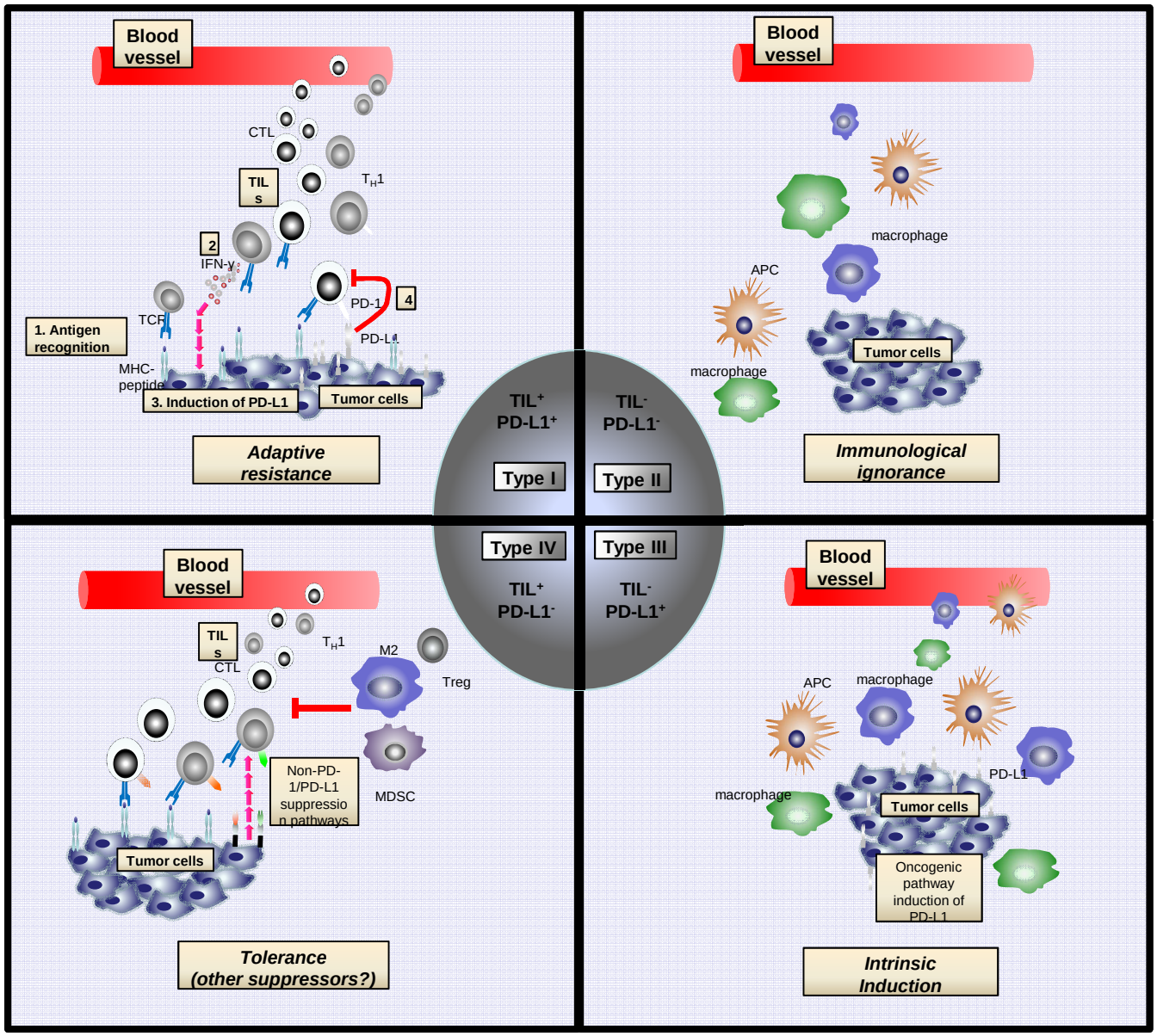
Discovery analysis of entire NanoString melanoma data set led to identification of new genes:

- IFNγ signaling
- MHC class I and II antigen presentation machinery
- T-cell activation markers



Ribas, Robert, Hodi, J Wolchok, Joshua, Hwu, Weber, Zarour,[8] Kefford, Loboda, Albright, Kang, Ebbinghaus, Yearley, Murphy, Nebozhyn, Lunceford, McClanahan, Ayers, Daud. ASCO 2015

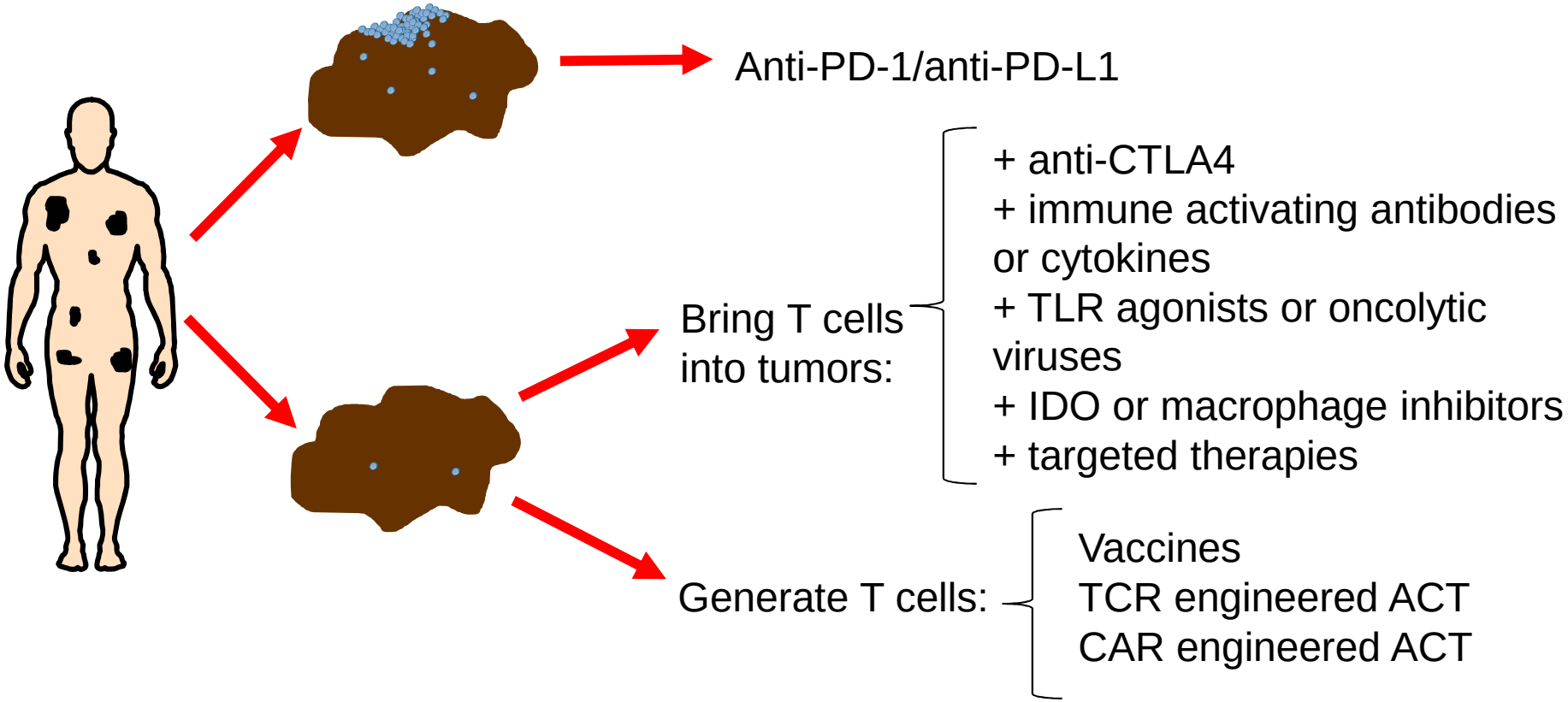
Classification of cancers depending on T cell infiltration and PD-L1 expression



Classification adapted from Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. Clinical Cancer Research 2013;19 (5): 1021-34.

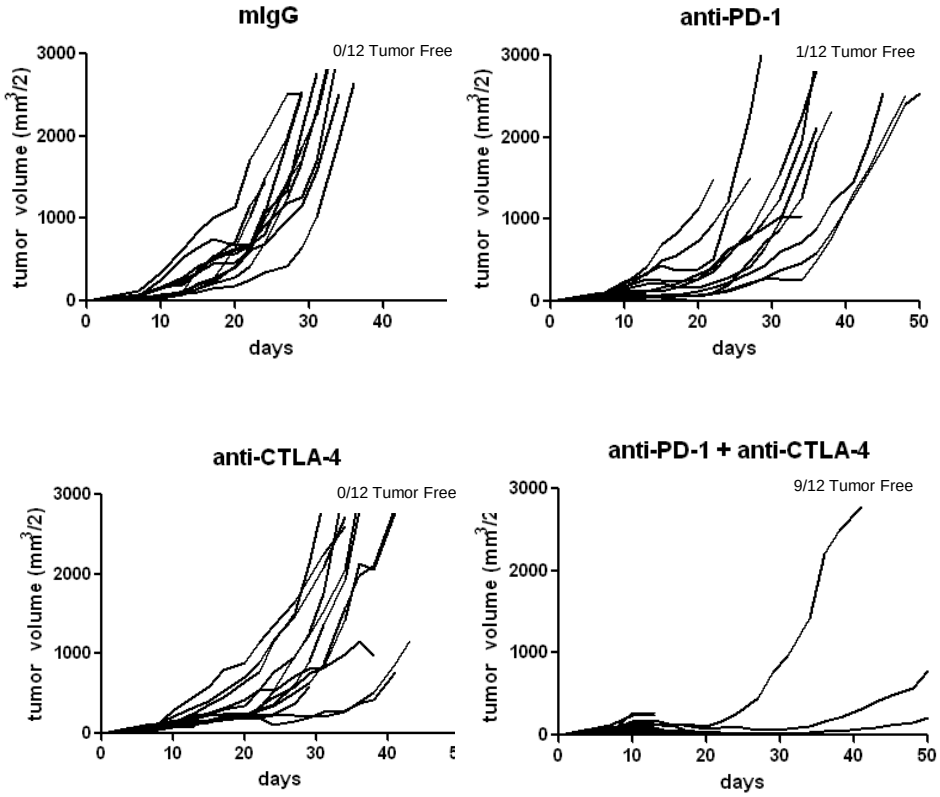
Teng MW, Ngiow SF, Ribas A, Smyth MJ. Cancer Res 2015

Management of cancer in the post-anti-PD-1/L1 era

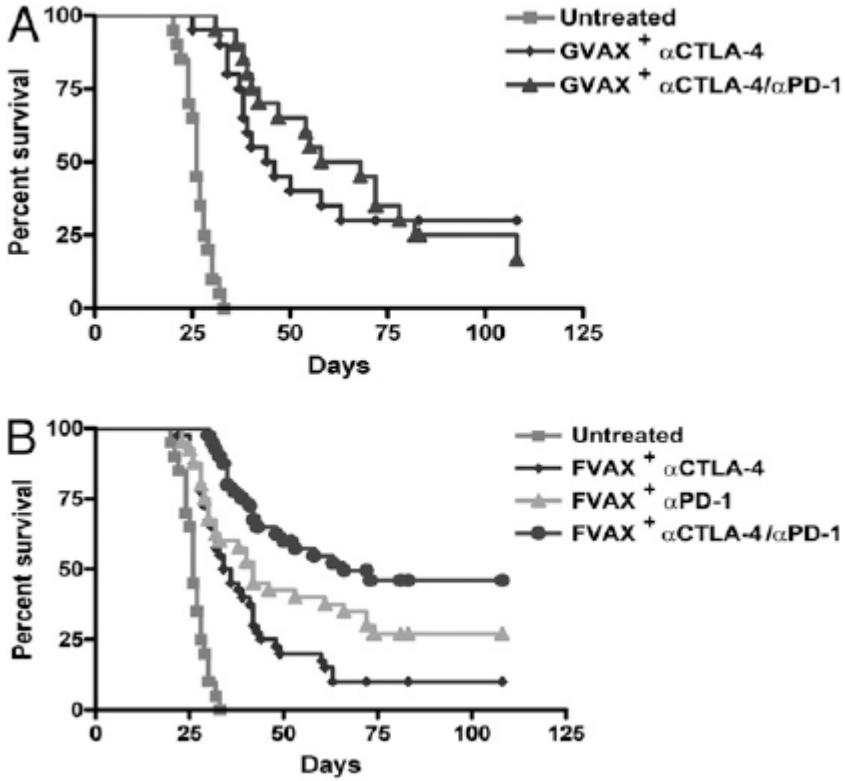


Antitumor Activity of Anti-CTLA-4 and Anti-PD-1 Antibodies in Murine Tumor Models

MC38 Colon Cancer
Antibody Rx Only [1, 2]



B16BL6 Melanoma
Antibody Rx + Cellular Vaccine[3]

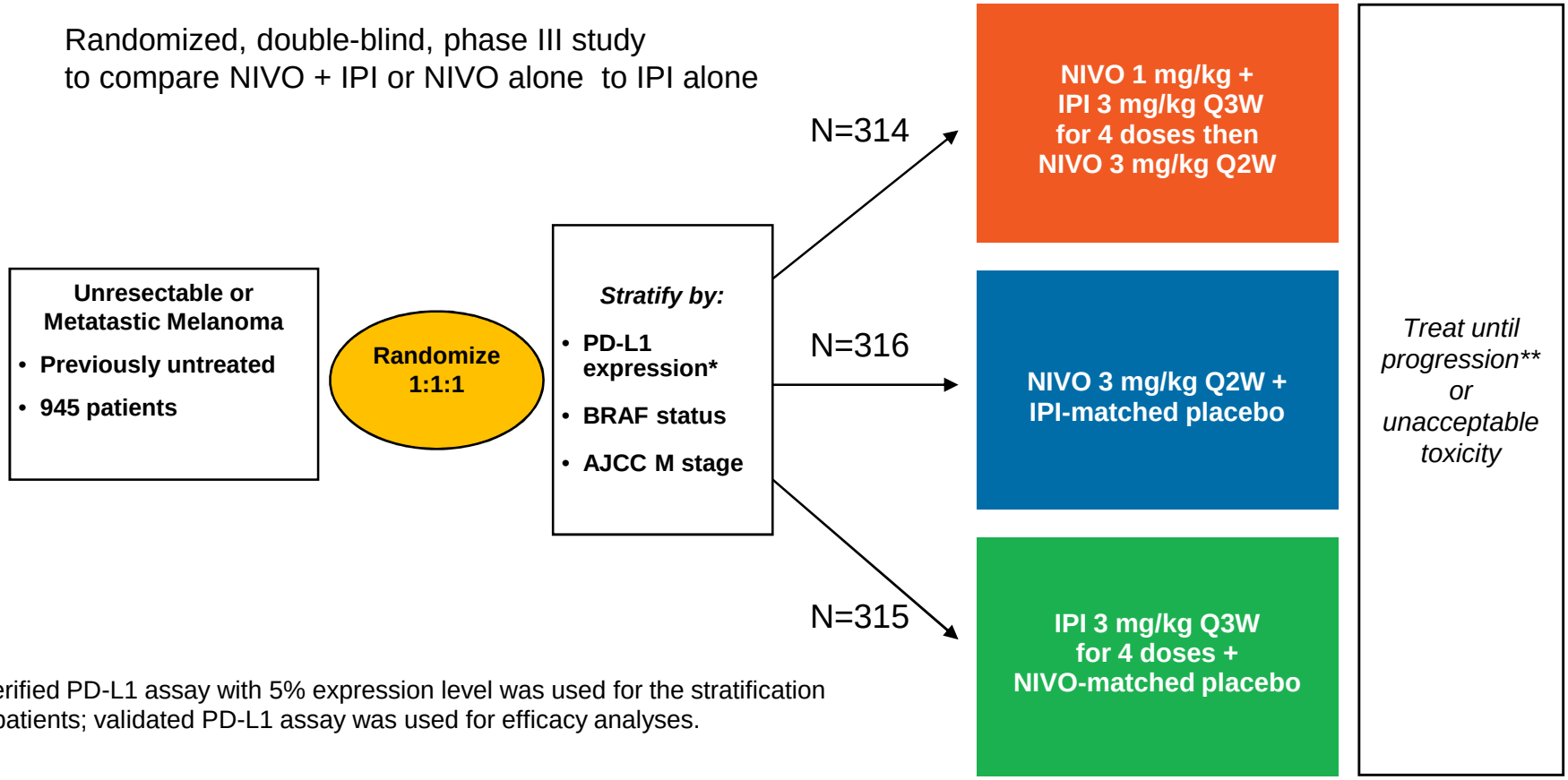


[1]Korman et al. J Immunol. 2007;178:48.37. [2]Selby et al. ASCO 2013, abs 3061. [3]Curran et al. Proc Natl Acad Sci. 2010;107:4275.

Presented by J. Wolchok, ASCO 2013

Phase III Trial of Nivolumab Alone or Combined With Ipilimumab vs. Ipilimumab Alone in Treatment-naïve Patients With Advanced Melanoma (CheckMate 067)

Randomized, double-blind, phase III study
to compare NIVO + IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

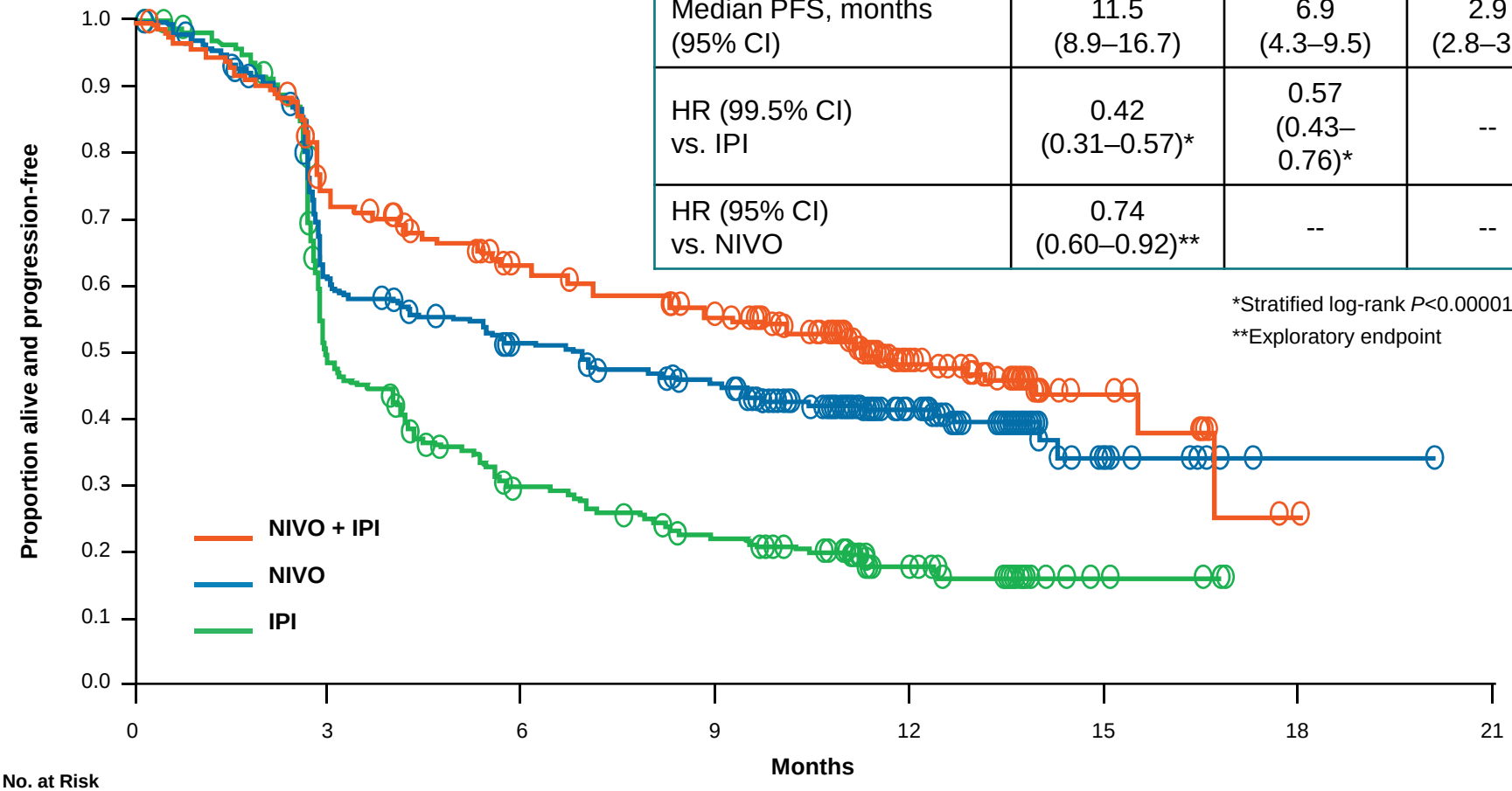
Wolchok, Chiarion-Sileni, Gonzalez, Rutkowski, Grob, Cowey, Lao, Schadendorf, Ferrucci, Smylie, Dummer, Hill, Haanen, Maio, McArthur, Yang, Rollin, Horak, Larkin, Hodi. LBA1, ASCO 2015

PFS (Intent-to-Treat)

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank *P*<0.00001 vs. IPI

**Exploratory endpoint



No. at Risk

NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

Wolchok *et al*. ASCO 2015

Safety Summary

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Wolchok *et al*. ASCO 2015

Conclusions

- Inhibiting the CTLA4 immune checkpoint results in durable responses in a subset of patients
  - Mediated by a diversification of the T cell repertoire

- Patients with advanced cancers will be studied for:
  - Pre-existing presence of T cells turned off by PD-1/PD-L1 interactions
    - Patients will be selected to get anti-PD-1/L1 therapy
  - If not present, then combinations will be designed to bring T cells to cancers
    - With CTLA4 blockade
    - BRAF and MEK inhibitors are a rational choice for such combinations
  - If no immune response to cancer, then patients will get engineered ACT therapies