Immuno-Oncology - “How it all got started…”

Christian Blank
The Netherlands Cancer Institute
EUFEMED Meeting
London, May 19, 2017

DISCLOSURES

Advisory role: BMS, MSD, Novartis, Roche, GSK, Pfizer

Honoraria: BMS, GSK, Roche, MSD, Pfizer

Research grant: Novartis

Shareholding: Verastem

The Father‘s of the Tumorimmunology Concept

Paul Ehrlich
1854-1915

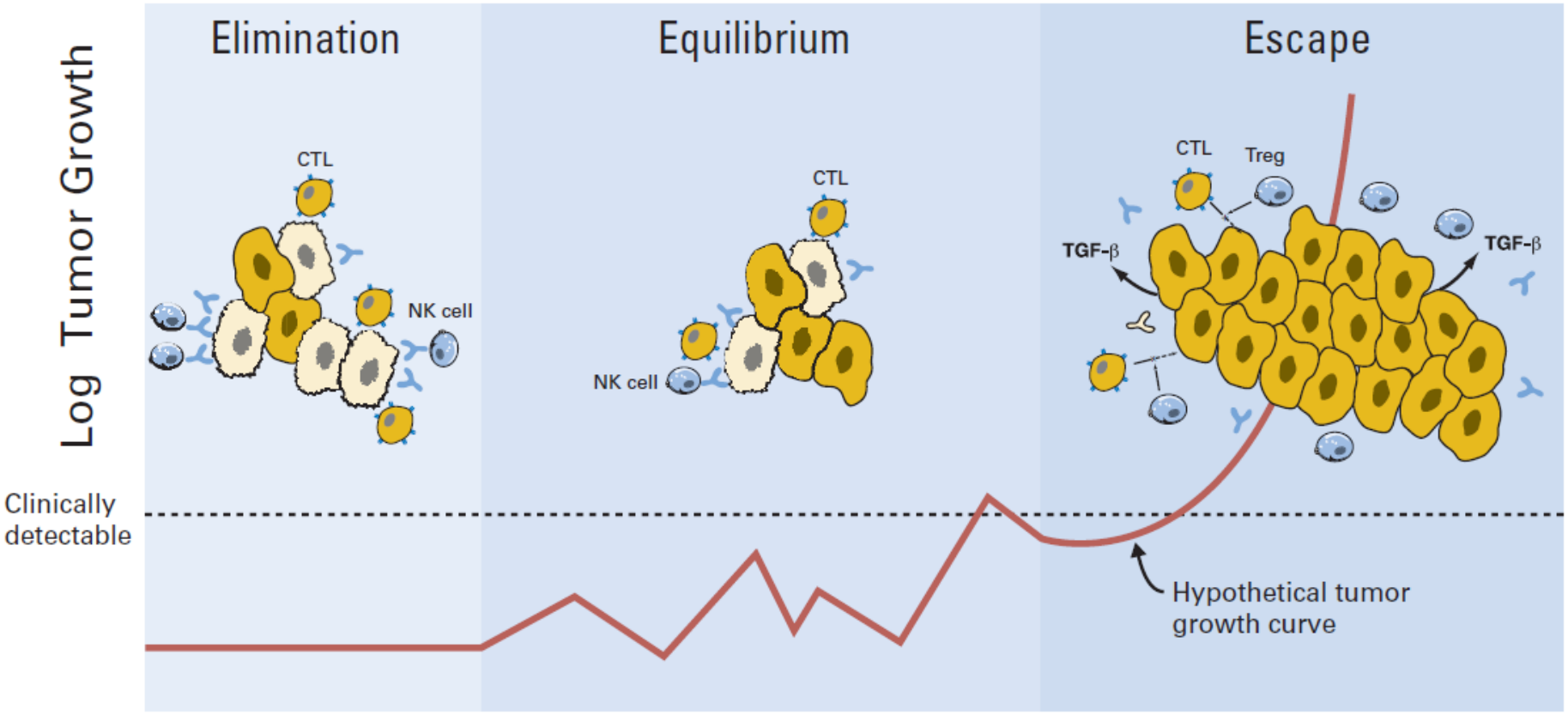
Frank Macfarlane Burnet
1899-1985

Lewis Thomas
1913-1993

„Die Häufigkeit maligner Erkrankungen müßte viel höher sein, wenn der Körper nicht in der Lage wäre, entartete Zellen zu eliminieren“

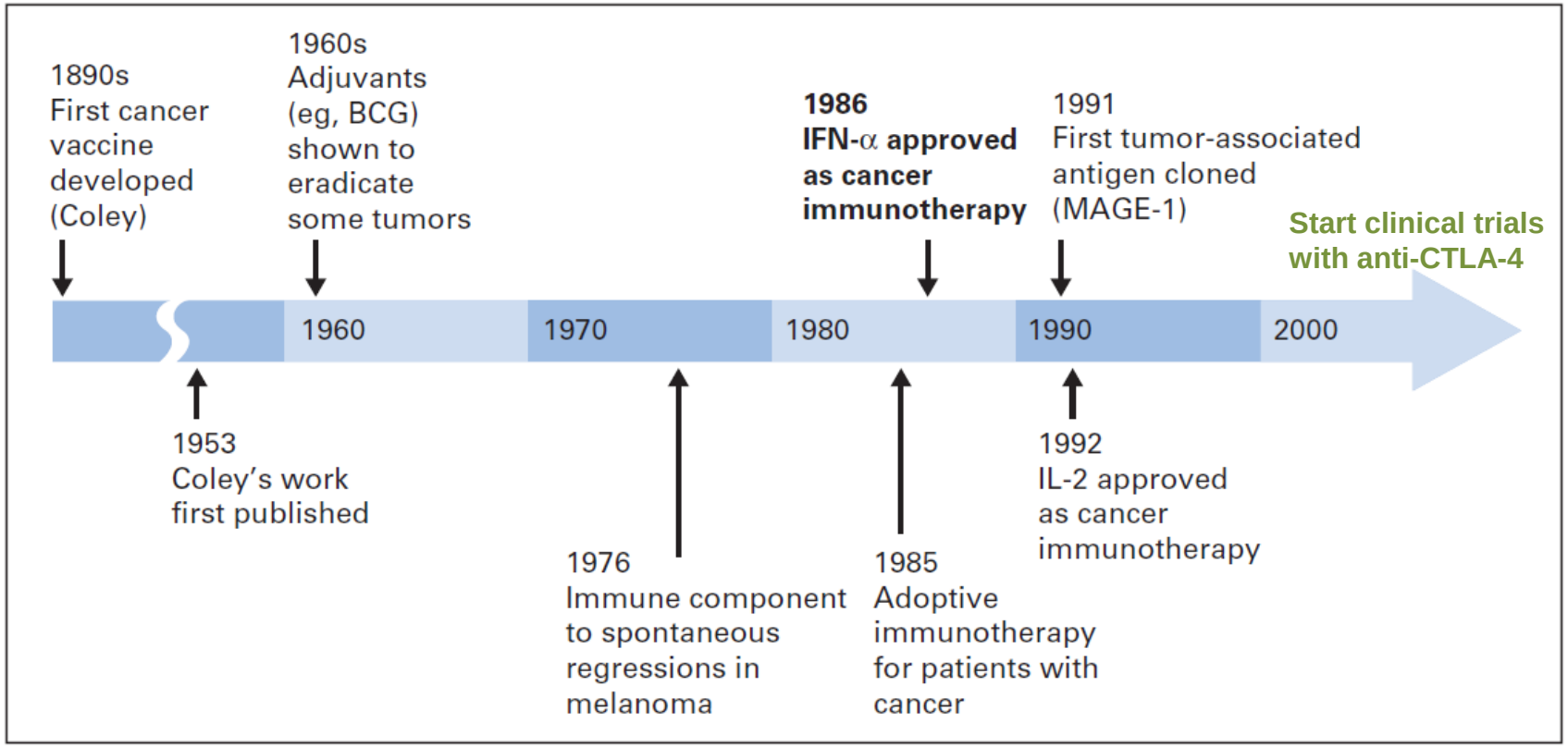
“The immune system is patrolling the body for signs of transformed cells and eliminates them upon detection, and its only rare that some escape to cause cancer”

Tumor Immune Escape

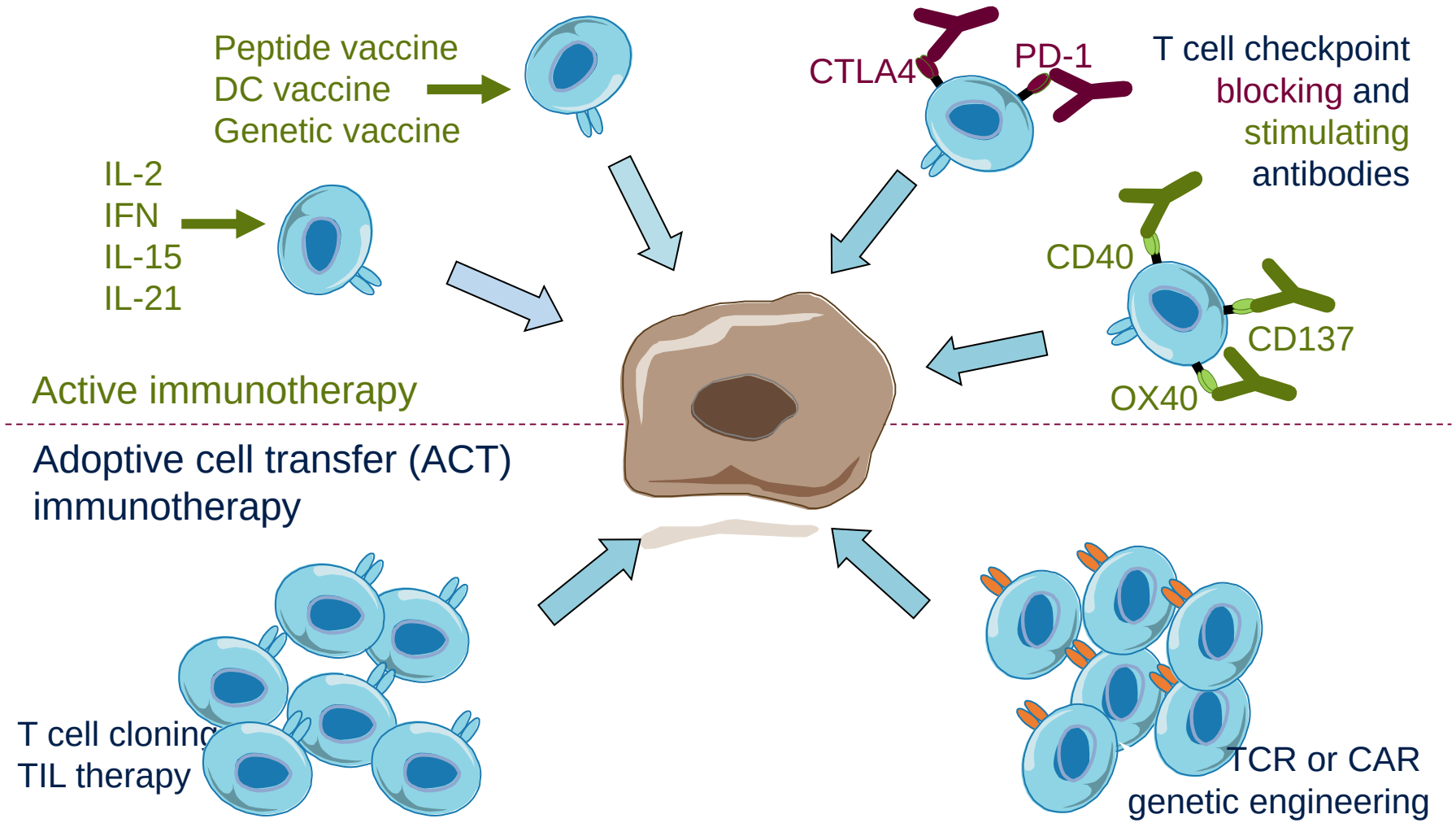


Kirkwood et al. JCO 2008

Key events in the history of cancer immunotherapy

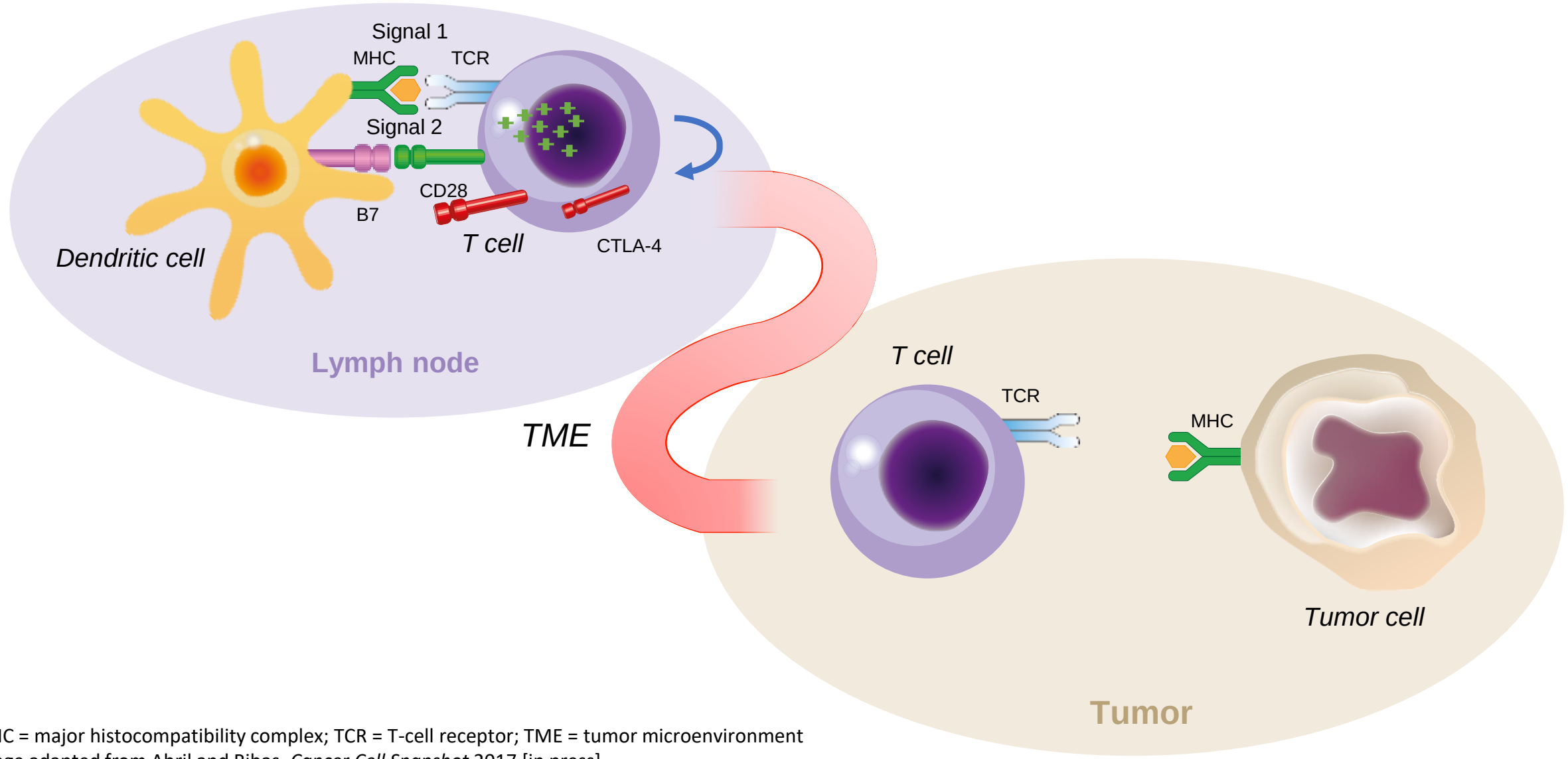


Immunotherapy– T cell versus melanoma



kindly provided by Toni Ribas

Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action



MHC = major histocompatibility complex; TCR = T-cell receptor; TME = tumor microenvironment
Image adapted from Abril and Ribas, *Cancer Cell Snapshot* 2017 [in press]

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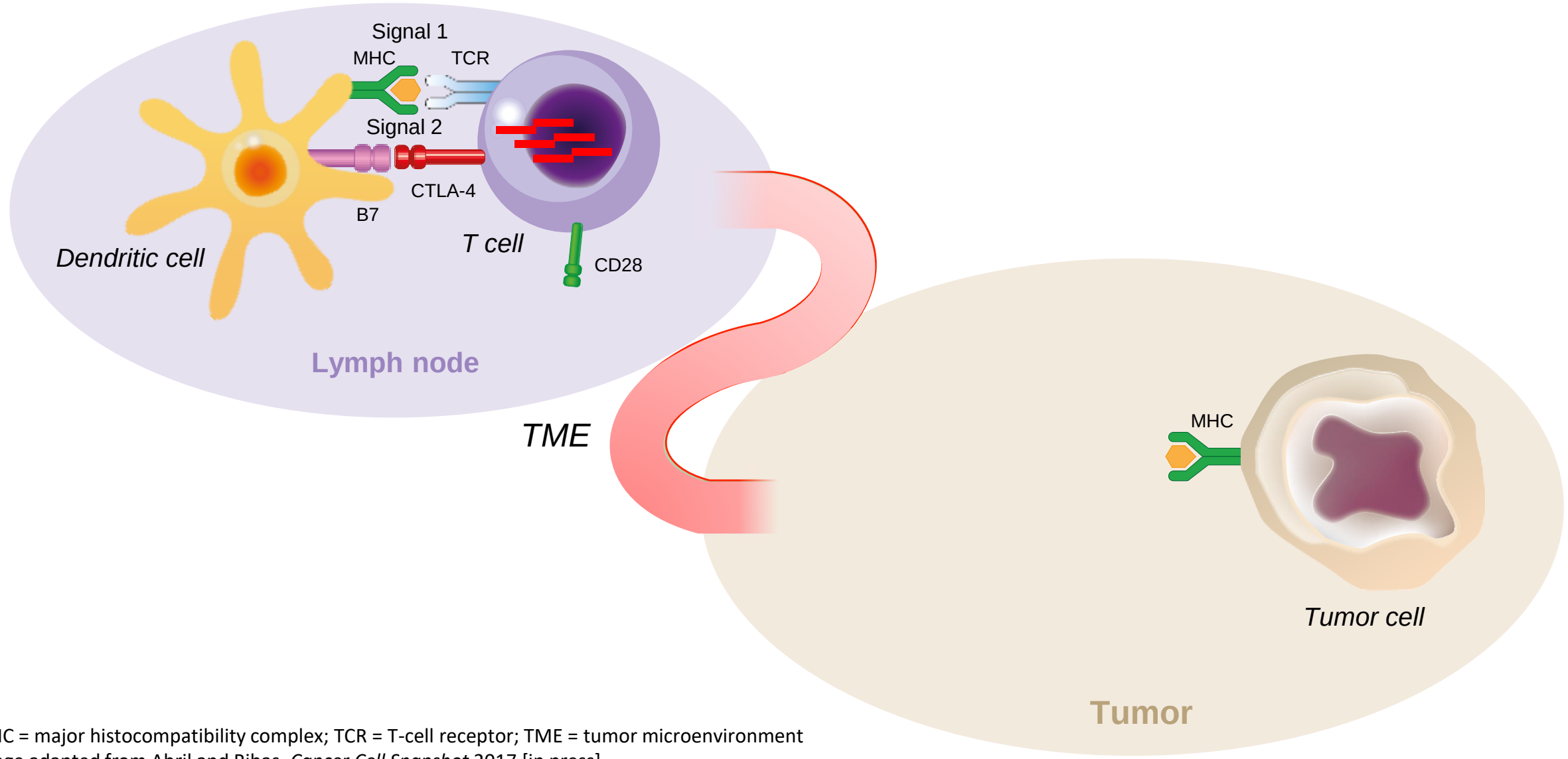

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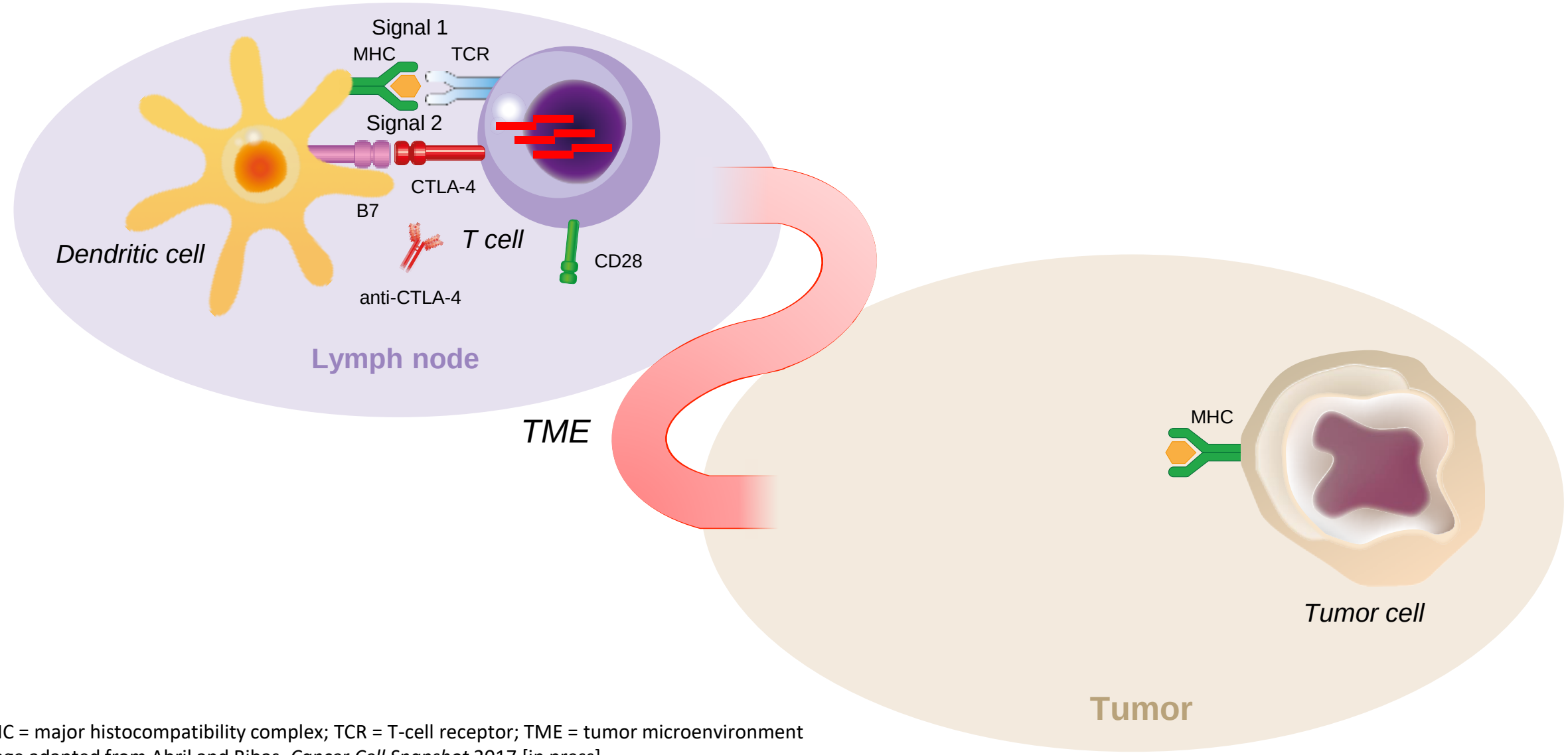

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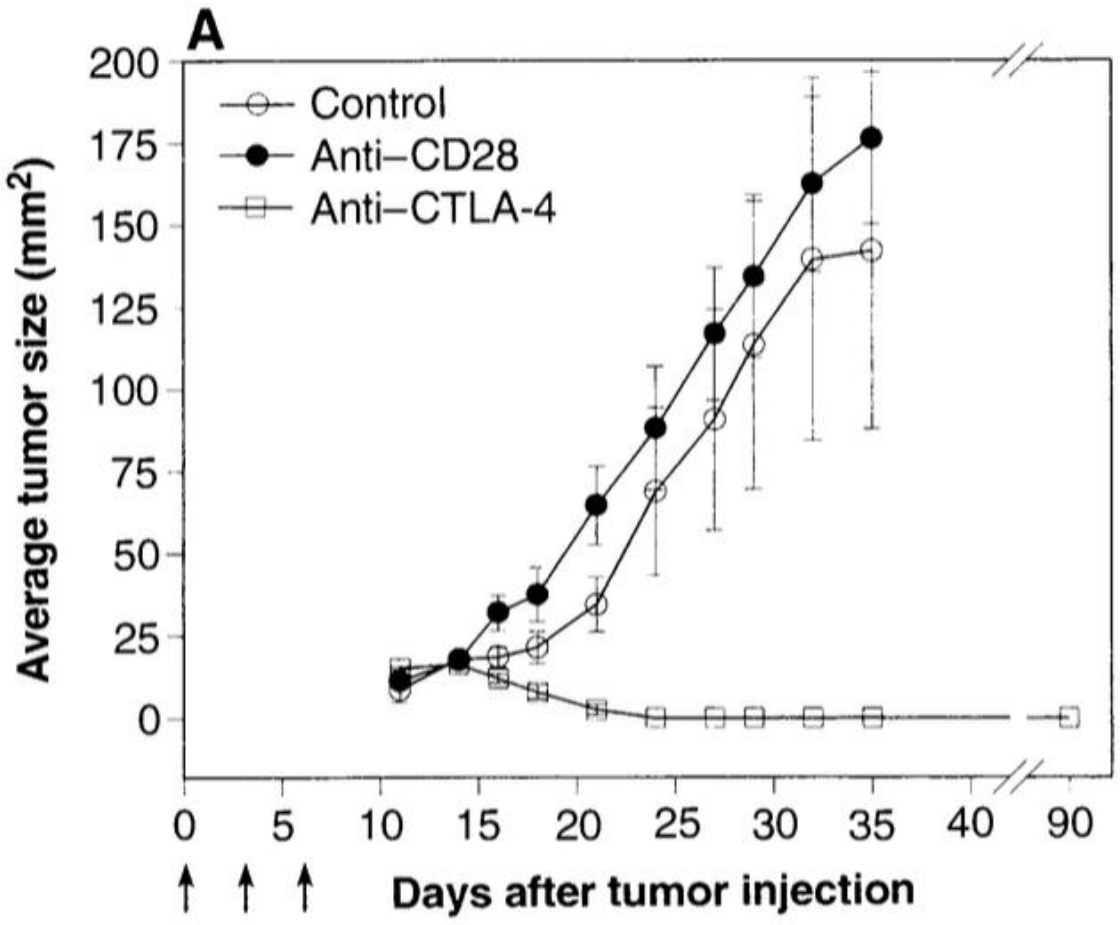
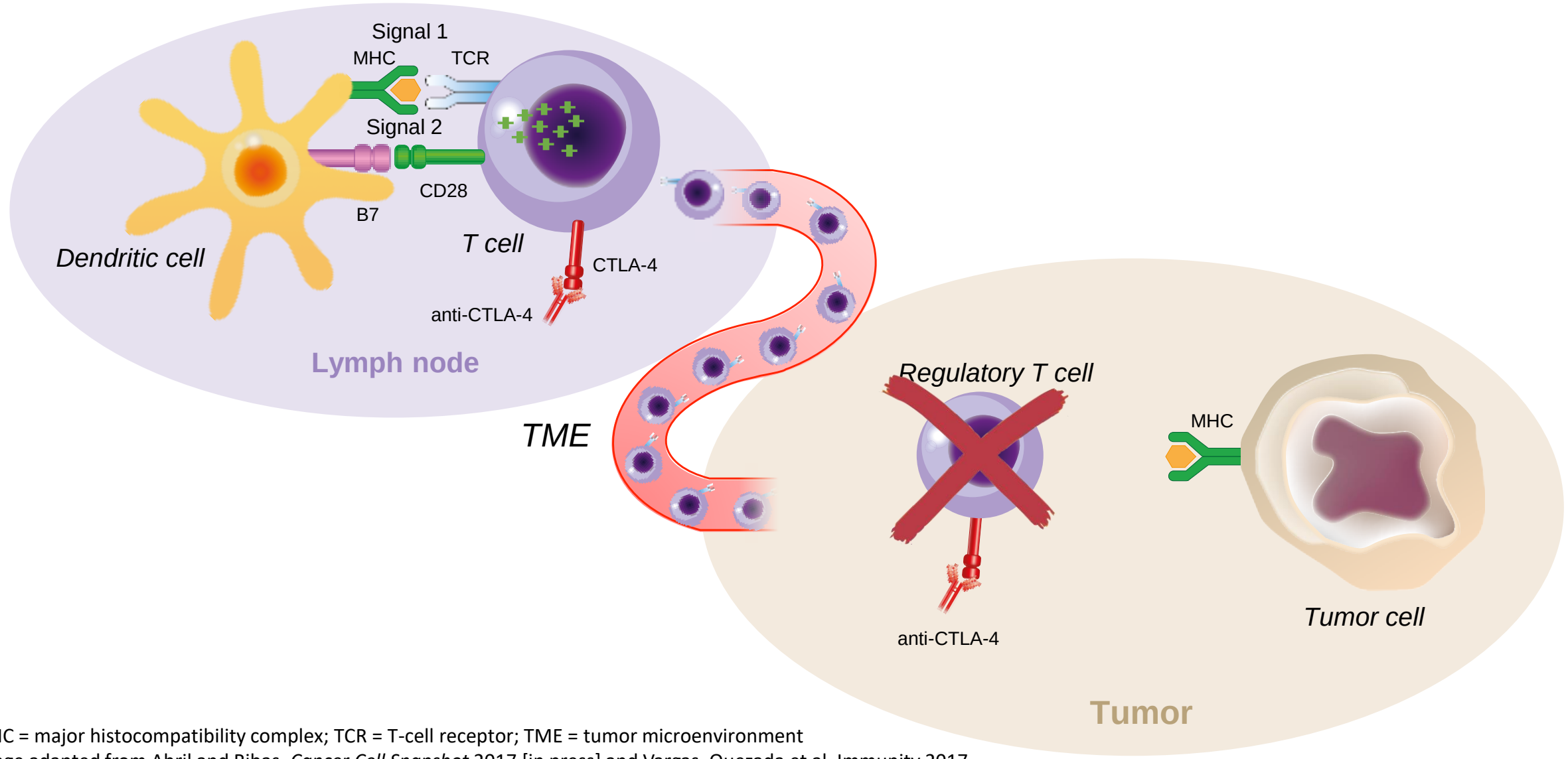
CTLA-4 blockade improves tumor control of B7-negative colon carcinoma line



Leach, Allison et al, Science, 1996

Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action



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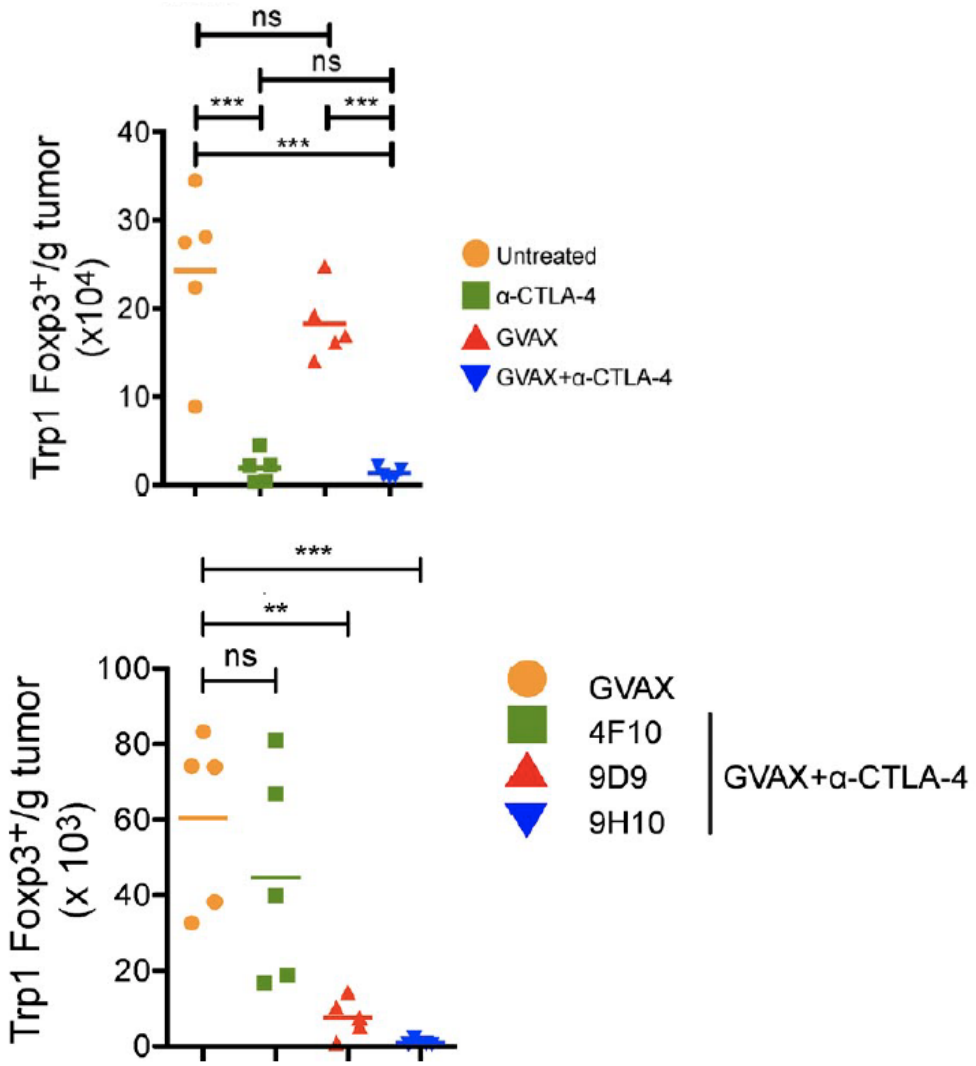
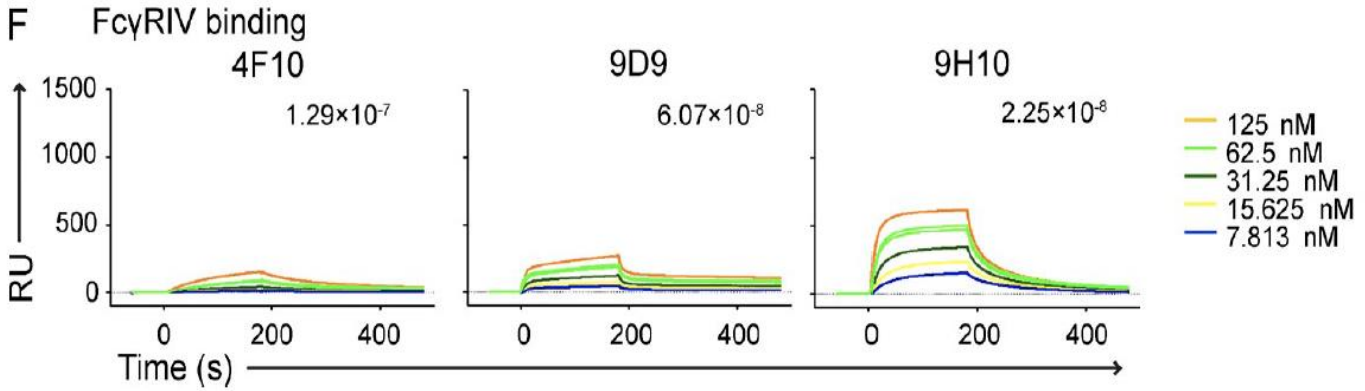
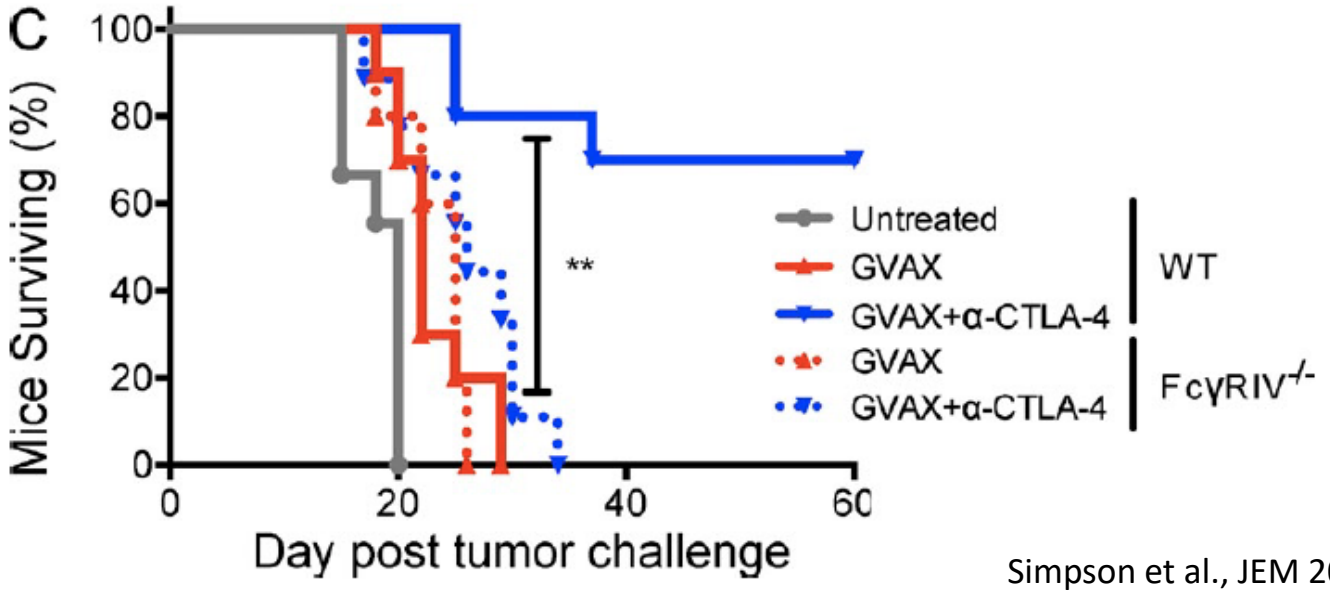
Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti–CTLA-4 therapy against melanoma







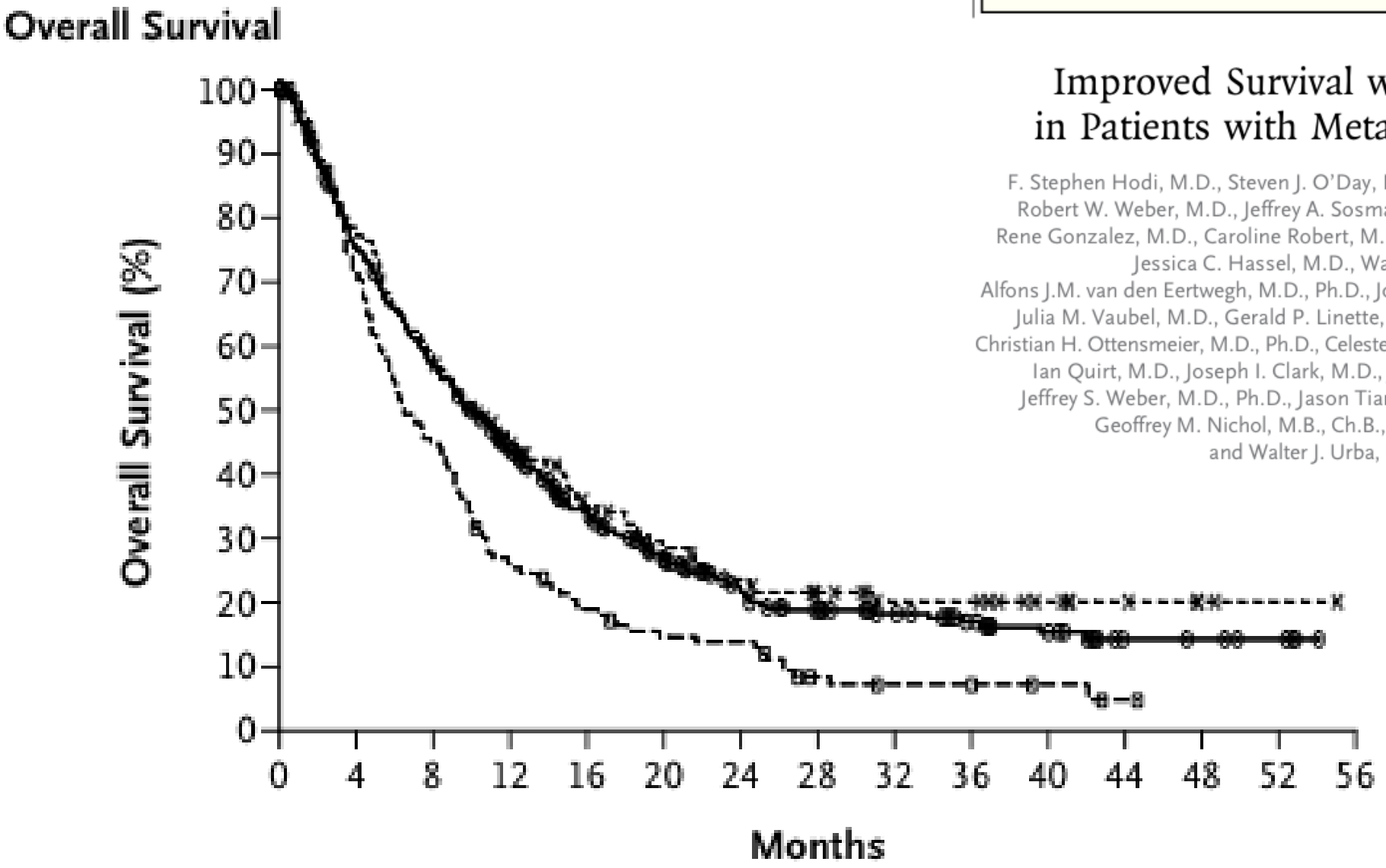
Simpson et al., JEM 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

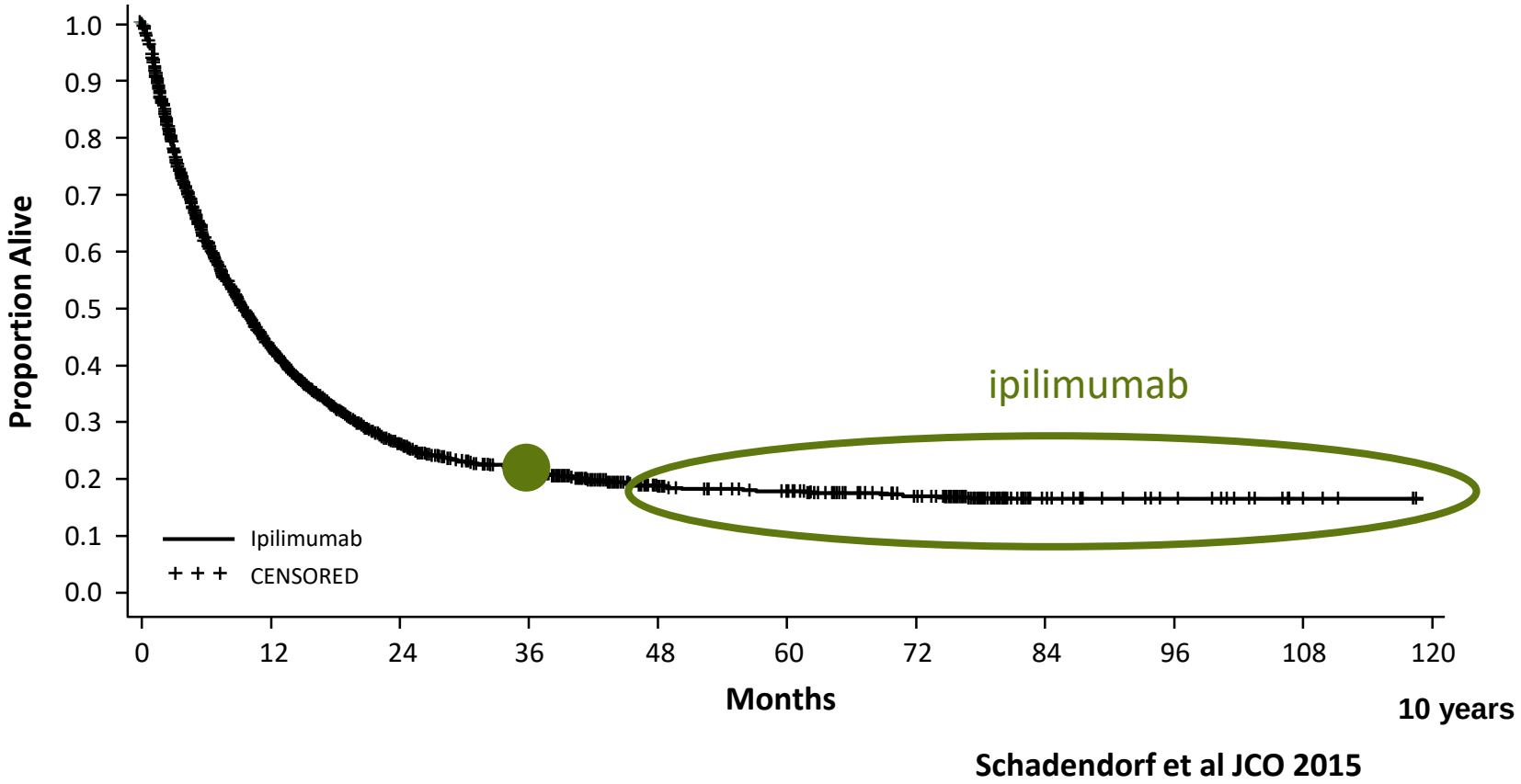
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



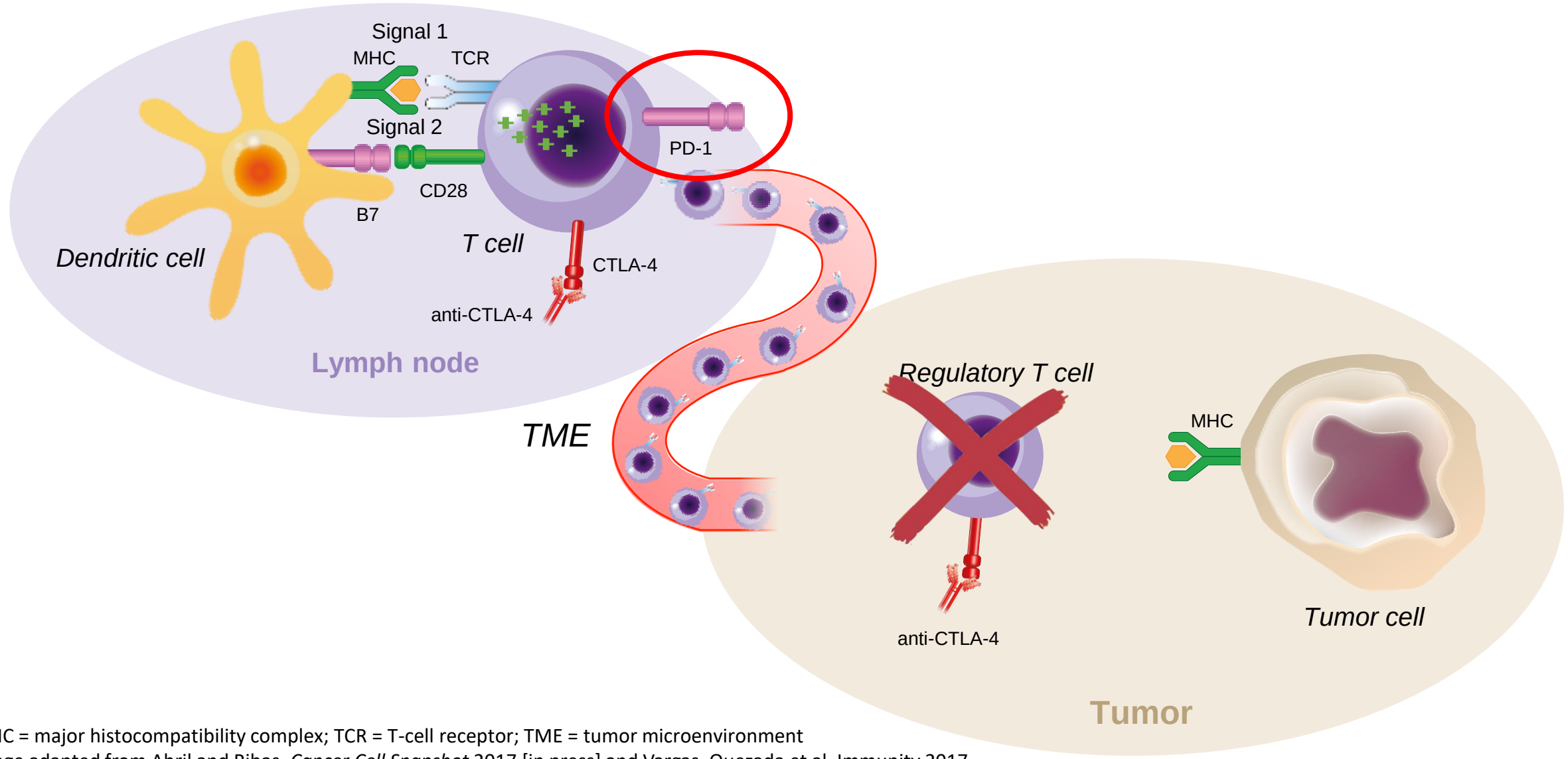
Hodi, Haanen, et al., NEJM 2010

Long-term benefit or even possibly cure from CTLA-4 blockade in melanoma



Schadendorf et al JCO 2015

Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action



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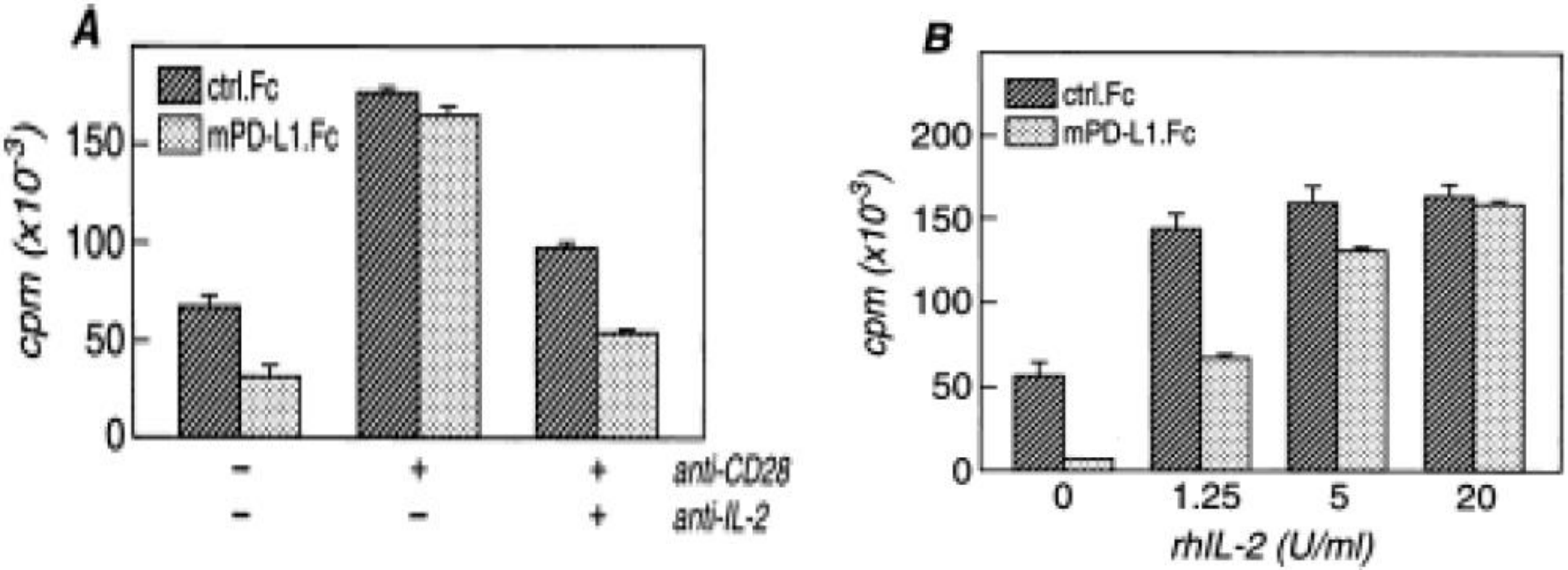
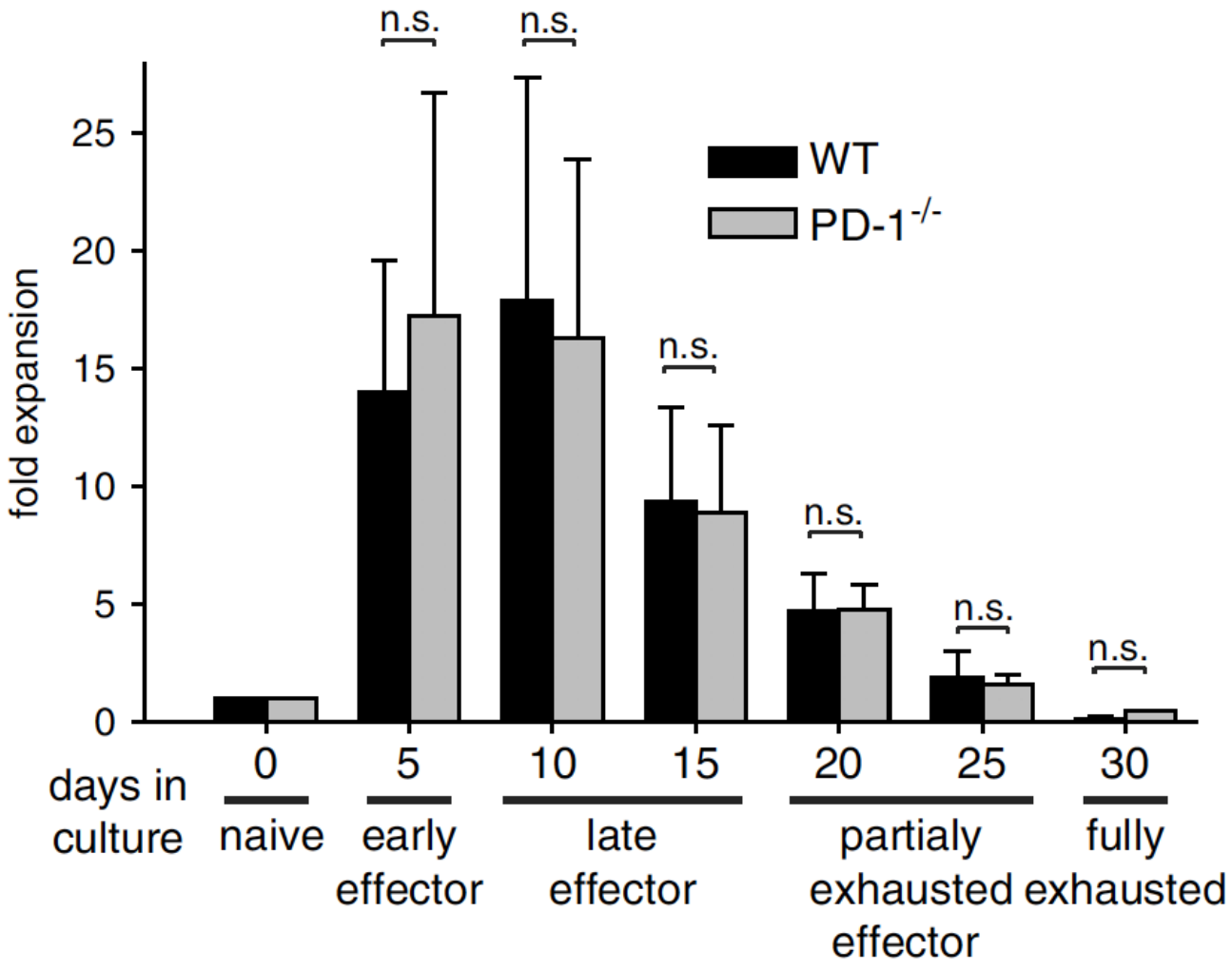
PD-L1 is not a negative prognosticator in melanoma



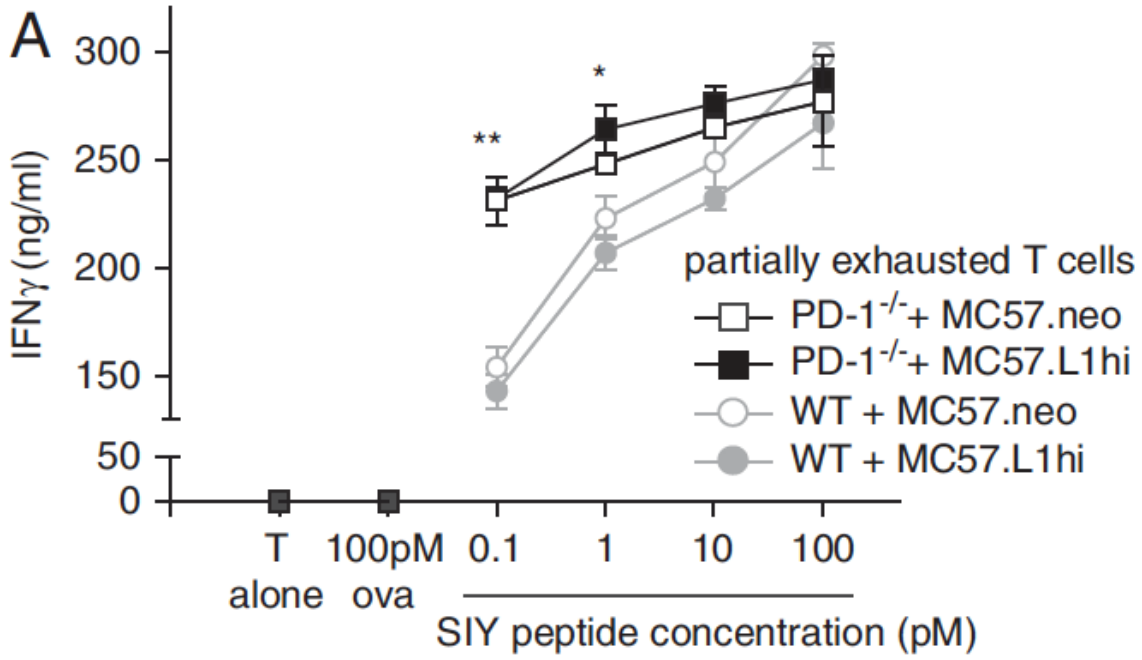
Carter et al., EJC 2002

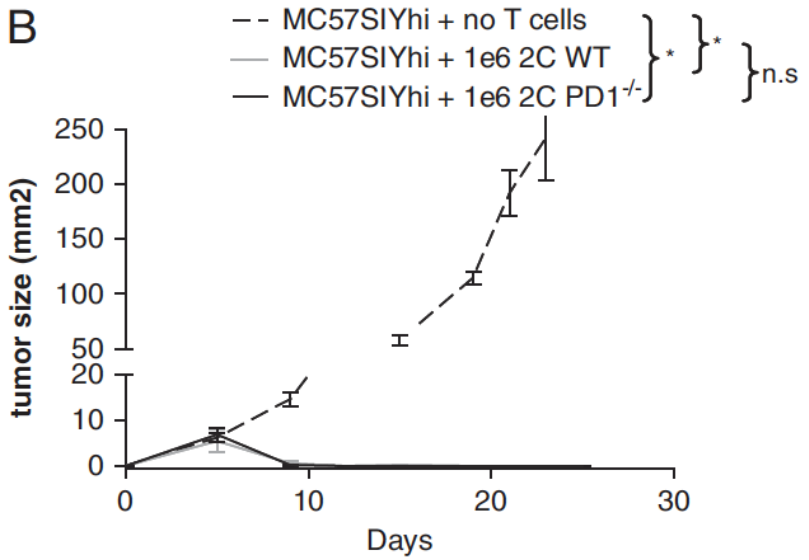
During optimal stimulation PD-1 signals are irrelevant

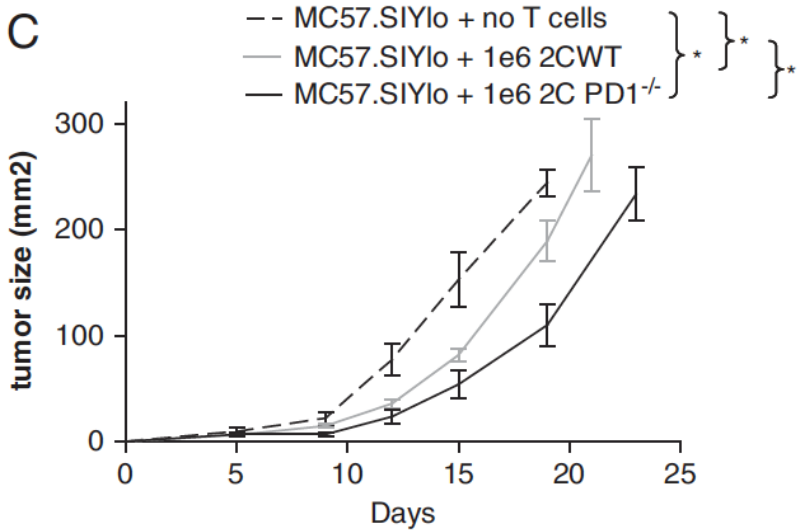


Kaiser, Blank, et al.
EJI 2012

Low tumor antigen density sensitizes for PD-1 signals

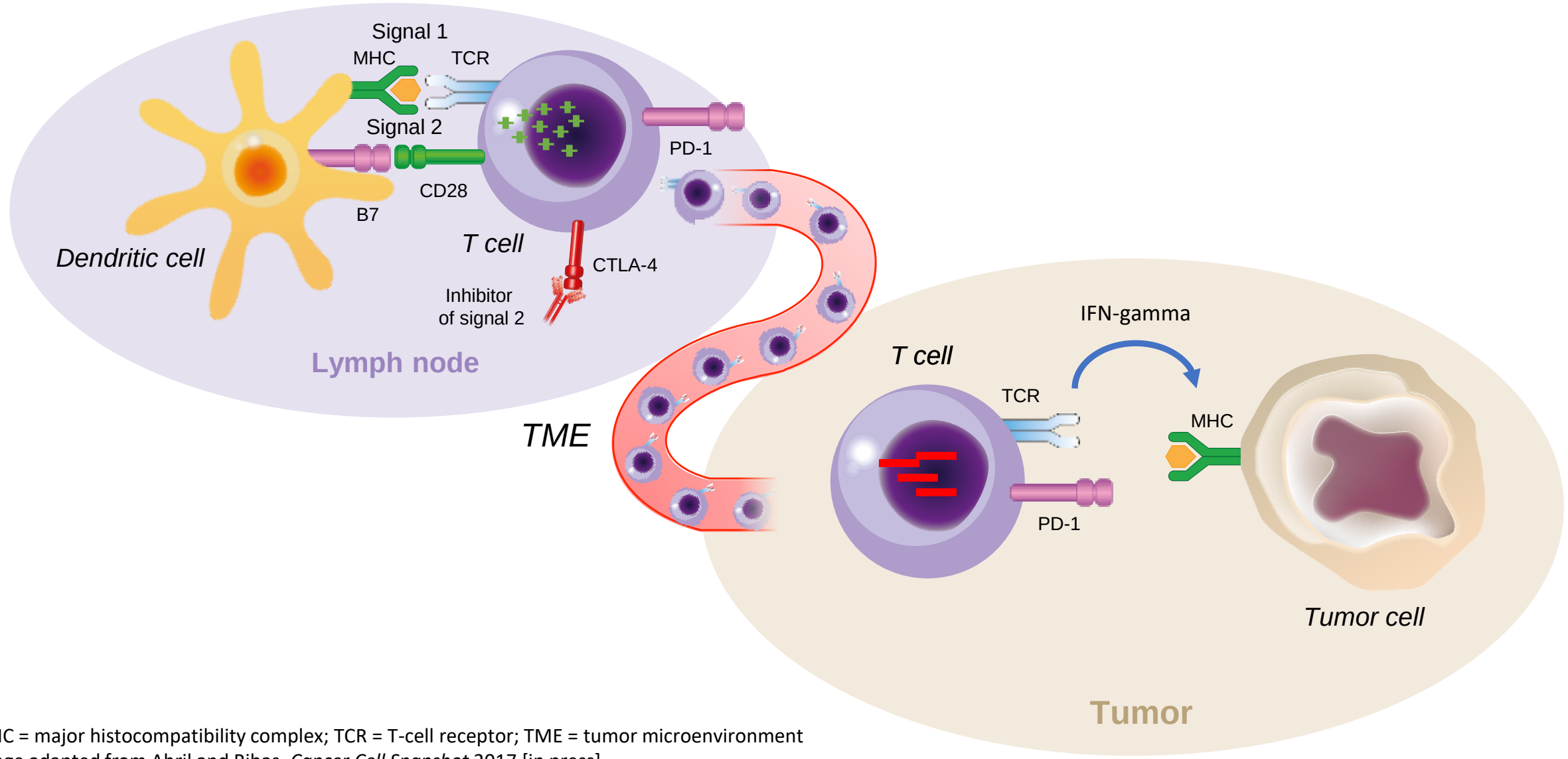






Kaiser, Blank, et al.
EJI 2012

Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action



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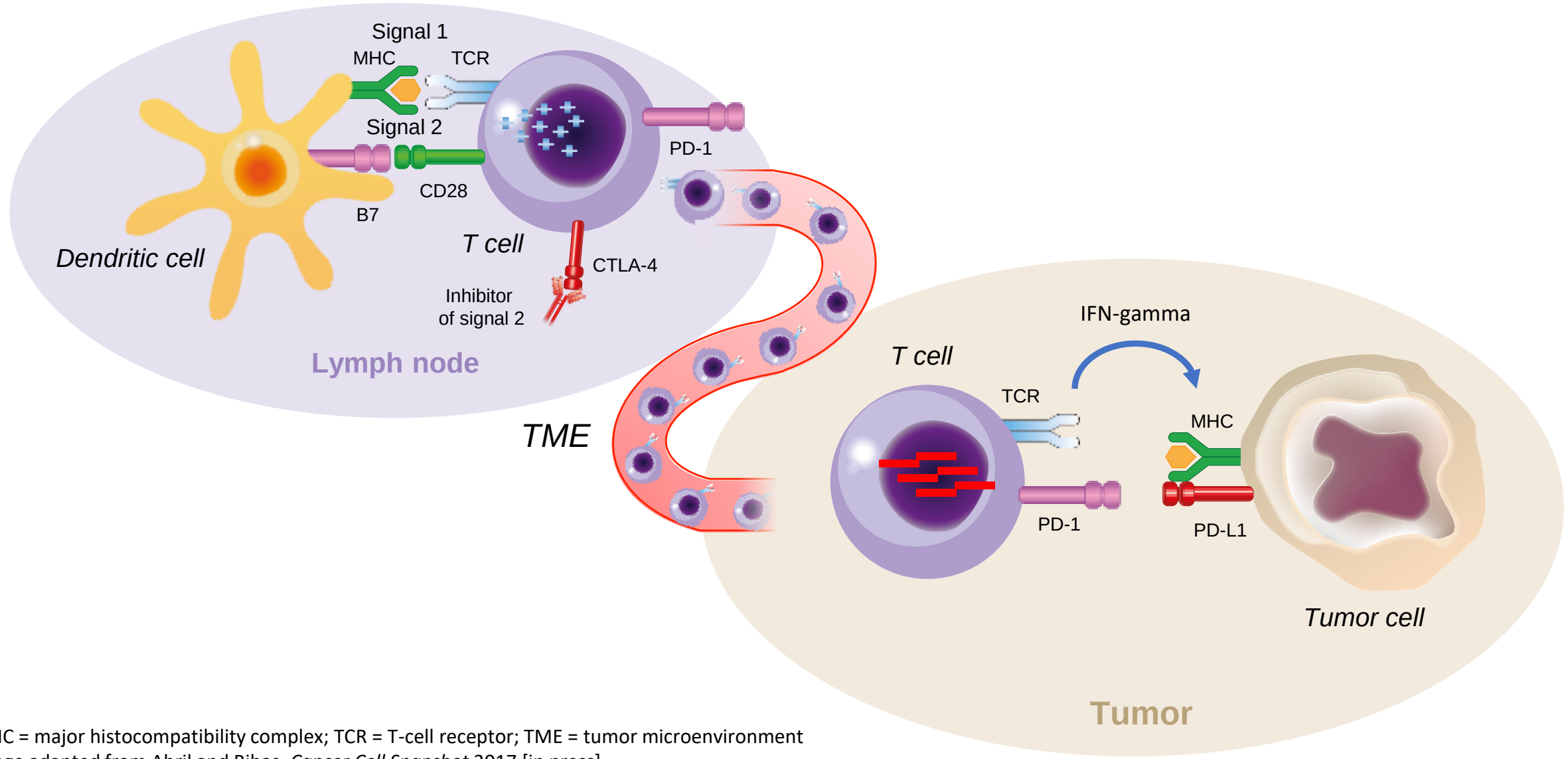

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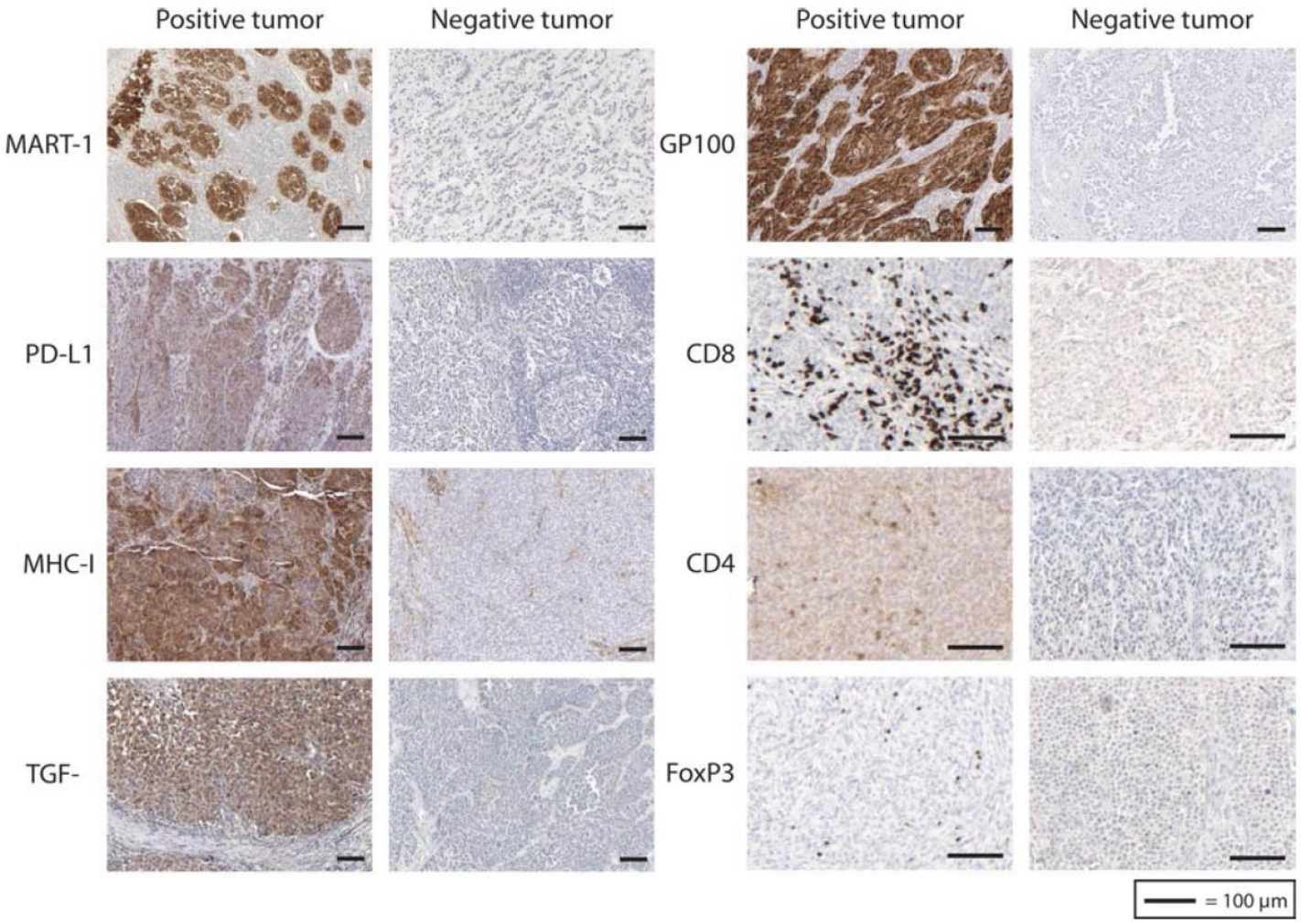
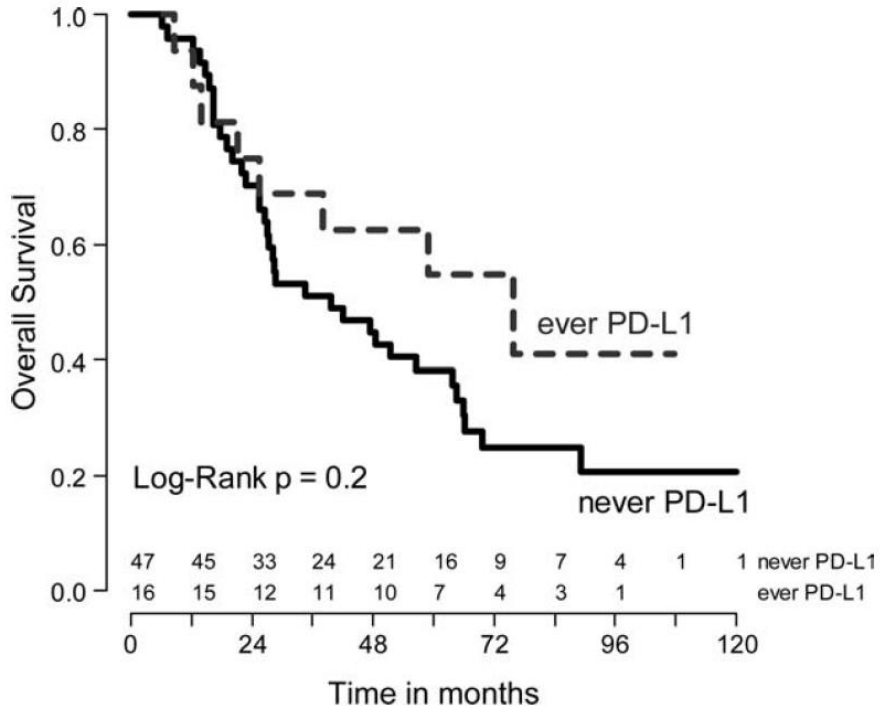
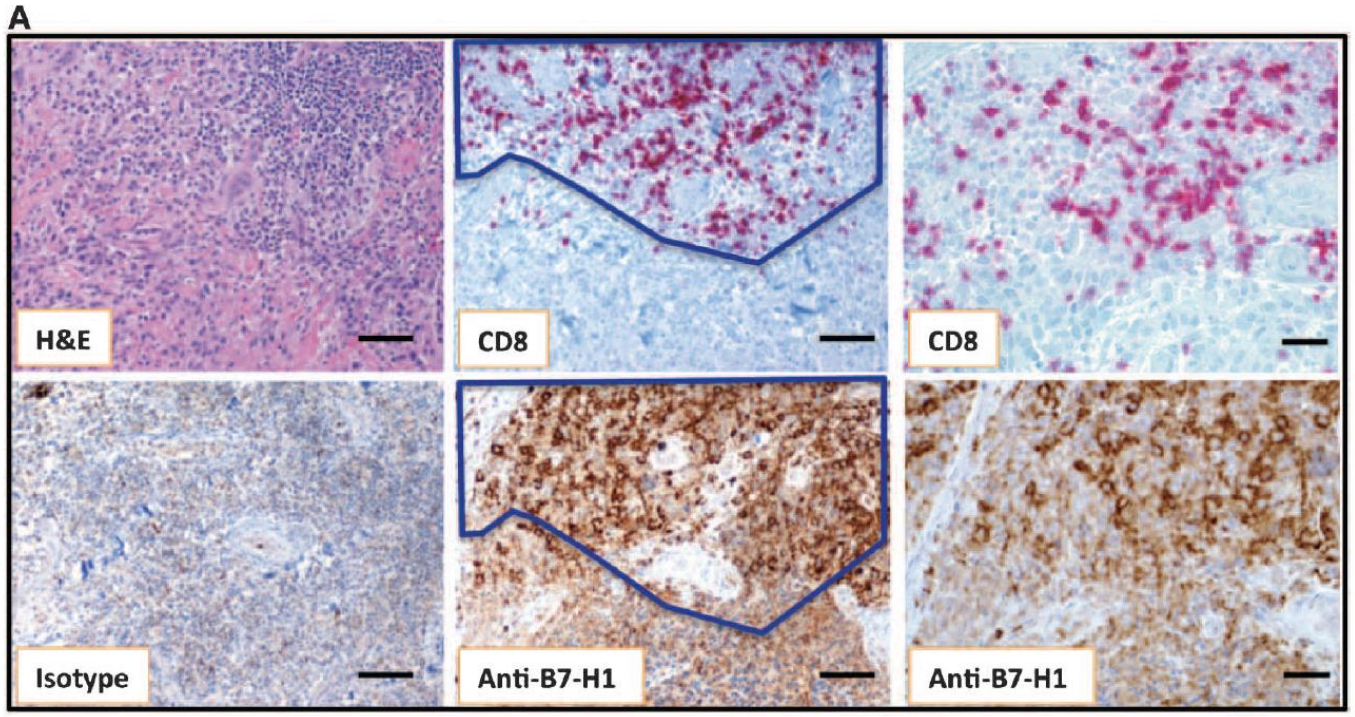
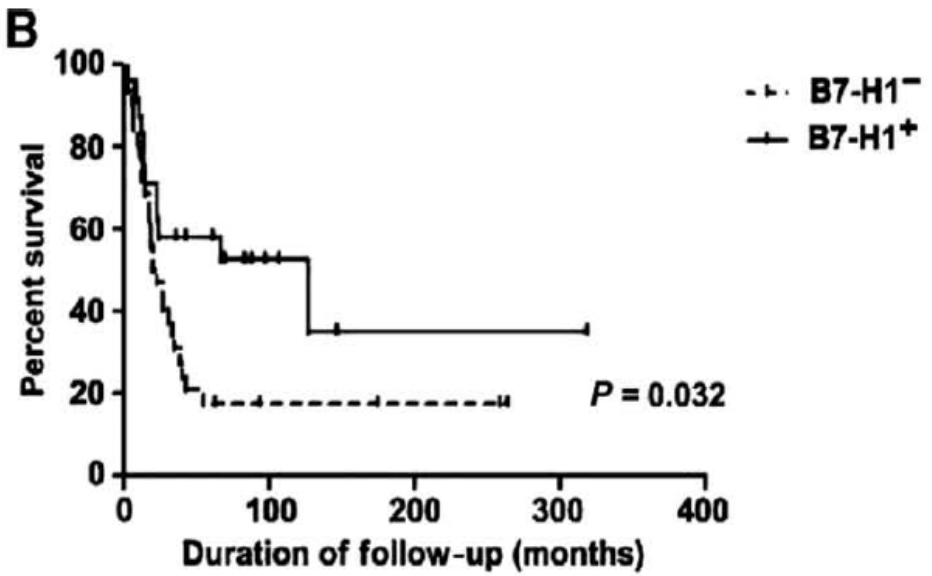




Gadiot, Blank, et al., Cancer 2011

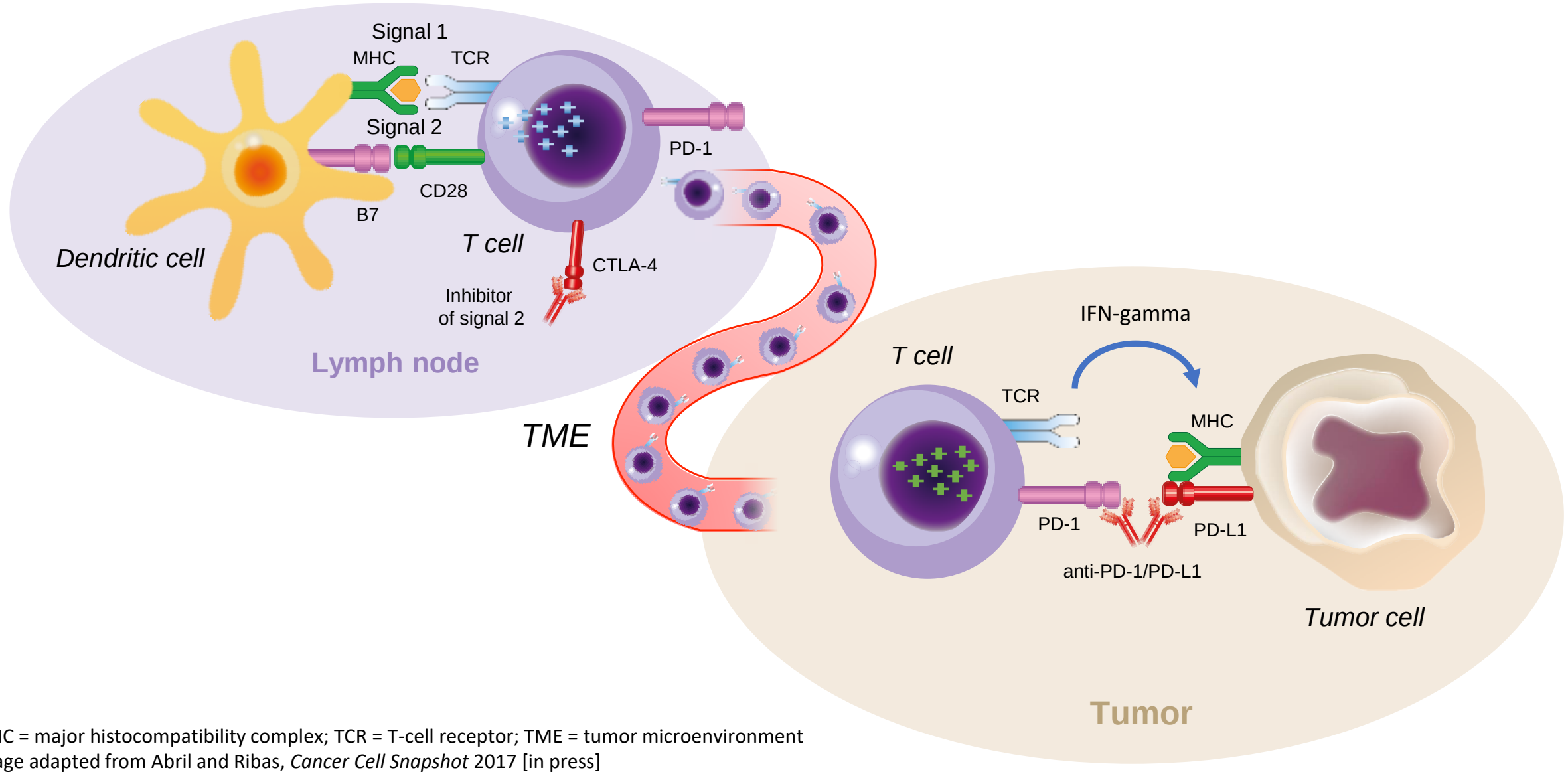
Interferon-producing tumor-infiltrating CD8 T cells induce PD-L1 upregulation – the concept of adaptive immune resistance





Taube et al., STM 2012

Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action



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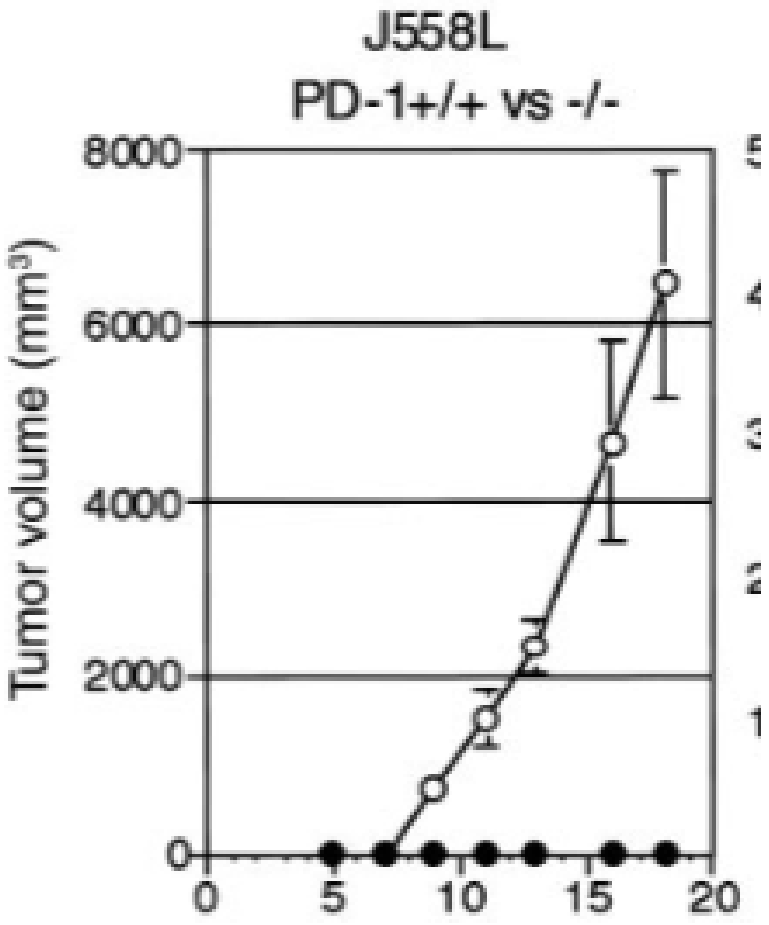
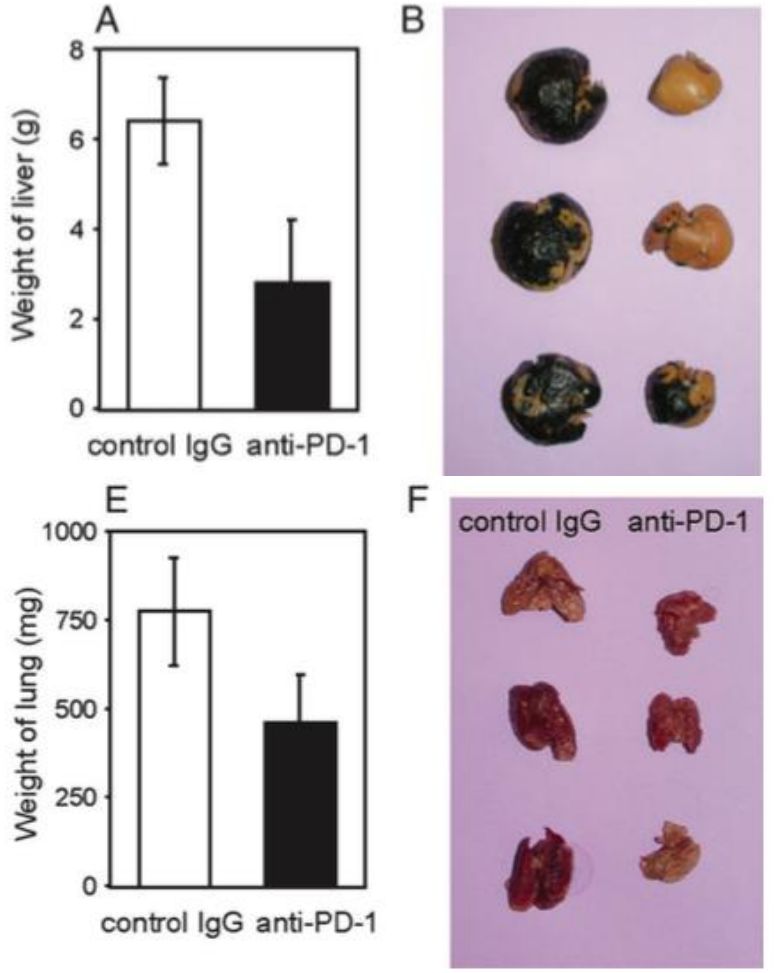
Absence of PD-1 or anti-PD-1 improves tumor control of murine myeloma, melanoma, and colon carcinoma

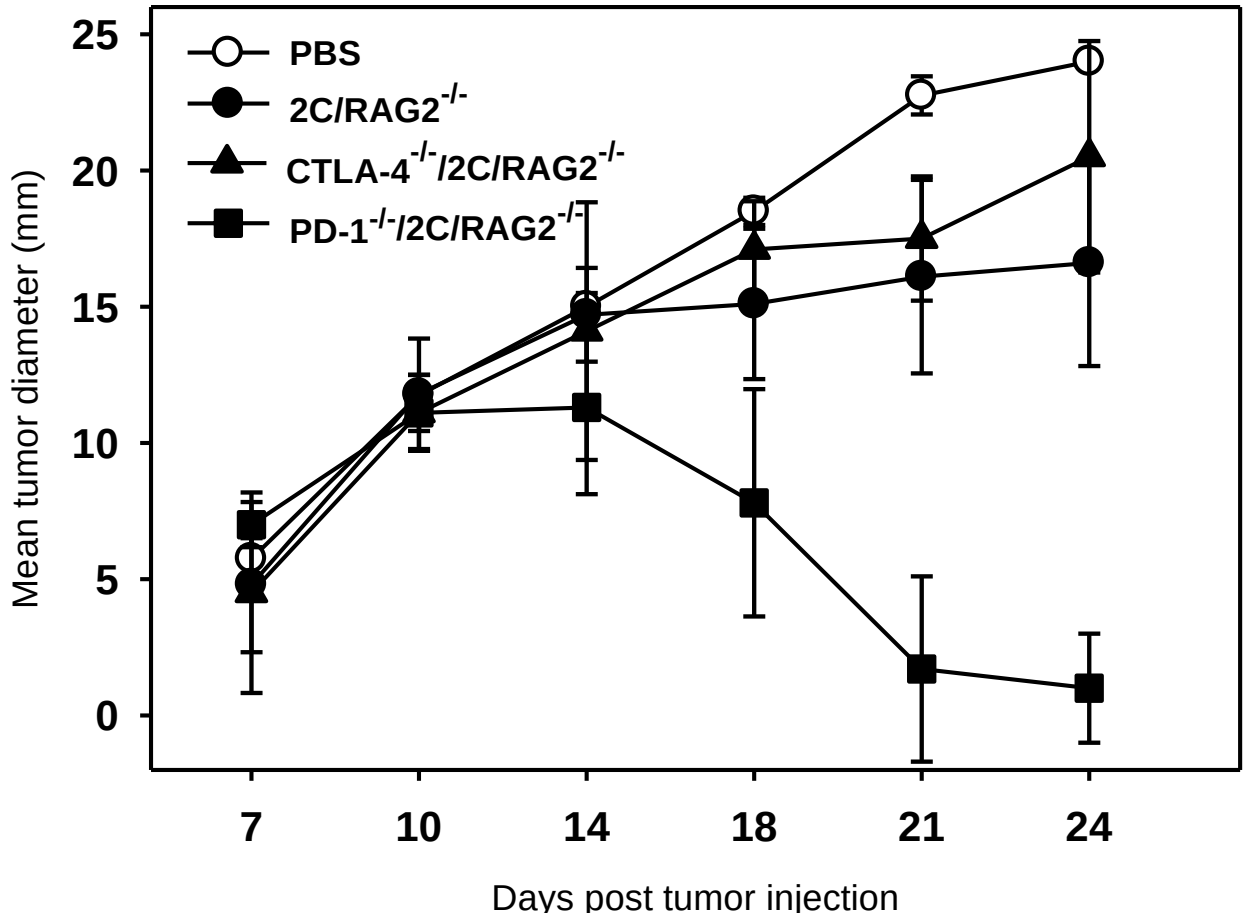


Iwai, Honjo et al.
PNAS 2002



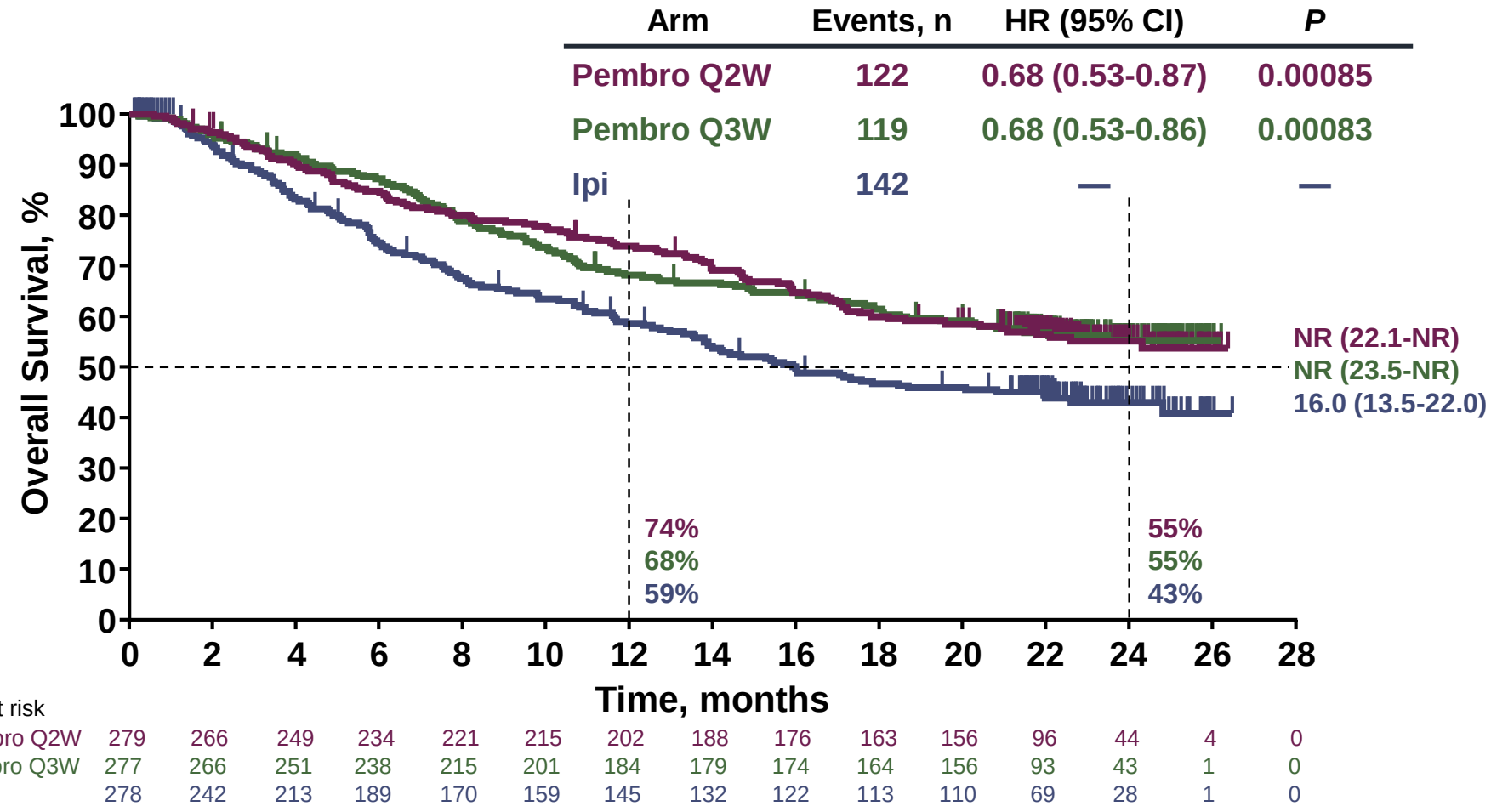
Iwai, Honjo et al.
Int Immunol 2005

Blockade of PD-L1/PD-1 interaction improves tumor control in mouse melanoma and is superior to anti-CTLA-4



Blank, Gajewski, et al. Cancer Res 2004

KEYNOTE-006: PD-1 blockade is superior to CTLA-4 blockade



Schachter J et al. Presented at ASCO 2016; Jun 2-7, 2016; Chicago, IL. Abstr. 9504.

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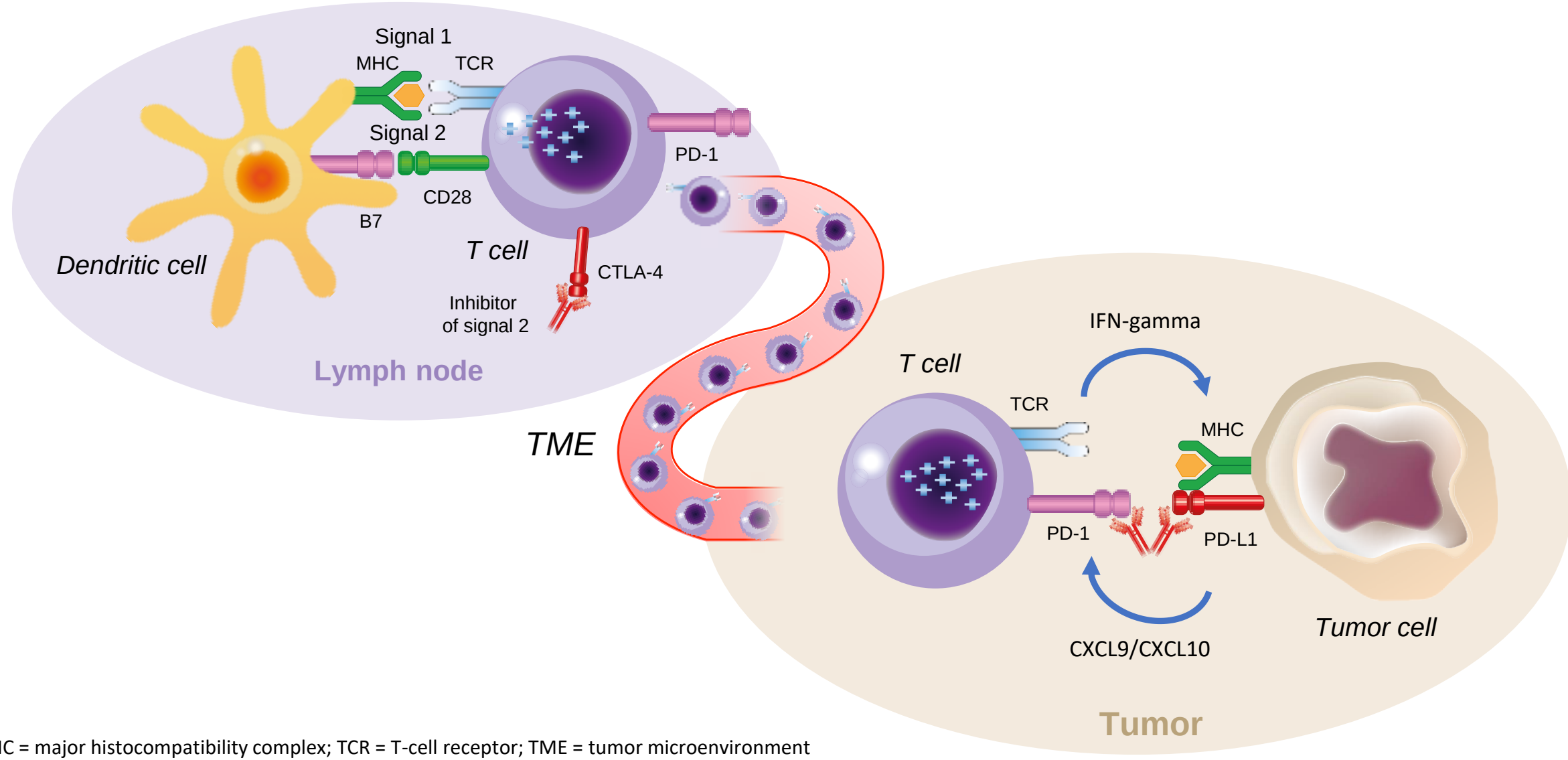

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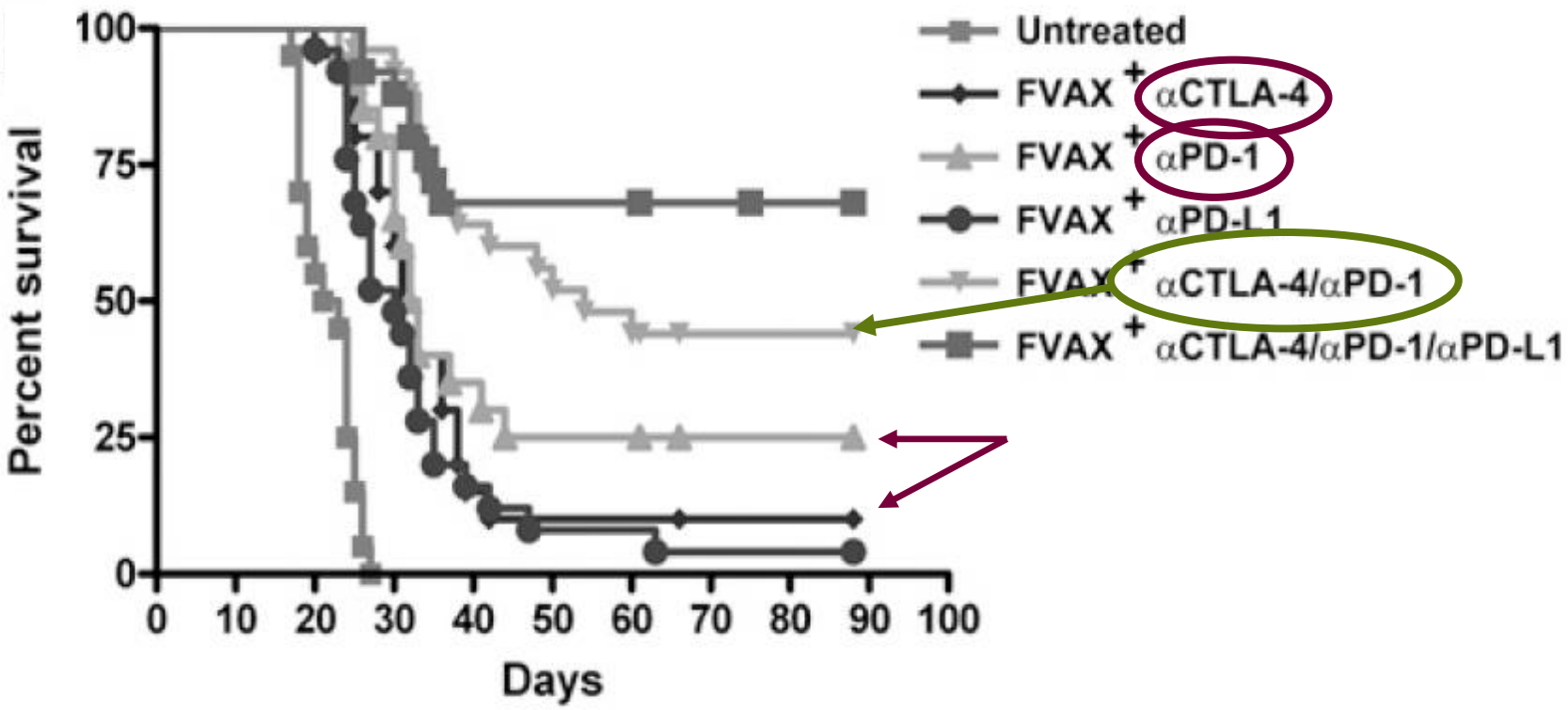
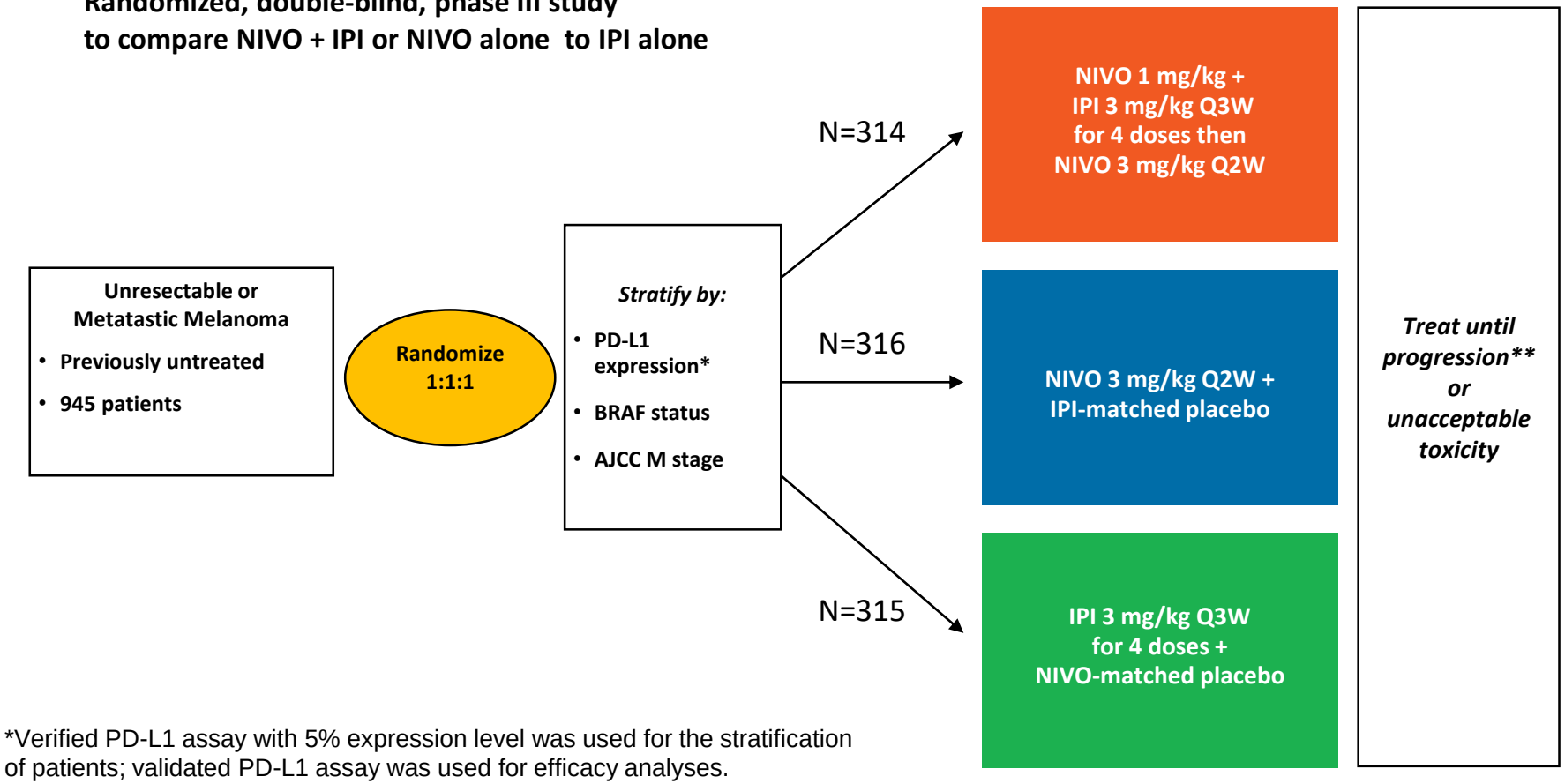
Combining PD-1 and CTLA-4 blockade improves tumor control further



Curran et al., PNAS 2010

PD-1+CTLA-4 blockade versusCTLA-4 blockade (Nivolumab + Ipilimumab vs Ipilimumab, Checkmate 067)

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



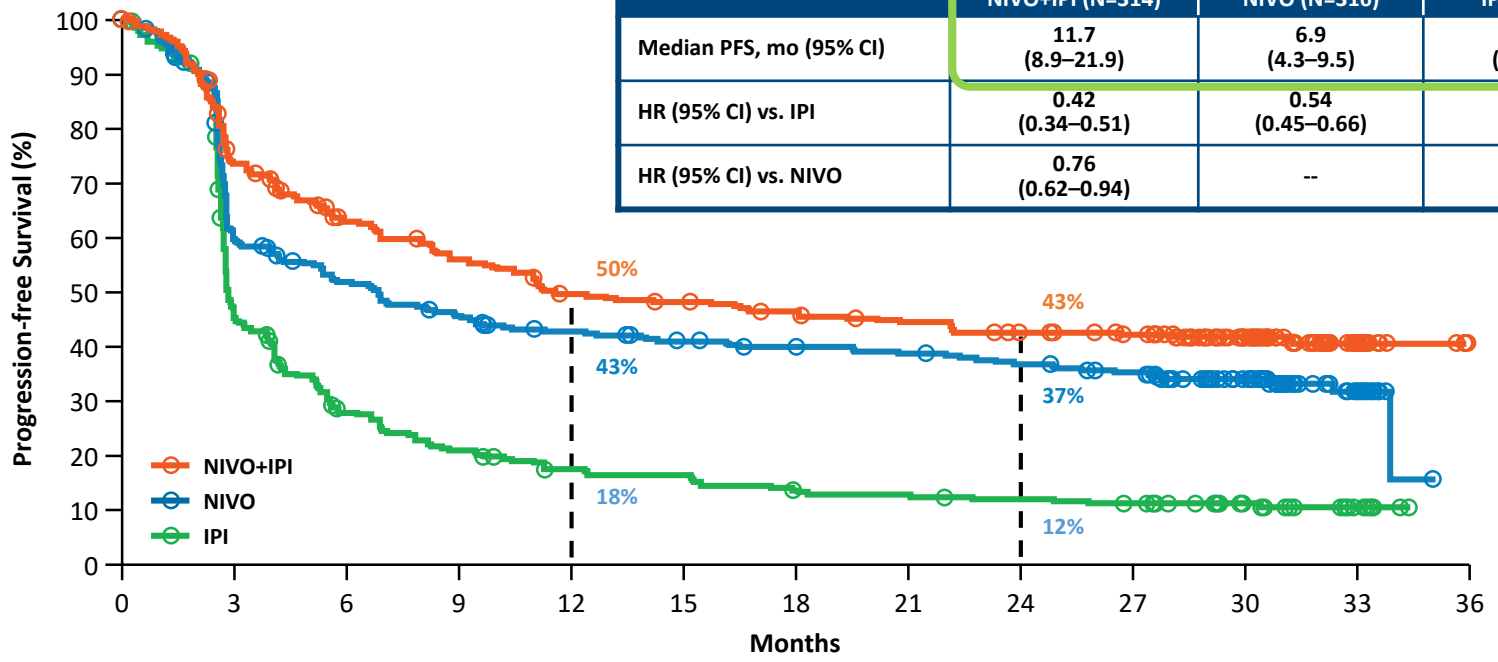
*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

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

Wolchok et al., ASCO 2015

Updated Progression-Free Survival 067 study

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, mo (95% CI)	11.7 (8.9–21.9)	6.9 (4.3–9.5)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.42 (0.34–0.51)	0.54 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.76 (0.62–0.94)	--	--



Patients at risk:

NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

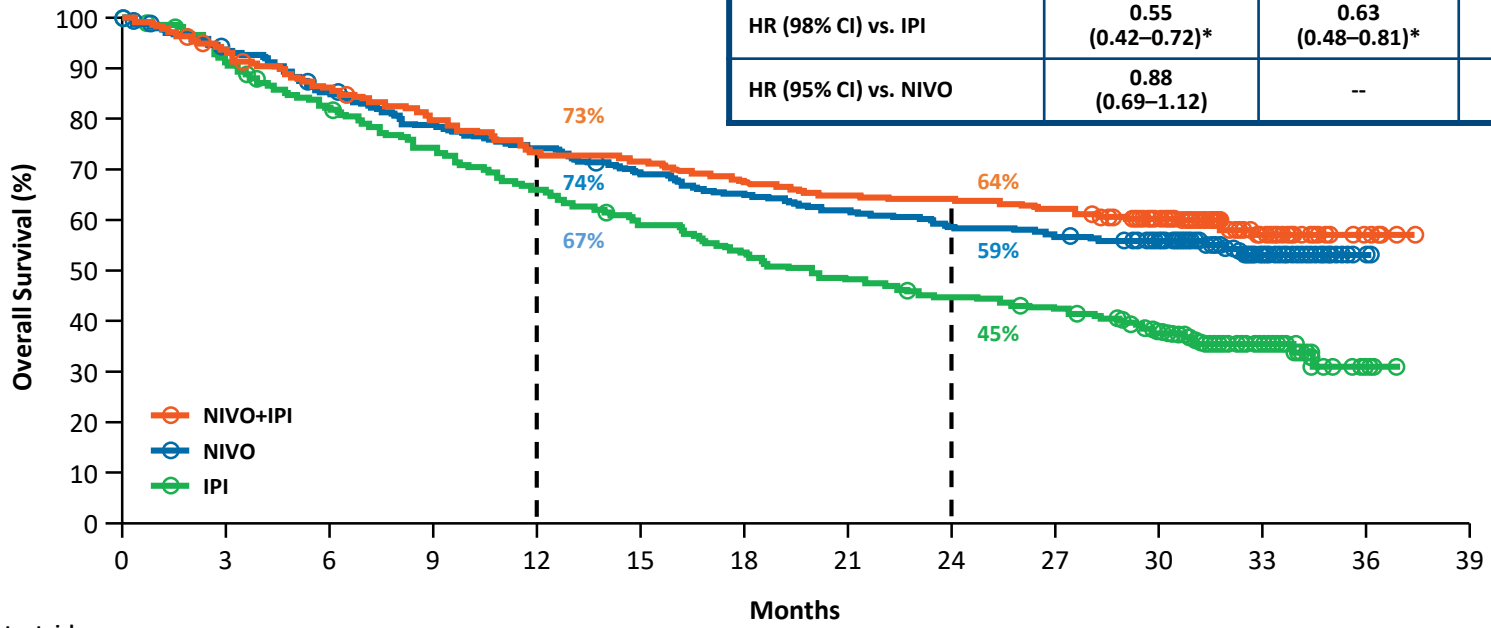
Database lock: Sept 13, 2016, minimum f/u of 28 months

Larkin et al., AACR 2017

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

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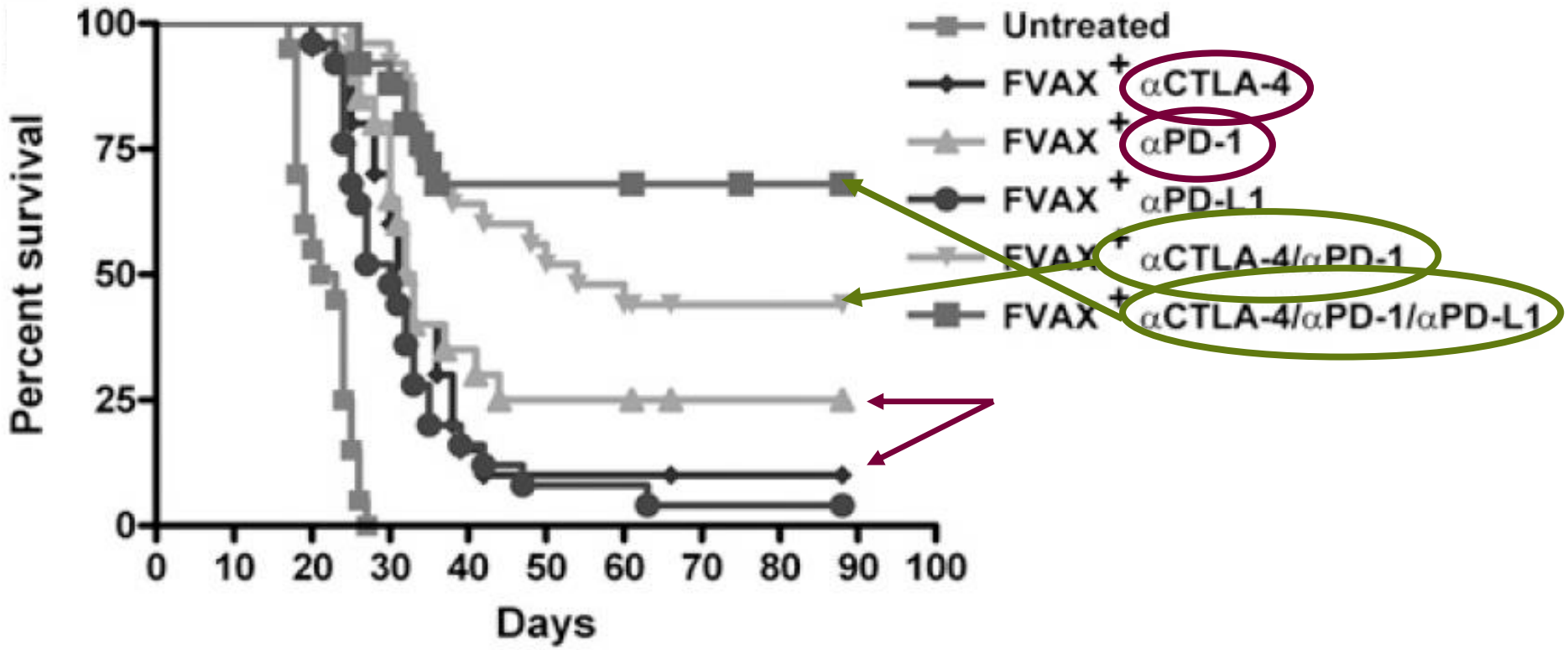
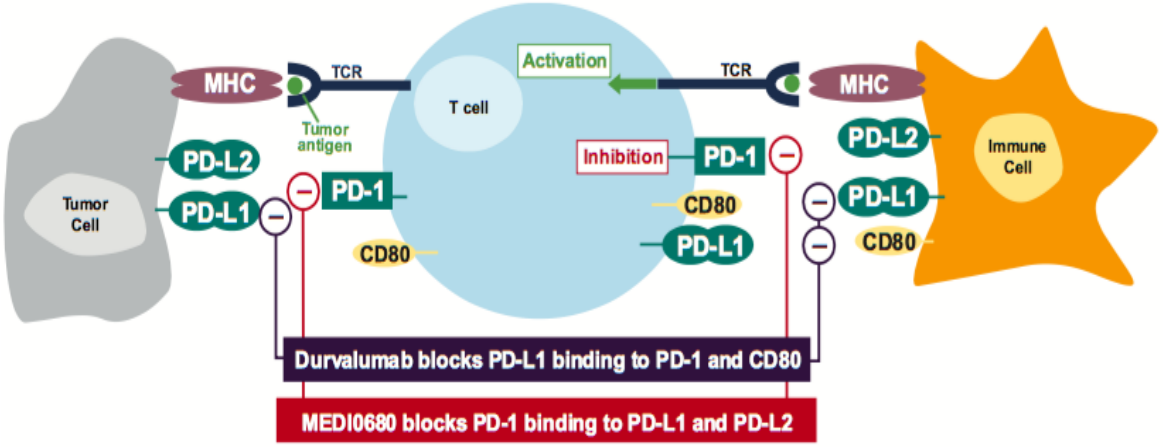
Larkin et al., AACR 2017

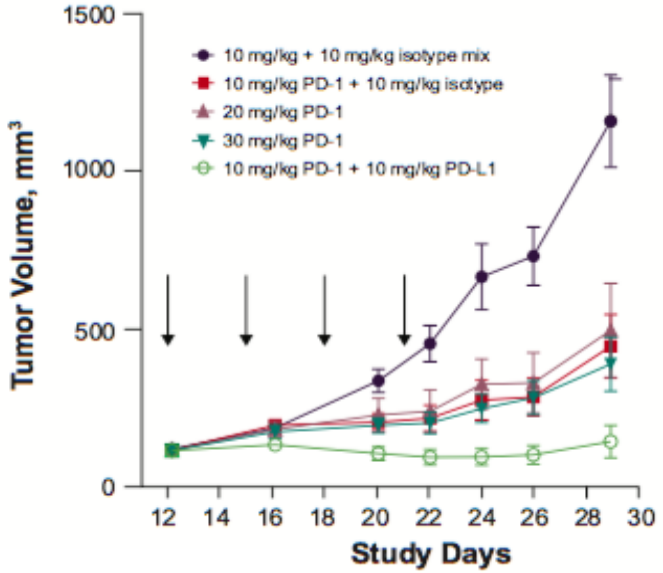
Combining PD-1 and PD-L1 and CTLA-4 blockade improves tumor control further

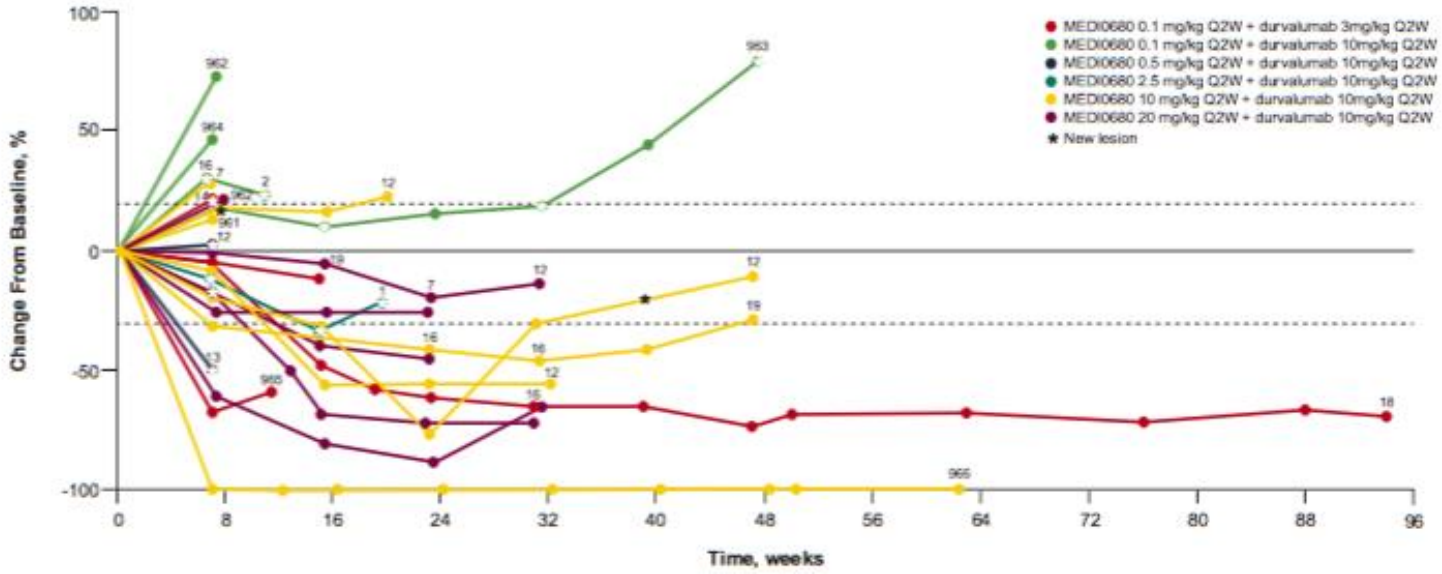


Curran et al., PNAS 2010

Combining PD-1 and PD-L1







Hamid et al., ESMO 2016

PD-1 and CTLA-4 are not alone

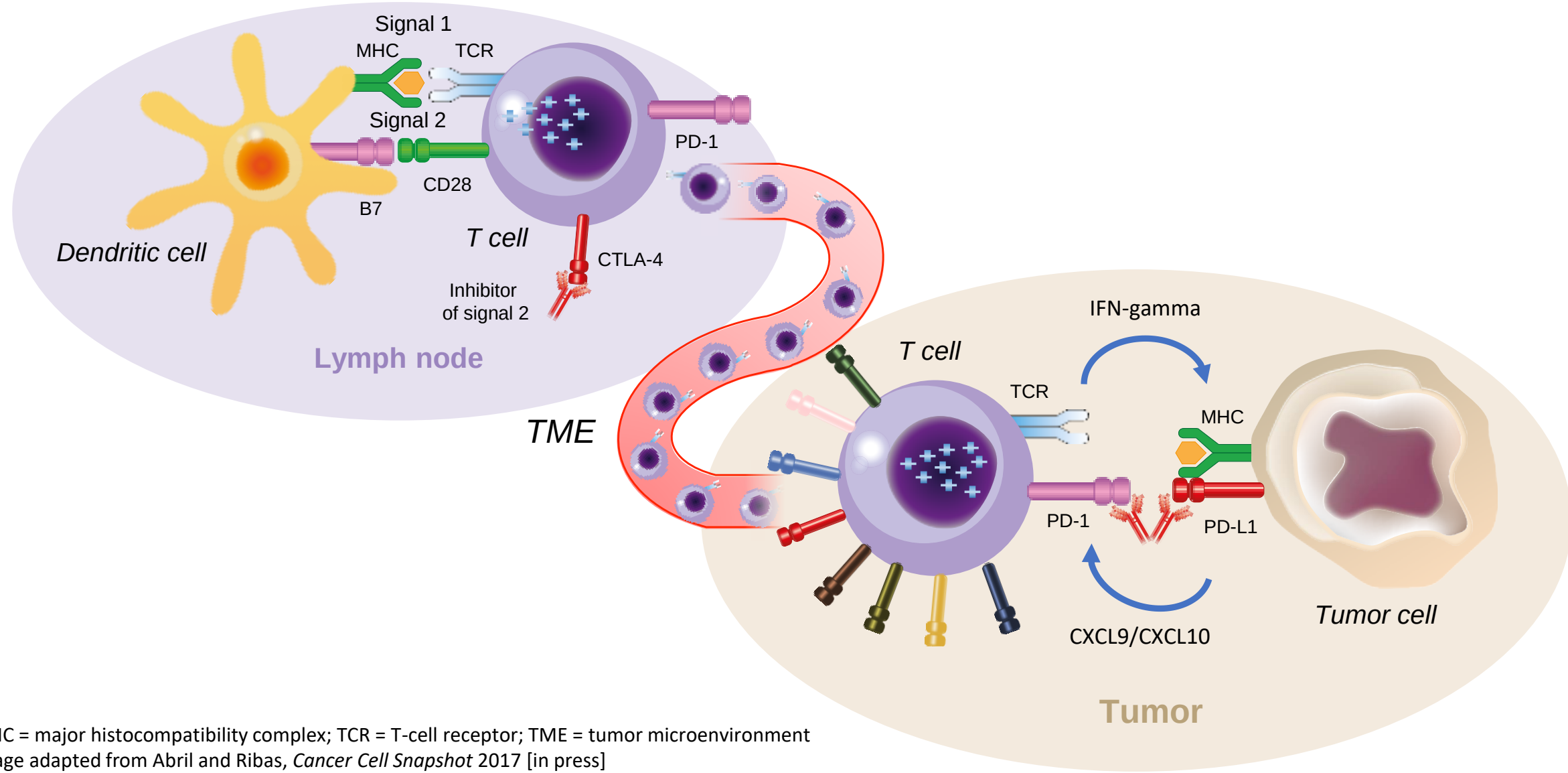


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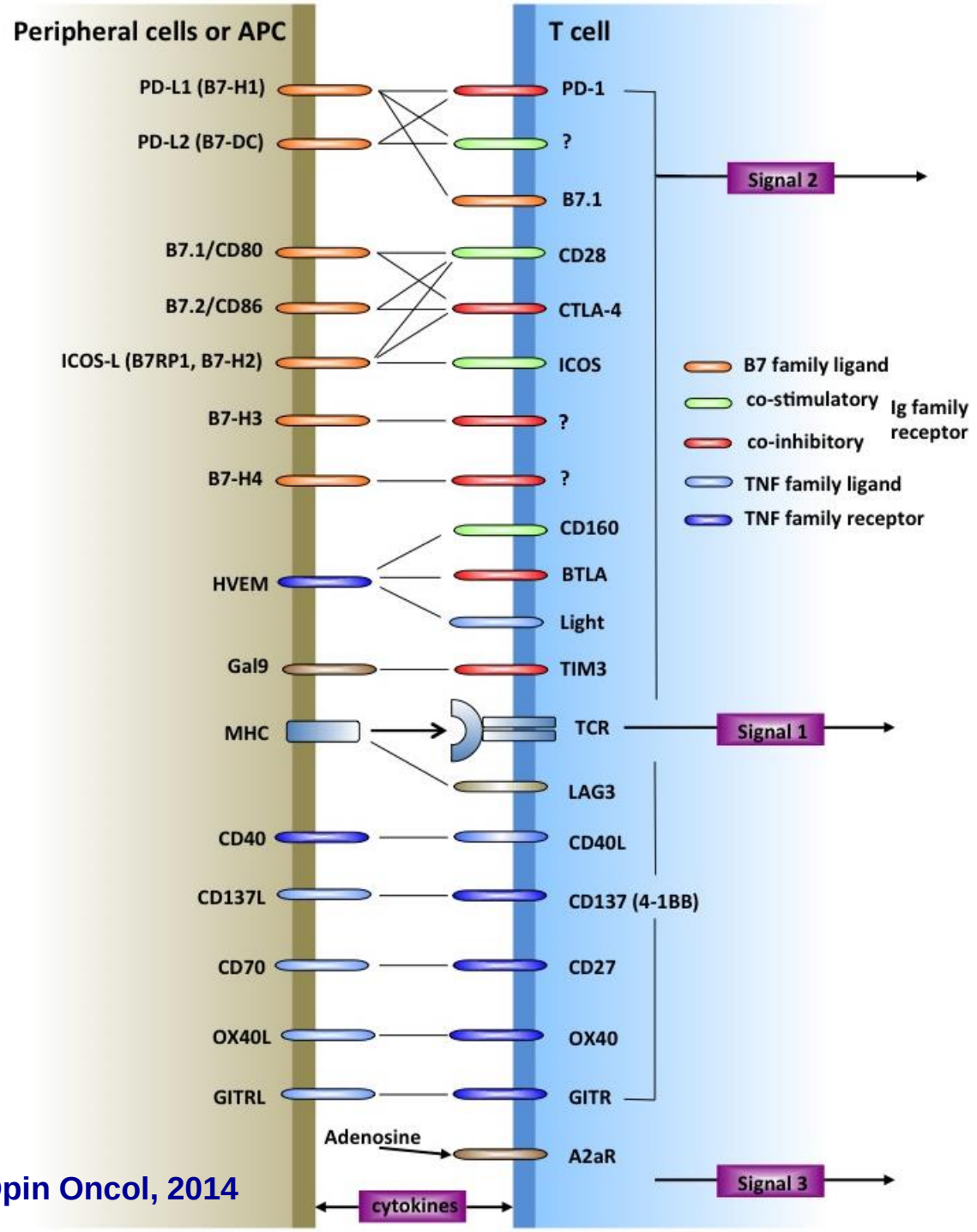
Image adapted from Abril and Ribas, *Cancer Cell Snapshot* 2017 [in press]

Checkpoint modulation is an orchestra of stimulatory and inhibitory signals.

And against all are currently mAbs developed.



Blank, Curr Opin Oncol, 2014

Postscript: Writing After Conceptual Art

Museum Of Contemporary Art Denver, October 2012 – February 2013
http://mcadenver.org/postscript.php

Anti-CTLA-4 broadens anti-tumor T cell repertoire of very low percentages of tumor-specific T cells

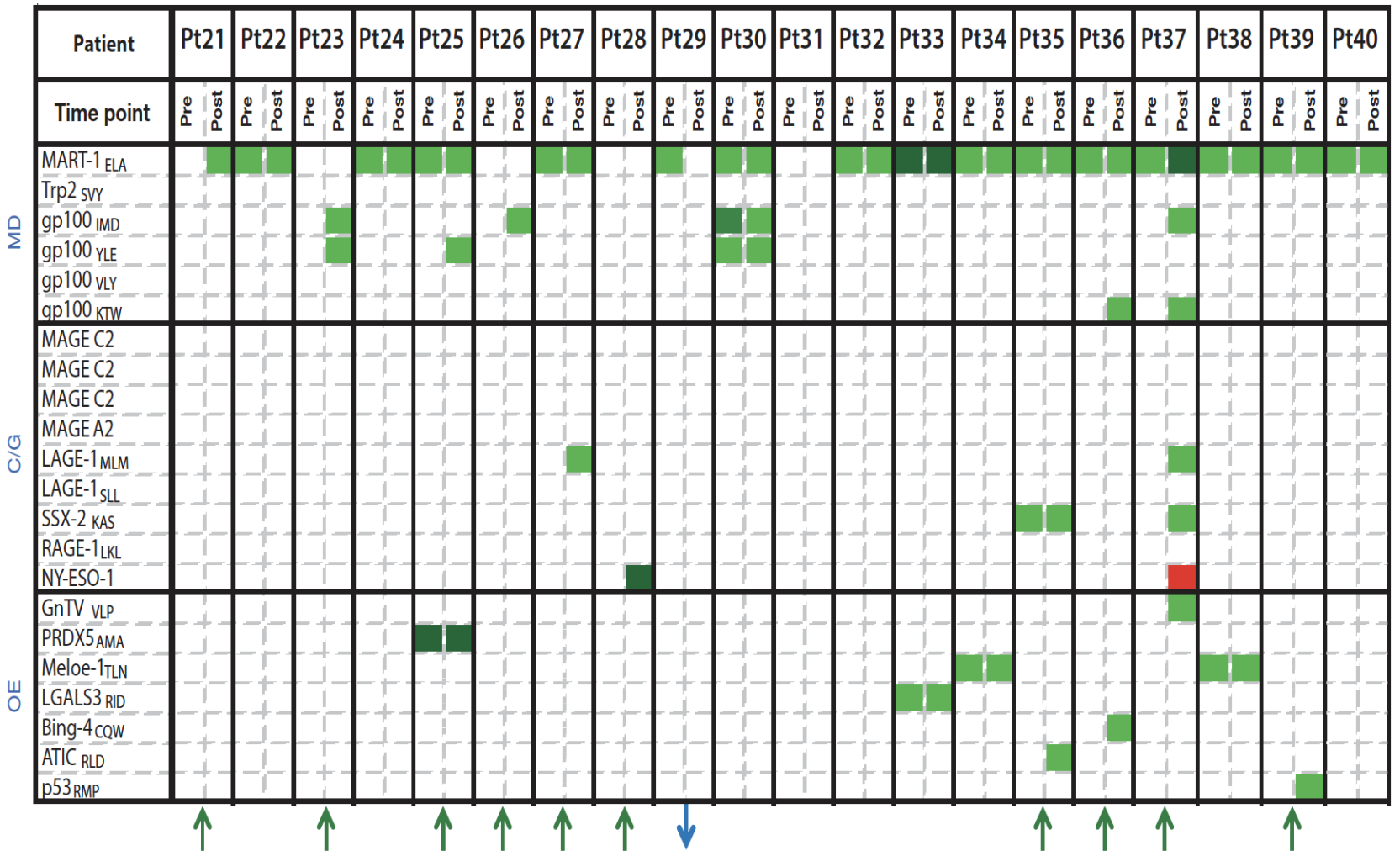
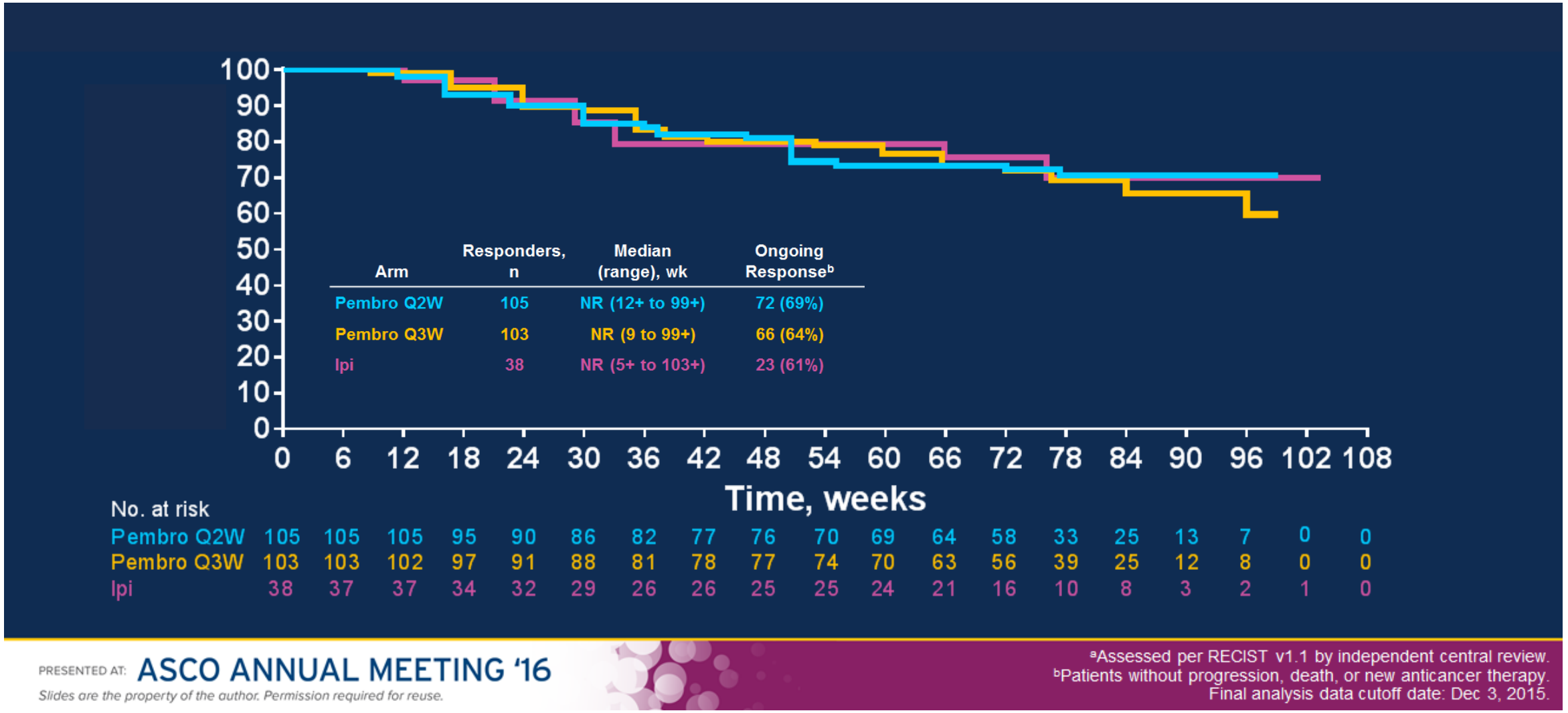


Fig. 3. Anti–CTLA-4 therapy selectively induces novel melanoma-reactive CD8 T cell responses. Heat map summarizing all melanoma-reactive T cell responses detected within this sample set, with the color scale indicating response magnitude pre- and posttherapy. Color code: light green, 0.005 to 0.099%; dark green, 0.1 to 0.99%; orange, 1.00 to 4.99%; and red, >4.99% pMHC multimer$^+$ CD8$^+$ of total CD8$^+$ cells. Only those epitopes against which reactivity was detected in at least one sample are shown.

Kvistborg, Blank, Schumacher et al. STM 2014

Duration of response upon checkpoint inhibition is independent of choice of treatment



PRESENTED AT: ASCO ANNUAL MEETING '16

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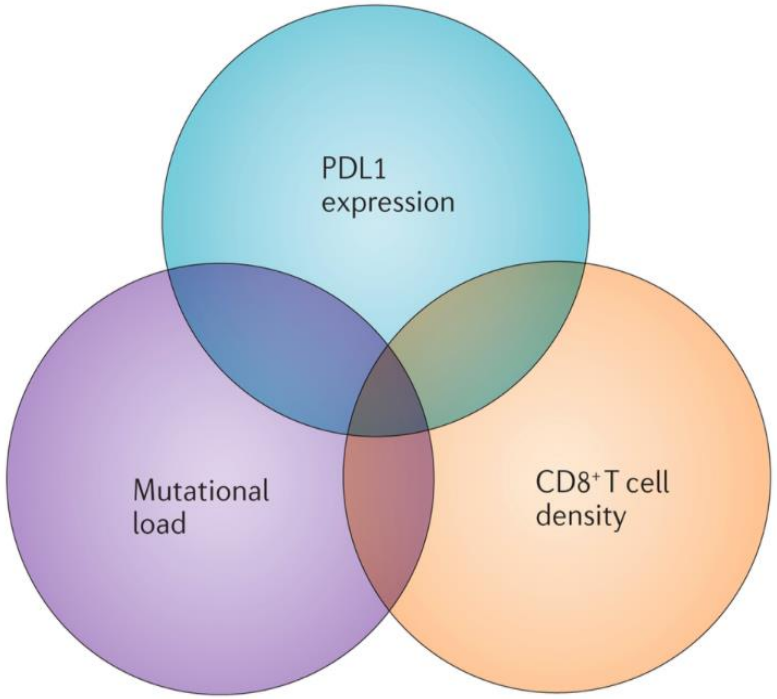
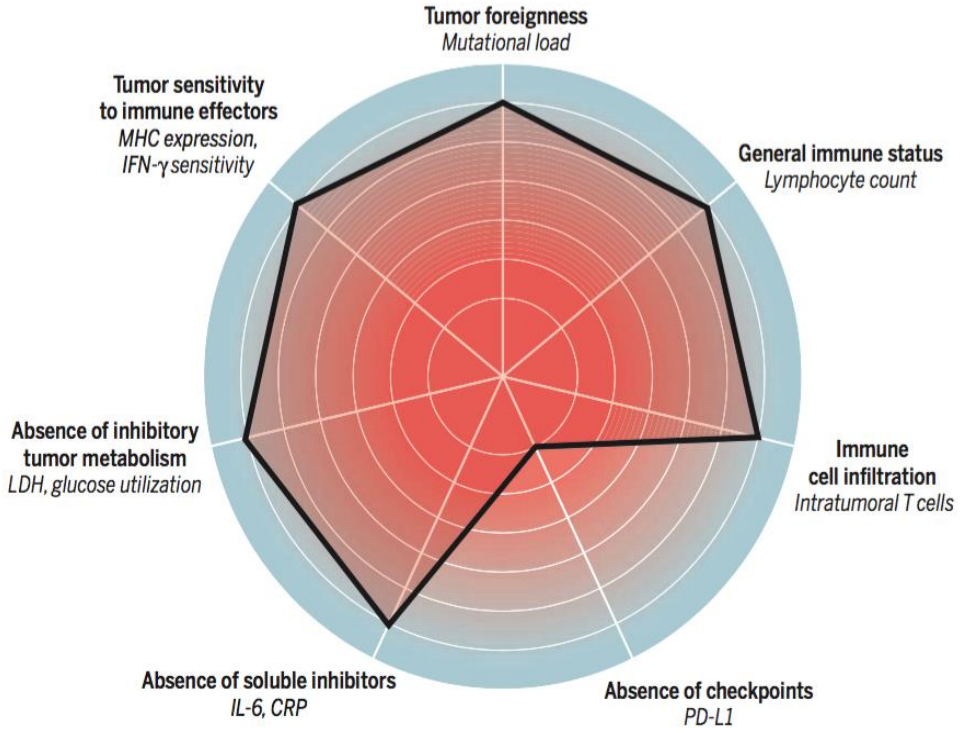
[a]Assessed per RECIST v1.1 by independent central review.
[b]Patients without progression, death, or new anticancer therapy.
Final analysis data cutoff date: Dec 3, 2015.

Schachter, et al. ASCO 2016

Is a single biomarker sufficient to identify long-term benefit?

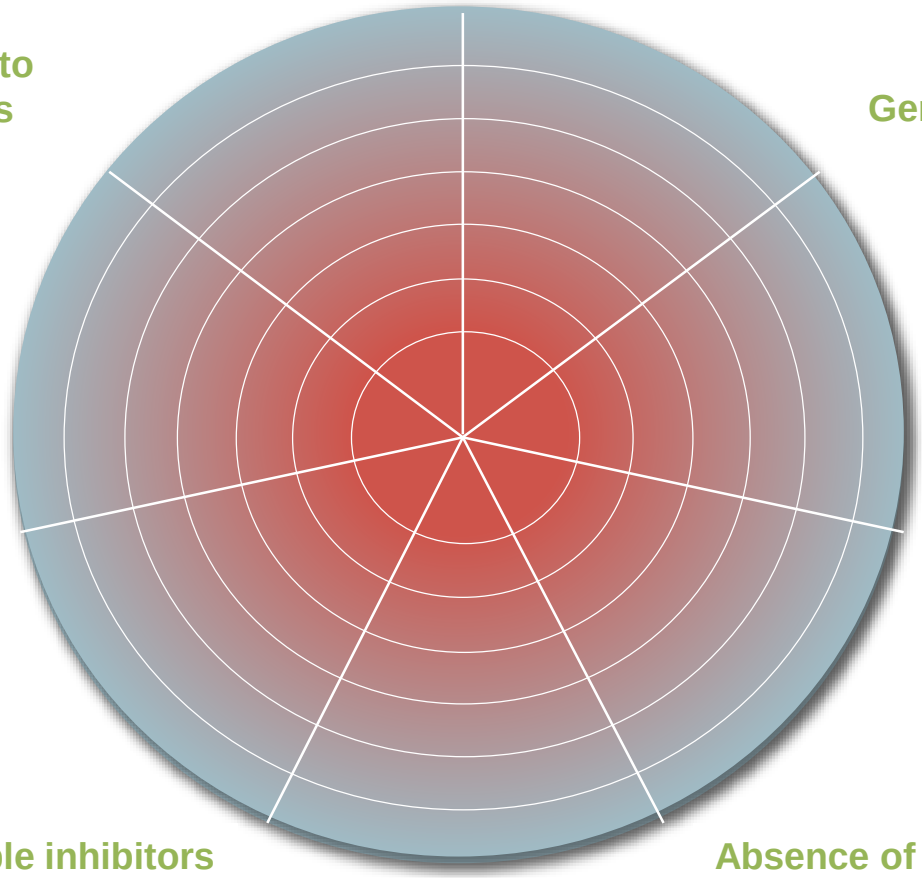


Topalian, Taube, Anders & Pardoll
Nature Reviews Cancer, 2016



Blank, Haanen, Ribas & Schumacher
Science, 2016

How to personalize Immunotherapy – The Cancer Immunogram



Tumor foreignness
Mutational load

Tumor sensitivity to immune effectors
MHC expression
IFN-γ sensitivity

General immune status
Lymphocyte count

Absence of inhibitory tumor metabolism
LDH, glucose utilization

Immune cell infiltration
Intratumoral T cells

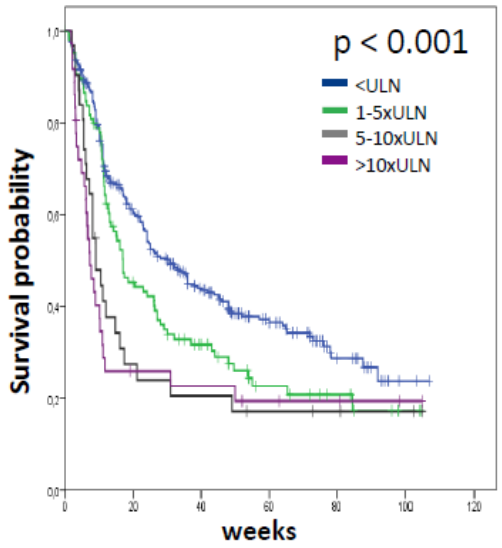
Absence of soluble inhibitors
IL6->CRP/ESR

Absence of Checkpoints
PD-L1

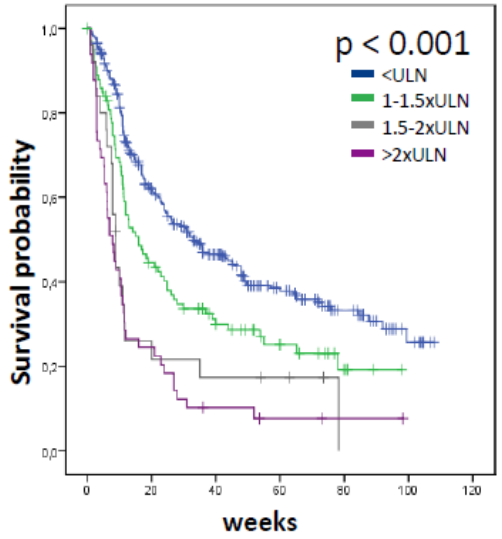
Blank, et al., Science 2016

CRP is aside LDH and ALC a strong parameter (European cohort, 500 patients)

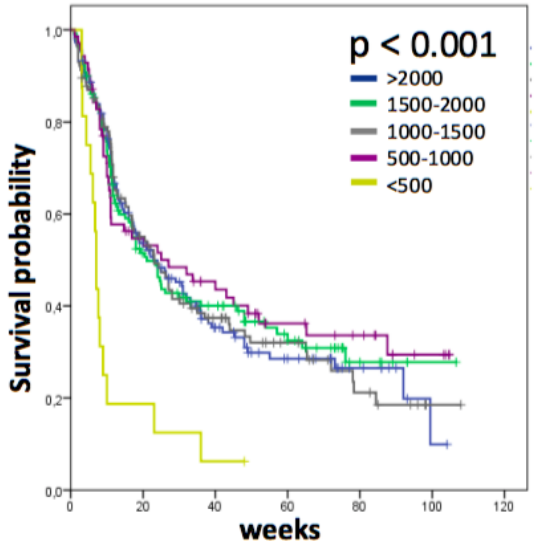
CRP



LDH



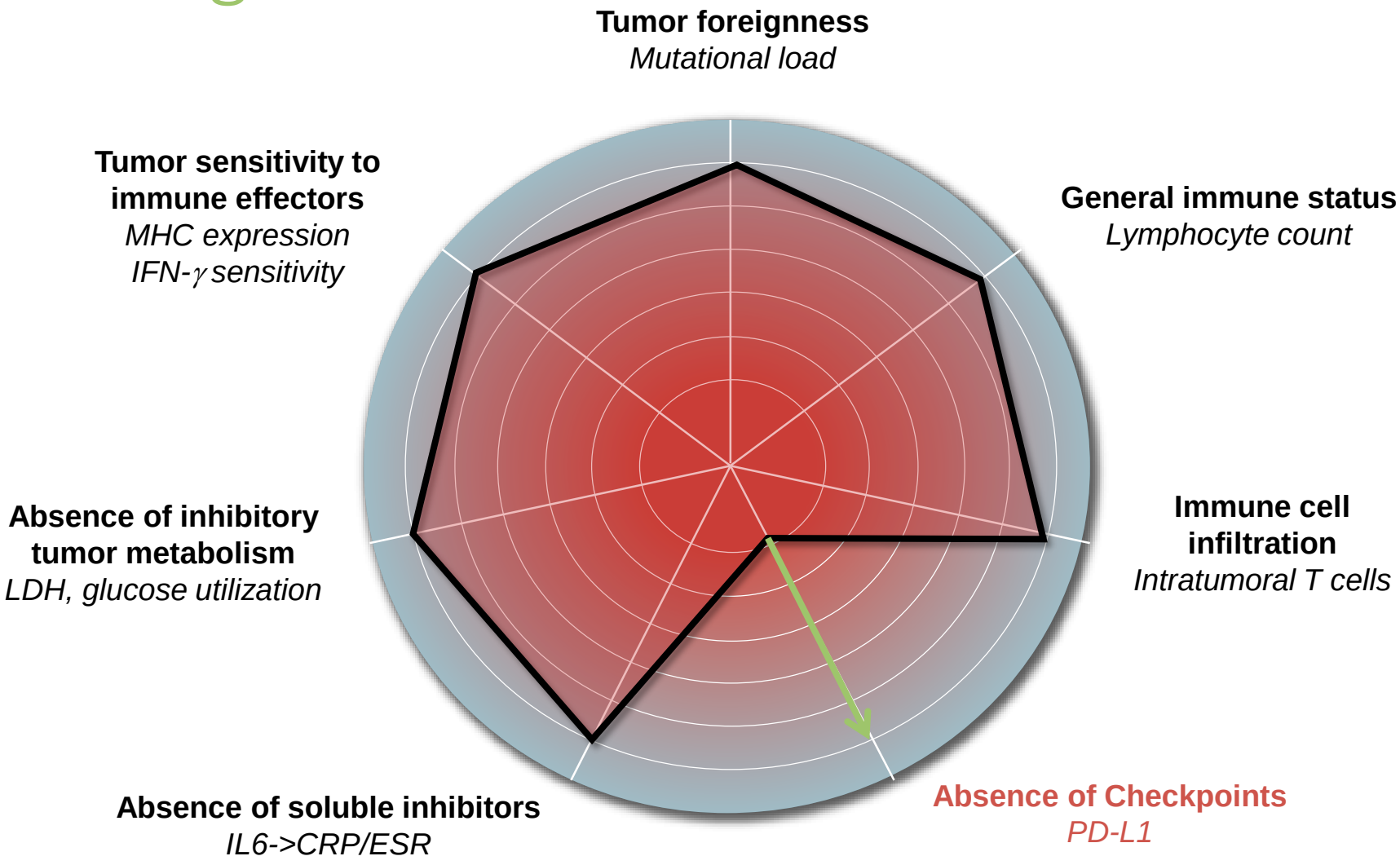
ALC



COPENHAGEN 2016 ESMO congress

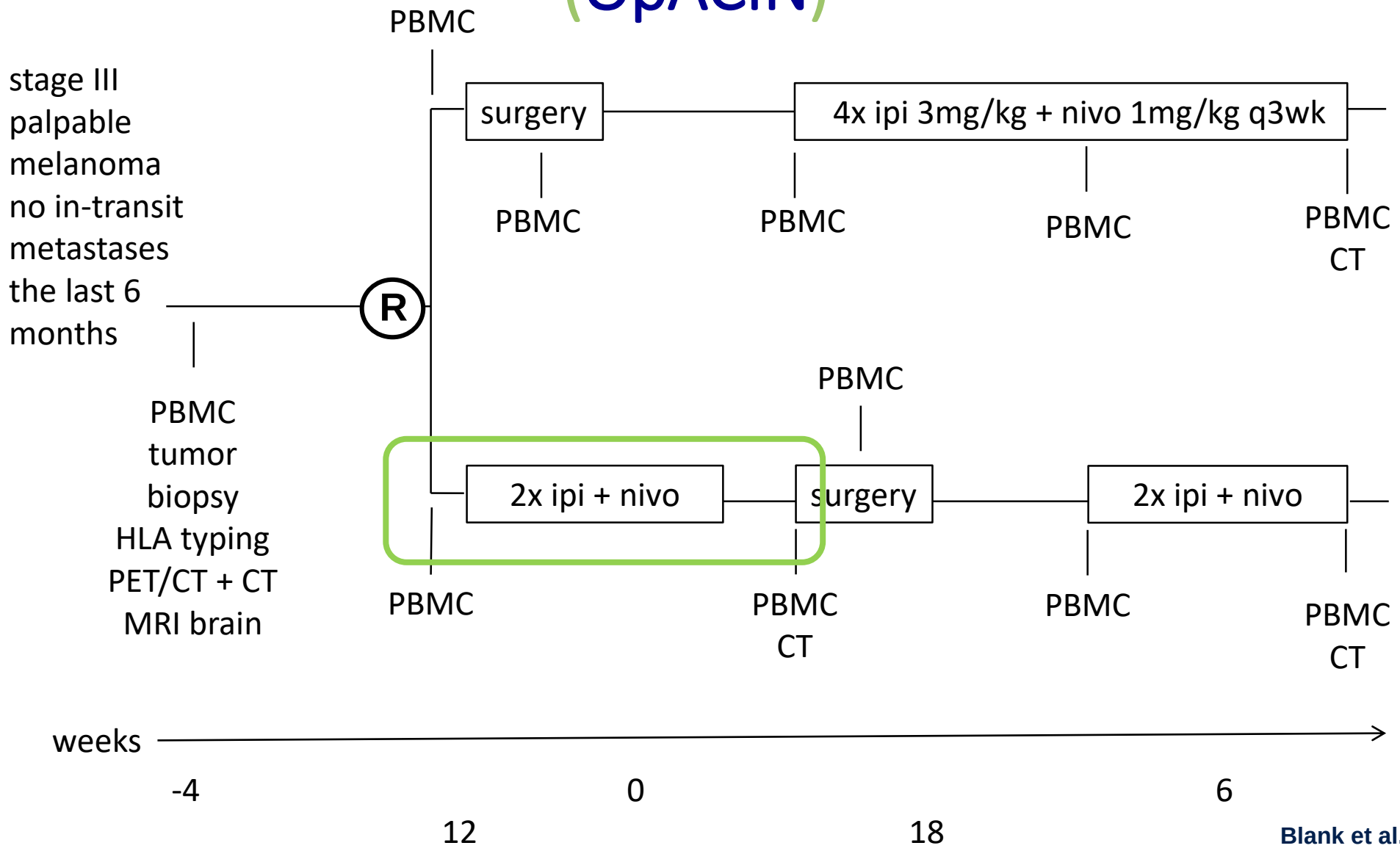
Jansen, Rozeman, Blank et al.,
Poster 1127, ESMO 2016

Who are typically “Cancer Immunogram-favorable” patients? Stage 3 melanoma!



Blank, Schumacher, et al., Science 2016

Feasibility Study to Identify of the Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab (OpACIN)



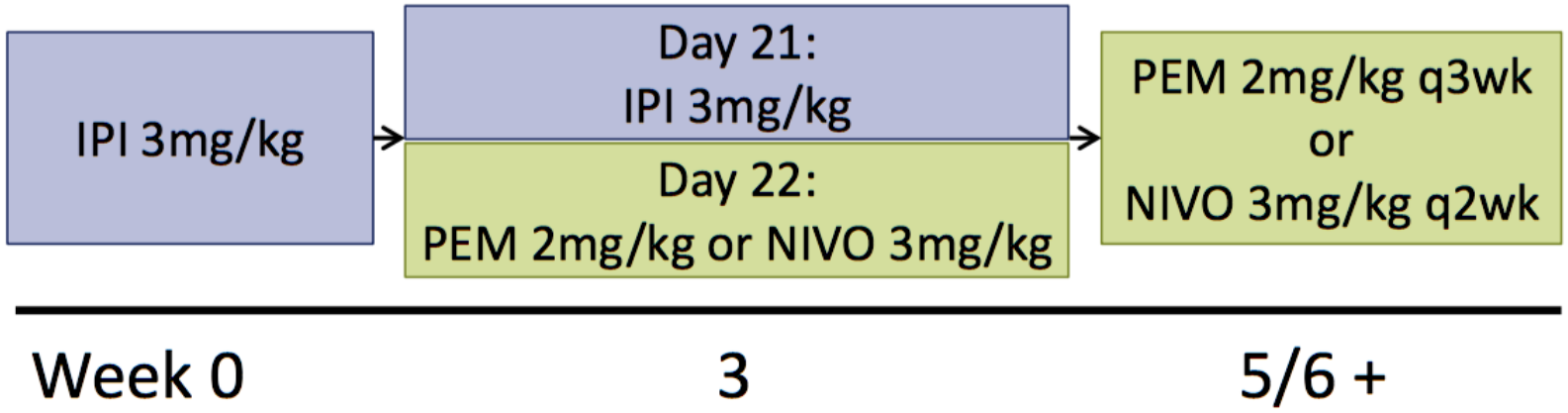
Blank et al., LBA ESMO 2016

8/10 (80%) OF PATIENTS HAVE A RESPONSE AFTER 6 WEEKS (NEO-ADJUVANT ARM ONLY)

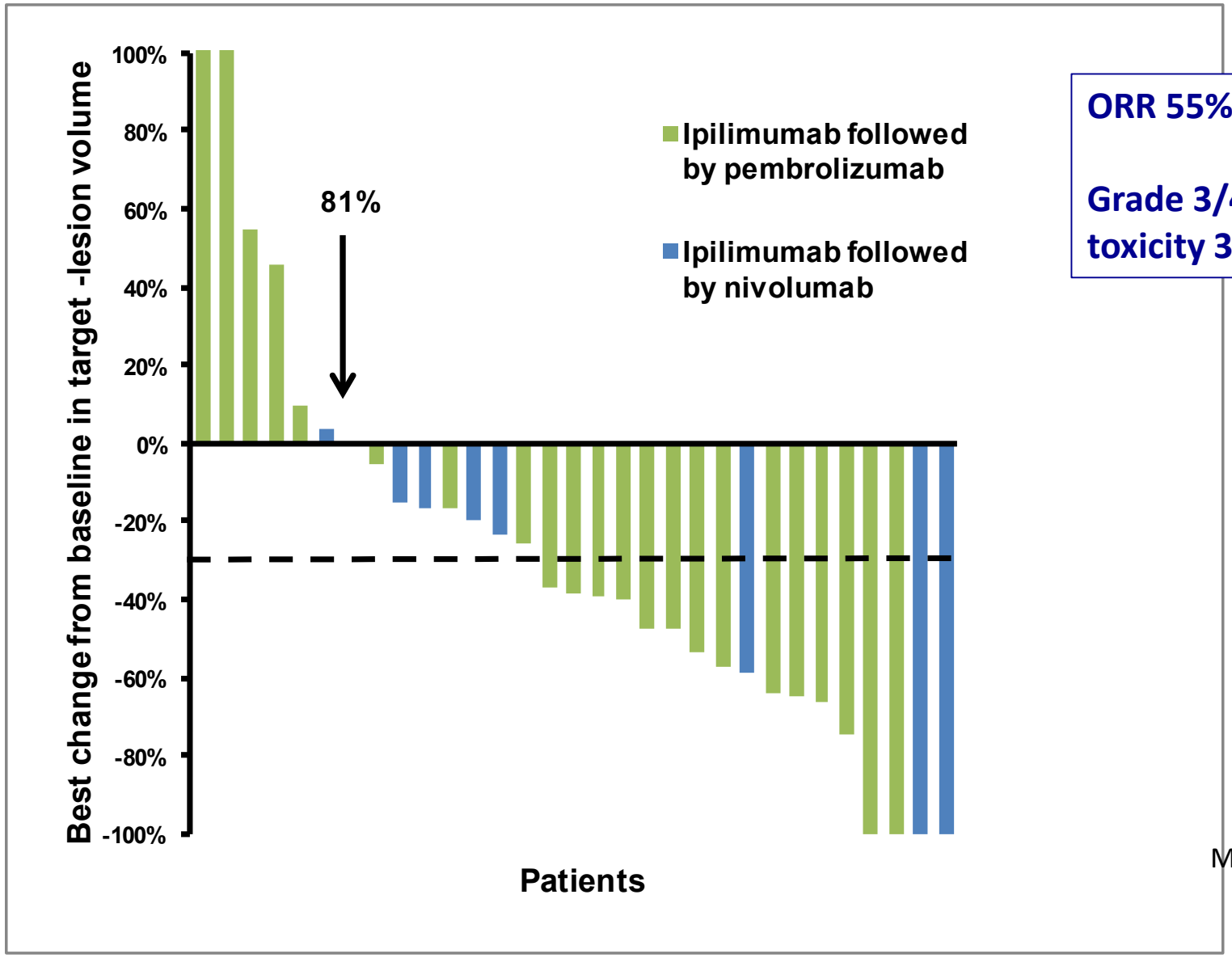
Pat ID	Courses	Radiologic response (CT scans, mm)	Pathologic response
7	2	31 x 50 → 18 x 31	pCR
16	2	23 x 36 → 17 x 23 & 22 x 24 →9 x 12	pCR
19	2	24 x 40 → 19 x 24	pCR
4	3	21 x 47 → 11 x 34	micrometastases (<1mm)
5	2	9 x 10 → ND	micrometastasis (0.5mm)
8	2	10 x 12 → 6 x 9	micrometastasis (sporadic tumor cells)
14	4	18 x 19 & 25 x 37 → ND	micrometastasis (sporadic tumor cells)
24	2	28 x 40 → 15 x 21	macrometastasis (75% necrosis)
13	2	22 x 40 → 22 x 40	LNs 35mm, 2mm, 1mm, 0.5mm, 0.1mm
17	1	11 x 18 → 17 x 25	LNs 30mm, 13mm, 6.0mm, 3.5mm

Blank et al., LBA ESMO 2016

Are there alternative checkpoint combination schemes?



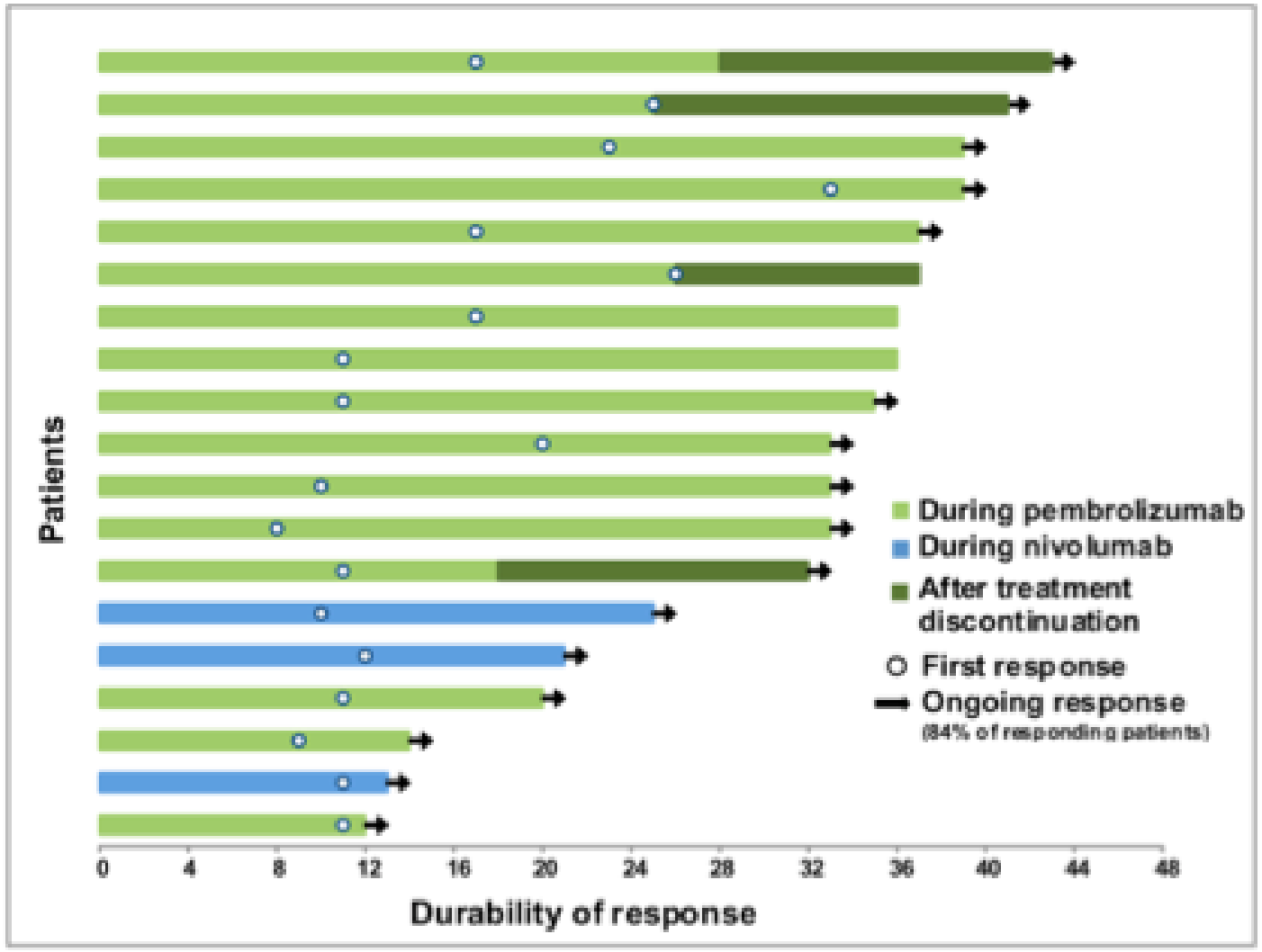
Meerveld, Rozeman, Blank et al.
OncoImmunology 2017



ORR 55%

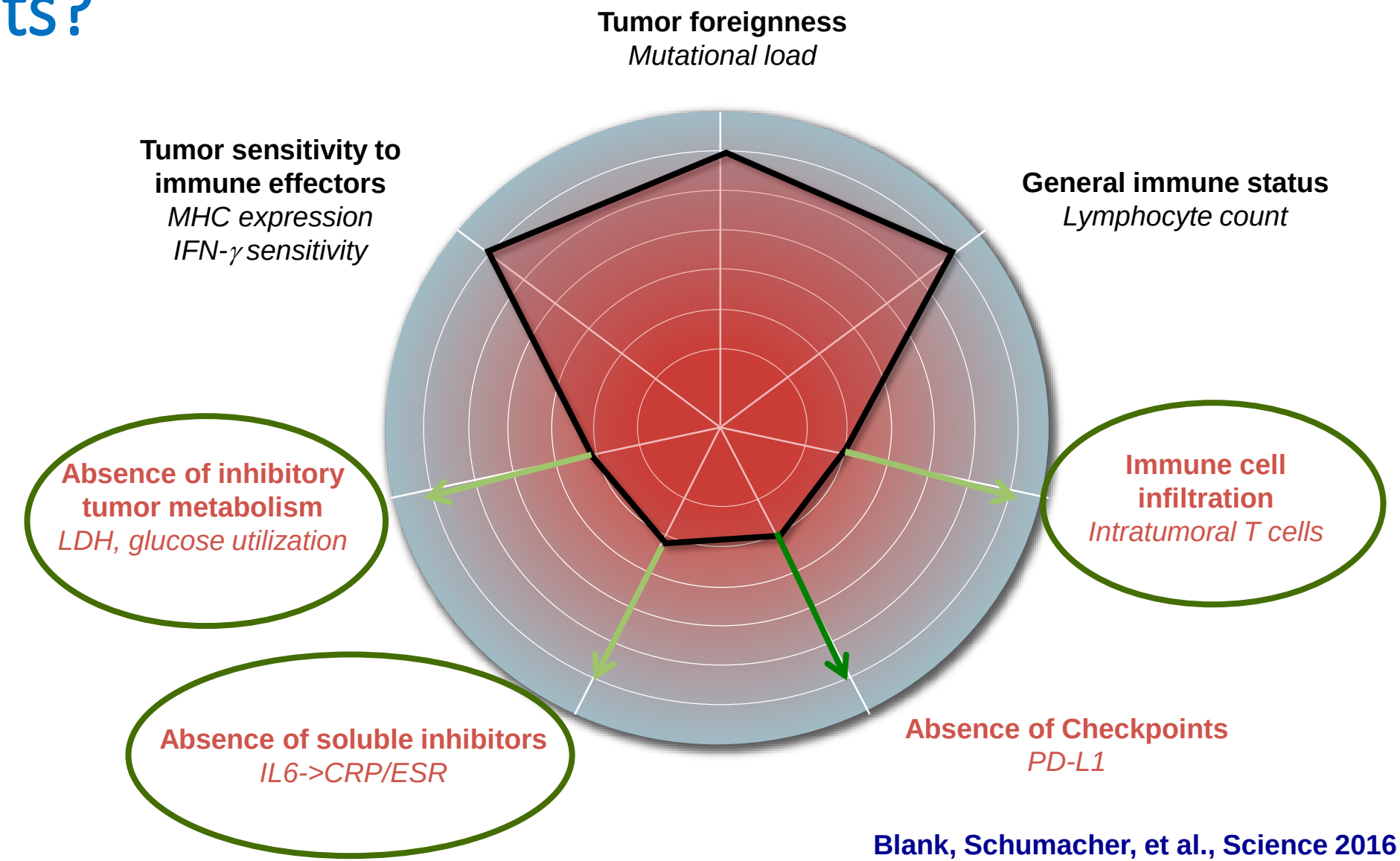
Grade 3/4 toxicity 38%

Meerveld, Rozeman, Blank et al. OncoImmunology 2017



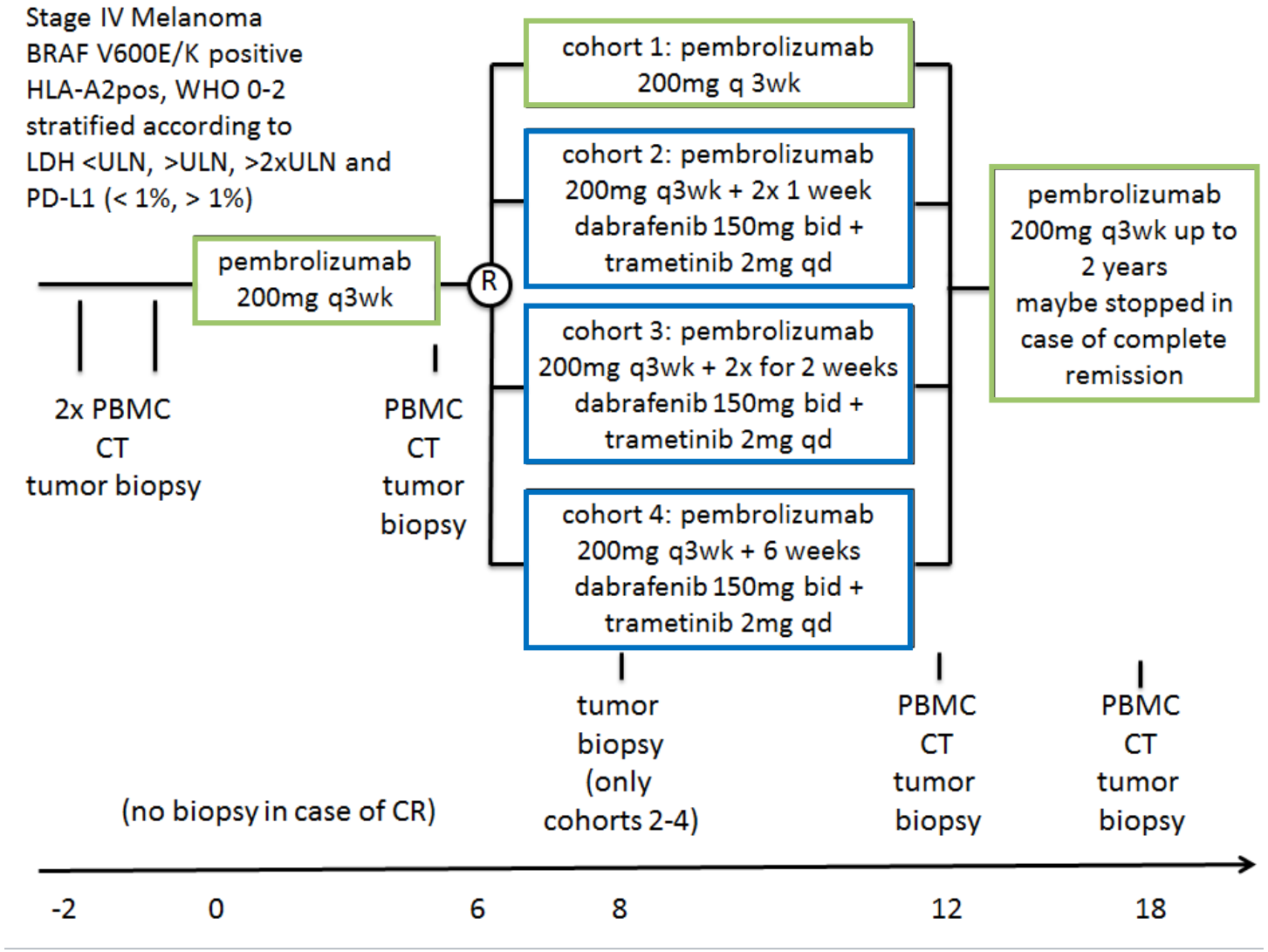
Meerveld, Rozeman, Blank et al.
OncoImmunology 2017

What to do with ”Cancer Immunogram-unfavorable“ patients?



Blank, Schumacher, et al., Science 2016

Phase1b Study of Intermittent MAPK Pathway Targeting in Melanoma Patients treated with Pembrolizumab and harboring the BRAFV600 mutation (IMPemBra)



PI CU Blank

Summary

- We do not yet understand which T cells are doing the job upon CTLA-4 +/- PD-1 blockade
- Unlikely that the same T cell clone mediates tumor responses upon PD-1 blockade and CTLA-4 blockade
- Repetitive checkpoint inhibition might not be needed or is even overdoing things
- Single biomarker analyses are out! Multiparameter analyses, like the Cancer Immunogram are the new standard
- TCR repertoire analyses are new markers for checkpoint inhibitor treatment characterization
- The optimal combination scheme has not yet been identified, sequential CTLA-4 and PD-1 blockade may see a revival
- CTLA-4 or PD-1+CTLA-4 blockade are options after failure upon PD-1 blockade (but be aware of deterioration of the patient)
- Combinations of Checkpoint inhibition with short-term targeted therapies is the way to go

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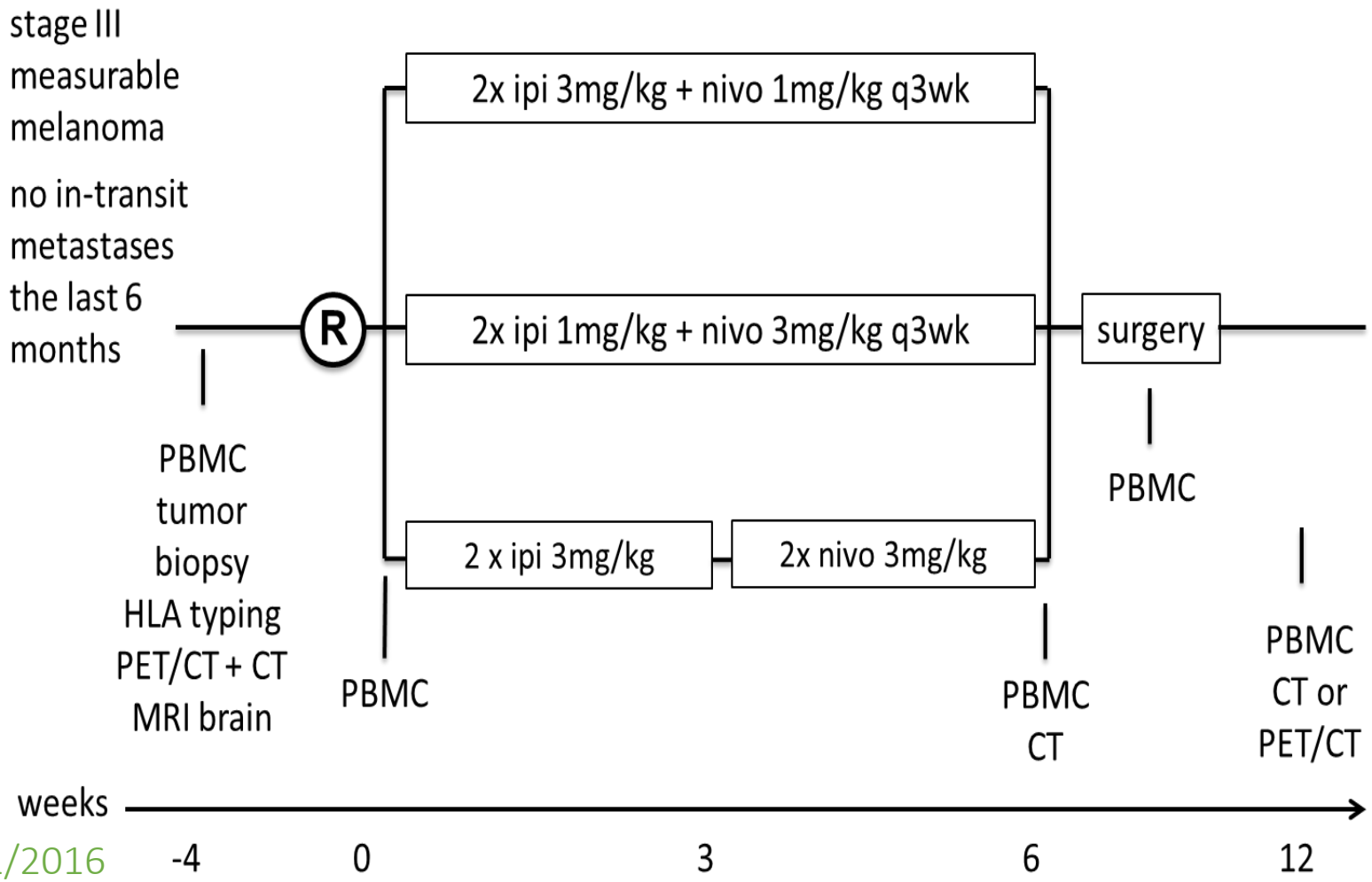
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

OPACIN-NEO TRIAL



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