Manipulating the immune system in GI cancer

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ESMO-Asia, Singapore, December 21, 2015

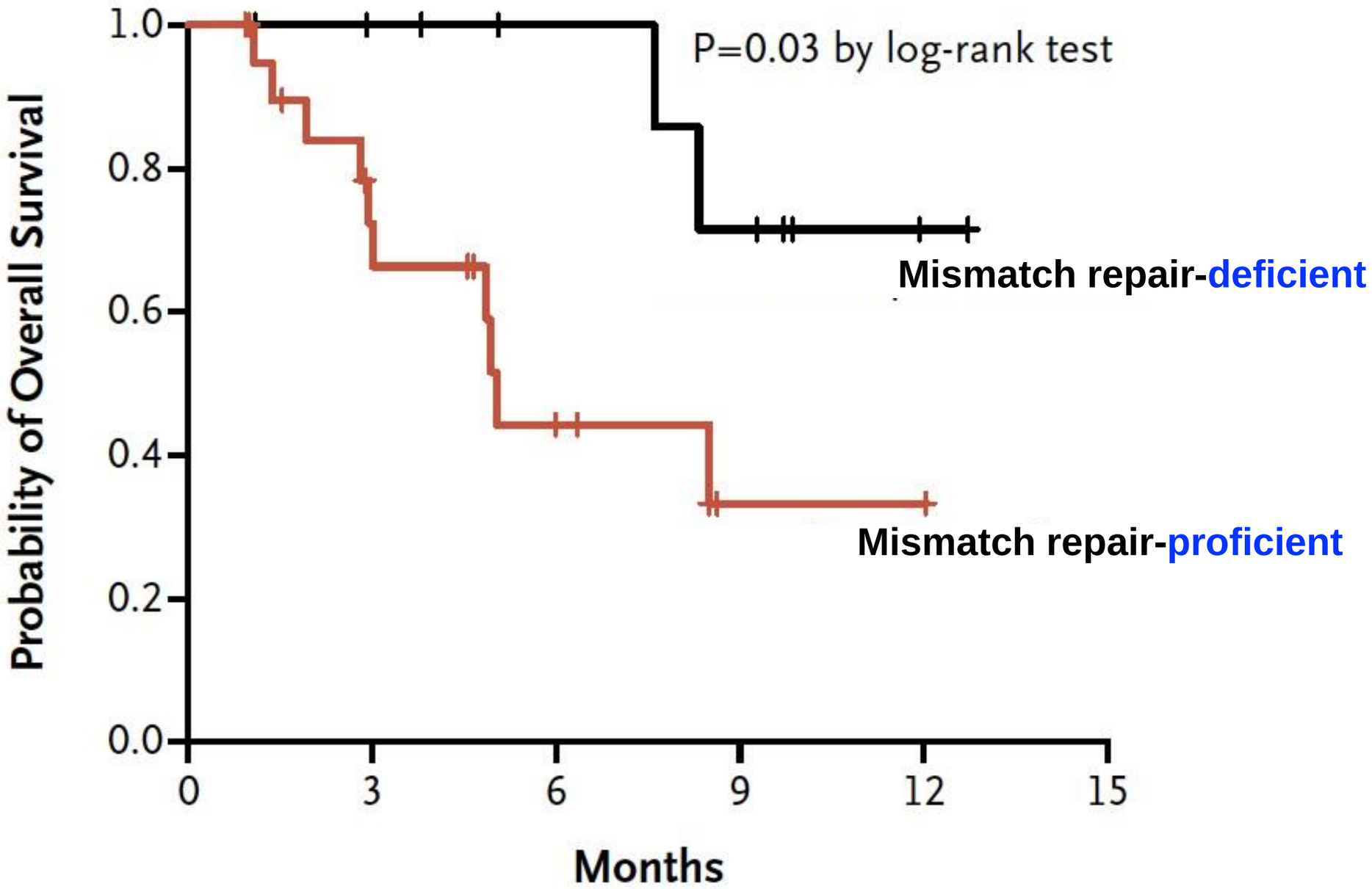
LUDWIG
CANCER
RESEARCH

Disclosures

- iTeos Therapeutics: co-founder and consultant
- Amgen: consultant

Pembrolizumab in treatment-refractory progressive metastatic CRC

(anti-PD-1 IgG4)



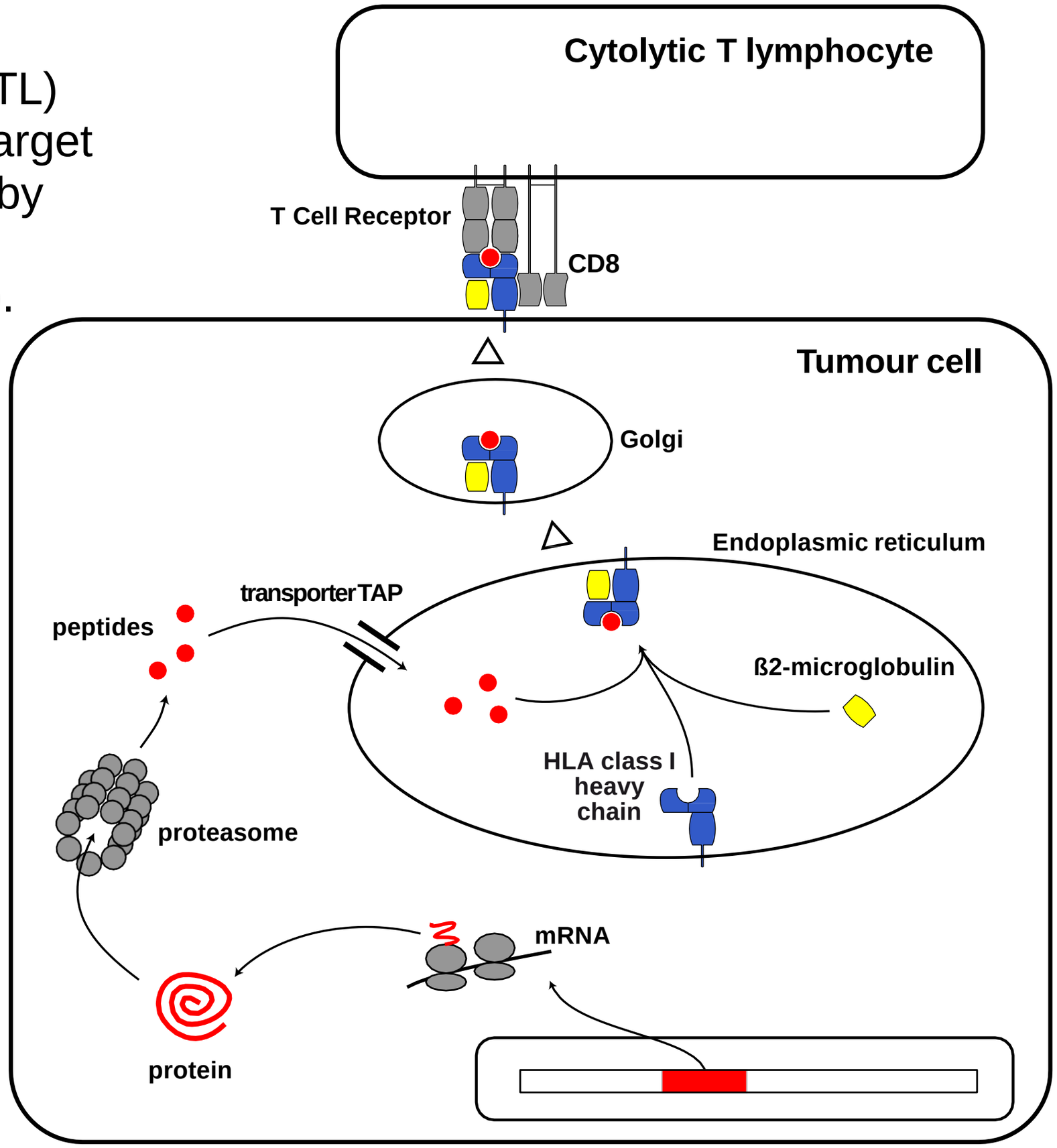
No. at Risk

Mismatch repair–deficient	11	9	7	5	1	0
Mismatch repair–proficient	21	12	5	1	1	0

Le et al. - 2015 - NEJM

Antigens recognized by CD8 T cells on the surface of tumor cells

Cytolytic T lymphocytes (CTL) recognize on the surface of target cells **peptides** presented by **HLA class I** molecules (HLA-A, B, C).

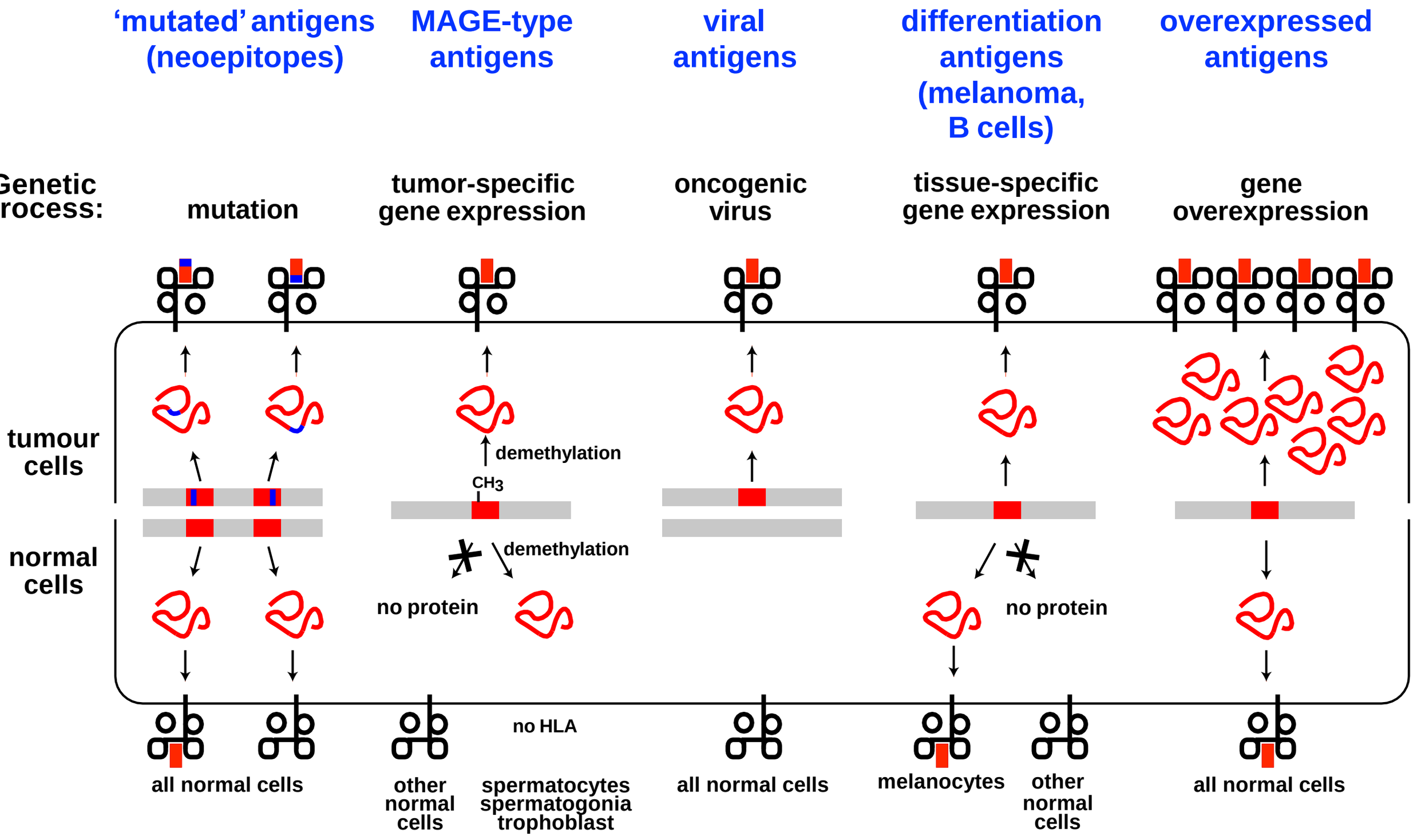


Five classes of tumor antigens recognized by CD8 T cells:

Antigen class	Advantages	Drawbacks
mutations	tumor-specific	individual
MAGE-type	tumor-specific (some exceptions) shared	tolerance ?
viruses	tumor-specific shared	only some tumor types
differentiation	shared	on normal cells (> autoimmunity)
overexpression	shared	on normal cells (> autoimmunity)

Coulie, Van dan Eynde, van der Bruggen, Boon - 2014 - Nat Rev Cancer

Classes of tumor antigens recognized by CD8 T cells



Only some tumor antigens recognized by T cells are tumor-specific

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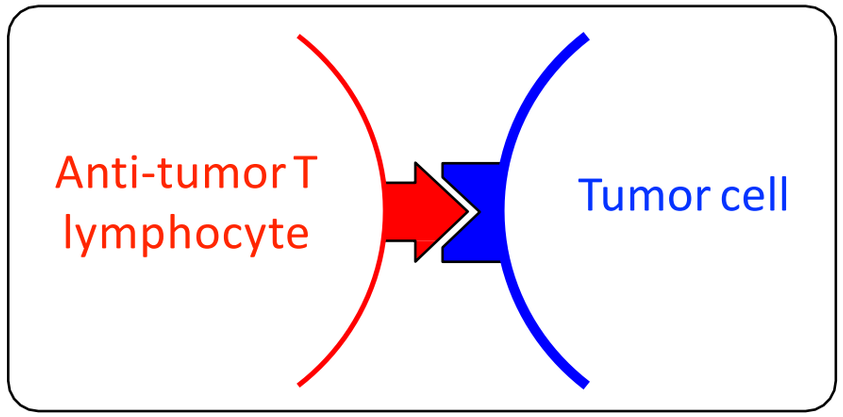
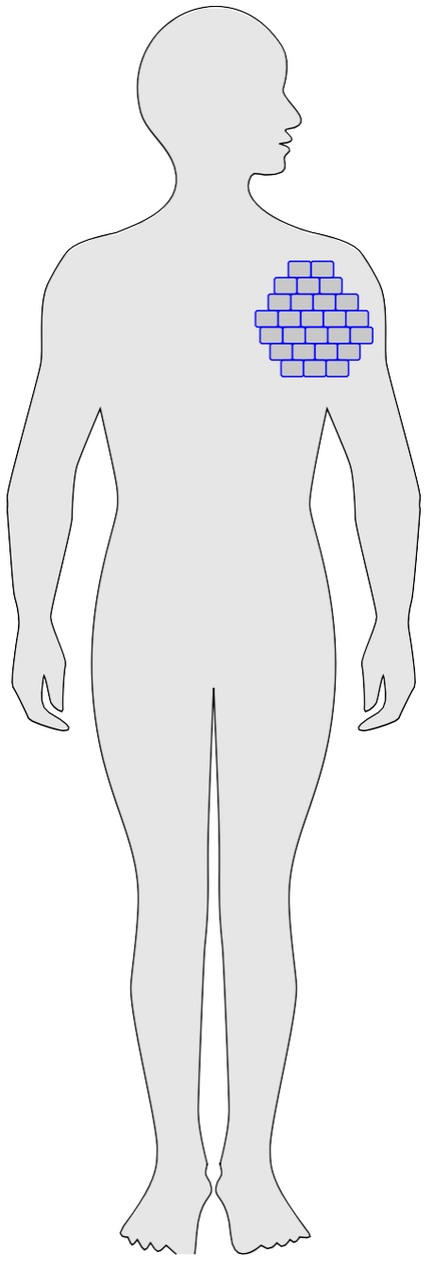


Cancer immunotherapy: 3 main modalities

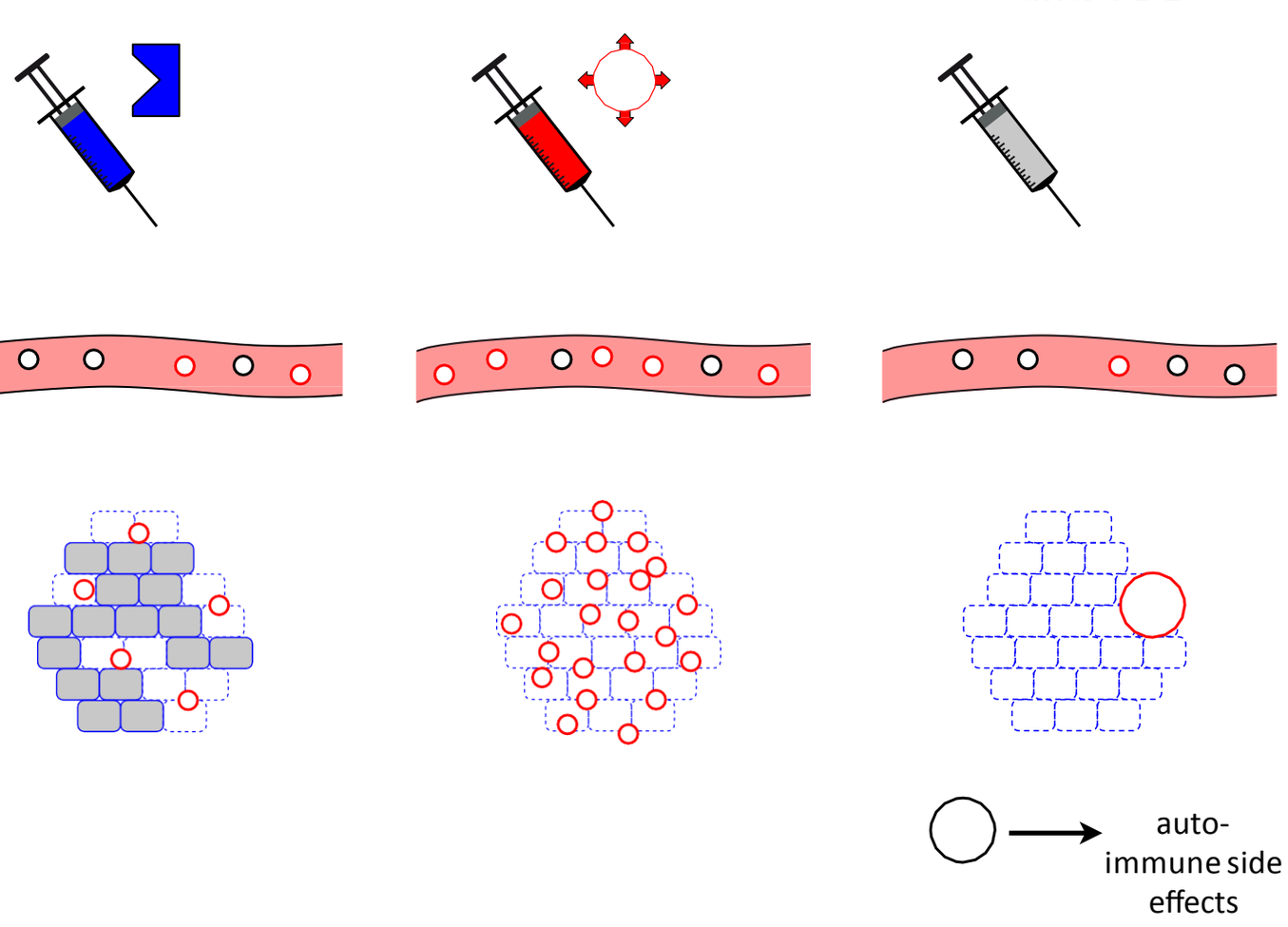


In patients:
weak «spontaneous» activity of anti-tumor T lymphocytes

Therapeutic vaccine

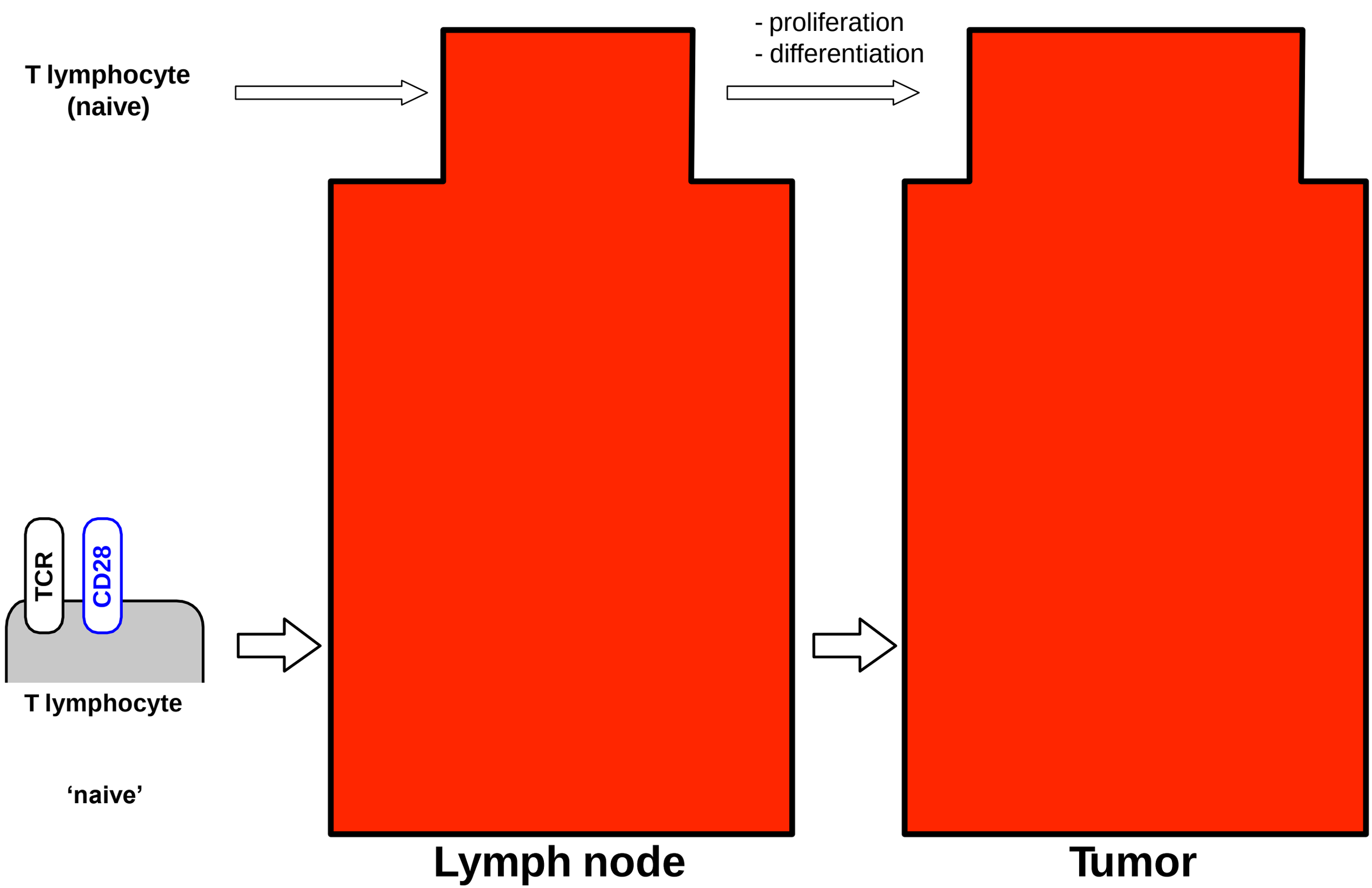
Adoptive transfer of anti-tumor T lymphocytes

Immunostimulating antibodies anti-CTLA4 anti-PD1

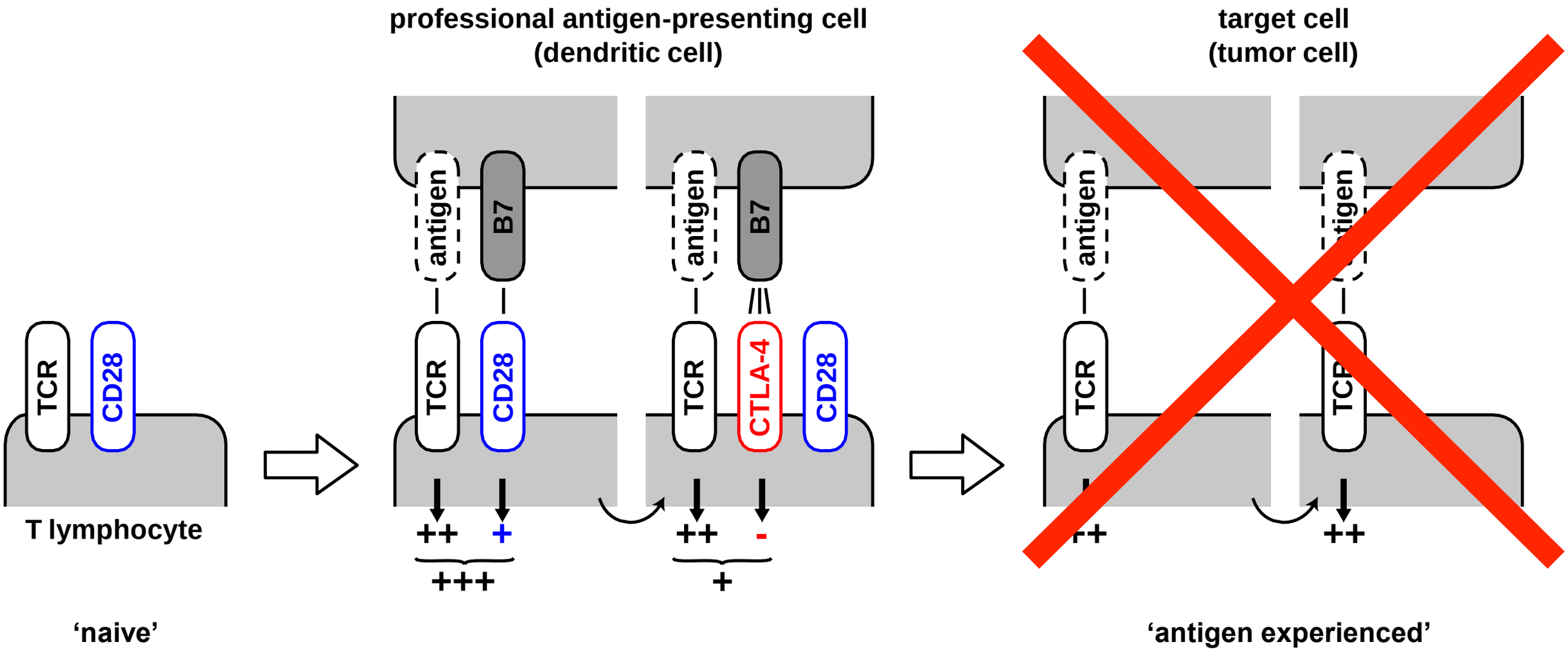


auto-immune side effects

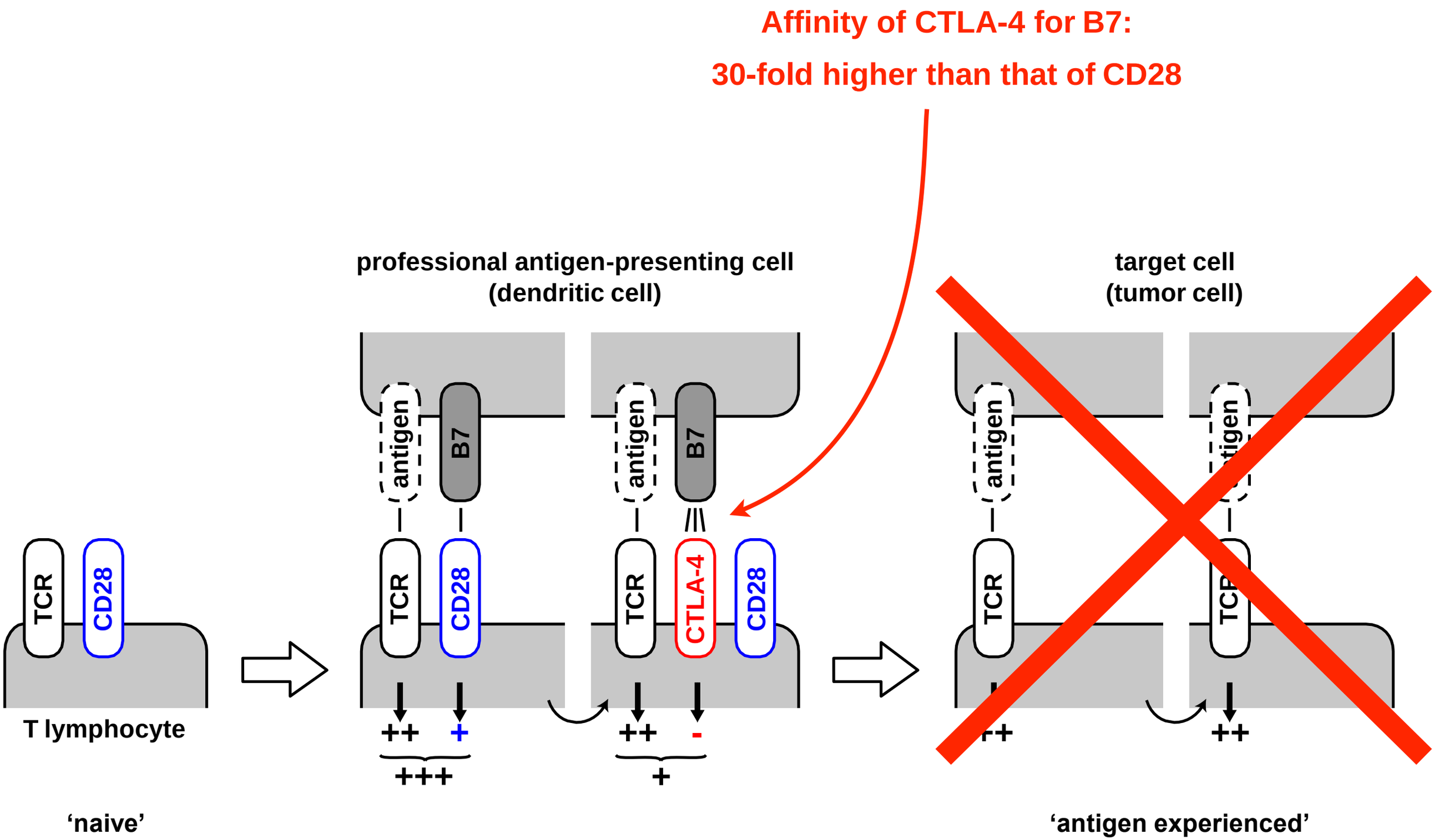
Two signals required for T cell priming



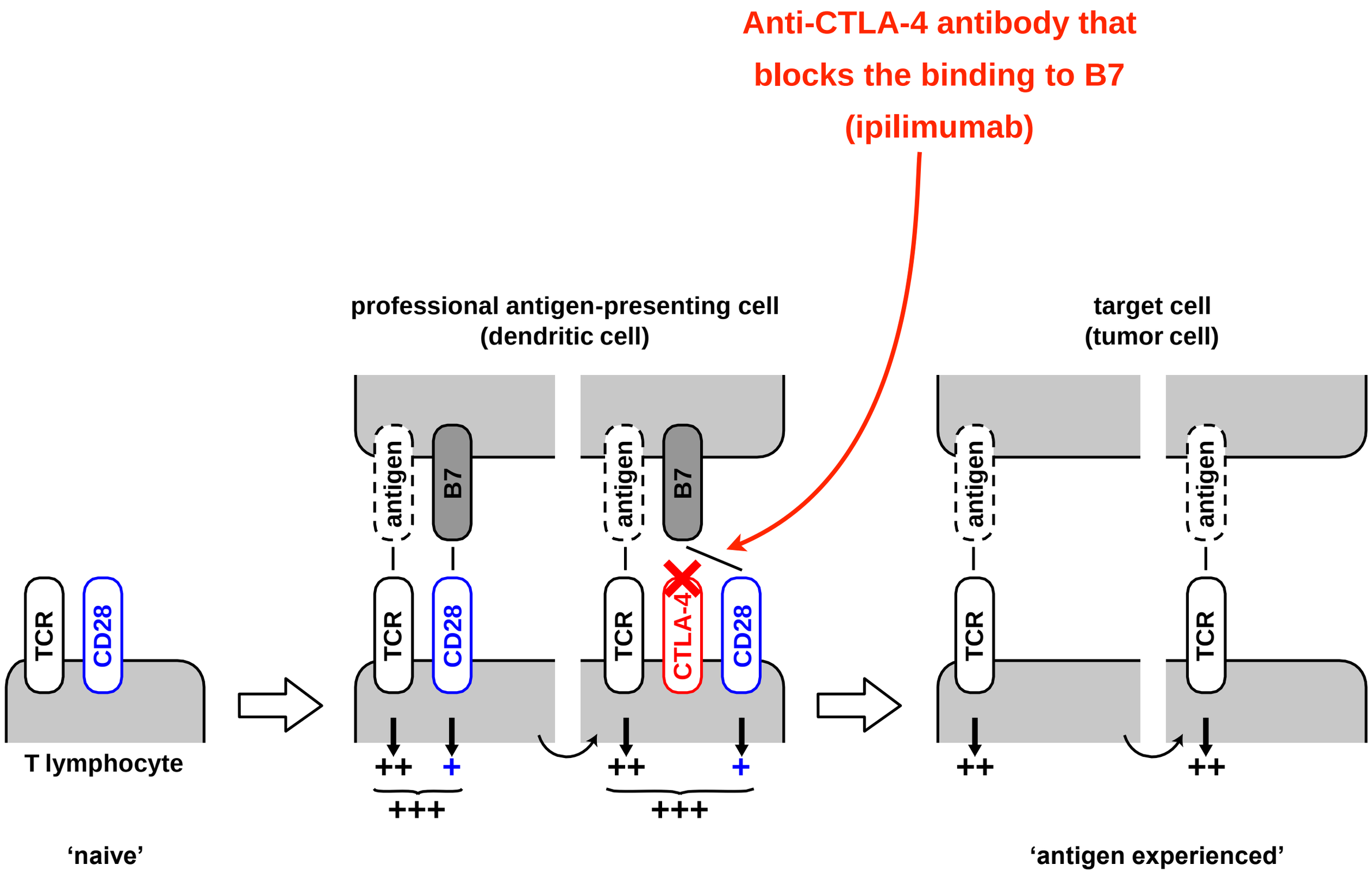
CTLA-4 surface expression 4-48h following T-cell activation



CTLA-4 is a physiological brake during T-cell activation

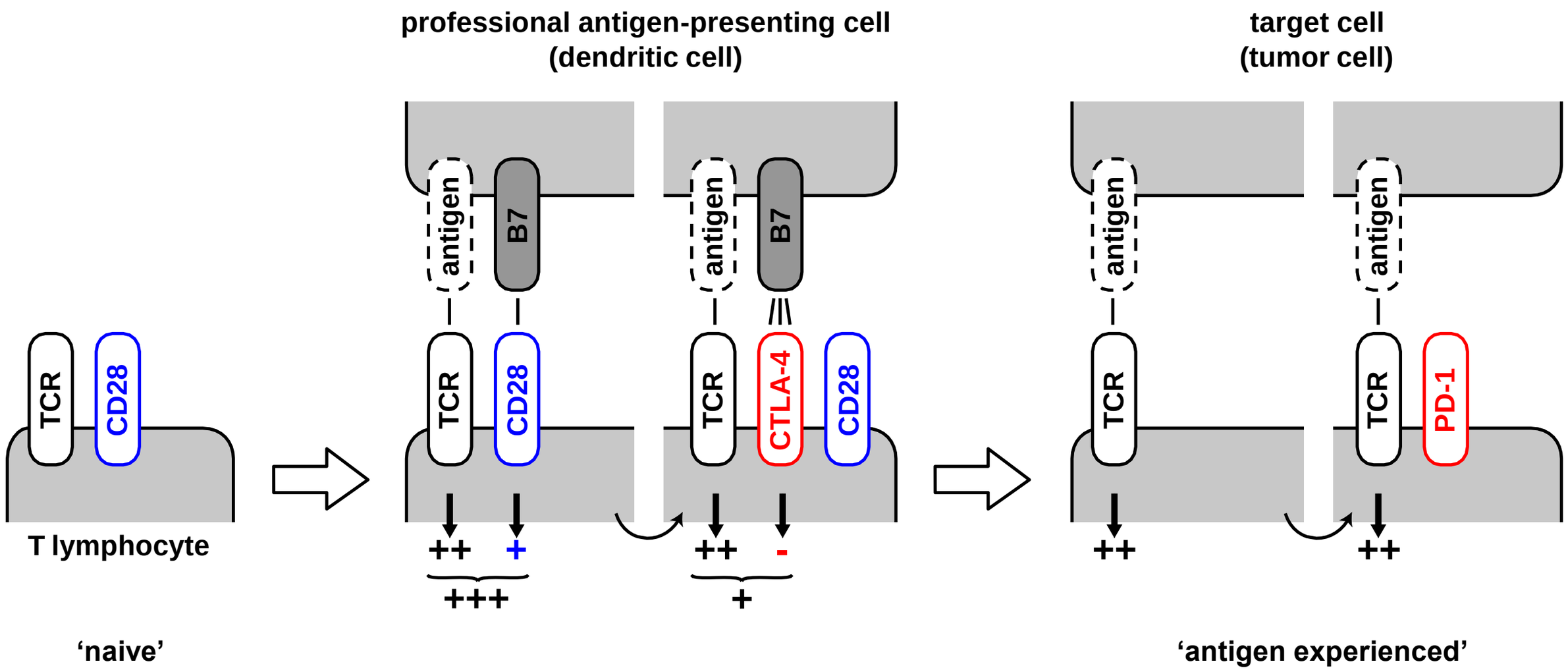


Immunostimulatory activity of anti-CTLA-4 antibodies

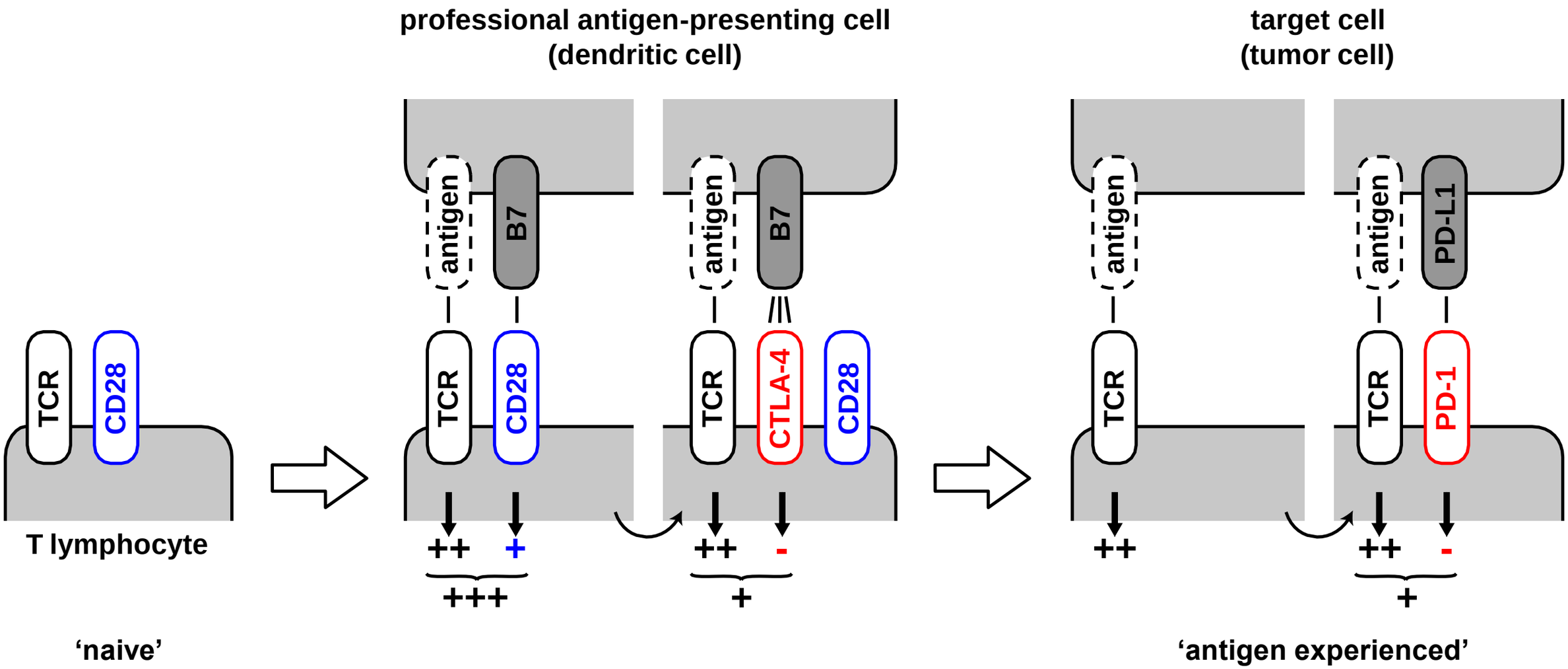


PD-1 expressed on activated effector T-cells

T lymphocyte (naive) → **Priming (first activation)** → **Effector function (subsequent activations)**



PD-1 dampens T cell activation

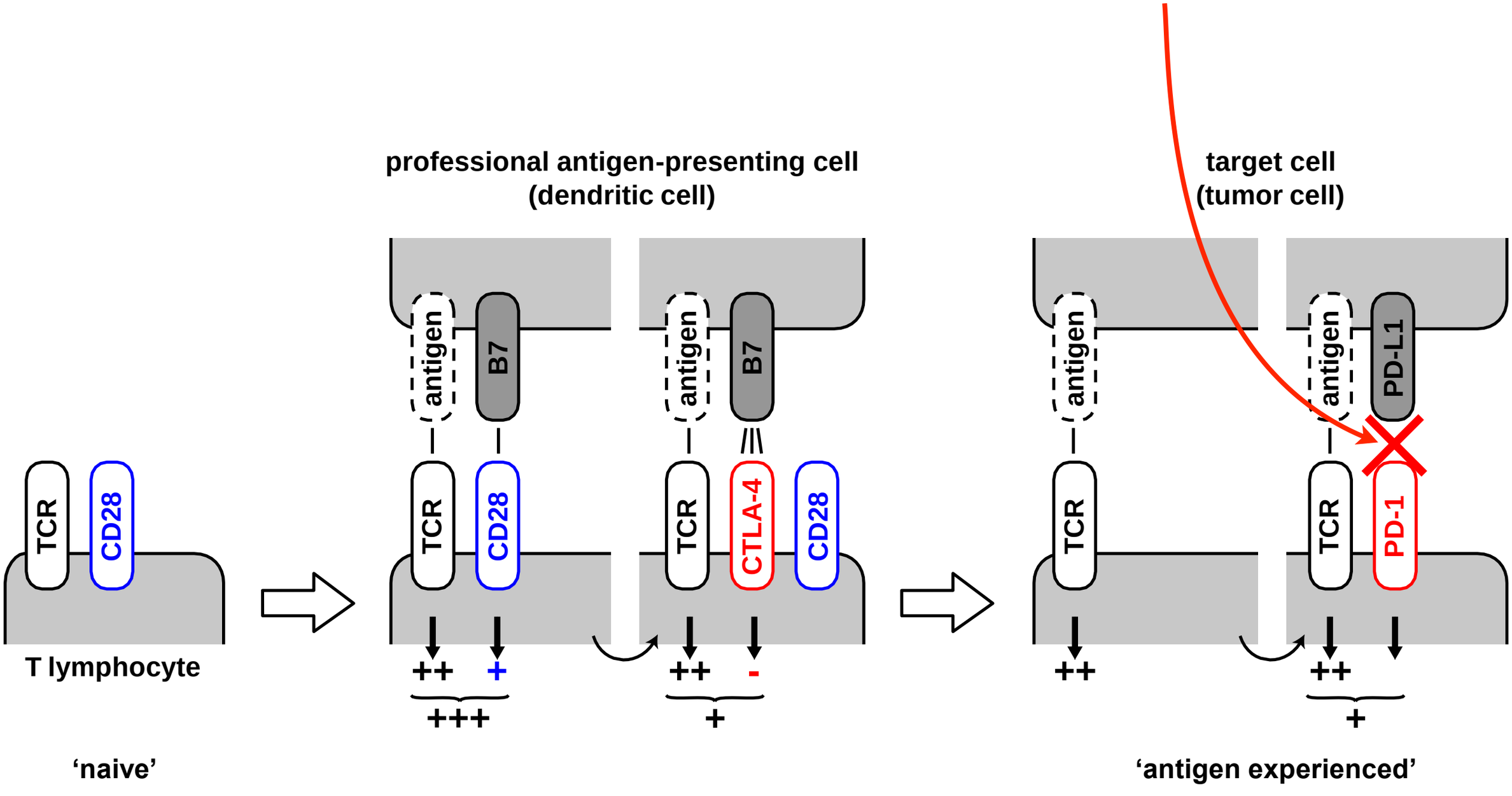


PD-1 dampens T cell activation

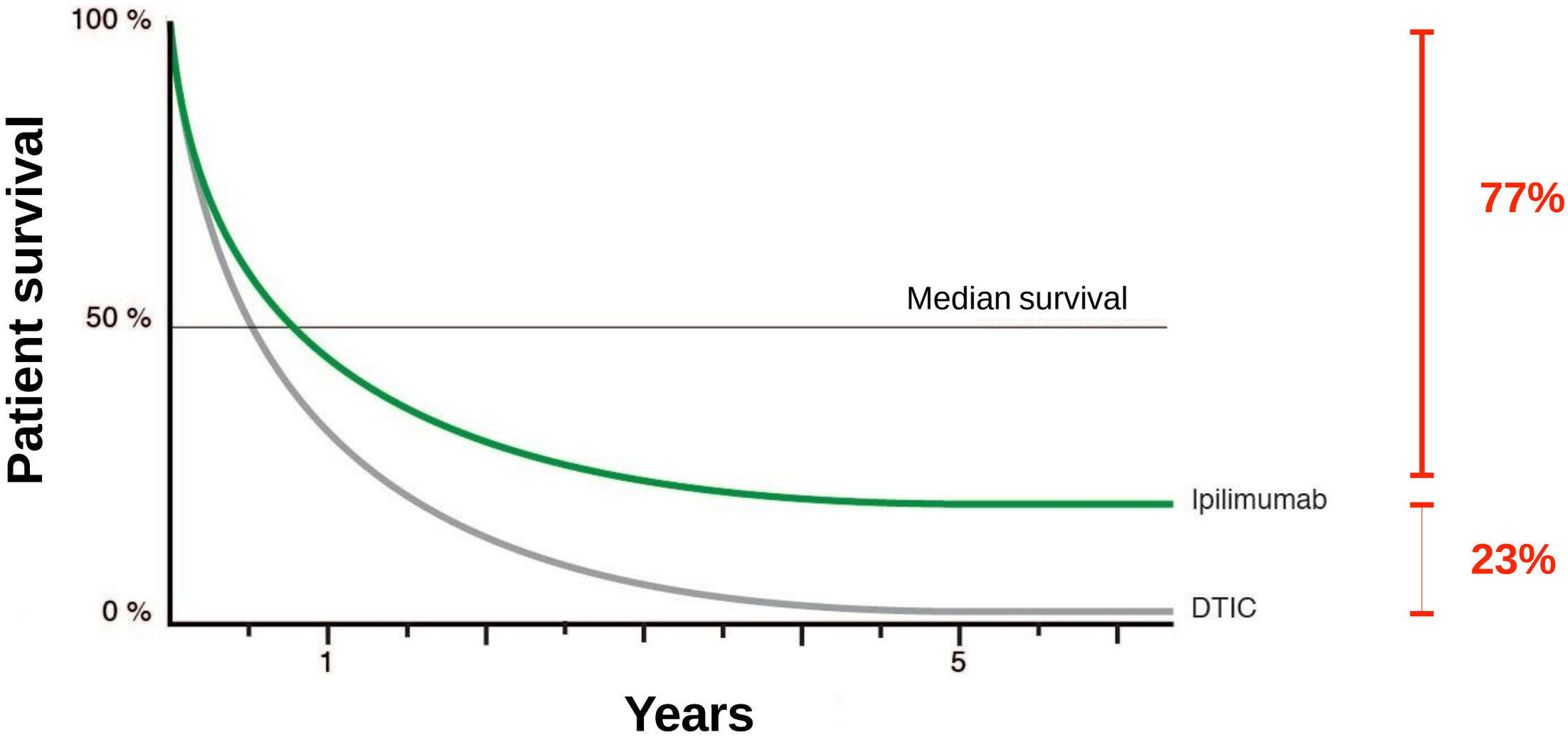
anti-PD1 (or anti-PDL1) antibody that blocks the PD1/PDL1 interaction

anti-PD1: nivolumab, pembrolizumab

anti-PDL1: BMS-936559



Clinical success of immunotherapy in metastatic melanoma: 23% patients are still alive 5 years a;er ipilimumab (anti--CTLA4)



- **long-term responses in a fraction of patients**
- **autoimmune toxicity, particularly with combos (anti-CTL4 + anti-PD1)**

Hodi FS et al. *New Engl J Med* 2010;363:711-723

Initial results with immunostimulatory antibodies in GI tumors

			Patients	RR	
CTLA-4	**Tremelimumab**	**refractory CRC**	**49**	**2%**	Chung et al - 2010 - JCO
PD-1	**Nivolumab**	**refractory CRC**	**19**	**0%**	Topalian et al - 2012 - NEJM
PD-L1	**BMS-936559**	**refractory CRC**	**18**	**0%**	Brahmer et al - 2012 - NEJM
PD-1	**Pembrolizumab**	**advanced gastric cancer**	**39**	**22%**	Muro et al - 2015 - ASCO

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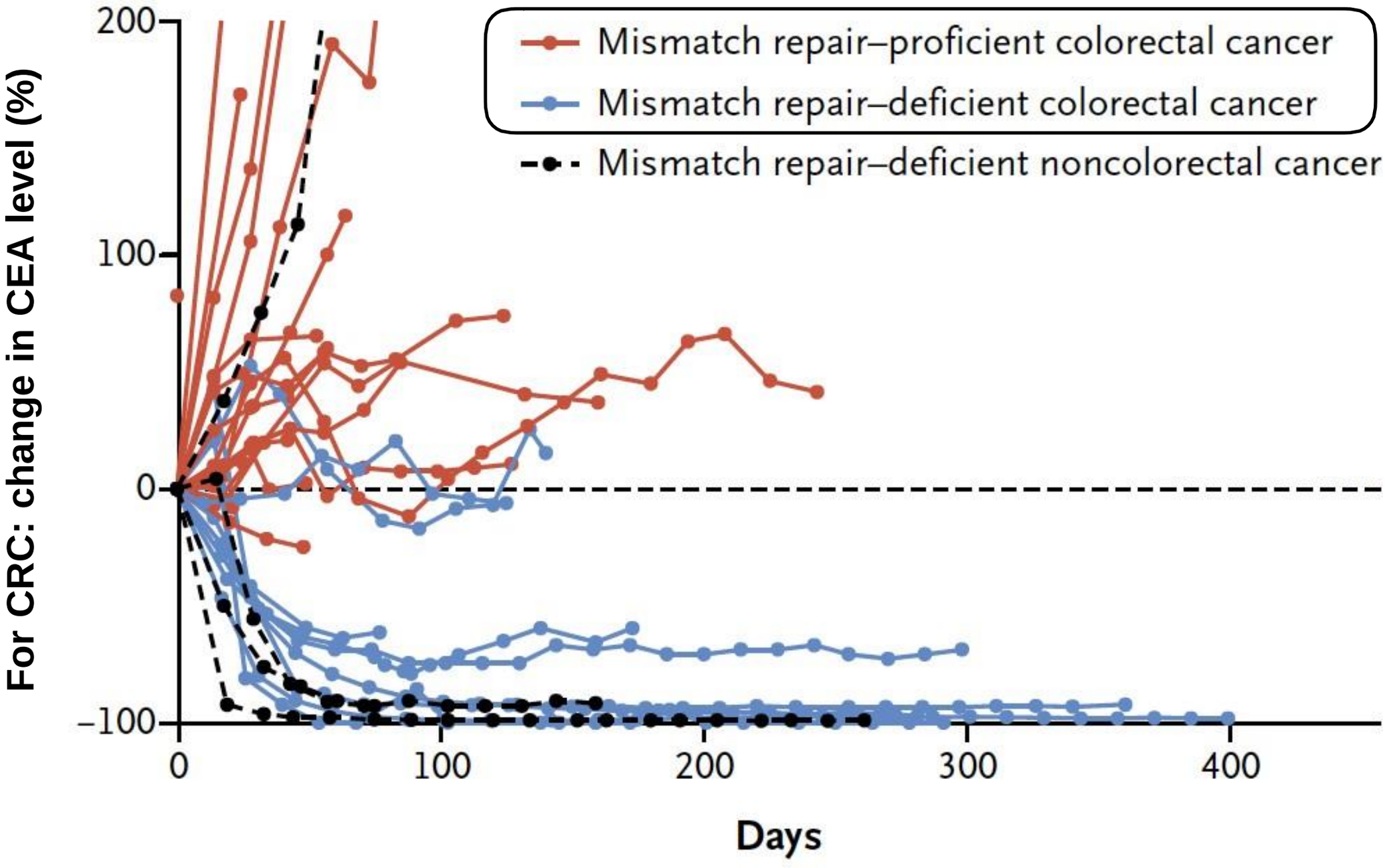
one patient with a complete response, ongoing at 3 years: MSI-H

Lipson et al - 2013 - Clin Cancer Res

Pembrolizumab in treatment-refractory progressive metastatic cancer

(anti-PD-1 IgG4)



Le et al. - 2015 - NEJM

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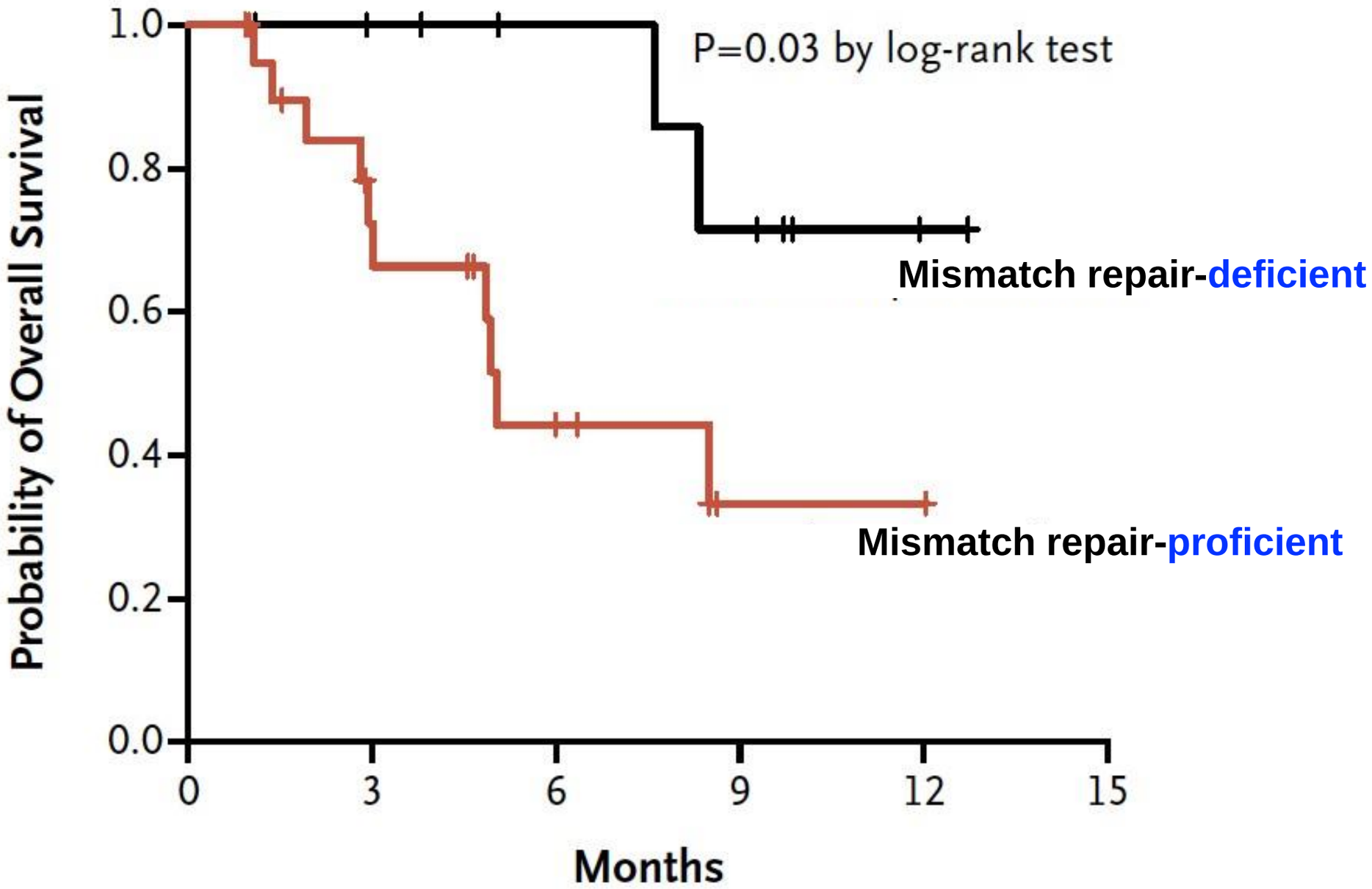

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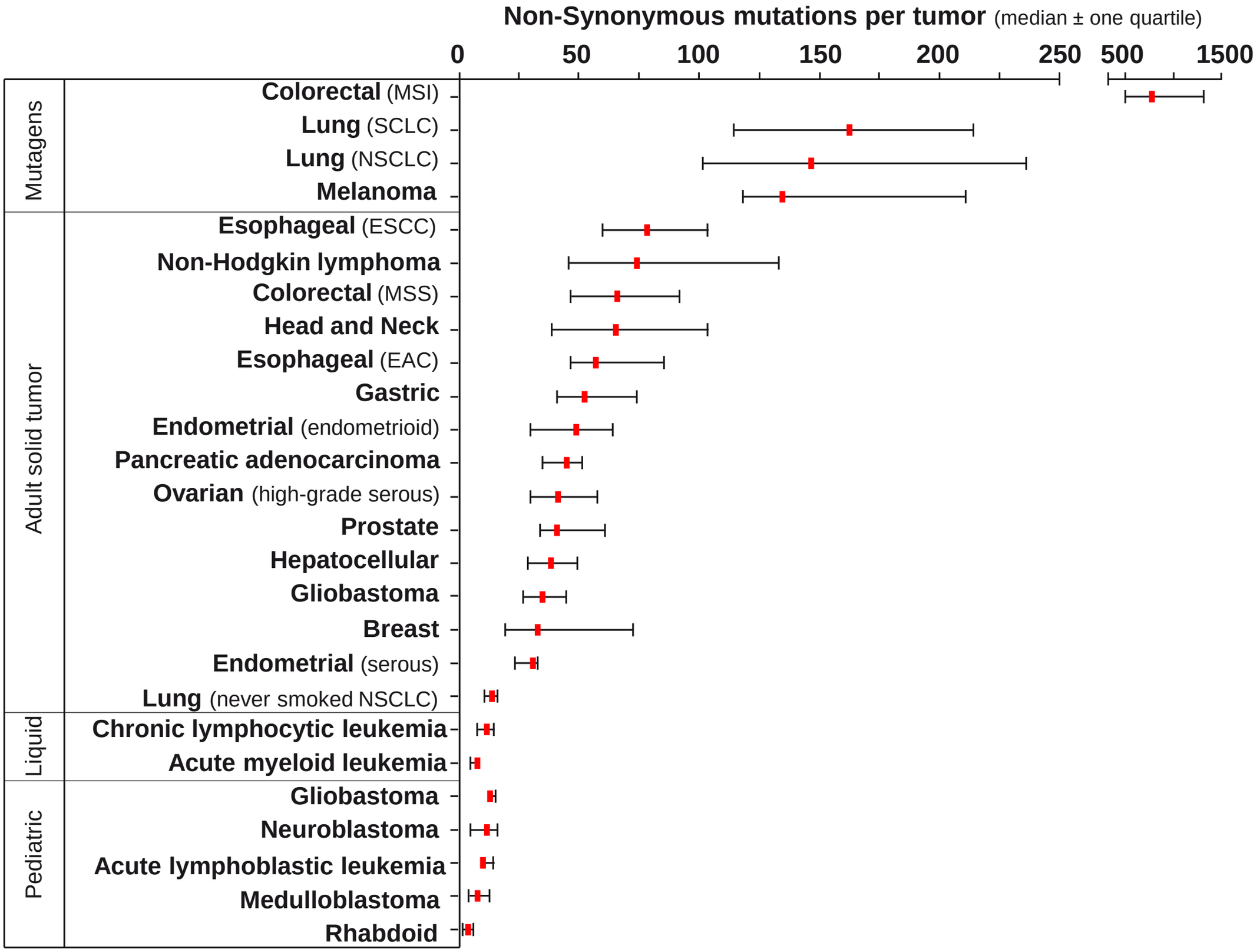
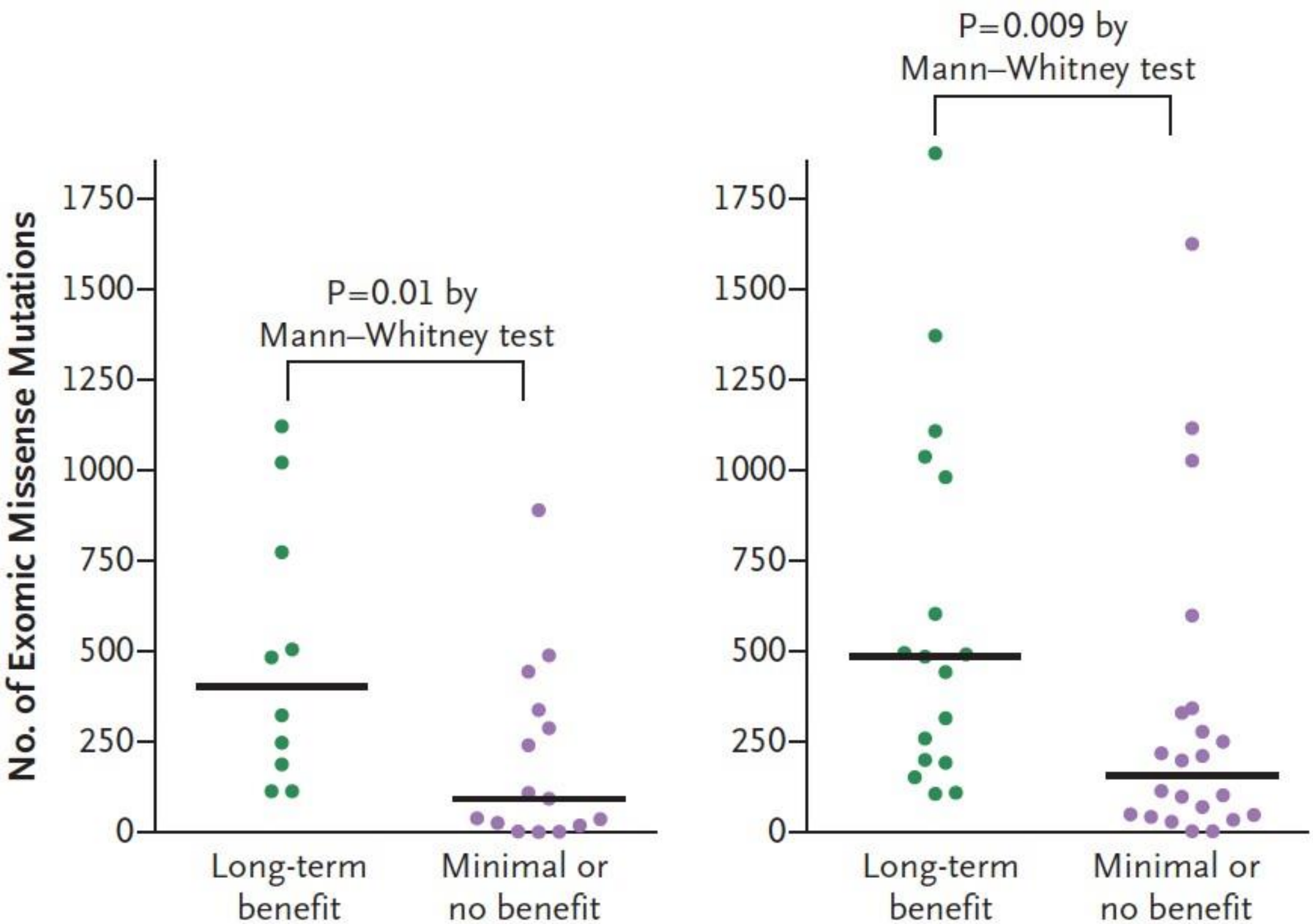
Antigens resulting from mutations (single nucleotide variations)



adapted from Vogelstein et al. 2013 Science 339:1546

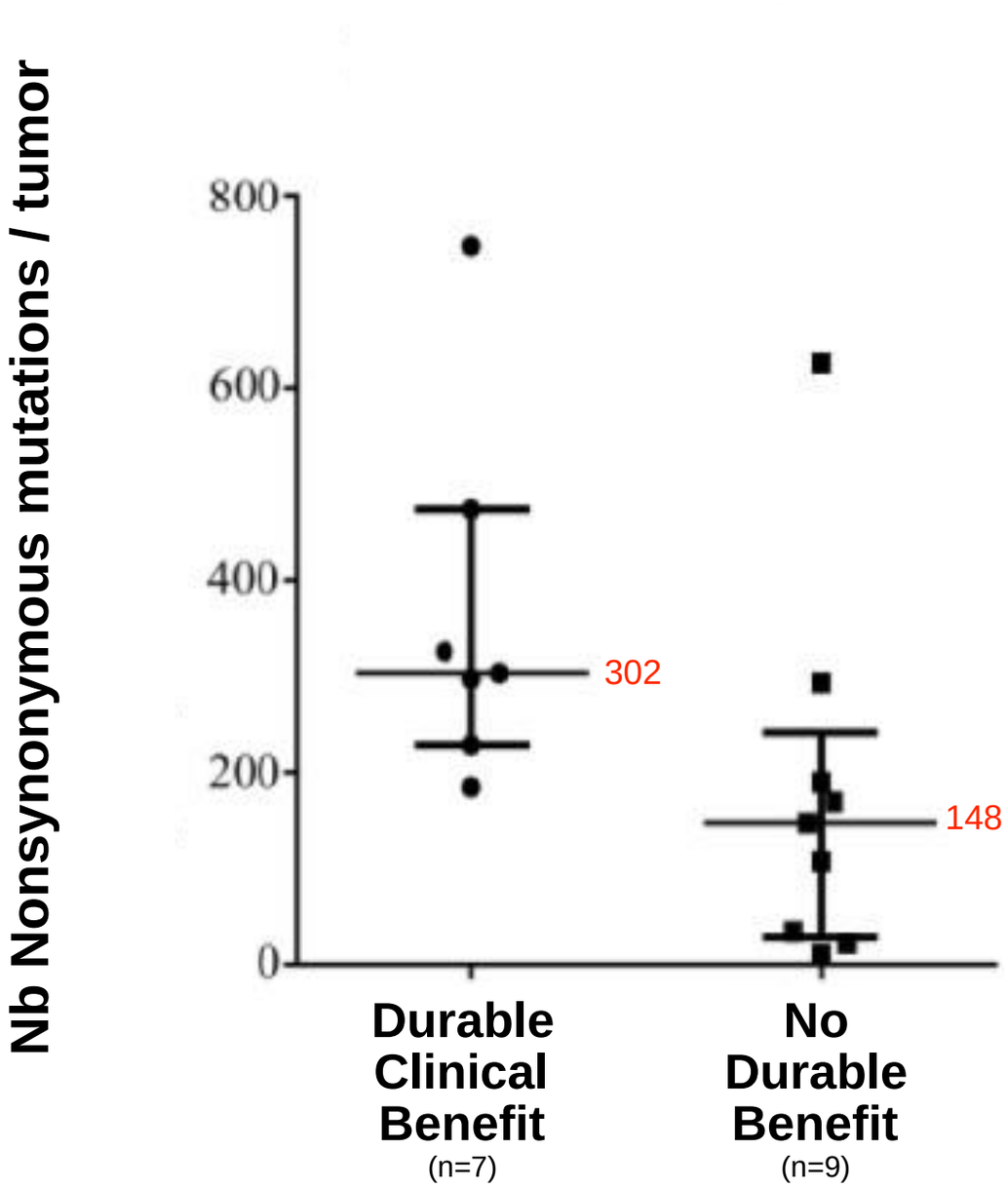
Mutational landscape of melanomas according to clinical benefit from ipilimumab treatment



Snyder et al. 2014 NEJM

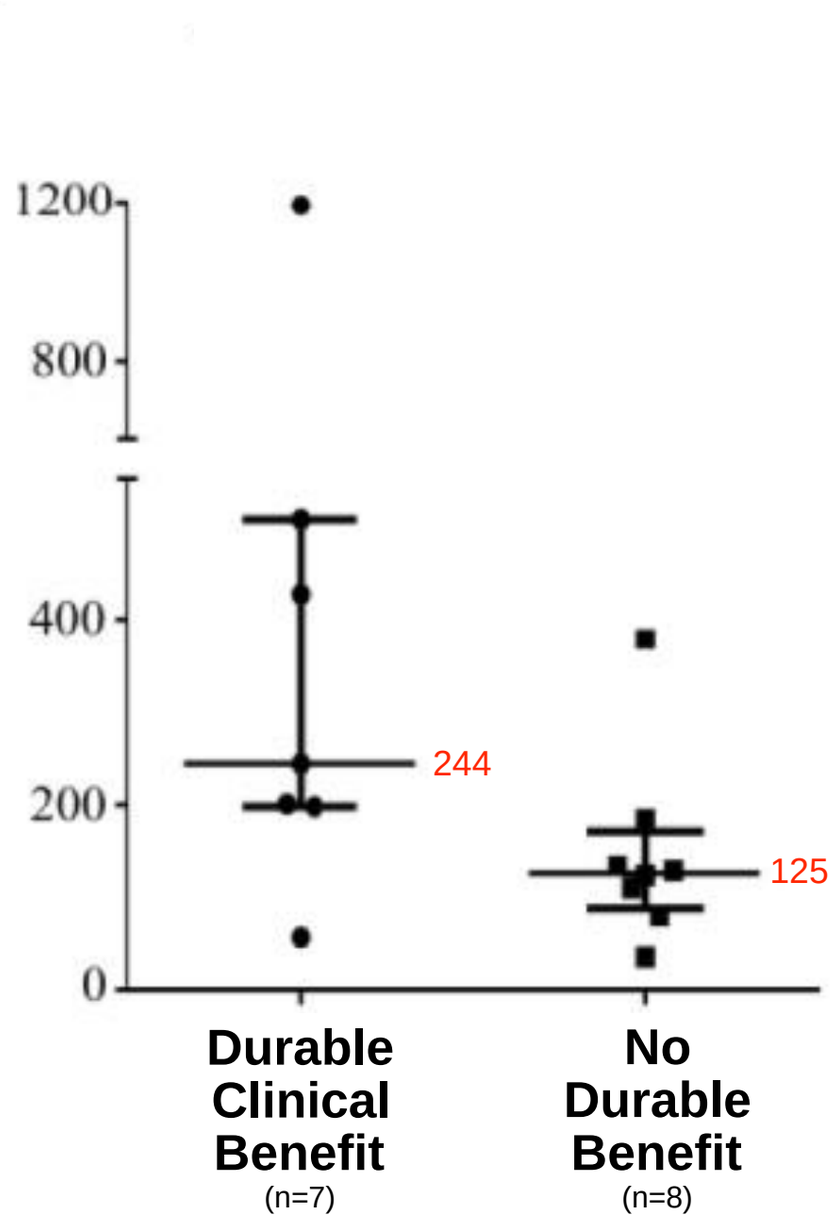
Nonsynonymous mutation burden in NSCLC treated with anti-PD1

Discovery Cohort



Mann-Whitney *P* = 0.02

Validation Cohort



Mann-Whitney *P* = 0.04

Rizvi et al. 2014 Science

Immunotherapy for GI tumors: towards improvements

1. Combinations of several immunostimulatory antibodies

probl: autoimmune **toxicity !**

2. Understanding and counteracting tumor resistance

blocking local immunosuppression + immunostimulatory antibodies

IDO inhibitor
Treg inhibitor
Microbiota
…

3. Trigger anti-tumor immune responses in « cold » tumors (non-MSI)

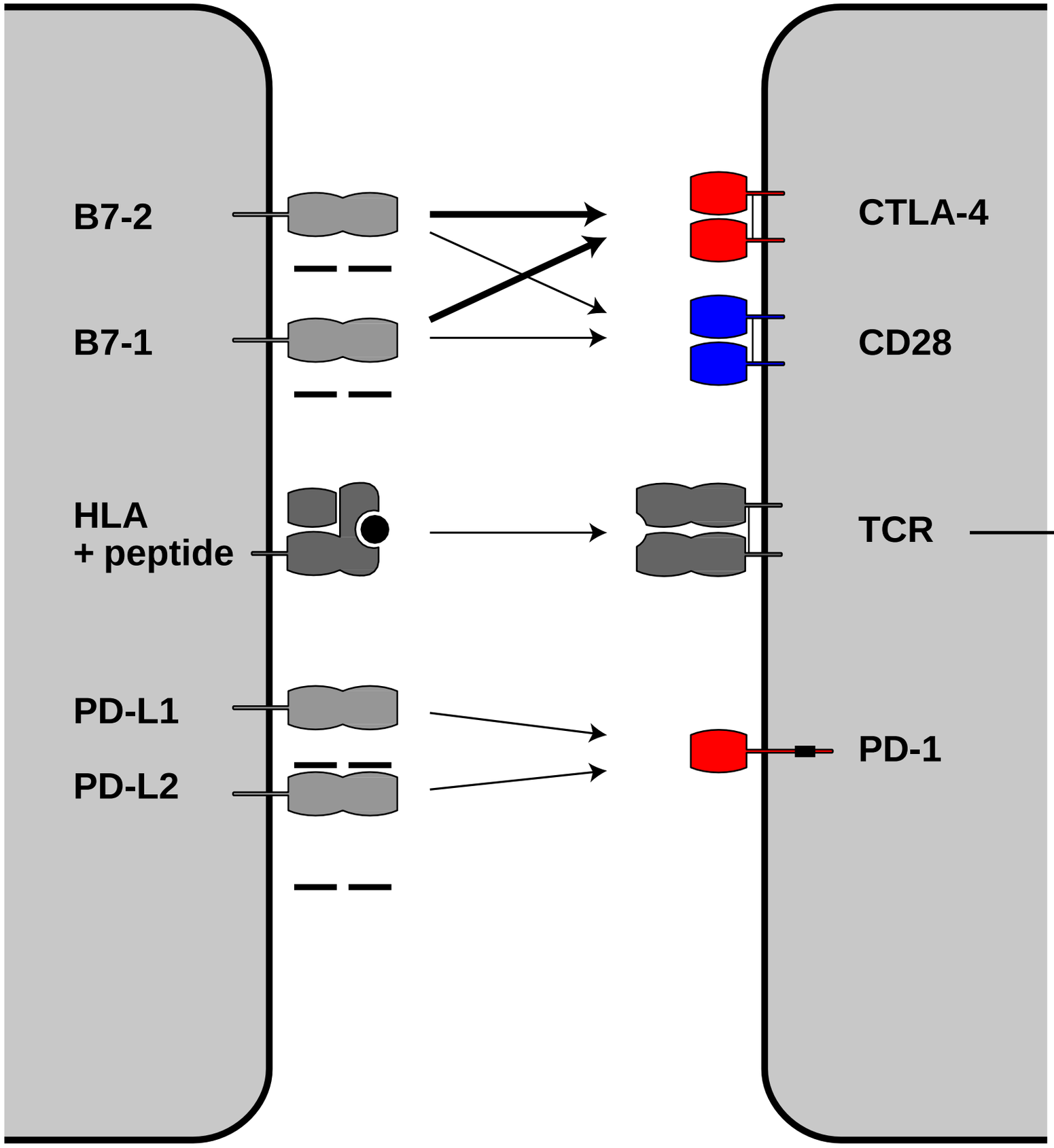
- **vaccines + immunostimulatory antibodies**

  individual mutated antigens (long peptides, RNA, viral vectors, …)
  MAGE-type antigens
  viral antigens

- **chemo ± radiotherapy + immunostimulatory antibodies**

antigen presenting cell

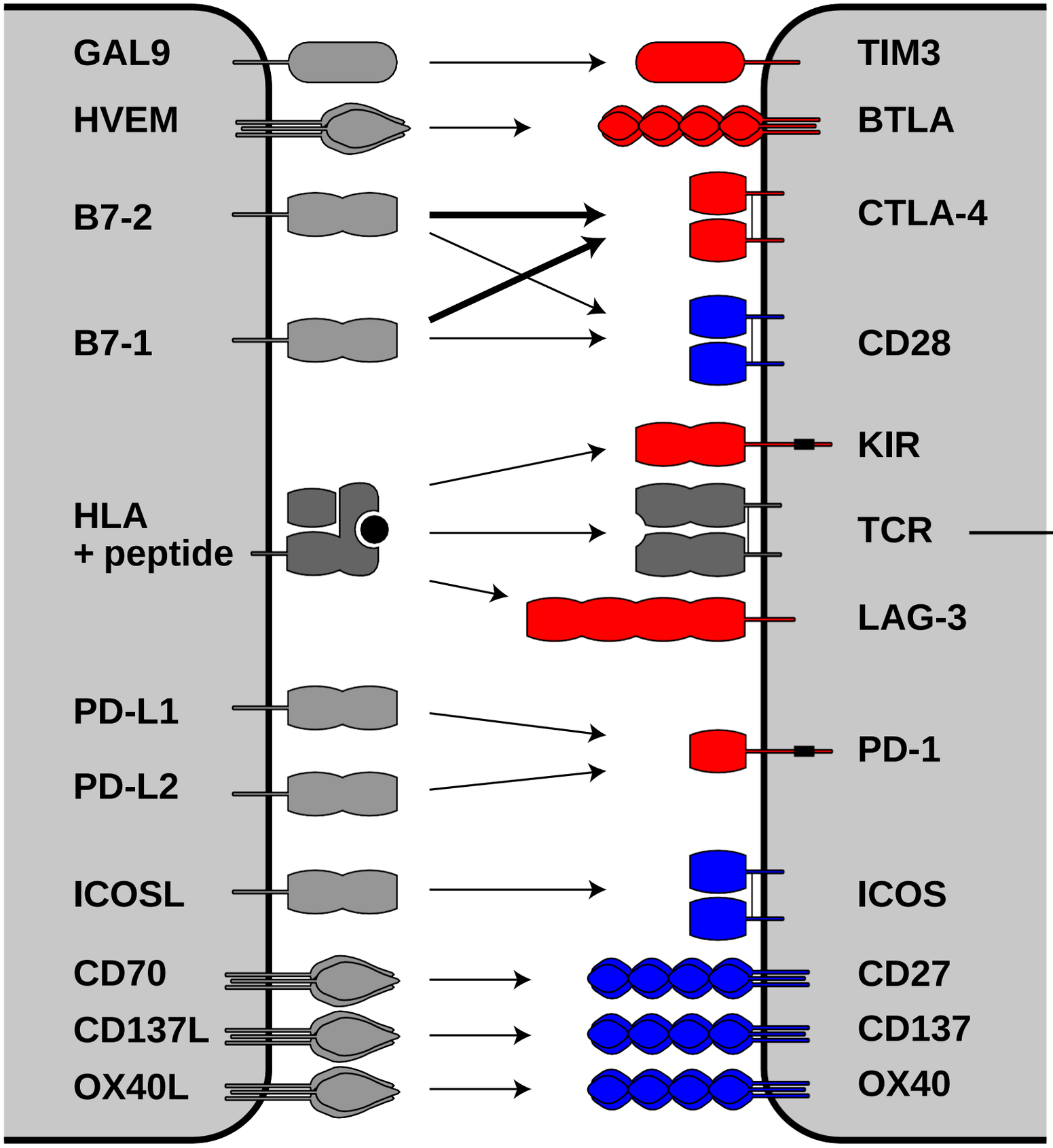
T lymphocyte



co-stimulatory receptor

inhibitory receptors

antigen presenting cell



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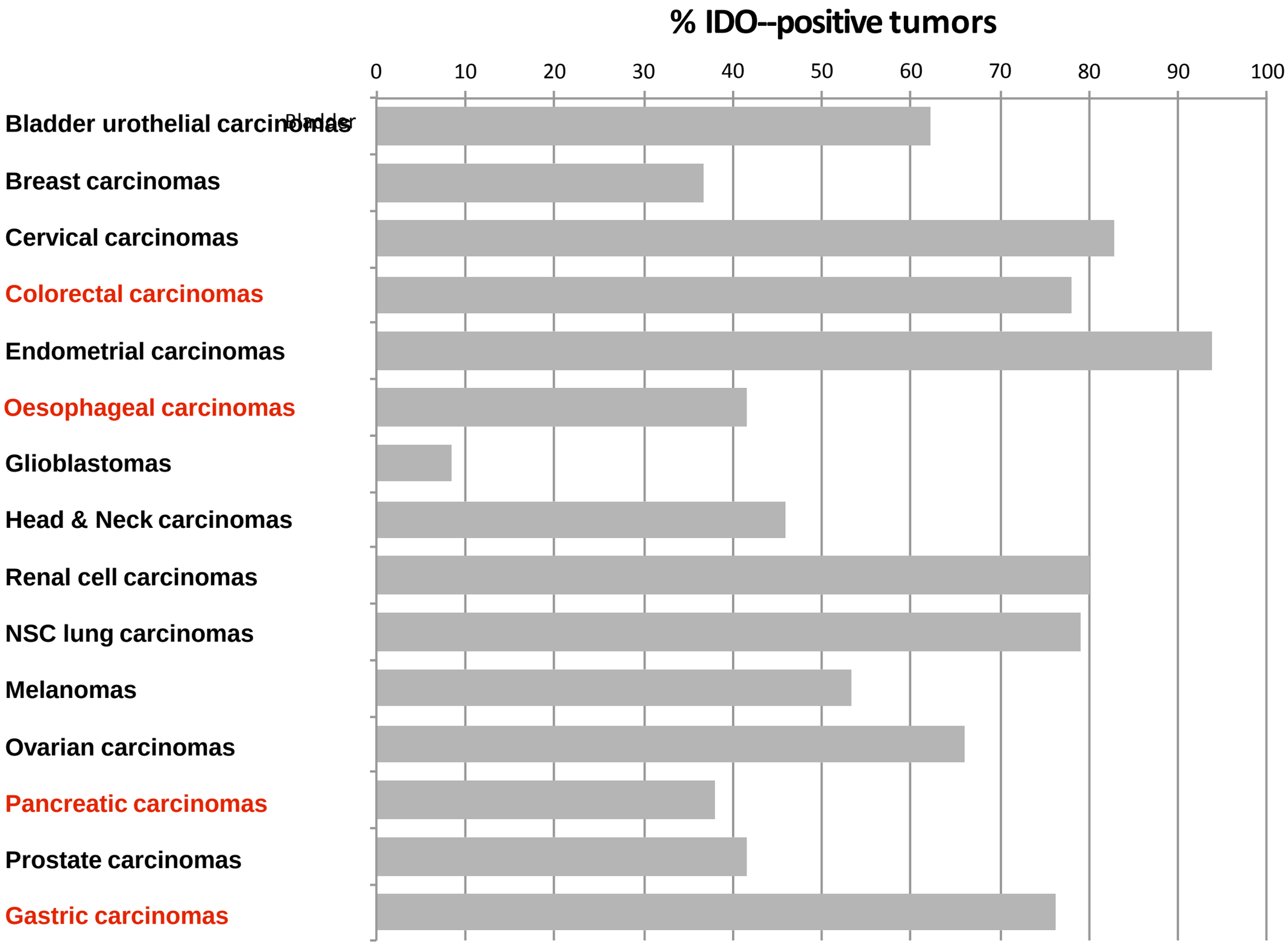
IDO1 protein expression (IHC) in human tumors (mAb 4.16H1)

(IDO: indoleamine dioxygenase)



Theate et al - 2015 - Cancer Immunol Res

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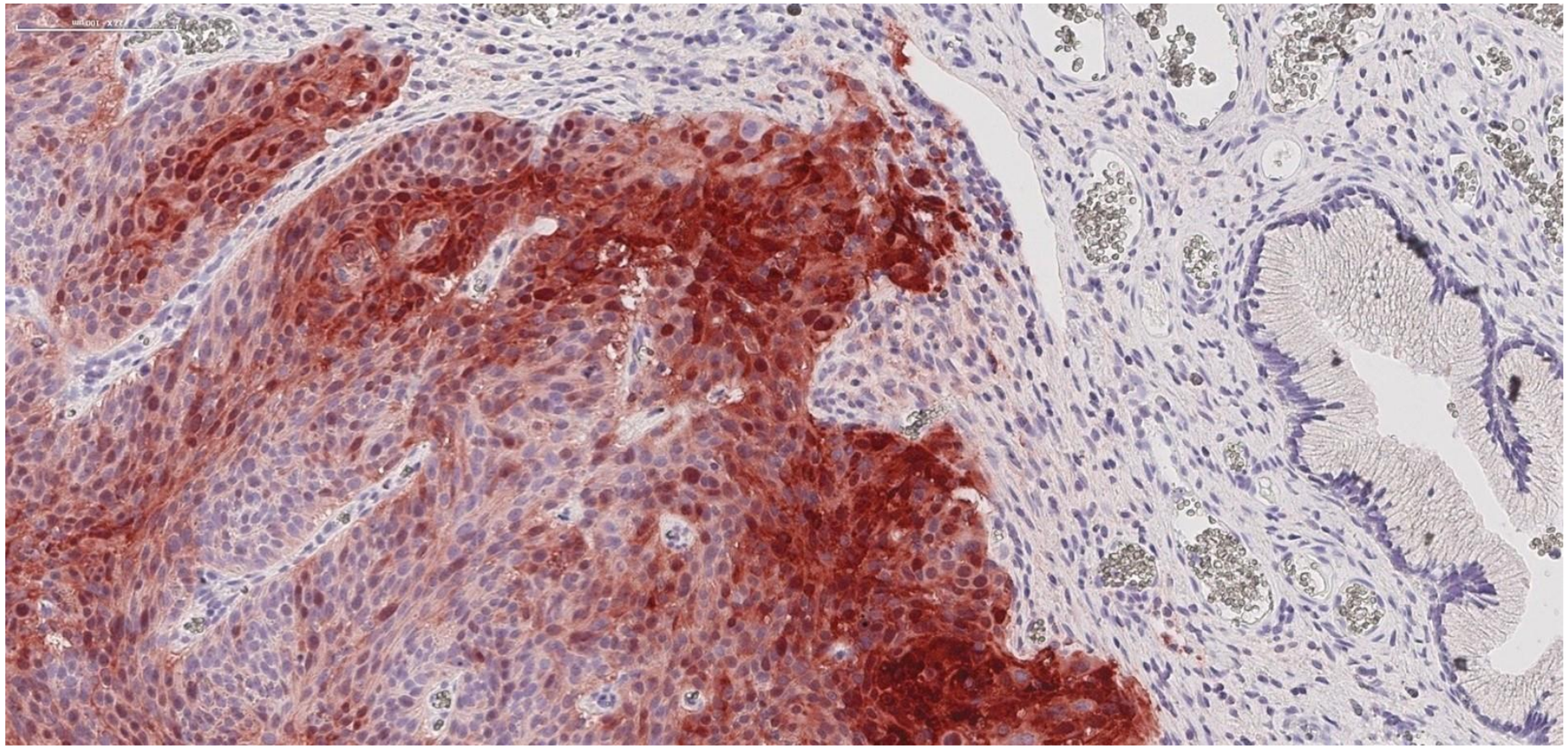
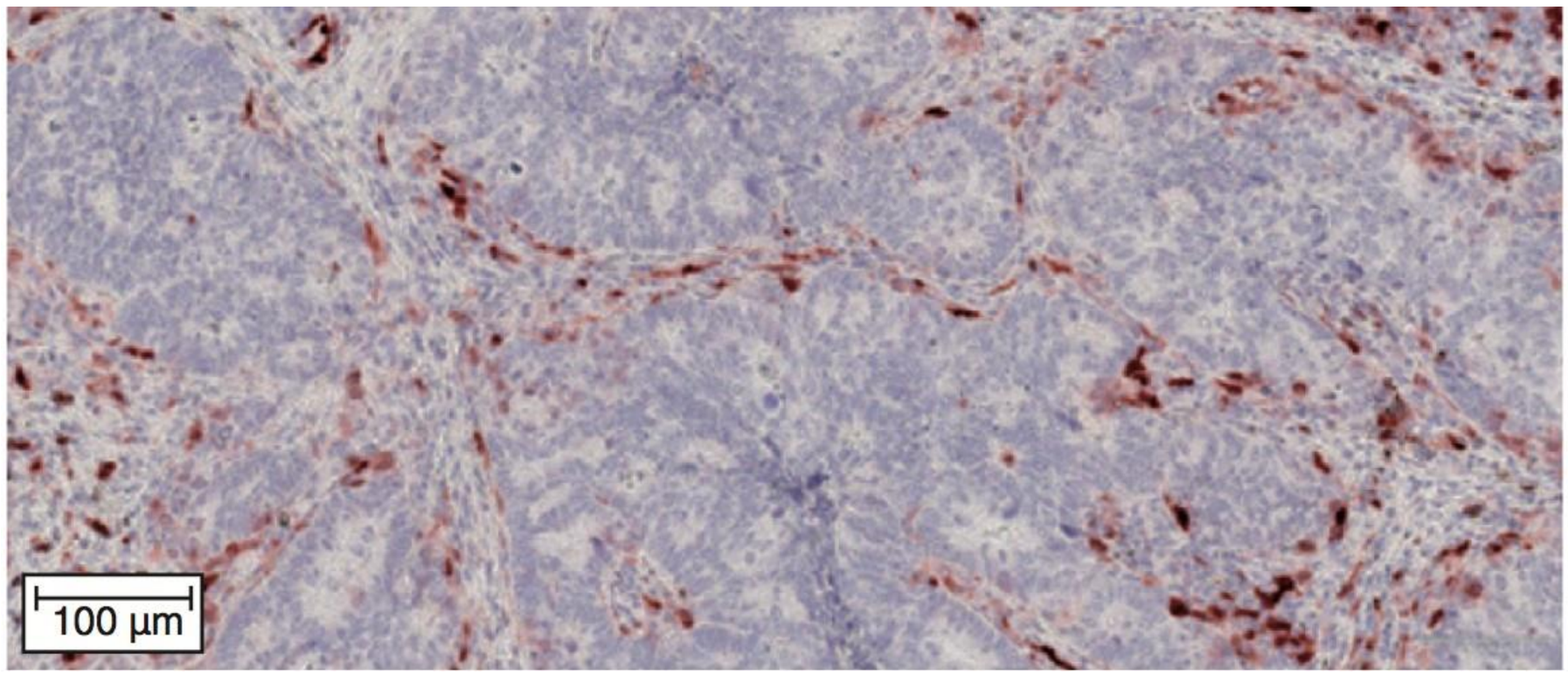
Cervical carcinoma

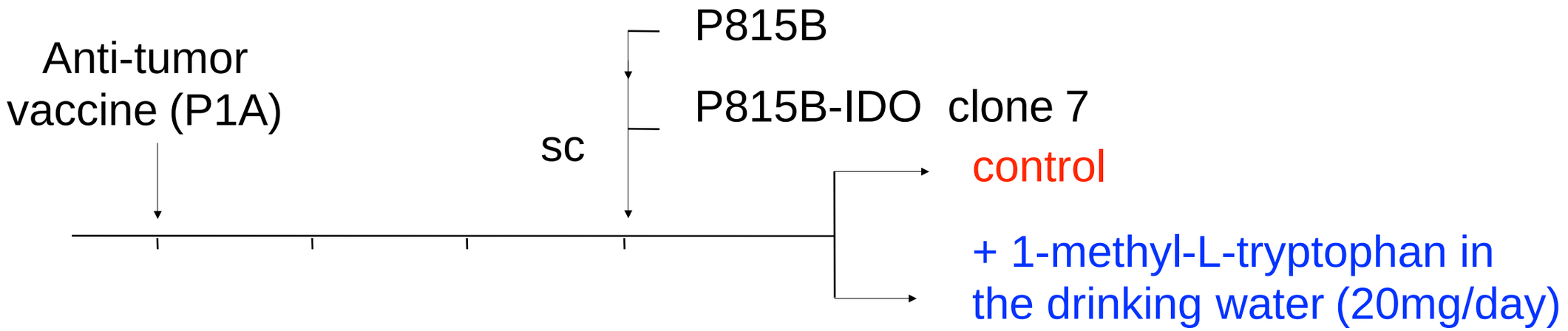


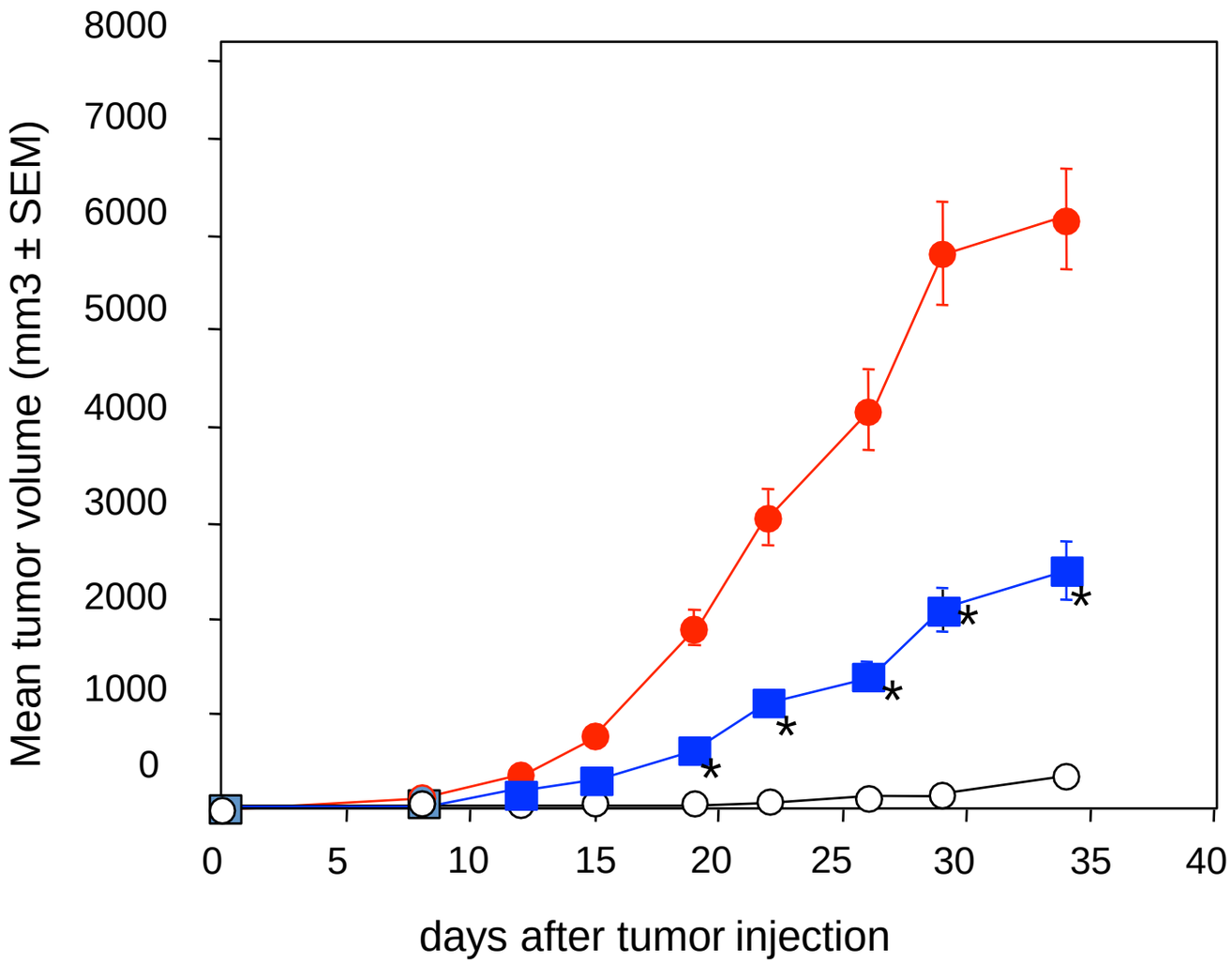
Gastric carcinoma



Theate et al - 2015 - Cancer Immunol Res

IDO1 inhibitors for cancer therapy





P815B-IDO clone 7

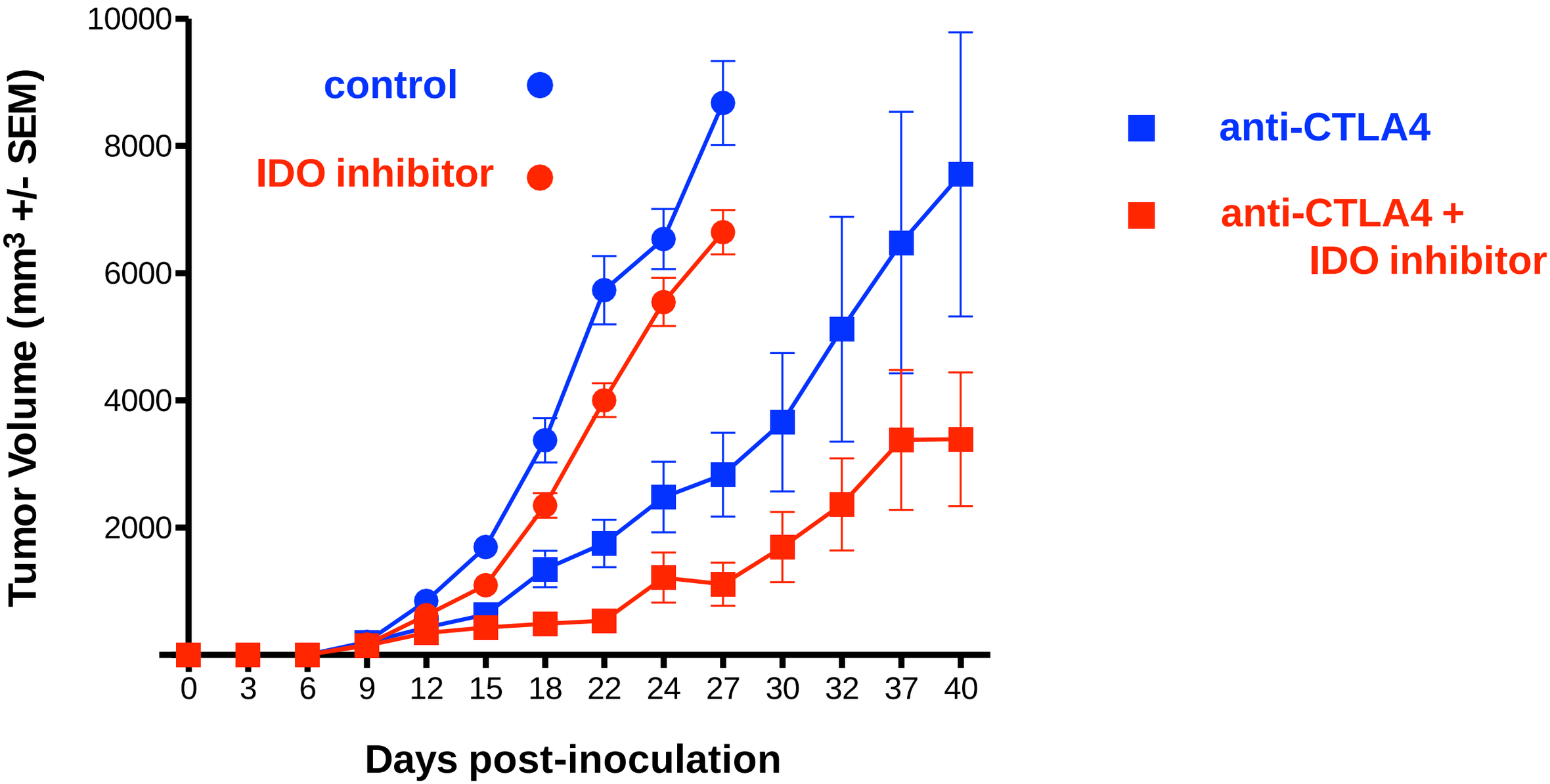
P815B-IDO clone 7
+ 1-methyl-L-tryptophan

P815B clone 1

Uyttenhove et al, 2003, Nat Med, 9, 1269-74

Colon carcinoma model CT26

subcutaneous inoculation (5 x 10^5 cells)
oral treatment with IDO inhibitor MMG-0358 (1mM in the drinking water)
starting day 3 (palpable tumor)



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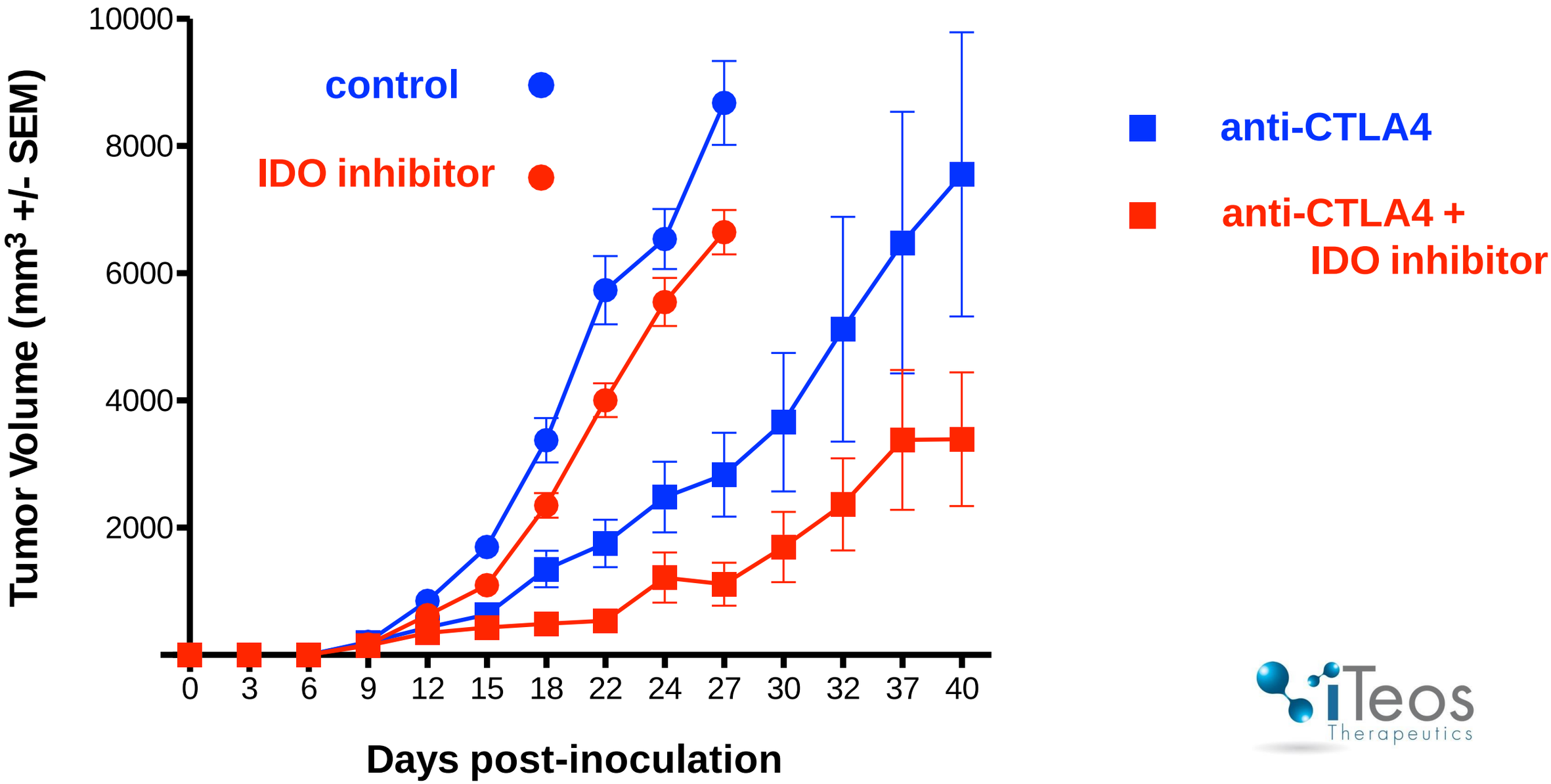

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Juliette Lamy
Wenbin Ma
Luc Pilotte
Céline Powis de Tenbossche
Florence Schramme
Marie Solvay
Vincent Stroobant
Catherine Uyttenhove
Nathalie Vigneron
JingJing Zhu

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