

Understanding the Relevant Immune Mechanisms in GI Cancers

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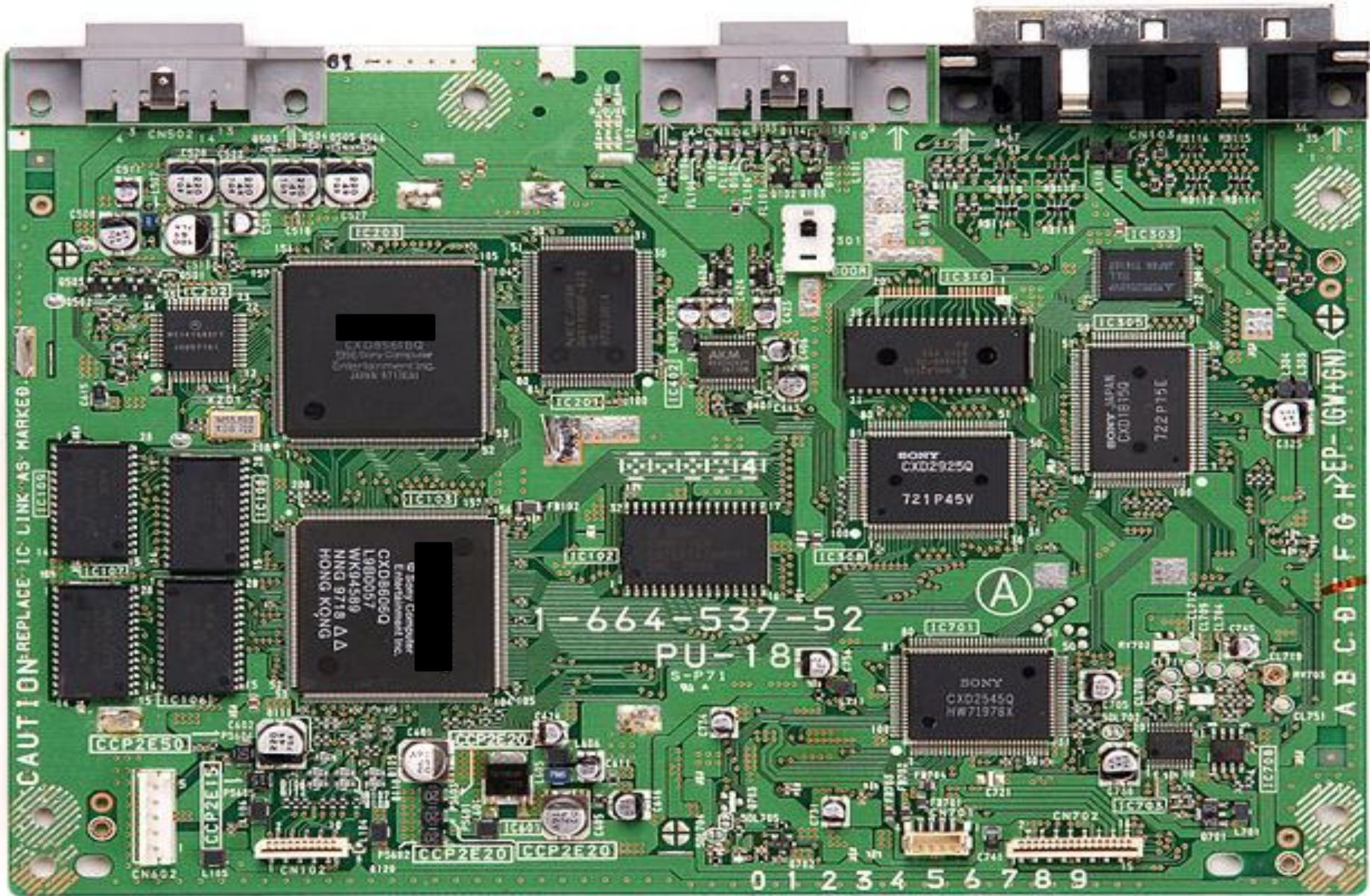
ESMO GI 2016



Immune Mechanisms in GI Cancers



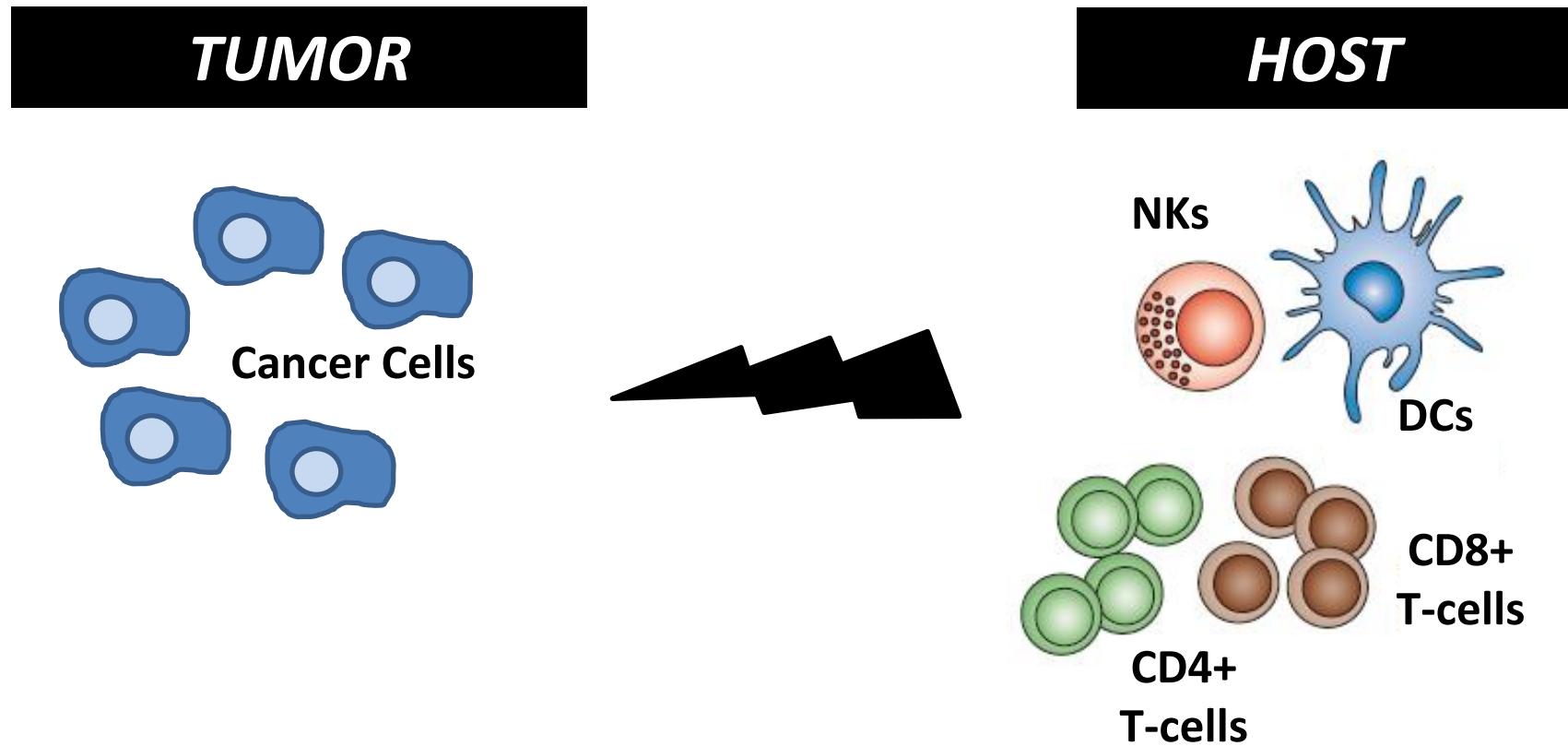
免疫機制在胃腸道腫瘤



Immuknowledgy

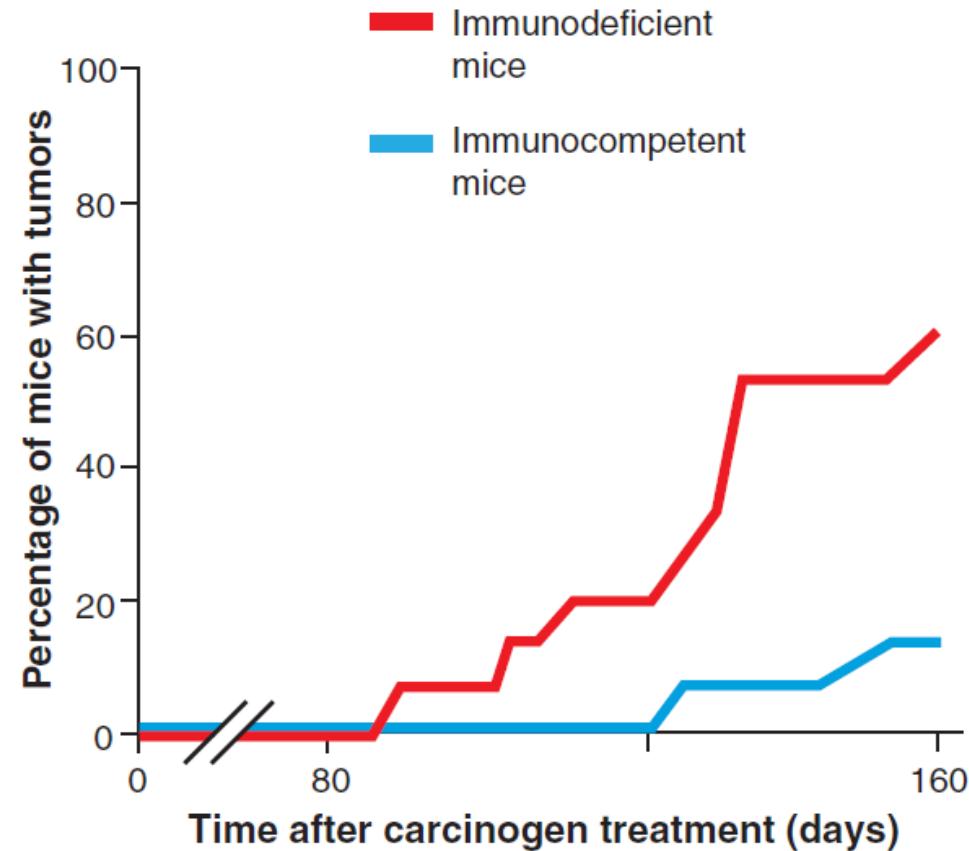


Role or the Immune System: Limited to Immuno-Surveillance ?



Adapted from Colombo MP, et al. Nat Rev Cancer. 2007.

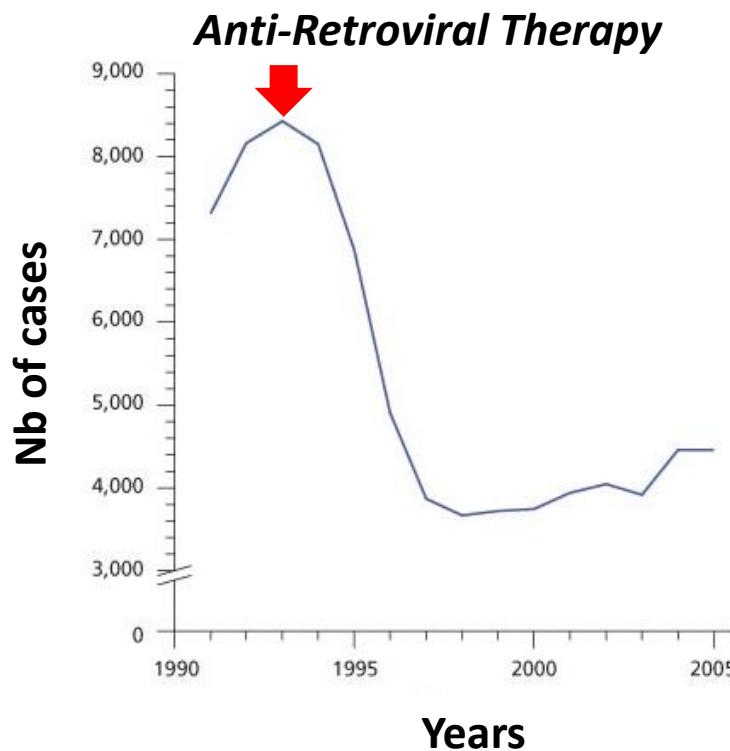
Immune Surveillance of Cancers (Mice)



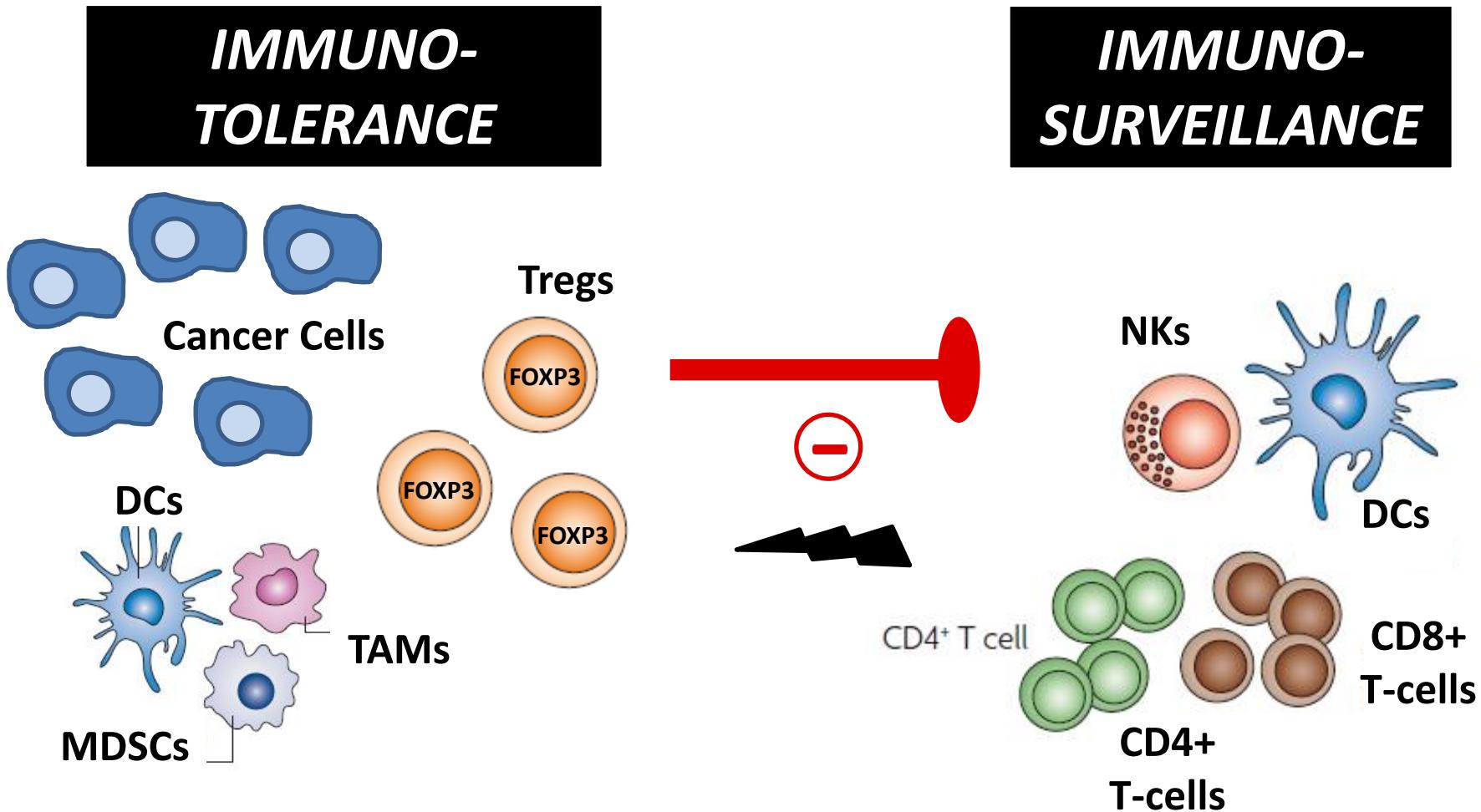
Schreiber RD, et al. Science 2011;331:1565–70.

Immune Surveillance of Cancers (Humans)

Cancers Among People Living with AIDS in the USA

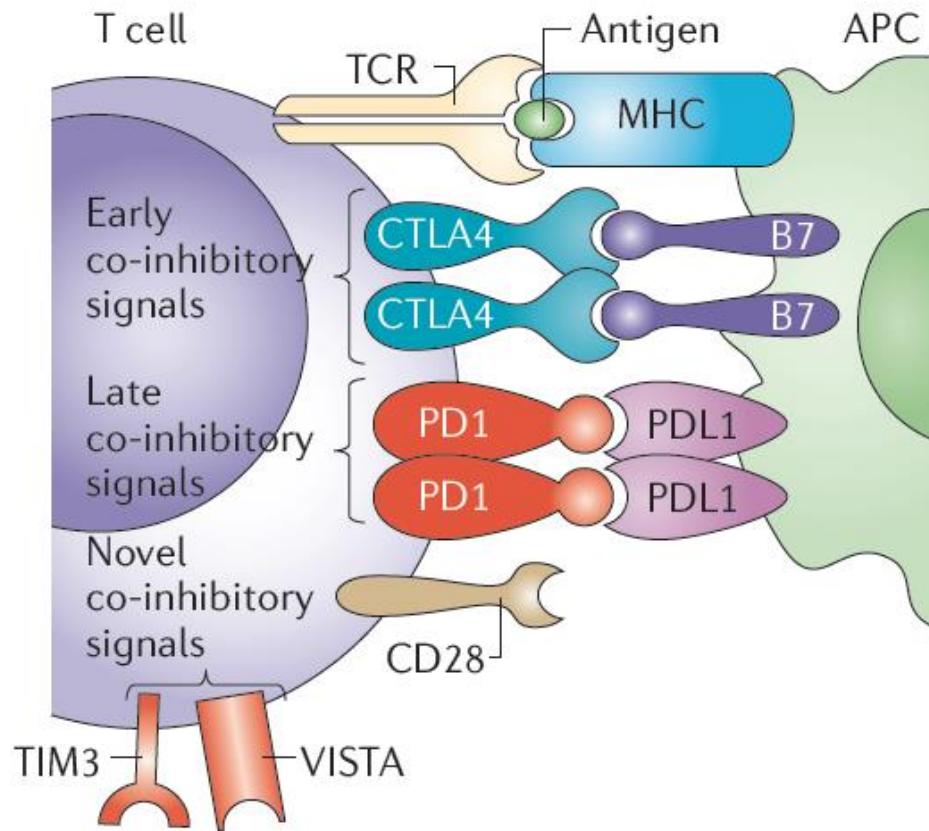


Subsets of Immune Cells can also Promote Cancers!



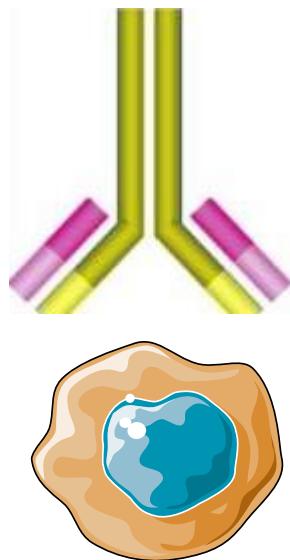
Adapted from Colombo MP, et al. *Nat Rev Cancer*. 2007.

Lymphocyte Inhibition



Paradigm Shift in Cancer Therapy

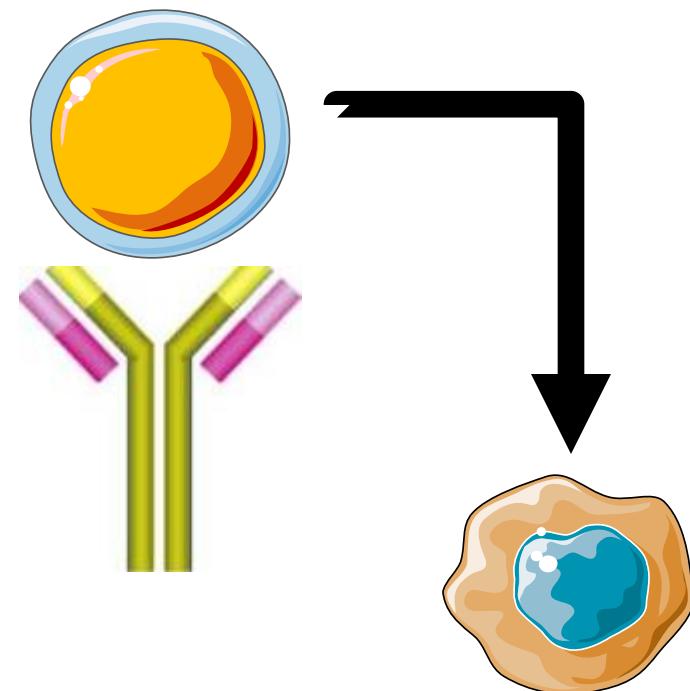
Historical Paradigm:
Targeting Tumor Cells



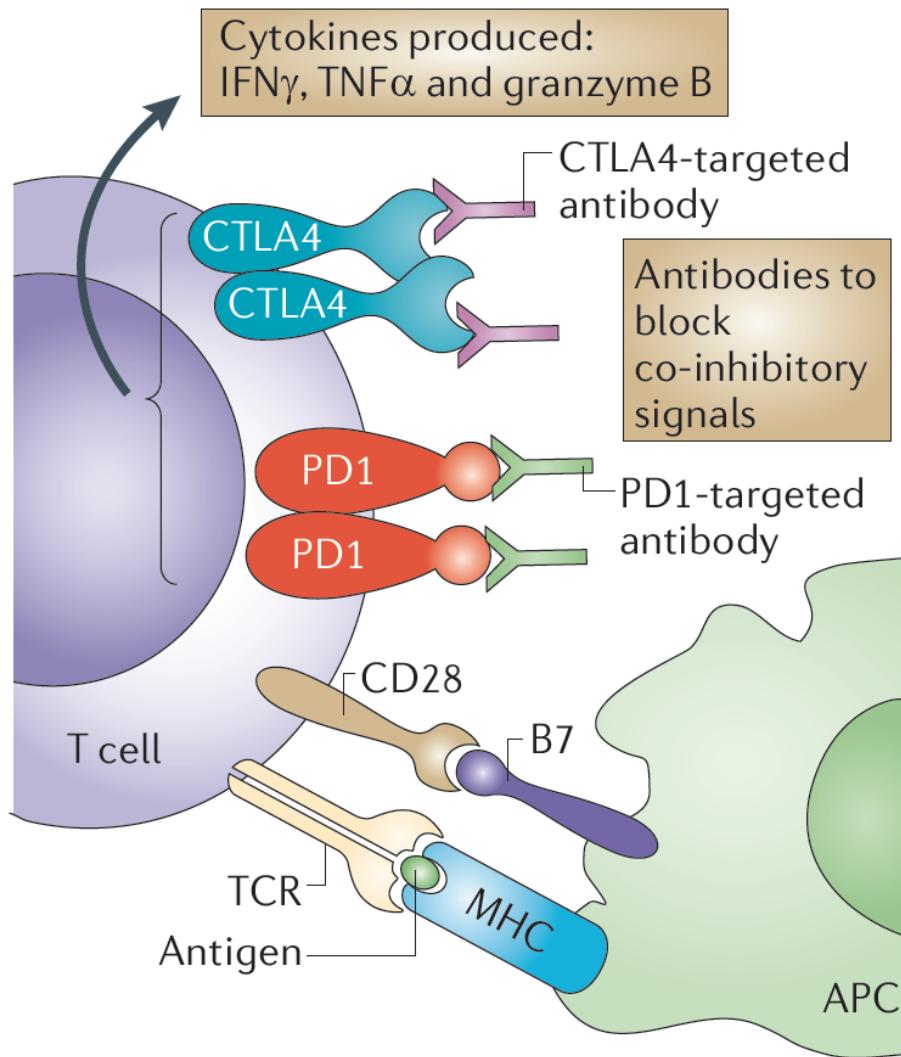
Tumor Cell

New Paradigm:
Targeting Immune Cells

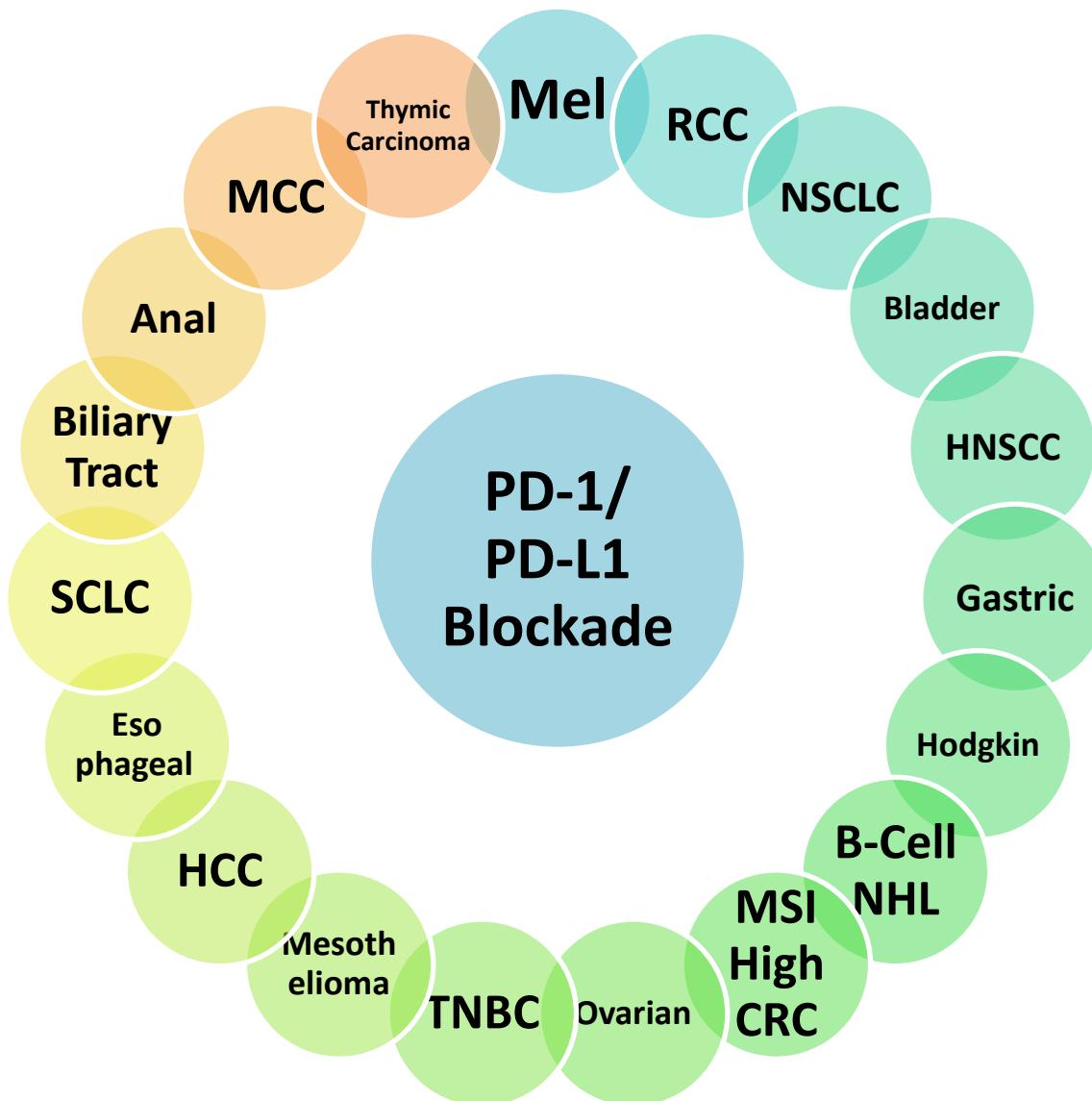
Lymphocyte



Immune Checkpoint Blockade Therapy

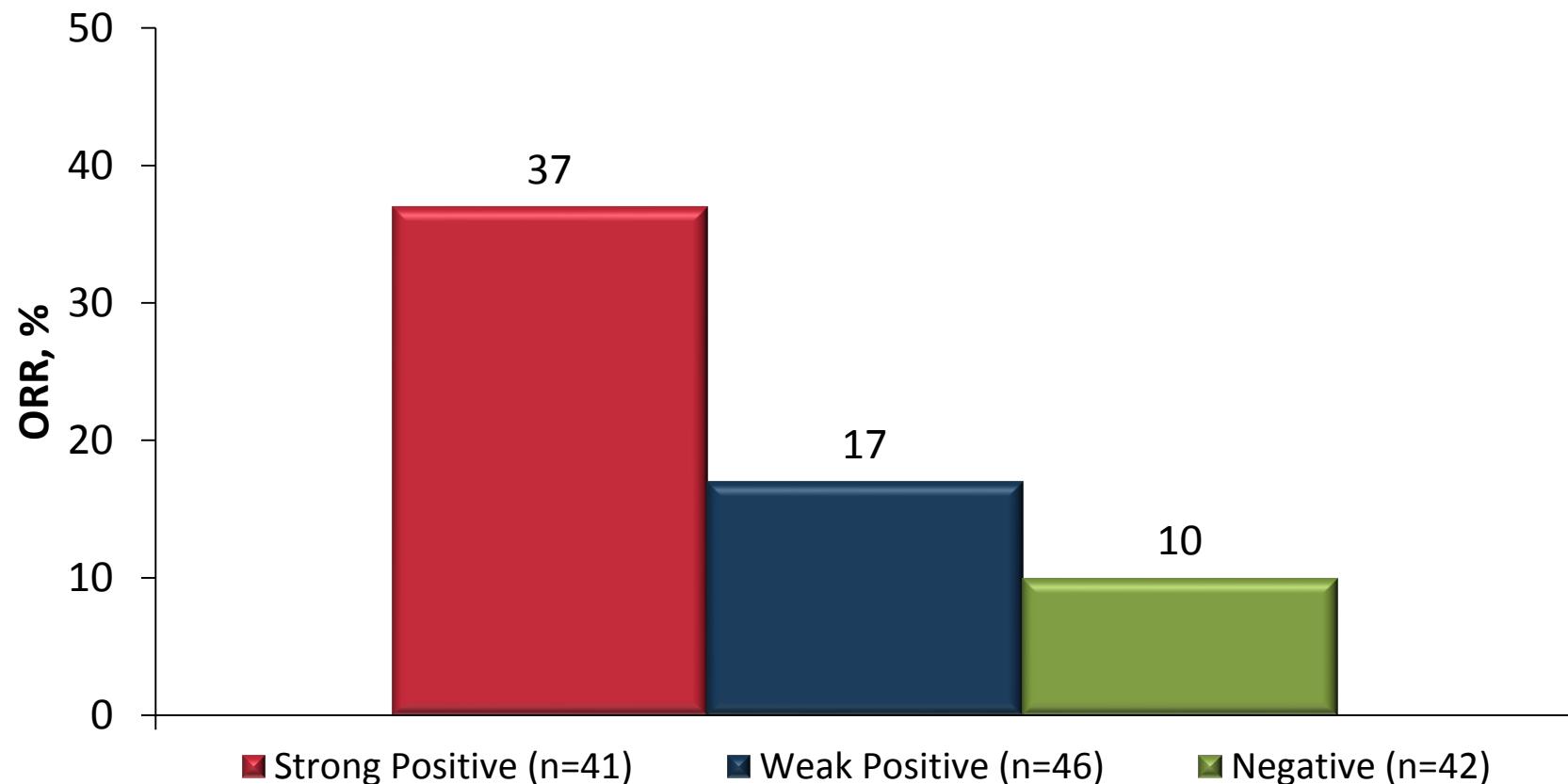


PD-Lomas 2016



PREDICTIVE VALUE OF PD-L1 EXPRESSION

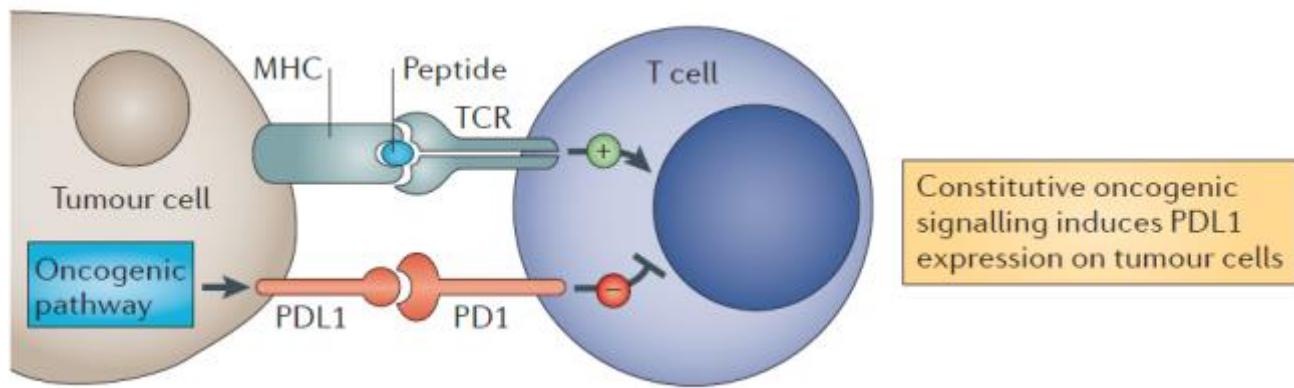
**Response Rate by Level of PD-L1 Expression in NSCLC with Pembrolizumab
(RECIST 1.1, Central Review)**



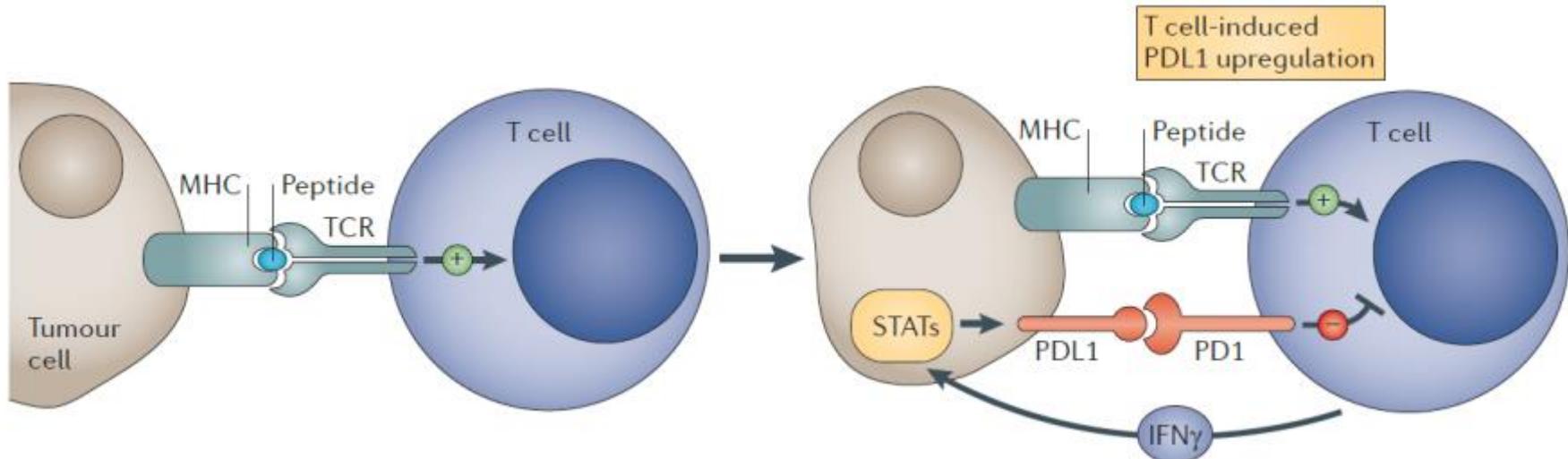
^aEvaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria.
Analysis cut-off date: March 3, 2014.

PD-L1 can be expressed in 2 ways

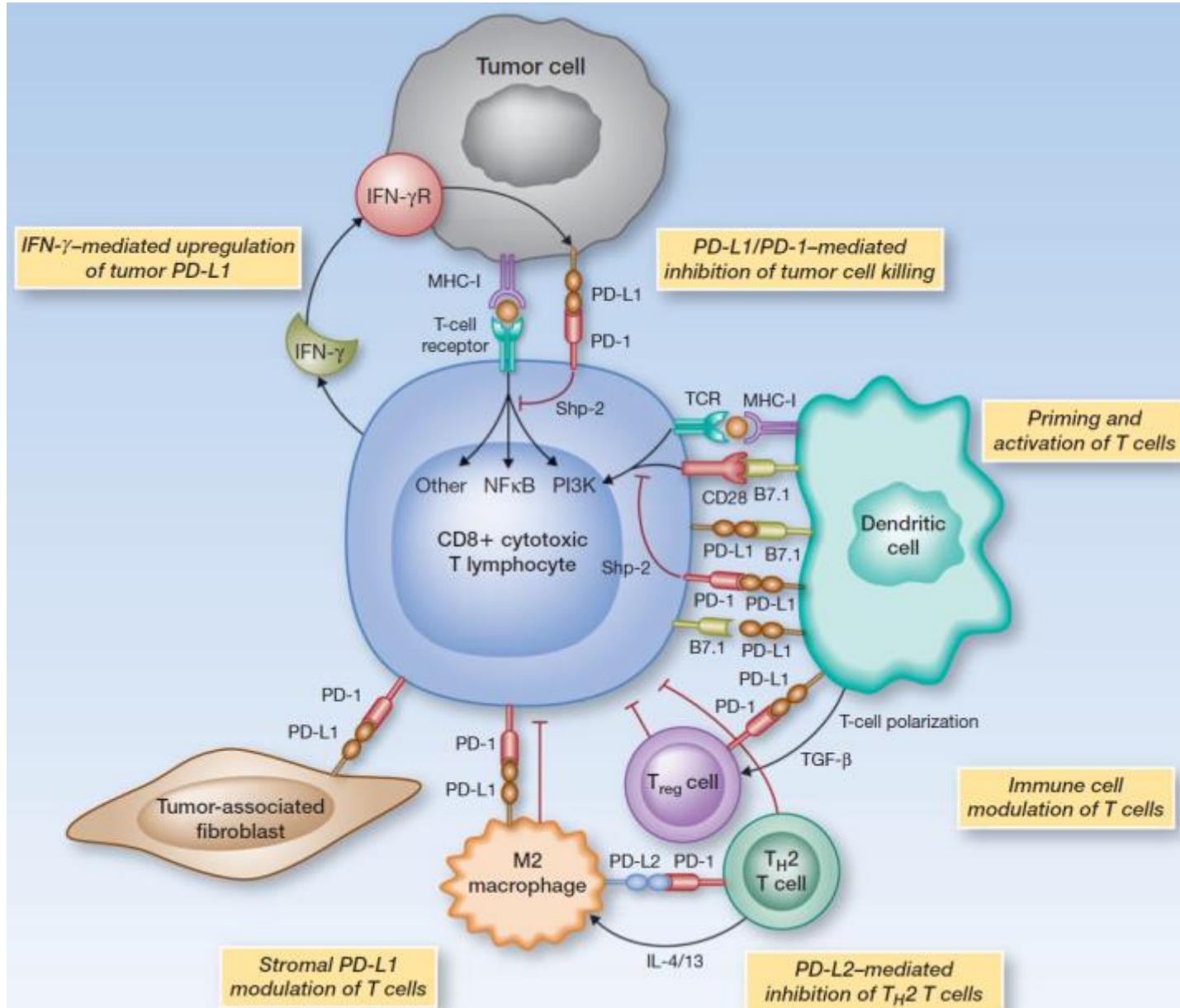
CONSTITUTIVE



INDUCTIBLE



Many Cell Types can be PD-L1+



PD-L1 IHC Stainings

Company	BMS	MERCK	ROCHE GENENTECH (3)
Clone	28–8 (Epitomics)	22C3 (Merck)	SP142 (Ventana)
Assay	Dako	Dako	Ventana
Scoring	Cancer Cells	Cancer Cells & stroma	Cancer & Immune Cells
Melanoma Threshold	5% ¹	1% ²	IHC 1,2,3 ³ : TC:1%, 5%, 50%
NSCLC Threshold	1-10% ⁴	50% ⁵	IC:1%, 5%, 10%

¹ Robert C, et al. N Engl J Med 2014.

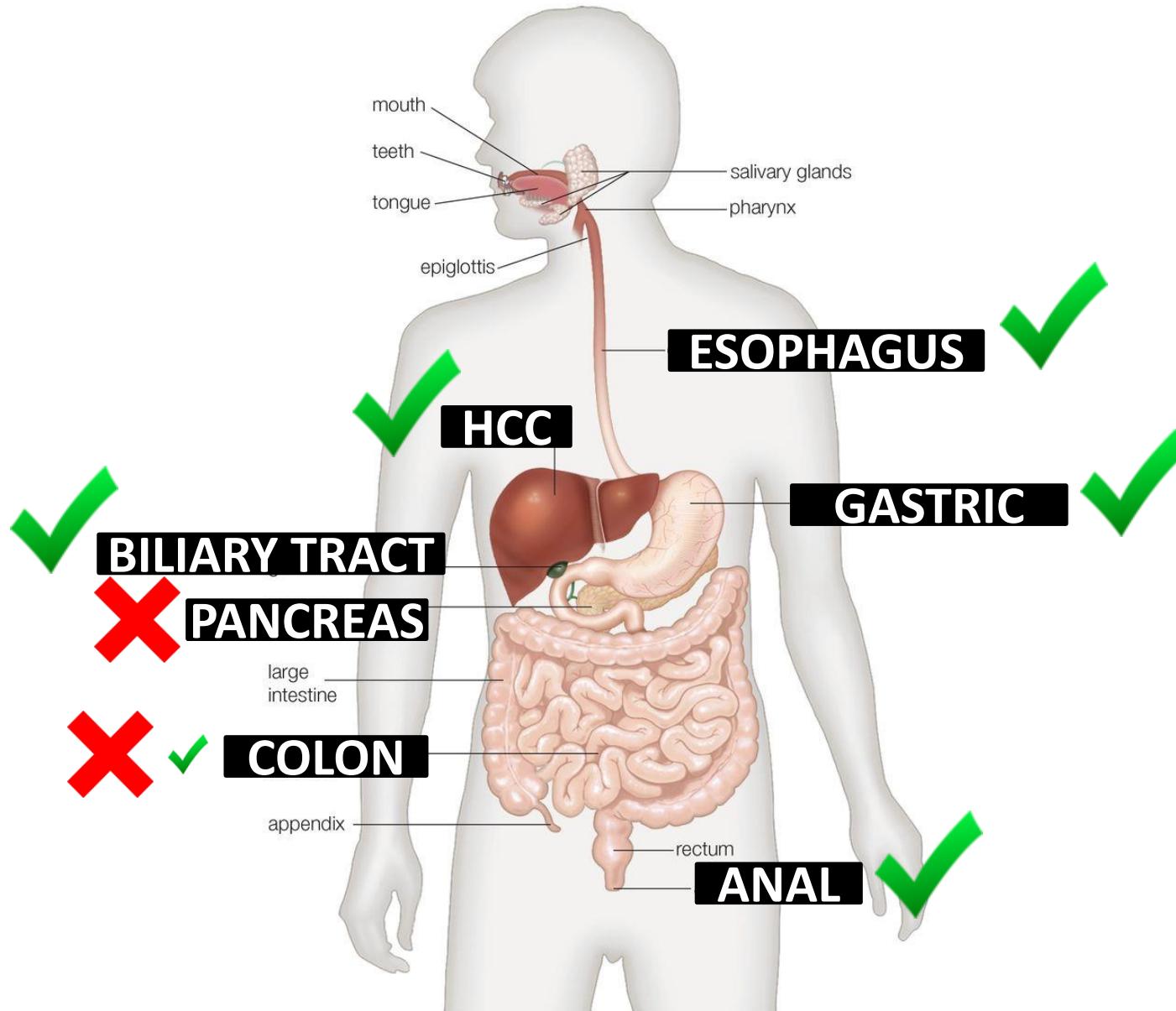
² Robert C et al. N Engl J Med 2015.

³ Herbst RS et al, Nature 2014.

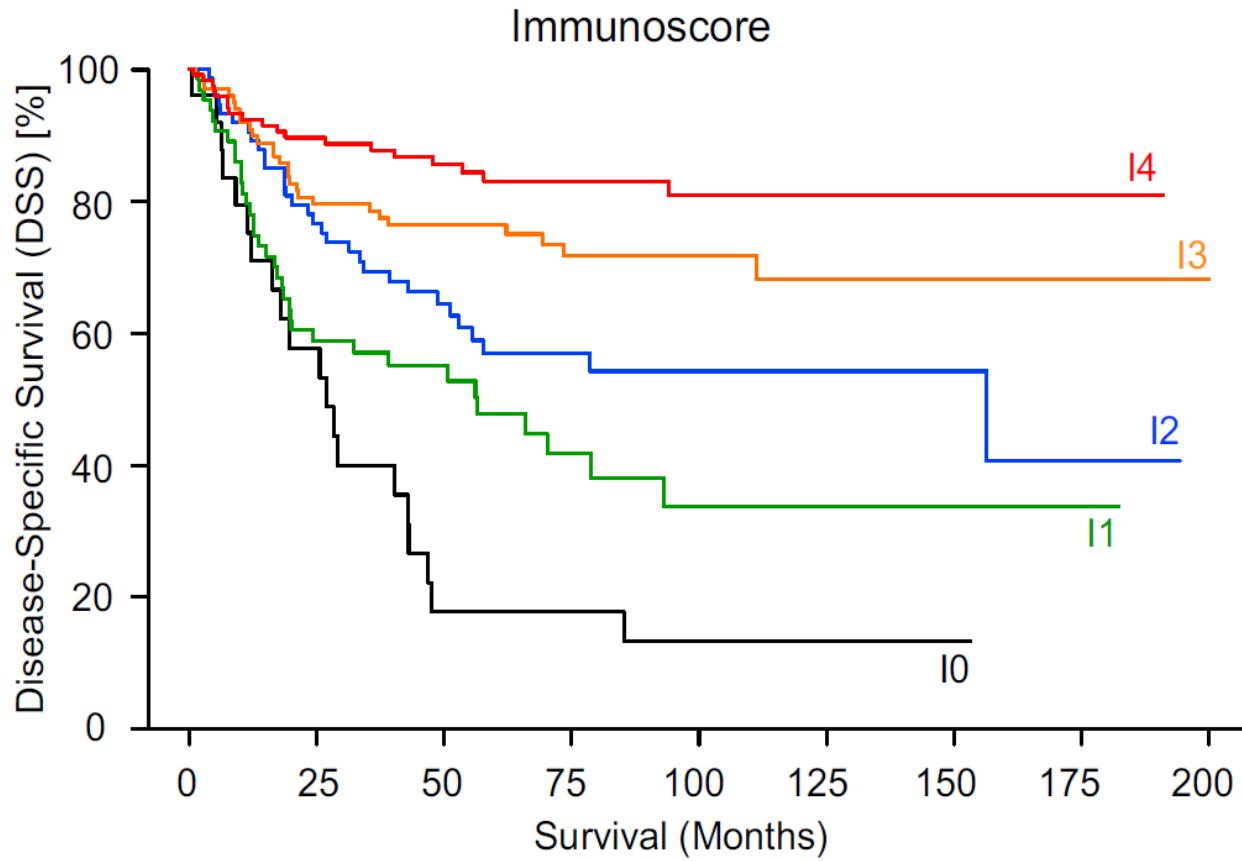
⁴ Dolled-Filhart M et al, Poster 11065, ASCO 2015

⁵ Brahmer J, et al. N Engl J Med 2015.

Sensitivity of GI Cancers to α PD-1/PD-L1

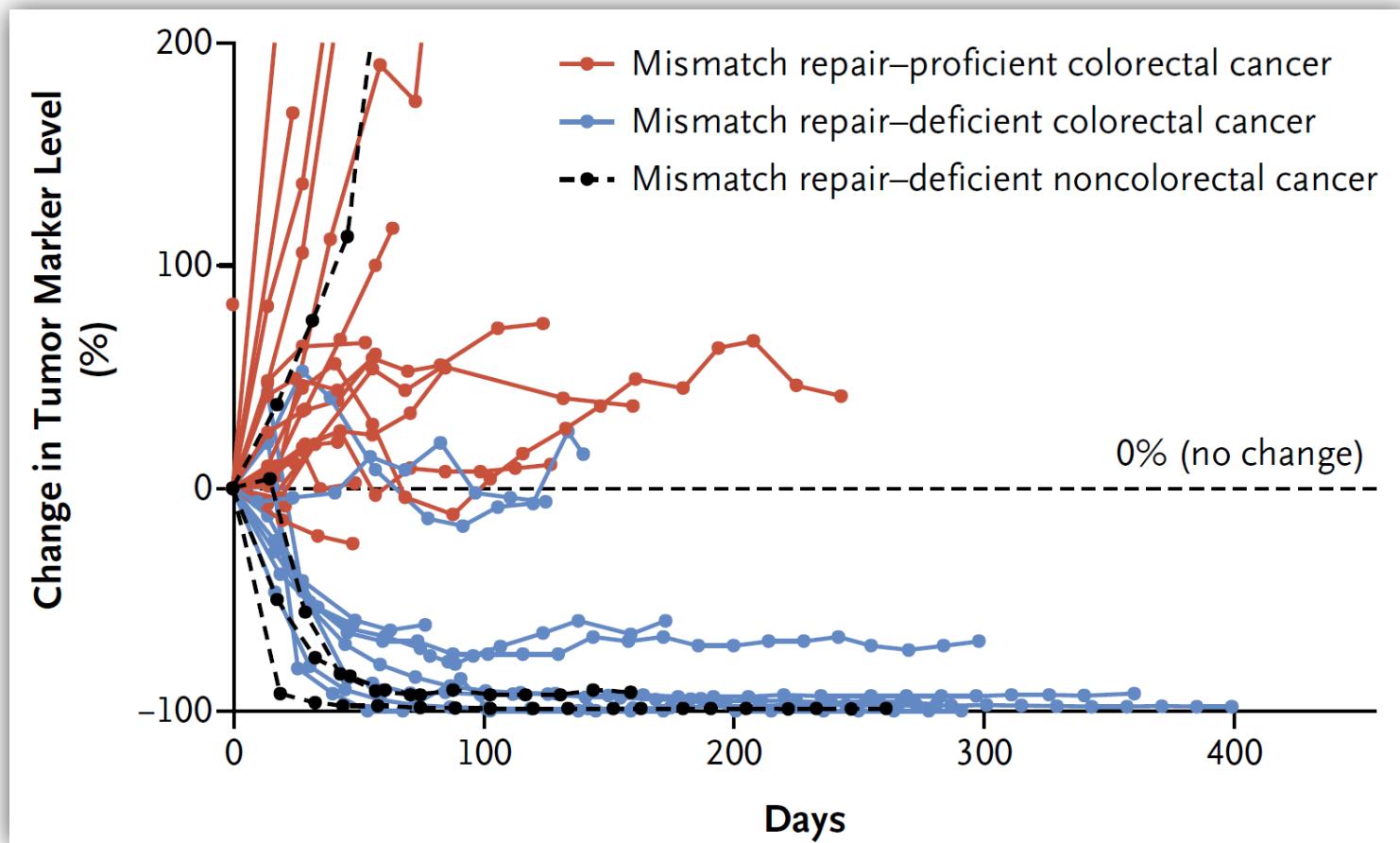


Impact of TILs in CRC

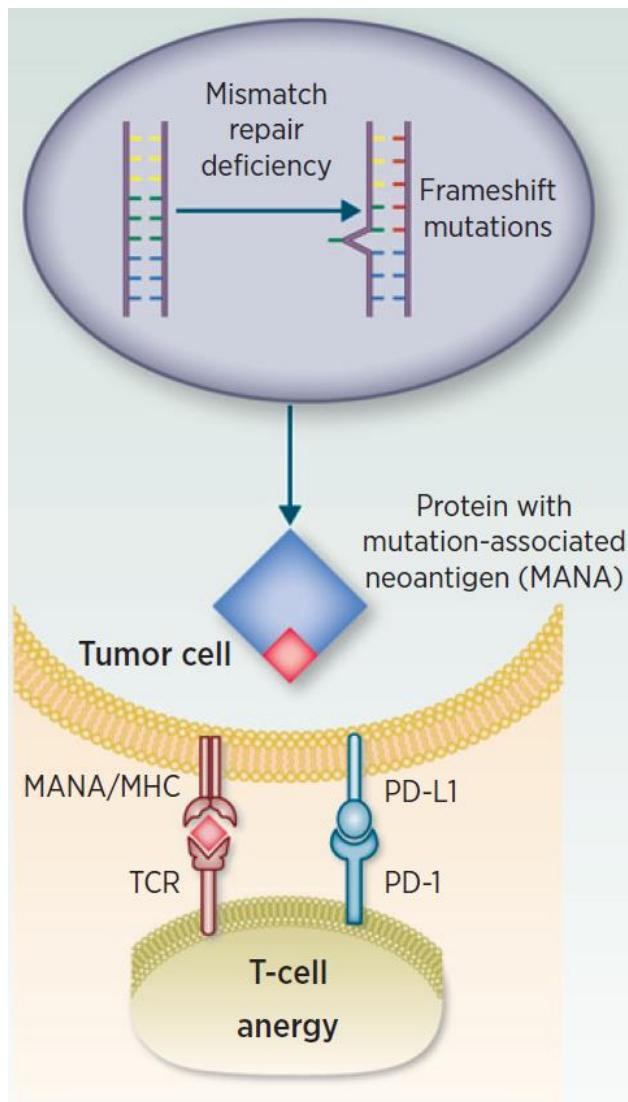


Mlecnik B, et al. *Immunity*. 2016.

MSI: best αPD-1 predictive biomarker

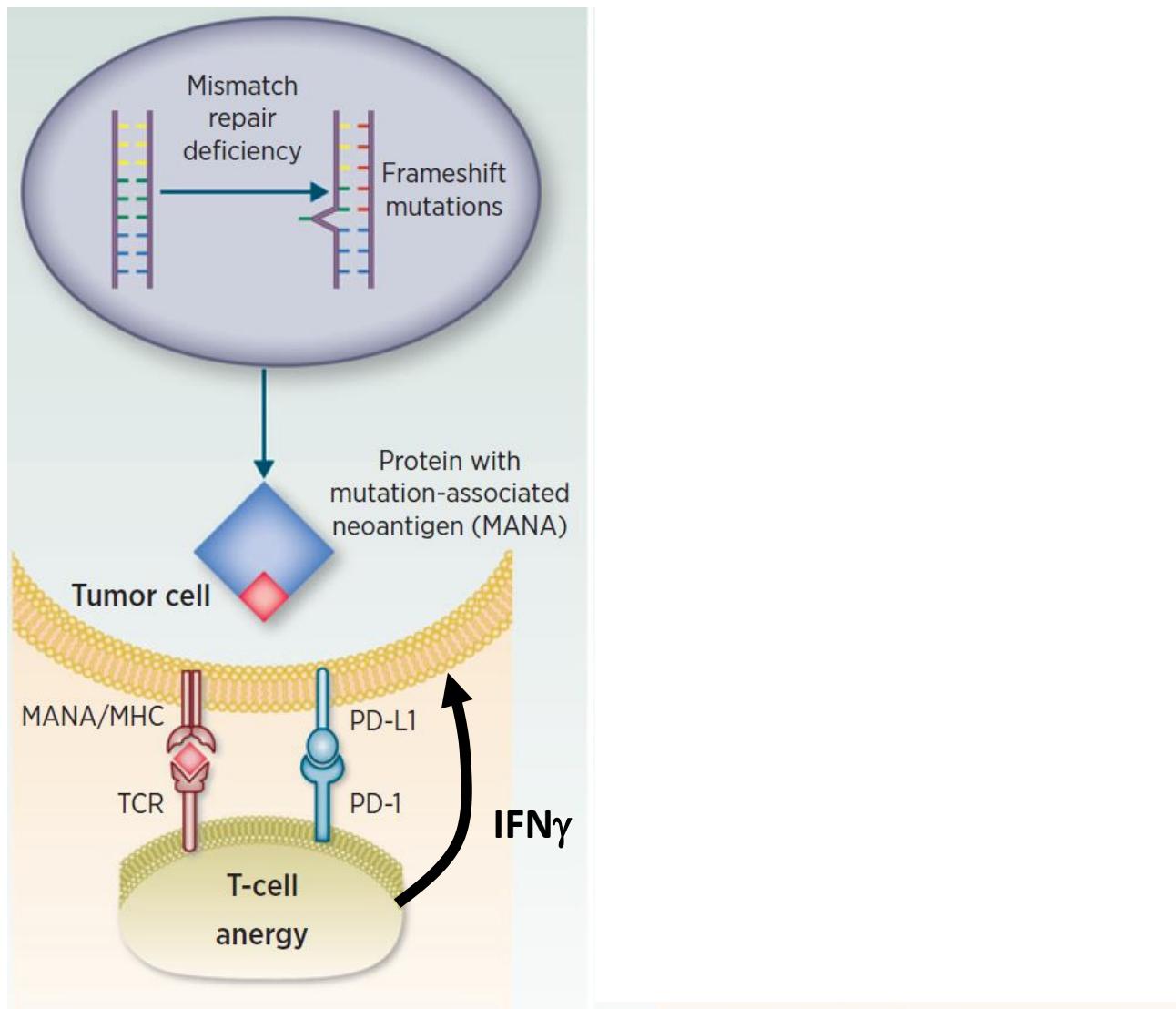


Immune Impact of MSI Status



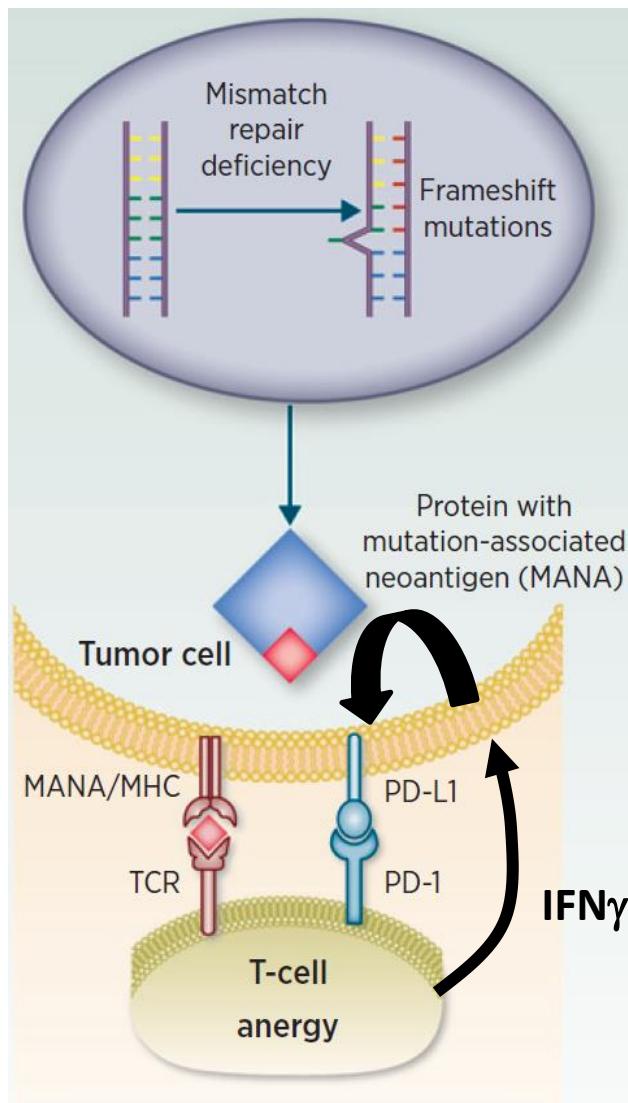
Dudley JC, et al. Clin. Cancer Res. 2016.

Immune Impact of MSI Status



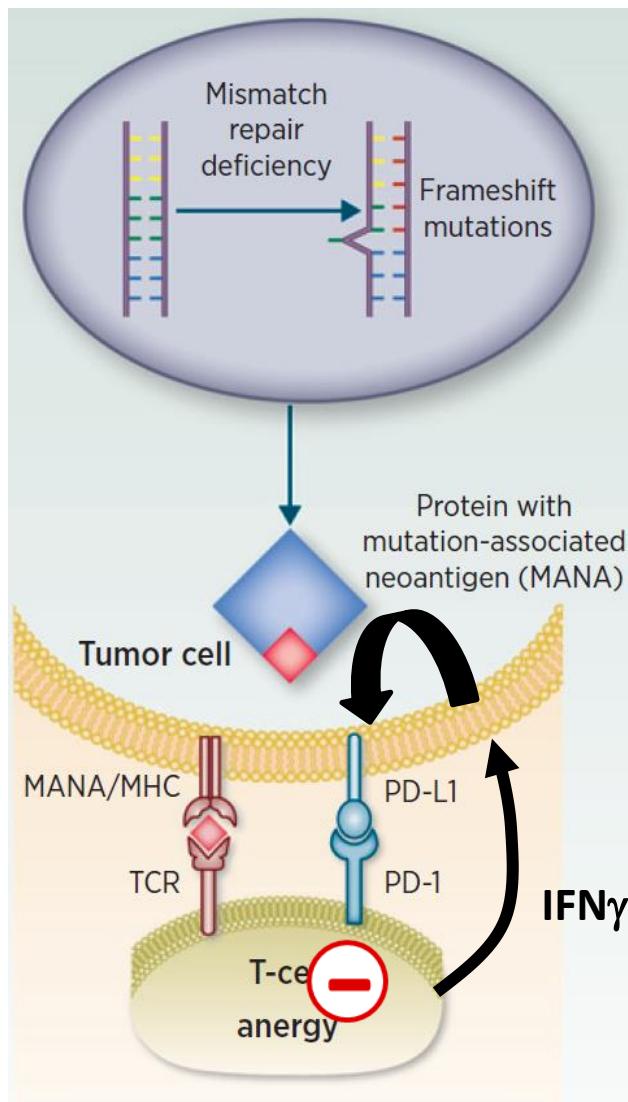
Dudley JC, et al. Clin. Cancer Res. 2016.

Immune Impact of MSI Status



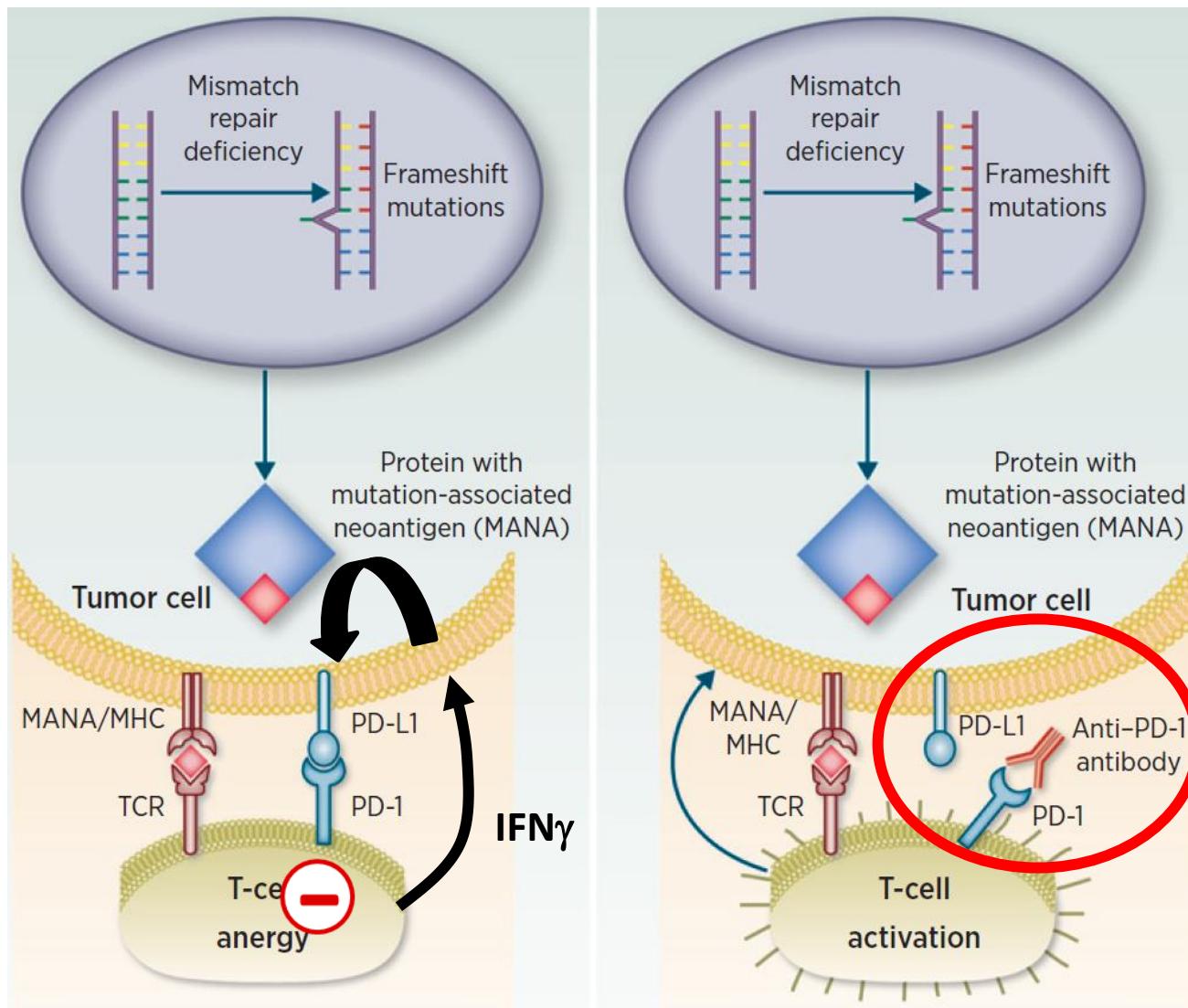
Dudley JC, et al. Clin. Cancer Res. 2016.

Immune Impact of MSI Status



Dudley JC, et al. Clin. Cancer Res. 2016.

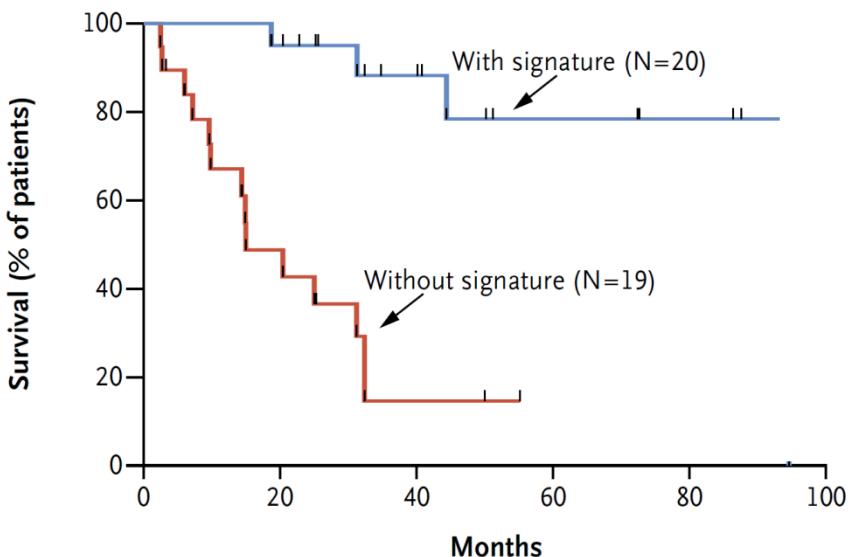
Immune Impact of MSI Status



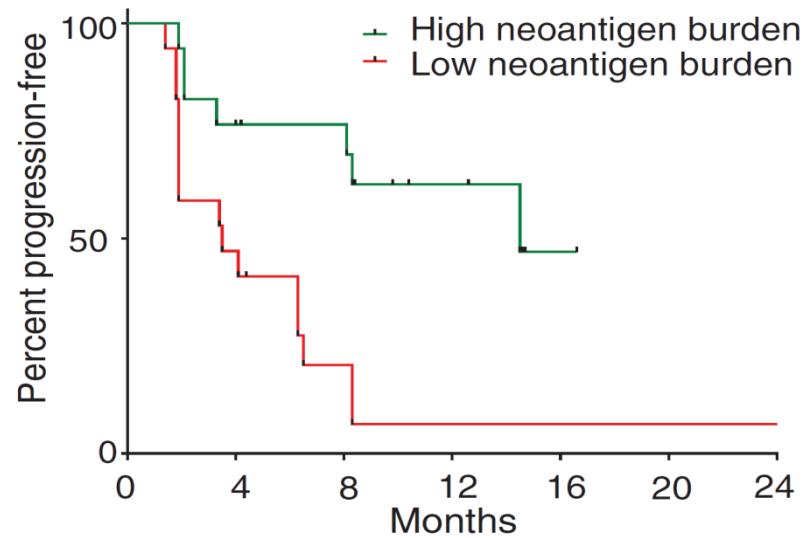
Dudley JC, et al. Clin. Cancer Res. 2016.

Anti-Neoepitopes Immune Responses

MELANOMA



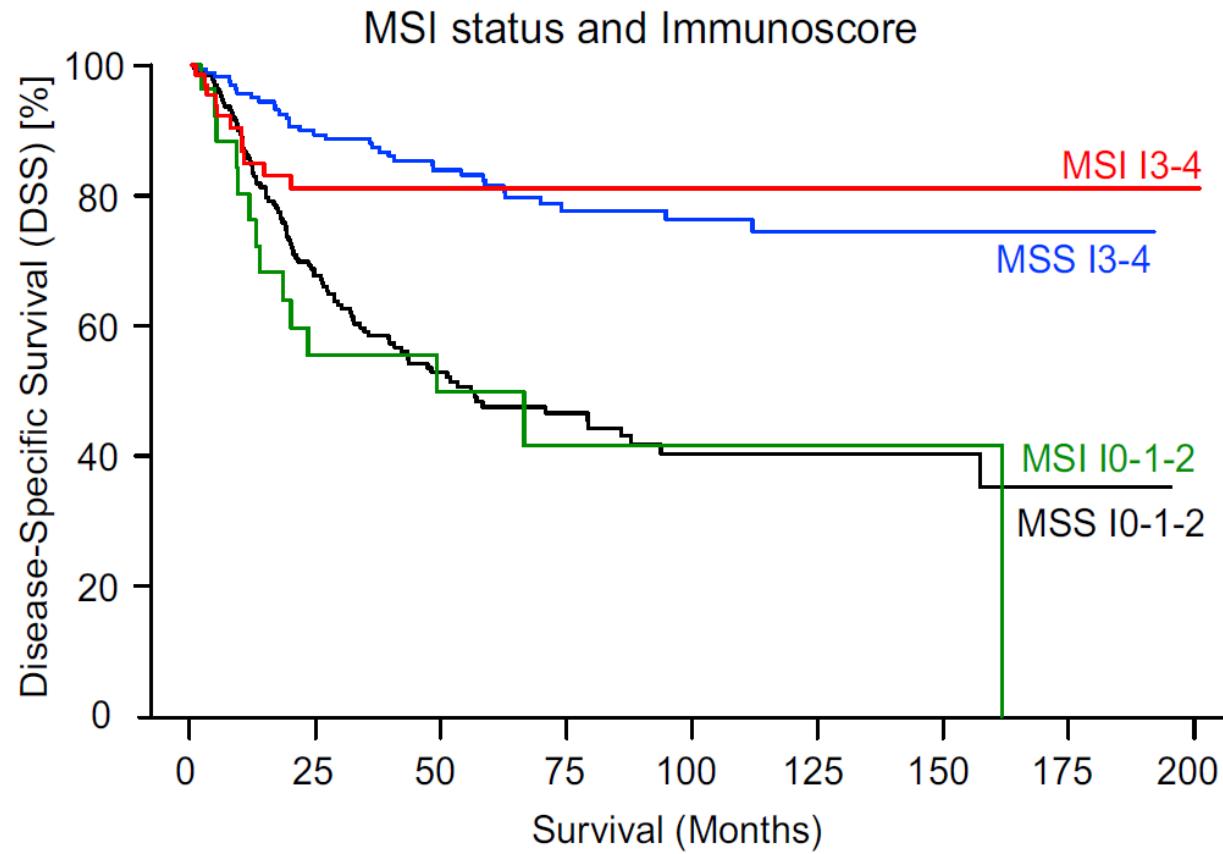
NSCLC



Snyder A, et al. N Engl J Med 2014.

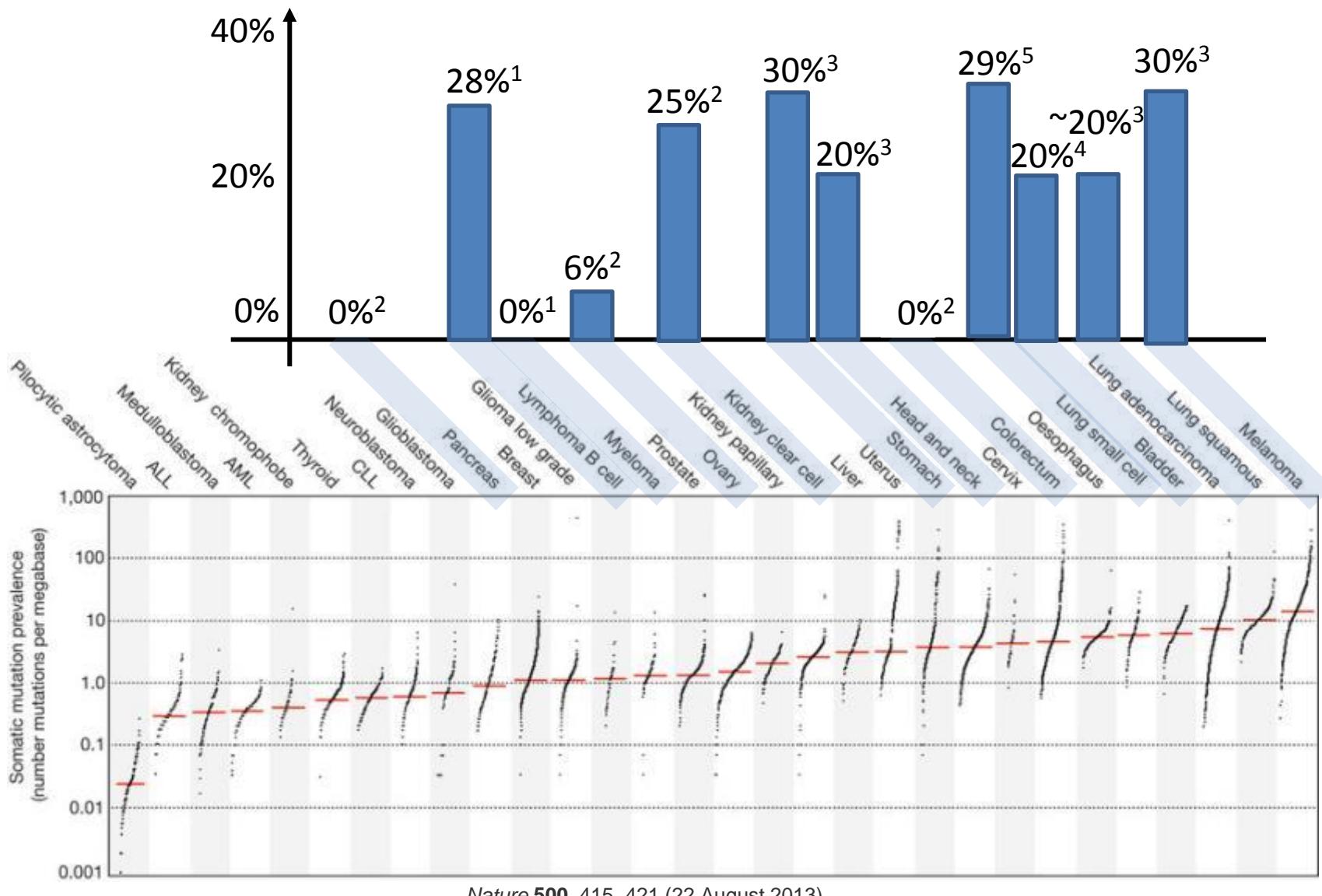
Rizvi NA, et al. Science (80) 2015.

Immunoscore > MSI status



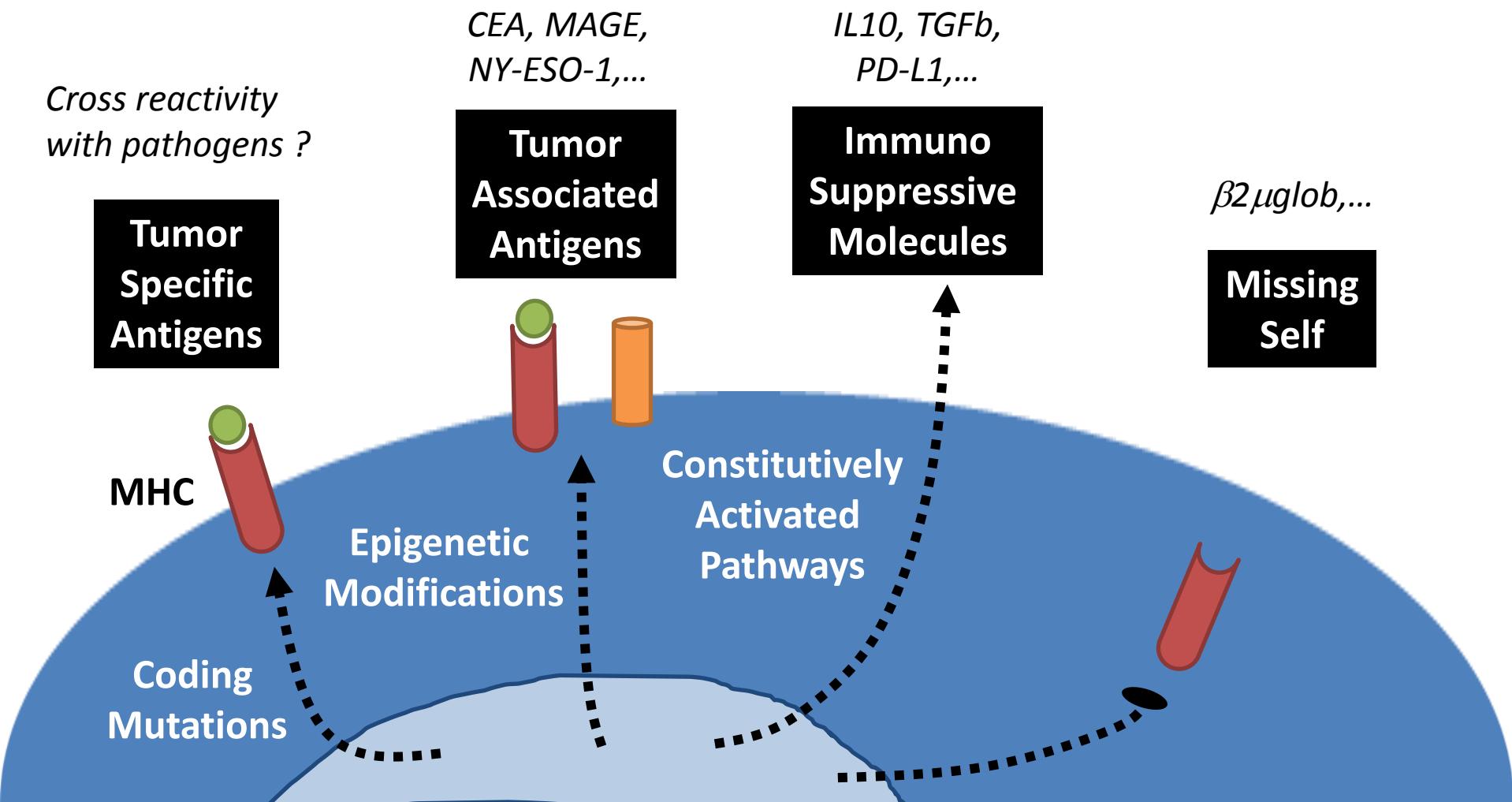
Mlecnik B, et al. Immunity. 2016.

Impact of Mutational Load on PD-1/PD-L1 Blockade ORR

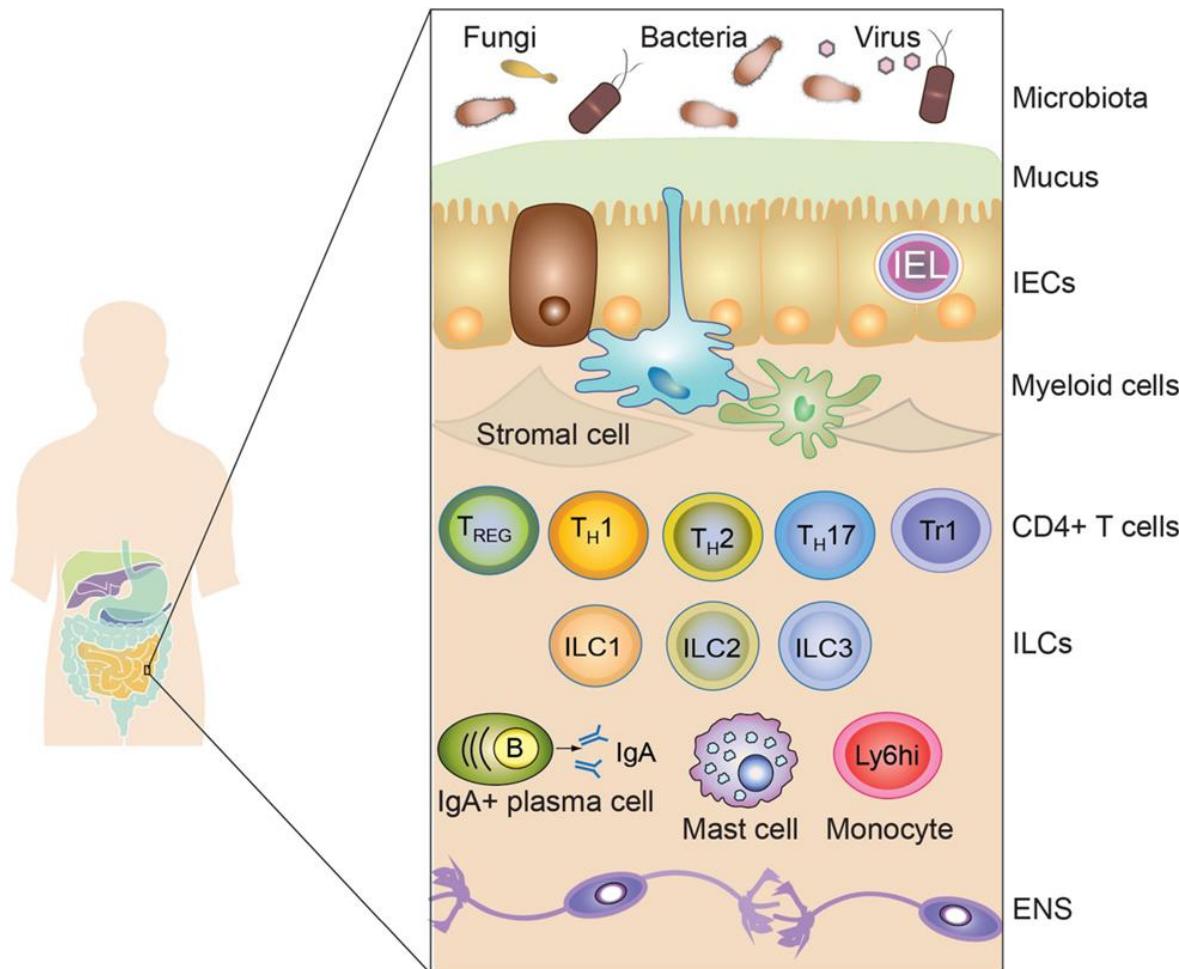


1: nivolumab, ASH 2014; 2:nivolumab, NEJM 2015; 3: pembrolizumab, ESMO 2014; 4: MPDL3280A, Nature 2014; ⁵ Ott, pembrolizumab WCLC2015

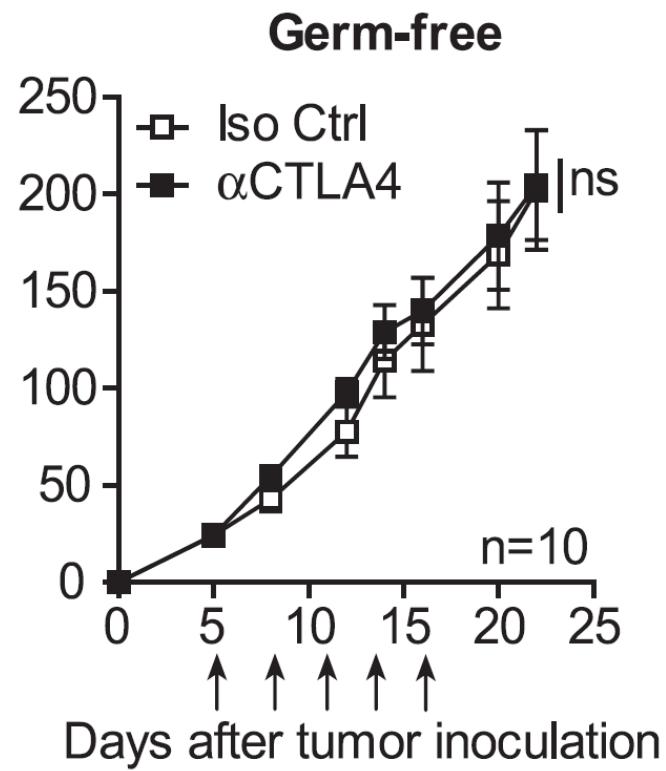
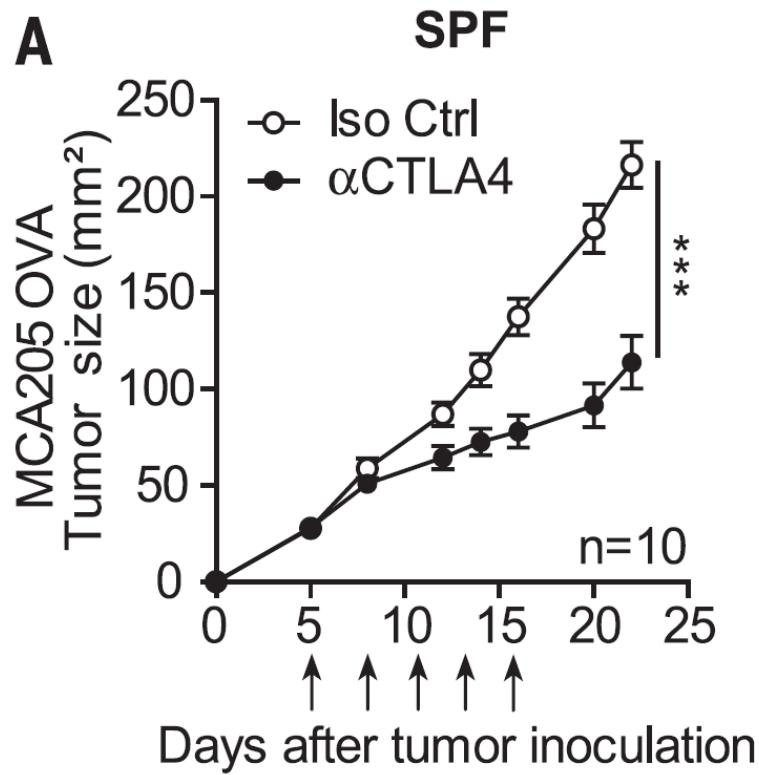
Impact of Somatic Genome Abnormalities on the Tumor Immunogenicity



Role of the Microbiota on the Immunity of GI Cancers

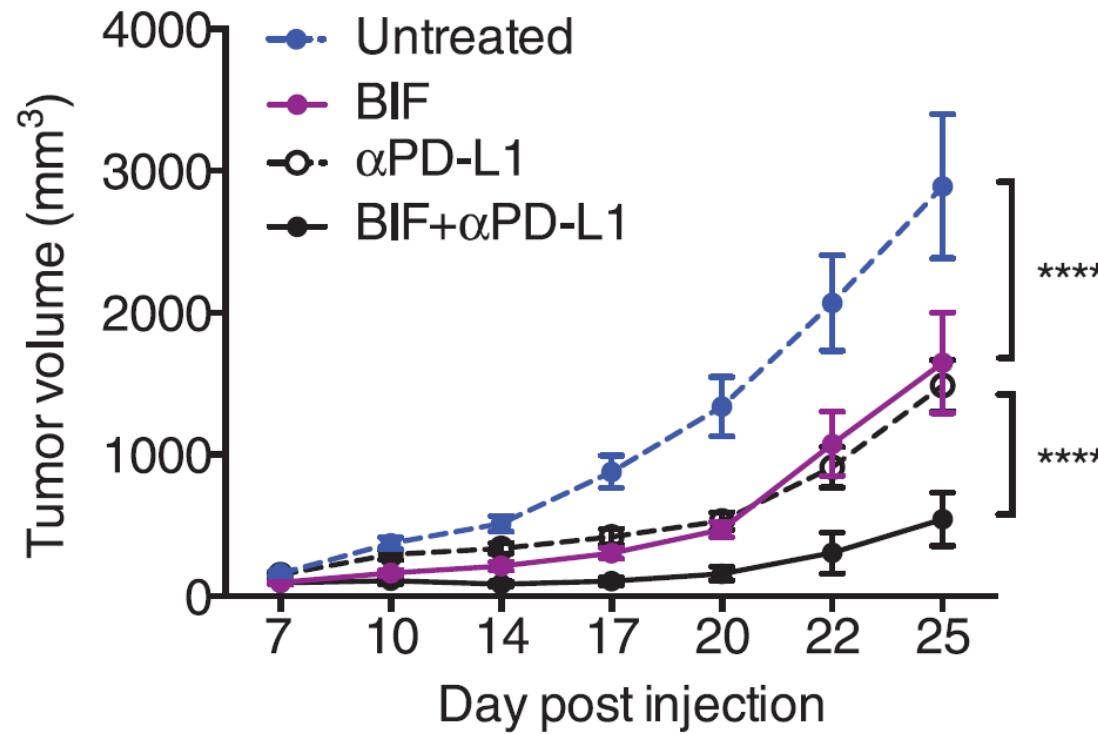


Impact of Gut Microbiota on α CTLA4



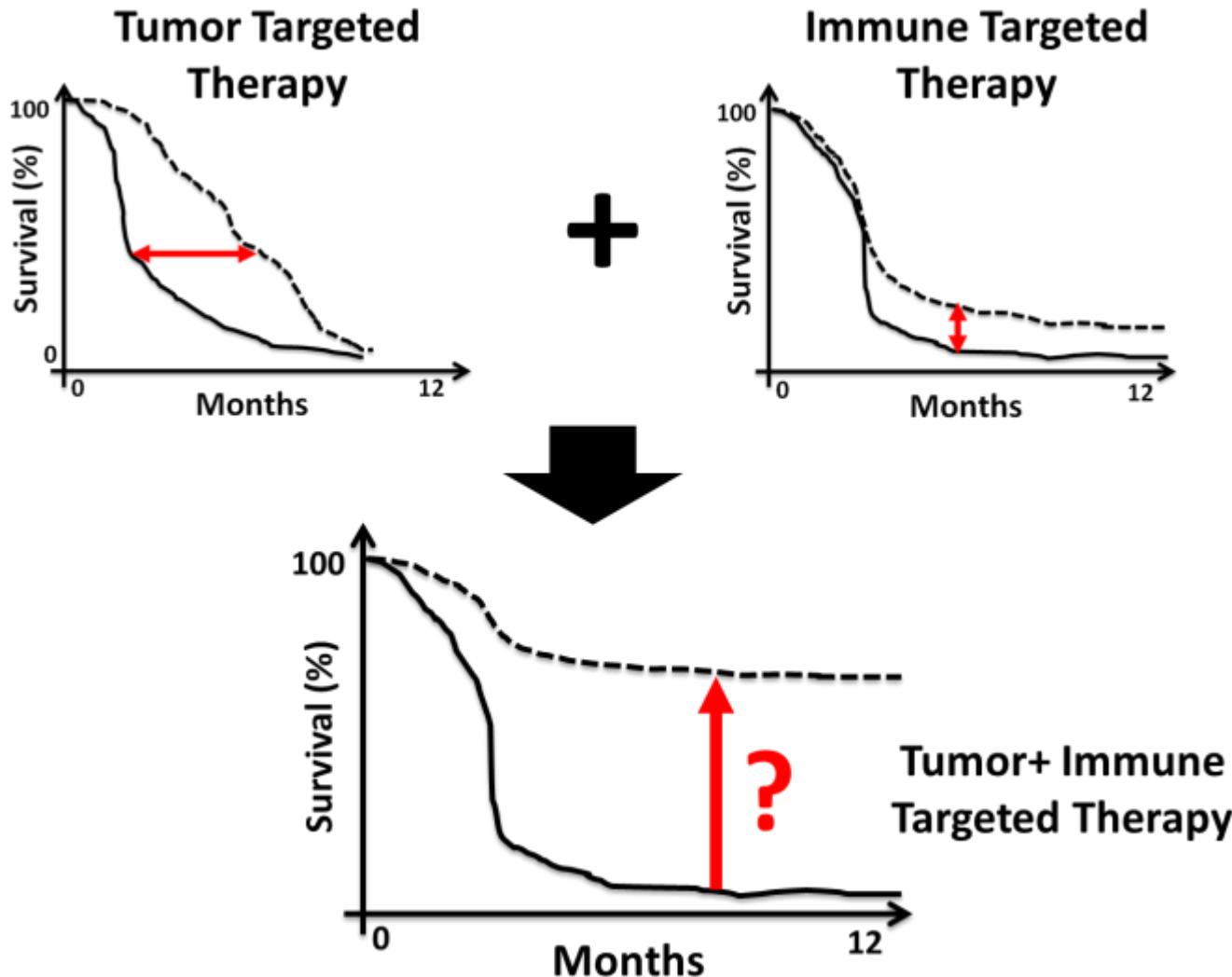
Vetizou M, et al. *Science*. 2015

Impact of Gut Microbiota on α PD-L1



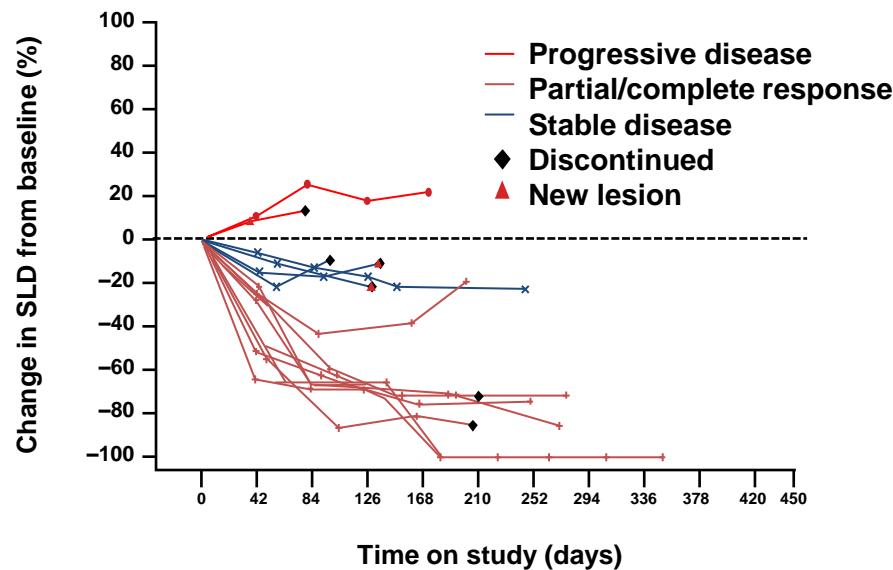
Sivan A, et al. Science. 2015

What is the Future of Oncology?



Chemotherapy + anti-PD-L1 in NSCLC

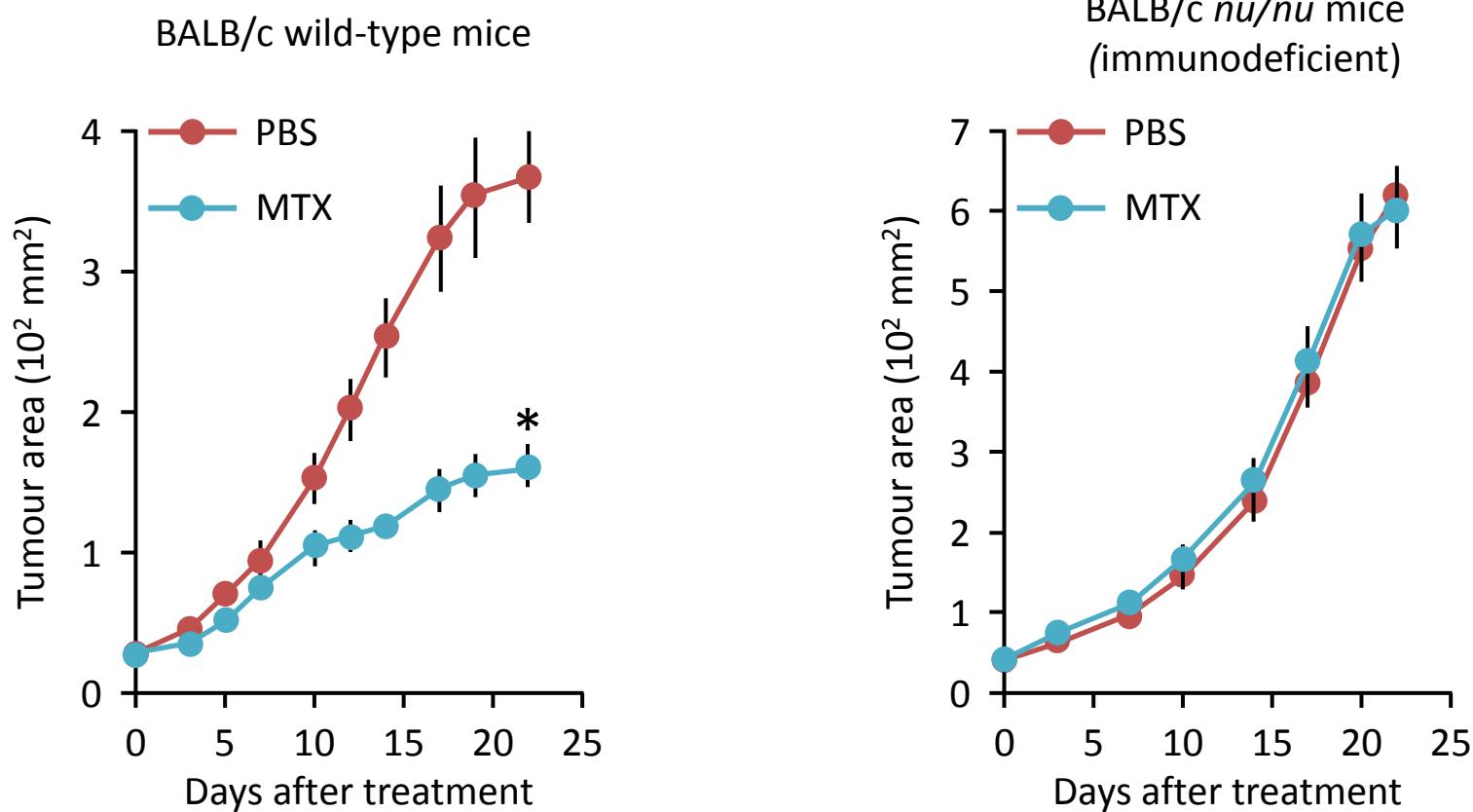
Carboplatin / Nabpaclitaxel + Atezolizumab



ORR = 56.3%
(9/16)

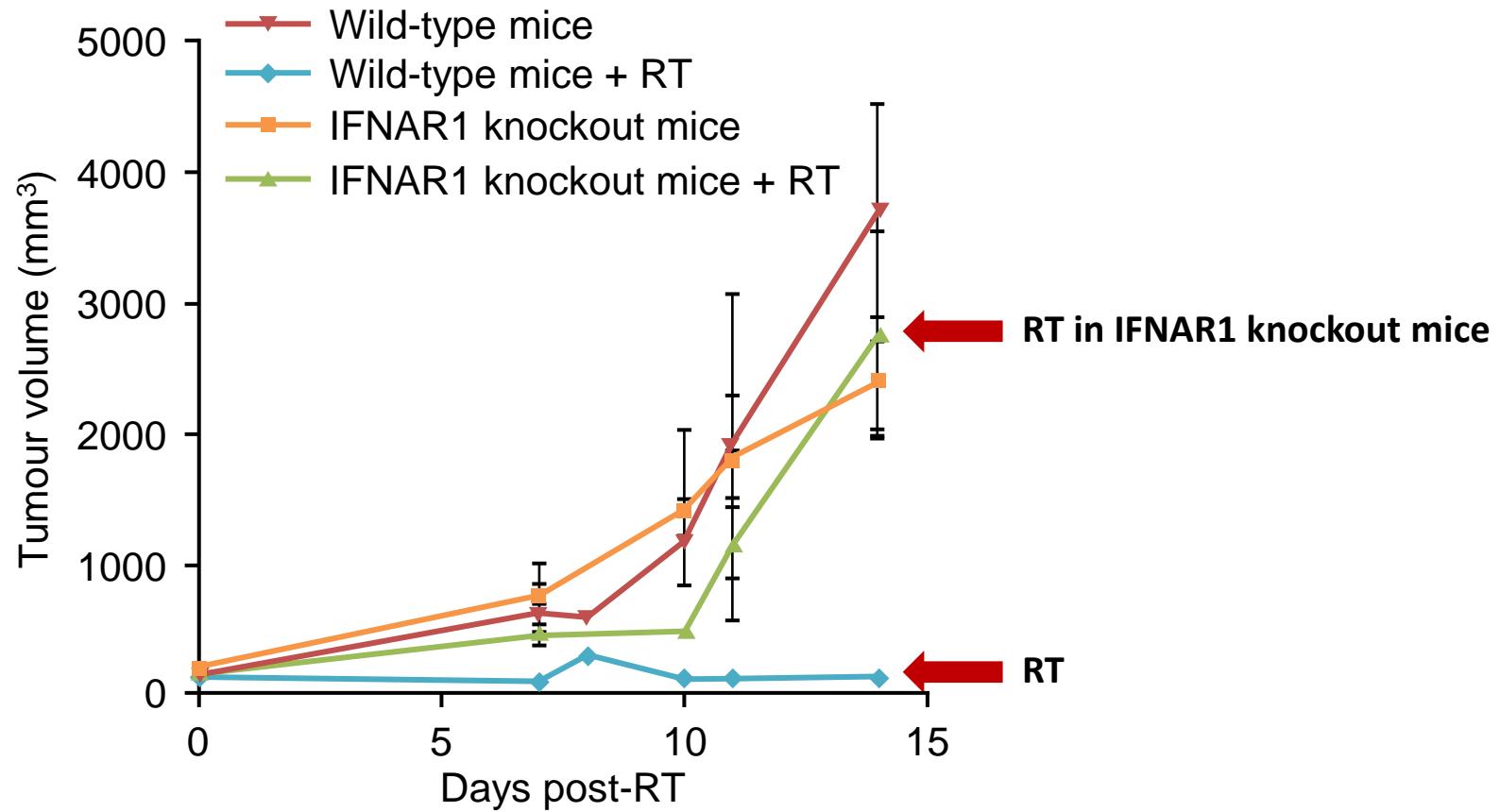
Giaccone et al, ESMO 2015

Chemotherapy Efficacy & the Immune System



* $P < 0.05$; $n = 10$ mice per group; means \pm SEM are shown.
MTX, mitoxantrone; PBS, phosphate-buffered saline (control).

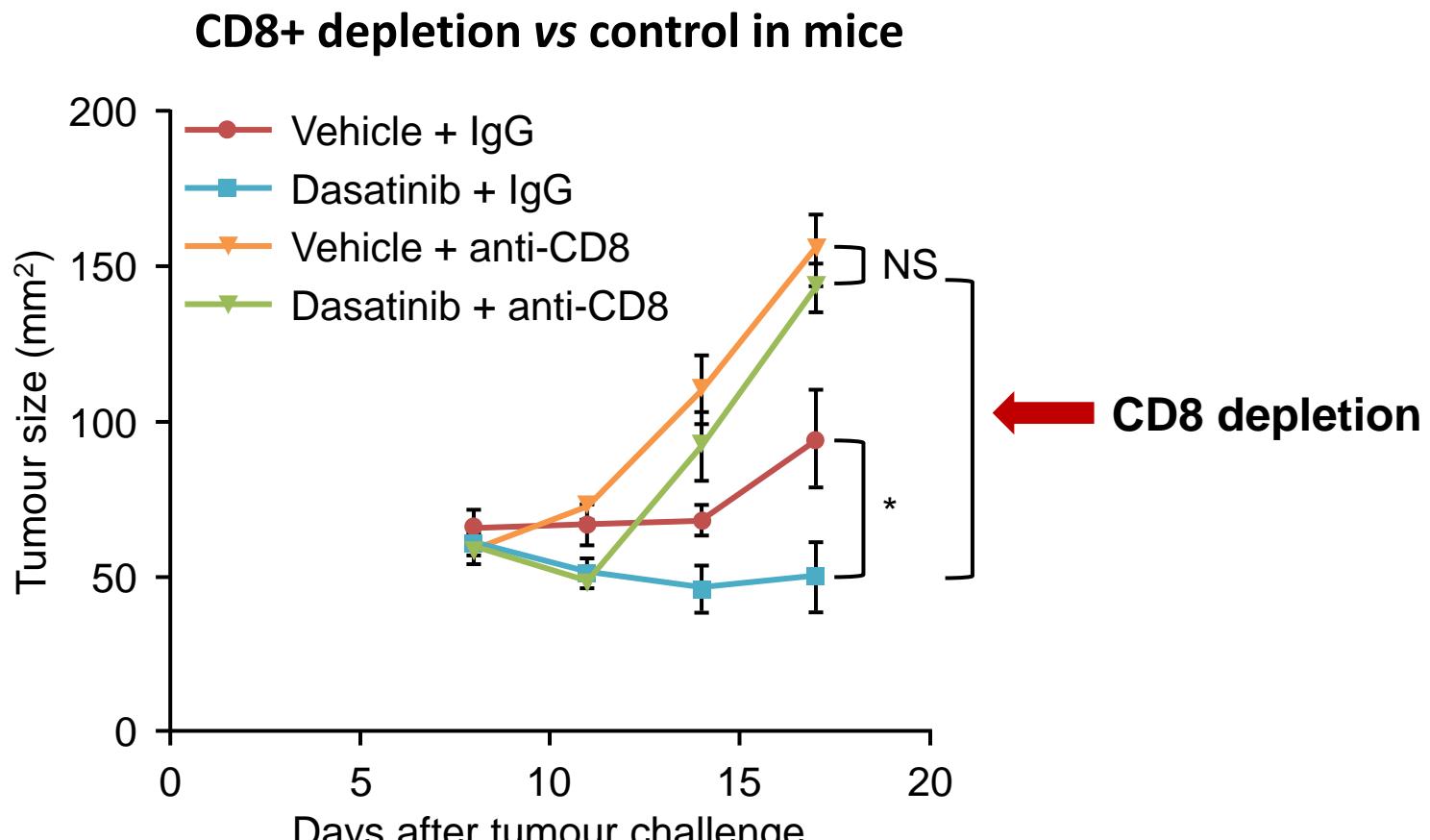
Radiotherapy Efficacy & the Immune System



Data shown are representative of at least 2 experiments with similar results with $n = 6\text{--}9$ mice per group.

IFNAR1, interferon (alpha, beta and omega) receptor 1; RT, radiotherapy.

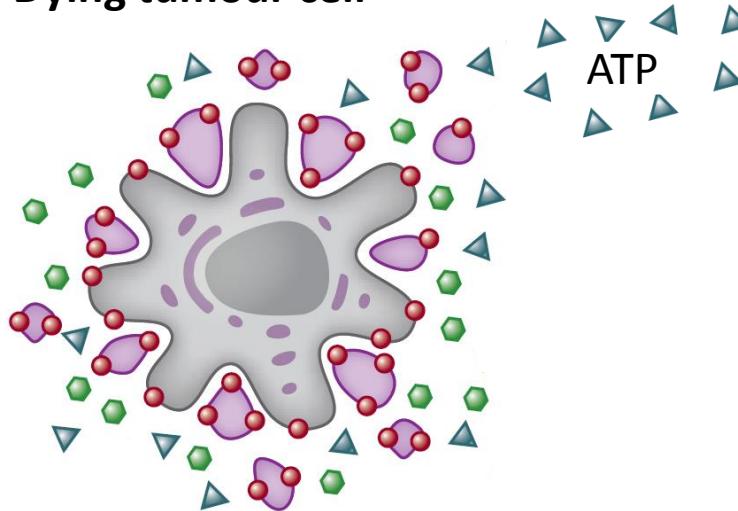
TKI Efficacy & the Immune System



* $P = 0.0427$; n = 6–10 mice per group
NS, not significant

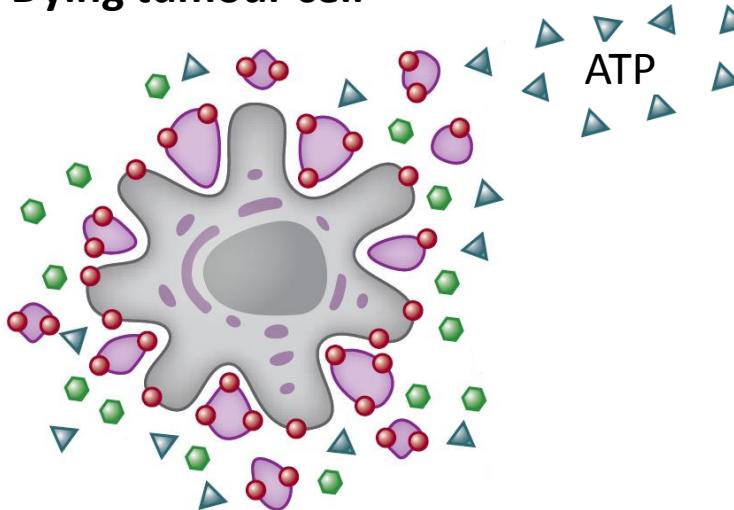
Immunogenic cell death

Dying tumour cell



Immunogenic cell death

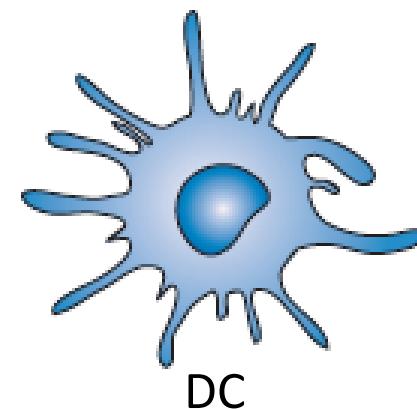
Dying tumour cell



Chemotaxis signal

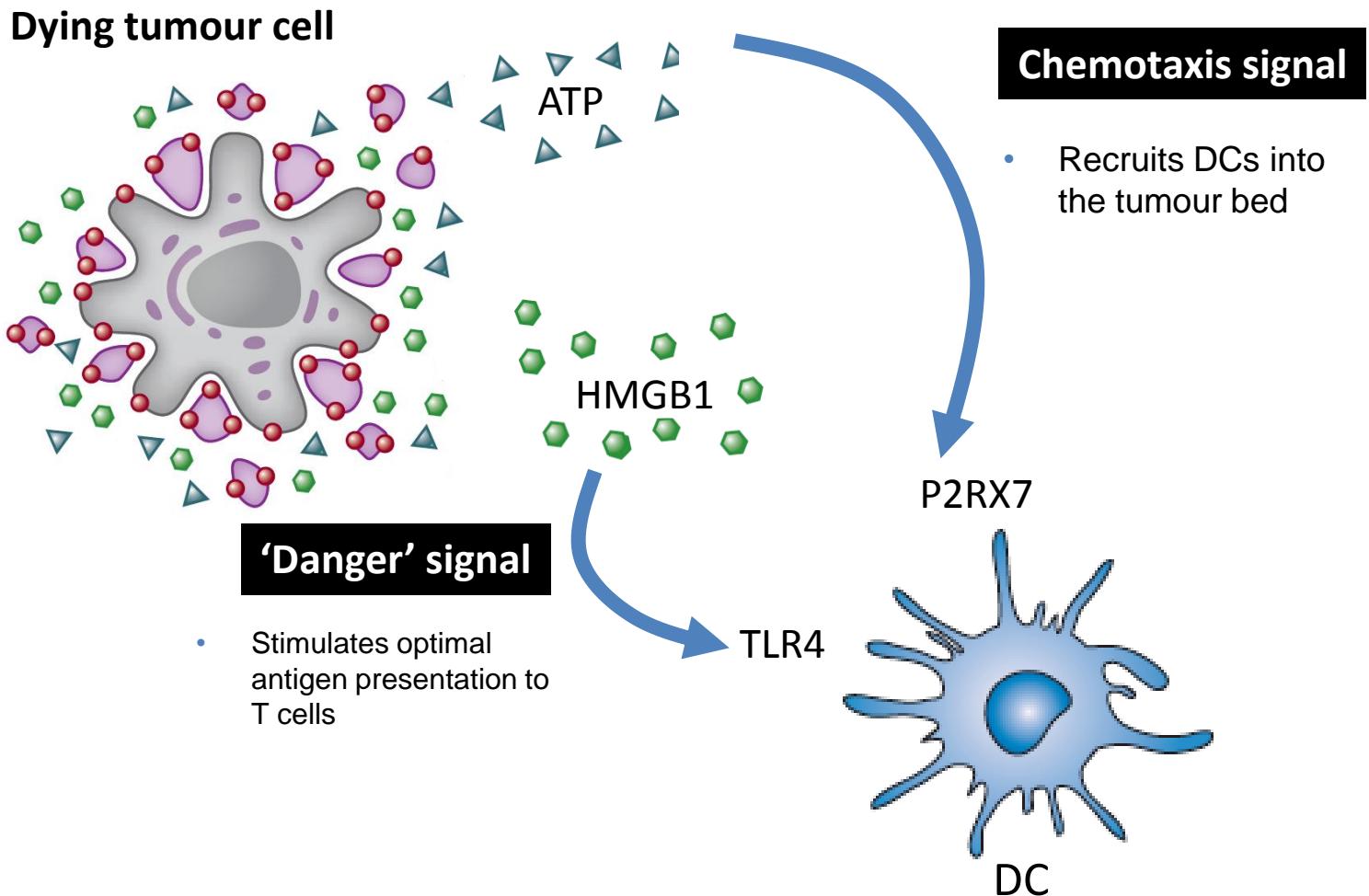
- Recruits DCs into the tumour bed

P2RX7



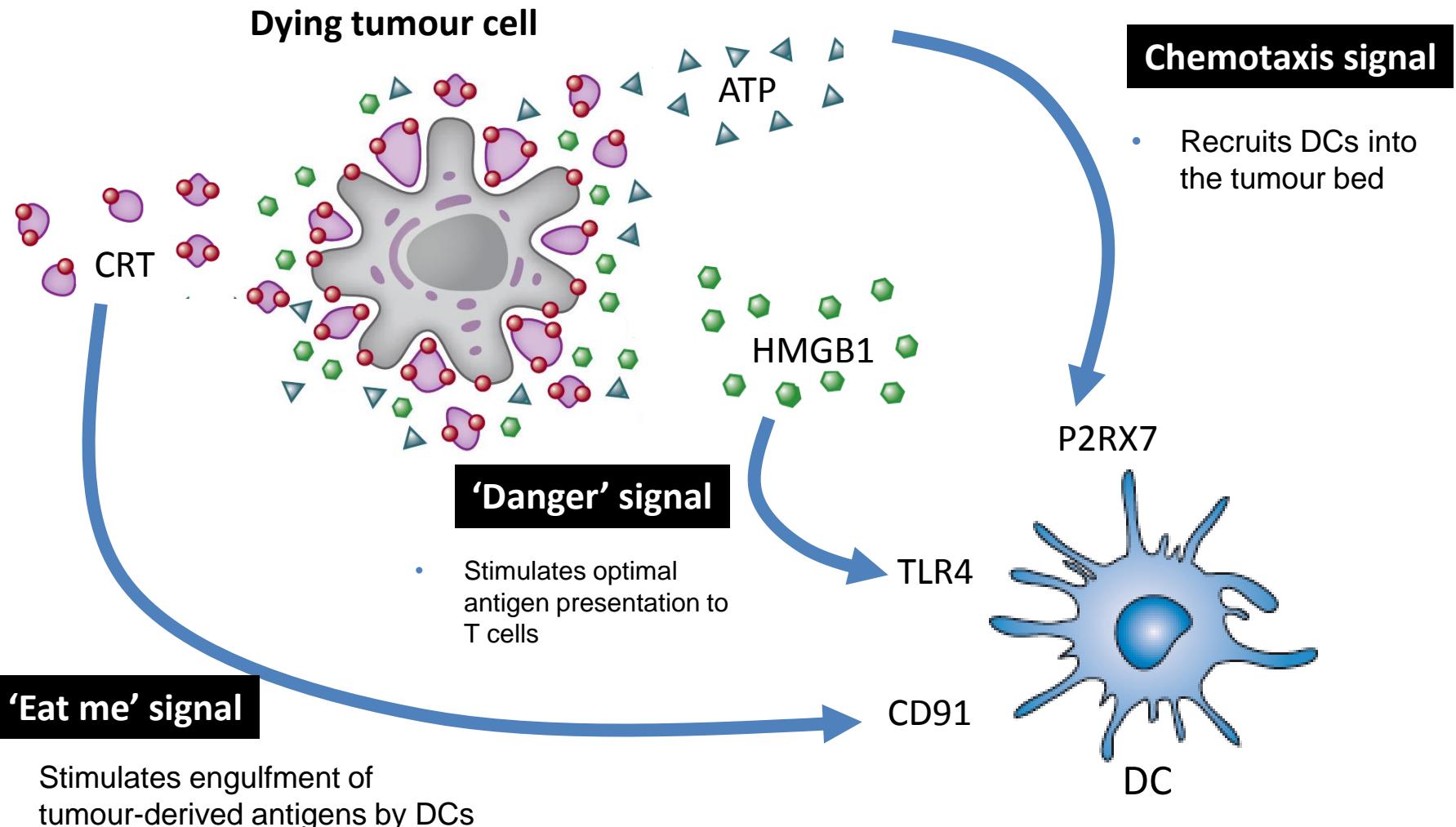
TLR4, toll-like receptor 4; P2RX7, P2X purinoceptor 7.

Immunogenic cell death



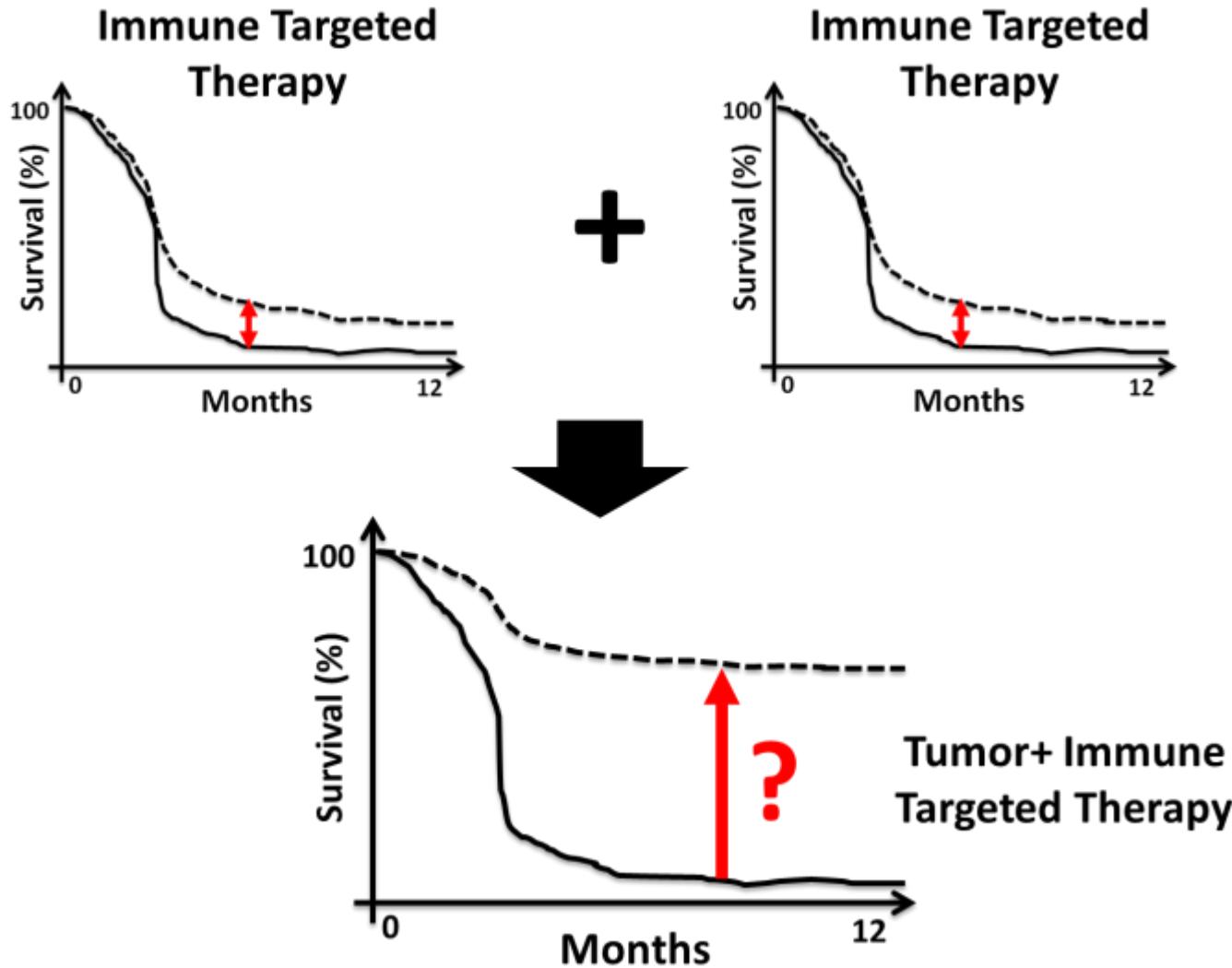
TLR4, toll-like receptor 4; P2RX7, P2X purinoceptor 7.

Immunogenic cell death

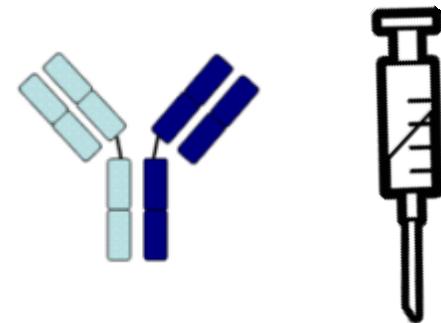
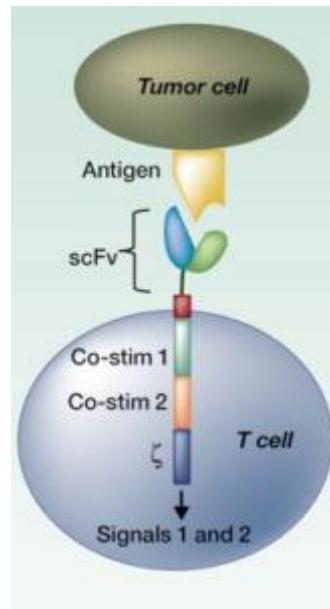
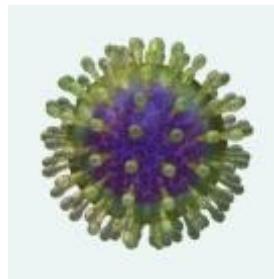
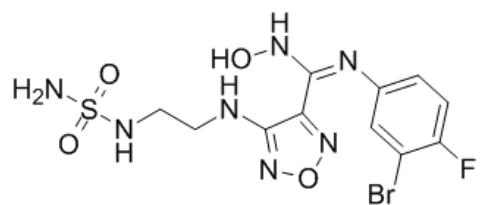


Adapted from Kroemer G et al. *Annu Rev Immunol.* 2013;31:51-72

The Future of Oncology?



OTHER IMMUNOTHERAPIES



Oral Immuno
Modulator

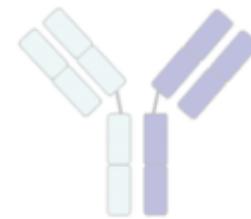
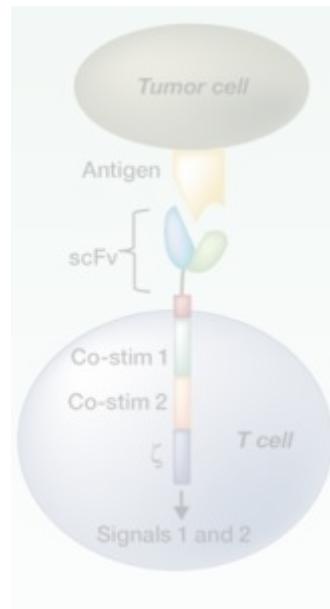
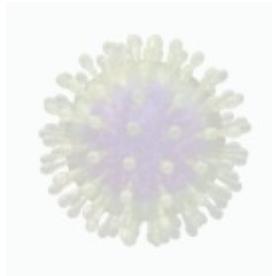
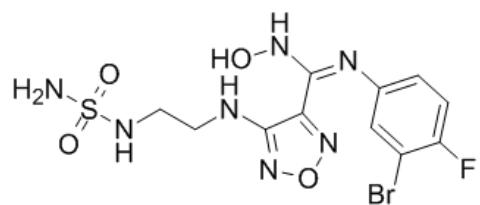
Oncolytic
Virus

CAR
T-cells

Bi
Spe

Cancer
Vaccines

OTHER IMMUNOTHERAPIES



Oral Immuno
Modulator

Oncolytic
Virus

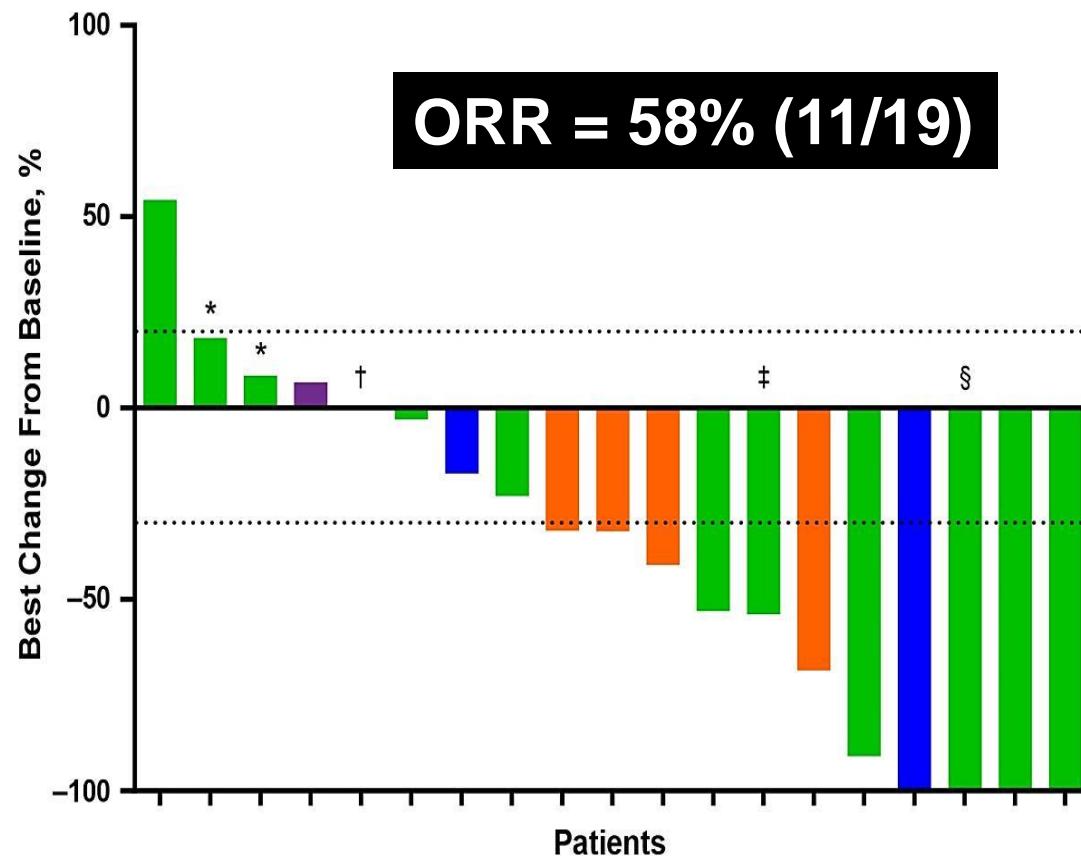
CAR
T-cells

Bi
Spe

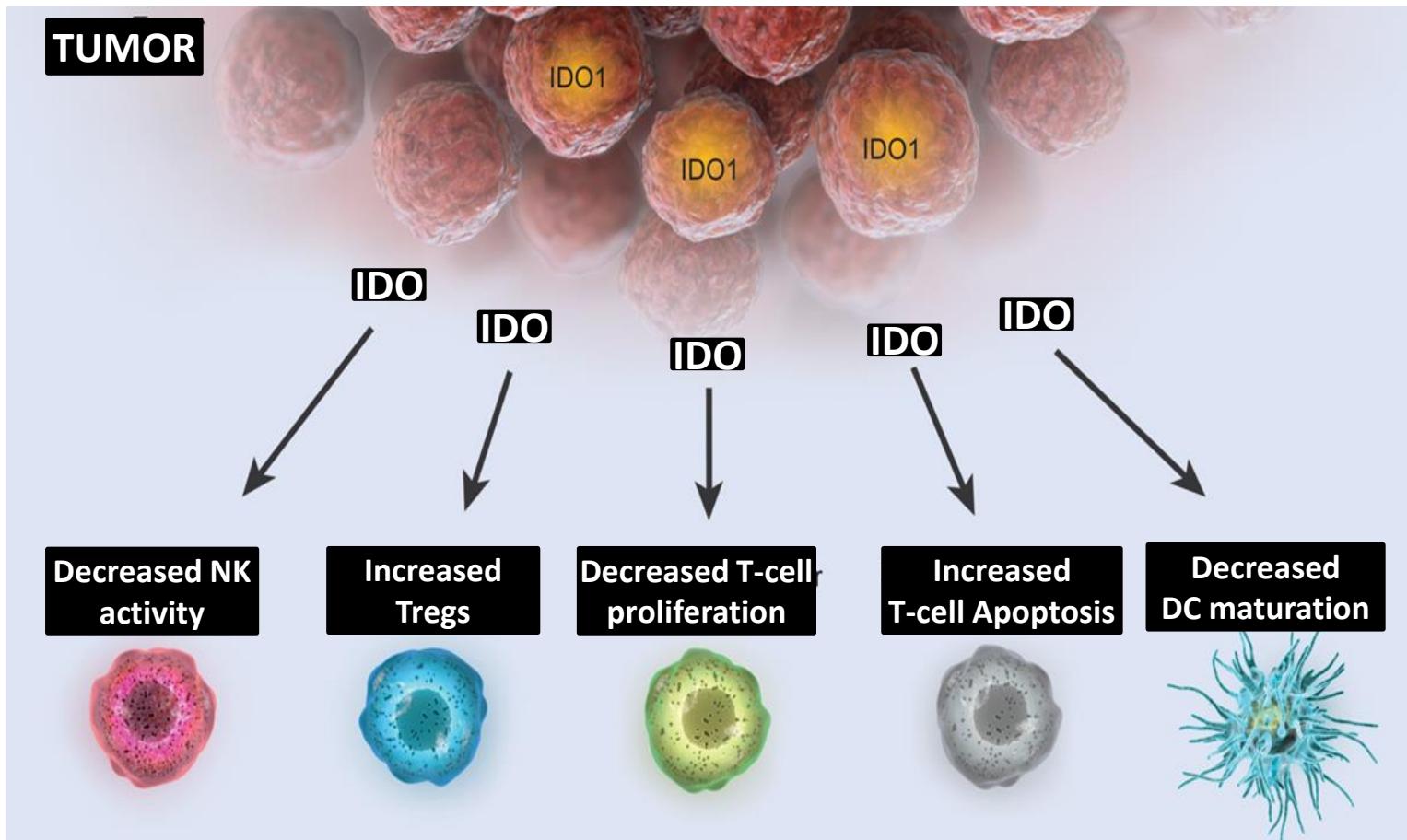
Cancer
Vaccines

Epacadostat + pembrolizumab in Metastatic Melanoma (Incyte, NCT02178722)

■ 25 mg BID ■ 50 mg BID ■ 100 mg BID ■ 300 mg BID ● Off study treatment



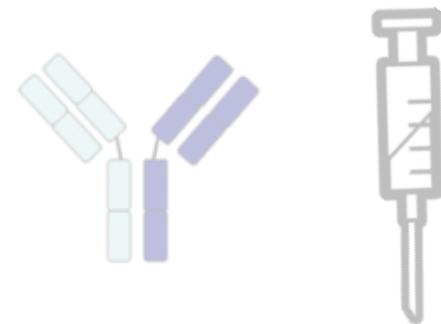
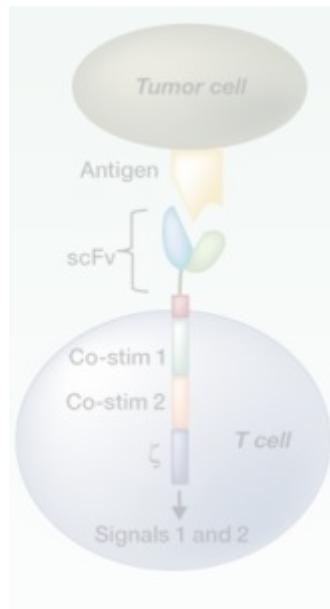
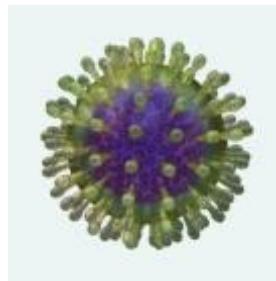
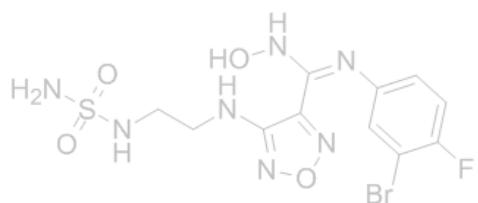
IDO inhibition



IDO1, indoleamine 2,3 dioxygenase 1.

Adapted from Gangadhar et al, SITC 2015

The Future is Bright



IDO inhibitors

Oncolytic
Virus

CAR
T-cells

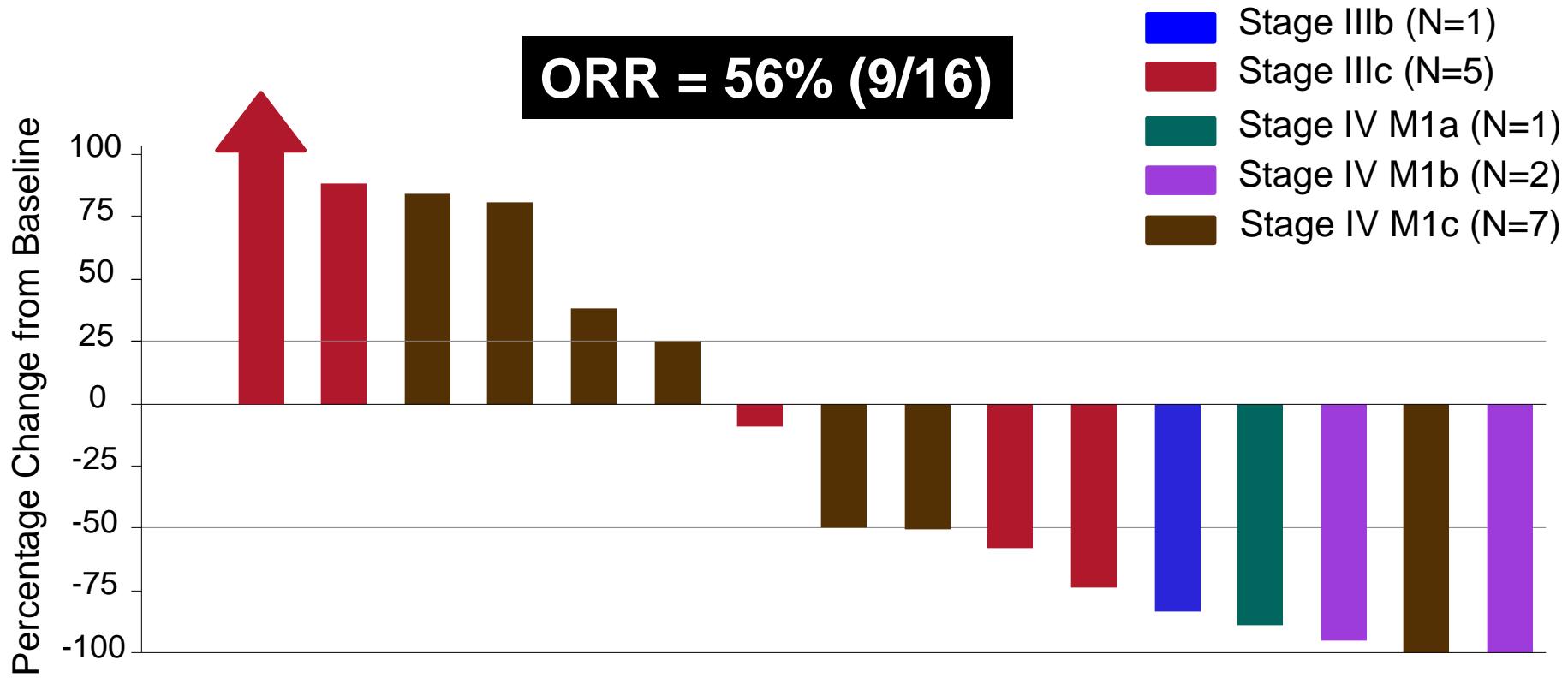
Bi
Spe

Cancer
Vaccines



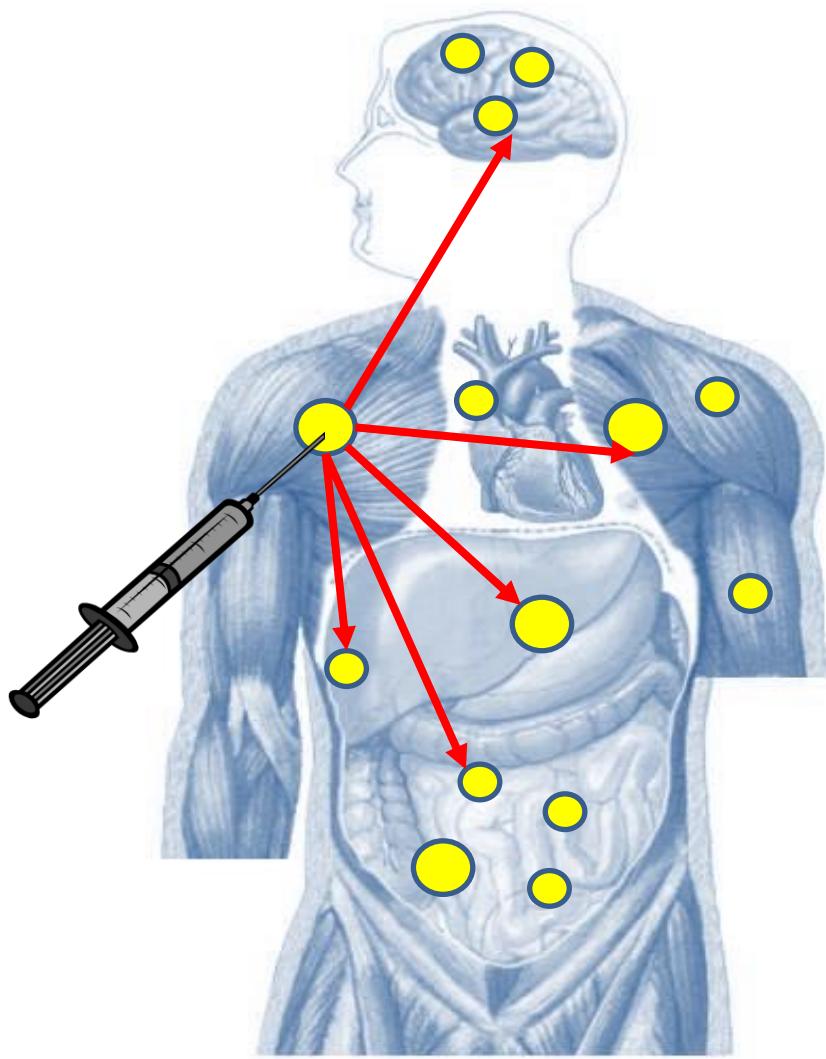
T-VEC EMA approval
Q4 2015

T-VEC + anti-PD-1 in Melanoma

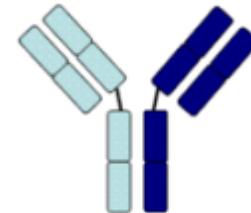
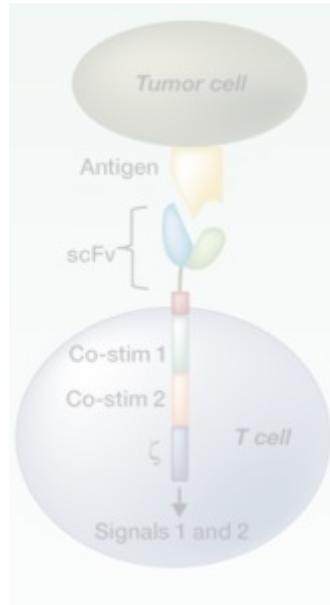
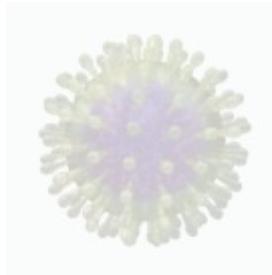
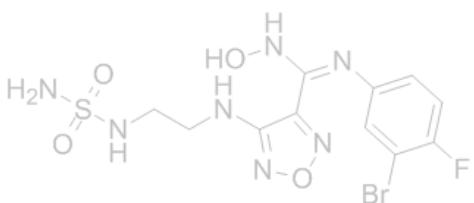


All 16 patients were followed at least 12 weeks from the first dose of pembrolizumab and must have had an evaluable response. Stable disease must be > 77 days to be considered evaluable.

in situ immunization



The Future is Bright



IDO inhibitors

Oncolytic
Virus

CAR
T-cells

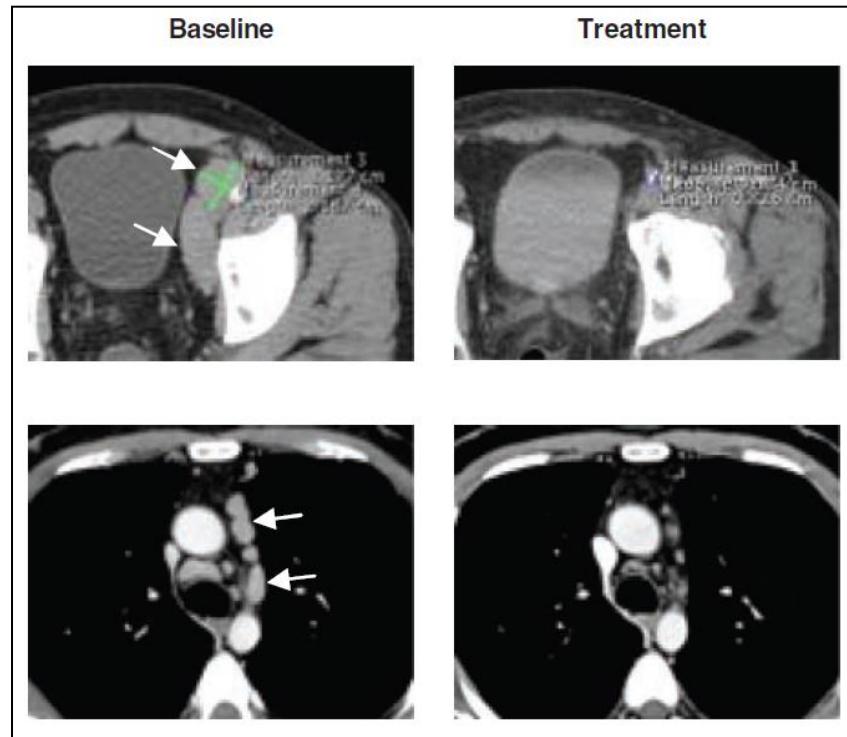
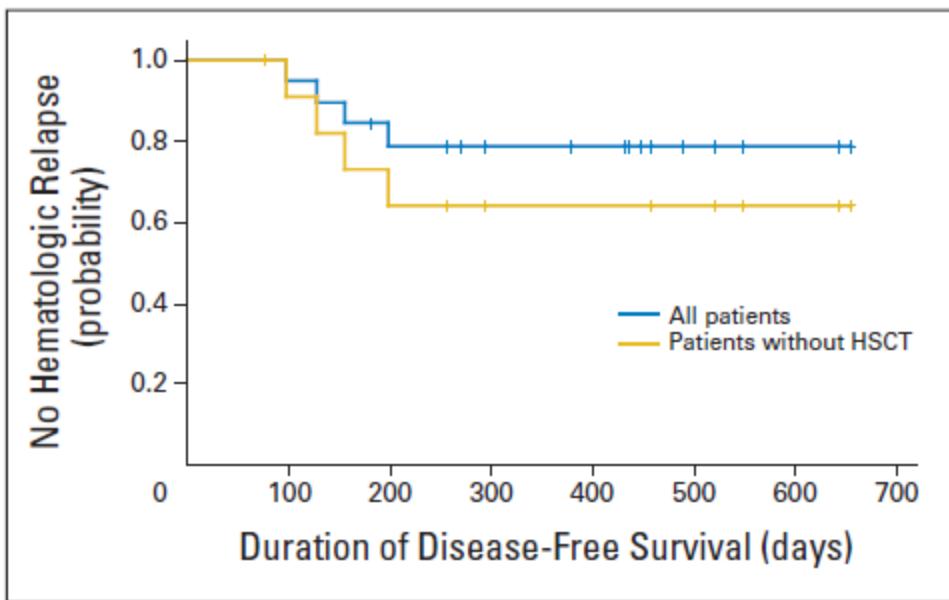
Bi
Spe

Cancer
Vaccines



Blinatumomab EMA approval
Q4 2015

Blinatumomab in ALL & NHL



Blinatumomab on Chemotherapy-Refractory MRD in B-ALL

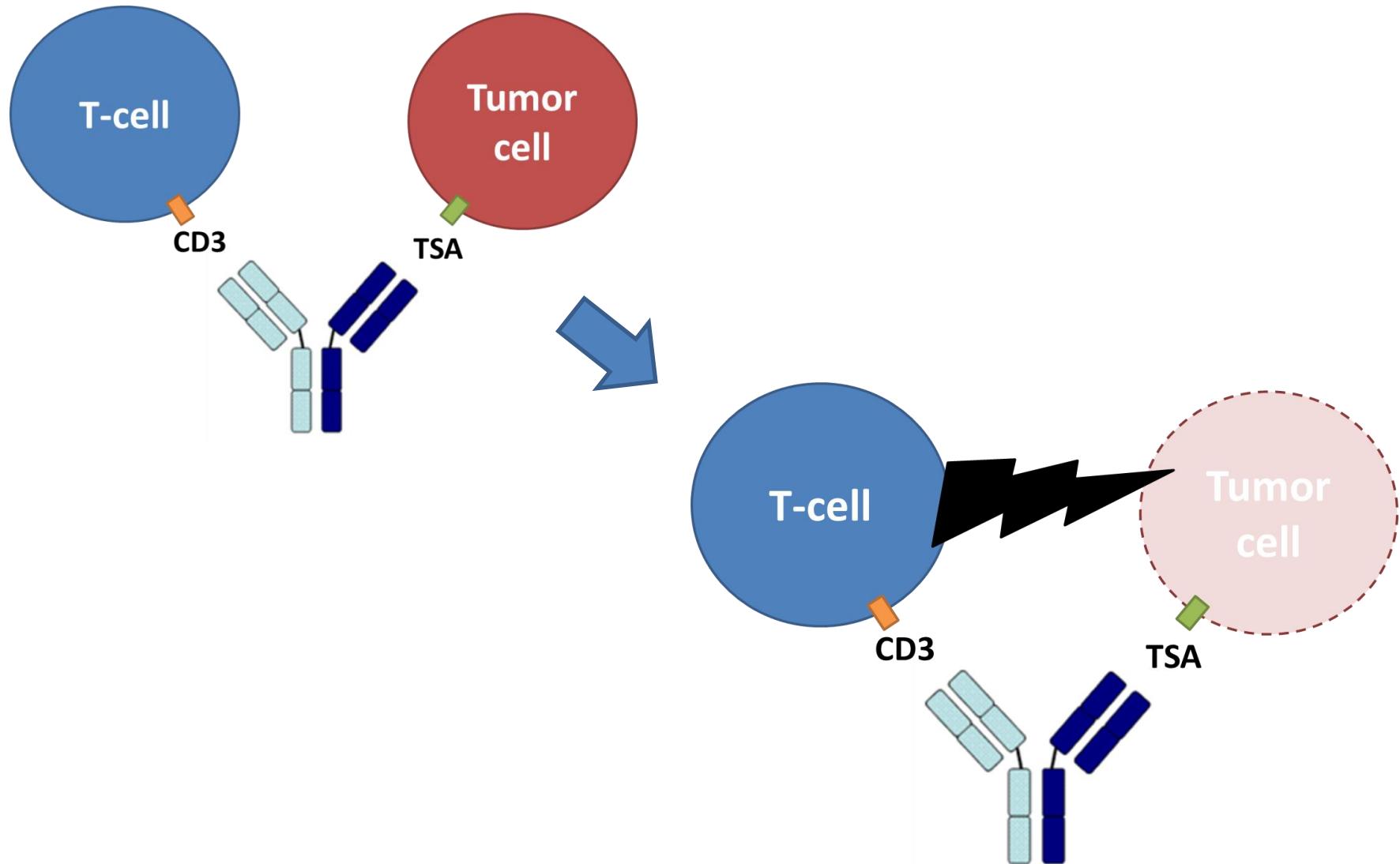
VOLUME 29 • NUMBER 18 • JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

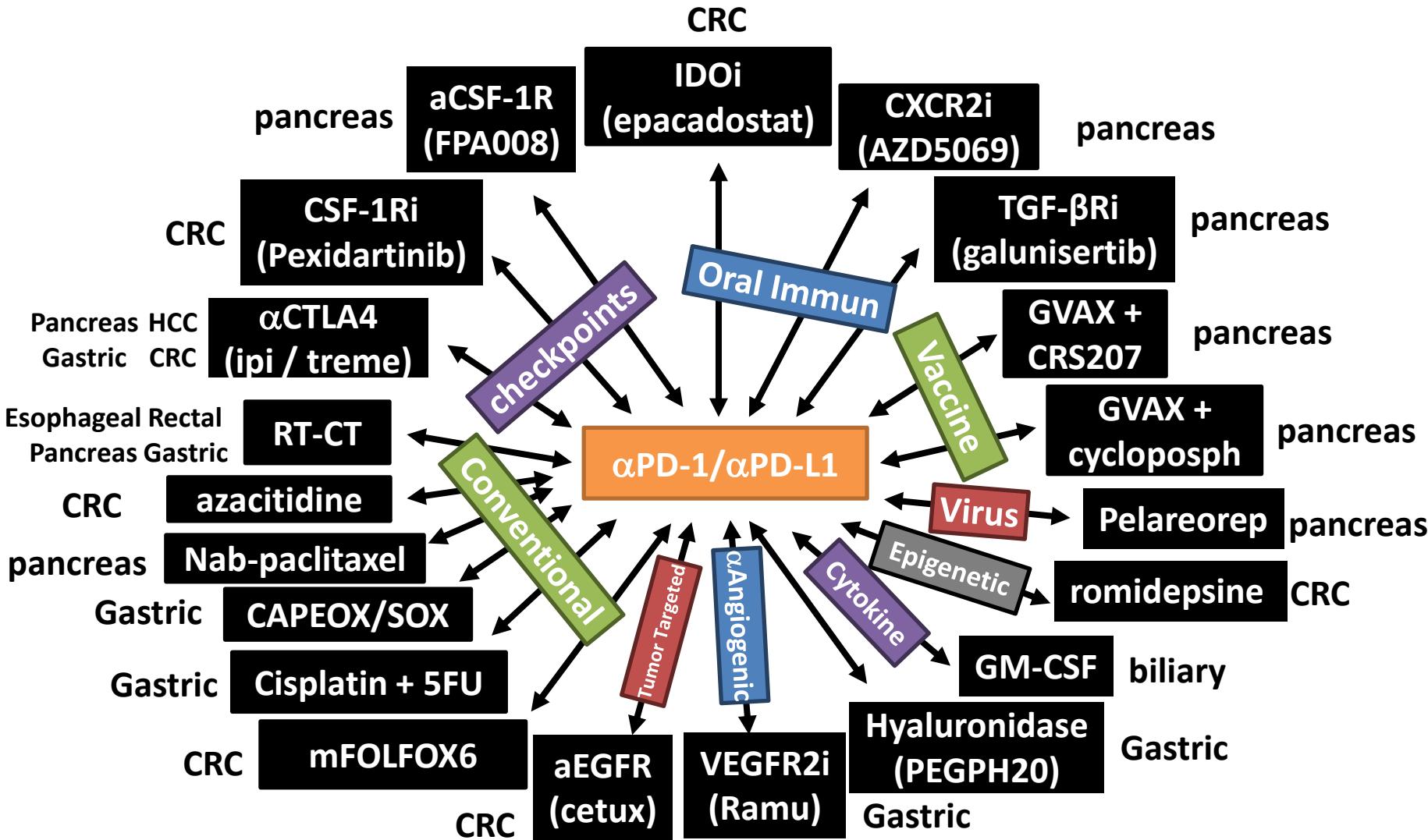
Tumor Regression in Cancer Patients by Very Low Doses of a T Cell-Engaging Antibody
Ralf Bargou et al.
Science 321, 974 (2008);
DOI: 10.1126/science.1158545

Science
AAAS

Bispecific T-cell Engaging mAbs



Ongoing I-O Combinations in GI Cancers



Understanding the Relevant Immune Mechanisms in GI Cancers

Aurélien Marabelle, MD, PhD

Clinical Director, Cancer Immunotherapy Pgm

Drug Development Department, Prof Soria

INSERM 1015, Prof Zitvogel Lab

ESMO GI 2016



CANCER CAMPUS
GRAND PARIS

