

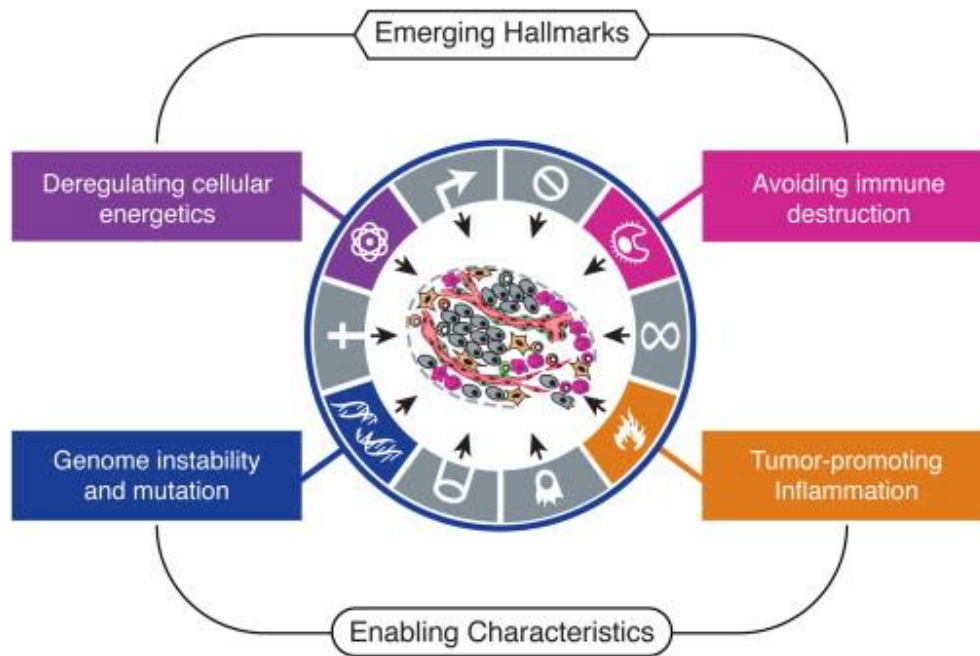
IMMUNOTERAPIA NEL 2015

LA VIA DEL SEGNALE PD-1 PD-L1

Alessandro Minisini
Dipartimento di Oncologia
Azienda Ospedaliero Universitaria
Udine

Negrar, 11 novembre 2015

HALLMARKS OF CANCER



Douglas Hanahan, Robert A. Weinberg, Cell 2011

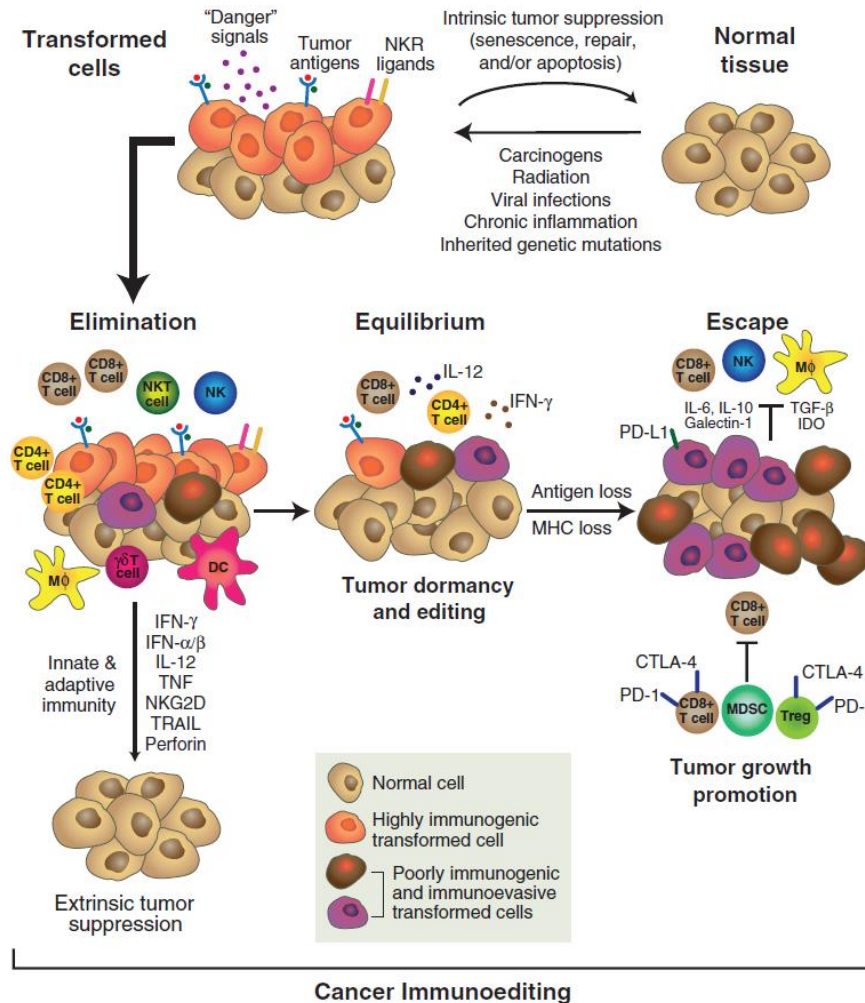


Paul Ehrlich (nobel Prize 1908): the first to hypothesize the role of immune system in tumors control

IMMUNOTHERAPY ERA REVOLUTION



IMMUNOEDITING MODEL



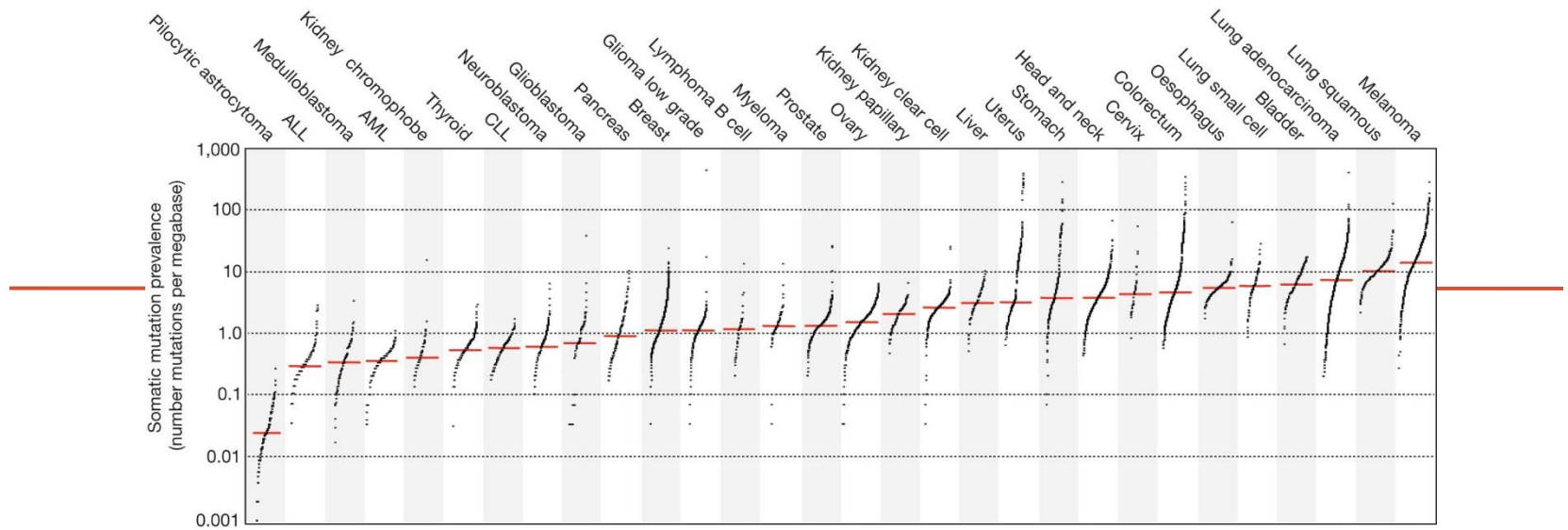
ANTIGEN PRESENTATION

- Active anticancer effect depends on efficient antigen presentation
 - Tumor Associated Antigens
- Professional Antigen Presenting Cells
 - Dendritic Cells (DCs)
 - Maturation of DCs
 - Maturation of co-stimulatory signals
 - Cytokines
 - Migration of DCs to secondary lymphoid tissues and presentation of antigens to T-cells

T-CELLS ACTIVATION

- CD4+ (T helper) and CD8+ (cytotoxic T lymphocytes)
 - Needs co-stimulatory signals
1. Activation
 2. Proliferation in a secondary lymphoid tissues
 3. Trafficking to sites of antigen and inflammation
 4. Direct effector function or help of a multitude of effector immune cells

The prevalence of somatic mutations across human cancer types.



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

CANCER IMMUNOTHERAPY

- **PASSIVE**

- Cytokines (IL-2, IFN)
- Monoclonal antibody

-IL-2 effective in a subset of patients with advanced melanoma/renal cell cancer

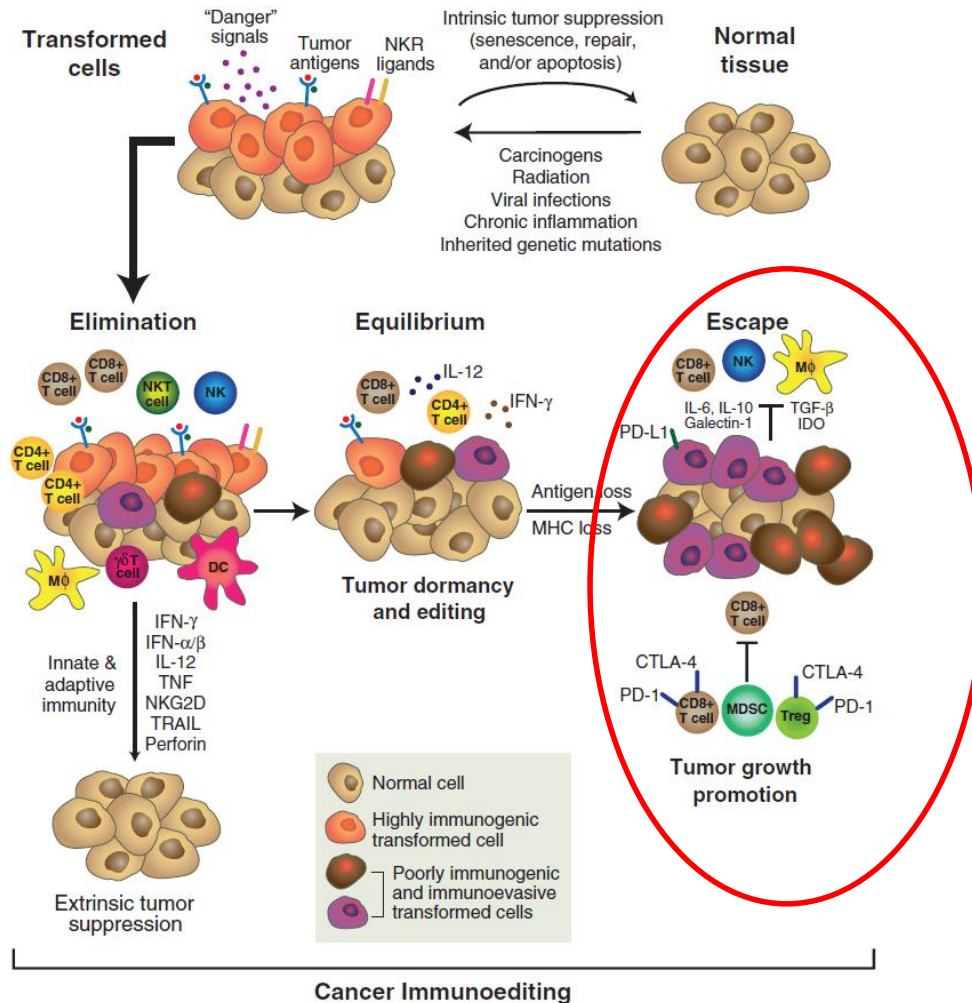
-Monoclonal antibody: a target therapy + immunotherapy?

- **ACTIVE**

- Dendritic cells manipulation
 - To achieve strong antigen presentation and activation of T cells
- Cancer vaccines

Experimental succes but low activity and efficacy in clinical setting

IMMUNOEDITING MODEL



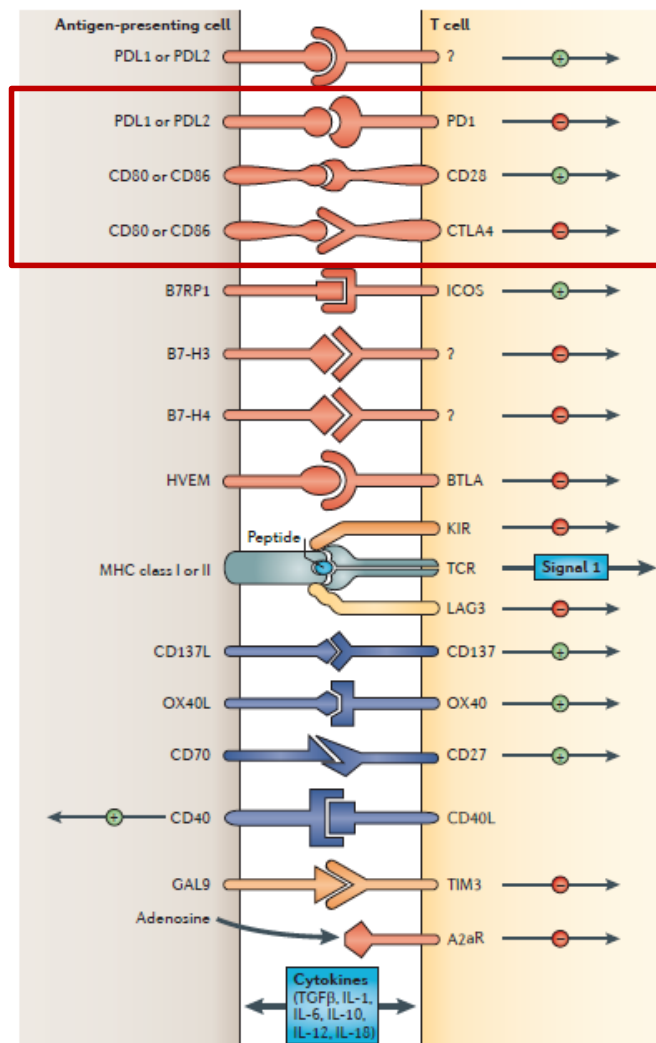
ESCAPE MECHANISMS

- Antigen masking
- Tolerance
 - Regulatory T cells (CD25+ FOXP3+)
 - Myeloid Derived Suppressor Cells (MDSC)
 - ***Inhibitory signals through Immune checkpoints***
 - Each step of T-cell mediated immunity is regulated by counterbalancing stimulatory and inhibitory signals
 - Fine-tuning of response
 - Knock-out mice for inhibitory signals (e.g. CTLA-4)
 - Lethal condition

WHAT DO YOU NEED FOR SAFE DRIVING?



IMMUNE CHECKPOINTS



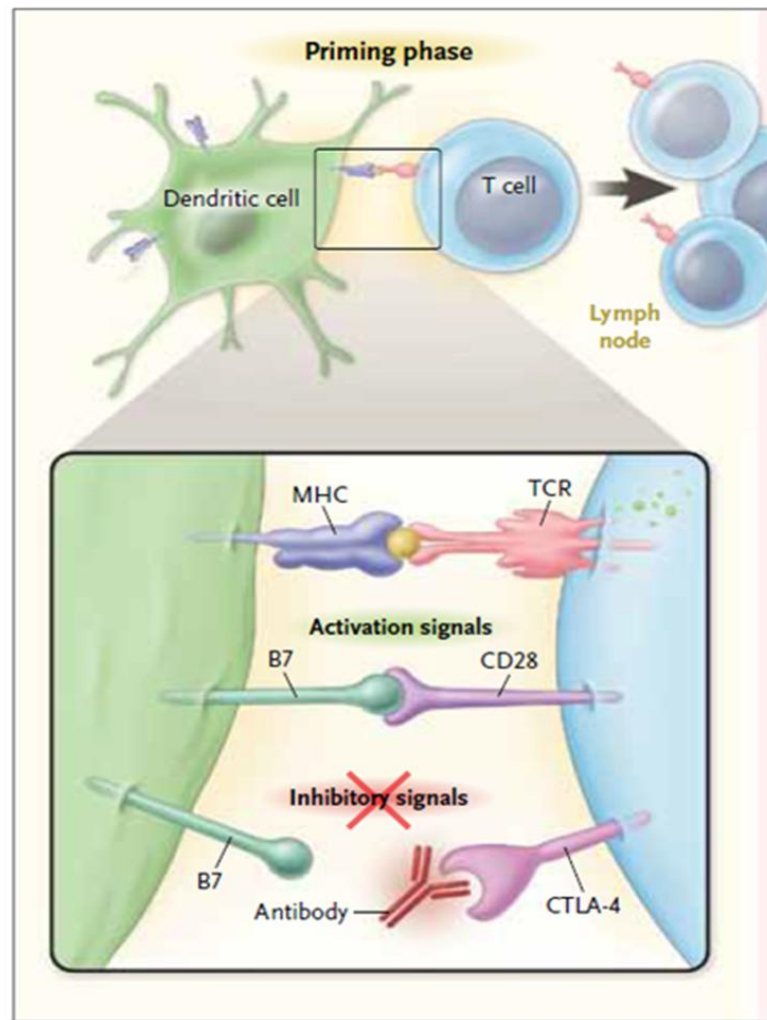
← ANTI-PD-1 ANTIBODIES

← IPILIMUMAB

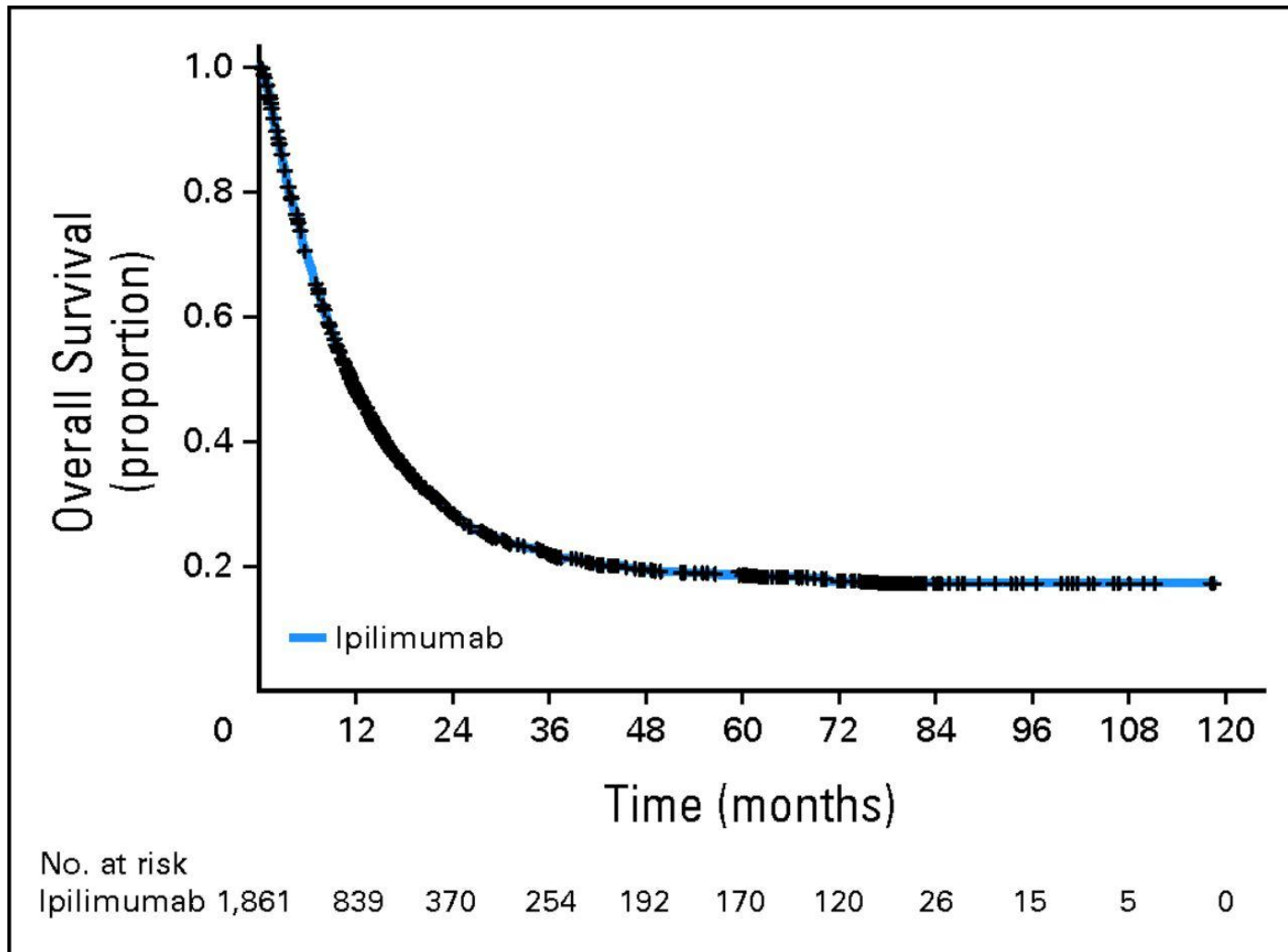
ANTI CTLA-4 AND ANTI-PD1

- Anti CTLA-4
 - Ipilimumab
 - (Tremelimumab)
- Anti PD-1
 - Nivolumab
 - Pembrolizumab
- Anti PD-L1
 - BMS-936559
 - MEDI-4736
 - MPDL-3280A
 - MSB-0010718C

ANTI CTLA-4



Primary analysis of pooled overall survival (OS) data.



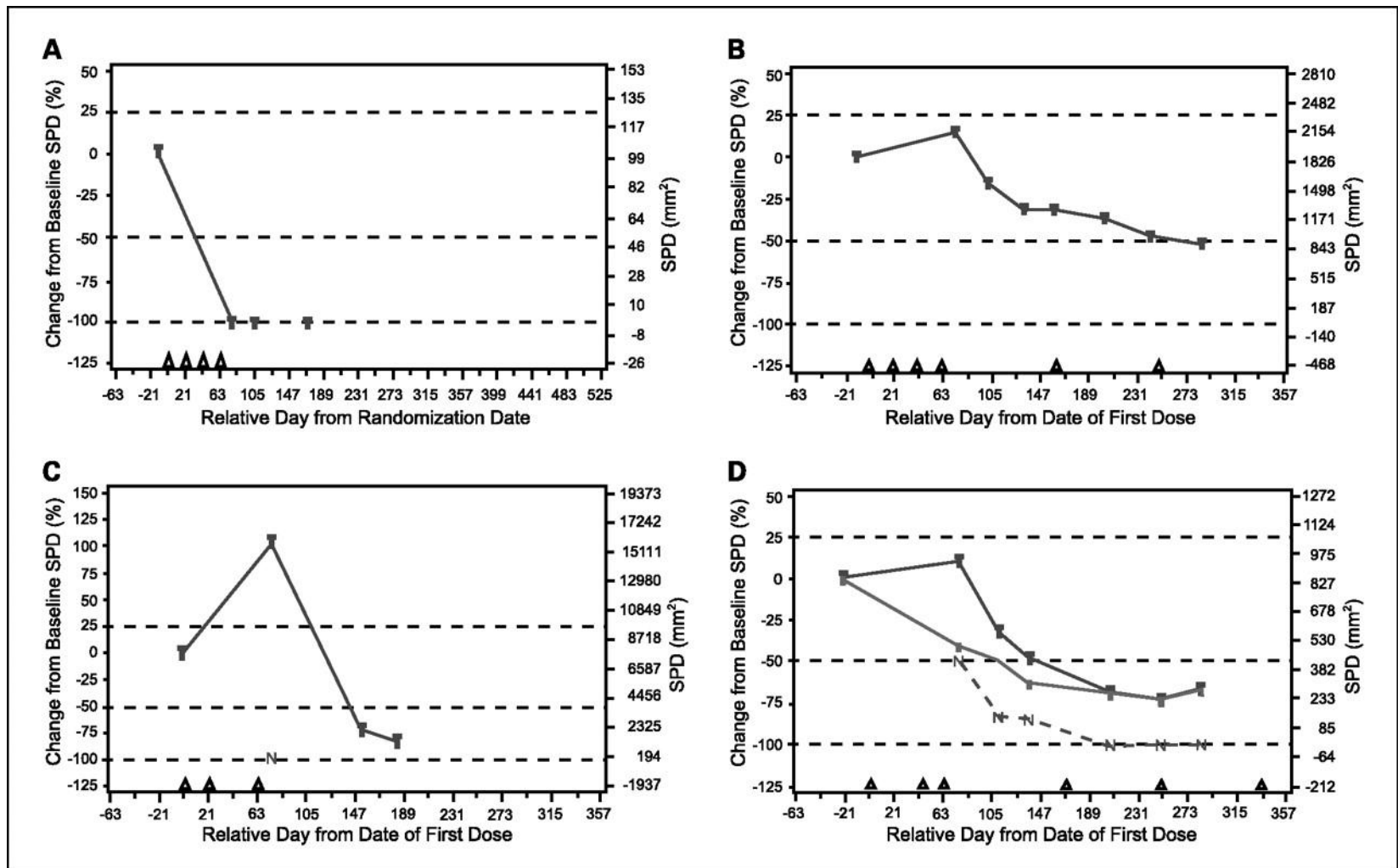
Dirk Schadendorf et al. JCO doi:10.1200/JCO.2014.56.2736

PATTERN OF RESPONSE

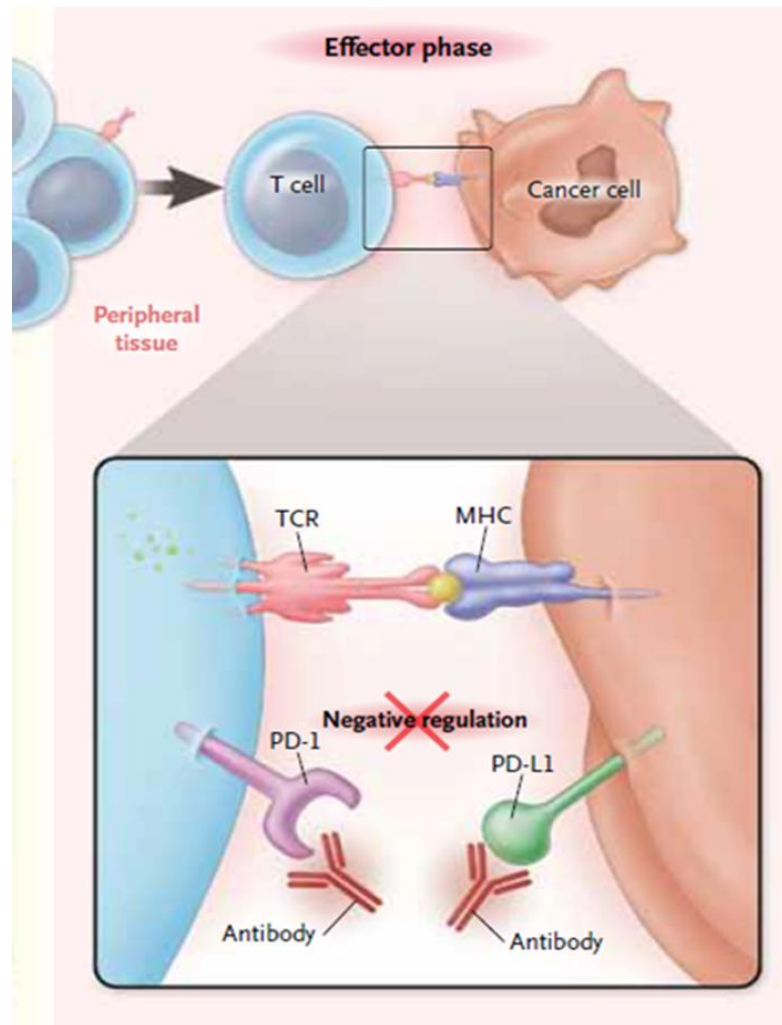
- Delayed onset of response and longterm benefit
 - Need to activate immune system
 - Initial progression could occur
 - Immurelated Response Criteria developed
 - To capture longterm benefit of ipilimumab

Wolchock et al, Clin Cancer Res 2008

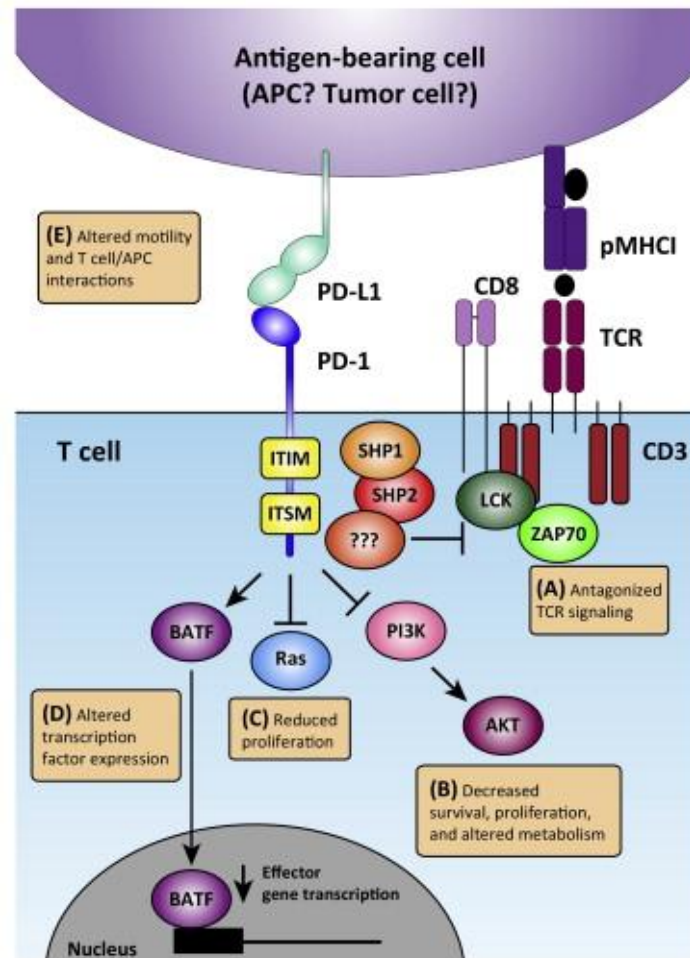
IPIILIMUMAB PATTERN OF RESPONSE



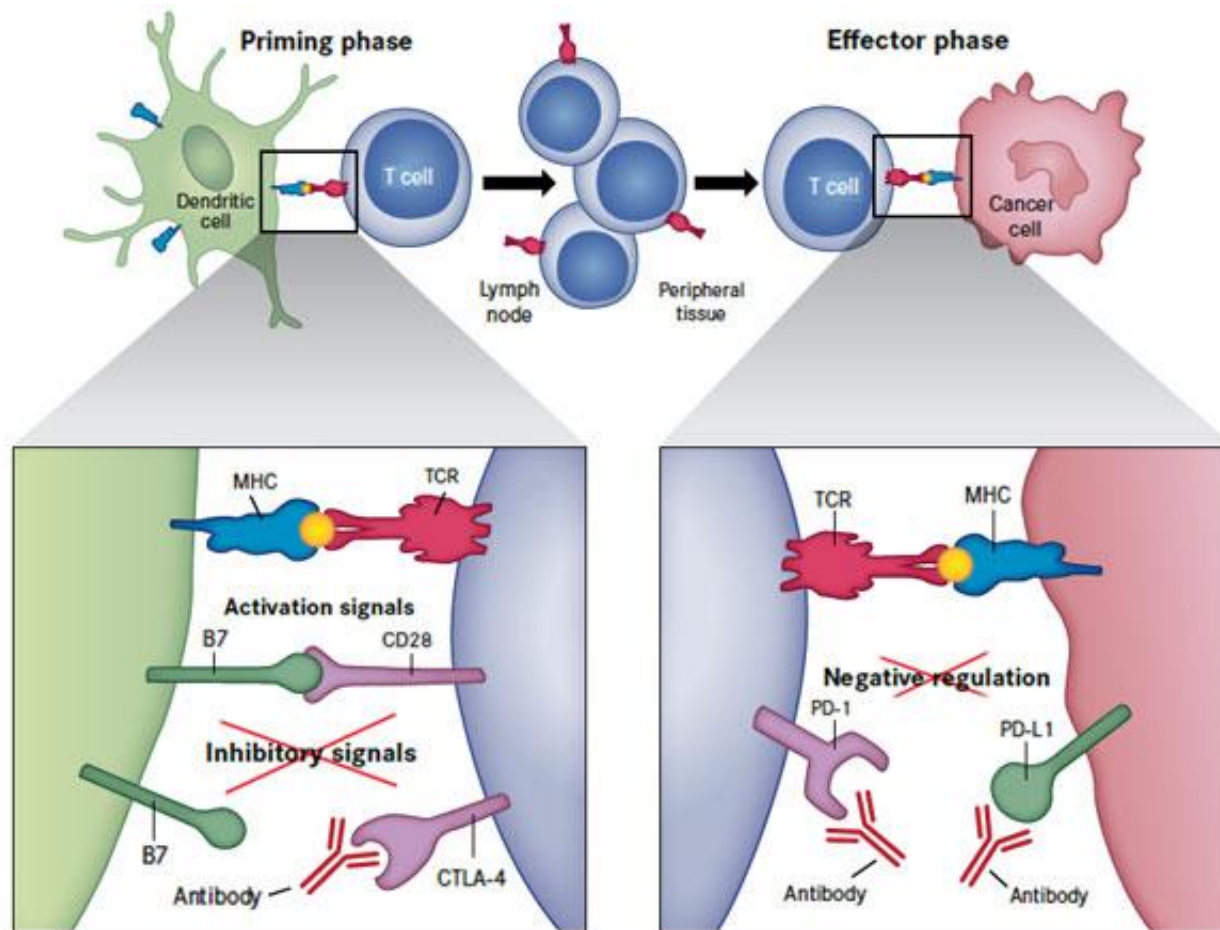
ANTI PD-1



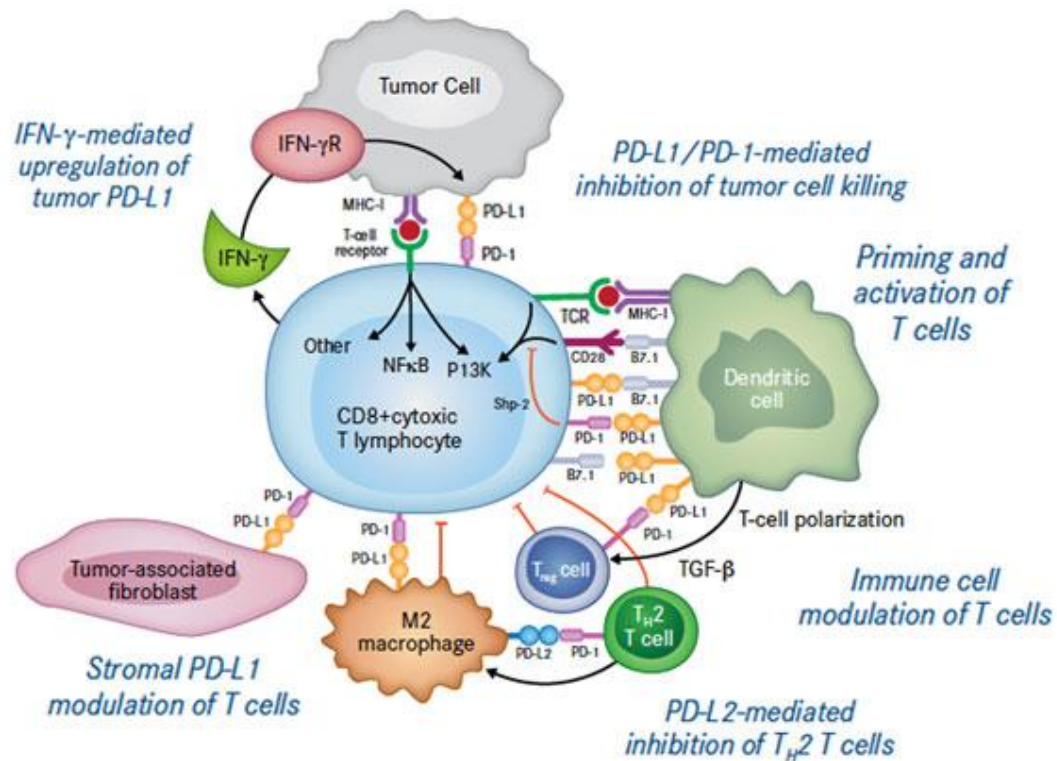
PD-1/PD-L1 SIGNAL



CTLA-4 AND PD-1



T CELLS IMMUNE MODULATION



Flogistic environment modulate T-cells

PD-L1 EXPRESSION

- Heterogeneity
 - Between primary tumor and metastases

Madore et al, Pigment Cell Melanoma Res 2015

- Dynamic marker
- Standardisation
 - Different cut-off
 - >1%, >5%
- PD-L1 positive
 - 30-50% in NSCLC
 - 35% (>5%), 80% (>1%) in melanoma
 - 25% (>1%) in renal cell carcinoma

PREDICTIVE FACTORS FOR IMMUNOTHERAPY

- **We do not have** a predictive factor for

- Anti CTLA-4

- moMDSCs

Gebhardt et al. Clin Cancer Res 2015

- mutational burden

- neoantigens landscape

Snyder et al, NEJM 2014

- Anti PD-1

- Data still no conclusive, but benefit shown even in PD-L1 neg

Robert et al, NEJM 2015 (nivolumab and pembrolizumab);

Postow et al, NEJM 2015 (nivolumab+ipilimumab)

An old story for a new era...

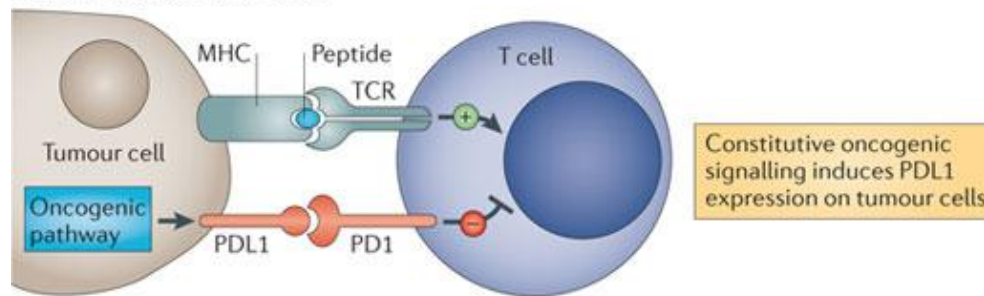


Van Gogh, il seminatore

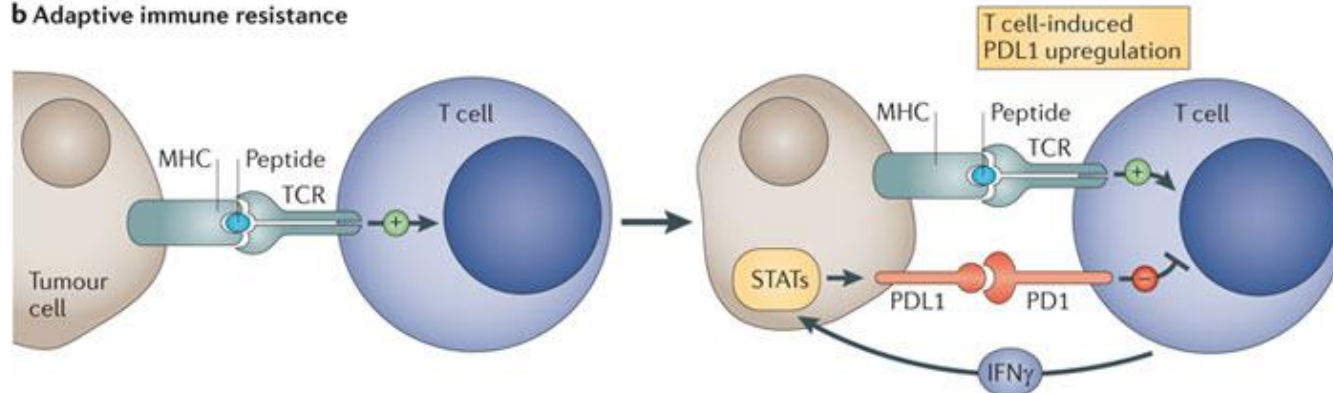
GRAZIE PER L'ATTENZIONE

INNATE AND ADOPTIVE IMMUNE RESISTANCE

a Innate immune resistance



b Adaptive immune resistance



Nature Reviews | Cancer