IMMUNOTARGET THERAPY: ASPETTI GENERALI

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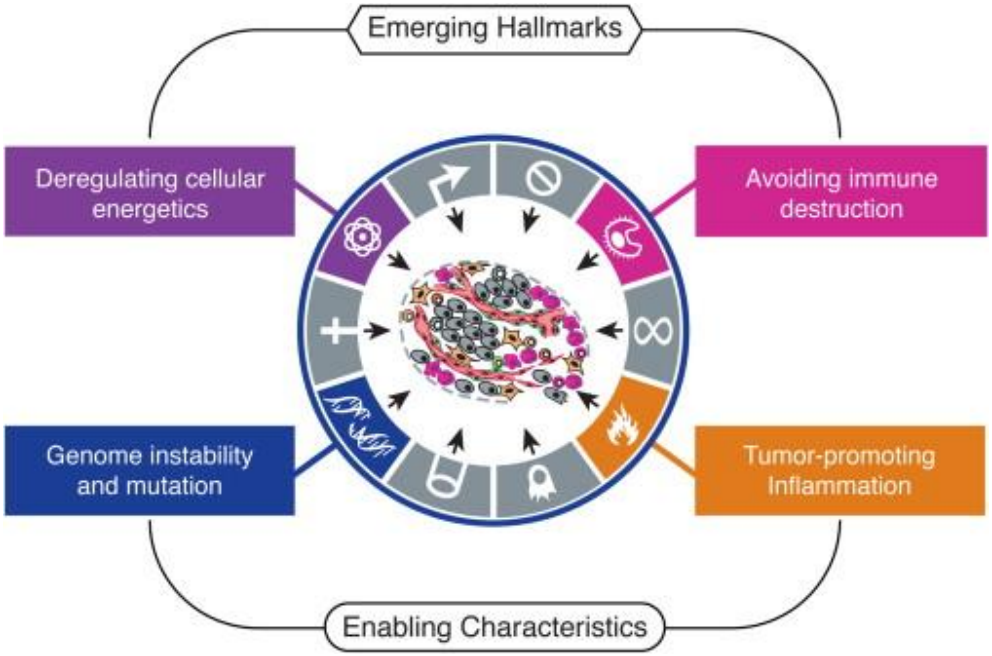
HALLMARKS OF CANCER

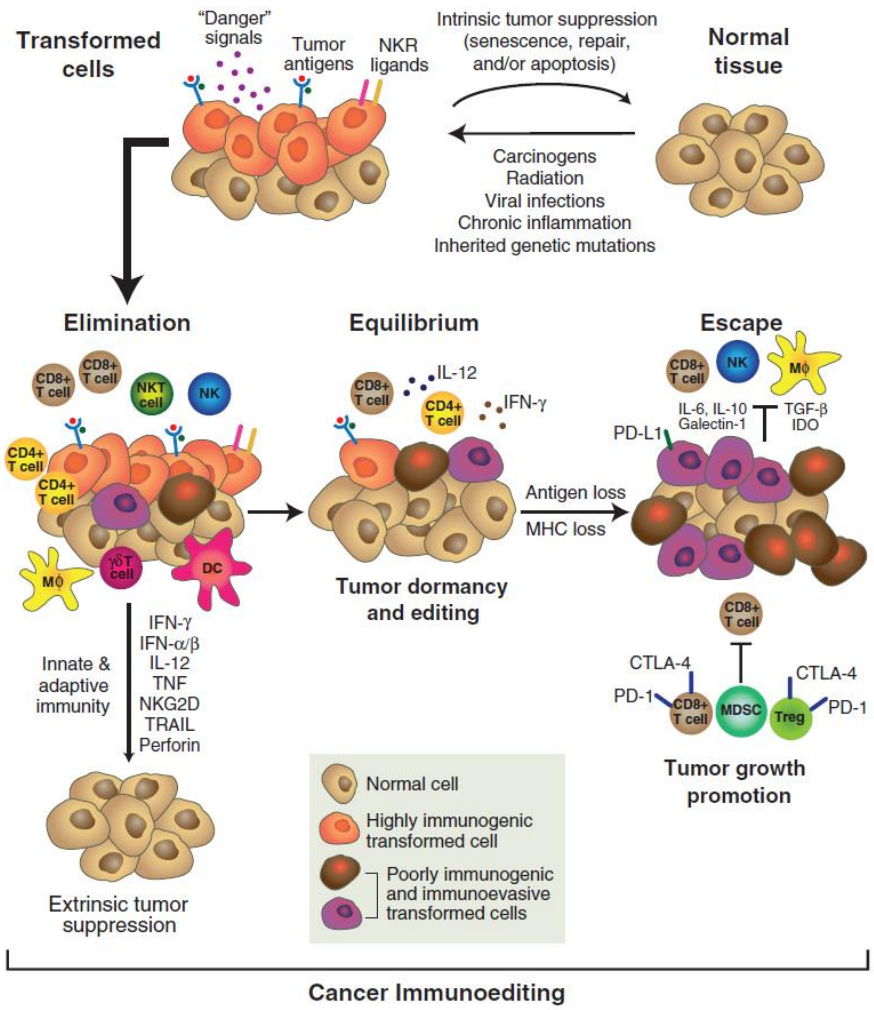


Douglas Hanahan, Robert A. Weinberg, Cell 2011

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

IMMUNOTHERAPY ERA REVOLUTION

IMMUNOEDITING MODEL



Schreiber RD et al, Science 2011

ANTIGEN PRESENTATION

- Active anticancer effect depends on efficient antigen presentation
  - Tumor Associated Antigens
  - Professional Antigen Presenting Cells
    - Dendritic Cells (DCs)
      - Maturation of DCs
        - Maturatin 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 lymphocites)
- Needs co-stimolatory 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

CANCER IMMUNOTHERAPY

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

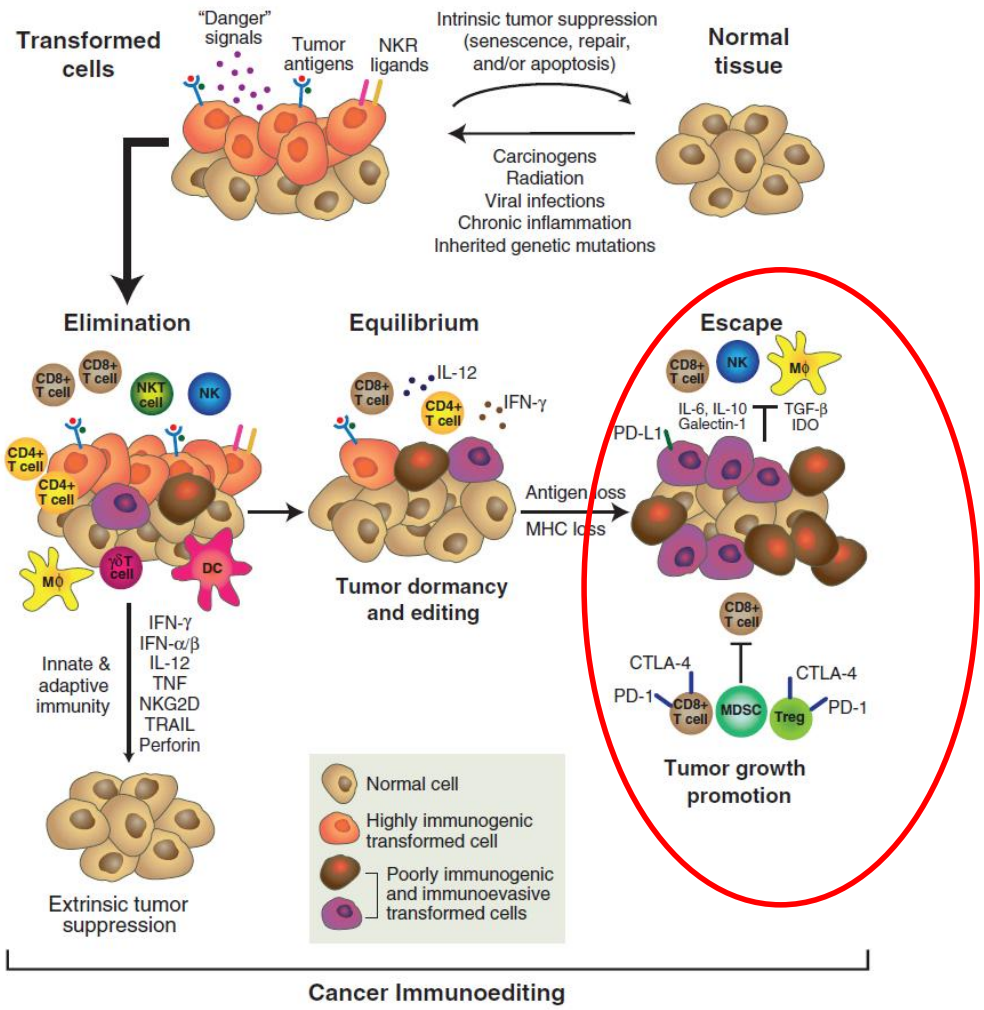
  -IL-2 effective in a subset of patients with advanced melanoma/renal cell cancer

  -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



Schreiber RD et al, Science 2011

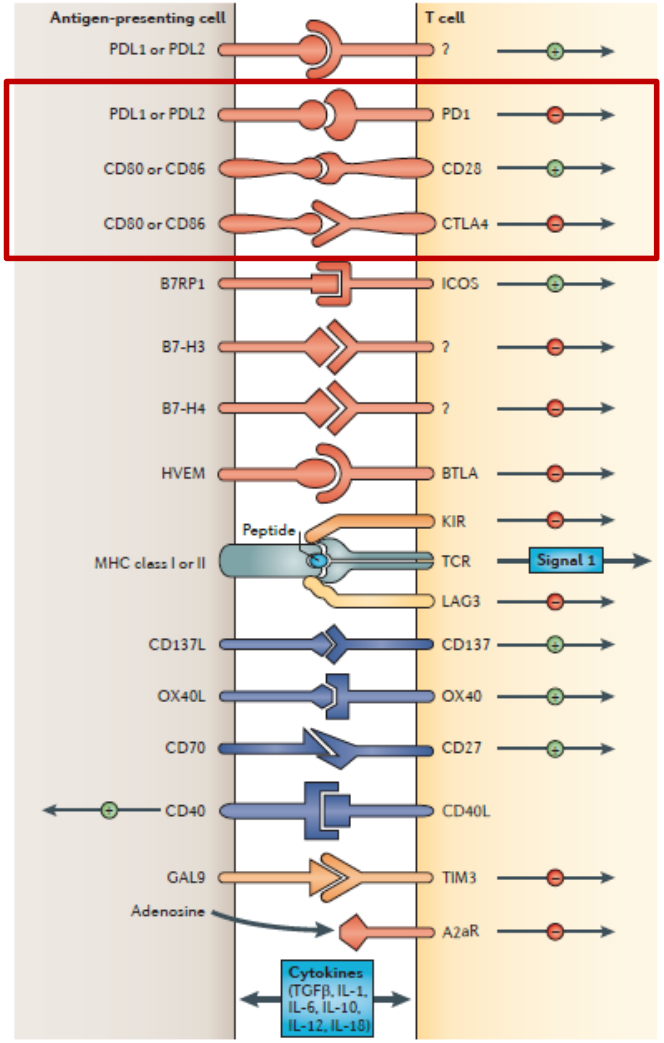
ESCAPE MECHANISMS

- Antigen masking

- Tolerance
  - Regulatory T cells (CD25+ FOXP3+)
  - Myeloid Derived Suppressor Cells (MDSC)
  - ***Inibitory signals through Immune chekpoints***
    - Each step of T-cell mediated immunity is regulated by counterbalancing stimulatory and inibitory 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

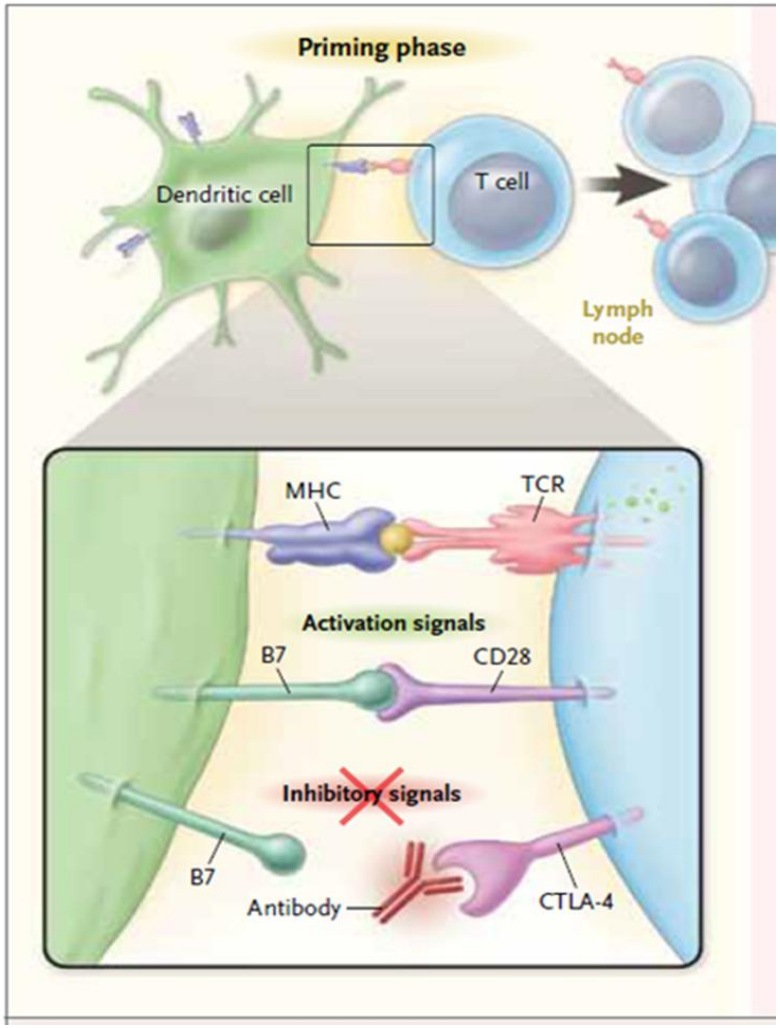
IPILIMUMAB

Pardoll DM, Nat Rev Cancer 2012

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

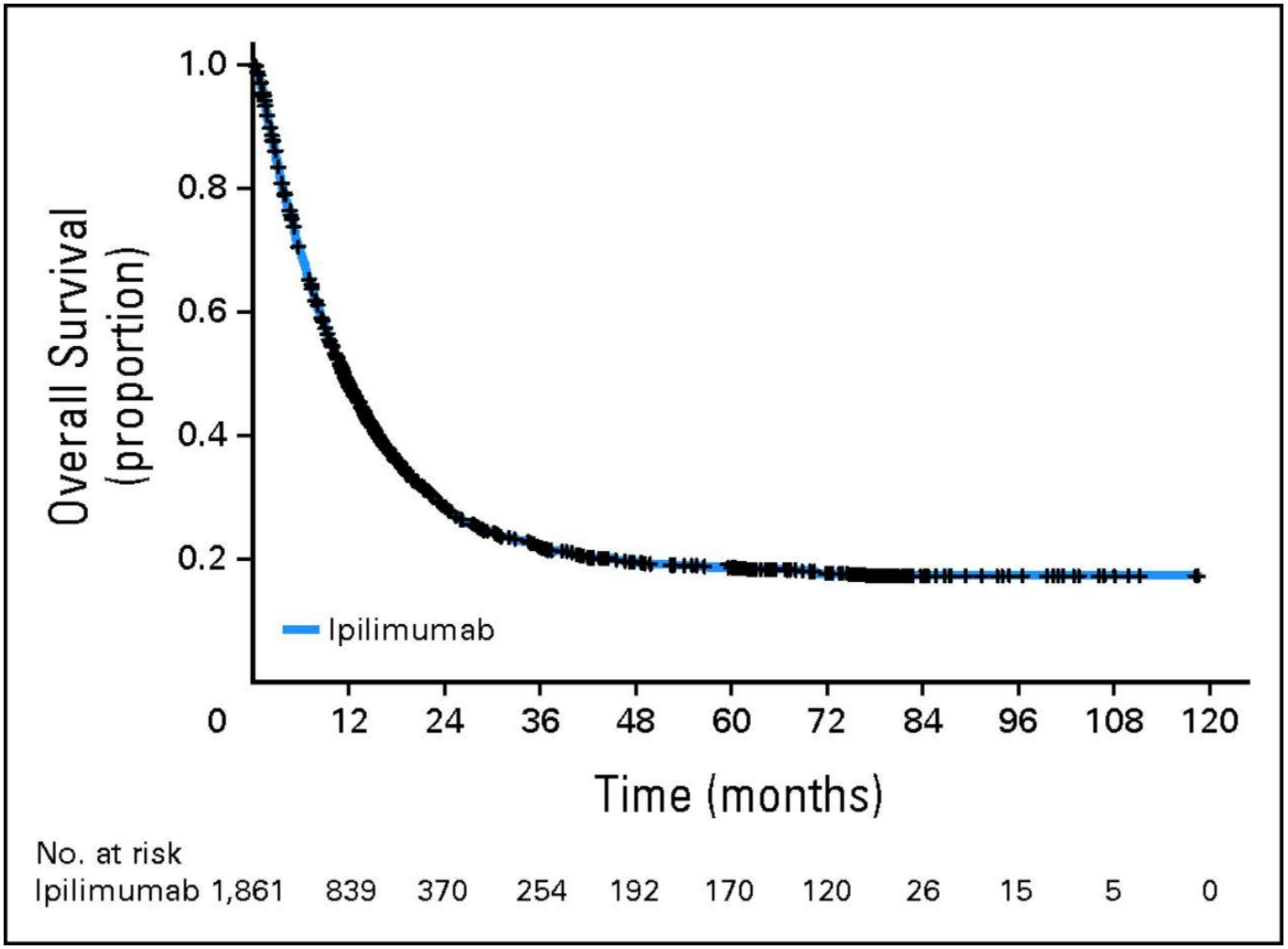
ANTI CTLA-4


Priming phase
Dendritic cell
T cell
Lymph node
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
Antibody
CTLA-4

IPILIMUMAB

- First in class
- First agent to demonstrate improvement in survival in advanced melanoma
  - But low response rate…
- Now data in adjuvant setting
  - Benefit in RFS in stage III melanoma
- One shot therapy: 4 courses at 3 mg/Kg q21
  - No reinduction approved

Primary analysis of pooled overall survival (OS) data.



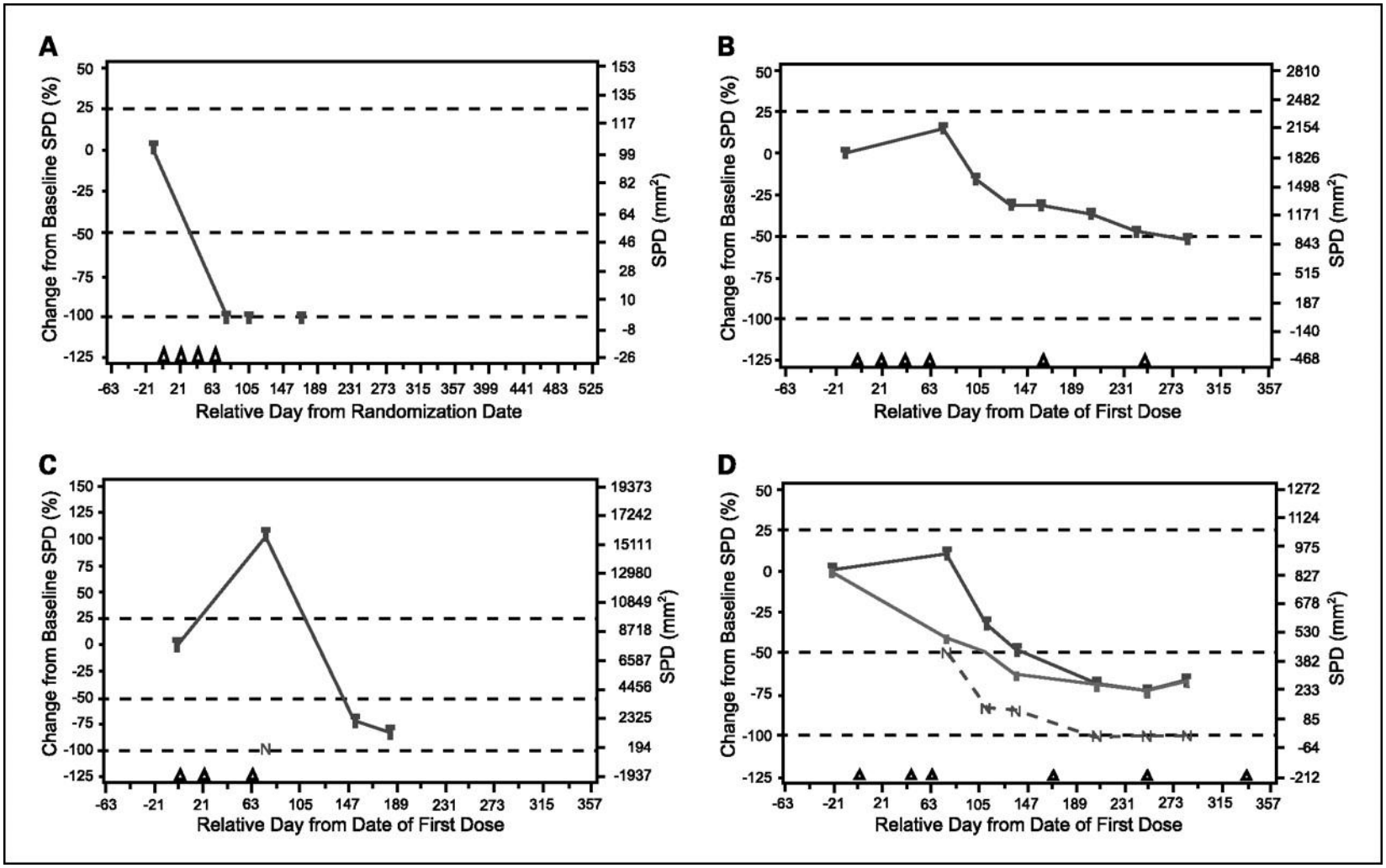
Dirk Schadendorf et al. JCO doi:10.1200/JCO.2014.56.2736

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

IPILIMUMAB PATTERN OF RESPONSE



Jedd D. Wolchok et al. Clin Cancer Res 2009;15:7412-7420

ABSCOPAL EFFECT

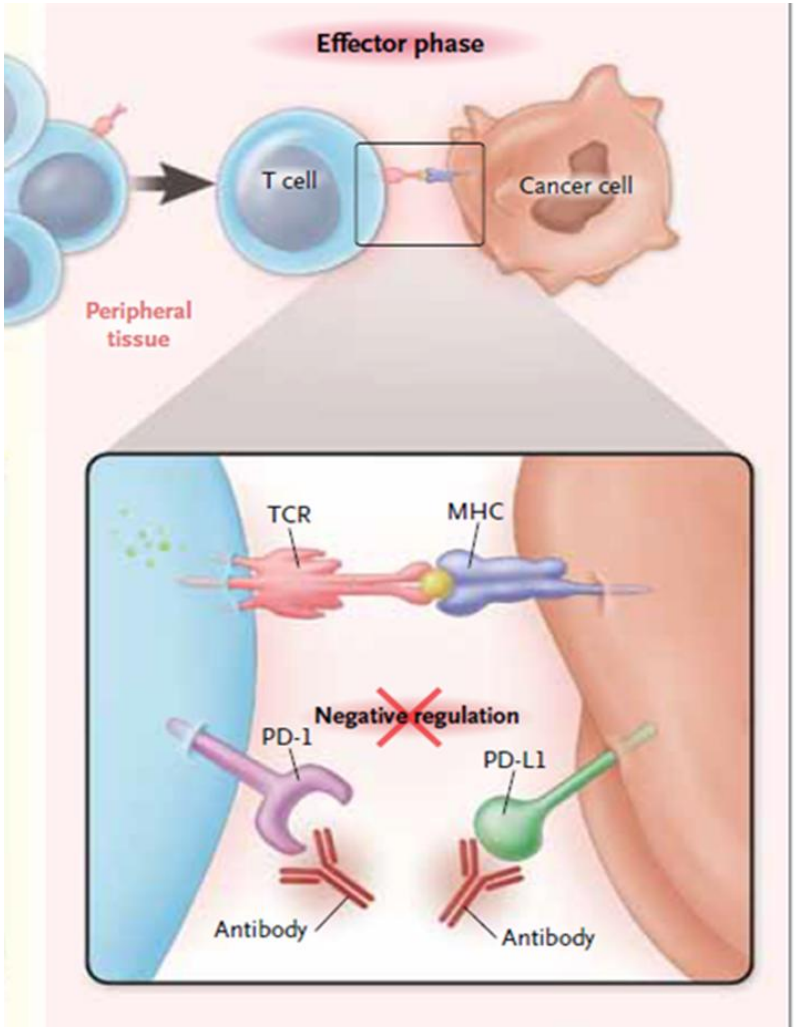
- Regression of non-irradiated metastatic lesions distant from the primary tumor site directly subject to irradiation

- Increase in antibody against CAA, modulation of peripheral immune cells (decrease of MDSC)

Postow et al, NEJM 2012

- *Radiotherapy could modulate immune response and enhance anti tumor effect of immunetherapy!*

ANTI PD-1


Effector phase
T cell
Cancer cell
Peripheral tissue
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

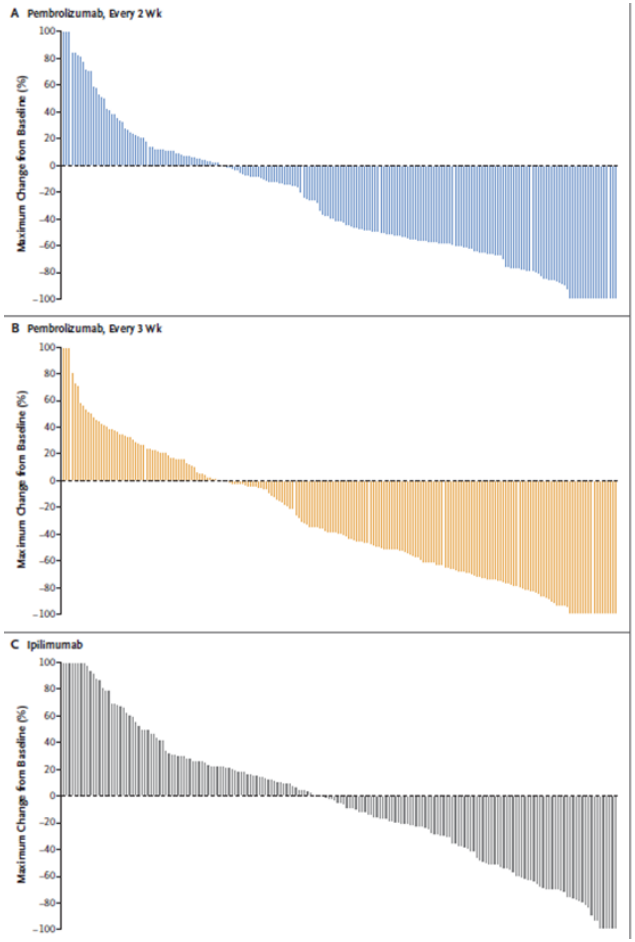
ANTI PD-1

- Nivolumab and Pembrolizumab both effective in first-line and in ipi-pretreated advanced melanoma
  - Pembrolizumab superior to ipilimumab in first-line
  - Higher and earlier Response Rate than ipilimumab
  - Treatment until progression
  - Convincing data in NSCLC

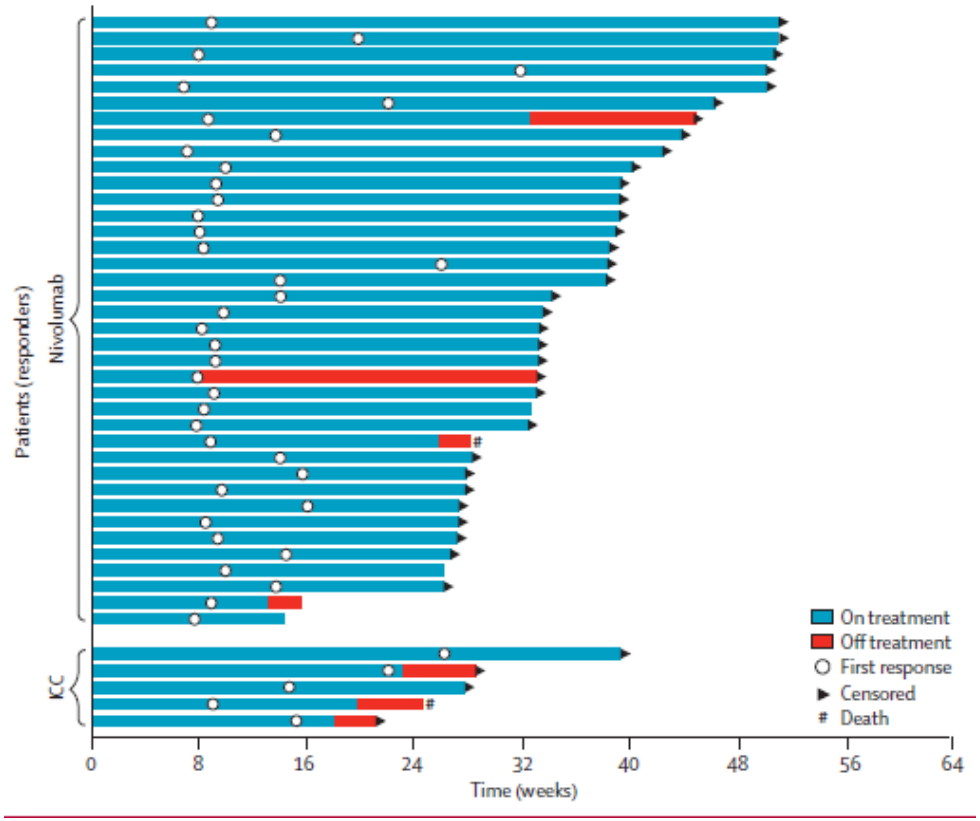
- Anti CTLA-4 + Anti PD-1
  - Combination immunotherapy in first-line advanced melanoma
    - Nivolumab+Ipilimumab
      - 22% of complete response!
      - Benefit in PFS with respect to ipilimumab alone

Postow et al, NEJM 2015

Plotting anti-PD1: higher/earlier RR (than ipi), durable response



Robert et al, NEJM 2015



Weber et al, Lancet Oncol 2015

SAFETY OF IMMUNE TARGET THERAPIES

- Immune related adverse events
  - Colitis (G3/4: 5%), diarrhea (G3/4: 10%)
  - Skin toxicity
  - Hepatitis
  - Endocrine toxicity
    - Hypofsitis, hyper/hypothiroidism
  - Neurologic toxicity
  - Ocular
    - Uveitis
- Management:
  - steroids
    - slow tapering
  - infliximab, micophenolate mofetil

PREDICTIVE FACTORS

- We do not have a strong 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
    - PD-L1 IHC expression?
      - Cut-off: 1 vs 10%
    - 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)
    - Dynamic marker

NOVEL PERSPECTIVES

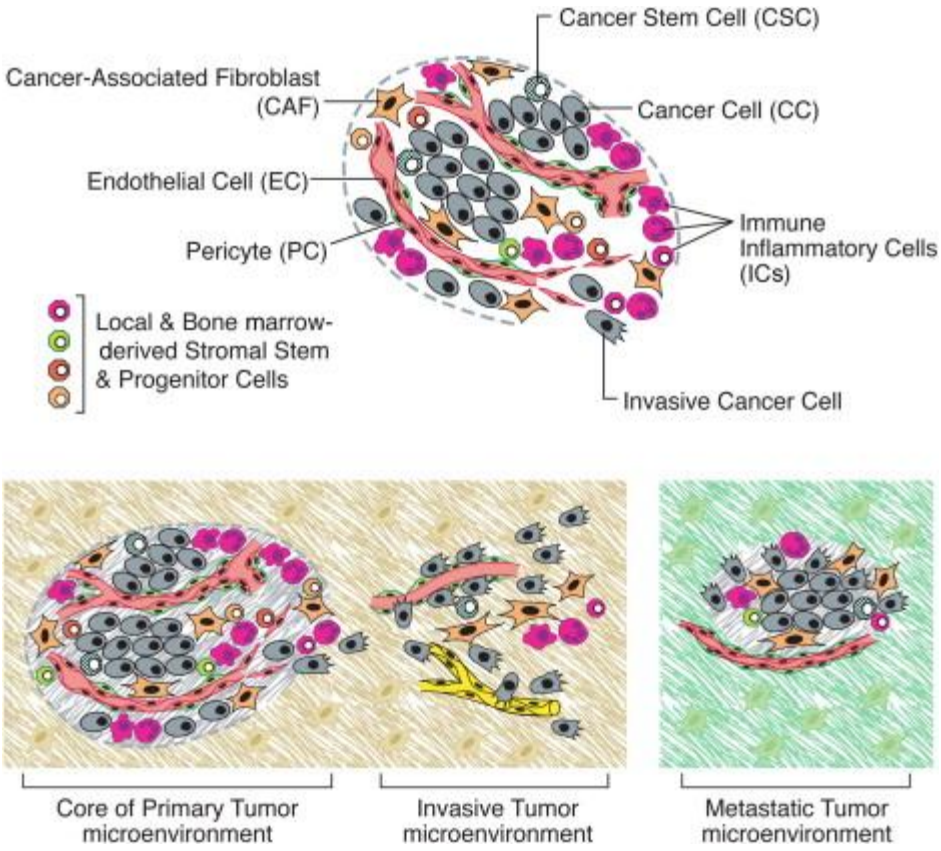
- **Integration of immunotherapy with other treatments**
  - Cancer vaccines
    - E.g. T-VEC+ipilimumab

      Puzanov et al, ASCO 2015
  - Small molecules
    - E.g. BRAF and MEK inhibitors in melanoma

      Ribas et al, ASCO 2015
  - Radiation therapy
- **Novel promising immune chekpoints**
  - VISTA, TIM-3
- **Patient selection**
  - We do need predictive factors for immune therapy too!

Vermeer, La ragazza con l'orecchino di perla

TUMOR MICROENVIRONMENT



Hanahan and Weinberg Cell 2011

An old story for a new era…

Van Gogh, il seminatore

GRAZIE PER L'ATTENZIONE