Rete Oncologica Veneta
Ricerca, innovazione, assistenza

ONCOLOGIA 4.0

IMMUNO-ONCOLOGIA TRA INNOVAZIONE E SOSTENIBILITÀ

L'immuno-oncologia come terapia del cancro

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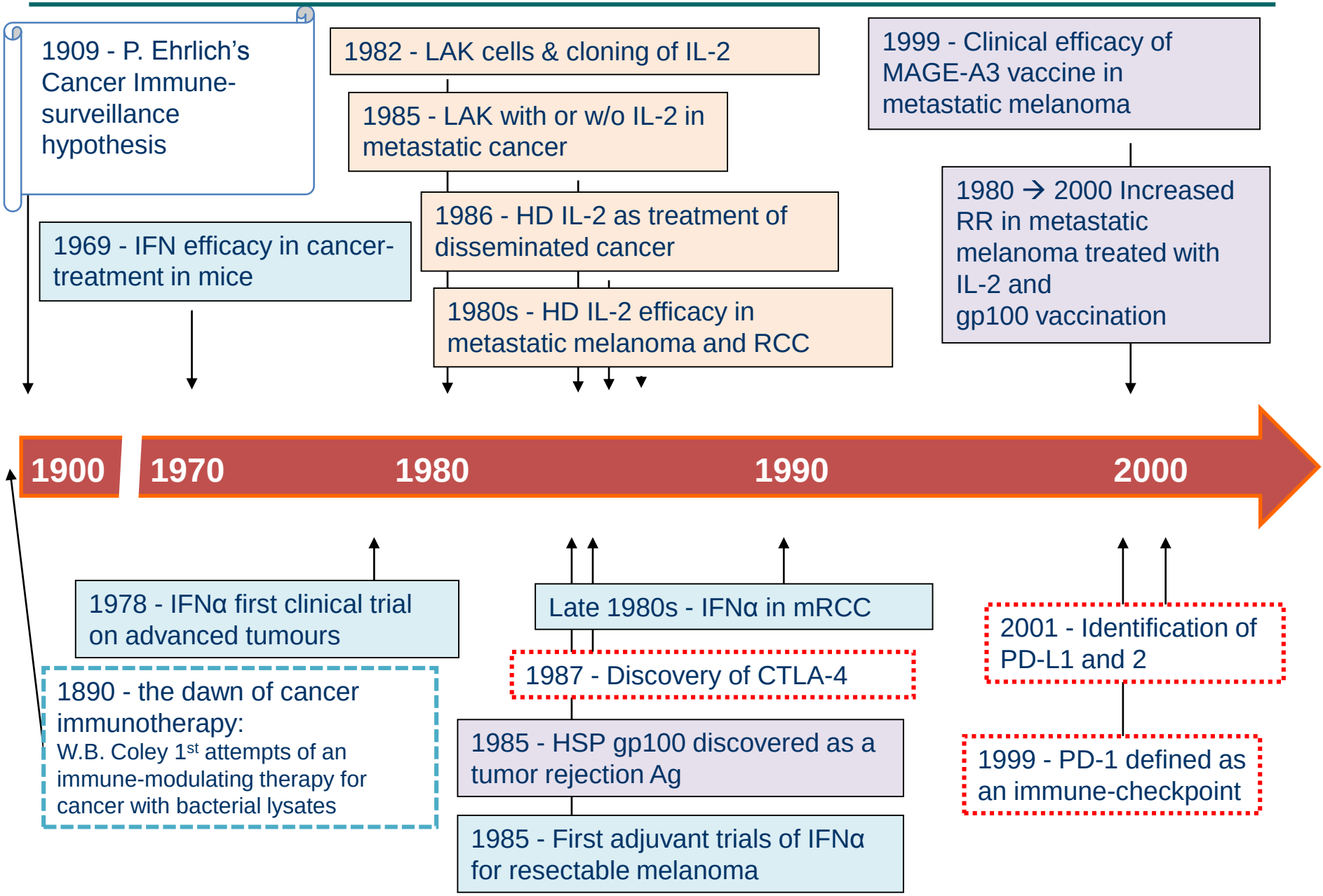
IOV - IRCCS

PADOVA 30 OTTOBRE 2017
Aula Magna Istituto Oncologico Veneto
Via Gattamelata 64 - ore 9 - 13

2017 MOTORE SANITÀ
sanità domani

Milestones in Cancer Immunotherapy (1)



Milestones in Cancer Immunotherapy (2)

2001 - The revival of the Cancer Immune-surveillance theory thanks to R.B Schreiber, L.J. Old and M.J. Smyth

2008 - Phase 3 trial with autologous tumor-derived HSP gp96 as adjuvant treatment in high risk RCC

2008 - Chimeric Antigen Receptors T-Cell (CAR-T) in cancer treatment

2003 - Adoptively transferred CTL mediate responses in refractory, metastatic melanoma

2010 - FDA approval of cellular vaccine Sipuleucel-T for advanced castrate-resistant prostate cancer

2007 - Ipilimumab causes regression in mRCC

2003 - Cancer regression induced by CTLA-4 blockade in metastatic melanoma

2001 - 3D structure of CTLA-4 in complex with its ligand B-7 solved

2012 - Anti-PD-1 dramatic results in refractory solid tumours

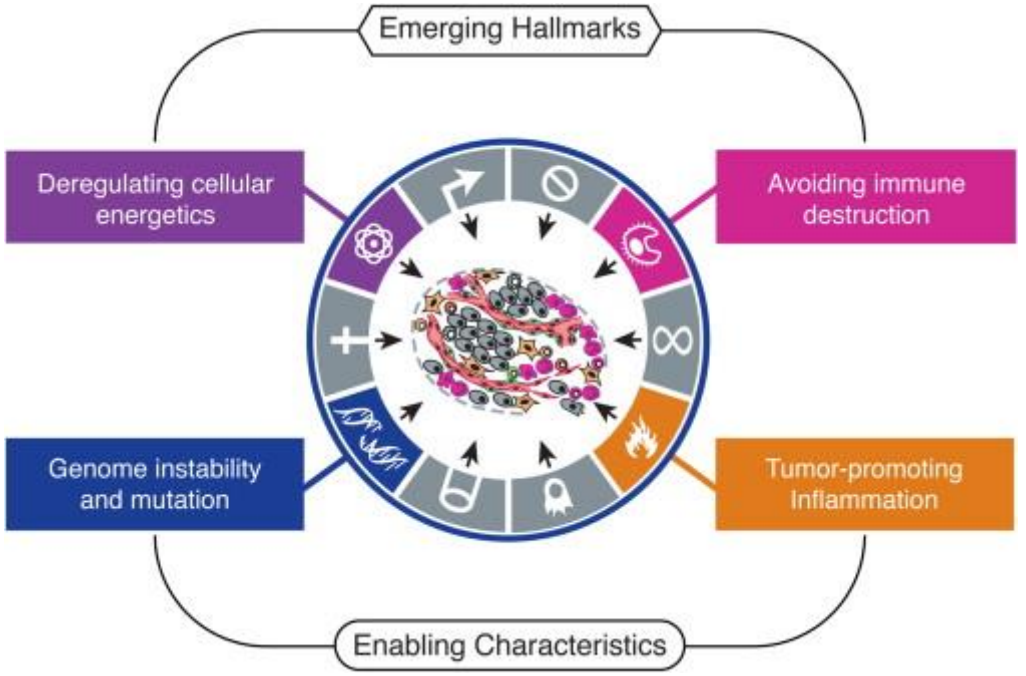
2011 - FDA approval of Ipilimumab for metastatic melanoma

2010 - Ipilimumab (vs gp100 alone), improved OS of pre-treated metastatic melanoma

2014-16 - FDA approval of anti PD1-PDL1 for:

- Advanced melanoma
- Advanced NSCLC
- mRCC
- Hodgkin Lymphoma
- Urothelial carcinoma
- Merkel Carcinoma

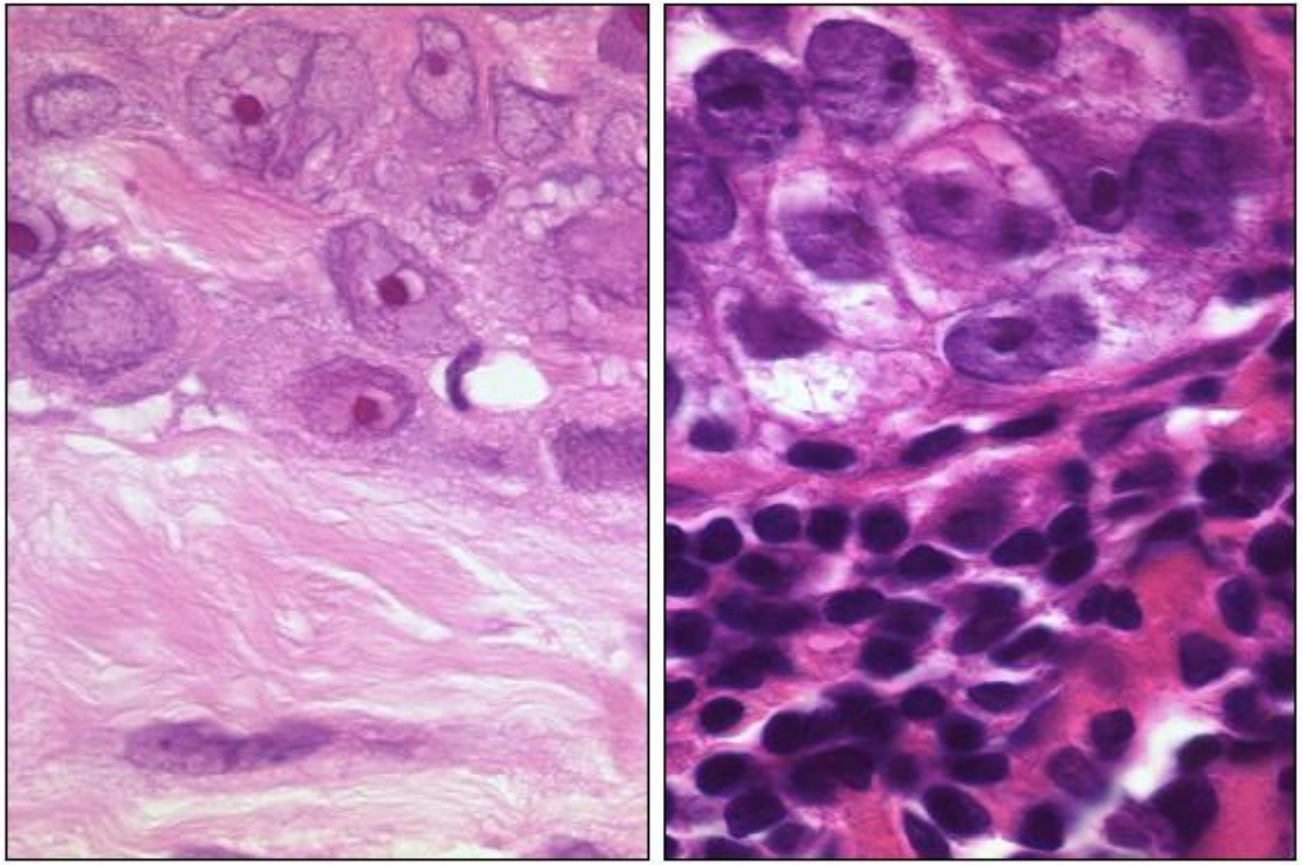
Antitumor immunity becomes a target



Hanahan D, Cell 2011, 144:646

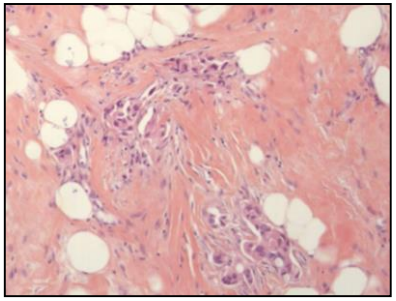
Heterogenous immune infiltrate in breast cancer

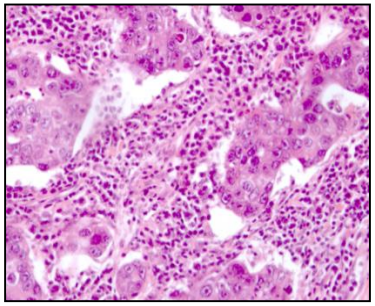
Lymphocyte-predominant breast cancer
(LPBC = more lymphocytes than tumor cells)



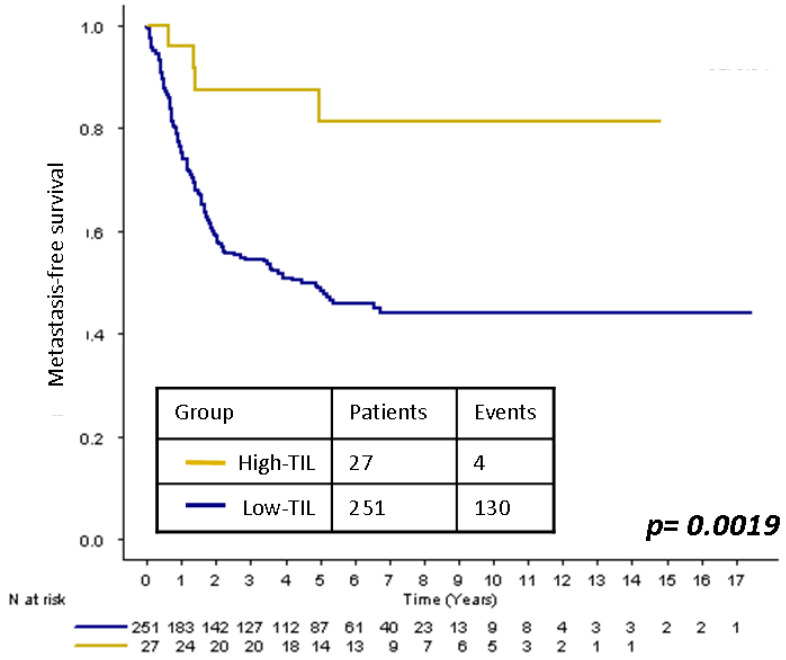
Prognostic value of TILs on residual disease after neoadjuvant chemotherapy for TNBC

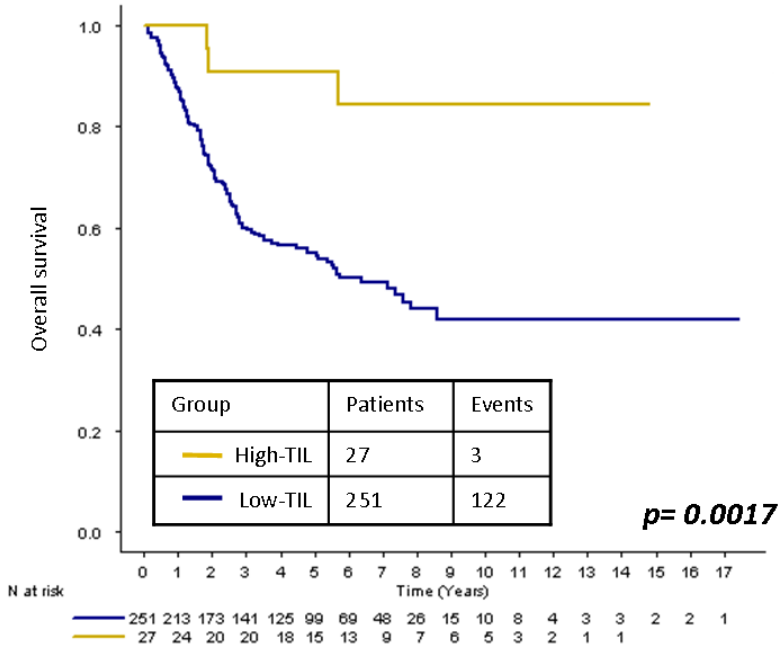
Low-TIL residual disease
(It and Str-TIL <=60%)





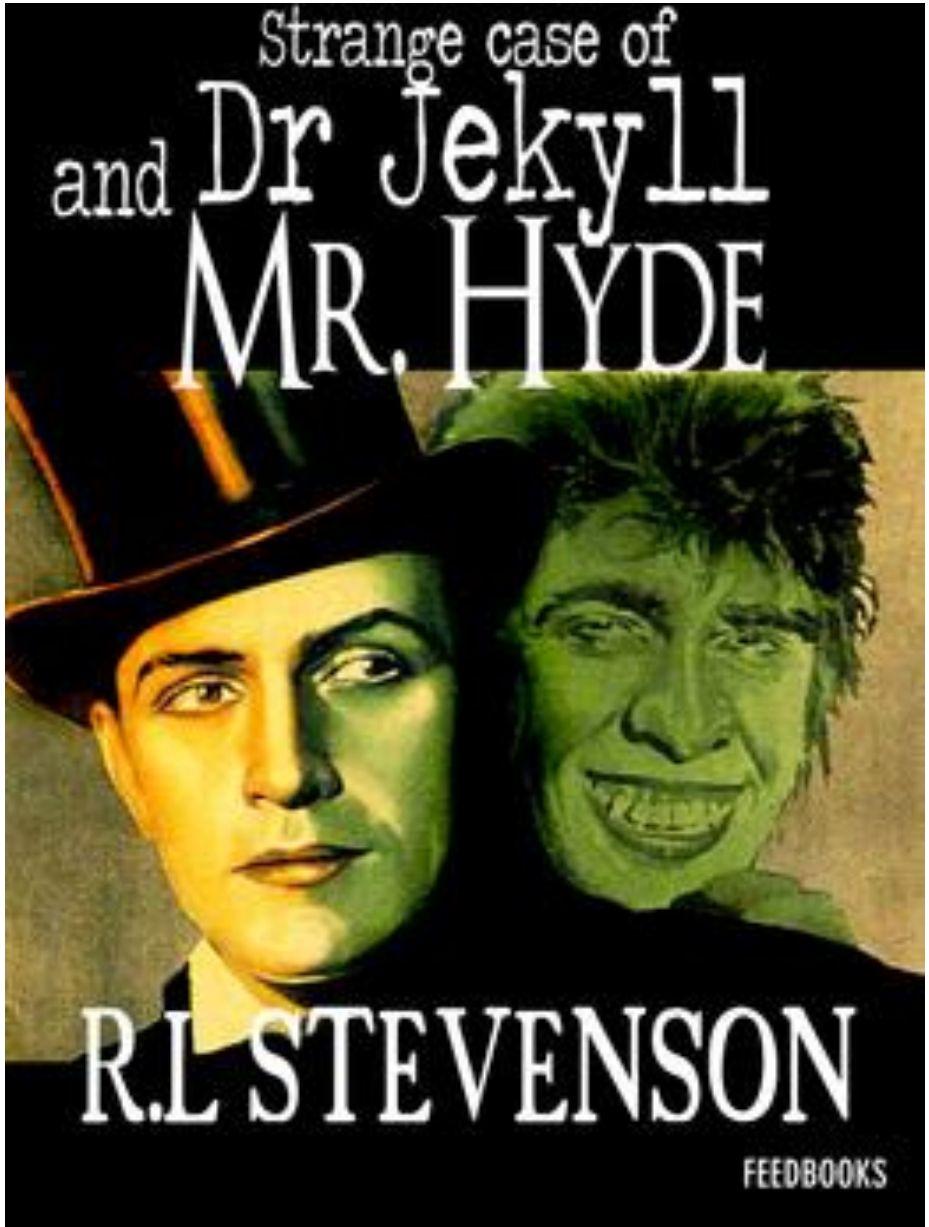
High-TIL residual disease
(It and/or Str-TIL >60%)





MV Dieci et al; Ann Oncol 2014

Immunity and Cancer

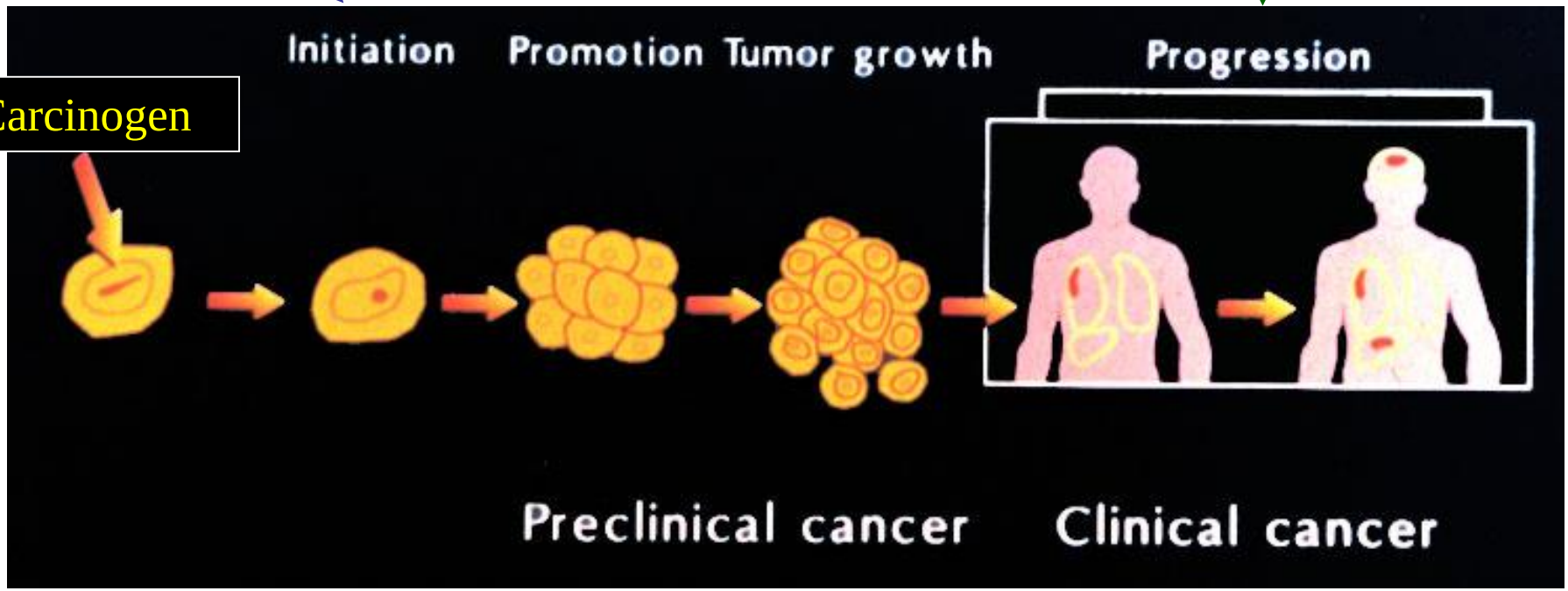


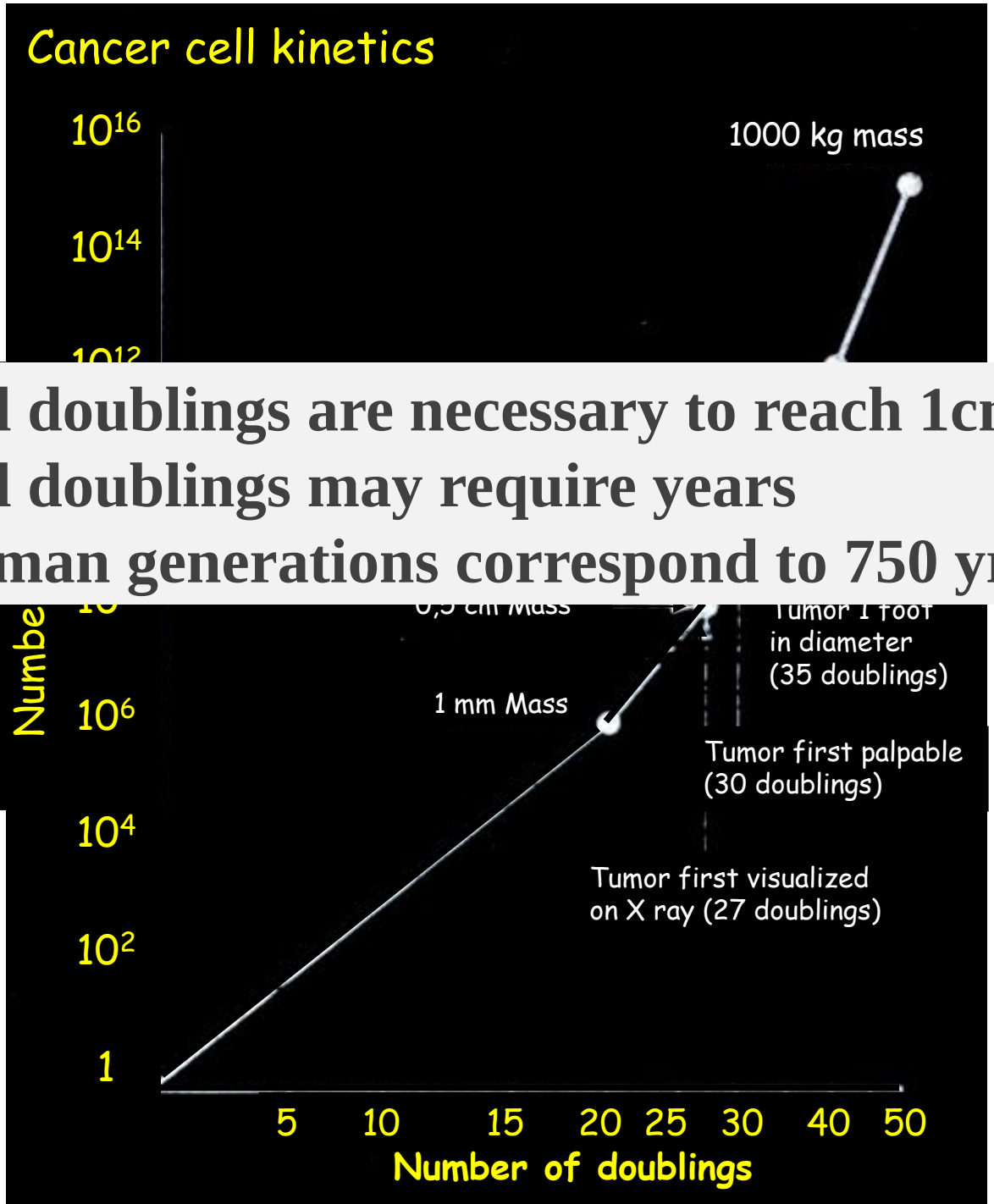
Multistep Carcinogenesis

Carcinogens induce irreversible and non lethal DNA alterations

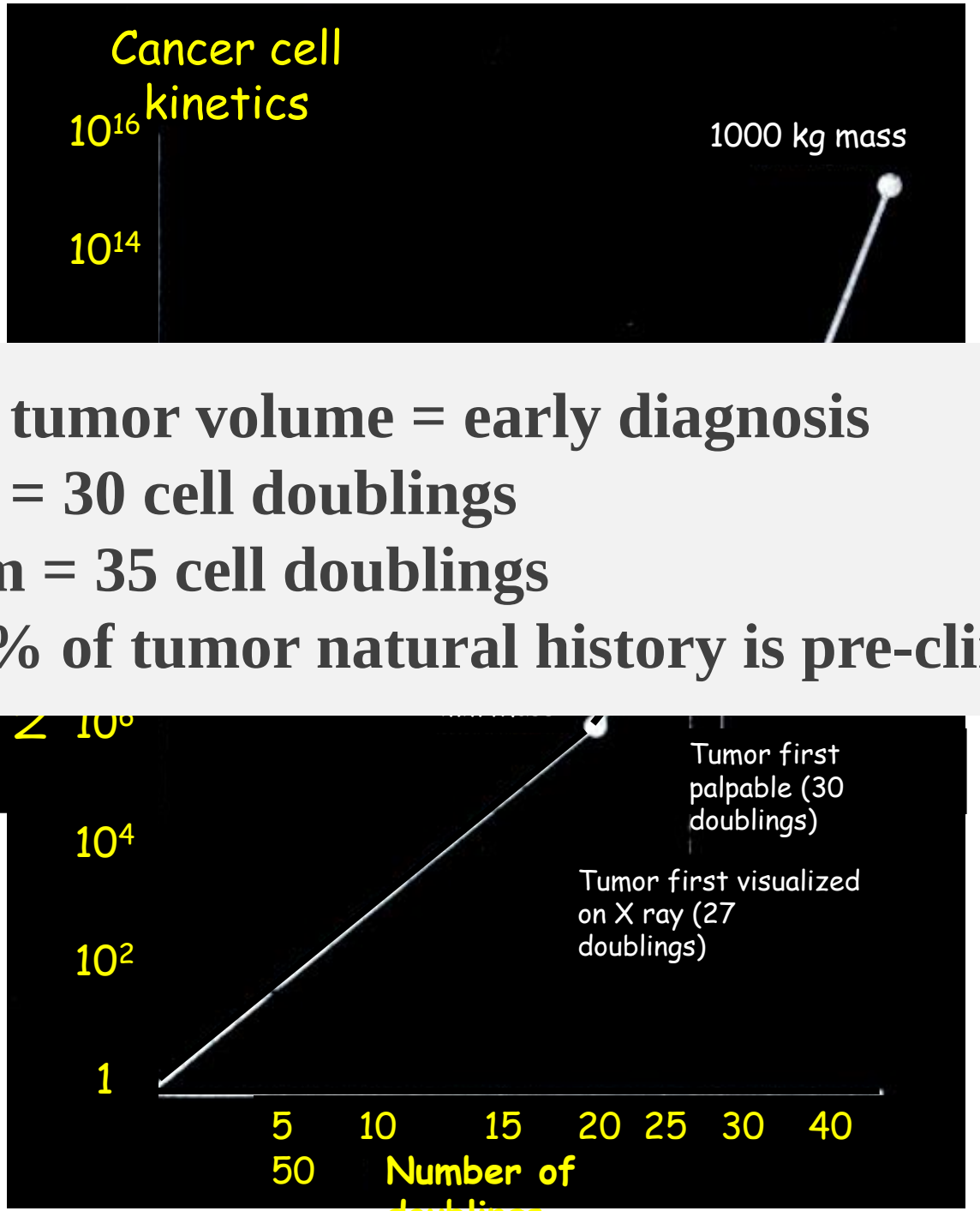
Slow and reversible development of cell clones bearing the same DNA dysregulations

Because of genetic instability, cancer cells acquire additional properties such as inhibition of apoptosis, promotion of neoangiogenesis, capability to penetrate blood vessel, disseminate, escape the immune system





30 cell doublings are necessary to reach 1cm volume
30 cell doublings may require years
30 human generations correspond to 750 yrs



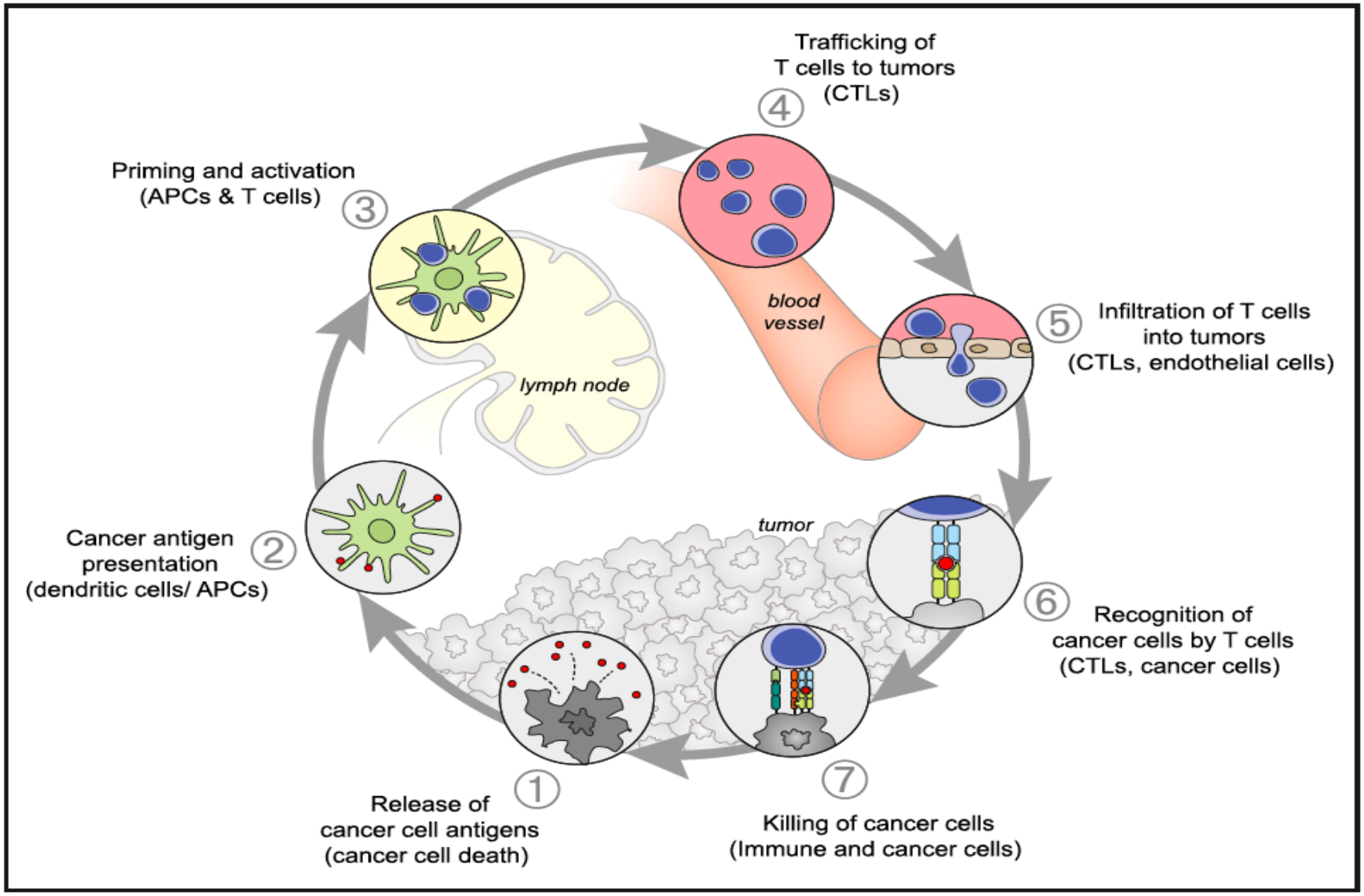
1 cm tumor volume = early diagnosis

1 cm = 30 cell doublings

32 cm = 35 cell doublings

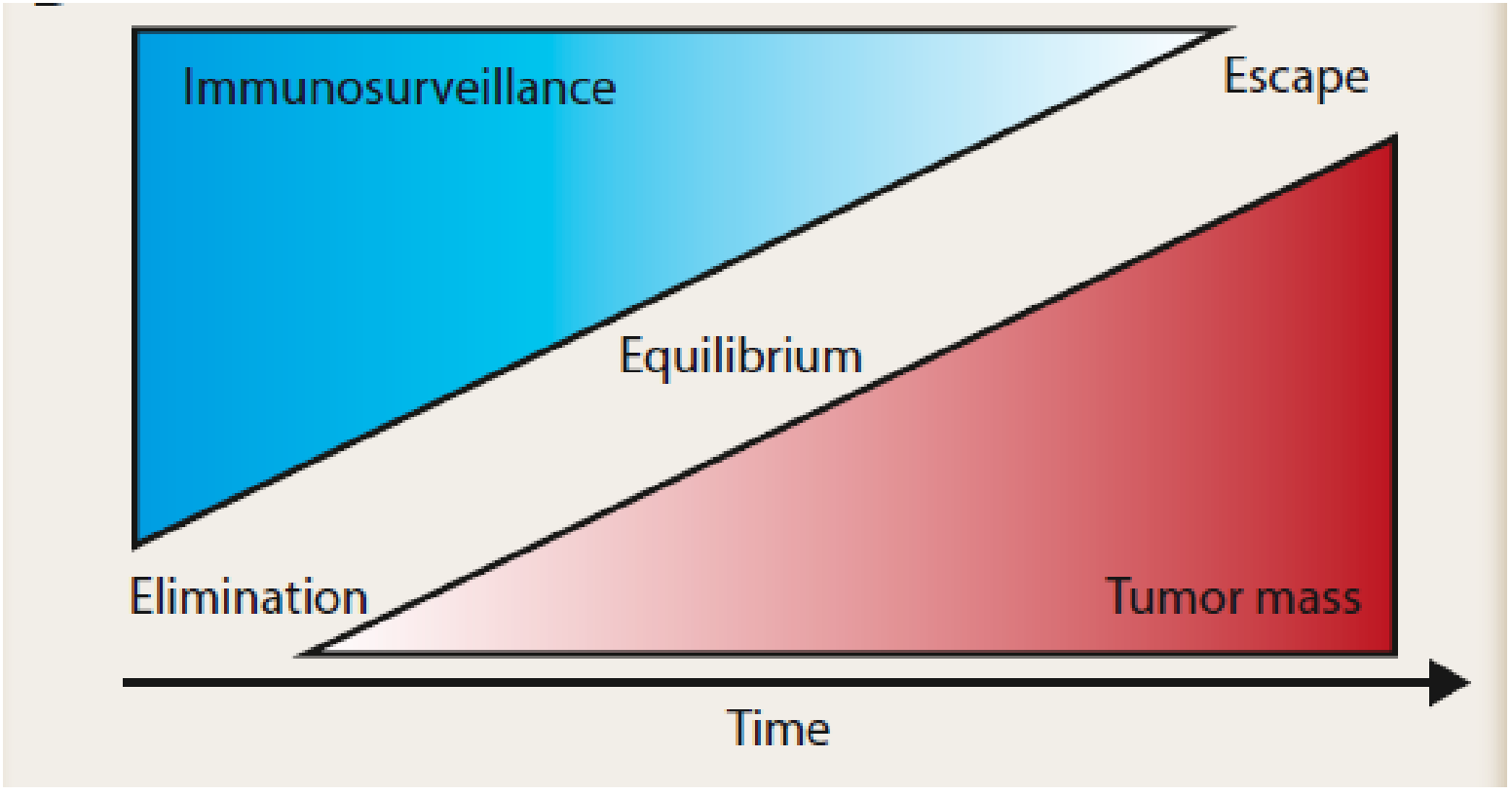
> 80% of tumor natural history is pre-clinical

The cancer immune cycle

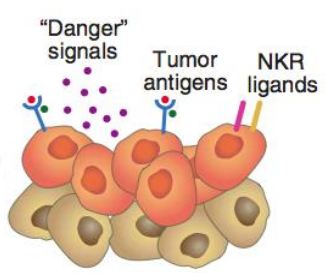


What is cancer?

- **Theory of immunoediting (3 E)**
  - Immunotherapy



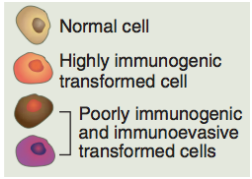
Cancer Immunoediting



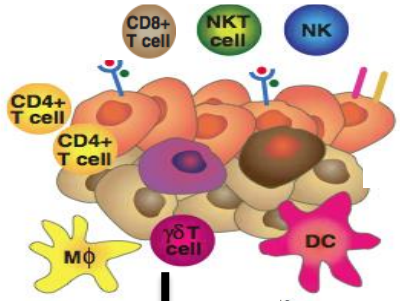
Intrinsic tumor suppression (senescence, repair, and/or apoptosis)

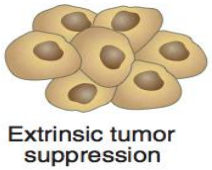
Carcinogens
Radiation
Viral infections
Chronic inflammation
Inherited genetic mutations

Normal tissue



Elimination Phase

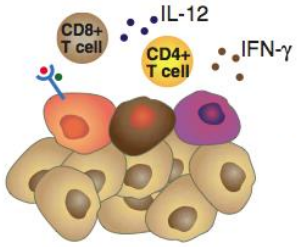




Extrinsic tumor suppression

"Danger signals" (e.g. IFNs) activate dendritic cells and promote induction of adaptive anti-tumor immune responses.

Equilibrium Phase



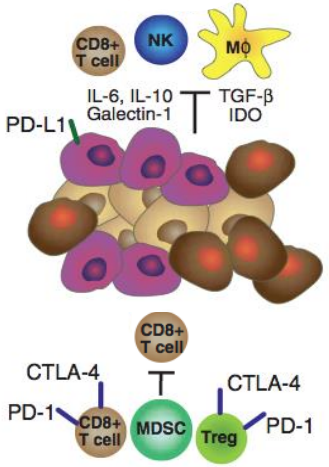
Tumor dormancy and editing

The adaptive immune system maintains residual tumor cells in a functional state of dormancy, before eventually resuming growth as either recurrent primary tumors or distant metastases

Antigen loss

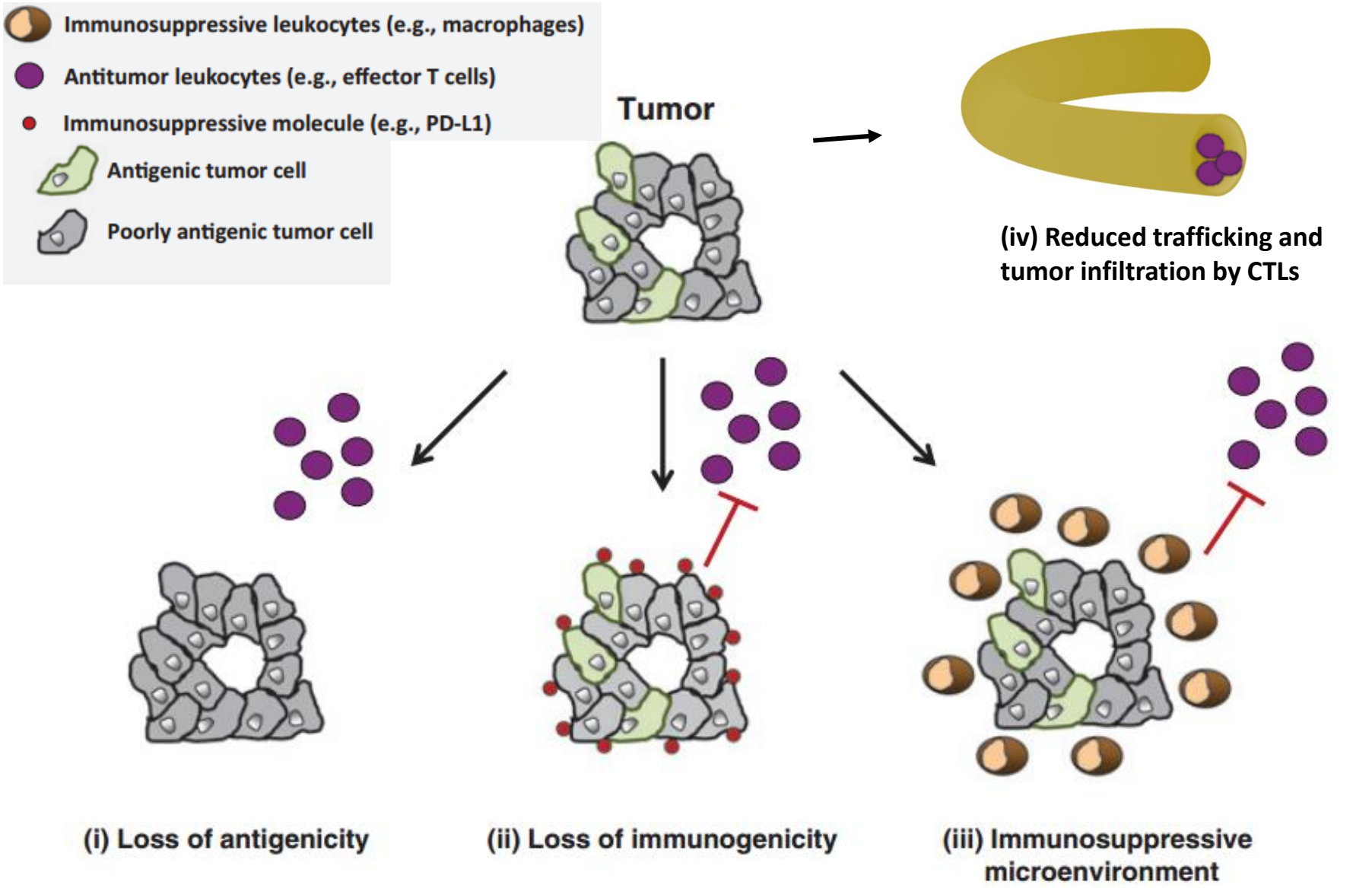
MHC loss

Escape Phase



Tumor growth promotion

Tumor cells that have acquired the ability to circumvent immune recognition and/or destruction emerge as progressively growing, visible tumors.



Selection
MHC downregulation

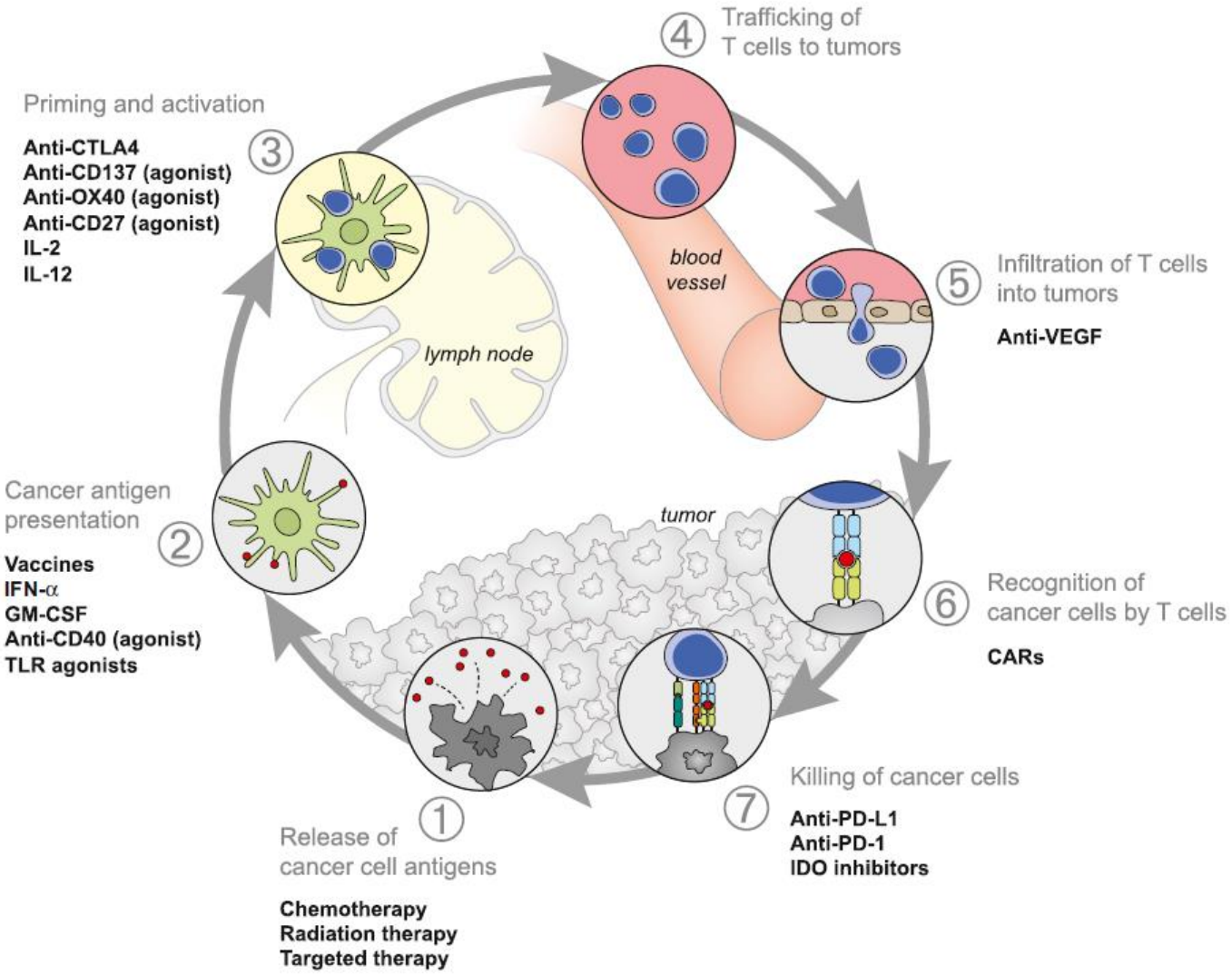
No co-stimulation
Inhibitory molecules
Inhibitory cytokines

Recruitment of immunesuppressive cells

Immunotherapeutic strategies

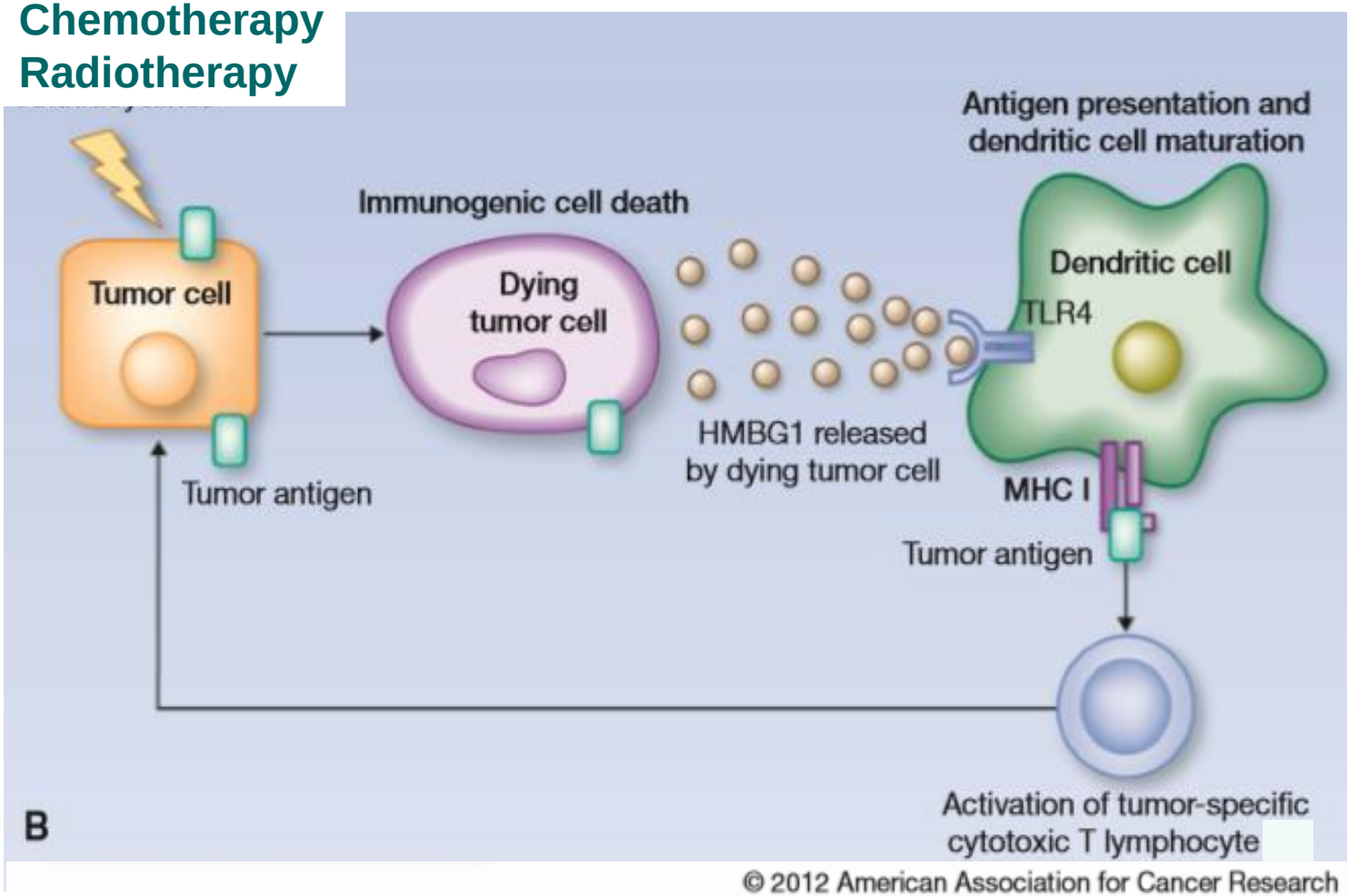
- Non-specific immune stimulation
  - Chemotherapy
  - Radiotherapy
  - Targeted therapies (moAbs)
  - Cytokines
- Vaccines
  - Preventive
  - Therapeutic
- Immune checkpoint inhibitors
- Adoptive cell transfer
- Antiangiogenic (indirect)

Immunotherapeutic strategies



Immunogenic cell death

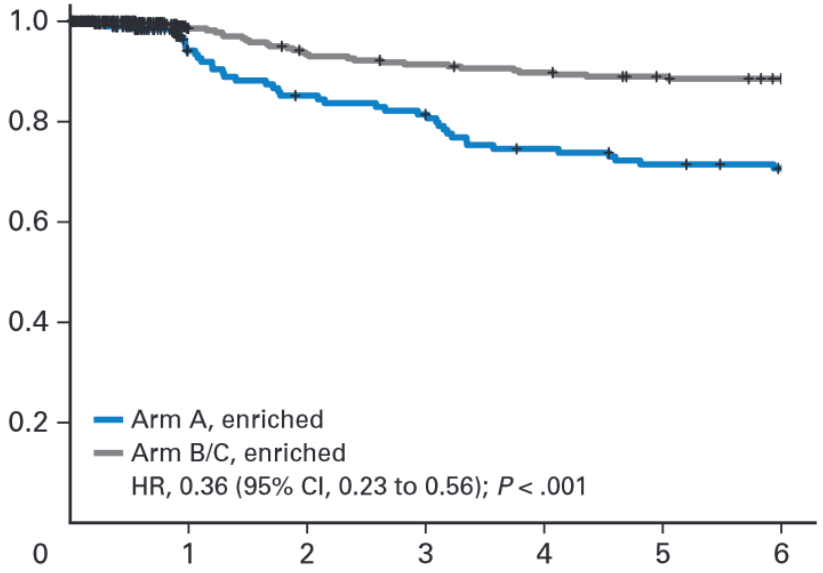
Chemotherapy
Radiotherapy



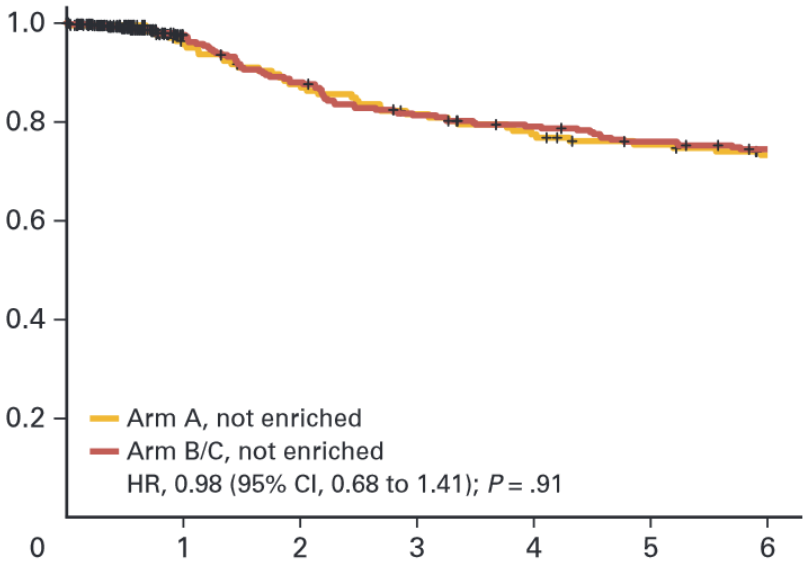
André F et al, CCR 2013

Immune function genes predict benefit from adjuvant trastuzumab

ENRICHED (n=677, 62.3%)



Non-ENRICHED (n=615, 47.7%)

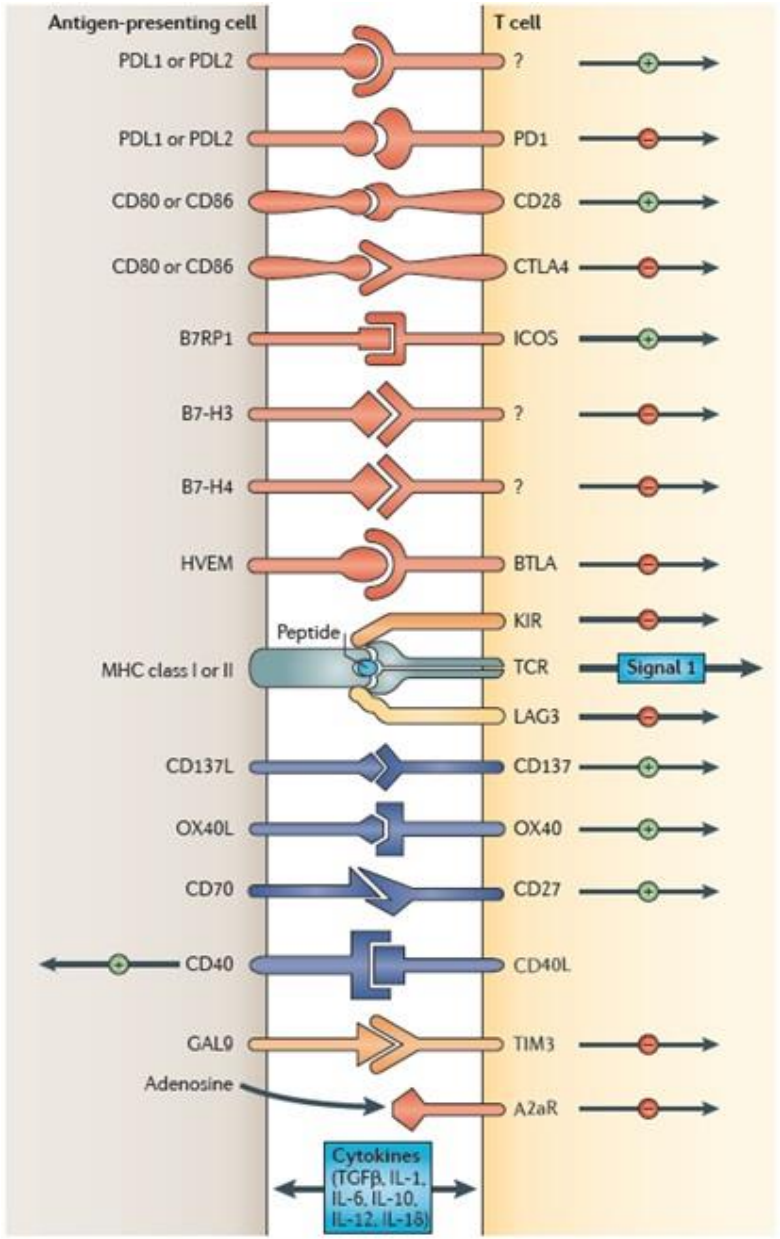


Perez E, et al. SABCS 2014, JCO 2015

Immune checkpoint

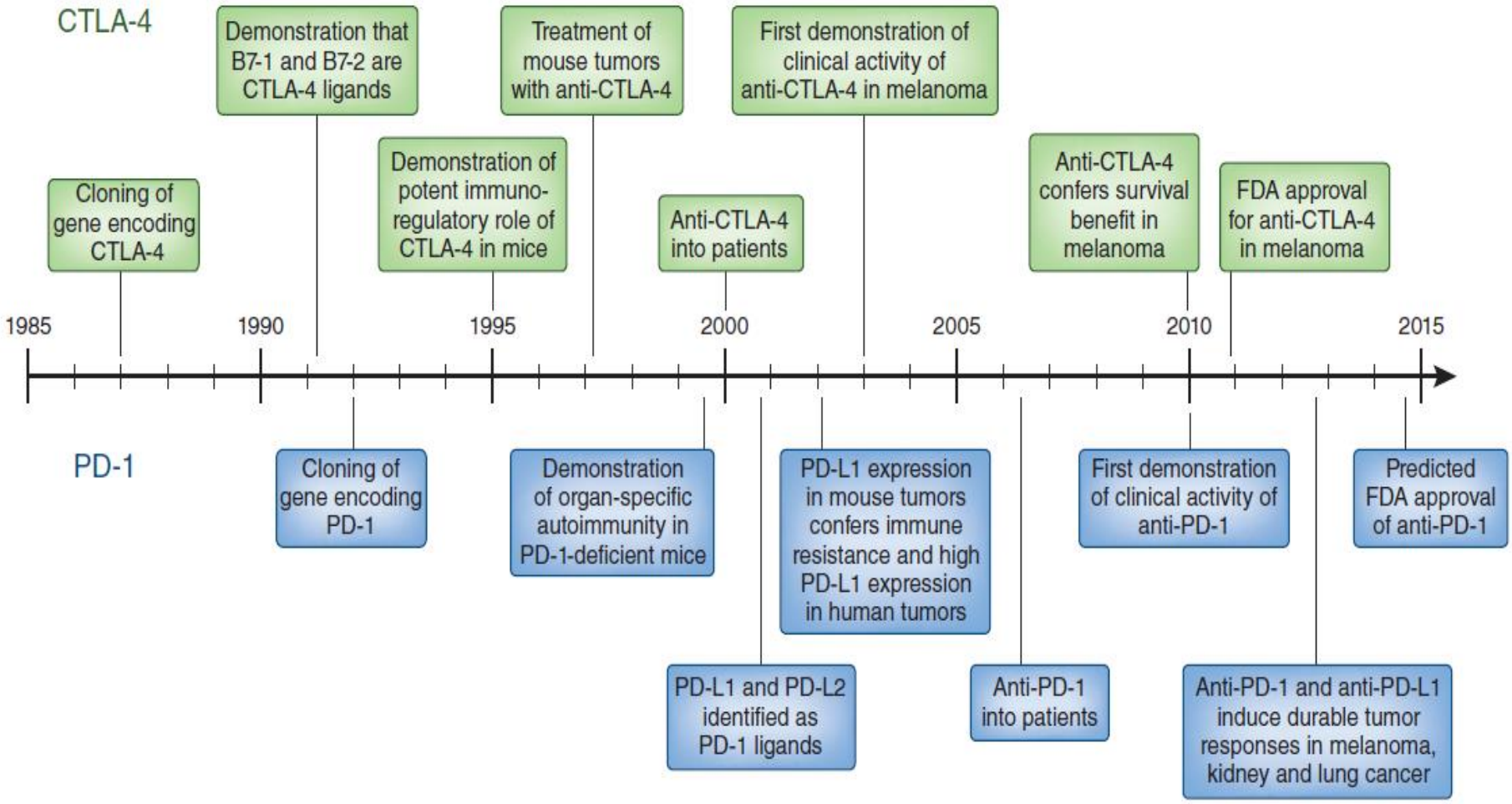
- Immune checkpoints refer to a plethora of inhibitory pathways of the immune system, that are crucial for *maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues* in order to minimize collateral tissue damage

Tumors co-opt certain immune-checkpoint pathways as a major machanism of immune resistance



DM Pardoll, Nature Reviews Cancer 201

Immune checkpoint inhibitors: Historical perspective



Pardoll DM, Nat Immunol 2012

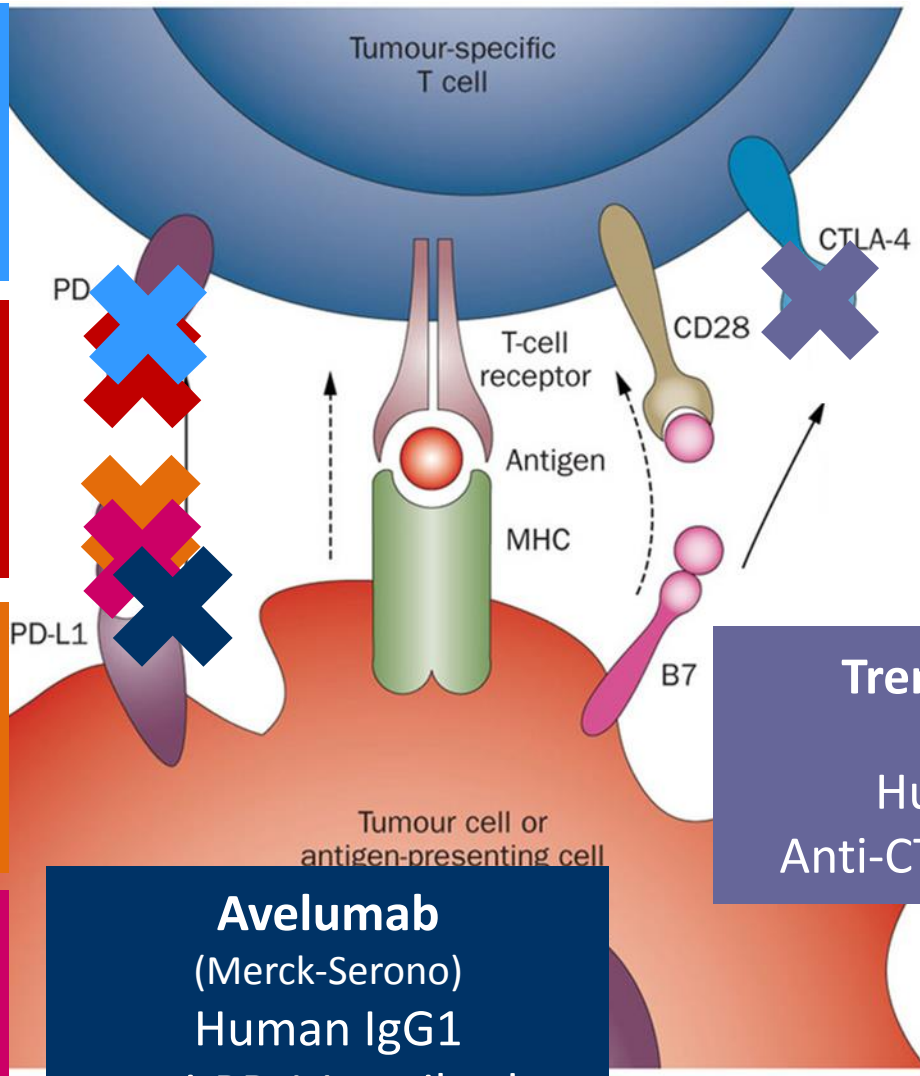
Immune checkpoint inhibitors under clinical development

Nivolumab
(BMS)
Human IgG4
anti-PD-1 antibody

Pembrolizumab (Merck)
Humanized IgG4
anti-PD-1 antibody

Atezolizumab
(Genentech)
engineered human IgG1
anti-PD-L1 antibody

Durvalumab
(AZ)
Human IgG1
anti-PD-L1 antibody

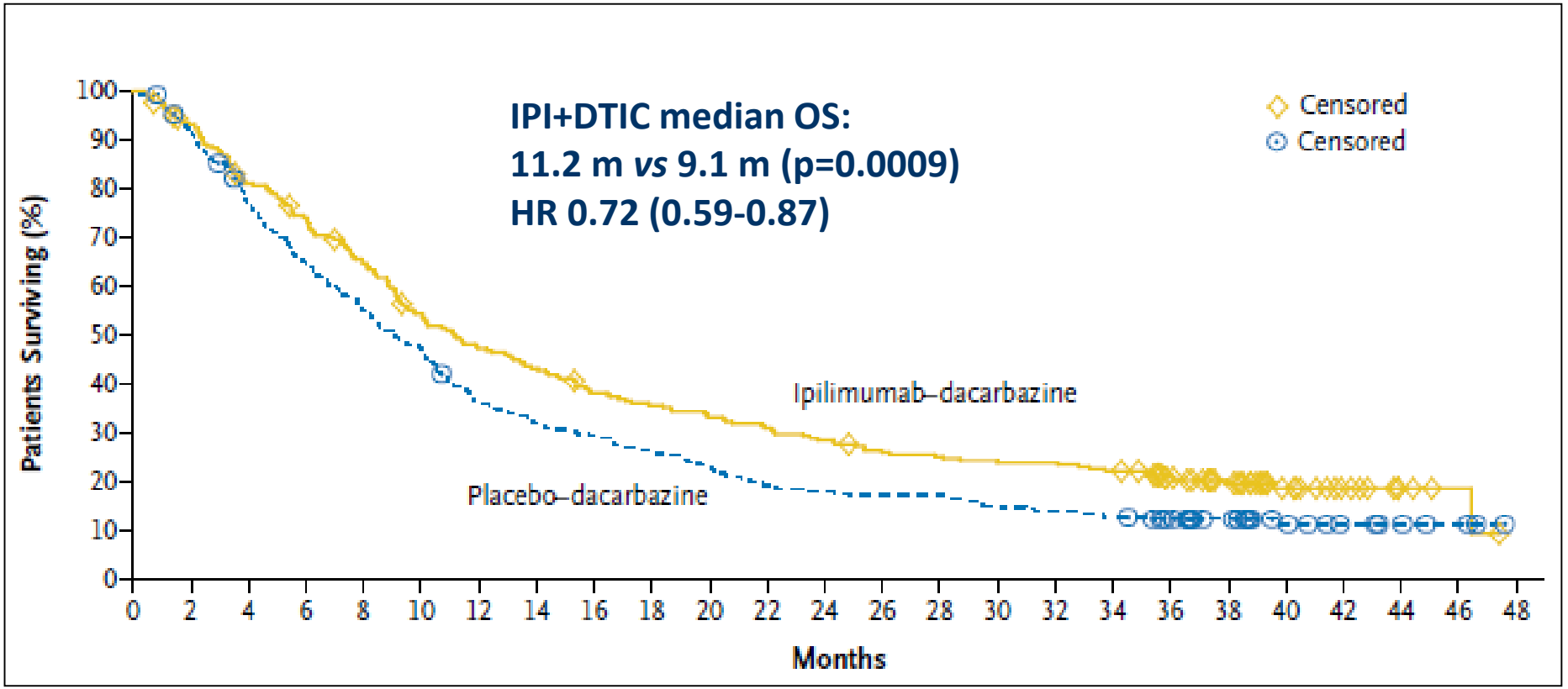


Avelumab
(Merck-Serono)
Human IgG1
anti-PD-L1 antibody

Tremelimumab
(AZ)
Human IgG2
Anti-CTLA-4 antibody

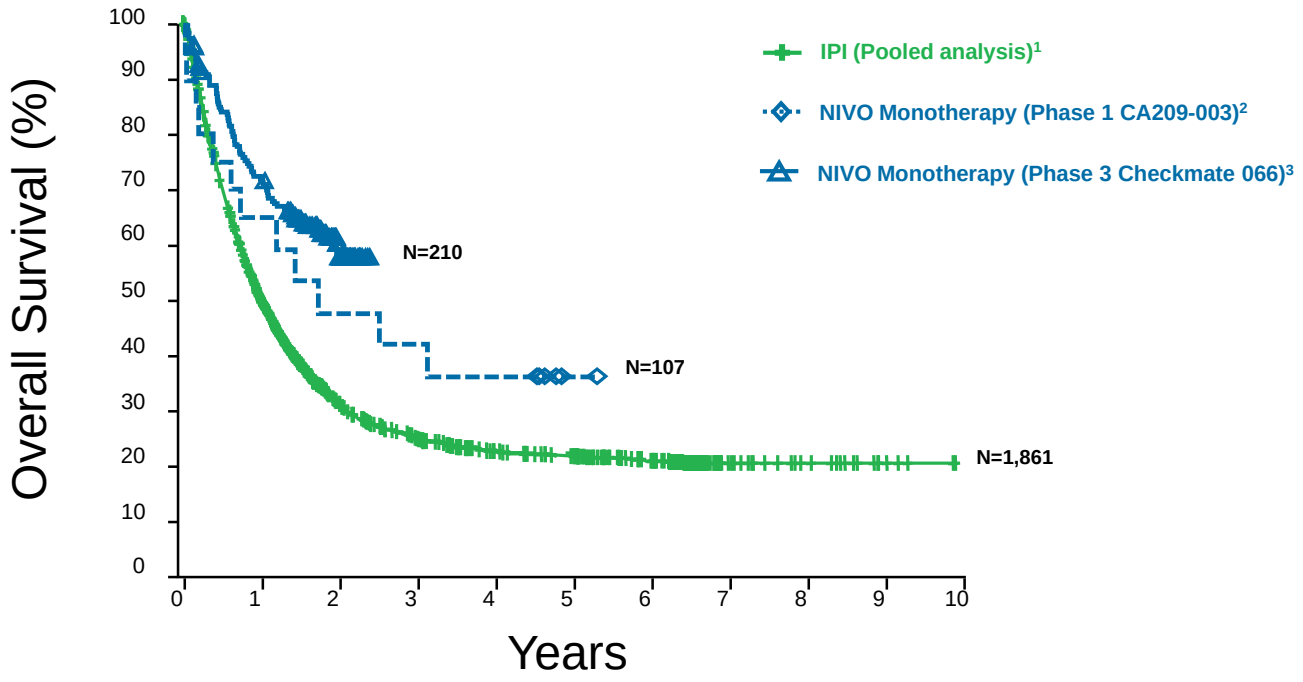
b:/ /v11/n1/images/nrclinonc.2013.208-f2.jpg

IPILIMUMAB in metastatic melanoma



C Robert et Al, N Engl J Med, 2011

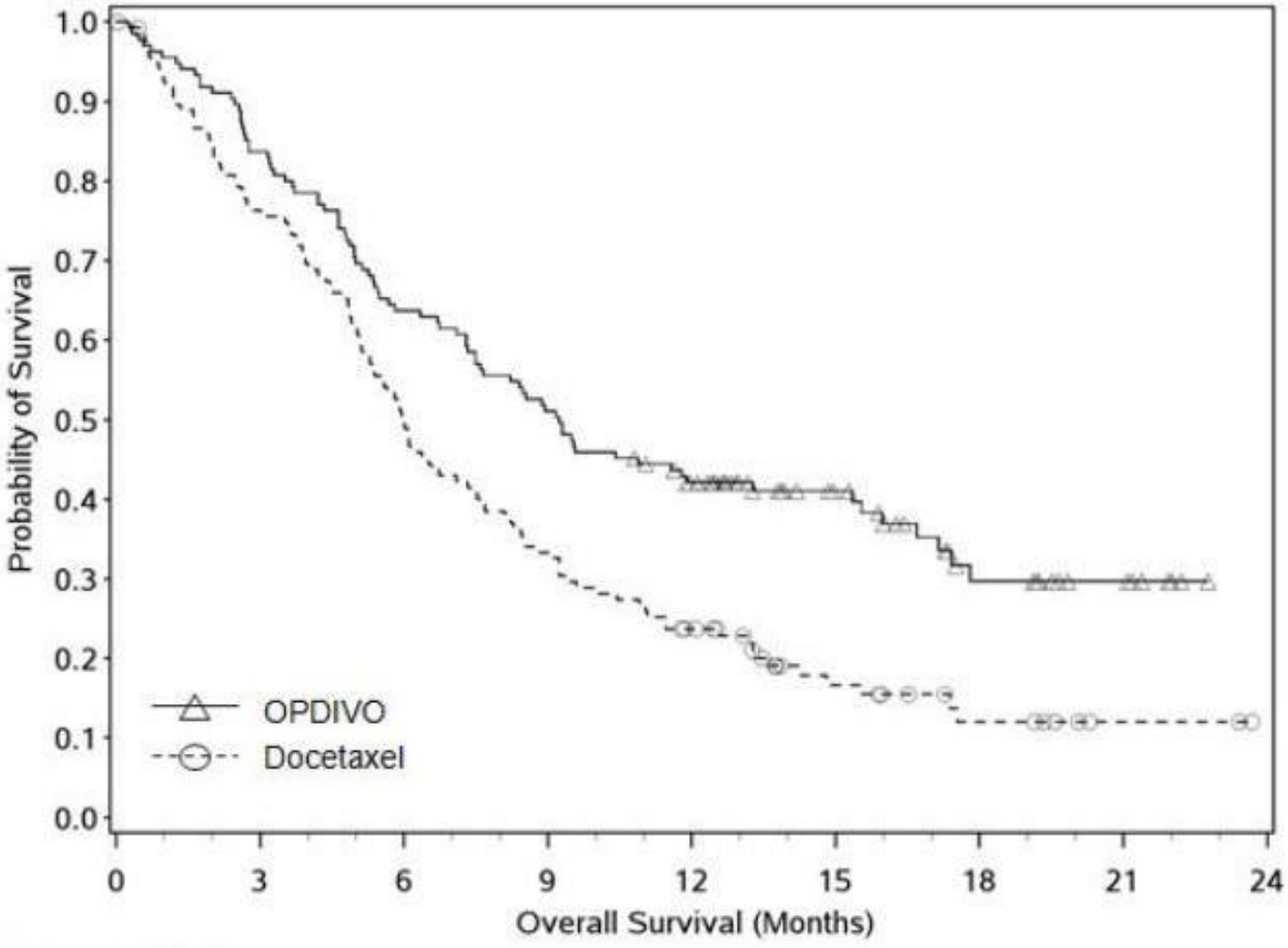
Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma



1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015

NIVOLUMAB and lung cancer (Checkmate 017)

Figure 1: **Overall Survival - Trial 2**

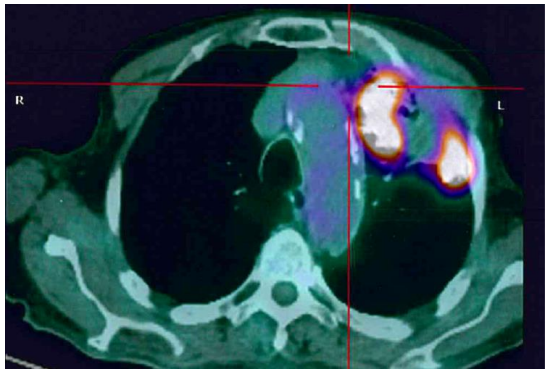


TARGETED THERAPIES: RESPONSE TO TREATMENT

- **INITIAL DISEASE PROGRESSION WITH IMMUNOTHERAPY**

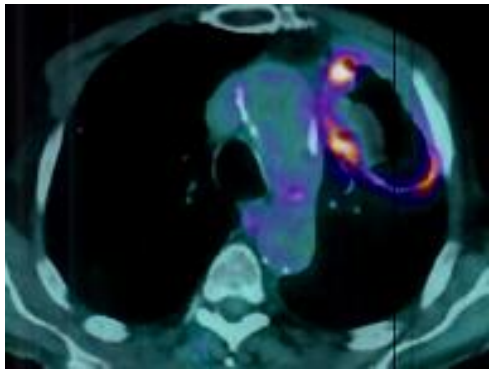
CLINICAL CASE - Stage IV NSCLC (SQ)

Baseline



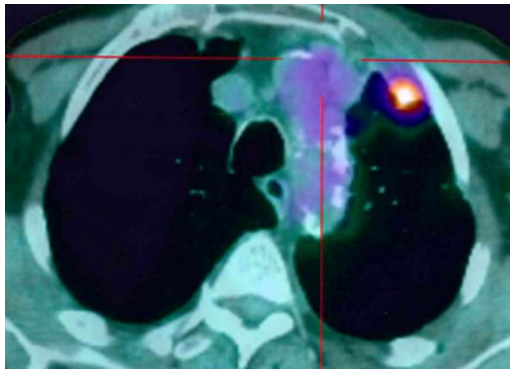
06/2015

W12



09/2015

W74



02/2017

Calabrò and Maio, unpublished

IPILIMUMAB: irAEs

Reticular erythematous rash

(Hodi SF et Al. Proc Natl Acad Sci 2003)

Pituitary swelling and disfunction

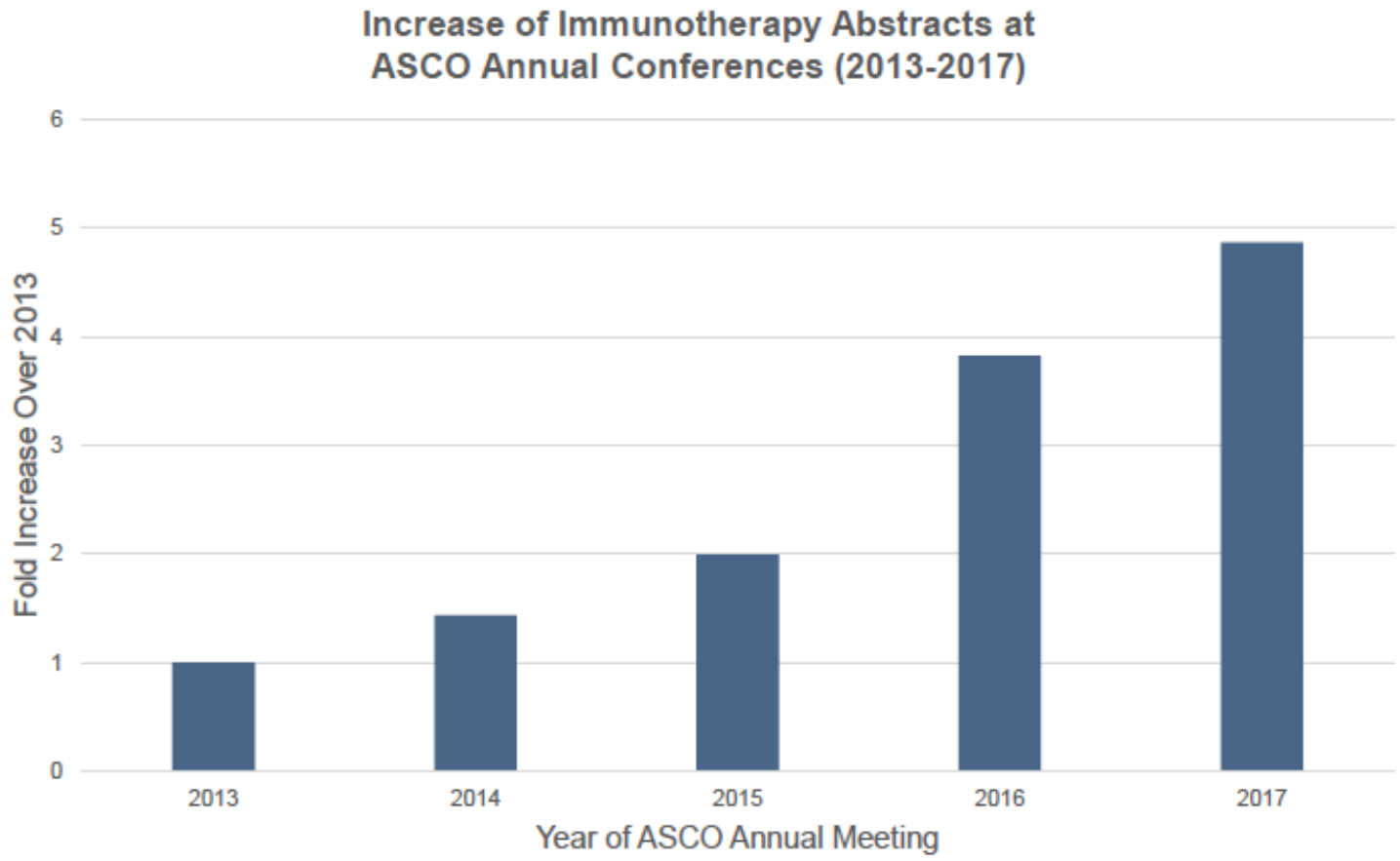
(Blansfield et Al. J Immunother 2005)

A. Bowel edema and ulceration (endoscopic view);
B. Focal active colitis (histopathologic analyses)

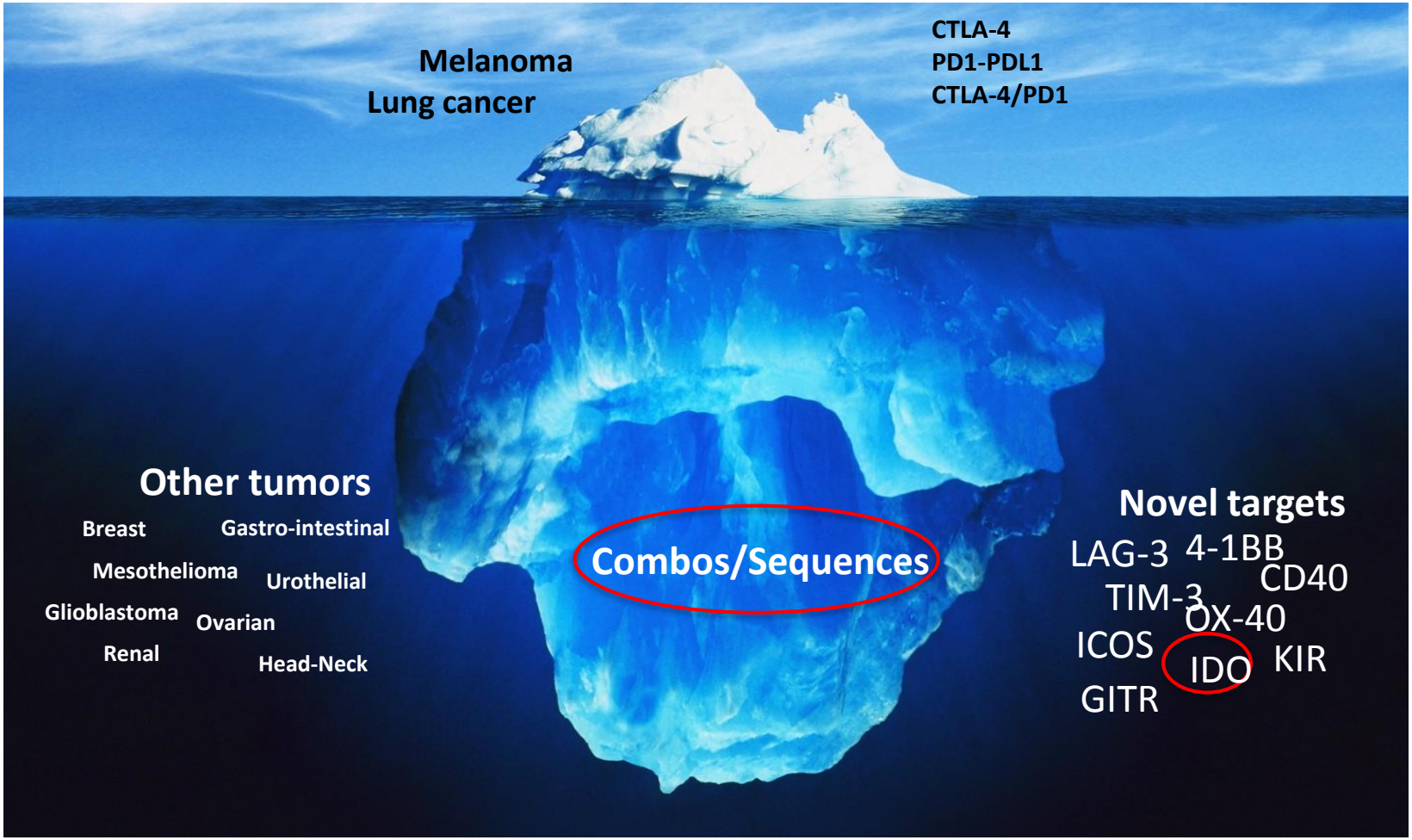
(Maker AV et Al. Ann Surg Oncol 2005)

2017 ASCO Annual Meeting

June 2-6, 2017, Chicago, Illinois



Schwartzberg LS, ASCO meeting 2017


Melanoma
Lung cancer
CTLA-4
PD1-PDL1
CTLA-4/PD1
Other tumors
Breast
Gastro-intestinal
Mesothelioma
Urothelial
Glioblastoma
Ovarian
Renal
Head-Neck
Combos/Sequences
Novel targets
LAG-3
4-1BB
CD40
TIM-3
OX-40
ICOS
IDO
KIR
GITR

Immunotherapy:
The third important wave in the history of oncology

1940s

Chemotherapy

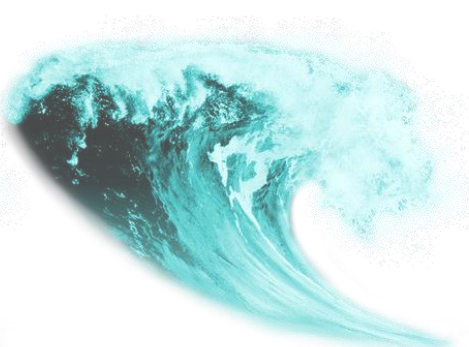
Alkylants, antimetabolites, CDDP, taxanes, ……

end of 1990s

Target Therapy

rituximab, trastuzumab, imatinib, …

2011-2015



Immunotherapy

ipilimumab, nivolumab, pembrolizumab, ….