IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

Targeting the Immune System to treat cancer

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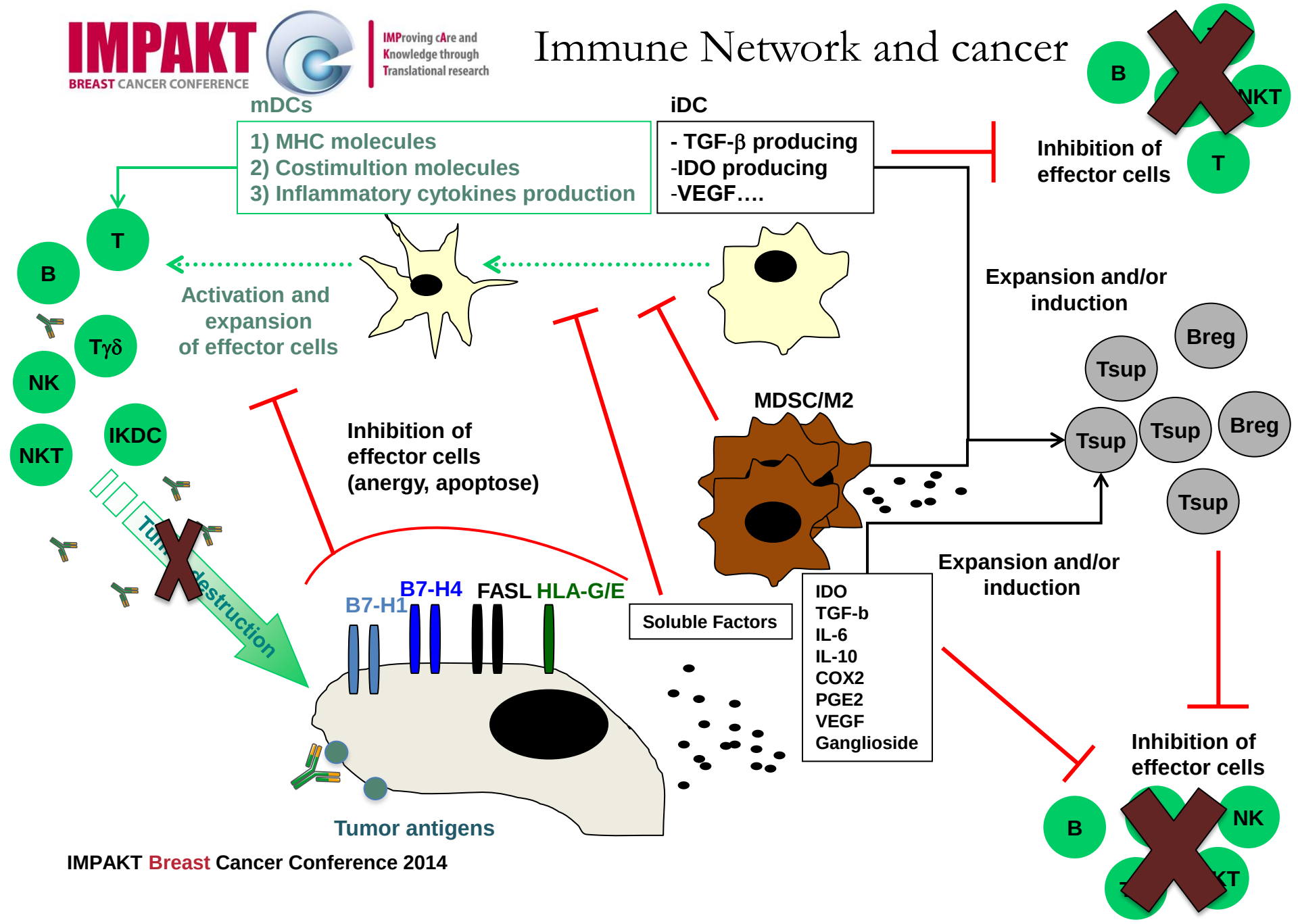
Immune Network and cancer

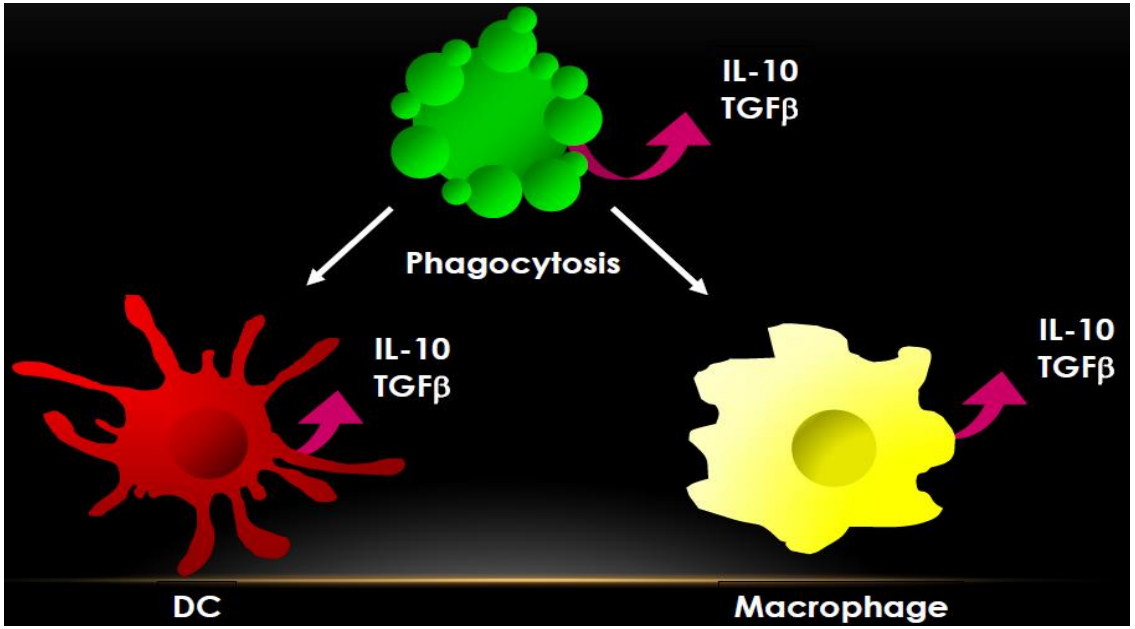


How can we restore immunity in cancer patients

- Block tolerance **and** restore/induce immunity
- With what tools can we make it
  - Monoclonal antibodies targeting antigens but also targeting the IS itself
  - Conventional treatment (Chemotherapy/radiotherapy)
  - Targeted therapy
  - Vaccines
  - Cytokines

Are conventional treatements immunogenic ?

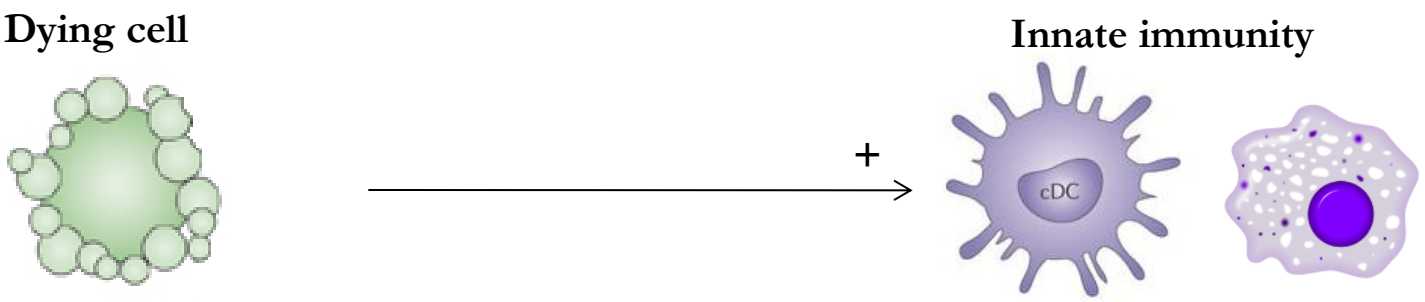
Tolerogenic Cell Death



Immunostimulatory effects of conventional anti-cancer therapies

- Lymphopenia and homeostatic T cells proliferation (Dummer W *et al, JCI, 2002)*
- Selective elimination of immunosuppressive populations : Treg, MDSC (Lutsiak, ME *et al*, Blood, 2005)
- ↑ recognition of tumor cells by immune effectors (Reits EA *et al, JEM, 2006)*
- Direct activation of effector immune cells (Tanaka H, Cancer Res, 2009; Rusakiewicz S; Nat med 2011; Balachandran, Nature Med, 2011)
- ↑T cell infiltration in the tumor bed (Matsumura S, JI, 2008)
- Immunogenicity of tumor cell death (Nowak AK, J Immunol, 2003; Casares N, JEM, 2005; Obeid Nature Med 2007; Apetoh Nature Med 2007; Ghiringhelli Nature Med 2009)

Endogenous danger signals that can lead to activation of innate immunity



Endogenous danger signals
Damage associated molecular pattern

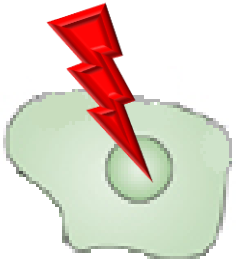
PRR

HMGB1, HSP	↔	TLR-2, -4
DNA	↔	TLR-9
RNA	↔	TLR-3
ATP, uric acid	↔	**NLRP3**
SAP130	↔	CLEC4A

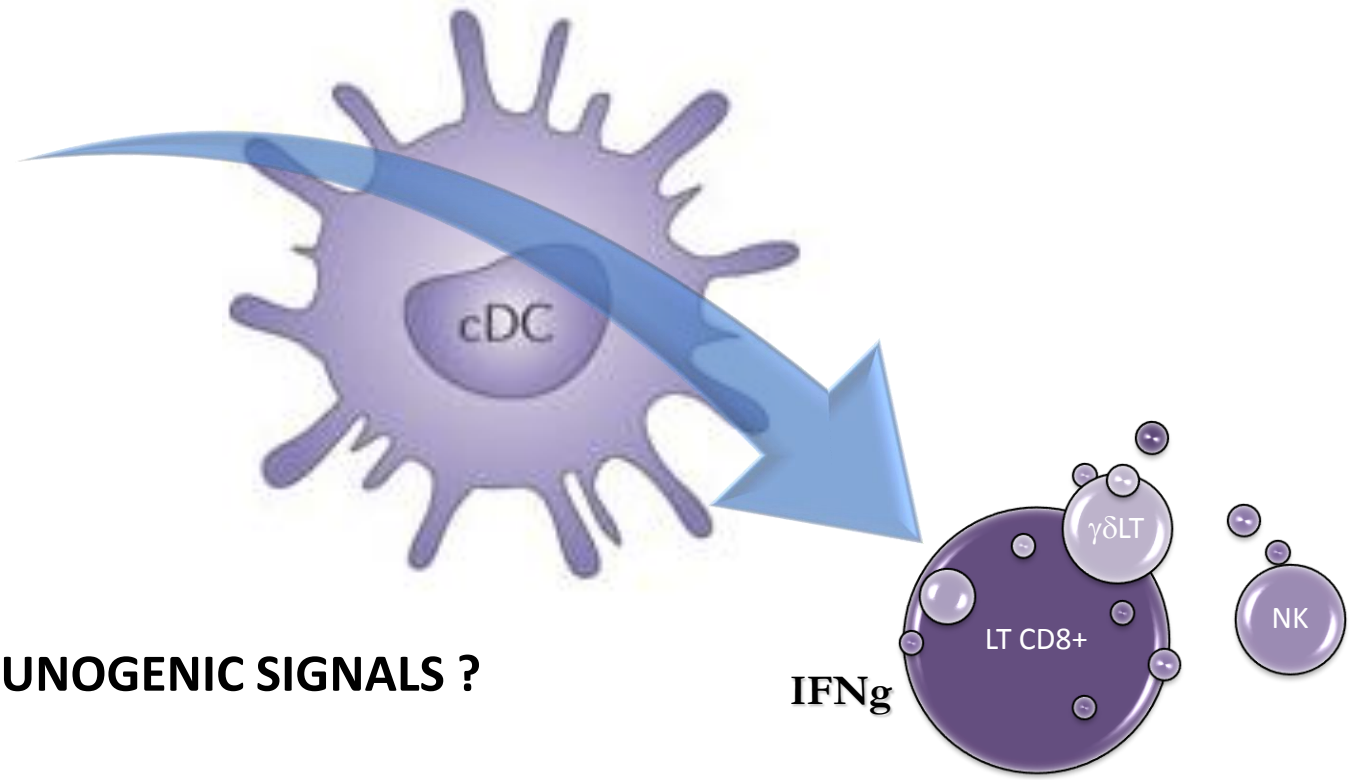
From Chen GY, Nat Rev Immunol, 2010

Can conventional anticancer treatments lead to immunogenic cell death?

Oxaliplatin, anthracyclins, Radiotherapy



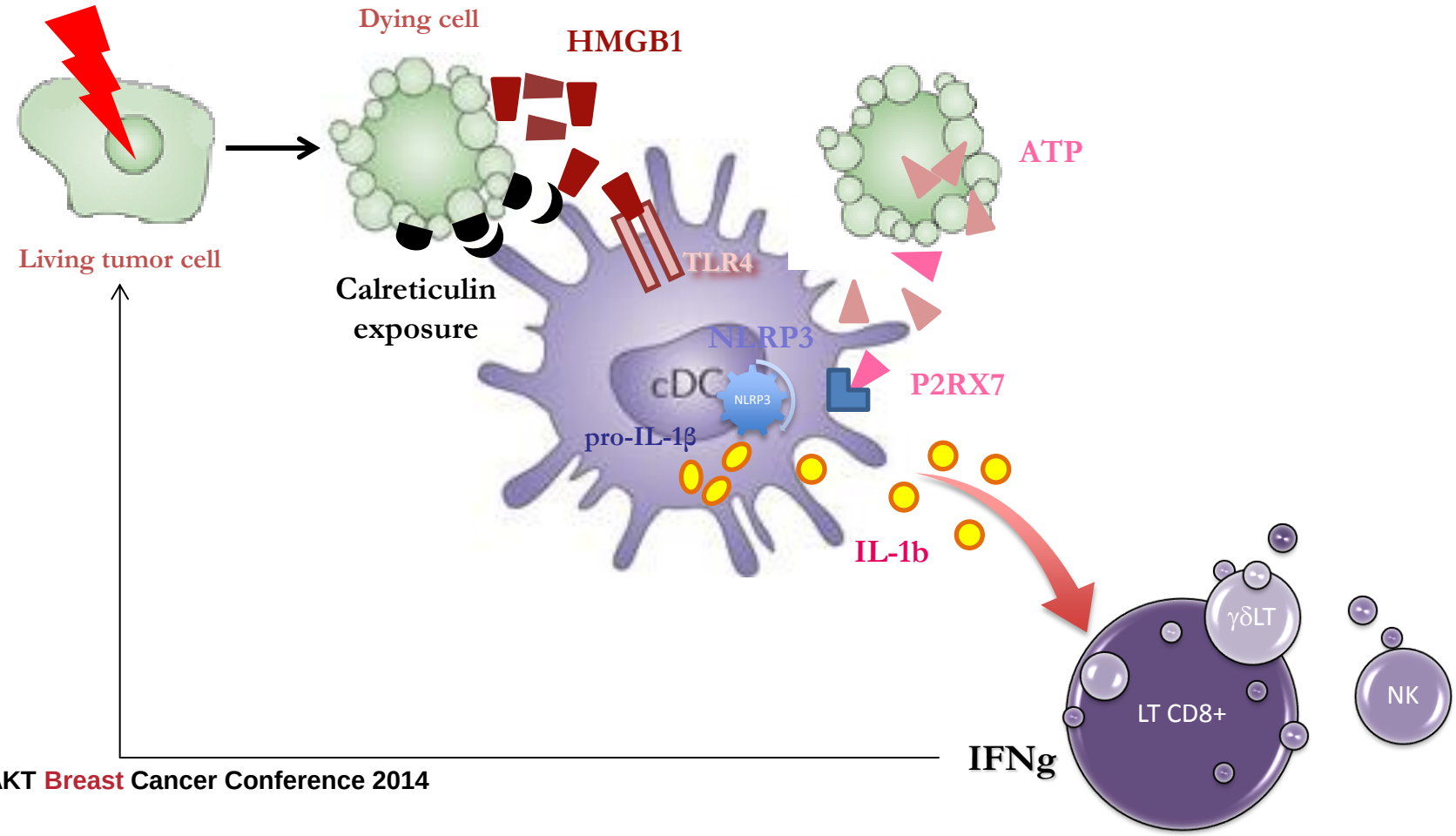
Living tumor cell



IMMUNOGENIC SIGNALS ?

Molecular events leading to immunogenic cell death

Oxaliplatin, anthracyclins, Radiotherapy



Calreticulin exposure dictates the immunogenicity of cancer cell death

VOLUME 13 | NUMBER 1 | JANUARY 2007 NATURE MEDICINE

Toll-like receptor 4–dependent contribution of the immune system to anticancer chemotherapy and radiotherapy

NATURE MEDICINE VOLUME 13 | NUMBER 9 | SEPTEMBER 2007

Activation of the NLRP3 inflammasome in dendritic cells induces IL-1β–dependent adaptive immunity against tumors

VOLUME 15 | NUMBER 10 | OCTOBER 2009 NATURE MEDICINE

Apetoh, Nat Med 2007

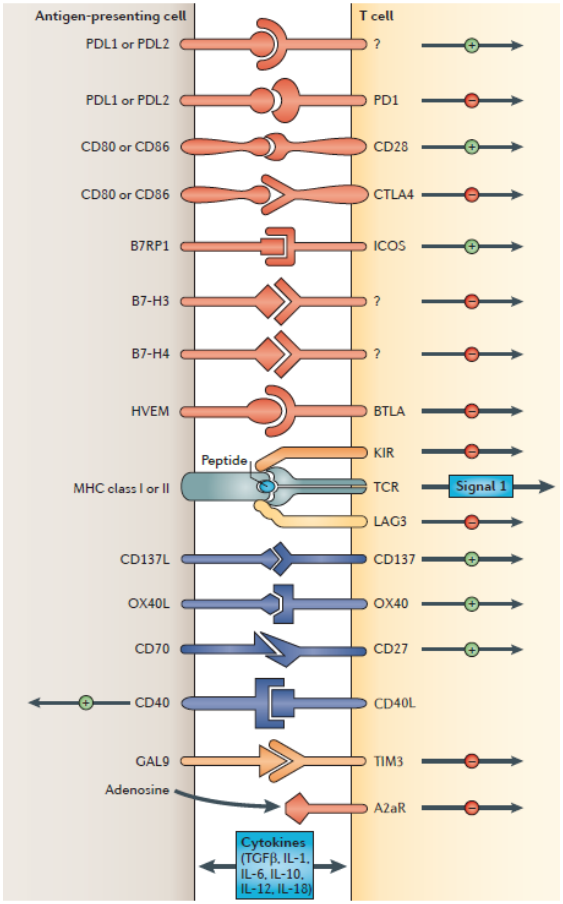
Taregtting Soluble Factors to diminish immunesupression

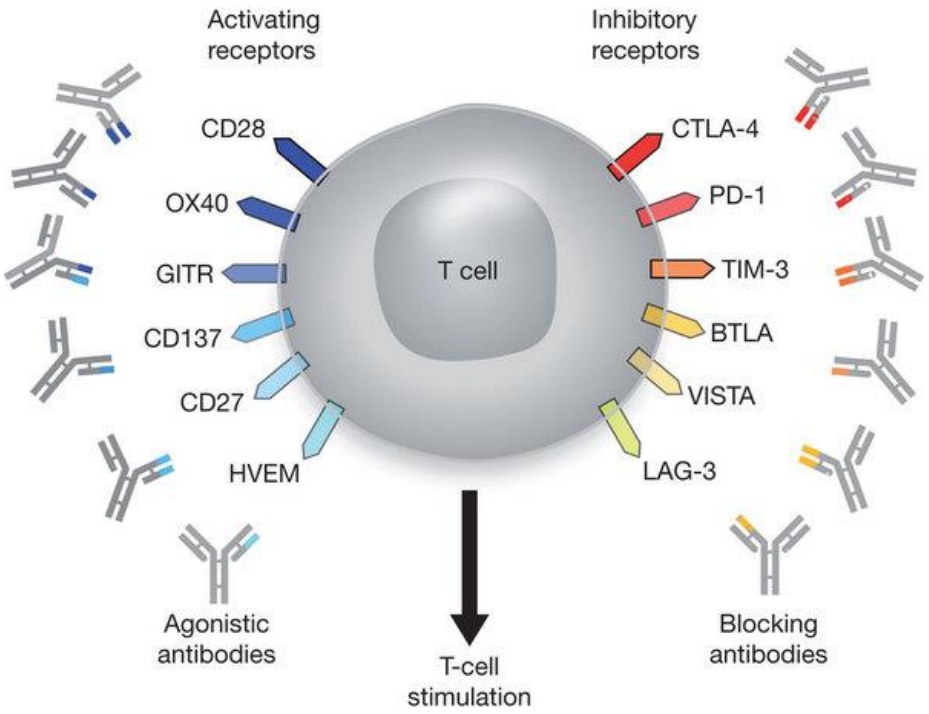
- Anti-VEGF ou VEGFR ➔ Treg & MDSC; diminution of FAS-L
- Anti-TGFb/TGFbR
- Anti-IL10/IL-10R
- Anti-IL-6 ou IL-6R (Tocilizumab)
- IDO inhibitors

Targeting immune cells to induce and/or reinvigorate anti-tumor immunity

- cytokines (non specific)
  - IL-2
  - IFNa
  - TNFα
  - Cytokines that are evaluated (Preclinical and phase I) l'IL-15; l'IL-7; la super-IL-2; la super-IL-15
- Therapeutic Vaccines (Specific)
  - BCG (ImmuncystTM) : Non invasive Bladder tumors
  - long peptides : HPV-16 onco-proteins E6 & E7 + incomplete Freund adjuvant (IFA) .
  - Sipuleucel-T (CPA + PSA-GMCSF) HR metastatic prostate cancer
  - CIMAvax-EGF approved Cuba (CBNPC) ➔ leads to anti-EGF Abs
- Monoclonal antibodies : *immune check point blockade* (Blockers)
  - Anti-CTLA4 - Ipilimumab (approved Melanoma)
  - Anti-PD1; anti-PD-L1 (Melanoma; Lung; RCC)
  - Others ?.... Clinical studies are ongoing (anti-LAG; Tim-3; GITR;)
- Monoclonal antibodies (agonists; Clinical studies are ongoing)
  - Anti-OX40; anti-4.1BB; ICOS…
- Trivalent antibodies
  - Catumaxomab targets CD3/Epcam and FcR : Treatment of malignant ascites : EpCAM positive tumors)

How to target T cells ?



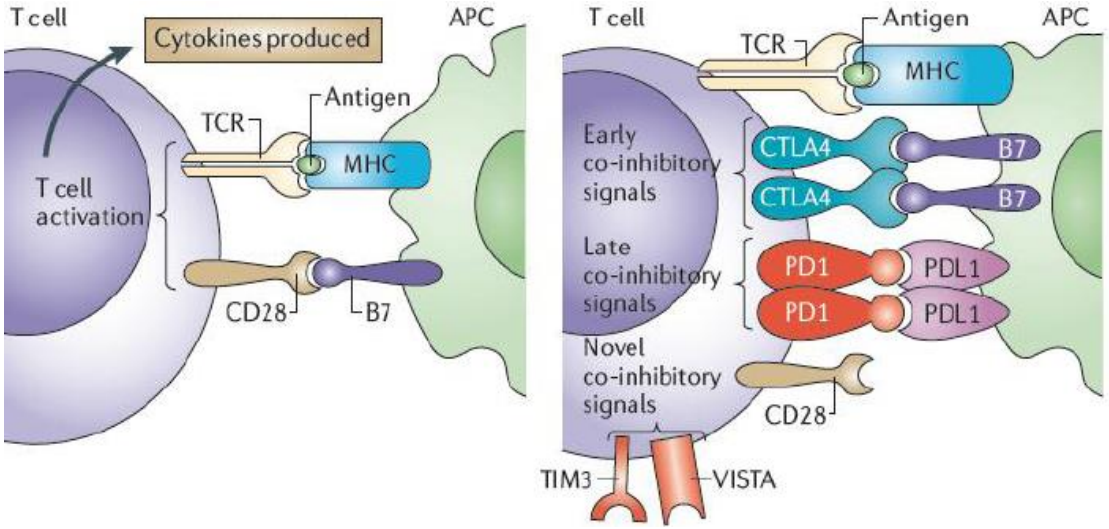


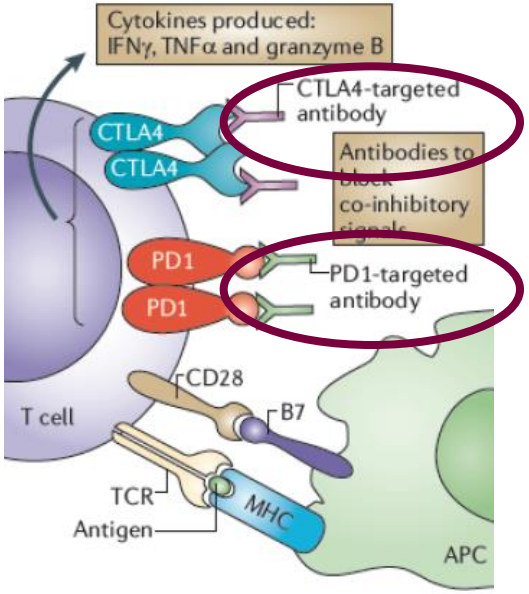
Anti-CTLA4 and anti-PD1: how it works?

- CTLA4
  - This system of peripheral tolerance intervenes at the time of the initiation of the immune response
  - Naïve or memory lymphocytes do not express CTLA4
  - The level of expression of CTLA4 is directly linked to the commitment of the TCR
  - Antigens of high affinity lead to a strong expression of CTLA4
  - Des antigènes de faible affinité induisent peu de CTLA4
  - It allows a sharp regulation of the amplitude of the immune response

- PD1
  - This system of peripheral tolerance intervenes on the site of the inflammatory reaction
  - Some inflammatory soluble factors allow the up-regulation of PD-L1 :
    - Decrease the amplitude of T cell activation
    - Limit collateral damages
    - IFNγ induces PD-L1
  - An excessive expression of PD1 ($PD1^{high}$) is associated with T cell anergy This excessive expression can be achieve during a chronic stimulation (ex : chronic infectious diseases (HIV; HCV); chronic inflammatory diseases as cancer.)

immune checkpoint blockade

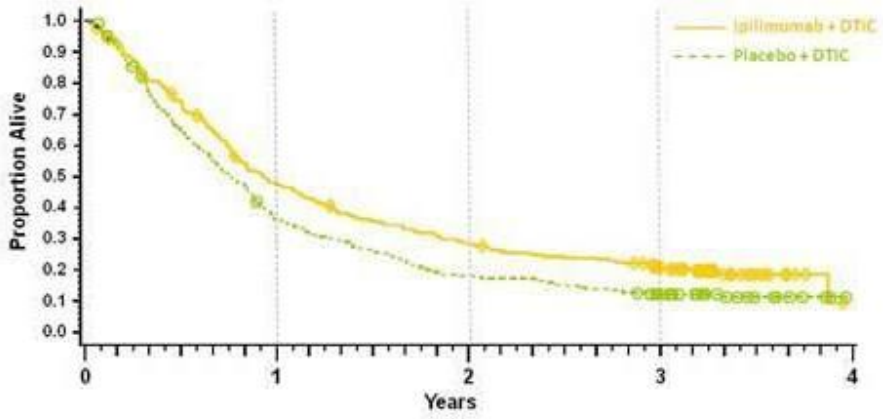




immune check point blockade anti-CTLA4

Ca184-024 study

modified from Robert et al. N Engl J Med. 2011[4]

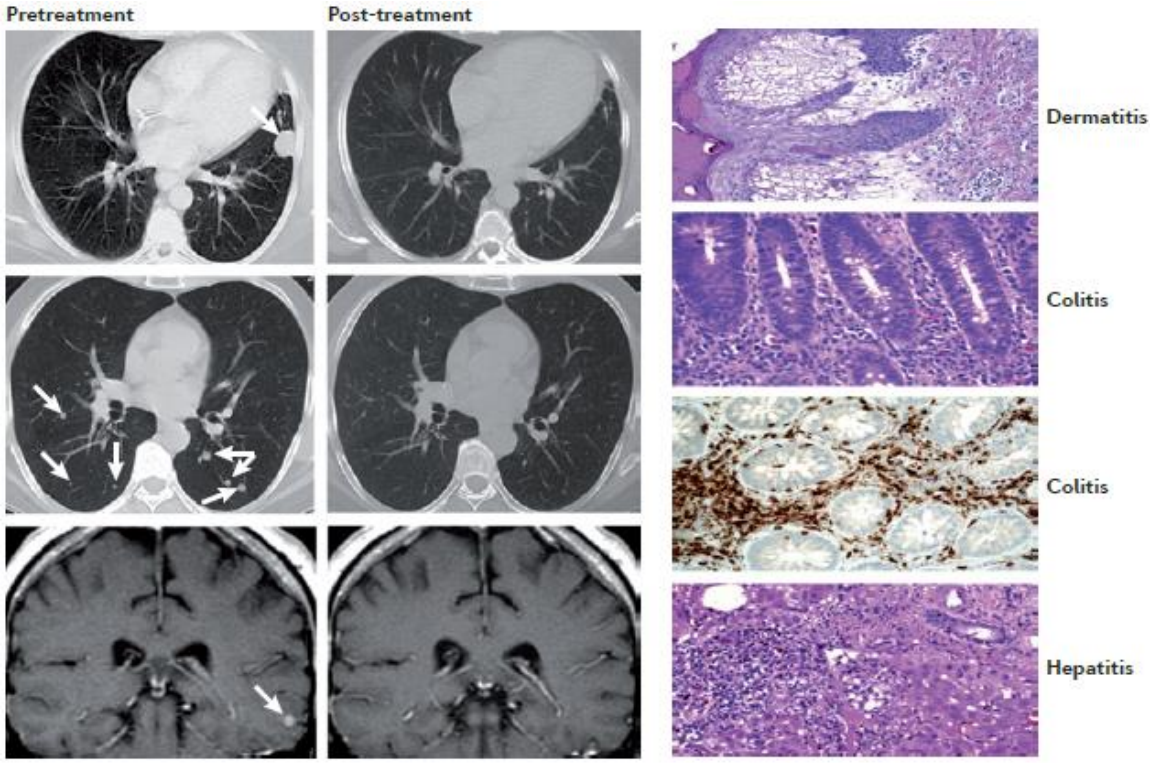


Survival Rate	1 Year	2 Year	3 Year
Ipilimumab + DTIC n=250	47.3	28.5	20.8
Placebo + DTIC n=252	36.3	17.9	12.2

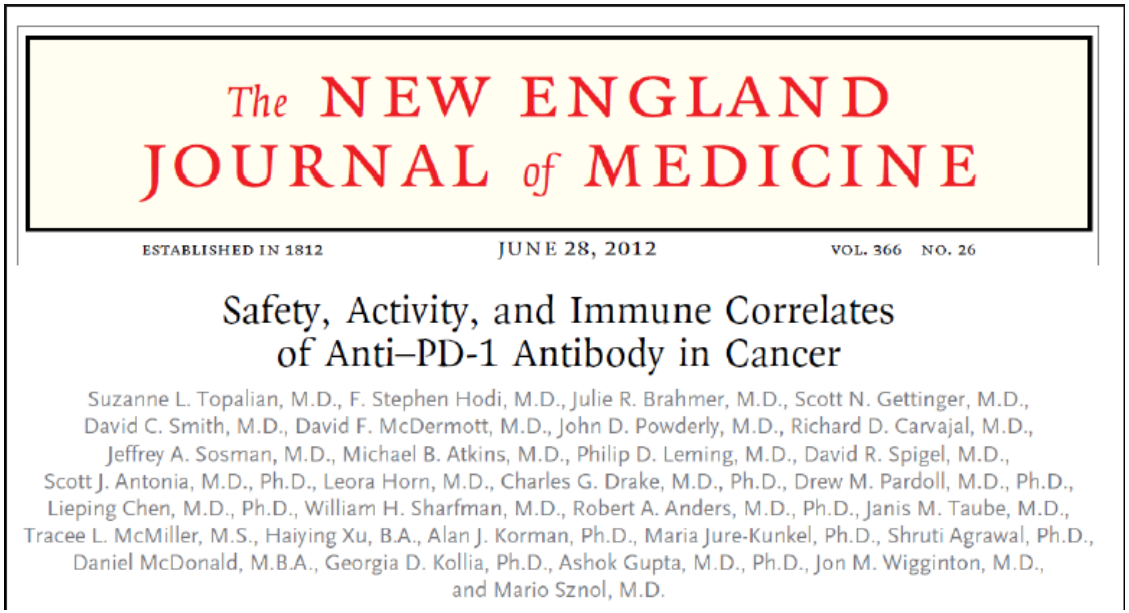
- **Response rate : 10-17%**
- **20-40% of Immune Related Adverse Effects** (irAE)
- **% patient alive at 3 years : 20%**

- Cost : 84.000 Euros/patients
- **A real need to find predictive marker of efficacy**
- Association with targeted treatment, with other immune check-point inhibitors?
- Association with local radiotherapy (MEL-IPI-RX trial)

immune check point blockade anti-CTLA4 : Immune Related Adverse Effects



immune check point blockade : anti-PD1 (melanoma, NSCL, Prostatic, Renal-cell or colorectal cancer patients)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

- Responses were observed in
  - 18% of patients with NSCL,
  - 27% renal-cell
  - 28% melanoma

immune check point blockade : anti-PDL1 (**NSCL, melanoma**, colorectal cancer, **Renal-cell**, ovarian cancer, pancreatic cancer, gastric or breast cancer patients)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

Combination anti-CTLA4 & Anti-PD1

Mélanome avancé Traitement	Réponses cliniques objectives	Diminution du cancer de plus de 80%	Survie à 2 ans
Anti-CTLA4 (1) (n=502)	11%	<2%	28%
Anti-PD1 (2) (n=135)	38%	<3%	43%
Anti-CTLA4 + Anti-PD1 (3) (n=70)	40%	31%	70%

(1) Robert et al NEJM 2012
(2) Hamid O et al. NEJM 2013
(3) Volchok et al. ASCO 2013

However high rate of IRAE (>50% grade III/IV) ➔ A real need to find combo-therapy with a good tolerance profile

Immune checkpoint blockers : A revolution for cancer treatment ?

- immunotherapy is not any more a myth
- These therapeutic approaches are rapidly growing and show impressive clinical results
- L'anti-CTLA4 (ipilimumab) approved in France in 2013

- However
  - Better understand mechanisms of action
  - Better understand the mechanisms that lead to IRAE (inflammatory diseases) to be able to anticipate and manage these IREA

Increase even more the survival of the patients

- Predictive biomarkers of Toxicity ➔ Better clinical management of IREA
- Predictive biomarkers of response/resistance ➔ better selection
- Compensate for the patients with a failing immune system
- Find effective combo-therapy

➔ Increase number of patients being able to benefit from these treatments

What about Breast cancer and immunotherapy
Innate Immunity

- MDSC are increased in BC ➔ Could be targeted with IDO inhibitors (Yu JI 2014)
- Plasmocytoide dendritic cell (pDC) and BC (Sisirak IJC 2013; Faget CR 2012; Sisirak CR 2012; Treilleux Clinical CR 2004)
  - associated with amplification of Treg cells ➔ linked to poor prognosis (Role of ICOS/ICOSL axis and IL-10)
  - Restoration of IFNα secreted by pDC could restore an effective immunity (use TLR-7 agonist Resiquimode)
- NK cells might play a role in human breast cancer (Mamessier CR 2011; Mamessier JCI 2011)
  - BC seems to escape from NK cell immunity

What about Breast cancer and immunotherapy
Adaptive Immunity

- Effector T cell infiltration and BC (Loi, JCO 2013; Dieci, Annal Oncol 2014; Ladoire J. Pathol 2011)
  - Effector T cell infiltration is associated with good prognosis in human breast cancer
  - Effector/Treg ratio, after NACT, is associated with a better prognosis in human breast cancer
  - High T cell infiltration after NACT is associated with a better prognosis in triple negative BC
  - TIL increased after NACT in triple negative BC
  - Doxorubicin could enhance T cell infiltration and immunogenicity of tumor cells (Immunogenic cell death ➔ Role of TLR4 in BC patients to be validated in prospective cohorts) (Apetoh, Nat Med 2009)
- PD-1 /PD-L1 and BC
  - PD-1-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer (Muenst; BCRT 2013)
  - PD-L1 expression is increased in tumors that have a higher proliferation index as measured by Ki-67. These observations suggest that the PD-L1/PD-1 pathway may be more important in certain breast cancer subtypes like **triple negative breast cancers** which have a higher proliferation rate, higher grade, and have a high lymphocytic response while in low grade tumors these molecules may play a role in the later stages contributing to their invasiveness (Ghebeh et al., 2007)
  - 20% triple negative breast cancers PD-L1+ (Mittendorf; CIR 2014)
  - Doxorubicin (but not docetaxel) could diminish surface expression of PD-L1 (Ghebeh ; 2010)…Implication for PD1/PD-L1 treatment?

There is a place for immunotherapy for the treatment of patients with BC

We must define which BC subtype
Triple negative BC should be a good target (highly infiltrated by T cells; express immune checkpoint ligands (PD-L1 and others as B7-H3)

Innate immunity as NK cells (good guys) or pDC/MDSC (bad Guys) could help for future immunomodulation approaches (RLI (super-IL-15) ; IDO inhibitors; TLR agonists…)

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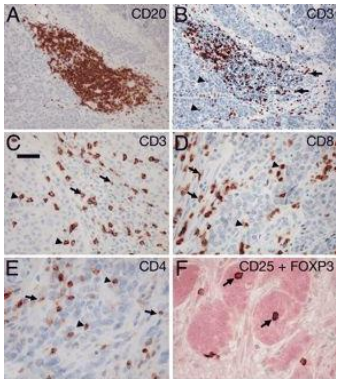
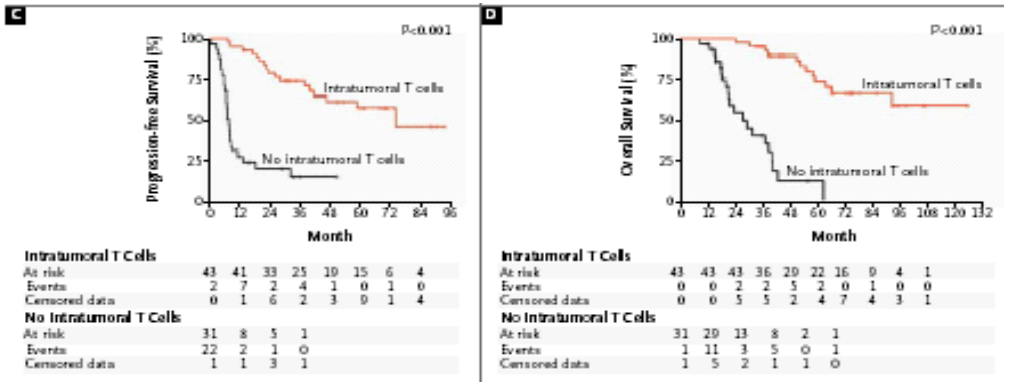
Thank you for your attention

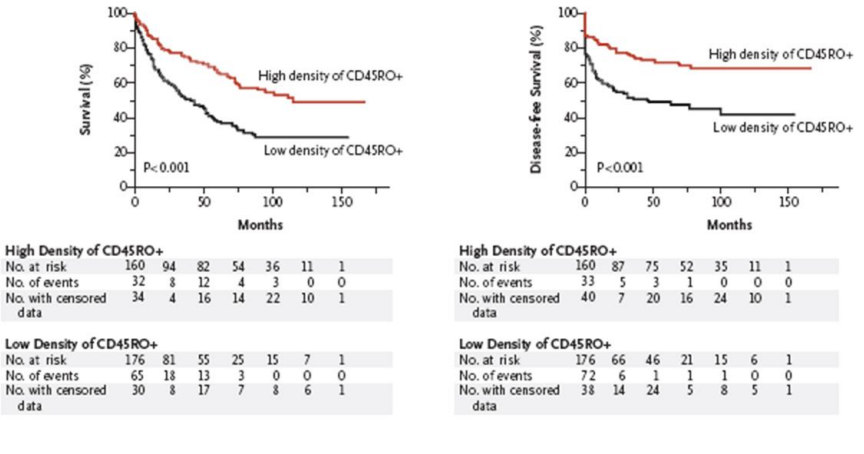
Can the Immune System (IS) recognize the tumor ?

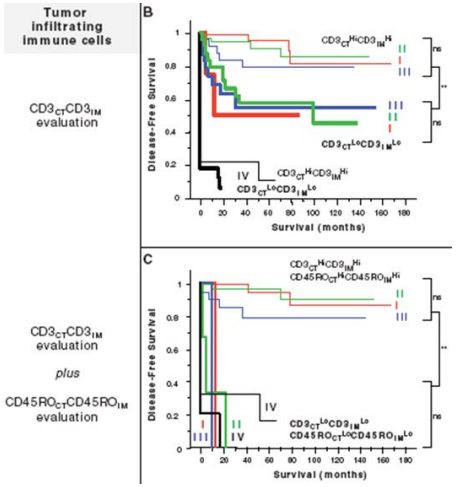
Zhang L et al. The NEJM. 2003

- **HUMAN**









Pagès et al, N EJM, 2005

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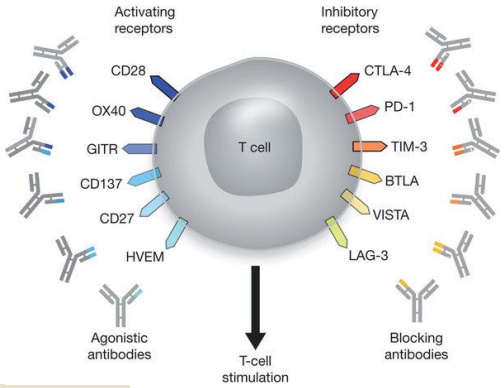
immune check point blockade



Target	Biological function	Antibody or Ig fusion protein	State of clinical development*
CTLA4	Inhibitory receptor	Ipilimumab	FDA approved for melanoma. Phase II and Phase III trials ongoing for multiple cancers
		Tremelimumab	Previously tested in a Phase III trial of patients with melanoma; not currently active
PD1	Inhibitory receptor	MDX-1106 (also known as BMS-936558)	Phase I/II trials in patients with melanoma and renal and lung cancers
		MK3475	Phase I trial in multiple cancers
		CT-011†	Phase I trial in multiple cancers
		AMP-224§	Phase I trial in multiple cancers
PDL1	Ligand for PD1	MDX-1105	Phase I trial in multiple cancers
		Multiple mAbs	Phase I trials planned for 2012
LAG3	Inhibitory receptor	IMP321‖	Phase III trial in breast cancer
		Multiple mAbs	Preclinical development
B7-H3	Inhibitory ligand	MGA271	Phase I trial in multiple cancers
B7-H4	Inhibitory ligand		Preclinical development
TIM3	Inhibitory receptor		Preclinical development

The Tumor **IS NOT** ignored by the IS

- Targeting the IS
  - Which targets ?
    - Tumor (Antigens; mutations…)
    - Soluble factors (VEGF; IL-10; TGFb…)
    - Immune cells (T cells; NK cells; Myeloid cells…)