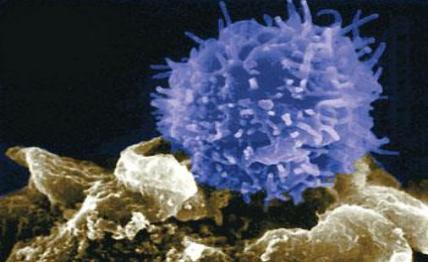




# Immunothérapies et Cancer Principe et succès

Pr Olivier ADOTEVI

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UMR 1098 INSERM/UFC/EFS  
[olivier.adotevi@univ-fcomte.fr](mailto:olivier.adotevi@univ-fcomte.fr)



**12<sup>eme</sup>** Biennale Monégasque  
de Cancérologie 

Cours Francophone d'Oncologie

**GRIMALDI FORUM ~ 3 – 6 Février 2016**  
**MONACO**

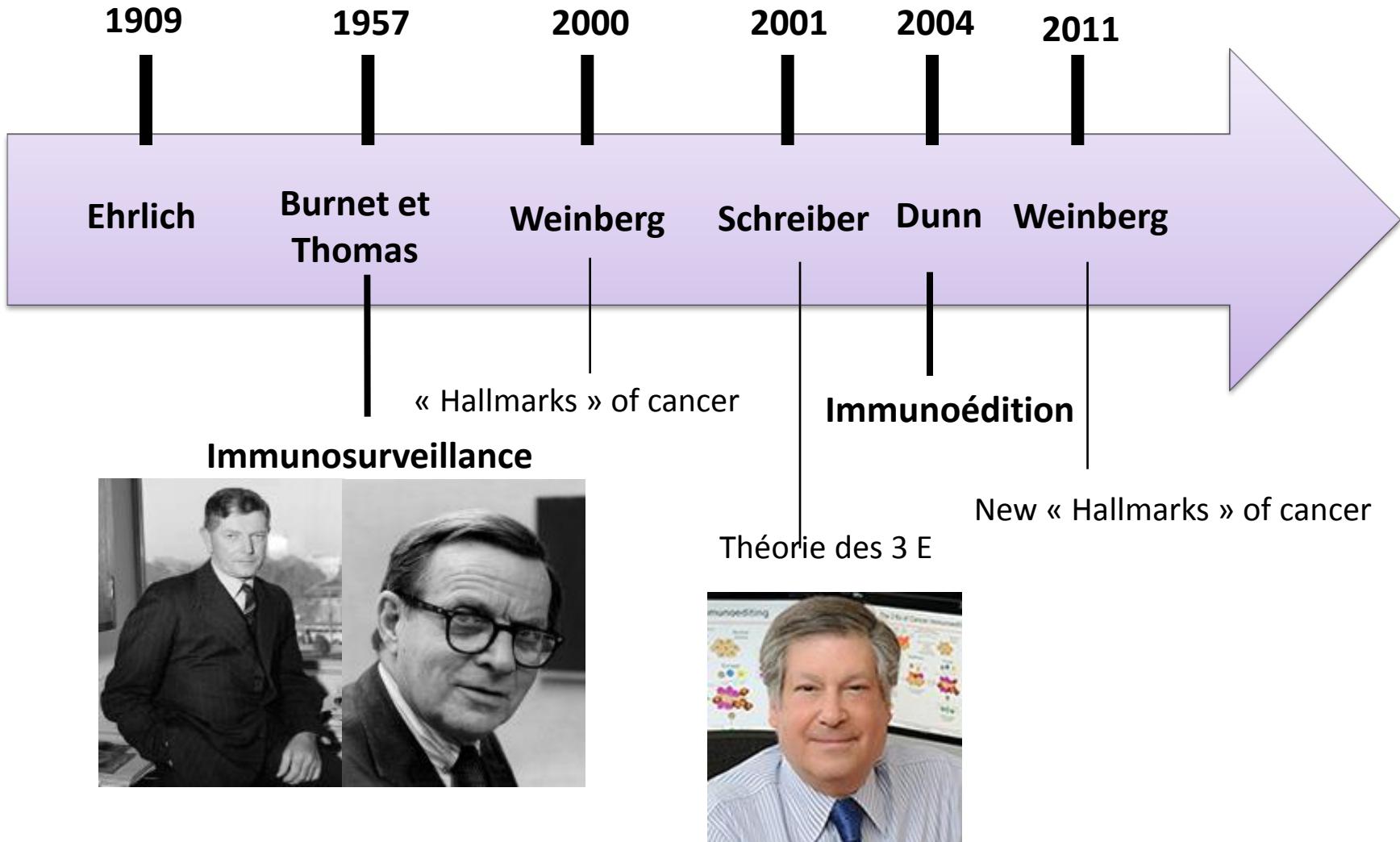
## Conflits d'intérêts

Regional Board : Boehringer Ingelheim, MSD

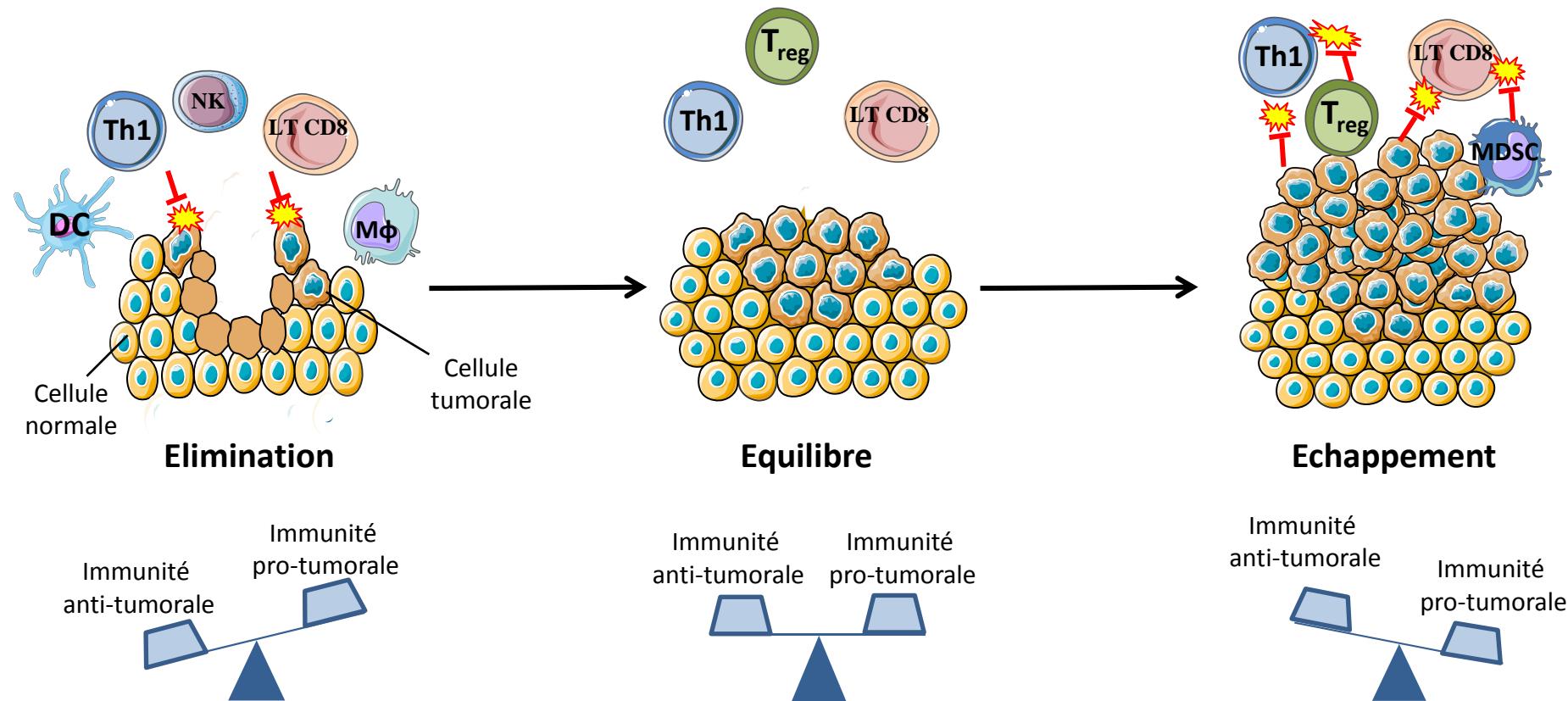
Scientific collaboration: Novartis, Gennetech,

Lab meeting: Roche, AstraZeneca, MSD

# Cancer et Système Immunitaire

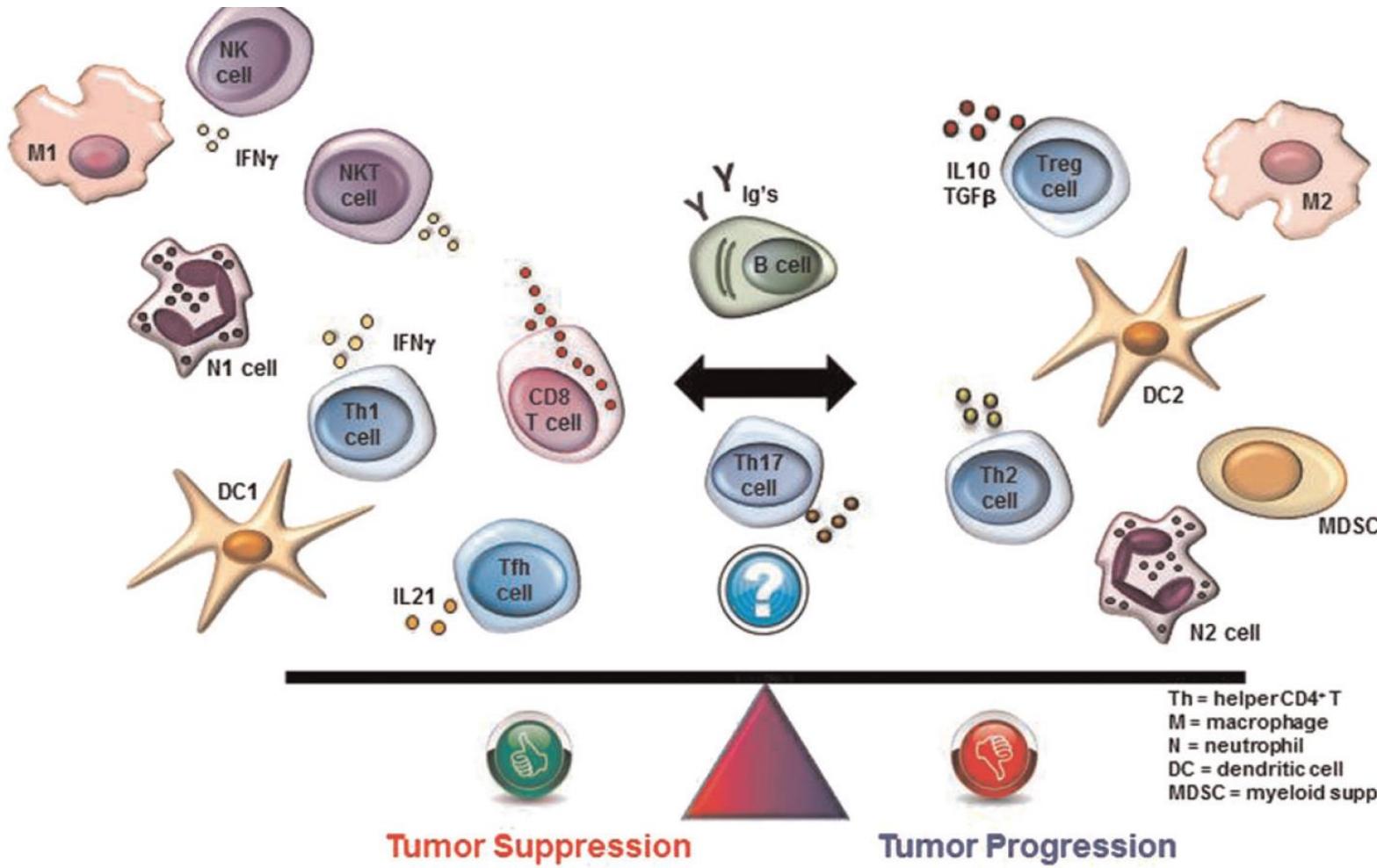


# Cancer et Système Immunitaire



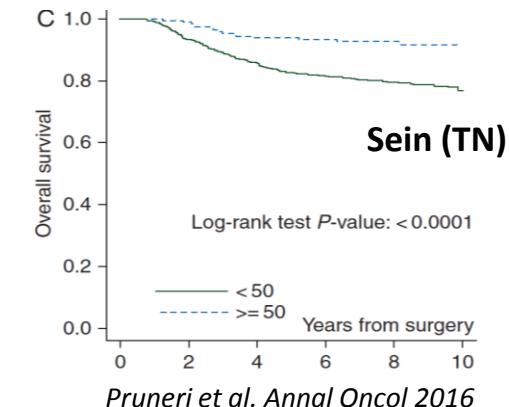
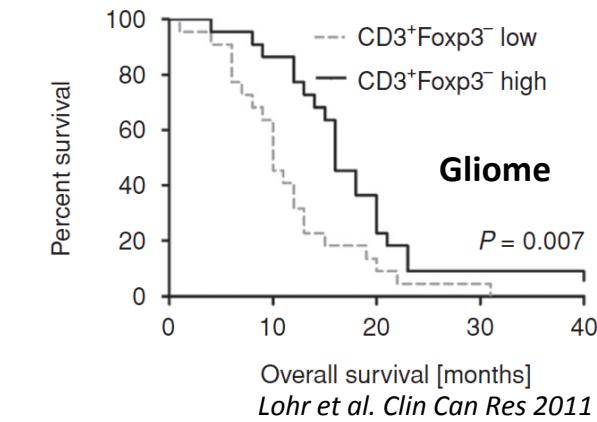
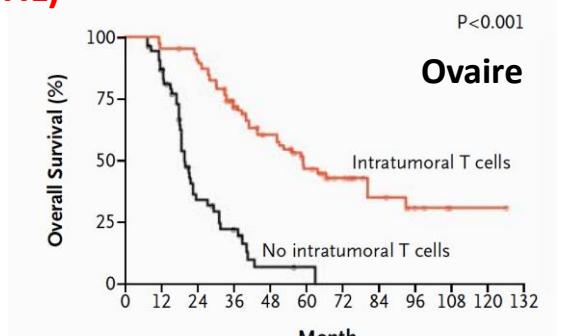
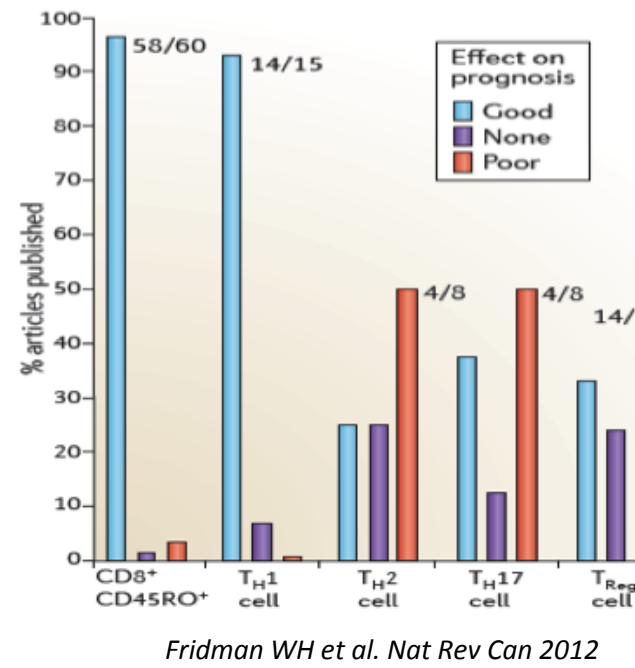
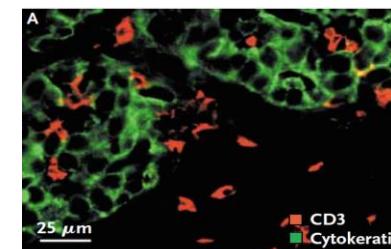
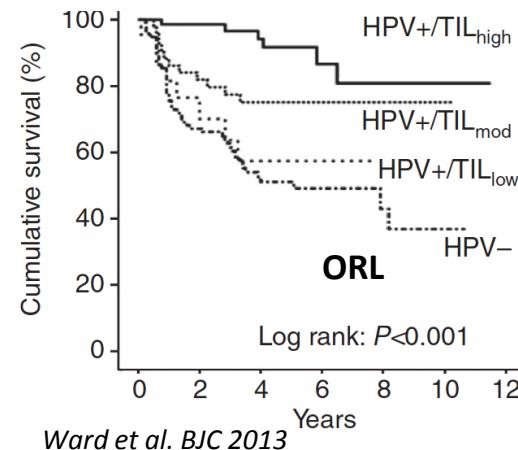
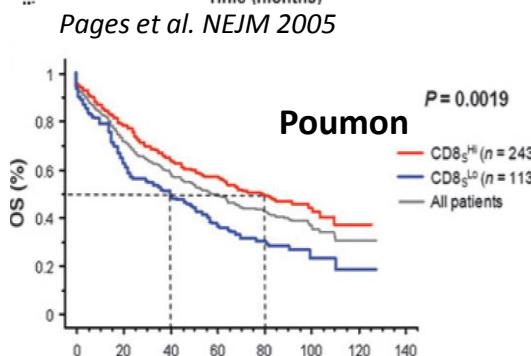
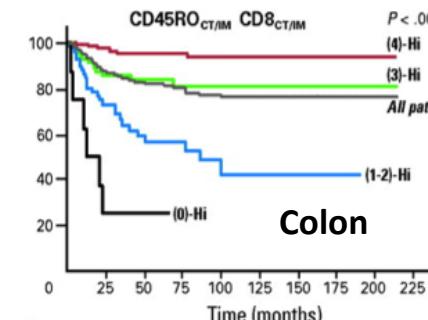
# Cancer et Système Immunitaire

Différentes cellules immunitaires coexistent au sein de la tumeur



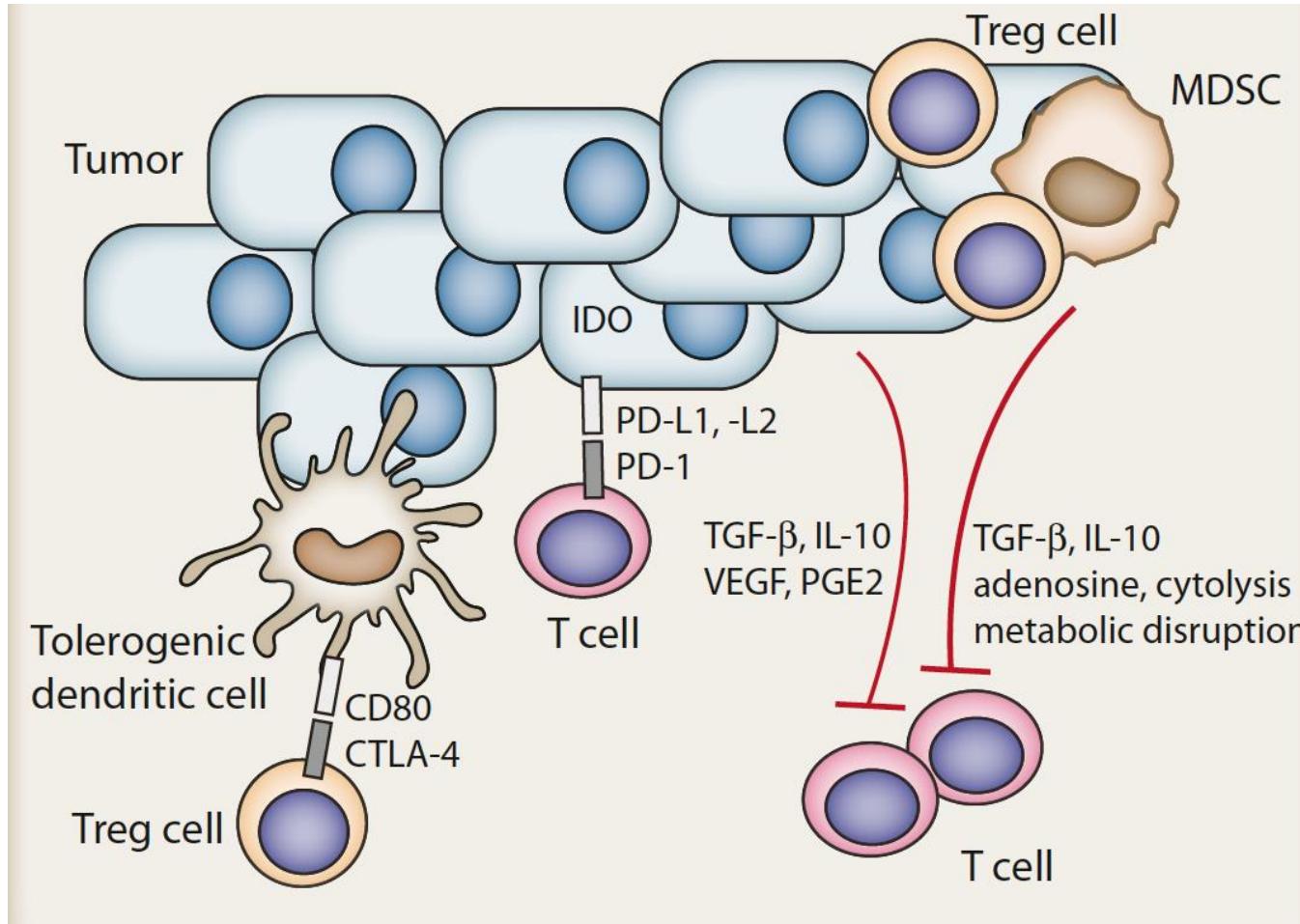
# Cancer et Système Immunitaire

## Rôle majeur des lymphocytes T intra-tumoraux (TIL)

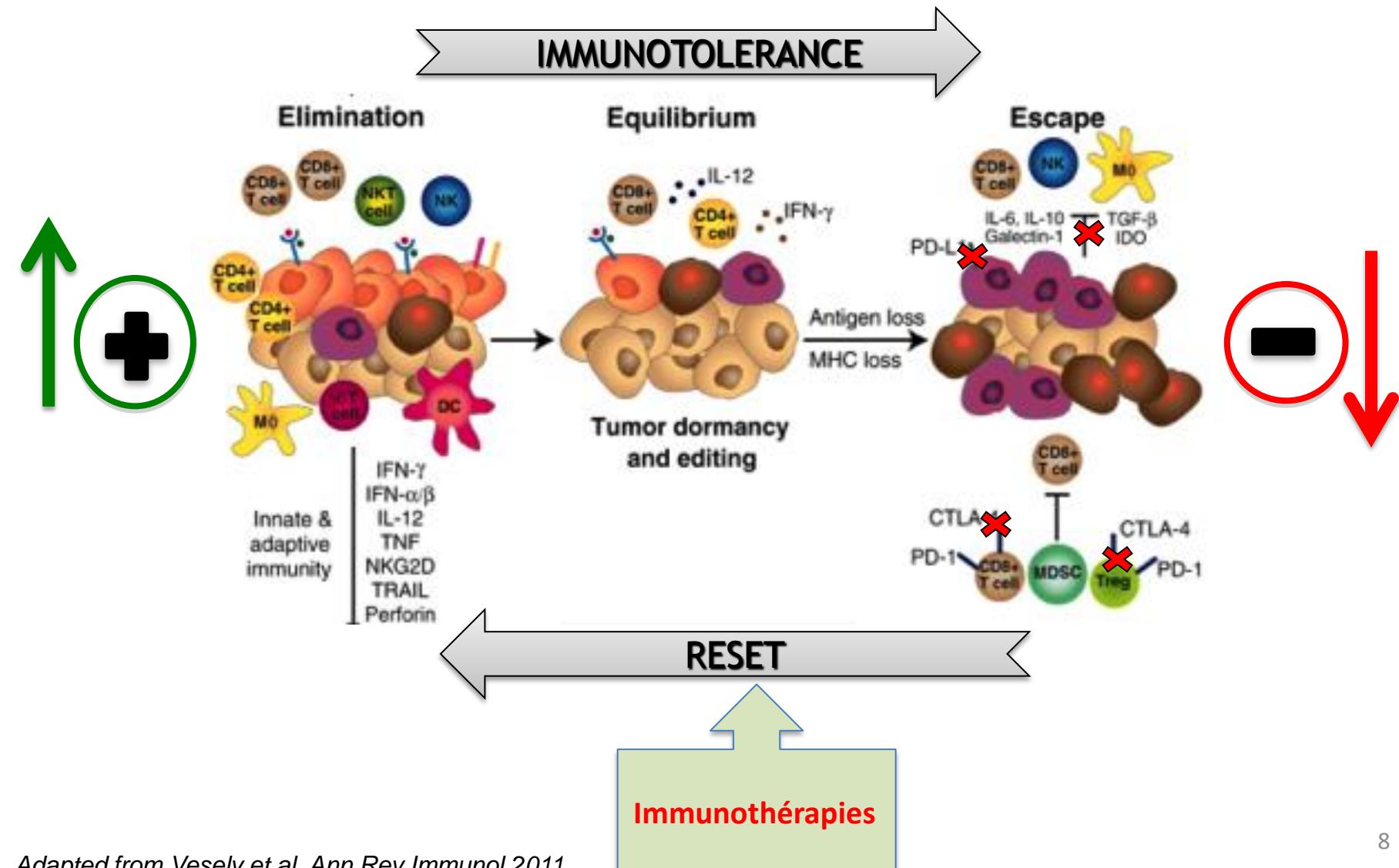


# Cancer et Système Immunitaire

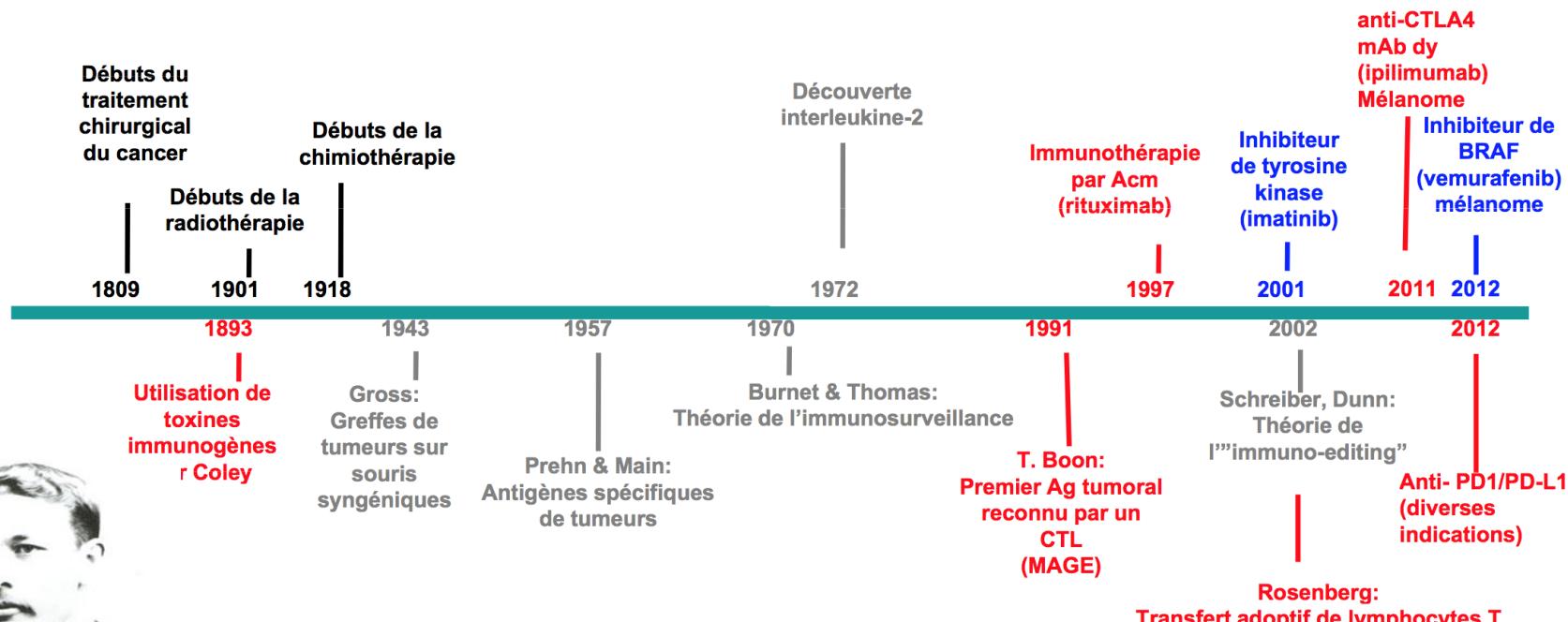
La tumeur met en place plusieurs mécanismes d'échappement aux lymphocytes T



# Principe de l'immunothérapie anticancer



# Place de l'immunothérapie dans le traitement des cancers



THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYsipelas: WITH A REPORT OF TEN ORIGINAL CASES.<sup>1</sup>

BY WILLIAM B. COLEY, M.D.,

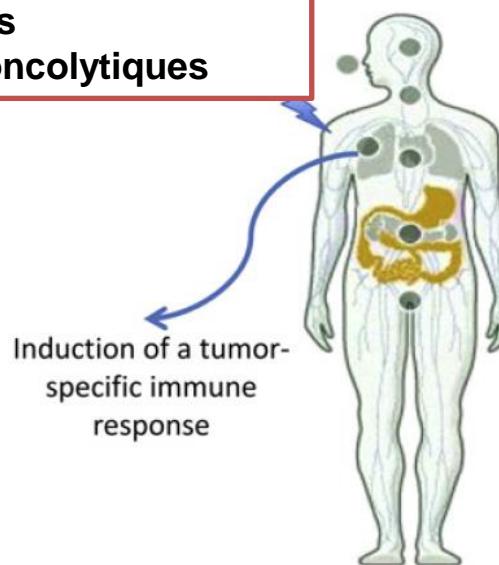
ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED; INSTRUCTOR IN SURGERY  
 IN THE POST-GRADUATE MEDICAL SCHOOL, NEW YORK.

## Deux grands types d'immunothérapies anticancer

❖ L'immunothérapie consiste à utiliser le système immunitaire comme cible ou médicament.

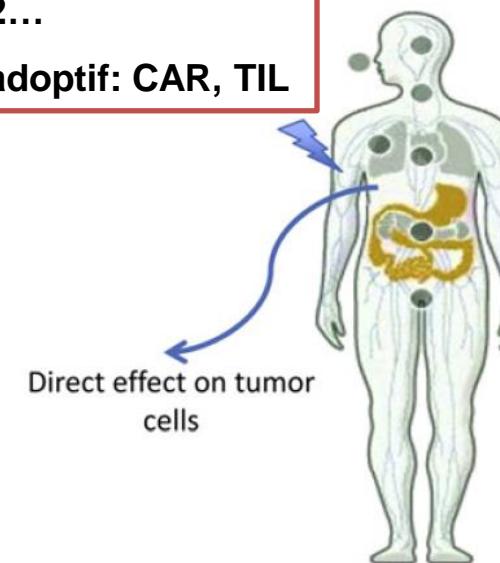
### Immunothérapie active

- Anti-CTLA4, anti-PD1...
- Vaccins
- Virus oncolytiques



### Immunothérapie passive

- Anti-EGFR, anti-VEGF, anti-HER2...
- Transfer adoptif: CAR, TIL

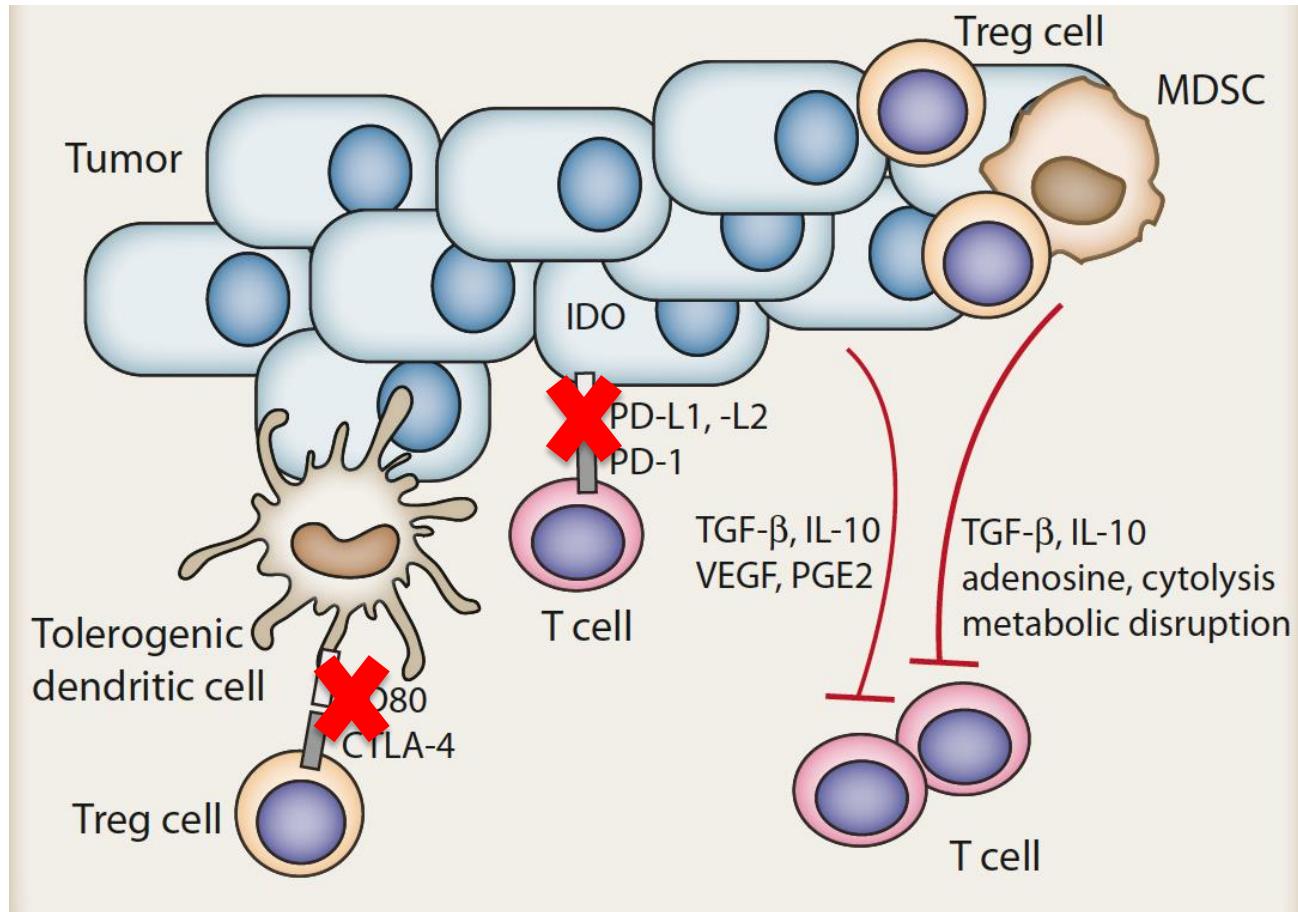
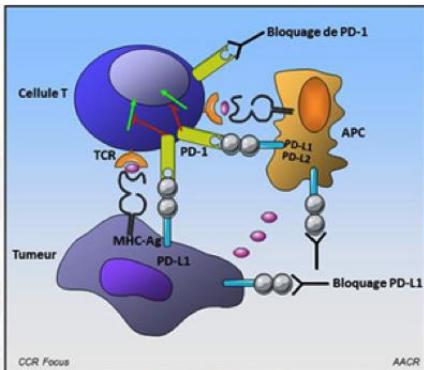


❖ Induction d'une mémoire immunologique

❖ Absence de mémoire immunologique

# Les Inhibiteurs de checkpoints Immunologiques

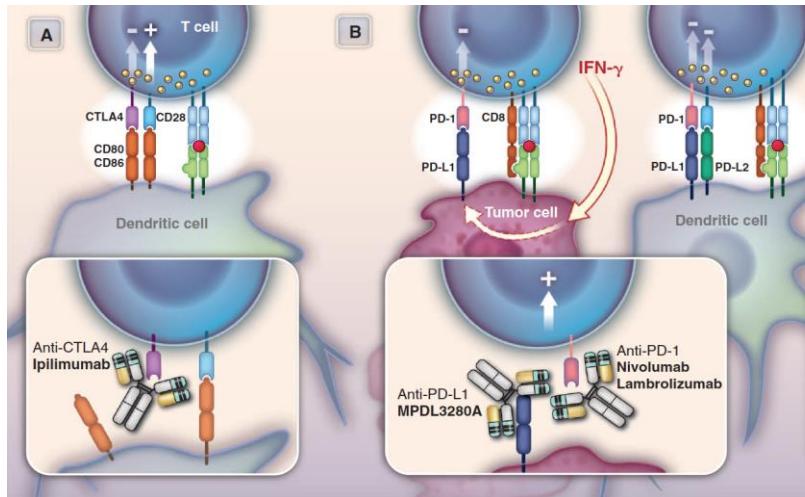
Principe = Bloquer les inhibiteurs des lymphocytes T antitumoraux



Vesely et al Ann Rev Immunol 2011  
Motz & Coukos Immunity 2013

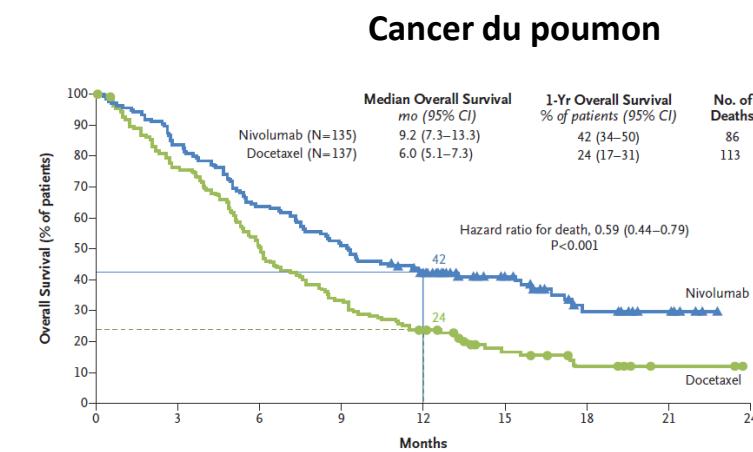
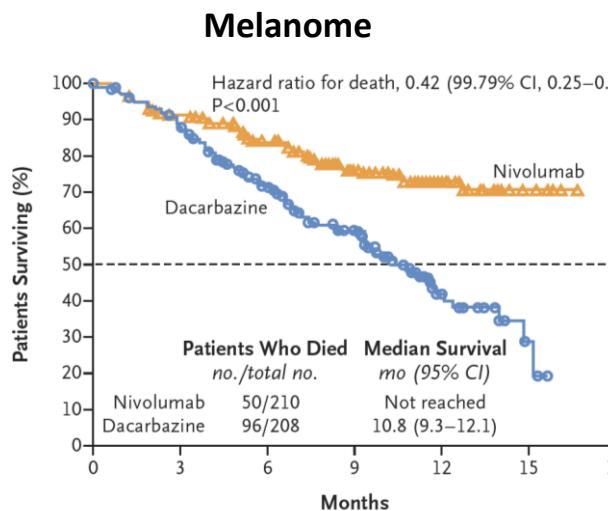
# Les Inhibiteurs de checkpoints Immunologiques

Efficacité = Oui et dans plusieurs cancers !!!



Association thérapeutique

Nécessité de Biomarqueurs



Topalian et al NEJM 2012; Robert C et al. NEJM 2014; Tumeh et al. Nature 2014; Ribas, NEJM, 2015; Brahmer, NEJM, 2015

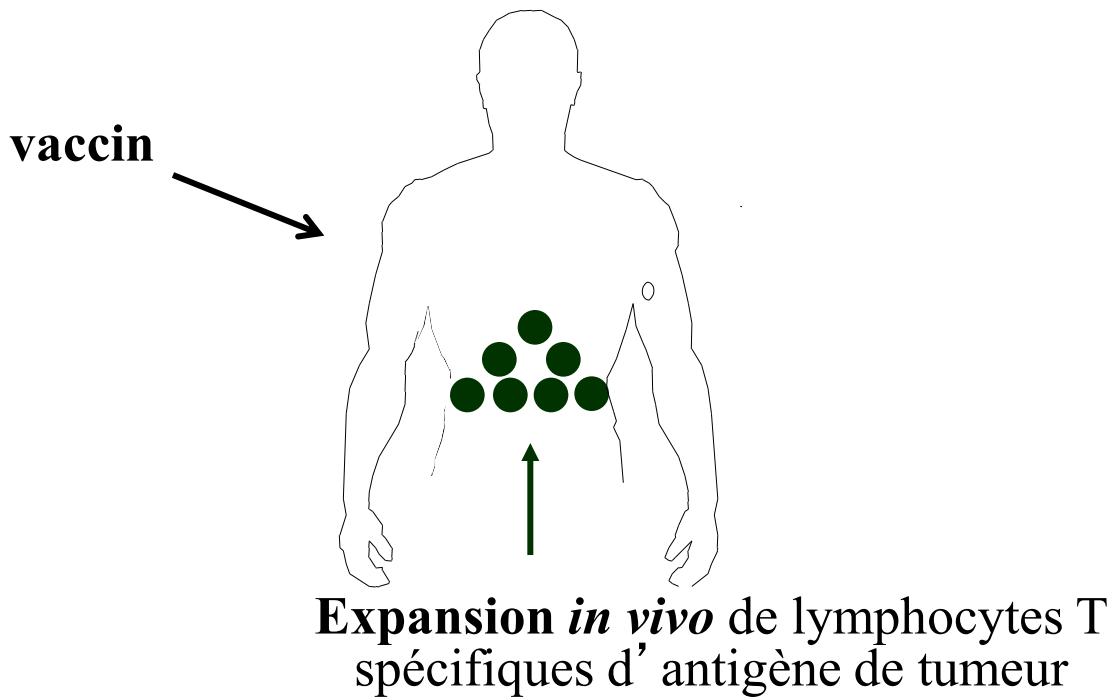
# Vaccin anticancer

# Les vaccins anticancers



Principe:

« stimuler chez le patient la multiplication de lymphocytes spécifiques de tumeur »



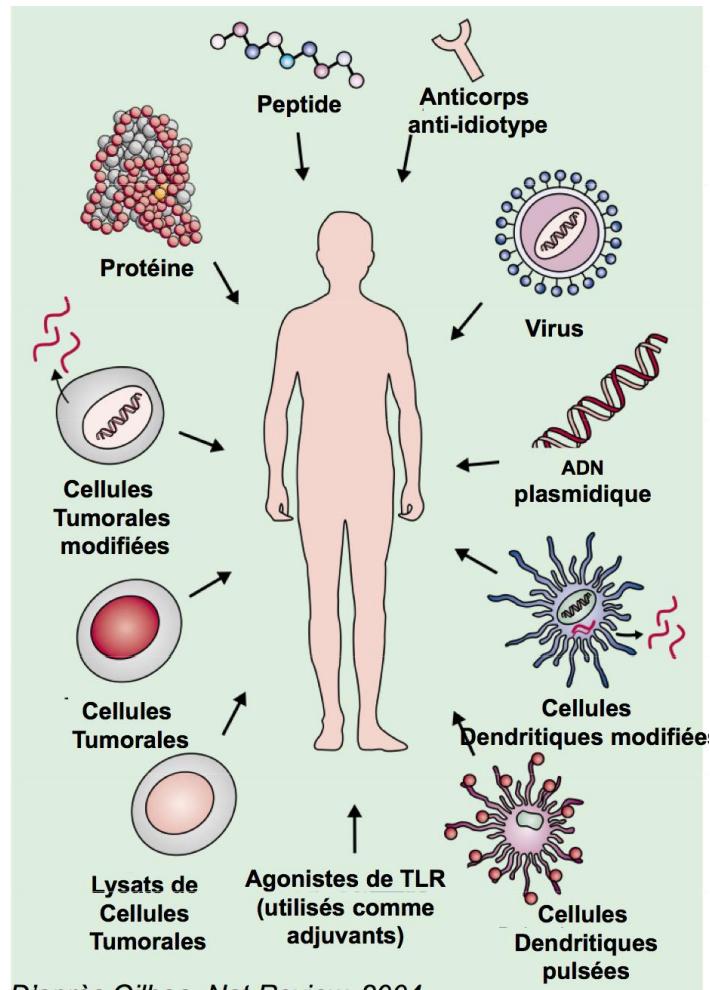
# Les vaccins anticancers



## Plusieurs sources d'antigènes tumoraux

	Exemples	Expression tumorale
Ag de différenciation	Mart 1, gp100, Melan A PSA, PAP, PSMA	Mélanome Cancer de la prostate
Ag du groupe cancer testis	Mage 1-10 NY-ESO1	Mélanome, sein, poumon, myélome Mélanome, poumon, vessie
Ag mutés	$\beta$ -caténine CDK-4 Ras	Mélanome, tumeur du foie Mélanome Cancer côlon, pancréas, poumon
Ag surexprimés	Her2/neu ACE	Adénocarcinome sein, poumon, rein, vessie Adénocarcinome côlon, poumon
Ag glycosidiques modifiés	Muc 1	Adénocarcinome sein, poumon, rein
Ag viraux	HPV HCV, HBV EBV <i>Helicobacter pylori</i>	Col de l'utérus, ORL, anus Cancer du foie Lymphome Cancer de l'estomac

## Plusieurs stratégies



D'après Gilboa, Nat Review. 2004

# Les vaccins anticancers



## Therapeutic vaccines for cancer: an overview of clinical trials

Ignacio Melero, Gustav Gaudernack, Winald Gerritsen, Christoph Huber, Giorgio Parmiani, Suzy Scholl, Nicholas Thatcher, John Wagstaff, Christoph Zielinski, Ian Faulkner and Håkan Mellstedt

> 7500 patients inclus dans essais de phase III

Immunotherapy	Targeted antigens	Adjuvants/immune modulators	Study population	n
<b>Prostate cancer</b>				
Autologous cell vaccine: sipuleucel-T, Provenge®	PAP <b>AMM</b>	GM-CSF	Metastatic, castration-resistant prostate cancer	512
Allogeneic tumour cell vaccine: GVAX	Tumour cell	GM-CSF	Castration-resistant prostate cancer	626
Allogeneic tumour cell vaccine: GVAX	Tumour cell	GM-CSF	Castration-resistant prostate cancer	408
<b>Breast cancer</b>				
Peptide vaccine: Theratope	Sialyl-Tn	KLH	Metastatic breast cancer, in remission after first-line chemotherapy	1,028
<b>Lung cancer</b>				
Peptide vaccine: tecemotide (L-BLP25)	MUC1	Liposomal monophosphoryl lipid A plus cyclophosphamide	Unresectable stage III NSCLC; after chemo-radiotherapy	1,239
Peptide vaccine: GSK1572932A	MAGE-A3	Liposomal AS15	Completely resected stage IB-II NSCLC	182
Allogeneic tumour cell vaccine: belagenpumatumab-L, Lucanix™	Tumour cell	Anti-TGF-β	Stage IIIB-IV NSCLC	532

Immunotherapy	Targeted antigens	Adjuvants/immune modulators	Study population	n
<b>Melanoma</b>				
Peptide vaccine	gp100	IL2 plus Montanide™ ISA51	Locally-advanced stage III or stage IV melanoma	185
Peptide vaccine: GSK 2132231A	MAGE-A3	QS-21	Resected melanoma	1,349
<b>Pancreatic cancer</b>				
Peptide vaccine: GV1001	Telomerase	GM-CSF	Locally-advanced and/or metastatic pancreatic cancer	1,062
<b>Colorectal cancer</b>				
Autologous tumour cell vaccine: OncoVAX®	Tumour cell	BCG	Resected stage II-III colon cancer; after resection	254
<b>Haematological malignancies</b>				
Autologous anti-idiotype vaccine	Idiotype	KLH	Advanced follicular lymphoma, with complete response after chemotherapy	177

# Les vaccins anticancers



## Therapeutic vaccines for cancer: an overview of clinical trials

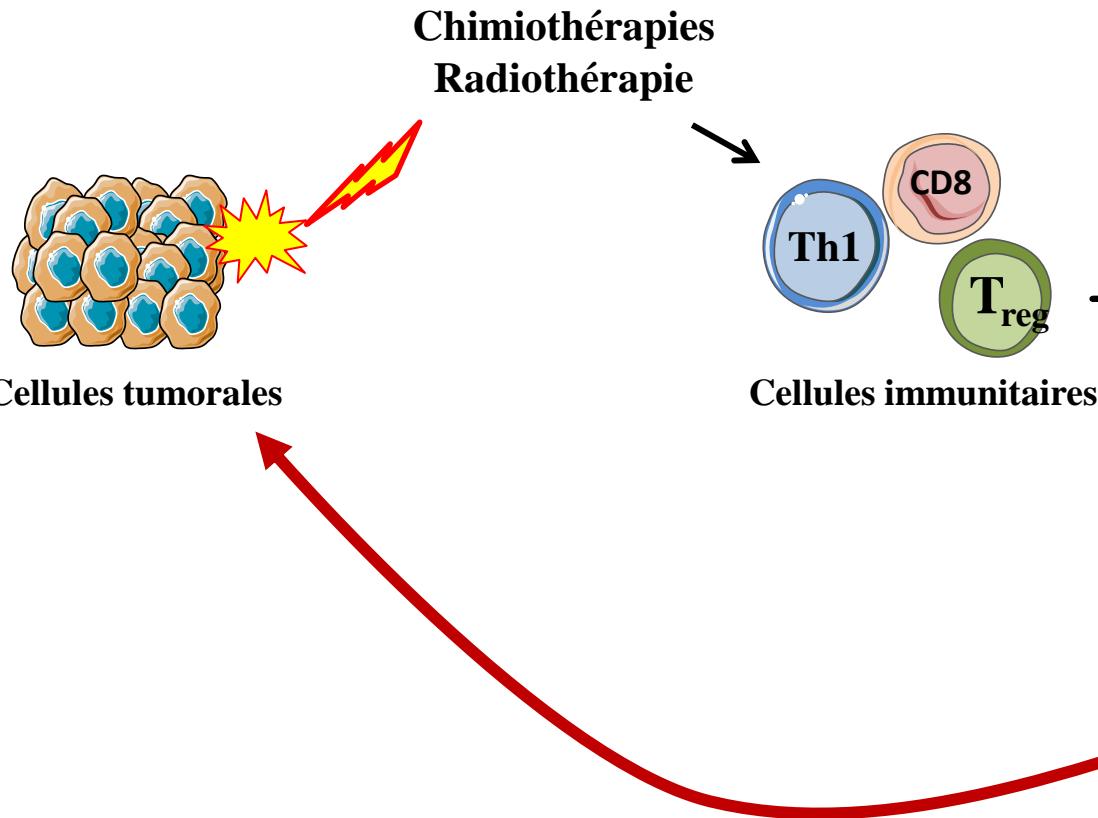
*Ignacio Melero, Gustav Gaudernack, Winald Gerritsen, Christoph Huber, Giorgio Parmiani, Suzy Scholl, Nicholas Thatcher, John Wagstaff, Christoph Zielinski, Ian Faulkner and Håkan Mellstedt*

### Paramètres pour améliorer l'efficacité des vaccins

- Choix de l'antigène tumoral
- Choix de l'adjuvant
- Qualité des réponses T induites (rôle des TCD4)
- Inhibition des mécanismes immunosupresseurs
- Combinaison avec traitements conventionnels

# Les Vaccins anti-cancers

## Rationnel pour combiner vaccin et traitements cytotoxiques



## Modulation des réponses immunitaires

Prolifération /recrutement de cellules effectrices

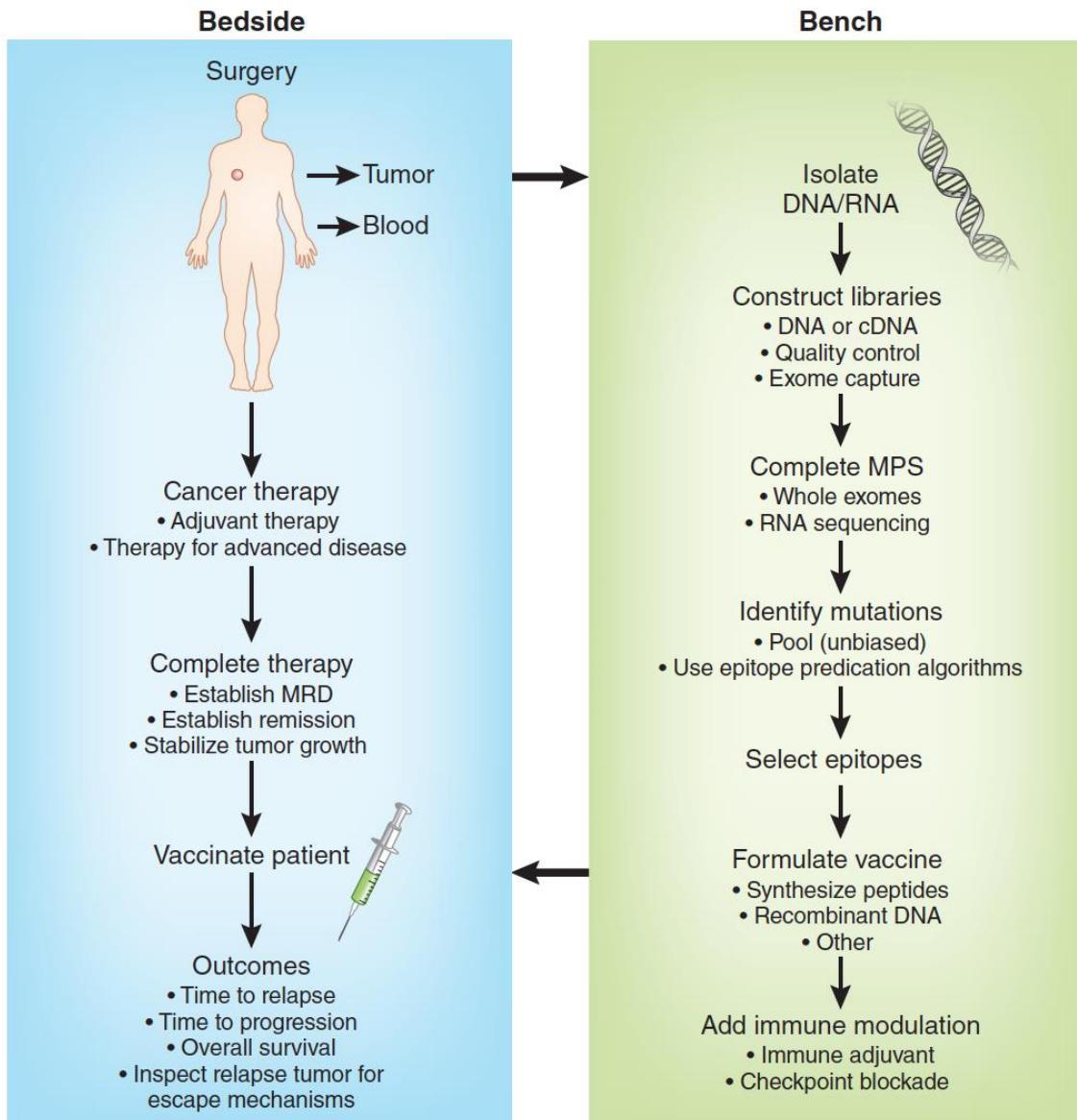
(Cisplatin, taxanes, cyclophosphamide...)

Diminution du microenvironnement immunosuppresseur

(Gemcitabine, 5-Fluoro-uracile, cyclophosphamide...)

(Vincent *et al.*, *Can. Res.*, 2010; Galluzzi *et al.*, *Nat. Rev. Drug Discov.*, 2012; Demaria and Formenti, *Front. Oncol.*, 2012 Formenti *et al.*, *J. Natl. Cancer Inst.*, 2013; Zitvogel *et al.*, *Immunity*, 2013, de Biasi *et al.*, *Clin. Cancer Res.*, 2014)

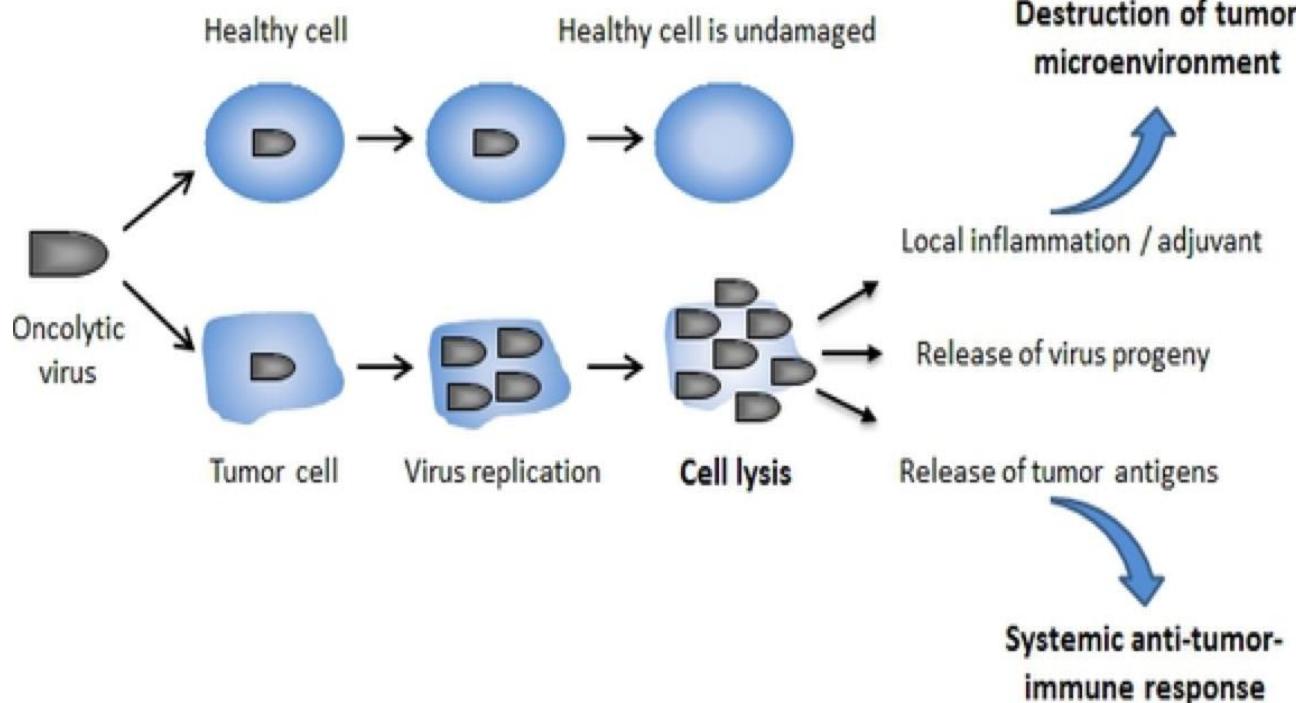
# Vers des vaccins personnalisés



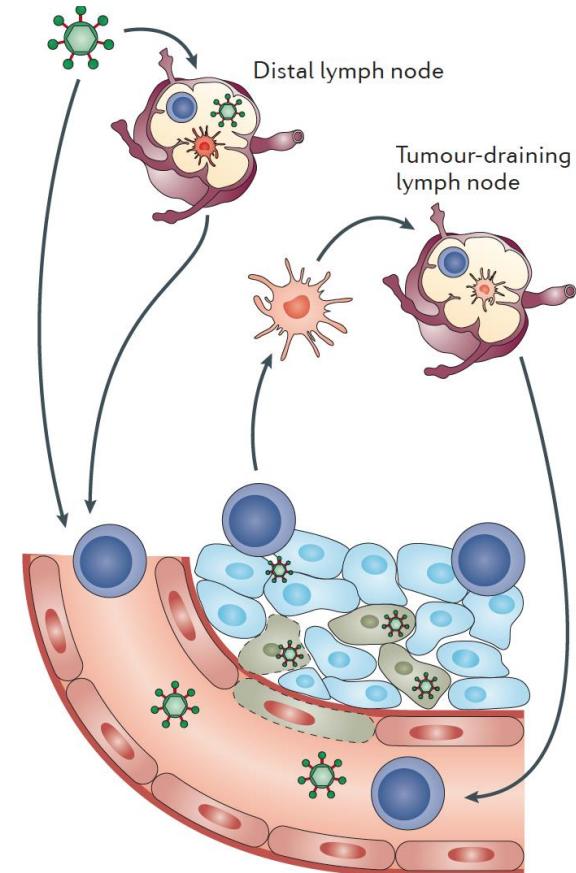
# **Virus Oncolytiques et Cancer**



## Virus Oncolytiques: « L'ennemi de mon ennemi est mon ami »



Adapted from [Viratherapeutics.com](http://Viratherapeutics.com)

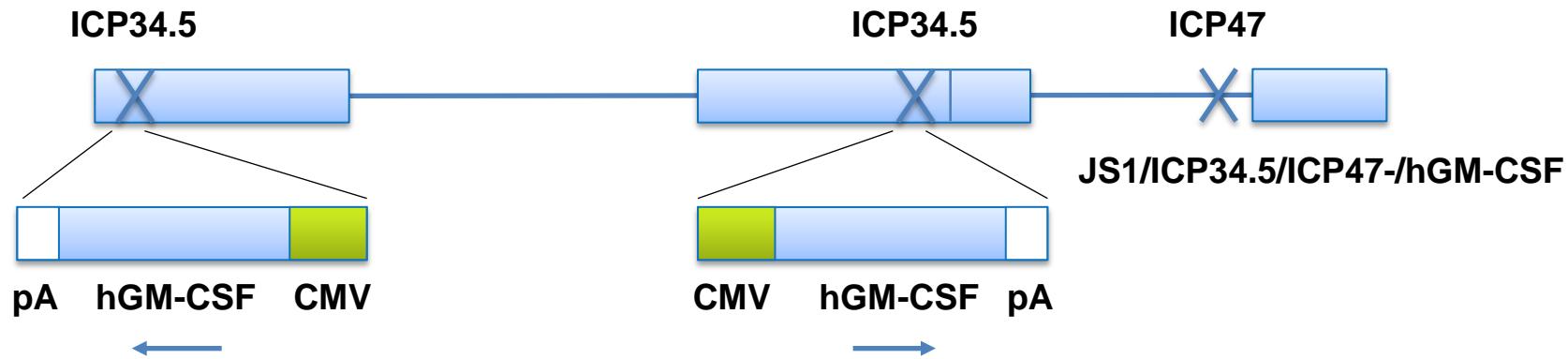


Lichty et al. *Nat Rev Can* 2015



### Talimogene laherparepvec (T-VEC) description

Modification	Rationale
Deletion of ICP34.5 (neurovirulence factor)	<ul style="list-style-type: none"> <li>Provides tumor selective replication</li> </ul>
Deletion of ICP47	<ul style="list-style-type: none"> <li>Prevents ICP47 from blocking antigen presentation (enhances antitumor immune response)</li> </ul>
Early/increased US11	<ul style="list-style-type: none"> <li>Increases replication of ICP34.5-deleted HSV</li> </ul>
Insertion of human GM-CSF gene	<ul style="list-style-type: none"> <li>Enhances antitumor response</li> </ul>
New HSV-1 strain: JS1	<ul style="list-style-type: none"> <li>Improves tumor cell lysis</li> </ul>



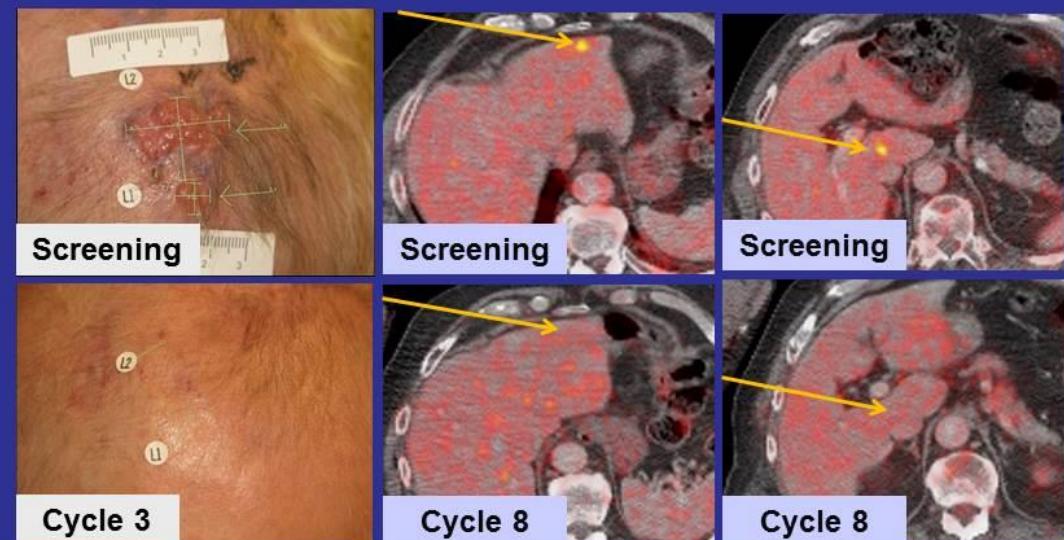
<sup>1</sup> Liu BL, et al. *Gene Therapy*. 2003;10:292-303.



**OPTiM: A Randomized Phase 3 Trial Of Talimogene Laherparepvec (T-VEC) Vs Subcutaneous Granulocyte-macrophage Colony-stimulating Factor (GM-CSF) For The Treatment Of Unresected Stage IIIB/C And IV**

Robert H.I. Andtbacka,<sup>1</sup> Frances Collichio,<sup>2</sup> Thomas Neil Senzer,<sup>4</sup> Jason Chesney,<sup>5</sup> Keith A. Delman,  
Igor Puzanov,<sup>8</sup> Susan Doleman,<sup>9</sup> Yining Ye,<sup>10</sup> Andrew Robert Coffin,<sup>9</sup> Howard L. Kaufman<sup>11</sup>

## Local And Distant Lesion Response to T-VEC



Patient had 2 liver lesions at baseline with a combined size of 2 cm, which were never injected



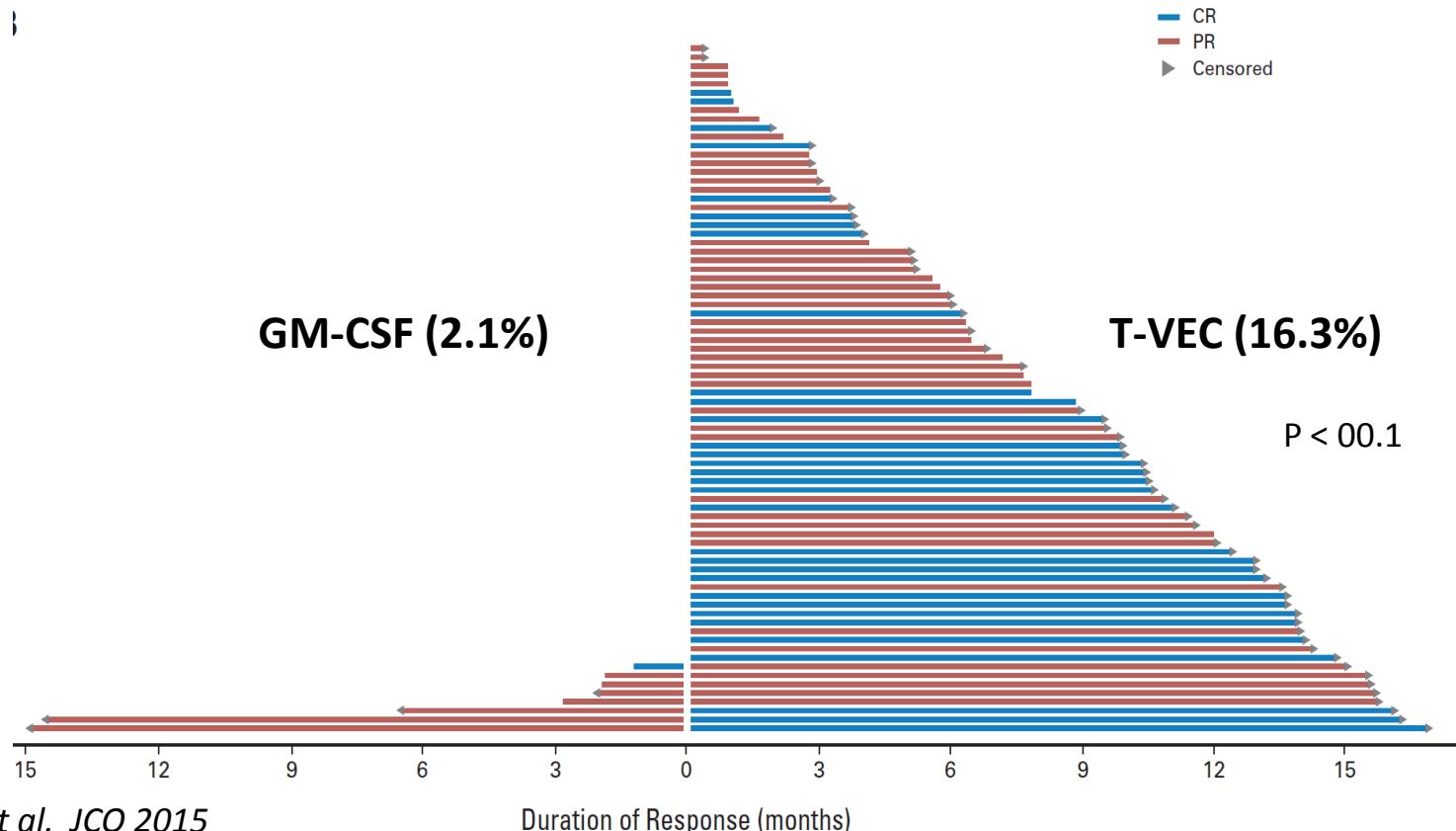
VOLUME 33 • NUMBER 25 • SEPTEMBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

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Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels,  
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# Virus Oncolytiques: « L'ennemi de mon ennemi est mon ami »

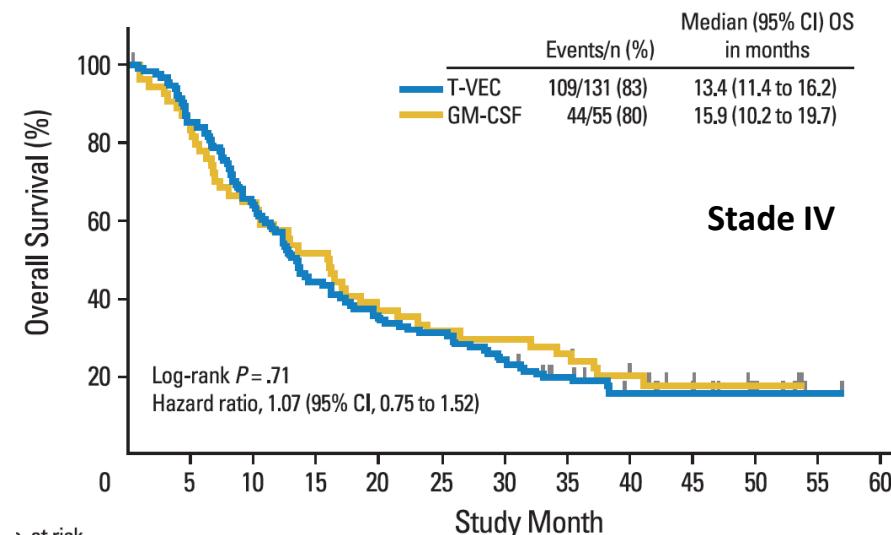
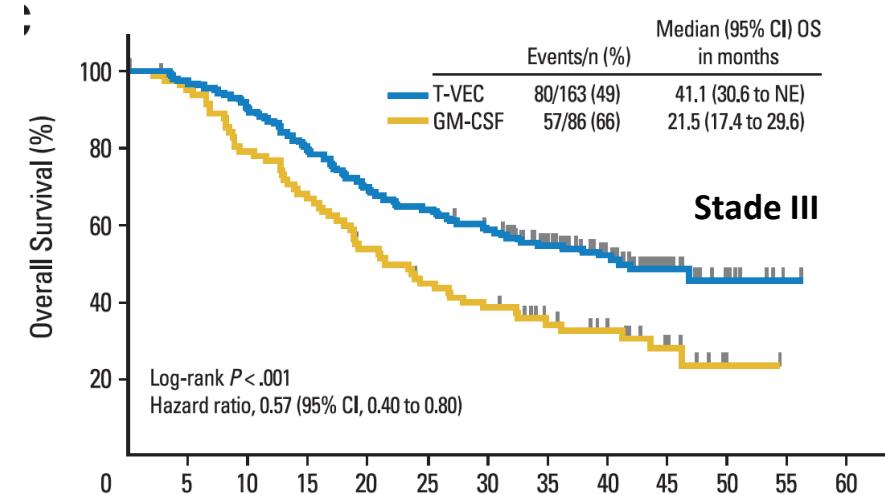
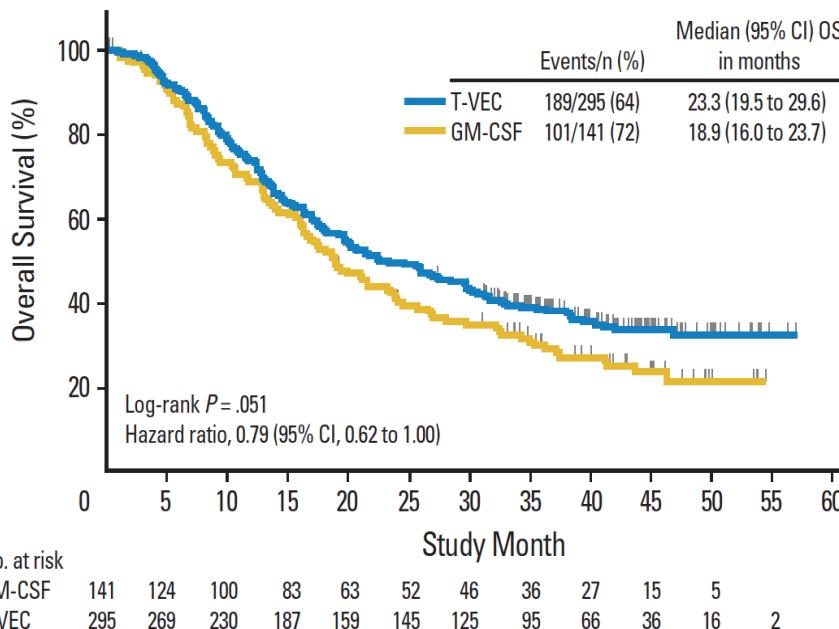
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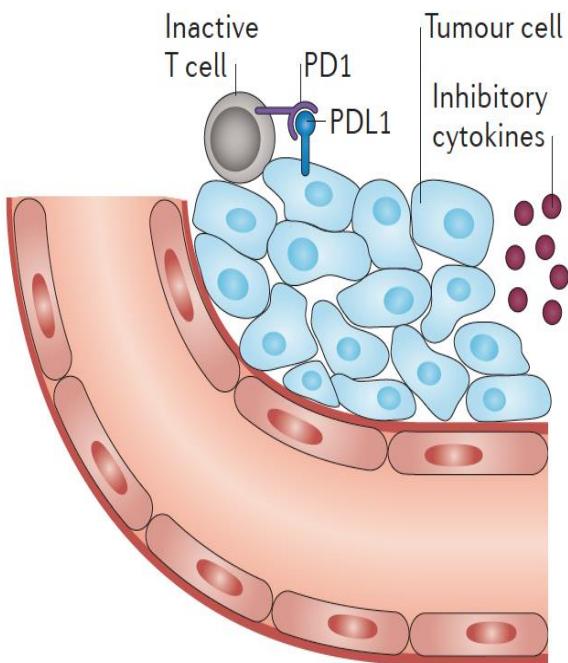


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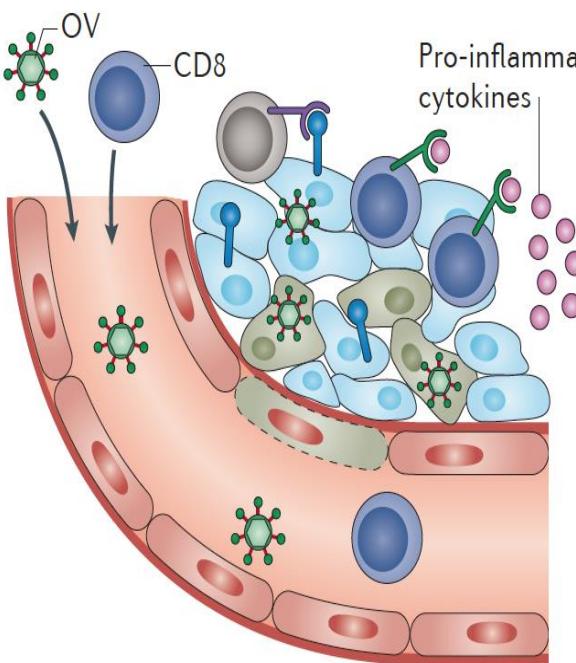


## Perspectives

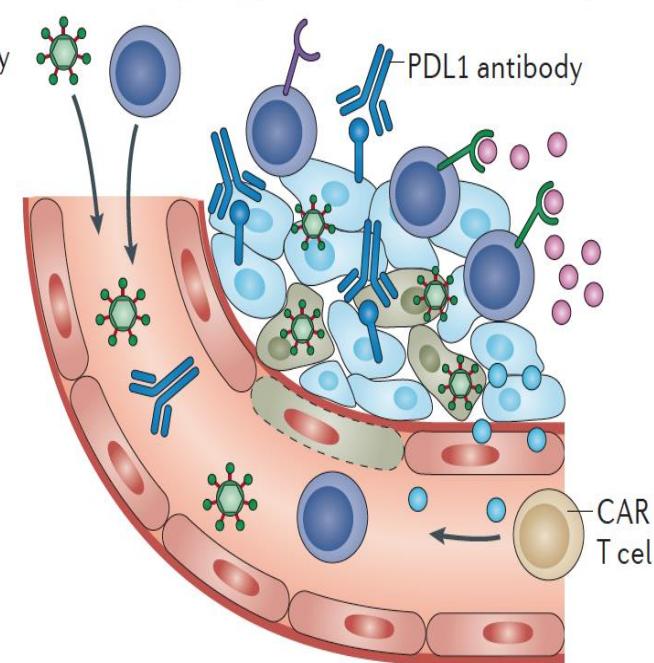
a Tumour at baseline



b Tumour after OV treatment



c Potential synergy with other immunotherapies



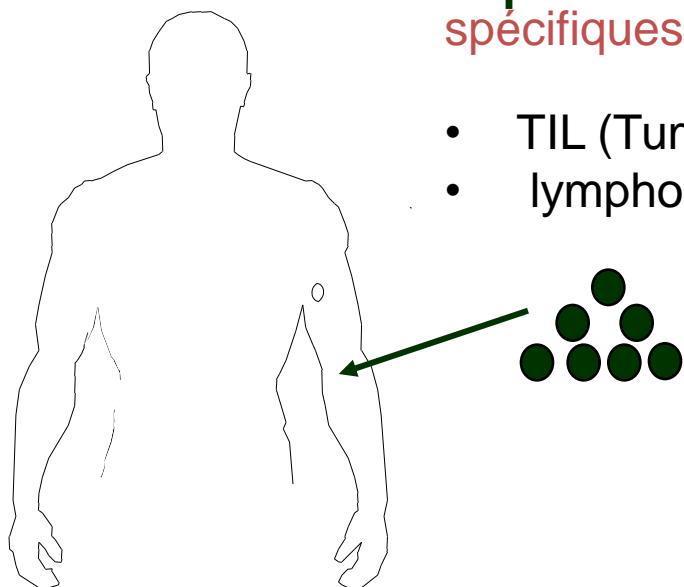
# **Transfert adoptif de lymphocytes T**

Objectif :

- \* Induire chez le patient une réponse immunitaire anti-tumorale par transfert de lymphocytes T spécifiques de tumeurs

**Expansion *ex vivo* de lymphocytes T autologues spécifiques des cellules tumorales:**

- TIL (Tumor Infiltrating Lymphocytes)
- lymphocytes T génétiquement modifiés (**CAR**)

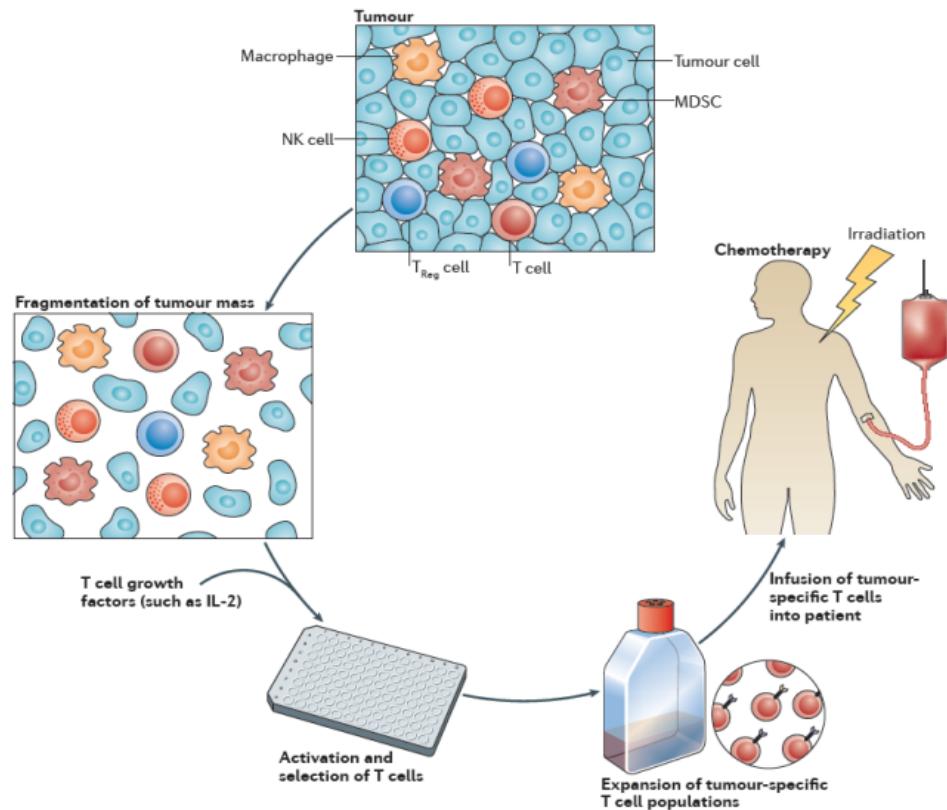


# Transfert adoptif de lymphocytes T intratumoraux (TIL)

## Transfert adoptif de (TIL)



S.A Rosenberg

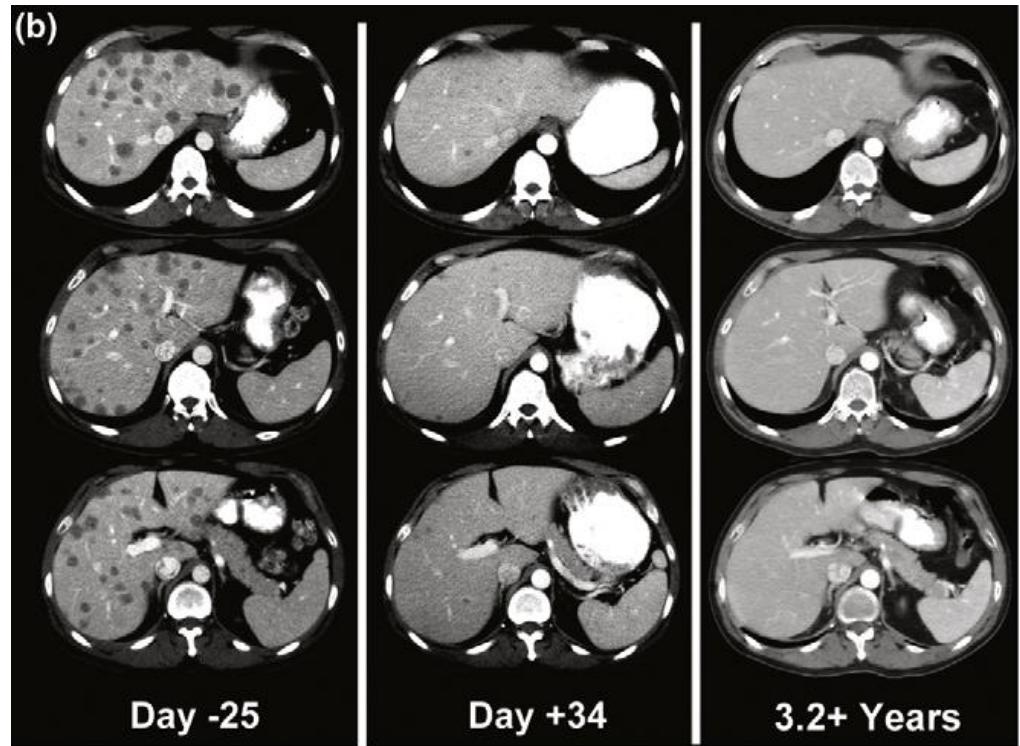


Premier essai de transfert de TIL chez l'homme dans le mélanome *Science*, 2002

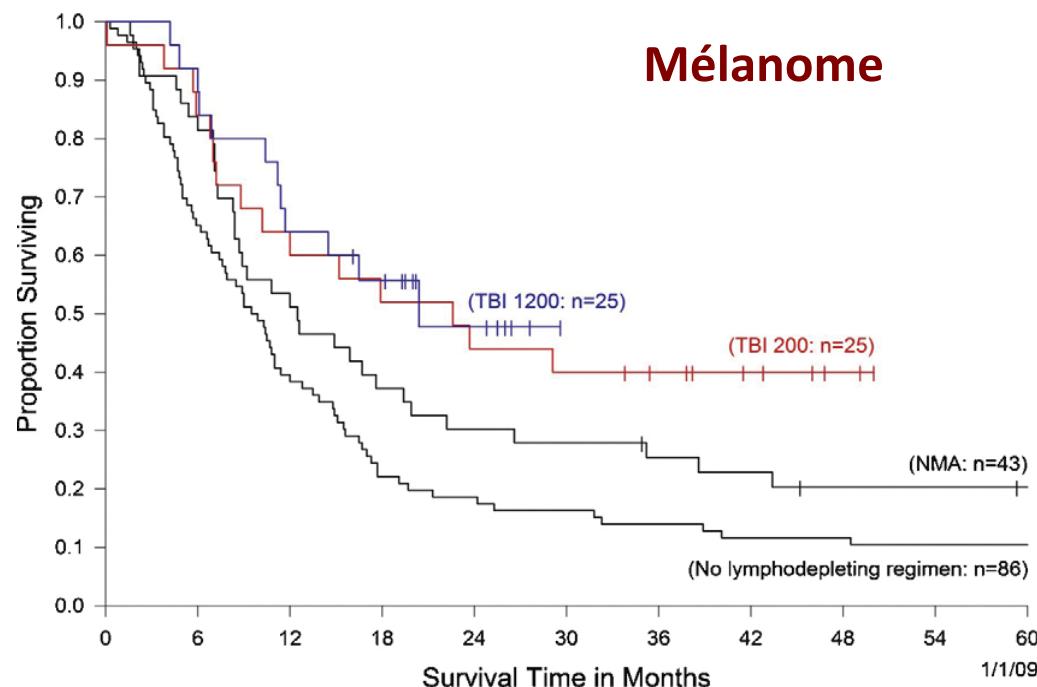
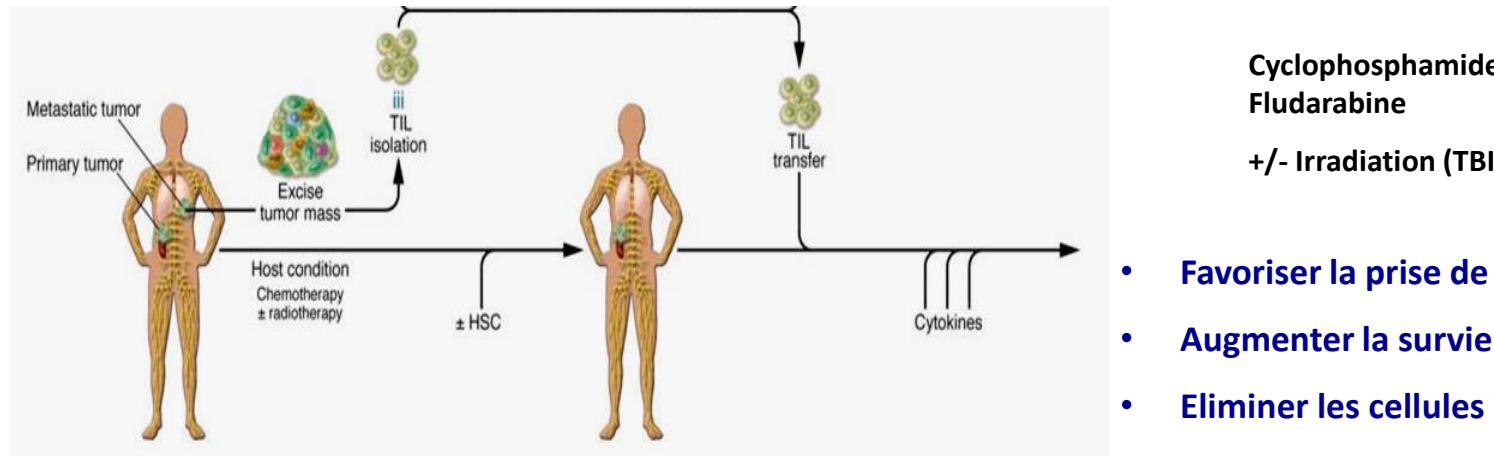
*Restifo et al. Nat Rev Immunol 2012*

# Transfert adoptif de lymphocytes T intratumoraux (TIL)

## Plusieurs essais dans le mélanome



# Transfert adoptif de lymphocytes T intratumoraux (TIL)



## TIL anti-HPV16 le cancer du col de l'utérus

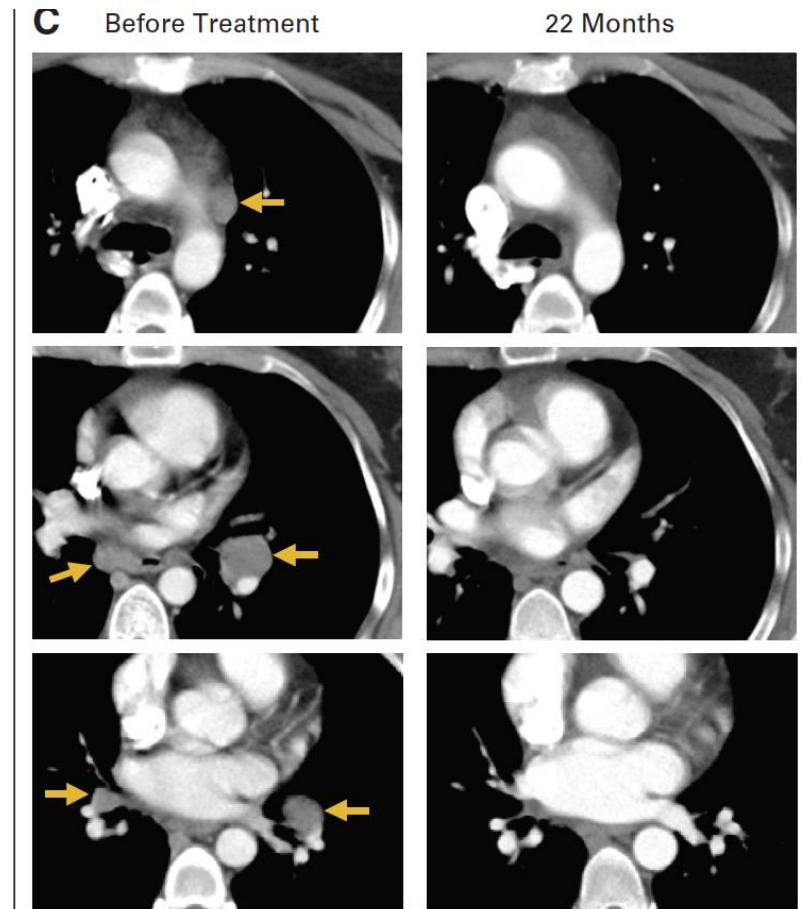
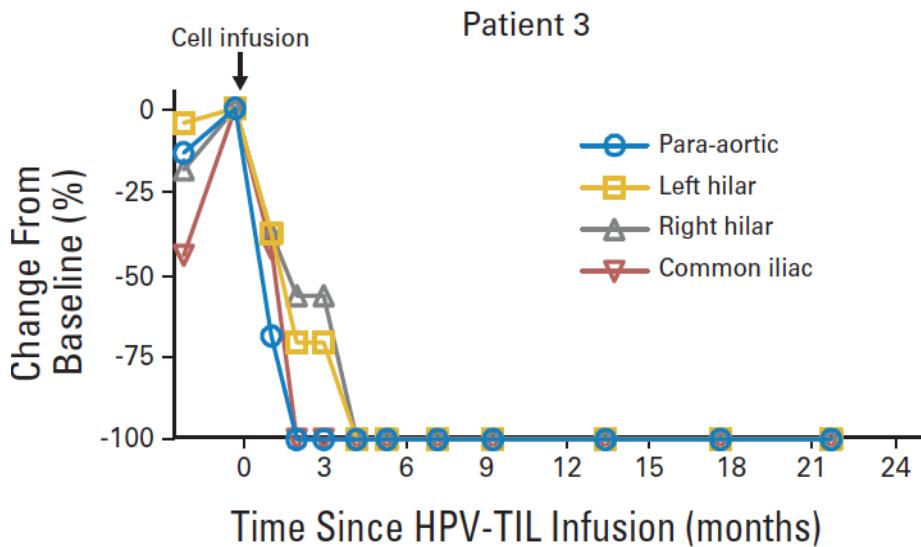
VOLUME 33 • NUMBER 14 • MAY 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

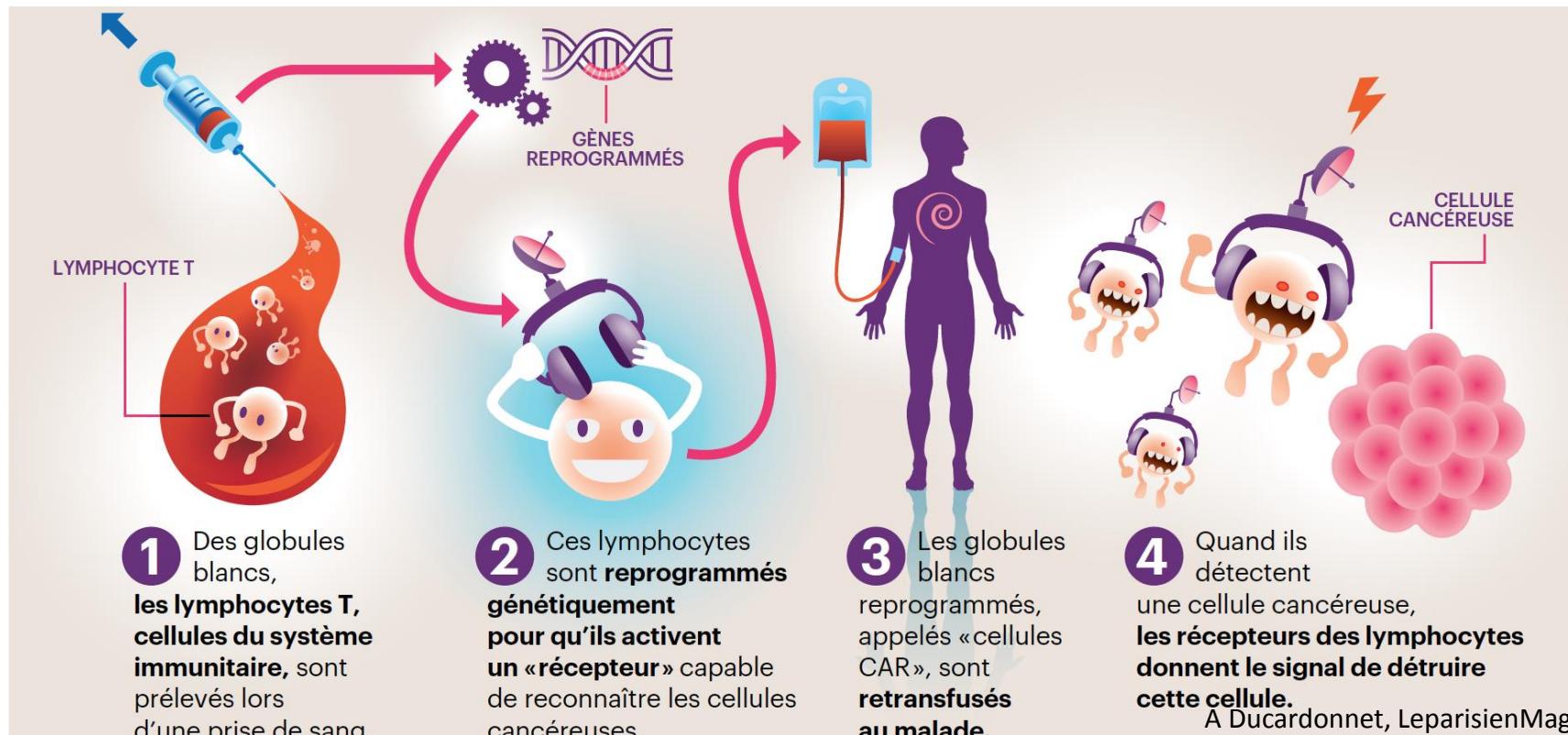
### Complete Regression of Metastatic Cervical Cancer After Treatment With Human Papillomavirus–Targeted Tumor-Infiltrating T Cells

Sanja Stevanović, Lindsey M. Draper, Michelle M. Langhan, Tracy E. Campbell, Mei Li Kwong, John R. Wunderlich, Mark E. Dudley, James C. Yang, Richard M. Sherry, Udai S. Kammula, Nicholas P. Restifo, Steven A. Rosenberg, and Christian S. Hinrichs



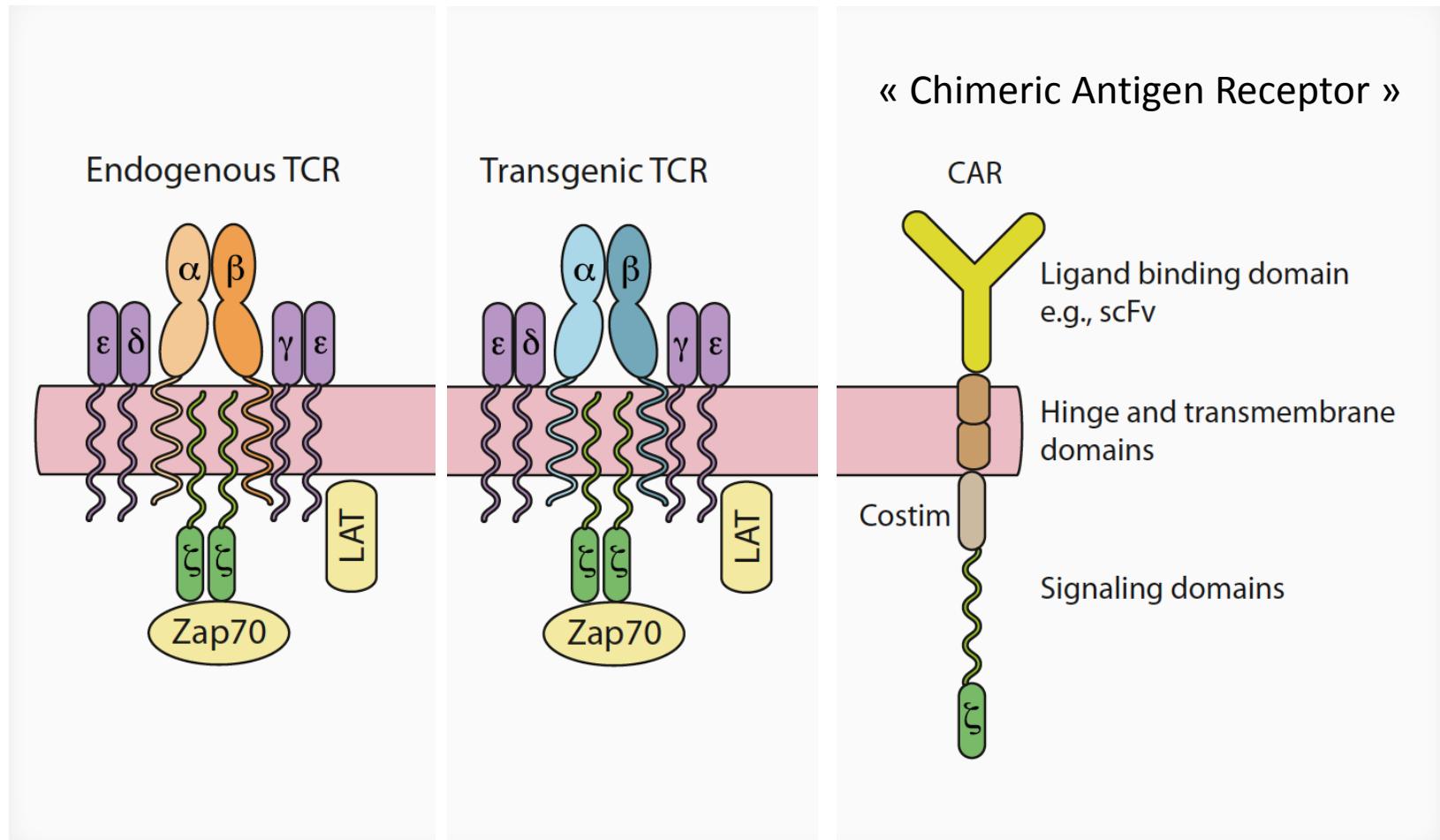
# Transfert adoptif de lymphocytes T génétiquement modifiés

## Reprogrammation génique des lymphocytes T antitumoraux

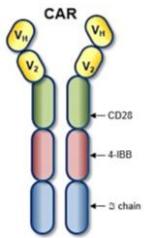


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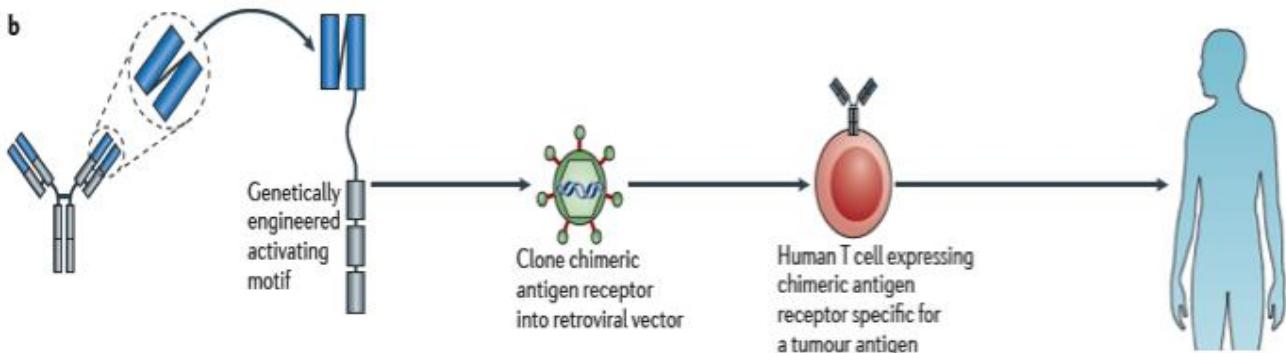
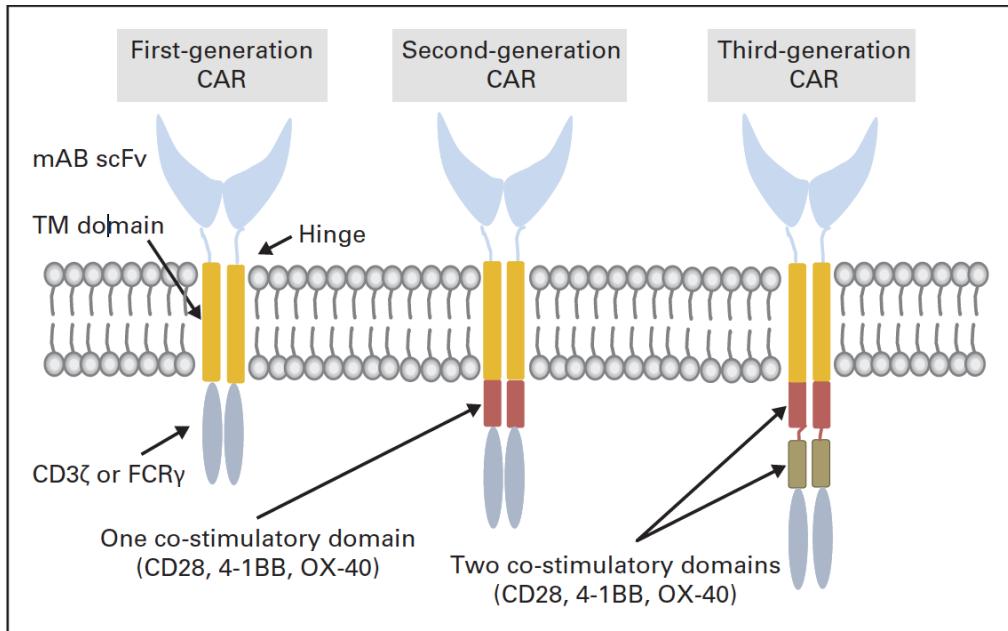
## Reprogrammation génique des lymphocytes T antitumoraux



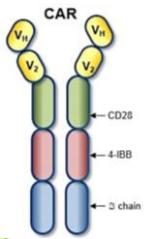
# Transfert adoptif: les CAR



## Différentes générations de CAR



## Transfert adoptif: les CAR



Efficacité CAR anti-CD19 = oui et dans les leucémies et lymphomes B !!!

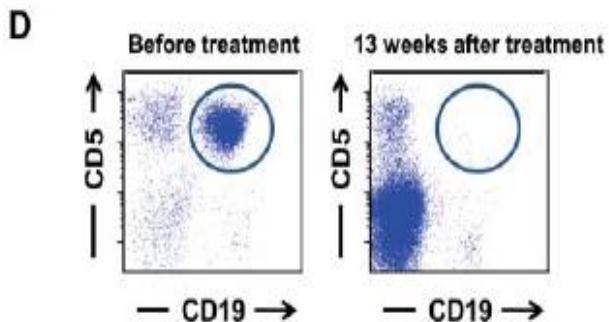
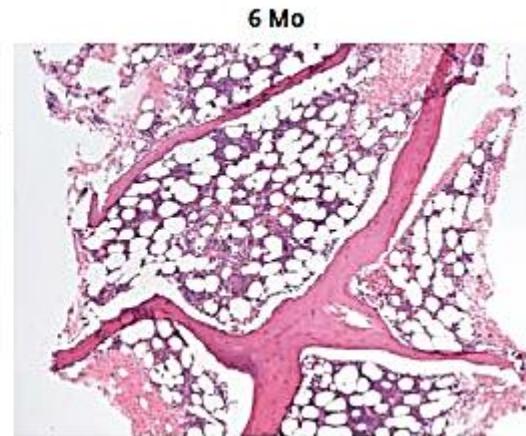
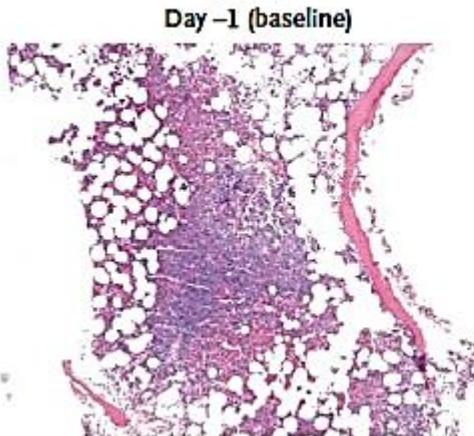
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

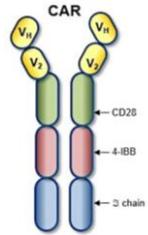
## Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D.,  
Adam Bagg, M.D., and Carl H. June, M.D.

### C Bone Marrow–Biopsy Specimens



# Transfert adoptif: les CAR



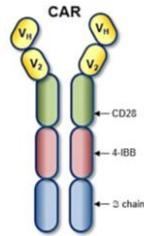
## CAR anti-CD19

The NEW ENGLAND JOURNAL of MEDICINE

### ORIGINAL ARTICLE

## Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

A total of 30 children and adults received CTL019. Complete remission was achieved in 27 patients (90%), including 2 patients with blinatumomab-refractory disease and 15 who had undergone stem-cell transplantation. CTL019 cells prolif-

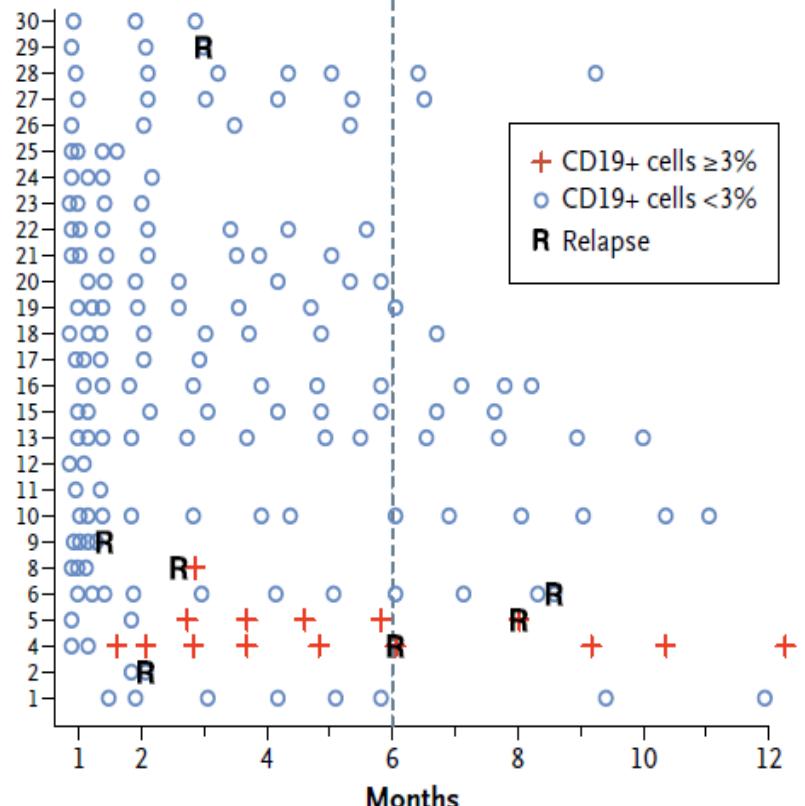


## CAR anti-CD19

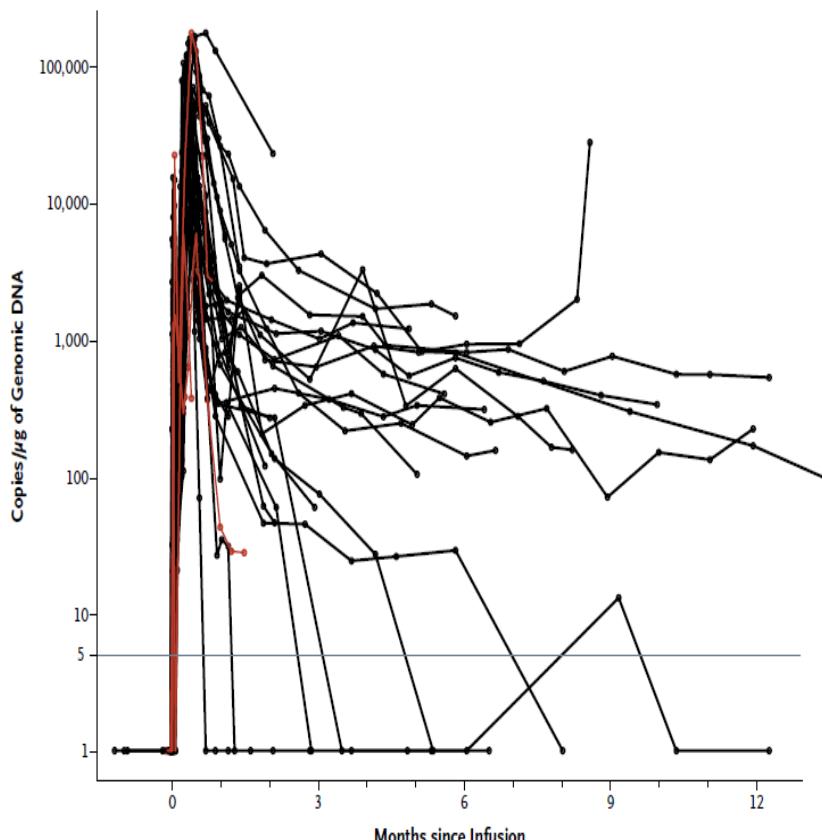
## ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells  
for Sustained Remissions in Leukemia

## A Positivity for CD19

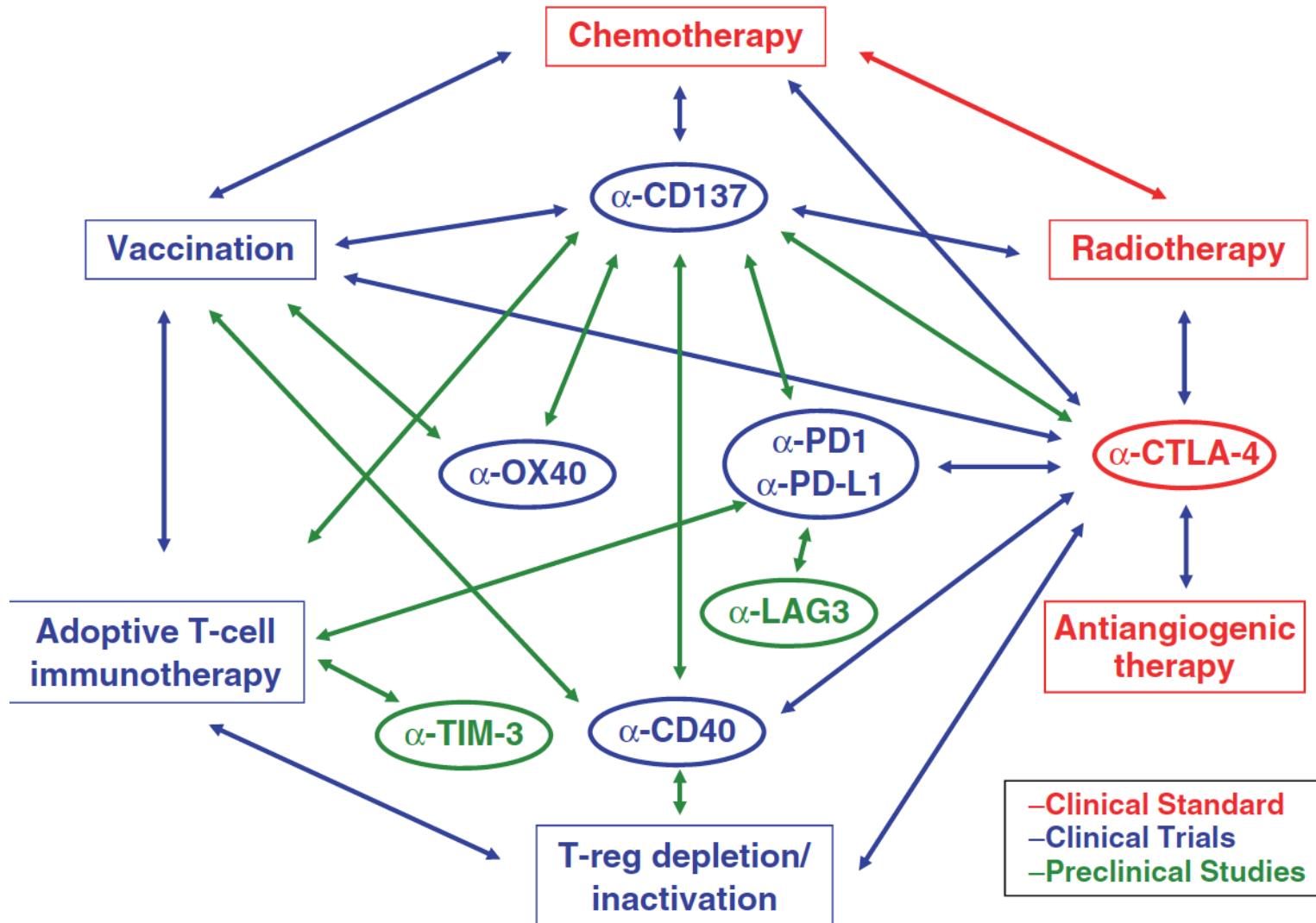


Levels of CTL019 DNA in Peripheral Blood



Maude S et al NEJM 2014

# L'avenir = combinaisons thérapeutiques



# Pipeline immunothérapies, Besançon

Dr C Ferrand,  
Dr M Deschamps,  
Pr F Garnache-Ottou)

**Development**  
**PHRT-K 2016**

**CAR-T cells (CD123) – BPDCN**

**CAR-T cells (IL-1RAP) – CML**

**Side by CIDe (iCasp9) – GvHD**

**ANSM**

**UCPVax – non-small cell lung cancer**

**PHRC-K 2013**  
Start Feb. 2016

**MTI**



# Merci pour votre attention

Equipe Immunothérapie anticancer, INSERM U1098 Besançon



Regional Institute for cancer  
(Pr X Pivot)



Biostatistic & QL Unit  
(Pr Bonnetain)

CLIP<sup>2</sup> Inca platform  
(Pr Borg)

CIC BT 1431,  
INSERM  
(Pr Haffen)

