Immunothérapie des cancers bronchiques: les vaccins

Pr Olivier ADOTEVI
Oncologie médicale, CHRU de Besançon
Cancer Immunotherpy
UMR 1098 INSERM, Labex LipsTic
olivier.adotevi@univ-fcomte.fr

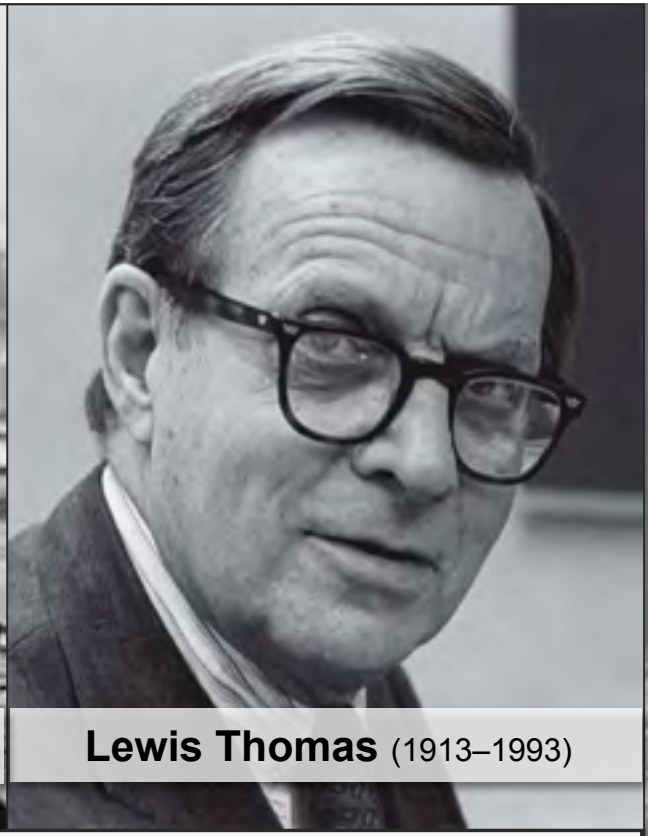
IRFC

CHRU Besançon
centre hospitalier régional universitaire

UNIVERSITÉ BOURGOGNE FRANCHE-COMTÉ

Inserm
Institut national de la santé et de la recherche médicale

McFarlane Burnet (1899-1985)



Lewis Thomas (1913–1993)

Théorie Burnet et Thomas, 1957 :

Tout au long de sa vie un individu est soumis à une cancérogénèse permanente, et le système immunitaire est capable d'identifier et de supprimer ces cellules génétiquement altérées et malignes.
Le développement d'un cancer résulte d'un échappement de la tumeur face au système immunitaire.

Contexte

Immunosurveillance des cancers

2011 : Weinberg RA, *Cell*
→ 'Hallmarks of cancer'

2007 : Schreiber RD, *Nature*
→ Implication de l'i
adaptive dans la phase
d'équilibre

2001 : Schreiber RD, *Nature*
→ Modèles de souris
immunodéficientes

2000 : Weinberg RA, *Cell*
→ 'Hallmarks of cancer'
6 critères nécessaires au
développement de
tumeurs malignes

selection

Autosuffisance en
signaux de croissance

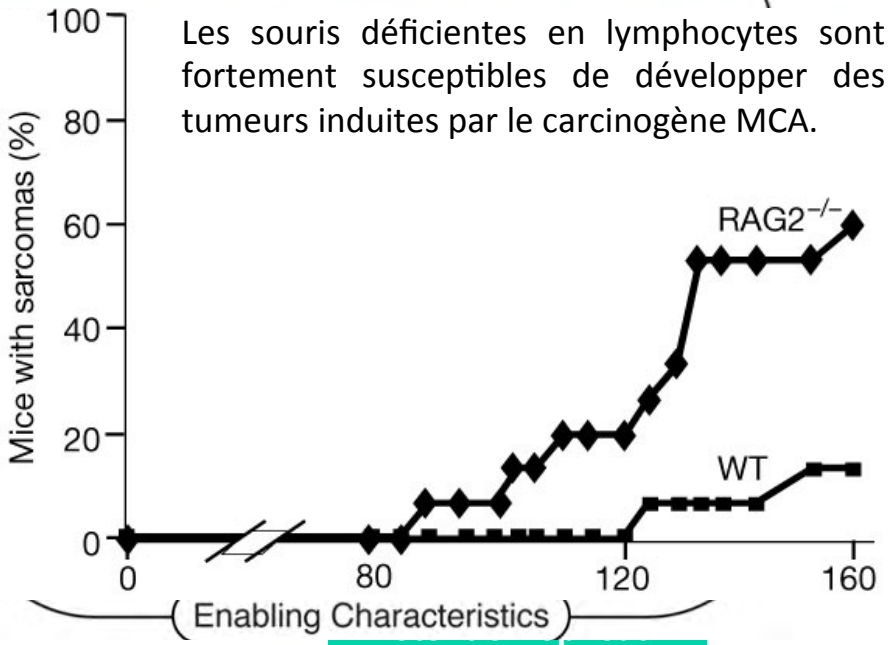
Emerging Hallmarks

Dérèglemer
métabolisme ce

Instabilité géno
et mutatio

Modèle de souris immunodéficientes : souris RAG$^{-/-}$

Les souris déficientes en lymphocytes sont fortement susceptibles de développer des tumeurs induites par le carcinogène MCA.



à
ar

luite
r

illimité

Aucun rôle de l'immunité dans l'échappement tumoral

Hung K et al. 1998. J Exp Med

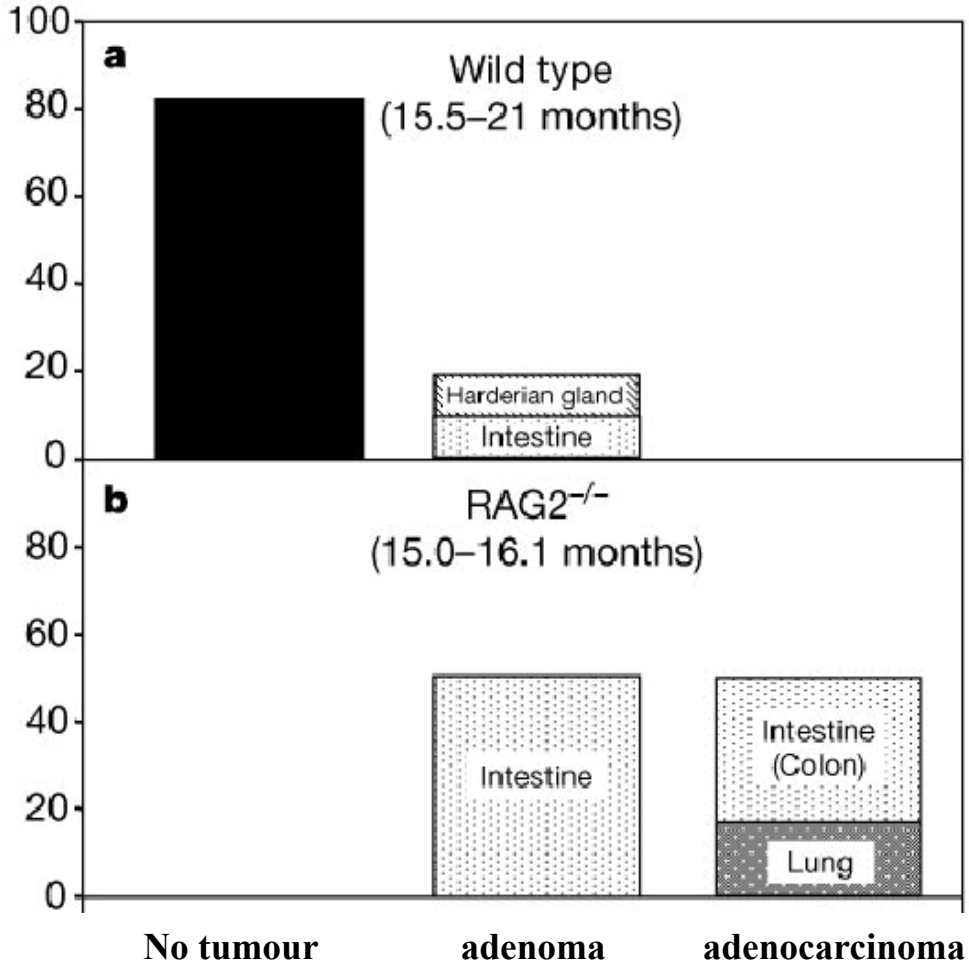
Contexte

Immunosurveillance des cancers

Increased development of spontaneous neoplastic disease in immunodeficient mice

Souris sauvages (15-21 mois)

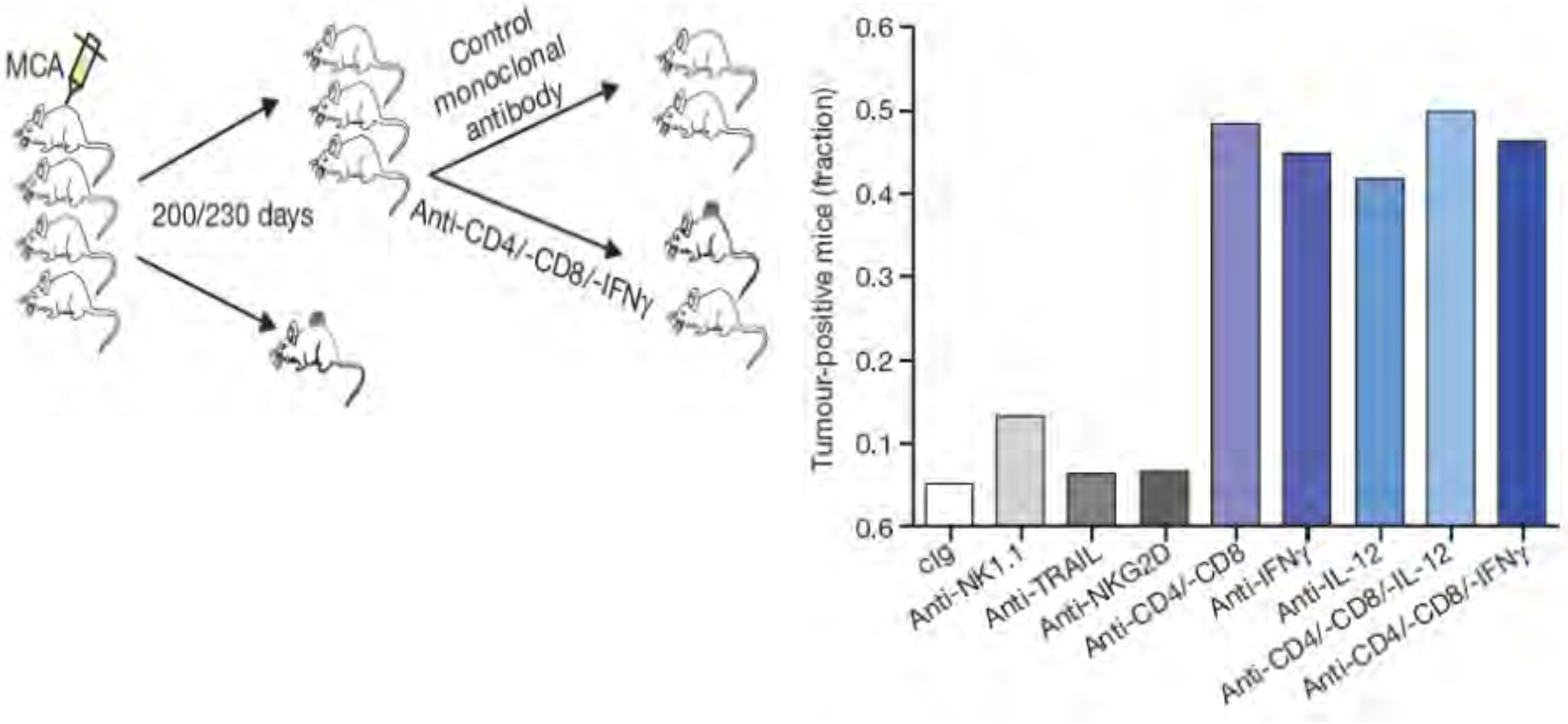
Souris RAG2 $^{-/-}$ Absence de LT et LB



(Shankaran et al. Nature 2001)

Immunosurveillance des cancers

Rôle majeur des lymphocytes T



M. Koebel, Nature 450, 2007

CONTEXTE

Immunosurveillance des cancers

Rôle majeur des lymphocytes T

Effet Graft versus leukemia, GVL

Transplantés - Infection VIH/SIDA...

Incidence plus élevée des cancers en situation d'immunodéficience lymphocytaire **T**

Immunosurveillance des cancers

Rôle majeur des lymphocytes T

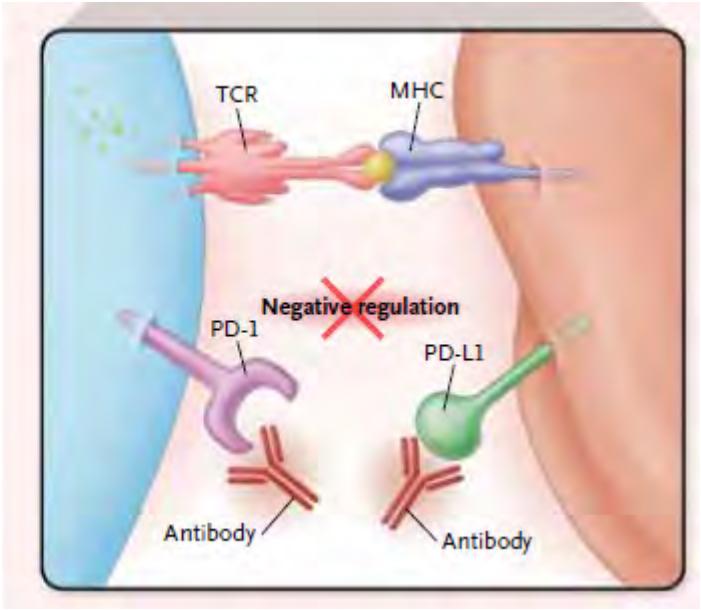
Tumor infiltrative lymphocytes (TIL) are present in many cancer types

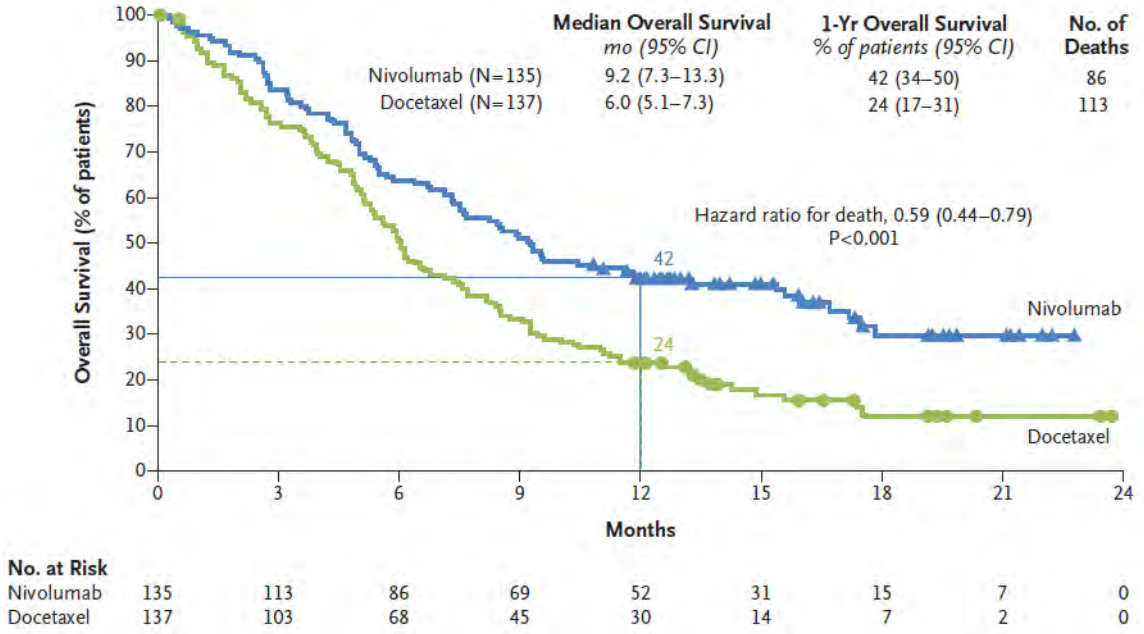
Cancers	References
Breast carcinoma	Bell *et al.* , 1999 Coronella *et al.* , 2002 Nzula *et al.* , 2003 Gobert *et al.* , 2009 Martinet *et al* ., 2011 Gu-Trantien *et al.* , 2013 Martinet *et al* ., 2013
Colorectal carcinoma	Suzuki *et al.* , 2002 McMullen *et al.* , 2010 Bergomas *et al.* , 2011 Coppola *et al* ., 2011 Martinet *et al* ., 2011 Remark et *al.* , 2013
Colorectal carcinoma liver metastasis	Miyagawa *et al.* , 2004
Colorectal carcinoma lung metastasis	Remark et *al.* , 2013
Lung carcinoma	Dieu-Nosjean et *al.* , 2008 Platonova *et al* ., 2011 de Chaisemartin et *al* ., 2011 Martinet *et al* ., 2011 Goc et *al* ., 2014
Melanoma	Ladányi *et al.* , 2007 Messina *et al* ., 2012 Martinet *et al.* , 2012 Cipponi *et al.* , 2012

Contexte

Immunosurveillance des cancers

Rôle majeur des lymphocytes T

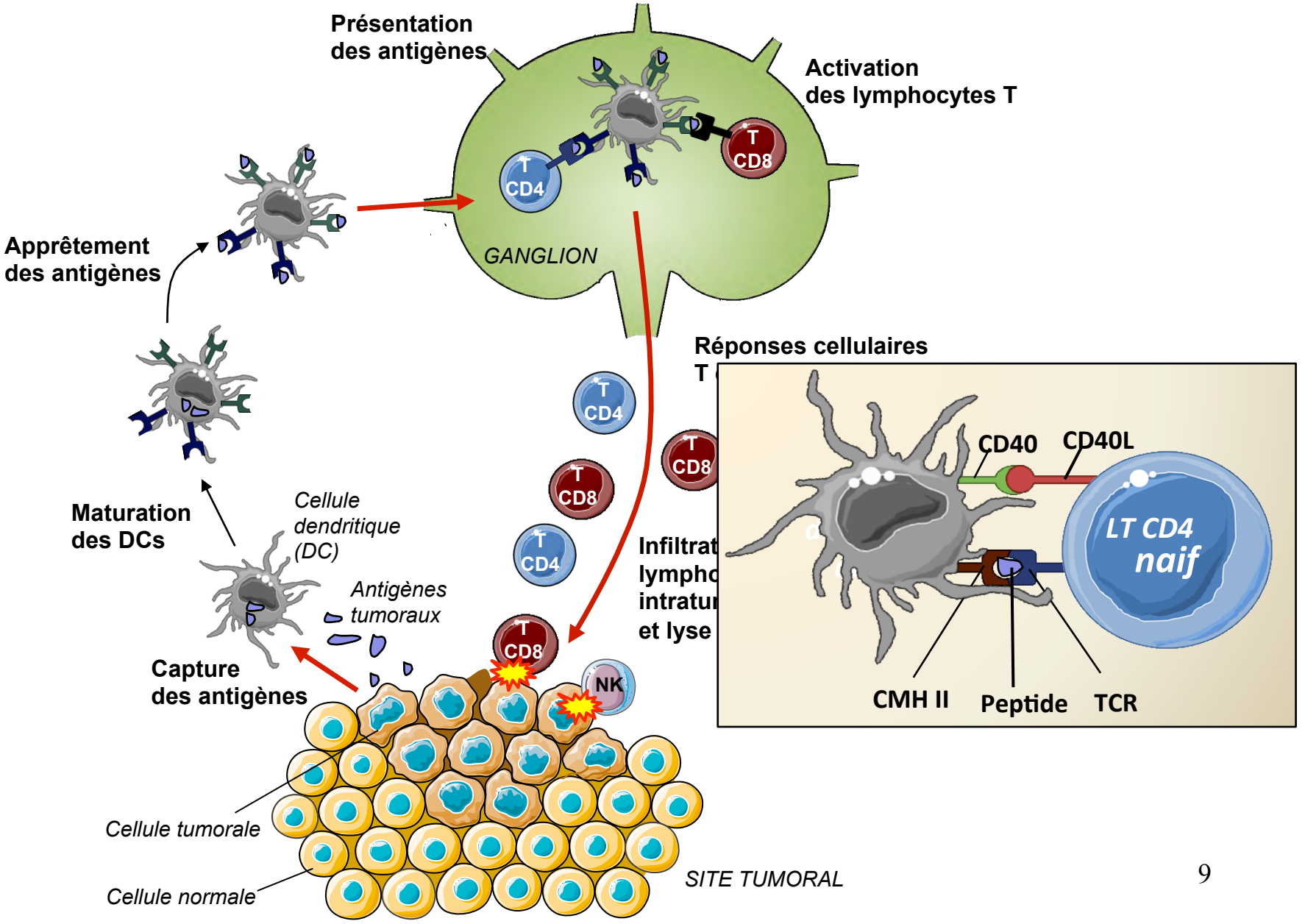




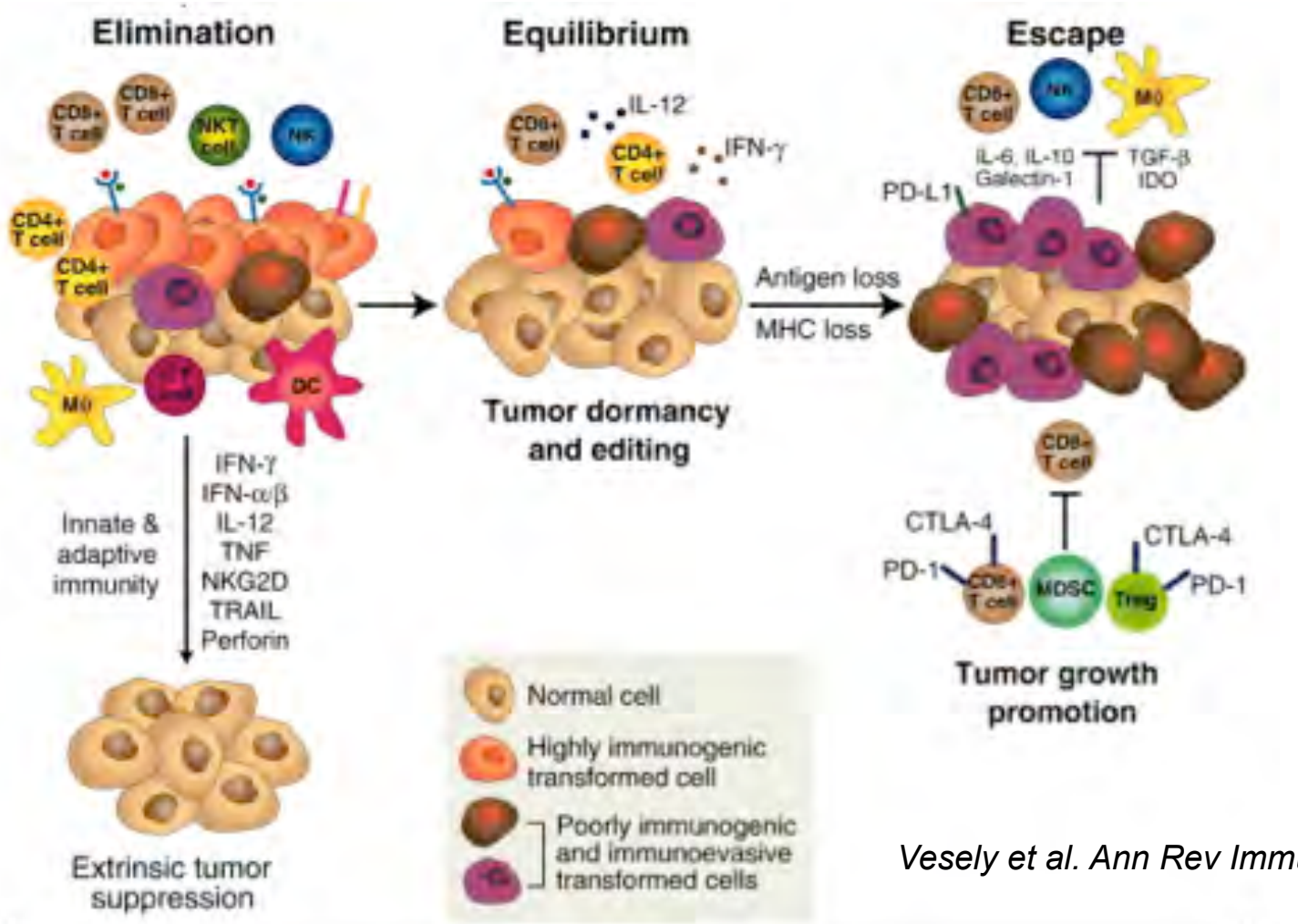
(Ribas, NEJM, 2012; Brahmer, NEJM, 2015)

CONTEXTE

Réponse T antitumorale, un processus dynamique



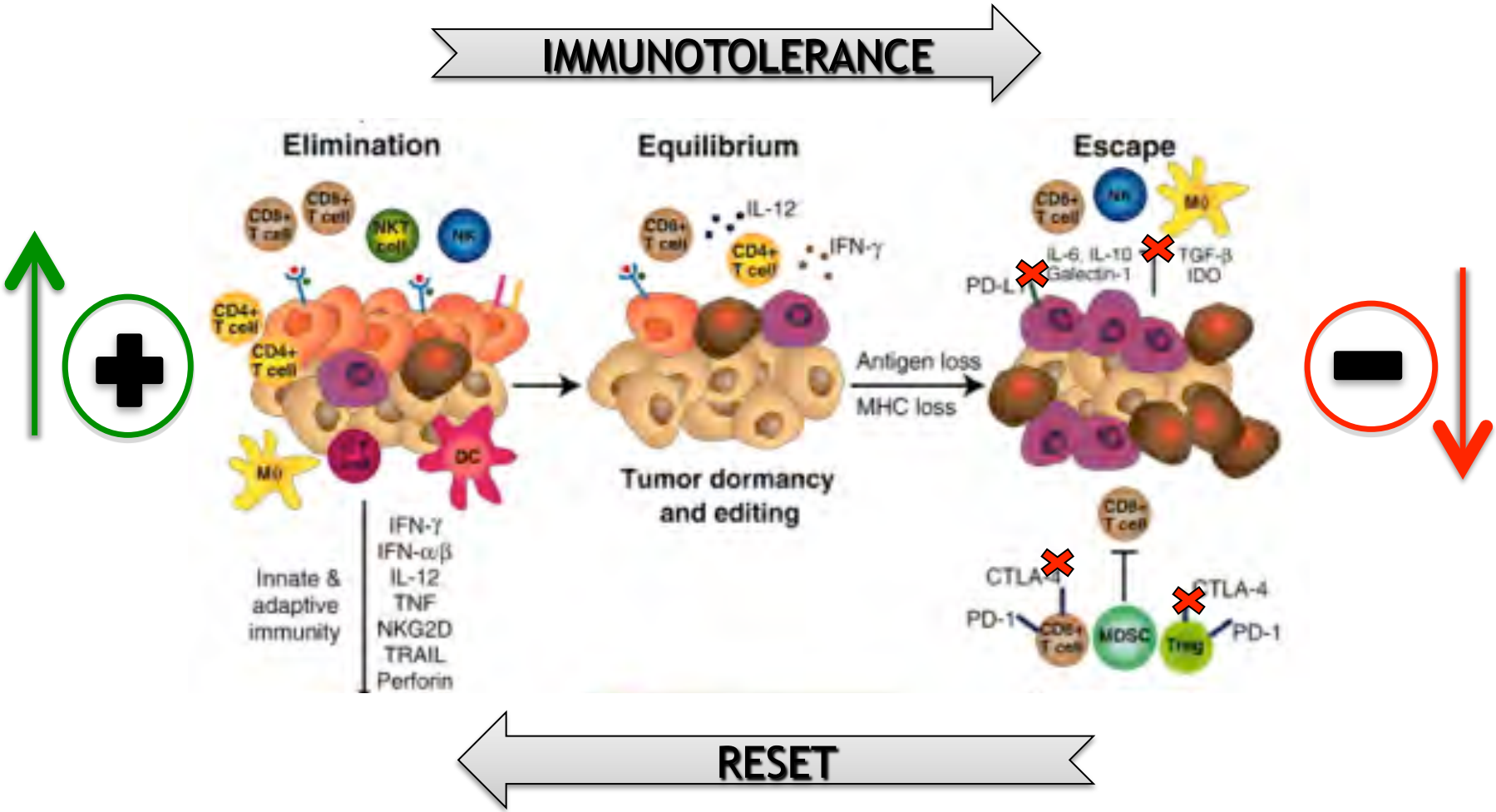
Cancer et immunité, les trois phases « E »



Vesely et al. Ann Rev Immunol 2011

Phase infra clinique | **Phase clinique**

Principe de l'immunothérapie anti-cancer

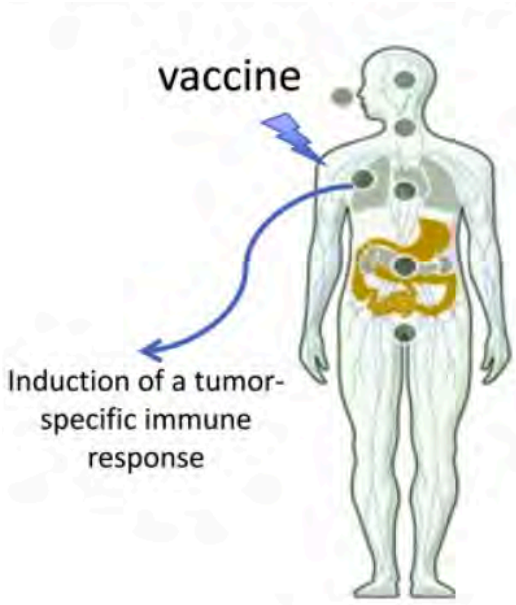


Adapted from Vesely et al. Ann Rev Immunol 2011

Principaux types d'immunothérapies

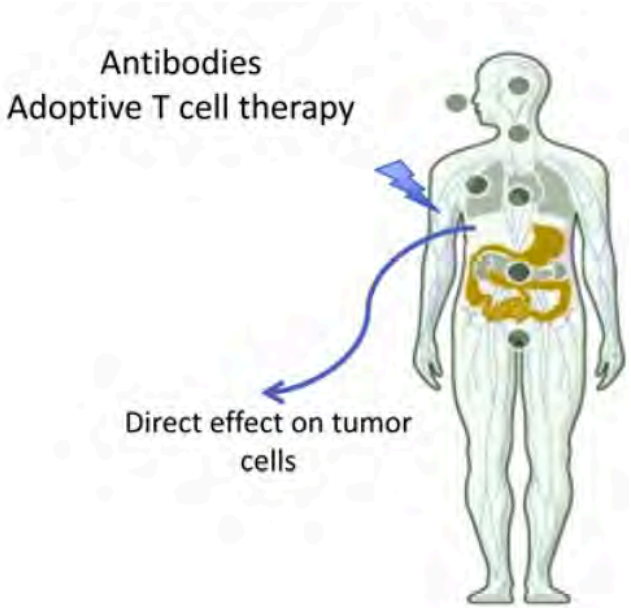
✧ L'immunothérapie consiste à utiliser le système immunitaire comme **cible** ou **médicament**.

Immunothérapie active



- **Induction d'une mémoire immunologique**
- **Effet indirect sur la masse tumorale**

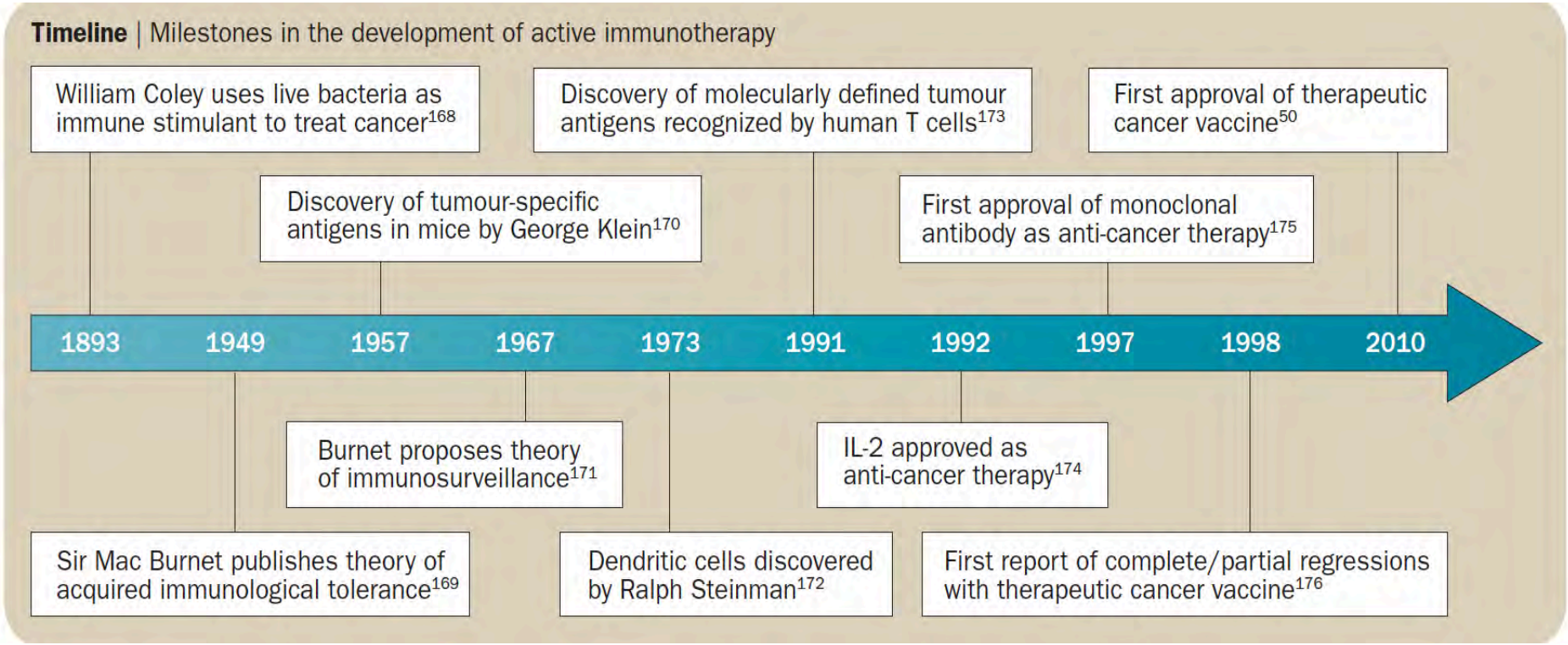
Immunothérapie passive



- **Action sur la masse tumorale**
- **Absence de mémoire immunologique**

De Pas et al. Crit Rev Onco Hem 2012

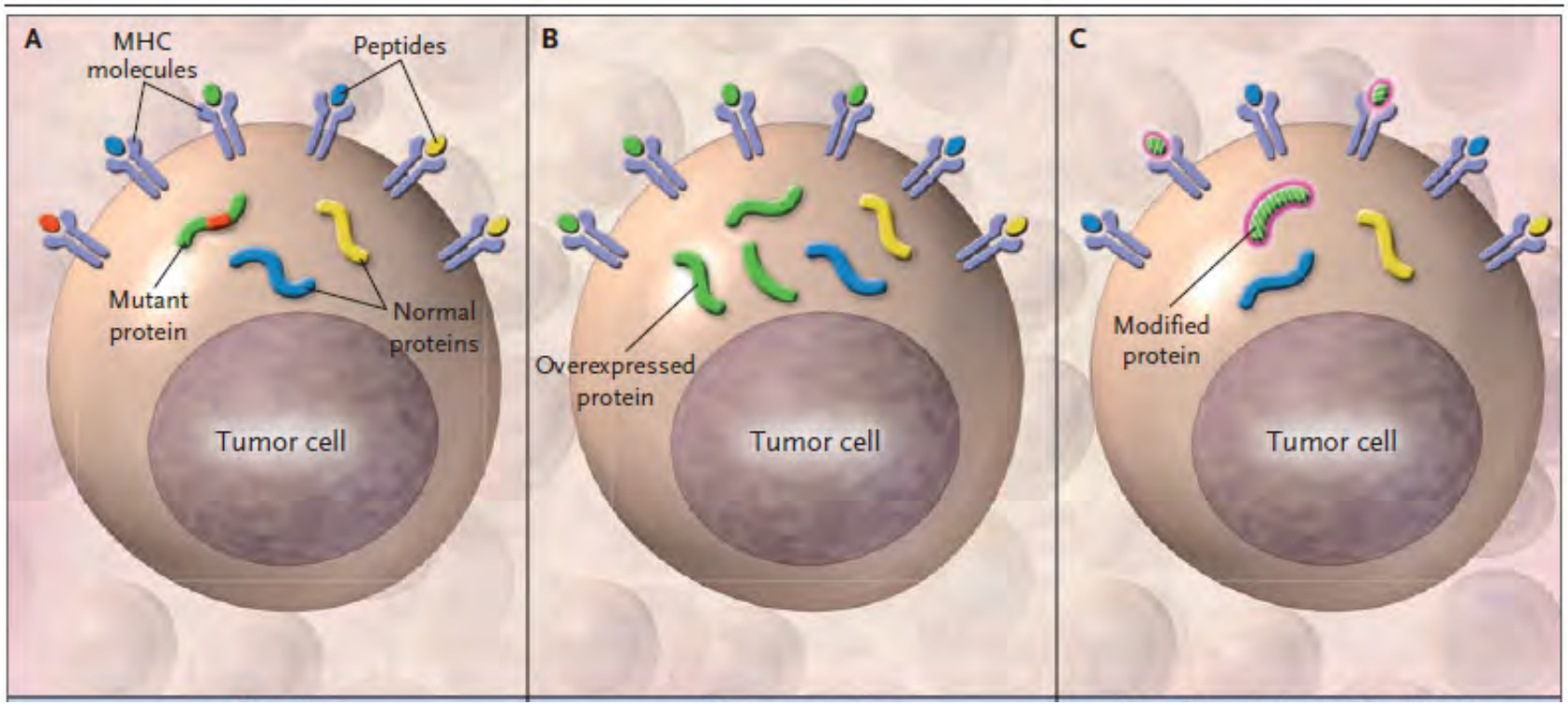
Les vaccins anti-cancers



Melero et al. Nat Rev Clin Oncol 2014

Les lymphocytes T reconnaissent des antigènes associés aux tumeurs

Plusieurs sources d'antigènes tumoraux



Ag mutés
N and K-Ras, mut-p53
BCR-ABL, mut-Jak2

Ag surexprimés
WT1, HER2-neu, p53
Survivine, TERT, CEA
Cyclin B1, PSA

Ag modifiés
hypoglyc Muc1

OJ. Finn N Engl J Med 2008

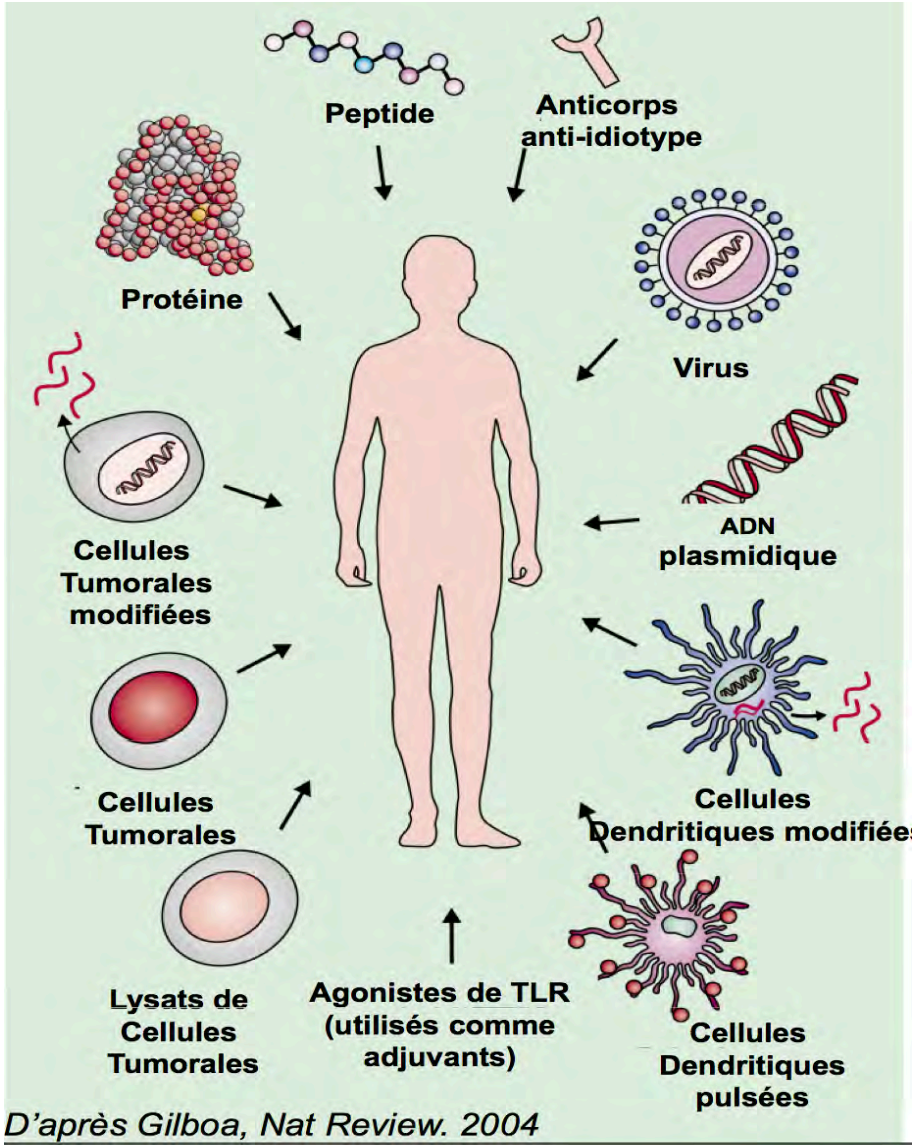
Les lymphocytes T reconnaissent des antigènes exprimés par les cellules tumorales

Plusieurs familles d'antigènes tumoraux

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

Tartour E et al. Med Sc 2011

Plusieurs types de vaccins et adjuvants



Vaccins thérapeutiques dans les cancers bronchiques

Vaccine target, composition and characteristics.

Target		Composition
Belagenpumatucel-l		Allogeneic tumor cells from 4 irradiated NSCLC cell lines
L-BLP25	**Tecemotide Essai START**	Tumor-associated MUC1
TG4010		Tumor-associated MUC1
EGF		Human recombinant EGF
MAGE-A3	**Essai MAGRIT**	Purified MAGE-A3 recombinant protein
Prame		Purified PRAME recombinant protein

De Pas et al. Crit Rev Onco Hem 2012

vaccins

Vaccins thérapeutiques dans les cancers bronchiques

Agent	Trial phase and disease stage	Number of patients	Results
Antigen specific immunotherapy			
MAGE-A3	Phase II, IB-II NSCLC	182	Trend in improved DFI (HR, 0.75; P=0.254)
MAGE-A3	Phase III, IA-IIIA NSCLC		Ongoing =Négatif
Liposomal BLP-25	Phase II, IIIB-IV NSCLC	171	No OS benefit (HR, 0.739; P=0.112). Patients with stage IIIB disease had 3-year survival of 49% with vaccination *vs.* 27% with BSC (P=0.070)
Liposomal BLP-25	Phase III, III NSCLC	1,239	No OS (HR, 0.88, P=0.123). Patients treated with concurrent CRT had prolonged OS (HR, 0.78; P=0.016) with vaccination
TG4010	Phase II, IIIB-IV NSCLC	148	6-month PFS 43.2% with vaccination *vs.* 35.1% with chemotherapy alone (P=0.307)
rHU-EGF	Phase II, IIB-IV NSCLC	80	OS was 11.7 months in GAR patients *vs.* 3.6 months in PAR patients
BEC2/BCG	Phase III, limited SCLC	515	OS was 16.4 *vs.* 14.3 months (P=0.28)
Tumor cell vaccines			
Belagenpumatucel-L	Phase II, II-IV NSCLC	75	OS of 14.5 months. OS in stage IIIB/IV patients with stable disease after chemotherapy was 44.4 months
Tergenpumatucel-L	Phase II, IV NSCLC	28	OS was 11.3 months

Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial

Critères d'inclusion principaux

- CBNPC stade III non opérable
- PS 0/1
- Absence de progression après RTCT (≥ 2 cycles à base de platine et ≥ 50 Gy)
- N = 1239

R 2:1

L-BLP25 806 µg lipopeptide SC hebdo x 8 puis toutes les 6 sem. (n = 829) → PD

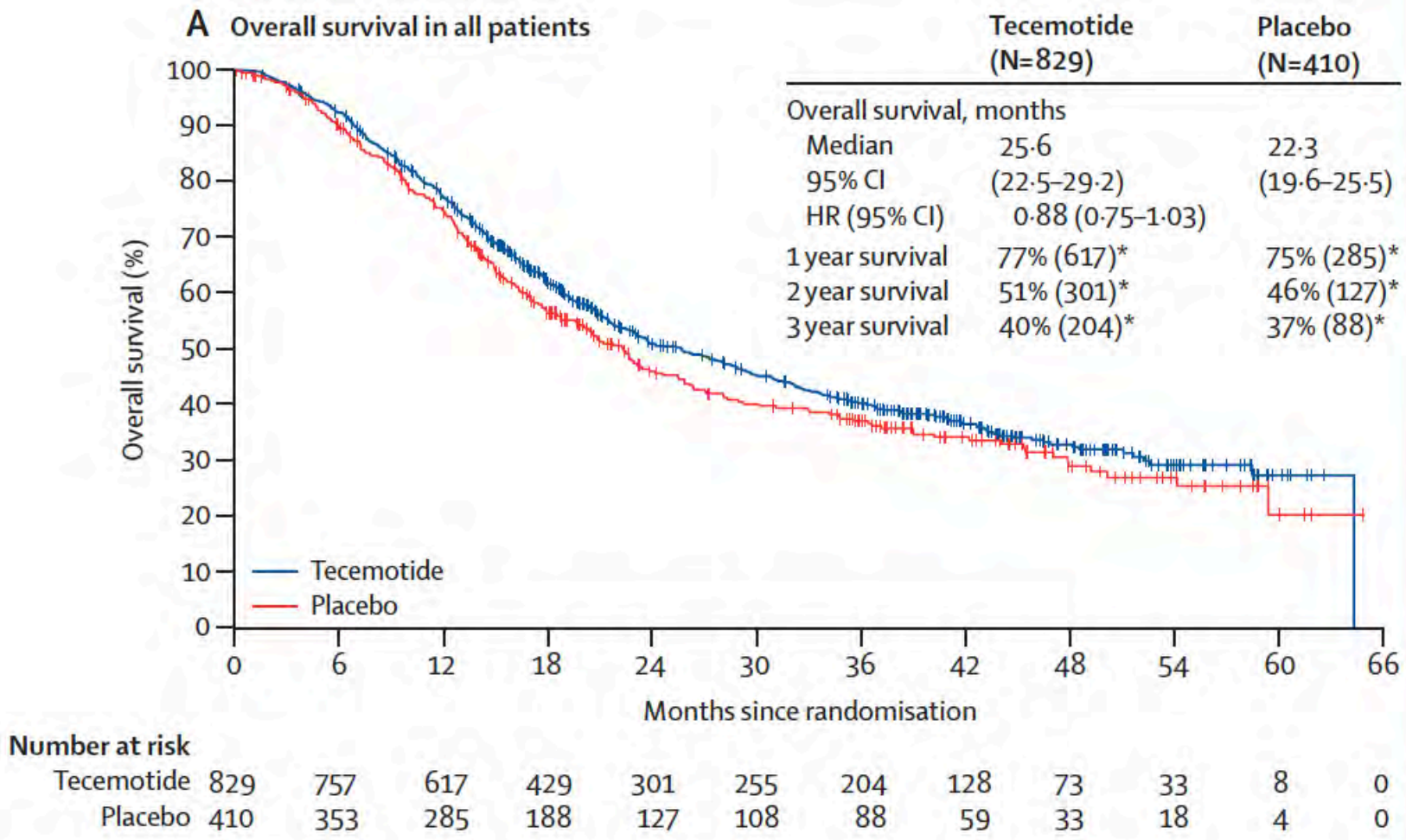
Placebo SC hebdo x8 puis toutes les 6 sem. (n = 410) → PD

Critère de jugement principal

•Survie globale

Butts et al. J Clin Oncol 31, 2013

Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial



	Tecemotide (N=829)	Placebo (N=410)
Overall survival, months		
Median	25·6	22·3
95% CI	(22·5–29·2)	(19·6–25·5)
HR (95% CI)	0·88 (0·75–1·03)	
1 year survival	77% (617)*	75% (285)*
2 year survival	51% (301)*	46% (127)*
3 year survival	40% (204)*	37% (88)*

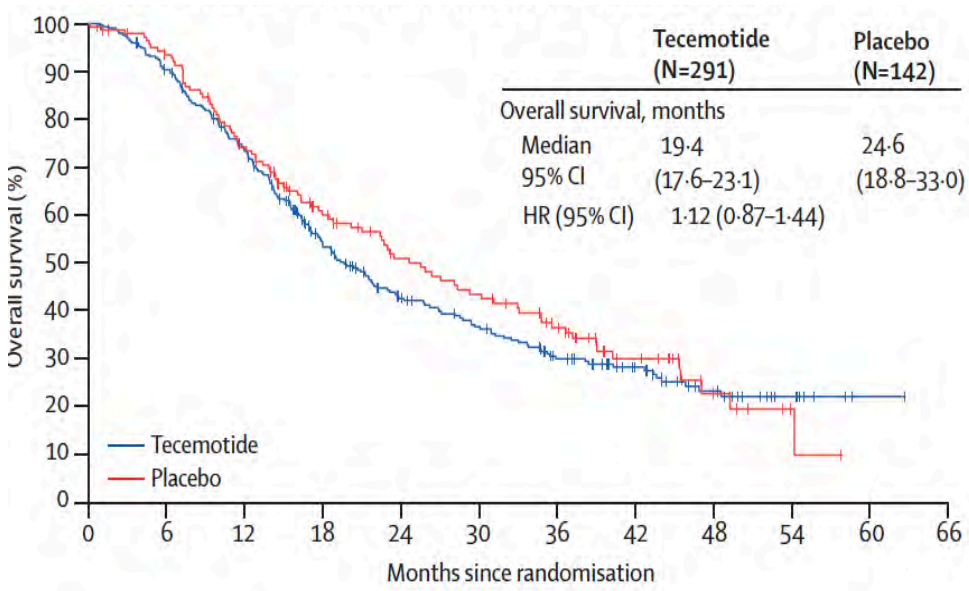
Number at risk

Tecemotide	829	757	617	429	301	255	204	128	73	33	8	0
Placebo	410	353	285	188	127	108	88	59	33	18	4	0

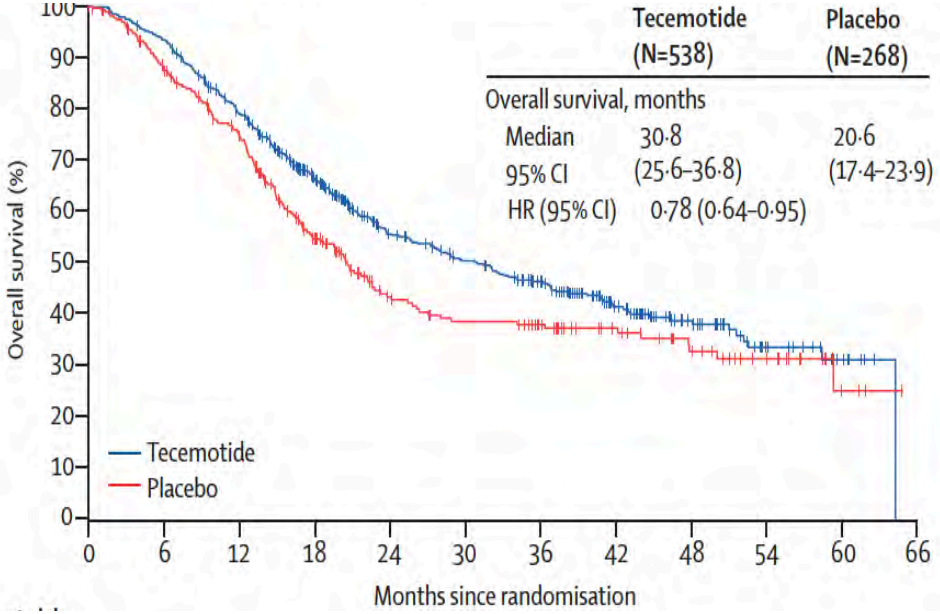
Butts et al. Lancet Oncol 2014

Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial

Inéfficace après RTCT séquentielle



Plus efficace après RTCT concomitante



Butts et al. Lancet Oncol 2014

Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial

Quelques enseignements de l'étude START

Positif	Negatif
• In residual disease after CT-RT • No severe adverse effects • Better immune response after concurrent chemotherapy?	• No selection of patients (MUC1 / immune status?) • The vaccine: – choice of the peptide – Liposomal vaccine – Immunogenicity the adjuvant

Paramètres pour améliorer l'efficacité des vaccins anti-cancers

- choix de l'antigène tumoral
- Inhibition des mécanismes immunosuppresseurs
- Qualité de la réponse T CD4 antitumorale
- Combinaison avec traitement conventionnel

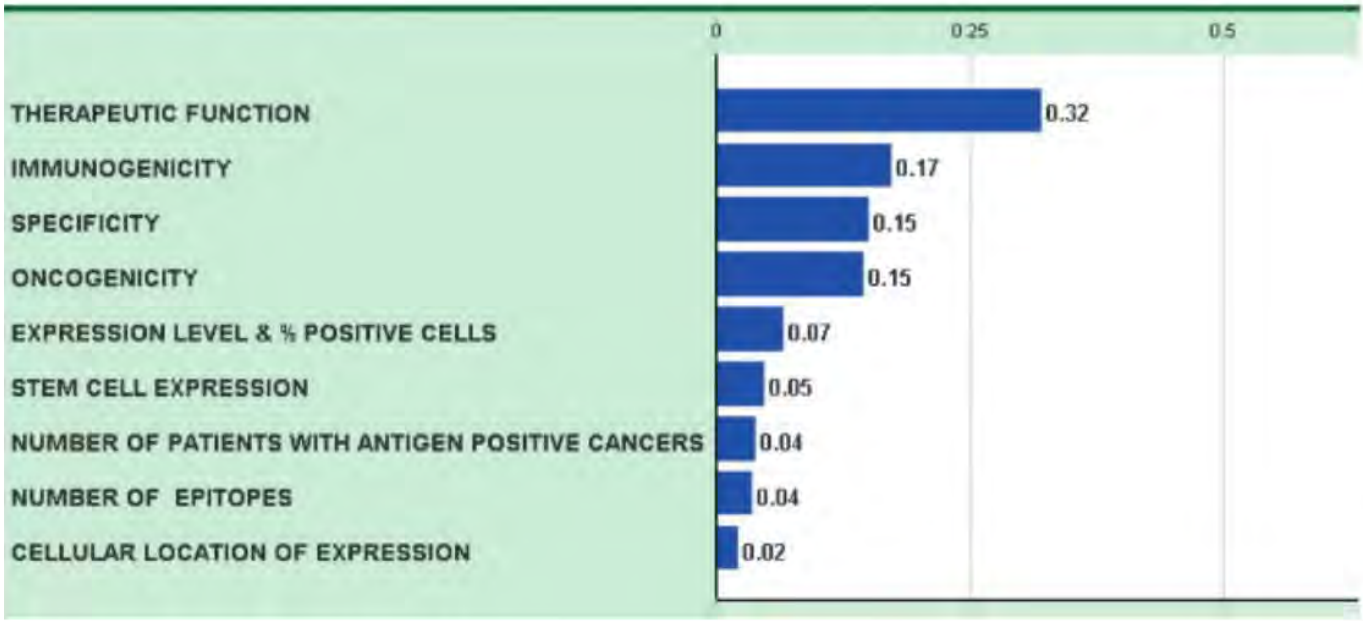
Perspectives

Quel antigène tumoral pour la vaccination ?

???
Differenciation
Overexpressed
Cancer germline
Viral
Mutated

The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research

Martin A. Cheever,[1] James P. Allison,[2] Andrea S. Ferris,[3] Olivera J. Finn,[4] Benjamin M. Hastings,[3] Toby T. Hecht,[5] Ira Mellman,[7] Sheila A. Prindiville,[6] Jaye L. Viner,[6] Louis M. Weiner,[8] and Lynn M. Matrisian[6]



Cheever et al. Clin Can Res 2009

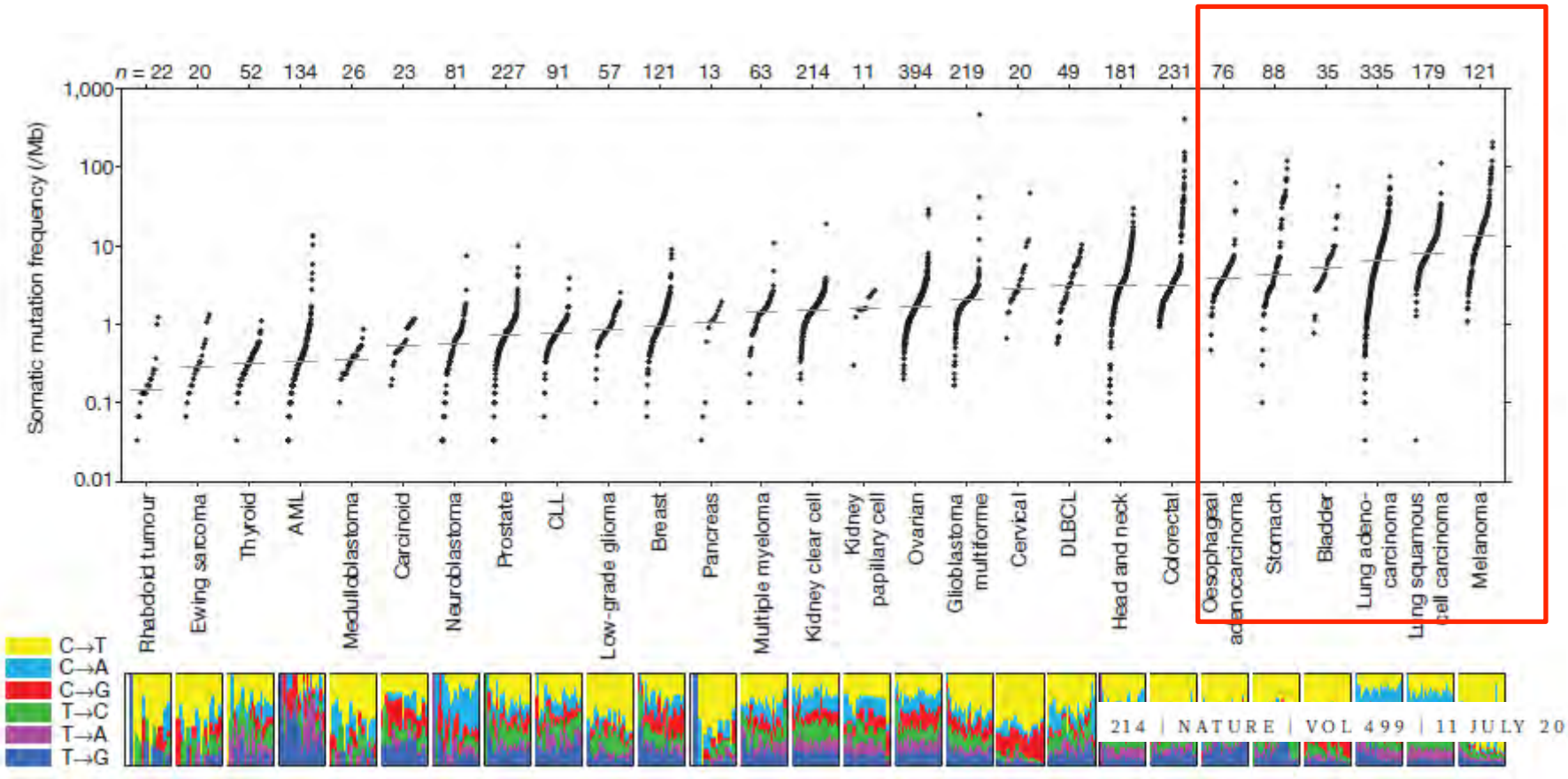
Perspectives

Quel antigène tumoral pour la vaccination ?

LETTER

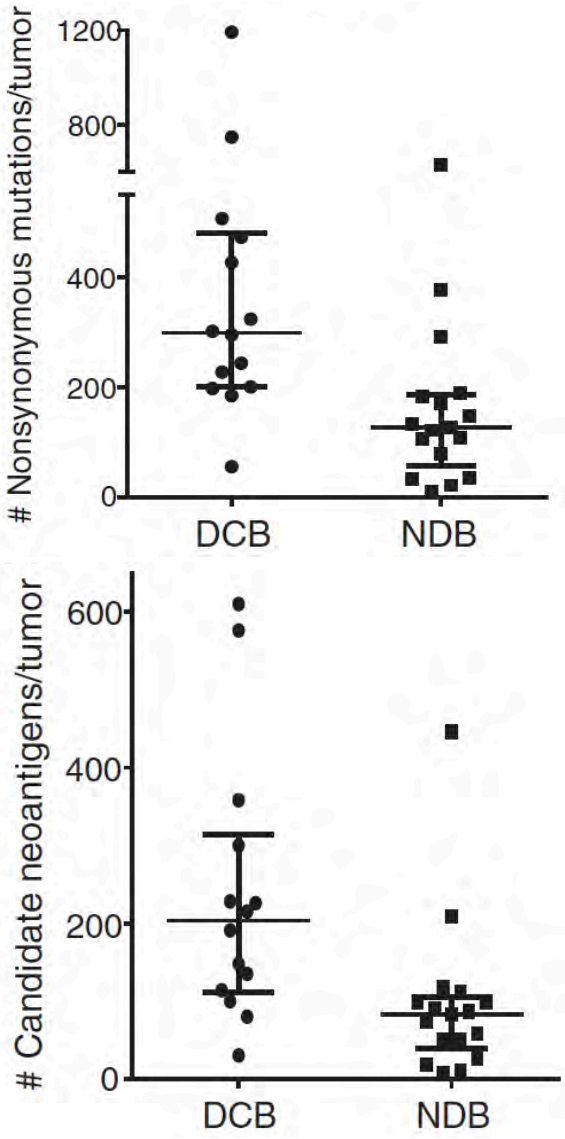
doi:10.1038/nature12213

Mutational heterogeneity in cancer and the search for new cancer-associated genes



Taux de mutation et efficacité des Immunothérapies

Rôle des néo-antigènes!!!

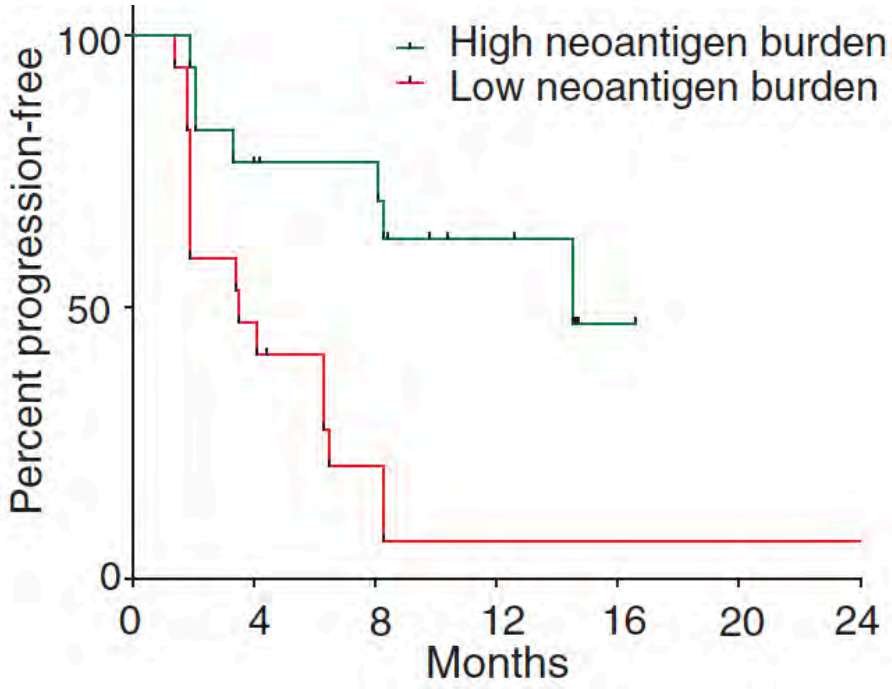


DCB= durable clinical benefit
NDB= no durable benefit

RESEARCH | REPORTS

CANCER IMMUNOLOGY

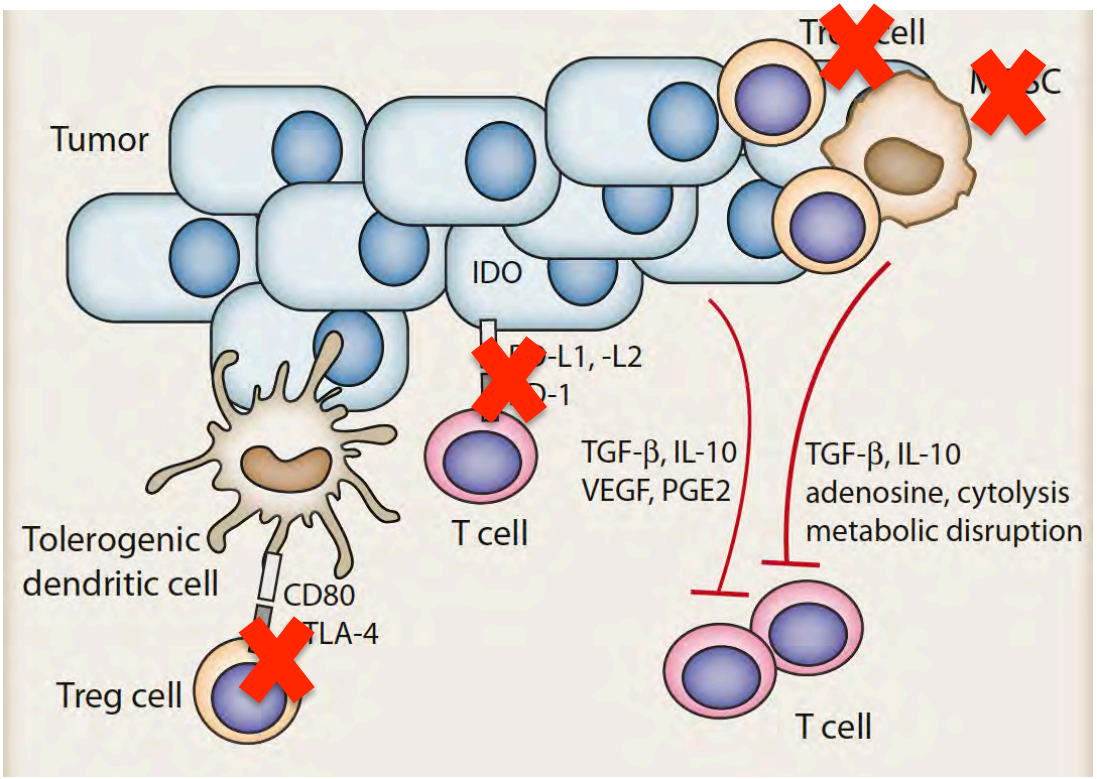
Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

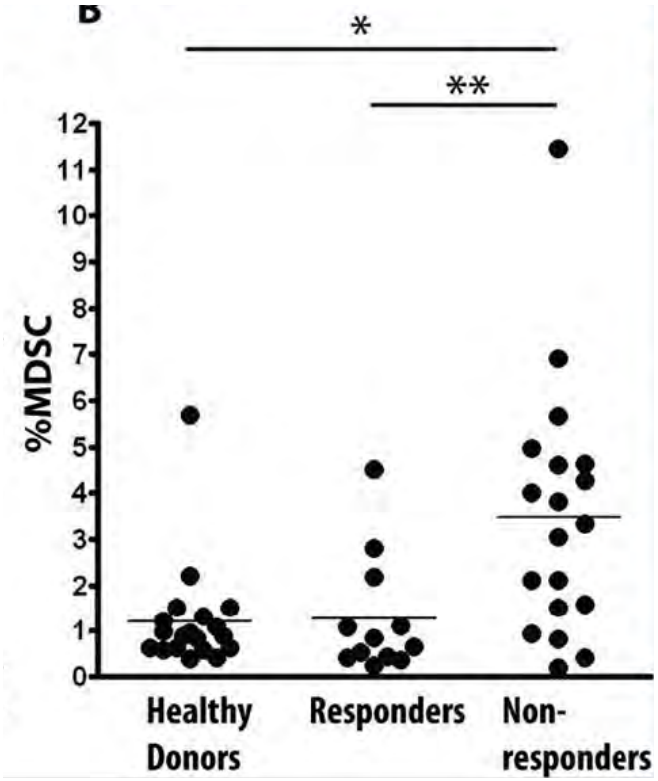


Rizvi N et al. Science 2015

Perspectives

Lutter contre les mécanismes d'immunosuppression

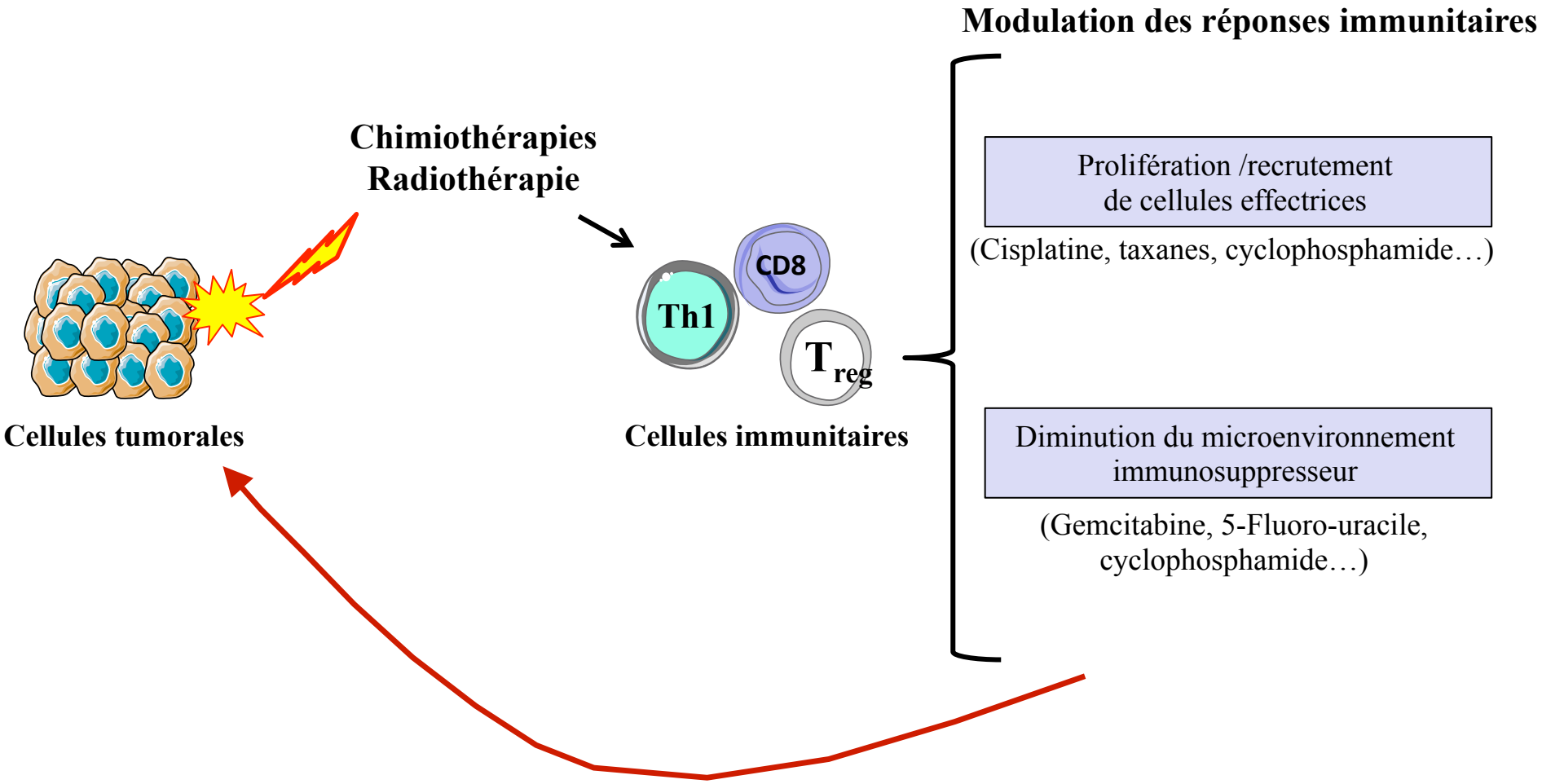




MDSC= cellules myéloïdes suppressives

Kimura et al. Cancer Prev Res 2013

Combinaison avec les traitements conventionnels



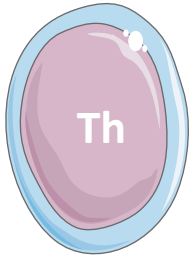
(Vincent et al., Can. Res., 2010; Galluzzi et al., Nat. Rev. Drug Discov., 2012; Demaria and Formenti, Front. Oncol., 2012 Formenti et al., J. Natl. Cancer Inst., 2013; Zitvogel et al., Immunity, 2013, de Biasi et al., Clin. Cancer Res., 2014)

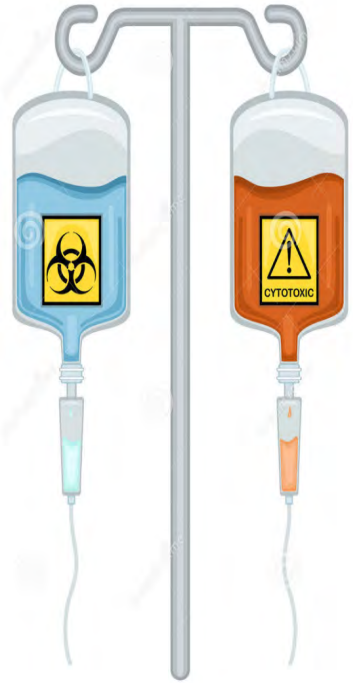
Perspectives

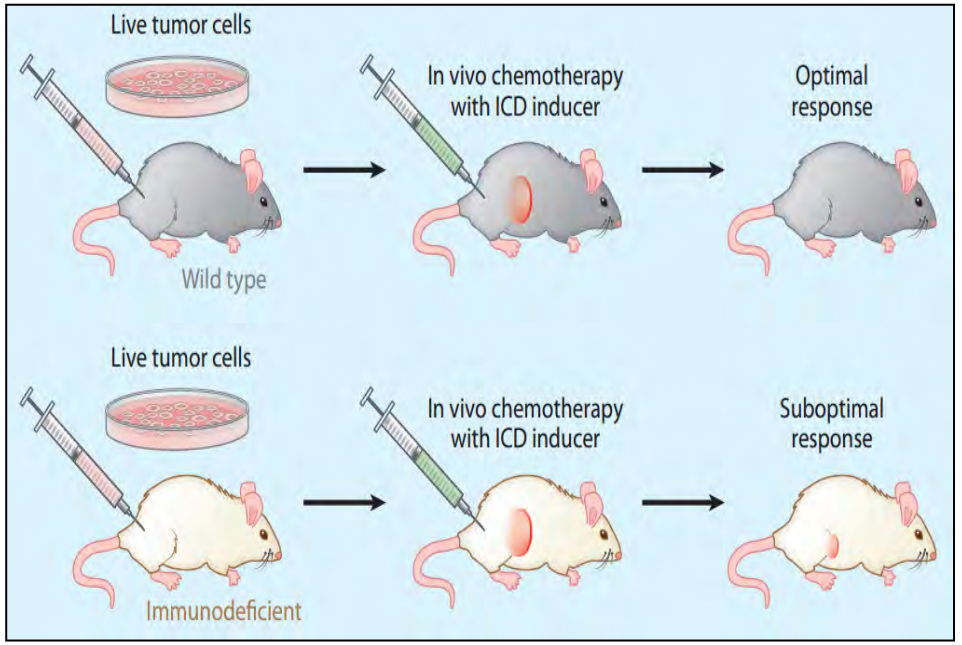
1 – AUGMENTER L'IMMUNOGENICITE TUMORALE

CHIMIOTHERAPIES

Oxaliplatine
Anthracycline
Radiothérapie







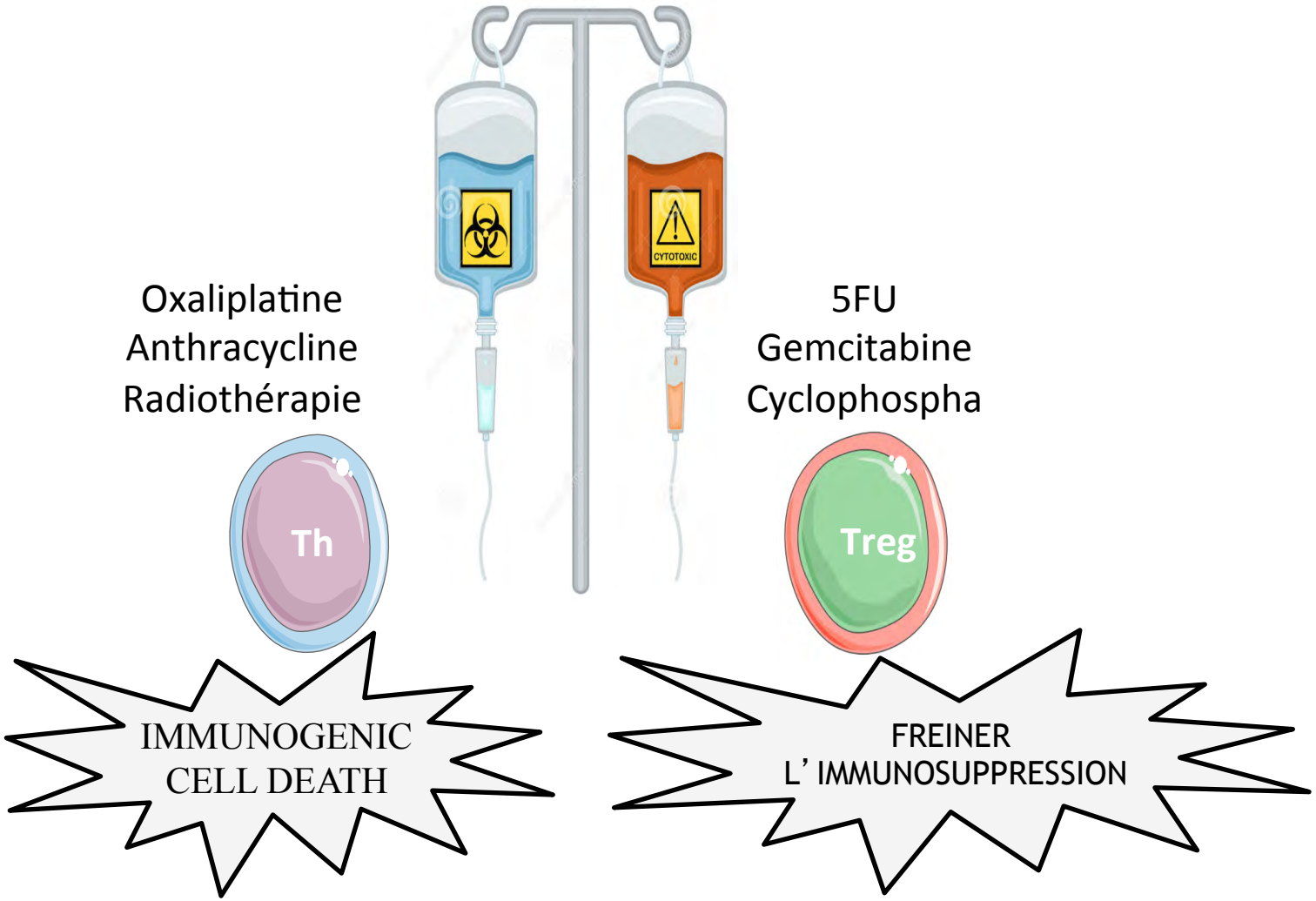
Kroemer et al. Nat med 2013

IMMUNOGENIC
CELL DEATH

Perspectives

2 – LIBERER LA REPONSE IMMUNITAIRE DU FREIN DE L'IMMUNOSUPPRESSION

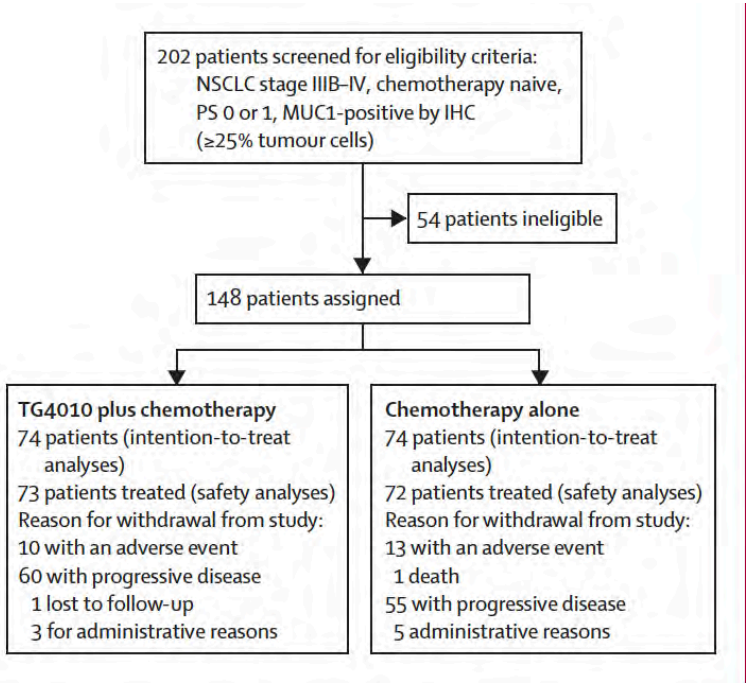
CHIMIOTHERAPIES

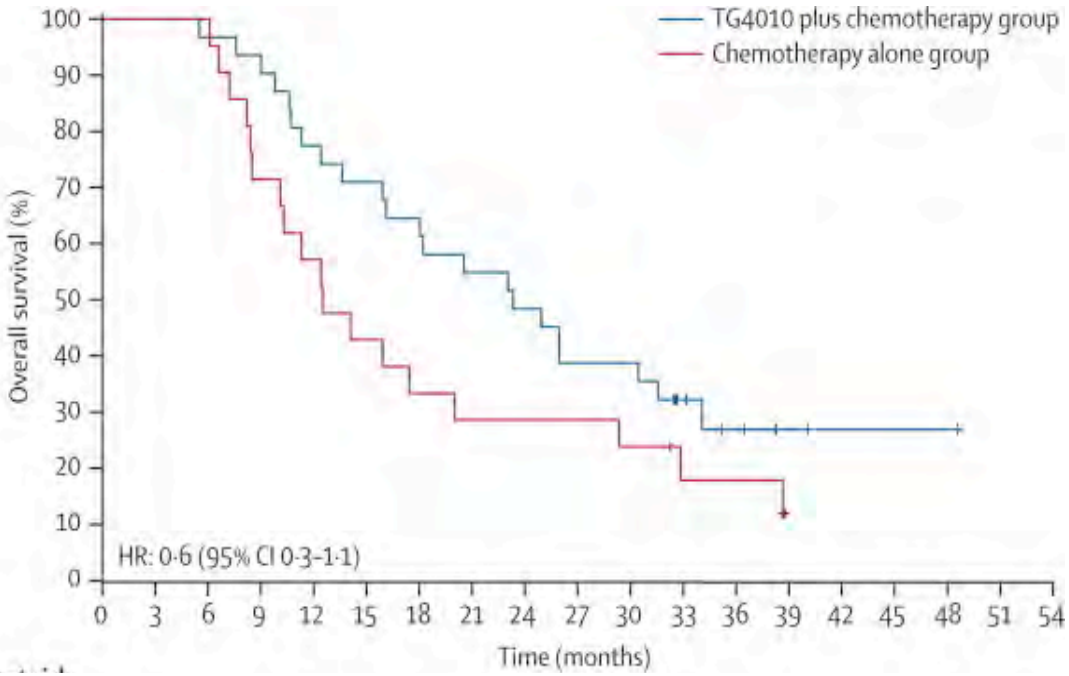


Perspectives

Therapeutic vaccination with TG4010 and first-line chemotherapy in advanced non-small-cell lung cancer: a controlled phase 2B trial

Elisabeth Quoix, Rodryg Ramlau, Virginie Westeel, Zsolt Papai, Anne Madroszyk, Alain Riviere, Piotr Koralewski, Jean-Luc Breton, Erich Stoelben, Denis Braun, Didier Debieuvre, Hervé Lena, Marc Buyse, Marie-Pierre Chenard, Bruce Acres, Gisèle Lacoste, Bérangère Bastien, Annette Tavernaro, Nadine Bizouarne, Jean-Yves Bonnefoy, Jean-Marc Limacher

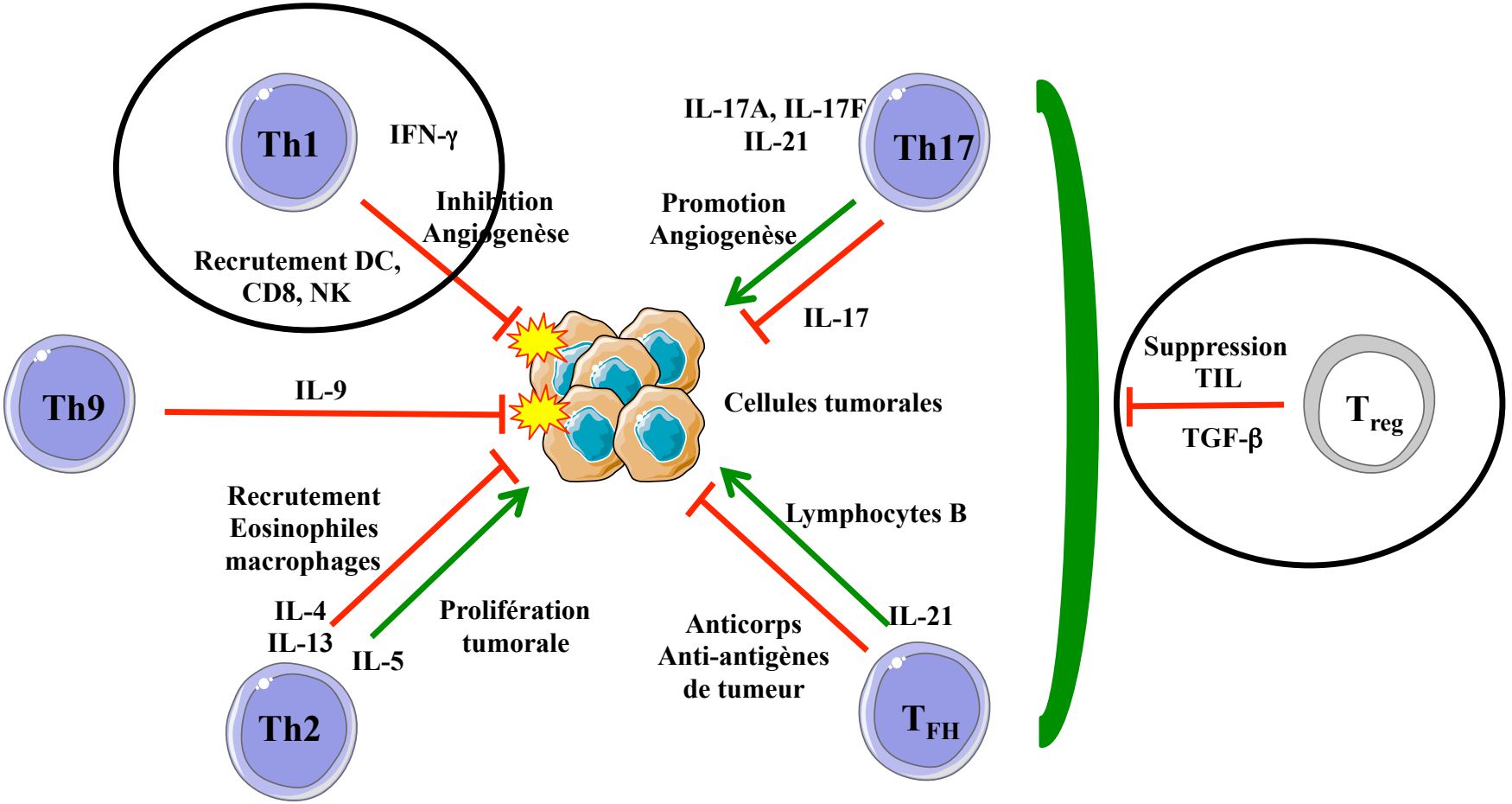




Quoix et al Lancel Oncol 2011

Perspectives

Stimulation d'une réponse T CD4 antitumorale adéquate et efficace

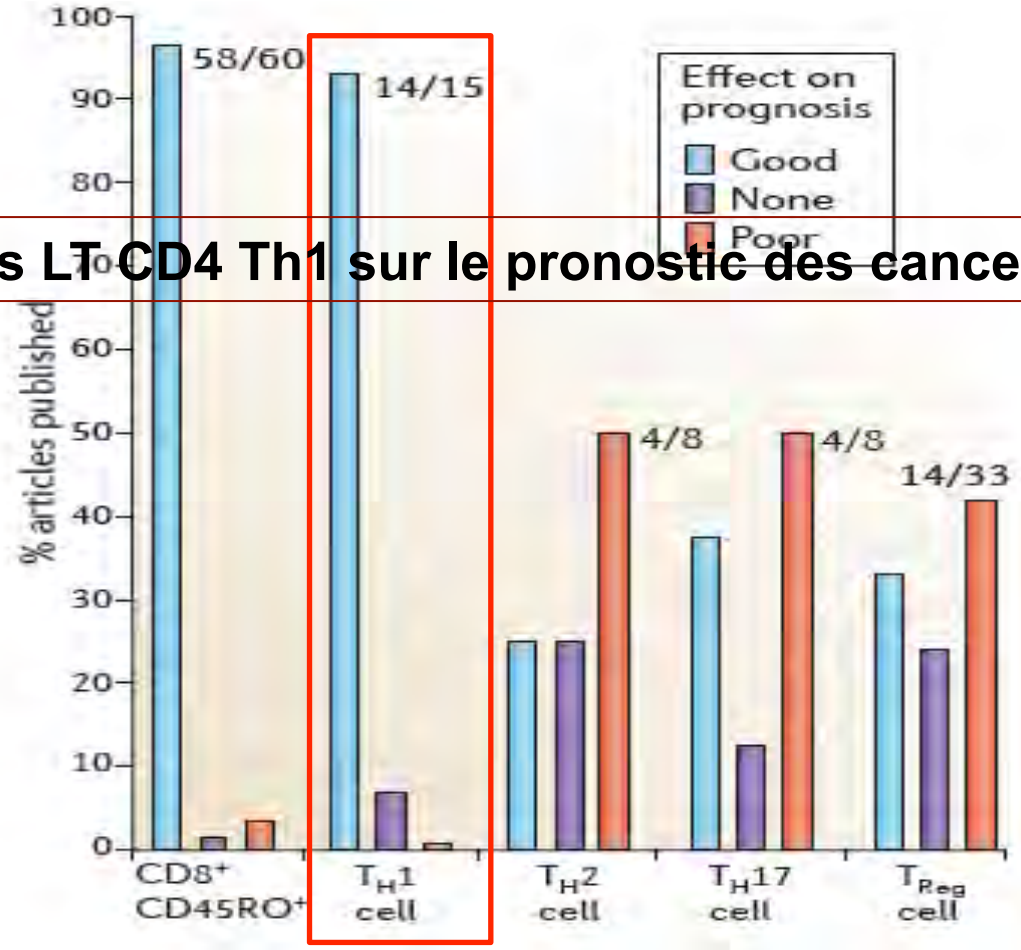


Rôle anti-tumoral des différentes populations de LT CD4 helper

(Kennedy and Celis, Immunol. Rev., 2008; O'Shea and Paul, Science, 2010; Kim and Cantor, Can. Immunol. Res., 201

Stimulation d'une réponse T CD4 antitumorale adéquate et efficace

Impact des LT CD4 Th1 sur le pronostic des cancers humains



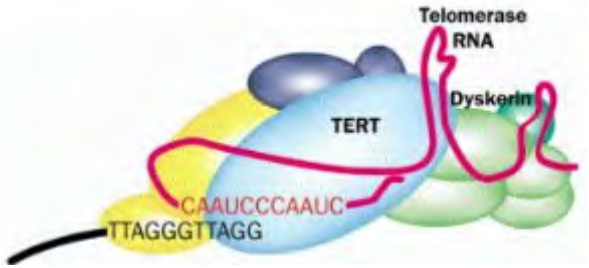
(Fridman et al., Nat. Rev. Cancer, 2012)

(Tosolini et al., Cancer Res., 2011)

Perspectives

UCPVax: vaccin dérivé de la télomérase capable de stimuler des réponses Th1 antitumorales

Localization	Type of cancer	TERT expression (%)
Lung	Non small cell carninoma	78
	Small cell carcinoma	100
Breast	*In situ* carcinoma	75
	intralobular carcinoma	88
Skin	Melanoma	86
	Basocellular carcinoma	95
Stomach	Carcinoma	85
Liver	Hepatocarcinoma	86
Pancreas	Carcinoma	95
Colon	Adenoma	45
	Carcinoma	89
Bladder	Carcinoma	92
Prostate	Adenocarcinoma	90
Testis		100
Womb	Cancer du col	100
Ovary	Carcinoma	91
Renal	Carcinoma	83
	Wilm's tumor	100
Nerve tissu	Neuroblastoma	94
	Meningiome malin	100
	Glioblastoma	75
	Retinoblastoma	50
	Oligodendroglioma	100
Hematological	Myeloma	100
	Lymphoma	86-100
	Chronic lymphoid leukemia	71-100
	Chronic lymphoid leukemia	57
	Acute leukemia	75-80
Thyroid		81



-Détection chez de **Th1 anti-TERT** chez des patients atteints de **cancers bronchiques**.

- Correlation avec une **meilleure survie** chez patients répondeurs après **chimiothérapie**.

Peptides UCP: vaccin anti-cancer ?

(Fan et al., Cancer Res., 2005; Martinez et Blasco, Nat. Rev. Cancer, 2011; Godet et al., Clin. Cancer Res., 2012; Godet et al., Oncoimmunology, 2012)

Perspectives

UCPVax: vaccin dérivé de la télomérase capable de stimuler des réponses Th1 antitumorales

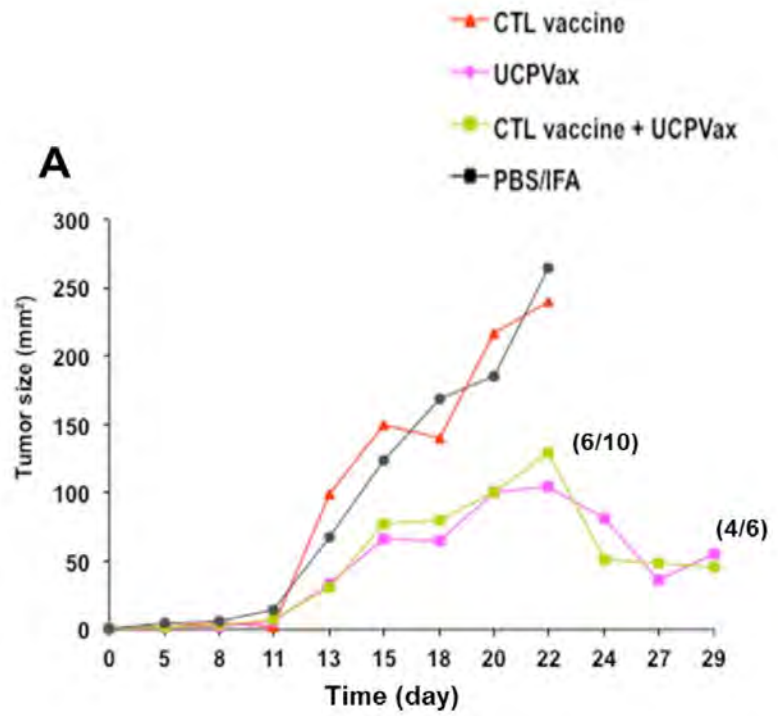
Tg A2DR1

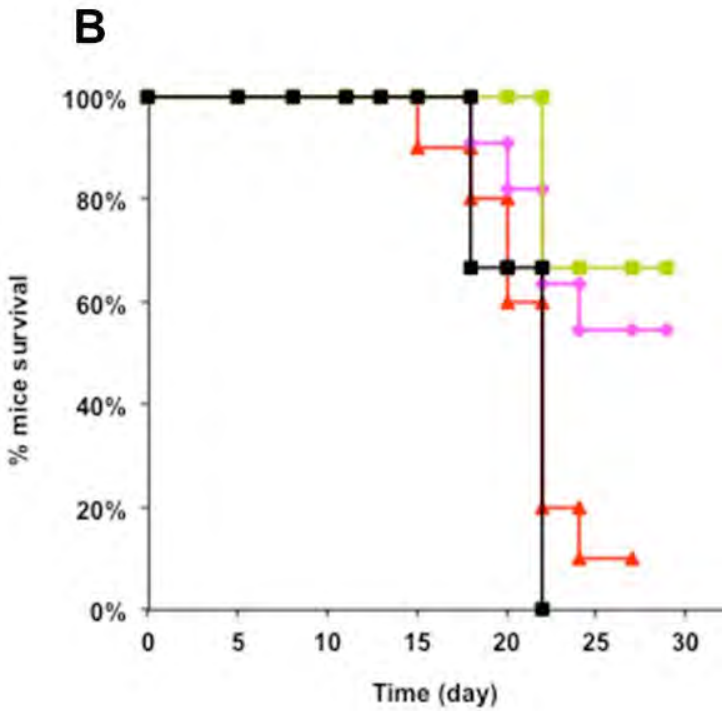
J0 — Tumor

J5 — vaccine

J16 — boost

- Réponse tumorale
- Survie





Dosset M et al. Clin Cancer Res. 2012, Dosset et al Onimmunol 2013, Adotévi et al. Hum Vaccin Immunother 2013

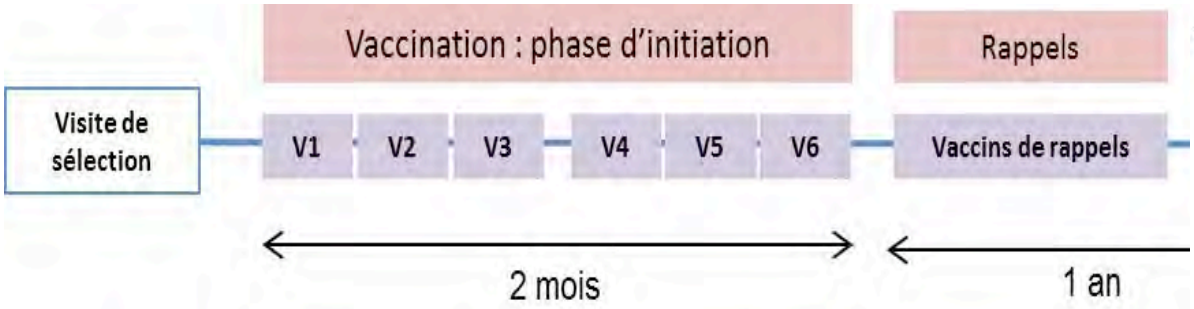
UCPVax: vaccin dérivé de la télomérase capable de stimuler des réponses Th1 antitumorales

Telomerase-derived T helper 1 inducer peptides in metastatic Non Small Cell Lung Cancer: a phase I/II study (PHRC-K13-063)

UCPVax plus Montanide ISA 51

Phase I: **Escalade dose** : 0,25 mg; 0,5mg; 1mg

Phase II: **Efficacité/dose**



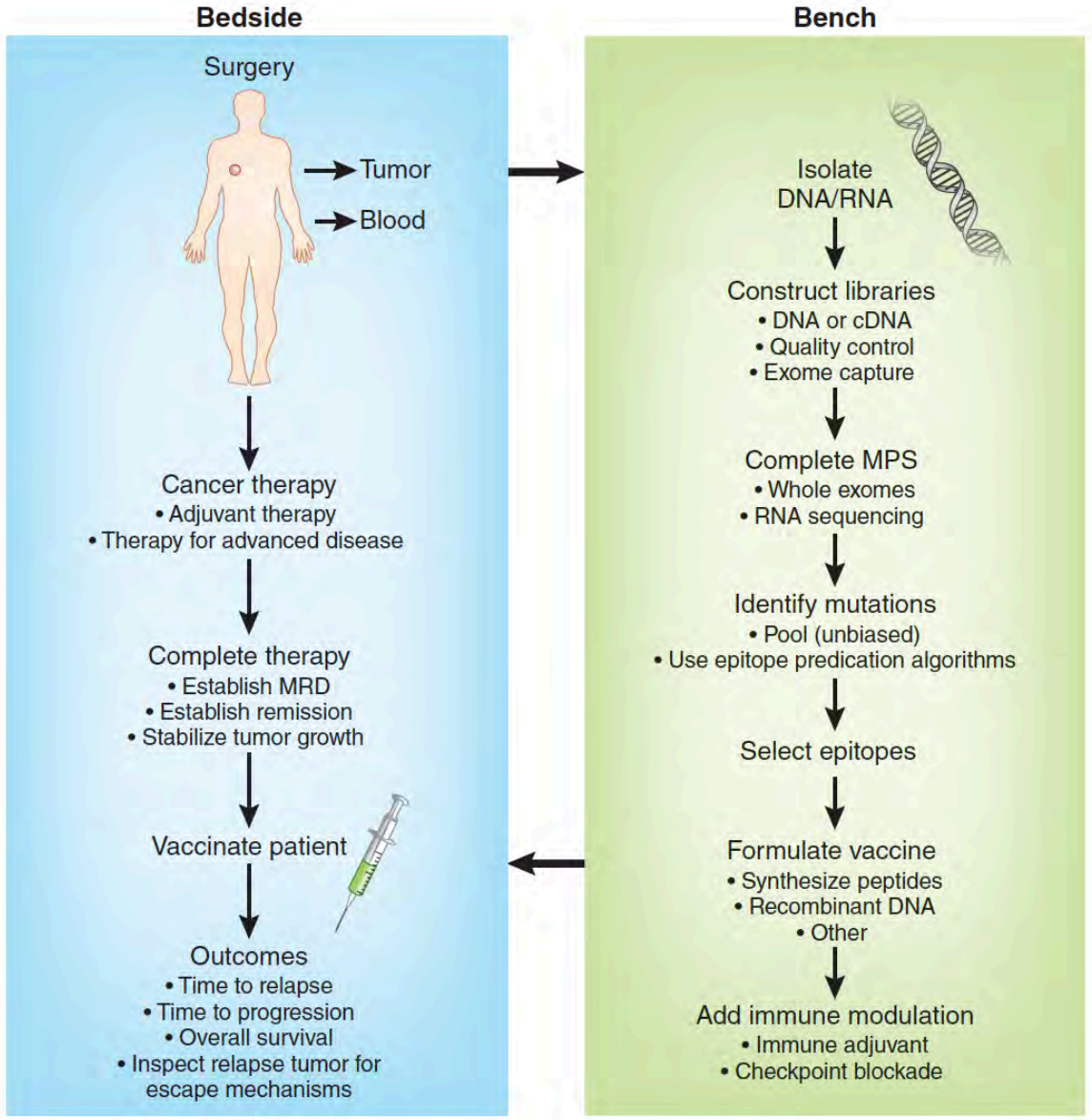
Nbre patients attendus : 54

Début des inclusions janvier 2016 !

INSTITUT NATIONAL DU CANCER

Perspectives

Vaccins personnalisés, l'avenir…



Vonderheide Nat Med 2013

Merci pour votre attention

UMR1098 INSERM, Besançon

Morganna Freeman-Keller et al Pharmacol & Therapeutic 2015, De Pas et al. Critical Reviews in Oncology/Hematology 2012, Melero etal Nat Rev Clin Oncol 2014, Rossana Ruiz et al. Curr Oncol Rep 2014

CHRU Besançon
centre hospitalier régional universitaire

CIC BIOTHÉRAPIE BESANÇON

Inserm
Institut national de la santé et de la recherche médicale

EFS

Bench
CANCÉROPÔLE DU GRAND-EST
LipSTIC Clinic
Laboratoire d'excellence

UNIVERSITÉ BOURGOGNE FRANCHE-COMTÉ

CONTRE LE CANCER
LA LIGUE
101 comités