

TRAITEMENTS CIBLANT LE MICROENVIRONNEMENT IMMUNITAIRE

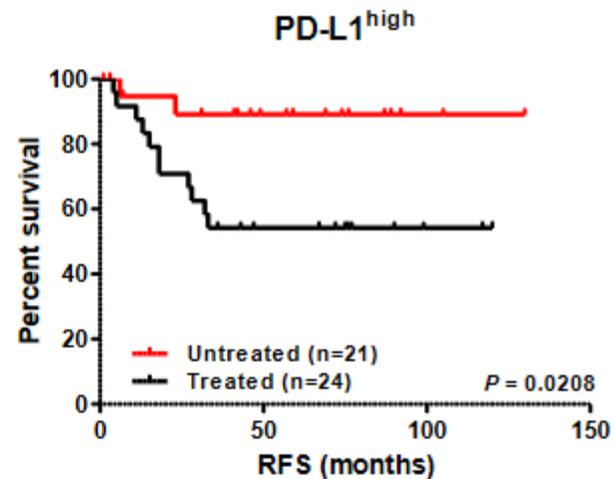
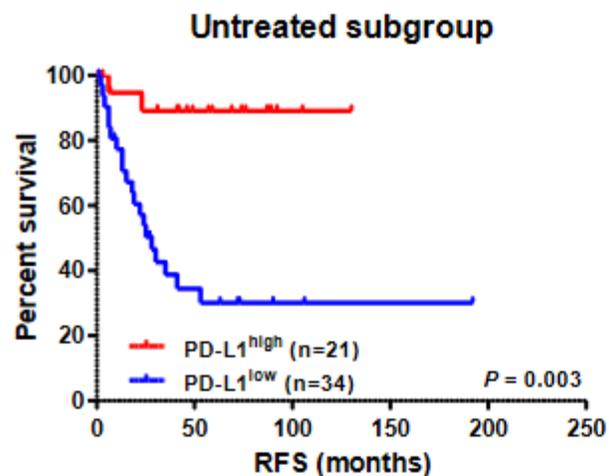
Chimiothérapie

TIME prédictif de l'efficacité de la chimiothérapie cytotoxique dans le cancer colorectal

- ▶ Chimiothérapie: **augmentation des réponses immunitaires**
 - ▶ directement (IFN γ)
 - ▶ inhibition de facteurs immunosuppresseurs
 - ▶ augmentation antigénicité/immunogénicité tumorale
- ▶ *Oxaliplatine*: active mort cellulaire immunogénique via DC et Th1
- ▶ *Irinitécan* : augmentation PDL1
- ▶ *FOLFOX* : augmentation infiltrat en CD8+/CD3+ et NK
- ▶ *5FU en néoadjuvant* : augmentation IS sur pièce opératoire rectale

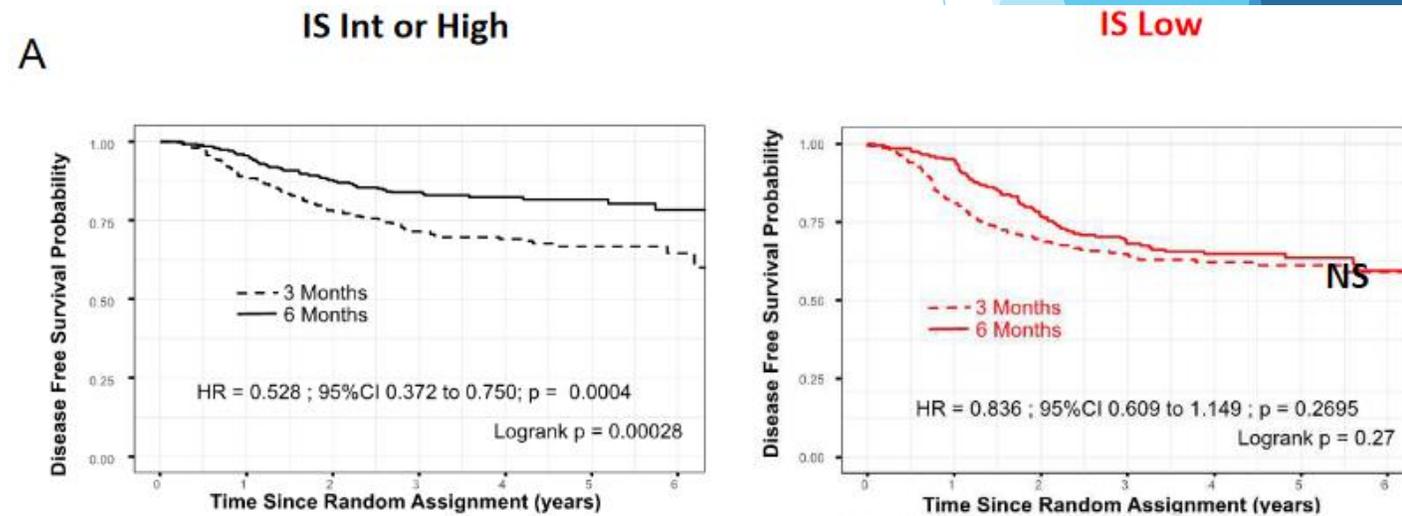
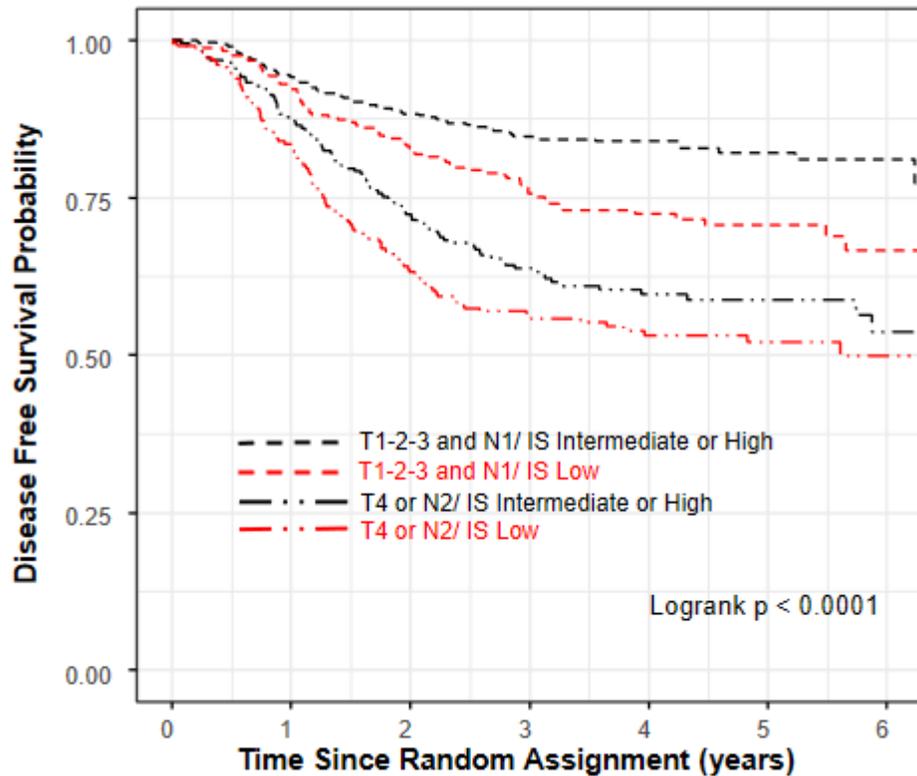
TIME prédictif de l'efficacité de la chimiothérapie cytotoxique dans le cancer colorectal - PDL1

- ▶ Association entre expression PDL1 et statut MSI dans stages précoces CRC
- ▶ Association entre taux de PDL1 et survie
- ▶ PD-L1^{high}/MSI/immune high stage II/III CRC ne doivent pas recevoir de la chimiothérapie standard

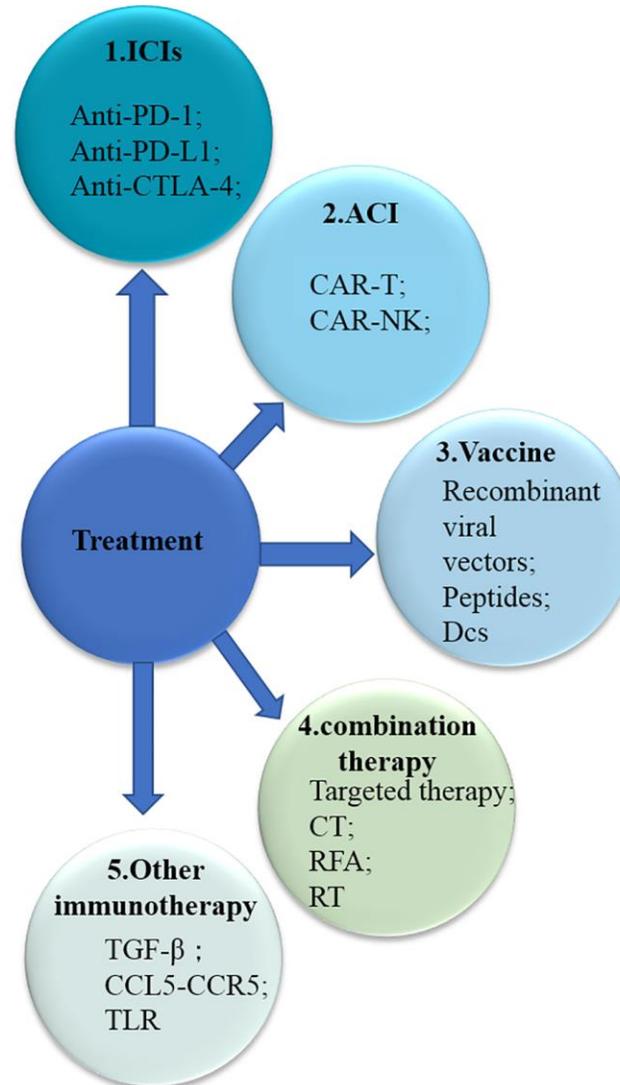
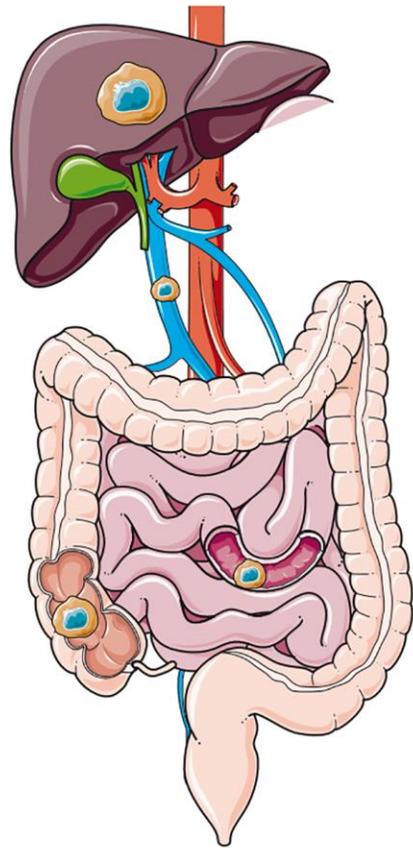


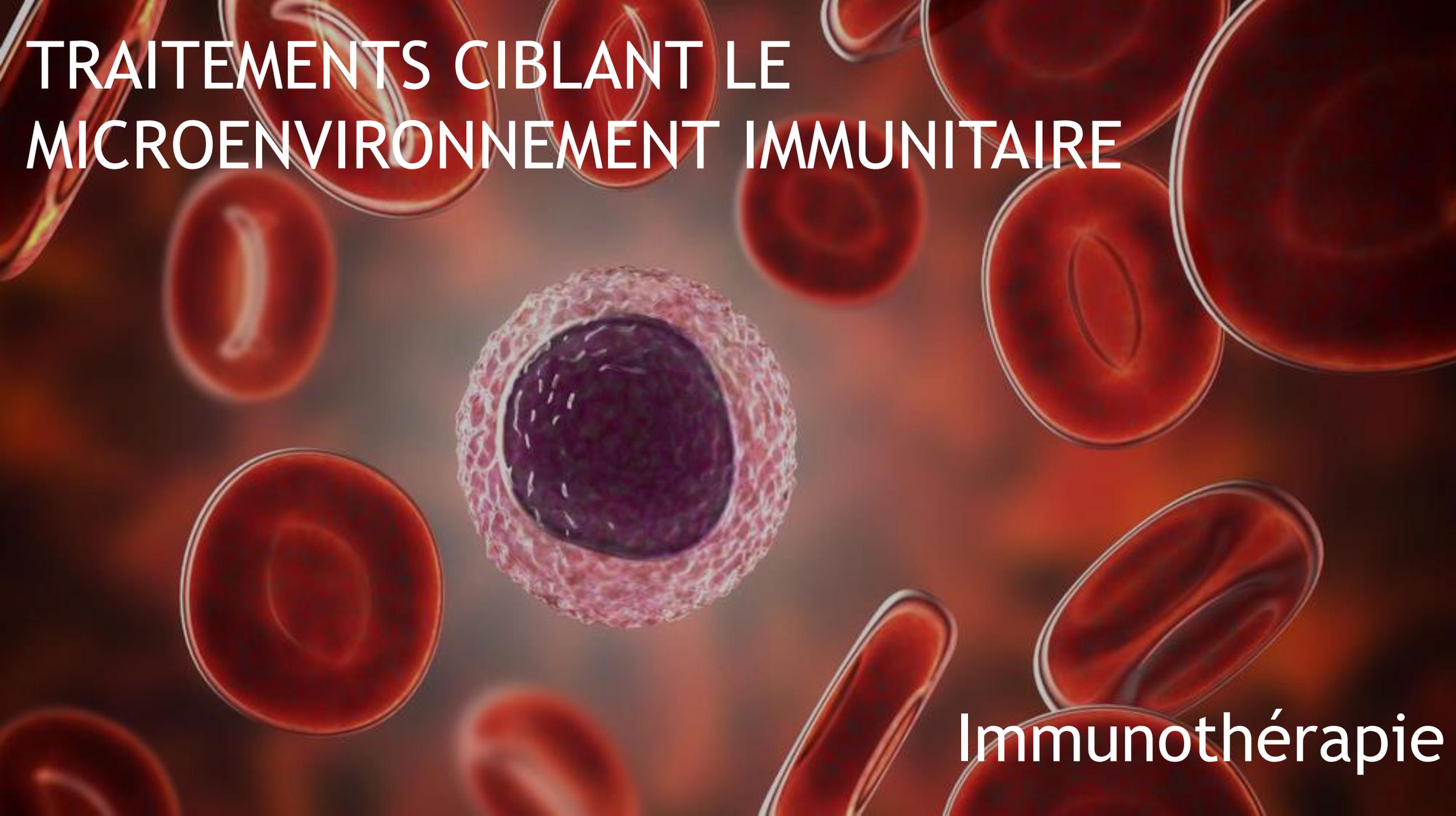
TIME prédictif de l'efficacité de la chimiothérapie cytotoxique dans le cancer colorectal - IS

- ▶ Sur la base des patients inclus dans IDEA



TRAITEMENTS CIBLANT LE MICROENVIRONNEMENT IMMUNITAIRE

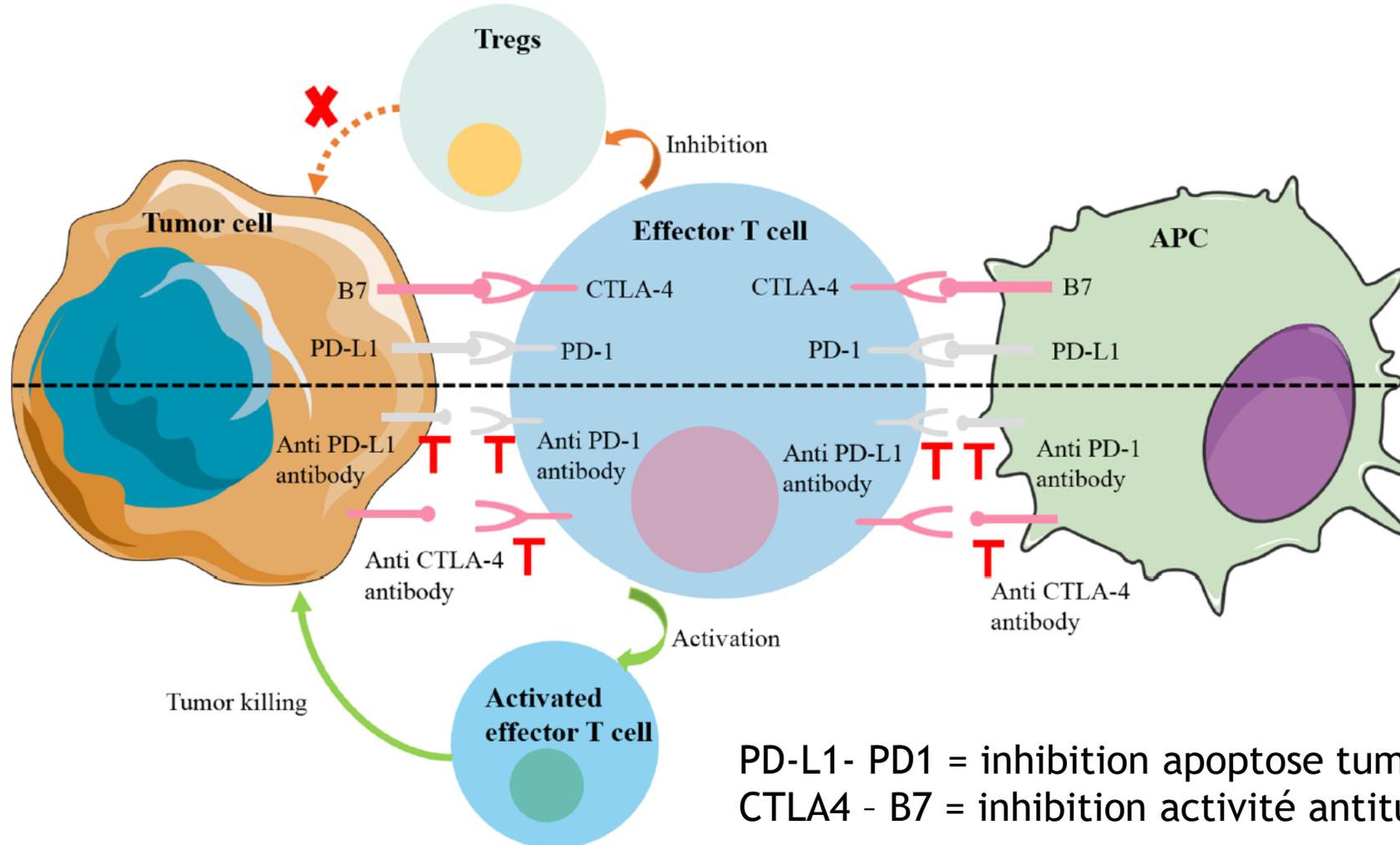




TRAITEMENTS CIBLANT LE MICROENVIRONNEMENT IMMUNITAIRE

Immunothérapie

Rappel



PD-L1- PD1 = inhibition apoptose tumorale
CTLA4 - B7 = inhibition activité antitumorale LT via APC

Immunothérapie - Efficacité

▶ Efficacité immunothérapie :

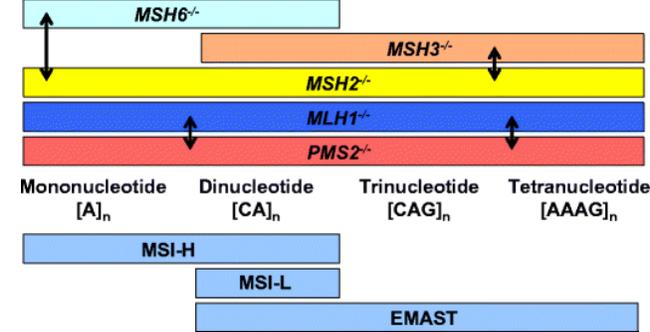
- ▶ Charge mutationnelle
- ▶ Niveau d'expression de PD-L1
- ▶ Infiltration preexistence d'une infiltration de cellules T (CD8+/3+)



Historiquement

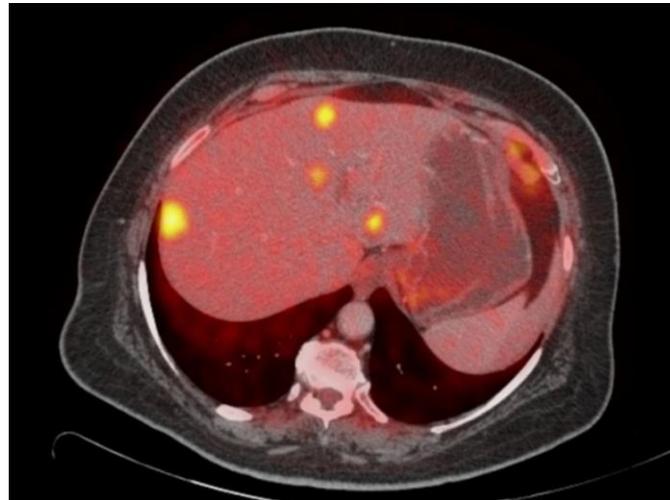
- ▶ 2009 : Sur 39 patients traité par Nivolumab = 1 seul répondeur
- ▶ 2010: 2% répondeurs au Tremelimumab chez mCRC
- ▶ 2012: 0% de répondeurs au Nivolumab dans mCRC

- ▶ **Pas effet de l'immunothérapie en monothérapie dans une population non sélectionnée en terme de statut MMR**



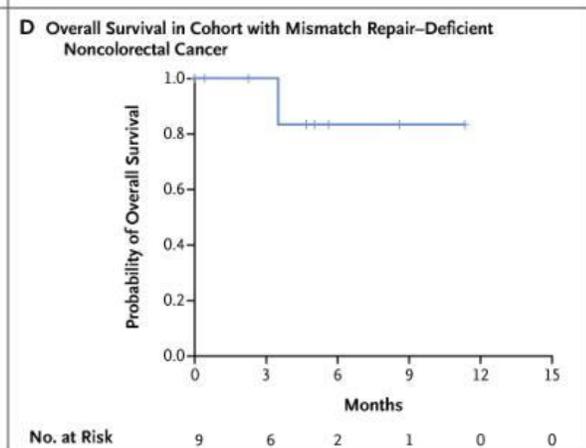
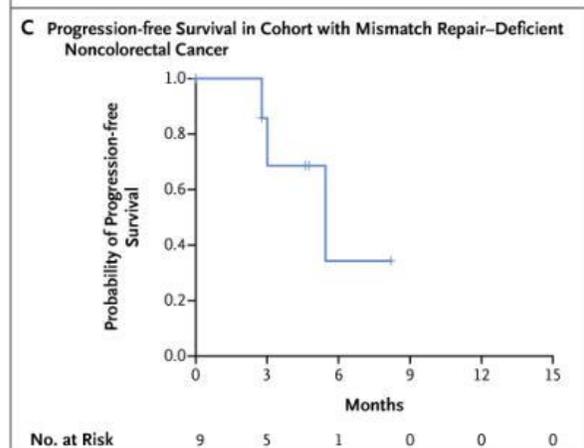
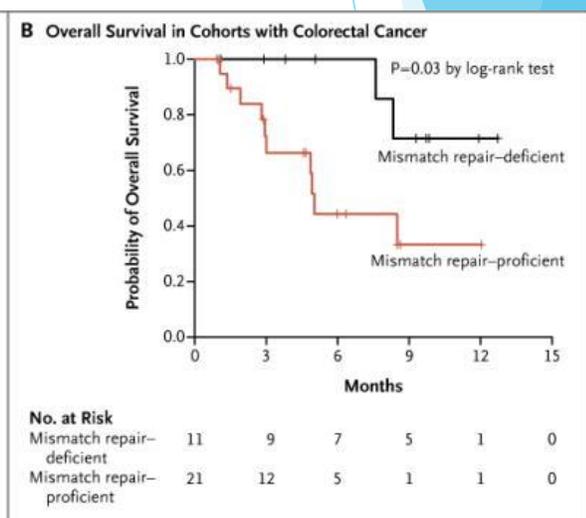
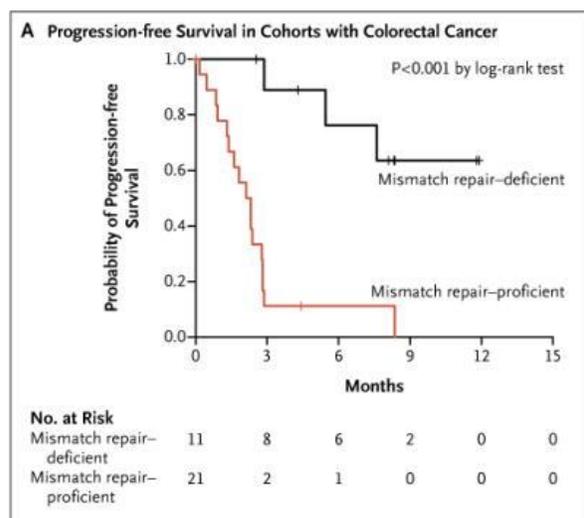
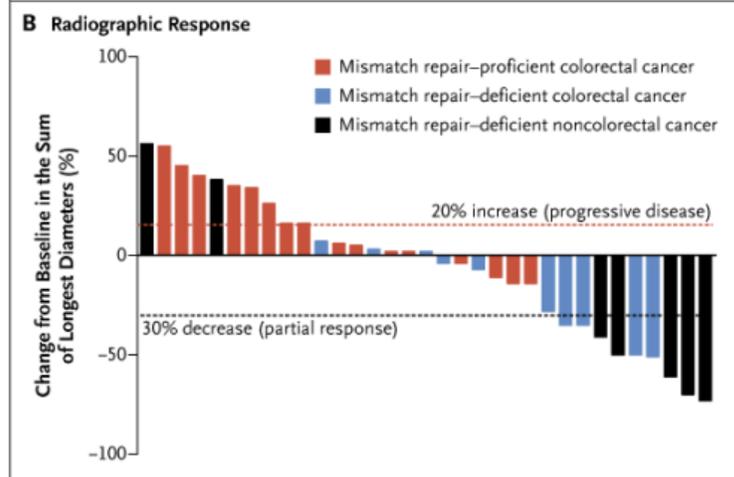
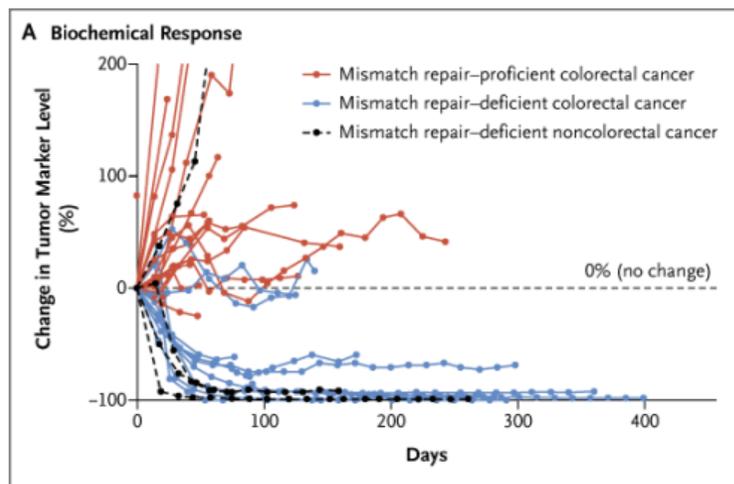
Statut MMR

- ▶ mCRC : 7% de patients MSI
- ▶ Pas de différences de statut entre le tumeur primitive et la métastase



PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

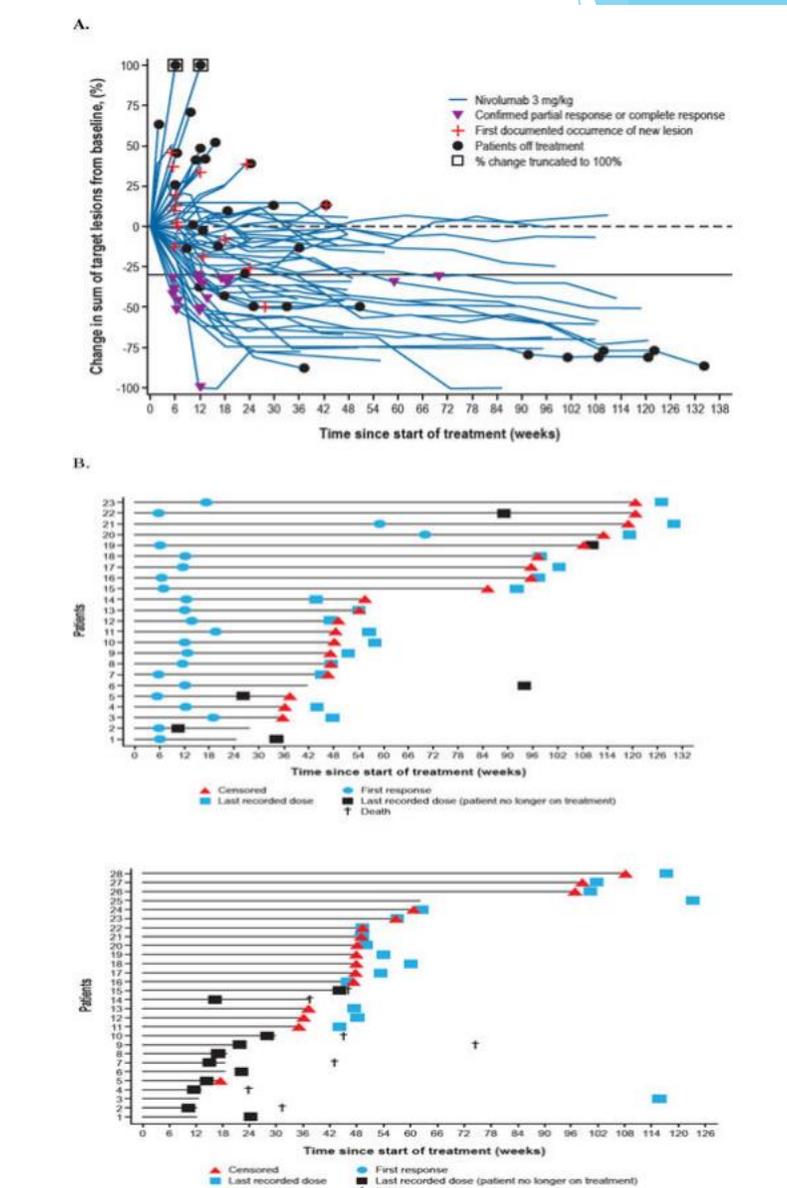
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Lubner, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz Jr.



Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability–high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study

Michael J. Overman, MD¹, Ray McDermott, MD², Joseph L. Leach, MD³, Sara Lonardi, MD⁴, Heinz-Josef Lenz, MD⁵, Michael A. Morse, MD⁶, Jayesh Desai, MBBS⁷, Andrew Hill, MBBS⁸, Michael Axelson, MD⁹, Rebecca A. Moss, MD⁹, Monica V. Goldberg, MD⁹, Z. Alexander Cao, PhD⁹, Jean-Marie Ledeine, MSc¹⁰, Gregory A. Maglinte, PhD⁹, Scott Kopetz, MD^{1,a}, and Thierry André, MD^{11,a}

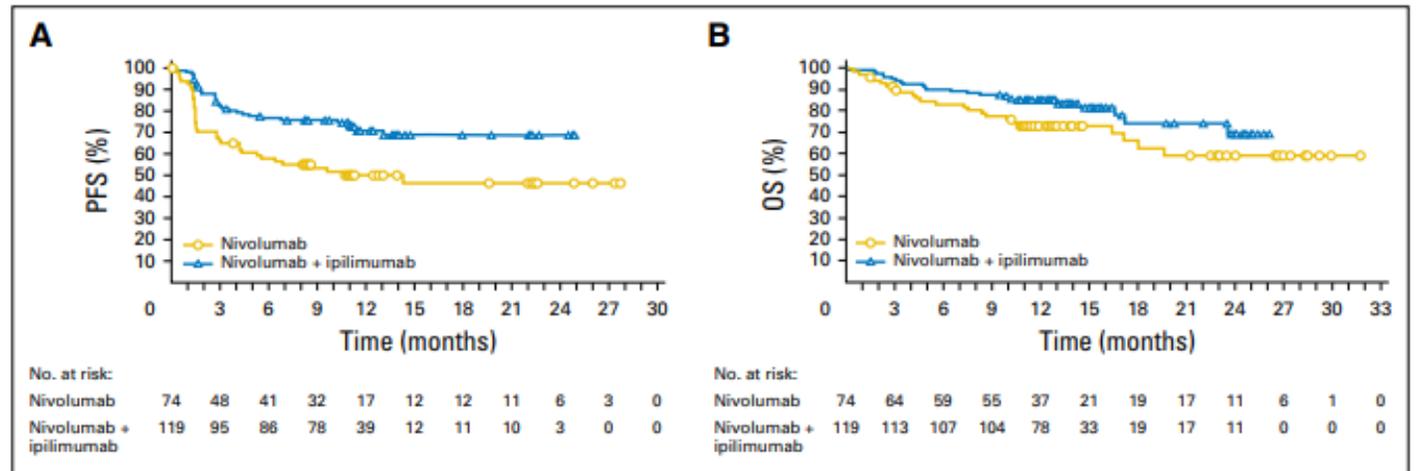
- Confirmation efficacité Nivolumab
- 31,1% réponse objective
- 2,7% réponse complète
- 29,7% réponse partielle



Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

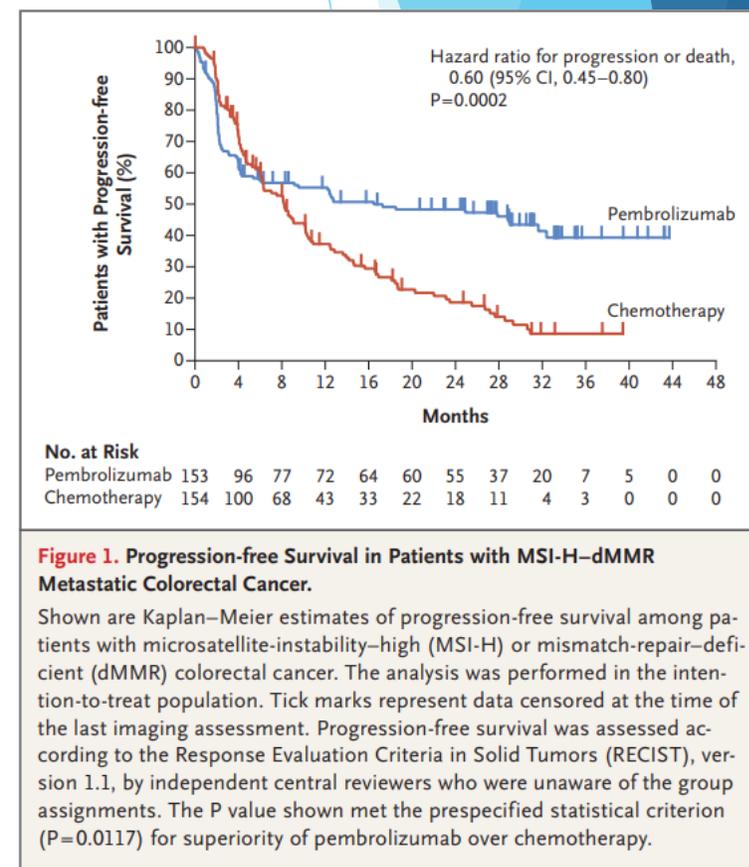
- ▶ 55% réponses objectives
- ▶ 71% PFS à 1 an
- ▶ 85% OS à 1 an



Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

Thierry André, M.D., Kai-Keen Shiu, F.R.C.P., Ph.D., Tae Won Kim, M.D., Ph.D., Benny Vittrup Jensen, M.D., Lars Henrik Jensen, M.D., Ph.D., Cornelis Punt, M.D., Ph.D., Denis Smith, M.D., Rocio Garcia-Carbonero, M.D., Ph.D., Manuel Benavides, M.D., Ph.D., Peter Gibbs, M.D., Christelle de la Fouchardiere, M.D., Fernando Rivera, M.D., Ph.D., *et al.*,
for the KEYNOTE-177 Investigators*

- ▶ MSI
- ▶ 50% métastases synchrones
- ▶ 25% BRAF V600E
- ▶ Median PFS Pembrolizumab : 16,5 mois
- ▶ Median PFS chimiothérapie (FOLFOX/FOLFIRI + TC) : 8,6 mois
- ▶ Réponse objective : 43,8% vs 33,1%
- ▶ Effets indésirables : 22% pour le Pembro vs 66% pour la chimio

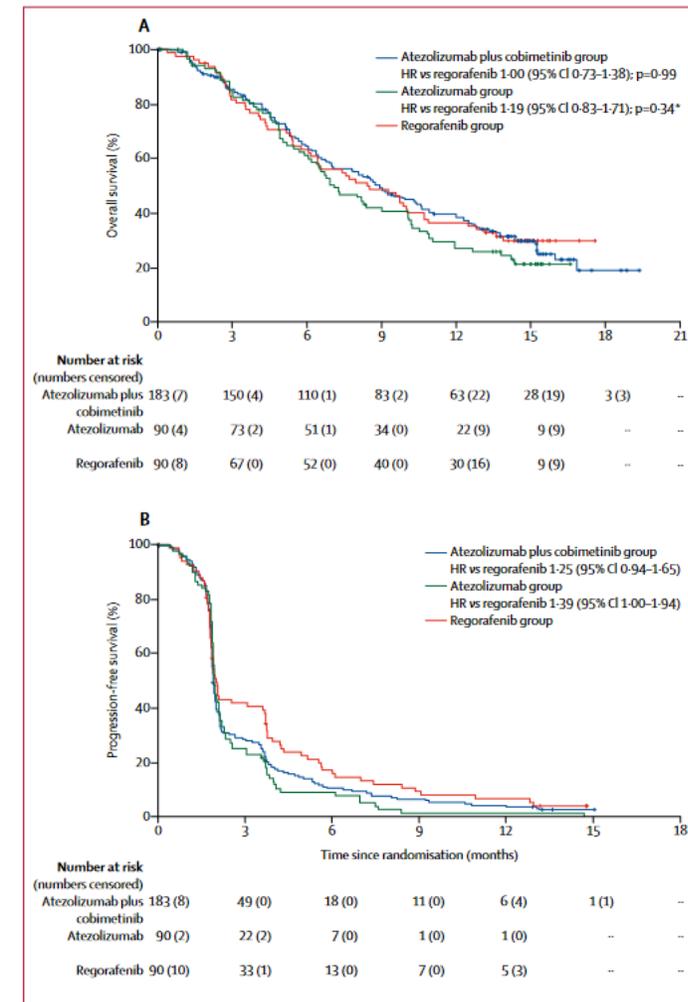


Chez les MSS : Inutile ?

Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial

*Cathy Eng, Tae Won Kim, Johanna Bendell, Guillem Argilés, Niall C Tebbutt, Maria Di Bartolomeo, Alfredo Falcone, Marwan Fakih, Mark Koz, Neil H Segal, Alberto Sobrero, Yibing Yan, Ilsung Chang, Anne Uyei, Louise Roberts, Fortunato Ciardiello, for the IMblaze370 Investigators**

- ▶ Phase III
- ▶ 363 patients mCRC MSS
- ▶ Atezo+Cobetinib / Atezo / Atezo+Rego
- ▶ 3^e ligne
- ▶ Aucune réponse complète
- ▶ PR: 3% association, 2% atezo seul, 2% rego seul
- ▶ Pas de différence entre les groupes



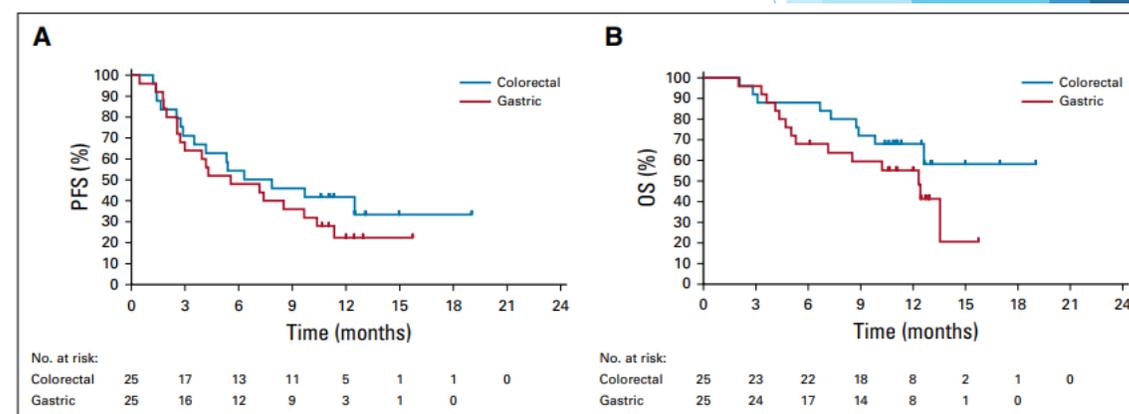
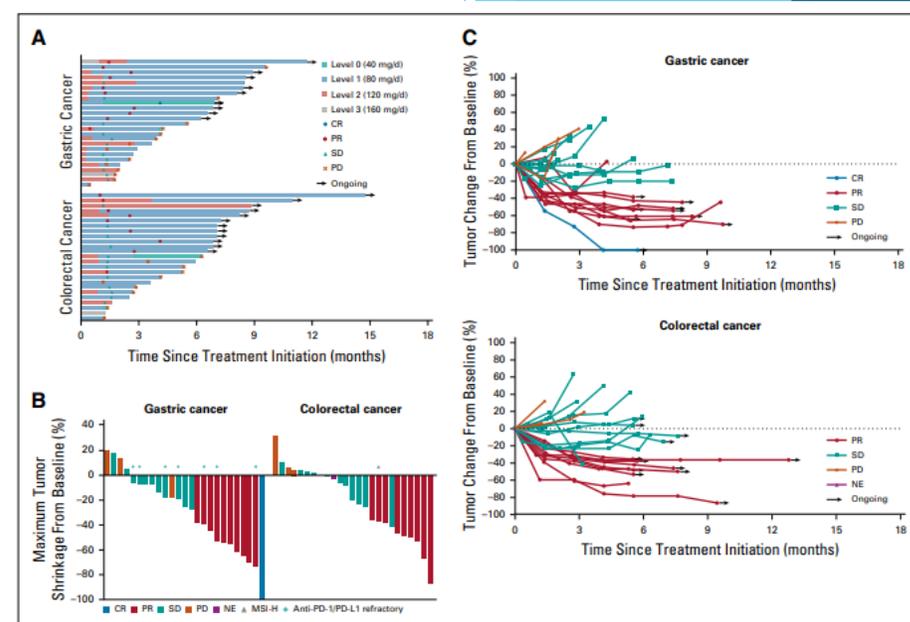
Chez les MSS : de l'espoir

original reports

Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603)

Shota Fukuoka, MD, PhD^{1,2}; Hiroki Hara, MD³; Naoki Takahashi, MD³; Takashi Kojima, MD¹; Akihito Kawazoe, MD¹; Masako Asayama, MD³; Takako Yoshii, MD, PhD³; Daisuke Kotani, MD¹; Hitomi Tamura, RN⁴; Yuichi Mikamoto, BPharm⁴; Nami Hirano, MLT⁴; Masashi Wakabayashi, ME⁵; Shogo Nomura, PhD⁴; Akihiro Sato, MD⁴; Takeshi Kuwata, MD, PhD⁵; Yosuke Togashi, MD, PhD²; Hiroyoshi Nishikawa, MD, PhD²; and Kohei Shitara, MD¹

- ▶ 2^e ligne, après chimiothérapie + TC
- ▶ Regorafenib + Nivolumab
- ▶ 36% réponse objective CRC (44% GC)
- ▶ Median PFS : 8 mois

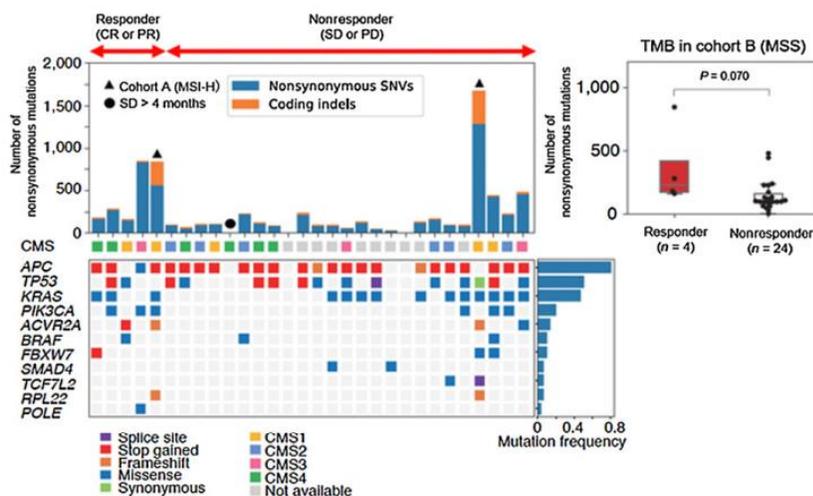


Chez les MSS : de l'espoir

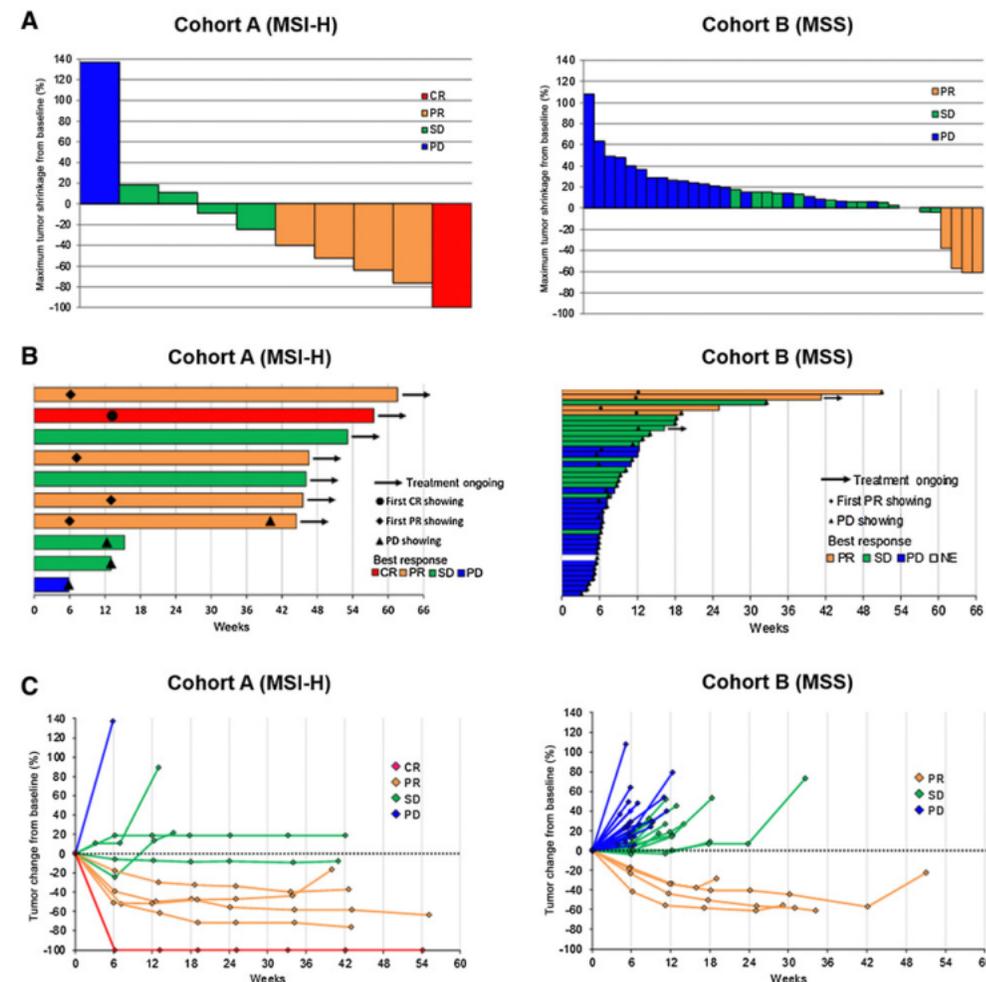
Multicenter Phase I/II Trial of Napabucasin and Pembrolizumab in Patients with Metastatic Colorectal Cancer (EPOC1503/SCOOP Trial)

Akihito Kawazoe¹, Yasutoshi Kuboki¹, Eiji Shinozaki², Hiroki Hara³, Tomohiro Nishina⁴, Yoshito Komatsu⁵, Satoshi Yuki⁶, Masashi Wakabayashi⁷, Shogo Nomura⁷, Akihiro Sato⁷, Takeshi Kuwata⁸, Masahito Kawazu⁹, Hiroyuki Mano⁹, Yosuke Togashi¹⁰, Hiroyoshi Nishikawa¹⁰, and Takayuki Yoshino¹

- ▶ Réponse objective dans 10% des cas MSS (vs 50% MSI)
- ▶ MAIS dans les MSS
 - ▶ Réponse 42,9% chez CPS>10%



CMS, consensus molecular subtype; SNV, single-nucleotide variant; TMB, tumor mutation burden

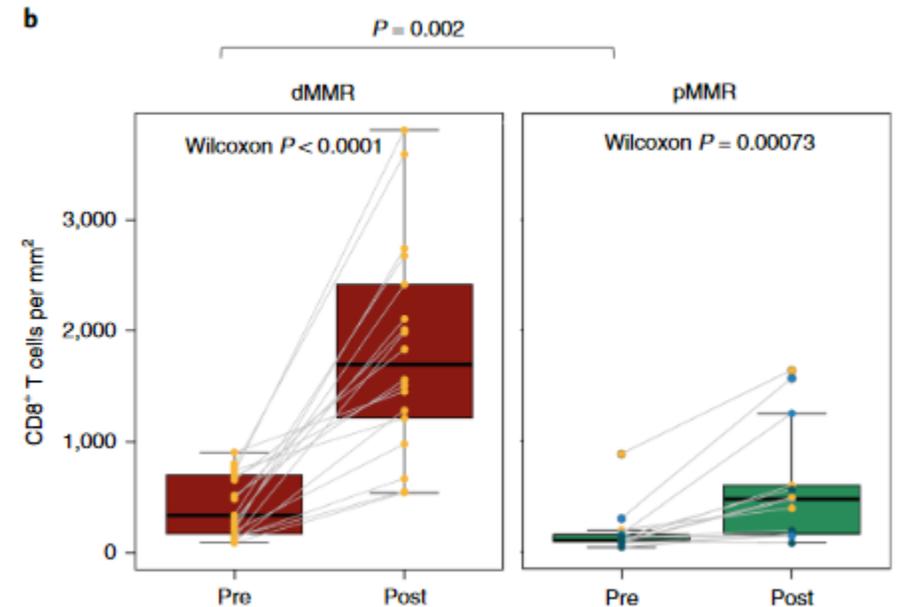
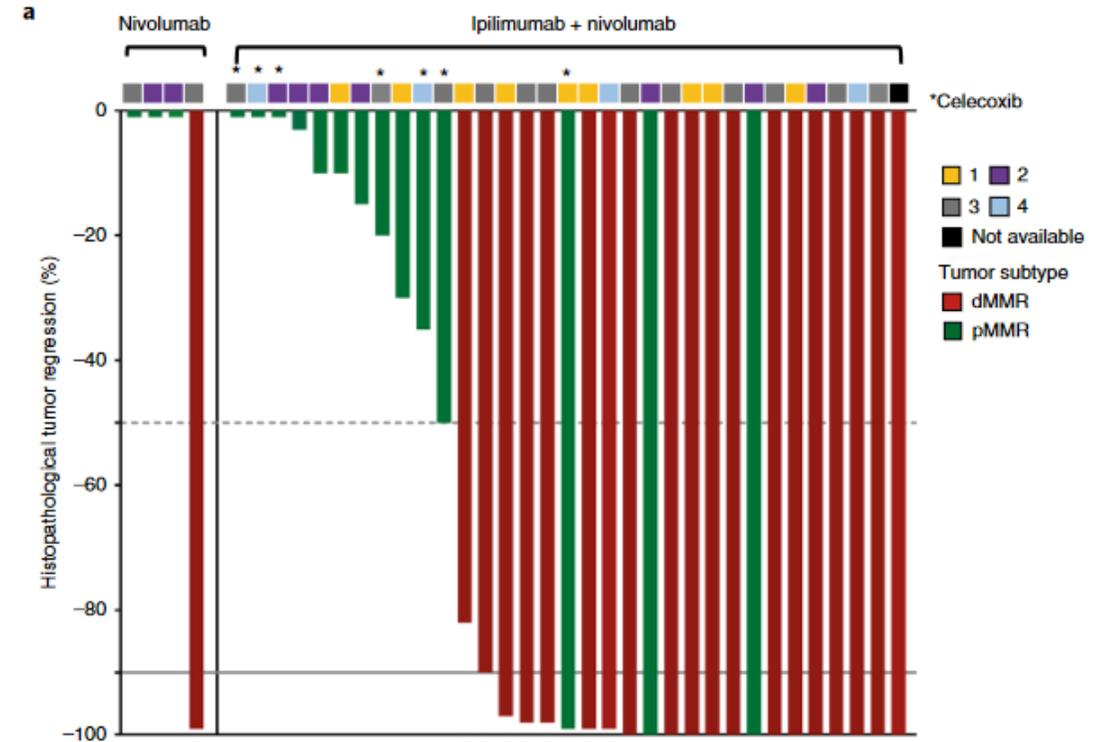
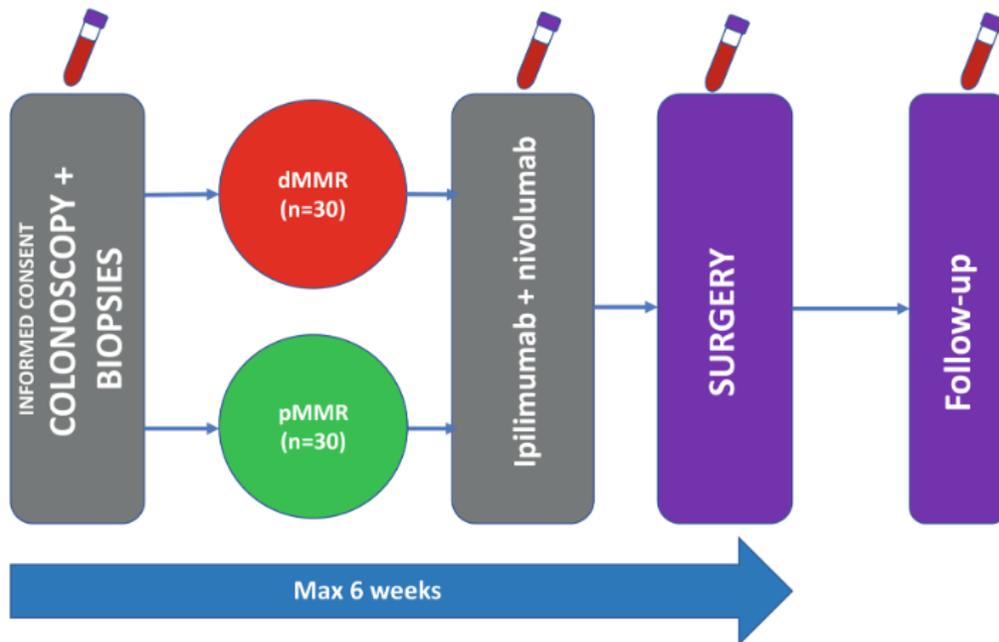


Chez les MSS : de l'espoir



Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi^{1,2,3}, Lorenzo F. Fanchi^{2,4,17}, Krijn K. Dijkstra^{2,4,17}, José G. Van den Berg^{5,17}, Arend G. Aalbers⁶, Karolina Sikorska⁷, Marta Lopez-Yurda^{7,8}, Cecile Grootscholten¹, Geerard L. Beets^{6,9}, Petur Snaebjornsson⁵, Monique Maas¹⁰, Marjolijn Mertz¹¹, Vivien Veninga^{2,4}, Gergana Bounova^{4,12}, Annegien Broeks¹³, Regina G. Beets-Tan^{9,10}, Thomas R. de Wijkerslooth¹, Anja U. van Lent¹⁴, Hendrik A. Marsman¹⁵, Elvira Nuijten⁷, Niels F. Kok⁶, Maria Kuiper¹, Wieke H. Verbeek¹, Marleen Kok^{3,16}, Monique E. Van Leerdam¹, Ton N. Schumacher^{2,4}, Emile E. Voest^{1,2,4,17} and John B. Haanen^{2,3,17}

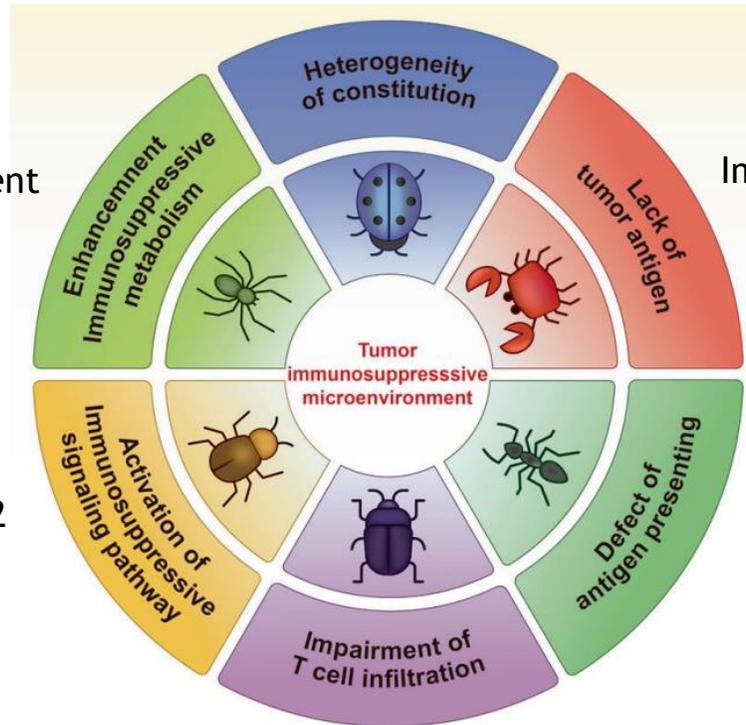


Causes d'inefficacité de l'immunothérapie

TAM, monocytes, granulocytes (IL10-35-TGFb)

Hyperexpression GLUT1 => epuiselement
LT par deficit Glc

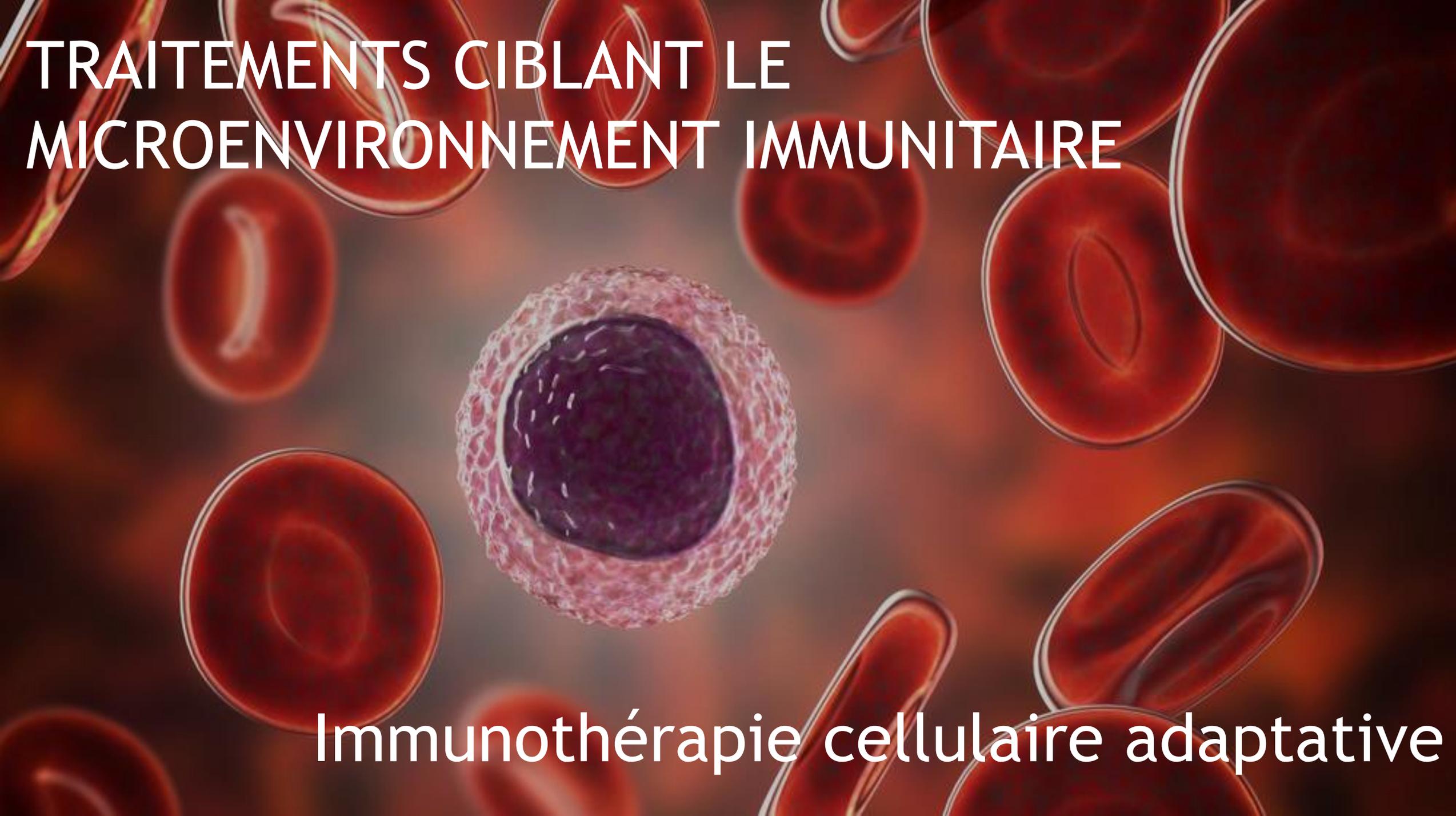
Mutation RAS, FAK, JAK1/2



Immunoediting, destruction MEC

Dédifférenciation DC de APC vers monocytes

CAF, endothéline B

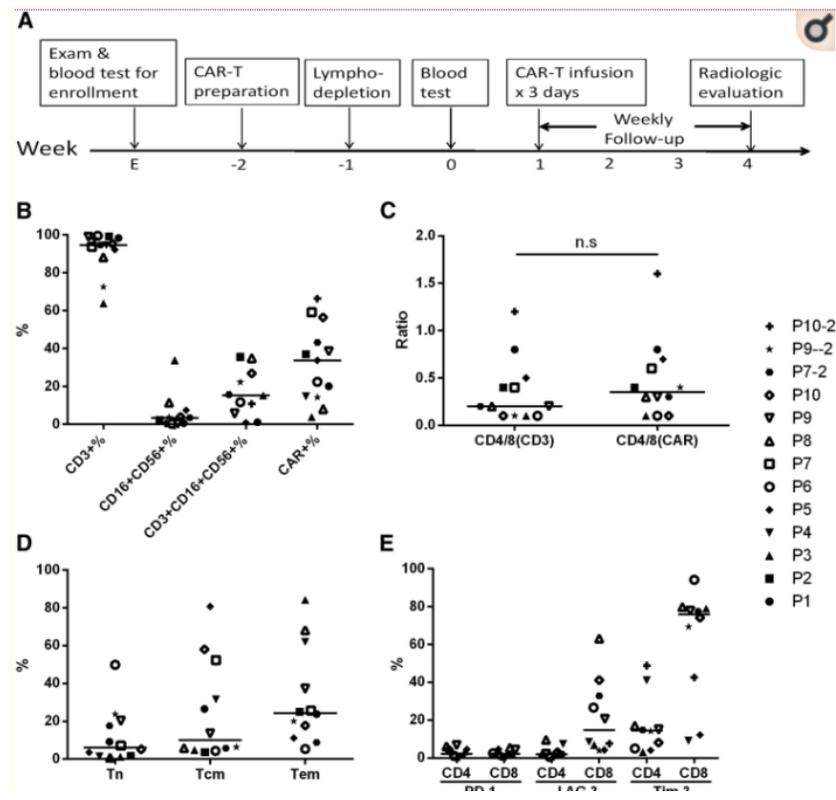


TRAITEMENTS CIBLANT LE MICROENVIRONNEMENT IMMUNITAIRE

Immunothérapie cellulaire adaptative

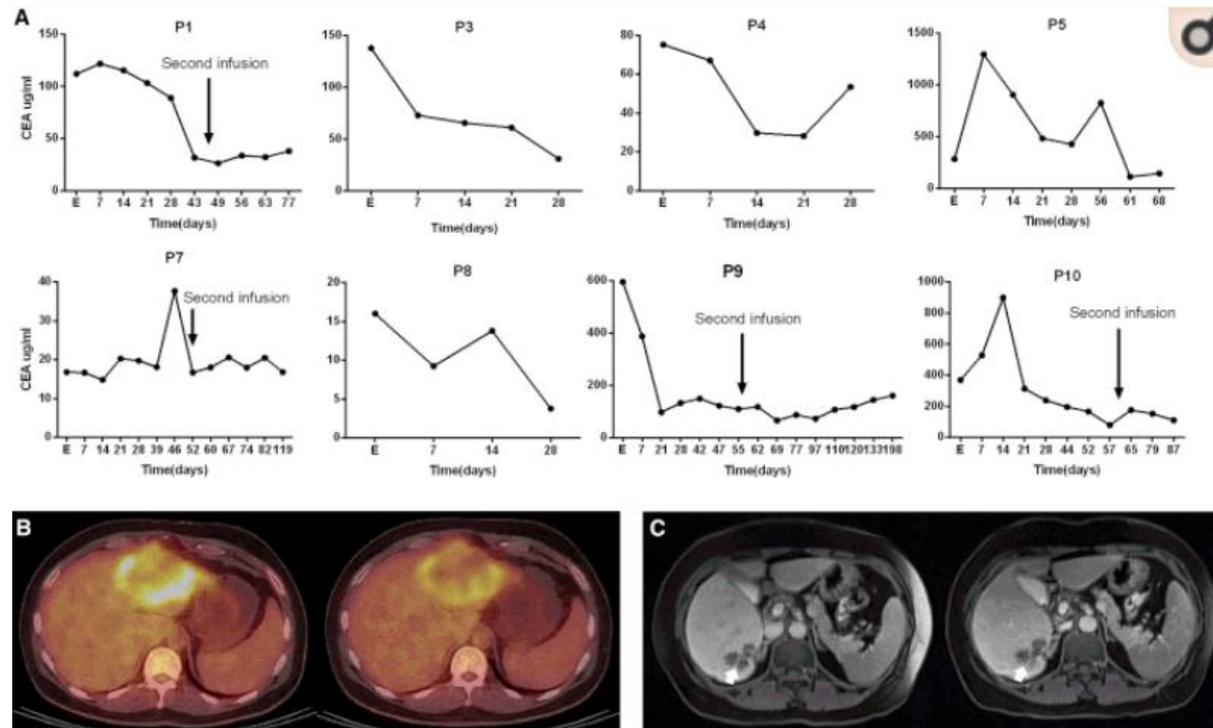
CAR-T

- ▶ Cellules T autologues dirigées contre Ag tumoraux spécifiques par édition génique => réinjectés aux patients pour stimuler la réponse immunitaire
- ▶ CRC: dirigé contre ACE



CAR-T

- ▶ Phase I
- ▶ mCRC ACE +
- ▶ Sur 10 pMMR : 7 stabilisation maladie avec CEA CAR-T, 2 réponses objectives

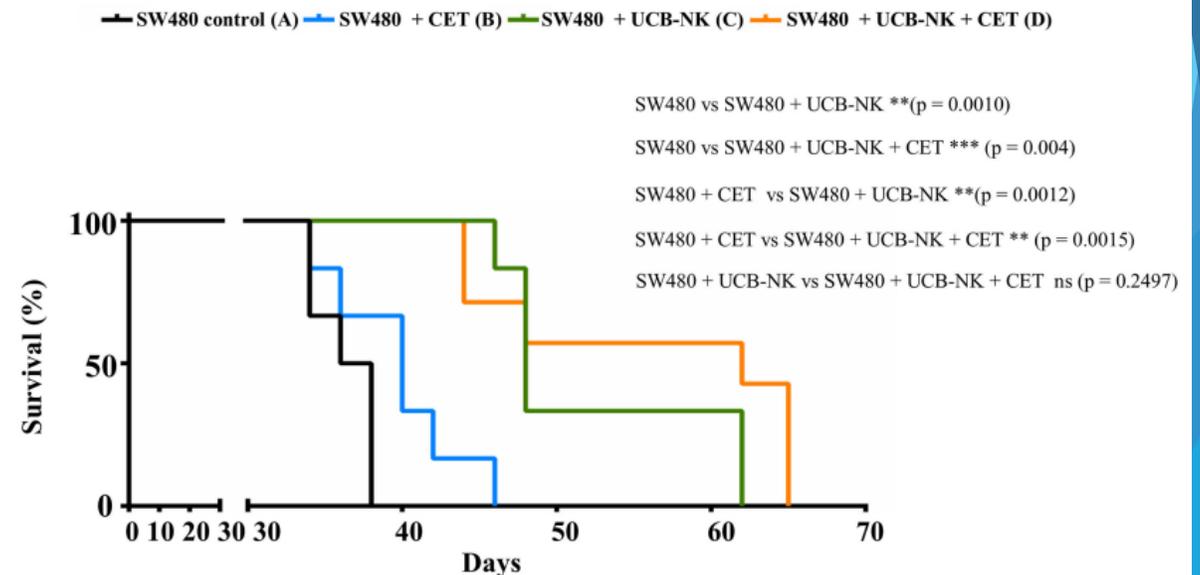
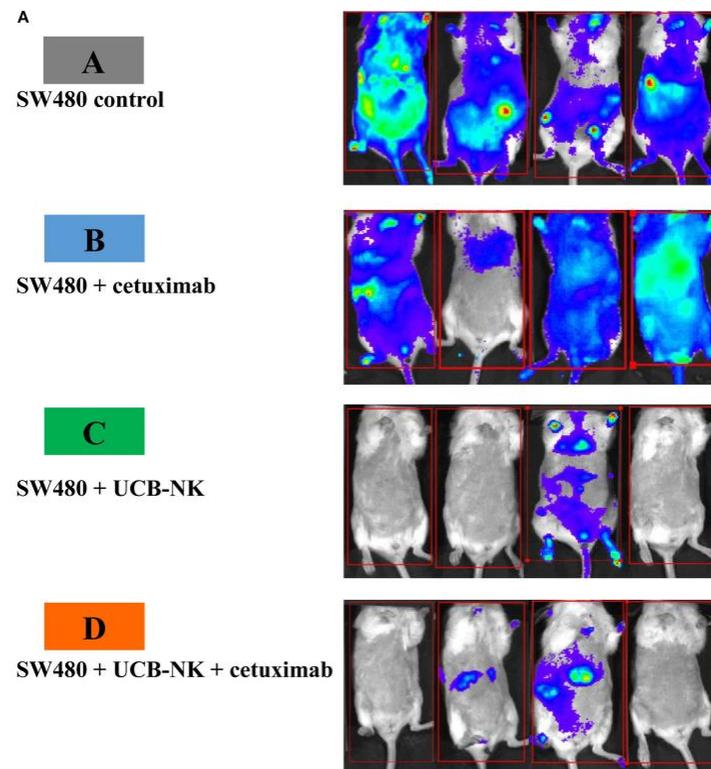


NK cells

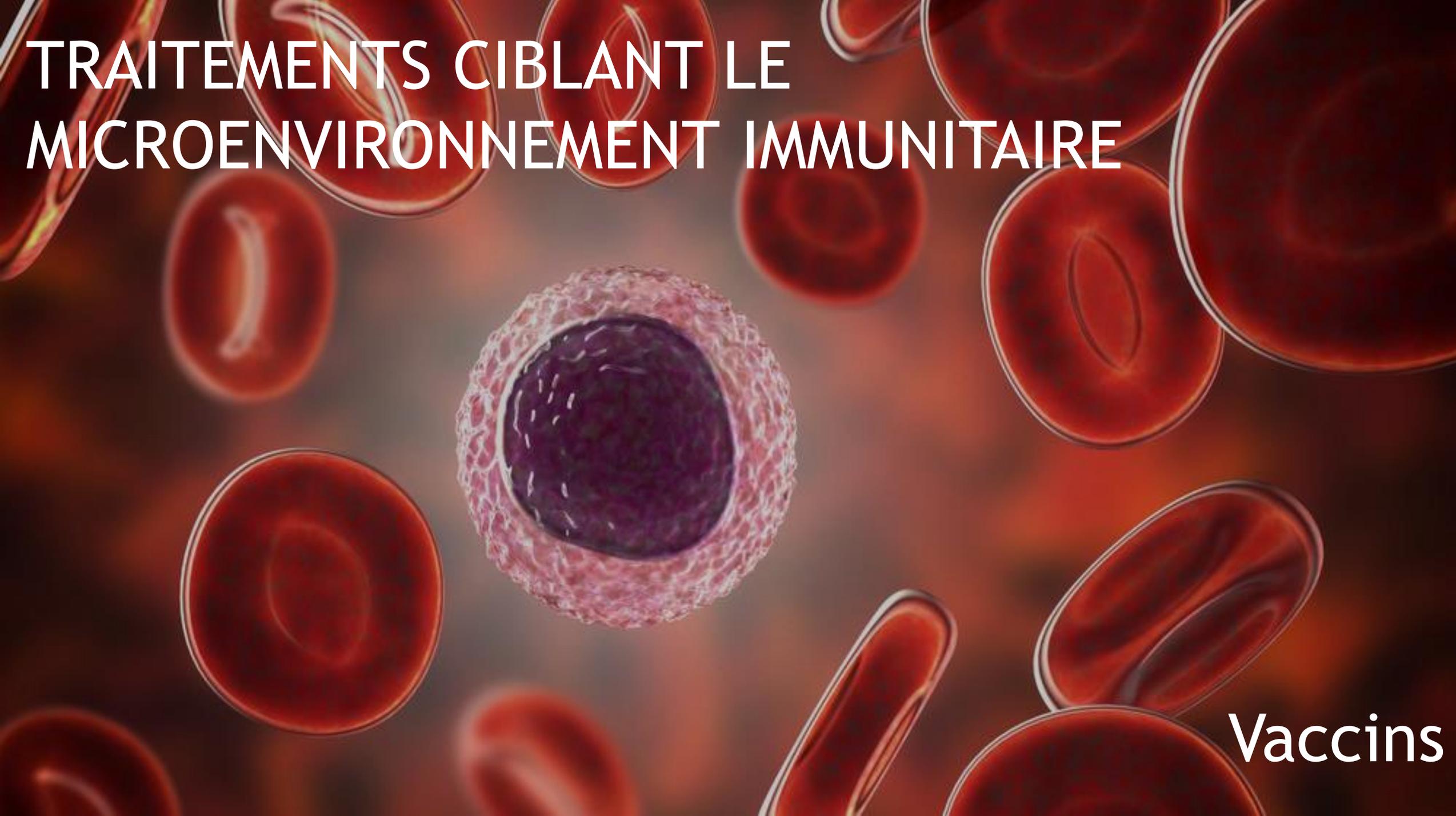
- ▶ NK therapy cell > CAR-T dans les cancers hématologiques
- ▶ Efficacité mCRC RASwt/mut

In Vivo Efficacy of Umbilical Cord Blood Stem Cell-Derived NK Cells in the Treatment of Metastatic Colorectal Cancer

John P. Veluchamy^{1,2†}, Silvia Lopez-Lastra^{3,4,5†}, Jan Spanholtz², Fenna Bohme², Nina Kok², Daniëlle A. M. Heideman⁶, Henk M. W. Verheul¹, James P. Di Santo^{3,4}, Tanja D. de Gruijl¹ and Hans J. van der Vliet^{1*}



Median survival (days)			
SW480 control	SW480 + CET	SW480 + UCB-NK	SW480 + UCB-NK + CET
37	40	48	62



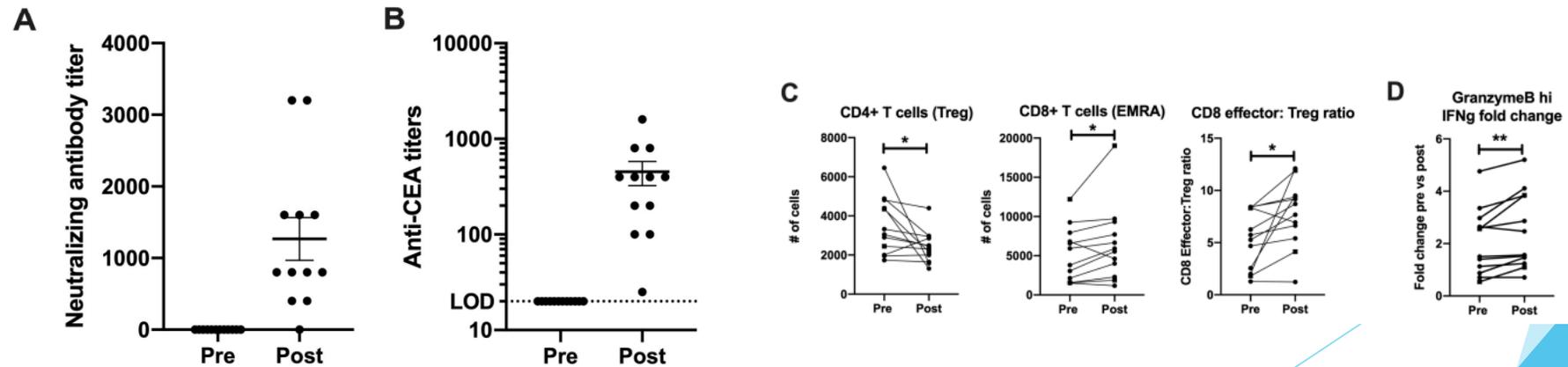
TRAITEMENTS CIBLANT LE MICROENVIRONNEMENT IMMUNITAIRE

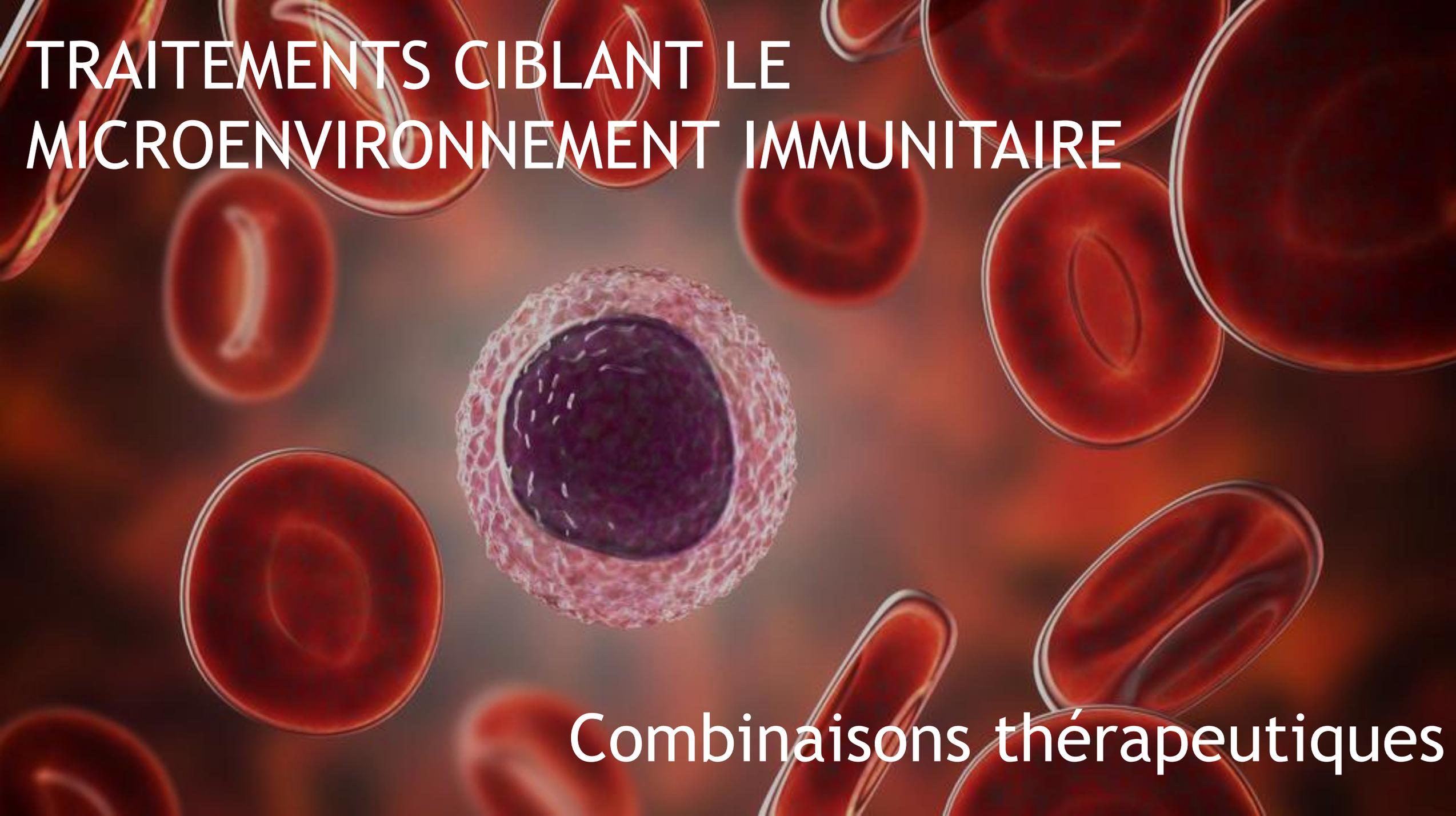
Vaccins

Vaccins

- ▶ CRC: expression de Tumor Associated Antigens
- ▶ Stimulation cellules T
- ▶ Switch Treg en Teff
- ▶ Réponse humorale et cellulaire
- ▶ Ex: virus-like replicon particle (VRP)-carcinoembryonic antigen (CEA): particule réplicon alphavirale codant pour un ACE modifié

Study	Phase	Agent	Population	MSI status	Endpoint
NCT01147965	1/2	AD5-CEA Vaccine	32 mCRC	-	The primary purpose: determine the safety The secondary objectives: evaluate CEA-specific immune responses and clinical response rate
NCT00529984	2	AWX701 (VRP-CEA Vaccine)	28 metastatic tumors; including 21 mCRC	-	the primary objectives: determine the safety The secondary objectives: evaluate CEA-specific immune responses and clinical response rate
NCT01890213	2	AWX701 (VRP-CEA Vaccine)	12 Stage III CRC	-	-
NCT00154713	1	CEA-pulsed DC	12 mCRC	-	The primary endpoint: safety
NCT01462513	2	Tecemotide (L-BLP25) or placebo	121 mCRC with R0/R1 resection	-	The primary endpoints: RFS and 3-year overall survival (OS) rate; The secondary endpoints: RFS and OS in subgroups with different MUC1 expression and safety
NCT01461148	1/2a	FSP-based vaccine	22 CRC	MSI	The primary endpoints: safety (phase I) and immunogenicity (phase IIa); The secondary endpoints: tumor response (both phases) and immunogenicity (phase I) and safety (phase IIa)
NCT00027833	2	ALVAC-CEA-B7.1 vaccine + FOLFIRI; FOLFIRI + ALVAC-CEA-B7.1 vaccine; ALVAC-CEA-B7.1 vaccine + tetanus toxoid + FOLFIRI	180 mCRC	-	The primary endpoints: Immune response to the vaccine.
NCT00676949	1	5 peptide vaccines of KOC1, TTK, CO16, DEPDC1, MPHOSPH1	18 metastatic Tumors, including nine mCRC	-	The primary end point: safety and tolerability. The secondary endpoints: MTD and immune response
NCT01413295	2	DC vaccine + BSC or BSC alone	52 mCRC	-	The primary endpoints: PFS; The secondary endpoints: PFS, OS, toxic effects, and ORR.
NCT01348256	2	DC vaccine	19 mCRC	-	-
-	1/2	p53-SLP	10 mCRC	-	-
-	-	MVA-5T4, metronomic low-dose cyclophosphamide, or a combination of both treatments	55 mCRC	-	The primary endpoints: magnitude of 5T4-specific responses at treatment day 43; The secondary end points: the kinetics of anti-5T4 immune responses overtime, PFS, OS
-	2	TroVax(MVA-5T4)	19 mCRC	-	-
-	2	a peptide vaccine combined with UFT/LV	46 stage III CRC	-	The primary end point: RFS; The secondary endpoints: OS, safety, tolerability and peptide-specific activities
-	-	DC vaccine	46 mCRC	-	-





TRAITEMENTS CIBLANT LE MICROENVIRONNEMENT IMMUNITAIRE

Combinaisons thérapeutiques

Immunothérapie + thérapie ciblée

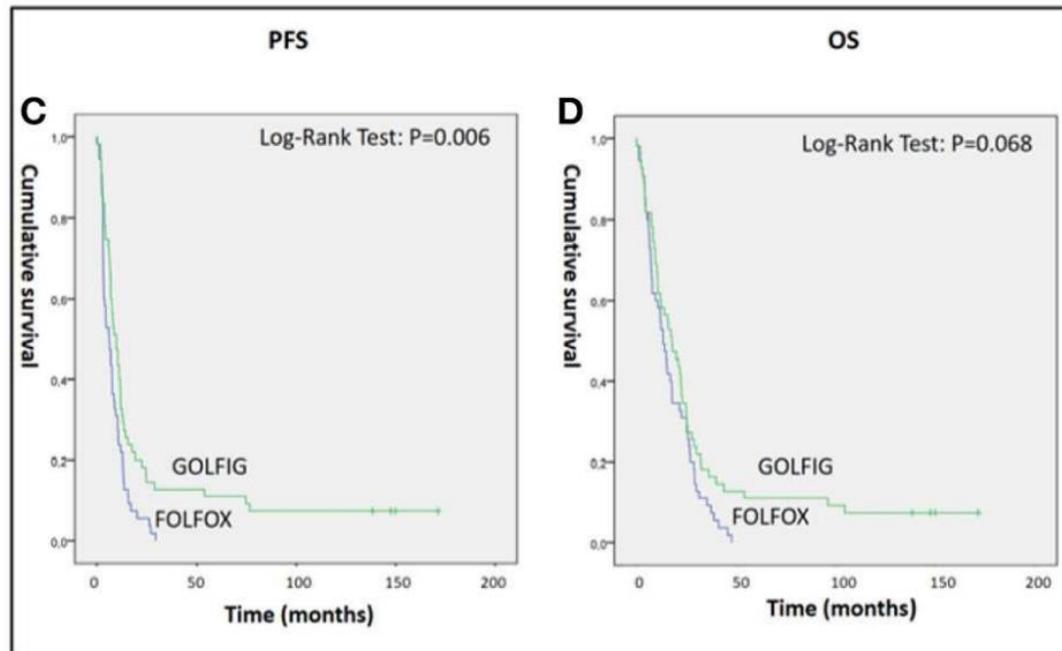
- ▶ Bevacizumab : augmentation CD3/4
- ▶ Cetuximab: augmentation infiltration CD3/8
- ▶ **Espoir pour les MSS**

- ▶ AVETUX II : FOLFOX + Cetuximab + avelumab
- ▶ 40 MSS, 4 MSI
- ▶ Taux réponse : 79,5% (6 complètes, 25 partielles)
- ▶ DFS: 92,3% à 1 an

- ▶ En cours: association antiMEK (cobimetinib)-Atezo, Cetux-NK graft

Immunothérapie + chimiothérapie

- ▶ Chimiothérapie => hyperexpression de TAA (dont ACE) => recrutement LT
- ▶ FOLFOX + IL2 + granocytes



Immunothérapie et ablation

- ▶ Chirurgie/traitement radiologique : déclenche réponse T Ag-spécifique pouvant augmenter l'efficacité de l'immunothérapie
- ▶ Effet abscopal : régression tumorale des lésions non traitées
- ▶ Augmentation taux PDL1 et LT au sein de la tumeur primitive et des lésions en place (murin) => résistance : d'où association IT
- ▶ Croissance moins rapide des lésions restantes

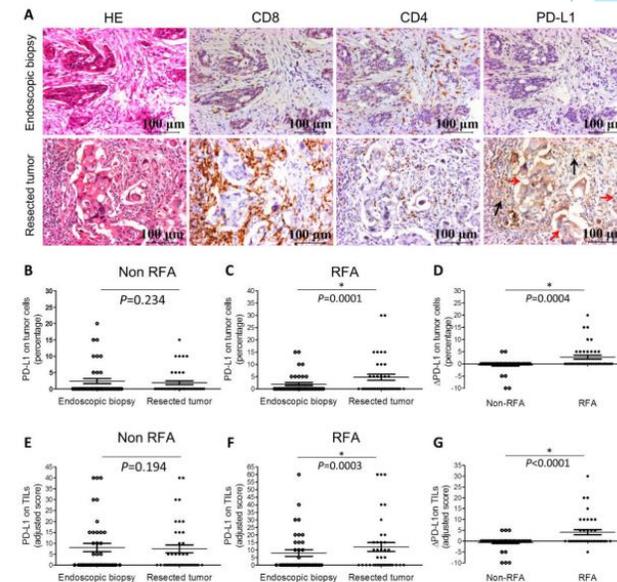
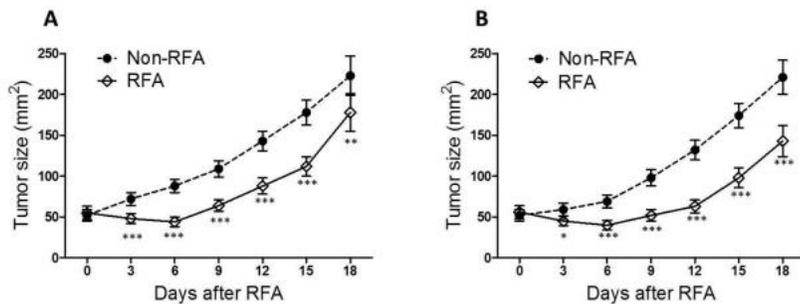
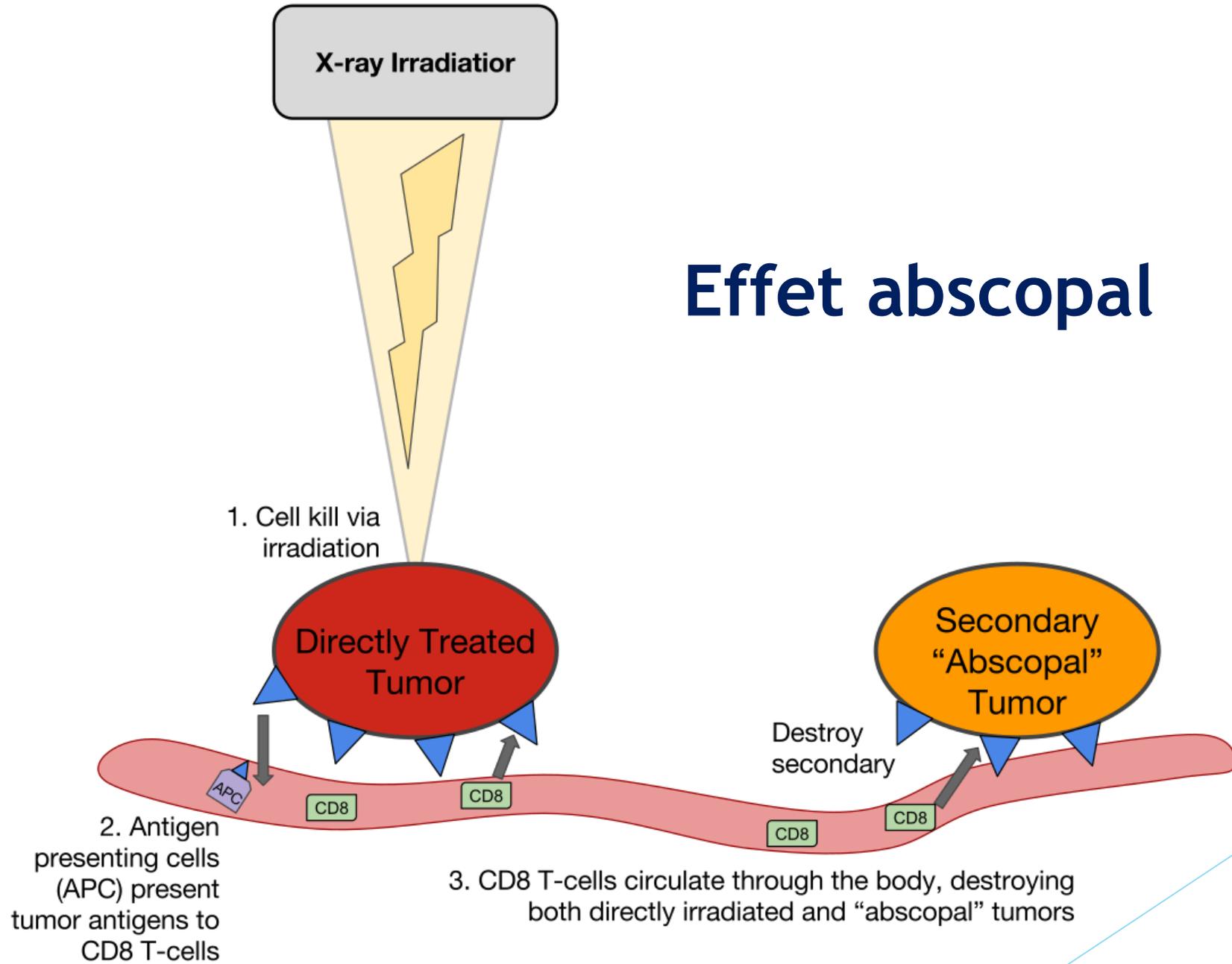


Figure 1. Both the number of TIL and expression of PD-L1 are increased in the primary tumor upon RFA of colorectal liver metastases

Effet abscopal

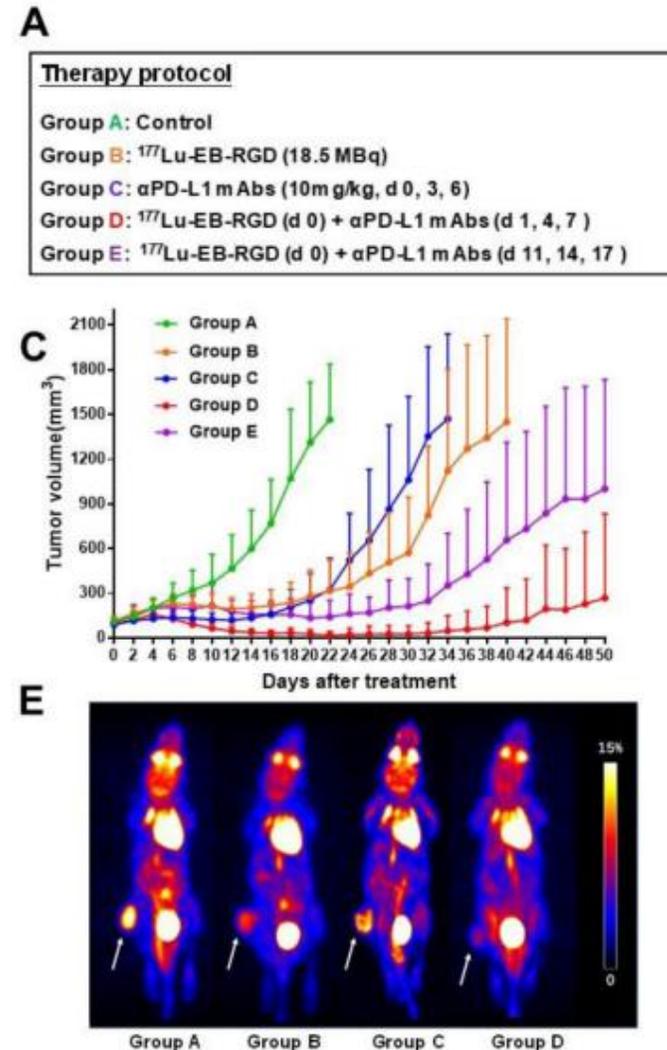


Immunothérapie et radiothérapie

Integrin $\alpha_v\beta_3$ -targeted radionuclide therapy combined with immune checkpoint blockade immunotherapy synergistically enhances anti-tumor efficacy

Haojun Chen^{1*}, Liang Zhao^{2*}, Kaili Fu², Qiuming Lin², Xuejun Wen³, Orit Jacobson⁴, Long Sun¹, Hua Wu¹, Xianzhong Zhang³, Zhide Guo³, Qin Lin², Xiaoyuan Chen⁴

- ▶ Effet abscopal : recrutement LT
- ▶ Diminution croissance tumorale : RT + IT



Conclusion

- ▶ Succès IT surtout chez MSI
- ▶ Mais taux de réponse pas encore assez élevé
- ▶ Envisager les associations IT et IT-biothérapies (en cours +++)
- ▶ Essors des CAR-T, cellules NK
- ▶ Vaccins: plutôt décevant, rôle limité, problème de sécurité / association thérapies NK
- ▶ Autres voies prometteuses : TGF-b, CCL5, CCR5
- ▶ Nanotechnologies : vecteurs de médicaments

