

Modulation des immune check points chez les PVVIH

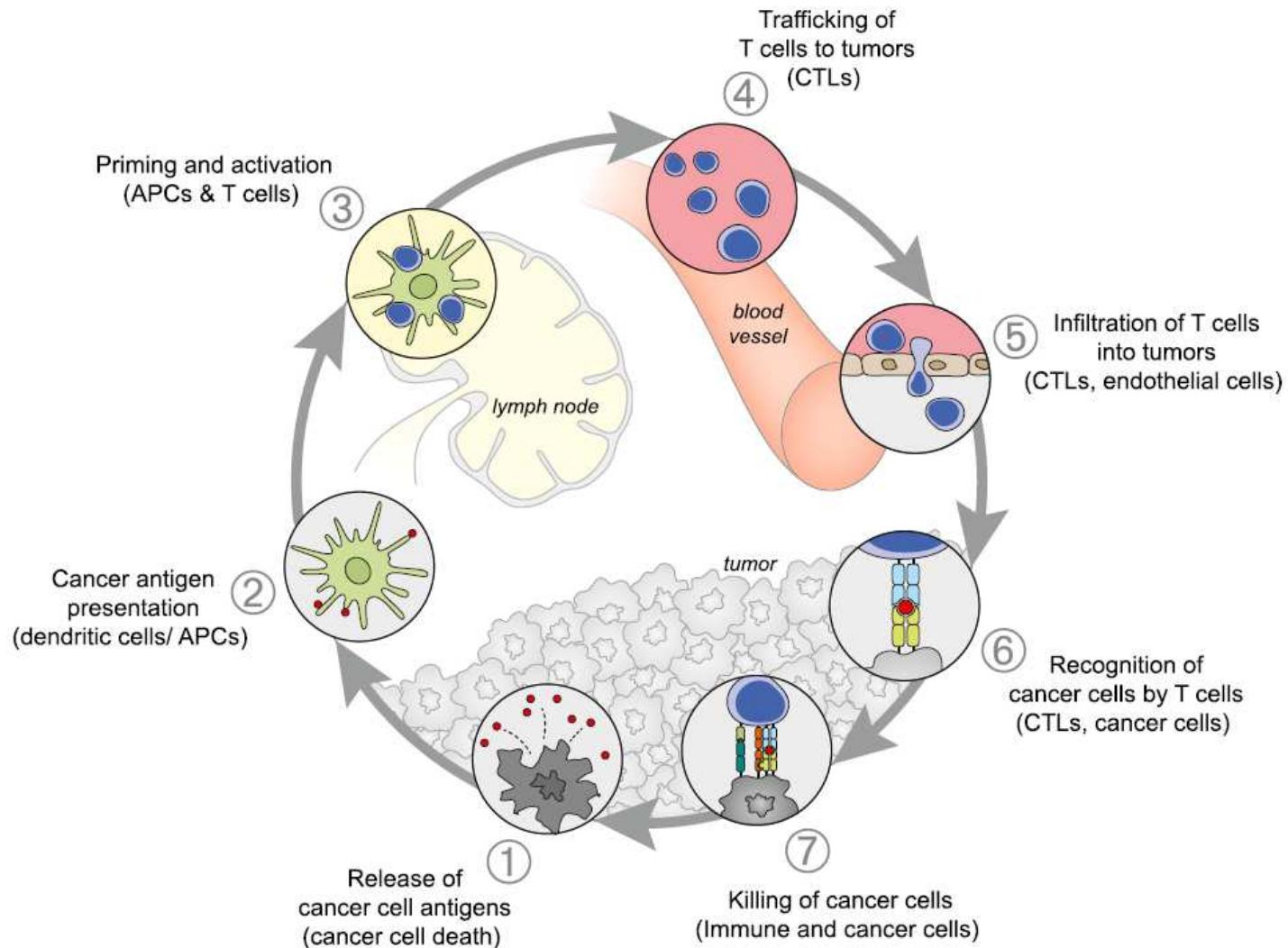
20 mai 2016

Dr. Amélie Guihot-Thévenin



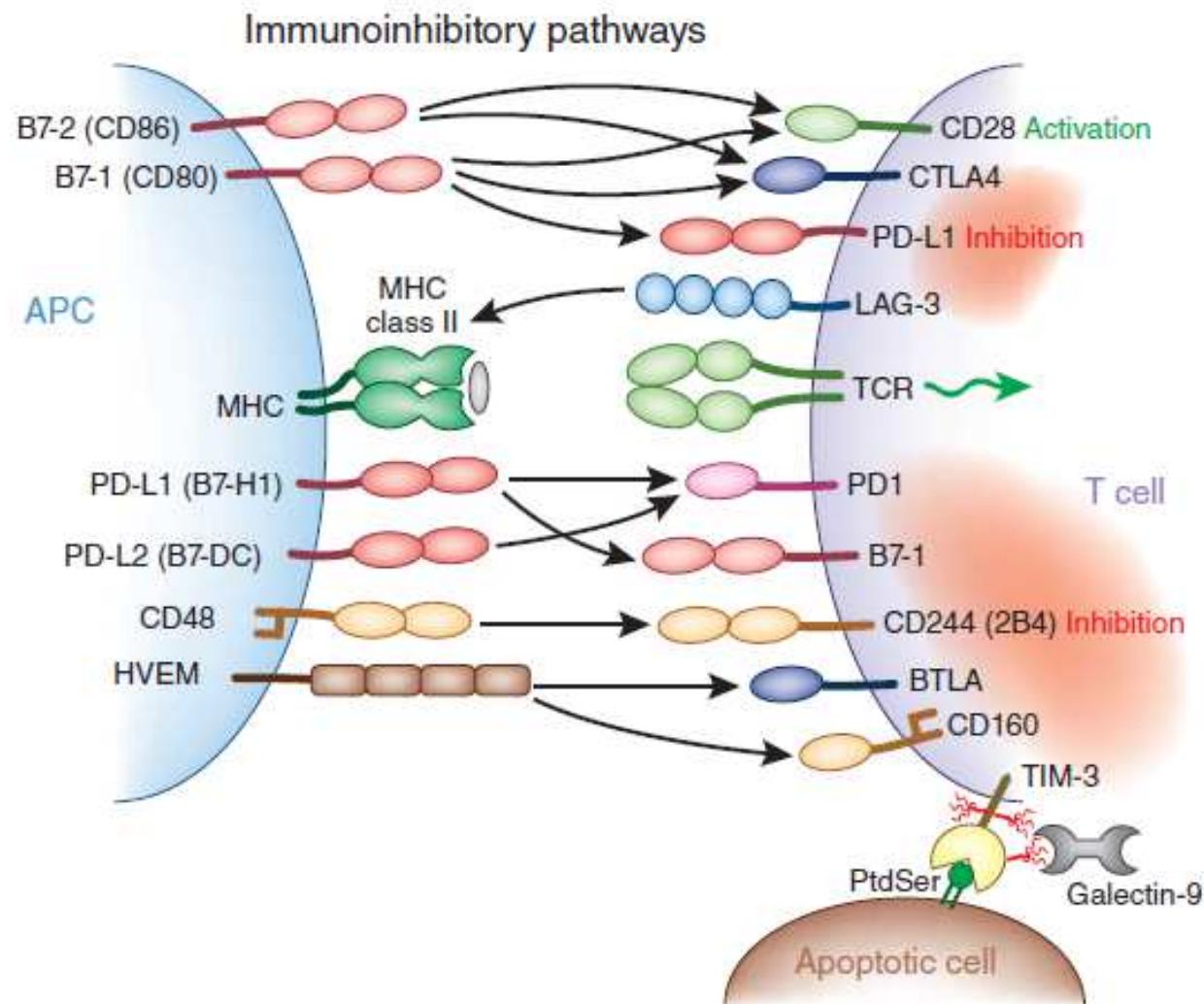
amelie.guihot@aphp.fr
Département d'Immunologie
Unité INSERM U1135 - CIMI
Groupe hospitalier Pitié-Salpêtrière, Paris

The Cancer-Immunity Cycle



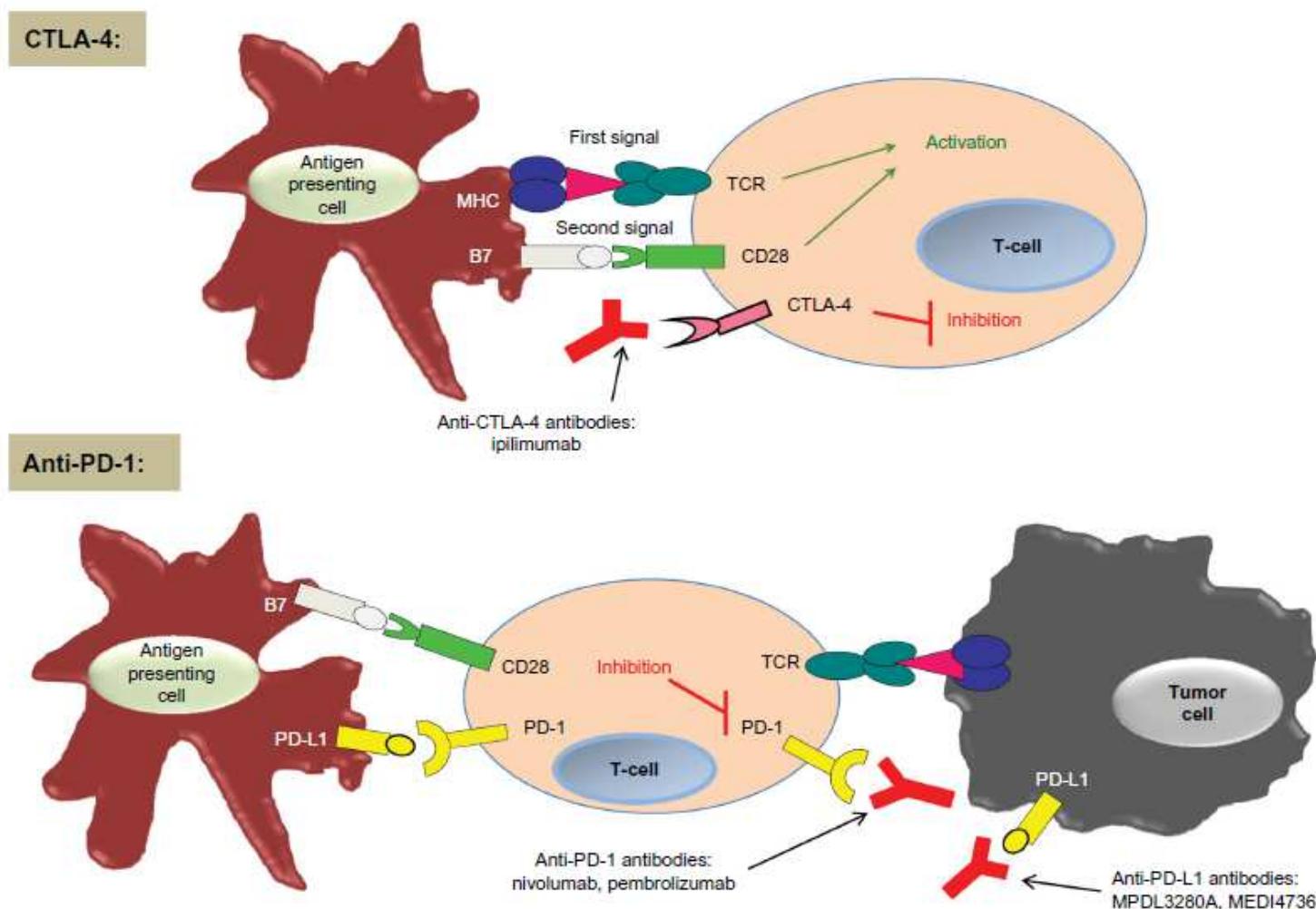
Chen & Mellman, *Immunity* 2013;39:1

T cell Coinhibitory pathways

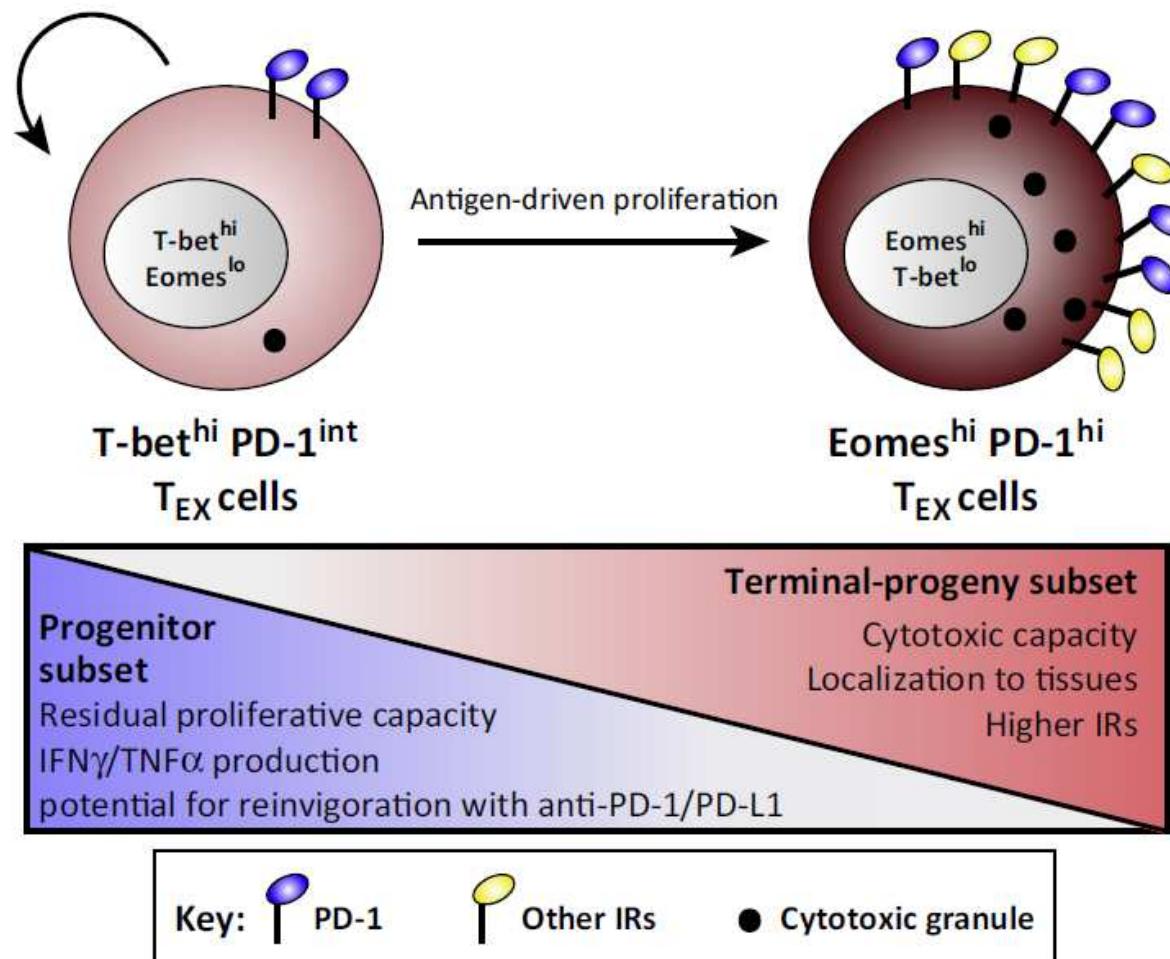


Freeman & Sharpe, *Nat Immunol* 2012;13:113

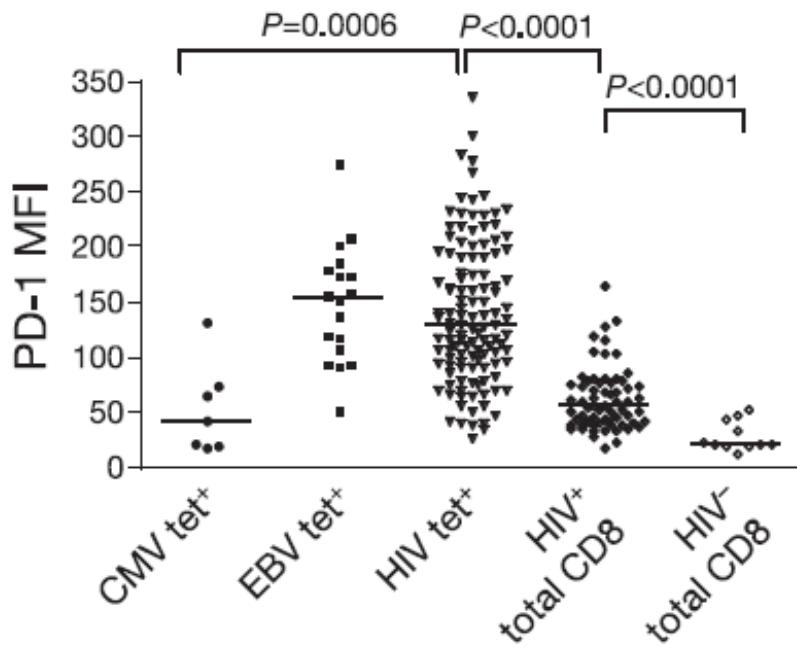
Concept of CTLA-4 and PD-1 immune checkpoints



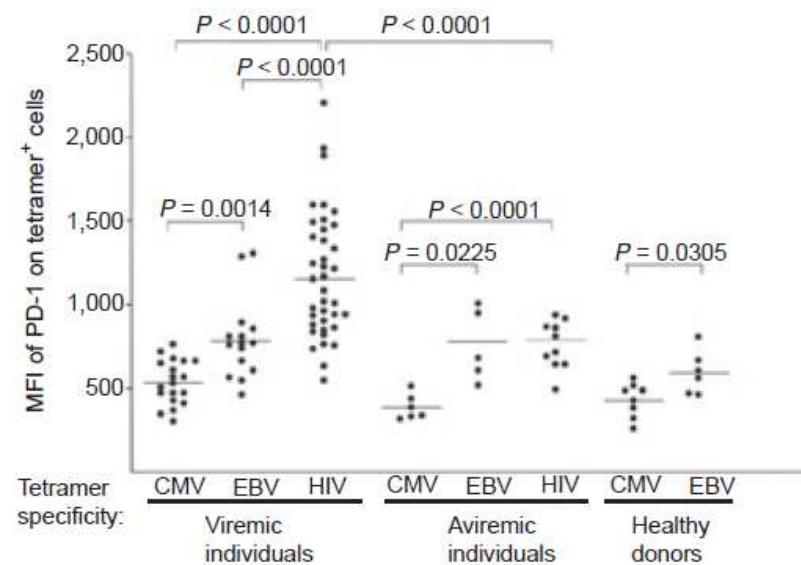
Heterogeneity in the exhausted T cell population



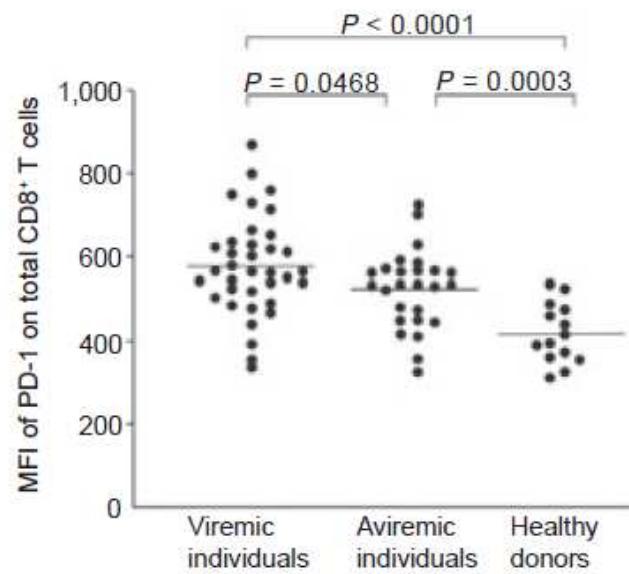
High levels of PD-1 expression on HIV/EBV-specific CD8 T cells



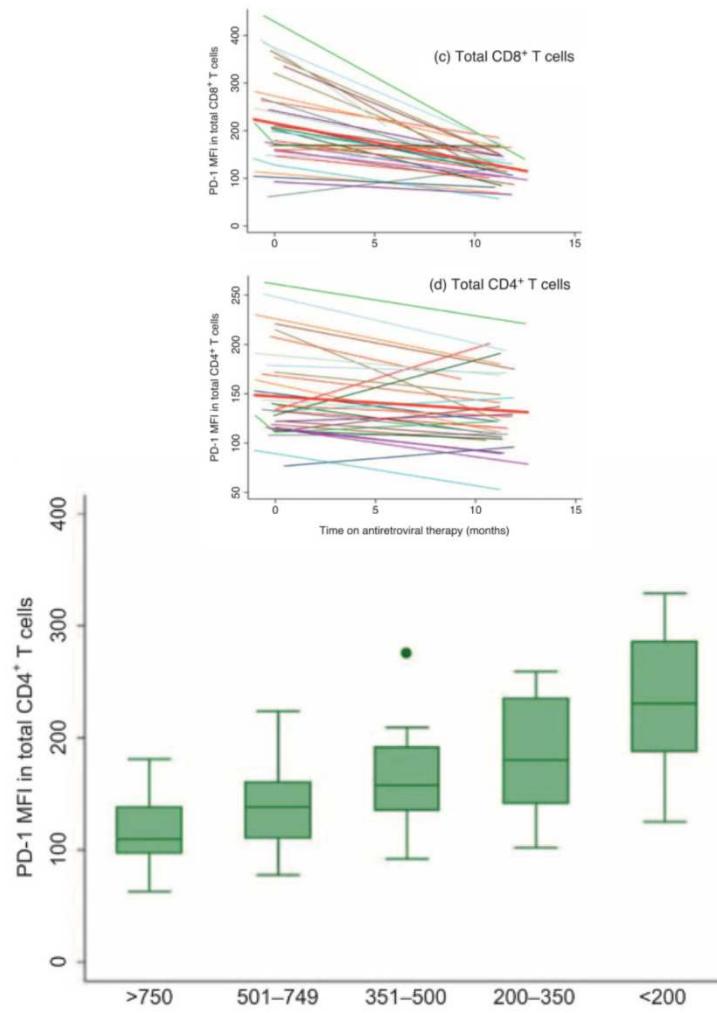
PD-1 expression on HIV-specific CD8 T cells in HIV+ cART-naïve pts (n = 71), versus HIV- controls (n = 11).



PD-1 expression on CD4 and CD8 T cells is not normalized with cART

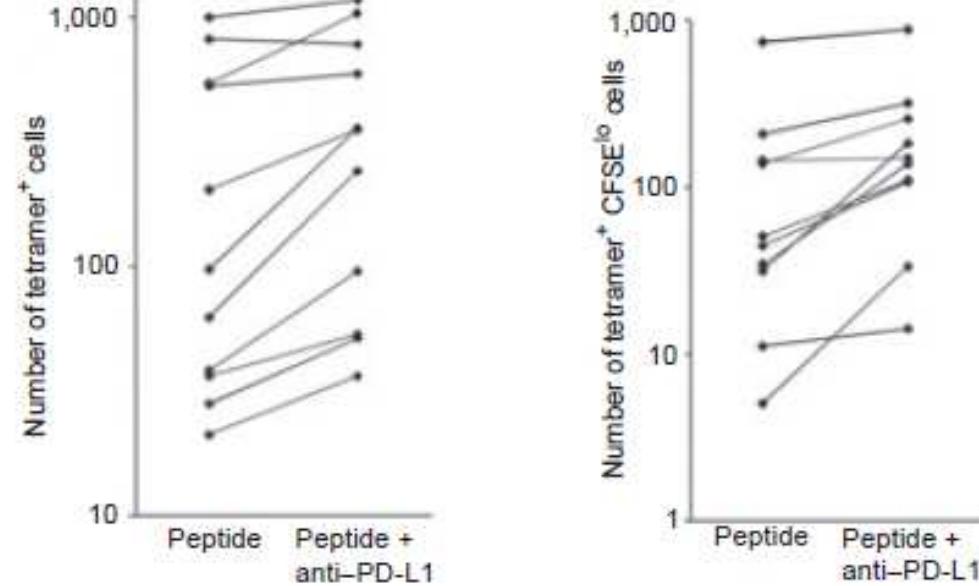
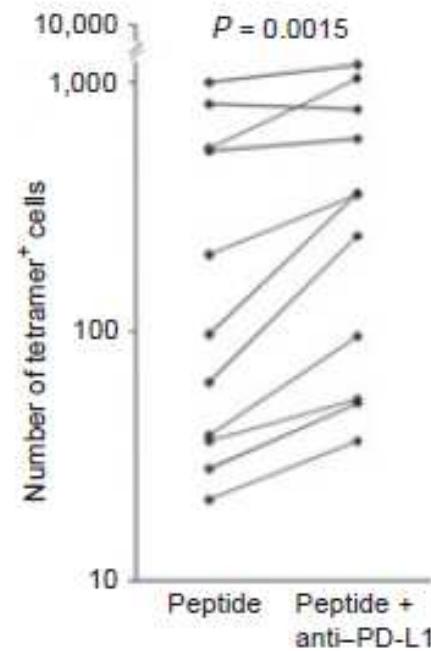
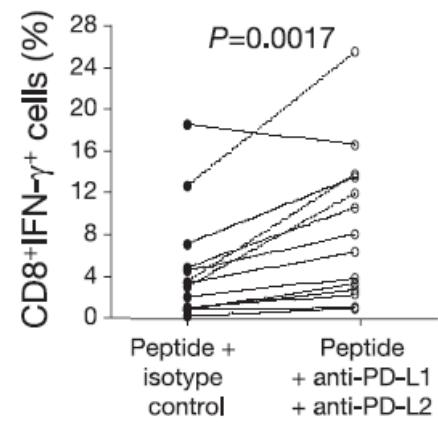
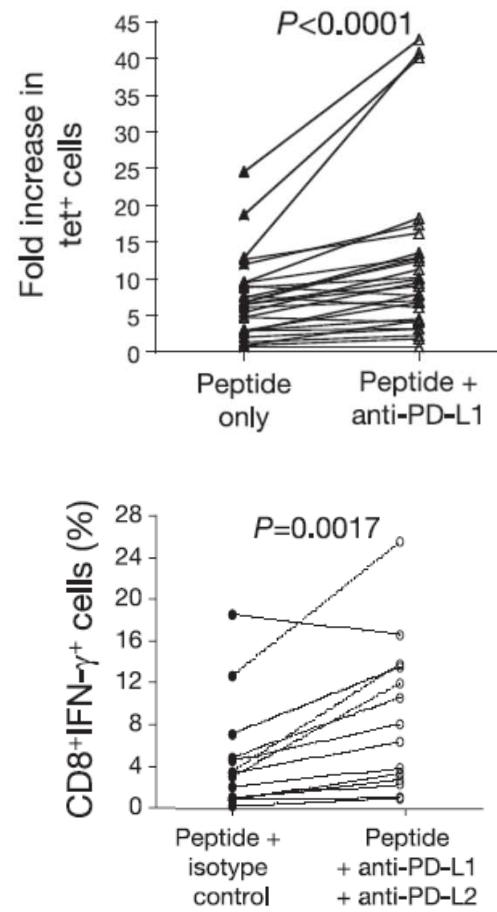


Trautmann *et al*, *Nat Med.* 2006;12:1198



Cockerham *et al*, *AIDS.* 2014; 28: 1749

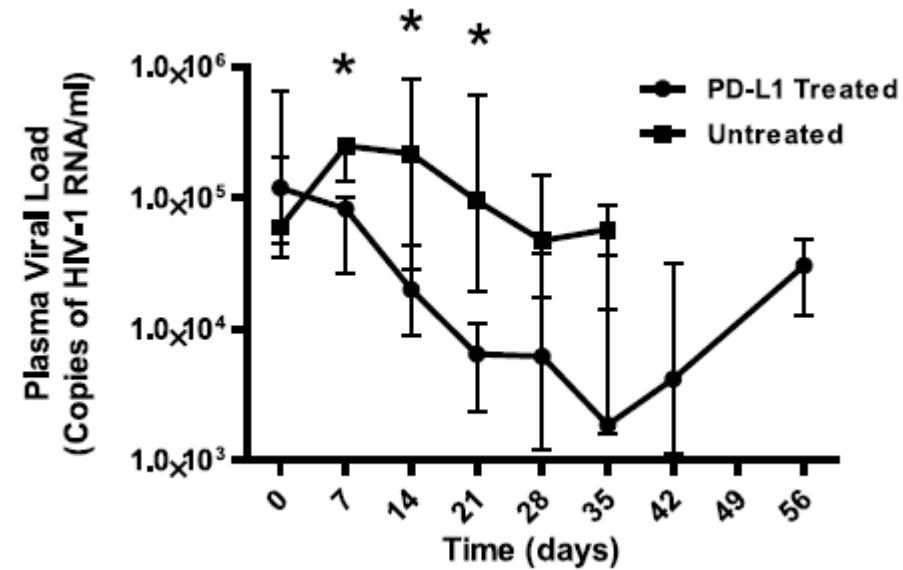
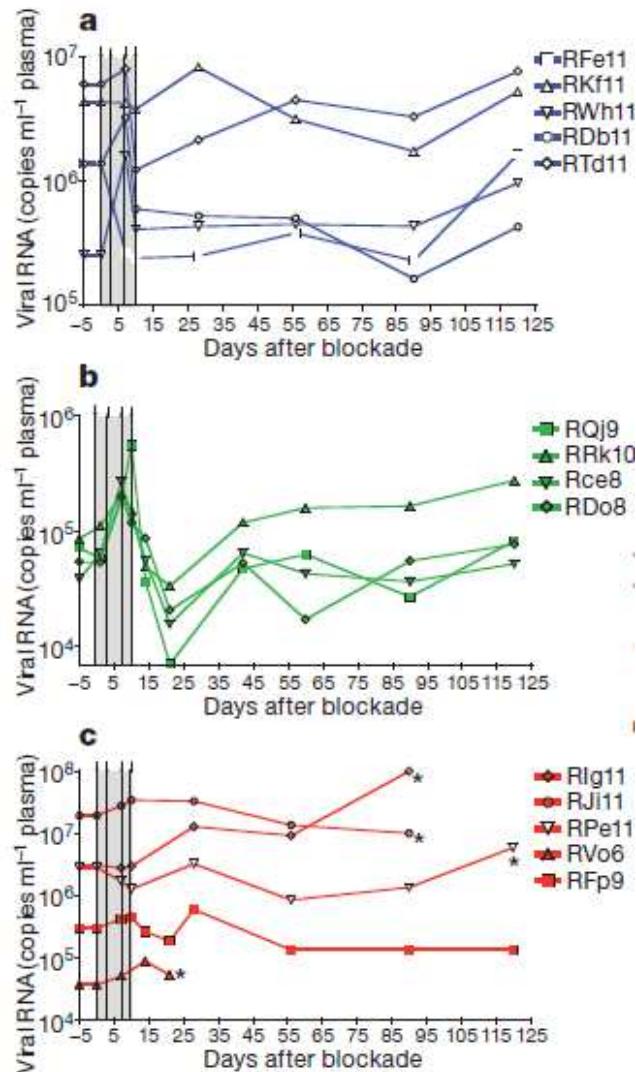
Blockade of the PD-1/PD-L1 pathway significantly increases expansion of HIV-sp. T cells and frequency of HIV-sp. IFNg producing CD8 T cells



Trautmann et al, Nat Med. 2006;12:1198

Day et al, Nature. 2006;443:350

Anti-PD-L1 and anti-PD-L2 antibodies increase HIV-specific CD4 and CD8 T-cell function in vivo (1)

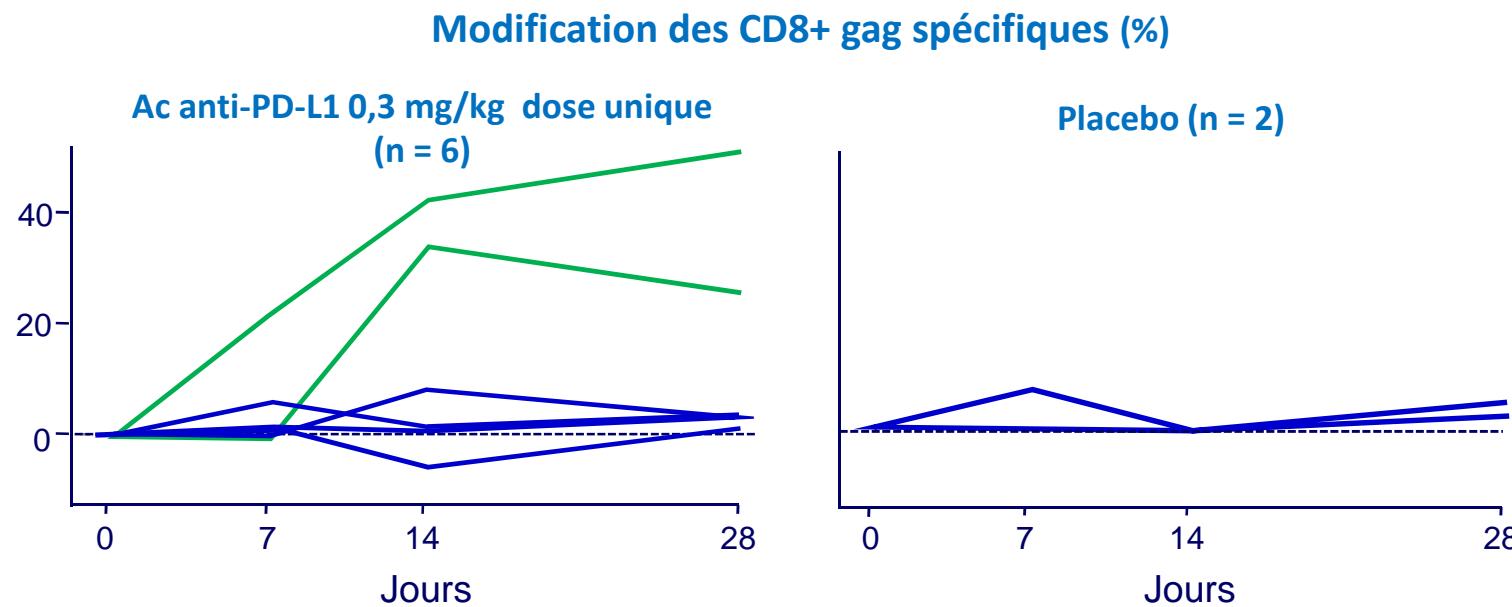


n=6 and n= 7 humanized mice treated with 200 mg of BMS humanized anti-PD-L1 mAb every 3 d for 4 wk (days 3–28)

Velu et al, *Nature* 2009;458:206

Palmer BE et al, *J Immunol.* 2013;190:211

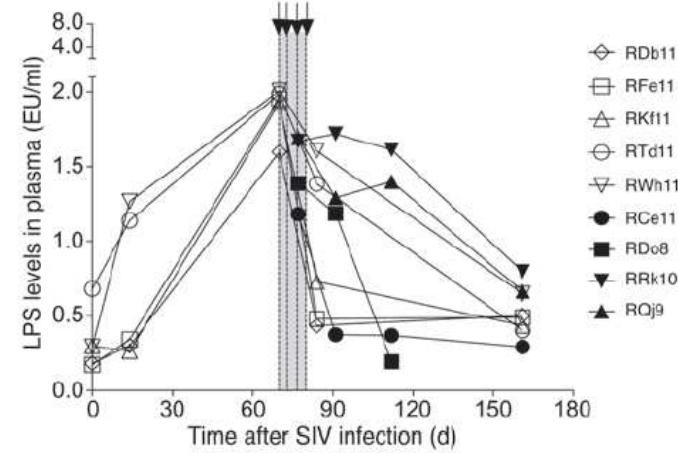
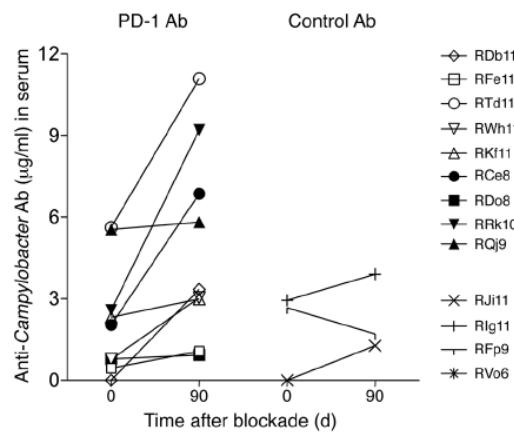
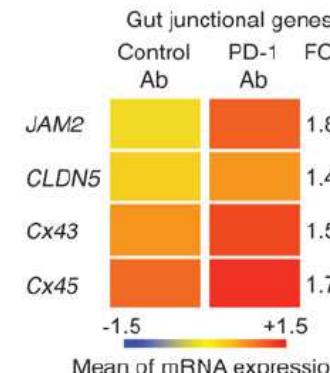
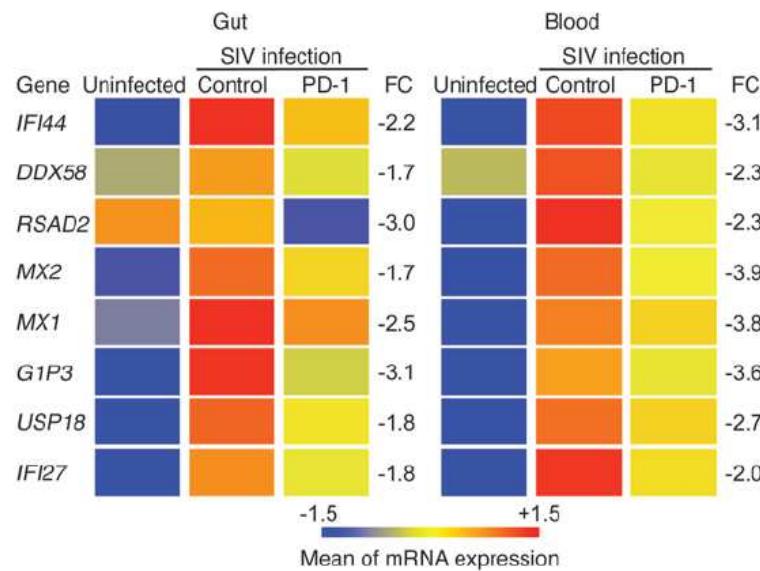
Anti-PD-L1 antibody increase HIV-specific CD8 T-cell function in vivo (2)



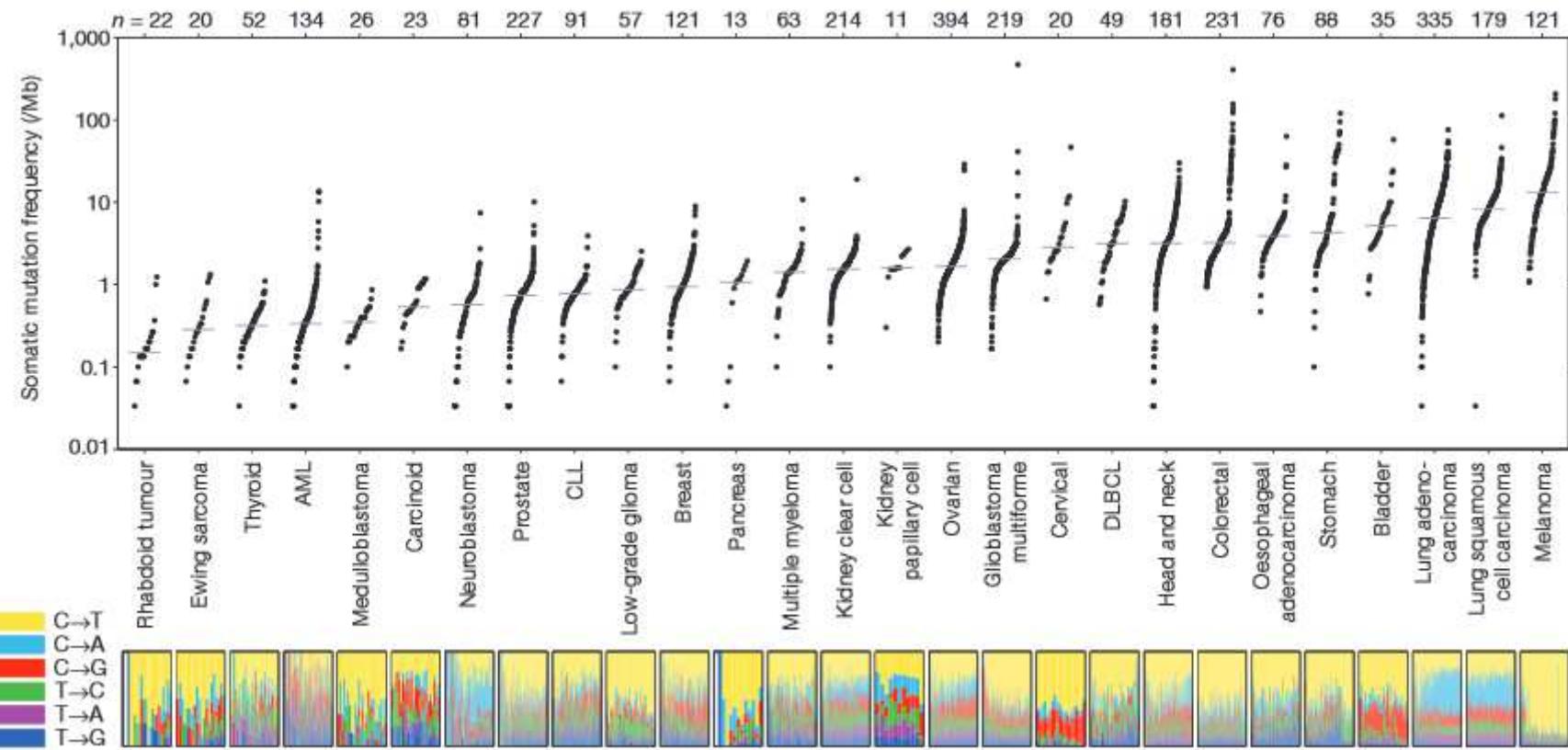
N=6 patients – 1 injection anti-PD-L1 0,3mg/kg

Virologie : pas d'impact sur virémie résiduelle, ARN VIH associé aux cellules, ADN VIH

PD-1 blockade during chronic SIV infection reduces hyperimmune activation and microbial translocation in rhesus macaques



Frequency of tumor somatic mutations: Exome compared to normal tissue (n = 3083 pairs)



Lawrence et al. *Nature* 2013;499:214

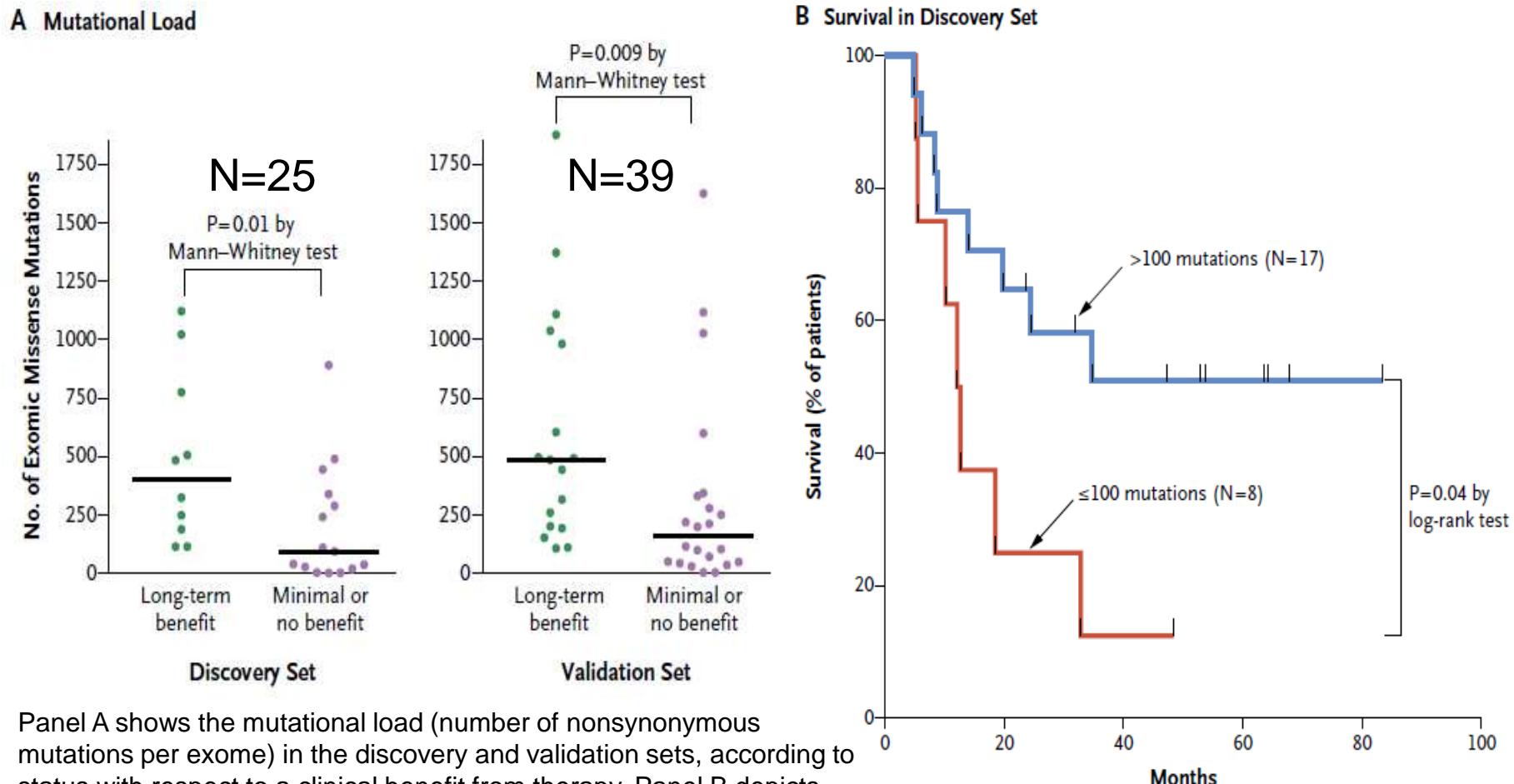
ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D.,
Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D.,
Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D.,
Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A.,
Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elpenahli, B.S.,
Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D.,
Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D.,
and Timothy A. Chan, M.D., Ph.D.

N Engl J Med 2014;371:2189-99.

Mutational load in melanoma, and clinical benefit from CTLA-4 blockade



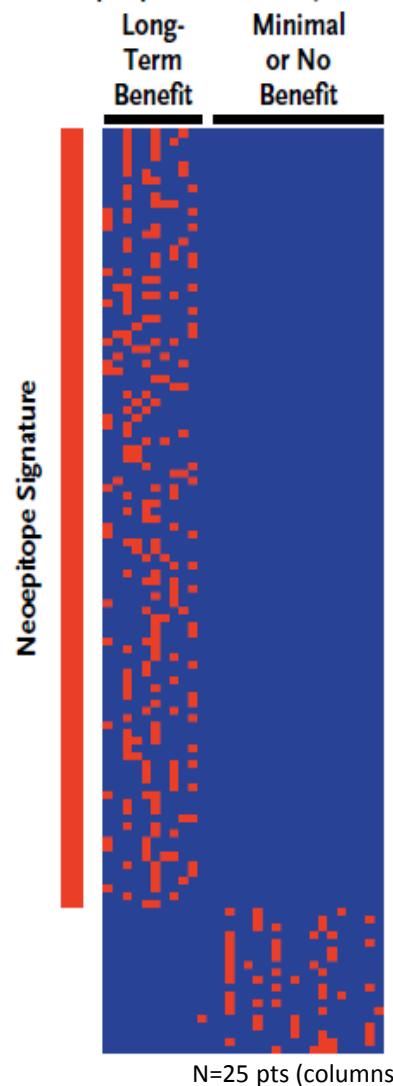
Panel A shows the mutational load (number of nonsynonymous mutations per exome) in the discovery and validation sets, according to status with respect to a clinical benefit from therapy. Panel B depicts the Kaplan-Meier curves for overall survival in the discovery set for patients with more than 100 nonsynonymous coding mutations per exome and patients with 100 or fewer mutations.

Mais qq tumeurs avec taux de mutation élevé ne répondent pas au tt

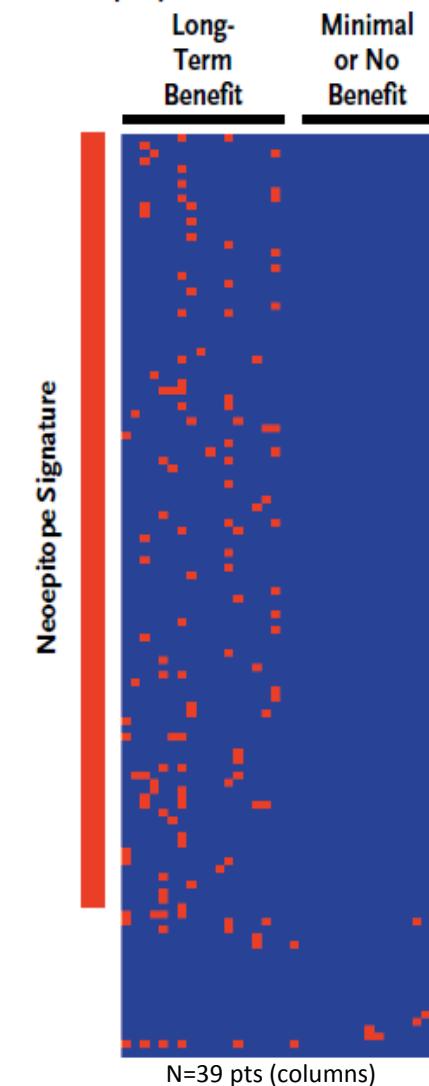
Snyder et al. NEJM 2014;371:2189

Neoepitopes signature and clinical benefit from CTLA-4 blockade

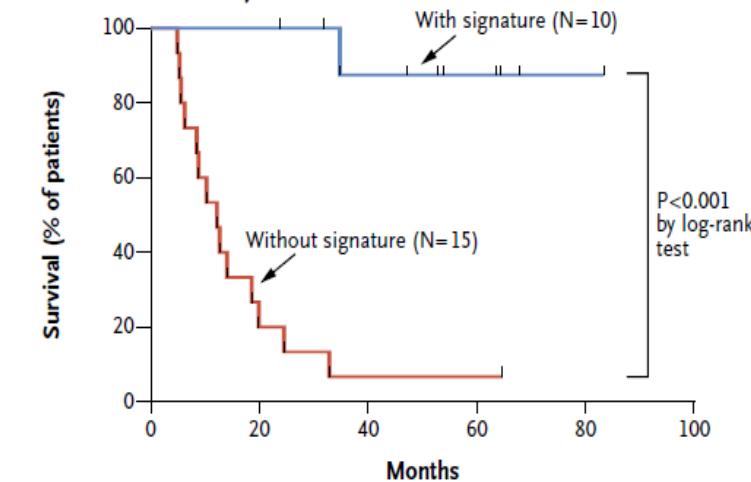
A Neoepitopes in Discovery Set



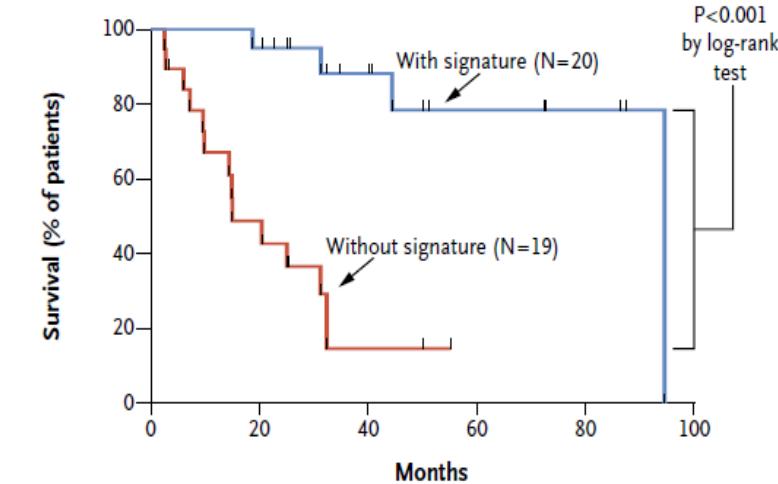
B Neoepitopes in Validation Set



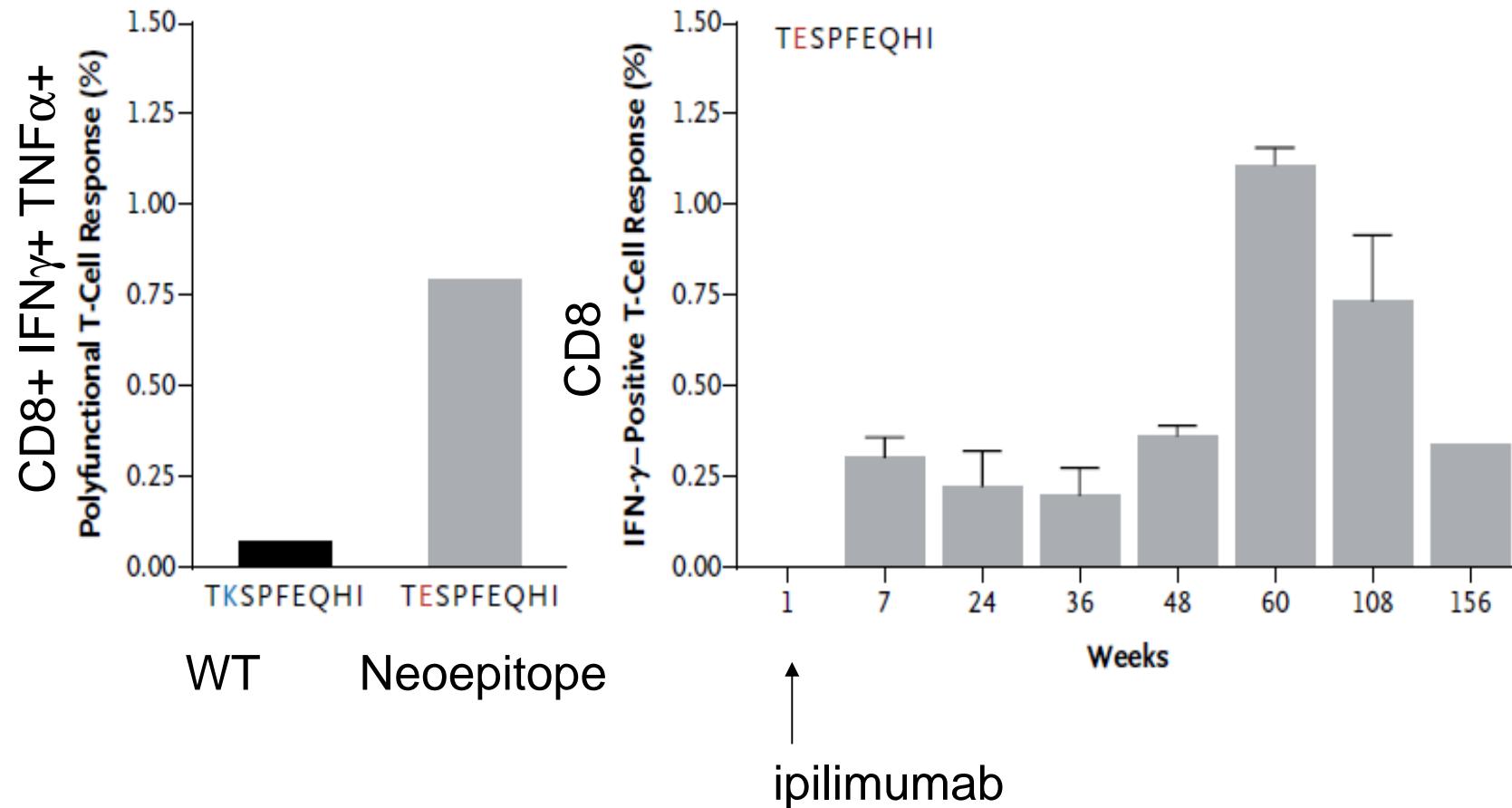
C Survival in Discovery Set



D Survival in Validation Set



Presence of neo-epitope-specific T Cells in Patients Treated with CTLA-4 Blockade



Snyder et al. NEJM 2014;371:2189

PD-1 CANCER-HIV

National program

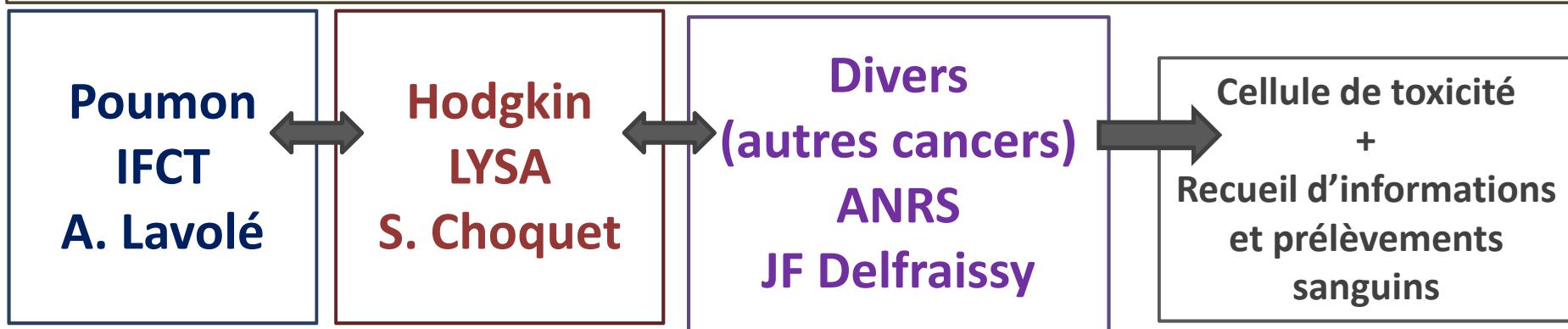
Immunothérapie chez les patients infectés par le VIH atteints de pathologies malignes

Pr. Jean-Philippe SPANO (CANCERVIH, CLIP²)

Pr. Brigitte AUTRAN/Dr Amélie GUIHOT – Dominique COSTAGLIOLA –

Pr. Christine KATLAMA- Pr Olivier LAMBOTTE

Méthodologie – COREVIH – Réseaux de cancérologie - Immunologie



Suivi biologique des PVVIH traitées par anti-PD-1/PD-L1

- **Au prélèvement initial (avant anti-PD-1/PD-L1) seulement :**
 - Charges virales EBV, CMV, HHV-8 si sérologie positive ; et ultérieurement en cas de positivité
 - Quantiféron®
- **Au prélèvement initial et à chaque cycle :**
 - NFS plaquettes, formule, iono, créat, ca, mg, ph, ASAT, ALAT, bili, PAL, gGT, glyc, lipase, albumine, LDH, BU
 - Numération CD4/CD8, charge virale VIH
- **Au prélèvement initial et tous les 3 cycles :**
 - TSH (T3, T4 libre si TSH anormale), anti-corps anti-nucléaires (AAN) avec anti-ADN natif et anti-ENA si AAN positifs, anti-TPO, anti-thyroglobuline
 - Antigène HBS, Charge virale VHB/VHC si co-infection VHB ou VHC
 - betaHCG si femme en âge de procréer

Sous étude Recherche : Objectifs (observatoire et/ou essais)

Virologie et réponses immunes antivirales :

- Impact sur la réponse immune anti-VIH et spécifique des autres virus (EBV, CMV)
- Impact sur les sous populations lymphocytaires circulantes T et expression des immune check points ; sur l'inflammation
- Impact sur la taille du réservoir et sur la réPLICATION VIH à bas bruit, sur la réPLICATION EBV, CMV, HHV-8, HBV, HCV

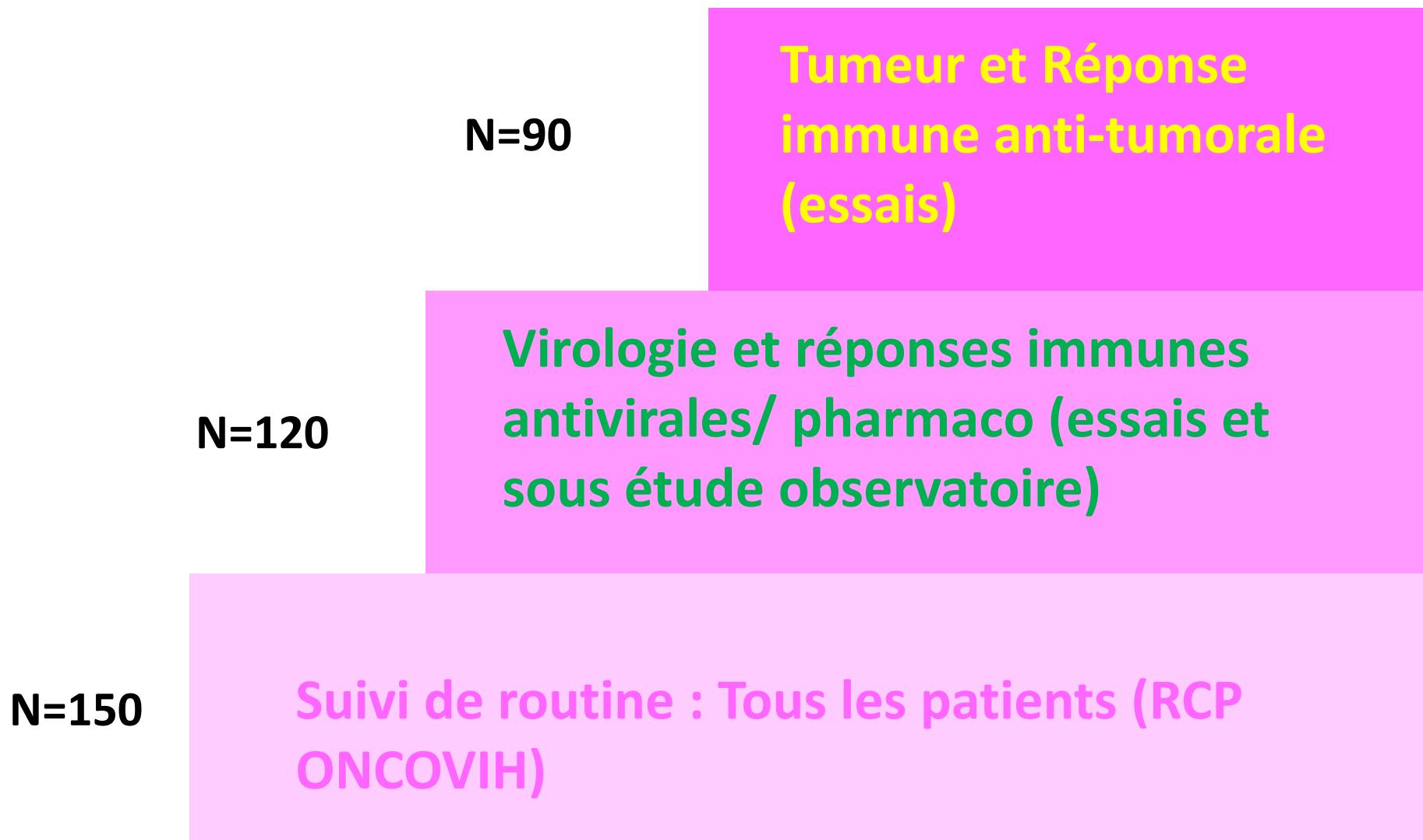
Tumeur et Réponses immunes anti-tumorale :

- Etude du mutanome tumoral, présence de néo-épitopes, présence de CTL spécifiques de néo-épitopes dans le sang périphérique
- Etude du microenvironnement tumoral avant et après chimiothérapie de première ligne

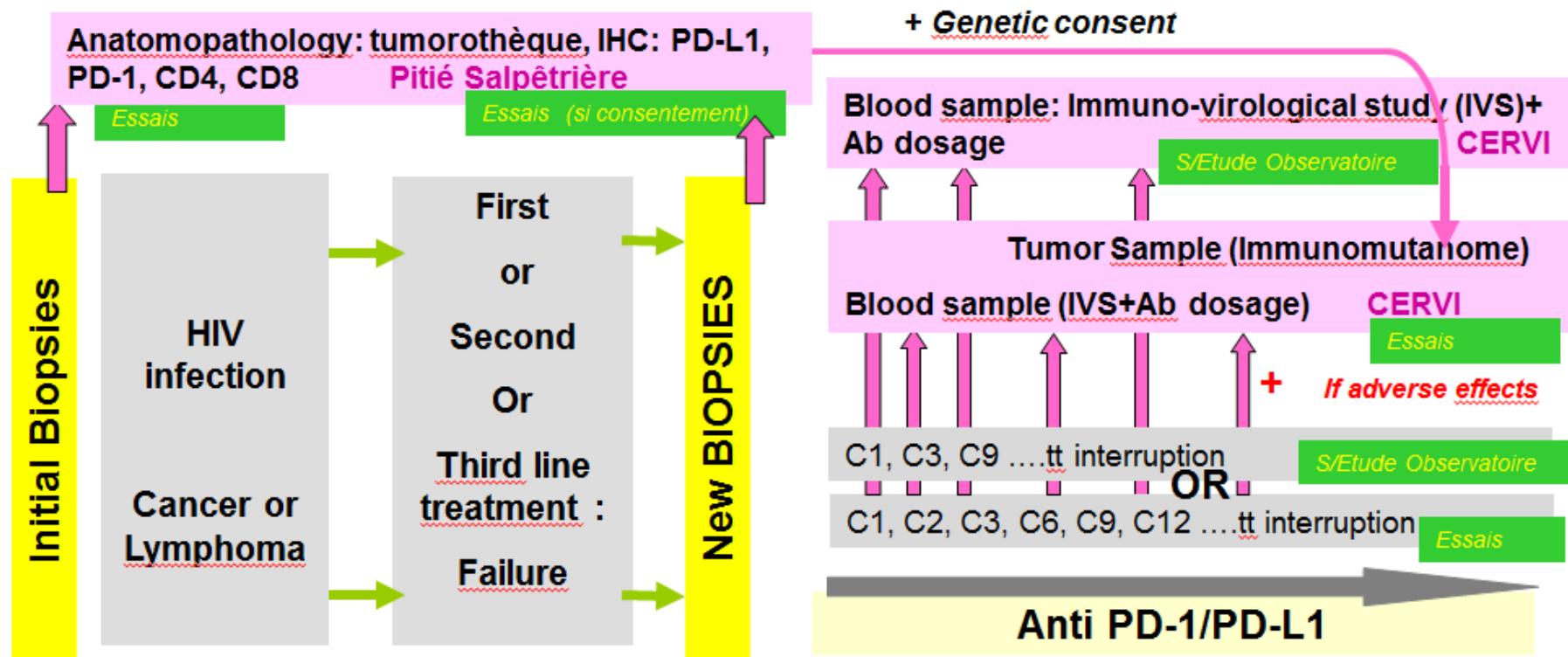
Immuno-Pharmacologie :

- Dosage des anticorps anti-PD-1 ou PD-L1

Inclusions dans les protocoles de recherche & prévisions d'Inclusions sur 3 ans



Research program : Flow Chart



Conclusion

Blocage de l'axe PD-1/ PD-L1 chez les PVVIH atteints de cancer :

1°/ Rompre la tolérance des CTL sp. de **tumeur** et/ou EBV

→ effet anti-tumoral curatif

2°/ Restaurer les réponses T spécifiques du VIH : contrôle optimal de la **réplication du VIH**

→ effet antiviral

3°/ Contrôler de façon optimale l'activation immunitaire et/ou l'inflammation induite par la réplication résiduelle du VIH

→ effet anti-tumoral préventif

- Effet sur le réservoir VIH (ADN viral intracellulaire) incertain : restauration de la prolifération des CD4
- Nécessité de définir des facteurs prédictifs de réponse