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Marine Baron

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Immunité T anti-tumorale et anti-virale chez les patients immunodéprimés

- 1. Paysage mutationnel, immunogénicité et microenvironnement tumoral des lymphomes non Hodgkiniens B survenant dans un contexte d'immunodépression*
- 2. Impact des inhibiteurs de PD-1 sur l'immunité T anti-virale et le réservoir VIH chez les patients vivant avec le VIH et atteints de cancers*

Par Marine BARON

Thèse de doctorat d'Immunologie

Dirigée par Vincent Vieillard et Amélie Guihot

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A Jennifer, disparue bien trop tôt

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Abréviations

ADN : acide désoxyribonucléique

AID : activation-induced cytidine deaminase

ARN: acide ribonucléique

ARV : anti rétroviraux

BART: BamH1-A rightward transcripts

BCR : B-cell receptor

B2M : béta2-microglobuline

CDR3: complementary determining region 3d

CIITA: class-II major histocompatibility complex transactivator

CLIP: class-II associated invariant chain peptideC

CMH: complexe majeur d'histocompatibilité

CMT: charge mutationnelle tumorale

CPA: cellule présentatrice d'antigène

CTLA-4 : cytotoxic T lymphocyte antigen-4 protein

DDR1 : discoidin domain receptor 1

EBER: EBV- encoded RNA

EBNA : Epstein Barr nuclear

EBV: Epstein-Barr Virus

ERAP: endoplasmic reticulum aminopeptidase

FR3 : framework region 3

ICP : points de contrôle immunitaires

ICPi : inhibiteur des points de contrôle immunitaire

IDO : indoleamine 2,3-dioxygenase

Ig: immunoglobuline

IL :interleukine

Indel : insertions-deletions

KLH : keyhole limpet hemocyanin

LAG-3 : lymphocyte activating 3

LBDGC: lymphome B diffus à grandes cellules

LCM : lymphome à cellules du manteau

LF : lymphome folliculaire

LH : lymphome de Hodgkin

Li : invariant chain

LLC: leucémie lymphoïde chronique

LMP : latent membrane protein

LNH: lymphome non hodgkinien

LPT : lymphome post-transplantation

LTC: lymphocytes T cytotoxiques

mTOR: mammalian target of rapamycin

NK: Natural Killer

MET: micro-environnement tumoral

MNI : mononucléose infectieuse

PD-1 : programmed cell death 1

RE: réticulum endoplasmique

RR: rechute ou réfractaire

SIR : standardized incidence ratio

SNV: single nucleotide variant

TAA: tumor associated antigen

SHM: somatic hypermutation

TAP 1 : transporter associated with antigen processing 1

TAP 2 : transporter associated with antigen processing 2

TCM: T centrale mémoire

TCR: T-cell receptor

TEM: T effectrice mémoire

TPM: T périphérique mémoire

TRM: T residente mémoire

TIM-3: T-cell immunoglobulin and mucin containing protein-3

TIGIT: T cell immunoreceptor with Ig and ITIM domains

TLR: Toll-like récepteur

VAF : variant allele frequency

VEGF: vascular endothelial growth factor

VIH: virus de l'immunodéficience humaine

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Introduction

1. Immunité anti-tumorale

L'importance du système immunitaire, et notamment de l'immunité médiée par les lymphocytes *Natural Killer* (NK) et les lymphocytes T, dans le contrôle des cellules cancéreuses est rapportée depuis de nombreuses années (Burnet, 1970, 1964; Kaplan, 1971).

1.1. Immunosurveillance

En 1909, Paul Ehrlich formule l'hypothèse que les défenses immunitaires de l'hôte peuvent prévenir le développement de cancers dans certaines situations, mais sans pouvoir le démontrer formellement (Ehrlich: Ueber den jetzigen Stand der Karzinomforschung - Google Scholar). En 1996, la démonstration que des souris peuvent être immunisées contre des tumeurs syngéniques (Old & Boyse, 1964; Klein, 1966) permet d'établir le concept d'antigènes spécifiques aux tumeurs et aboutit à la définition du concept **d'immunosurveillance** par Burnet en 1970 qui écrit: « *in large, long-lived animals, like most of the warm-blooded vertebrates, inherited genetic changes must be common in somatic cells and a proportion of these changes will represent a step toward malignancy. It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially, dangerous mutant cells and it is postulated that this mechanism is of immunological character* » (Burnet, 1970). Ce concept est ensuite confirmé chez l'humain, notamment par le constat d'une augmentation du risque de cancers, viro- mais également non viro-induits, chez les patients immunodéprimés et d'un lien de corrélation entre le taux de lymphocytes T, notamment T CD8+, infiltrant les tumeurs et une augmentation de la survie des patients, notamment dans le contexte du mélanome et du cancer colorectal (Clemente *et al*, 1996; Dunn *et al*, 2002; Pagès *et al*, 2018; Angell *et al*, 2020; Bruni *et al*, 2020) (**Figure 1**). Pendant de nombreuses années, la recherche des antigènes tumoraux s'est concentrée sur des auto-antigènes, appelés antigènes associés aux tumeurs (**TAA**), qui sont anormalement exprimés ou surexprimés dans les tissus tumoraux, mais qui sont donc sujets à la **tolérance** périphérique ou centrale. Des décennies plus tard, la définition et la caractérisation des **antigènes spécifiques des tumeurs** impliqués dans la reconnaissance immunologique spécifique, et donc non sujets à la tolérance, étaient finalement faites sous le nom de **néoépitopes**. Les néoépitopes sont définis comme des peptides dérivés

des **protéines mutées spécifiques** de la tumeur et sont donc issus de la transcription et de la traduction de l'ADN génomique tumoral muté (mutations somatiques). De ce fait, ils n'ont pu être caractérisés que récemment grâce à l'avènement des techniques de séquençage de l'exome à haut débit et de détection des lymphocytes T spécifiques (Schumacher & Schreiber, 2015a). La majorité des mutations tumorales survenant de façon spécifique chez chaque patient, les techniques de séquençage rapides et peu coûteuses de l'exome tumoral étaient effectivement indispensables à leur caractérisation.

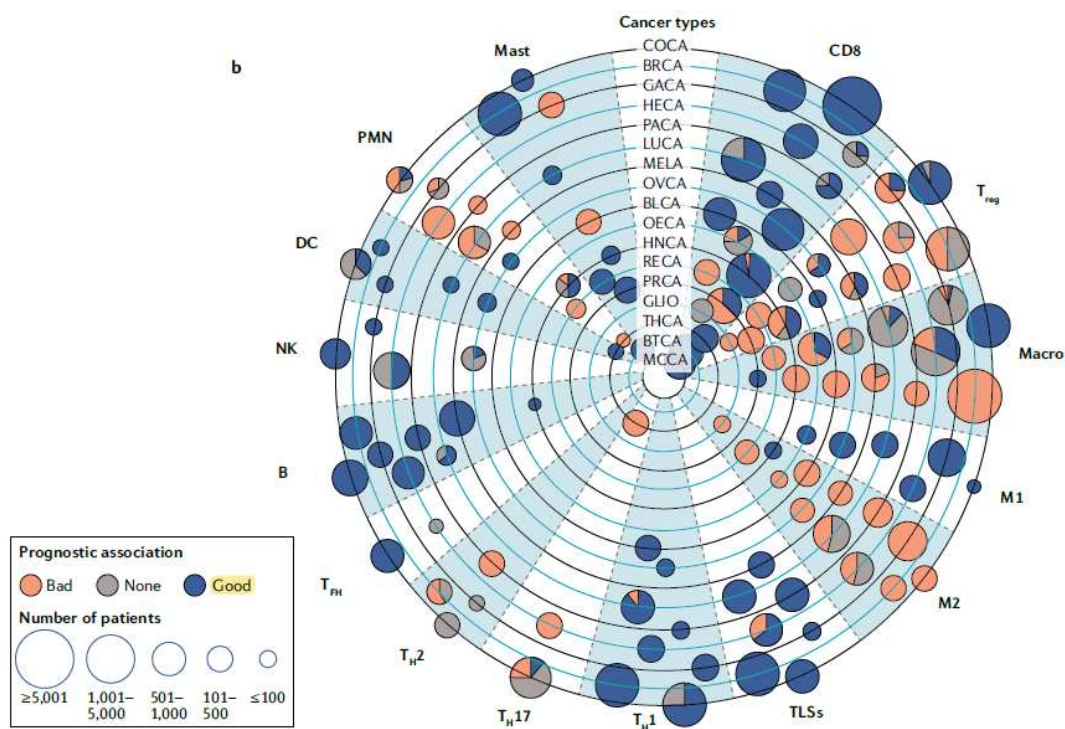


Figure 1. Effets de l'infiltrat immunologique sur le pronostic des patients avec cancer. Les datas sont issues de 300 études avec plus de 70 000 patients atteints de cancers de différents types, en fonction de 14 populations immunologiques différentes au sein de la tumeur : les lymphocytes : T CD8+ cytotoxiques (CD8), les T régulateurs (T_{reg}), les macrophages (macro), les macrophages M1 (M1), les macrophages M2 (M2), les structures tertiaires lymphoïdes (TLSs), les lymphocytes T helper 1 (T_{H1}), T helper 17 (T_{H17}), T helper 2 (T_{H2}), T follicular helper (T_{FH}), les lymphocytes B (B), les lymphocytes NK (NK), les cellules dendritiques (DCs), les cellules suppressives d'origine myéloïde (PMNs) et les mastocytes (mast). La couleur des cercles indique le caractère : bon (good, en bleu), mauvais (bad, en rose) ou sans effet (none, en gris) de la population cellulaire en question sur le pronostic des patients. La taille des cercles

indique le nombre de patients inclus dans les études. BLCA : bladder cancer; BRCA : breast cancer; BTCA : biliary tract cancer; COCA: colorectal cancer; GACA: gastric cancer; GLIO : glioma; HECA : hepatocellular carcinoma ; HNCA : head and neck cancer ; LUCA : lung cancer ; MCCA : Merkel cell carcinoma ; MELA : melanoma ; OECA : oesophageal cancer ; OVCA : ovarian cancer ; PACA : pancreatic cancer ; PRCA : prostate cancer ; RECA : renal cell carcinoma ; THCA : thyroid cancer. Tiré de (Bruni *et al*, 2020).

1.2. Immunogénicité des tumeurs

1.2.A. Présentation des néoépitopes tumoraux

Les néoépitopes tumoraux peuvent être issus d'altérations survenant à tous les stades de biosynthèse d'une protéine (anomalies mutationnelles, translocations chromosomiques et gènes de fusion, anomalies de l'épissage ou encore anomalies post-traductionnelle telle que phosphorylation ou glycosylation) (Malaker *et al*, 2017; De Mattos-Arruda *et al*, 2020a; Zeneyedpour *et al*, 2020; Wang *et al*, 2021; Jhunjunwala *et al*, 2021; Sabdia *et al*, 2022) et sont présentés aux lymphocytes T CD8+ par l'intermédiaire du complexe majeur d'histocompatibilité de type 1 (CMH-1) exprimé à la surface des cellules tumorales. Une multitude d'étapes et d'acteurs sont impliqués dans la présentation des néoépitopes à la surface des cellules (**Figure 2**). Le **protéasome** est le principal complexe enzymatique qui dégrade les polypeptides et protéines cellulaires en peptides. Ces peptides sont ensuite transportés vers le réticulum endoplasmique (RE) grâce à l'intervention des « transporter associated with antigen processing » (TAP1 et TAP2), où ils peuvent être de nouveau coupés par des « aminopeptidases du RE » (ERAP). Le **processus de chargement des peptides** dans les molécules du CMH-1 se fait en plusieurs étapes et fait intervenir différentes protéines chaperonnes (calnexine, tapasine, calreticuline, Erp57). Seuls les complexes peptides-CMH-1 formés d'un peptide avec une forte affinité (score d'affinité au moins <500 nM) pour le CMH quittent finalement le RE pour rejoindre la surface de la cellule où ils peuvent être reconnus par le récepteur T (TCR) spécifique des lymphocytes T CD8+, sous réserve d'une durée de liaison du complexe CMH-peptide (évaluée par le paramètre de stabilité) suffisante et de la présence d'un clonotype spécifique du TCR.

En parallèle, les cellules présentatrices d'antigènes (**CPA**) du microenvironnement tumoral (MET), telles que les cellules dendritiques, les macrophages et les lymphocytes B présentent

également ces néoépitopes, issus des peptides tumoraux captés du milieu extra-cellulaire, aux LT CD4+ **via le CMH de classe II**. La captation des antigènes extra-cellulaires par les CPA se fait grâce à des mécanismes de phagocytose et d'endocytose par l'intermédiaire du récepteur des cellules B (BCR) pour les lymphocytes B ou des récepteurs du mannose, du complément, du fragment constant (Fc) des immunoglobulines (Ig) et des récepteurs éboueurs (« scavengers ») pour les cellules dendritiques et les macrophages respectivement (Pishesha *et al*, 2022). Par ailleurs, des mécanismes de macro et micropinocytose (ingestion de gouttelettes lipidiques issues du milieu extra-cellulaire) participent également à la captation de substances extra-cellulaires. En parallèle, les molécules du CMH-II sont synthétisées dans le RE où elles s'associent à une chaîne invariante (invariant chain ou Ii) qui empêchent la fixation de peptides sur les molécules du CMH-II au cours de leur migration cytoplasmique. Elles migrent ensuite, en passant par l'appareil de Golgi, dans les **compartiments endolysosomiques** au sein desquels la chaîne invariante est dégradée enzymatiquement par une endoprotéase pour produire un fragment de Ii (nommé CLIP pour class-II associated invariant chain peptide). Sous l'influence d'HLA-DM (molécule analogue structurellement aux molécules de CMH-II et dont l'activité est régulée par HLA-DO), le CLIP est finalement expulsé et remplacé par un peptide ayant une stabilité suffisante pour les molécules du CMH grâce à un processus « **d'édition peptidique** » (ou « peptide editing ») (le peptide étant échangé jusqu'à obtention d'une stabilité importante du complexe). Cet étape permet ainsi de créer un **complexe peptide-CMH II fonctionnel** qui peut alors être transporté à la surface cellulaire dans des vésicules pour interagir avec les LT CD4+. L'expression des molécules du CMH-II est notamment régulée par un facteur de transcription nommé « Class II major Histocompatibility Complex Transactivator » ou **CIITA** dont l'activité, en se fixant sur les promoteurs des gènes codant pour les molécules du CMH-II, en augmente l'expression.

Il est important de souligner ici qu'une présentation croisée (« cross-presentation ») de ces néoépitopes par les cellules dendritiques aux lymphocytes T CD8+ est indispensable à l'initiation (« **priming** ») de la réponse immunitaire initialement.

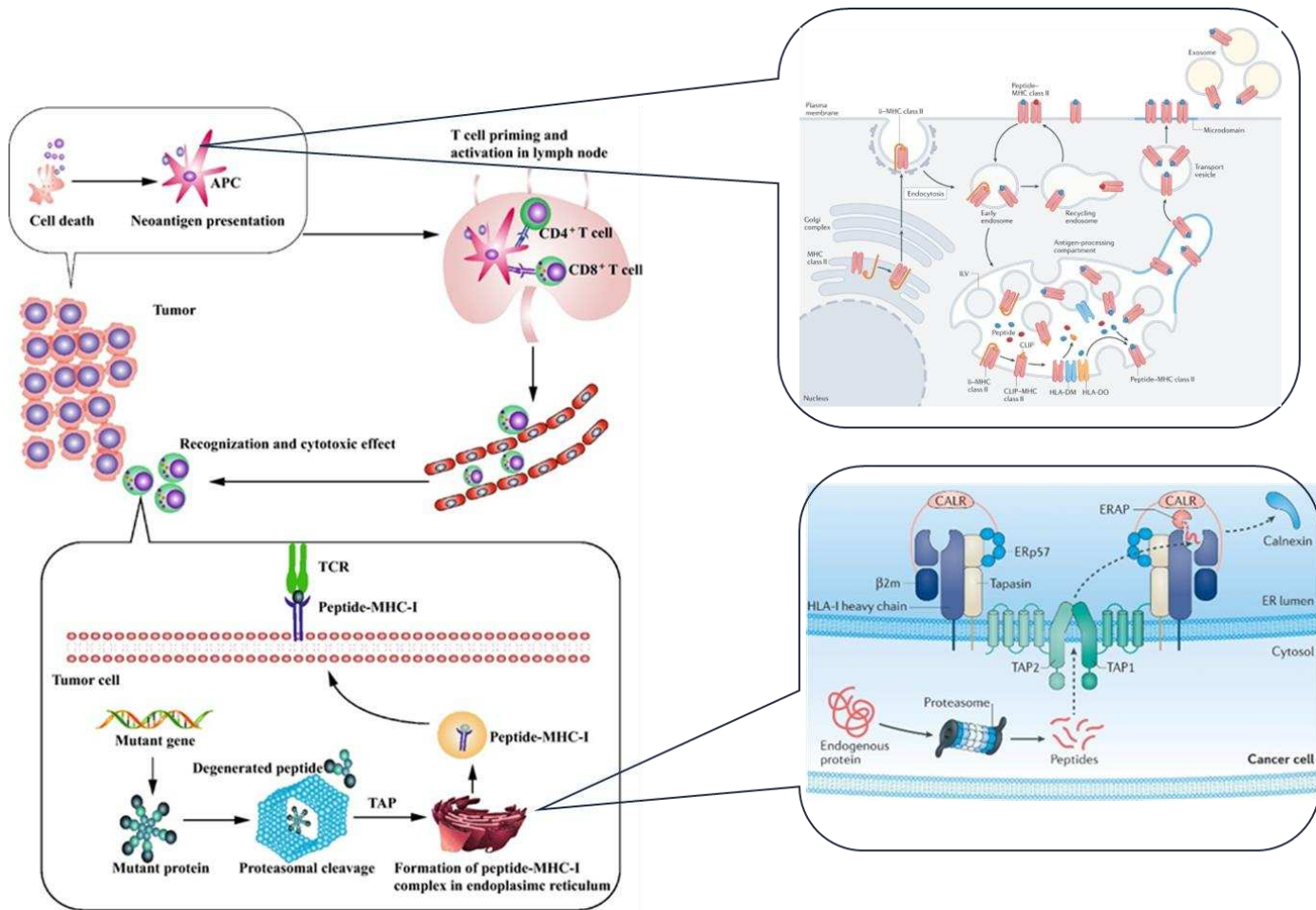


Figure 2. Cycle de l'immunité anti-tumorale et présentation antigénique. Cycle : les néoépitopes relargués par les cellules tumorales mortes sont capturés par les CPA qui initient la réponse immunitaire périphérique spécifique des néoépitopes (« priming ») au sein des organes lymphoïdes secondaires. Les cellules T périphériques activées migrent et infiltrent les tissus tumoraux et tuent les cellules tumorales après reconnaissance des néoépitopes exprimés à leur surface. **Encart haut : Présentation antigénique par les molécules du CMH-II :** Les molécules du CMH-II s'associent à la chaîne invariante chaîne invariante (Ii) dans le RE et migrent à la surface de la cellule via l'appareil de Golgi. A partir de là, le complexe est acheminé vers les compartiments endosomaux ou atteint la surface de la cellule d'où il peut être internalisé et livré aux compartiments de présentation de l'antigène. Il est ensuite dégradé enzymatiquement pour produire le CLIP qui reste lié au sillon de liaison peptidique du CMH-II. Le CLIP est ensuite éliminé lors d'un échange avec un peptide antigénique dans une réaction assistée par le chaperon HLA-DM dont l'activité est elle-même régulée par HLA-DO. Les molécules de CMH-II sont ensuite transportées vers la membrane plasmique. Les complexes peptide-CMH-II présents à la surface de la cellule peuvent être internalisés et subir une

dégradation lysosomale ou être recyclés vers la membrane plasmique. **Encart bas: Présentation antigénique par les molécules du CMH-I:** les protéines mutantes dérivées des mutations somatiques tumorales sont dégradées en peptides par le protéasome et transportées ensuite vers le RE grâce notamment à l'intervention des transporteurs TAP où ils peuvent être de nouveau coupés par des « aminopeptidases du RE » (ERAP). Le peptide muté se lie au CMH-I sous réserve d'une affinité suffisante. Le complexe peptide-CMH-I est ensuite transporté à la surface de la cellule tumorale où il pourra être reconnu par les lymphocytes T cytotoxiques qui tueront la cellule. ILV, vésicule intraluminaire CALR : calreticuline ; HLA: human leucocyte antigen ; TAP1 et 2 : transporters associated with antigen presentation ; ER : endoplasmic reticulum; ERAP: ER aminopeptidase; β 2M: β 2-microglobulin ; . Tiré de (Yi *et al*, 2018; Jhunjhunwala *et al*, 2021; Pishesha *et al*, 2022).

Les **mutations** peptidiques issues des mutations somatiques tumorales peuvent affecter la reconnaissance par les lymphocytes T de 3 façons différentes : 1. En créant un acide aminé d'ancrage permettant la liaison du peptide à une molécule du CMH (« mutation d'ancrage »), 2. En créant un peptide reconnu par un autre clonotype T non affecté par la tolérance centrale (« mutations en regard du TCR »), 3. En modifiant le processus de présentation du peptide en question (**Figure 3**) (Vormehr *et al*, 2016).

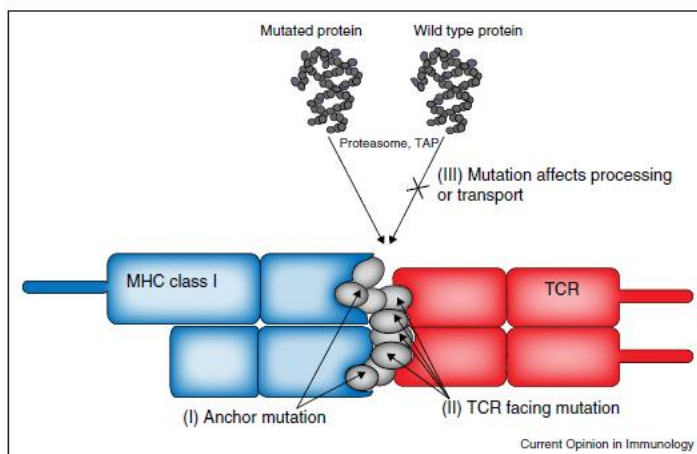


Figure 3. Les mutations somatiques peuvent induire des néoépitopes selon 3 différents mécanismes. Mutations affectant : les acides aminés d'ancrage (I), les résidus reconnus par les TCR en regard (II), le processus de présentation (III). Tiré de (Vormehr *et al*, 2016).

1.2.B. Quantité et qualité des néoépitopes tumoraux

La capacité du système immunitaire à déclencher une réponse contre un néoépitope donné dépend d'un ensemble de **facteurs** incluant 1. la **quantité** des néoépitopes, 2. la capacité de **présentation** de ces néoépitopes 3. les **qualités** d'immunogénicité des néoépitopes présentés et 4. la capacité de **reconnaissance** des TCR en regard (McGranahan & Swanton, 2019; Wells *et al*, 2020; De Mattos-Arruda *et al*, 2020a; Sabdia *et al*, 2022). La **quantité** de néoépitopes présentés est notamment dépendante du nombre de mutations présentes au sein du génome tumoral (charge mutationnelle tumorale, ou CMT). Plus un génome tumoral est muté, plus la cellule est en théorie capable de présenter des néoépitopes à sa surface, et il est désormais clairement admis qu'une CMT élevée et/ou un nombre de néoépitopes élevé sont associés à une meilleure réponse aux immunothérapies non spécifiques de type inhibiteurs d'immunité checkpoint (ICPi) (Brown *et al*, 2014; Rizvi *et al*, 2015, 2018). De fait, les 2 cancers bénéficiant le plus actuellement des ICPi, le cancer du poumon et le mélanome, sont des cancers médiés par une exposition à des carcinogènes tels que le tabac et le soleil responsables de charges mutationnelles élevées généralement supérieures à 10 mutations/mégabase (Australian Pancreatic Cancer Genome Initiative *et al*, 2013; Alexandrov *et al*, 2020).

Si la quantité des néoépitopes présentés apparaît donc fondamentale à l'instauration d'une réponse immunitaire efficace, la **qualité** des néoépitopes en est également un enjeu majeur. Mc Granahan titrait ainsi en 2019 une revue traitant du choix des néoépitopes à privilégier « neoantigen quality, not quantity » (McGranahan & Swanton, 2019) et rapportait les différents paramètres théoriques garantissant une meilleure qualité d'immunogénicité aux néoépitopes. Le **type** d'anomalies dont sont issus les néoépitopes en est un premier paramètre majeur. Les peptides tumoraux doivent être **suffisamment uniques** (et donc différents des peptides sauvages) pour ne pas être sujets à la tolérance de l'hôte. Les variants d'un seul nucléotide (single nucleotide variant, ou SNV) sont les mutations les plus fréquemment retrouvées dans les génomes tumoraux mais les néoépitopes qui en découlent sont souvent peu différents des peptides sauvages (De Mattos-Arruda *et al*, 2020a). A l'inverse, les anomalies mutationnelles de type insertion-délétion (indel) avec décalage du cadre de lecture (Turajlic *et al*, 2017), ou variations de l'épissage (mutations des sites d'épissage, mutation des facteurs impliqués dans l'épissage, rétention d'intro) (Hoyos & Abdel-Wahab, 2018), ou issues de gènes de fusion (Wei *et al*, 2019; Yang *et al*, 2019; Wang *et al*, 2021) modifient davantage les séquences peptidiques mutées et sont génératrices de néoépitopes plus immunogènes (9 et 2.5

fois plus immunogènes que les SNV pour les indels et les anomalies de l'épissage respectivement). Les autres facteurs théoriques impliqués dans la qualité d'immunogénicité des néoépitopes ont fait l'objet de nombreux rapports ces dernières années au vu de leur implication thérapeutique potentielle et comportent notamment : la fréquence de l'allèle muté reflétant notamment le caractère potentiellement « driver » de la mutation, le niveau d'expression du gène, le niveau d'affinité du néoépitope pour le complexe du CMH, la capacité du néoépitope à être présenté par différentes molécules du CMH, le type de molécules du CMH, la stabilité du complexe et la présence de néoépitopes partagés (Heemskerk *et al*, 2012; McGranahan & Swanton, 2019; De Mattos-Arruda *et al*, 2020a; Wells *et al*, 2020). Une **fréquence de l'allèle muté** (variant allele frequency, ou VAF) élevée peut refléter à la fois la présence d'une mutation « driver » (et donc avec une faible possibilité d'échappement par perte de néoépitope) et la possibilité d'une réponse T spécifique dirigée contre l'ensemble des cellules tumorales (Miao *et al*, 2018; McGranahan *et al*). Une **hétérogénéité intra-tumorale** est ainsi associée à une réponse immunitaire moins efficace. A l'inverse, les mutations « **passengers** », non indispensables à la cellule tumorale, représentent 85% des mutations tumorales et sont en théorie plus à risque d'échappement tumoral par perte d'expression de la mutation (par délétion de régions chromosomiques par exemple) (Heemskerk *et al*, 2012; Anagnostou *et al*, 2017). **L'expression de l'ARN muté** est quant à elle un paramètre indispensable à connaître puisque la majorité des mutations faux-sens survenant dans un génome tumoral ne sont pas exprimées ou qu'il existe des phénomènes de répression transcriptionnelle, ne permettant donc pas la génération d'un néoépitope. Le **CMH** est très polymorphe et certains travaux ont suggéré que les molécules du CMH hétérozygotes et/ou les néoépitopes putatifs présentés par plusieurs molécules du CMH pourraient être particulièrement intéressants (car avec moins de risque de perte de présentation par perte d'hétérozygotie), ou encore que certains types du CMH étaient associés à une meilleure survie chez des patients traités par ICPI (Chowell *et al*, 2018; De Mattos-Arruda *et al*, 2020a). Enfin, les néoépitopes décrits comme **partagés** (« shared » ou « public ») entre différents patients, et donc issus de mutations stéréotypées survenant dans les génomes tumoraux, sont particulièrement attirants car ils peuvent permettre le développement de thérapies ciblées pour l'ensemble des patients partageant ces mutations. La **reconnaissance** du complexe peptide-CMH par les lymphocytes T en regard et la mise en place d'une réponse immunitaire dédiée et efficace font ensuite intervenir différents facteurs, dont le paramètre de stabilité du complexe, l'avidité du TCR pour le néoépitope en question et la diversité du répertoire T intra-tumoral mais également la qualité du **MET**, qui seront traités ultérieurement.

1.2.C. Immunogénicité des tumeurs viro-induites

Dans la plus grande majorité des cas, les cancers ne sont pas viro-induits et les néoépitopes capables de déclencher une réponse immunitaire sont uniquement les néoépitopes tumoraux. Plus rarement, dans 10% des cas, et notamment dans un contexte d'immunosuppression, les cellules tumorales sont infectées par un virus et les néoépitopes peuvent alors découler à la fois des altérations de l'ADN tumoral mais également des protéines virales (Chen *et al*, 2021). En particulier, l'Epstein Barr Virus (EBV) infecte les cellules épithéliales de l'oropharynx et les lymphocytes B et peut être associé au développement de carcinomes oro-pharyngés et de lymphomes B contre lesquels l'immunité anti-virale a un rôle anti-tumoral.

L'immunité T anti-EBV se fait au cours des 2 phases différentes de l'infection par l'EBV (traitée dans la **partie 3**) (Taylor *et al*, 2015). En premier lieu, la réponse T au cours de la primo-infection ou mononucléose infectieuse (MNI) est un des exemples les plus florissants de réponses immunologiques à un pathogène au sein de notre organisme avec une expansion spectaculaire des LT CD8+ spécifiques qui peuvent représenter presque 50% des lymphocytes T totaux. Ces LT CD8+ reconnaissent majoritairement les épitopes lytiques de l'EBV tandis que 5% seulement sont dirigés contre les épitopes latents (Hislop *et al*, 2005). Secondairement, la diminution de la charge virale EBV, témoignant notamment de l'efficacité de la réponse immunologique, s'associe à une contraction du compartiment T périphérique et spécifique. L'EBV est alors présent dans les lymphocytes B dans un état de latence avec une expression réduite des différentes protéines virales tandis que les LT CD8+ spécifiques dirigés contre les épitopes lytiques (BZLF1, BMRF1 et BRLF1) et latents (EBNA3) peuvent représenter jusqu'à 2 et 0.5% des LT totaux respectivement chez des donneurs sains. La présence de ces cellules T mémoire permet normalement de prévenir l'activation non contrôlée des cellules B au cours d'épisodes de réactivation. Les peptides viraux présents dans le contexte des tumeurs viro-induites représentent donc également des néoépitopes d'intérêt capables de déclencher une réponse immunitaire dirigée contre la tumeur, et de d'autant plus qu'ils sont généralement très éloignés du « soi ».

1.3. Immunoédition et échappement tumoral

1.3.A. Immunoédition

Néanmoins, le développement de tumeurs chez des sujets immunocompétents témoigne notamment d'un équilibre imparfait entre tumeur et système immunitaire, qui a fait secondairement évoluer le concept d'immunosurveillance en concept **d'immuno-édition** (Dunn *et al*, 2002) (**Figure 4**). L'immuno-édition rend compte de la **plasticité** des interactions entre ces 2 systèmes vivants (tumoral et immunologique) et des capacités de modulation du système immunitaire par les cellules tumorales aboutissant finalement à l'échappement tumoral. Il définit les 3E du cancer : élimination/ équilibre/échappement. La première phase **d'élimination** correspond à un système immunitaire fonctionnel ; majoritairement composé de cellules NK et de lymphocytes T, qui reconnaît et élimine complètement les cellules tumorales. La deuxième phase **d'équilibre** correspond à la présence de cellules tumorales partiellement contrôlées par le système immunitaire et sans expression clinique. Pendant cette phase, différents mécanismes de **sélection tumorale** aboutissent notamment à la troisième phase **d'échappement** caractérisée par une prolifération tumorale non contrôlée et responsable d'une symptomatologie clinique (Dunn *et al*, 2002; Jhunjhunwala *et al*, 2021).

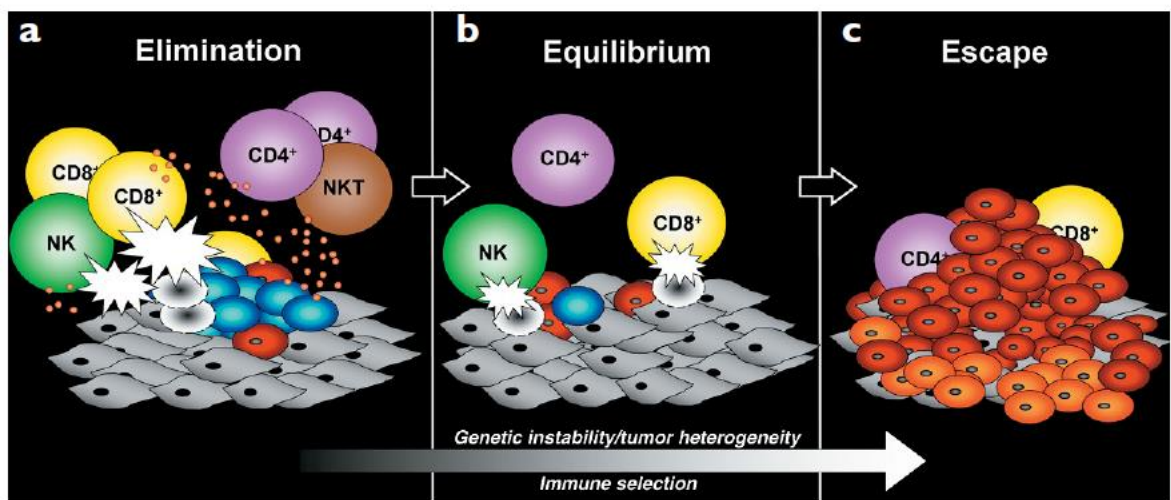


Figure 4. Les 3 E de « l'immunoédition du cancer ». a). L'élimination correspond à l'immunosurveillance. b). L'équilibre correspond au processus pendant lequel le système immunitaire sélectionne ou promeut la génération de cellules tumorales variantes avec des capacités augmentées de survie, c). L'échappement correspond à la phase où la tumeur « sculptée immunologiquement » n'est plus contrôlée. Cellules tumorales : bleu ; cellules

tumorales variantes : rouge et orange ; stroma et cellules non transformées : gris ; petits ronds orange : cytokines ; éclair blanc : activité cytotoxique des lymphocytes. Tiré de (Dunn *et al*, 2002).

1.3.B. Echappement tumoral

L'**échappement** des cellules tumorales au système immunitaire est médié par de très nombreux mécanismes faisant intervenir différents acteurs cellulaires (Jhunjhunwala *et al*, 2021; Sadeghi Rad *et al*, 2021). Au premier rang, la **cellule tumorale** peut diminuer ses capacités de présentation antigénique (perte d'expression, perte d'hétérozygotie ou mutation des molécules du CMH ou de la bêta-2 microglobuline (B2M), diminuer l'expression du CD58 impliqué dans l'activation des lymphocytes T et NK, ou encore muter ou perdre l'expression de néoépitopes immunogènes (Challa-Malladi *et al*, 2011; Matsushita *et al*, 2016; Anagnostou *et al*, 2017; The TRACERx consortium *et al*, 2019). Par ailleurs, le **MET** est constitué de populations immunologiques hétérogènes qui peuvent inhiber ou promouvoir la croissance tumorale (**Figure 5**) (Sadeghi Rad *et al*, 2021). La présence de fibroblastes associés aux tumeurs, de macrophages de type M2 et de lymphocytes T régulateurs, ou encore la production d'IL-10 et de TGF- β participent à la construction d'un MET **tolérogène** facilitant la prolifération tumorale. La fonction des lymphocytes T CD8 cytotoxiques et des CD4 non régulateurs peut quant à elle être altérée par la production de cytokines immunosuppressives mais également par l'expression à leur surface de molécules de points de contrôle immunitaire (ICP). Les ICP sont des molécules exprimées à la surface des cellules de l'immunité, et notamment des lymphocytes, et sont responsables d'une anergie lymphocytaire lorsqu'elles se lient à leur ligand. Ces molécules seront traitées ultérieurement dans la **partie 5**.

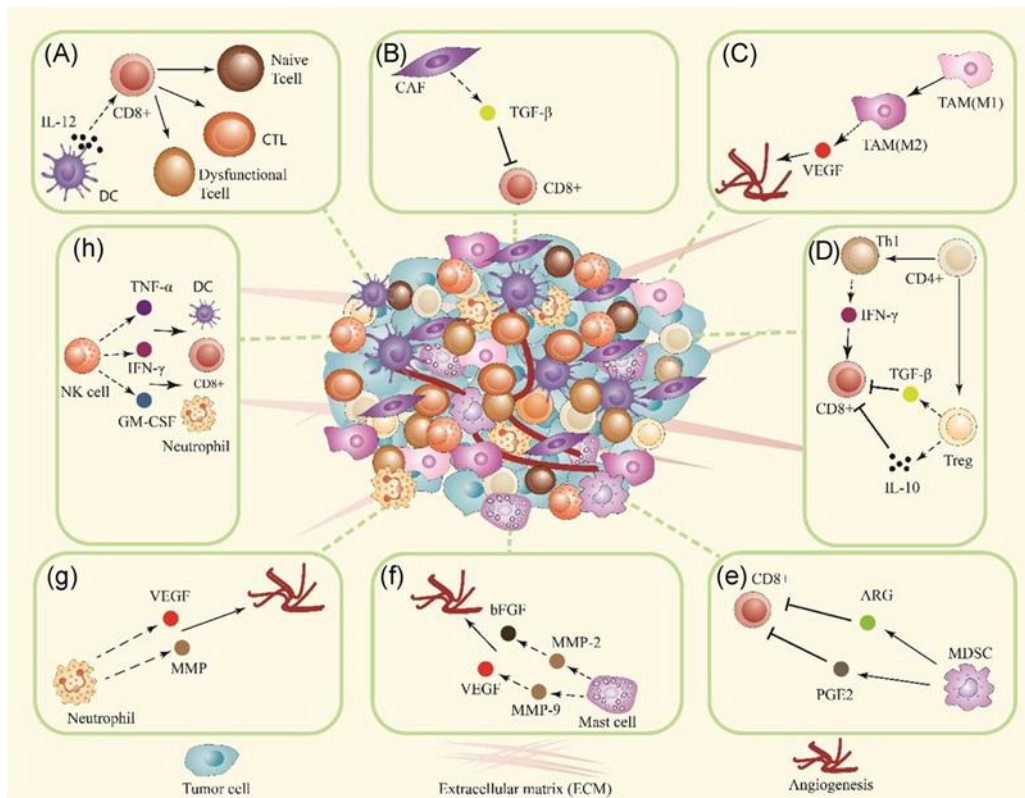


Figure 5. Rôles des différentes populations cellulaires du MET dans la progression du cancer. Les populations cellulaires du MET modulent les conditions d'activation immunitaire ou d'immunosuppression pour prévenir ou favoriser la croissance tumorale. (A) La fonction effectrice des cellules T et les signaux de différenciation peuvent être soutenus par les cellules dendritiques (CD) par le biais de la sécrétion d'interleukine 12 (IL-12). (B) Les fibroblastes associés au cancer (CAF) jouent un rôle immunosuppresseur en inhibant l'infiltration et la fonction des lymphocytes T CD8+ par la sécrétion du facteur de croissance transformant bêta (TGF- β). (C) Les macrophages associés à la tumeur (TAM) sont principalement des macrophages M2, qui sont tumorigènes. Les TAM (M2) contribuent à l'angiogenèse par la sécrétion de facteur de croissance de l'endothélium vasculaire (VEGF). (D) Les cellules T CD4+ peuvent jouer un rôle immunoactif ou immunosuppresseur en se différenciant respectivement en cellules T helper de type 1 (Th1) ou en cellules T régulatrices (Treg). Les cellules Th1 sont capables d'induire les cellules T CD8+ en libérant des cytokines activatrices telles que l'interféron-gamma (IFN- γ) ; à l'inverse, les Treg ont une activité immunosuppressive par l'inhibition de la fonction des cellules T CD8+ en libérant de l'IL-10 et du TGF- β . (E) Les cellules suppressives d'origine myéloïde (MDSC) suppriment la réponse des cellules T CD8+ spécifiques de la tumeur en augmentant les niveaux de prostaglandine E2 (PGE2) et d'arginase (ARG). (F) Les mastocytes peuvent favoriser la progression de la tumeur par le développement

de l'angiogenèse en sécrétant certaines protéases, telles que la métalloprotéinase matricielle 2 (MMP-2) et la MMP-9, ainsi qu'en libérant du VEGF et le facteur de croissance des fibroblastes (bFGF) de la matrice extracellulaire (ECM). (G) Le neutrophile est également capable de développer l'angiogenèse par la sécrétion de VEGF et de MMPs. (H) Les cellules Natural killer (NK) peuvent induire des réponses immunitaires innées et adaptatives par la sécrétion de cytokines pro-inflammatoires, notamment l'IFN- γ , le facteur de nécrose tumorale alpha (TNF- α) et le facteur de stimulation des colonies de granulocytes/monocytes (GM-CSF). TME, microenvironnement tumoral. Tiré de (Sadeghi Rad *et al*, 2021).

2. Lymphomes et immunodépression

2.1 Lymphomes chez les patients transplantés d'organe

Le risque de cancers chez les patients transplantés d'organe est largement augmenté par rapport à la population générale. Les lymphomes post-transplantation (LPT) sont la deuxième cause de cancers chez ces patients avec un « **standardized incidence ratio** » (SIR, reflétant l'augmentation du risque par rapport à la population générale) évalué à 10 pour les lymphomes non-Hodgkiniens (LNH) et à 4 pour les lymphomes Hodgkiniens (LH), et sont responsables d'une morbi-mortalité importante (de Fijter, 2017; Dierickx & Habermann, 2018). Les études de registre de ces dernières années rapportent une **augmentation de l'incidence** des LPT, témoignant à la fois d'une augmentation du nombre de transplantations, d'un âge plus avancé à la transplantation, de l'utilisation de nouvelles drogues immunosuppressives ou encore d'une diminution de la morbi-mortalité liée aux autres causes (notamment infectieuses et cardiovasculaires) (Engels *et al*, 2011; Styczynski *et al*, 2013).

Si le **déficit de l'immunosurveillance** prend une part importante dans le processus de lymphomagenèse chez ces patients, d'autres mécanismes sont également impliqués. Ainsi, l'infection par l'Epstein Barr Virus (**EBV**) des lymphocytes B tumoraux est particulièrement fréquente dans cette population (environ 50%) et est responsable d'un signal oncogénique fort mimant notamment l'activation chronique du lymphocyte B par l'intermédiaire de la Latent Membrane Protein (LMP) exprimée à la surface de la cellule. Dans le contexte des LPT-EBV-négatif, il est même suggéré qu'une infection par l'EBV de type « hit and run » pourrait être responsable d'une infection des lymphocytes B initiant la lymphomagenèse avant de disparaître

(Niller *et al*, 2011; Mundo *et al*, 2020; Ababneh *et al*, 2021). L'EBV infecterait les lymphocytes B et leur conférerait un avantage prolifératif avant qu'une activité de recombinaison ne soit responsable d'une perte du virus mais les données restent controversées à ce jour quant à cette hypothèse. Ces dernières années ont été marquées par une diminution de la proportion des LPT associés à l'EBV, reflétant probablement à la fois la modification des régimes d'immunosuppression (notamment la transition de la ciclosporine vers le tacrolimus, et de l'azathioprine vers le mycophenolate mofetil) et l'augmentation de l'espérance de vie de ces patients (Luskin *et al*, 2015) (**Tableau 1**). Ainsi, la proportion des LPT EBV-positif était rapportée à 90% entre 1990 et 1995 contre 51% entre 2008 et 2013 dans le travail de Luskin.

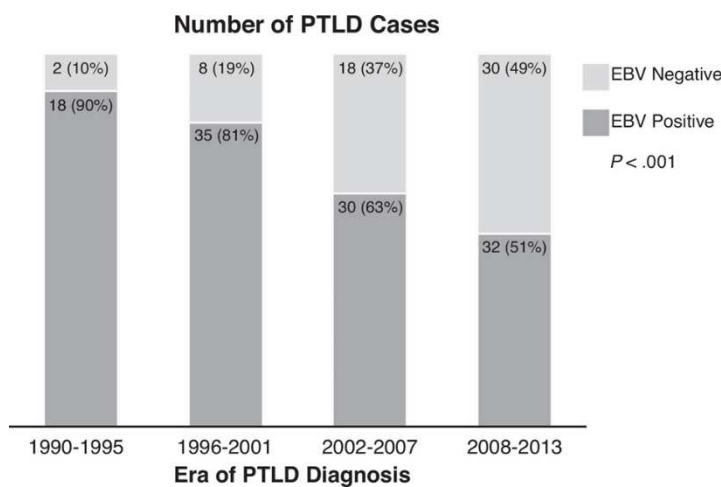


Tableau 1. Evolution du statut EBV des LPT en fonction de l'époque du diagnostic.
PTLD : post-transplant lymphoproliferative disorder. Tiré de (Luskin *et al*, 2015).

La **stimulation antigénique chronique** par les allo-antigènes de l'organe greffé participe également à l'activation polyclonale des lymphocytes B au sein desquels peuvent secondairement survenir des événements oncogéniques. Enfin, il a été suggéré que certains **immunosuppresseurs** pouvaient avoir un impact direct sur le développement des cancers. Les inhibiteurs de calcineurine altèrent notamment les voies de réparation de l'ADN et augmentent l'expression du TGF-béta et du VEGF, ce qui peut aider au développement des cancers (Hojo *et al*, 1999; Basu *et al*, 2008; Han *et al*, 2012). Par ailleurs, des travaux suggèrent que certains immunosuppresseurs de type inhibiteurs de mTOR pourraient avoir un effet protecteur sur l'incidence des cancers survenant chez les patients transplantés (l'oncoprotéine Akt ayant besoin d'une activation en aval de mTORC1) (Kauffman *et al*, 2005; Yanik *et al*, 2015a,

2015b). Néanmoins, ces données sont encore aujourd'hui très parcellaires dans le contexte des LPT.

Le risque de développer un LPT après une transplantation dépend de différents paramètres tels que **l'intensité du régime d'immunosuppression** (induction et maintenance), le type de transplantation, le statut EBV séronégatif du receveur ou encore l'âge à la transplantation. Le **type de transplantation** reflète à la fois l'utilisation de régimes d'immunosuppression plus ou moins intensifs et une quantité de tissu lymphoïde transplanté plus ou moins importante. Ainsi, les transplantés de rein ont le plus faible risque de développer un LPT, suivis des transplantés de foie, de pancréas, de cœur, de poumons et enfin des transplantés multi-organes et intestinaux (Dierickx & Habermann, 2018). Le risque de PTLN chez un patient **EBV séronégatif** est quant à lui augmenté d'un facteur 12 par rapport aux receveurs séropositifs, soulignant l'importance d'une immunité anti-virale antérieure à l'instauration des immunosuppresseurs dans le contrôle de l'infection (Dharnidharka & Araya, 2009). De ce fait, l'incidence des LPT est 100 fois plus importante chez les enfants comparée aux adultes, reflétant la séronégativité EBV beaucoup plus fréquente des enfants (50%).

L'incidence des LPT suit une **courbe bimodale** avec un pic initial (majoritairement constitué de LPT EBV-positif) survenant dans la première année et un second pic (constitué davantage de LPT EBV-négatif) plus tardif survenant dans les 5 à 15 ans post transplantation. Par ailleurs, il existe un nombre croissant de LPT très tardifs survenant plus de 20 ans après (Evens *et al*, 2010). La présentation clinique des LPT est caractérisée par une fréquence très largement accrue des **localisations extra-nodales**, notamment au niveau du tractus gastro-intestinal (20-30%), de l'organe greffé (10-15%) et du **système nerveux central** (5-20%) (Styczynski *et al*, 2013; Caillard *et al*, 2013; Dierickx *et al*, 2013). La présentation histologique est également différente des lymphomes de l'immunocompétent et est notamment caractérisée par des **entités histopathologiques non décrites chez l'immunocompétent**. La classification de l'OMS 2016 détaille ainsi 6 sous-types histologiques de LPT: 3 de type non destructif (hyperplasie plasmocytaire, LPT-MNI like et hyperplasie folliculaire floride), les LPT polymorphes, les LPT monomorphes (de phénotype B le plus souvent, mais T ou NK également) et les LPT-LH like (Swerdlow *et al*, 2016). Cette classification a été révisée en 2022 et a donné lieu à la 5^{ème} classification qui a introduit des changements importants concernant les lymphoproliférations survenant dans un contexte d'immunosuppression. (**Tableau 2**) (Alaggio *et al*, 2022). Les lymphoproliférations survenant dans un contexte de déficit immunitaire primitif, d'infection par le VIH, de transplantation (LPT) et sous

immunosuppresseurs au long cours sont désormais regroupées dans un même chapitre en raison de chevauchements morphologique et biologique fréquents au sein de ces différentes entités (**Figure 6**). Les LPT font désormais partie du groupe plus large des « **lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation** » et sont définies par leurs caractéristiques histologiques, leur association ou non à un virus oncogène et leur statut d'immunosuppression sous-jacente. Par ailleurs, les lymphomes B diffus à grandes cellules (LBDGC) du système nerveux central (SNC), particulièrement fréquents au sein des LPT, font désormais partie du groupe des lymphomes B à grandes cellules primitifs des sites « immunologiquement privilégiés », au même titre que les lymphomes vitréo-rétiens et testiculaires.

Histological diagnosis	Viral association	Immune deficiency/dysregulation setting
<ul style="list-style-type: none"> ○ Hyperplasia (specify type) ○ Polymorphic lymphoproliferative disorder ○ Mucocutaneous ulcer ○ Lymphoma (classify as for immunocompetent patients) 	<ul style="list-style-type: none"> ○ EBV +/- ○ KSHV/HHV8 +/- 	<ul style="list-style-type: none"> ○ Inborn error of immunity (specify type) ○ HIV infection ○ Posttransplant (specify: solid organ/bone marrow) ○ Autoimmune disease ○ Iatrogenic/therapy-related (specify) ○ Immune senescence

Tableau 2. Nouvelle nomenclature en 3 parties des proliférations lymphoïdes et des lymphomes survenant dans un contexte d'immunodéficience/ dysfonction. Tiré de la 5^{ème} classification des tumeurs lymphoïdes (Alaggio *et al*, 2022).

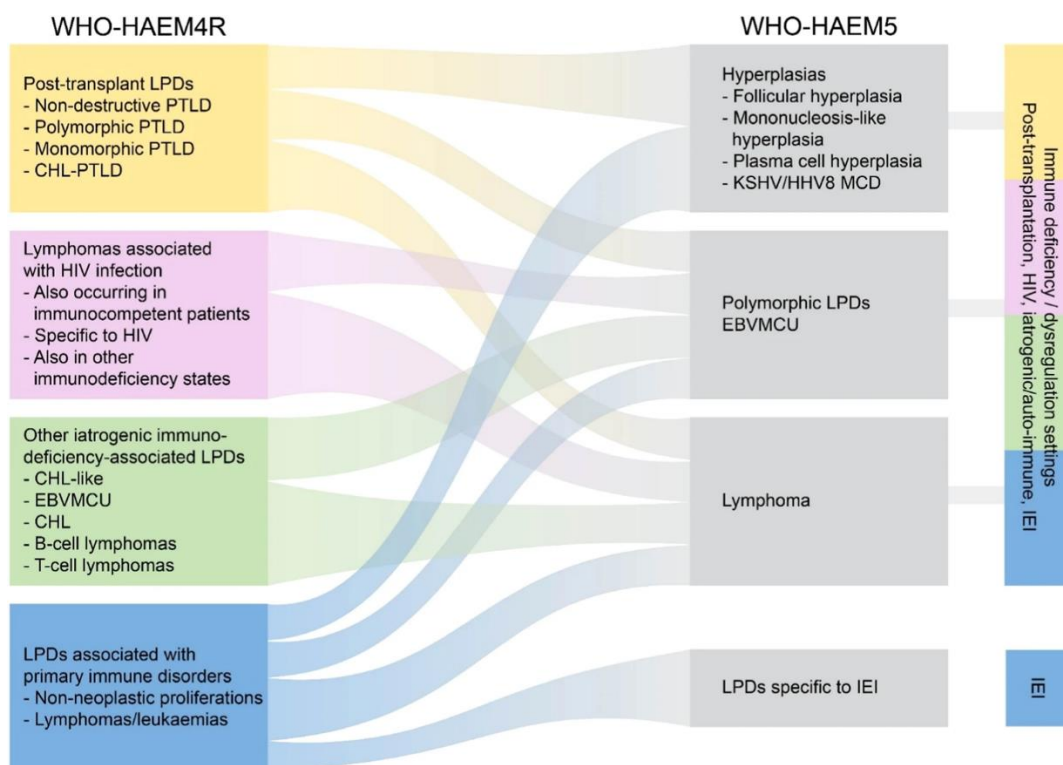


Figure 6. Résumé de la nouvelle classification des proliférations lymphoïdes et des lymphomes associés à un statut d'immunodéficience. La colonne de gauche représente la quatrième et ancienne classification (WHO-HAEM4R) et celle de droite la cinquième et nouvelle classification (WHO-HAEM5R). Cette nouvelle classification reconnaît les similarités histologiques et biologiques des proliférations survenant dans différents types d'immunosuppression, tout en reconnaissant leurs aspects spécifiques. LPD : lymphoproliférative disorder ; PTLD : post-transplant lymphoproliférative disorder ; CHL : classical Hodgkin lymphoma ; EBVMCU : EBV-positive mucocutaneous ulcer; MCD : multicentric Castelman disease ; IEI : inborn errors of immunity. Tiré de la 5^{ème} classification des tumeurs lymphoïdes (Alaggio *et al*, 2022).

Le traitement des LPT est tout à fait particulier car il fait intervenir une **réduction de l'immunosuppression** et un traitement initial par **anticorps monoclonal anti-CD20** seul pour 4 injections qui est ensuite poursuivi seul ou complété par de la **chimiothérapie** en fonction de la réponse obtenue à la première phase de traitement. Cette stratégie de **traitement dite « stratifiée »**, qui n'existe pas chez les patients immunocompétents, est notamment issue d'une étude menée par les groupes français et allemands ayant démontré une nette diminution de la mortalité liée au traitement avec cette procédure (Trappe *et al*, 2012, 2017). Dans ces conditions, la médiane de survie globale est de 6.6 ans avec une survie à 3 ans de 75%.

2.2. Lymphomes chez les patients VIH

Chez les personnes vivant avec le VIH (PVVIH), les pathologies tumorales sont également un enjeu majeur de la prise en charge, le cancer représentant leur première cause de mortalité (Spano *et al*, 2016; Vandenhende *et al*, 2015). Au sein de ces cancers, les LNH font partie des tumeurs les plus fréquentes, leurs **SIR** étant évalués à 12 pour les LBDGC bien que leur fréquence se soit drastiquement effondrée depuis ces 30 dernières années avec l'avènement des traitements anti-rétroviraux (ARV) (**Figure 7**) (Hernández-Ramírez *et al*, 2017a; de Martel *et al*, 2012). Ainsi, le risque relatif de développer un lymphome avant les ARV était estimé entre 60 et 200 par rapport à la population générale (Polesel *et al*, 2008). L'incidence des lymphomes de Hodgkin et des lymphomes de Burkitt a quant à elle tendance à augmenter sur ces dernières années avec un SIR actuellement estimé à 8 et à 20 respectivement, témoignant de maladies associées à une immunosuppression plus modeste (Hernández-Ramírez *et al*, 2017a). Le **tableau 3** illustre la modification de la distribution de ces différents types de lymphomes en fonction des périodes.

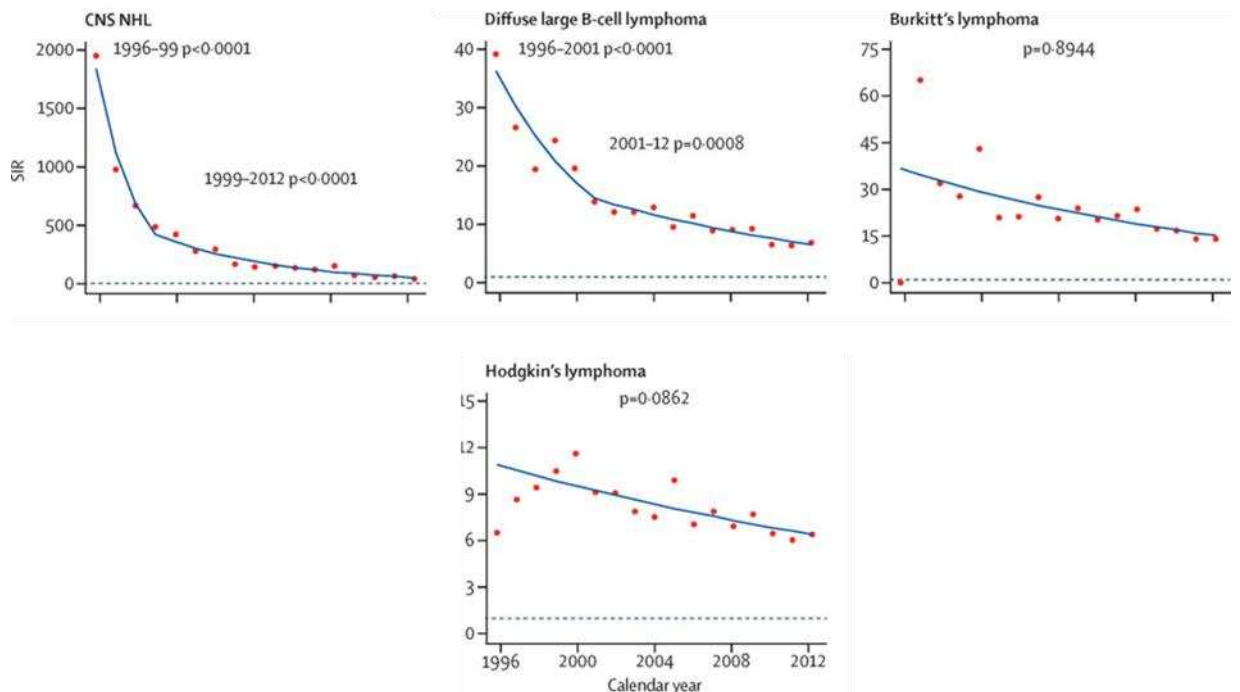


Figure 7. Evolution des SIR pour les lymphomes chez les PVVIH en fonction des périodes.

SIR : standardized incidence ratio ; CNS : central nervous system ; NHL : non-hodgkin lymphoma. Tiré de (Hernández-Ramírez *et al*, 2017a).

Actuellement, 42% des PVVIH diagnostiquées avec un lymphome ont une charge virale VIH indétectable, et leur taux de CD4 médian est compris entre $166/\text{mm}^3$ (IQR, 52-346) et $221/\text{mm}^3$ (range, 2-2308) (Gopal *et al*, 2013; Ramaswami *et al*, 2016). La persistance d'un sur-risque chez des patients avec un contrôle immuno-virologique satisfaisant témoigne à la fois de l'histoire du VIH antérieure au diagnostic du LNH avec des périodes d'immunodéficience profonde dont peut témoigner le **nadir** des patients (nadir médian à $73/\text{mm}^3$, IQR 20-195) mais également de la présence d'autres facteurs impliqués dans la lymphomagenèse (de Carvalho *et al*, 2021). Au premier rang, l'**EBV** est impliqué dans plus de la moitié des LNH VIH+ (Hernández-Ramírez *et al*, 2017a). Par ailleurs, différents mécanismes médiés directement ou indirectement par le VIH sont à l'origine d'une stimulation lymphocytaire B chronique anormale sur laquelle peuvent venir se greffer des évènements oncogéniques secondairement. La **stimulation antigénique chronique** médiée par les protéines virales ainsi que la **production de cytokines** telles que l'interleukine 6 (IL-6) par les lymphocytes T CD4+ ou l'IL-10 par les monocytes, sous le contrôle notamment des protéines Tat ou gp120, contribuent à une **activation lymphocytaire B chronique** (Kundu *et al*, 1999; Vendrame *et al*, 2020). L'une des principales sources de variabilité génétique, et donc d'altérations oncogéniques, au sein des lymphocytes B est médiée par l'enzyme Activation-Induced-Cytidine Deaminase (AID). AID est une enzyme qui génère des mutations au sein des régions constantes des Ig pour la commutation isotypique de classe et au sein des régions variables pour l'hypermutation d'affinité. Ce processus peut participer à la lymphomagenèse de 2 moyens différents. Les mutations peuvent être suivies de cassures de l'ADN responsables de translocations chromosomiques oncogéniques d'une part, et l'introduction de mutations par AID dans des gènes non-Ig, et notamment dans des proto-oncogènes, nommée « hypermutation aberrante », est désormais clairement reconnue comme contribuant de façon majeure à la lymphomagenèse d'autre part (Pasqualucci *et al*, 2001). Dans le contexte de l'infection par le VIH, l'interaction entre les lymphocytes B et la gp120 (Cagigi *et al*, 2009) ou le CD40 ligand exprimé par certaines particules virales (et issu des cellules hôtes initialement) (Epeldegui *et al*, 2010, 2007) est responsable d'une **surexpression d'AID** et donc d'un risque d'introduction d'évènements

oncogéniques. Enfin, outre la contribution du VIH dans l'activation des lymphocytes B et la surexpression d'AID, certaines études ont démontré la **participation directe** des protéines virales du VIH dans la lymphomagenèse et l'angiogenèse. Ainsi, la protéine virale p17 est capable de stimuler les voies de **prolifération et anti-apoptotique** des lymphocytes B (Dolcetti *et al*, 2015, 2016) *in vitro*, et d'interagir avec les cellules endothéliales, par l'intermédiaire de CXCR1 et CXCR2, afin de promouvoir l'angiogenèse (Caccuri *et al*, 2012). D'autres protéines virales ont également été impliquées. Ainsi, Tat favorise l'émergence de lymphomes chez la souris dans 30% des cas (Kundu *et al*, 1999), et est capable d'induire une relocalisation de *Myc* (puissant oncogène) à côté du gène *IgH* (Germini *et al*, 2017). L'impact du VIH sur le nombre de mutations tumorales reste assez controversé (Grulich *et al*, 2007; Bhatia *et al*, 2012; Gleber-Netto *et al*, 2018; Ziada *et al*, 2019). Récemment, le travail de Gandhi *et al* sur les lymphomes primitifs du SNC EBV+ chez des patients VIH-positifs (n=20) ou négatifs (n=16) a mis en évidence un nombre de mutations plus important dans les lymphomes VIH+, suggérant que le VIH en lui-même pourrait contribuer à l'accumulation de mutations au sein de la tumeur (Gandhi *et al*, 2021). Le rôle mutagène d'APOBEC, classiquement mobilisé dans les infections chroniques par le VIH, pourrait être soulevé.

La présentation clinique des LNH survenant chez les PVVIH est **différente** de la population générale immunocompétente. Elle est notamment caractérisée par un âge plus jeune au diagnostic (âge moyen : 45 ans), et une fréquence accrue de maladie disséminée (stade Ann Arbor 3 ou 4), de localisations extra-nodales, d'altération de l'état général et de symptômes B (Carbone *et al*, 2022a). Les localisations au niveau du **SNC** restent encore aujourd'hui particulièrement fréquentes avec un SIR évalué à 153. Au niveau **histopathologique**, les LBDGC représentent le sous-type le plus fréquent (37%) des LNH des PVVIH mais les lymphomes de Burkitt et de Hodgkin comptent désormais à eux 2 pour presque 50% des lymphomes (Ramaswami *et al*, 2016; Carbone *et al*, 2022a). Par ailleurs, les lymphomes survenant spécifiquement chez les PVVIH telles que les lymphomes primitifs des séreuses et les lymphomes plasmablastiques représentent environ 10% des cas.

Histotype	1986-1995; London (158 patients)	1996-2005; London (200 patients)	2006-2015; London (257 patients)	1996-2000; CNICS (132 patients)	2001-2005; CNICS (201 patients)	2006-2010; CNICS (143 patients)
BL	3%	10%	20% ↑	7.6%	10.9%	16.8% ↑
DLBCL	63%	59%	37% ↓	43.9%	45.8%	35.7% ↓
HL	4%	11%	26% ↑	15.2%	15.4%	19.6% ↑
PCNSL				14.4%	10.4%	9.8% ↓
PBL	0	2%	6% ↑			
PEL	2%	1%	5% ↑			
Other				18.9%	17.4%	18.2%

Tableau 3. Distribution des différents sous-types histologiques de lymphomes survenant chez les PVVIH sur ces 30 dernières années dans une cohorte européenne (London) de 615 patients et une cohorte américaine (CNICS USA) de 476 patients. Période 1986-1995 : pré-ARV ; Période 1996-2005 : période ARV précoce ; Période 2006-2015 : période ARV tardive. Tiré de (Carbone *et al*, 2022a).

Le traitement des lymphomes des PVVIH **rejoint** celui des patients immunocompétents et est adapté au type de lymphomes. Si la mortalité liée au traitement et les taux de réussite se sont nettement améliorées en combinant les ARV et la chimiothérapie et en proposant un traitement optimal calqué sur les patients immunocompétents ces dernières années, il persiste néanmoins un plus haut risque de mortalité comparé à la population générale (Han *et al*, 2017; Trickey *et al*, 2020). Cette différence peut être en partie expliquée par une présentation plus agressive au diagnostic (stade, infiltration extra-ganglionnaire, signes généraux) mais également par des prises en charge thérapeutiques hétérogènes et non optimales et par le fait que les PVVIH sont exclues de la majorité des essais cliniques. Actuellement, la **survie globale** à 5 ans est de 70% (contre 13% en pré ARV, 1986-1995) (Carbone *et al*, 2022a).

3. Lymphomes de l'immunodéprimé et immunogénicité

3.1. Spécificités des LNH et implication sur l'immunogénicité

La cellule B, et à fortiori les lymphomes développés aux dépens des cellules B, sont tout à fait particuliers en termes d'immunogénicité. En effet, le lymphocyte B tumoral possède un **BCR unique et hautement muté** qui peut donner naissance à des néoépitopes et il a par

ailleurs, en tant que CPA professionnelle, une capacité de présentation antigénique à la fois par l'intermédiaire du CMH-I mais également par l'intermédiaire du **CMH-II**.

Le réarrangement productif des régions variables de la chaîne légère et de la chaîne lourde des Ig (nommé réarrangement VDJ) intervient au cours de la différenciation lymphocytaire au niveau médullaire et aboutit à l'expression à la surface des lymphocytes d'un BCR unique impliqué dans la reconnaissance antigénique et les réponses adaptatives humorales. Une fois la différenciation lymphocytaire médullaire achevée, les lymphocytes B rejoignent les organes lymphoïdes secondaires où ils subissent, après rencontre avec l'antigène, le processus d'hypermutation somatique (SHM) initié par AID afin d'augmenter la spécificité antigénique. Les régions « hotspot » cibles de ces mutations sont la région « charpente » 3 (FR3) et la « région déterminant la complémentarité » (CDR) 3 (Pilzecker & Jacobs, 2019). Le réarrangement VDJ et la SHM génèrent ainsi des BCR uniques et hautement mutés, spécifiques de chaque lymphocyte B. Dans un contexte de lymphome B avec une expansion de cellules B monoclonales, ce BCR constitue donc une **altération génétique spécifique de la tumeur** potentiellement ciblable par la réponse T immunologique, et donc un néoépitope dérivé des Ig (**Figure 8**).

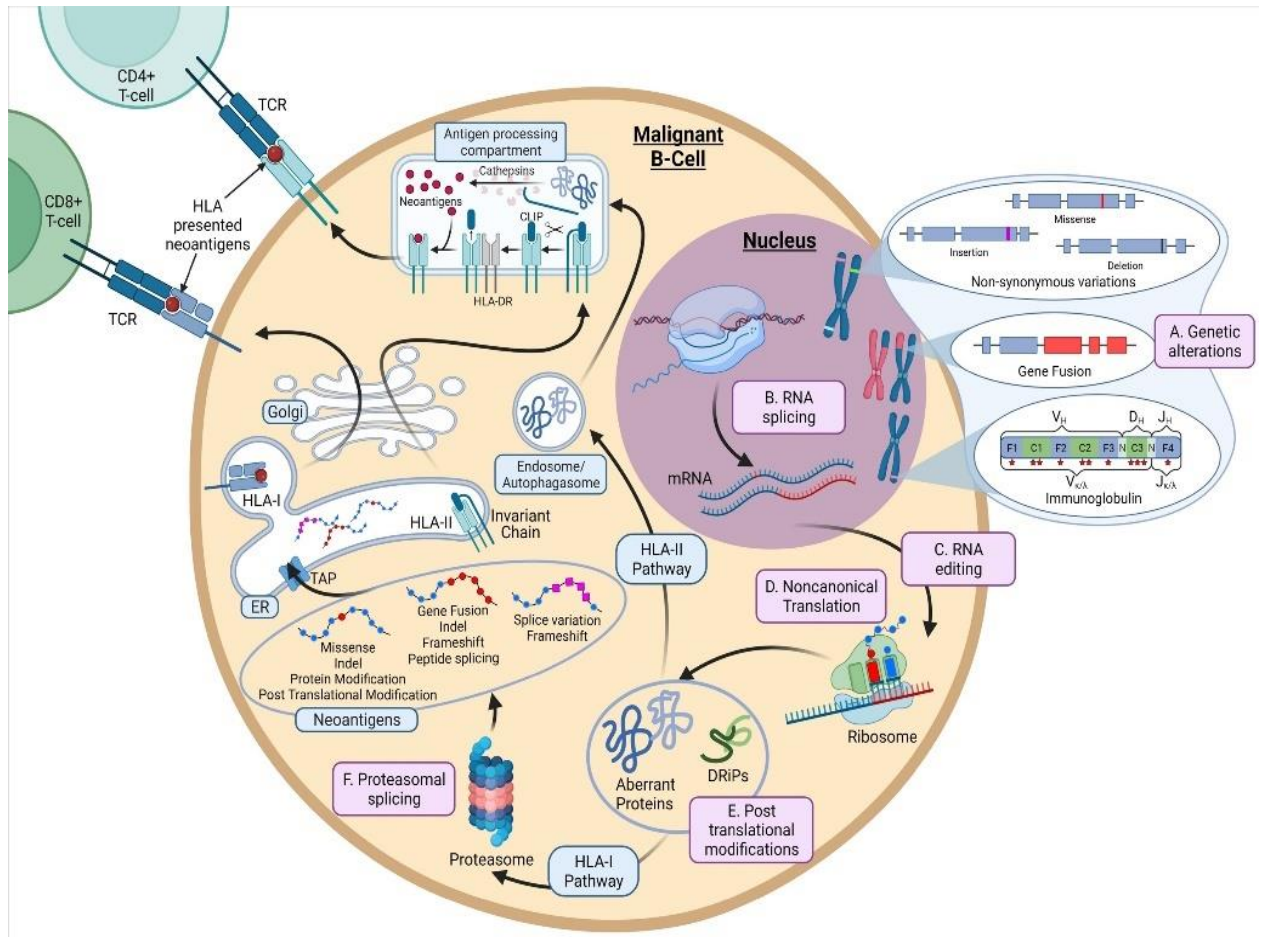


Figure 8. Génération et présentation des néoépitopes par les molécules de CMH-I et CMH-II dans les cellules B malignes. Les étapes de génération des peptides et la manière dont elles peuvent être "détournées" pour induire un néoépitope sont illustrées. A) La première étape commence par des **altérations génomiques** (SNV, indels, translocations chromosomiques entraînant des gènes de fusion, hypermutation somatique de la région variable des gènes des Ig). L'étape suivante est la **transcription** de la région concernée, qui peut être soumise à des modifications telles que B) des événements d'épissage alternatif de l'ARN impliquant la rétention d'introns et le saut d'exon. Elle est suivie d'une **traduction** médiée par le ribosome, qui peut également être soumise à: C) **la modification** de l'ARN : insertion, suppression et/ou substitution de paires de bases, ou D) la **traduction non canonique** telle que la lecture de codons d'arrêt ou le décalage des cadres ribosomiques. Ces altérations peuvent conduire à une expression aberrante des protéines tumorales spécifiques ainsi qu'à des produits ribosomiques défectueux (DRiP). E). Des **modifications post-traductionnelles** des protéines telles que la glycosylation, la méthylation et la phosphorylation peuvent se produire avant une éventuelle dégradation protéasomique. Pour la présentation par l'intermédiaire du CMH-I, les protéines

sont dégradées par le protéasome en peptides, avec des F) altérations au sein des **sous-unités protéasomiques** pouvant également générer des néoépitopes épissés alternativement. Les peptides épissés par le protéasome sont transportés dans le RE par l'intermédiaire des protéines TAP. Les peptides sont ensuite chargés dans les molécules du CMH et, après formation d'un complexe CMH-peptide stable, le complexe est exporté à surface cellulaire via l'appareil de Golgi. Les complexes **CMH-I**-antigène peuvent interagir avec le TCR des lymphocytes T CD8+. La présentation d'antigènes endogènes par le **CMH-II** se produit par la dégradation des protéines cellulaires dans les autophagosomes et les endosomes à l'aide des cathepsines. Les molécules du CMH-II nouvellement synthétisées se combinent à ces compartiments, où les peptides sont chargés et transportés à la surface des cellules. Les complexes CMH-II-antigènes interagissent avec le TCR des cellules T CD4+. Tiré de (Sardia *et al*, 2022).

De fait, différents travaux récents ont caractérisé la réponse T dirigée contre des néoépitopes dans le contexte des lymphomes (Trojan *et al*, 2000; Khodadoust *et al*, 2017, 2019). Trojan démontre dès 2009 que les néoépitopes dérivés de la région FR3 des Ig est immunogène chez des donneurs sains (Trojan *et al*, 2000). Plus récemment, le premier travail de Khodadoust s'est intéressé à caractériser les néoépitopes de 17 patients atteints de lymphomes à cellules du manteau (**LCM**) et immunocompétents (Khodadoust *et al*, 2017). L'analyse immuno-peptidomique par spectrométrie de masse et chromatographie sur tissus tumoraux mettaient en évidence un nombre élevé de complexes peptides-CMH-I et CMH-II, avec un biais pour le CMH-I (ratio I/II=1.9), concernant notamment les gènes impliqués dans la signalisation du BCR (*IGHM*, *CD79B*, *BTK*, *LYN*, *SYK*, *CD20* and *CD22*). Le séquençage de l'exome démontrait des mutations dans les gènes connus tels que les régions variables des Ig, *TP53*, *CCDN1*, *ATM*, *UBR5*, *SMARCA4*, *NOTCH1*, *FAT4*, *TRAF2*, and *WHSC1*. Néanmoins, de façon très marquante, à l'exception des **peptides dérivés des Ig** (chaîne lourde ou légère), les peptides présentés dérivait tous des régions non mutées des gènes. Les néoépitopes découverts dérivait donc tous des gènes des Ig, et majoritairement de la **région variable**, et étaient préférentiellement présentés par le **CMH-II**. La région constante des Ig était présentée à la fois par les molécules de CMH-I et de CMH-II tandis que la région variable, et notamment la jonction entre **CDR3 et FR3** dans 93% des cas, était très majoritairement présentée par les molécules de CMH-II. Presque la moitié des peptides présentés par le CMH-II étaient issus de la SHM ou du réarrangement V(D)J. Enfin, des cellules T CD4+ mémoire spécifiques de ces néoépitopes étaient identifiées chez 1 patient/3 et s'expandaient en post-vaccination. Secondairement, la même équipe s'est attachée à caractériser les néoépitopes uniquement

dérivés des Ig dans d'autres hémopathies telles que les **lymphomes folliculaires** (LF) (n=6), les **LBDGC** (n=1), et les **leucémies lymphoïdes chroniques** (LLC) (n=2) (Khodadoust *et al*, 2019). Cette seconde étude confirmait les résultats obtenus dans les LCM : les néoépitopes présentés étaient préférentiellement présentés par le CMH-II et la région la plus fréquemment présentée était la région **FR3**. Par ailleurs, l'ajout de Toll-like receptor 9 (TLR9) en tant qu'activateur des lymphocytes B permettait d'augmenter la présentation antigénique par les CMH-II.

Ces différents résultats générés suggèrent que les **régions FR3 et CDR3 des Ig** pourraient être la **cible** des stratégies thérapeutiques ciblant les Ig qui fera l'objet d'un paragraphe ultérieur. La présentation préférentielle par le CMH-II suggère également que les stratégies médiées par les CD4 devraient être plus efficaces.

3.2. Association avec l'EBV et implication sur l'immunogénicité

3.2.A. EBV : cycle et lymphomagenèse

L'EBV est un γ -herpès virus ubiquitaire qui infecte plus de 90% de la population mondiale, se transmet par contact avec la salive d'un porteur et pénètre ensuite dans l'hôte par le tractus **oropharyngé** où il infecte les **cellules épithéliales** et les **cellules B** (**Figure 9**) (Niller *et al*, 2011; Taylor *et al*, 2015; Dharnidharka *et al*, 2016a). Le virus est initialement responsable d'une infection **lytique** caractérisée par la production de nouvelles particules virales qui peuvent infecter les cellules B amygdaliennes naïves et transmettre le virus à d'autres individus. Par la suite, l'EBV établit une infection **latente**, au cours de laquelle il reste sous forme épisomale dans un sous-ensemble de cellules B mémoires au repos ou s'intègre dans le génome de l'hôte.

Ainsi, après infection par l'EBV, les cellules B infectées exprimant un programme génétique viral, appelé **latence III**, se propagent. Elles sont caractérisées par l'expression de neuf protéines (LMP1, LMP2A, LMP2B, antigène nucléaire d'Epstein Barr 1 (EBNA1), EBNA2, EBNA3A, EBNA3B, EBNA3C et EBNA-LP), ainsi que les transcrits BamH1-A rightward (BART) et les transcrits non codants EBV encoded ARN 1 (EBER1) et EBER2. Les protéines de latence III sont hautement immunogènes et sont donc ciblées par les lymphocytes T cytotoxiques des hôtes immunocompétents qui limitent généralement l'expansion de cette population. Par la suite, le virus peut passer du programme génétique de la latence III à celui

de **latence II** (caractérisé par l'expression des gènes EBNA1, LMP1, LMP2A et EBERs) afin d'échapper à la réponse T de l'hôte. Lorsque ces cellules B infectées pénètrent dans le centre germinatif, les protéines virales LMP1 et LMP2A fournissent des signaux de substitution du CD40 (indispensable à la survie du lymphocyte dans le centre germinatif) et du BCR respectivement, en promouvant ainsi la survie et la différenciation des cellules malgré l'absence de présentation d'antigène. Ces cellules B infectées ayant transité par le centre germinatif émergent ensuite en tant que pool de cellules B mémoires recirculant préférentiellement entre le sang et les tissus lymphoïdes pharyngés. L'EBV adapte alors un programme de **latence 0** au sein de ce réservoir de cellules B mémoire, caractérisé par l'expression unique de l'EBER et ainsi dissimulé à la réponse immunitaire de l'hôte. Les cellules B infectées latentes persistent pendant toute la vie de l'hôte, bien qu'occasionnellement le virus puisse être réactivé et entrer à nouveau dans un cycle lytique.

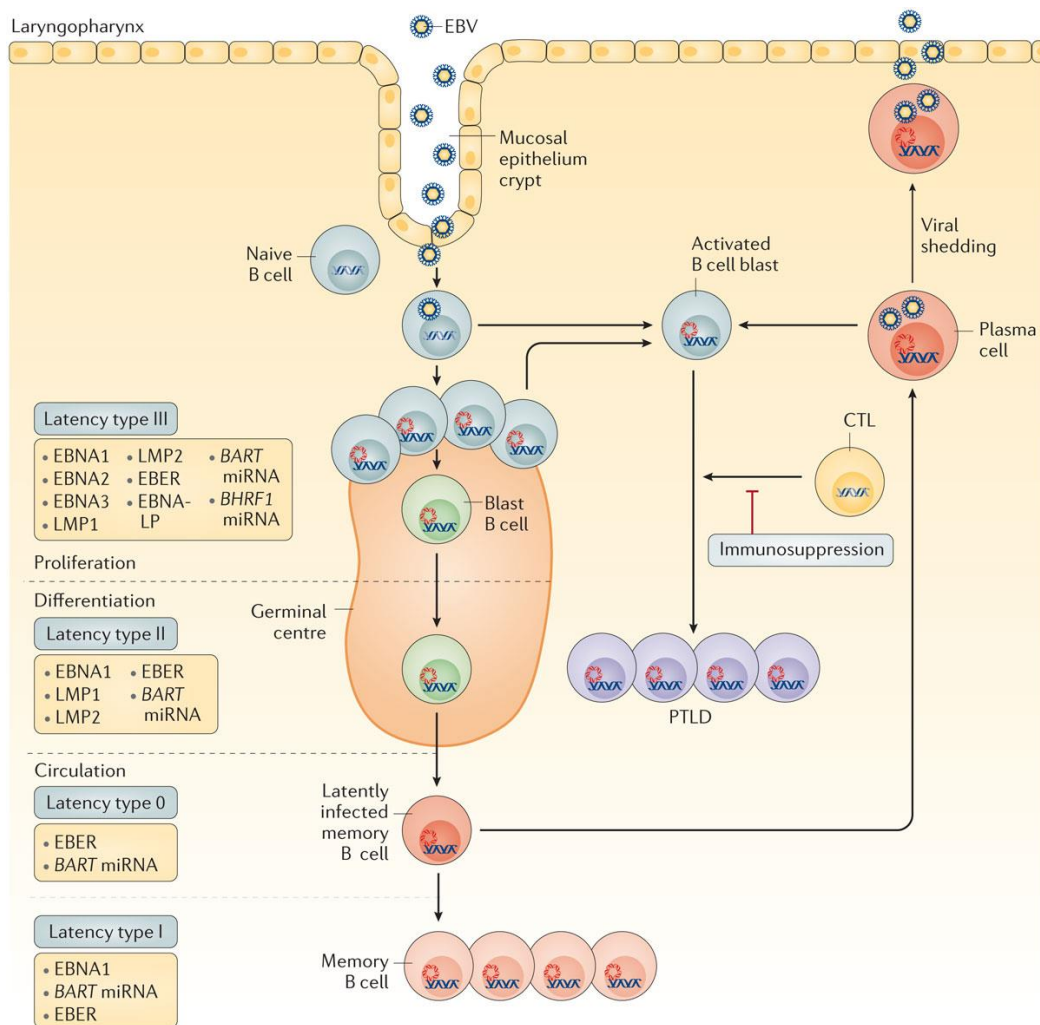


Figure 9. Cycle de l'EBV et développement des LPT. Le virus de l'EBV pénètre dans l'organisme par l'oropharynx, traverse l'épithélium des muqueuses et infecte les cellules B sous-muqueuses. Certaines cellules B mémoire infectées de manière latente quittent le centre germinatif et persistent, tandis qu'occasionnellement, certaines cellules mémoire infectées se différencient en plasmocytes libérant dans la salive de nouveaux virions. Les cellules T cytotoxiques (CTL) CD8+ spécifiques empêchent la prolifération des blastes B. Néanmoins, l'immunosuppression extrinsèque et non spécifique, retrouvée notamment chez les patients transplantés d'organe, peut compromettre cette suppression médiée par les CTL, permettant ainsi la prolifération des cellules B et le développement d'un LPT. Les différents stades de latence virale et les profils d'expression protéique caractéristiques sont illustrés. *BART*, BamH1-A rightward transcript; *BHRF1*, BamH1 fragment H rightward open reading frame; EBER, EBV-encoded RNA; EBNA1, Epstein Barr nuclear antigen 1; LMP1, latent membrane protein 1. Tiré de (Dharnidharka *et al*, 2016a).

LMP1, EBNA2 et EBNA3 sont trois protéines clés de la **latence virale** participant à la lymphomagenèse B. **LMP-1** est une protéine transmembranaire exprimée au cours de la latence II et III et est considérée comme un des oncogènes majeurs de l'EBV car elle mime (grâce à une similarité structurale) la fonction du CD40 et est ainsi responsable d'une activation constitutive de la signalisation B en aval (voies PI3-kinase- AKT, N κ FB, JAK, STAT, p38, responsable d'une up-régulation de l'IL-10, et MAPK) (Snow *et al*, 2006; Lambert & Martinez, 2007; Vaysberg *et al*, 2008). En effet, l'interaction de CD40, exprimé à la surface des lymphocytes B, avec son ligand (CD40L), exprimé par les lymphocytes T helper (LTh), est une des étapes critiques pour la survie de la cellule B activée (Abbas *et al*, 2014). De ce fait, des souris transgéniques LMP-positives développent des lymphomes agressifs dans un contexte d'immunosuppression alors que l'expansion B est contrôlée dans des souris immunocompétentes (Zhang *et al*, 2012). **EBNA-2**, exprimée au cours de la latence III, est un facteur de transcription régulant l'expression de protéines virales de latence telles que LMP-1 et 2 qui est essentiel au processus d'immortalisation des lymphocytes B. Les souches d'EBV délétées pour EBNA-2 ne sont pas capables d'immortalisation des lymphocytes B *in vitro* tandis que la restauration d'EBNA-2 leur confère de nouveau un pouvoir de transformation des cellules hôtes (Rabson *et al*, 1982). **EBNA-3A et C** sont exprimées au cours de la latence III et sont également des facteurs de transcription nécessaires à la transformation des cellules B *in vitro* en régulant la transcription génique des cellules hôtes. **EBNA-1** est quant à elle une protéine **exprimée à tous les stades de latence** excepté la latence 0 qui facilite notamment la

réplication virale et diminue la présentation antigénique des peptides viraux par l'intermédiaire du CMH-I (Blake *et al*, 1997). Chez un hôte immunocompétent, la prolifération des lymphocytes B est empêchée par une réponse T cytotoxique CD8+ adaptée. Chez les sujets transplantés d'organe ou les PVVIH, l'immunosuppression iatrogène ou induite par le VIH permet la prolifération des lymphocytes B EBV-positif aboutissant au développement d'un lymphome. La majorité des **LPT** et des **LBDGC VIH+** expriment les gènes de latence de **type III et II**.

3.2.B. EBV et profil moléculaire

La présence de l'EBV au sein des cellules tumorales est associée à une **instabilité génomique plus faible** et de ce fait impacte profondément le profil mutationnel et transcriptomique de ces tumeurs (Ferla *et al*, 2020).

Les anomalies du nombre de copies (**CNA**) des gènes sont moins fréquentes dans les LBDGC post-transplantation (PT) EBV-positif comparé aux autres LBDGC (Poirel *et al*, 2005; Yoon *et al*, 2015; Finalet Ferreiro *et al*, 2016). Notamment, Finalet Ferreiro démontre en 2016, en comparant 21 LBDGC PT EBV-positif/ 6 LBDGC PT EBV-négatif et 11 LBDGC IC, que les CNA sont moins fréquentes dans les LPT EBV-positif (48%) *versus* les LBDGC IC (64%) et les LPT EBV-négatif (83%) et que les profils de CNA sont beaucoup plus largement partagés entre LBDGC PT EBV-négatif et LBDGC IC. Les gains ou amplifications du **9p24** responsables d'une surexpression de PDL-1 ou PDL-2 (ligand de PD-1) sont quant à eux beaucoup plus largement rapportés dans les LPT EBV-positif et représentent les CNA les plus fréquentes (24%) dans ce contexte (Yoon *et al*, 2015; Finalet Ferreiro *et al*, 2016). Il est intéressant à ce propos de noter qu'une uprégulation de **PDL-1** est rapportée dans la majorité des LPT EBV-positif (85%) (Chen *et al*, 2013; Veloza *et al*, 2019) et qu'il existe probablement un mécanisme alternatif aux CNA et notamment médié par l'EBV (Green *et al*, 2012). Ainsi, Green et al ont démontré que la protéine de membrane LMP augmentait l'activité du promoteur de PDL-1 par l'intermédiaire de **JAK3** dans les lymphomes de hodgkin EBV-positif.

Par la suite, différents travaux ayant évalué le **profil mutationnel** des LPT par **séquencage ciblé** ont démontré un nombre de mutations moins important dans les LBDGC PT EBV-positif, et notamment dans les gènes impliqués dans les voies de signalisation de NF- κ B (Courville *et al*, 2016; Menter *et al*, 2017). Les LBDGC PT EBV-négatif sont quant à eux caractérisés par une similarité mutationnelle importante avec les LBDGC IC, excepté une

fréquence de mutations de **TP53** particulièrement importante (44%). Par ailleurs, et indépendamment du statut EBV, les LBDGC PT ne présentent pas de mutation de **B2M** (0% *versus* 22% pour les LBDGC IC) (Menter *et al*, 2017). Plus récemment, le travail de séquençage ciblé de Gandhi sur 47 patients avec un lymphome primitif du SNC (LPSNC) EBV-négatif et 44 patients avec un LPSNC EBV-positif (dont 18 LPT et 23 lymphomes VIH+) a rapporté des différences importantes également médiées par l'EBV. Le nombre de gènes mutés était moins important dans les maladies EBV-positives et les mutations de **MYD88**, **CD79B** et **PIMI** étaient absentes, renforçant la notion de sous-représentation des mutations impliquées dans la voie NF- κ B alors que 81% des lymphomes EBV-négatif présentaient une mutation dans au moins un de ces gènes (Gandhi *et al*, 2021). Par ailleurs, les CNA étaient beaucoup moins fréquentes dans les maladies EBV-positives et l'analyse de la « **cell of origin** » retrouvait 63% d'origine centro-germinative chez les EBV-positif *versus* 19% chez les EBV-négatif. Enfin, les CNA et/ou mutations impliquant la présentation antigénique, les molécules du CMH-I et II (notamment les **délétions du chromosome 6**), la régulation épigénétique et le cycle cellulaire étaient beaucoup moins fréquentes dans les lymphomes EBV-positif.

De la même façon, les analyses non supervisées **d'expression génique** ségrégent les LBDGC PT EBV-positif du groupe LDGBC PT EBV-négatif +LBDGC IC, avec notamment une surexpression des gènes impliqués dans l'immunité cytotoxique et anti-virale et la tolérance pour les LBDGC PT EBV-positif (Craig *et al*, 2007; Yoon *et al*, 2015; Morscio *et al*, 2013).

Ces résultats rejoignent les constatations faites dans les LBDGC EBV-positif sans autre particularité (NOS) survenant chez des patients sans immunosuppression avérée, ou encore dans d'autres sous-types de lymphomes EBV-positif survenant chez des patients immunodéprimés (lymphome de la zone marginale PT EBV-positif) (Nicolae *et al*, 2015; Kataoka *et al*, 2019; Gebauer *et al*, 2021; Sarkozy *et al*, 2021; Rea *et al*, 2022).

3.2.C. EBV et microenvironnement tumoral

Le **MET** des lymphomes EBV-positif, survenant chez des patients immunodéprimés ou non, présente des spécificités particulières. Il existe tout d'abord une surexpression des gènes impliqués dans l'immunité anti-virale, et notamment de l'IFN- γ et du TNF- α (Morscio *et al*, 2013; Gandhi *et al*, 2021). En regard de la surexpression fréquente de PDL-1 ou PDL-2 par les cellules tumorales (qui a été décrite dans les paragraphes précédents), l'expression des **points de contrôle immunitaire** tels que LAG-3 et TIM-3 est plus élevée dans les maladies EBV-

positive, qu'elles soient de localisation cérébrale ou systémique, et la distribution des **macrophages** intra-tumoraux est orientée vers une distribution de type **M2** tolérogène (évaluée par le ratio CD163/CD68) (Keane *et al*, 2019; Gandhi *et al*, 2021). Par ailleurs, d'autres molécules impliquée dans l'immunorégulation négative telles que l'indoleamine 2, 3-dioxygénase (**IDO**) ont un haut niveau d'expression (Nicolae *et al*, 2015). Enfin, la protéine LMP pourrait également intervenir sur le MET indépendamment de la surexpression des ligands de PD-1. En effet, elle est responsable, dans les lymphomes de Hodgkin, d'une surexpression d'un récepteur nommé discoidin domain receptor 1 (DDR1) activé par le collagène (particulièrement riche dans le MET des LH) et impliqué dans le cycle cellulaire (Cader *et al*, 2013). L'ensemble de ces constatations témoigne d'un MET plus **tolérogène** dans ce type de maladies.

Le **répertoire** T intra-tumoral est un paramètre du MET témoignant de la diversité des lymphocytes T recrutés au niveau du site tumoral. Dans le contexte des infections virales chroniques, il est depuis longtemps reconnu qu'un répertoire polyclonal est indispensable à une immunité anti-virale efficace permettant de contrer l'échappement viral médié notamment par des mutations (Phillips *et al*, 1991; Erickson *et al*, 2001; Gandhi & Khanna, 2004; Costa *et al*, 2015). Il a été émise l'hypothèse que le répertoire T dans les cancers, et notamment dans les lymphomes, pouvait avoir un impact identique à celui des infections virales chroniques mais les données sont encore assez parcellaires. Ainsi, une diversité intra-tumorale moins importante du répertoire est associée à une réponse au traitement moins élevée dans les LBDGC des IC (Shanavas *et al*, 2021) et à une survie globale moins importante dans les LB (Rieken *et al*, 2021). Dans les LBGCC EBV-positif des IC, Keane *et al* ont démontré quant à eux que l'EBV était associé à un petit nombre de clonotypes très expandus, témoignant d'une **clonalité** plus élevée et d'une **diversité** moins importante que les LBDGC EBV-négatifs, et qui se traduisait notamment par une **survie globale** moins importante (Keane *et al*, 2017) bien que ces résultats n'aient été confirmés que par une tendance dans les LB EBV-positif (Rieken *et al*, 2021). Ces données suggèrent que le répertoire T intra-tumoral des lymphomes EBV-positif est associé à un répertoire moins divers qui peut témoigner d'une immunodominance des protéines virales.

3.3. Localisation au sein du SNC et implication sur l'immunogénicité

Le SNC est depuis longtemps reconnu comme étant un « **site de privilège immunitaire** », nécessaire à la prévention d'une réponse immunitaire excessive qui pourrait

être responsable de dommages parenchymateux irréversibles. En effet, l'administration précautionneuse d'antigènes viraux, bactériens ou encore tumoraux au sein du parenchyme cérébral n'induit pas de réponse immunitaire adaptative, témoignant d'une forme d'échappement immunologique (Galea *et al*, 2007). Un certain nombre de caractéristiques, anatomiques, cellulaires et moléculaires spécifiques à ce site anatomique concourent à cette qualité. En premier lieu, la **barrière hémato-encéphalique** (BHE) est caractérisée par la présence de jonctions serrées entre les cellules endothéliales ainsi que de pieds astrocytaires et de péricytes (cellules musculaires lisses qui sont enchâssées dans la membrane basale) mais également par des capacités de macropinocytose limitée et par un système de transporteurs de relargage qui limitent l'accessibilité des toxiques mais également des molécules impliquées dans la réponse immunitaire ou encore des cellules au sein du parenchyme cérébral (Cecchelli *et al*, 2007). Par ailleurs, les **vaisseaux lymphatiques** sont absents, gênant ainsi la migration des antigènes vers les organes lymphoïdes secondaires qui est finalement assurée par le liquide céphalo-rachidien (LCR) jusqu'à la muqueuse nasale où ils sont pris en charge par des vaisseaux lymphatiques afférents jusqu'aux ganglions cervicaux (Figure 10) (Ransohoff & Engelhardt, 2012).

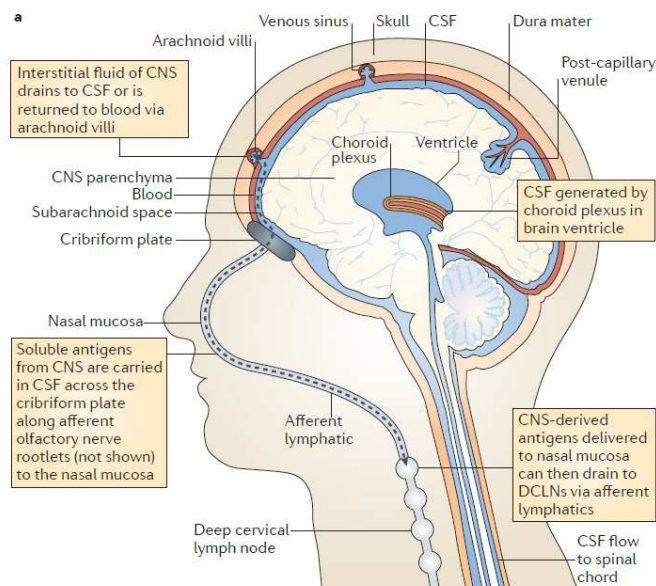


Figure 10. Drainage par le LCR des antigènes du SNC vers les ganglions lymphatiques cervicaux profonds. Tête humaine en coupe sagittale médiane, montrant les différentes structures anatomiques (à savoir le ventricule, les plexus choroïdes, le parenchyme cérébral, les lymphatiques et les ganglions lymphatiques cervicaux profonds). CSF : cerebrospinal fluid. Tiré de (Ransohoff & Engelhardt, 2012).

Au niveau cellulaire, le SNC est caractérisé par un **faible nombre de CPA**, et notamment de cellules dendritiques. En particulier, les cellules microgliales, macrophages résidents du SNC, sont **quiescentes** à l'état physiologique, notamment du fait d'interactions entre le récepteur neuronal CD200 et son ligand exprimé à la surface des cellules microgliales. Ce point a été notamment démontré dans des souris déficientes pour le CD200 au sein desquelles les cellules microgliales exprimaient spontanément des marqueurs d'activation (Hoek *et al*, 2000). Les **molécules d'adhésion** permettant la migration des cellules immunitaires, notamment lymphocytaires, sont quant à elle exprimées de façon beaucoup moins importante que dans d'autres organes (10 fois moins), diminuant leurs possibilités d'interaction avec le parenchyme cérébral (Carvalho-Tavares *et al*, 2000). Il a été suggéré également que l'expression des **molécules de CMH-I** et des molécules de co-stimulation positive telles que CD86 et CD40 était diminuée à la surface des cellules microgliales (Neumann *et al*, 1998; Wei & Jonakait, 1999). Il existe par ailleurs une production de **molécules immunosuppressives** et **anti-inflammatoire** telles que le TGF- β et l'interleukine-10 par les cellules de la microglie ou les astrocytes qui limitent l'activité immunitaire localement (Aloisi *J Immunol* 1997/ Vincent *Glia* 1997). Enfin, un autre mécanisme contribuant à la suppression des réactions immunitaires au niveau cérébral est l'expression constitutive de **Fas** ligand sur les neurones qui peut promouvoir la mort médiée par Fas des cellules immunitaires infiltrant le SNC (Flügel *et al*, 2000).

Dans ce contexte de « site de privilège immunitaire », le **MET des lymphomes primitifs du SNC (LPSNC)** présente des particularités. Ainsi, le travail de Marcelis en 2020 permettait de mettre en évidence une expression plus importante du récepteur du TGF- β (TGF- β R), et une fréquence moins importante de lymphocytes TCD8+ dans le MET des LPSNC comparé à celui des LBDGC systémiques (Marcelis *et al*, 2020). De la même façon, l'expression de marqueur d'activation et de présentation tel que HLA-DR ou encore la fréquence des cellules dendritiques et des cellules T cytotoxiques, et notamment effectrices, ont été rapportées comme moins importantes dans les LPSNC comparé aux lymphomes systémiques (Chang *et al*, 2015). Enfin, l'expression de PD-1 sur les lymphocytes infiltrant la tumeur et de PDL-1 sur les cellules tumorales est plus importante dans les LPSNC que dans les lymphomes systémiques (Four *et al*, 2017; Miyasato *et al*, 2018).

4. Immunogénicité et immunothérapies

L'intérêt croissant pour caractériser la CMT, les néoépitopes d'intérêt, l'immunité anti-tumorale et les interactions entre les tumeurs et le MET tient évidemment à la volonté d'une meilleure compréhension entre ces 2 systèmes « mouvants » mais également au développement de thérapies anti-tumorales basées sur **l'immunité anti-tumorale**. S'il existe d'ores et déjà des immunothérapies très largement utilisées telles que les ICPI qui sont « non spécifiques » d'un antigène donné, d'autres traitements tels que la vaccination anti-tumorale ou encore les lymphocytes T cytotoxiques dirigés contre l'EBV sont encore en cours de développement ou en attente d'accord des autorités de santé.

4.1. Inhibiteurs des points de contrôle immunitaire

Les **ICPI** seront traités dans une partie ultérieure (**Partie 5**) et sont des anticorps monoclonaux qui ciblent les points de contrôle immunitaires responsables d'un épuisement lymphocytaire. La fixation de l'anticorps monoclonal thérapeutique permet d'inhiber l'interaction entre l'ICP et son ligand et de restaurer ainsi une immunité anti-tumorale robuste.

4.2. Vaccination anti-tumorale

Les **vaccins** ont traditionnellement été utilisés dans la prévention des maladies infectieuses mais leur capacité à initier ou à amplifier une réponse immunologique spécifique est interprétée depuis longtemps comme une **voie précieuse** de développement de traitements anti-tumoraux. Les premières **stratégies vaccinales anti-tumorales** se sont concentrées sur les **TAA** et n'ont pas réussi à générer des réponses immunitaires efficaces cliniquement. Ces résultats s'expliquent probablement en raison de la cible thérapeutique choisie : les TAA étant notamment sujets à la **tolérance** périphérique ou centrale. Par ailleurs, leur expression au sein d'autres tissus non tumoraux soulève le risque de développer des toxicités dirigées contre ces tissus en question. A l'inverse, l'immense avantage de développer des vaccins dirigés non pas contre les TAA mais contre les **néoépitopes** issus des mutations somatiques propres à la cellule tumorale et donc **spécifiques** de la tumeur permet d'augmenter la possibilité de développer une réponse immunitaire spécifique (le néoépitope est propre à la cellule tumorale et donc non sujet à la tolérance) tout en limitant la toxicité dirigée contre les autres tissus (le néoépitope n'est pas exprimé par les tissus non tumoraux). Par ailleurs, le potentiel de **persistance** et de **mémoire**

lymphocytaire induite par ce type de traitement permet en théorie un effet anti-tumoral prolongé évitant les rechutes. Les **inconvénients** de ce type d'approche sont la difficulté de caractérisation des néoépitopes présentés par le CMH-II, des coûts élevés, le temps nécessaire à la caractérisation des néoépitopes et à la construction des vaccins, et l'absence de consensus international sur le choix des néoépitopes et le type de vaccins à développer (Blass & Ott, 2021). Il est enfin probablement nécessaire de construire des vaccins dirigés contre plusieurs néoépitopes afin d'éviter des mécanismes d'immunoédition avec perte des néoépitopes ciblés. Les procédures d'identification et de développement de ce type de stratégies vaccinales et les réponses immunitaires induites sont illustrées dans la **Figure 11**.

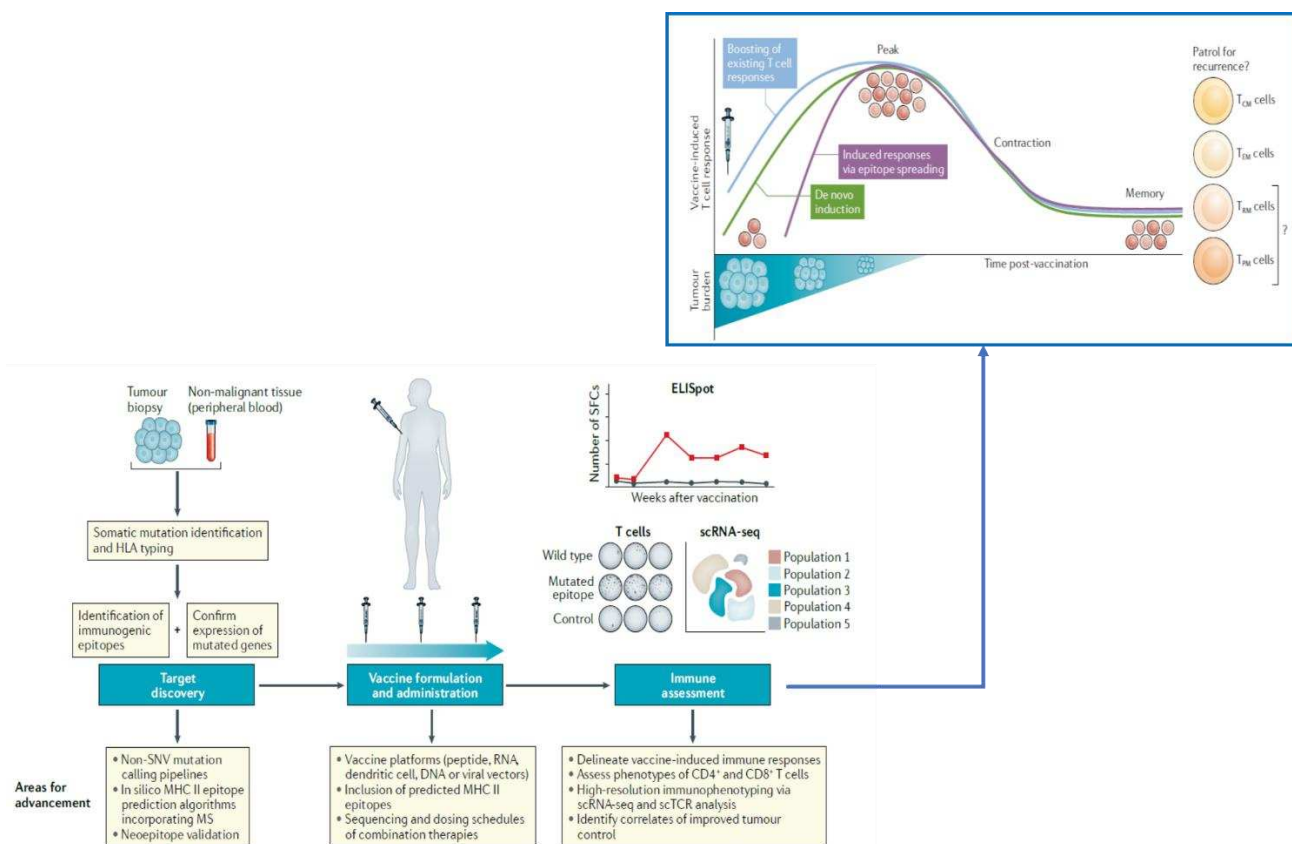


Figure 11. Procédures d'identification et de construction des vaccins thérapeutiques, et réponses immunitaires induites. Une première étape permet de définir les néoépitopes d'intérêt à partir de la tumeur. Une seconde étape consiste en la conception et l'administration du vaccin selon différentes modalités et différents schémas d'administration. Une dernière étape permet de caractériser les réponses immunitaires induites (ELISpot mais aussi séquençage de l'ARN en single cell (scRNAseq)). **Encart : réponses immunitaires induites.** Après la vaccination, les cellules T CD4⁺ et les cellules T CD8⁺ induites et spécifiques d'un néoépitope

prolifèrent et tuent les cellules tumorales exprimant le néoépitope en question. Lorsque les cellules tumorales sont éliminées, la libération d'antigènes tumoraux peut contribuer à l'apparition de nouveaux néoépitopes, permettant ainsi une augmentation de l'intensité de la réponse immunitaire. Après l'éradication de la tumeur, les populations de cellules T se contractent, mais des sous-populations mémoires à longue durée de vie, telles que les cellules T mémoire centrale (TCM) ou T mémoire effectrice (TEM) persistent. La génération de T mémoire résidente (TRM) et/ou de T mémoire périphérique (TMP) n'est pas encore bien définie. **Abréviations** : MHC II, CMH de classe II; MS, spectrométrie de masse; scTCR, single cell TCR ; SFC, cellule formant un spot. Tiré de (Blass & Ott, 2021).

Dans le contexte des lymphomes, les **néoépitopes** à cibler peuvent être dérivés des gènes des *Ig* ou non. La majorité des néoépitopes reconnus par le système immunitaires dans les lymphomes (LBDGC, LLC et LF) étant dérivés de la région variable de la chaîne lourde des **Ig**, la majorité des essais cliniques se sont pour le moment intéressés à la vaccination anti-idiotypes (Khodadoust *et al*, 2017, 2019; Xu-Monette & Young, 2020). La plupart des études ont porté sur des patients atteints de lymphomes **folliculaires** et, bien que les données biologiques témoignent d'une réponse immunitaire induite par la vaccination anti-idiotype, les 3 essais cliniques de phase 3 et comparés n'ont pas tous réussi à mettre en évidence de bénéfice clinique (Kwak *et al*, 1992; Hsu *et al*, 1997; Freedman *et al*, 2009; Rizvi *et al*, 2015; Khodadoust *et al*, 2017; Tusé *et al*, 2015). Le premier essai comparait chez 349 patients atteints de LF en première ligne ou en rechute/ réfractaires (RR) une consolidation par une vaccination anti-idiotype+ KLH (keyhole limpet hemocyanin) (à visée d'adjuvant) vs placebo et retrouvait un temps à la progression plus court dans le groupe de patients vaccinés (Freedman *et al*, 2009). La différence disparaissait après ajustement des scores pronostiques à la baseline. Le second essai comparait chez 117 patients atteints d'un LF en première ligne une consolidation par une vaccination anti-idiotype + KLH vs placebo et démontrait un gain de survie sans progression (SSP) pour le groupe de patients vaccinés (médiane 44 vs 30 mois respectivement, $p=0.05$), qui ne se traduisait pas en gain de survie globale (Schuster *et al*, 2011). Le dernier essai comparait chez 287 patients atteints de LF en première ligne une consolidation par une vaccination anti-idiotype + KLH vs placebo et ne mettait pas en évidence de différence de SSP (Levy *et al*, 2014). Néanmoins, la SPP était nettement plus importante chez les patients ayant développé des anticorps anti Ig (2.9 vs 1.2 ans respectivement, $p= 0.02$), témoignant de l'importance du développement d'une réponse immune dans l'obtention d'un bénéfice clinique. Dans le contexte des lymphomes **lymphoplasmocytaires**, un essai clinique testant une vaccination anti-

idiotype + KLH est en cours chez des patients asymptomatiques n'ayant jamais été traités auparavant afin d'évaluer son efficacité dans ce contexte de faible masse tumorale et de système immunitaire « compétent » (Thomas *et al*, 2018). Dans le contexte des **lymphomes à cellules du manteau**, un essai de phase I/II proposé à 45 patients a démontré la faisabilité et la sécurité d'un vaccin dirigé à la fois contre des néoépitopes dérivés des Ig et des néoépitopes non dérivés des Ig avec développement d'une réponse T spécifique persistante plus de 2 ans après le traitement pour certains patients (Frank *et al*, 2020). Dans le contexte des **LBDGC**, les données sont beaucoup plus parcellaires et il existe un essai clinique de phase 3 évaluant l'efficacité thérapeutique d'un vaccin anti idiotype couplé à du KLH et du GM-CSF (à visée d'adjuvants) en association avec le traitement classique d'immunochimiothérapie (R-CHOP) pour des patients atteints de LBDGC en première ligne thérapeutique. (NTC00324831). Enfin, des réponses T spécifiques de néoépitopes dérivés de **mutations drivers**, tels que *MYD88 L265P* dans les LNH, ou *CRBBP* et *MEF2B* dans les lymphomes folliculaires, ont également été démontrées et témoignent d'une possibilité de développement de vaccins dirigés contre ces néoépitopes (Nelde *et al*, 2017; Nielsen *et al*, 2017). Le développement de la vaccination anti-tumorale dans d'autres pathologies que les lymphomes, tels que les mélanomes, les gliomes ou encore les cancers du poumon, est actuellement en plein essor et peut être combinée avec d'autres traitements d'immunothérapies tels que les ICPi avec des résultats particulièrement intéressants (Khattak *et al*, 2023).

4.3 Lymphocytes T cytotoxiques anti-EBV

Dans le contexte des lymphomes survenant chez des patients ID, l'association fréquente à l'EBV a conduit au développement des lymphocytes T cytotoxiques (LTC) anti-EBV à visée anti-tumorale. A partir des années 1990, différentes équipes ont rapporté l'obtention de réponses complètes durables chez 50 à 70% des patients transplantés de moelle et atteints de lymphomes grâce à l'utilisation de **LTC anti-EBV dérivés des donneurs** (Rooney *et al*, 1995; Heslop *et al*, 1996; Doubrovina *et al*, 2012; Icheva *et al*, 2013; Comoli *et al*, 2007). Dans le cadre des transplantation d'organe solide, les **LTC autologues anti-EBV** peuvent également induire des rémissions complètes mais moins fréquemment (Savoldo *et al*, 2006; Khanna *et al*, 1999; Comoli *et al*, 2005; Sherritt *et al*, 2003). Néanmoins, les lymphocytes T autologues anti-EBV sont difficiles à générer en cas de séronégativité du receveur et nécessitent des temps de culture et d'organisation souvent trop longs pour des maladies qui progressent rapidement.

Pour répondre à ce besoin d'accéder rapidement à des LTC anti-EBV, des équipes ont secondairement développé des LTC anti-EBV dérivés de donneurs sains et matchés pour les molécules du CMH des receveurs, nommés « **third-party donor** » en anglais. La procédure de manufacturing de ces LTC est illustrée dans la **Figure 12**. Les résultats d'expériences issues de petits effectifs de patients de ces LTC sont résumés dans le **Tableau 4**.

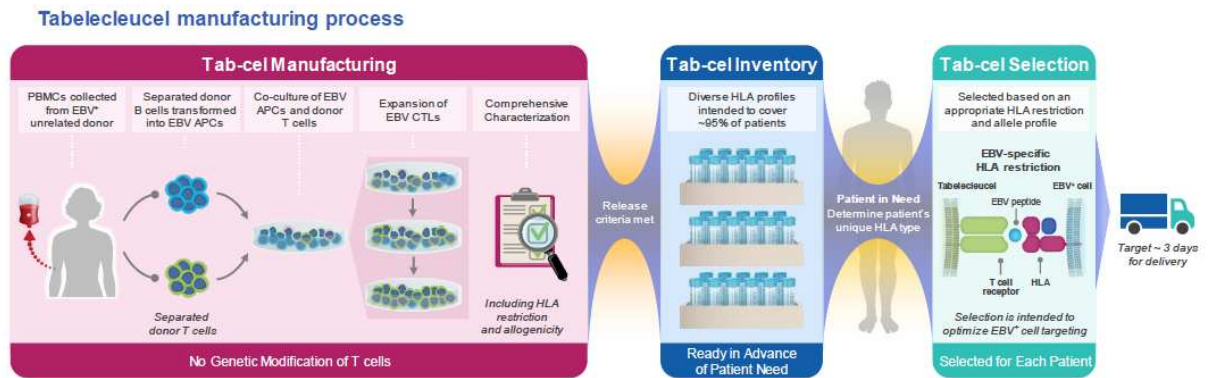


Figure 12. Procédure de manufacturing des LTC anti-EBV issus de donneurs sains.

Center	Method of selection	Indication for CTLs	Prior therapy failed	N	HLA match	CR	PR	SD	POD	NE
Edinburgh, Haque et al. (28, 29)	EBV-BLCL-sensitized EBV-CTLs	EBV polymorph lymphoma	HCT	RIS	2	2-5/6	2	0	0	0
Alabama, Sun et al. (33)	EBV-BLCL-sensitized EBV-CTLs	EBV-PTLD	SOT	RT	1	4/6	1	0	0	0
Karolinska, Uhlén et al. (34)	EBV pentamer-sorted T cells	EBV lymphoma	HCT	None	1	5/10	1	0	0	0
MSKCC, Barker et al. (30)	EBV-BLCL-sensitized T cell line	EBV lymphoma	HCT	Rituximab +/- C	5	>2/10	4	0	0	1
Baylor, Leen et al. (32)	Transduced multivirus CTLs	8 EBV-PTLD	HCT	Rituximab	8	≥1	3	3	0	2
INSERM, Gallot et al. (35)	EBV-BLCL-sensitized EBV-CTLs	1 EBV viremia	HCT	Rituximab	1	1 HLA	0	0	0	1
INSERM, Gallot et al. (35)	EBV-BLCL-sensitized EBV-CTLs		HCT	Rituximab +/- C	6	≥2	2	1	0	2
Multicenter, Naik et al. (31)	EBV-BLCL- or multi-virus-sensitized EBV-CTLs	EBV-PTLD	HCT	C +/- rituximab	3	≥2	1	0	0	2
Multicenter, Naik et al. (31)	EBV-BLCL- or multi-virus-sensitized EBV-CTLs	EBV-PTLD	HCT	immuno-deficiency	5	≥3	1	1	0	3
Aberdeen, Vickers et al. (36)	EBV-BLCL-stimulated EBV-CTLs	EBV-PTLD	HCT	NA	6	≥3	4	0	0	2
Aberdeen, Vickers et al. (36)	EBV-BLCL-stimulated EBV-CTLs	EBV-PTLD	SOT	NA	4	≥3	4	0	0	0
Baylor, Tzannou et al. (37)	Peptide-stimulated	EBV-PTLD	HCT	None	1	3/8	1			
Hannover, Schultze-Florey et al. (38)	Peptide-stimulated IFN-γ capture	EBV-PTLD in remission	HCT	None	2	5/8, 5/8	2			
Aberdeen, Chiou et al. (39)	EBV-BLCL-stimulated EBV-CTLs	EBV-PTLD	SOT	Rituximab RIS	10		8	2		

C, chemotherapy; MSKCC, Memorial Sloan Kettering Cancer Center; RIS, reduction in immune suppression; RT, radiation therapy.

Tableau 4. Résumé des expériences de thérapie adoptive avec des LTC « **third-party donor** » anti-EBV. Tiré de (Prockop *et al*, 2020).

En 2020, Prockop et al rapportaient ensuite les résultats d'une série de 46 patients (33 transplantés de moelle et 13 transplantés d'organes solides) atteints de LPT réfractaires ou en

réponse partielle au rituximab en monothérapie et traités par 3 injections hebdomadaires au moins de LTC anti-EBV « third-party donor ». La tolérance des injections étaient très bonnes (1 réaction du greffon contre l'hôte de grade 1) et ce traitement permettait d'obtenir une réponse hématologique (réponses complète et partielle) chez 68% et 54% des patients transplantés de moelle et d'organes solides respectivement, pour une survie globale à 2 ans de 57 et 54%. Il est important de noter que toutes les réponses complètes, mais également partielles, étaient durables (6-115 mois), témoignant d'une efficacité thérapeutique au long cours ; et que des injections ultérieures de LTC restreints par des molécules du CMH différentes des premières injections permettaient d'améliorer la réponse chez certains patients. Enfin, l'expansion des LTC était beaucoup plus marquée chez les patients répondeurs (x294) versus les patients non répondeurs (x3.4) ($p=0.001$), et il persistait des LTC 24 mois après la première injection chez 1/5 patients testés à plusieurs reprises témoignant de la capacité des LTC à persister dans certains cas sans rejet de la part de l'hôte. Ces résultats tout à fait encourageants ont abouti à 2 études prospectives actuellement en cours (NCT04554914 (ATA-205) et NCT03394365 (ATA-302 ; Allele). Les résultats préliminaires d'ATA-302 présentés à l'ASH 2022 rapportaient qu'un traitement par Tabelecleucel permettait d'obtenir chez 43 patients avec un LPT réfractaires une réponse globale dans 51% des cas avec une durée médiane de réponse de 23 mois et sans effet secondaire particulier (pas de flare tumoral, pas de réaction à l'injection, pas de syndrome de relargage cytokinique, pas de réaction des LTC contre l'hôte, pas de rejet d'organe) (Mahadeo *et al*, 2022). Actuellement, le Tabelecleucel peut être obtenu de façon compassionnelle dans l'attente de l'obtention du remboursement.

5. Immune checkpoint et infection par le VIH, et implications thérapeutiques

La pérennisation des infections virales chroniques témoignent notamment d'une réponse immunitaire dysfonctionnelle empêchant l'éradication complète des agents pathogènes. La réponse immunitaire est soumise à de nombreux mécanismes d'autorégulation afin de maintenir l'homéostasie. Les principaux mécanismes impliqués dans la limitation de la réponse T sont l'expression de points de contrôle immunitaire T, la production de cytokines

immunosuppressives (IL-10, TGF-béta) par des cellules régulatrices telles que les T régulateurs ou les macrophages de type M2 ou encore l'apoptose (expression progressive de Fas).

5.1. ICP et immunité anti-tumorale

Les points de contrôle immunitaire, ou immune checkpoint (ICP), sont des récepteurs inhibiteurs exprimés de façon physiologique à la surface des cellules du système immunitaire afin de prévenir les dommages potentiels sur les tissus d'une réponse immunitaire prolongée (Wherry, 2011). Divers ICP ont été décrits tels que le « program cell death protein 1 » (PD-1), le « cytotoxic T lymphocytes antigen 4 » (CTLA-4), le T cell immunoglobulin mucin receptor 3 (TIM-3) ou encore le « lymphocyte activation gene 3 protein » (LAG-3) et sont illustrés dans la **Figure 13**.

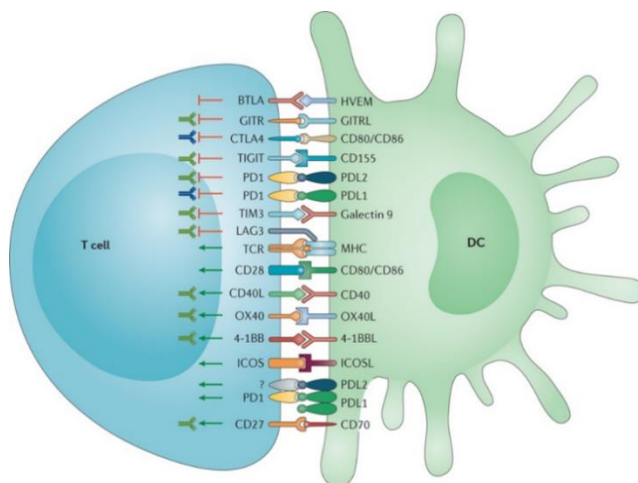


Figure 13. Régulation des réponses T par les CPA. Les CPA telles que les cellules dendritiques régulent les réponses des lymphocytes T spécifiques aux agents pathogènes ou aux cellules malignes. Les TCR exprimés par les cellules T reconnaissent d'abord l'antigène présenté par les molécules du CMH (**signal 1**). Cette étape est ensuite suivie d'un signal envoyé au CD28 des cellules T par le CD80 des CPA, et est décrit comme le "**signal 2**". Plusieurs ligands différents sur les cellules dendritiques fournissent alors des signaux aux cellules T, déterminant ainsi la qualité et la durée de la réponse effectrice. Les interactions récepteur-ligand qui **amplifient** les réponses des cellules T effectrices (flèches vertes) comprennent le CD40-CD40 ligand (CD40L), OX40-OX40L, 4-1BB-4-1BBL (également connu sous le nom de CD137L), co-stimulateur de cellules T inductibles (ICOS)-ICOSL et CD27-CD70. Il existe également des interactions récepteur-ligand qui **suppriment** les réponses des cellules T

effectrices (traits rouges) afin de maintenir la tolérance et de prémunir les tissus des dommages occasionnés par une réponse immunitaire prolongée. Il s'agit notamment de l'interaction « lymphocyte activation gene 3 » (LAG3) - CMH de classe II, de « T-cell immunoglobulin mucin protein 3 » (TIM3) -galectine 9, de « program cell death protein 1 » (PD-1-) -PDL-1, et de PDL-1-PDL-2, « T cell immunoreceptor with immunoglobulin and ITIM domains » (TIGIT)-CD155, « cytotoxic T lymphocyte antigen 4 » (CTLA4)-CD86 ou encore CTLA4-CD80, « glucocorticoid-induced TNFR-related protein » (GITR)-GITR ligand (GITRL) et « B and T lymphocyte attenuator » (BTLA)-herpes virus entry mediator (HVEM). Le symbole "?" fait référence à un récepteur inconnu qui "active" les cellules T. Les symboles des anticorps représentent des voies testées dans le cadre d'essais cliniques en cours. Les anticorps vert indiquent les voies faisant l'objet d'essais cliniques pour le cancer, et les anticorps bleu foncé indiquent ceux qui sont déjà utilisés en clinique. Tiré de (Wykes & Lewin, 2018).

Ils sont de ce fait cruciaux dans le maintien de la tolérance et la protection contre les maladies auto-immunes. L'interaction ICP-ligand est responsable d'un signal négatif d'inhibition des cellules effectrices du système immunitaire, au premier rang desquelles les lymphocytes T CD4 et CD8, provoquant une diminution de leurs capacités de prolifération et effectrices (production cytokinique et cytotoxicité). Les différents mécanismes moléculaires impliqués dans l'épuisement lymphocytaire sont décrits dans la **Figure 14**.

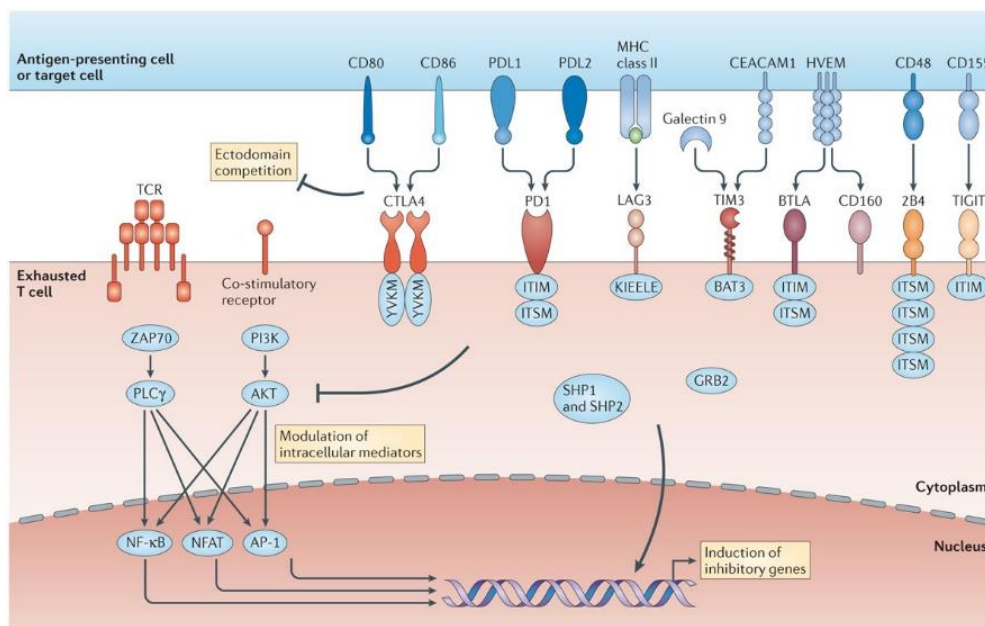


Figure 14. Signalisation moléculaire des récepteurs inhibiteurs Les couples ligands/récepteurs pour les voies inhibitrices sont représentés avec les domaines intracellulaires des récepteurs qui contribuent à l'épuisement des cellules T. De nombreux récepteurs inhibiteurs ont des motifs de type « immunoreceptor tyrosine-based inhibitory motifs » (ITIM) et/ou de type ITSM dans leurs domaines intracellulaires ; néanmoins, certains récepteurs ont d'autres motifs spécifiques. Les **mécanismes** moléculaires de la signalisation des récepteurs inhibiteurs sont classés comme suit : **compétition** des ectodomains (les récepteurs inhibiteurs séquestrent les récepteurs cibles ou les ligands); **modulation** des **médiateurs intracellulaires** (atténuation intracellulaire locale et transitoire des signaux positifs provenant des récepteurs activateurs tels que les récepteurs des lymphocytes T et les récepteurs co-stimulateurs) et **induction de gènes inhibiteurs**. De multiples récepteurs inhibiteurs sont responsables de ces trois mécanismes. AP-1, protéine activatrice 1; BAT3, HLA-B-associated transcript 3; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; GRB2, growth factor receptor-bound protein 2; NFAT, facteur nucléaire des cellules T activées; PI3K, phosphoinositide 3-kinase; PLC γ , phospholipase C γ ; TIGIT, « T cell immunoreceptor with immunoglobulin and ITIM domains ». Tiré de (Wherry, 2011).

Si ces ICP sont indispensables à une homéostasie immunitaire correcte, il est désormais clairement admis que leur **surexpression ou la surexpression** de leurs ligands sont impliquées dans des pathologies tumorales et infectieuses chroniques responsables d'une stimulation antigénique chronique (Pardoll, 2012; Wykes & Lewin, 2018). Ainsi, la surexpression d'ICP au sein des lymphocytes intra-tumoraux des mélanomes ou encore de PDL-1 (ligand de PD-1) par les cellules tumorales dans les cancers du poumon, des ovaires, du colon, les mélanomes ou encore les LH a été rapportée (Dong *et al*, 2002; Ahmadzadeh *et al*, 2009; Green *et al*, 2012; Daud *et al*, 2016; Roemer *et al*, 2016). Il est par exemple tout à fait notable que les cellules tumorales du LH, dont le MET est caractérisé par la présence d'une population immunitaire floride, présentent des anomalies du 9p24 de type amplification, gain ou polysomie dans presque 100% des cas (Roemer *et al*, 2016). Ces anomalies sont responsables d'une surexpression de PDL-1 ou PDL-2. De ce fait, de nombreux anticorps monoclonaux bloquant les ICP, les **ICPi**, ont été développés afin de restaurer une immunité anti-tumorale dans le traitement des cancers, tels que les anti-PD-1 (Nivolumab, Pembrolizumab), les anti-PD-L1 (Atezolizumab, Avelumab), les anti-CTLA-4 (Ipililumab) et plus récemment les anti-LAG-3 et les anti-TIM-3, avec des taux de réponses variant entre 20 et 30% en fonction des études et des types de cancers. Actuellement, en France, ces traitements sont utilisés dans le traitement des

mélanomes, des cancers broncho-pulmonaires, de la vessie, du rein, de la tête et du cou, des LH et des carcinomes de Merkel.

5.2. ICP et immunité anti-virale

De la même façon, les ICP sont impliqués dans **l'épuisement lymphocytaire T** contribuant à la persistance de différentes infections virales chroniques, telles que le VIH (ce sujet est traité dans le paragraphe suivant), le **VHB**, le **VHC**, le **JC-virus** ou encore **l'EBV**. Dans l'infection par le VHB, la surexpression de différents ICP, tels que PD-1, CTLA-4 ou TIM-3, à la surface des LT CD8+ spécifiques a été rapportée, et un traitement *in vitro* par des ICPi permettait d'augmenter la fréquence des LT CD8+ (Bengsch *et al*, 2014; Schurich *et al*, 2011; Nebbia *et al*, 2012; Zhang *et al*, 2008). De ce fait, un **essai clinique** a proposé un traitement par Nivolumab, associé ou non à une vaccination thérapeutique, à 20 patients avec une hépatite B chronique à charge virale indétectable et sans cancer (Gane *et al*, 2019). Ce traitement a permis une séroconversion et une perte de l'antigène HBs persistantes à un an chez un patient, et une réduction $> 0.5 \log_{10}$ de l'antigène HBs chez 2 autres patients, suggérant que ce type de traitement pourrait jouer un rôle dans le traitement du VHB. Dans l'infection par le VHC, PD-1 est également surexprimé par les lymphocytes T spécifiques (Rutebemberwa *et al*, 2008; Golden-Mason *et al*, 2007; Burke & Cox, 2010), et certaines données suggèrent également que les ICPi pourraient jouer un rôle dans le contrôle de l'infection chronique (Gardiner *et al*, 2013; Fukuda *et al*, 2020). Un essai clinique testant une monothérapie par anti-PD-1 a mis en évidence une réduction $> 0.5 \log_{10}$ de la CV VHC sous traitement chez 5/45 patients naïfs de traitement ou en échec d'un traitement antérieur (Gardiner *et al*, 2013). Néanmoins, ces résultats n'ont été confirmés que très partiellement chez les patients infectés par le VHB ou le VHC et traités par ICPi pour un cancer (El-Khoueiry *et al*, 2017; Pertejo-Fernandez *et al*, 2020).

5.3 ICP et VIH : immunité et réservoir

5.3.A. ICP et VIH : implication dans l'immunité anti-virale

Au cours de l'infection chronique par le VIH, les ICP sont impliqués à la fois dans **l'épuisement lymphocytaire** et dans la **latence du réservoir**. En effet, les LT CD8+ spécifiques du VIH expriment des taux plus élevés de PD-1 que les LT spécifiques des autres

virus et que les LT CD8+ des donneurs sains et il existe en conséquence une diminution des capacités de production cytokinique de ces cellules (Trautmann *et al*, 2006). Les LT CD8+ spécifiques du VIH expriment également des niveaux plus élevés de TIGIT et ont une production cytokinique altérée tandis que TIM-3 et LAG-3 sont surexprimés par les LT CD8+ totaux (Tian *et al*, 2015; Chew *et al*, 2016; Rallón *et al*, 2018). Les LT CD4+ spécifiques du VIH, quant à eux, sur-expriment PD-1 et CTLA-4 (D'Souza *et al*, 2007).

Ex vivo, le blocage des ICP est responsable d'une augmentation des LT CD8+ spécifiques du VIH (Trautmann *et al*, 2006; Kaufmann *et al*, 2007; Tian *et al*, 2015; Chew *et al*, 2016). *In vivo*, la première démonstration de **l'augmentation de l'immunité anti-VIH** après blocage des ICP a été apportée en 2009 chez des macaques SIV+ (Velu *et al*, 2009). Ainsi, 9 + 5 macaques SIV+ répliatifs et non traités par ARV ont été respectivement traités par anticorps anti-PD-1 (3 mg/kg, J0, 3, 7 et 10) ou placebo. Ce traitement était responsable d'une expansion rapide, entre J7 et J21, des LT CD8+ spécifiques du SIV (Gag) du sang périphérique avec une augmentation de leur fréquence allant de 2.5 à 11 fois plus qu'au J0, et qui se maintenait jusqu'à 28 à 45 jours après. Cette expansion était également décrite au niveau du tissu digestif avec une augmentation plus tardive (J42) et moins importante (2 à 3 fois plus qu'au J0) que celle du sang périphérique. De façon encore plus intéressante, le traitement était également associé à une augmentation de la qualité fonctionnelle de cette réponse spécifique puisqu'il existait une augmentation de la fréquence des cellules polyfonctionnelles capables de produire à la fois de l'IFN- γ , du TNF- α et de l'IL-2. Ces observations immunologiques se traduisaient par une amélioration des paramètres virologiques et cliniques. En effet, le blocage de PD-1 s'accompagnait d'une diminution significative de la charge virale VIH (divisée par 210, à J21 ou J28) et d'une nette **augmentation de la survie globale** comparé aux macaques traités par placebo. D'autres études menées secondairement *in vivo* dans des modèles animaux ont également suggéré ou démontré une diminution de la charge virale SIV ou VIH après blocage de l'axe PD-1 (Seung *et al*, 2013; Palmer *et al*, 2013; Gill *et al*, 2016). Les études *in vivo* chez l'homme sont survenues plus tardivement. Une étude chez 6 PVVIH sans cancer traitées par une seule injection d'anticorps anti-PD-L1 a démontré une augmentation modérée des LT CD8+ spécifiques du VIH chez 2 d'entre eux (Gay *et al*, 2017).

5.3.B. ICP et VIH : implication dans le réservoir

Par ailleurs, la constitution précoce d'un réservoir VIH est un **obstacle majeur** au traitement curatif de l'infection (Siliciano *et al*, 2003). Les traitements anti-rétroviraux (ARV)

permettent de supprimer la réplication virale au long cours mais ne sont pas capables d'éradiquer complètement la maladie, ainsi qu'en témoignent les classiques « rebonds viraux » de la CV VIH à l'arrêt des traitements. Le virus persiste dans des cellules infectées (LT CD4+, majoritairement mémoire, mais aussi macrophages, astrocytes, hépatocytes) à longue durée de vie et sans activité transcriptionnelle, sous la forme d'ADN VIH intégré dans le génome de l'hôte (appelé provirus) (Churchill *et al*, 2009; Kumar *et al*, 2014; Jambo *et al*, 2014; Zerbato *et al*, 2019) (**Figure 15**). Cet état de quiescence de la cellule hôte et l'absence d'activité transcriptionnelle, et donc d'expression de protéines virales, permet au virus de rester invisible aux yeux du système immunitaire et de le prémunir d'une éradication complète. Si la très grande majorité de l'ADN VIH intégré est défectif du fait de l'acquisition de mutations, et donc incapable d'infection productive, 2 à 5% en est **intact** et donc capable de réplication (Ho *et al*, 2013; Bruner *et al*, 2016). L'état de latence du VIH au sein de la cellule est maintenu par **divers facteurs** dont la localisation du site d'intégration, du silencing épigénétique, une faible disponibilité des facteurs de transcription, une rétention des transcrits et des miRNA au niveau nucléaire, ou encore l'expression d'ICP (Deeks *et al*, 2016).

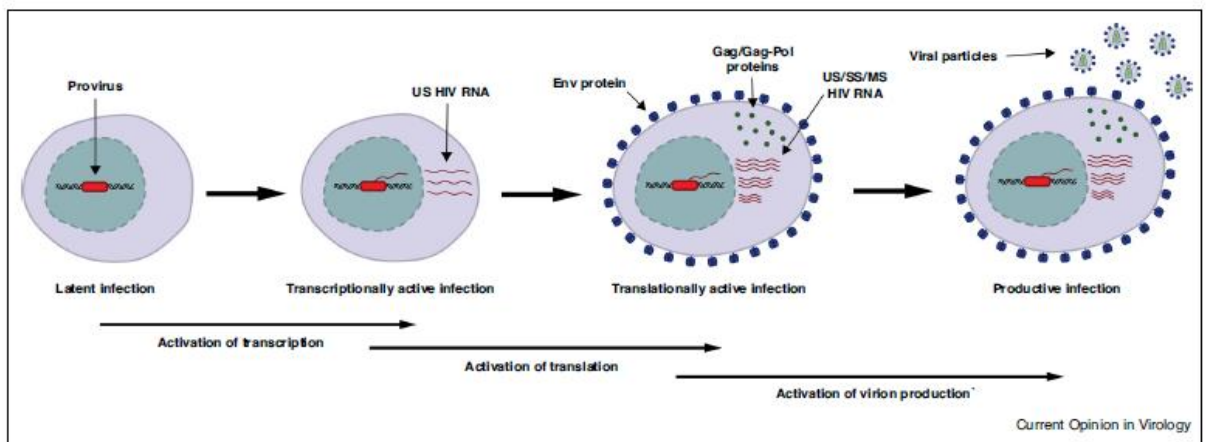


Figure 15. Etapes de la latence. L'inversion de la latence du VIH nécessite de multiples étapes aboutissant à une cellule infectée productive. *In vivo*, les cellules infectées par le VIH persistant sous traitement antirétroviral se trouvent à différents stades de latence, allant de la latence **réelle** (ADN+, ARN-) à l'activité **transcriptionnelle** (ADN+, ARN US+) et à l'activité **traductionnelle** (ADN+, ARN US+, ARN MS+, protéine+). Env : protéine d'enveloppe, US : non épissé, SS : épissé simple, MS : épissé multiple. Tiré de (Zerbato *et al*, 2019).

Une des premières démonstrations de l'implication des ICP dans le réservoir a rapporté un **enrichissement** en ADN VIH dix fois plus important dans les LT CD4+ PD-1+ comparé aux LT CD4+ PD-1^{low} (Chomont *et al*, 2009). Par ailleurs, ces cellules réservoir surexpriment

d'autres ICP tels que LAG-3 et TIGIT et la co-expression de PD-1, LAG-3 et TIGIT définit des LT CD4+ très enrichis en génome viral intégré (Fromentin *et al*, 2016). La démonstration formelle de l'implication fonctionnelle des ICP dans la latence a été finalement apportée par l'équipe de N. Chomont (Fromentin *et al*, 2019). Ainsi, la production de protéines virales p24 après stimulation *ex vivo* de LT CD4+ infectés par le VIH était largement diminuée en présence de PD-L1 comparé à une stimulation sans PD-L1 (98% d'inhibition), et cette inhibition persistait au neuvième jour de culture. *Ex vivo*, les inhibiteurs de PD-1 associés à la bryostatine permettaient de rétablir une production virale au sein des cellules réservoir.

5.4 La théorie du shock and kill : concept et état des lieux

Si l'espérance de vie des PVVIH a largement augmenté avec l'utilisation massive des ARV, l'infection par le VIH continue à être un réel **enjeu de santé publique** en raison de la pénibilité et des effets secondaires des ARV au long cours, du coût de ce traitement et de l'augmentation du risque de cancer chez ces patients. La mortalité par **cancer** représente en effet la première cause de mortalité dans cette population (Vandenhende *et al*, 2015). Dans une stratégie curative du VIH, la théorie du « **shock and kill** » a été développée qui consiste à coupler une induction de la transcription virale (le « shock ») dans les cellules réservoir latentes à un traitement dirigé contre le virus (« le kill ») (**Figure 16**). Diverses molécules, appelées **agents inversant la latence**, ont été proposées à visée de « shock » (inhibiteurs d'histone acétylase, inhibiteurs de bromodomaine, disulfiram, inhibiteurs de mTOR) sans qu'il n'y ait eu de réelle efficacité cliniquement démontrée *in vivo* à ce jour (Zerbato *et al*, 2019).

Récemment, les **ICPi** sont apparus comme des candidats intéressants pour servir cette théorie. *In vitro*, les travaux mentionnés ci-dessus ont démontré l'efficacité des ICPi dans l'induction de la transcription virale et donc le recrutement du réservoir (Chomont *et al*, 2009; Fromentin *et al*, 2016, 2019). *In vivo*, les données sont plus **parcellaires et contradictoires** (Abbar *et al*, 2020)/ divers case report témoignant pour ou contre leur efficacité sur le réservoir. Au sein du laboratoire d'accueil, un patient infecté par le VIH et traité par anticorps anti-PD-1 pour un cancer a baissé son réservoir pendant presque un an sans modification par ailleurs du traitement ARV (Guihot *et al*, 2018). Par ailleurs, au début de ce travail de thèse, 3 autres rapports avaient respectivement démontré une augmentation transitoire de la transcription virale chez un patient, une diminution persistante du réservoir VIH chez un patient et une augmentation transitoire de la transcription virale au sein de 29 patients (Evans *et al*, 2018; Fromentin *et al*, 2019; Uldrick). Depuis que notre travail a été réalisé et finalisé, deux sous-

études biologiques d'essais cliniques ont également évalué l'impact des ICPi dans l'infection par le VIH dans un contexte de cancer (Rasmussen *et al*, 2021; Uldrick *et al*, 2022) dont les résultats seront développés dans la discussion.

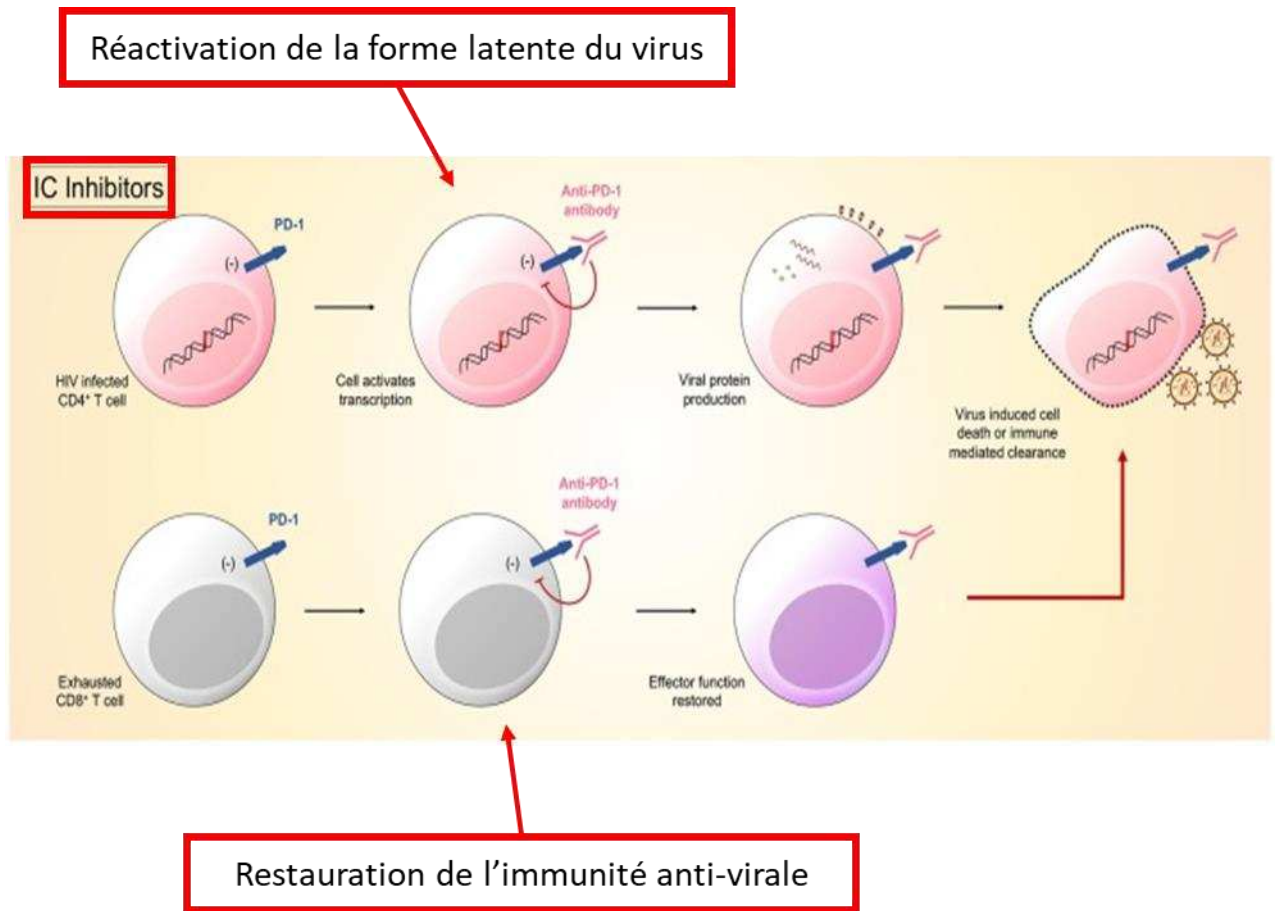


Figure 16. Shock and kill et ICPi. Les ICPi pourraient jouer le rôle d'agents inversant la latence. Les anticorps anti-PD-1 se fixent au PD-1 à la fois sur les cellules T CD4+ infectées par le VIH réservoir et sur les cellules T CD8+ spécifiques du VIH. La liaison de PD-1 par l'anticorps lève l'inhibition des signaux envoyés par les ICP au niveau intra-cellulaire. Les cellules infectées deviennent transcriptionnellement actives et produisent des produits viraux entraînant la mort de la cellule. Les cellules T CD8+ quant à elles ont une fonction effectrice restaurée par l'anticorps qui leur permet de cibler les cellules T CD4+ infectées transcriptionnellement actives. D'après (Boyer & Palmer, 2018).

Objectifs

Première partie. Paysage mutationnel, immunogénicité et microenvironnement tumoral des LNH B survenant dans un contexte d'immunodépression

La caractérisation de l'immunogénicité des tumeurs et de l'immunité anti-tumorale est devenue un enjeu majeur de la compréhension de la tumorigénèse en général et du développement d'immunothérapies innovatrices. Au sein des tumeurs, les lymphomes B sont particuliers par leur capacité de présentation par l'intermédiaire du CMH-II et par la production importante d'Ig avec un profil muté. Au sein des lymphomes B, les lymphomes survenant dans un contexte d'immunodépression (VIH et transplantation) sont particuliers par la faible pression immunologique exercée, la fréquence d'association avec l'EBV et la fréquence des localisations au niveau du SNC.

Nous émettons l'hypothèse que la faible pression immunologique, la positivité d'EBV, la localisation au niveau du SNC, et que les fonctions de CPA et de production d'Ig des LNH B pourraient avoir un impact sur la CMT et le paysage mutationnel, l'immunogénicité des tumeurs et le MET.

Les objectifs de ce premier projet sont, au sein des LNH B survenant chez des patients VIH ou transplantés d'organe (et comparés à des LNH B de l'immunocompétent), de:

- Caractériser la **charge mutationnelle tumorale** et analyser les associations avec le statut immunologique, le statut EBV EBV et la localisation de la maladie
- Caractériser le **paysage mutationnel tumoral** et analyser les associations avec le statut immunologique, le statut EBV et la localisation de la maladie
- Définir les **filtres immunologiques de prédiction *in silico*** des néoépitopes à partir du séquençage de l'exome et de l'ARN
- Caractériser le **nombre de néoépitopes** qui découlent de la prédiction et analyser les associations avec le statut immunologique, le statut EBV et la localisation de la maladie
- Développer une **stratégie de sélection** des néoépitopes les plus pertinents immunologiquement

- Caractériser la **réponse immune T anti-néoépitopes** par des tests fonctionnels sur les cellules mononuclées sanguines périphériques (CMNS) après une phase d'expansion en culture
- Caractériser la **distribution des populations immunologiques** du MET et analyser les associations avec le statut immunologique, le statut EBV et la localisation de la maladie
- Caractériser le **répertoire T intra-tumoral** et analyser les associations avec le statut immunologique, le statut EBV et la localisation de la maladie
- Caractériser le **profil d'expression de différents gènes** impliqués dans la réponse immune au sein du MET et analyser les associations avec le statut immunologique, le statut EBV et la localisation de la maladie

Cette étude a été menée dans le cadre du projet **Idéation** proposant de caractériser l'immunogénomique et le MET des tumeurs survenant dans un contexte d'immunosuppression (lymphomes, cancer du poumon chez les PVVIH et gliomes) et financé par **MSD Avenir** et le **Siric Curamus**. Les résultats rapportés dans ce travail ne concernent que les lymphomes.

Seconde partie. Impact des inhibiteurs de PD-1 (PD-1I) sur l'immunité T anti-virale et sur le réservoir VIH chez les PVVIH atteintes de cancer

Dans l'infection par le VIH, les ICP sont impliqués à la fois dans la dysfonction cellulaire T et dans la latence du réservoir ainsi que démontré plus en amont.

Nous émettons l'hypothèse que l'utilisation d'inhibiteurs d'immune checkpoint chez ces patients pourrait permettre à la fois une réactivation des cellules infectées latentes et une restauration de l'immunité anti-virale, selon la stratégie du « shock and kill » au service d'une « HIV cure ».

Les objectifs de ce second projet sont de caractériser chez les PVVIH atteintes de cancer et traitées par PD-1I:

- L'impact des PD-1I sur le **phénotype des lymphocytes T totaux périphériques** (activation, prolifération, expression des ICP, distribution des sous-populations lymphocytaires) au cours du traitement
- L'impact des PD-1I sur la **fréquence des lymphocytes T spécifiques périphériques** : anti-VIH, mais aussi anti-HBV, HCV, EBV, CMV et HHV-8 en cas de séropositivité associée au cours du traitement
- L'impact des PD-1I sur **l'infection par le VIH** avec évaluation de l'évolution de la charge virale et du **réservoir VIH** au cours du traitement
- L'impact des PD-1I sur **les co-infections virales** avec évaluation de l'évolution des charges virales HBV, HCV, EBV, CMV et HHV-8 au cours du traitement

Cette étude a été menée à partir de 2 sous-études biologiques : **ONCOVIRIM** dans le cadre d'une cohorte prospective ANRS CO24 ONCOVIHAC de PVVIH traitées par ICPi pour un cancer menée par l'Agence Nationale de Recherche sur le SIDA (ANRS), et **CHIVA-BIO** dans le cadre d'un essai clinique CHIVA2 évaluant un traitement par Nivolumab pour les PVVIH avec un cancer du poumon non à petites cellules en rechute ou réfractaires mené par l'Intergroupe Francophone de Cancérologie Thoracique (IFCT) .

6. Résultats : Première partie

Paysage mutationnel, immunogénicité et microenvironnement tumoral des LNH B survenant dans un contexte d'immunodépression

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EBV and immune status imprint the immunogenomics of
non-Hodgkin lymphomas occurring in immune-suppressed
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EBV and immune status imprint the immunogenomics of non-Hodgkin lymphomas occurring in immune-suppressed environments

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Running heads: Immunogenomics of immune-suppressed NHL

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ABSTRACT

Non-Hodgkin lymphomas (NHL) commonly occur in immune-deficient (ID) patients, both HIV-infected and transplanted, and are often EBV-driven with cerebral localization, raising the question of tumor immunogenicity, a critical issue for treatment responses. We investigated the immunogenomics of 68 lymphoproliferative disorders from 51 ID (34 post-transplant, 17 HIV+) and 17 immunocompetent patients. Overall, 72% were Large B Cells Lymphoma (LBCL) and 25% were primary central-nervous-system lymphoma (PCNSL) while 40% were EBV-positive. Tumor whole-exome and RNA sequencing, along with a bioinformatics pipeline allowed analysis of tumor mutational burden (TMB), tumor landscape and microenvironment (TME) and prediction of tumor neoepitopes. Both TMB (2.2 vs 3.4/Mb, $p=0.0014$) and neoepitopes numbers (40 vs 200, $p=0.00019$) were lower in EBV-positive than in EBV-negative NHL, regardless of the immune status. In contrast both EBV and the immune status influenced the tumor mutational profile, with *HNRNPF* and *STAT3* mutations exclusively observed in EBV-positive and ID NHL, respectively. Peripheral blood T-cell responses against tumor neoepitopes were detected in all EBV-negative cases but in only half EBV-positive ones, including responses against *IgH*-derived MHC-class-II restricted neoepitopes. The TME analysis showed higher CD8 T cell infiltrates in EBV-positive vs EBV-negative NHL, together with a more tolerogenic profile composed of Tregs, type-M2 macrophages and an increased expression of negative immune-regulators.

Our results highlight that the immunogenomics of NHL in patients with immunodeficiency primarily relies on the tumor EBV status, while T cell recognition of tumor- and *IgH*-specific neoepitopes is conserved in EBV-negative patients, offering potential opportunities for future T cell-based immune therapies.

INTRODUCTION

Non-Hodgkin lymphomas (NHL) are highly prevalent in severe immune-deficient (ID) patients such as HIV-infected patients and transplant recipients. In both cases, the incidence is higher than in immunocompetent individuals, with a standardized incidence ratio of 11.5 for HIV-related lymphomas and 8 for post-transplant lymphoproliferative disorders (PTLD)(Engels, 2017; Hernández-Ramírez *et al*, 2017b; Blosser *et al*, 2021). The Epstein-Barr virus (EBV) is present in 50–70% of the ID NHL and has been established as a strong oncogene(Carbone *et al*, 2022b; Dharnidharka *et al*, 2016b). Several targeted sequencing approaches have shown that the mutational landscape of EBV-positive NHL differs from that of EBV-negative NHL, with lower number of mutated genes(Finalet Ferreiro *et al*, 2016; Gandhi *et al*, 2021; Menter *et al*, 2017; Yoon *et al*, 2015; Kaulen; Guney *et al*, 2023). In addition, ID patients display alterations of the normally potent cellular immunity directed against viral antigens(Nakid-Cordero *et al*, 2019; Nakid-Cordero *et al*, 2021), potentially leading to immune escape(Green *et al*, 2012; Nicolae *et al*, 2015; Keane *et al*, 2019, 2017). Finally, almost 10% of ID patients, the majority of whom EBV+, have a central-nervous-system (CNS) localization compared to 1% in the general population. As the CNS acts as an immunologically isolated site with very specific immune features, it is hypothesized that the tumor-specific and EBV-specific immune responses are even less active in this tissue, thus favoring immune escape.

The remarkable successes of immunotherapies in solid tumors relay on the level of tumor immunogenicity(Li *et al*, 2017; Schumacher & Schreiber, 2015b; Yarchoan *et al*, 2017). The tumor neoantigens (NeoAg) that surround tumor mutations and are presented by the patients' MHC molecules allow the immune system to distinguish cancer from noncancer cells and emerge as major factors for anti-tumor immunity, response to immunotherapies and the development of targeted treatments. Indeed, the tumor mutational burden (TMB) and the abundance of predicted immunogenic mutations are associated with higher levels of responses

to immune checkpoint inhibitors (ICPi) and increased patient survival (Brown *et al*, 2014; Rizvi *et al*, 2018, 2015) while personalized NeoAg vaccine approaches have successfully induced NeoAg-specific T cells associated with clinical responses (Leidner *et al*, 2022; Li *et al*, 2021, 2017; Platten *et al*, 2021; Sahin *et al*, 2017). However limited data exist for B-cell malignancies which are very specific due to the ability of tumor cells to present tumor NeoAg with MHC class-II molecules and to produce highly mutated immunoglobulins (Ig) that may be immunogenic. Furthermore, studies in immunocompetent patients suggested that NeoAg derived from the lymphoma Ig heavy- or light-chain variable regions with a strong bias for an MHC-II presentation may be particularly critical immune targets (Khodadoust *et al*, 2017, 2019). However, the recognition of these peculiar Ig-based neoantigens has never been analyzed in ID patients.

We hypothesized that the immunogenomics and the tumor microenvironment (TME) of NHL occurring in ID patients might be influenced by the lower immune pressure, the frequent EBV oncogenesis and the immune-privileged sites in these patients. To further investigate this hypothesis, we developed the IDeATion project, a multicentric, prospective study of PTLD and HIV-related lymphoproliferative disorders occurring in a large series of ID patients or in immune-privileged sites such as the CNS. We took advantage of whole tumor DNA and RNA sequencing to compare the TMB, numbers of tumor neoepitopes, neoepitope-specific T cell responses and TME as a function of both tumor EBV status and patient immune status.

MATERIAL AND METHODS

Patient cohort

Patients were enrolled in the IDeATion project ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03706625) NCT03706625). From January 2019 to December 2022, consecutive HIV-infected patients or transplant recipients with treatment-naïve lymphoproliferative disorders from the Hematology or Neuro-Oncology

departments at Pitié-Salpêtrière Hospital, Paris, France or the lymphoid malignancies unit at Henri Mondor Hospital, Créteil, France, were included. Immunocompetent (IC) patients with diffuse large B-cell lymphomas (DLBCL) not otherwise specified (NOS) were included as comparators. All patients gave written informed consent authorizing the use of their biological samples (CRB authorization no. 18.06.46). The protocol was approved by the French national IRB (no. 2018-A01099-46) and the “Commission Nationale de l’Informatique et des Libertés” (CNIL no. 918222) and performed in accordance with the Declaration of Helsinki.

The lymphoma subtype was defined on the diagnostic tumor biopsy according to the 2016 WHO classification (Swerdlow *et al*, 2016). The EBV status was assessed using EBV-encoded small RNA (EBER) *in situ* hybridization analysis. Diagnostic tissue biopsies and blood were collected at inclusion before any treatment.

Whole exome and RNA sequencing, and MHC class-I and class-II restricted neoepitope prediction are detailed in **Supplementary materials** (Text, Tables and Figures).

Immunoglobulin neoepitope prediction

Using RNAseq fastq files, MixCR-V3.0 (Bolotin *et al*, 2015) was employed to derive the sequences and frequencies of the Ig productive clonotypes (heavy and light chains). Reads were aligned to reference V, D, J and C genes of BCR. Each final IgH chain clonotype was identified by a CDR3 sequence and clonotype count. The FR3-CDR3-FR4 sequence of the dominant clonotype (at least $\geq 15\%$ of all clonotypes) was then tested for binding affinity score in NetMHC version 4.0 (Andreatta & Nielsen, 2016) and NetMHCIIpan version 3.2 (Jensen *et al*, 2018) asking for 8–10 mers and 15 mers for MHC I and II binding respectively. The number of neoepitopes with a binding affinity score ≤ 500 nM was determined.

Neoepitopes-specific T cell expansion and functional validation

The most relevant non-Ig derived neoepitopes were selected upon their presentation by expressed HLA molecules or beta-2 microglobulin (B2M) (reads per kilo base per million

(RPKM) ≥ 1), and the highest pVACseq priority score for SNV (**Supplementary materials**), and the highest binding affinity score for indels derived from the same somatic variant. When numbers of candidate neoepitopes were >60 , the stability filter (NetMHCstab) was used to select the 60 strongest binders.

For Ig-derived neoepitopes, 8–14 mer peptides surrounding the mutation for MHC-I peptides and 25 mer peptides overlapping by 20–24 amino-acids and spanning the complete mutated predicted sequences for MHC-II peptides were selected.

A maximum of 60 peptides corresponding to neoepitopes were synthesized per patient (GeneCust, Boynes, France). Frozen PBMCs were thawed and co-cultured with each patient's personalized pooled peptides (2 $\mu\text{g}/\text{mL}$) in RPMI medium enriched with human AB serum, IL2 (10 UI/mL) (Roche, Bâle, Suisse), IL-7 (25 ng/mL) and IL-15 (25 ng/mL) (both from BioLegend, San Diego, CA). On day 10, cell reactivity was tested in a triplicate IFN- γ ELISPOT assay after stimulation with personalized pooled peptides (2 $\mu\text{g}/\text{mL}$ per pool), medium alone and phytohemagglutinin (PHA, Sigma-Aldrich) as negative and positive controls, respectively. When enough cells were available, additional assays were performed with MHC-I or MHC-II pooled peptides, or each individual peptide (2 $\mu\text{g}/\text{mL}$). After a 20-hour stimulation, numbers of spot-forming-cells (SFC) were read (AID Elispot reader, Auto-immun Diagnostika, Strassberg, Germany) and mean triplicate SFC numbers were calculated, after background subtraction, with a positivity threshold of 50 SFC/ 10^6 cells (Nakid-Cordero *et al*, 2019; Nakid-Cordero *et al*, 2021).

Gene expression and cell type abundance profiling

Tumors were digitally quantified for immune genes with a targeted gene panel including T cell function (*IFN- γ* , *TNF- α* , *CD107a*, *granzyme B*, *perforin*), positive immune regulation (*ICOS*, *ICOSL*, *CD28*, *CD40*, *CD40L*, *OX40*, *OX40L*, *4.1BB*) and negative immune regulation (*PD-1*, *PD-L1*, *PD-L2*, *LAG-3*, *TIM-3*, *Galectin9*, *TIGIT*, *CD47*, *IL-10*, *TGF- β* , *IDO*). Each sample

enrichment scores and gene set pairing was computed separately using Single-sample Gene Set Enrichment Analysis (ssGSEA)(Subramanian *et al*, 2005) (<https://www.gsea-msigdb.org/gsea/index.jsp>). Immune deconvolution analysis was performed with CIBERSORTx(Steen *et al*, 2020) version, using expression matrix estimating 22 immune cell types using 547 signature genes (LM22).(Newman *et al*, 2015)

Differential gene expression (DGE), gene ontology (GO) enrichment analysis, T cell receptor analysis and statistical analysis are detailed in **Supplementary materials**.

RESULTS

Patient characteristics

Sixty-eight patients with NHL were enrolled, including 51 immunodeficient (ID) patients, either transplant recipients (N=34 PTLN) or HIV-positive (N=17), and 17 immunocompetent (IC) patients with DLBCL (**Table 1**). The median age was 57 years and 72% of patients were male. Diseases were systemic in 75% and cerebral in 25% cases. The most frequent lymphoproliferative disorder subtypes were Large B Cell Lymphoma (LBCL) (72%: 34 DLBCL NOS + 12 Primary CNS Lymphoma (PCNSL) + 2 DLBCL NOS HHV8+ and 1 HGBL NOS), followed by polymorphic lymphoproliferation (9%), Burkitt lymphoma (BL) and plasmablastic lymphoma (PL) (6% each). The tumors were EBV-positive in 40% cases, all in the ID group (47% and 65% in PTLN and HIV+ patients, respectively). Both CNS and systemic localizations were equally distributed between EBV-positive and negative NHL. All but one CNS NHL from ID patients were EBV-positive. No significant differences were observed between EBV-positive and -negative NHL regarding time from transplantation to NHL diagnosis (6.9 [IQR:2.85-13.11] vs 10.2 [IQR:8.80-20.41] years, p=0.06), median CD4 counts at NHL diagnosis (266 and 222/mm³), time from diagnosed HIV infection to NHL diagnosis (4.1 [IQR:2.49-21.53] vs 21.6 [IQR:4.92-23.94] years, p=0.7) and overall survival (OS) (NA

and 5.3 years, $p=0.21$) (**Supplementary Figure 1**). The median follow-up from NHL diagnosis was 1.8 years.

The tumor mutational burden is lower in EBV-positive compared to EBV-negative NHL

We investigated the TMB in a WES analysis of paired tumor and normal samples (**Methods in Supplementary data; Supplementary Figure 2.A**). The median TMB was 3.01/Mb [IQR : 1.81-5.06] similar to the previously described burden for DLBCL patients (**Supplementary Figure 3**)(Australian Pancreatic Cancer Genome Initiative *et al*, 2013). However, the median TMB was lower in the EBV-positive compared to EBV-negative NHL, both among the whole (ID+IC) NHL population (2.2 *versus* 3.4/Mb, $p=0.0014$) and among the ID only NHL (2.2 *versus* 4.6/Mb, $p=0.0075$) (**Figure 1.A**). Similarly, when restricting the analysis to the predominant LBCL subgroup ($n=49$), a lower median TMB was observed in EBV-positive compared to EBV-negative LBCL (2.2 *versus* 3.4/Mb, $p=0.0007$) (**Figure 1.A**). There were no TMB differences according to immune status when comparing IC, PTL and HIV patients both in the overall population (**Figure 1.B**) and in the EBV-negative one (**Supplementary Figure 4**). By contrast, the TMB differed slightly according to disease localization (3.2 in systemic *versus* 2.3 in CNS disease, $p=0.046$) (**Figure 1.C**). Importantly, a higher TMB was associated with a significantly longer OS in EBV-negative patients (OS=NA for TMB >3/Mb *vs* 2.2 years for TMB <3/Mb, $p=0.01$) while there was no difference in EBV-positive ones (**Figure 1.D**) (**Supplementary methods** for the determination of the TMB cut point).

EBV, immune status and disease localization impact the mutational profile of NHL.

Next, we deciphered the mutational profile of these lymphomas and observed some frequently mutated genes such as *PCLO* (25% cases), *CSMD3* (24%), *TP53* (24%), *FAT4* (19%) and *MYD88* (16%) as expected (**Figure 2A**). However when focusing on the LBCL we observed a

dysbalance in the mutational profile depending on both EBV and patients immune status. Indeed in EBV-positive LBCL the most frequently mutated genes were: *TYWI* (27%) and *STAT3*, *HNRNPF*, *TNRC18*, *PARP10* and *KDM3A* (20% each), while *TP53* (35%), *MYD88* (32%), *CD79B* (24%) and *FOXQ1*, *STAT3*, *KRT3* and *ZNF574* (15% each) were the most frequently mutated in EBV-negative ones (**Figure 2.B and Supplementary Table 1**).

Furthermore, some mutations were observed only in EBV-positive NHL, such as *HNRNPF* (20%), or only in EBV-negative ones, such as *MYD88* and *CD79B* mutations (32 and 24% respectively). Finally, *TP53* mutations were observed almost exclusively in EBV-negative NHL (35% vs 7%). After FDR correction, no significant differences remained yet.

The immune status (IC or ID) co-influenced this tumor profile with *TP53* present in 34% of ID-LBCL (vs 12% in IC-DLBCL), all but one of which were in the EBV-negative group. Furthermore, the *STAT3*, *TYWI* and *KDM3A* mutations were found only in ID-LBCL (25%, 25% and 19%, respectively), regardless of EBV status, while they were absent in IC-DLBCL. (**Figure 2.C and Supplementary Table 2**). As expected, the disease localization had also an impact, with *TP53* mutations found only in systemic diseases (37% vs 0%) and *MYD88* and *CD79B* mutations being more frequent in CNS than in systemic diseases (50% vs 11% and 43% vs 6%, respectively) (**Supplementary Figure 5.A**). Finally, the 6 polymorphic lymphoproliferations (5 EBV+ and 1 EBV-) showed a distinct mutational profile with *PCLC* as the most recurrently mutated gene (**Supplementary Figure 5.B**). Within the 4 BL, the 2 genes recurrently mutated were: *MYC* and *IGLL5* (**Supplementary Figure 5.C**).

In addition, we identified significant recurrent Somatic Copy Number Alterations (SCNAs) on the WES data (Methods in **Supplementary data**). When focusing on the 47 LBCL, we successfully identified a total of 13 arm-level and 12 focal regions displaying copy gain, along with 5 arm-level and 6 focal regions with copy loss (arm q value ≤ 0.1 , focal regions q value ≤ 0.25 **Supplementary Figure 6.A**). These SCNAs observed frequencies ranged from

2% to 55%. In IC DLBCL, SCNAs encompassed amplifications of 1q, 18q, 21q, 7q22, 8q24, and 19q13, and deletions involving 6q, 17p, 1p36, and 1p13, consistently with prior reports (Chapuy *et al*, 2018). Additionally, we observed SCNAs in genes previously reported in DLBCL (Schmitz *et al*, 2018), including *PIK3CA* (25%), *PRDM1* (38%), *MYC* (19%), *CDKN2A* (21%), *PTEN* (14%), *ETV6* (42%), *STAT6* (42%), *B2M* (23%), and *TP53* (42%) (**Supplementary Table 3**). Furthermore, we uncovered previously unreported amplifications of chromosome 16 in 34% of LBCL patients in our dataset.

Notably, factors influencing those SCNAs included the EBV status with focal amplification peaks, in EBV-positive cases, of the 9q34.13, a region encompassing the *NOTCH1* and *JAK2* genes (**Supplementary Figure 6.B**). The immune status as well influenced SCNAs with more frequent amplification at 1q22, 7q22.1, 8q24.3, 9q34.3, 11q13.1, 11p15.5, 16q24.3, 17q25.3, 22q13.31 genomic regions in the ID-LBCL vs IC-DLBCL groups. Additionally, some deletions were prevalent at 1p36.32, 1p13.3, and 15q12 (**Supplementary Figure 6.C**), affecting genes like *IL10*, *CDK6*, *MYC*, *CD45*, *CD27*, *CDKN1A*, *IRF8*, *CCR4*, *IL17RA*, *CDKN2C*, *CD4*, *IGHV*, among others. Systemic localizations also played a role with more frequent deletions affecting the human-leukocyte-antigen (HLA) locus (6p21.31), *BCL6* (3q29) and Immunoglobulin genes (15q12), together with amplifications of the 7q22 and 8q24 locus (**Supplementary Figure 6.D**).

The EBV status influences the tumor immunogenicity dominated by MHC class-II restricted neoepitopes

We first predicted the neoepitopes derived from non-Ig tumor variants by including parameters from the RNA sequencing. In the 30 tumors with available RNAseq (Methods in **Supplementary data; Supplementary Figure 2.B**), we found a median of 149 neoepitopes per tumor, with lower numbers in EBV-positive compared to EBV-negative NHL (40 vs 200,

p=0.00016), independently of the immune status (**Figure 3.A**). These values were not influenced by the expression levels of the MHC molecules and B2M that did not differ between EBV-positive and negative NHL, ID and IC patients and systemic *versus* CNS localization (**Data not shown**). Furthermore, very few down-regulations (RPKM <1) of HLA class I and class II were observed (3% and 9% of tumors, respectively) and no B2M down-regulation or mutations were observed despite the presence of heterozygote deletions in four tested patients. Most neoepitopes were predicted to be presented by MHC class-II molecules with a median class-II/ class-I CMH ratio of 4, independently of the EBV status.

As RNAseq was not available in more than half tumors, we conducted the same analysis solely based on WES. Similarly, we observed lower numbers of neoepitopes in EBV-positive compared to EBV-negative tumors (159 *versus* 501, p=0.0024) (**Figure 3.B**), with a highly significant positive correlation between WES and RNA-based results (r=0.93, p<0.001) (**Figure 3.C**). Importantly, the neoepitopes numbers were positively correlated to the TMB (r=0.8, p<0.001) (**Figure 3.C**). Furthermore clonal-derived neoepitopes accounted for 89% of the entire WES predicted neoepitopes with significantly higher neoepitopes numbers originating from clonal compared to subclonal populations (median per patient: 301 and 32, respectively, p=0.02) (**Supplementary Figure 7.A**).

Then, we analyzed the neoepitopes derived from Ig variable regions genes by using the available RNAseq data from the FR3-CDR3-FR4 region. A dominant tumor Ig clonotype ($\geq 15\%$) was found in 24 NHL patients, with frequencies ranging from 15% to 100% (median 81%). A median of 15 neoepitopes derived from the tumor heavy chain variable region genes was found, independently of the EBV (15 and 18 for EBV-positive and negative samples, respectively) or immune status (15 and 15 for ID and IC samples, respectively) (**Figure 3.D**). These Ig-derived neoepitopes were also predicted to be more frequently presented by the MHC class II, with an MHC class-II/class-I ratio of 1.5.

Circulating T-cells specific for tumor neoepitopes, including *Ig*-derived neoepitopes, are detectable in 71% of NHL

To confirm that the predicted NHL neoepitopes could drive effective anti-tumor immunity in ID patients, we analyzed the peripheral blood T cell responses against the corresponding peptides in 14 samples (13 ID and 1 IC patient). We tested a similar number of variant-derived peptides from EBV-positive and -negative tumors with a median of 48 peptides per patient. Neoepitope-specific responses were detectable in 10 out of the 14 (71%) patients samples tested, among whom 93% were ID and 50% had CNS disease. These neoepitope-specific responses were more frequently detectable, though non significantly, in the EBV-negative patients, as observed among all 6 (5 ID + 1 IC) tested cases, than in EBV-positive ones as observed in only 4 of the 8 ID cases tested ($p=0.08$). The median magnitude of positive T-cell responses was 746 SFC/ 10^6 cells per patient's peptide pool, and above 500 SFC/ 10^6 cells in the 7 ID patient samples (**Figure 4 and Supplementary Figure 8**). The magnitudes above SFC $>500/10^6$ cells were associated with a trend towards higher, though non significantly different, time from transplantation or HIV diagnosis to NHL diagnosis and CD4 count in HIV patients, (12 vs 8 years, 27 vs 9 years, 135 vs 1087/ mm^3 , respectively, $p>0.4$).

The *Ig*-derived neoepitopes were tested in 5 cases with a median number of 22 tested neoepitopes per patient (16 MHC-II and 8 MHC-I restricted) and were recognized in 3 cases with a 1.5- to 3-fold higher magnitude (median 697 SFC/ 10^6 cells) than against autologous non-*Ig* neoepitopes. All recognized *Ig* epitopes were localized in the heavy chain region and predicted to be MHC-class II restricted.

Finally, there were no neoepitopes shared between tumors, although some derived from frequently mutated genes (in $\geq 10\%$ NHL) such as *FAT4*, *SETD1B*, *ZFP36L1*, *HMCN1*, *MTMR1*, *UBR4*, *KLF2*, *RBMX1*, *ALMS1* and *C2ORF49*. These tumor-derived neoepitopes

were not found in the public immune epitope database (IEDB) for T cell epitopes from pathogens and autoimmunity.

EBV drives the tumor microenvironment.

These immunogenicity results prompted us to analyze the intra-tumoral TCR repertoire in RNA seq data of 27 patients' samples with sufficient numbers of TCR β reads (≥ 100). The EBV-positive NHL contained higher numbers of unique productive clonotypes than the EBV-negative ones (412 *versus* 134, $p=0.003$) (**Figure 5**). These numbers were also higher among ID NHL compared to the IC ones, both in the EBV-negative NHL (157 *versus* 90, $p=0.04$) and in the overall population (**Supplementary Figure 9**). In contrast, the repertoire diversity was similar between the NHL subgroups (**Supplementary Figure 10**) without any shared dominant clonotypes between patients. Finally, the TCR sequences with clone frequencies $>10\%$, suggestive of tumor-neoantigen selection, did not show any evidence of known antigen specificity using the VDJ database.

We then analyzed the TME immune cell composition to determine whether such higher TCR abundance in ID NHL was associated with selected T cell populations (**Supplementary Figure 11**). The frequencies of CD8+ T cells, regulatory T cells (Tregs), resting NK cells, type-M1 and M2 macrophages and monocytes were significantly higher in EBV-positive compared to EBV-negative NHL, but were not influenced by the immune status or disease localization (**Figure 6.A and Supplementary Figure 12**). In EBV-positive NHL, the frequencies of CD8 T cells and of activated memory CD4 T cells were positively correlated with the TMB ($r=0.79$, $p=0.048$; $r=0.96$, $p=0.024$, respectively) (**Figure 6.B**). A similar trend of association was observed among EBV-negative cases, though not statistically significant.

Finally, we studied the expression of a selected customized panel of relevant genes involved in intra-tumoral immune responses. Whereas there was no difference for genes involved in

positive immune regulation or T-cell lymphocyte function, a trend to a higher expression of genes involved in negative immune regulation was observed in EBV-positive NHL samples (**Figure 7**).

DISCUSSION

Our comprehensive large study of the immunogenomics of NHL occurring in ID patients revealed that the presence of EBV influences both the tumor mutational burdens and profiles, along with the immune status, but also influences the tumor variant immunogenicity and the microenvironment. Altogether, a limitation of our study might be the size of our series of NHL from immunodeficient patients, though the largest so far to be studied at the unbiased immunogenomics level, in addition to some heterogeneity in the lymphoproliferative disorders studied

Our unbiased WES-based analysis allowed us to demonstrate a lower TMB in EBV-positive NHL of immunodeficient patients compared to EBV-negative ones, confirming previously suggested data obtained by targeted approaches (Finalet Ferreiro *et al*, 2016; Gandhi *et al*, 2021; Menter *et al*, 2017; Ferla *et al*, 2020). Our data further indicate that the strong viral signaling present in EBV-positive NHL reduces the need for other driver tumor mutations in lymphomagenesis, in accordance with the concept of EBV alone acting as a strong oncogene in infected B cells, especially in the context of low immune pressure (Dharnidharka *et al*, 2016b). In line with this hypothesis, we showed that the numbers of tumor neoepitopes determined by these mutations were also lower in EBV-positive NHL, suggesting that each additional mutation increases the probability of generating a significant neoantigen, thereby contributing to the overall tumor immunogenicity.

Additionally, the presence of EBV also drives specific mutational profiles. The finding that *HNRNPF* was significantly mutated only in EBV-positive NHL might be in accordance with

data showing that other ribonucleoproteins from the same HNRNPK family bind to the EBV nuclear antigen-2 (EBNA-2) and enhance viral LMP2A antigen expression (Gross *et al*, 2012). We also confirmed previous targeted approaches reporting the almost complete lack of *MYD88*, *CD79B* or *TP53* mutations in EBV-positive NHL. More importantly, our WES approach enabled us to show that the immunodeficient status was associated with *STAT3* and *TYWI* mutations regardless of the EBV status, with *STAT3* being mutated only among ID patients, both HIV-positive and transplant recipients. The *STAT3* protein is involved in a key signaling pathway modulating multiple physiological processes and inflammatory responses, especially in the B-cell lineage. *STAT3* mutations, which are rare in IC EBV-negative DLBCL had been reported in half EBV-positive diseases, such as PL or polymorphic lymphoproliferations, particularly in HIV-positive patients (Chapman *et al*, 2021; Sarkozy *et al*, 2021; Ramis-Zaldivar *et al*, 2021; Liu *et al*, 2020). However, data for *STAT3* mutations in PTLN patients are limited (Leeman-Neill *et al*, 2022). Our findings suggest for the first time that chronic immune stimulation and/or inflammation in these two immunodeficient settings associated with permanent antigenic stimuli (allogeneic transplant or HIV) might favor such *STAT3* mutations, thus highlighting the potential of JAK inhibitors as a promising treatment option. In addition, *STAT3* mutations have been reported very recently to be linked with a “hot” microenvironment in PCNSL (Hernández-Verdin *et al*, 2023).

The prediction and validation of the most relevant neoepitopes were allowed by our development of a robust bioinformatic method based on tumor DNA and RNA sequencing, along with *in silico* algorithms and inferred rules for tumor neoepitope immunogenicity. In order to consider all steps of the antigen processing required for successful neoepitope selection (Garcia Alvarez *et al*, 2022), we included factors in our pipeline that are involved in the presentation machinery, such as the HLA molecules and B2MG expression, in addition to key parameters for effective anti-tumor immune responses (Schumacher & Schreiber, 2015b; Wells

et al, 2020; De Mattos-Arruda *et al*, 2020b). The strong correlation observed between neoepitope numbers selected from WES and RNA sequencing should facilitate future routine use. We confirmed that our neoantigen predictions could effectively drive blood T cell responses that were detectable in 71% of our tested patients, even with CNS diseases and ID status. In addition to these non-viral neoepitopes, we showed, as previously suggested in IC patients (Khodadoust *et al*, 2019, 2017), that NHL *Ig*-derived neoantigens contain immunodominant neoantigens, mostly presented by MHC-class II, in these ID patients. The low levels of T cell responses against non-viral neoepitopes in EBV-positive NHL might reflect a strong immunodominance of EBV rather than the lower number of neoepitopes.

The higher T cell infiltrate observed in the TME analysis of EBV-positive NHL might be in accordance with the strong EBV immunodominance, regardless of the immune status and without evidence for enrichment in specific TCR clonotypes. This T cell microenvironment was composed of both CD8 and activated CD4 T cells. In addition, a tolerogenic profile, composed of Tregs, type M2 macrophages and a higher expression of negative immune regulation molecules, tended to predominate in EBV-positive NHL, thus confirming that EBV might promote a more tolerogenic TME (Keane *et al*, 2019, 2017).

In conclusion, our exhaustive analysis of the immunogenomics characteristics of NHL occurring in immunodeficient patients shows the major influence of EBV on tumor mutational burden and profile and on tumor neo-antigenicity and suggests that future treatments should be adapted to the EBV status. Despite the lack of frequent or public NHL driver mutations and neoepitopes preventing the development of shared immune strategies as in other cancers (Li *et al*, 2021; Platten *et al*, 2021), the existence of T-cell responses in these immunodeficient contexts, directed against non-viral tumor neoepitopes, and particularly against *IgH* ones in ID patients, could pave the way for the development of future *Ig*-based immune therapies.

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Data sharing statement: All the data can be shared with the authors by mailing the corresponding author. All whole-exome sequencing and transcriptome data have been deposited at the European Genome-phenome Archive (EGA), which is hosted by the European Bioinformatics Institute (EBI), under the accession code EGASXXXXXXXXXX (submission in progress).

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TABLES

Table 1 : Patients characteristics at diagnosis

Patients characteristics	Overall NHL (n=68)	EBV-negative NHL (n=41)	EBV-positive NHL (n=27)	P
Median age at diagnosis(range)	57 (21-85)	59 (21-85)	57 (30-76)	0.2
Sex : M/F	49/19	28/13	21/6	0.42
Immune status : n (%)				
- Transplant recipients	34 (50)	18 (44)	16 (60)	0.234
- HIV patients	17 (25)	6 (15)	11 (41)	
- IC patients	17 (25)	17 (41)	NA	
Allograft type: n (%)				
- Kidney	12 (35)	4 (22)	8 (50)	0.09

- Liver	12 (35)	9 (50)	3 (19)	
- Heart	9 (27)	5 (28)	4 (25)	
- Heart/lung	1 (3)	0	1 (6)	
Time from transplantation to NHL diagnosis: years, median (range)	9 (0.4-32)	10 (2-33)	7 (0.4-28)	0.06
Time from diagnosed HIV infection to NHL diagnosis: years, median (range)	9 (0-35)	22 (0.1-33)	4 (0-35)	0.7
HIV viral load at NHL diagnosis: cp/mL(range) (available for 14 HIV patients)	78 (<20-1700000)	121 (<20-1700000)	40 (<20-353000)	0.26
CD4 count at NHL diagnosis: /mm3 (range) (available for 14 HIV patients)	245 (24-1846)	223 (160-1846)	267 (24-596)	0.22
WHO classification: n (%)				
- LBCL*	49 (72)	34 (83)	15 (55)	0.01
- Polymorphic lymphoma	6 (9)	1 (2)	5 (19)	
- Burkitt Lymphoma	4 (6)	2 (5)	2 (7)	
- Plasmablastic lymphoma	4 (6)	1 (2)	3 (11)	
- Marginal zone lymphoma	2 (3)	1 (2)	1 (4)	
- Plasmocytoma	2 (3)	1 (2)	1 (4)	
- Mantle cell lymphoma	1 (1)	1 (2)	0	
Cell of origin (DLBCL NOS) Available for	43	31	12	
- GC	24	20 (65)	4 (33)	0.09
- Non GC	19	11 (35)	8 (67)	
EBV status: n(%)				
- Positive	27 (40)	0	27 (100)	NA
- Negative	41 (60)	41 (100)	0	
Disease localization: n (%)				
- Systemic	51 (75)	32 (78)	19 (70)	0.57
- Central nervous system	17 (25)	9 (22)	8 (30)	
Extranodal localization for systemic disease: n (%) Available for	48	37	19	
- Yes	43 (90)	34 (92)	17 (90)	1
- No	5 (10)	3 (7)	2 (10)	
LDH above upper limit: n (%), available for 50 patients	37 (74)	20 (74)	18 (78)	0.15
Ann Arbor Stage for systemic disease: n(%) Available for:	46	28	18	0.4
- I-II	10 (22)	5 (18)	5 (28)	
- III-IV	36 (78)	23 (82)	13 (72)	
Age-adjusted IPI for systemic disease: n (%) Available for:	44	26	17	1
- 0-1	14 (32)	8 (31)	6 (35)	

- 2-3	29 (68)	18 (69)	11 (65)	
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Abbreviations: EBV, Epstein Barr Virus; NHL, non-Hodgkin lymphoma; IC, immunocompetent; ID, immunodeficient; M, male; F, female; DLBCL, diffuse large B-cell lymphoma; GC: germinal center, EBV, Epstein-Barr Virus; LDH, lactate deshydrogenase; IPI, international prognosis index; NA: not applicable. *: LBCL included 34 DLBCL NOS + 12 primary CNSL + 2 DLBCL NOS HHV8-positive + 1 high-grade B-cell lymphoma NOS.

FIGURE LEGENDS

Figure 1. The tumor mutational burden is lower in EBV-positive NHL compared to EBV-negative ones.

Tumor mutational burden (defined as the number of mutations per Megabase) according to **A.** the EBV status among the 65 NHL patients on the left (3 outliers were excluded from the analysis, all in the EBV-negative group), the 48 immunodeficient NHL patients in the middle, and the 47 LBCL patients on the right. Red and green color denote EBV-negative and positive NHL respectively. **B.** the immune status. Salmon, blue and yellow colors denote immunocompetent, transplant and HIV patients respectively. **C.** the disease localization. Pink and blue color denote systemic and CNS localization respectively. *Wilcoxon Test*. **D.** and **E.** Overall survival depending on TMB>3/Mb among EBV-negative (**D**) et positive (**E**) diseases. *Kaplan Meier*. IC: immunocompetent, CNS: central nervous localization.

Figure 2. The mutational landscape of ID NHL differs by EBV and immune status, and disease localization.

A. Oncoplot of the top 50 most recurrently mutated genes within the overall population of 68 NHL patients. **B.** Co-oncoplot of the most recurrently mutated genes ($\geq 15\%$) within the 49 LBCL samples according to the EBV status (EBV-negative on the left, EBV-positive on the right). *TP53*, *MYD88* and *HNRNFP* were differently mutated between the 2 groups but these results lost their significant value after FDR correction was applied. **C**

.Co-oncoplot of the most recurrently mutated genes ($\geq 15\%$) within the 49 LBCL samples according to the immune status (immunocompetent on the left, immunodeficient on the right). *STAT3*, *TYWI* and *MYD88* were differently mutated between the 2 groups but these results lost their significant value after FDR correction was applied. *Fisher exact test* were used to compare categorical data. **D.** The GISTIC2.0 results of significantly recurring (events with a q-value of < 0.25) focal amplifications (red) and deletions (blue) are shown. The chromosomes are plotted in the x-axis and the GISTIC-scores (G-score) are plotted in the y-axis.

Figure 3. The number of neoepitopes is lower in EBV-positive NHL compared to EBV-negative ones. Number of predicted neoepitopes (\log_{10}) **A.** from the non *Ig* variants within the 31 RNA samples, according to the EBV status on the left and the immune status (in EBV-negative NHL) on the right. *Wilcoxon test*. **B.** from the non *Ig* variants within the 63 WES samples (5 samples were excluded because of outliers ($n=3$) or absence of germline assessment ($n=2$)) according to the EBV status. *Wilcoxon test*. **C.** Correlation study between the number of predicted neoepitopes from the RNA and the WES data on the left, and between the number of predicted neoepitopes from the RNA data and the tumor mutational burden on the right. *Spearman correlation*. **D.** Number of predicted neoepitopes (\log_{10}) from *Ig* variants within the 24 RNA samples (7 samples were excluded because of dominant *IgH* clone $< 15\%$). *Wilcoxon test*. IC: immunocompetent; ID: immunodeficient.

Figure 4. Neoepitopes-specific T-cells are detectable among 71% cases, including responses directed against Ig-derived neoepitopes. Number of IFN- γ spots ($/10^6$ cells) after peptide stimulation for the 14 tested patients (represented on the *x* axis). Green squares denote responses directed against the complete pool, red circles denote responses directed against Ig-derived neoepitopes and black circle denote responses directed against individual non-Ig neoepitopes. Thawed PBMC were co-cultured with personalized pooled peptides during 10 days and next tested for reactivity using IFN- γ enzyme linked immunoSpot (ELISPOT) assays.

Patients were all tested for their personalized pooled peptides (named “complete pool”) and eventually for each individual peptide if the number of cells were adequate (named as the mutated gene). The mean numbers of spot forming cells (SFC) from triplicates were normalized to number of IFN- γ spots detected per 1×10^6 PBMC after background subtraction, and ELISPOT-IFN- γ positivity threshold was 50 SFC per million cells.

Figure 5. The intra-tumoral TCR repertoire diversity does not differ between EBV-positive and negative NHL. Number of unique productive TCR- β clonotypes according to the EBV status (left), the immune status (middle) and the disease localization (right).

Wilcoxon Test. IC: immunocompetent; ID: immunodeficient; CNS: central nervous system.

Figure 6. EBV drives the tumor microenvironment in NHL in immune-suppressed and immune-competent patients. A. Cell type abundance assessed with CIBERSORTx, according to the EBV status. *Wilcoxon Test.* **B.** Correlation study between TMB and memory resting CD4 T cell and CD8 T cell within EBV-positive NHL (green circles, upper) and EBV-negative NHL (red circles, lower). *Spearman correlation.*

Figure 7. The gene expression profiling tends to differ from EBV positive and negative NHL. Single sample gene set enrichment analysis (ssGSEA) scores of negative immune stimulation (upper panel), positive immune stimulation (middle panel) and T-cell function (lower panel). SsGSEA calculates separate enrichment scores for each pairing of a sample and gene set. Each ssGSEA enrichment score represents the degree to which the genes in a particular gene set are coordinately up- or down-regulated within a sample. *Wilcoxon test.*

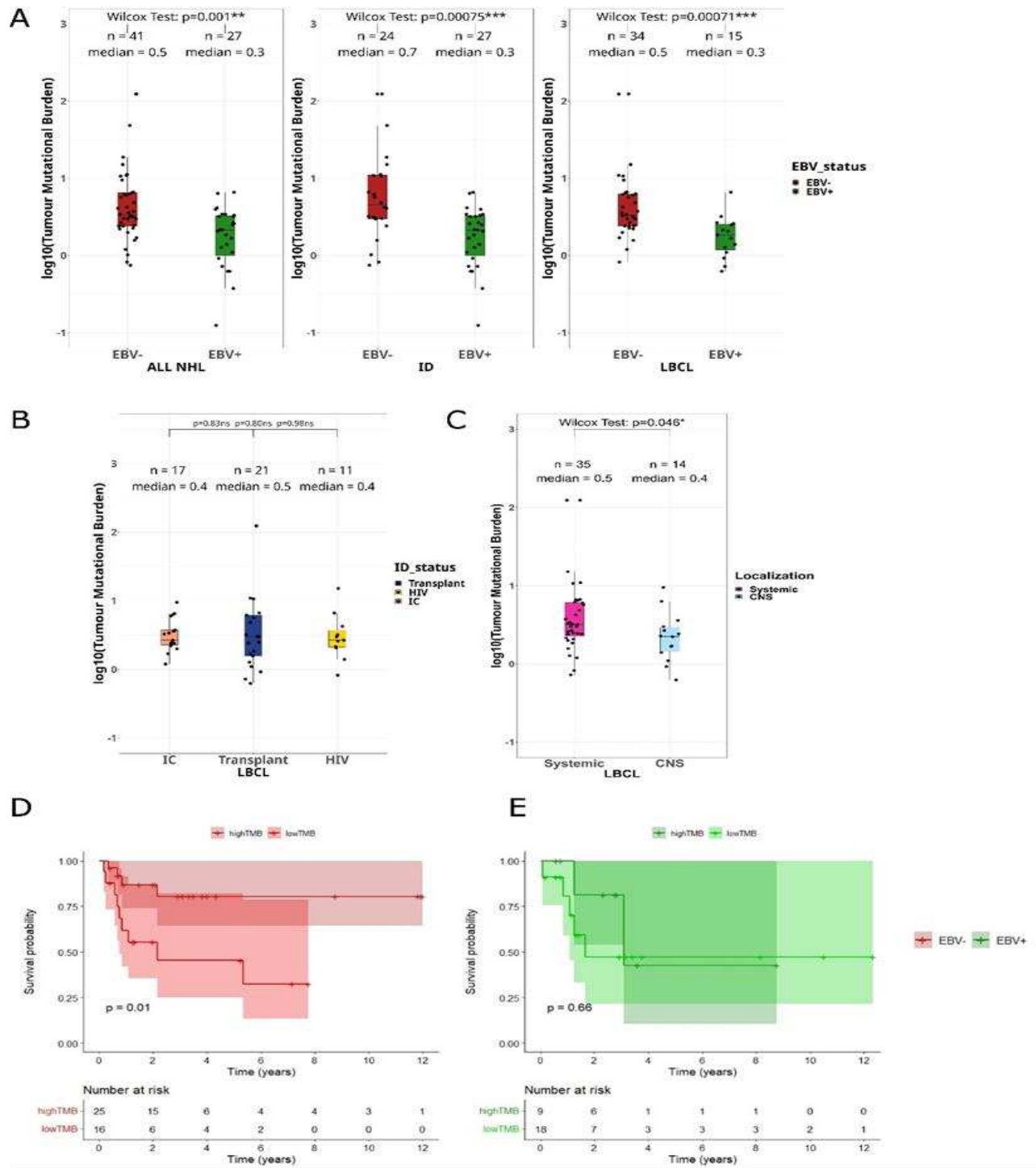


Figure 1

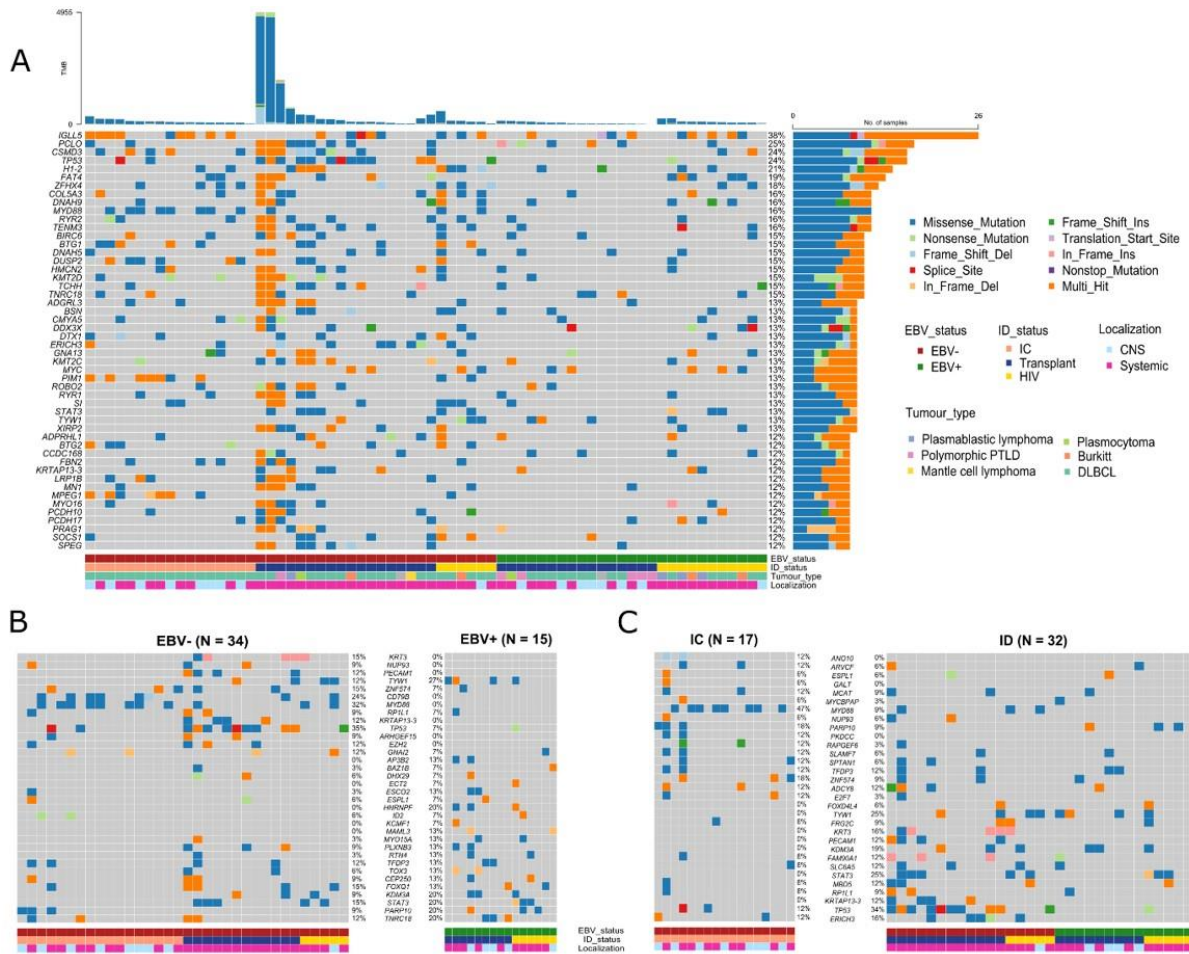


Figure 2

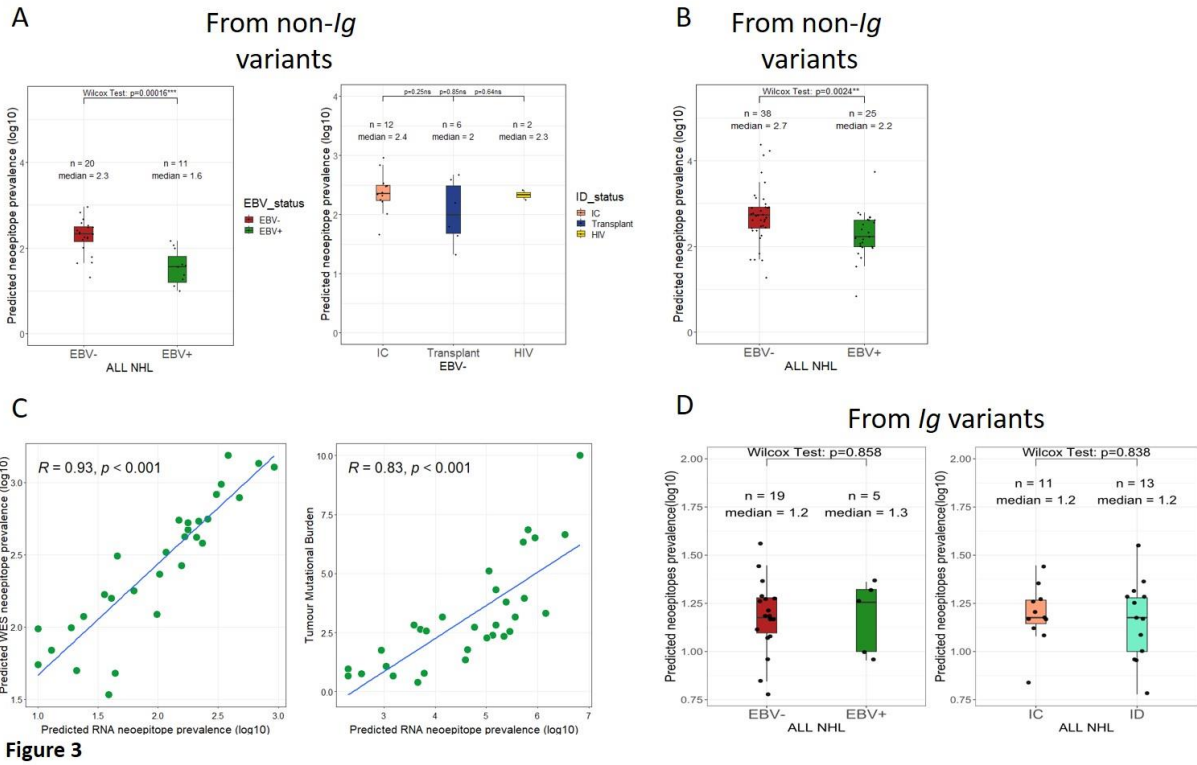


Figure 3

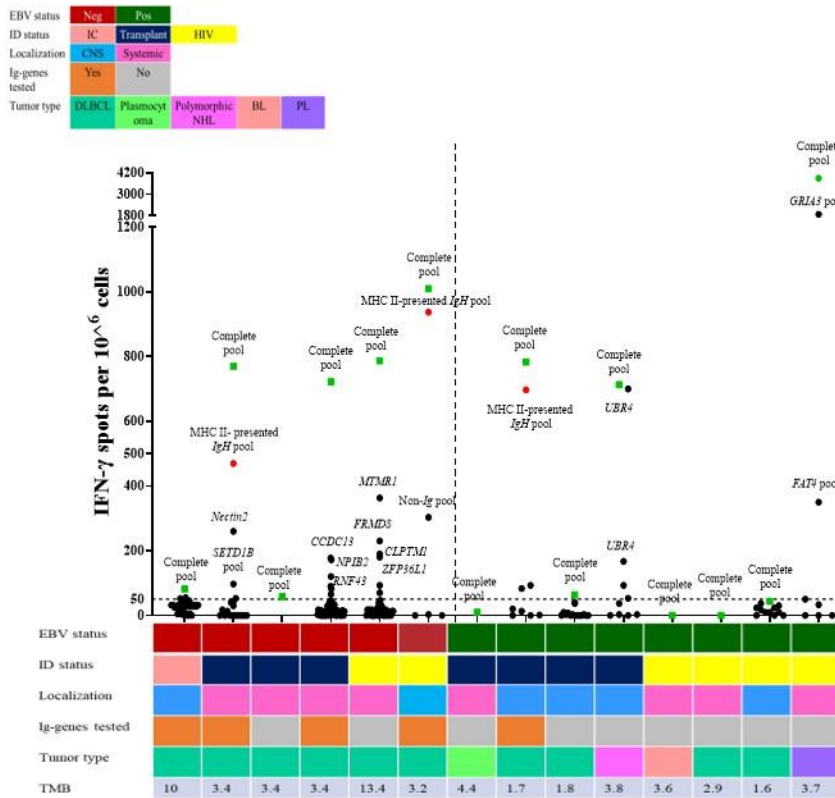


Figure 4

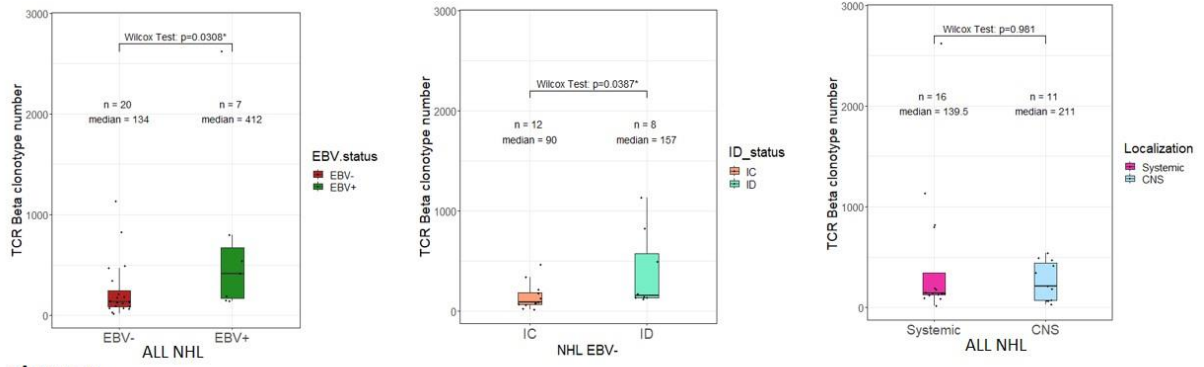


Figure 5

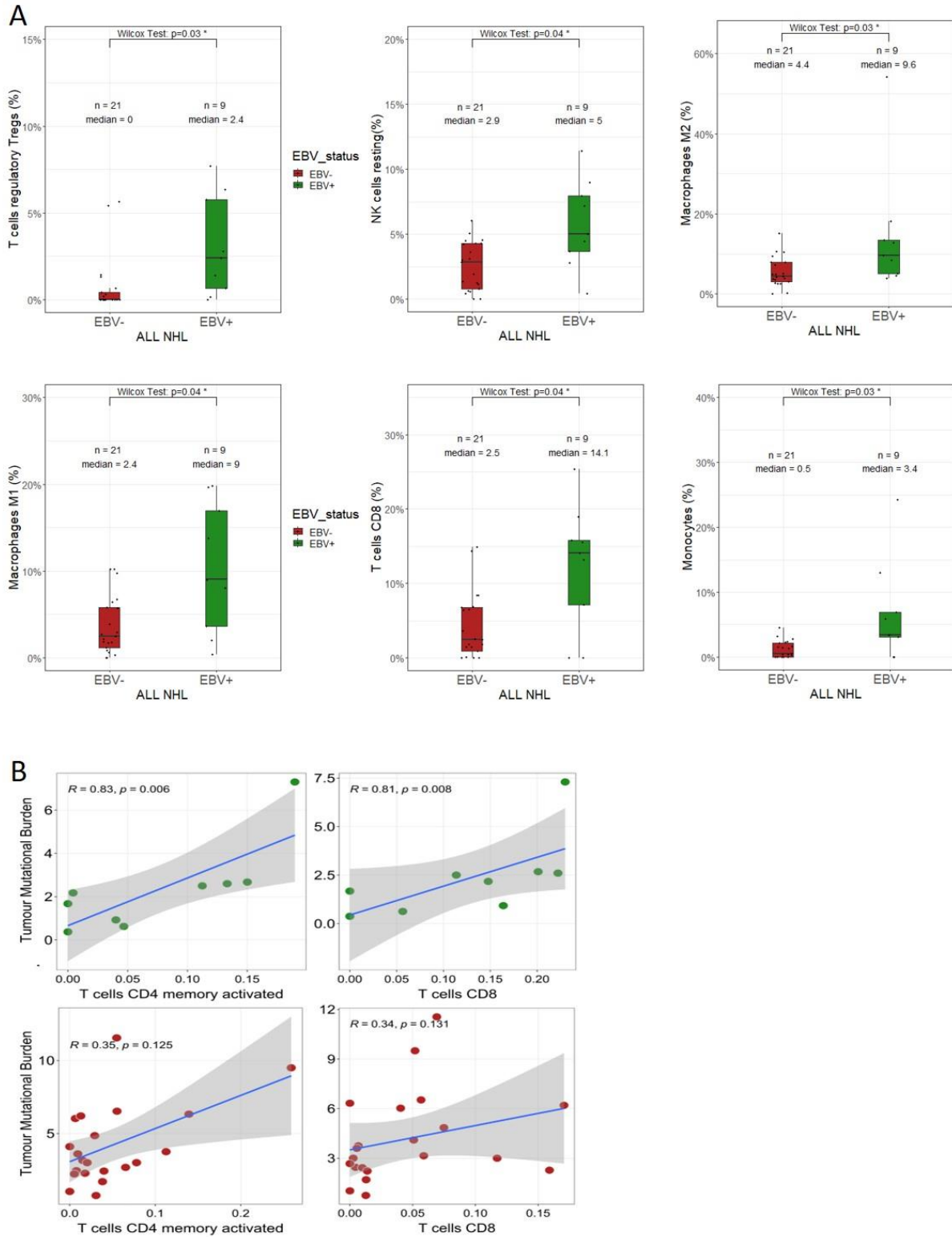


Figure 6

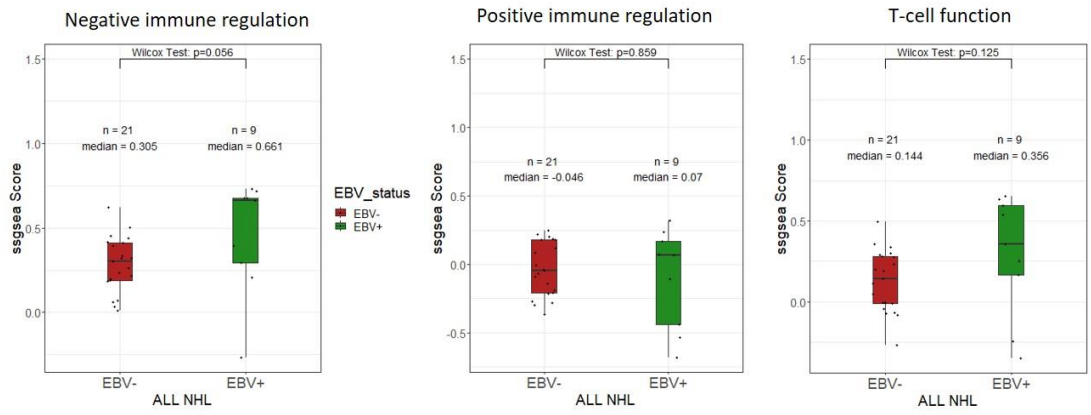


Figure 7

SUPPLEMENTARY METHODS AND MATERIALS

Methods:

Whole exome sequencing

WES was performed on tumor genomic DNA from tumor tissue biopsies and on germline DNA from blood. DNA was isolated from fresh frozen or formalin-fixed paraffin-embedded (FFPE) biopsies and from blood using a QIAamp-DNA Mini-Kit, FFPE Tissue-Kit or blood kit (Qiagen) respectively. Libraries were prepared and hybrid-captured using the SeqCap-EZ MedExome-Enrichment Kit (Roche) with 200 ng DNA input. Sequencing was performed on an Illumina Novaseq system with 150-bp paired-end reads. Raw paired-end fastq files were pre-processed using fastp(Chen *et al*, 2019) for adapter trimming and quality filtering. The filtered reads were aligned to the hg38 human reference genome using BWA-MEM(Adalsteinsson *et al*, 2017). The mean sequencing coverage across targeted bases was 200× and 150× for tumour and germline, respectively (**Supplementary Figure 2.A**). Somatic single nucleotide variants (SNVs) and indels were called using MuTect(Cibulskis *et al*, 2013) and Strelka2(Kim *et al*, 2018), respectively. We excluded potential oxidative damage-induced and low base quality mutations using in-house scripts(Costello *et al*, 2013). For two patients with missing germline DNA, we used Mutect2 (v4.1.4.1) using a Panel of Normal (PoN) generated from 38 normal DNA. Variants detected (marked PASS, coverage AD ≥ 10 in both normal and tumor, at least 3 tumor variant reads, VAF ≥ 0.05 , gnomAD_AF ≤ 0.0001) were annotated using VEP(McLaren *et al*, 2016). Candidate driver genes and significantly mutated genes were defined using OncodriveCLUST(Tamborero *et al*, 2013).

Detection of copy number alteration (CNV)

We employed FACETS (ref) tool to accurately infer CNV and tumour purity estimation for the paired samples (n=66). Moreover, GISTIC2 were used for the identification of recurrent copy

number alterations. By leveraging data from high-throughput genomic profiling technologies, GISTIC2 aids in the detection of focal and arm-level copy number variations that are statistically significant across a cohort of samples. GISTIC2's allow to discern between true somatic events and random fluctuations in copy number.

CCF inference

PyCloneVI (ref) was employed to estimate the cancer cell fractions within each tumor sample. FACETS CNV segments and raw variant allele frequencies were provided as input, along with a specified mutation prevalence threshold of 0.05 to exclude low-frequency variants. The 'pyclone-vi fit' and 'pyclone-vi write-results-file' command was executed with default settings.

We determined if a peptide was clonal for each patient by looking at the mutation's CCF that forms the peptide. A peptide is considered clonal when its CCF is 0.8 or higher.

RNA sequencing

RNA was extracted from fresh frozen biopsies using an RNeasy Micro-Kit (Qiagen). Libraries were prepared from 500 ng RNA. After end-repair, A-tailing, ligation and purification, sequencing was performed on an Illumina Novaseq with 150-bp paired-end reads. Reads were aligned to the human hg38 reference genome after an index was generated using STAR v2.7.2(Dobin *et al*, 2013) by applying per-sample two-pass mapping. The generated BAM files were pre-processed according to GATK v4.1 RNA-seq best practice (SplitNcigarReads and BQSR), duplicates reads were marked then removed using STAR option '--bamRemoveDuplicatesType UniqueIdentical --bamRemoveDuplicatesMate2basesN 15' and Samtools, respectively. Finally, gene counts were obtained using Htseq⁹ (RNAseq library size range: 24.8-154.9 Million reads, see **Supplementary Figure 2.B** and transformed into CPM (Counts Per Million) values.

Differential gene expression (DGE) and gene ontology (GO) enrichment analysis

CPM values were normalized using the Trimmed Mean of M-values normalization method from edgeR package (Robinson & Oshlack, 2010). To filter out low read counts, a CPM threshold of 0.5 was applied, equivalent to a count of 10 for the library sizes in this dataset. Subsequently, the data were log₂ normalized (see **Supplementary Figure 2.C**). DGE analysis was performed with edgeR. DE genes were identified using a p-value cut-off of 5% without fold-change cut-off. A GO analysis was used to predict putative biological functions based on DGE. The DE genes between CNS vs Systemic, EBV+ vs EBV- and ID vs IC groups were inserted to the goana function in limma-R packages (Ritchie *et al*, 2015) with focus on the biological process ontology.

Since the MHC class-I and class-II locus expression was computed using seq2HLA and measured in RPKM, we opted to calculate the *B2M* expression in RPKM as well.

MHC class-I and class-II restricted neoepitope prediction

Neoepitopes were predicted using the Ideation@SiRIC pipeline combining several software packages. First, we used seq2HLA to determine MHC class-I and class-II types [PMID: 23259685] using default parameters for all 31 RNAseq tumors and 68 normal-WES preprocessed fastq files using fastp. Next, somatic mutation-filtered VCF files were annotated by Variant Effect Predictor (Version 99) with default parameters and additionally with the 'Frameshift' and 'wild-type' plugins (from the pVACtools suite [version 3.0.3 PMID: 31907209]). The annotated non-synonymous mutations were extracted for downstream analysis. For each variant, the transcript expression levels (from RNA sequencing data) were then added using vcf-expression-annotator from VAtools v5.0.1. All parameters were then processed with the pVACseq for neoantigen prediction. For each pVACseq run, epitope prediction was done by the NetMHC [PMID: 18463140] NetMHCpan and NetMHCIIpan

[PMID: 32406916] algorithms packed in the pVACseq toolkit; epitope length was set to 8–10 amino-acids long for class-I and 15 for class-II presentation with default parameters for all other settings. Predicted neoepitopes were filtered based on coverage >10X, DNA VAF $\geq 10\%$, transcript level expression ≥ 0.5 counts per million (CPM), TSL (Transcript Support Level) =1 and median affinity binding ≤ 500 nM. When RNA samples were unavailable, selection from the WES data used all of these parameters except the transcript level expression. The number of neoepitopes per tumor was defined as the overall number of unique filtered mutant peptide sequences per tumor.

Neoepitope priority score: the priority score is one way to prioritize neoepitope candidates proposed by pVACseq: each of the following 4 criteria are assigned a rank-ordered value: B= rank of the mutant IC50 binding affinity/ F= rank of fold change between MT and WT alleles/ M= rank of mutant allele expression/ D= rank of tumor DNA VAF. The score is calculated with the following formula: $B + F + (M*2) + (D/2)$, and then converted to a rank.

T cell receptor (TCR) analysis

From the RNAseq fastq files, the productive TCR β clonotypes numbers and sequences and their frequencies were generated with MixCR V3.0(Bolotin *et al*, 2015) (<https://mixcr.readthedocs.io/>). Reads were aligned to reference TCR V, D, J and C genes. Each final clonotype was identified by a unique CDR3 sequence and clonotype count. Further analyses were restricted to samples with numbers of productive TCRs >100. The TCR repertoire abundance was defined as the number of unique productive clonotypes. Shannons' entropy index, computed using vjtools V1.2.1 software(Shugay *et al*, 2015), was used to compute the TCR repertoire entropy based on the frequency of particular sequences and normalized after division by clonotype log numbers (lower values indicate greater diversity). The clonotypes with frequencies $\geq 10\%$ were considered to be suggestive of a tumor-neoantigen

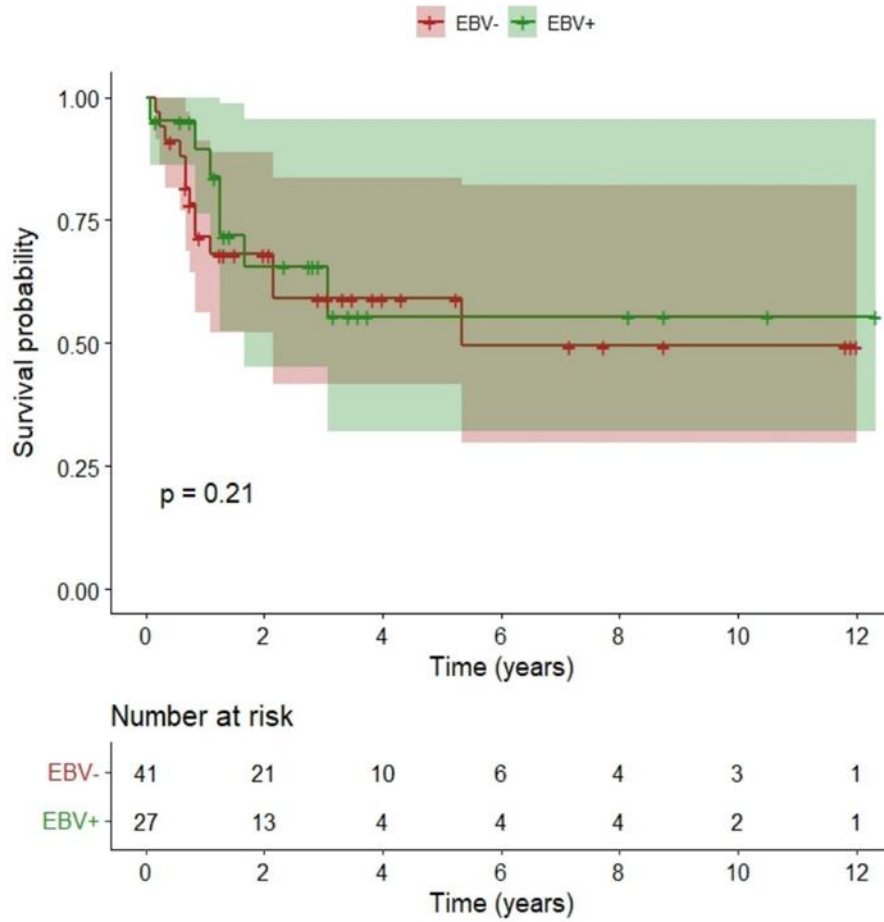
selection and investigated for known antigen specificities in public dataset (VDJdb)(Goncharov *et al*, 2022).

Statistical Analysis

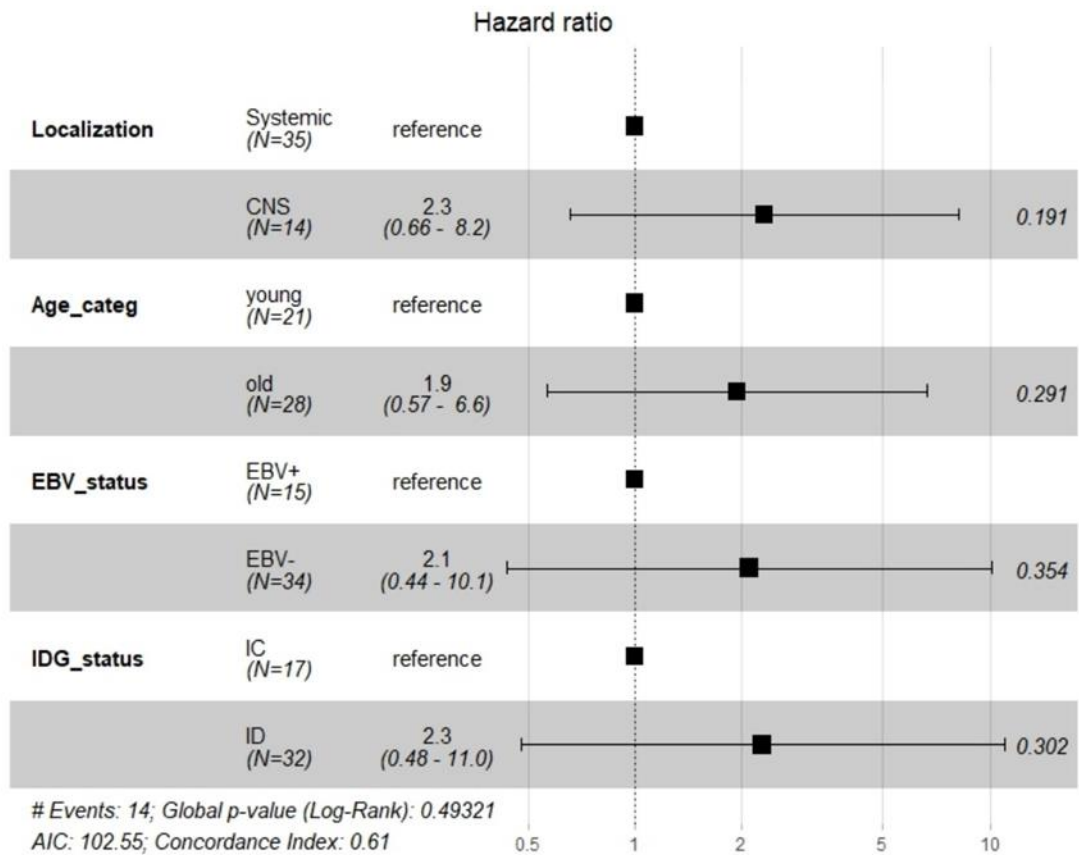
Statistical analysis was performed using R (version 4.2.1). The Fisher exact test was used to compare categorical data and the Wilcoxon test was used to compare quantitative variables between groups. All tests were 2-sided at the threshold of $p=0.05$. In the case of multiple testing, we controlled FDR at the 5% level. Survival plots were generated using the Kaplan–Meier method. The Log-rank test was used to compare survival curves between groups. The Cox proportional-hazards regression model was used to compute hazard ratios summarizing the association between survival and age, EBV status, immune status, and localization. We made use of the “`surv_cutpoint`” function from `survminer` R package to determine the optimal TMB cutpoint that corresponds to the most significant relation with survival.

Figures

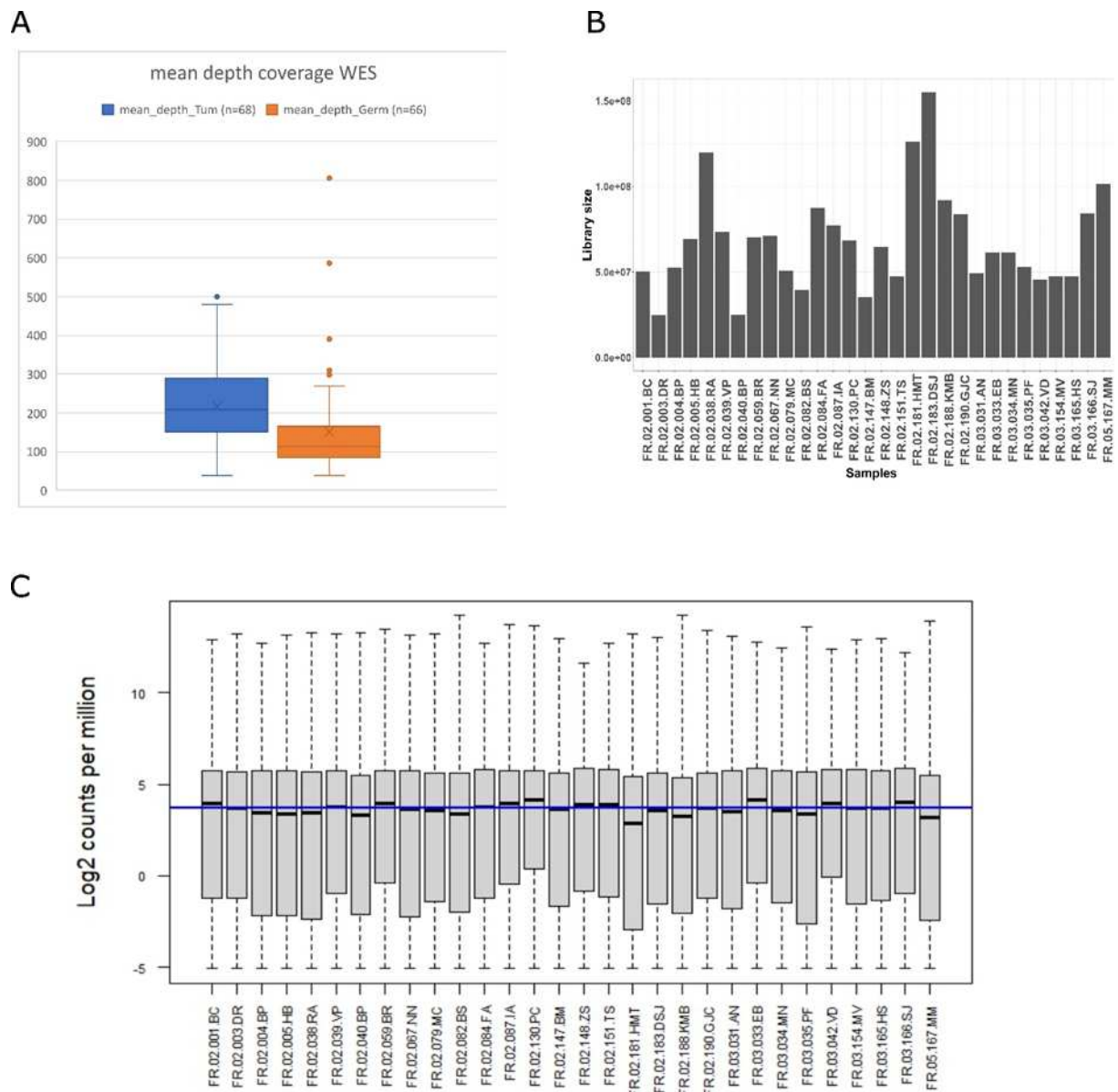
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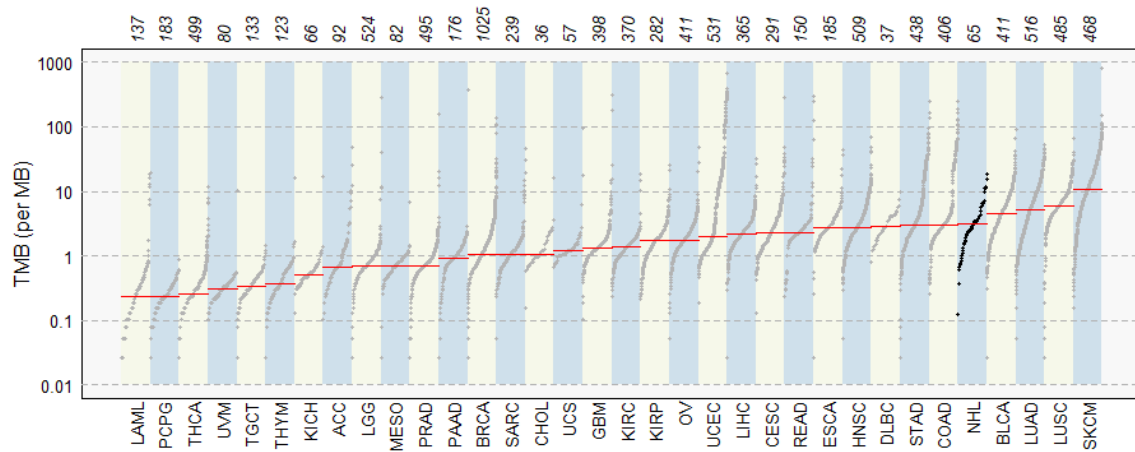


Supplementary Figure 1. A. Overall survival within NHL patients according to the EBV status (negative: red line; positive: green line) with adjustments made for patient age. **B.** Table representing a Cox regression model using tumor localization, age stratified into an old (≥ 58 years old) and a young group (< 58 years old), EBV status, immune status stratified into immunocompetent (IC) group and immune-deficient group (ID : HIV + PTLD).

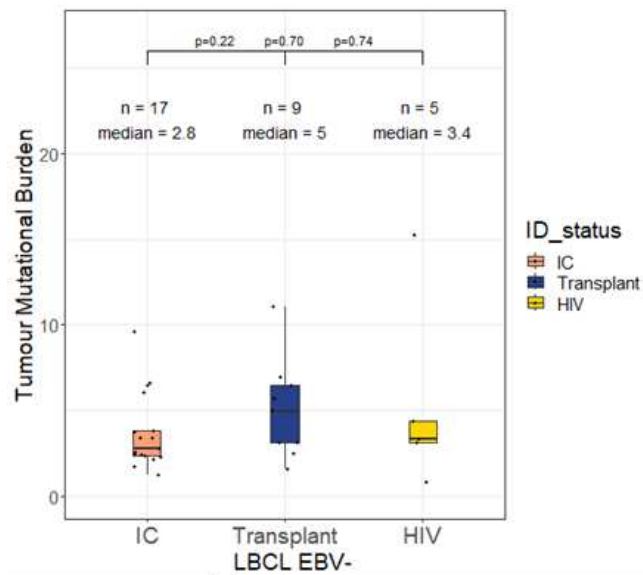


Supplementary Figure 2. A. Coverage of exome sequencing for tumors and their normal counterparts. Boxes are divided by median values. Length of boxes corresponds to interquartile

range and whiskers correspond to 1.5 interquartile ranges. **B.** RNA seq library size. **C.** CPM distribution across tumors.

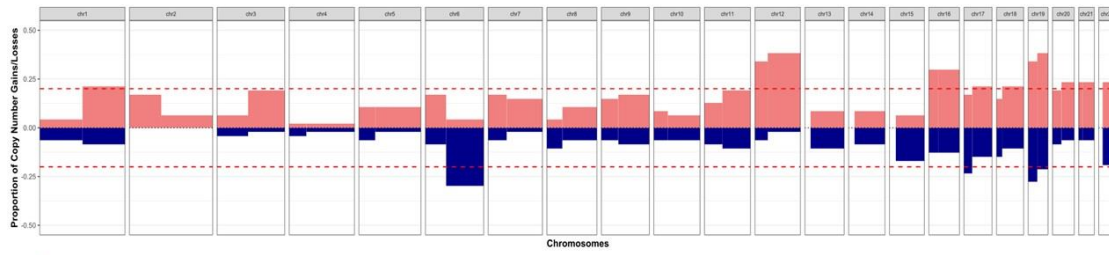


Supplementary Figure 3. Tumor mutational burden. The prevalence of somatic mutations in our cohort of NHL patients is illustrated among the ones of human cancer types described previously by (Australian Pancreatic Cancer Genome Initiative *et al*, 2013). Our cohort is named “NHL” and appears close to the “DLBCL” one. The TMB is defined as the number of mutations per megabase.

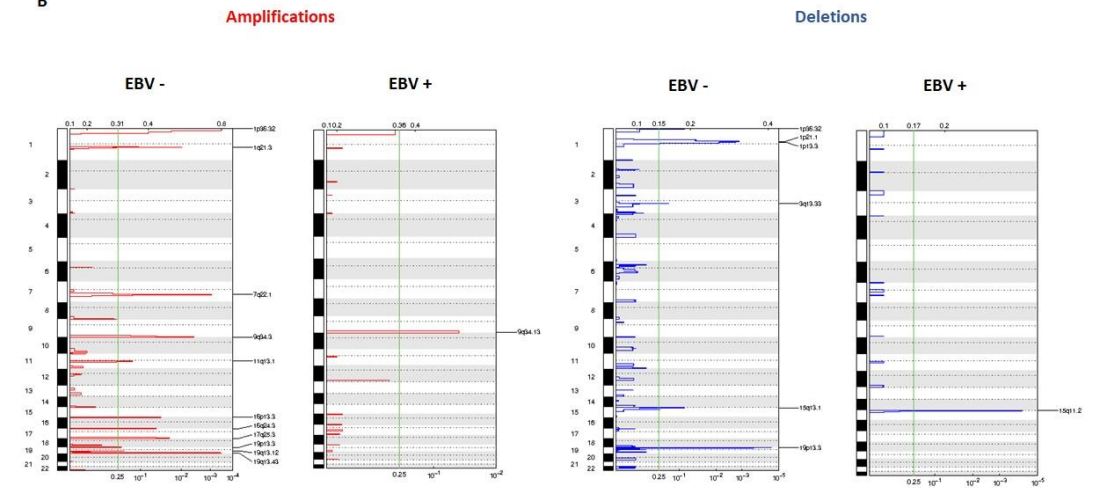


Supplementary Figure 4. Tumor mutational burden (TMB) according to the immune status among the EBV-negative LBCL patients (n=31): IC, transplant and HIV patients are illustrated with salmon, blue and HIV bars respectively. The TMB is defined as the number of mutations per megabase. IC: immunocompetent. *Wilcoxon Test*.

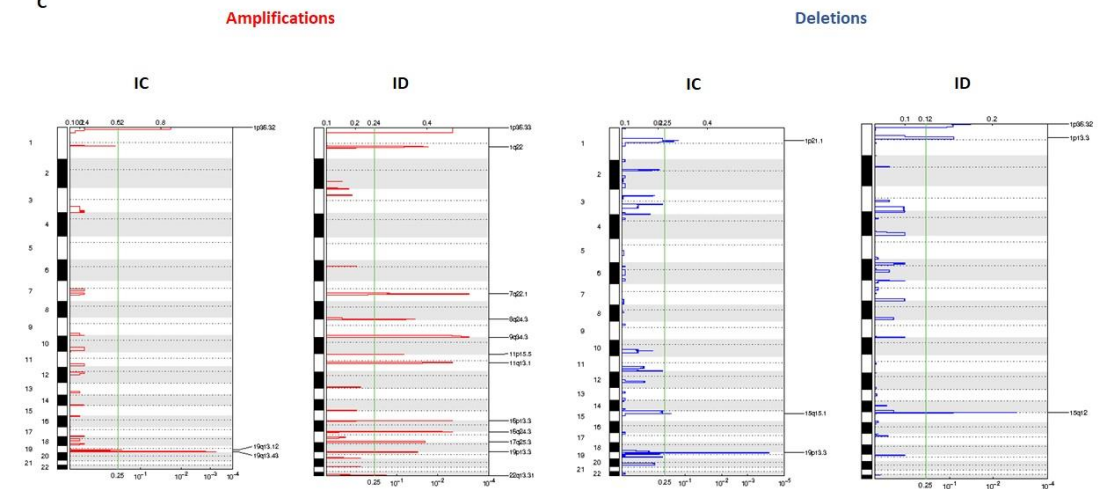
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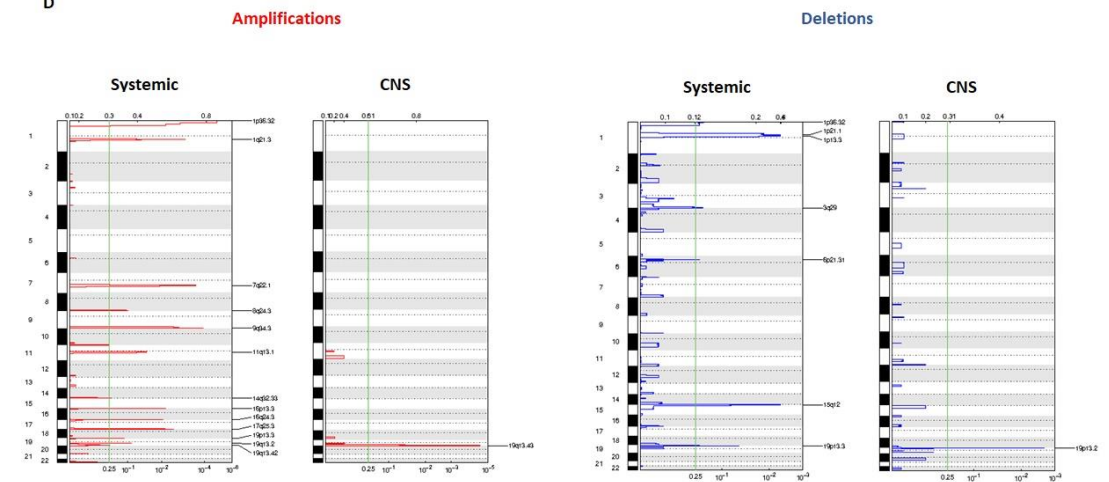
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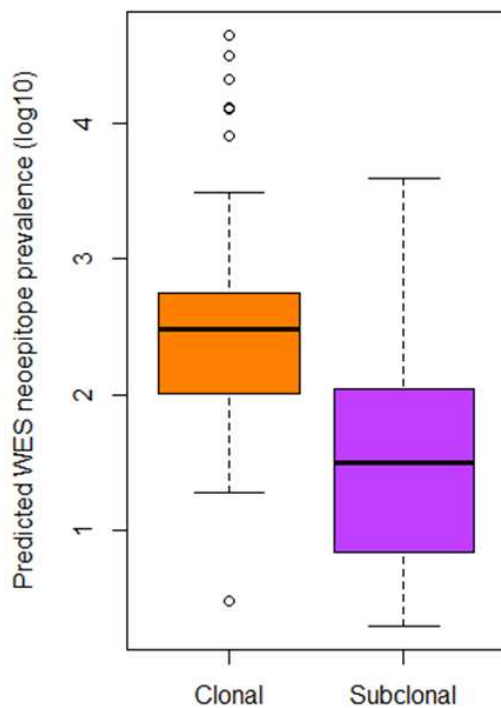
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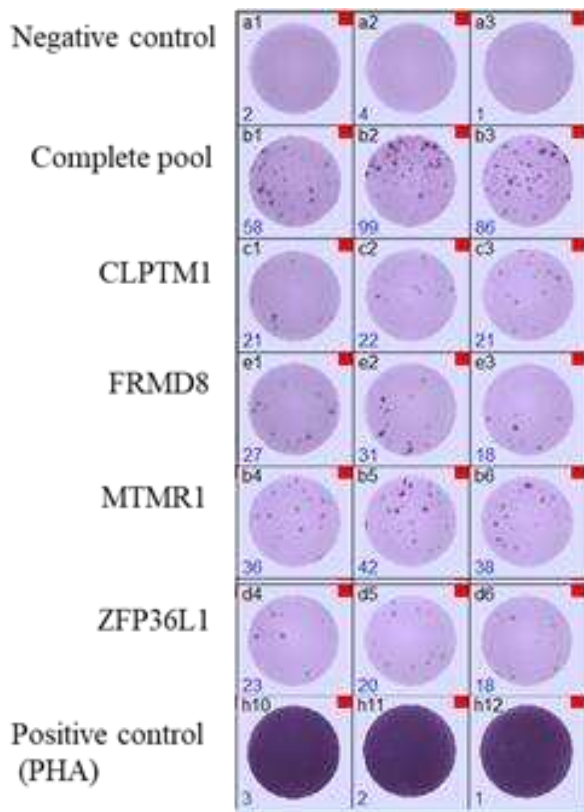
D



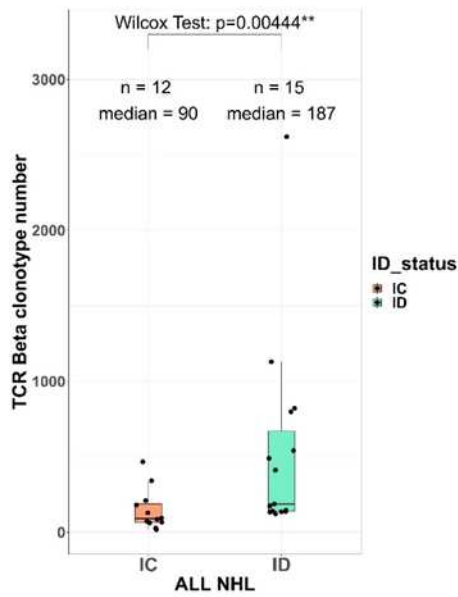
Supplementary Figure 6. A. Frequency of arm-level somatic copy number alterations (SCNAs) among LBCL tumors. dashed line indicating the threshold of arm-level SCNA frequency at 20% or higher. **B, C and D. Comparisons of GISTIC2.0-defined recurrent focal copy number gains (red, left) and losses (blue, right).** Chromosomes are shown on the vertical axis. Green line denotes q-value of 0.25. Somatic copy number alterations (SCNAs) are labeled with their associated cytoband. **A.** Based on EBV status **B.** based on immune status. **C.** Based on disease localization. CNS: central nervous system; ID: immunocompetent; ID: immunodeficient.



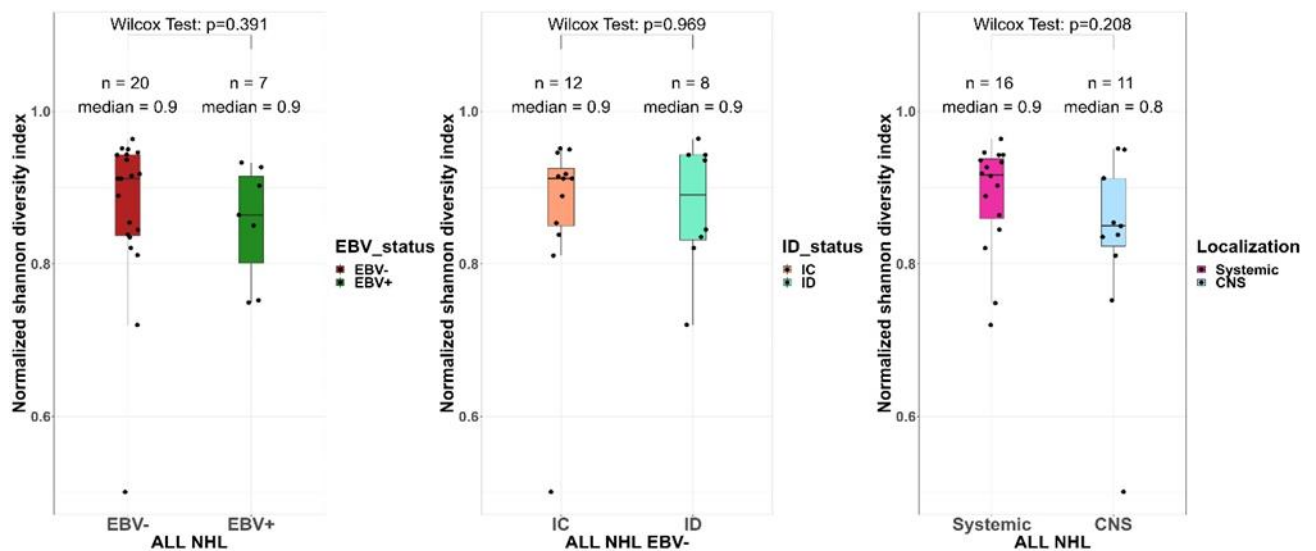
Supplementary Figure 7. Number of Clonal and Subclonal predicted neopeptides (log₁₀) per patient based on WES sequencing.



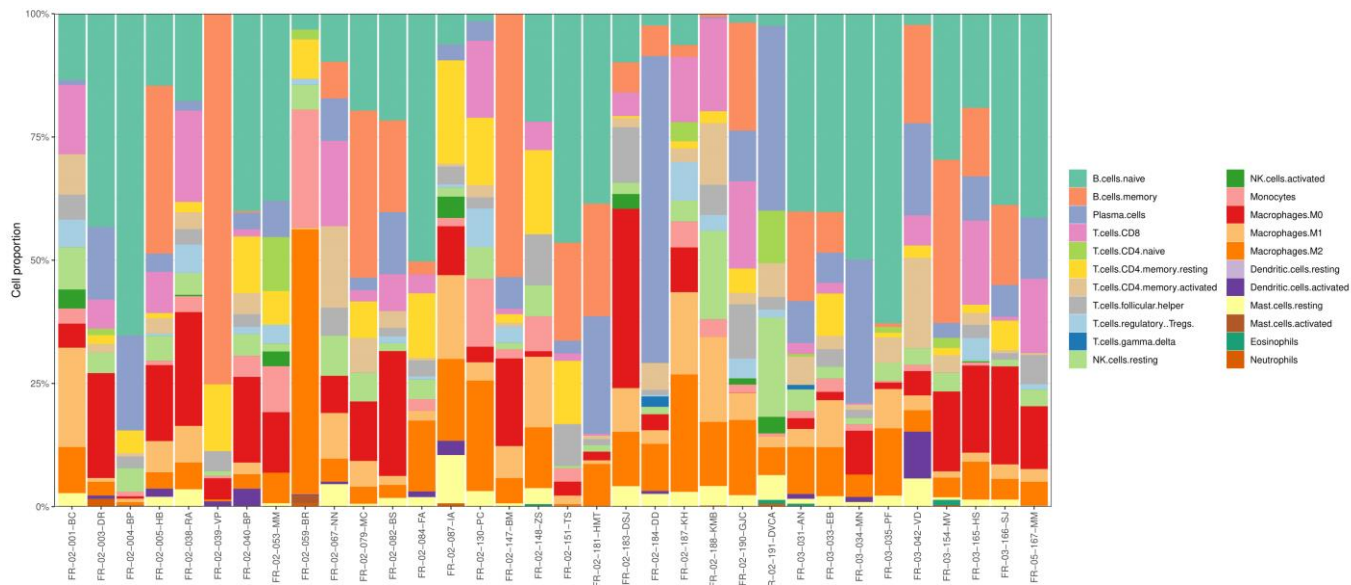
Supplementary Figure 8. Example ELISPOT results among one HIV patient with EBV-negative NHL: the patient was tested for 41 different peptides (only positive results against CLPTM1, FRMD8, MTMR1 and ZFP36L1 peptides are shown), negative control (at the top) and positive control (at the bottom). Thawed PBMC were co-cultured with personalized pooled peptides during 10 days and next tested for reactivity using IFN- γ enzyme linked immunoSpot (ELISPOT) assays. Patients were all tested for their personalized pooled peptides (named “complete pool”) and eventually for each individual peptide if the number of cells were adequate (named as the mutated gene). The mean numbers of spot forming cells (SFC) from triplicates were normalized to number of IFN- γ spots detected per 1×10^6 PBMC after background subtraction, and ELISPOT-IFN- γ positivity threshold was 50 SFC per million cells.



Supplementary Figure 9. Intra-tumoral TCR repertoire abundance according to the immune status within 27 NHL samples. *Wilcoxon Test*.

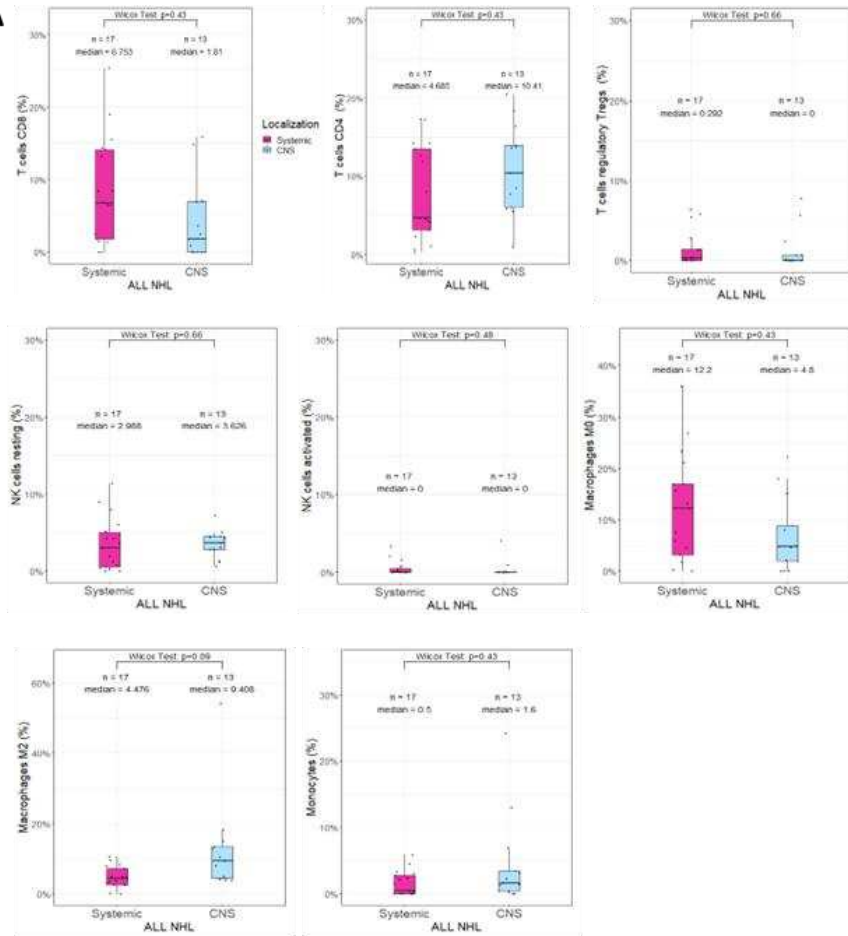


Supplementary Figure 10. Normalized Shannon index diversity index according to the EBV status (left), the immune status (middle) and the disease localization (right). Shannons' entropy was calculated using vjtools V1.2.1 software(Shugay *et al*, 2015) and was divided by (log (number of clonotypes)) to be independent of the abundance: lower values indicate more diversity. IC: immunocompetent; ID: immunodeficient; CNS: central nervous system. *Wilcoxon Test*

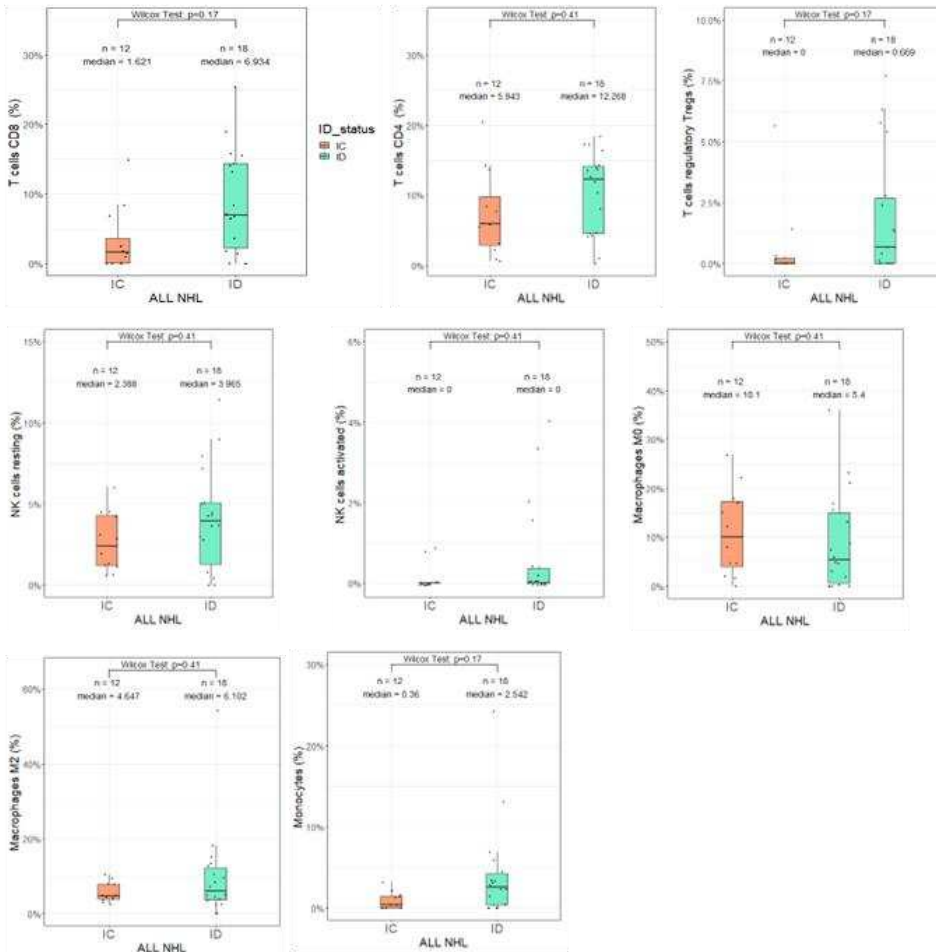


Supplementary Figure 11. Cell type abundance distribution for each patient using CIBERSORTx.

A



B



Supplementary Figure 12. Cell type abundance according to **A.** the disease localization, and **B.** the immune status. Cell type abundance was assessed using CIBERSORTx. CNS: central nervous system; IC: immunocompetent; ID: immunodeficient. *Wilcoxon Test.*

Tables

Supplementary Table 1. Comparison of the mutational frequencies stratified by EBV status.

Mutational frequencies in the 34 EBV-negative lymphomas were compared to the 15 EBV-positive ones. Genes are ranked by uncorrected p values (with corrected p values shown in the adjacent column).

Hugo_Symbol	EBV -	EBV +	pval	OR	Cl. low	Cl. up	Adj.Pval
			0.0112409			1.35253987	0.348470
MYD88	11	0	7	Inf	Inf	1	2
			0.0246960	0.000000		0.00000000	0.382788
HNRNPF	0	3	5	0	0.9941339	0	8
			0.0426308	7.391435	348.708670	0.90091266	0.440519
TP53	12	1	9	8	9	2	2
			0.0868316			0.83163418	0.461309
CD79B	8	0	9	Inf	Inf	8	5
			0.0892857	0.000000		0.00000000	0.461309
AP3B2	0	2	1	0	2.2852181	0	5
			0.0892857	0.000000		0.00000000	0.461309
MAML3	0	2	1	0	2.2852181	0	5
			0.2184650	0.204646		0.00325014	0.676895
ESCO2	1	2	5	4	4.2426528	2	0
			0.2184650	0.204646		0.00325014	0.676895
MYO15A	1	2	5	4	4.2426528	2	0
			0.2184650	0.204646		0.00325014	0.676895
RTN4	1	2	5	4	4.2426528	2	0
			0.2272004	0.375225		0.05844879	0.676895
TYW1	4	4	6	3	2.3835301	3	0
			0.2983395			0.29190527	0.676895
EZH2	4	0	9	Inf	Inf	6	0
			0.2983395			0.29190527	0.676895
KRTAP13-3	4	0	9	Inf	Inf	6	0
			0.2983395			0.29190527	0.676895
PECAM1	4	0	9	Inf	Inf	6	0
			0.3056945			0.41278848	0.676895
KRT3	5	0	3	Inf	Inf	4	0
			0.3533009	0.395617		0.04617551	0.684520
KDM3A	3	3	9	8	3.3716730	0	7
			0.3533009	0.395617		0.04617551	0.684520
PARP10	3	3	9	8	3.3716730	0	7
			0.5432587			0.18055683	0.887206
ARHGEF15	3	0	9	Inf	Inf	4	6

NUP93	3	0	0.5432587	Inf	Inf	0.18055683	0.887206
			0.5763559	0.414709		0.02732475	0.887206
TOX3	2	2	8	5	6.2831643	0	6
			0.6351954	0.635417		0.06451601	0.887206
CEP250	3	2	3	7	8.4440603	0	6
			0.6351954	0.635417		0.06451601	0.887206
PLXNB3	3	2	3	7	8.4440603	0	6
			0.6517774	2.376899	122.123263	0.23228939	0.887206
ZNF574	5	1	5	3	1	2	6
			0.6598756	0.540778		0.07791716	0.887206
TNRC18	4	3	5	0	4.2502025	8	6
			0.6868696	0.695146		0.11302161	0.887206
STAT3	5	3	5	9	5.1882401	3	6
			1.0000000	0.877450		0.04234219	1.000000
DHX29	2	1	0	0	55.2479011	7	0
			1.0000000	0.877450		0.04234219	1.000000
ESPL1	2	1	0	0	55.2479011	7	0
			1.0000000	0.877450		0.04234219	1.000000
ID2	2	1	0	0	55.2479011	7	0
			1.0000000	1.118145		0.15620253	1.000000
FOXQ1	5	2	0	4	13.2050937	7	0
			1.0000000	1.845523		0.16198090	1.000000
GNAI2	4	1	0	7	98.3507357	6	0
			1.0000000	1.346926		0.09781330	1.000000
RP1L1	3	1	0	8	76.1064554	7	0
			1.0000000	0.869263		0.10814205	1.000000
TFDP3	4	2	0	7	10.7397691	4	0

Supplementary Table 2. Comparison of the mutational frequencies stratified by immune status. Mutational frequencies in the 32 ID LBCL were compared to the 15 IC DLBCL. Genes are ranked by uncorrected p values (with corrected p values shown in the adjacent column).

Hugo_Symbol	ID	IC	pval	OR	Cl. up	Cl. low	Adj. Pval
MYD88	3	8	0.004574082	0.1228121	0.644494	0.01724404	0.1326484
STAT3	8	0	0.038368700	Inf	Inf	1.02551071	0.3708974
TYW1	8	0	0.038368700	Inf	Inf	1.02551071	0.3708974
KDM3A	6	0	0.079848305	Inf	Inf	0.66525774	0.4791059
TP53	11	2	0.105125508	3.8314402	40.600568	0.68100497	0.4791059
ANO10	0	2	0.115646259	0.0000000	2.767552	0.00000000	0.4791059
PKDCC	0	2	0.115646259	0.0000000	2.767552	0.00000000	0.4791059
KRT3	5	0	0.148789334	Inf	Inf	0.50449696	0.5393613
E2F7	1	2	0.273122015	0.2496756	5.148406	0.00398254	0.6855032
RAPGEF6	1	2	0.273122015	0.2496756	5.148406	0.00398254	0.6855032

KRTAP13-3	4	0	0.283656478	Inf	Inf	0.35569410	0.6855032
PECAM1	4	0	0.283656478	Inf	Inf	0.35569410	0.6855032
PARP10	3	3	0.405458996	0.4905080	4.138715	0.05794602	0.8398793
ZNF574	3	3	0.405458996	0.4905080	4.138715	0.05794602	0.8398793
FOXD4L4	2	0	0.537414966	Inf	Inf	0.09910238	0.8924406
ARVCF	2	2	0.602031377	0.5076208	7.640914	0.03367628	0.8924406
SLAMF7	2	2	0.602031377	0.5076208	7.640914	0.03367628	0.8924406
SPTAN1	2	2	0.602031377	0.5076208	7.640914	0.03367628	0.8924406
FAM90A1	4	1	0.646250113	2.2520240	119.418697	0.19933525	0.8924406
MBD5	4	1	0.646250113	2.2520240	119.418697	0.19933525	0.8924406
SLC6A5	4	1	0.646250113	2.2520240	119.418697	0.19933525	0.8924406
ADCY8	4	2	1.000000000	1.0699424	13.119541	0.13457850	1.0000000
ERICH3	5	2	1.000000000	1.3799652	16.160751	0.19512568	1.0000000
ESPL1	2	1	1.000000000	1.0652809	66.787013	0.05166123	1.0000000
FRG2C	3	1	1.000000000	1.6394834	92.199004	0.11990355	1.0000000
MCAT	3	2	1.000000000	0.7800302	10.287934	0.07993619	1.0000000
NUP93	2	1	1.000000000	1.0652809	66.787013	0.05166123	1.0000000
RP1L1	3	1	1.000000000	1.6394834	92.199004	0.11990355	1.0000000
TFDP3	4	2	1.000000000	1.0699424	13.119541	0.13457850	1.0000000

IC: immunocompetent; ID: immunodeficient; Adj. P value: adjusted P value after FDR correction.

Supplementary Table 3 is available in a separate excel spreadsheet. All GISTIC2 thresholded SCNA by gene.

Supplementary R

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7. Résultats : Seconde partie

Impact des inhibiteurs de PD-1 (PD-1I) sur l'immunité T anti-virale et sur le réservoir VIH chez les PVVIH atteintes de cancer

Article

Impact of Anti PD-1 Immunotherapy on HIV Reservoir and Anti-Viral Immune Responses in People Living with HIV and Cancer

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Abstract: The role of immune checkpoints (ICPs) in both anti-HIV T cell exhaustion and HIV reservoir persistence, has suggested that an HIV cure therapeutic strategy could involve ICP blockade. We studied the impact of anti-PD-1 therapy on HIV reservoirs and anti-viral immune responses in people living with HIV and treated for cancer. At several timepoints, we monitored CD4 cell counts, plasma HIV-RNA, cell associated (CA) HIV-DNA, EBV, CMV, HBV, HCV, and HHV-8 viral loads, activation markers, ICP expression and virus-specific T cells. Thirty-two patients were included, with median follow-up of 5 months. The CA HIV-DNA tended to decrease before cycle 2 ($p = 0.049$). Six patients exhibited a $\geq 0.5 \log_{10}$ HIV-DNA decrease at least once. Among those, HIV-DNA became undetectable for 10 months in one patient. Overall, no significant increase in HIV-specific immunity was observed. In contrast, we detected an early increase in CTLA-4 + CD4 + T cells in all patients

($p = 0.004$) and a greater increase in CTLA-4+ and TIM-3 + CD8+ T cells in patients without HIV-DNA reduction compared to the others ($p \leq 0.03$). Our results suggest that ICP replacement compensatory mechanisms might limit the impact of anti-PD-1 monotherapy on HIV reservoirs, and pave the way for combination ICP blockade in HIV cure strategies.

Keywords: immune checkpoint blockade; HIV reservoir; anti-HIV immune responses; compensatory mechanisms

1. Background

Immune checkpoints (ICPs), such as programmed cell death protein 1 (PD-1), cytotoxic T lymphocytes antigen 4 (CTLA-4), T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) and lymphocyte activation gene (LAG-3) are T cell inhibitory receptors that are activated on immune cells after TCR engagement to counterbalance chronic antigenic stimulation [1]. In cancers, ICPs are involved in immune control escape, promoting anti-tumor T-cell exhaustion. Nowadays, ICP blockade (ICB) by monoclonal antibodies is used for restoring anti-tumor immunity and is a major advance in cancer therapy [2].

During HIV-1 infection, ICPs are involved in both reservoir latency and anti-viral T cell exhaustion. On the one hand, PD-1, TIGIT and LAG-3 expression is positively associated with the frequency of CD4 + T cells harboring integrated HIV-DNA, and PD-1 engagement has been showed to inhibit HIV production and reactivation in latently infected cells *ex vivo* [3,4]. Accordingly, ICB reverses latency and reactivates viral production [3,5]. On the other hand, increased levels of PD-1 expression on total and HIV-specific CD8 + and CD4+ T cells in untreated HIV-1 infection are significantly correlated with both increased HIV viral load (VL) and with reduced capacity of cytokine production and of proliferation of HIV-specific T cells [6–8]. Anti-PD-1 and anti-PD-L1 antibodies demonstrated immune dysfunction reverse [8–10]. Taken together, these data suggest that ICB used as a “shock and kill” strategy could at the same time reverse latency and make the virus visible to the immune system, and restore anti-HIV immunity towards an HIV cure. The impact of ICB monotherapy on HIV-1 infection *in vivo* has been reported with controversies [11]. In our experience, one patient treated with nivolumab for cancer demonstrated a drastic and persistent decrease in cell-associated (CA) HIV-DNA [12]. Three other reports revealed latency reversal in patients [3,5,13]. A more recent study with very short follow-up including 33 people living with HIV (PLWH) with cancer showed no modification of the replication-competent reservoir [14].

During other co-infecting chronic viral infections, such as HBV, HCV, JC-virus or EBV infections, pathogens also exploit ICPs for immune evasion [15–17]. Several studies have suggested that ICB could be used as anti-infectious treatment for chronic HBV and HCV infection or for progressive multifocal leukoencephalopathy [18–20]. Finally, EBV-associated lymphomas and HHV-8-associated Kaposi sarcoma (KS) could benefit from ICB [21,22]. Of note, no predictive biomarker of ICB efficacy is available concerning chronic viral infections.

A biological sub-study was set-up, from both the ANRS CO24 OncoVIHAC prospective multicenter cohort (OncoVIRIM) and clinical trial IFCT-1602 CHIVA-2 (BIO-CHIVA-2), including PLWH with cancer treated with ICB. Here, we present the results of the largest cohort of patients assessing *in vivo* CA HIV-DNA, immunological changes and the evolution of virus-specific T cells among PLWH treated with ICB for cancer.

2. Methods

2.1. Study Design and Population

Patients were included from December 2017 to March 2020 from ten French centers on behalf the Agence nationale de recherche sur le SIDA et les hépatites virales (ANRS) and Intergroupe Francophone de cancérologie thoracique (IFCT) groups. Inclusion criteria:

were age above 18 years old, proven HIV-1 or 2 infection, viral load below 50 cps/mL in OncoVIRIM or 200 cps/mL in BIO-CHIVA-2 under ART, ICB for cancer. Patients received nivolumab or cemiplimab 3 mg/kg every 2 weeks or pembrolizumab 2 mg/kg every 3 weeks until tumor progression, toxicity or patient decision to cease treatment. All patients signed a written informed consent form. The protocol was approved by an institutional review board (ANRS CO-24 OncoVIHAC: CPP17-020/2017-A00699-44; IFCT-1602 CHIVA2: CPP-Sud-Est V/17-IFCT-01) and was performed in accordance with the Helsinki declaration. Fresh blood samples were obtained at baseline and before cycles 2, 3 or 4, 9, 15 or 18, 27 or 36 and 51 and at the end of treatment.

2.2. HLA-Typing

HLA typing was performed using PCR-SSO hybridization methods in a Luminex FLEXMAP-3D[®] platform and analyzed on the HLA-Fusion[™] software (LABtype SSO class I/II tests: LABtype XR Class I locus A, B, C and Labtype SSO class II DRB1, DQA1/B1, OneLambda Inc., West Hills, CA, USA).

2.3. Viral Assays

Serologies for CMV and EBV (DiaSorin, Saluggia, Italy), HBV and HCV (Abbott, Chicago, IL, USA), HHV-8 [23] were analyzed at baseline. The HIV, HBV and HCV viral loads (VL) were analyzed in plasma using AmpliPrep/COBAS TaqMan (Roche Diagnostics, Basel, Switzerland) and the CMV and EBV loads were measured in whole blood (Qiagen, Hilden, Germany). HHV-8 was quantified by RT-PCR [24]. CA HIV-1 DNA was quantified by ultrasensitive RT-PCR (Biocentric, Bandol, France) [25].

2.4. Flow Cytometric Analysis

Flow cytometry testing was performed on fresh blood with two mixes of antibodies assessing first lymphocyte subsets and ICP: TIM3-BB515 (BD, Franklin Lakes, NJ, USA, 7D3), CXCR5-PE (BioLegend, San Diego, CA, USA, J252D4), CD45RA-ECD (BC, Fullerton, CA, USA, 2H4LDH11LDB9), CD27-PerCP-Cy5.5 (BD, Franklin Lakes, NJ, USA, L128), CCR7-Pe-Cy7 (BD, Franklin Lakes, NJ, USA, 3D12), CTLA4-APC (BD, Franklin Lakes, NJ, USA, BNI3), CD4-APC-R700 (BD, RPA-T4, Franklin Lakes, NJ, USA), CD3-APC-Cy7 (BD, SK7, Franklin Lakes, NJ, USA), PD1-BV421 (BD, EH12.1, Franklin Lakes, NJ, USA) and CD8-BV510 (BD, SK1, Franklin Lakes, NJ, USA), and intracellular staining with CTLA4-APC (BD, BNI3, Franklin Lakes, NJ, USA); second, activation markers were assessed: CD4-FITC (BD, RPA-T4, Franklin Lakes, NJ, USA), CD25-PE (BC, B1.49.9, Fullerton, CA, USA), CD69-PE-CF594 (BD, FN50, Franklin Lakes, NJ, USA), PD1-PE-Cy7 (BD, EH12.1, Franklin Lakes, NJ, USA), HLA-DR-AF700 (BioLegend, San Diego, CA, USA, L243), CD3-APC-AF750 (BC, Fullerton, CA, USA, UCHT1), CD38-BV421 (BioLegend, San Diego, CA, USA, HB7) and CD8 BV510 (BD, Franklin Lakes, NJ, USA, SK1), and intracellular staining with Ki67-APC (ThermoFisher, Waltham, MA, USA, 20Raj1). Cell permeabilization (Cytofix/Cytoperm, BD, Franklin Lakes, NJ, USA), fixation (CellFIX, BD, Franklin Lakes, NJ, USA), acquisition (10-colors Gallios) and analysis (FlowJo 10.5) were performed as previously described [26]. T cell subsets were defined as: naive T cells (TN): CD27 + 45RA + CCR7+, central memory T cells (TCM): CD27 + 45RA-CCR7+, transitional memory T cells (TTM): CD27 + 45RA-CCR7-, effector memory T cells (TEM): CD27-45RA-CCR7-, CD45RA re-expressing TEM (TEMRA): CD27-45RA + CCR7-. Boolean ICP analysis defined single, double and triple expressers displaying only one, two or three ICP.

2.5. Intracellular Cytokine Staining Assays

Virus-specific T cells were analyzed using an ICS assay [27]. Briefly, 1×10^6 thawed PBMC were stimulated overnight with each virus peptides pool (Supplementary Methods S1 and Supplementary Table S1) or staphylococcal enterotoxin B toxin as the positive control and medium alone as negative control. Cells were surface-stained with Live/Dead Fixable Aqua Dead Cell (Invitrogen, Carlsbad, CA, USA, L34957) and anti PD1-BV421

(BD, Franklin Lakes, NJ, USA, EH12.1), CD4-APC (BD, Franklin Lakes, NJ, USA, RPA-T4) and CD8-PerCP-Cy5.5 (BD, Franklin Lakes, NJ, USA, SK1); then intracellular staining was performed for interleukin-2 (IL2)-PE (BD, Franklin Lakes, NJ, USA, 5344.111), interferon- γ (IFN- γ)-FITC (BD, Franklin Lakes, NJ, USA, 25723.11), tumor necrosis factor- α (TNF- α)-PE-Cy7 (BD, Franklin Lakes, NJ, USA, Mab11) and CD3-APC-Cy7 (BD, Franklin Lakes, NJ, USA, SK7).

The HIV-stimulated cells from 18 patients were also analyzed for the expression of ICP and surface stained with anti CD4-ECD (BC, Fullerton, CA, USA, UCHT1, 7448079F), CD8-PerCP-Cy5.5 (BD, Franklin Lakes, NJ, USA, SK1), PD1-BV421 (BD, Franklin Lakes, NJ, USA, EH12.1), TIM3-PeCy7 (ThermoFisher; Waltham, MA, USA, F38-2E2), CTLA4-APC (BD, Franklin Lakes, NJ, USA, BNI3), LAG3-AlexaFluor700 (ThermoFisher, Waltham, MA, USA, 3DS223H) and IgG 4-PE (Southern Biotech, Birmingham, AL, USA, HP6025); then intracellular staining was performed for IFN- γ -FITC (BD, Franklin Lakes, NJ, USA, 25723.11), CD3-APC-Cy7 (BD, Franklin Lakes, NJ, USA, SK7) and CTLA4-APC (BD, Franklin Lakes, NJ, USA, BNI3).

Percentages of CD8+ and CD4 + T cells producing cytokines were determined after subtraction of negative controls and by adding the various peptide pools for each virus. Phenotypes of specific T cells were evaluated only on cytokine-producing cells with more than 50 events.

2.6. Statistical Analysis

The non-parametric Wilcoxon test was used to test differences between paired groups. The Mann-Whitney test was used to test differences between unpaired groups. Statistical significance was considered for *p*-values below 0.05. When multiple comparisons were performed, the Bonferroni correction was used to correct the significance level, as stated in the figure legends.

3. Results

3.1. Patients Characteristics

Thirty-two patients with HIV-1 infection were included: *n* = 22 in OncoVIRIM, *n* = 10 in BIO-CHIVA-2 (Table 1). The cancer types were non-small cell lung-cancer (*n* = 20), bladder cancer (*n* = 3), melanoma (*n* = 2), head and neck cancer (*n* = 2), Hodgkin lymphoma, KS, anal, oropharynx and orbit cancer (1 patient each). Viral co-infections included HHV-8 infection (53%), resolved HBV infection (38%), resolved HCV infection (38%) and chronic HBV infection (22%). At baseline, the median CA HIV-DNA was 184 cps/10⁶ cells (range 40–1749) and the median HIV VL was 20 cps/mL (range <1–352). The median baseline CD4 cell count was 369/mm³ (range 45–915) and the CD4/CD8 ratio was 1 (range 0.2–2.1). All patients were treated with anti-PD-1: nivolumab (69%), pembrolizumab (28%) and cemiplimab (3%). Six of the patients received ICB as a first line treatment and the others had refractory or relapse diseases. The median follow-up duration was five months (range 1–30) and the median number of cycles received was six (range 2–36). At last follow-up, all but one patient had discontinued ICB. Eighteen patients died: 15 from tumor progression, one from an immune-related adverse event (myocarditis), one from COVID-19 infection and one from an unknown cause.

Table 1. Clinical and biological characteristics at baseline.

Pt	Cohort	Age	Sex	Type of Cancers	Pv Line	ICB Type	ART	CD4 Count (/mm ³)	CD4/CD8 Ratio	HIV VL (cp/mL)	HIV-DNA(cp/10 cells)	HLA Typing
1	CHIVA-2	71	M	NSCLC	2	Nivo	Rilpivirine, Dolutegravir	183	0.5	28	<40	A*01:03 B*37:49
2	CHIVA-2	68	M	NSCLC	2	Nivo	Abacavir, Nevirapine, Emtricitabine	NA	NA	<1	227	A*03:11 B*07:27
3	CHIVA-2	56	M	NSCLC	1	Nivo	tenofovir disoproxil, Maraviroc	831	0.4	193	818	A*24:29 B*38:44
4	CHIVA-2	59	M	NSCLC	1	Nivo	Emtricitabine, Rilpivirine, Tenofovir alafenamide	596	0.9	<1	<40	A*02:29 B*49:58
5	CHIVA-2	65	M	NSCLC	2	Nivo	Tenofovir, Emtricitabine, Bictegravir	451	0.9 *	352	904	A*02:29 B*07:15
6	CHIVA-2	55	F	NSCLC	1	Nivo	Dolutegravir, Abacavir, Lamivudine	499	0.6	138	1287	A*29:30 B*37:44
7	CHIVA-2	68	M	NSCLC	1	Nivo	Abacavir, Efavirenz	241	0.7	<20	187	A*02:11 B*39:40
8	CHIVA-2	53	F	NSCLC	1	Nivo	Emtricitabine, Tenofovir	291	0.4	<20	66	A*02:66 B*49:52
9	CHIVA-2	58	M	NSCLC	1	Nivo	Dolutegravir, Abacavir, Lamivudine	249	0.2	<20	851	A*01:03 B*08:51
10	CHIVA-2	59	M	NSCLC	1	Nivo	Lamivudine, Dolutegravir, Abacavir	583	0.4	<1	231	A*02:03 B*18:27
11	Onco VIHAC	62	M	Melanoma	0	Nivo	Elvitegravir, Emtricitabine, Tenofovir	455	0.8	<1	166	A*02:26 B*07:08
12	Onco VIHAC	69	M	NSCLC	0	Pembro	Emtricitabine, Rilpivirine, Tenofovir	273	0.4	<1	<40	A*02:24 B*35:57
13	Onco VIHAC	75	M	NSCLC	1	Nivo	Lamivudine, Dolutegravir	217	1	42	218	A*25:31 B*40:51
14	Onco VIHAC	60	F	NSCLC	0	Pembro	Darunavir, Norvir, Raltegravir	888	2.1	21	1749	A*31:68 B*07:07
15	Onco VIHAC	63	M	NSCLC	1	Nivo	Dolutegravir, Abacavir, Lamivudine	238	1.8	<1	<40	A*03:23 B*44:53
16	Onco VIHAC	53	M	HL	3	Nivo	Dolutegravir, Lamivudine	373	0.3	<20	173	A*33:68 B*14:44
17	Onco VIHAC	53	M	NSCLC	2	Nivo	Abacavir, Lamivudine	405	0.6	<1	620	A*02:29 B*40:49
18	Onco VIHAC	64	M	Bladder	2	Pembro	Abacavir, Lamivudine, Nivirapine	449	1.1	<1	213	A*02:31 B*07:40
19	Onco VIHAC	62	M	Oropharynx	2	Nivo	Darunavir, Ritonavir	162	0.5	<20	80	A*02:11 B*15:40
20	Onco VIHAC	58	M	Kaposi Sarcoma	4	Nivo	Dolutegravir, Abacavir, Lamivudine	728	2.1	47	409	A*33:68 B*14:44
21	Onco VIHAC	62	M	Anal	2	Nivo	Dolutegravir, Lamivudine	209	1.2	<20	231	A*02:24 B*35:44
22	Onco VIHAC	52	M	Head and neck	1	Nivo	Darunavir, Norvir, Raltegravir	369	0.8	<20	191	A*30:33 B*07:15
23	Onco VIHAC	71	F	Head and neck	1	Nivo	Dolutegravir	333	1.1	<1	<40	A*02:24 B*44:50
24	Onco VIHAC	63	M	Eye	2	Cemi	Bictegravir, Emtricitabine, Tenofovir	45	0.2	29	<40	A*02:33 B*14:53
25	Onco VIHAC	70	M	Melanoma	0	Pembro	Emtricitabine, Tenofovir, Nivirapine	434	0.5	<1	181	A*01:03 B*07:51

Table 1. Cont.

Pt	Cohort	Age	Sex	Type of Cancers	Pv Line	ICB Type	ART	CD4 Count (/mm ³)	CD4/CD8 Ratio	HIV VL (cp/mL)	HIV-DNA(cps/10 ⁶ cells)	HLA Typing
26	OncO VIHAC	56	M	NSCLC	2	Pembro	Emtricitabine, Tenofovir, Darunavir, Ritonavir, Efavirenz,	424	0.8	<20	166	A*11:11 B*15:27
27	OncO VIHAC	62	M	Bladder	1	Pembro	Emtricitabine, Tenofovir, Darunavir,	915	1.4	<20	99	A*24:24 B*44:44
28	OncO VIHAC	58	M	NSCLC	0	Pembro	Doletugravir, Ritonavir, Tenofovir,	192	0.4	<1	73	A*02:32 B*44:51
29	OncO VIHAC	62	M	NSCLC	1	Nivo	Raltegravir, Emtricitabine, Tenofovir	534	0.3	<1	99	NA
30	OncO VIHAC	60	M	Bladder	2	Pembro	Bictegravir, Emtricitabine, Tenofovir	969	0.6	<1	363	NA
31	OncO VIHAC	59	M	NSCLC	1	Nivo	Darunavir, Ritonavir,	699	1	<1	251	NA
32	OncO VIHAC	60	M	NSCLC	0	Pembro	Bictegravir, Emtricitabine, Tenofovir	169	0.4	<1	59	NA
all	OncO VIHAC 69%	61	M 88%	NSCLC 63% Bladder 9%	1	Nivo 69% Pembro 28%		369	1	20	184	

Abbreviations: Pt, patient; Pv, previous; ICB, immune checkpoint blockade; ART, antiretroviral therapy; M, male; F, female; NSCLC, non-small cell lung cancer; HL: Hodgkin lymphoma, Nivo, nivolumab; Pembro, pembrolizumab; Cemi, cemiplimab; NA, Not Available, %, percentage. In the line named "all", absolute values are medians.

3.2. Early Two-Fold Decrease of CA-HIV-DNA following Anti-PD-1

Evaluating as a first step the total CA HIV-DNA at each time point, we observed a 1.9-fold decrease from a median 184 to 99 cps/10⁶ cells at C2 when compared to baseline ($p = 0.0499$), without reaching the significance level after the Bonferroni correction (Figure 1). In addition, as 0.3 log₁₀ physiological fluctuations are commonly described in this assay, we used a threshold of 0.5 log₁₀ to further evaluate this decay. A more than 0.5 log₁₀ decrease in HIV-DNA cps/10⁶ cells was observed at once after anti-PD-1 initiation in six patients (Pt #7, #14, #17, #21, #30 and #31). We further identified these patients with reservoir size reduction as "RR" patients, and we studied if they exhibited specific immunological characteristics to better understand which factors could be involved. Baseline CA HIV DNA was higher in RR compared to those without reservoir size reduction (further identified as "NoRR" patients): 307 versus 166 cps/10⁶ cells ($p = 0.002$) (Supplementary Figure S1). Amongst the six RR, patient #7 demonstrated a persistent and stable HIV-DNA decrease below the detection threshold at the three consecutive last samples. Among the 26 other patients, 4 had a transient increase of ≥ 0.5 log₁₀ HIV-DNA cps/10⁶ cells and there was no change below or above 0.5 log₁₀ for the 22 other patients. Because age potentially impacts the expression of PD-1 on T lymphocytes, we looked at baseline HIV-DNA between younger (<60 years) and older (≥ 60 years) patients and found no difference between groups (median values 191 and 181 cps/10⁶ cells, respectively, $p = 0.9018$). We also compared the median age in RR and in NR and found no significant difference ($p = 0.6974$).

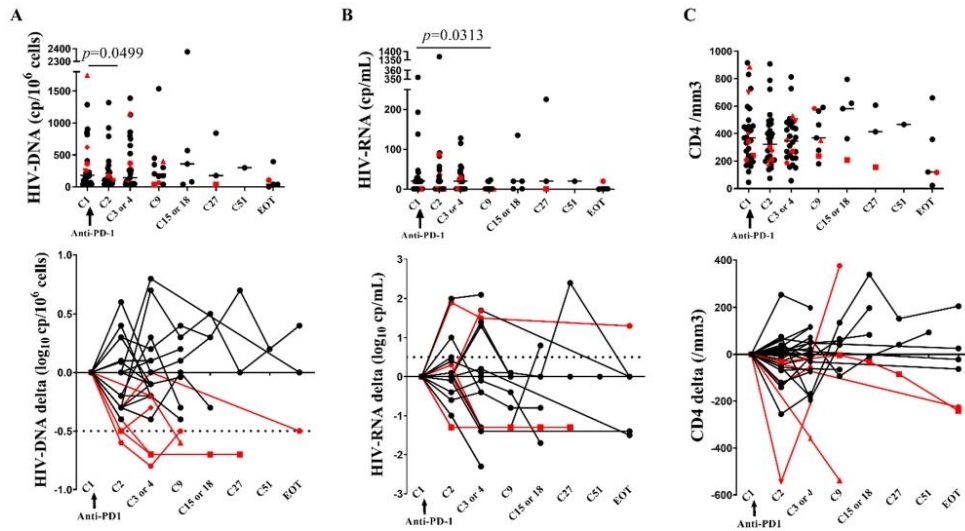


Figure 1. Anti-PD-1 therapy in PLWH with cancer does not significantly impact the biology of HIV. (A), HIV-DNA (cp/ 10^6 cells) (upper panel) and HIV-DNA (\log_{10} cp/ 10^6 cells) delta from baseline (lower panel), (B), HIV-RNA (cp/mL) (upper panel) and HIV-RNA (\log_{10} cp/mL) delta from baseline (lower panel), (C), CD4 count ($/\text{mm}^3$) (upper panel) and CD4 count ($/\text{mm}^3$) delta from baseline (lower panel). Dotted lines denote decrease $\leq 0.5 \log_{10}$ for CA HIV-DNA and increase $\geq 0.5 \log_{10}$ for HIV-RNA. Red color denotes the RR patients represented with different shapes. EOT: end of treatment. Bonferroni corrected p -value: $p \leq 0.007$, Wilcoxon-matched pairs signed Rank test. At cycle 1, $n = 32$; at cycle 2, $n = 29$; at cycle 3 or 4, $n = 29$; at cycle 9, $n = 11$; at cycle 15, $n = 5$; at cycle 27, $n = 3$; at cycle 51, $n = 1$; at end of treatment, $n = 5$. Experiments were monoplicates.

3.3. CD4 Stability and Early T Cell Activation

There was no difference in baseline CD4 count and HIV-VL between RR and NoRR patients (Supplementary Figure S1). The HIV-VL decreased from a median baseline of 20 cp/mL to 1 cp/mL at cycle 9 ($p = 0.0313$) without reaching the significance level after the Bonferroni correction, and there was no change in the CD4 cell counts (Figure 1), nor in the CD4/CD8 ratios, in the CD3, CD8, NK and B cell counts or in lymphocyte differentiation (Supplementary Figure S2). Overall, the proportions of HLA-DR + CD4+ and CD8 + T cells and of CD38+ and HLA-DR + CD38 + CD8 + T cells significantly increased at C2 or C3: respectively 1.8, 1.6, 1.4 and 1.7 fold increase from baseline ($p < 0.0001$, Figure 2, Supplementary Figures S3 and S4). Similarly, there was an early increase in Ki67 + CD4+ and CD8 + T cells at C2 or C3: respectively 2.1 and 2.3 fold increase from baseline ($p \leq 0.0003$). Among RR, the baseline proportions of CD25 + CD8+ T cells (33%) in patient #7 and of HLA-DR + CD8 + T cells (25%) in patient #21 were the highest of the cohort, while patient #14 displayed an early major increase of CD4 + Ki67+ and CD4 + HLA-DR T cells at C3. Nevertheless, there was no statistical difference between activation markers at baseline or kinetics among patients with and without reservoir size reduction (Supplementary Figure S5). These results confirm that ICB induces early immunological activation and show that some RR patients had high baseline levels of activation markers.

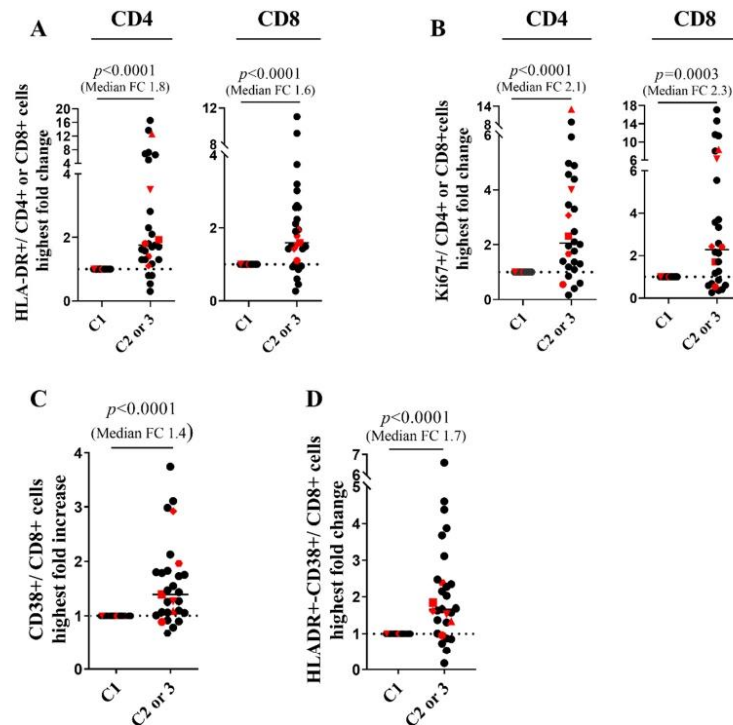


Figure 2. Anti-PD-1 treatment in PLWH with cancer results in T cell immunological activation. (A), Highest fold change at C2 or 3 from baseline in HLA-DR + cells among CD4+ and CD8 + T cells. (B), Highest fold change at C2 or 3 from baseline in Ki67+ cells among CD4+ and CD8+ T cells. (C), Highest fold change at C2 or 3 from baseline in CD38+ cells among CD8+ T cells. (D), Highest fold change at C2 or 3 from baseline in CD38 + HLA-DR + cells among CD8 + T cells. Red spots denote the RR patients and dotted lines denote fold change of 1. Wilcoxon- signed Rank test. FC: fold change. Experiments were monoplicates.

3.4. CTLA-4 Is Upregulated on CD4 Cells and ICP Compensatory Mechanisms Are Less Pronounced in Patients RR

Next, we assessed at each time point the co-expression of PD-1 together with CTLA-4 and TIM-3 on T cells to explore whether inhibitory compensation of ICP blockade occurred (Figure 3, Supplementary Figures S6–S8). At baseline, RR patients did not demonstrate any specific profile except patient RR #21 who showed the highest proportion of PD-1 + CD8 + T cells (99%) in the cohort. (Supplementary Figure S8). At C2 and overtime, the membrane PD-1 molecule became barely detectable on CD4+ and CD8 + T cells ($p < 0.0001$). In contrast, we observed a significant but transient increase in CTLA-4 + CD4 + T cells at C2 (fold change: 1.5, $p = 0.004$) and a trend for an increase of CTLA-4 + CD8+ T cells at C2 which did not reach statistical significance ($p = 0.03$). Of note, the proportions of CD8+ T cells displaying CTLA-4 and TIM-3 increased more at C2 or C3 in NoRR patients compared to RR patients (respectively 2.4 versus 1.1 for CTLA-4 + CD8 + fold change, and 1.4 versus 0.9 for TIM-3 + CD8 + fold change) ($p \leq 0.03$) (Figure 3). Taken together, these results suggest that anti-PD-1 monotherapy could be associated with some compensatory increase of other ICP molecules on T cells which is less pronounced in the RR patients.

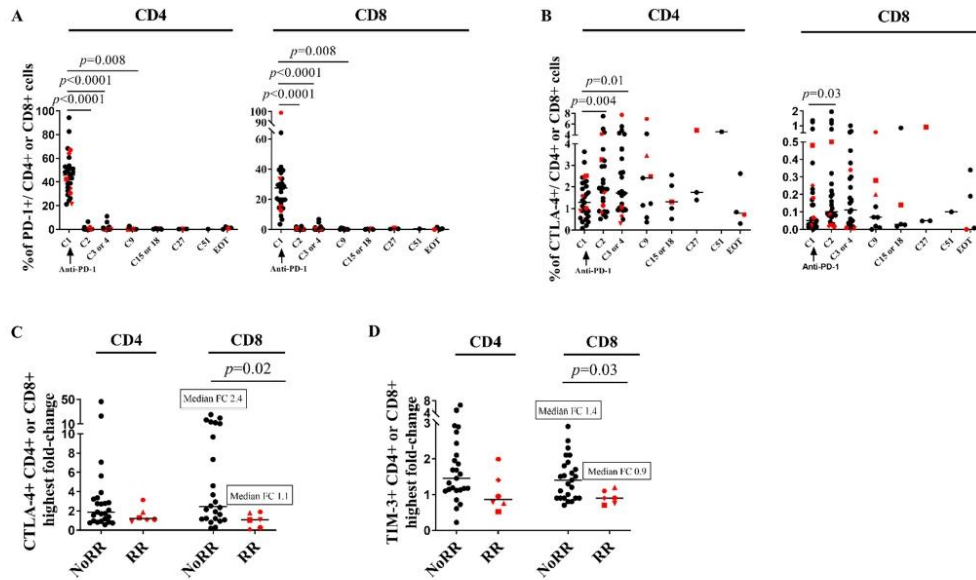


Figure 3. Anti-PD-1 therapy in PLWH with cancer induces dramatic decrease of PD-1 detection and slight and transient CTLA-4 expression increase. (A), Changes overtime in PD-1 expression on CD4 + (left) and CD8 + (right) T cells. (B), Changes overtime in CTLA-4 expression on CD4 + (left) and CD8 + (right) T cells. Bonferroni corrected p -value: $p \leq 0.007$, Wilcoxon-matched pairs signed Rank test. Highest fold change at cycle 2 or 3 of (C), CTLA-4 + CD4 + (left) and CD8 + (right) T cells, and of (D), TIM-3 + CD4 + T (left) and CD8 + (right) among the patients without reservoir reduction (NoRR) and with reservoir reduction (RR). Mann-Whitney test. In each graph, red spots denote the patients RR. EOT: end of treatment. FC: fold change. At cycle 1, $n = 32$; at cycle 2, $n = 29$; at cycle 3 or 4, $n = 29$; at cycle 9, $n = 11$; at cycle 15, $n = 5$; at cycle 27, $n = 3$; at cycle 51, $n = 1$; at end of treatment, $n = 5$. Experiments were monoplicates.

3.5. Stability of Peripheral HIV-Specific T Cells Despite PD-1 Overexpression at Baseline

We next evaluated whether ICB could enhance HIV-specific T cell responses in vivo, defined as IFN- γ producing CD8+ T cells. At baseline, the median proportion of HIV-specific CD8 + T cells was 0.48% (range 0–6.52) of total CD8+ T cells. Those frequencies did not differ in the RR patients compared to the NoRR patients, although the patient RR #21 had the third highest proportion of HIV-specific CD8+ T cells among the cohort (2.63%) (Supplementary Figure S9). Overall, the percentages of HIV-specific CD8+ T cells did not statistically change over time (Figure 4) and there was no difference in the kinetics of HIV-specific CD8+ T cells between the RR and NoRR patients (Supplementary Figure S9). The frequencies of IL-2 + CD8+ and TNF- α + CD8+ T cells were much lower at baseline (0.02% each) than the IFN- γ + CD8+ T cells frequencies and did not change over time (Supplementary Figure S10). The cell poly-functionality defined as the co-production of IFN- γ , and/or IL-2 and/or TNF- α also remained stable over time without differences between RR patients and the others (Supplementary Figure S11). Similarly, CD4 HIV-specific T cell responses did not change over time (Supplementary Figure S10).

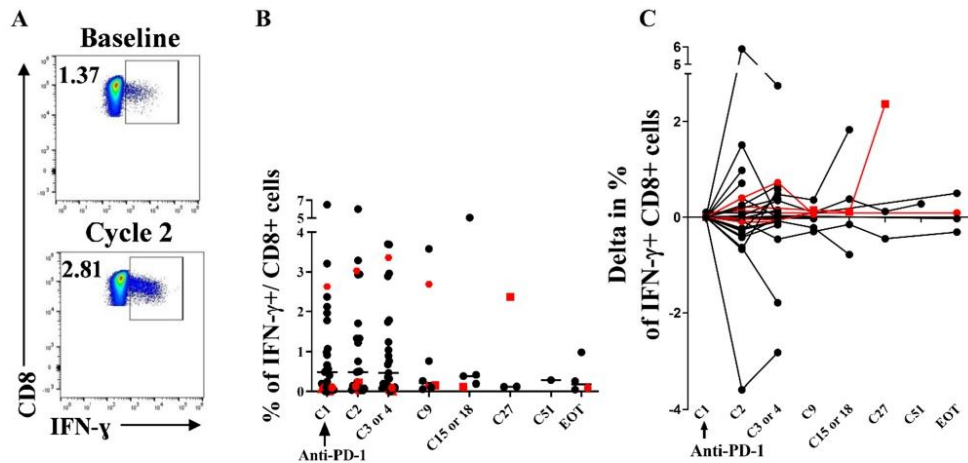


Figure 4. Anti-PD-1 therapy in PLWH with cancer does not significantly increase the in vivo frequency of HIV-specific CD8 + T cells. Thawed PBMC were stimulated during 6 h with HIV peptides (15 mers overlapping peptides covering RT, Nef and Gag) and then stained with intra-cellular anti-cytokine antibodies (anti-IFN- γ , anti-IL-2 and anti-TNF- α). HIV-specific CD8 + T cells were defined as IFN- γ producing CD8 + T cells after HIV stimulation. (A), Example dot plots of IFN- γ expression among CD8 + T cells after HIV stimulation at baseline and at cycle 2. (B), frequency of HIV-specific CD8 + T cells under ICB. (C), HIV-specific CD8 + T cells delta from baseline under ICB. Red colors denote the RR patients. EOT: end of treatment. At cycle 1, $n = 32$; at cycle 2, $n = 29$; at cycle 3 or 4, $n = 29$; at cycle 9, $n = 11$; at cycle 15, $n = 5$; at cycle 27, $n = 3$; at cycle 51, $n = 1$; at end of treatment, $n = 5$. Experiments were monoplicates.

When analysing PD1 expression on HIV-specific T cells at baseline, we observed that HIV-specific T cells displayed higher percentages of PD-1+ cells and CTLA-4+ cells (Figure 5 and Figure S12) and higher mean fluorescence intensity (MFI) of PD-1 (Supplementary Figure S13) compared to non-HIV-specific CD8 + T cells ($p < 0.001$). PD-1 expression on HIV-specific CD8 + T cells was non significantly lower in RR compared to NoRR patients (Supplementary Figure S9). We then tested in 18 patients whether such a lack of immune enhancement could reflect an upregulation of other ICP on HIV-specific CD8 T cells. However, CTLA-4, TIM-3 and LAG-3 expression on HIV-specific T cells did not increase over time (Figure 5).

Taken together, these results suggest that ICB monotherapy is insufficient for enhancing an HIV-specific response despite high PD1-expression on HIV-specific CD8+ T cells at baseline.

3.6. Immunological and Virological Parameters of Other Viruses Are Not Modified

As ICB have been proposed to be used against other chronic viral co-infections such as EBV, CMV and HBV, we aimed at evaluating the effects of ICB on other viruses in these poly-infected patients, and whether anti-PD-1 could enhance these other virus-specific T cell responses. In patients seropositive for HHV-8, HCV, HBV and CMV, there was no corresponding viral replication at baseline, except in 2 patients with active HBV infection and for whom anti-HBV treatment was changed at the start of ICB. After anti-PD-1 initiation, there was no significant change in HHV-8, HBV, HCV, EBV and CMV loads over time (Supplementary Figure S14). There was no significant change in virus-specific CD8 + T cells over time despite highly heterogeneous profiles (Figure 6). When studying PD-1 expression on virus-specific CD8 + T cells, we observed at baseline higher percentages of PD-1 expression (Figure 5) and higher MFI of PD-1 (Supplementary Figure S13) on EBV-

and HBV-specific CD8+ T cells ($p < 0.007$). Taken together, these results suggest that ICB can be safely used in PLWH with viral co-infections and that PD-1 overexpression on EBV and HBV-specific CD8+ T cells could be targeted, even though we failed to demonstrate specific invigoration in peripheral blood.

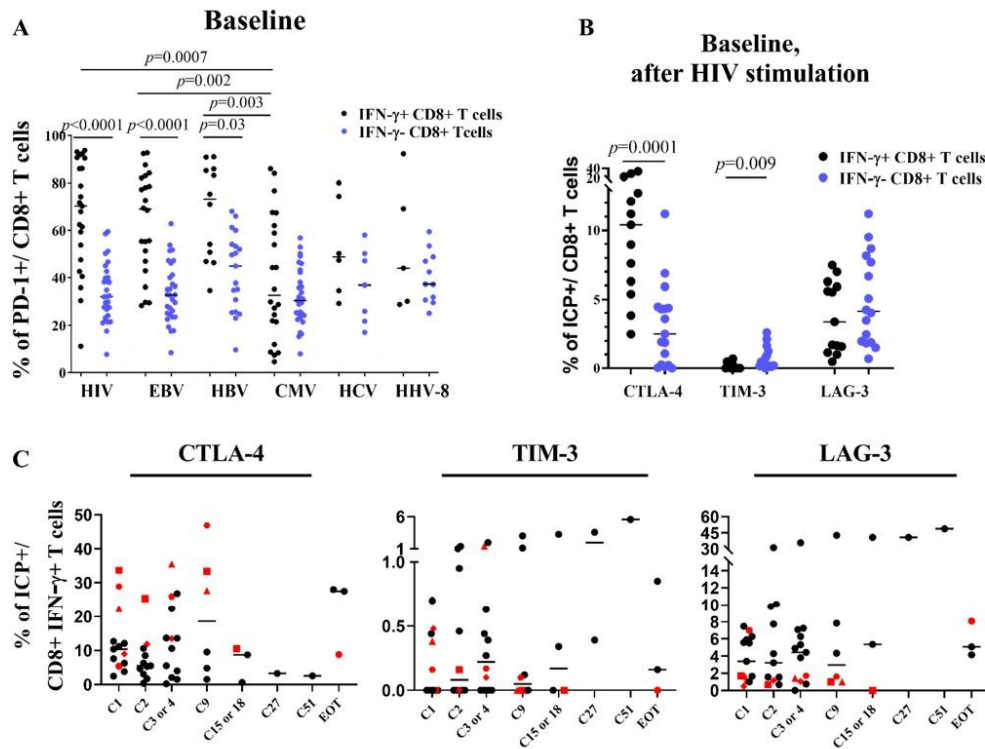


Figure 5. In PLWH with cancer, high levels of ICP expression are detected on HIV-specific T cells, without upregulation on anti-PD-1 therapy. Thawed PBMC were stimulated during 6 h with viral peptides and then stained with intra-cellular anti-cytokine antibodies (anti-IFN- γ , anti-IL-2 and anti-TNF- α). HIV-specific CD8+ T cells were defined as IFN- γ producing CD8+ T cells after HIV stimulation. (A), PD-1 expression among specific (black spots) and non-specific (blue square) CD8+ T cells at baseline depending on viral stimulations. Mann Whitney test. (B), CTLA-4, TIM-3 and LAG-3 expression among HIV-specific and non-specific CD8+ T cells after HIV stimulation ($n = 18$). Mann Whitney test. (C), expression of CTLA-4 (left), TIM-3 (middle) and LAG-3 (right) on HIV specific CD8+ T cells overtime. Red spots denote the patients with reservoir reduction. EOT: end of treatment. At cycle 1, $n = 32$; at cycle 2, $n = 29$; at cycle 3 or 4, $n = 29$; at cycle 9, $n = 11$; at cycle 15, $n = 5$; at cycle 27, $n = 3$; at cycle 51, $n = 1$; at end of treatment, $n = 5$. Experiments were monoplicates.

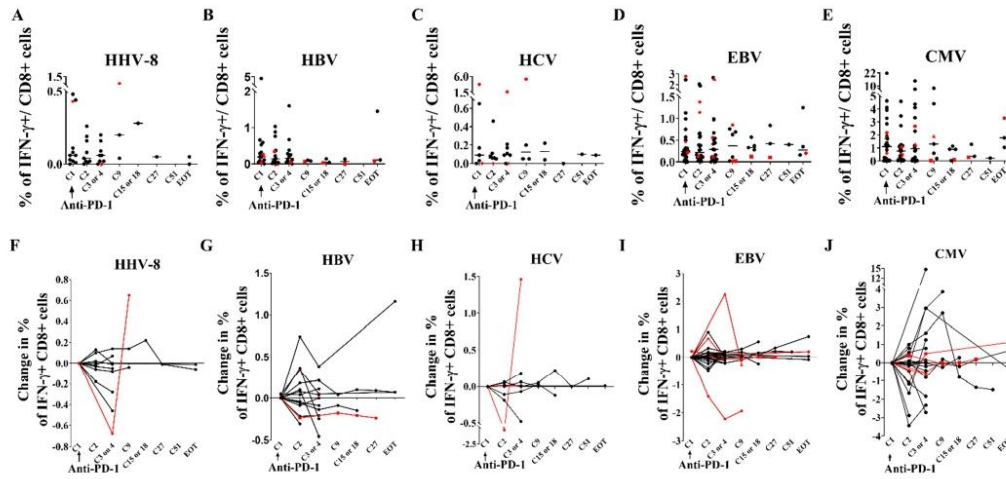


Figure 6. Anti-PD-1 therapy in PLWH with cancer does not significantly increase the frequency of virus-specific CD8 + cells. Thawed PBMC were stimulated during 6 h with viral peptides and then stained with intra-cellular anti-cytokine antibodies (anti-IFN-γ, anti-IL-2 and anti-TNF-α). Virus-specific CD8 + T cells were defined as IFN-γ producing CD8+ T cells after viral stimulation. Frequencies of (A), HHV-8, (B), HBV, (C), HCV, (D), EBV, and (E), CMV-specific-CD8+ T cells overtime. Delta from baseline of (F), HHV-8, (G), HBV, (H), HCV, (I), EBV, and (J), CMV-specific CD8 + T cells under ICB. Red colors denote the patients with reservoir reduction. EOT: end of treatment. Experiments were monoplicates.

3.7. Immuno-Virological Profiling of RRs

The individual profiles (HIV-RNA, CA HIV-DNA and HIV-specific T cells) of RR patients are summarized in Figure 7. None of these patients with available HLA typing ($n = 4$) had the HLA-B27 or B57 protective alleles. Patient #7 had the longest follow-up of 14 months and his HIV-DNA decreased from 187 cps/ 10^6 cells to become persistently undetectable at the last three time points (C9, 15 and C27). Patient #14 displayed the highest HIV-DNA at baseline (1749 cps/ 10^6 cells) which decreased by 0.6 \log_{10} down to 403 cps/ 10^6 cells six months later. Patient #17 experienced an early 0.5 \log_{10} decrease in HIV-DNA from 620 to 178 cps/ 10^6 cells at C2. Patient #21 demonstrated a persistent CA HIV-DNA reduction from 231 to 66 cps/ 10^6 cells 4 months later ($-0.5 \log_{10}$). Patient #30 HIV-DNA decreased from 363 to 106 cps/ 10^6 cells ($-0.5 \log_{10}$) 4 months later. Finally, the HIV-DNA of patient #31 decreased gradually from 251 to 53 cps/ 10^6 cells 2 months later ($-0.7 \log_{10}$). ICB was stopped because of tumor progression in 4 cases and of cutaneous toxicity in 1 case, and monitoring was stopped in 1 case because of patient relocation.

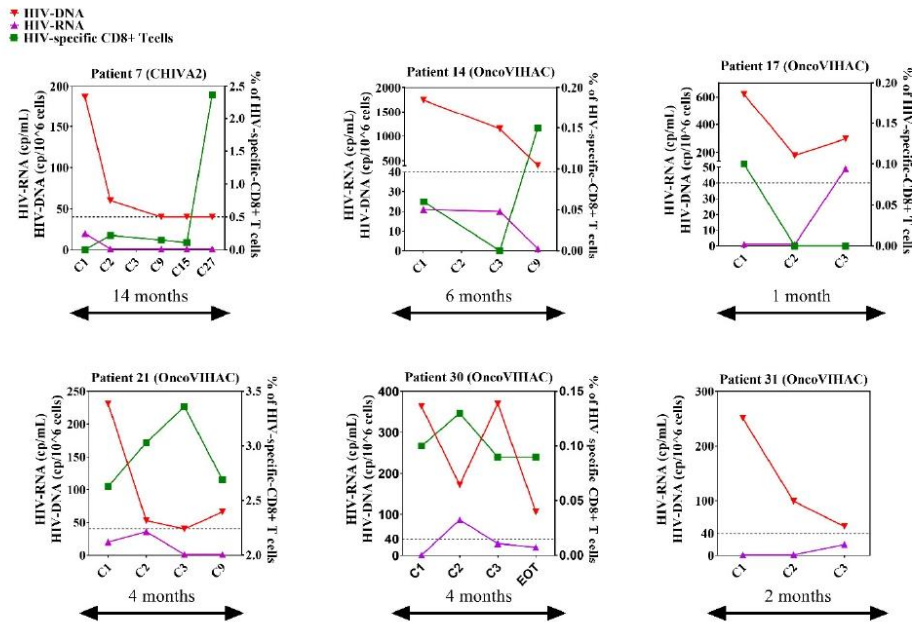


Figure 7. Immunovirological-profiles of the six PLWH patients treated with anti-PD-1 with a CA HIV-DNA decrease $\geq 0.5 \log_{10}$. In each graph, red inverted triangles represent HIV-DNA (cp/10⁶ cells), purple triangles represent HIV-RNA (cp/mL) and green squares represent HIV-specific CD8 + cells (% of total CD8 + T cells). Dotted lines represent CA HIV-DNA = 40 cp/10⁶ cells, which is the detection threshold. EOT: end of treatment. The frequency of HIV-specific CD8 + T cells was not available for patient #31. Experiments were monoplicates.

4. Discussion

Here, we report the largest comprehensive and homogeneous immunological and virological assessment of the influence of immune check-point blockade on HIV reservoirs and T cell functions in a series of 32 PLWH treated with anti-PD-1 for cancer.

Despite some cancers heterogeneity, there was a majority of lung cancers and no evidence that the cancer type might influence the ICB action on the HIV reservoir and on HIV-specific T cells.

We chose to focus as a first step of reservoir size analysis on the measurement of total CA HIV-DNA since our final aim was to study the evolution of the HIV-reservoir as a result of both HIV latent cell reactivation and immune invigoration. We assume that it provides less understanding of the potential influence of ICB on the reservoirs, but such evaluation appeared to us to be more relevant on a clinical perspective. The CA HIV-DNA decrease observed after the cycle 1 was only transient and such ICB could have impacted more profoundly and durably the HIV-reservoir, though still transiently, in only 19% of cases. The threshold of CA HIV-DNA reduction of 0.5 log is above the usual 0.3 log₁₀ fluctuations of the methods and was an acceptable cut-off in other studies [28,29]. This proportion of 19% RR could be mis-estimated given that CA HIV-DNA was undetectable at baseline in six patients. The 6 patients with a CA HIV-DNA decrease $\geq 0.5 \log_{10}$ under ICB included one with CA HIV-DNA becoming persistently undetectable for 14 months and one with features of a “shock and kill”. Although follow-up was short due to frequent tumor progression, four patients with RR were followed during more than three months, which represents one of the longest descriptions of CA-HIV DNA under ICB. Of note, two

out of six patients RR (patient #14 and #17) had a decrease of CD4+ T cells frequencies at the same time, which may have impacted the results of HIV reservoir. Overall, no significant immunological differences in terms of immune activation or HIV-specific T cell responses were observed between these rare RR and NoRR patients. The weak HIV-specific T cell responses observed in our patients and the lack of ICB effect might reflect the consequences of previous multiple chemotherapies in those PLWH with cancers

Our results suggest one mechanism to explain such limited ICB impact on HIV reservoirs is that the virus persists preferentially in CD4 + T cells expressing other ICP than PD-1. The greater increase in CTLA-4 and TIM-3 expression on CD8 + T cells in the NoRR compared to the RR patients reinforces this hypothesis. Such ICP compensation and upregulation on CD8 + T cells could have hampered the CTL response to the virus and prevent an efficient “shock and kill” mechanism. These observations are consistent with the recently published demonstration of ICP overexpression in Hodgkin lymphoma tumor microenvironment exposed to anti-PD-1 [30]. Thus, a combination of IC blockade could be necessary to bypass multiple ICP expression both on HIV reservoir cells and on HIV-specific T cells as suggested by others, although such combinations are limited by an increased and barely acceptable toxicity in PLWH [4,14,31–33]. Finally, the dramatic decrease in PD-1 expression on T cells reflects the antigenic occupancy with the monoclonal antibody of detection which recognizes the same epitope as the therapeutic one, as it has been demonstrated previously [34].

Finally, we provide insights into the virological safety of ICB and its impact on immune responses against other viruses. Indeed, ICB is safe and can be widely used in co-infected patients, although the great majority of patients had very low viral antigen loads with undetectable HBV, HCV, CMV and HHV-8 VL at baseline. Of note, the two patients with active HBV infection at baseline benefited from anti-HBV treatment at the same time, which also hinders the interpretation of VL decrease under ICB.

In conclusion, our study shows that ICB with anti-PD1 antibodies in PLWH with cancer had a very limited impact on HIV reservoirs and immunity to HIV which might be explained by an ICP compensatory phenomenon as assessed by the early increase in CTLA-4 and Tim-3 expression. Further studies are warranted to evaluate the impact of combined immune checkpoint blockade on the HIV reservoirs and immunity of PLWH suffering from cancers.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cells11061015/s1>, Supplementary Methods S1: Viral stimulations before ICS assays are detailed [26,27,35–42]; Figure S1: Cell-associated HIV DNA at baseline is higher in patients with virological reduction compared to the others; Figure S2: Lymphocytes’ subsets and subpopulations are not modified under anti-PD-1 therapy; Figure S3: Example dot plots of A, HLA-DR and of B, Ki-67 expression among CD4 and CD8 T cells at baseline and at cycle 2; of C, CD38 and of D, CD38+ HLA-DR+ expression among CD8 T cells at baseline and at cycle 2; Figure S4: CD69 and CD25 expression on CD4+ and CD8+ T cells are not modified under anti-PD-1 therapy; Figure S5: Activation markers expression at baseline and activation markers kinetics are not different between the RR patients and the others; Figure S6: PD-1, CTLA-4 and TIM-3 expression profile on total CD8+ and CD4+ T cells at baseline before anti-PD-1 therapy; Figure S7: Example dot plots of PD-1, CTLA-4 and TIM-3 expression among CD4+ and CD8+ T cells at baseline and at cycle 2; Figure S8: ICP expression at baseline are not different between the RR patients and the others; Figure S9: HIV-specific CD8+ T cells proportions at baseline and kinetics are not different between the RR patients and the others; Figure S10: Intra-cellular cytokine expression after HIV-peptide stimulation is not modified under anti-PD-1 therapy; Figure S11: Polyfunctionality profile amongst HIV-specific CD8+ T cells is not modified under anti-PD-1 therapy; Figure S12: Example dot plots of A, IFN- γ + CD8+ T cells after stimulation with medium alone (negative control on the left) and with staphylococcal enterotoxin B toxin (positive control on the right); Figure S13: High levels of mean fluorescence intensity (MFI) are detected on HIV, EBV and HBV-specific CD8+ T cells baseline after viral stimulation; Figure S14: Viral loads under ICB; Table S1: Immunodominant HBV peptides sequences, genotype, HLA restriction and amino acids number.

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SUPPLEMENTARY MATERIAL

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SECTION I: Supplementary Methods

Viral stimulations before ICS assays are detailed below. All stimulations, except HBV, have been previously described.

- HIV-Gag pooled peptides 15mers overlapping by 11 amino acids and spanning the complete sequence of p17 and p24 (final concentration 2µg/mL of each peptide, provided by NeoSystem).[1].
- HIV-Gag pooled and RT and Nef pooled peptides 15mers overlapping by 11 amino acids and spanning the complete sequence of P1, P2, P6, P7, RT and Nef (final concentration 2µg/mL of each peptide, provided by NeoSystem) [1].
- EBV peptides 8-11mers representing immunodominant epitopes restricted to different class-I MHC molecules from EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, LMP-2, BMLF-1, BZLF-1, - (final concentration 2µg/mL, provided by GeneCust Europe) [2].
- IE1 CMV 15mers peptides overlapping by 10 amino acids and spanning the complete sequence of IE1 (final concentration 2 µg/ml, provided by the « INSERM « Action-thématique-Concertée on antiviral immunity ») [3].
- PP65 CMV 15mers peptides overlapping by 10 amino acids and spanning the complete sequence of PP65 (final concentration 2 µg/ml, provided by the « INSERM « Action-thématique-Concertée on antiviral immunity »)[3].
- HBV 8-15mers peptides overlapping by 11 and spanning the complete sequence of Enveloppe (genotype A: one of the most common french genotype) and HBV peptides representing immunodominant epitopes restricted to different class-I MHC molecules from Enveloppe, Core, HbX and Polymerase (genotypes A and D: the 2 most common french genotype) (final concentration 2µg/mL, provided by Genecust, France) These ninety peptides were selected from immunodominant peptides, prioritizing peptides

- from HBV genotype A and D because of their frequency in Europe and prioritizing the more frequent European HLAs, and from the complete sequence of Envelope protein with overlapping peptides (genotype A) [4–8]. HbYX peptides represent peptides derived from HbX protein with tyrosine substitutions at position 1 and whose immunogenicity was demonstrated. HBV peptides sequences, genotype, HLA restriction and amino acids number are summarized in **Supplementary Table 1**.
- HCV 18mers peptides overlapping by 11 amino acids and spanning the complete sequence of NS-3, NS-5a, NS-5b and core (final concentration 0,5 µg/mL, provided by the NIH-AIDS-Reagent-Program) [9].
 - HHV8 9-22mers peptides representing immunodominant epitopes from lytic viral glycoprotein (gp) B246, gp H, gp 35, and latent viral LANA-1, K12, K15, ORF-57 (final concentration 2 µg/mL, provided by EpiTop) [10].

SECTION II: Supplementary Table

Table S1: Immunodominant HBV peptides sequences, genotype, HLA restriction and amino acids number.

HBV peptides	Sequence	HBV genotype	HLA restriction	Amino acids number
Core 18-27	FLPSDFPSPV	A and D	A2	10
Core 107-115	CLTFGRETV	A and D	A2	9
Env 183-191	FLLTRILTI	A and D	A2	9
Env 335-343	WLSLLVPFV	A and D	A2	9
Env 338-347	LLVPFVQWFV	A and D	A2	10
Env 348-357	GLSPTVWLSA	A	A2	10
Env 348-357	GLSPTVWLSV	D	A2	10
Pol 455-463	GLSRYVARL	A and D	A2	9
Pol 502-510	KLHLYSHPI	A and D	A2	9
Pol 575-583	FLLSLGIHLFLLSLGIHL	A and D	A2	19
Pol 655-663	ALMPLYACI	A and D	A2	9
Pol 816-824	SLYAVSPSV	A	A2	9
Pol 816-824	SLYADSPSV	D	A2	9
Core 419-428	DLDTASALY	A and D	A2	10
Pol 538-546	YMDDVVLGA	A and D	A2	9
Pol 149-159	HTLWKAGILYK	A and D	A11	11
Pol 388-397	LVVDFSQFSR	A and D	A11	10
Pol 531-539	SAICSVVRR	A and D	A11	9
Core 141-151	STLPETTIVRR	A and D	A11	11
HbX1 4-12	RLCCQLDPA	A and D	A2	9
HbX6 84-92	NAHQILPKV	A	A2	9
HbX6 84-92	NAHQFLPKV	D	A2	9
HbYX7 92-100	YLHKRTLGL	A and D	A2	9
HbYX10 115-123	YLFKDWEEL	A and D	A2	9
HbYX12 99-108	YLSAMSTTDL	A	A2	10
HbYX12 99-108	YLSVMSTTDL	D	A2	10
Core 8-16	EFGATVELL	A and D	A2	9
Core 75-83	LEDPASRDL	A	B4001	9
Core 75-83	LEDPASREL	D	B4001	9
Core 88-96	YVNTNMGLK	A and D	A1101	9
Core 117-125	EYLVQFGVW	A and D	A2402	9
Core 141-151	TLPETTVVRR	A and D	A1101	10
Env 61-70	GLLGWSPQA	A and D	A0201	9
Env 171-180	FLGPLLVLQA	A and D	C0801	10
Env 356-364	SAIWMWYW	A and D	B5801	9
Env 370-379	SIVSPFIPLL	A	A0201	10
Env 370-379	SILSPFLPLL	D	A0201	10
Pol 165-174	ASFCGSPYSW	A and D	B5801	10
Pol 386-395	SRLVVDFSQF	A and D	B1301	10
Pol 756-764	KYTSPWLL	A and D	A2402	10
Env 177-185	VLQAGFFIL	A and D	A2	9
Env 204-212	FLGGTRVCL	A	A2	9
Env 204-212	FLGGTTVCL	D	A2	9
Env 250-258	LLCLIFLV	A and D	A2	9
Env 260-269	LLDYQGMLPV	A and D	A2	10

Abbreviation: Env : envelope : Pol : polymerase.

SECTION III: Supplementary Figures

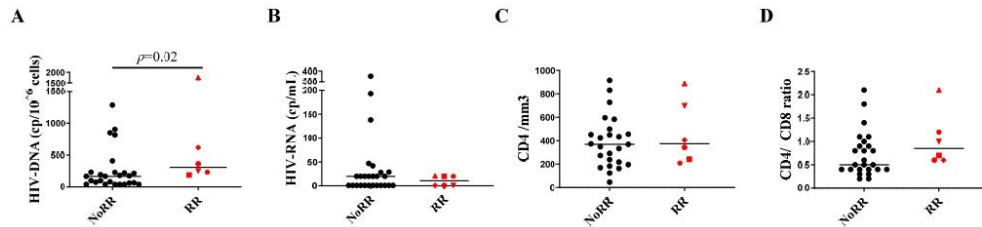


Figure S1. Cell-associated HIV DNA at baseline is higher in patients with virological reduction compared to the others. At baseline **A**, HIV-DNA (cp/10⁶ cells). **B**, HIV-RNA (cp/mL). **C**, CD4 count /mm³. **D**, CD4/ CD8 ratio. NoRR: patients without reservoir reduction; RR: patients with reservoir reduction. Mann-Whitney test. For the HIV-RNA results, the undetectable results were depicted at the threshold of detection (1 cp/mL), the detectable but unmeasurable results (1-<20 cp/mL) were depicted at the threshold detection (20 cps/mL). Experiments were monoplicates.

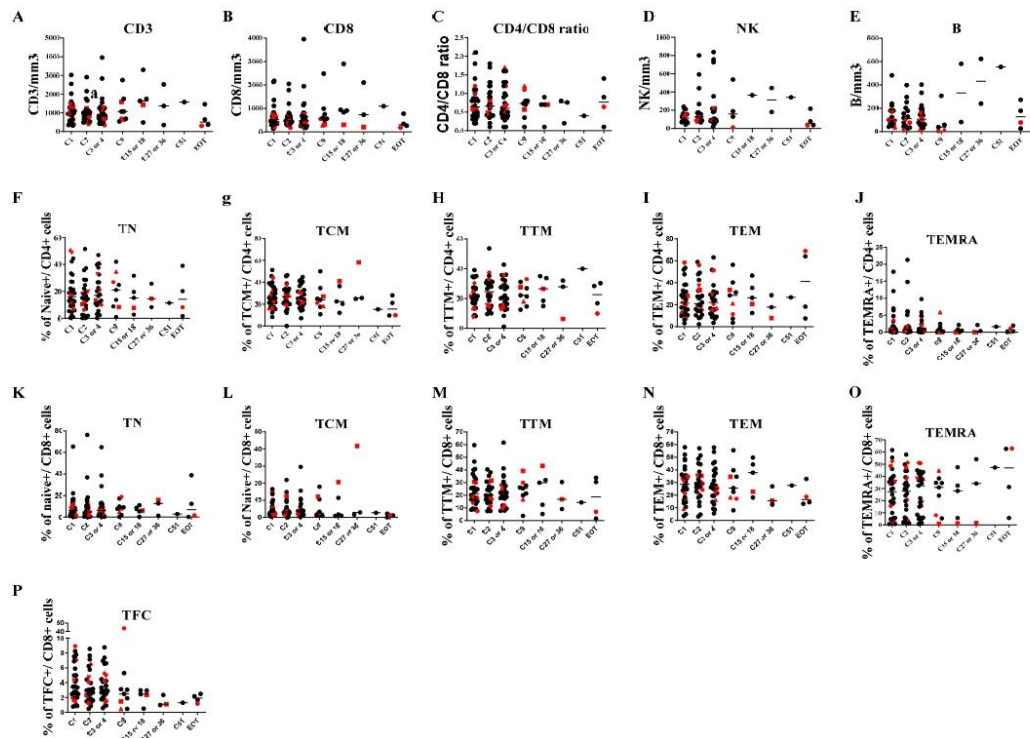


Figure S2. Lymphocytes' subsets and subpopulations are not modified under anti-PD-1 therapy. **A**, CD3 count (/mm3). **B**, CD8 count (/mm3). **C**, CD4/ CD8 ratio. **D**, NK count (/mm3). **E**, B count (/mm3) % of **F**, naive CD4+ T cells. **G**, central memory CD4+ T cells. **H**, transitional memory CD4+ T cells. **I**, effector memory CD4+ T cells. **J**, TEMRA CD4+ T cells. **K**, naive CD8+ T cells. **L**, central memory CD8+ T cells. **M**, transitional memory CD8+ T cells. **N**, effector memory CD8+ T cells. **O**, TEMRA CD8+ T cells. **P**, follicular cytotoxic CD8+ T cells. Abbreviations. TN: naive T cells; TCM: central memory T cells; TTM: transitional memory T cells, TEM: effector memory T cells; TEMRA: effector memory RA T cells; TFC: follicular cytotoxic T cells. EOT, end of treatment. Red symbols denote the RR patients. Experiments were monoplex.

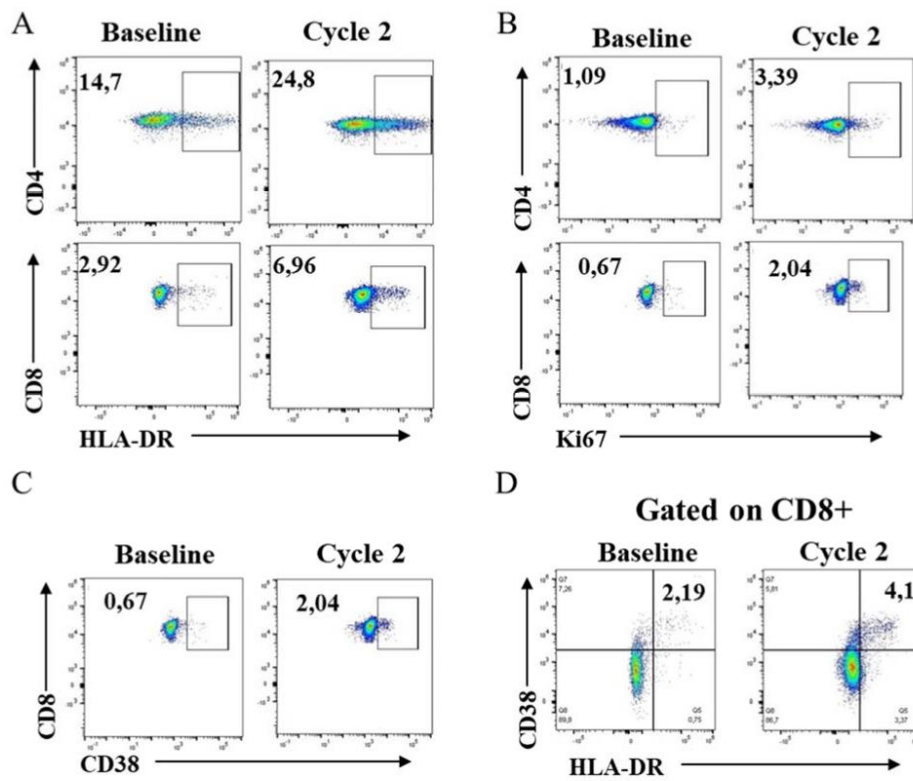


Figure S3. Example dot plots of **A**, HLA-DR and of **B**, Ki-67 expression among CD4 and CD8 T cells at baseline and at cycle 2; of **C**, CD38 and of **D**, CD38+ HLA-DR+ expression among CD8 T cells at baseline and at cycle 2. Experiments were monoplicates.

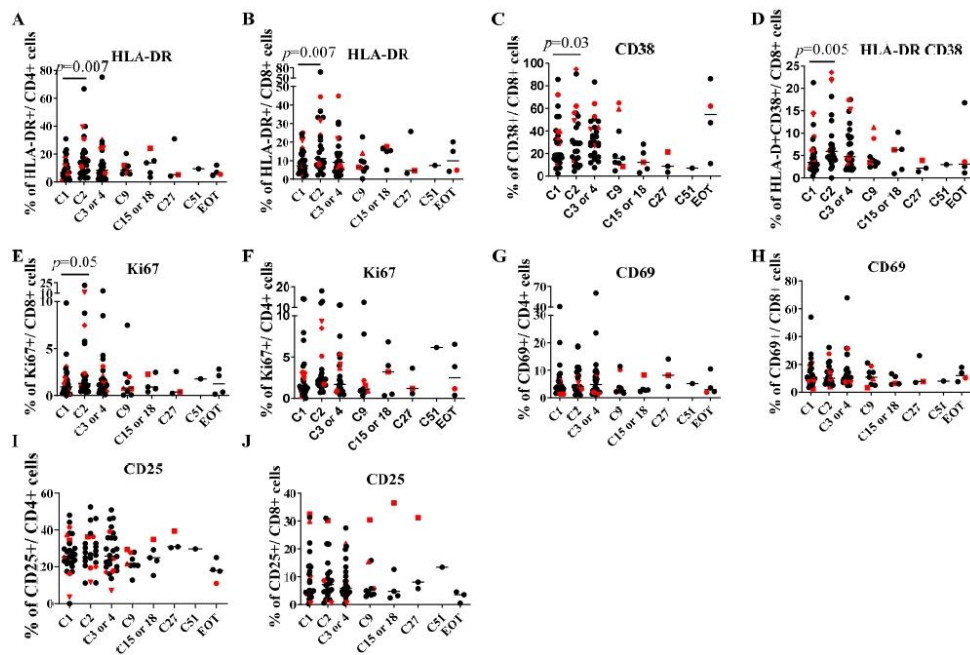


Figure S4. CD69 and CD25 expression on CD4+ and CD8+ T cells are not modified under anti-PD-1 therapy. % of **A** HLA-DR+ CD4+ T cells. **B**, HLA-DR+ CD8+ T cells. **C**, CD38+ CD8+ T cells. **D**, CD38+ HLA-DR+ CD8+ T cells. **E**, Ki67+ CD4+ T cells. **F**, Ki67+ CD8+ T cells. **G**, CD69+ CD4+ T cells. **H**, CD69+ CD8+ T cells. **I**, CD25+ CD4+ T cells. **J**, CD25+ CD8+ T cells. EOT, end of treatment. Red symbols denote the six RR patients. Bonferroni corrected p-value: $p \leq 0.007$, Wilcoxon-matched pairs signed Rank test. Experiments were monoplicates.

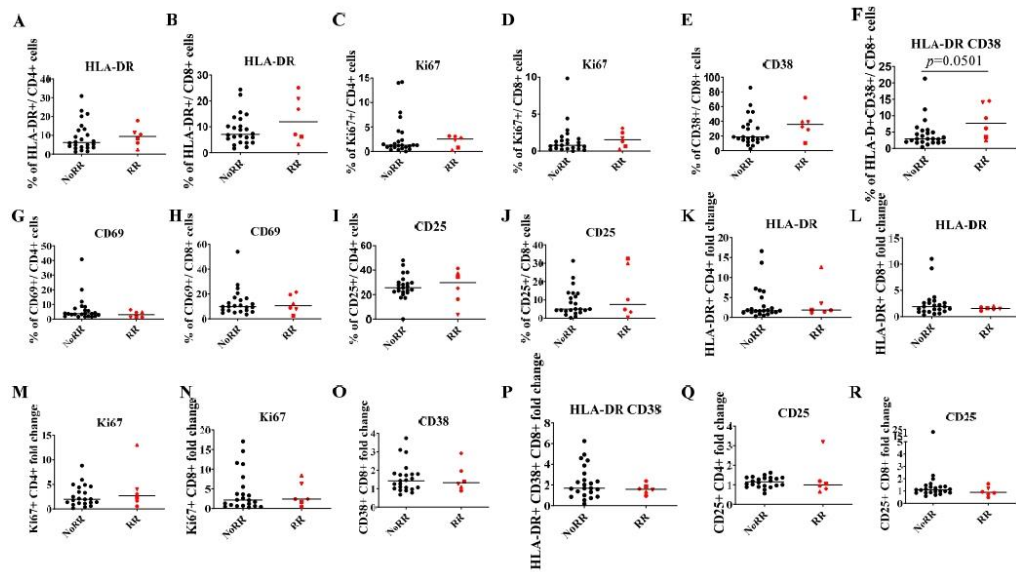


Figure S5. Activation markers expression at baseline and activation markers kinetics are not different between the RR patients and the others. % at baseline of **A**, HLA-DR+ CD4+ T cells. **B**, HLA-DR+ CD8+ T cells. **C**, Ki67+ CD4+ T cells. **D**, Ki67+ CD8+ T cells. **E**, CD38+ CD8+ T cells. **F**, CD38+ HLA-DR+ CD8+ T cells. **G**, CD69+ CD4+ T cells. **H**, CD69+ CD8+ T cells. **I**, CD25+ CD4+ T cells. **J**, CD25+ CD8+ T cells. Highest fold change at C2 or C3 of **J**, HLA-DR+ CD4+ T cells. **K**, HLA-DR+ CD8+ T cells. **L**, Ki67+ CD4+ T cells. **M**, Ki67+ CD8+ T cells. **N**, CD38+ CD8+ T cells. **O**, CD38+ HLA-DR+ CD8+ T cells. **P** CD25+ CD4+ T cells. **Q**, CD25+ CD8+ T cells. RR: patients with reservoir reduction, NoRR: patients without reservoir reduction. Mann-Whitney test. Experiments were monoplicates.

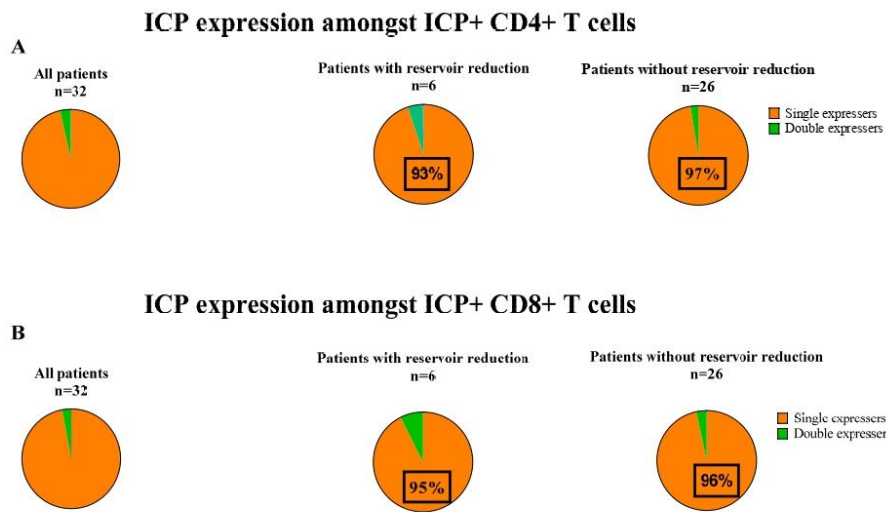


Figure S6. PD-1, CTLA-4 and TIM-3 expression profile on total CD8+ and CD4+ T cells at baseline before anti-PD-1 therapy. The percentages of (A) CD4+ or (B) CD8+ among CD4+ICP+ or CD8+ ICP+ T cells expressing one (single), two (double) or three (triple) ICP among PD-1, CTLA-4 and TIM-3 are represented for all patients at the left and for the RR patients (n=6) and the others (n=26) at the right. Experiments were monoplicates.

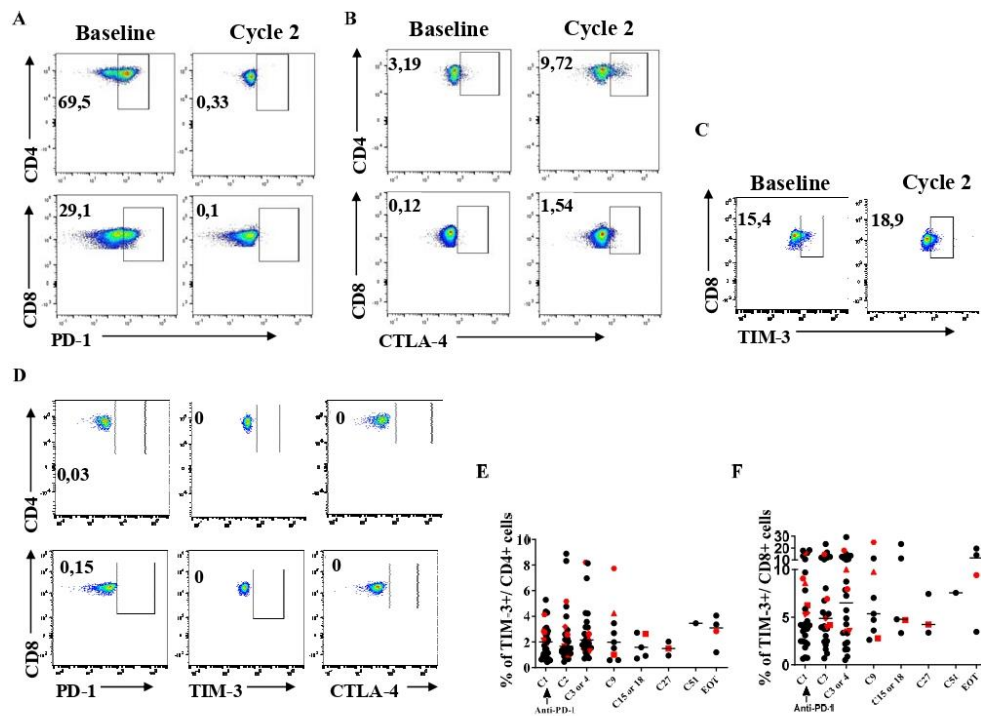


Figure S7. Example dot plots of **A**, PD-1, **B**, CTLA-4 and **C**, TIM-3 expression among CD4+ and CD8+ T cells at baseline and at cycle 2. **D**, Fluorescence Minus One controls of PD-1, CTLA-4 and TIM-3. **TIM-3 expression** in **E**, CD4+ and in **F**, CD8+ T cells. Experiments were monoplicates.

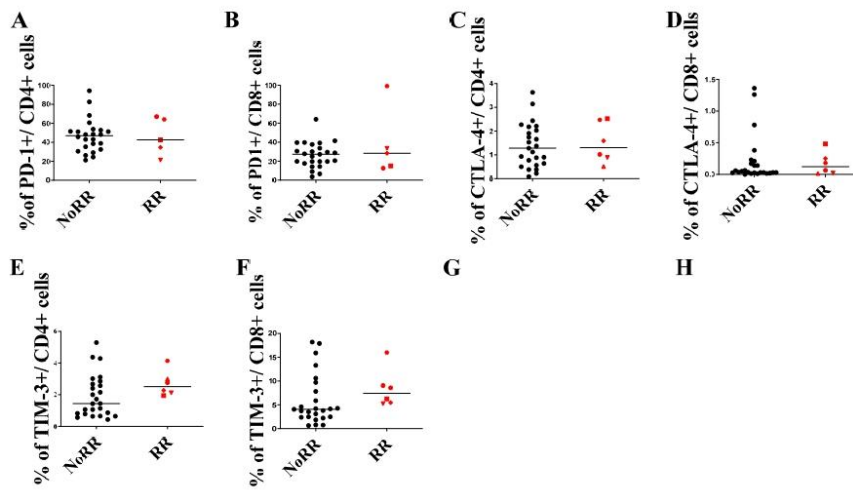


Figure S8. ICP expression at baseline are not different between the RR patients and the others. % at baseline of **A**, PD-1+ CD4+ T cells. **B**, PD-1+ CD8+ T cells. **C**, CTLA-4+ CD4+ T cells. **D**, CTLA-4+ CD8+ T cells. **E**, TIM-3+ CD4+ T cells. **F**, TIM-3+ CD8+ T cells. Highest fold change at C2 or C3 of **G**, CTLA-4+ CD4+ T cells. **H**, TIM-3+ CD4+ T cells. RR: patients with reservoir reduction, NoRR: patients without reservoir reduction. Experiments were monoplicates.

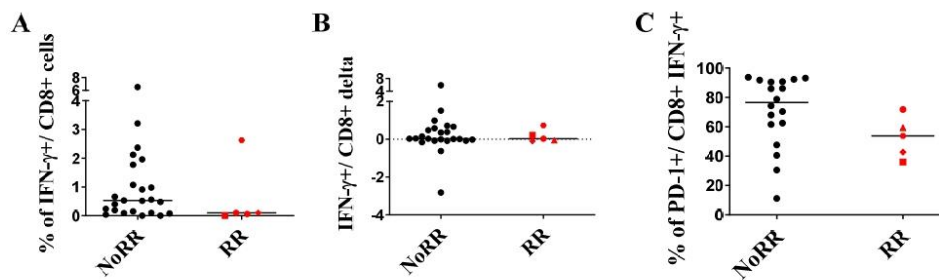


Figure S9. HIV-specific CD8+ T cells proportions at baseline and kinetics are not different between the RR patients and the others. HIV-specific CD8 + T cells are defines as IFN- γ producing CD8 + T cells. **A**, % of HIV-specific CD8+ T cells at baseline. **B**, HIV-specific CD8+ T cells best delta at C2 or C3. **C**, % of PD-1 on HIV-specific CD8+ T cells at baseline. RR: patients with reservoir reduction, NoRR: patients without reservoir reduction. Experiments were monoplicates.

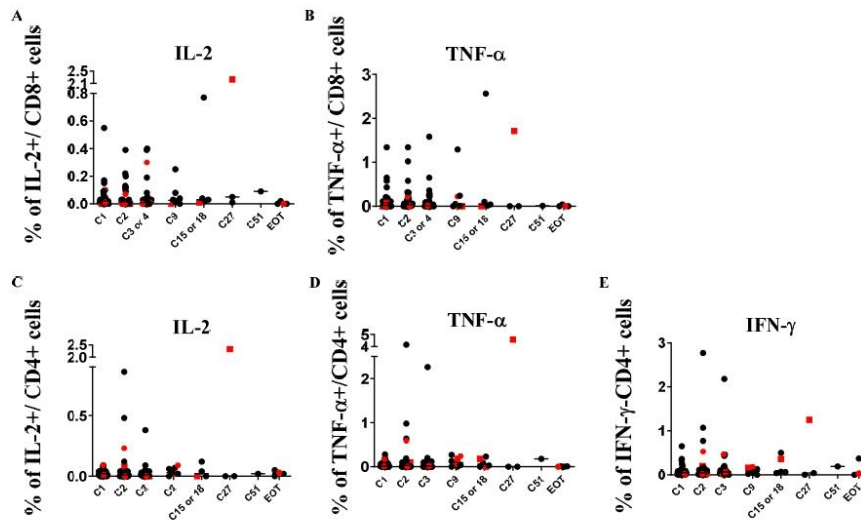


Figure S10. Intra-cellular cytokine expression after HIV-peptide stimulation is not modified under anti-PD-1 therapy. Thawed PBMC were stimulated during 6 hours with HIV peptides (15mers overlapping peptides covering RT, Nef and Gag) and incubated overnight. Then, they were stained with intra-cellular cytokine (IFN- γ , IL-2, TNF- α). % of **A**, IL-2+ CD8+ T cells. **B**, TNF- α + CD8+ T cells. **C**, IL-2+ CD4+ T cells. **D**, TNF- α + CD4+ T cells. **E**, IFN- γ + CD4+ T cells. Red symbols denote the 6 patients with reservoir reduction. Experiments were monoplicates.

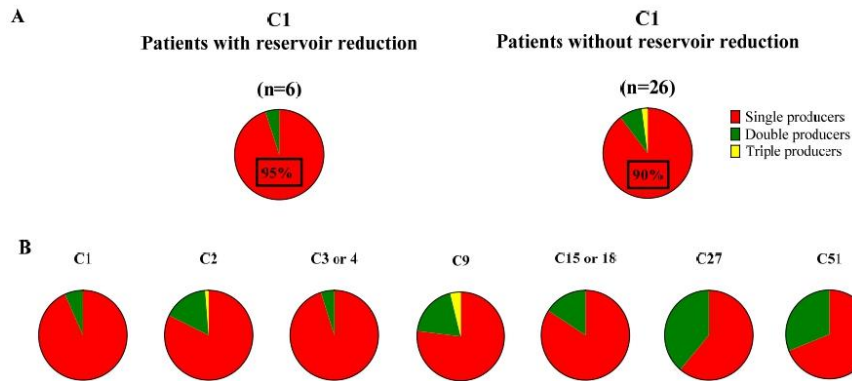


Figure S11. Polyfunctionality profile amongst HIV-specific CD8⁺ T cells is not modified under anti-PD-1 therapy. Cytokine production (IFN- γ , IL-2, TNF- α) was assessed with intracellular cytokine staining after stimulation during 6 hours with HIV-15mers overlapping peptides. **A**, Example dot plots of TNF- α + IFN- γ + CD8⁺ T cells. **B**, cytokine production profile at baseline in patients RR and NoRR. **C**, cytokine production profile for all patients overtime. Red pies represent the percentage of CD8⁺ T cells producing only 1 cytokine, green pies the percentage of CD8⁺ T cells producing 2 cytokines and yellow pies the percentage of CD8⁺ T cells producing 3 cytokines. Experiments were monoplicates.

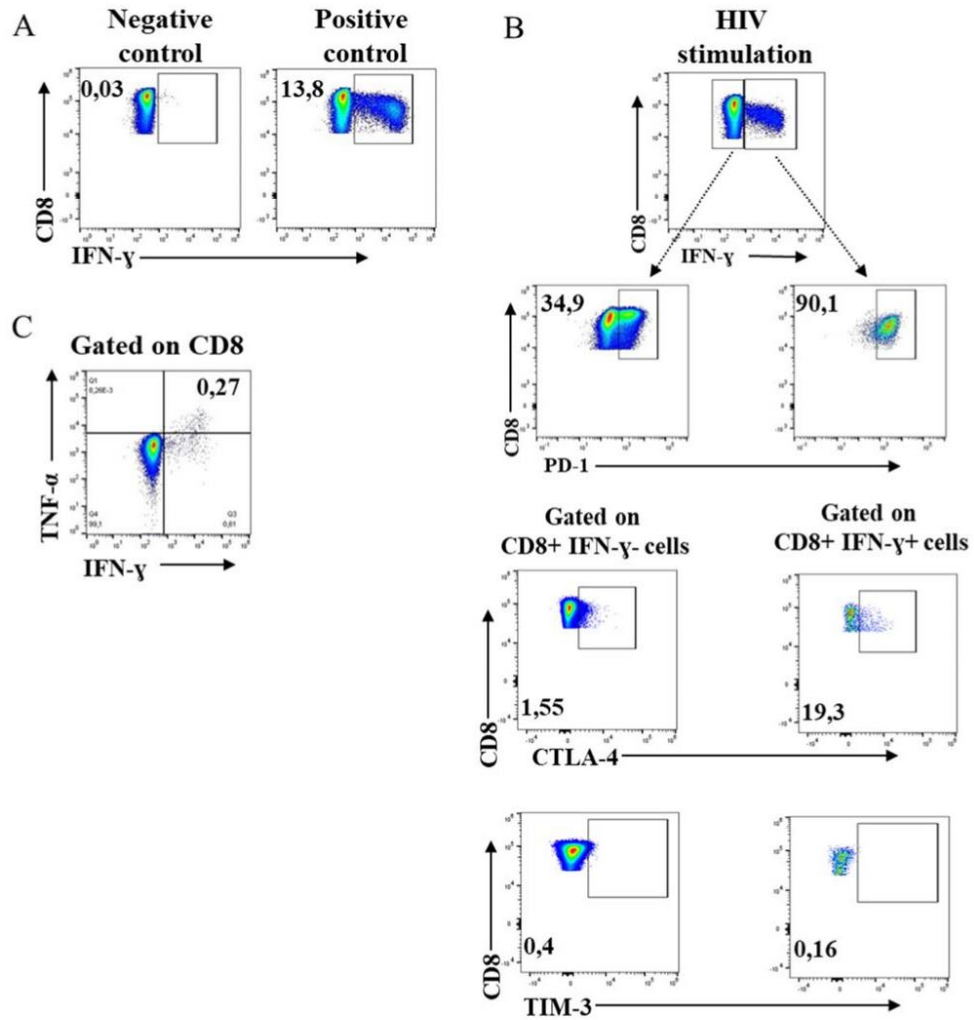


Figure S12. Example dot plots of A, IFN- γ + CD8+ T cells after stimulation with medium alone (negative control on the left) and with staphylococcal enterotoxin B toxin (positive control on the right). B, PD-1, CTLA-4 and TIM-3 expression among HIV non-specific (IFN- γ -) and HIV-specific (IFN- γ +) CD8+ T cells after HIV stimulation at baseline, of, C, CD8+ cells producing both IFN- γ and TNF- α . Experiments were monoplicates.

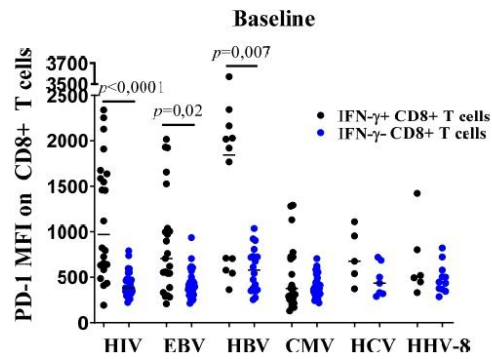


Figure S13. High levels of mean fluorescence intensity (MFI) are detected on HIV, EBV and HBV-specific CD8+ T cells baseline after viral stimulation. PD-1 MFI among specific (black spots) and non-specific (blue square) CD8+ T cells at baseline depending on viral (HIV, EBV, HBV, CMV, HCV and HHV-8) stimulations during 6 hours. Mann Whitney test. Experiments were monoplicates.

Conclusion et perspectives

Première partie. Paysage mutationnel, immunogénicité et microenvironnement tumoral des LNH B survenant dans un contexte d'immunodépression

Notre étude représente le premier travail ayant étudié en parallèle et de manière exhaustive (en partant du génome tumoral pour aller jusqu'au microenvironnement immunologique) le profil tumoral et l'immunogénicité des lymphomes B survenant dans un contexte d'immunosuppression, afin de caractériser l'ensemble des interactions présentes au sein du tissu tumoral. Nous avons initialement émis l'hypothèse que le statut d'immunodépression et/ou le statut EBV et/ou la localisation au sein du SNC pouvaient impacter ces différentes interactions. Nous démontrons finalement que la présence d'EBV influence à la fois la CMT et le profil mutationnel mais également l'immunogénicité et le MET des lymphomes.

Hétérogénéité de la cohorte. Nous assumons une certaine **hétérogénéité** de notre population de patients en terme de sous-types de lymphomes, de localisations (systémique et SNC) et de statuts immunologiques (IC, transplantés et VIH) qui peut influencer les différents paramètres étudiés. Cette hétérogénéité dans notre recrutement reflète **l'hétérogénéité de présentation** des lymphomes survenant dans un contexte d'ID, et les caractéristiques histopathologiques et cliniques de nos patients au diagnostic rejoignent les caractéristiques rapportées habituellement. Néanmoins, afin de procéder à nos analyses de la façon la plus rigoureuse possible et ne pas méconnaître notamment un biais lié aux sous-types histologiques, nous avons également décliné nos analyses dans le sous-groupe majoritaire des **lymphomes B à grandes cellules** (constitué à 94% de LBDGC) qui nous a permis de confirmer nos résultats trouvés dans l'ensemble de la cohorte. Pour ce qui est de la **localisation**, nous nous sommes attachés, à chaque étape, à décliner également les analyses en sous-groupes (systémique et SNC) sans mettre en évidence de différence particulière.

Charge mutationnelle tumorale. Nous avons démontré pour la première fois par une technique de séquençage de l'exome complet que la **CMT** des lymphomes EBV-positif était **moins élevée**

que celle des lymphomes EBV-négatif (ID ou IC), confirmant ainsi les données suggérées par les techniques de séquençage ciblé (Craig *et al*, 2007; Morscio *et al*, 2013; Yoon *et al*, 2015; Courville *et al*, 2016; Menter *et al*, 2017; Gandhi *et al*, 2021). Cette CMT était par ailleurs comparable au sein des lymphomes EBV-négatif entre IC, transplantés et VIH, témoignant du fait que **la diminution de la pression immunologique ne semblait pas avoir d'impact sur la CMT**. Ces résultats démontrent que la signalisation B médiée par l'EBV au sein des cellules tumorales est suffisante à la lymphomagenèse et diminue la nécessité de nouvelles mutations drivers. Cette notion de **plus faible instabilité génomique** et de diminution de mutations dans les gènes drivers a été questionnée récemment dans les LB EBV-positifs où le séquençage de LB EBV-positif (endémiques) et EBV-négatif (sporadiques) mettait en évidence un nombre de mutations non synonymes plus important dans les maladies EBV-positif (Grande *et al*, 2019). Néanmoins, cette différence était en partie expliquée par une surexpression d'AID, responsable d'une SHM aberrante dans les régions codantes et non codantes du génome, et des anomalies des voies de réparation MMR dans les LB EBV-positif. Par ailleurs, le nombre de mutations dans les gènes drivers récurrentement mutés dans les LB, tels que *SMARCA4*, *CCND3*, *ID3*, *TCF3*, était moins important dans les maladies EBV-positives (Grande *et al*, 2019; Chakravorty *et al*, 2019). Notre travail n'ayant pas étudié le génome dans son ensemble mais uniquement l'exome, nous n'avons pas pu statuer sur la possibilité d'une activité SHM aberrante dans les régions non codantes plus importante dans les lymphomes EBV-positif. Enfin, en lien avec cette CMT moins élevée dans les lymphomes EBV-positif, nous avons démontré un **nombre de néoépitopes** moins élevé également avec une forte **corrélation** positive entre CMT et nombre de néoépitopes, confirmant que chaque nouvelle mutation somatique augmente la possibilité de générer un nouvel néoépitope. De la même façon, la corrélation positive mise en évidence entre le nombre de néoépitopes prédits à partir des données de séquençage de l'ARN et ceux prédits à partir des données de séquençage de l'exome corrobore notre démarche à partir de l'exome en cas de matériel insuffisant et pourra être applicable plus facilement en routine.

Profil mutationnel. Grâce à notre recrutement de patients et à notre démarche systématique de comparaison entre les différents groupes, nous avons rapporté un profil mutationnel spécifique à la fois du statut EBV et du statut immunologique. Nous avons démontré pour la première fois que les mutations de *STAT3* étaient associées non pas à la présence d'EBV mais à une situation **d'immunodépression** (fréquemment associée à la présence d'EBV elle-même). En effet, *STAT3* était muté uniquement chez les patient ID (25%), transplantés ou VIH, indépendamment de leur statut EBV (EBV positif ou négatif), tandis qu'aucune mutation n'était retrouvée chez

les patients IC. La protéine STAT3 est impliquée dans différentes voies de signalisation clé des lymphocytes B. Les mutations de *STAT3* sont rares dans les LBDGC de l'IC, comptant pour moins de 5% des cas, mais ont été rapportées dans presque la moitié des cas des lymphomes polymorphes et de lymphomes plasmablastiques EBV-positif (survenant tous chez des patients ID) (Reddy *et al*, 2017; Liu *et al*, 2020; Chapman *et al*, 2021; Sarkozy *et al*, 2021; Ramis-Zaldivar *et al*, 2021), alors que très peu de données étaient disponibles dans le contexte des LPT indépendamment de leur statut EBV (Leeman-Neill *et al*, 2022). Grâce à nos analyses en sous-groupes, il est désormais établi que ces mutations sont associées à la présence d'une **immunodéficience** (associée ou non à l'EBV) et cela suggère que la stimulation immunologique chronique par le biais des alloantigènes de la transplantation ou des protéines virales pourrait faciliter l'apparition de mutations de *STAT3*. Ces résultats soulignent le potentiel de développement d'inhibiteurs de JAK à visée thérapeutique. *TYWI* est quant à lui un gène très peu fréquemment muté dans les lymphomes et sans rôle particulier, dont la signification devra être ré-interrogée. La présence d'EBV était quant à elle associée à une fréquence élevée des mutations d'*HNRNPF* (20%), qui n'étaient retrouvées dans aucune tumeur EBV-négative, et qui sont habituellement présentes dans moins de 2% des LBDGC de l'IC. Ce constat est réminiscent de données antérieures ayant montré que d'autres ribonucléoprotéines de la même famille hnRNPK pouvaient se lier à EBNA2 et augmenter l'expression de LMP2A (Gross *et al*, 2012). Enfin, nous avons confirmé l'absence des mutations de gènes impliqués dans la signalisation du BCR, le cycle cellulaire ou encore l'apoptose, tels que *MYD78*, *CD79B*, *PIMI* et *TP53* confirmant les données antérieures de séquençage ciblé. (Menter *et al*, 2017; Gandhi *et al*, 2021).

Choix des paramètres d'analyses de l'immunogénicité. La prédiction des néoépitopes *in silico* a fait un appel à un **pipeline bio-informatique robuste** que nous avons développé pour ce travail. A des fins de définition des néoépitopes d'une tumeur, une autre technique, appelée technique de caractérisation de **l'immunopeptidome** (ou encore HLA ligandome) peut être utilisée. Elle consiste à identifier les complexes peptides-CMH exprimés à la surface des cellules afin d'isoler les peptides en question par une technique de chromatographie et de spectrométrie de masse. Les peptides extraits constituent donc « l'immunopeptidome » d'un tissu et peuvent ensuite être filtrés par des databases afin de ne garder que les peptides tumoraux mutés. Cette technique a l'immense avantage d'apporter une **preuve directe de l'interaction** du peptide avec le CMH et de n'identifier donc que les peptides effectivement présentés. Par ailleurs, elle permet également d'identifier les peptides issus de **modifications post-**

transcriptionnelles comme la glycosylation ou encore la phosphorylation (cf **Figure 8**). Néanmoins, elle présente une **limitation** claire: sa lourdeur expérimentale et les différentes étapes de purification et d'éluion sont responsables de nombreuses pertes et le rendement est estimé à 0.5-3% (Hassan *et al*, 2014). Afin de contrebalancer ce faible rendement, des quantités très importantes de tissu congelé sont nécessaires, qui empêchent souvent la réalisation de cette technique. Dans ces conditions, nous avons pris le parti de définir les néoépitopes *in silico* à partir des données de séquençage, d'autant que le séquençage permettait par ailleurs les analyses tumorales et du MET, en assumant le fait que nous n'avions pas de « preuve » de la présentation antigénique effective. Nous avons choisi les paramètres immunologiques les plus pertinents pour décider des **filtres** intervenant dans la prédiction des néoépitopes. Actuellement, le choix des filtres reste assez différent en fonction des équipes avec un **manque d'uniformité** au niveau international, et de rentabilité (Wells *et al*, 2020; Kishton *et al*, 2020; McGranahan & Swanton, 2019; De Mattos-Arruda *et al*, 2020a). Ainsi, Wells et al ont rapporté, dans un très élégant travail, un **consortium de 28 équipes** ayant accès aux prélèvements tumoraux de patients identiques afin d'utiliser leur pipeline propre de prédiction de néoépitopes pour définir les néoépitopes présentés par le CMH-I (Wells *et al*, 2020). Les néoépitopes sélectionnés étaient ensuite testés pour leur immunogénicité *in vitro*. Seulement 6% des néoépitopes étaient effectivement validés fonctionnellement et le taux médian de chevauchement des néoépitopes prédits entre les différentes équipes étaient seulement de 13%, soulignant la très grande hétérogénéité des différentes procédures. Par ailleurs, Wells démontrait que le score **d'affinité** (majoritairement inférieur à 100 nM), « **l'abondance tumorale** » (illustrant l'expression des néoépitopes, et majoritairement supérieure à 10 TPM), la **stabilité** de l'interaction CMH-peptide (majoritairement supérieure à 1 heure) et un paramètre impliqué dans la **reconnaissance** du complexe peptide-CMH par les lymphocytes T (**l'agrétopicité** estimée par le ratio d'affinité du peptide muté sur le sauvage) étaient **4 filtres** particulièrement importants pour différencier les néoépitopes immunogènes des non-immunogènes, et un score avec des seuils (affinité < 34 nM, expression > 33 TPM et stabilité > 1.4 h) était proposé. Au début de ce travail, nous avons défini **nos paramètres** ainsi : VAF > 10%, affinité < 500 nM, expression > 1 TPM +/- score de stabilité élevé, et nous avons fait intervenir l'expression des molécules du CMH et de la B2M afin d'éliminer les peptides qui ne pouvaient pas être présentés. Quoique les néoépitopes issus de mutations clonales (+/- drivers) ne soient ni les plus fréquents ni les meilleurs en termes de qualité, nous avons fait intervenir le filtre de la VAF dans l'hypothèse du développement de traitements ciblés dirigés contre les néoépitopes. En effet, les stratégies

dirigées contre les néoépitopes clonaux permettent à la fois de cibler l'ensemble de la population tumorale et d'être à priori « partageables » entre différents patients. Dans l'avenir, il faudrait probablement incorporer systématiquement le filtre de stabilité et introduire un paramètre d'agrément afin d'être plus à même de caractériser les néoépitopes les plus immunogènes.

Réponses T spécifiques anti-néoépitopes. Grâce à notre validation fonctionnelle, nous avons démontré que 71% des 14 patients testés avaient une **réponse T spécifique dirigée** contre des néoépitopes en dépit de leur statut d'immunodépression et/ou d'une localisation dans un sanctuaire immunologique tel que le SNC. La tendance à une **plus faible réponse** dans le groupe des lymphomes EBV-positif reflète soit le nombre de néoépitopes moins important dans les lymphomes EBV-positif soit une forte immunodominance de l'EBV. Nous n'avons pas été en mesure d'analyser les réponses T anti-EBV pour répondre à cette question par manque de cellules. Par ailleurs, nous avons confirmé que les néoépitopes dérivés des *IgH* étaient immunogènes et probablement immunodominants, et qu'ils étaient majoritairement présentés par le CMH-II. Cette constatation renforce l'idée que des **stratégies thérapeutiques futures** pourraient faire intervenir des vaccinations anti-idiotypes médiées par les lymphocytes CD4+. A l'inverse, nous n'avons pas mis en évidence de **néoépitopes immunogènes partagés** entres les 14 patients testés, empêchant l'idée de développer des thérapeutiques anti néoépitopes partagés ainsi que dans d'autres cancers (Platten *et al*, 2021; Chandran *et al*, 2022; Hsiue *et al*, 2021; Poole *et al*, 2022). Pour les patients sans réponse T spécifique détectable, plusieurs hypothèses peuvent être émises : échec de prédiction des néoépitopes, absence de présentation des néoépitopes au niveau tumoral ou absence de lymphocytes T spécifiques en regard. Enfin, les **paramètres immunologiques** individuels (VAF, expression, affinité, stabilité) des néoépitopes effectivement immunogènes n'ont pas pu être définis en raison d'un nombre insuffisant de cellules qui nous a empêché de tester les peptides individuellement dans la majorité des cas. Néanmoins, le projet Idéation proposait d'étudier également d'autres tumeurs que les lymphomes et l'ensemble des filtres immunologiques, des critères de sélection des néoépitopes, du protocole expérimental de co-culture et d'expansion, et de la validation fonctionnelle ont été développés par mes soins initialement autour des **glioblastomes**. J'ai réalisé la validation fonctionnelle de 18 patients avec glioblastomes, avec mise en évidence de réponses T spécifiques des néoépitopes dans 72% des cas. Il est important de noter à cet endroit que les réponses T spécifiques étaient rapportées beaucoup plus fréquemment chez les patients naïfs de traitement (100%) comparé aux patients en cours de traitement par chimiothérapie

(n=29%). Dans ce contexte tumoral, où les CMNS étaient le plus souvent beaucoup plus nombreuses que pour les patients avec lymphomes, j'ai pu tester les peptides individuellement pour 10 patients et nous sommes en train d'analyser, en étroite collaboration avec les neuro-oncologues, les résultats afin de caractériser quels paramètres immunologiques sont les plus à même de prédire la présence d'une réponse T spécifique. Dans le contexte des lymphomes, un prochain travail avec un nombre de cellules plus important disponible devrait nous permettre de répondre à cette question. nt,

Microenvironnement tumoral. Notre analyse du MET (répertoire, population cellulaire et expression génique) a montré que les lymphomes B EBV-positif étaient associés à un **infiltrat T plus riche**, témoignant probablement du recrutement de lymphocytes T anti-viraux, mais sans caractéristique de répertoire particulières. Par ailleurs, la fréquence de **populations régulatrices** telles que les lymphocytes T régulateurs, les macrophages de type M2 et les cellules NK quiescentes était plus élevée dans les lymphomes EBV-positif, et il existait une tendance à la surexpression des gènes impliqués dans une **immunorégulation négative**. L'ensemble de ces données confirmaient que l'EBV pouvait promouvoir un MET plus **tolérogène**. Il est important de rappeler à cet effet que les manipulations réalisées *in vitro* de validation fonctionnelle ne reproduisent pas les différentes interactions et les éventuels signaux négatifs présents au sein du MET et que de ce fait la présence d'une réponse T périphérique spécifique des néoépitopes ne coïncide pas forcément avec une réponse T anti-tumorale efficace au niveau tumoral. Ces résultats suggèrent que le MET pourrait également être une cible **d'intervention thérapeutique** à venir afin de faciliter la réponse anti-tumorale. Les ICPI pourraient évidemment être envisagés mais l'utilisation de ces traitements dans un contexte de transplantation d'organe est associée à des rejets dans environ 30% des cas (fréquence dépendant du type de transplantation). En revanche, il n'existe aucune contre-indication particulière dans le contexte de l'infection par le VIH, au cours de laquelle la tolérance et l'efficacité anti-tumorale de ce type de traitement ont d'ores et déjà été largement décrites (Uldrick *et al*, 2019).

Immunoédition et SNC. Nous avons émis l'hypothèse au début de ce travail que le statut immunologique (IC ou ID) des patients atteints de lymphome pourrait avoir un impact sur l'immunogénomique, et notamment sur la charge mutationnelle tumorale et le MET. En effet, le principe d'immunoédition, et donc d'interactions permanentes entre cellules tumorales et système immunitaire modulant la tumeur pouvait suggérer une CMT moins élevée et un MET

moins tolérogène chez les patients ID. Néanmoins, à l'exception d'un infiltrat T plus élevé chez les patients ID, il n'existait pas de différence entre patients ID et IC, et ce même lorsque nous comparions les ID et les IC au sein des tumeurs EBV-négative afin de s'affranchir des biais de l'EBV. De la même façon, la localisation au sein du SNC ne semblait pas avoir d'impact particulier sur ces différents paramètres par rapport à la localisation systémique. Nous pouvons émettre l'hypothèse que le poids de l'EBV est tel qu'il « écrase » les autres comportements tumoraux.

Au total, nous présentons ici les résultats d'une étude immunogénomique exhaustive des lymphomes survenant dans un contexte d'immunosuppression, en partant de la tumeur, en passant par les réponses T spécifique et en finissant avec le MET. Nous avons démontré l'influence majeure de l'EBV sur la CMT, le nombre de néoépitopes, la réponse T spécifique périphérique et le MET, qui pourrait suggérer une adaptation des traitements au statut EBV. Nous rapportons pour la première fois une fréquence élevée et exclusive des mutations de *STAT3* dans le groupe des patients ID, qui suggère le développement de traitement ciblé contre la signalisation JAK/ STAT dans ce type de tumeurs. Enfin, la caractérisation de réponses T CD4+ spécifiques dirigées contre les *IgH* ouvre le chemin au développement de thérapeutiques ciblées.

Seconde partie. Impact des inhibiteurs de PD-1 (PD-1I) sur l'immunité T anti-virale et sur le réservoir VIH chez les PVVIH atteintes de cancer

Notre étude représente le seul travail ayant étudié en parallèle immunité anti-virale et réservoir VIH, et avec le plus long suivi publié jusqu'ici, afin de documenter précisément les différents mécanismes d'action des ICPi sur l'infection par le VIH. Ce projet a été construit alors qu'il existait des données *in vitro* et *in vivo* suggérant un effet « shock and kill » des ICPi dans l'infection par le VIH. En particulier, mon laboratoire d'accueil avait décrit une diminution jusqu'au seuil d'indélectabilité du réservoir VIH pendant plus d'un an (données mises à jour secondairement) chez un patient traité par anticorps anti-PD-1 pour un cancer du poumon (Guihot *et al*, 2018). Ces différentes observations nécessitaient la mise en place d'une cohorte de validation.

Diminution du réservoir et sur-expression des ICP. Nous avons démontré qu'il existait une **diminution précoce, modérée** (fold change à 1.9) et **transitoire** du réservoir VIH survenant après la première injection d'ICPi et sans augmentation de la charge virale VIH par ailleurs. Nos résultats rejoignent en partie ceux des 2 autres études publiées en parallèle de notre travail chez des PVVIH traitées pour des cancers (Rasmussen *et al*, 2021; Uldrick *et al*, 2022). Le travail d'Uldrick, publié en 2022, rapportait l'impact d'un traitement par pembrolizumab sur l'infection par le VIH chez 32 PVVIH traitées pour un cancer et avec une charge virale VIH indétectable pour 29 d'entre elles (et = à 21, 21 et 168 cp/mL pour les 3 restantes). Une diminution modérée et transitoire de l'ADN VIH à J2 (fold change= 0.78) associée à une augmentation modérée et transitoire de l'ARN VIH associé aux cellules à J8 étaient notées, suggérant qu'un traitement par anti PD-1 pouvait effectivement inverser la latence. Le travail de Rasmussen, publié quant à lui en 2021, rapportait chez 33 PVVIH avec une charge virale VIH indétectable et traitées par nivolumab une diminution transitoire de l'ADN VIH (-45%) à J2 sans modification de l'ARN VIH associé aux cellules par ailleurs. Dans notre cohorte de patients, l'évaluation de l'expression **d'autres ICP tels que CTLA-4 et TIM-3** nous a permis de mettre en évidence une augmentation modérée et transitoire de leur expression (quoique non significative pour TIM-3) à la surface des LT après la première injection d'ICPi. Cette observation était consistante avec la démonstration d'une surexpression de LAG-3 dans le microenvironnement tumoral de patients traités par anti-PD-1 pour un lymphome de Hodgkin (Michot *et al*, 2021). Dans notre cohorte, cette surexpression était d'autant plus marquée chez les patients non-répondeurs suggérant fortement, et pour la première fois, que ces **mécanismes de compensation** pourraient participer à l'absence d'efficacité des ICPi sur l'infection par le VIH chez ces patients. En parallèle, l'équipe de Rasmussen a également rapporté l'impact d'une bithérapie de type nivolumab + ipililumab chez 7 PVVIH traités pour un cancer et avec une CV VIH indétectable (Rasmussen *et al*, 2021). Il était noté une augmentation modérée et transitoire de l'ARN VIH associé aux cellules (fold change 1.44) à J2 spécifiquement dans ce groupe de patients, suggérant effectivement une augmentation plus importante de l'activité transcriptionnelle comparée à la monothérapie. De la même façon, un test fonctionnel réalisé par QVOA au cycle 16 ou à la fin du traitement chez 2 patients traités par bithérapie témoignait d'une nette diminution du réservoir inductible tandis qu'aucune diminution significative n'était notée pour le groupe de patients traités en monothérapie (n= 8). Nos observations ainsi que ces résultats rapportés récemment, quoique sur un très petit groupe de patients, pourraient suggérer l'utilisation d'une **bithérapie d'ICPi** afin d'en augmenter l'impact sur l'infection par le VIH.

Néanmoins, bien que la fréquence de survenue d'effets secondaires des ICPi est identique entre PVVIH et patients non infectés, la bithérapie d'ICPi en augmente très clairement le risque. Et il est important de rappeler que la **tolérance** vis-à-vis des effets secondaires de grade>3 doit être très basse dans une population de patients sous ARV avec une bonne qualité de vie et une espérance de vie équivalente à la population générale (Uldrick *et al*, 2019). D'autres études seront nécessaire pour déterminer si la toxicité pourrait être diminuée, sans modifier l'efficacité, notamment en diminuant le nombre d'injections ainsi que suggéré récemment par un essai clinique proposant une seule et unique injection de nivolumab dans le contexte de l'hépatite B chronique (Gay *et al*, 2017).

Mesure du réservoir. Le réservoir VIH est retrouvé majoritairement dans les lymphocytes T CD4+, plus particulièrement dans les CD4 mémoires et dans les tissus périphériques, et avec une distribution non homogène (les lymphocytes sanguins ne représentant que 1 à 2% des lymphocytes totaux). On estime que 1/ 10⁵-10⁸ lymphocytes T CD4+ est réservoir, ce qui représente une quantité d'environ 10⁴-10⁷ lymphocytes T CD4+ réservoir pour l'ensemble de l'organisme (en assumant un chiffre total de lymphocytes de 10¹¹ T CD4+) (Strain *et al*, 2005; Zhang *et al*, 1998). Le réservoir est par ailleurs constitué de 95% d'ADN défectif muté qui ne peut pas être transcrit en ARN et de 2 à 5% % d'ADN non défectif (ou **intact**) capable de transcription, de traduction puis de production de virion (Massanella & Richman, 2016; Chomont *et al*, 2009; Bruner *et al*, 2016; Zerbato *et al*, 2019; Bruner *et al*, 2019). C'est ce réservoir non défectif qui fait obstacle à l'« HIV cure » et qui doit être l'objet des stratégies du « shock and kill ». Différentes techniques d'analyse du réservoir sont actuellement disponibles : des analyses « **fonctionnelles** » mesurant le réservoir capable de transcription (Tat/Rev induced dilution assay, ou TILDA) ou de réplication (Quantitative Viral Outgrowth Assay, ou QVOA) et des analyses **non fonctionnelles** de type Intact Proviral DNA Assay (ou IPDA) capable de mesurer l'ADN intact, ou encore la mesure de l'ADN VIH total ou intégré ou de l'ARN VIH associé aux cellules (Massanella & Richman, 2016; Chen *et al*, 2022). Au sein de notre cohorte, le réservoir a été quantifié par la mesure de **l'ADN VIH total sur cellules non triées**. Ce test est probablement critiquable car il ne permet notamment pas de distinguer l'ADN défectif de l'ADN non défectif potentiellement mobilisable mais il a été choisi du fait d'un coût économique, d'un temps de technique et d'un volume de sang acceptables, et ce d'autant plus que les analyses immunologiques réalisées en parallèle nécessitaient déjà des volumes sanguins importants. Ce point a pu participer à la sous-estimation de l'impact du traitement sur le réservoir VIH intact. Pour les même raisons, nous n'avons pas étudié **l'activité**

transcriptionnelle du réservoir (mesure de l'ARN VIH associé aux cellules) qui nous aurait permis d'avoir une description mécanistique plus fine mais nous assumons le fait que l'objectif final de notre d'approche était avant tout chose la réduction du réservoir (et donc la quantification de l'ADN VIH). Enfin, la stabilité du taux de CD4 au cours du temps pour nos 31 patients nous a permis d'analyser la mesure de l'ADN VIH malgré le fait qu'il ne soit pas rapporté aux taux de CD4 individuels des patients. En effet, une diminution du nombre des lymphocytes après traitement par anti-PD-1, suggérant des phénomènes de migration tissulaire, a d'ores et déjà été décrit (Gardiner *et al*, 2013).

Population d'étude. Par ailleurs, notre population d'étude de PVVIH, ainsi que les populations rapportées par Uldrick et Rasmussen, était différente en termes immuno-virologiques de la population de macaques SIV+ au sein de laquelle avait été démontré initialement un bénéfice virologique et/ou clinique après traitement par ICPi (Velu *et al*, 2009; Uldrick *et al*, 2022; Rasmussen *et al*, 2021; Abbar *et al*, 2020; Gill *et al*, 2016; Seung *et al*, 2013; Palmer *et al*, 2013). En effet, nos patients, traités pour la plupart depuis des années par ARV (temps médian entre le diagnostic de l'infection et du cancer=31 ans, taux de CD4 médian au traitement par ICPi= 369/mm³), étaient caractérisés par une **charge virale VIH indétectable** pour 24/32 patients et la médiane de charge virale était de 45 cp/mL pour les 7 autres patients détectables. Dans ce contexte, le **réservoir VIH était inférieur** au seuil de détection de la technique utilisée (< 40 cps/10⁶ cellules) pour 6 patients et inférieur à 150 cp/10⁶ cellules pour 6 patients supplémentaires au J0 du début du traitement, «ne permettant donc pas » de réduction de plus de 0.5 log₁₀ du réservoir pour ces 12 patients au total. Cette particularité a pu participer à la **minoration** de l'efficacité des ICPi sur le réservoir VIH. De la même façon, nous pouvons émettre l'hypothèse que la faible charge antigénique virale et la poursuite des traitements **ARV** en parallèle des ICPi ont gêné la stimulation immunologique en regard ainsi qu'en témoigne l'absence d'augmentation des lymphocytes T spécifiques du VIH après le traitement. Enfin, **l'altération du système immunitaire** de nos patients, en raison du cancer et des traitements anti-tumoraux utilisés antérieurement pour la majorité de nos patients (26/32 patients), a pu également participer à une diminution de l'impact des traitements sur l'infection par le VIH. L'ensemble de ces considérations pourraient suggérer l'utilisation des ICPi chez des PVVIH sans cancer et/ou avec un mauvais contrôle immuno-virologique, voire non traitées par ARV sur une certaine période. A notre connaissance, une seule équipe a proposé dans le cadre d'un essai de phase 1 randomisé un traitement par une seule injection d'anticorps anti-PDL-1 (BMS-936559) dans une petite cohorte de 6 (bras avec traitement) + 2 (bras placebo) PVVIH sans

cancer avec une charge virale VIH indétectable et des $CD4 > 350/mm^3$ avant traitement, avec un suivi de 48 semaines (Gay *et al*, 2017). La cohorte d'escalade de dose n'a pas été réalisée en raison d'une toxicité rétinienne survenue en parallèle chez des macaques traités avec des doses supérieures. Il était noté, pour les 6 patients traités avec une posologie de 0.3 mg/kg, une augmentation transitoire plus importante des lymphocytes T spécifiques du VIH, quoique non significative, à J28 comparé aux patients traités par placebo, et majoritairement médiée par 2 patients. Néanmoins, il n'existait pas de modification de l'ARN et de l'ADN VIH associé aux cellules chez ces 6 patients traités et il est difficile d'émettre des conclusions avec ces doses peu importantes d'anticorps thérapeutiques utilisés. D'autres études seront donc nécessaires pour conclure quant à l'efficacité des ICPI sur l'infection par le VIH chez des PVVIH mal ou non contrôlés par ARV et/ ou sans cancers.

Profil des patients répondeurs. Nous avons isolé au sein de notre cohorte **6 patients** ayant démontré une diminution de plus de $0.5 \log_{10}$ du réservoir VIH au moins une fois au cours du traitement. Au sein de ces 6 patients, 3 avaient une diminution persistante ≥ 4 mois (patient.#7, #14 et #21, avec un suivi à 14, 6 et 4 mois respectivement). Nous n'avons pas réussi à mettre en évidence de différences, entre les patients répondeurs et non répondeurs, en termes de paramètres immuno-virologiques (excepté un ADN VIH plus important chez les patients répondeurs au J0), de marqueurs d'activation, d'expression des ICP et de fréquence des LT spécifiques du VIH au J0 et/ou en termes de cinétique après ICPI. Néanmoins, il est intéressant de noter que les 3 patients répondeurs persistants présentaient une expression des différents marqueurs d'activation la plus élevée au J0 ou en termes de cinétique, et que le patient #14 avait un des taux de $CD4 (888/mm^3)$ les plus élevés et une quantification du réservoir la plus élevée au J0 ($1749/10^6$ cellules). De la même façon, le patient #21 présentait l'expression de PD-1 à la surface des LT $CD8+$ la plus élevée de la cohorte au J0. Ces observations suggèrent qu'un état d'activation élevé avant traitement et/ou une activation importante du système immunitaire sous traitement pourraient avoir un impact sur l'efficacité des ICPI mais elles devront être confirmées par des études ultérieures. Enfin, nous n'avons pas pu évaluer les liens de corrélation éventuels entre « réponse virale » (réduction du réservoir VIH) et réponse anti-tumorale car les données de réponse anti-tumorale étaient disponibles uniquement pour les patients répondeurs ($n=6$). Néanmoins, le traitement par ICPI a été arrêté en raison d'une progression tumorale chez 4 de nos 6 patients répondeurs, ce qui semble infirmer la possibilité d'une corrélation entre ces 2 paramètres. De la même façon, il n'existait pas de différence de durée de traitement entre les patients répondeurs et les non répondeurs, suggérant une durée de réponse au traitement

similaire entre les 2 groupes, la majorité des patients ayant arrêté le traitement pour progression dans les 2 groupes (79% pour toute la population, 67% pour les RR et 83% pour les NoRR).

Disponibilité des ICPI. Nous pouvons nous interroger sur l'efficacité des ICPI dans la mobilisation du réservoir pour les cellules macrophagiques de type microglie présentes au niveau du SNC. En effet, l'utilisation « classique » des ICPI à visée de restauration d'une immunité anti-tumorale ou anti-virale ne nécessite pas le **passage de l'anticorps monoclonal thérapeutique à travers la barrière hémato-encéphalique (BHE)**. L'anticorps monoclonal se fixe sur les lymphocytes de l'organisme qui peuvent ensuite migrer au sein des tissus tumoraux ou infectés. De fait, ils ont d'ores et déjà prouvé leur efficacité dans le traitement des métastases cérébrales de cancers broncho-pulmonaires ou rénaux, ou encore de la leuco-encéphalopathie multifocale progressive (Medikonda *et al*, 2023; Uzunov *et al*, 2020; Cortese *et al*, 2019; Beck & Cortese, 2020; Peng *et al*, 2021). La survenue d'effets secondaires immunologiquement médiés au niveau du SNC sous ICPI, quoique rares, tels que des encéphalites, des méningo-encéphalites, des ataxies cérébelleuses ou encore des hypophysites renforcent également ces affirmations (Martins *et al*, 2019; Valencia-Sanchez *et al*, 2023). En revanche, l'action supposée de ces traitements sur le réservoir VIH avec l'étape du « shock » nécessite une liaison directe de l'anticorps sur les cellules en question, et donc un passage de la BHE, non altérée par ailleurs, dans le contexte des cellules réservoir microgliales. A notre connaissance, il n'y a pas de travaux ayant étudié la fixation des anticorps monoclonaux dans ces tissus particuliers, notamment en raison de son accessibilité difficile et il est donc difficile de conclure quant à la distribution des ICPI dans ces tissus (Kapoor & Tan, 2020).

Au total, nous avons démontré que les anticorps anti-PD-1 utilisés en monothérapie chez les PVVIH avec un cancer avaient un impact limité sur le réservoir VIH et l'immunité anti-virale. Cet impact limité peut notamment s'expliquer par la présence de mécanismes compensatoires de surexpression des autres ICP suggérant l'utilisation de bithérapies sous réserve d'une toxicité acceptable, ou par une infection virale trop bien contrôlée qui pourrait suggérer de tester ces traitements dans une population de PVVIH non traitées par ailleurs.

Pour conclure, ces 2 travaux ont été menés dans des populations de patients **immunodéprimés** (transplantés d'organe ou VIH) afin d'étudier, dans ces contextes immunologiques particuliers, la capacité des patients à développer une réponse immune dirigée respectivement contre des **antigènes tumoraux**, et des **antigènes viraux** en situation d'ICPI. Nos résultats démontrent

notamment, malgré la situation d'immunodépression, la présence d'une réponse immune de moyenne amplitude contre les antigènes tumoraux, et sans possibilité d'amplification par les ICPI en monothérapie contre les antigènes viraux. La démonstration de l'implication importante de l'**EBV** dans l'immunogénicité des tumeurs (profil mutationnel, nombre de néoépitopes, MET et réponses T spécifiques), nous a notamment conduit à développer un nouveau projet de recherche autour du microenvironnement tumoral des LPT et des LNH du VIH afin d'étudier les différentes populations cellulaires par cytométrie de masse au diagnostic et à la rechute. Ce projet nous permettra de caractériser des marqueurs de résistance et/ou de réponse aux traitements qui pourront être ciblés à visée thérapeutique.

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Annexes

Annexe 1. Immune checkpoint inhibitors in people living with HIV: what about anti-HIV effects? Article de revue en tant que second auteur, 2019.

Immune checkpoint inhibitors in people living with HIV: what about anti-HIV effects?

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Immune checkpoint inhibitors (ICPi) have shown major therapeutic successes when used in various cancers. In the HIV field a double benefit of such ICPi should result from their dual ability to restore in-vitro HIV-specific CD8⁺ T-cell functions and to enhance HIV production from reservoir cells, thus fulfilling the goals of the 'shock and kill' concept proposed as an HIV cure therapeutic strategy. We conducted a systematic review to identify studies reporting the tolerance profile of ICPi and their effects on HIV plasma loads (pVL), CD4⁺ cell count, HIV reservoirs (cell-associated HIV-DNA) and/or HIV-specific CD8⁺ T cells in PLWH. Thirty-one articles were included for a total 176 participants. Twelve percent of the participants experienced severe adverse events and 49% nonsevere adverse events. pVL remained stable in 91.9% participant, showed increases in 5.8% participant, and decreases in 2.3%. CD4⁺ cell count remained stable in 60.7% participants, showed increases in 24.6%, and decreases in 14.7%. Regarding ICPi effects on HIV-DNA and HIV-specific immunity, we identified three distinct profiles: profile I, transient pVL increases followed by a boost in HIV-specific CD8⁺ T cells concomitant to a decrease in HIV-DNA, reported in one participant. Profile II: increase in HIV-specific CD8⁺ T cells without changes in pVL or HIV-DNA, reported in three participants. III: no effect, reported in five participants. In conclusion, the clinical, virological and immunological safety profiles of ICPi reported in about 200 PLWH appear to be favorable but there are still modest results in terms of HIV cure strategy.

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Introduction

High performance of combined antiretroviral therapies (cART) on suppressing HIV replication has led to massive improvement in survival and prevention of transmission. As no clear strategy to maintain viral suppression without antiretroviral therapy is yet at hand, a long-life cART is mandatory with the consequent issues of long-term

fatigue of therapy, toxicity, drug supplies, and cost. Therefore, HIV cure remains the biggest expectation from people living with HIV (PLWH) and one of the strongest challenges in curative therapy for this persistent retroviral infection [1]. The major obstacle to HIV cure is the life-long persistence of HIV reservoirs composed of proviral genomes integrated in several compartments of latently infected CD4⁺ cells [2–4]. Various mechanisms

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are at play among which silencing of viral transcription in host CD4⁺ T cells [5–7] plays a key role whereas a persisting low-level viral replication in tissues might also contribute to permanently reseeding HIV reservoirs [8,9]. Such inducible and replication-competent HIV reservoirs are preferentially harbored by CD4⁺ T cells over-expressing immune check-points (ICPs) [10,11] in which levels of integrated HIV-DNA strongly correlate with the combined ICP expression [4]. Indeed, chronically activated exhausted T lymphocytes over-express ICPs, such as programmed cell death-1 (PD-1), cytotoxic lymphocyte antigen-4 (CTLA4), T-cell immunoglobulin and mucin-domain-containing 3 (TIM3), lymphocyte-activation gene 3 (LAG3) and T-cell immune receptor with Ig and ITIM domains (TIGIT). Engagement of PD-1 or others, down-regulates T-cell proliferation and functions [12] and inhibits in-vitro viral replication in infected cells [13,14]. Importantly the over-expression of PD-1 and CTLA-4, used as markers of T-cell exhaustion and HIV disease progression, partially regresses under cART [15–18].

Monoclonal antibodies antagonizing those ICPs potently restore exhausted T-cell functions and have shown major therapeutic successes when used in various cancers [19–22]. In the HIV field, a double benefit of such immune check-point inhibitors (ICPi) should result from their dual ability to restore in-vitro HIV-specific CD8⁺ T-cell functions [15–17] and to enhance HIV production from reservoir cells [13], thus fulfilling the goals of the ‘shock and kill’ concept proposed as an HIV cure therapeutic strategy. This strategy indeed combines a reactivation of latent HIV reservoirs under cART (‘the shock’) and their elimination thanks to boosted HIV-specific immunity with appropriate immune-based therapy (‘the kill’). Yet, while in-vitro promising results had been obtained [23] the feasibility and the efficacy of this concept remained to be demonstrated *in vivo*. So far modest if any clinically relevant efficacy was obtained *in vivo* when using various ‘shock’ strategies, mostly histone-deacetylase inhibitors (HDACi) [24–26], disulfiram [27] or ‘kill’ strategies mostly based on still weakly immunogenic HIV therapeutic vaccines [28,29]. The dual properties of ICPi might provide in theory an easier ‘shock and kill’ approach for HIV cure or remission. Yet using ICPi in PLWH without cancer requires solid information on the safety and tolerability of these agents known for clinical and immunologic adverse events that limit their usage in some cancer patients [30]. So far, only limited case series and clinical trials of PLWH treated with ICPi, mostly for a cancer, have been reported with discordant and heterogeneous effects on the HIV reservoirs and immunity [31–33].

Therefore, we conducted here-in a systematic review of the literature to summarize first the safety profile of the ICPi reported in those participants then their anti-HIV effects, and discuss these promising compounds as a potential therapeutic strategy towards HIV remission.

Methods

We conducted a systematic review of the literature according with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines. A literature search of Pubmed database was performed on 13 August 2019 to identify every clinical study reporting safety, effects on HIV viral load (HIV-RNA), CD4⁺ cell count, HIV reservoir (cell-associated HIV-DNA) and/or HIV-specific CD8⁺ T cells of ICPi in PLWH, using the following search terms: HIV nivolumab, HIV pembrolizumab, HIV atezolizumab, HIV durvalumab, HIV avelumab, HIV ipilimumab, HIV anti-PD-L1, HIV PD-1 blockade, HIV anti-PD-1 and HIV anti-CTLA-4. The inclusion criteria were case report, case series, cohort study or clinical trial reporting safety and/or immunovirological effects of ICPi among PLWH. The exclusion criteria were not evaluating ICPi, not involving PLWH, preclinical study and review. Two hundred and sixty-three records were identified after duplicates removed; among these, 232 were excluded (126 not evaluating ICPi, 40 not involving PLWH, 37 preclinical studies and 29 reviews). Thirty-one studies fitted the inclusion criteria (Fig. 1: flow chart) including 19 case reports [31,34–49,14,13], nine patient series [32,50–57] and three clinical trials [33,58,59] for a total of 176 cases of PLWH treated with ICPi (63 and 113 from prospective and retrospectives studies, respectively).

Overall 146/176 (83%) participants had concomitant cancer, the remaining 30 (17%) were cancer-free and included in clinical trials assessing the anti-HIV effects of ICPi [33,58]. At time of ICPi initiation, HIV-related data were available for 167 participants, among them 136 (81%) were virally-suppressed under cART (<200 copies/ml) and 31 (19%) displayed detectable HIV viremia, whether or not they received cART. Regarding ICPi 125 participants (71.0%) were treated with anti-PD-1, 31 (17.6%) with anti-CTLA-4, 9 (5.1%) with anti-PD-L1 and 11 (6.3%) with combined or sequential ICPis (anti-PD-1 and anti-CTLA-4).

Immune checkpoint inhibitor safety in people living with HIV

Safety data were available for 165 participants regarding severe adverse events (CTCAE grade>2) and for 156 participants regarding nonsevere adverse events (CTCAE grade 1 and 2). Adverse events are presented in Table 1.

A total of 26 severe adverse events were reported in 20 among 165 participants (12.1%) including six pneumonitis; four anemia; three colitis, two hepatitis; two neutropenia; two lymphopenia, one skin eruption, one myositis, one soft tissue infection, one edema limbs, one hyper eosinophilia, one uveitis and one nephritis. Interestingly only one severe adverse event was reported among the 30 cancer-free participants. Nonsevere adverse events were reported in about half participants with a total

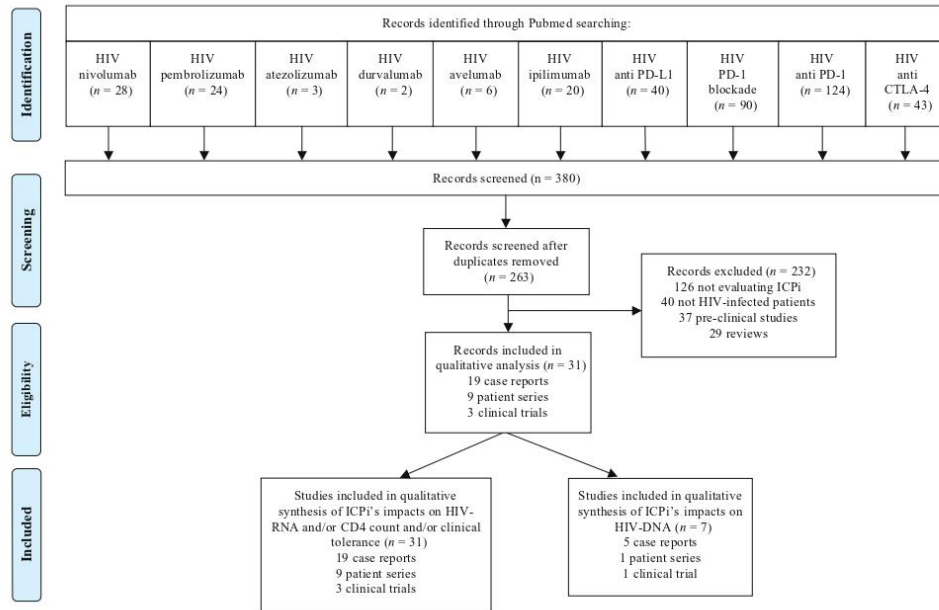


Fig. 1. Flow chart.

of 224 in 77 among 156 (49.4%) (Table 1). The most frequently reported events were gastrointestinal disorders (33 cases), general disorders (30 cases), skin disorders (28 cases) and hematological disorders (25 cases).

Noteworthy, no immune reconstitution inflammatory syndrome (IRIS) was reported. Similarly, no hepatic toxicity was reported among the 30 participants with medical history of chronic viral hepatitis B or C virus (HBV, HCV). One case of active neurosyphilis was reported early after nivolumab initiation with favorable outcome under antibiotics [50] and one case of lethal Kaposi's sarcoma-associated lymphoproliferation with a likely undiagnosed multicentric Castlemans disease was reported [59].

In-vivo effects on plasma HIV loads and CD4⁺ cell counts

HIV-related data were available for two thirds participants (117/176), regarding pVL changes under treatment, and for half participants (92/176) regarding CD4⁺ cell counts. Among them, 31 were excluded from the analysis because of uncontrolled pVL (>200 copies/ml) at time of ICPi initiation or change in cART regimen during treatment course. We arbitrarily considered as stable, changes of pVL from baseline of less than 50 copies/ml. Overall, viral loads remained stable in 91.9% participants (79/86), showed early (between D14 and D180) increases in 5.8% participants (5/86, mean: 1.03 log₁₀ copies/ml, range: 0.53–2), or decreases in 2.3% (2/96, mean: 0.57 log₁₀ copies/ml, range: 0.49–0.65) (Table 1).

Median CD4⁺ cell counts at baseline were 385/μl (ranges: 10–1156). We arbitrarily considered as stable changes from baseline lower than 100 CD4⁺ cell counts/μl. Overall 60.7% (37/61) participants had stable CD4⁺ cell counts, 24.6% (15/61) experienced a CD4⁺ cell count increase (median: +171/μl, range: 105–290) at a median 84 days (ranges: 60–210) after ICPi initiation and 14.7% (9/61) displayed a substantial CD4⁺ cell count decrease (median: –200/μl, range: 109–552) at a median 84 days (range: 30–420) after ICPi initiation (Table 1).

In-vivo effects of immune checkpoint inhibitors on HIV reservoirs and HIV immunity

We then reviewed the impact of ICPi therapy on HIV reservoirs (cell-associated HIV-DNA) and HIV-specific CD8⁺ T-cell responses. Overall, we identified data available from 13 participants among whom we identified three distinct profiles (Table 2): profile I, transient pVL increases followed by a boost in HIV-specific CD8⁺ T cells concomitant to a decrease in HIV reservoirs, as reported in participant 1 [31]; Profile II, an isolated increase in HIV-specific CD8⁺ T cells without changes in pVL or HIV reservoir levels, as reported in three participants (#2, #9, #10) [33,34]. Profile III: no effect, as reported in five participants (#4, #7, #8, #11, #12) [32,33].

Information on blood cell-associated HIV-DNA alone were reported in four participants (#3, #5, #6, #13) [13,14,32,35] showing a second case of decrease in HIV reservoirs occurred under pembrolizumab in pt#13, but

Table 1. Full-text records reporting HIV-infected patients treated with immune checkpoint inhibitors.

Articles	N	Cancer (n)	ICPi	Change in viral load ^a	Change in CD4 ⁺ count ^b	Safety (CTCAE grade)
Tio <i>et al.</i> , <i>European Journal of Cancer</i> , 2018 [55] Retrospective	12	Melanoma (9) Urothelial carcinoma (1) HCC (1) RCC (1)	Ipilimumab + nivolumab (3) Ipilimumab then pembrolizumab (2) Pembrolizumab (5) Nivolumab (1) Atezolizumab (1)	7/12 NA 2 excluded ^c 3 stable non-US-VL	8 NA 2 excluded ^c 1 stable 1 increase	Grade 1-2: 4/12 (33%) Grade >2: 1/12 (8%)
Ostios-Garcia <i>et al.</i> , <i>Journal of Thoracic Oncology</i> , 2018 [51] Retrospective	7	NSCLC (7)	Nivolumab (2) Pembrolizumab (5)	1 excluded ^c 6 stable non-US-VL	1 NA 1 excluded ^c 5 stable	Grade 0-2: 4/7 (57%) Grade >2: 0/7 (0%)
Chang <i>et al.</i> , <i>Journal of Immunotherapy</i> , 2018 [52] Retrospective	16	NSCLC (8) SCLC (1), HL (2), anal SCC (1) RCC (2) HCC (2)	Nivolumab (10)	5/16 NA 10 stable 1 decrease non-US-VL 2 excluded ^c 5 stable 2 increase non-US-VL	5 NA 6 stable 3 increase 2 excluded ^c 3 stable 3 increase 1 decrease non-US-VL	Grade 1-2: 3/16 (19%) Grade >2: 4/16 (25%) Grade 1-2: NA Grade >2: 0/9 (0%)
Galanina <i>et al.</i> , <i>Cancer Immunology Research</i> , 2018 [53] Retrospective	9	Kaposi (9)	Nivolumab (8) Pembrolizumab (1)	4/10 NA 1 excluded ^c 4 stable 1 increase non-US-VL	7 NA 1 excluded ^c 1 increase 1 decrease	Grade 1-2: 3/10 (30%) Grade >2: 2/10 (20%)
Heppt <i>et al.</i> , <i>Annals of Oncology</i> , 2017 [54] Retrospective	10	Melanoma (9) Merkel (1)	Pembrolizumab (3) Nivolumab (1) Ipilimumab (3) Ipilimumab + nivolumab (3)	6/17 NA 10 stable 1 decrease	6/17 NA 6/11 stable 3/11 increase 2/11 decrease	Grade 1-2: 8/17 (47%) Grade >2: 3/11 increase 1/17 (6%)
Bari <i>et al.</i> , <i>Journal of Oncology</i> , 2019 [57] Retrospective	17	NSCLC (10), anal SCC (2), HCC (2), RCC (1), NHL (1), invasive basal (1)	Nivolumab (13) Pembrolizumab (3) Atezolizumab (1)	1/23 NA 1 excluded ^c 21 stable non-US-VL	13/23 NA 1 excluded ^c 7 stable 2 decrease	6/23 NA Grade 1-2: 4/17 (24%) Grade >2: 2/17 (12%)
Lavolè <i>et al.</i> , <i>Annals of Oncology</i> , 2018 [50] and Spano <i>et al.</i> , <i>AIDS</i> , 2019 [56] Retrospective	23	NSCLC (21), melanoma (1), head and neck SCC (1)	Nivolumab (21) Pembrolizumab (2)	5/19 NA 11/14 non-US-VL 3/14 US-VL 12 stable 2 increase 0 decrease	7/19 NA 7/12 (58.3%) stable 4/12 (33.3%) increase 1/12 (8.3%) decrease	5/19 NA Grade 1-2: 6/14 (43%) Grade >2: 3/14 (21%)
Case reports Retrospective [13,14,31,34-49]	19	NSCLC (6) melanoma (7) HL (3) Merkel carcinoma (2) Pancreas (1)	Nivolumab (8) Ipilimumab (4) Pembrolizumab (3) Avelumab (1) Combined (3)	2 stable 1 NA US-VL	2 stable 1 NA	Grade 1-2: 1/3 (33%) Grade >2: 0/3 (0%)
Scully <i>et al.</i> , <i>Annals of Oncology</i> , 2018 [32] Prospective	3	Head and neck SCC (2) Skin SCC (1)	Nivolumab (2) Pembrolizumab (1)	6 stable US-VL	6 NA	Grade 1-2: 3/6 (50%) Grade >2: 0/6 (0%)
Gay <i>et al.</i> , <i>Journal of Infectious Diseases</i> , 2017 [33] Phase I clinical trial	6	None	BMS-936559 (6) (Anti PD-L1)	24 excluded ^c	24 excluded ^c	Grade 1-2: 19/24 (79%) Grade >2: 1/24 (4%)
Colston <i>et al.</i> , <i>PLoS One</i> , 2018 [58] Phase I clinical trial	24	None	Ipilimumab (24)	NA	NA	Grade 1-2: 22/30 (73%) Grade >2: 6/30 (20%)
Uldrick <i>et al.</i> , <i>JAMA Oncology</i> , 2019 [59] Phase I clinical trial	30	Kaposi (6), anal (6), NHL (5), skin SCC (3), NSCLC (2), cystic carcinoma (1), bladder (1), tonsillar (1), cholangiocarcinoma (1), HCC (1), Prostate (1), pancreatic (1) Urothelial (1)	Pembrolizumab (30)	59/176 NA 31/117 excluded ^c 79/86 (91.9%) stable 5/86 (5.8%) increase 2/86 (2.3%) decrease	84/176 NA 31/92 excluded ^c 37/61 (60.7%) stable 15/61 (24.6%) increase 9/61 (14.7%) decrease	Grade 1-2: 20/176 NA 77/156 (49.4%) Grade >2: 11/176 NA 20/165 (12.1%)
Total	176	146/176 with cancer 30/176 without cancer	Anti PD-1 n=125 Anti PD-L1 n=9 Anti CTLA4 n=31 combined n=11			

AE, adverse events; CTCAE, common terminology criteria for adverse events; CTLA4, cytotoxic T-lymphocyte-associated protein 4; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; ICPi, immune checkpoint inhibitor; NA, not available; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell-death 1; PD-L1, programmed cell-death ligand 1; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; US-VL, ultra-sensible viral load.

^aChange from baseline HIV-RNA of at least 50 copies/ml.

^bChange from baseline CD4⁺ cell count of at least 100/μl.

^cUncontrolled HIV load (>200 copies/ml) at time of ICPi initiation and/or cART regimen change during treatment course.

Table 2. Studies reporting HIV-infected patients treated with immune checkpoint inhibitors with HIV reservoir monitoring.

Article	Cancer	ICPi	HIV-RNA (copies/ml) US-VL	Cell-associated HIV-DNA	Percent HIV-1-specific CD8 ⁺ cells producing IFN γ (antigens targeted)	Profiles
Guihot <i>et al.</i> , <i>Ann Oncol</i> , 2018 [31] Patient #1	NSCLC	Nivolumab (anti-PD-1)	D0: 1 D44: 101 D120: 31	D0: 369 D120: 30 (cp/10 ⁶ PBMC)	D0: 0.53 D120: 1.31 (Cag, RT, Nef)	Transient \uparrow in HIV pVL followed by a boost in HIV-specific CD8 ⁺ T cells concomitant to a \downarrow HIV-DNA
Le Garriff <i>et al.</i> , <i>AIDS</i> , 2017 [34] Patient #2	NSCLC	Nivolumab (anti-PD-1)	D0: 14 D30: 1 D60: 19 D0: 20–25 D70: 5	D0: 116 D30: 213 D60: 117 (cp/10 ⁶ PBMC) Stable	D0: 0.2 D30: 0.5 D60: 0.2 (Cag, RT, Nef) NA	\uparrow in HIV-specific CD8 T cells No changes in pVL No changes in HIV-DNA Unknown
Wightman <i>et al.</i> , <i>AIDS</i> , 2015 [35] Patient #3	Melanoma	Ipilimumab (Anti CTLA-4)	D0: 30–40 D7: NA	D0: 100–200 D7: 400–500 (cp/10 ⁶ PBMC)	NA	Unknown
Evans <i>et al.</i> , <i>AIDS</i> , 2018 [14] (following Wightman <i>et al.</i>) Patient #3	Melanoma	Nivolumab (anti-PD-1) post-ipilimumab (anti-CTLA-4)	D0: 0–1 D29: 2–3 D45: 1–2	D0: 200–300 D29: 200–300 D45: 300–400 (cp/10 ⁶ CD4+)	D0: 0–0.1 D29: 0.1–0.2 D45: 0–0.1 (Cag)	No effect
Scully <i>et al.</i> , <i>Ann Oncol</i> , 2018 [32] n°1 Patient #4	Head and neck SCC	Nivolumab (anti-PD-1)	D0: 1–2 D28: 0–1 D45: 1–2	D0: 10–20 D28: 20–30 D45: 40–50 (cp/10 ⁶ CD4)	NA	Unknown
Scully <i>et al.</i> , <i>Ann Oncol</i> , 2018 [32] n°2 Patient #5	Head and neck SCC	Nivolumab (anti-PD-1)	D0: NA D50: 1–5 D105: 5–10 D150: 10–20 D150: > 30	D0: NA D50: 1–5 D105: 5–10 D150: 10–20 (cp/10 ⁶ CD4)	NA	Unknown
Scully <i>et al.</i> , <i>Ann Oncol</i> , 2018 [32] n°3 Patient #6	Skin SCC	Pembrolizumab (anti-PD-1)	Means: D0: 1.1 D28: 1.3	Means: D0: 435 D28: 513 (cp/10 ⁶ CD4)	D0: 0.134 D28: no increase >0.1% (Cag)	No effect
Gay <i>et al.</i> , <i>J Infect Dis</i> , 2017 [33] n°1 Patient #7	None	BMS-936559 (Anti PD-L1)	Means: D0: 1.1 D28: 1.3	Means: D0: 435 D28: 513 (cp/10 ⁶ CD4)	D0: 0.134 D28: no increase >0.1% (Cag)	No effect
Gay <i>et al.</i> , <i>J Infect Dis</i> , 2017 [33] n°2 Patient #8	None	BMS-936559 (Anti PD-L1)	Means: D0: 1.1 D28: 1.3	Means: D0: 435 D28: 513 (cp/10 ⁶ CD4)	D0: 0.078 D28: no increase >0.1% (Cag)	No effect
Gay <i>et al.</i> , <i>J Infect Dis</i> , 2017 [33] n°3 Patient #9	None	BMS-936559 (anti-PD-L1)	Means: D0: 1.1 D28: 1.3	Means: D0: 435 D28: 513 (cp/10 ⁶ CD4)	D0: 0.167 D28: 0.43 (Cag)	\uparrow in HIV-specific CD8 T cells No changes in pVL
Gay <i>et al.</i> , <i>J Infect Dis</i> , 2017 [33] n°4 Patient #10	None	BMS-936559 (anti-PD-L1)	Means: D0: 1.1 D28: 1.3	Means: D0: 435 D28: 513 (cp/10 ⁶ CD4)	D0: 0.065 D28: 0.57 (Cag)	No changes in HIV-DNA \uparrow in HIV-specific CD8 T cells
Gay <i>et al.</i> , <i>J Infect Dis</i> , 2017 [33] n°5 Patient #11	None	BMS-936559 (anti-PD-L1)	Means: D0: 1.1 D28: 1.3	Means: D0: 435 D28: 513 (cp/10 ⁶ CD4)	D0: 0.094 D28: no increase >0.1% (Cag)	No changes in HIV-DNA No effect
Gay <i>et al.</i> , <i>J Infect Dis</i> , 2017 [33] n°6 Patient #12	None	BMS-936559 (anti-PD-L1)	Means: D0: 1.1 D28: 1.3	Means: D0: 435 D28: 513 (cp/10 ⁶ CD4)	D0: 0.007 D28: no increase >0.1% (Cag)	No effect
Fromentin <i>et al.</i> , <i>Nat Commun</i> [13] #13	Melanoma	Pembrolizumab (anti-PD-1)	NA	D0: >100 D120: >50 (cp/10 ⁶ CD4)	NA	Unknown

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; D, day; ICPi, immune checkpoint inhibitors; IFN γ , interferon gamma; NA, not available; NSCLC, nonsmall cell lung cancer; PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death ligand 1; PD-L1, programmed cell death ligand 1; SCC, squamous cell carcinoma; US-VL, ultra-sensible viral load; Y, year.

to a much lesser degree than in participant #1. However, no changes were observed in the three other cases: in participant #3 treated for a metastatic melanoma in whom HIV-DNA levels were first stable under ipilimumab [35] then increased later-on while under nivolumab [14]; in two participants, #5 and #6, in whom both HIV plasma loads and reservoirs remained stable under nivolumab and pembrolizumab respectively. Furthermore, an ancillary study of the CITN-12 trial reported a short 3-month follow-up with significant but transient decreases in cell-associated HIV-DNA ($P=0.02$) 1 day after ICPi initiation, with rapid return to baseline values [60].

Discussion

The increasing interest for ICPi as an innovative therapeutic strategy towards an HIV remission together with the increasing usage of ICPis in cancer and the high numbers of cancers in PLWH, prompted us to perform a comprehensive review of the reported real-life experience from close to 200 PLWH treated with ICPi, mainly for cancer.

Overall data are somewhat reassuring in terms of safety profile, with a 12% rate of severe adverse events similar to the 13–14% rate reported in HIV-negative patients [61]. These findings are also in accordance with the 9% rate of severe adverse events recently reported among PLWH treated with ICPi [62]. However, the two cases of neurosyphilis and of lethal Castleman disease reported in PLWH should remind us the risk of intercurrent infections in this fragile population. Importantly, plasma HIV loads and CD4⁺ cell counts remain roughly stable upon treatment and the slight increase in HIV-RNA observed in about 6% participants did not require ICPi discontinuation or change in ART regimen. While keeping in mind, the potential bias resulting in the retrospective nature of most collected data, the safety profile of ICPi among PLWH and the lack of substantial alterations in HIV disease provide favorable signals for future clinical trials assessing ICPi as an HIV cure strategy in healthy PLWH without cancer.

As potential therapeutic tools for a 'shock and kill' strategy, ICPi were expected to re-activate both latently infected CD4⁺ T cells to produce HIV and HIV-specific CD8⁺ T cells to eliminate the re-activated HIV-infected cells. Limited and heterogeneous data were available from less than 10% of the participants, with still modest results. Our group reported the single case of a substantial decrease of HIV reservoir associated to a transient increase of pVL and a durable increase of HIV-specific CD8⁺ T cells [31]. The only modest fluctuations in CD4 cell counts could not explain the changes in HIV reservoirs. These events might rather be interpreted as resulting from a 'shock and kill' in-vivo effect [31].

These results have yet to be compared with those obtained *in vivo* with latency reversal agents (LRAs), either HDACi, such as vorinostat, panobinostat and romidepsin, or disulfiram, which appear to be slightly more efficient than ICPi to reverse HIV latency *in vivo* with significant increases in pVL and cell associated HIV-RNA in most of patients treated. However, contrarily to ICPi, those LRAs failed at decreasing the HIV reservoirs or enhancing HIV-specific T cells when used alone [24–27]. Furthermore, they also differ from effects of other agents, such as interleukin 7 combined to cART, which induced some HIV-blips, but with major effects on CD4⁺ T-cell homeostatic proliferation resulting in transient increases in HIV reservoirs [63–65]. In addition, similarly to ICPi, IL-7 can increase virus-specific CD8⁺ T cells [66].

Indeed, ICPi treatments appear more consistently able to boost HIV-specific CD8⁺ T cells as observed in four of the nine studied participants. Interestingly, such increase followed viral blips in participant #1 and might result from a combined effect of an auto-vaccination phenomenon induced by re-exposure to patient's virus, and of a direct enhancement of immune functions. In contrast, HIV-specific T cells increased in three other cases without detectable blips, suggesting here ICPi might have directly favored restoration of immune functions. Such a modest immune benefit on HIV immunity contrasts with a strongest antitumoral effect and might reflect a prior decrease in ICP expression on T cells as a result of the immune restoration induced by cART [18]. Alternatively, persistently high ICP levels despite cART might assess that the exhausted CD8⁺ T cells were directed against old HIV variants preexisting before cART as a remnant of an already failed immunity, and their inefficacy at eliminating new variants [67]. It might be interesting to explore in the future whether levels of ICP on CD8⁺ T cells prior to ICPi initiation are correlated with a boosting of anti-HIV CD8⁺ T cells. These modest results are also close to those reported with some therapeutic vaccines that had failed at decreasing HIV reservoirs when used as a single immunotherapy despite modest or even substantial enhancements of anti-HIV immunity [28,29]. Finally, one cannot eliminate the hypothesis that important immune alterations caused in these cancer patients by previous chemotherapies might have limited the immune benefits of ICPis.

These first field results on immunovirological ICPi effects on HIV reservoirs should be taken cautiously. Indeed, the heterogeneity in the responses reported might reflect the diversity and the limitation of the methods used. The level of standardization in methods to quantify HIV reservoirs is still a major issue to assess those 'shock and kill' strategy. For participants #1 and #2, levels of HIV reservoirs had been assessed by using the well standardized, clinically applicable method quantifying total cell-associated HIV-DNA, though with a coefficient of variation around 30% [68]. Beyond ICPi, several mechanisms could be involved

Table 3. Ongoing trials with immune checkpoint inhibitors among people living with HIV.

NCT	Phase	Treatment	Population	Outcomes	Country
NCT03304093 CHIVA 2 IFCT-1602	Phase II	Nivolumab (anti-PD-1)	HIV-infected patients with advanced NSCLC in second line of treatment	Clinical trial: DCR and safety BIOCHIVA2: HIV-RNA, HIV-DNA and HIV-specific immunity follow-ups; identification of biomarkers associated with ICPi antiviral and antitumoral efficacy	France
NCT03094286	Phase II	Durvalumab (anti-PD-L1)	HIV-infected with advanced cancer	Feasibility, safety, DCR à 4 months	Spain
NCT02595866	Phase I	Pembrolizumab (anti-PD-1)	HIV-infected patients with advanced solid malignancy	Safety, ORR, PFS	USA
NCT02408861	Phase I	Nivolumab + ipilimumab (anti-PD-1 + anti-CTLA4)	HIV-infected patients with advanced solid malignancy or HL	Safety, ORR HIV-RNA, CD4 and HIV-specific immunity follow-ups	USA
NCT03316274	Phase I	Intralesional nivolumab (anti-PD-1)	HIV-infected with Kaposi sarcoma	Safety Changes in HIV-RNA and in anti-HIV and HHV8 T cells	USA
NCT03354936 ANRSO24 Oncovihac	Noninterventional	ICPi	HIV-infected patients with advanced solid malignancy or HL	Clinical safety Biomarkers associated with ICPi antiviral and antitumoral efficacy Changes in HIV-RNA, HIV-DNA and HIV-specific T cells	France
NCT03767465 PembroHIV	Noninterventional	Pembrolizumab (anti-PD-1)	HIV-infected patients with advanced cancer	Changes in HIV-RNA, HIV-DNA and in anti-HIV T cells	Germany Spain
NCT03787095	Phase I-II	Cemiplimab (anti-PD-1)	HIV-infected under ART (no cancer)	Safety Changes in anti-HIV T cells	USA
NCT03239899	Phase I	Pembrolizumab (anti-PD-1)	HIV-infected under ART (no cancer)	Safety Changes in anti-HIV T cells	USA
NCT03367754	Phase I-II	Pembrolizumab (anti-PD-1)	HIV-infected under ART with CD4 ⁺ less than 350/ μ l (no cancer)	Safety Changes in lymphocytes' PD-1 expression	USA

ANRS, agence nationale de recherche sur le sida et les hépatites virales; ART, antiretroviral therapy; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; DCR, disease control rate; HHV8, human herpes virus 8; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; ICPi, immune checkpoint inhibitors; IFCT, intergroupe francophone de cancérologie thoracique; NSCLC, nonsmall-cell lung cancer; ORR, objective response rate; PD-1, programmed cell-death 1; PD-L1, programmed cell-death ligand 1; PFS, progression free survival; USA, United States of America.

in shifts in the HIV-DNA and HIV-RNA observed in these patients. Furthermore, the timing of the HIV-DNA/RNA, measurement seems to be important because immediate measurement of plasma HIV-RNA after ipilimumab infusion decreases substantially [35]. Another issue is that all measurements were performed in peripheral blood cells but not in lymphoid tissues where reside the HIV reservoirs. Similarly, all studies evaluated CD8⁺ T-cell responses in blood cells while reinvigorated HIV-specific CD8⁺ T cells are to be located in lymphoid tissues where the virus production is re-activated. Finally, increases of HIV-DNA levels observed might also result from clonal expansion of HIV-infected CD4⁺ T cells, though usually not resulting in substantial virus production, while decreases of HIV-DNA values might reflect the immune control mediated by anti-HIV T cells expanding with ICPi.

Altogether these modest and relatively disappointing 'shock and kill' in-vivo effects of ICPi require further investigations to better understand the mechanisms underlying those results and their limitations. In addition, defining the factors able to predict the success of both the mobilization of the reservoirs and the restoration of anti-HIV immunity is of the utmost importance, in view of

avoiding undue exposure to potential adverse events in future clinical applications of ICPis. Several prospective studies are ongoing to confirm these very preliminary results and define predictive markers for ICPi effects on HIV immunity and reservoirs (Table 3).

Our review suggests that a strategy built on ICPi alone is unlikely to be the unique solution toward an HIV-free world. Combining ICPi with other LRAs might help synergize the latency reversing potential of ICPi but might increase the risks of toxicity, especially in healthy PLWH without cancer. Similarly, to the cancer field [69], combining ICPi with the new therapeutic vaccines providing recent encouraging efficacy results in animals models [70,71] might help enhance more efficacious HIV-specific T cells.

In conclusion, the clinical, virological and immunological safety profiles of ICPi reported in about 200 PLWH appear to be favorable but their still modest results in terms of HIV cure strategy suggest they would have to be combined with other synergistic approaches in future clinical trials aiming at building efficient therapeutic strategies toward HIV remission or cure as currently explored in several ongoing clinical studies.

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Conflicts of interest

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Annexe 2. Natural Killer Cells in Post-Transplant Lymphoproliferative Disorders. Article de revue en tant que co-premier auteur, 2020.

Review

Natural Killer Cells in Post-Transplant Lymphoproliferative Disorders

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Simple Summary: Post-transplant lymphoproliferative disorders (PTLDs) are life-threatening complications. The clinical and pathological spectrum of PTLD is broad; however, most cases of PTLD are associated with Epstein–Barr virus (EBV) infection and the use of immunosuppression treatment required to prevent graft rejection. While T-cell impairment is known to play a critical role in the immunopathogenesis of EBV complications post-transplantation, the role of natural killer (NK) cells remains more elusive. NK cells are key elements of the innate immune system that use a sophisticated array of activating, costimulatory, and inhibitory receptors to kill virally infected and/or cancerous cells. In this review we highlight the role of NK cells in the pathogenesis of PTLD, and also identify future avenues for NK cell therapy research.

Abstract: Post-transplant lymphoproliferative disorders (PTLDs) are life-threatening complications arising after solid organ or hematopoietic stem cell transplantations. Although the majority of these lymphoproliferations are of B cell origin, and are frequently associated with primary Epstein–Barr virus (EBV) infection or reactivation in the post-transplant period, rare cases of T cell and natural killer (NK) cell-originated PTLDs have also been described. A general assumption is that PTLDs result from the impairment of anti-viral and anti-tumoral immunosurveillance due to the long-term use of immunosuppressants in transplant recipients. T cell impairment is known to play a critical role in the immune-pathogenesis of post-transplant EBV-linked complications, while the role of NK cells has been less investigated, and is probably different between EBV-positive and EBV-negative PTLDs. As a part of the innate immune response, NK cells are critical for protecting hosts during the early response to virus-induced tumors. The complexity of their function is modulated by a myriad of activating and inhibitory receptors expressed on cell surfaces. This review outlines our current understanding of NK cells in the pathogenesis of PTLD, and discusses their potential implications for current PTLD therapies and novel NK cell-based therapies for the containment of these disorders.

Keywords: natural killer cells; post-transplant lymphoproliferative disorders; Epstein–Barr virus

1. Introduction

Natural killer (NK) cells were identified more than four decades ago as innate lymphocytes with the ability to lyse tumor cells without the need for prior sensitization [1,2]. NK cells are mounted with a panoply of activating and inhibitory receptors on their surface, suggesting that different NK cell subsets can be identified based on the assortment of NK receptors that are expressed. The integration and balance of the activating and

inhibitory signals from the ligand/receptor interactions dictates the status of NK cell activation. For instance, healthy cells express no or a minimal level of ligands for NK cell activating receptors, such as NKG2D and the natural cytotoxicity receptors (NCR: NKp30, NKp44 and NKp46), but express high levels of the major histocompatibility complex class I (MHC-I) molecules, which ligate to inhibitory receptors, such as NKG2A, Ig-like transcript 2 (ILT-2) and the killer immunoglobulin-like (KIR) family, to protect them from NK attack. Conversely, pathogenic target cells can downregulate MHC-I expression and/or overexpress ligands for NK cell activating receptors to trigger NK cell functions [3]. Thus, upon activation, NK cells release cytotoxic granules containing perforin and granzymes to directly lyse tumor cells, in a similar fashion to activated cytotoxic T cells, or indirectly by antibody-dependent cellular cytotoxicity (ADCC), triggered through binding of the FcγRIIIA receptor (CD16) on NK cells by the Fc fragment of IgG antibodies. In addition, NK cells produce large amounts of chemokines and cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), which also play major roles in tuning and controlling adaptive immune responses [4].

Due to their intrinsic capacities, NK cells play important roles in protection against viruses and tumor growth [5,6]. Studies in both animals and humans suggest that NK cells are critical in the host defense against Epstein–Barr virus (EBV), persistently carried by more than 85% of the adult human population. In vitro studies have clearly shown killing of EBV-infected B cells by autologous NK cells [7,8], whereas individuals with selective primary NK cell deficiency exhibit an increased susceptibility to EBV, associated with fatal primary infection or the development of EBV-associated cancers [9–11]. In addition, depletion of NK cells upon EBV infection of humanized mice favors EBV-associated tumorigenesis and exacerbates infectious mononucleosis (IM) [12,13], a self-limiting disorder characterized by extensive proliferation of polyclonal EBV-specific CD8⁺ T cells in response to primary EBV infection. Importantly, preferential proliferation and accumulation of early-differentiated CD56^{dim}NKG2A⁺KIR[−] NK cells was observed in immunocompetent children with acute IM [8], or after in vitro co-culture of NKG2A⁺ NK cells with autologous EBV-infected B cells [14,15]. Mechanistically, it was reported that peptides derived from EBV latent proteins can impair the recognition of the inhibitory NKG2A receptor, despite being presented by HLA-E, resulting in activation of differentiated, cytotoxic NK cells for the immune control of EBV [16,17].

Compared to IM, less is known about EBV-specific immune control by NK cells in EBV-driven lymphomas, such as in post-transplant lymphoproliferative disorders (PTLDs). PTLDs are heterogeneous tumors arising after solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT), often related to EBV [18,19]. EBV-positive PTLDs usually arise early after transplantation, in close relation with heavy immunosuppressive therapy, and are believed to result from altered NK and T cell responses against EBV-infected lymphocytes, while the pathogenesis of EBV-negative PTLD is less clear [18,20–22] (Table 1). Although most PTLDs are of B cell origin, the emergence of post-transplant NK lymphoproliferative diseases has also been observed in PTLD development. These malignancies are usually classified amongst T/NK cell PTLD in the World Health Organization (WHO) classification [23]. Previously, an analysis of 130 cases of T/NK cell PTLD reported that they occurred late, at a median of 66 months after transplantation, and that they were frequently extranodal [24]. Since, eight other central nervous system or nasal NK/T cell lymphoma patients have been reported, all but two being EBV-related [25,26]. T/NK PTLDs usually do not respond to a decrease in immunosuppression and the median survival is six months. Notably, overall survival for patients with EBV+ T/NK PTLD was described to be significantly better than for patients with EBV disease. This reveals that true NK cell PTLDs are very rare entities with poor prognosis. Diagnosis relies on pathologic examination, immunohistochemistry, peripheral blood immunophenotyping and, when necessary, T-cell receptor (TCR) sequencing showing the germline configuration.

Table 1. Characteristics of EBV-positive and EBV-negative PTLDs.

WHO Classification	Post-Transplant Onset	Age at Transplant	EBV Association
Nondestructive PTLD	Generally early	Adult and pediatric	Generally EBV-positive
Polymorphic PTLD	Frequently early	Adult and pediatric	Generally EBV-positive
Monomorphic PTLD			
B-cell lymphomas	Both early and late	More frequent in adult than pediatric	EBV-positive and EBV-negative
T-cell and NK-cell lymphomas	Generally late	Generally adult	Frequently EBV-negative
Classic Hodgkin Lymphoma-like PTLD	Generally late	Generally adult	Frequently EBV-positive

2. The Role of NK Cells in the Immunopathology of PTLDs

NK cells are critical actors in innate immunity during early responses against both viral infections and tumor growth. In the context of PTLDs, NK cells probably play different roles according to EBV status of the tumor. Indeed, EBV-positive and EBV-negative PTLDs show different patterns in terms of time from transplantation to PTLD development, age at PTLD diagnosis, and tumor morphologies (Table 1).

2.1. NK Cells and EBV-Positive PTLDs

EBV-positive PTLDs frequently develop early after transplantation, when immunosuppression is at its highest level and immune surveillance is weak. During this critical period, EBV reactivation is frequently observed in transplant recipients, resulting from a loss in the balance between infected cells and cytotoxic lymphocytes. Additionally, transplant recipients who develop primary EBV infection are at high risk of PTLD development due to uncontrolled EBV-driven proliferation of infected lymphocytes.

NK cells are known to play a major role in the control of EBV infection in the early post-transplant period, as NK cell reconstitution in peripheral blood reaches normal values within the first month after SOT or HSCT, several months before T cell and B cell restoration [27–31]. In a recent study in adult SOT recipients, NK cell lymphopenia was observed in 70% of EBV-positive PTLD diagnoses [32]. In that same study, the proportion of peripheral blood CD56^{bright} CD16[−] and CD56^{dim} CD16⁺ NK cells was similar between PTLD patients and transplant controls, independently of SOT type. Previous work by Baychelier et al. described increased proportions of CD56^{bright} CD16[−] cells in 11 adult lung or liver recipients who developed EBV-positive PTLD, when compared to healthy SOT recipients [33]. Meanwhile, a study by Wiesmayr et al. in pediatric heart or lung transplant recipients showed that EBV-positive PTLD patients displayed increased proportions of early-differentiated CD56^{dim} CD16[−] cells and CD56[−] CD16⁺ NK cells in peripheral blood [34]. Interestingly, early-differentiated CD56^{dim} NKG2A⁺ KIR[−] CD16[−] NK cells also accumulate in immunocompetent children with acute IM and are known to preferentially recognize autologous B cells with lytic EBV infection [8].

The scarcity of data about NK cell phenotype and subtype distribution reported at PTLD diagnosis might be related to the variability between studies in terms of type of organs transplanted. Transplant-related alterations are associated with differences in pre-transplant conditioning regimes and maintenance immunosuppressive therapy. In allo-HSCT patients and SOT recipients who received anti-thymocyte globulin (ATG), NK cells are depleted during pre-transplant conditioning treatment, which is followed by post-transplant NK cell reconstitution, starting with CD56^{bright} cells [35–37]. An accumulation of CD56^{bright} NK cells in blood may also be seen in patients treated with azathioprine-based regimens, which selectively deplete CD56^{dim} NK cells (Lord and Shows, 2017), or with cyclosporine, which preferentially blocks CD56^{dim} cell proliferation and favors an accumulation of CD56^{bright} NK cells in blood [38]. On the other hand, it has been observed

that CD56^{bright} and CD56^{dim} subsets regain normal proportions within the first year in hepatic transplant recipients [39].

The age at transplantation and at PTLD diagnosis are other factors that probably influence NK cell phenotype. The early-differentiated CD56^{dim} NKG2A⁺ KIR⁻ CD16⁻ NK cell subset is progressively replaced by differentiated CD56^{dim} KIR⁺ during the first decade of life [8,40], while the level of expression of NKG2D, NKp30 and NKp46 decreases with age [40]. The modulation of activating receptors NKp46 and NKG2D is also observed in the NK cells of adult and pediatric SOT recipients at EBV-positive PTLD diagnosis. NKG2D is an important activating receptor against EBV-positive PTLD tumors, as they express NKG2D ligands such as MIC-B [41]. However, EBV miRNAs from the BART (Bam HI-A region rightward transcript-2) family are also expressed in EBV-transformed B cells during PTLD and have been found to traffic with MIC-B mRNA, limiting the expression of MIC-B protein at the surface of tumor cells [42]. The specific ligands of NKp46 in EBV-positive PTLDs remain undescribed, but NKp46 downmodulation is also observed in different virus-induced cancers and has been related to low cytotoxic capacity [34,37,43,44].

A recent concept in NK-cell biology is that of functional exhaustion. In contrast with T cells, NK cell exhaustion probably results from the progressive loss of expression of several activating receptors, followed by the accumulation of inhibiting receptors, including the expression of inhibitory immune checkpoints, such as PD-1, Tim-3 and Lag-3, leading to cell dysfunction [45] (Figure 1). Another alteration of the NK cell phenotype at EBV-positive PTLD diagnosis, which often appears alongside one or several of the previously mentioned alterations, is the expression of the PD-1 receptor [32,34]. PD-1 expression by NK cells is rare in healthy individuals [46], but is often observed in association with gamma-herpesvirus infection in kidney transplant recipients with chronic EBV reactivation [47], in pediatric thoracic recipients with high EBV loads [34], and in human-herpesvirus-8 (HHV-8)-related Kaposi sarcoma patients [44]. PD-1 expression by NK cells is also frequently observed in the context of cancers in which the PD-1 ligands PD-L1/L2 are highly expressed by tumor cells [48,49], which is frequently the case for EBV-positive PTLDs [50,51]. In pediatric EBV-positive PTLD patients with high PD-1 expression by NK cells, the low functional capacity of NK cells, in terms of both IFN- γ production and CD107a cytotoxicity marker expression, can be recovered after *in vitro* PD-1/PD-L1 blockade [34]. A study of adult lung recipients observed diminished NK cell cytotoxicity against various lymphoma cell lines at PTLD diagnosis [33], while IFN- γ production after IL-12 and IL-18 stimulation was superior in NK cells of adult SOT recipients at PTLD diagnosis, compared to transplant controls [32,33]. Treatment with anti-PD-1 antibodies resulted in increased cytotoxicity and IFN- γ production of peripheral NK cells from multiple myeloma patients carrying high proportions of PD-1⁺ NK cells, suggesting that PD-1 could be a target for an immunotherapeutic strategy in EBV-positive PTLD patients [52]. However, immune-checkpoint blockade in transplant recipients is a delicate task due to the risk of transplant rejection, an issue that currently limits the utilization of anti-PD-1 and anti-PD-L1 antibodies in PTLD patients [53,54].

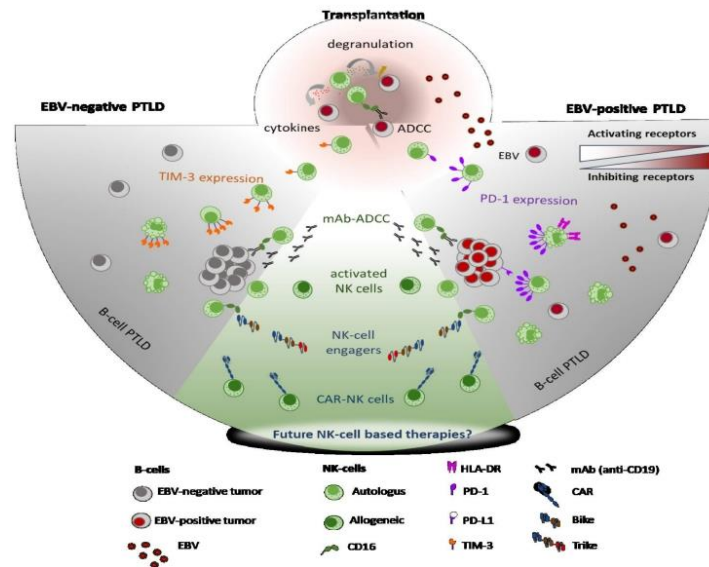


Figure 1. Natural killer (NK) cells are the first lymphocyte compartment to be quantitatively and functionally restored after solid organ or hematopoietic stem-cell transplantation and are the first line of protection against Epstein–Barr virus (EBV)-infected cells and tumor development. At the recognition of EBV-infected or tumor targets, NK cells release perforin and granzymes to mediate the lysis of target cells. Meanwhile, NK cells produce IFN- γ to limit viral infection. Transplant recipients with increasing EBV loads are at high risk of EBV-positive PTLD development and are often treated with rituximab, a monoclonal antibody (mAb) that binds to the CD20 molecule expressed at the surface of B cells. In such cases, NK cells also contribute to the defense of the host by inducing antibody-dependent cell cytotoxicity (ADCC) through the recognition of therapeutic mAbs by CD16. However, solid organ transplantation (SOT) recipients often present increased proportions of NK cells expressing the PD-1 inhibiting immune checkpoint receptor in relation with high EBV loads in blood. During EBV-positive post-transplant lymphoproliferative disorders (PTLDs), NK cells progressively increase PD-1 expression together with the NKG2A inhibiting receptor, while NKG2D and Nkp46 activating receptors are downmodulated, a phenotype that might impact NK cell functional capacity against the tumor. In addition to this phenotype, constant NK cell activation has been observed and related to increased activation-induced cell death (AICD), resulting in peripheral NK cell lymphopenia at PTLD diagnosis. In the case of EBV-negative PTLDs, NK cells show increased expression of the Tim-3 inhibiting immune checkpoint receptor, and increased apoptosis has also been associated with mild NK cell lymphopenia at EBV-negative PTLD diagnosis. Besides their central role as cytotoxic innate lymphocytes, NK cells can also be exploited for therapeutic use. Their most frequent role is their cytotoxic activity through ADCC in the context of mAb treatments such as chimeric (rituximab) or humanized (obinutuzumab) anti-CD20 mAbs. Furthermore, autologous infusions of activated NK cells have been used in HSCT recipients with PTLD. Currently, several strategies for NK cell activity enhancement are under development and present characteristics that could allow their utilization in transplanted populations. Bi-specific and tri-specific NK cell engagers, for example, facilitate NK cell synapsing with tumor targets in a very specific manner, and offer the advantage that they can be administered to boost NK cell responses of the host or be coupled with either autologous or allogeneic infusions of NK cells. CAR-NK cells, on the other hand, promise an “off-the-shelf” cellular therapy, so far showing low toxicity and high specificity in immunocompetent recipients.

Another important parameter to consider when studying NK cell phenotype in transplant recipients is the EBV pre-transplant serology. While most adult transplant recipients have encountered EBV before transplantation, pediatric transplant recipients are less likely to and therefore more frequently develop primary EBV infection after transplantation. A recent study by our team observed that the NK cells of adult PTLD patients overexpress the HLA-DR activation marker, with the highest levels observed in patients who acquired primary EBV infection post-transplant [32]. In that same study, NK cell activation was associated with high EBV loads and seemed to cause NK cell apoptosis, as those patients also presented with high proportions of IFN- γ -producing NK cells, PD-1 overexpression and profound NK cell lymphopenia [32] (Figure 1). Altogether, the different alterations of NK cells that have been described at EBV-positive PTLD diagnosis seem to be directly related to the interaction between EBV and NK cells in the context of immunosuppression and reduced presence of adaptive T lymphocytes.

Besides the direct role of NK cells in the control of both EBV infection and tumor development, NK cells also share complementary roles with other cellular components of immunity. Given the impaired state of the immune system under immunosuppressive therapy, such complementary roles become essential to maintain the delicate balance between immunity and virus/tumor development. The increased capacity of NK cells to produce IFN- γ at EBV-positive PTLD diagnosis might partially compensate for the low levels of latent EBV-specific CD4⁺ Th1 cells frequently observed after transplantation [47,55,56]. Thus, concomitant reduction of Th1 and NK cells limits two subsets specialized in producing high levels of the anti-viral cytokines IFN- γ and TNF- α . Furthermore, the cytotoxic capacity of NK cells is probably essential for keeping EBV-infected cells under control, especially when considering that EBV-specific CD8⁺ T cells also show several defects in EBV-positive PTLD patients. Finally, the synergistic work between the B and NK cell compartments results in interaction between antibody production and CD56^{dim} CD16⁺ NK cell-directed ADCC.

Although most studies describing NK cells in EBV-positive PTLDs are based on observations made in peripheral blood populations, the genetic characterization of the EBV-positive PTLD tumor microenvironment (TME) has started to demonstrate the role of NK cells. The comparison of gene expression profiles between EBV-positive and EBV-negative tumors showed positive regulation of genes associated with innate immunity and cytotoxicity in EBV-positive PTLDs [57]. However, the actual capacity of NK cells to infiltrate the tumor microenvironment (TME) has not been proven and NK cell anti-tumor cytotoxicity might be limited due to the tolerogenic environment created by EBV latent proteins and miRNAs [17,58–60].

2.2. NK Cells and EBV-Negative PTLDs

The role of NK cells in EBV-negative PTLD has been less described than in its EBV-positive counterpart. EBV-negative PTLDs have historically represented a small minority of PTLDs, but their proportion has constantly increased in recent years [21], currently representing 30–50% of PTLDs depending on different cohorts [20,21,61–63]. As EBV-negative PTLDs develop late after transplantation, 5–10 years or more [64], the identification of predictive biomarkers, and therefore prevention, is difficult. EBV-negative PTLDs generally present as aggressive monomorphic lymphomas (Table 1).

A recent immunological characterization of 39 EBV-negative PTLDs allowed us to observe different immune alterations between EBV-positive and EBV-negative PTLDs [32]. We observed a mild NK cell lymphopenia in EBV-negative PTLD patients, suggesting that NK cell lymphopenia could be a common aspect between PTLDs, although the presence of EBV clearly exacerbated NK cell depletion. More interestingly, NK cells from EBV-negative PTLD patients displayed higher Tim-3 expression than NK cells from EBV-positive samples [32] (Figure 1). The Tim-3 immune checkpoint is an inhibitory receptor normally expressed by mature NK cells [65], but its expression is generally increased in various types of cancer [66–70]. In patients with lung adenocarcinoma, treatment with anti-Tim-3 antibodies resulted in increased cytotoxicity and IFN- γ production of peripheral NK

cells [70], suggesting that Tim-3 could be a target for an immunotherapeutic strategy in EBV-negative PTLN patients. However, the safety of the Tim-3 immune-checkpoint blockade in transplant recipients remains unknown, especially when considering the risk of graft rejection.

3. Putative Strategies Exploiting NK Cell Therapy to Treat PTLNs

Considering the major role of NK cells in the immunopathology of PTLN, we asked if effector functions of NK cells could be used as a therapeutic option in PTLN, whatever their origin. However, very few data are available for PTLN patients because of the rarity of the disease and the frequent exclusion of these patients from clinical trials. Thus, we focused on NK-based regimens in non-Hodgkin lymphoma (NHL) patients, assuming that they could be extended to PTLN, subject to confirmation of safety. Indeed, safety is a major concern in transplant recipients because of the risk of graft rejection in the case of non-targeted immunotherapy.

3.1. NK Cell-Mediated ADCC

In the context of lymphoma, NK cell-mediated ADCC can be exploited through the use of therapeutic monoclonal antibodies (mAbs) targeting an antigen, such as CD20. Several reports have demonstrated that ADCC is an important mechanism contributing to the efficacy of rituximab in follicular lymphoma [71–73]. It is known that the valine (V) to phenylalanine (F) transition at amino-acid position 176 of Fc γ R1IIa induces a higher affinity to human IgG1 to lead a more effective mediation of ADCC [74]. Indeed, polymorphisms of Fc γ R1IIa (homozygous V/V allele) are independently associated with response to rituximab and progression-free survival (PFS) in follicular lymphoma patients [71,72]. In the same way, favorable genotypes of Fc γ R1IIa positively affect the outcomes of lymphoma patients treated with idiotype vaccination [75]. Conversely, Fc γ R1IIa polymorphisms do not correlate with outcomes for lymphoma patients treated with chemotherapy without rituximab, confirming that the positive effects of favorable genotypes are not due to the underlying clinical behavior of the disease, but to immunologic mechanisms. [76]. A new generation of glycoengineered anti-CD20 mAbs, such as obinutuzumab, leading to afucosylation and enhanced affinity for the Fc γ R1IIa, induced greater ADCC than rituximab and are currently used for NHL treatment [77] (Figure 1). Of note, Fc γ R1IIa expression is negatively regulated by the metalloproteinase ADAM17, which cleaves this receptor from the surface of NK cells after activation. Preventing this downregulation in tumor-infiltrating NK cells could be a potential target of treatment. A phase I/II trial testing rituximab combined with an ADAM17 inhibitor is currently being conducted in patients with large B cell lymphoma (NCT02141451).

3.2. NK Cell Engagers

In another attempt to enhance the natural function of tumor-infiltrating NK cells, antibody constructs known as bispecific killer engagers (BiKE) have been developed, which bring these cells into contact with tumor cells in an antigen-specific manner via CD16 [78–82]. In addition to bridging contact, the juxtaposition of NK cells and targets facilitates other activating receptor interactions and other missing-self signals. Nevertheless, BiKE failed to target NK cell expansion, as CD16 ligation does not trigger proliferation and survival [83]. To resolve this issue, tri-specific killer engager (TriKE) molecules were designed to induce specific NK cell-mediated killing, while providing a cytokine signal to drive NK cell expansion (Figure 1). Indeed, these molecules are composed of two single-chain variable fragments (scFvs), one engaging the CD16 on NK cells and one engaging a tumor-associated antigen, connected by small linkers and IL-15, a cytokine that stimulates the expansion of NK cells, and their ADCC functions. TriKE demonstrated a superior capacity for stimulating NK proliferation and persistence, and a higher killing capacity of these NK cells compared to that seen when treated using BiKE [84–86]. Considering lymphoid malignancies, AFM13 is the first BiKE that specifically recruits NK cells through CD16A

binding while targeting CD30, and which was given to relapsed or refractory Hodgkin lymphoma (R/R HL) patients. In a phase 1 study, AFM13 showed a good safety profile, but only short-term NK cell activation, low response rates (23% for patients receiving optimal doses) and short response duration (median five months) [87]. It was combined with pembrolizumab to facilitate innate and adaptive immune system recruitment in R/R HL [88]. Outcomes were very positive, with an 83% overall response rate (ORR) and a median response duration of 10 months, however it is difficult to assess the individual contributions of AFM13 and pembrolizumab to the efficacy observed. Several trials testing AFM13 in lymphoma treatment are currently under way (NCT02321592, NCT03192202, NCT04074746). For B cell proliferations such as chronic lymphoid leukemias (CLL) and lymphomas, TriKE therapies have been tested *in vitro* and have demonstrated stimulation of NK cell expansion and enhancement of effector functions associated with tumor growth delay and survival improvement, compared to untreated or BiKE-treated mice [86,89,90].

3.3. NK Cell Enhancement with Cytokines

Another way to enhance NK cell function *in vivo* is through the use of IL-2 or IL-15, which are known to be key regulators of NK cell activity. While an increase in NK cell activity against malignant cells was seen with this method, limited success was observed in patients treated with cytokines such as IL-2. In that respect, we have learned that IL-2 therapy results in activation of regulatory T cells (Tregs), which inhibits NK cell function and limits their anti-tumor activity [91,92]. Treatment with IL-15 was associated with lower toxicities than IL-2 treatment, and few objective responses [93–95]. To augment the antitumor immunity induced by such approaches, N-803 IL-15 “superagonist” is now being tested in combination with NK cell adoptive treatment, immune checkpoint inhibitors or tumor-targeting mAbs in several clinical trials. In patients with R/R NHL, N-803 combined with rituximab resulted in an ORR of 48% in a phase 1 study [96].

3.4. Adoptive NK Cell Transfer

The advantages of anti-tumor immunity mediated by NK cells can also be implemented using adoptive cellular therapy. Autologous NK cell infusions were the first major focus of adoptive NK cell therapy, but failed to produce significant therapeutic effects in hematological or solid malignancies, possibly due to the lack of KIR-ligand mismatch [97–99]. Moreover, the expansion efficiency and functional status of autologous NK cells were still limited because patients were often heavily pretreated, whereas allogeneic NK cells from healthy donors could have a stronger graft-versus-tumor effect. These considerations motivated the development of treatments based on allogeneic NK cells, which can usually be collected from haploidentical or unrelated donors, or from umbilical cord blood, clonal cell line NK-92 or stem cell-derived NK cells. The first studies were undertaken in the setting of HSCT or acute myeloid leukemia (AML), because of the major role of NK cells in post-transplantation immune reconstitution [100–102]. For B cell lymphoma patients, haploidentical NK cell infusions plus IL-2 and rituximab after lymphodepleting chemotherapy induced a 29% ORR ($n = 4$). Donor NK cells persisted for at least one week after infusion and beyond day 28 in one responding patient [103]. Notably, levels of IL-15 in peripheral blood prior to NK cell infusion were almost twofold higher in patients who showed a clinical response (Figure 1). Thus, in order to improve expansion and efficacy of NK cell therapy, recombinant (r) human IL-15 was tested in association with lymphodepleting chemotherapy and haploidentical NK cell infusion in AML patients [102]. The trial reported a high rate of adverse events, such as cytokine release syndrome (CRS) and neurotoxicity, after subcutaneous injection of IL-15, while achieving a 40% ORR. These results suggest that future studies should be undertaken to clarify the best way to use these agents.

Another approach to improve expansion, functionality and “memory” of NK cells is to use cytokine-induced memory-like (CIML) NK cells. These cells are obtained after IL-2, IL-15 and IL-18 cytokine preactivation, and low-dose IL-2 administration. They exhibit

longer persistence and higher effector functions than control NK cells [104]. Currently, CIML NK cell therapy has only been tested in AML patients, and induced a clinical response in 50% of patients with poor prognosis, however no clinical trials have been performed for lymphoma patients [105]. Finally, exciting results have been reported more recently at an American Society of Hematology meeting, for a treatment called GCA-201 combining nicotinamide (NAM) and IL-15, which expanded allogeneic NK cells from healthy donors [106]. NAM plays a key role in metabolic reprogramming of cells and preserves cellular functionality and phenotype during *ex vivo* expansion. Nineteen R/R NHL patients were treated with GDA-201 and rituximab after lymphodepleting chemotherapy and achieved an ORR of 74% and a complete response (CR) rate of 67%, without any remarkable toxicities. Median duration of response was 8.7 months, eight patients remained in CR without other treatment, and one of them maintained the response for 24 months. Flow cytometry confirmed the persistence of GDA-201 in peripheral blood for 7–10 days, as well as enhanced *in vivo* proliferation and trafficking to the bone marrow and lymph nodes.

3.5. Chimeric Antigen-Receptor NK Cells (CAR-NK)

Finally, interest is growing surrounding CAR-NK cells, which could overcome the limits of other adoptive therapies. CAR-NK cells have the potential to be rapid, off-the-shelf and cheaper products, without the need for HLA-matching and without major adverse effects (permitting repeated doses) (Figure 1). Anti-CD19 CAR-NK cells were constructed from umbilical cord blood using a retroviral vector that expresses genes that encode anti-CD19 CAR, IL-15 and inducible caspase 9 to trigger apoptosis in the case of unacceptable toxicity. This product was tested in phase 1 and 2 trials for the treatment of heavily pre-treated R/R CLL and NHL, and persisted for at least 12 months in the peripheral blood. It was associated with a 73% ORR and a 64% CR rate (7 of 11 patients), without any major toxicity [107]. All of the responses occurred during the first month after infusion and one patient maintained the CR for 13 months without further treatment. Nevertheless, the majority of responding patients were given other treatment after the CAR-NK cell infusion, which makes it difficult to draw conclusions about the durability of the response. These results are very encouraging and further studies are needed to address the issue of response duration. Several clinical trials of CAR-NK cells targeting CD19 or CD22 are ongoing for lymphoma patients (NCT04639739, NCT03056339, NCT04245722). Notably, CIML-CAR-NK cells are also in development for use in NK-resistant lymphoma patients [108].

4. Conclusions

Throughout this review, we have highlighted the many different roles that NK cells perform in the context of PTLDs. NK cells as innate cytotoxic sentinels against tumors and viral infections are the first line of protection that limits cellular transformation at the early stages. Although rare, NK cells can also be the origin of PTLD and develop as NK cell lymphomas. Yet, the primary role of NK cells is their participation in PTLD immunopathology through the acquired alterations that limit their capacity to control tumor growth, as well as their complementary role with other cellular components of the immune system. Finally, the most recently discovered role of NK cells in PTLDs is their use in PTLD therapy, both as ADCC effectors and as a therapeutic product by themselves through the different applications of NK cell infusions in current development.

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Abbreviations

Acute myeloid leukemia (AML); ADAM Metallopeptidase Domain 17 (ADAM17); antibody dependent cellular cytotoxicity (ADCC); BamHI-A rightward transcript-2 (BART2); bispecific killer engagers (BiKE); chimeric antigen-receptor NK cells (CAR-NK); chronic lymphoid leukemias (CLL); cytokine-induced memory-like (CIML); cytokine release syndrome (CRS); Epstein-Barr virus (EBV); hematopoietic stem cell transplantation (HSCT); human herpesvirus-8 (HHV-8); human leukocyte antigens (HLA); Ig-like transcript-2 (ILT-2); interferon gamma (IFN- γ); immunoglobulin (Ig); interleukin (IL); infectious mononucleosis (IM); killer cell immunoglobulin-like receptor (KIR); lymphocyte-activation gene 3 (Lag-3); low affinity immunoglobulin gamma Fc region receptor III-A (Fc γ RIII); microARN (miRNA); major histocompatibility complex class I (MHC-I); MHC class I polypeptide-related sequence B (MIC-B); natural cytotoxicity receptor (NCR); natural killer (NK); NK group 2 member A (NKG2A); NK group 2 member D (NKG2D); overall response rate (ORR); post-transplant lymphoproliferative disorders (PTLDs); programmed cell death protein 1 (PD1); programmed death-ligand 1 (PD-L1); progression-free survival (PFS); regulatory T cells (Tregs); single-chain variable fragments (scFvs); solid organ transplantation (SOT); T-cell receptor (TCR); T cell immunoglobulin and mucin domain-containing-3 (Tim-3); tri-specific killer engager (TriKE); tumor microenvironment (TME); tumor necrosis factor alpha (TNF- α); World Health Organization (WHO).

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Table des illustrations

Figure 1. Effets de l'infiltrat immunologique sur le pronostic des patients avec cancer. Les datas sont issues de 300 études avec plus de 70 000 patients atteints de cancers de différents types, en fonction de 14 populations immunologiques différentes : les lymphocytes : T CD8+ cytotoxiques (CD8), les T régulateurs (T_{reg}), les macrophages (macro), les macrophages M1 (1), les macrophages M2 (M2), les structures tertiaires lymphoïdes (TLS), les lymphocytes T helper 1 (T_H1), T helper 17 (T_H17), T helper 2 (T_H2), T follicular helper (T_{FH}), les lymphocytes B (B), les lymphocytes NK (NK), les cellules dendritiques (DCs), les cellules suppressives d'origine myéloïde (PMNs) et les mastocytes (mast). La couleur des cercles indique le caractère : bon (good, en bleu), mauvais (bad, en rose) ou sans effet (none, en gris) de la population cellulaire en question sur le pronostic des patients. La taille des cercles indique le nombre de patients inclus dans les études. Tiré de (Bruni *et al*, 2020).

Figure 2. Cycle de l'immunité anti-tumorale et présentation antigénique. Cycle : les néoépitoques relargués par les cellules tumorales mortes sont capturés par les CPA qui initient la réponse immunitaire périphérique spécifique des néoépitoques (« priming ») au sein des organes lymphoïdes secondaires. Les cellules T périphériques activés migrent et infiltrent les tissus tumoraux et tuent les cellules tumorales après reconnaissance des néoépitoques exprimés à leur surface. **Encart haut : Présentation antigénique par les molécules du CMH-II :** Les molécules du CMH-II s'associent à la chaîne invariante chaîne invariante (Ii) dans le RE et migrent à la surface de la cellule via l'appareil de Golgi. A partir de là, le complexe est acheminé vers les compartiments endosomaux ou atteint la surface de la cellule d'où il peut être internalisé et livré aux compartiments de présentation de l'antigène. Ii est ensuite dégradée enzymatiquement pour produire le CLIP qui reste lié au sillon de liaison peptidique du CMH-II. Le CLIP est ensuite éliminé lors d'un échange avec un peptide antigénique dans une réaction assistée par le chaperon HLA-DM dont l'activité est elle-même régulée par HLA-DO. Les molécules de CMH-II sont ensuite transportées vers la membrane plasmique. Les complexes peptide-CMH-II présents à la surface de la cellule peuvent être internalisés et subir une dégradation lysosomale ou être recyclés vers la membrane plasmique. **Encart bas: Présentation antigénique par les molécules du CMH-I:** les protéines mutantes dérivées des mutations somatiques tumorales sont dégradées en peptides par le protéasome et transportées ensuite vers le RE grâce notamment à l'intervention des transporteurs TAP où ils peuvent être

de nouveau coupés par des « aminopeptidases du RE » (ERAP). Le peptide muté se lie au CMH-I sous réserve d'une affinité suffisante. Le complexe peptide-CMH-I est ensuite transporté à la surface de la cellule tumorale où il pourra être reconnu par les lymphocytes T cytotoxiques qui tueront la cellule. ILV, vésicule intraluminale CALR : calreticuline ; HLA: human leucocyte antigen ; TAP1 et 2 : transporters associated with antigen presentation ; ER : endoplasmic reticulum; ERAP: ER aminopeptidase; β 2M: β 2-microglobulin ; . Tiré de (Yi *et al*, 2018; Jhunjhunwala *et al*, 2021; Pishesha *et al*, 2022).

Figure 3. Les mutations somatiques peuvent induire des néoépitopes selon 3 différents mécanismes. Mutations affectant les acides aminés d'ancrage (I), les résidus reconnus par les TCR en regard (II), le processus de présentation (III). Tiré de (Vormehr *et al*, 2016).

Figure 4. Les 3 E de « l'immunoédition du cancer ». a). L'élimination correspond à l'immunosurveillance. b). L'équilibre correspond au processus pendant lequel le système immunitaire sélectionne ou promeut la génération de cellules tumorales variantes avec des capacités augmentées de survie, c). L'échappement correspond à la phase où la tumeur « sculptée immunologiquement » n'est plus contrôlée. Cellules tumorales : bleu ; cellules tumorales variantes : rouge et orange ; stroma et cellules non transformées : gris ; petits ronds orange : cytokines ; éclair blanc : activité cytotoxique des lymphocytes. Tiré de (Dunn *et al*, 2002).

Figure 5. Différents rôles des populations cellulaires du MET dans la progression du cancer. Les populations cellulaires du MET modulent les conditions d'activation immunitaire ou d'immunosuppression pour prévenir ou favoriser la croissance tumorale. (A) La fonction effectrice des cellules T et les signaux de différenciation peuvent être soutenus par les cellules dendritiques (CD) par le biais de la sécrétion d'interleukine 12 (IL-12). (B) Les fibroblastes associés au cancer (CAF) jouent un rôle immunosuppresseur en inhibant l'infiltration et la fonction des lymphocytes T CD8+ par la sécrétion du facteur de croissance transformant bêta (TGF- β). (C) Les macrophages associés à la tumeur (TAM) sont principalement des macrophages M2, qui sont tumorigènes. Les TAM (M2) contribuent à l'angiogenèse par la sécrétion de facteur de croissance de l'endothélium vasculaire (VEGF). (D) Les cellules T CD4+ peuvent jouer un rôle immunoactif ou immunosuppresseur en se différenciant respectivement en cellules T helper de type 1 (Th1) ou en cellules T régulatrices (Treg). Les cellules Th1 sont capables d'induire les cellules T CD8+ en libérant des cytokines activatrices

telles que l'interféron-gamma (IFN- γ) ; à l'inverse, les Treg ont une activité immunosuppressive par l'inhibition de la fonction des cellules T CD8+ en libérant de l'IL-10 et du TGF- β . (E) Les cellules suppressives d'origine myéloïde (MDSC) suppriment la réponse des cellules T CD8+ spécifiques de la tumeur en augmentant les niveaux de prostaglandine E2 (PGE2) et d'arginase (ARG). (F) Les mastocytes peuvent favoriser la progression de la tumeur par le développement de l'angiogènèse en sécrétant certaines protéases, telles que la métalloprotéinase matricielle 2 (MMP-2) et la MMP-9, ainsi qu'en libérant du VEGF et le facteur de croissance des fibroblastes (bFGF) de la matrice extracellulaire (ECM). (G) Le neutrophile est également capable de développer l'angiogènèse par la sécrétion de VEGF et de MMPs. (H) Les cellules Natural killer (NK) peuvent induire des réponses immunitaires innées et adaptatives par la sécrétion de cytokines pro-inflammatoires, notamment l'IFN- γ , le facteur de nécrose tumorale alpha (TNF- α) et le facteur de stimulation des colonies de granulocytes/monocytes (GM-CSF). Tiré de (Sadeghi Rad *et al*, 2021) :

Figure 6. Résumé de la nouvelle classification des proliférations lymphoïdes et des lymphomes associés à un statut d'immunodéficience. La colonne de gauche représente la quatrième et ancienne classification (WHO-HAEM4R) et celle de droite la cinquième et nouvelle classification (WHO-HAEM5R). Cette nouvelle classification reconnaît les similarités histologiques et biologiques des proliférations survenant dans différents types d'immunosuppression, tout en reconnaissant leurs aspects spécifiques. LPD : lymphoproliférative disorder ; PTLN : post-transplant lymphoproliférative disorder ; CHL : classical Hodgkin lymphoma ; EBVMCU : EBV-positive mucocutaneous ulcer; MCD : multicentric Castelman disease ; IEI : inborn errors of immunity. Tiré de la 5^{ème} classification des tumeurs lymphoïdes (Alaggio *et al*, 2022).

Figure 7. Evolution des SIR pour les lymphomes chez les PVVIH en fonction des périodes. SIR : standarized incidence ratio ; CNS : central nervous system ; NHL : non-hodgkin lymphoma. Tiré de (Hernández-Ramírez *et al*, 2017b).

Figure 8. Génération et présentation des néoépitopes par les molécules HLA-I et HLA-II dans les cellules B malignes. Les étapes de génération des peptides et la manière dont elles peuvent être "détournées" pour induire un néoépitope sont illustrées. A) La première étape commence par des **altérations génomiques**, (SNV, indels, translocations chromosomiques entraînant des gènes de fusion, hypermutation somatique de la région variable des gènes des

Ig). L'étape suivante est la **transcription** de la région concernée, qui peut entraîner des modifications telles que B) des événements d'épissage alternatif de l'ARN impliquant la rétention d'introns et le saut d'exon. Elle est suivie d'une **traduction** médiée par le ribosome, qui peut impliquer : C) **la modification** de l'ARN; l'insertion, la suppression et/ou la substitution de paires de bases, ou D) la **traduction non canonique** telle que la lecture de codons d'arrêt, le décalage des cadres ribosomiques et le contournement de la traduction. Ces altérations peuvent conduire à une expression aberrante des protéines tumorales spécifiques ainsi qu'à des produits ribosomiques défectueux (DRiP). (E) Des **modifications post-traductionnelles** des protéines telles que la glycosylation, la méthylation et la phosphorylation peuvent se produire avant une éventuelle dégradation protéasomique. Pour la présentation par l'intermédiaire du CMH-I, les protéines sont dégradées par le protéasome en peptides, avec des F) altérations au sein des **sous-unités protéasomiques** pouvant également générer des néoépitopes épissés alternativement (Vigneron *et al*, 2004). Les peptides épissés par le protéasome sont transportés dans le RE par l'intermédiaire des protéines TAP. Les peptides sont ensuite chargés dans les molécules du CMH et, après formation d'un complexe HLA-peptide stable, le complexe est exporté vers la surface cellulaire via l'appareil de Golgi. Les complexes CMH-I-antigène peuvent interagir avec le TCR des lymphocytes T CD8+. La présentation d'antigènes endogènes par le CMH-II se produit par la dégradation des protéines cellulaires dans les autophagosomes et les endosomes à l'aide des cathepsines. Les molécules CMH-II nouvellement synthétisées se combinent à ces compartiments, où les peptides sont chargés et transportés à la surface des cellules. Les complexes CMH-II-antigènes interagissent avec le TCR des cellules T CD4+. Tiré de (Sardia *et al*, 2022).

Figure 9. Cycle de l'EBV et développement des LPT. Le virus de l'EBV pénètre dans l'organisme par l'oropharynx, traverse l'épithélium des muqueuses et infecte les cellules B sous-muqueuses. Certaines cellules B mémoire infectées de manière latente quittent le centre germinatif et persistent, tandis qu'occasionnellement, certaines cellules mémoire infectées se différencient en plasmocytes libérant dans la salive de nouveaux virions. Les cellules T cytotoxiques (CTL) CD8+ spécifiques empêchent la prolifération des blastes B. Néanmoins, l'immunosuppression extrinsèque et non spécifique, retrouvée notamment chez les patients transplantés d'organe, peut compromettre cette suppression médiée par les CTL, permettant ainsi la prolifération des cellules B et le développement d'un LPT. Les différents stades de latence virale et les profils d'expression protéique caractéristiques sont illustrés. *BART*, BamH1-A rightward transcript; *BHRF1*, BamH1 fragment H rightward open reading frame; EBER,

EBV-encoded RNA; EBNA1, Epstein Barr nuclear antigen 1; LMP1, latent membrane protein 1. Tiré de (Dharnidharka *et al*, 2016).

Figure 10. Drainage par le LCR des antigènes du SNC vers les ganglions lymphatiques cervicaux profonds. Tête humaine en coupe sagittale médiane, montrant les différentes structures anatomiques (à savoir le ventricule, les plexus choroïdes, le parenchyme cérébral, les lymphatiques et les ganglions lymphatiques cervicaux profonds). CSF : cerebrospinal fluid.. Tiré de (Ransohoff & Engelhardt, 2012).

Figure 11. Procédures d'identification et de construction des vaccins thérapeutiques, et réponses immunitaires induites. Une première étape permet de définir les néoépitopes d'intérêt à partir de la tumeur. Une seconde étape consiste en la conception et l'administration du vaccin selon différentes modalités et différents schémas d'administration. Une dernière étape permet de caractériser les réponses immunitaires induites (ELISpot mais aussi séquençage de l'ARN en single cell (scRNAseq). **Encart : réponses immunitaires induites.** Après la vaccination, les cellules T CD4+ et les cellules T CD8+ induites et spécifiques d'un néoépitope prolifèrent et tuent les cellules tumorales exprimant le néoépitope en question. Lorsque les cellules tumorales sont éliminées, la libération d'antigènes tumoraux peut contribuer à la propagation de l'épitope et à l'apparition de nouveaux néoépitopes, permettant ainsi une augmentation de l'intensité de la réponse immunitaire. Après l'éradication de la tumeur, les populations de cellules T se contractent, mais des sous-populations mémoires à longue durée de vie, telles que les cellules T mémoire centrale (TCM) ou T mémoire effectrice (TEM) persistent. La génération de T mémoire résidente (TRM) et/ou de T mémoire périphérique (TMP) n'est pas encore bien définie. **Abréviations :** MHC II, CMH de classe II; MS, spectrométrie de masse; scTCR, single cell TCR ; SFC, cellule formant une tache. Tiré de (Blass & Ott, 2021).

Figure 12. Procédure de manufacturing des LTC anti-EBV issus de donneurs sains.

Figure 13. Régulation des réponse T par les CPA. Les CPA telles que les cellules dendritiques régulent les réponses des lymphocytes T spécifiques aux agents pathogènes ou aux cellules malignes. Les TCR exprimés par ces cellules T reconnaissent d'abord l' antigène présenté par les molécules du CMH (**signal 1**). Cette étape est ensuite suivie d'un signal envoyé au CD28 des cellules T par le CD80 des CPA, et est décrit comme le "**signal 2**". Plusieurs ligands différents sur les cellules dendritiques fournissent alors des signaux aux cellules T,

déterminant ainsi la qualité et la durée de la réponse effectrice. Les interactions récepteur-ligand qui **amplifient** les réponses des cellules T effectrices (flèches vertes) comprennent le CD40-CD40 ligand (CD40L), OX40-OX40L, 4-1BB-4-1BBL (également connu sous le nom de CD137L), co-stimulateur de cellules T inductibles (ICOS)-ICOSL et CD27-CD70. Il existe également des interactions récepteur-ligand qui **suppriment** les réponses des cellules T effectrices (traits rouges) afin de maintenir la tolérance et de prémunir les tissus des dommages occasionnés par une réponse immunitaire prolongée. Il s'agit notamment de l'interaction « lymphocyte activation gene 3 » (LAG3) - CMH de classe II, de « T-cell immunoglobulin mucin protein 3 » (TIM3) -galectine 9, de la « program cell death protein 1 » (PD1-) -PDL1, et de PD1-PDL2, « T cell immunoreceptor with immunoglobulin and ITIM domains » (TIGIT)-CD155, « cytotoxic T lymphocyte antigen 4 » (CTLA4)-CD86 ou CTLA4-CD80, « glucocorticoid-induced TNFR-related protein » (GITR)-GITR ligand (GITRL) et « B and T lymphocyte attenuator » (BTLA)-herpes virus entry mediator (HVEM). Le symbole "?" fait référence à un récepteur inconnu qui "active" les cellules T. Les symboles des anticorps représentent des voies testées dans le cadre d'essais cliniques en cours. Les anticorps verts indiquent les voies faisant l'objet d'essais cliniques pour le cancer, et les anticorps bleu foncé indiquent celles qui sont déjà utilisées en clinique. Tiré de (Wykes & Lewin, 2018).

Figure 14. Signalisation moléculaire des récepteurs inhibiteurs. Les couples ligands/récepteurs pour les voies inhibitrices sont représentés avec les domaines intracellulaires des récepteurs qui contribuent à l'épuisement des cellules T. De nombreux récepteurs inhibiteurs ont des motifs de type « immunoreceptor tyrosine-based inhibitory motifs » (ITIM) et/ou de type ITSM dans leurs domaines intracellulaires ; néanmoins, certains récepteurs ont d'autres motifs spécifiques. Les **mécanismes** moléculaires de la signalisation des récepteurs inhibiteurs sont classés comme suit : **compétition** des ectodomains (les récepteurs inhibiteurs séquestrent les récepteurs cibles ou les ligands); **modulation** des **médiateurs intracellulaires** (atténuation intracellulaire locale et transitoire des signaux positifs provenant des récepteurs activateurs tels que les récepteurs des lymphocytes T et les récepteurs co-stimulateurs) et **induction de gènes inhibiteurs**. De multiples récepteurs inhibiteurs sont responsables de ces trois mécanismes. Tiré de (Wherry, 2011).

Figure 15. Etapes de la latence. L'inversion de la latence du VIH nécessite de multiples étapes aboutissant à une cellule infectée productive. *In vivo*, les cellules infectées par le VIH persistant sous traitement antirétroviral se trouvent à différents stades de latence, allant de la latence **réelle**

(ADN+, ARN-) à l'activité **transcriptionnelle** (ADN+, ARN US+) et à l'activité **traductionnelle** (ADN+, ARN US+, ARN MS+, protéine+). Env : protéine d'enveloppe, US : non épissé, SS : épissé simple, MS : épissé multiple. Tiré de (Zerbato *et al*, 2019).

Figure 16. Shock and kill et ICPI. Les ICPI pourraient jouer le rôle d'agents réversant la latence. Les anticorps anti-PD-1 se fixent au PD-1 à la fois sur les cellules T CD4+ infectées par le VIH réservoir et sur les cellules T CD8+ spécifiques du VIH. La liaison de PD-1 par l'anticorps lève l'inhibition des signaux envoyés par les ICP au niveau intra-cellulaire. Les cellules deviennent transcriptionnellement actives, les cellules T CD4+ produisant des produits viraux qui entraînant la mort de la cellule, et les cellules T CD8+ ayant une fonction effectrice restaurée leur permettant de cibler les cellules T CD4+ infectées. D'après (Boyer & Palmer, 2018).

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Tableau 3. Distribution des différents sous-types histologiques de lymphomes survenant chez les PVVIH sur ces 30 dernières années dans une cohorte européenne (London) de 615 patients et une cohorte américaine (CNICS USA) de 476 patients.

Tableau 4. Résumé des expériences de thérapie adoptive avec des LTC « third-party donor » anti-EBV. Tiré de (Prockop *et al*, 2020).

Résumé :

Les cancers, notamment les lymphomes non hodgkiniens (LNH), sont particulièrement fréquents chez les patients **immunodéprimés** (ID : transplantés ou VIH+). Les LNH des ID sont caractérisés par une association fréquente à l'**EBV** et/ou à une localisation **cérébrale** qui peuvent tous 2 impacter la réponse immune anti-tumorale. Les cancers des patients VIH+ peuvent quant à eux bénéficier de traitement par inhibiteurs d'immune checkpoint (**ICPi**). Dans ces différentes situations, le développement, la profondeur et la caractérisation de la **réponse immune** dirigée contre les antigènes tumoraux ou contre les antigènes viraux sont d'une importance capitale pour définir des marqueurs de réponse et/ou de résistance au traitement et des cibles thérapeutiques.

Dans la **première partie**, nous avons étudié l'**immunogénomique** de 68 patients avec des lymphoproliférations B : 51 ID (34 transplantés, 17 VIH+) et 17 immunocompétents, en caractérisant la charge (CMT) et le profil mutationnel tumoral, le nombre de néoépitopes, le microenvironnement tumoral (MET) et les réponses T spécifiques, à partir du séquençage de l'exome entier et de l'ARN tumoral et des cellules mononuclées sanguines périphériques respectivement. La prédiction des néoépitopes a été réalisée grâce à un pipeline bio-informatique développée au sein de notre structure.

72% des patients avaient un lymphome B à grandes cellules, 25 % une localisation cérébrale et 40 % des tumeurs étaient EBV+. La **CMT** (2,2 vs 3,4/Mb, $p=0,004$) et le **nombre de néoépitopes** (40 vs 200, $p=0,0002$) étaient plus faibles dans les LNH EBV+ comparé aux EBV-, quel que soit le statut immunitaire. Le profil mutationnel tumoral différait à la fois en fonction du statut EBV et du statut immunitaire avec des **mutations** d'*HNRNPF* et de *STAT3* exclusivement observées dans les LNH EBV+ et ID respectivement. Des **réponses lymphocytaires T spécifiques** des néoépitopes étaient détectées chez tous les LNH EBV-, mais seulement 50% des LNH EBV+ ($p=0,08$), et étaient notamment dirigées contre les néoépitopes dérivés d'*IgH* restreints par la classe II du CMH. L'analyse du **MET** montrait une augmentation de l'infiltrat T CD8+ dans les LNH EBV+ ainsi qu'un profil plus tolérogène composé de Tregs, de macrophages de type M2 et d'une expression accrue de gènes impliqués dans l'immunorégulation négative.

Dans la **deuxième partie**, nous avons étudié l'**impact des anti-PD-1** sur les réservoirs VIH et les réponses immunitaires antivirales chez les patients VIH+ traités pour un cancer, afin d'étudier la possibilité d'une stratégie du « shock and kill ». Nous avons évalué à différents points biologiques, dans le sang périphérique, le nombre de CD4+, l'ARN-VIH plasmatique, l'ADN-VIH, les charges virales EBV, CMV, VHB, VHC et HHV-8, les marqueurs d'activation et l'expression de différents ICP sur les lymphocytes, et les cellules T spécifiques anti-virales. 32 patients ont été inclus, avec un suivi médian de 5 mois. L'**ADN-VIH** avait tendance à diminuer avant le cycle 2 ($p = 0,049$). Notamment, 6 patients ont présenté une diminution $\geq 0,5$ log10 de l'ADN-VIH au moins une fois et l'ADN-VIH d'un de ces patients est devenu indétectable pendant 10 mois. Aucune augmentation significative de l'**immunité spécifique** anti-VIH n'était observée. En revanche, une **augmentation** précoce de l'expression de **CTLA-4** à la surface des CD4+ ($p = 0,004$), et de **TIM-3** et de **CTLA-4** à la surface des CD8+ était plus marquée chez les patients sans réduction de l'ADN-VIH par rapport aux autres ($p \leq 0,03$).

Nos résultats suggèrent la présence d'une **réponse immunologique** spécifique d'antigènes **tumoraux**, et notamment de néoépitopes dérivés des *IgH* présentés par le CMH II, dans les LNH de l'ID. Chez les VIH+, il existe également une réponse T spécifique **anti VIH** mais sans amplification significative par les ICPi en monothérapie. Nous avons démontré une implication

forte de l'EBV dans l'immunogénomique des LNH, et un potentiel mécanisme de résistance aux ICPI par surexpression d'autres ICP, qui peuvent permettre le développement de traitements ciblés.

Mots clés : [lymphomes, cancers, immunodéficience, EBV, charge mutationnelle tumorale, profil mutationnel, réponses T spécifiques anti-tumorales, microenvironnement tumoral, inhibiteurs d'immune checkpoint, réservoir VIH, réponses T spécifiques anti-virales]

Abstract :

Tumors, especially non-Hodgkin lymphomas (NHL), are particularly common in **immunocompromised** patients (ID: transplant recipients or HIV+ individuals). NHL in ID patients is characterized by a frequent association with **EBV** infection and/ or **cerebral** localization, both of which can impact the anti-tumor immune response. Cancer in HIV+ patients can benefit from treatment with immune checkpoint inhibitors (**ICPi**). In these different situations, the development, depth, and characterization of the immune response directed against tumor antigens or viral antigens are of paramount importance in defining markers of treatment response and/ or resistance and therapeutic targets.

In the **first part** of this work, we studied the **immunogenomics** of 68 B-cell lymphoproliferations: 51 ID patients (34 transplant recipients, 17 HIV+) and 17 immunocompetent individuals (IC), characterizing tumor mutational burden (TMB), mutational profile, the number of neoepitopes, the tumor microenvironment (TME), and peripheral-specific T-cell responses, based on tumor whole-exome and RNA sequencing data and peripheral blood mononuclear cells. Neoepitope prediction from RNA sequencing data was performed using a bioinformatics pipeline developed within our institution.

Seventy-two percent of patients had diffuse large-B-cell lymphoma, 25% had cerebral localization, and 40% of tumors were EBV-positive. **TMB** (2.2 vs. 3.4/Mb, $p=0.004$) and the number of neoepitopes (40 vs. 200, $p=0.00019$) were lower in EBV-positive NHL compared to EBV-negative NHL, regardless of immune status. The **tumor mutational profile** differed based on both EBV status and immune status. *HNRNPF* and *STAT3* mutations were exclusively observed in EBV-positive NHL and ID, respectively. **Specific T-cell responses** to tumor neoepitopes were detected in all cases of EBV-negative lymphomas but only in half of the cases of EBV-positive lymphomas ($p=0.08$). Responses were notably directed against neoepitopes derived from *IgH* and restricted by class II MHC. **TME** analysis showed increased CD8+ T-cell infiltrate in EBV-positive NHL and a more tolerogenic profile composed of Tregs, M2 macrophages, and increased expression of genes involved in negative immunoregulation.

In the **second part** of this work, we studied **the impact of anti-PD-1 antibodies** on HIV reservoirs and antiviral immune responses in people living with HIV (PLWH) and treated for cancer, to investigate the possibility of a “shock and kill” strategy with these treatments. We evaluated, at various time points in peripheral blood, the number of CD4+ lymphocytes, plasma HIV RNA, HIV DNA, viral loads of EBV, CMV, HBV, HCV, and HHV-8, activation markers and the expression of different ICP on lymphocytes, and anti-viral specific T cells.

Thirty-two patients were included, with a median follow-up of 5 months. **HIV DNA** tended to decrease before cycle 2 ($p = 0.049$). Notably, six patients showed a ≥ 0.5 log₁₀ decrease in HIV DNA at least once, and the HIV DNA of one of these patients became undetectable for a prolonged period of 10 months. However, no significant increase **in specific immunity** against

HIV was observed during treatment. Conversely, an **early increase in CTLA-4** expression on the surface of CD4+ T cells ($p = 0.004$), and **TIM-3** and **CTLA-4** on the surface of CD8+ T cells, was more pronounced in patients without a reduction in HIV DNA compared to others ($p \leq 0.03$).

In **conclusion**, our results suggest the presence of an **immune response** directed against **tumor antigens**, especially against neopeptides derived from *IgH* and presented by class II MHC, in ID NHL. In PLWH, there is also a specific **anti-HIV** T-cell response but without the possibility of significant amplification by ICPI in monotherapy. Moreover, we demonstrated a strong involvement of EBV in the immunogenomics of ID NHL (from mutational profile to TME), and a potential mechanism of resistance to ICPI by overexpression of other, which can both allow the development of targeted treatments.

Keywords: [lymphomas, cancers, immunodeficiency, EBV, tumor mutational profile, mutational profile, specific anti-tumor T-cell responses, tumor microenvironment, immune checkpoint inhibitors, HIV reservoir, specific anti-viral T-cell responses]