Les lymphomes en 2017 : progrès thérapeutiques et de prise en charge

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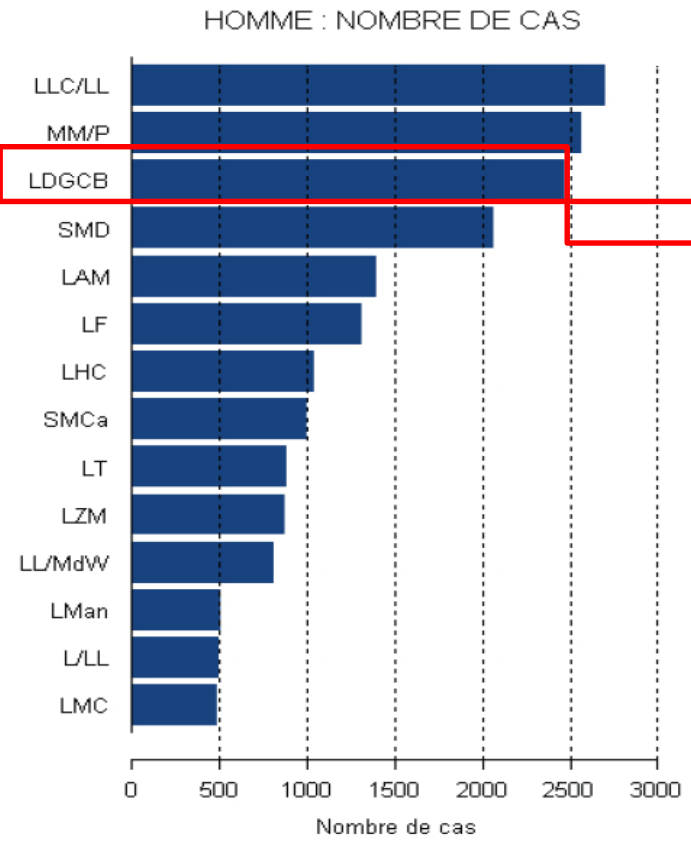
Introduction: définitions

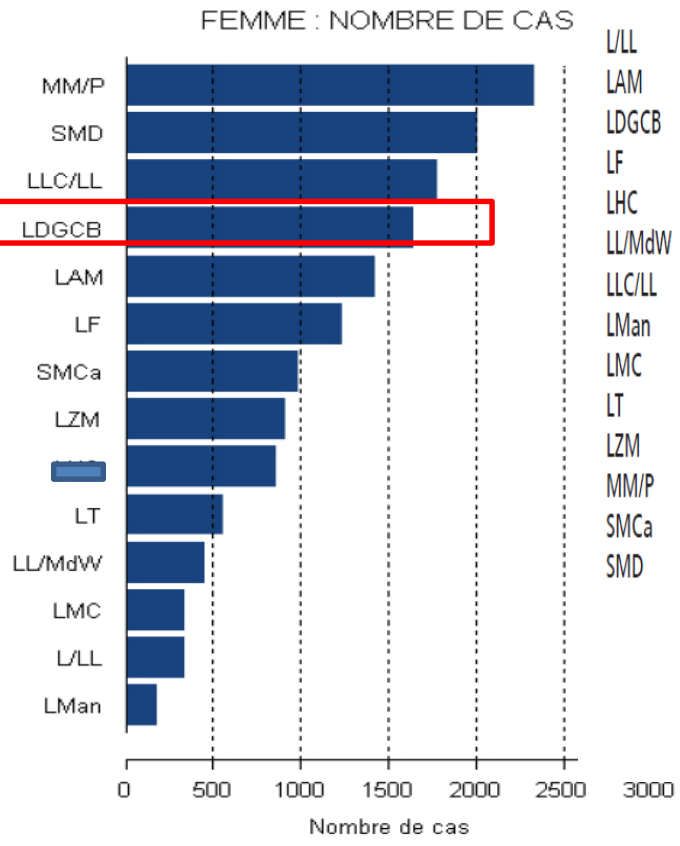
- Les lymphomes:
  - Néoplasies lymphoïdes → proliférations clonales de cellules des lignées lymphocytaires B (85%)ou T(15%) à leurs différents stades de différenciation et d'activation.
  - Atteignent dans 60% des cas des territoires lymphoïdes en particulier ganglionnaires mais aussi les territoires non lymphoïdes.
  - On distingue:
    - Lymphome de hodgkin
    - Lymphome malin non hodgkinien B ou T
    - Mais aussi:
      - LLC ou lymphome lymphocytique
      - myélomes

Epidémiologie des lymphomes

- 6è rang de cancer en France
- Les facteurs étiologiques ou de risque ne sont pas très bien connus, mais:
  - Fréquence accrue de l'immunodéppression dont **l'infection par le VIH** qui multiplie le risquex10 malgré les progrès du Traitement anti rétroviral.
- D'autres facteurs:
  - Immunosuppression congénitale ou acquise(PTLD)
  - Virus: VHC, HTLV-I
  - Bactériens: Helicobacter pylori, chlamydiae
  - Auto-immunité: syndrome de gougerot sjogren

Estimation du nombre de nouveaux cas des hémopathies malignes en France en 2012





L/LL	Leucémie / lymphome lymphoblastique à cellules (B, T ou SAI)
LAM	Leucémies aiguës myéloïdes
LDGCB	Lymphome diffus à grandes cellules B
LF	Lymphome folliculaire
LHC	Lymphome de Hodgkin classique
LL/MdW	Lymphome lymphoplasmocytaire / macroglobulinémie de Waldens
LLC/LL	Leucémie lymphoïde chronique / lymphome lymphocytique
LMan	Lymphome du manteau
LMC	Leucémie myéloïde chronique
LT	Lymphome T/NK à cellules matures
LZM	Lymphome de la zone marginale
MM/P	Myélome multiple & plasmocytome
SMCa	Autres syndromes myéloprolifératifs chroniques
SMD	Syndromes myélodysplasiques

- En 2012 sur 35000 cas d'hémopathie malignes, 2/3 sont lymphoïdes, H>F
- Age>60 ans sauf Lymphome de Hodgkin.

Monneraeau A. InVs 2014

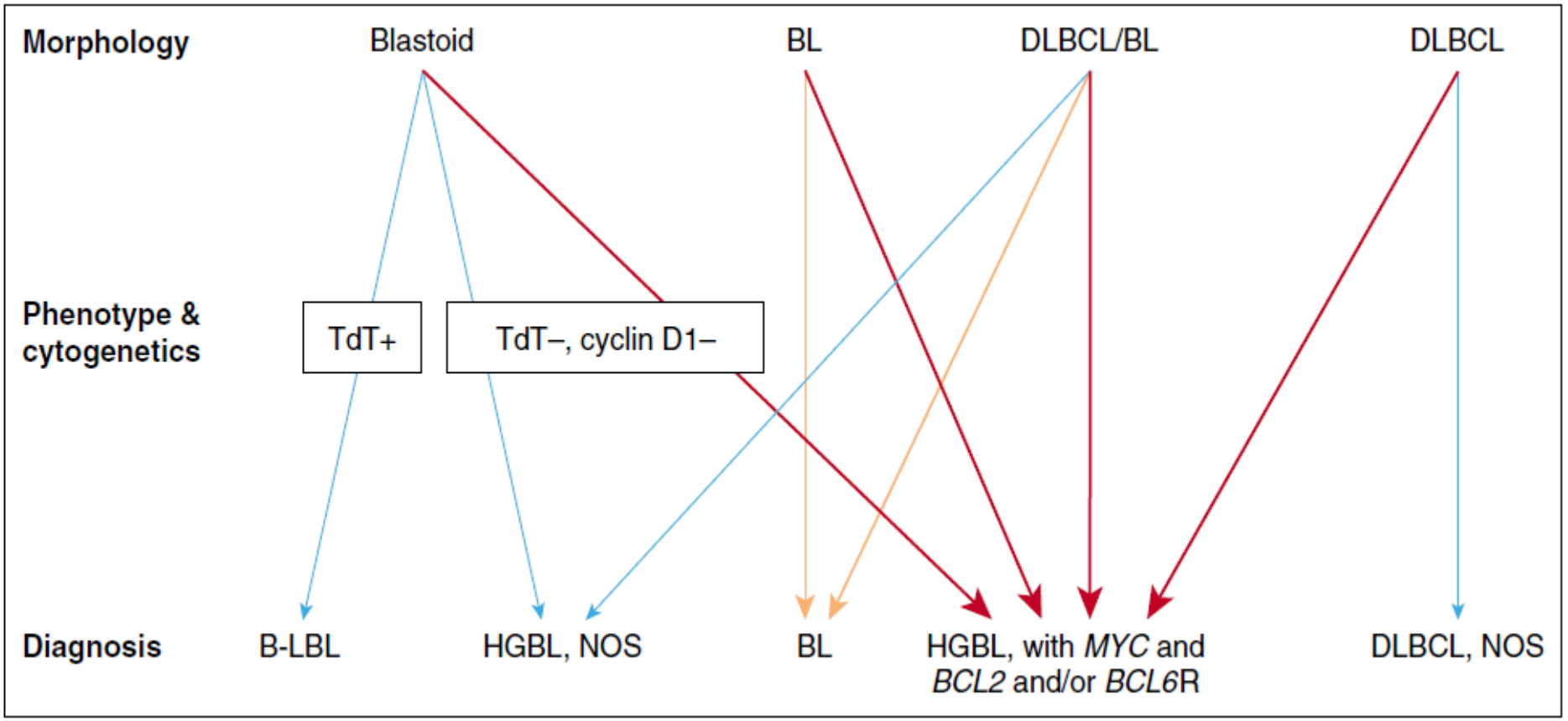
Le diagnostic et bilan d'extension

- Evoquer devant des signes cliniques et ou biologiques: des adénopathies superficielles persistantes, organomégalie.....

- Organiser la biopsie: → prélèvement histologique par chirurgie exérèse:
  - Une partie est fixée en paraffine
  - Une autre partie congelée, permet la réalisation d'études morphologiques et phénotypiques, cytogénétiques et moléculaires. → Classification selon la classification OMS et traitement.

- Attention pas de corticoïdes avant biopsie

Approche diagnostique des DLBCL



Swerdlow SH et al.
Blood. 2016;127:2375-2390

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7]

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
Large B-cell lymphoma with IRF4 rearrangem
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
*EBV$^+$ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*HHV8$^+$ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Table 1. (continued)

Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**
nt Hodgkin lymphoma
odgkin lymphoma
odgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
tic cell neoplasms
cytosis
oma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

- Multiples types histologiques
- Pas de référence au VIH

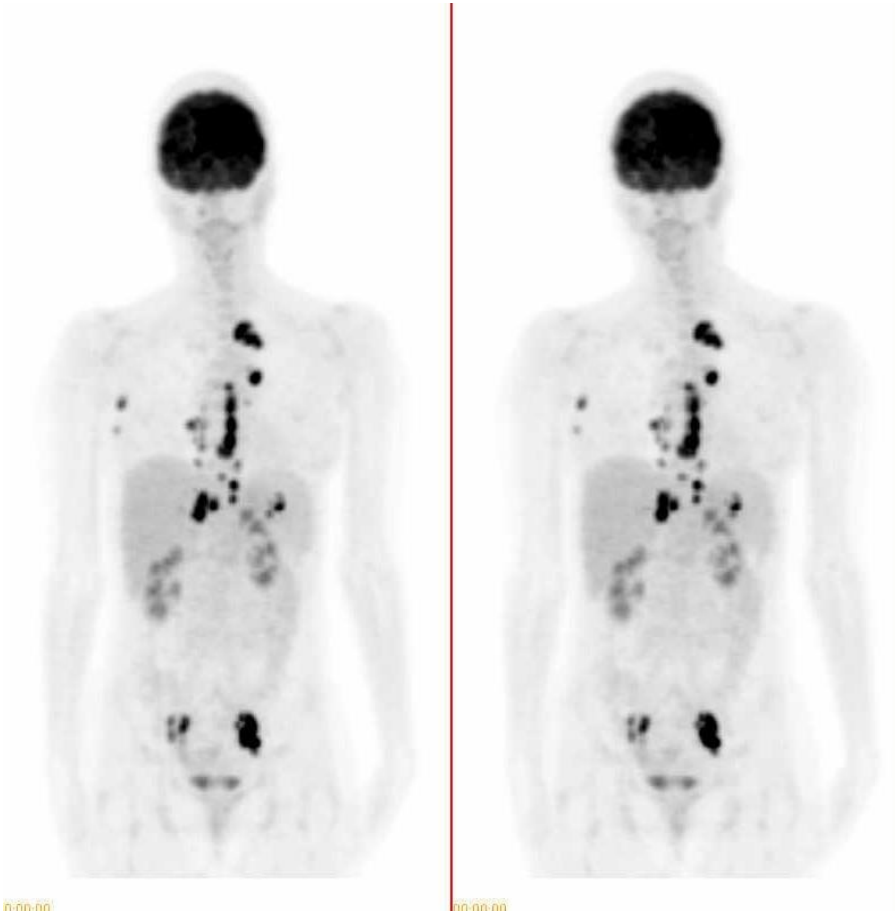
Swerdlow SH et al.
Blood. 2016;127:2375-2390

Le diagnostic et bilan d'extension

Bilan d'extension:

- Clinique
- Biologie
- BOM
- LCR
- Imagerie:
  - TDM
  - TEP
  - IRM

- Bilan pré thérapeutique:
  - Organes: cœur, poumons
  - Sérologies virales**: VIH**, VHB et VHC, EBV, (HTLV-I), HHV8
  - CD4



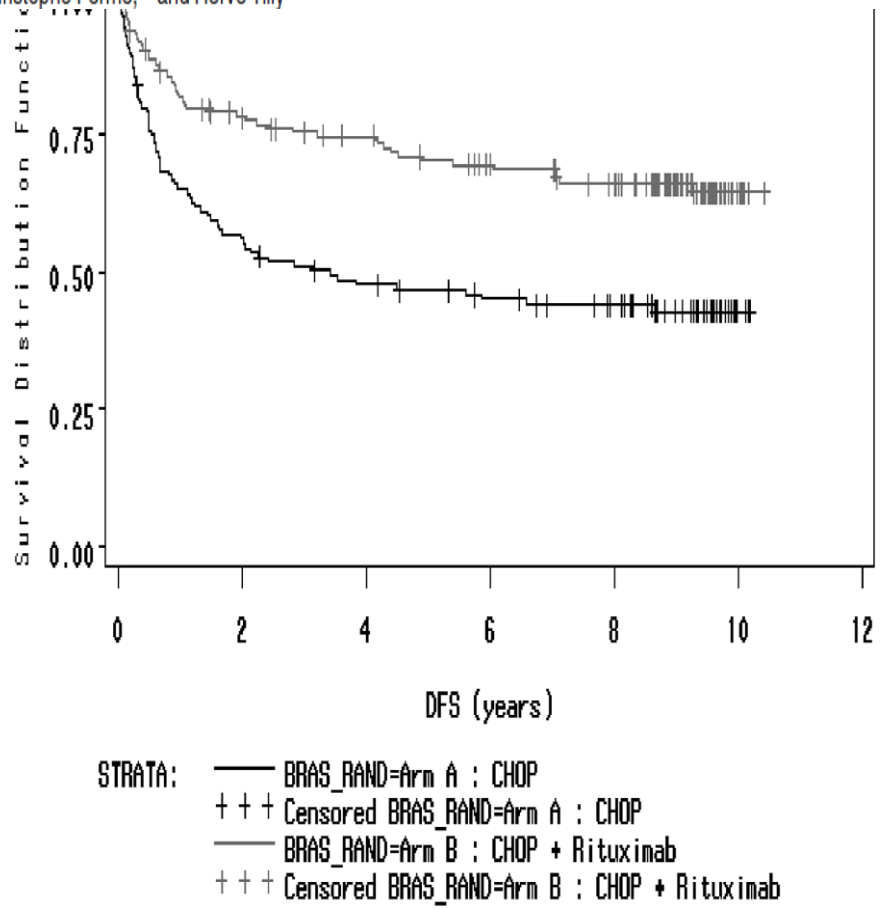
Type histologique et traitement

On distingue:

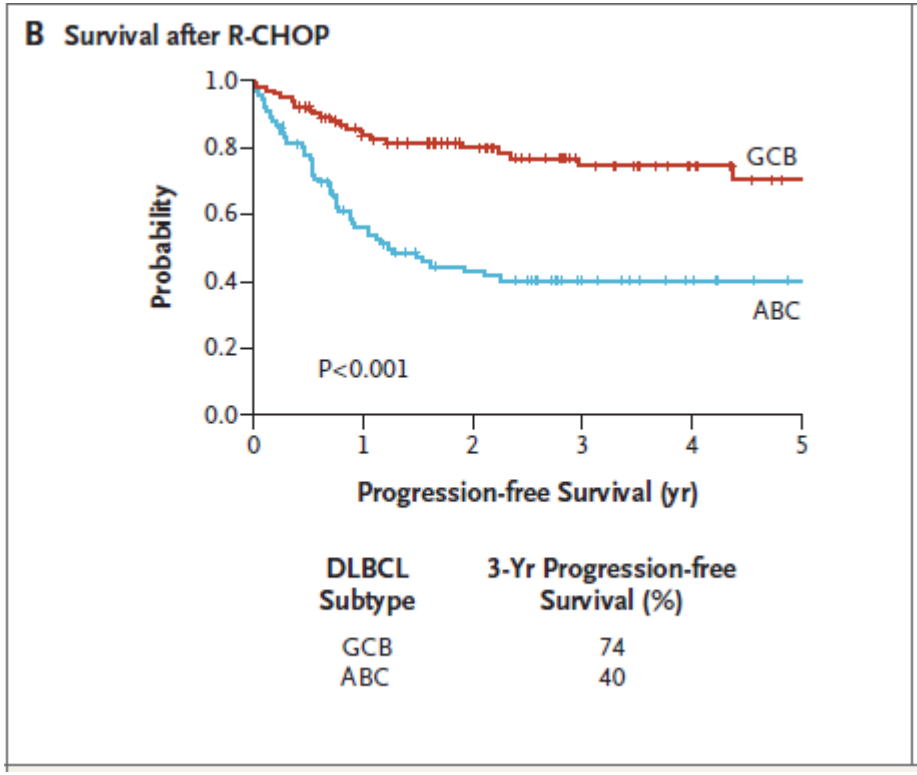
- LNH agressifs: 50-60% (retrouvés dans infection par VIH)
  - Traitement obligatoire
  - Guérison
- LMNH indolents: 40-50%
  - Traitement si symptômes ou critères forte masse
  - Incurable, récidives fréquentes

Long-term outcome of patients in the LNH-98.5 trial, the first randomized st comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte

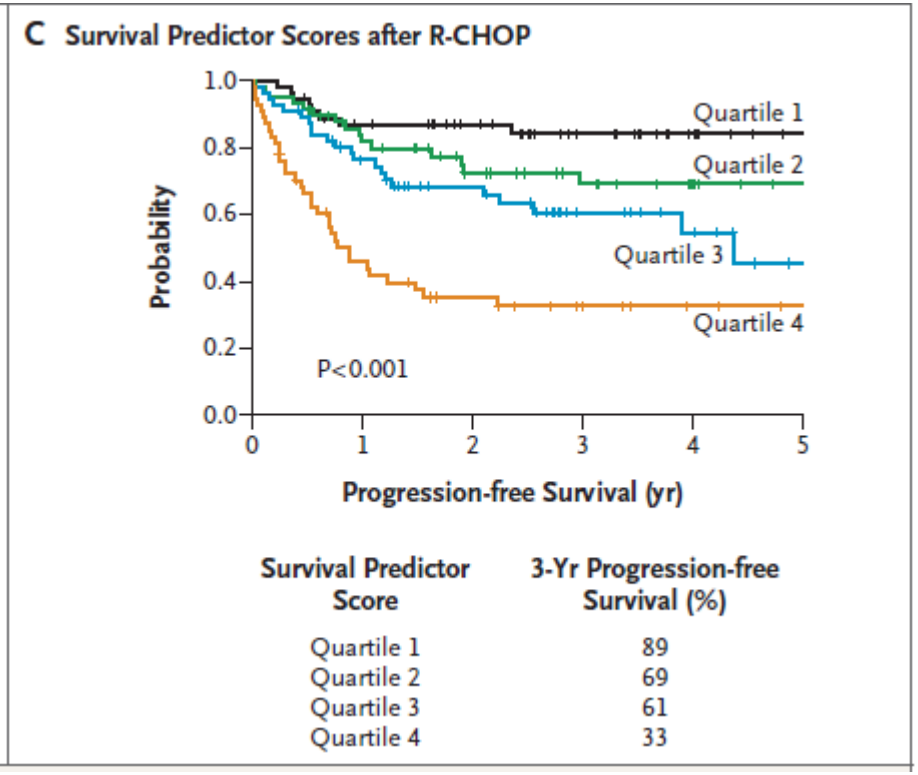
Bertrand Coiffier,[1] Catherine Thieblemont,[2] Eric Van Den Neste,[3] Gérard Lepeu,[4] Isabelle Plantier,[5] Sylvie Castaign Sophie Lefort,[7] Gérald Marit,[8] Margaret Macro,[9] Catherine Sebban,[10] Karim Belhadj,[11] Dominique Bordessoule,[12] Christophe Fermé,[13] and Hervé Tilly[14]



DLBCL: la réponse au R-CHOP est corrélée à l'expression génique



DLBCL Subtype	3-Yr Progression-free Survival (%)
GCB	74
ABC	40



Survival Predictor Score	3-Yr Progression-free Survival (%)
Quartile 1	89
Quartile 2	69
Quartile 3	61
Quartile 4	33

Mais aussi en 2017: C-MYC et BCL2
Facteurs pronostics importants.

N Engl J Med 2010;362:1417-29.

Lymphomes et VIH

Lymphomes et infection VIH

- Mécanismes pathogéniques

- Présentations cliniques et pronostic

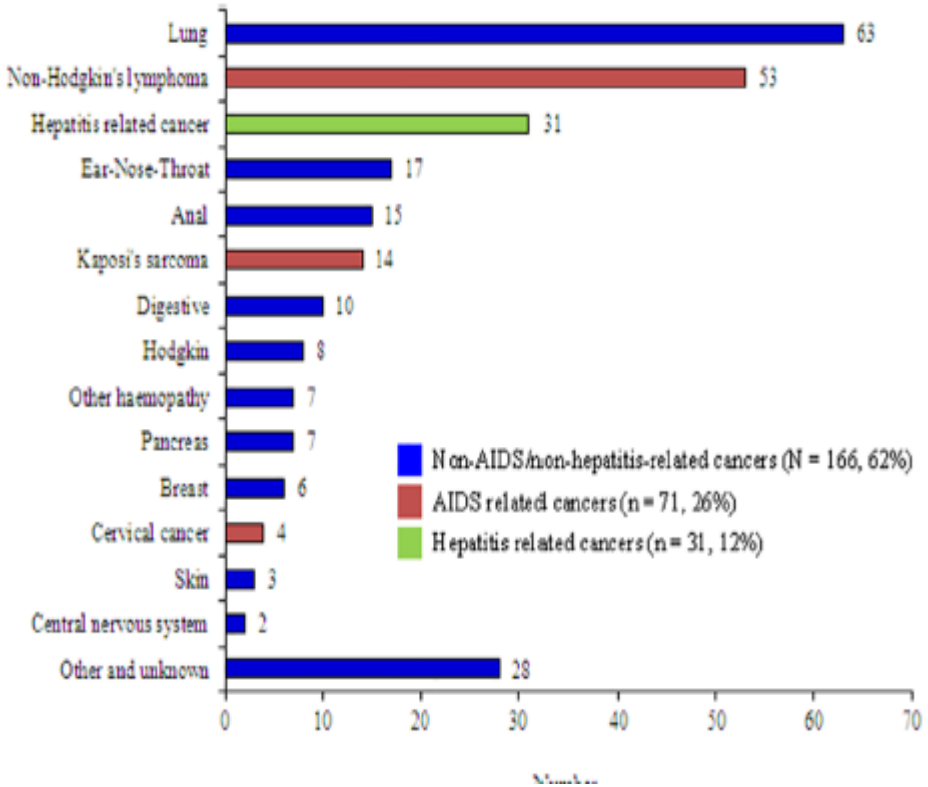
- Aspects thérapeutiques → controverses :
  - Dose intensité des chimiothérapies
  - Place des anticorps monoclonaux
  - Introduction, maintien ou non de la trithérapie antirétrovirale
  - Particularités des différentes entités: DLBCL, BL, L H,PEL

Aspects épidémiologiques: à l'ère de la trithérapie

- L'incidence du LNH associé au VIH, a considérablement diminué mais reste plus élevée comparée aux Personnes séronégatives = **10 fois**.
- Parfois révélatrice de l'infection.
- Hétérogénéité des présentations, Formes **agressives:** DLBCL, L Burkitt, LCP,…
- Stabilité voir augmentation des lymphomes survenant avec immunodépression légère: L Hodgkin et Burkitt.

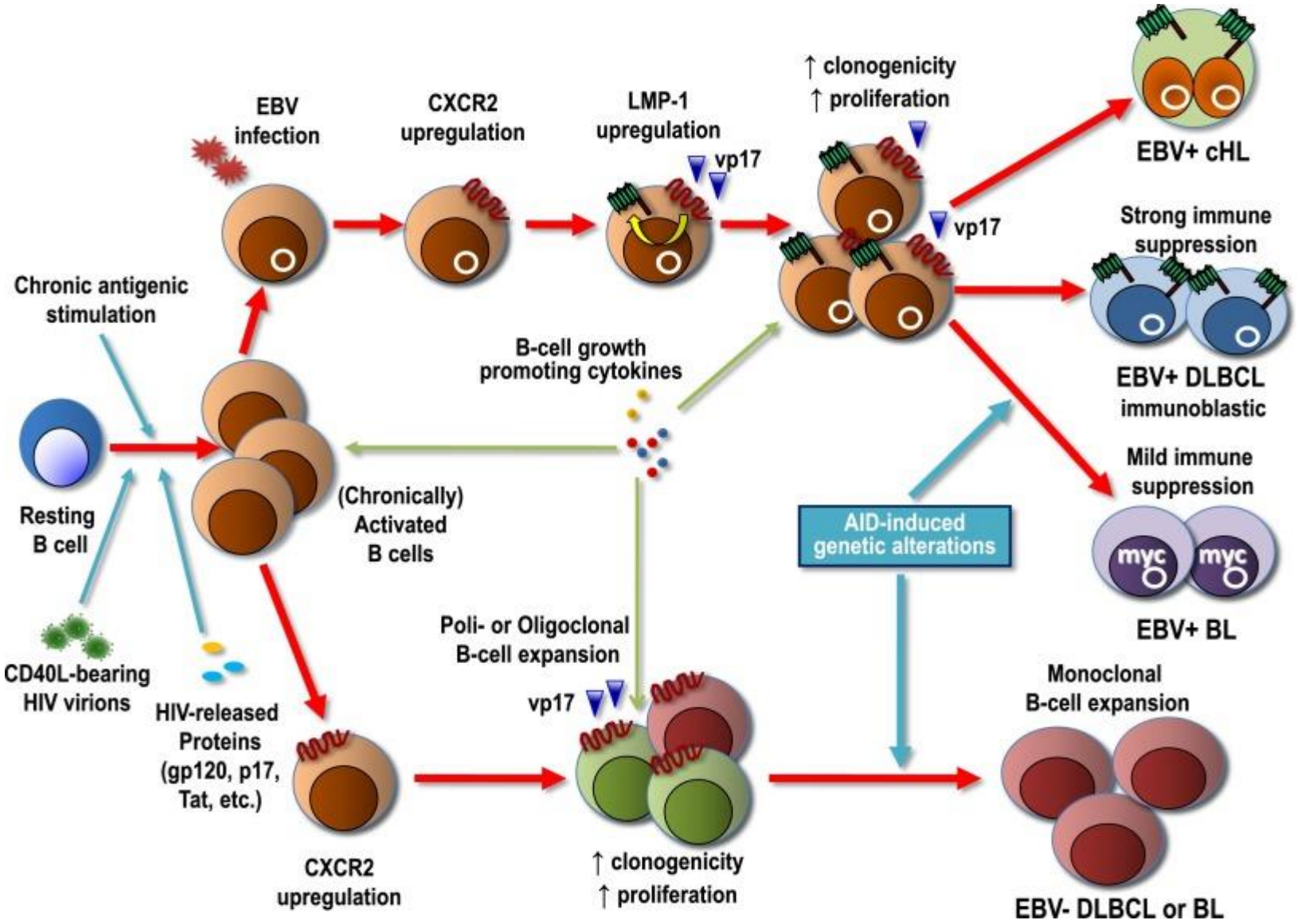
• Powles T et al JCO 2009.27:884
•Cobucci R J infect public health 2015;8:1-10
• ShielsCurr Opin HIV AIDS 2017, 12:6–11

Aspects épidémiologiques: à l'ère de la trithérapie



Marie-Anne Vandenhende. PLOS 2014

Aspects étiologiques: Modèle rôle EBV et HIV



Dolcetti R. Blood. 2016:127: 1403–1409.

Place EBV et HIV- Lymphome

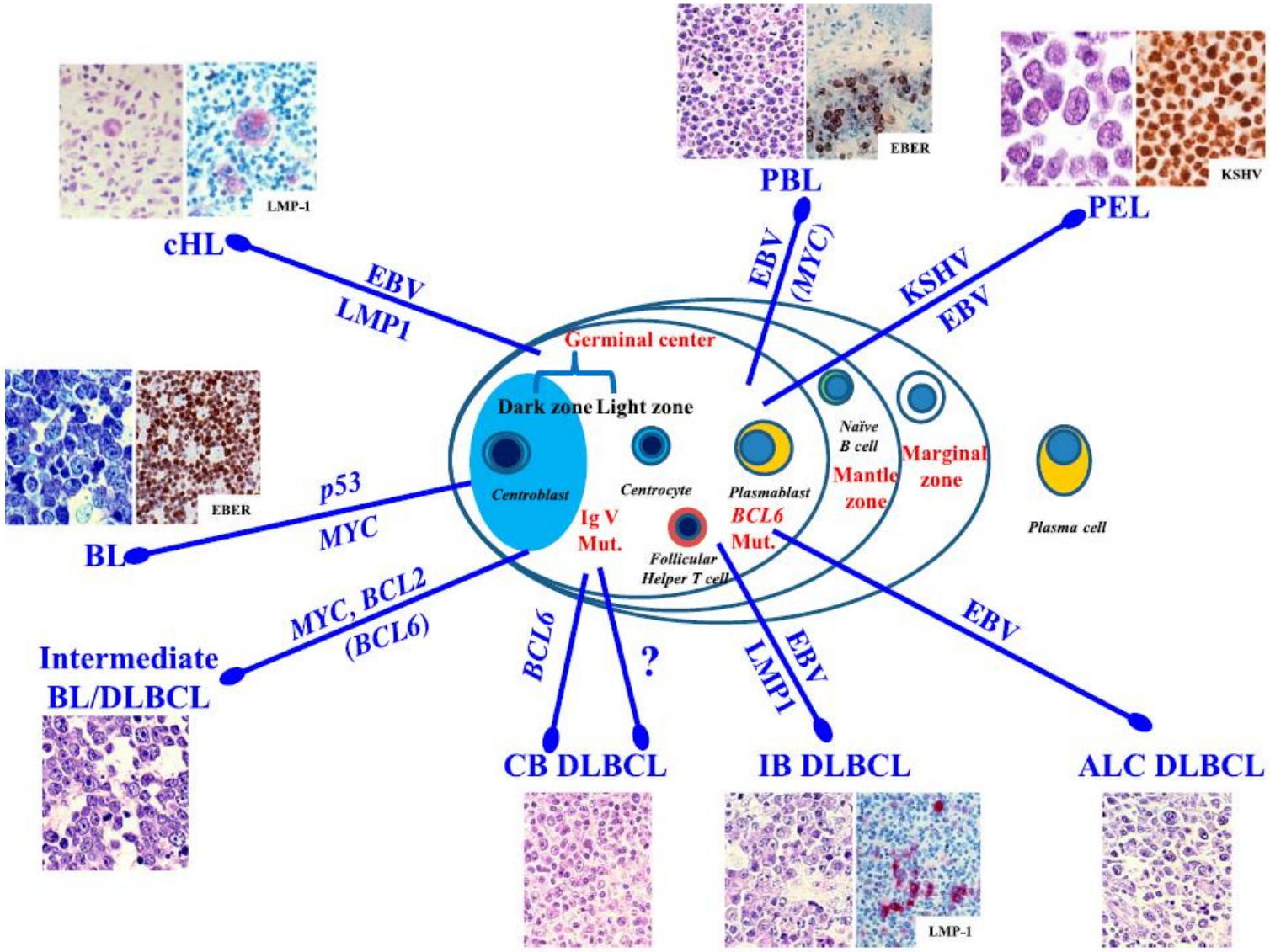
Table 1. Viral and genetic abnormalities in human immunodeficiency virus (HIV)–associated lymphomas

Histologic subtype	EBV +	KSHV/HHV-8+	Common recurring chromosomal abnormalities
Diffuse large B-cell lymphoma			*MYC* (10%); *BCL6* (20% of centroblastic DLBCL)[19,20] *TP53* (40%)[5,88]
Centroblastic	30%[2,10,11]	0	
Immunoblastic	80-90%[2,10,11]	0	
Plasmablastic lymphoma	>50%[2]	80%[81]	None
Primary effusion lymphoma	100%[2,8]	100%[2,8]	None
Burkitt lymphoma	30-50%[2,9]	0	*MYC* (100%)[2]; *TP53* (50-60%)[5,88]
Primary CNS lymphoma	100%[10]	0	*BCL6* (30-40%)[2]
Hodgkin lymphoma	80-100%[2]	0	None

EBV, Epstein-Barr virus; KSHV/HHV-8, Kaposi sarcoma herpes virus/human herpes virus 8; CNS, central nervous system.

Dolcetti R. Blood. 2016:127: 1403–1409

Main viral and molecular pathogenic pathways



Différents types histologiques

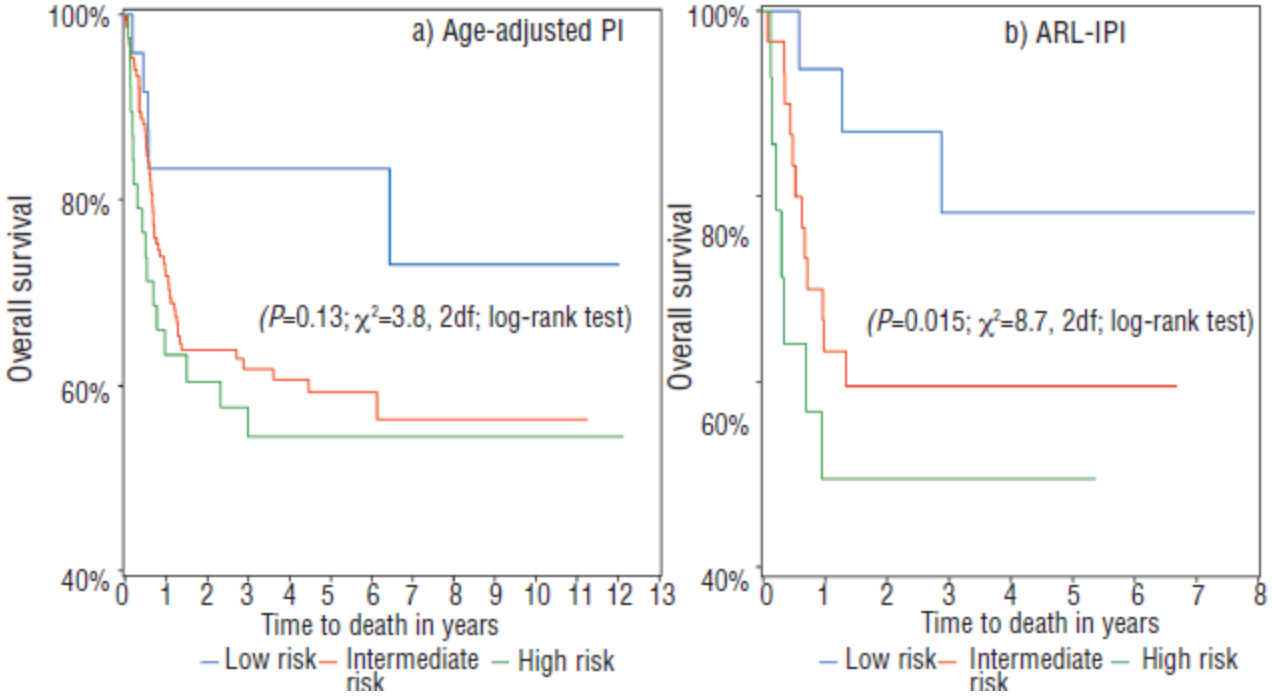
Types histologiques	Sous type	Fréquence(%)
LNH	L B diffus à grandes cellules	40
	Lymphome de burkitt	20
	Primitif cérébral	5
Lymphoproliferations associées à HHV-8	Maladie de castleman	10
	Lymphome plasmablastique	
	Lymphome des séreuses	
Lymphome de Hodgkin	Cellularité mixte	25
	scleronodulaire	
	Déplétion lymphocytaire	

Formes agressives, souvent EBV positive:
DLBCL systémique et localisation extra ganglionnaires(LCP)

• Dolcetti R. Blood. 2016:127: 1403–1409
•Mounier blood 2016

A new prognostic score for AIDS-related lymphomas in the rituximab-era

Stefan K. Barta,[1] Xiaonan Xue,[2] Dan Wang,[2] Jeannette Y. Lee,[3] Lawrence D. Kaplan,[4] Josep-Maria Ribera,[5]



- N=487, dont 244 test et 243 validation
- ARL- IPI:
  - aIPI
  - atteinte extra nodale
  - HIV score*

haematologica | 2014; 99(11)

*: CD4, CV, IO

Lymphomes et infection VIH: Aspects thérapeutiques

1) Avant thérapie antivirale: Immunodépression sévère = patient s fragiles comorbdites , majoration complications infectieuses et nutritionnelles → Sous traités

- **Intérêt dose intensité**: lymphomes agressifs curables

2) Depuis cART: patients moins immunodéprimés, moins d'IO, mais:

  - Interactions médicamenteuses: suspendre cART?
  - Malades non inclus dans des protocoles: critères d'exclusion
  - Etudes dédiées rares
  - Extrapolation études faites chez séronégatives

Comment on Noy et al, page 160

To be or not to be HIV+, that is no longer the question

Stefan K. Barta FOX CHASE CANCER CENTER/TEMPLE UNIVERSITY HEALTH SYSTEM

The results of AMC 048 will hopefully go a long way in reducing the hesitancy in the medical community to allow HIV-infected patients with hematologic malignancies access to adequate care.--→ chimio intensive adaptée L Burkitt

Barta S. BLOOD, 9 JULY 2015 x VOLUME 126, page 124

Noy A et al.Blood. 2015;126(2):160-166)

SHORT COMMUNICATION

BJC

British Journal of Cancer (2015) 113, 861–863 | doi: 10.1038/bjc.2015.301

Keywords: AIDS; HIV; lymphoma; clinical trials

The exclusion of people living with HIV (PLWH) from clinical trials in lymphoma

ground: The prognosis of non-Hodgkin lymphoma and Hodgkin lymphoma is not affected by HIV serostatus, yet peo with HIV (PLWH) are frequently excluded from clinical trials in lymphoma.

hods: The UK NIHR Clinical Research Network Study Portfolio website was used to identify all the open clinical trials homa in the United Kingdom in January 2015. Trials that excluded PLWH were further investigated to evaluate if the exclus justified by scientific evidence.

lts: We identified 56 multicentre open clinical trials in lymphoma including 46 interventional trials. People living with HIV w uded from 32 interventional trials (70%). We identified a biologically valid reason (a potential increased risk of grea unosuppression) for excluding PLWH from one trial and possibly for one optional arm in another study.

clusions: There was no scientific or safety justification for excluding PLWH from most lymphoma clinical trials included on R portfolio. A clear justification for excluding PLWH was not offered in the available protocols. The exclusion of PLWH sho xplicitly justified on scientific grounds in protocols to minimise stigmatisation.

Lymphomes et infection VIH: DLBCL

- Traitement de référence en dehors VIH: R-CHOP
  - Guérison >50%

⟹ Actuellement Traitement comme VIH négative

- Mais attention interactions médicamenteuses et infections

- <u>Les différentes études</u>:
  - Confirment la bonne réponse corrélée à l'intensité de la chimiothérapie
  - Les complications infectieuses
  - L'intérêt de la trithérapie associée

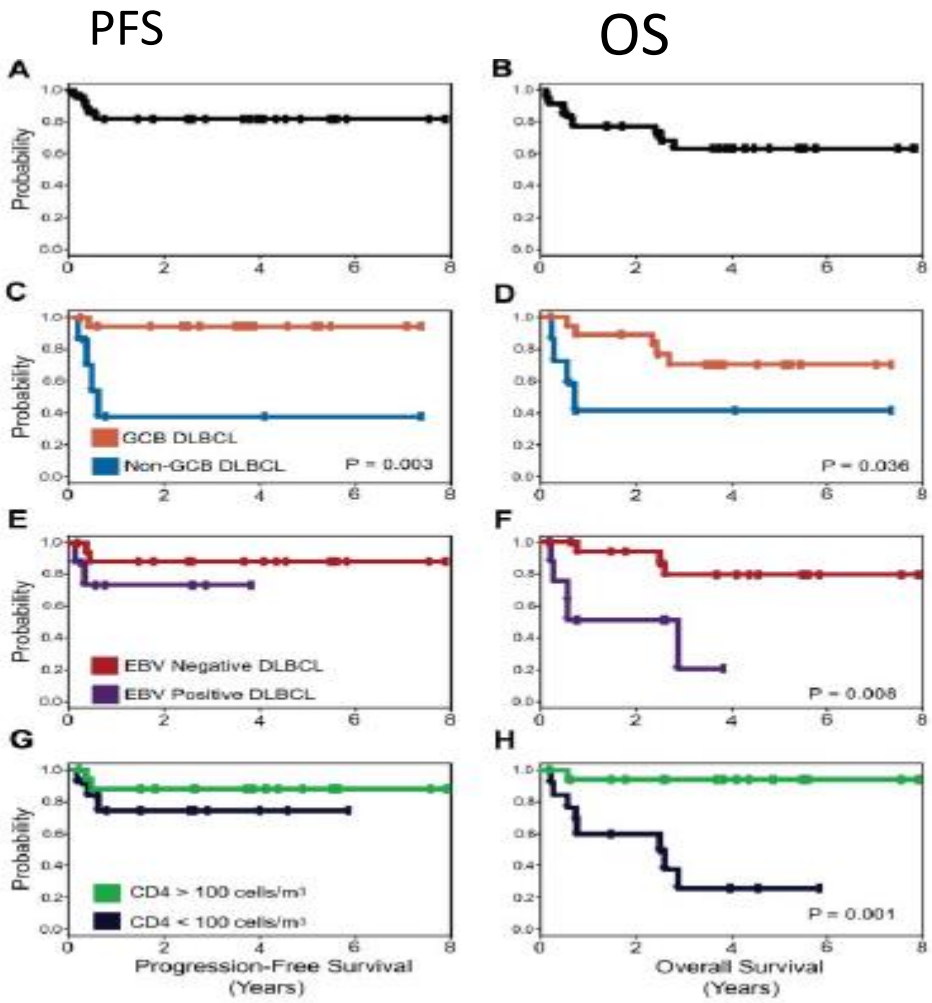
Traitement DLBCL

Table 2. Pivotal trials in HIV-associated lymphomas

Study	Study type	Study design	Results
Kaplan et al[53]	Prospective multicenter randomized phase III (n=192)	Randomization to standard-dose m-BACOD with GM-CSF versus low-dose m-BACOD without GM-CSF. No cART	Similar efficiacy of both regimens but less hematological toxicity with low-dose m-BACOD
Ratner et al[62]	Prospective multicenter sequential phase II (n=65)	First 40 patients received modified-dose (m) CHOP (50% cyclophosphamide and doxorubicin) and the next 25 patients received standard-dose CHOP. cART was administered	CR higher with full dose CHOP compared to mCHOP (48% vs 30%). Authors concluded that concomitant cART was safe but unable to conclude superiority of one regimen over another
Sparano et al[65]	Prospective multicenter sequential phase II (n=98)	First 43 patients received didanosine and the next 55 patients received cART with CDE	At 2 years, FFS and OS were 36% and 43%. Patients receiving concomitant cART had better survival and less toxicity
Mounier et al[56]	Prospective multicenter phase III study	485 patients were randomly assigned to different CHOP-based chemotherapy regimens according to an HIV score that was based on performance status, prior AIDS and CD4 count	Though HIV score, IPI score and cART affected survival, the intensity of CHOP-based chemotherapy had no effect on survival
Little et al[37]	Prospective single center phase II (n=39)	All patients received EPOCH and G-CSF with cART suspension	CR was 74%. At 53 months, DFS and OS were 92% and 60%. Patients in CR achieved CD4 recovery and HIV control following treatment. Conclusion that EPOCH with cART suspension is feasible and highly effective
Kaplan et al[54]	Prospective multicenter randomized phase III (n=150)	Randomization (2:1) to R-CHOP versus CHOP with concomitant cART. Some patients received maintenance rituximab.	CR rate higher with R-CHOP compared to CHOP (57.6% vs 47%). Increased infectious deaths with R-CHOP mostly in patients with low CD4 counts. Conclusion that rituximab does not improve clinical outcome
Boue et al[63]	Prospective multicenter phase II (n=61)	All patients received R-CHOP	CR in 77% of patients. Estimated 2 year OS was 75%
Spina et al[60]	Retrospective analysis of 3 phase II trials	Pooled results from 3 trials of CDE with rituximab	CR rate was 70%. At 2 years, FFS and OS were 59% and 64%. Conclusion that R-CDE is effective but rituximab may increase infections
Sparano et al[49]	Prospective multicenter phase II study	101 patients were randomized to receive either concurrent or sequential rituximab with DA-EPOCH	There was a superior outcome with concurrent rituximab and DA-EPOCH (CR rate 75%) and this was considerably better when compared to the previous ANC results with CHOP +/- R
Dunleavy et al[47]	Prospective single center phase II (n=33)	All patients received SC-EPOCH-RR with cART suspension	79% of patients needed only 3 cycles of treatment. At 5 year follow-up, PFS and OS were 84% and 68%. Outcome was better for GCB versus non-GCB DLBCL (5 year PFS of 95% versus 44%).

GM-CSF, granulocyte macrophage colony-stimulating factor; G-CSF, granulocyte colony stimulating factor; cART, combined anti-retroviral therapy; CR, complete remission; FFS, failure-free survival; OS, overall urvival; DFS, disease-free survival, m-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R, rituximab; CDE, Cyclophosphamide, doxorubicin, and etoposide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DA, dose adjusted; SC short course

Traitement DLBCL



PFS et OS :

1) A et B: global
2) C et D: statut moléculaire
3) E et F Statut EBV
4) G et H: selon taux CD4.

Dunleavy K ***Blood. 2012;119:*3245-3255**

Traitement DLBCL en rechute: autogreffe faisable?

CLINICAL TRIALS AND OBSERVATIONS

Comment on Alvarnas et al, page 1050

A new standard for HIV-associated lymphoma ?

Andrew R. Rezvani STANFORD UNIVERSITY

In this issue of *Blood*, Alvarnas et al report a prospective multicenter clinical trial demonstrating that autologous hematopoietic cell transplantation (AHCT) can be performed safely and effectively in patients with HIV-associated lymphomas, with success rates comparable to those in the HIV-negative population.[1]

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Autologous hematopoietic cell transplantation for H lymphoma: results of the BMT CTN 0803/AMC 07

Joseph C. Alvarnas,[1] Jennifer Le Rademacher,[2] Yanli Wang,[3] Richard F. Little,[4] Gorgu

Key Points

- Autologous hematopoietic cell transplantation is safe and effective in patients with HIV-related lymphoma who meet standard transplant criteria.
- Patients with HIV-related lymphomas should not be precluded from participating in AHCT clinical trials.

TRM: 5.2%

Rechute Autogreffe faisable

- Phase 2
- N=43
- TRM 5,2%
- Comparaison historique
- Conclusion: VIH ne devrait pas etre une CI

1. Alvarnas JC,. Blood. 2016;128:1050-1058

Lymphome cérébral primitif=LCP

Mme LAV M âgée de 63 ans:

- Antécédents: Thyroïdectomie en 2004 (hyperthyroïdie),
- Céphalées frontales d'aggravation progressive,
- TDM cérébral+ IRM cérébral : lésion temporo pariétale gauche hémorragique,
- Biopsie neurochirurgicale, anapath: **DLBCL= lymphome B diffus à grande cellules, post-centro-germinatif. -ABC. EBV+(EBER positive).**
- Bilan d'extension: - ponction lombaire : non envahie.
- Scanner TAP : pas de lésion extra cérébrale
- Moelle normale.

Conclusion: LCP

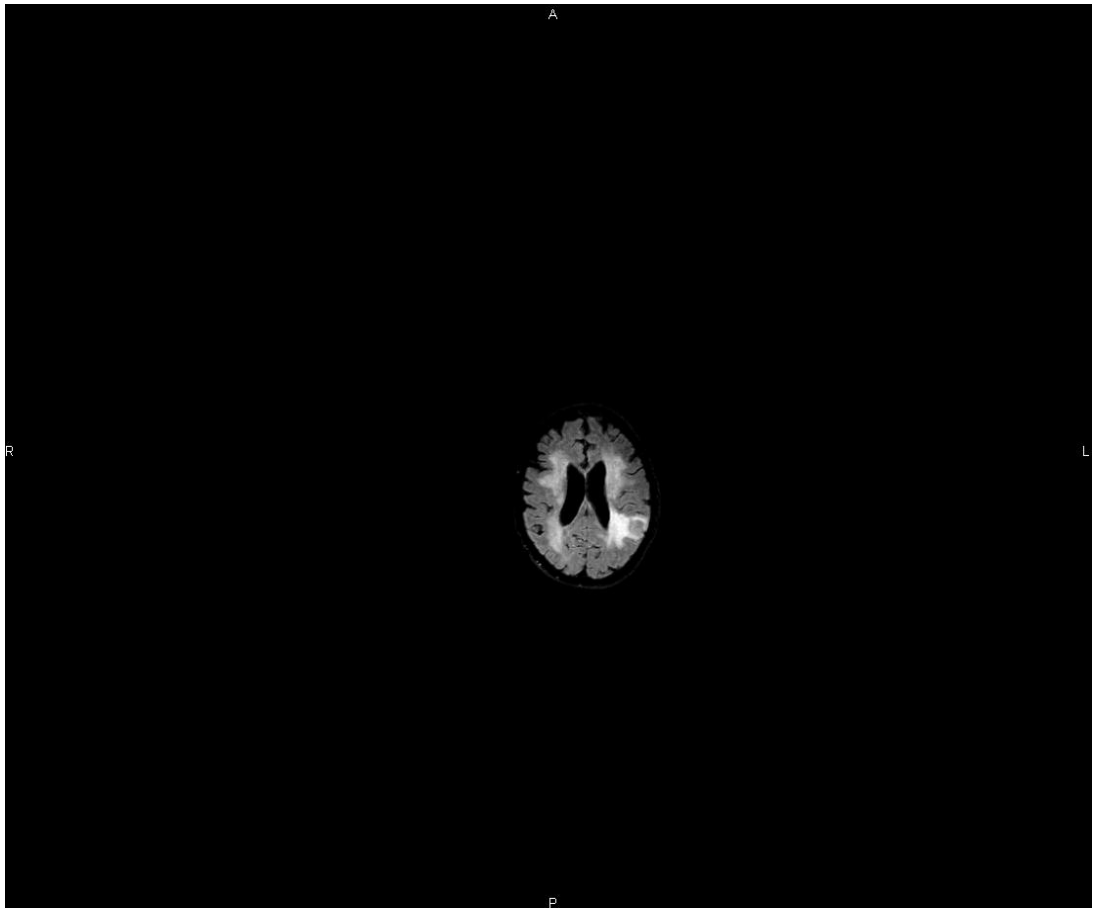
Bilan PR thérapeutique:

- découverte **sérologie VIH positive, charge virale 152000, taux de CD4** à **51/mm3.** immuno chimiothérapie R-MPVA et transfert infectiologie introduction : ATR par raltegravir et truvada.

Evolution: Plusieurs complications, AEG avec alitement prolongé, embolie pulmonaire, hématome sous dural, hématologique, infections.. Echec du Traitement malgré 2 lignes. Immuno CD4 toujours<100 malgré amorce baisse CV.

Décès.

Mme LAV M: IRM au diagnostic avec plusieurs lésions



Lymphome cérébral primitif et VIH

- Survient au stade immunosuppression sévère= Définition SIDA
- Lésions cérébrales surtout multiples
- Diagnostic différentiel multiples dans ce contexte: toxoplasmose…
- Immuno-chimiothérapie: Rituximab et méthotrexate aracytine comme chez séronégative. Rôle radiothérapie? Toxicité
- Pronostic sombre
- Chez certains patients, l'autogreffe peut être faisable

- A O'Neill. Bone Marrow Transplantation (2015) 50, 999–1000
- Blood 2012

LETTER TO THE EDITOR

Outcomes for HIV-positive patients with primary central nervous system lymphoma after high-dose chemotherapy and auto-SCT

Table 1. Initial ART and chemotherapy regimens

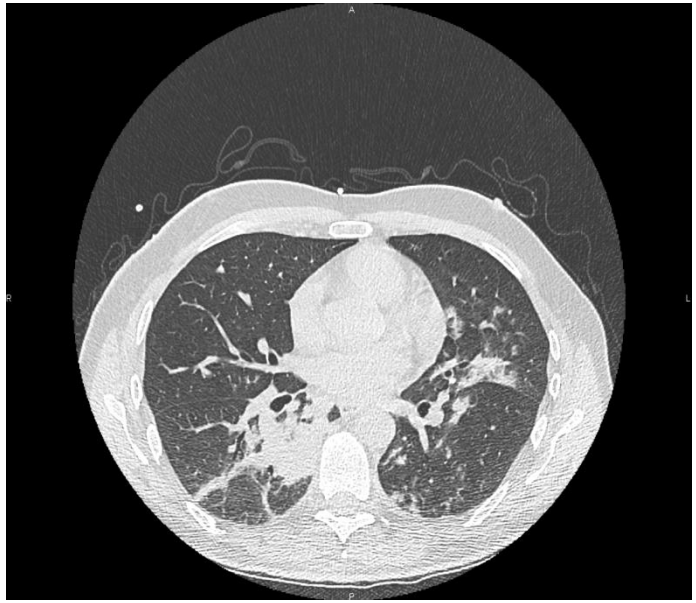
	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
HIV VL (copies/mL) at diagnosis	6052	578 144	5.7 million	847 000	< 40
CD4+ cell count ($\times 10^6$/L) at diagnosis	21	165	44	100	1046
Initial ART	Kal, RAL, Truv	RAL, Truv,	EFV, FTC, TDF	RAL, Truv	RAL, Truv
Initial chemotherapy	MTX, Ara-C, R[a]	MTX, Ara-C, R	MTX, Ara-C, R, Thio	MTX, Ara-C, R, Thio	MTX, Ara-C, R
SCT conditioning chemotherapy	Car, Thio	Car, Thio	Car, Thio	Car, Thio	Car, Thio
Outcome	CR, maintained 30 months after transplant	Death from transplant-related complications	CR, maintained 36 months after transplant	Death from transplant-related complications	CR, maintained 7 months after transplant

Abbreviations: Ara-C = cytarabine; ART = antiretroviral therapy; Car = carmustine; EFV = efavirenz; FTC = emtricitabin; Kal = Kaletra; MTX = high-dose MTX; R = rituximab; RAL = raltegravir; TDF = tenofovir; Thio = thiotepa; Truv = Truvada; VL = viral load. [a]Rituximab in the first cycle only.

Bone Marrow Transplantation (2015) **50,** 999–1000

Lymphome de burkitt et VIH

- Mr CHA C , 45 ans
  - VIH diagnostiqué en avril 2014, avec coïnfections syphilis, condylomes, traitement : Truvada – Prezistar-Norvir, **charge virale = 57 et CD4 = 381**
  - volumineuse adénopathie axillaire droite (10 x 10 cm)évoluant< 1 mois. apparition de céphalées et d'une diplopie binoculaire par paralysie du VI droit.= Atteinte SNC clinique et IRM. **Biopsie lymphome de Burkitt**.
  - R chimiothérapie(COPADM, CYVE). RC mais toxicité hématologiques+++ complications infectieuses,
  - Vivant RC avec séquelles OPH 18 mois post chimiothérapie



Probable aspergillose

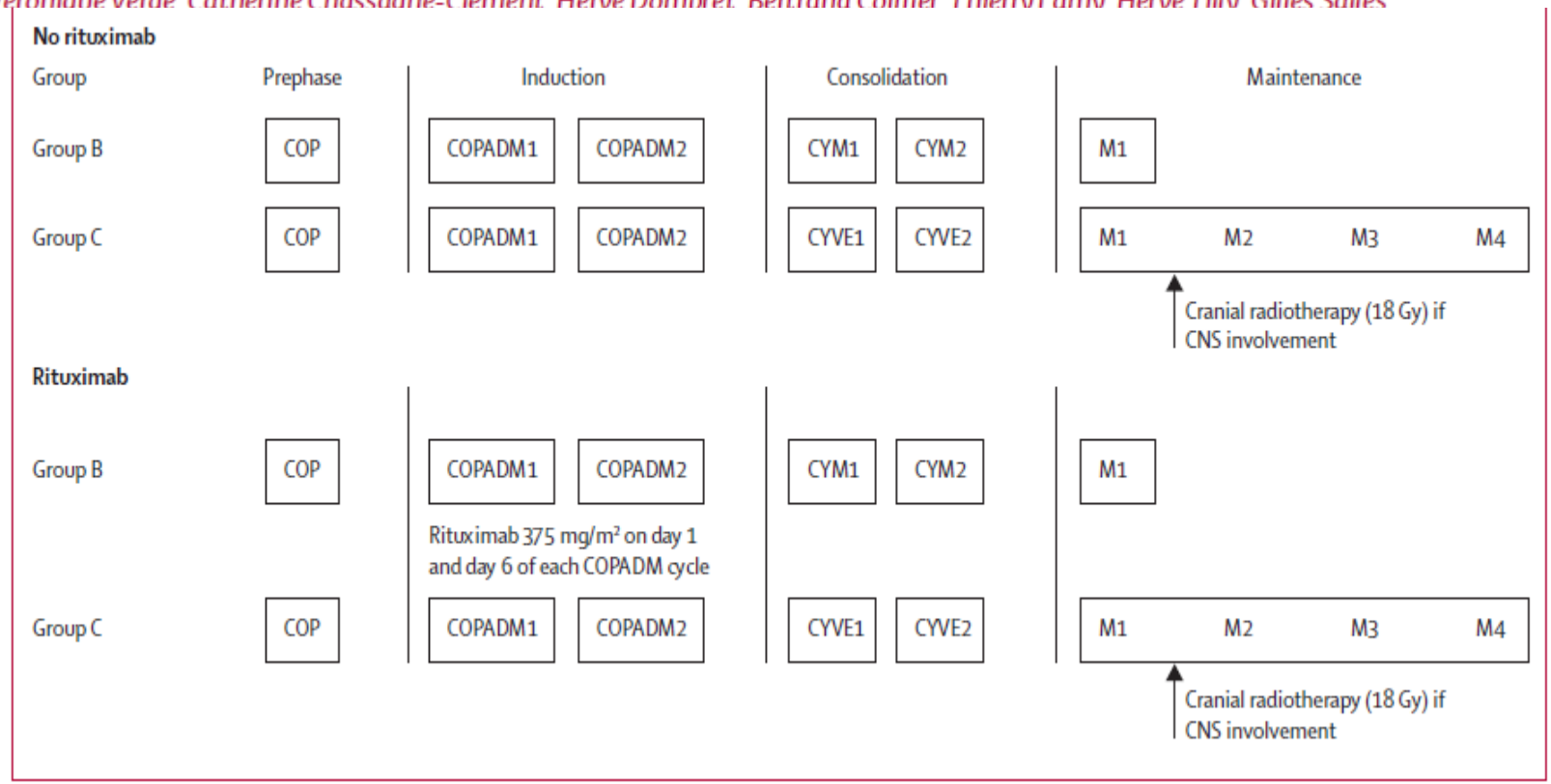
lymphomes de Burkitt et VIH

- Immunosuppression souvent légère
- Présentation très agressive
- Fréquence atteinte extra nodale: MO, SNC, tube digestif,..
- Urgence thérapeutique, syndrome de lyse, réa
- Chimiothérapie intensive
- Toxicité hématologique
- Malgré complications infectieuses, résultats comparables VIH-

Noy A et al.Blood. 2015;126(2):160-166

Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial

Vincent Ribrag, Serge Koscielny, Jacques Bosq, Thibaut Leguay, Olivier Casasnovas, Luc-Mathieu Fornecker, Christian Recher, Hervé Ghesquieres, Franck Morschhauser, Stéphane Girault, Steven Le Gouill, Mario Ojeda-Uribe, Clara Mariette, Jerome Cornillon, Guillaume Cartron, Veronique Verge, Catherine Chassagne-Clément, Hervé Dombret, Bertrand Coiffier, Thierry Lamy, Hervé Tilly, Gilles Salles



Ribrag V et al. ***Lancet 2016; 387: 2402–11***

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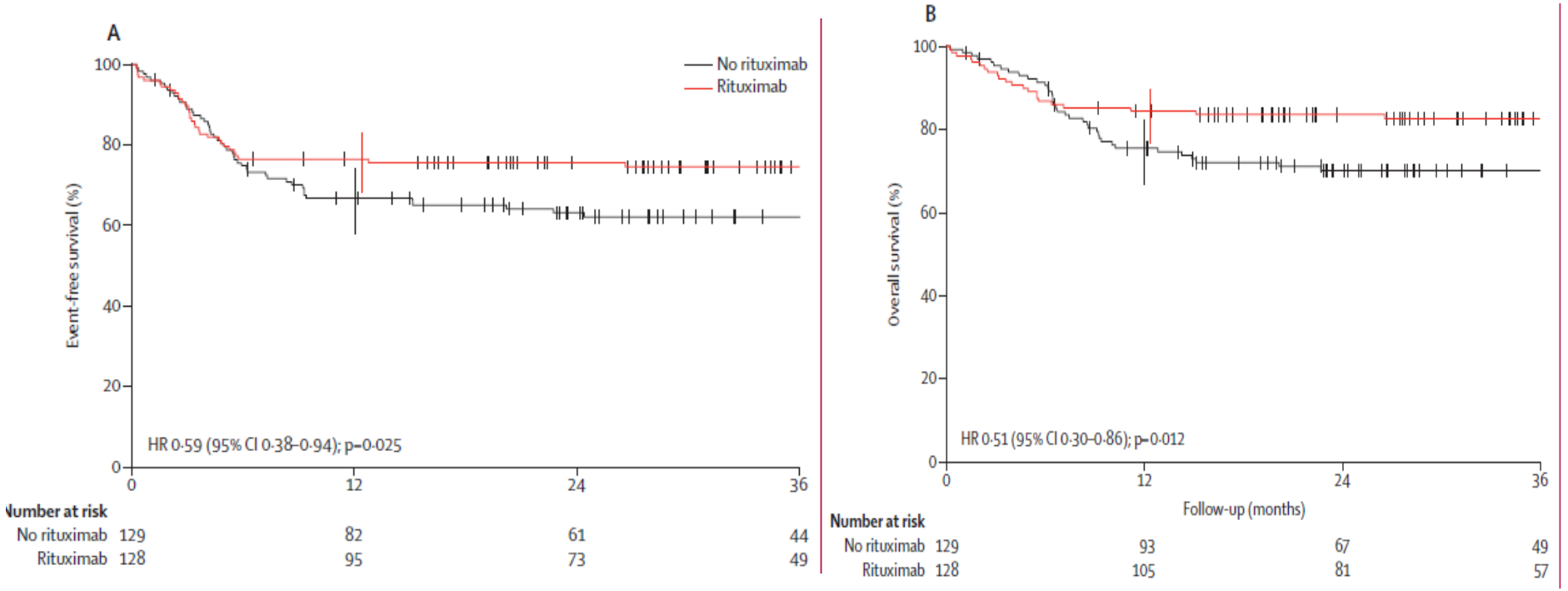

Figure 3: (A) Event-free and (B) overall survival

Ribrag V et al. ***Lancet 2016; 387: 2402–11***

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective f HIV-associated Burkitt lymphoma

Ariela Noy,[1] Jeannette Y. Lee,[2] Ethel Cesarman,[3] Richard Ambinder,[4] Robert Baiocchi,[5] Erin Reid,[6] Lee Ratner,[7] Nina Wagner-Johnston,[7] and Lawrence Kaplan,[8] for the AIDS Malignancy Consortium

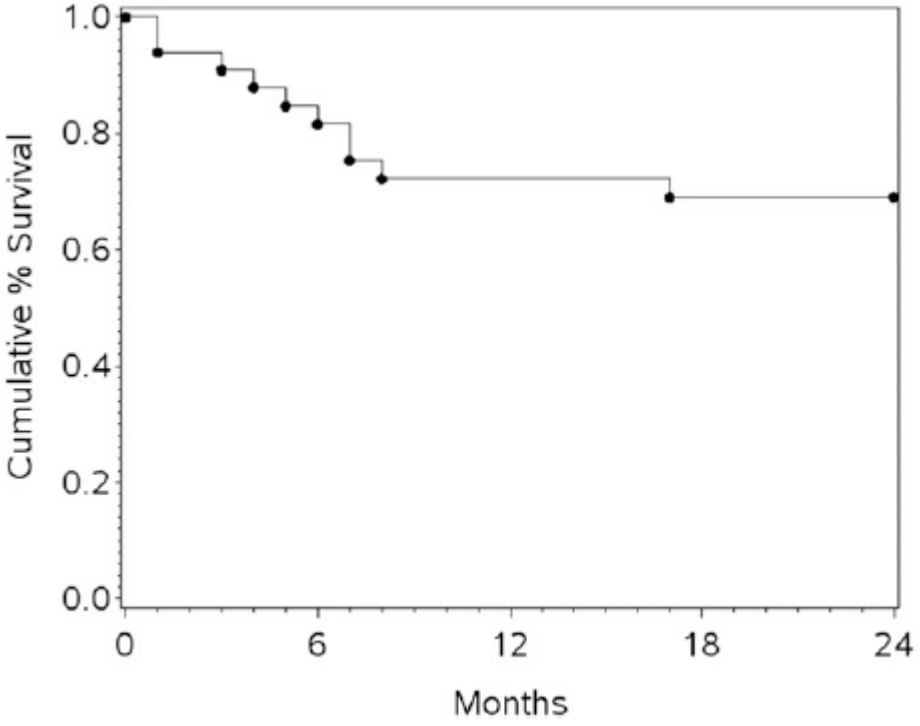

Figure 1. Cumulative survival for all enrolled patients.

Etude prospective, multicentrique
N=34
Réduction des doses de chimiothérapie
Maintien efficacité

Noy A et al.Blood. 2015;126(2):160-166)

VIH et lymphomes de Burkitt: schéma court

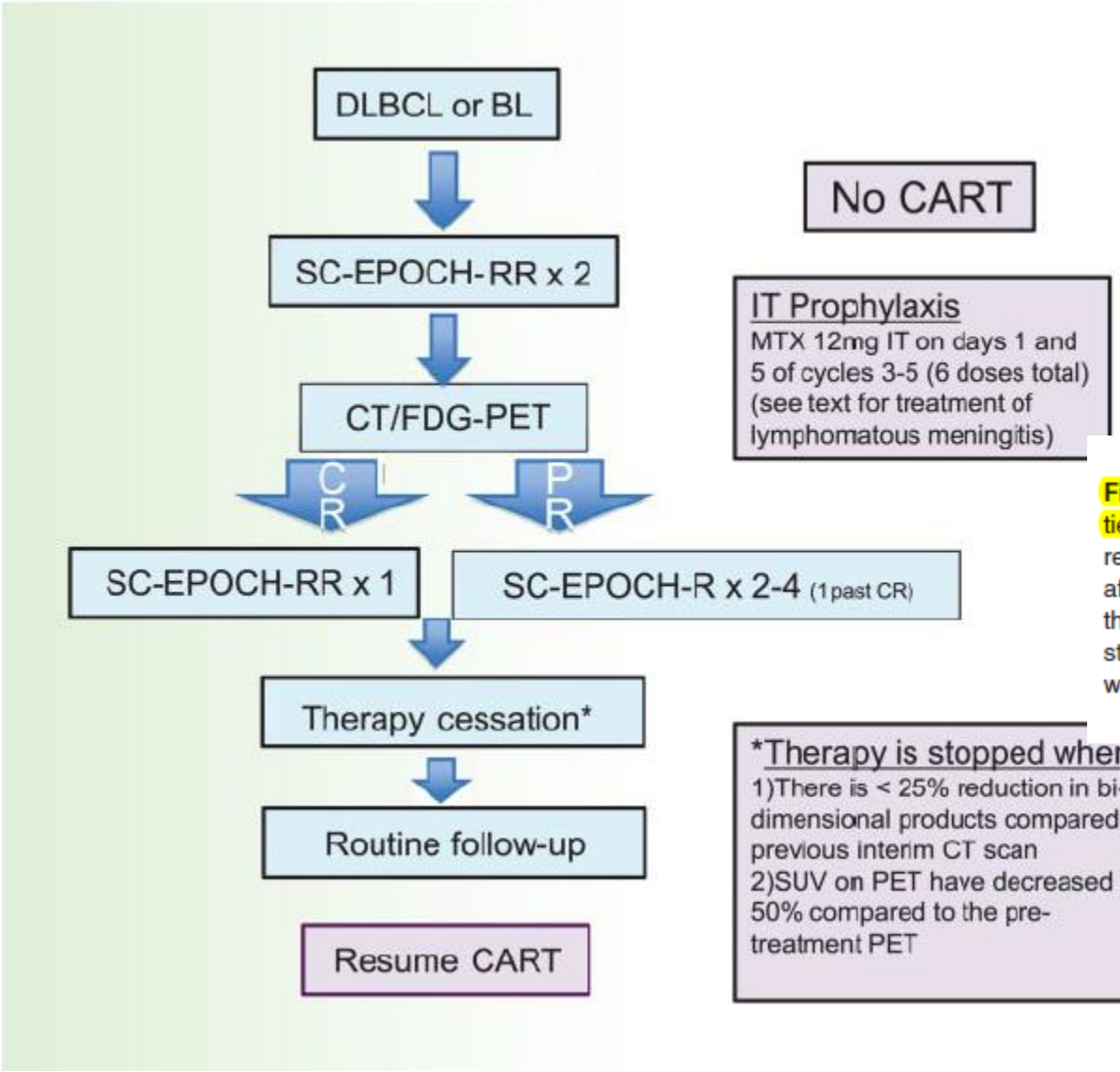

Figure 3. SC-EPOCH-RR treatment paradigm. Pa
tients receive 2 cycles of SC-EPOCH-RR and are the
restaged by CT and FDG-PET scanning. Patients in C
after 2 cycles receive one more cycle (minimum 3)
therapy. Patients with a "positive" CT and/or FDG-PE
study after 2 cycles receive additional cycles until the
were negative, for a maximum of 6 cycles.

Autres lymphomes

- L Hodgkin: traitement comparable VIH négative
- PEL
- L Plasmablastique
- Maladie de castelman

- Entité rare
- Pronostic mauvais

Coïnfection: VHC VHB VIH

- MR CO L 28 ans. VIH diagnostic âge 9 ans, traité que début 2016. CD4 291, CV?
- Découverte myélome grave avec PT 144g/l, pic 106, anémie sévère 5g, hypercalcémie, insuffisance rénale créatinine 335 µmol, lésions osseuses, multiples. Poly adénopathies<2 cm et splénomégalie. MO 18% plasmocytes. Caryotype échec.
- Coïnfections:
  - Vih: CD4 CV?
  - HVB: Ag Hbs+, Ac-
  - HVC+
- Traitement:
- 1) myélome: bortezomib-dexamethasone+/-thalidomide
- 2) VIH: isentress+Ziagen
- 3) VHB: lamivudine
- 4) prophylaxie TBC: Rimifon

Coïnfection: VHC VHB VIH

- Complications:
  - très rapidement cytolyse dépassant parfois transa>1000. arrêt rimifon et thalidomide
  - Pic transa après injection bortezomib-→ réduction des doses amélioration, mais
  - Perte réponse sur le myélome. Discussion pluridisciplinaire
  - Malgré augmentation doses, échappement, mais poursuite amélioration BH, négativation des charges virales.
  - Décision RCSP mobilisées par chimiothérapie endoxan FD. Bonne tolérance
  - Autogreffe melphalan FD octobre 2016. Bien tolérée

Actuellement: va bien, en rémission de son myélome sous traitement d'entretien, charges virales indétectables, CD4 250 mais post autogreffe.

Cette observation montre, sujet très jeune, les difficultés de prise en charge, interactions médicamenteuses

Intérêt prise en charge pluridisciplinaire

Maintien si possible le programme de Traitement selon patient séronégatif

Perspectives: Le futur

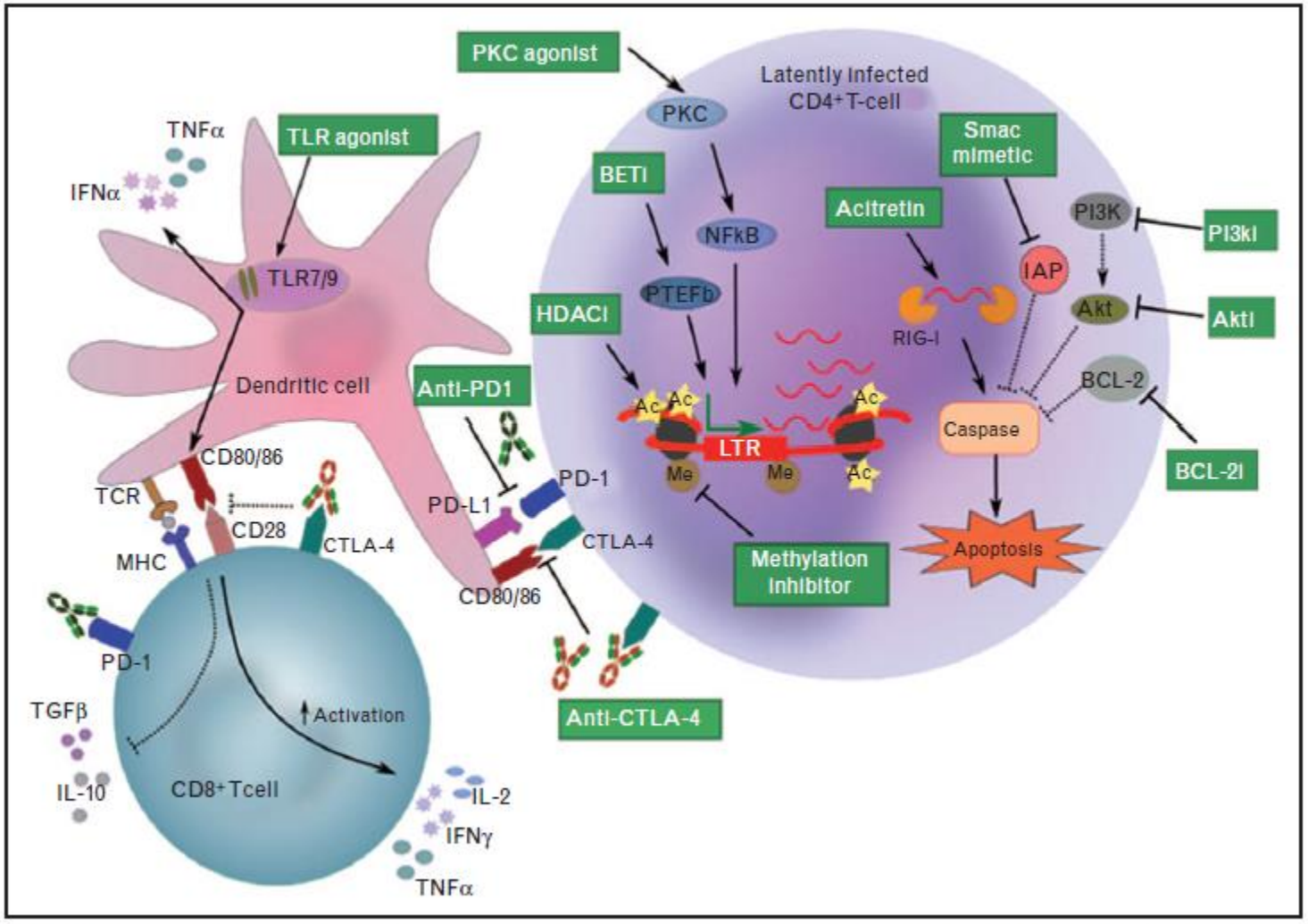

FIGURE 1. Anticancer compounds with potential to target HIV persistence. Latency reversing agents (LRAs) that induce HIV

Molécules actives à la fois sur le virus VIH et le cancer

Perspectives: Le futur

Table 1. Cancer therapies investigated in HIV

Drug class	Promising compounds in HIV research	Clinical development phase in oncology	Proposed effect in HIV infection	Clinical studies in HIV
(i) Latency reversing agents				
HDAC inhibitors	Vorinostat, romidepsin, panobinostat	Licensed (CTCL, MM)	Reversing HIV latency by chromatin remodelling	Yes, refs [9–13]
BET inhibitors	OTX015, JQ1	Phase 1/2	Reversing HIV latency by promoting recruitment of P-TEFb to the HIV LTR	No
Histone methyltransferase inhibitors	Low doses only of chaetocin, BIX-01294 or DNZep	Not safe at doses tested/preclinical	Prevents histone 3 methylation that represses HIV transcription, thereby reactivating latent HIV	No
DNA methyltransferase inhibitors	Azacitidine, decitabine	Licensed (MDS)	Prevents CpG methylation at the HIV promoter that represses HIV transcription	No
PKC agonists	Bryostatin-1, prostratin	Phase 1/2	Reversing HIV latency by activating NF-κB signalling pathways	Yes, ref. [17•]
(ii) Apoptosis promoting compounds				
BCL-2 antagonists	Venetoclax	Licensed (CLL), phases 1–3	Inhibits antiapoptotic BCL-2, sensitizing cells to apoptosis. When combined with LRA reactivation, leads to preferential apoptosis of HIV-infected cells	No
RIG-I inducers	Acitretin	Licensed (psoriasis only)	Reactivates HIV transcription and activates RIG-I induced apoptosis, leading to selective apoptosis of HIV-infected cells	No
PI3k/Akt inhibitors	Perifosine, arctigenin	Phase 1/2	Blocks PI3K/Akt pathway signalling, sensitizing HIV-infected cells for apoptosis	No
SMAC mimetics	Birinapant, SBI-0637142, LCL161	Phase 1/2	Inhibits inhibitor of apoptosis proteins (IAPs), sensitizing HIV-infected cells for apoptosis, induces viral replication	No
Tyrosine kinase inhibitors	Ibrutinib	Licensed	Impairs Bruton's tyrosine kinase on the surface of HIV-infected cells, inducing selective depletion of HIV-infected cells	No
(iii) Immune modulation				
Immune checkpoint inhibitors	Ipilimumab, pembrolizumab, nivolumab	Licensed (melanoma, NSCLC)	Enhancing HIV-specific T cell responses; reversing HIV latency	Yes, ref [60]
TLR agonists	GS-9620, MGN1703	Phase 1, 2	Activating DCs and NK cells; reversing HIV latency	Yes, refs [76,78]

Lymphomes et VIH: Conclusion

- Malgré la trithérapie, le risque de lymphome reste élevé
- Lymphomes agressifs potentiellement curables
- Malgré la paucité d'études randomisées, expérience croissante étude prospectives
- Traitement comme VIH négative moyennant précautions
- A quand inclusions protocoles?

JE VOUS REMERCIE