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2022 : Une année particulière pour la classification des lymphomes ?

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IMRB INSTITUT MONDOR DE RECHERCHE BIOMÉDICALE

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Retour à des temps anciens ….
2 classifications des lymphomes en 2022

Retour à des temps anciens ….
2 classifications des lymphomes en 2022

blood® Special Report

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

Elias Campo,[1] Elaine S. Jaffe,[2] James R. Cook,[3] Leticia Quintanilla-Martinez,[4] Steven H. Swerdlow,[5] Kenneth C. Anderson,[6] Pierre Brousset,[7] Lorenzo Cerroni,[8] Laurence de Leval,[9] Stefan Dirnhofer,[10] Ahmet Dogan,[11] Andrew L. Feldman,[12] Falko Fend,[4] Jonathan W. Friedberg,[13] Philippe Gaulard,[14,15] Paolo Ghia,[16] Steven M. Horwitz,[17] Rebecca L. King,[12] Gilles Salles,[17] Jesus San-Miguel,[18] John F. Seymour,[19] Steven P. Treon,[6] Julie M. Vose,[20] Emanuele Zucca,[21] Ranjana Advani,[22] Stephen Ansell,[23] Wing-Yan Au,[24] Carlos Barrionuevo,[25] Leif Bergsagel,[26] Wing C. Chan,[27] Jeffrey I. Cohen,[28] Francesco d'Amore,[29] Andrew Davies,[30] Brunangelo Falini,[31] Irene M. Ghobrial,[6,32] John R. Goodlad,[33] John G. Gribben,[34] Eric D. Hsi,[35] Brad S. Kahl,[36] Won-Seog Kim,[37] Shaji Kumar,[23] Ann S. LaCasce,[6] Camille Laurent,[7] Georg Lenz,[38] John P. Leonard,[39] Michael P. Link,[40] Armando Lopez-Guillermo,[41] Maria Victoria Mateos,[42] Elizabeth Macintyre,[43] Ari M. Melnick,[44] Franck Morschhauser,[45] Shigeo Nakamura,[46] Marina Narbaitz,[47] Astrid Pavlovsky,[48] Stefano A. Pileri,[49] Miguel Piris,[50] Barbara Pro,[51] Vincent Rajkumar,[12] Steven T. Rosen,[52] Birgitta Sander,[53] Laurie Sehn,[54] Margaret A. Shipp,[6] Sonali M. Smith,[55] Louis M. Staudt,[56] Catherine Thieblemont,[57,58] Thomas Tousseyn,[59] Wyndham H. Wilson,[56] Tadashi Yoshino,[60] Pier-Luigi Zinzani,[61] Martin Dreyling,[62] David W. Scott,[54] Jane N. Winter,[63] and Andrew D. Zelenetz[17,64]

Leukemia www.nature.com/leu

REVIEW ARTICLE OPEN

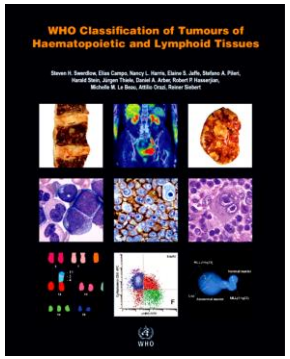
LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20]✉, Kojo S. Elenitoba-Johnson[21], Judith Ferry[22]✉, Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51]✉, Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62]✉, Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

- Les 2 représentent une actualisation de la classification OMS 2017
- ICC a été précédé d'un meeting du « Clinical Advisory Committee » à Chicago en sept. 2021
- OMS (5ème édition; WHO5) a été construite par des éditeurs choisis par l'IARC (Dr I. Cree)

Heureusement, les différences entre les 2 classifications sont limitées…



- Intégration des avancées biologiques/génétiques ayant un impact dans la définition des maladies et constituent des critères diagnostiques ou prognostiques/predictifs

- Quelques différences entre les classification ICC et OMS dans la dénomination ou en terme d'entités nouvelles

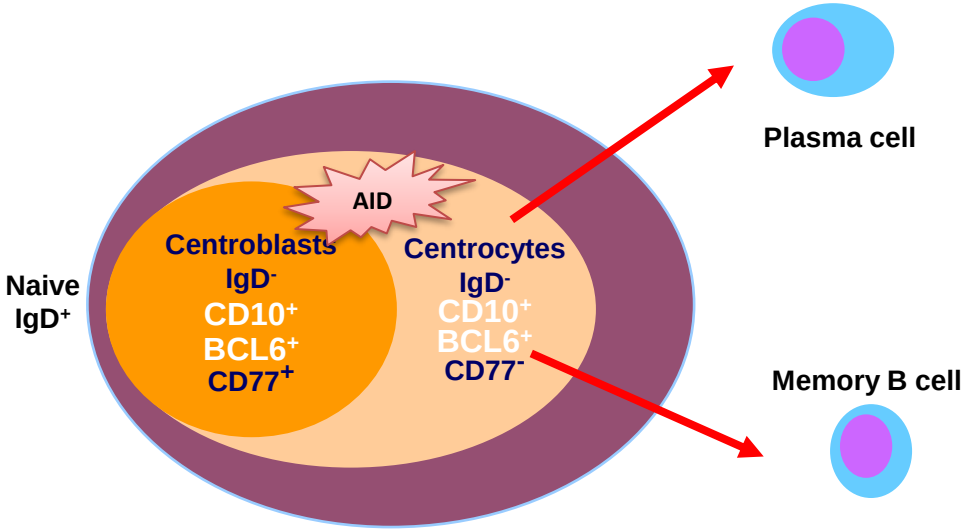
- Entités provisoires listées dans ICC, pas dans l'OMS

- OMS: - critères « souhaitables /essentiels »
  - lésions trompeuses (« tumour-like »)

Concept d'entité anatomo-clinique

Concept d'entités anatomo-cliniques

- Cellule d'origine



MCL	*FL- DLBCL (GC)* *Burkitt*	*MZL/DLBCL(ABC)* *WM/Myeloma*

- Evènements oncogèniques

✓ *Virus, autres agents infectieux (EBV, HHV8, HTLV1, HP,…)*

✓ *Translocations (t(14;18) et LF, t(11;14) et LM, t(8;14) et Burkitt,…*

✓ *Mutations ++*

Anomalies primaires ou secondaires

✓ **Morphologie**
✓ **Phénotype (IHC, CMF), HIS**
✓ **IHC, Cytogénétique, FISH,..**
✓ **Séquençage (ciblé ou non, NGS …)**
✓ **Présentation clinique, évolution, traitement**

Approche intégrée

2022: Contribution de la génétique

blood Special Report

Genomic profiling for clinical decision making in lymphoid neoplasms

Laurence de Leval,[1,*] Ash A. Alizadeh,[2-5] P. Leif Bergsagel,[6] Elias Campo,[7] Andrew Davies,[8] Ahmet Dogan,[9] Jude Fitzgibbon,[10] Steven M. Horwitz,[11] Ari M. Melnick,[12] William G. Morice,[13] Ryan D. Morin,[14-16] Bertrand Nadel,[17] Stefano A. Pileri,[18] Richard Rosenquist,[19,20] Davide Rossi,[21] Itziar Salaverria,[22] Christian Steidl,[23] Steven P. Treon,[24] Andrew D. Zelenetz,[11,12] Ranjana H. Advani,[25] Carl E. Allen,[26] Stephen M. Ansell,[27] Wing C. Chan,[28] James R. Cook,[29] Lucy B. Cook,[30] Francesco d'Amore,[31] Stefan Dirnhofer,[32] Martin Dreyling,[33] Kieron Dunleavy,[34] Andrew L. Feldman,[13] Falko Fend,[35] Philippe Gaulard,[36,37] Paolo Ghia,[38] John G. Gribben,[10] Olivier Hermine,[39] Daniel J. Hodson,[40,41] Eric D. Hsi,[42] Giorgio Inghirami,[43] Elaine S. Jaffe,[44] Kennosuke Karube,[45] Keisuke Kataoka,[46,47] Wolfram Klapper,[48] Won Seog Kim,[49] Rebecca L. King,[13] Young H. Ko,[50] Ann S. LaCasce,[24] Georg Lenz,[51] José I. Martin-Subero,[52] Miguel A. Piris,[53] Stefania Pittaluga,[44] Laura Pasqualucci,[54] Leticia Quintanilla-Martinez,[35] Scott J. Rodig,[55] Andreas Rosenwald,[56] Gilles A. Salles,[11] Jesus San-Miguel,[57] Kerry J. Savage,[23] Laurie H. Sehn,[23] Gianpietro Semenzato,[58] Louis M. Staudt,[59] Steven H. Swerdlow,[60] Constantine S. Tam,[61] Judith Trotman,[62] Julie M. Vose,[63] Oliver Weigert,[33] Wyndham H. Wilson,[59] Jane N. Winter,[64] Catherine J. Wu,[24] Pier L. Zinzani,[65] Emanuele Zucca,[21] Adam Bagg,[66] and David W. Scott[23,*]

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Mantle cell lymphoma	*CCND1* rearrangement†: FISH	Consider if CCND1 IHC is negative		MRD testing using HTS to guide treatment decisions WTS or targeted gene expression panel for proliferation and signatures of nnMCL vs cMCL
	CCND2 and *CCND3* rearrangement†: FISH	Consider in *CCND1*-R–negative tumors		
	TP53 mutation*: HTS‡		Prognostic and guide management[111]	

- ICC companion papers (lymphoid and myeloid) with current recommendations and perspective on the contribution of genomic profiling to clinical decision making
- Clinical impact:
  - test(s)
  - diagnosis
  - treatment
  - perspectives
- Selected experts for the companion papers include WHO authors

2022: quid de la Biopsie à l'aiguille …?

blood

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Lymph node excisions provide more precise lymphoma diagnoses than core biopsies: a French *Lymphopath* network survey.

Tracking no: BLD-2022-015520R1

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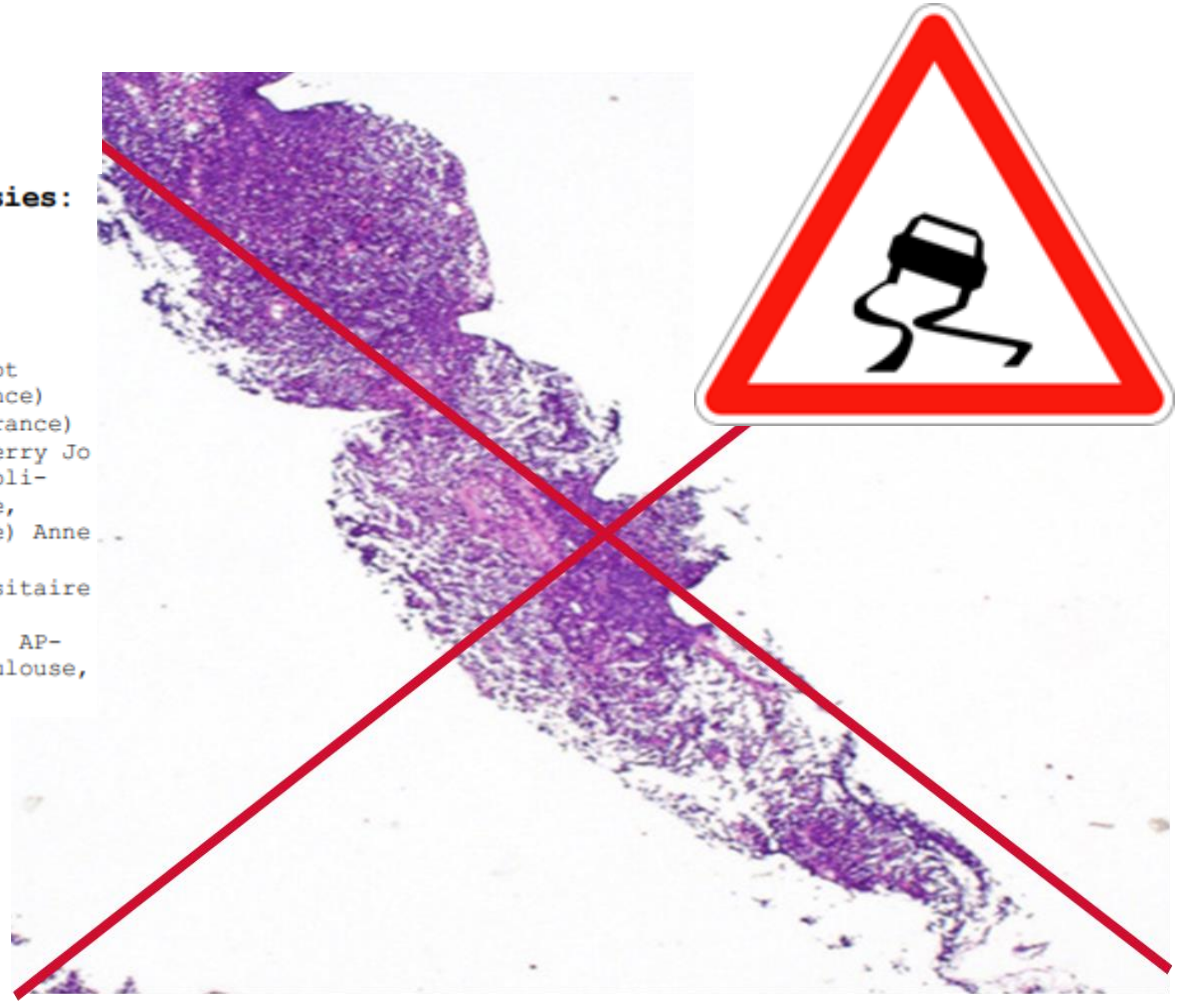


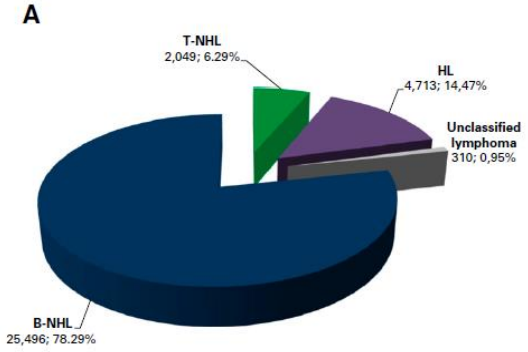
Lymphopath
- 32.285 cases
- CNB: 92.3% complete Diagnosis
- SE: 98.1%
- Expert review
- Difficult situations

Syrykh C et al. Blood, 2022

2022: quelques avancées dans le domaine des lymphomes (*)

- Lymphomes B « à petites cellules »
- Lymphomes B « agressifs »
- Lymphomes de Hodgkin
- Lymphomes T

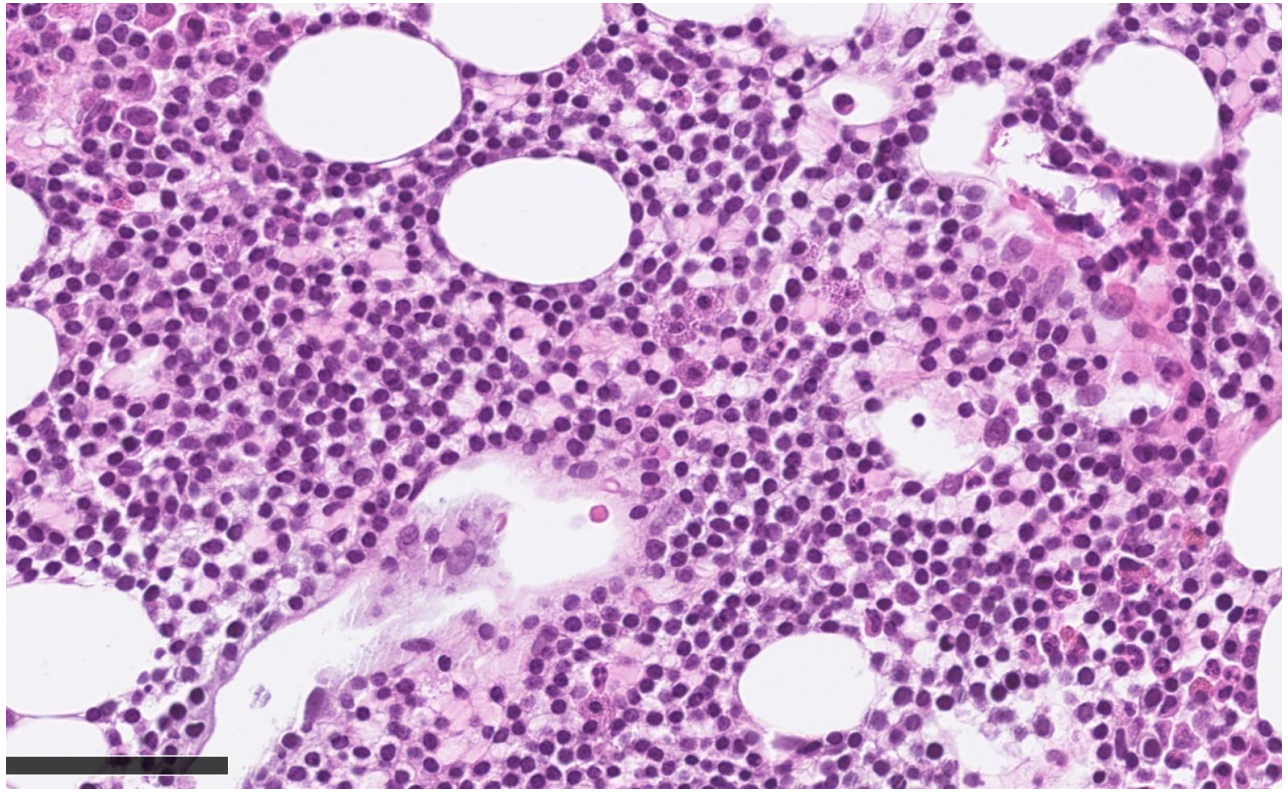
- **Précisions diagnostiques**
- **Dénominations, terminologie**
- **Nouvelles entités (rares), nouveaux concepts**

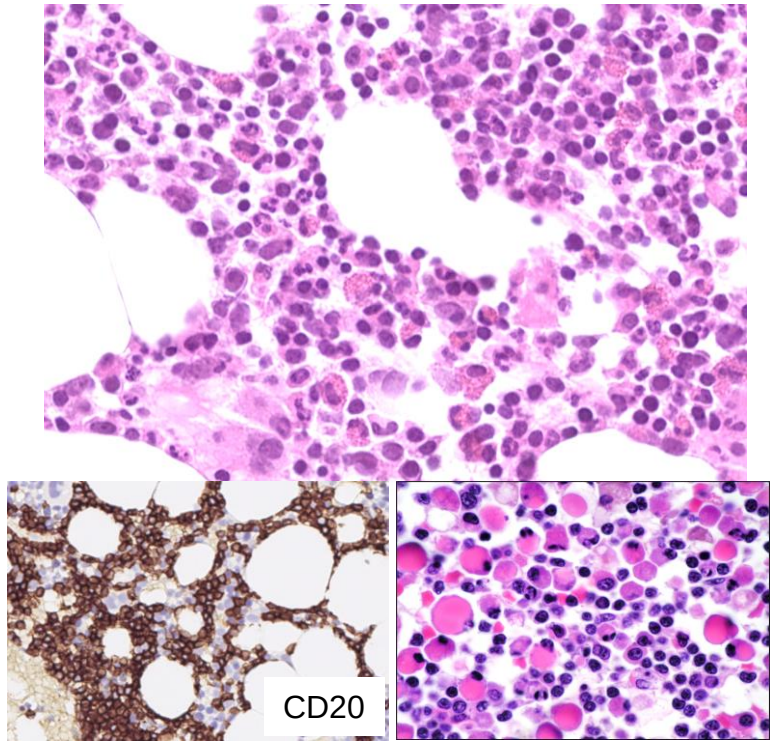


Lymphopath, 2010-2013

(*) introduites dans les classifications ICC et/ou OMS

Préciser la définition du lymphome lymphoplasmacytique (LPL)/Macroglobulinémie de Waldenström





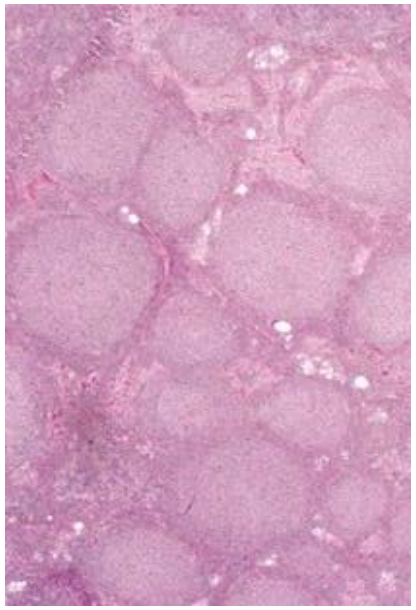
LPL/WM: infiltration médullaire

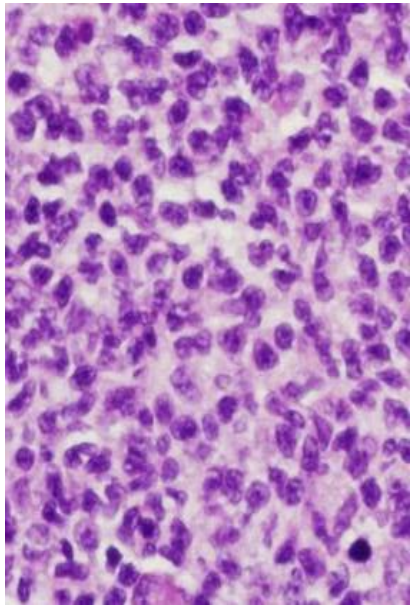
- ✓ ICC (2022): agrégats de cell B Clonales +/- diff plasmo (CMF)/monotypiques (IHC) dans <u>BOM</u> , même si <10% de la cellularité
- ✓ Importance diagnostique de mise en évidence de la mutation *MYD88 (p.265P)* (>90%); diagnostic différentiel avec nMZL ou MALT avec diff. Plasmocytaire et MM
- ✓ Recommandation de rechercher mut *CXCR*4 (40% des cas) avant décision traitement par Ibrutinib (CXCR4 confère résistance)

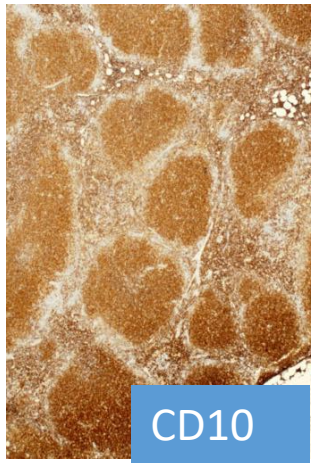
WHO et ICC: Une nouveauté : mal. Des agglutinines froides (rare)

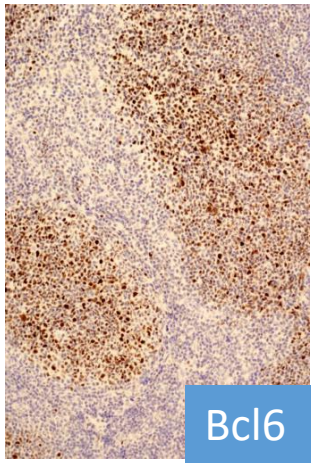
Le ou les lymphome(s) folliculaire(s) ?

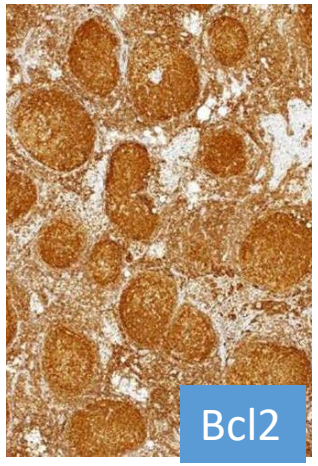
- Environ 20-25 % des lymphomes
- Variation géographique
- Âge médian : > 60 ans
- Ganglions disséminés, état général conservé
- **Centrocytes et centroblastes**
- **Cell B du GC**: CD10+, BCL6+, CD23-/+, **BCL2+ (80-90%)**
- **Translocation t(14;18)**
- **Grades cytologiques (1-2, et 3A) sans valeur clinique/pronostique → Facultatif selon OMS**
- Evolution indolente, mais difficile à éradiquer







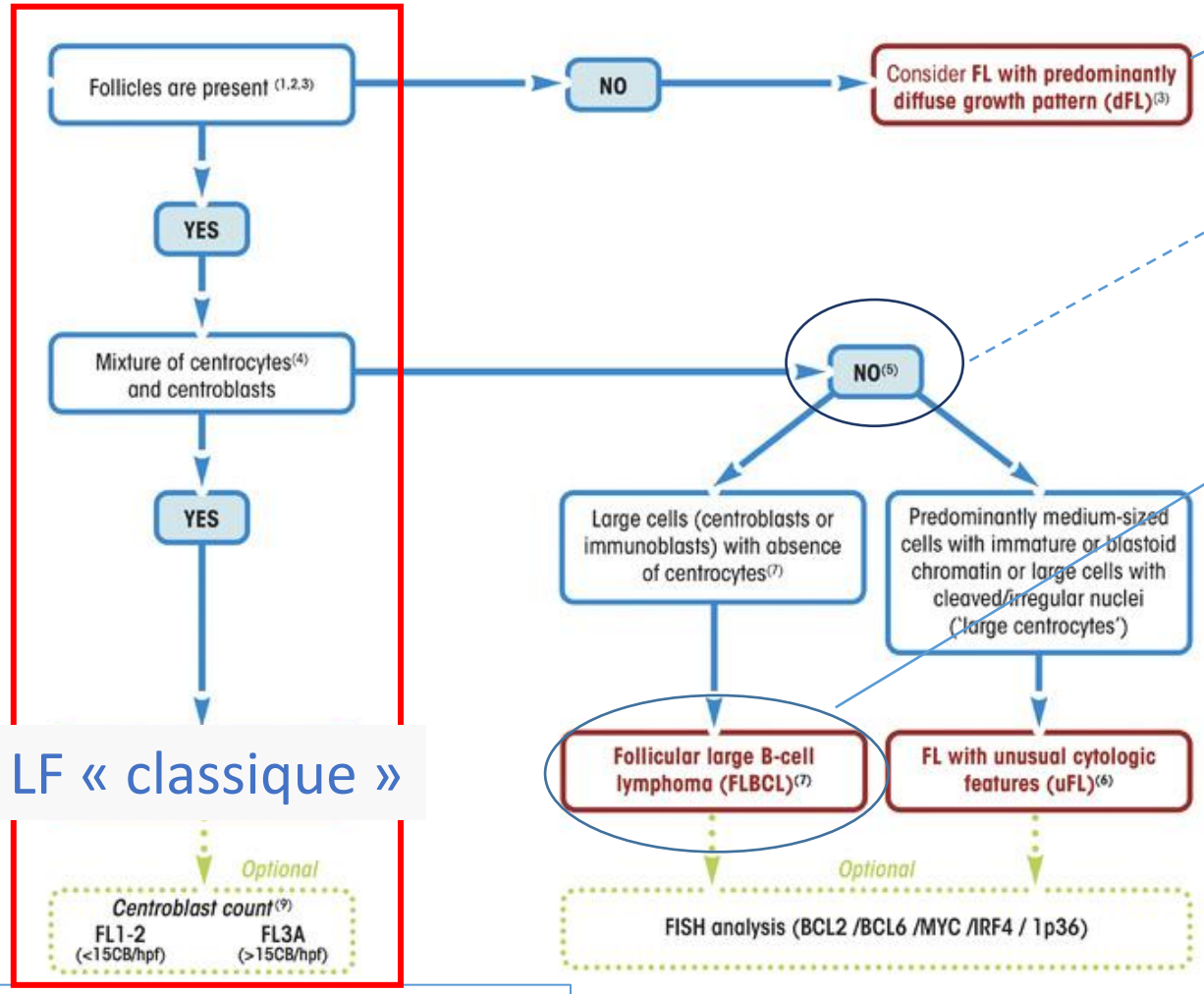




QQ « difficultés » dans les lymphomes folliculaires

Attention, micro-biopsies!

Si CD10-, exclure MZL



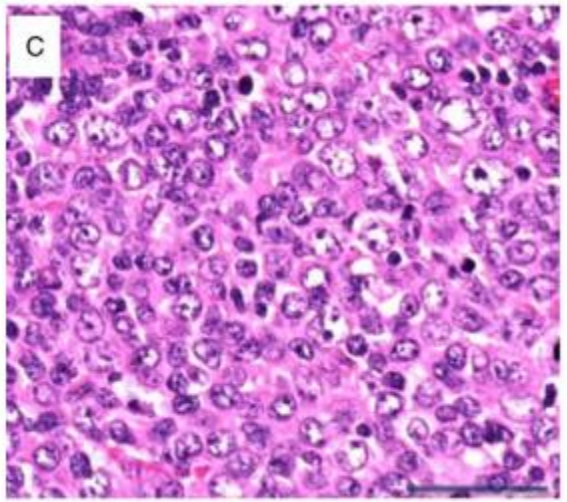
LF « classique »

- CD10+, BCL6+, MEF2B, LMO2, GCET…
- BCL2-R (>85%)

L Xerri et al. WHO 2022

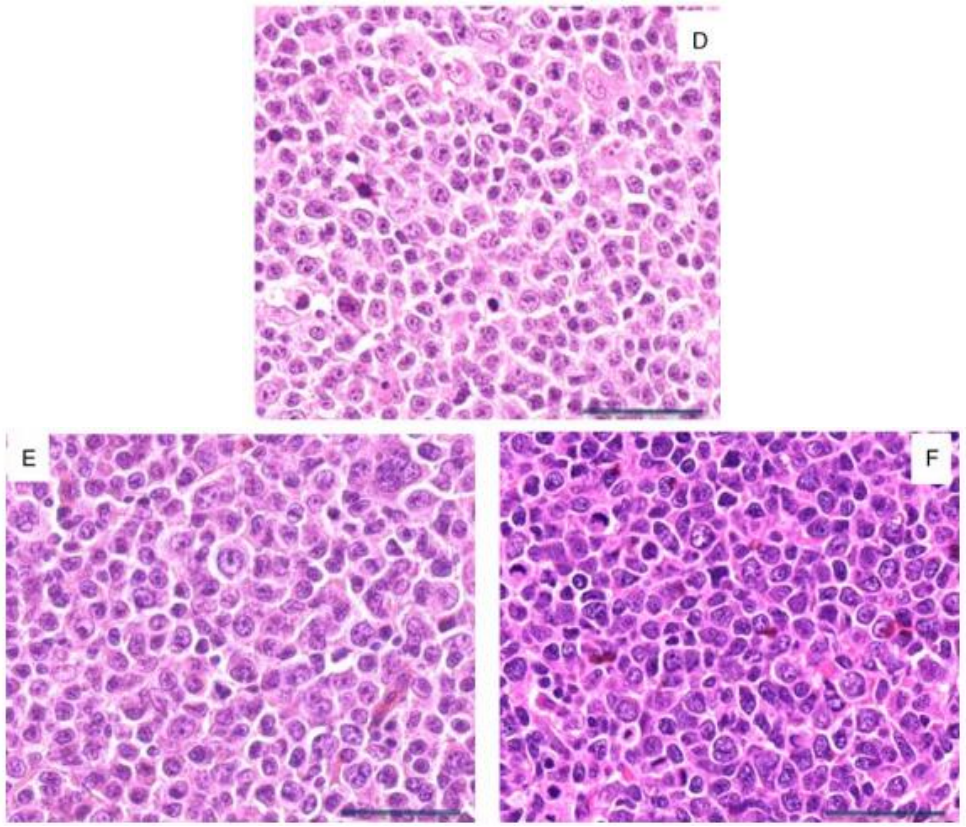
FL 3B (ICC 2022)

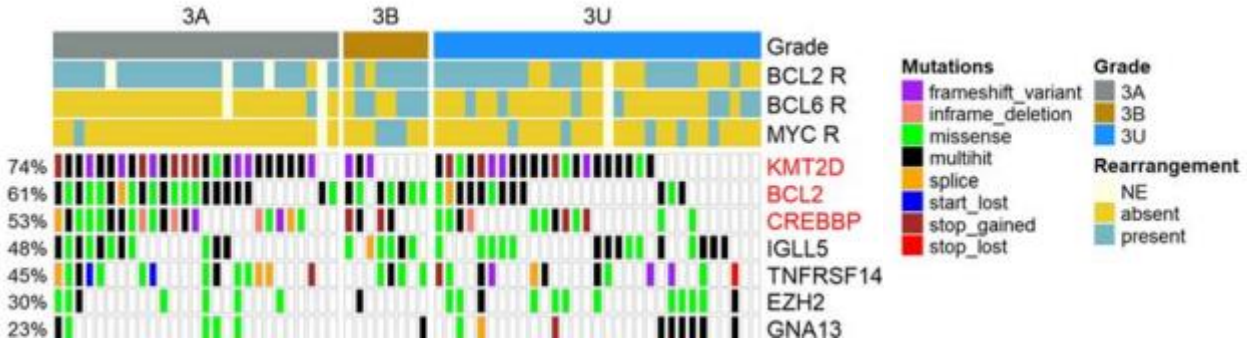
- Distinction with FL 3A critical
- Usually treated as DLBCL
- BCL2R and CD10+ favor FL3A
- BCL6R more frequent



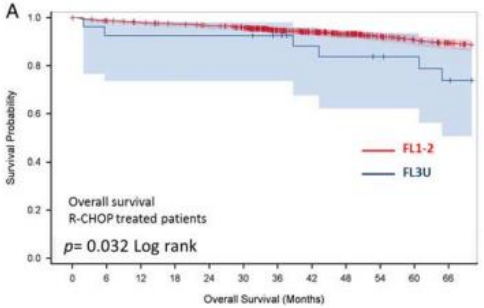
C Laurent et al. AJSP 2021

LF avec cytologie inhabituelle (« uFL », WHO)





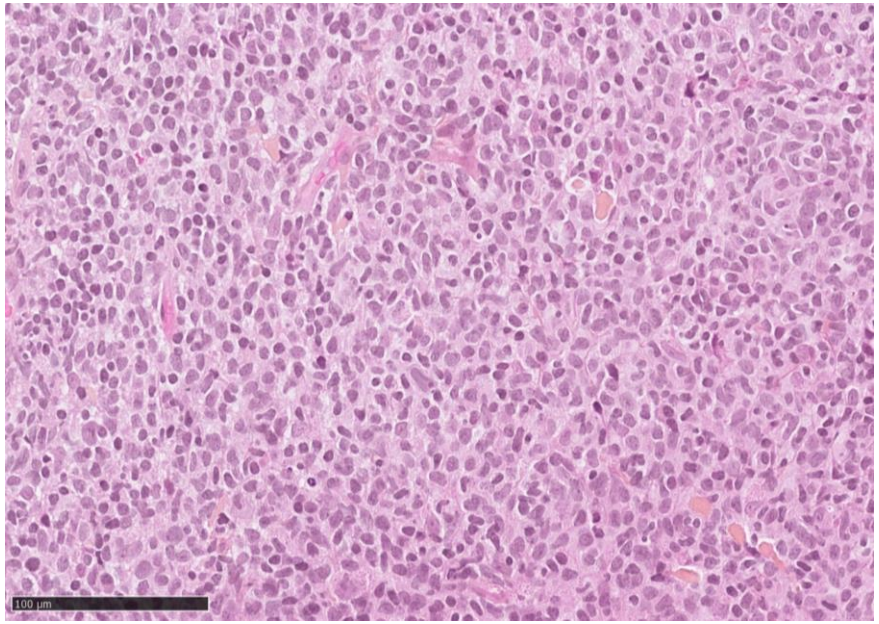
- ✓ Rare (2,5% des FL)
- ✓ Cell. Moyennes, + blastoides, gds cc
- ✓ Par rapport au FL classique:
  - moins de BCL2R
  - Ki67+ élevé, MUM1+ élevé
  - Éliminer FL avec IRF4R
  - Profil mutationel moins caractéristique
  - Evoluution plus agressive à confirmer?

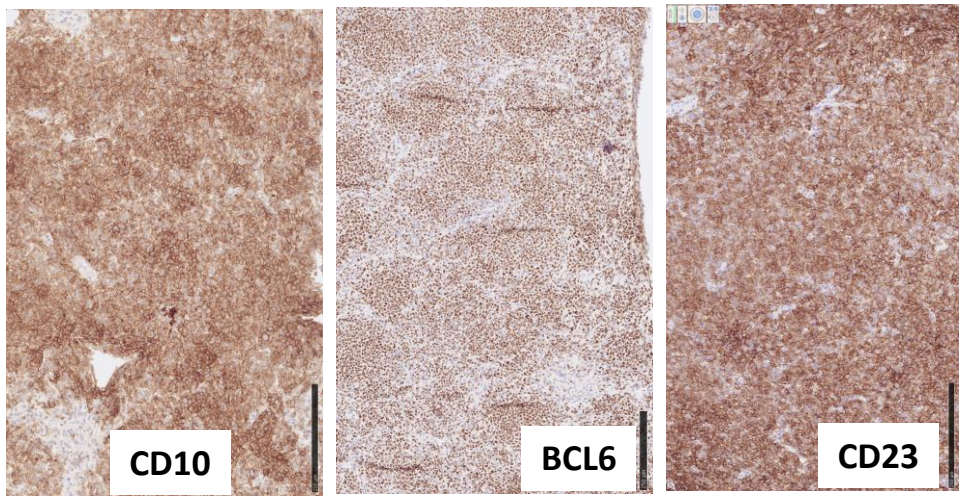


Laurent et al. AJSP 2021

LF sans R-BCL2 et CD23+

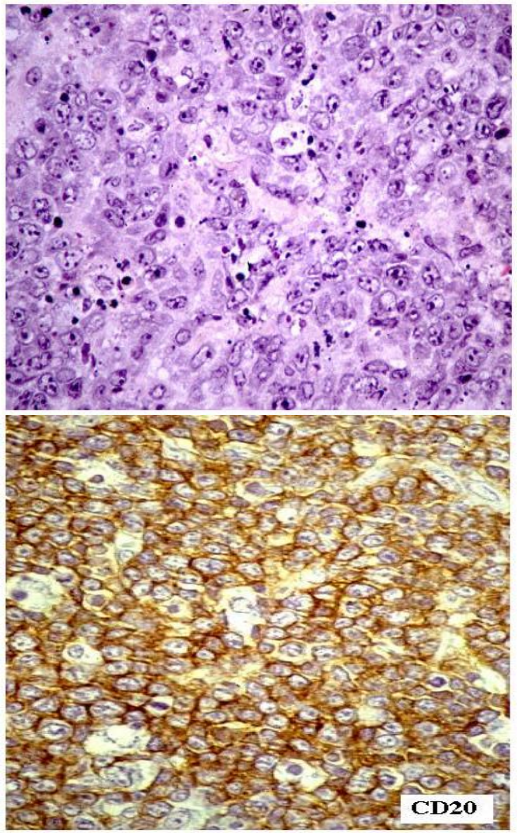
- **ICC : entité provisoire**
- **WHO : FL avec architecture essentiellement dif**fuse
- Prédominance féminine (M:F ratio 1:2)
- Présentation volontiers localisée
  - gg inguinal > axillaire ou cervical
- Architecture souvent **diffuse**, plus rarement fofficulaire (35%)
- **Expression de CD23** (surrogate de STAT6 mutations)
- Absence de réarrangement de BCL2
- **Mutations de *CREBPP* et *STAT6***
- **Délétion 1p36 et/ou mutations *TNFRS14***
- Pronostic favorable

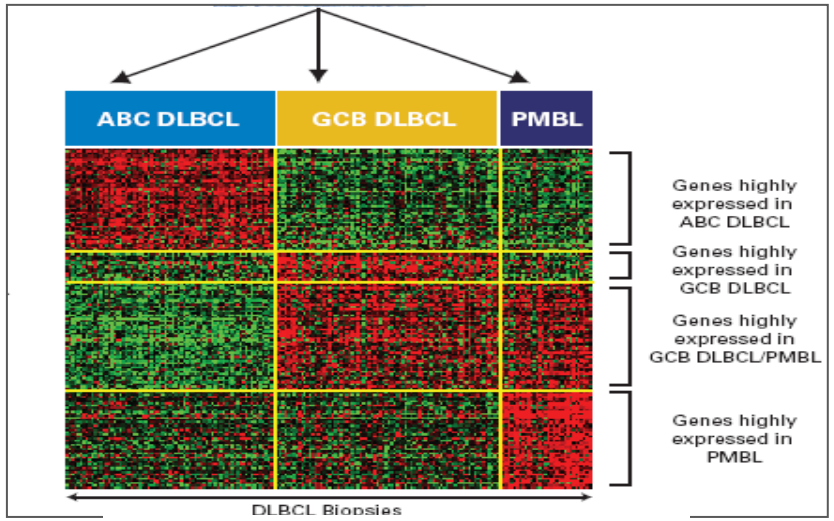


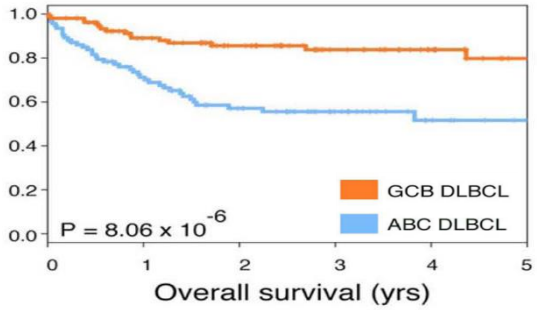


Blood 2009;113:1053-1061; Mod Pathol 2016;29:570-581;Blood Adv 2020;4:5652-5665

Et les lymphomes B à grandes cellules ?







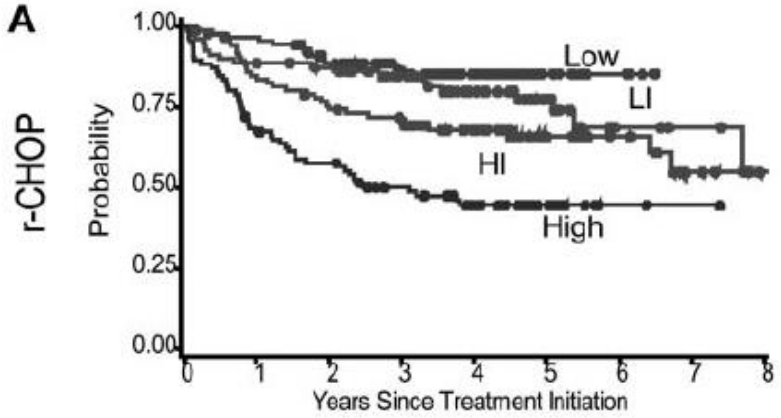
- Plusieurs entités
- Sous-types « GC » et « ABC »
- Biomarqueurs pronostiques/ prédictifs

- 30-40 % des lymphomes de l'adulte (4-5000 nouveaux cas/an en France)
- Grande hétérogénéité morphologique, clinique et biologique
- Evolution spontanée «agressive»

Rosenwald et al. NEJM 2002
Rosenwald et al. J Exp Med 2003
Lenz et al. 2008; H Nohai et al, J Clin Oncol 2011

DLBCL (, NOS) en 2022: où en sommes-nous ?

- R-CHOP: ~30-40% DLBCL vont rechuter ou ne répondront pas à l'immuno-chimiothérapie
- Meilleure compréhension des aspects moléculaires, **complexes**
- Progrès – hélas surtout décevants - vers des traitements ciblés, basés sur des sous-types de DLBCL
  - Cell. d'origine (GCB # ABC)
  - Voies moléculaires
- Identification des lymphomes B de haut grade (« HGBL », double hit)



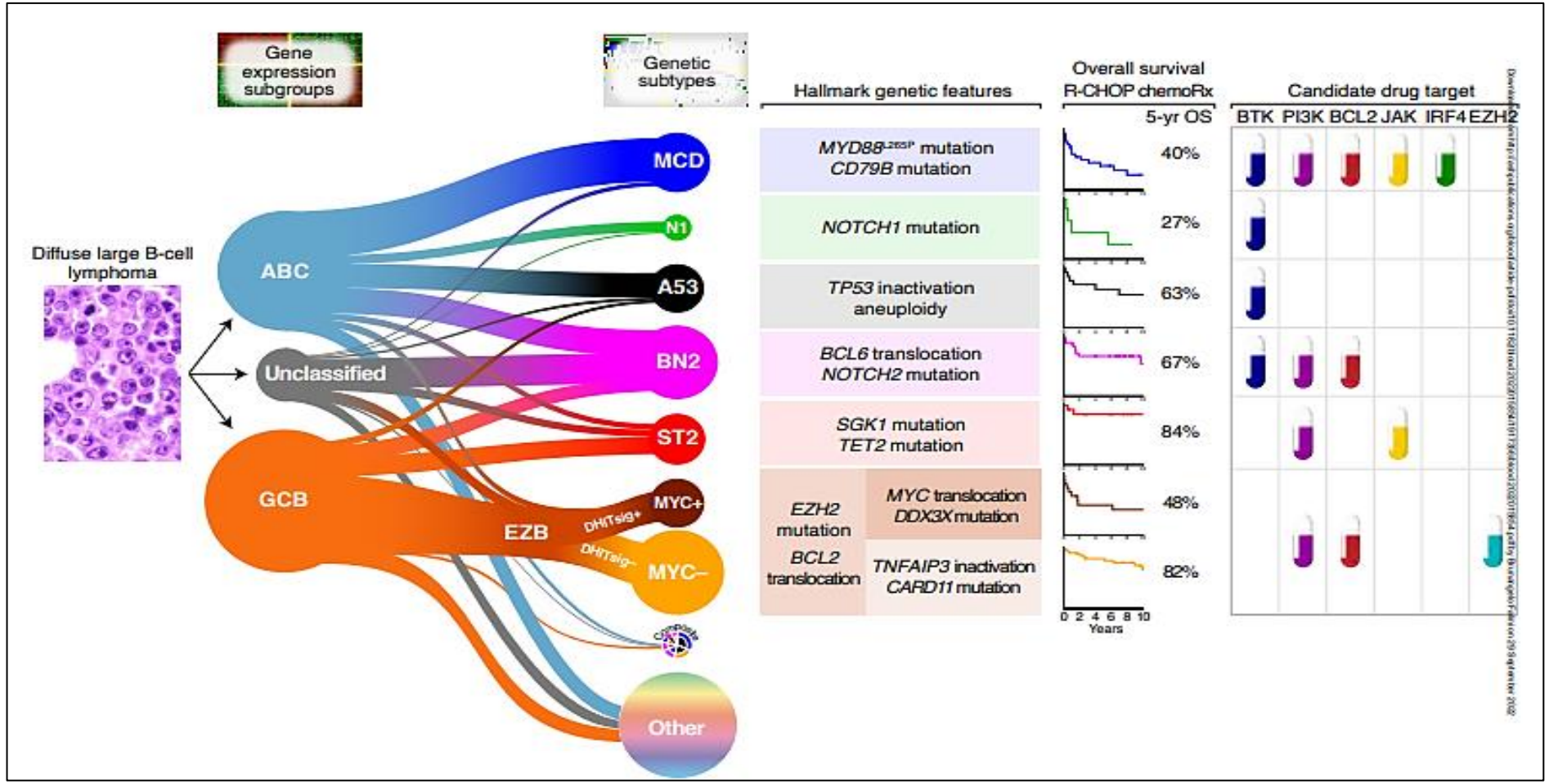
G Salles et al. Blood 2011

Staiger et al. JCO 2017

Staiger et al. JCO 2017
J Clin Oncol 2019; 37(15): 1285-1295
J Clin Oncol 2021; 39(12): 1317-1328

2022: la complexité moléculaire des « DLBCL » dépasse la compartimentation selon la cell. d'origine

Transfert à la routine ?



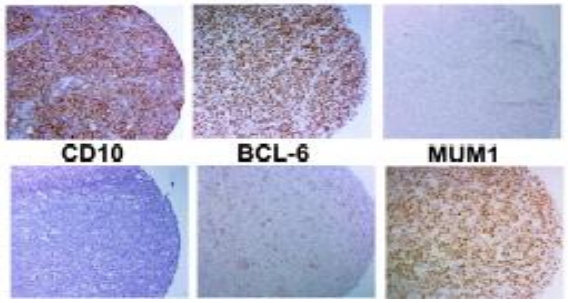
Chapuy B et al. Nature Medecine 2018
Schmitz et al. NEJM 2018
S Lacy et al. Blood 2020

According to Schmitz, Wright et al Cancer Cell 2020

DLBCL, NOS : Faut-il déterminer le profil "cell d'origine" et faut-il faire une "FISH" ?

Marqueurs GCB -DLBCL	Marqueurs post GC (ABC)
CD10	
BCL6	MUM1/IRF4
GCET1	FOXP11
MEF2B	CD138
LMO2	
t (14;18)	

IHC : Algorithme Hans



Profil expression moléculaire (FFPE)

° nCounter system (Nanostring)

° RT-MLPA (F Jardin et al)

- ✓ **La determination de la "cell d'origine" est maintenue dans l'ICC, facultative dans la WHO-HAEM5**
- ✓ La dichotomie binaire « GC vs ABC » est biologiquement relevante, mais elle ne reflète pas entièrement la complexité génétique et n'a pas d'impact clinique démontré à ce jour (°)
- ✓ **En théorie, la recherche des translocations *MYC (BCL2, BCL6)* est à réaliser (FISH) devant tout « DLBCL » afin d'identifier les HGBL**

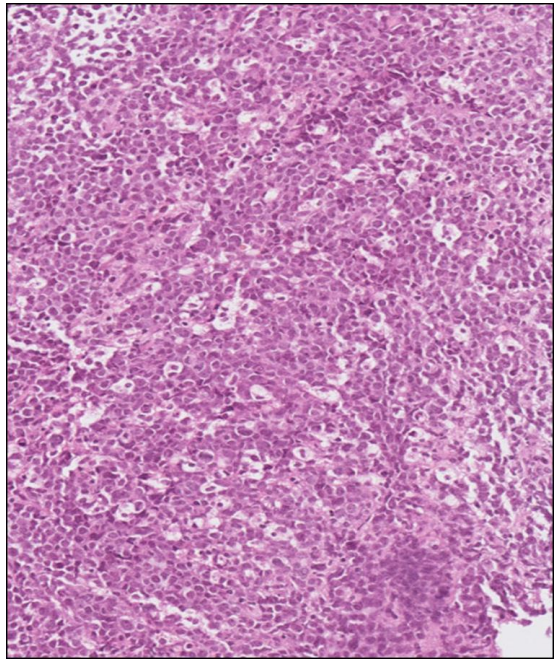
(°) Staiger et al. JCO 2017; J Clin Oncol 2019; 37(15): 1285-1295; J Clin Oncol 2021; 39(12): 1317-1328

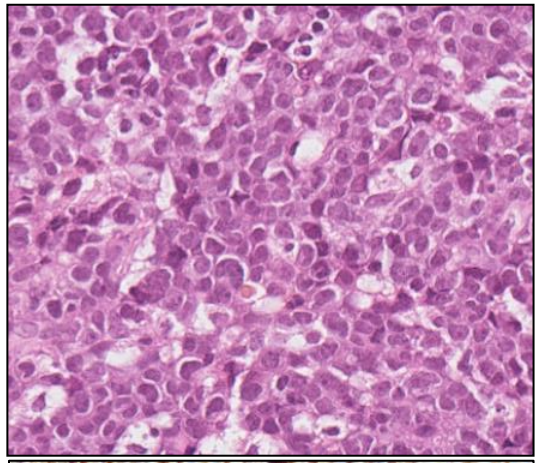
A côté du « DLBCL, NOS »….

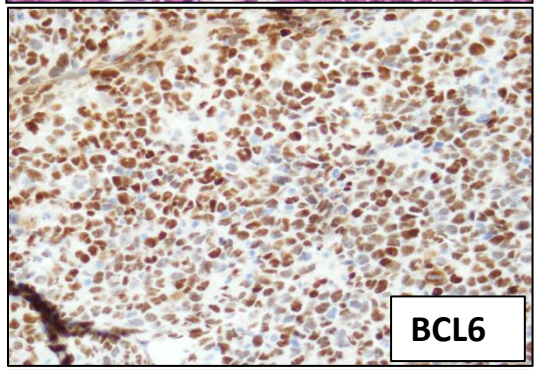
WHO-HAEM4	WHO-HAEM5	ICC
DLBCL, NOS	Recommended	Germinal center B-cell subtype (GBC)
DLBCL, NOS	Recommended	Activated B-cell subtype (ABC)
Burkitt-like lymphoma with 11q aberration (provisional entity)	**High grade B-cell lymphoma with 11q aberrations**	**Large B-cell lymphoma with 11q aberration (provisional entity)**
Large B-cell lymphoma with IRF4 rearrangement (provisional entity)	**Large B-cell lymphoma with IRF4 rearrangement (upgraded to distinct entity)**	**Large B-cell lymphoma with IRF4 rearrangement (upgraded to a distinct entity)**
Primary diffuse large B-cell lymphoma of the CNS	**Lymphoma of the immune privileged sites** **- testis** **- vitreus** **- CNS**	**Primary diffuse large B-cell lymphoma of the CNS** **Primary diffuse large B-cell lymphoma of the testis**
Primary cutaneous diffuse large B-cell lymphoma, leg-type **Intravascular large B-cell lymphoma**	Primary cutaneous diffuse large B-cell lymphoma, leg-type Intravascular large B-cell lymphoma	Primary cutaneous diffuse large B-cell lymphoma, leg-type Intravascular large B-cell lymphoma
T cell/Histiocyte-rich large B-cell lymphoma	T-cell/histiocyte-rich large B-cell lymphoma Transformation of indolent B-cell lymphomas	T cell/Histiocyte-rich large B-cell lymphoma

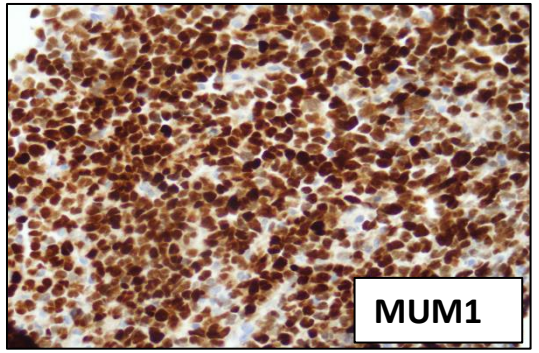
Lymphome B à grandes cellules avec réarrangement d'*IRF4*

- Children and young adults , but…
- Predominantly head and neck / Waldeyer ring
- Nodular or diffuse – variable morphology (large cell +/- blastoid)
- CD10 variable, BCL6+, **strong MUM1 (100%)**, high proliferation rate,
- CD5+ (30-40%)
- *IRF4* rearrangement with IGH partner
- **Good prognosis**
- **Frequent *IRF4* mutations**, often multiple (exons 1 and 2)
- Other mutations in **NF-kB pathway** genes (*CD79b, MYD88, CARD11*….)





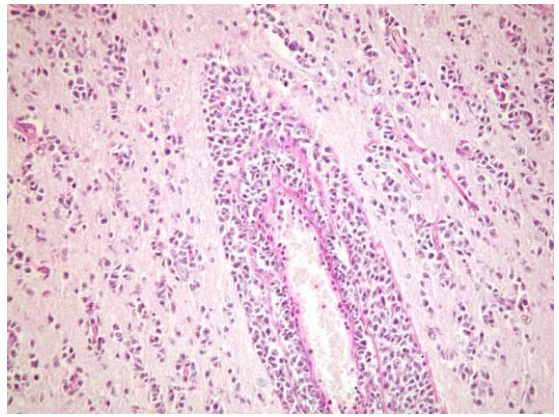


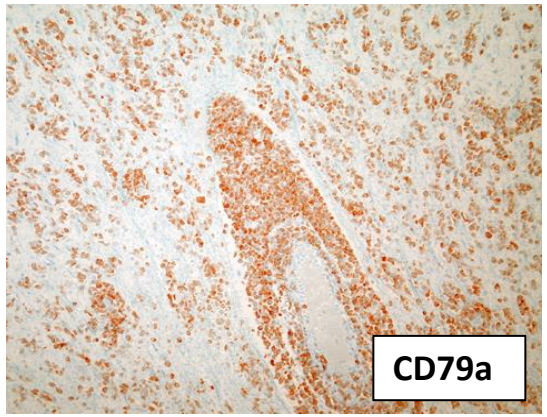


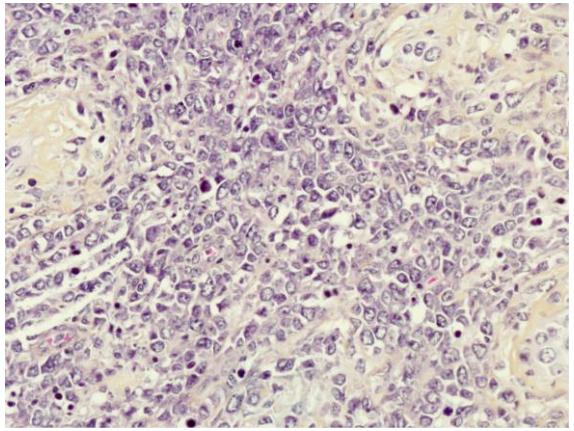
Salaverria I.et al, Blood 2011; Liu Q. et al, Am J Surg Pathol 2013; Quintanilla-Martinez L. et al, Virchows Arch 2016; Chisholm K. et al, Ped Blood Cancer 2019; Ramis Zaldivar J. et al, Blood 2020; Nasim M. et al, Int J Surg Pathol 2020; Zhang L. et al, J Clin Pathol 2020; Au-Yeung R. et al, Br J Haematol 2020

Lymphome B à grandes cell. des sites exclus du système immunitaire : testicule, SNC, vitrée (OMS)
- « DLBCL » primitif du testicule (ICC)
- « DLBCL » primitif du CNS (ICC)

- Adultes >60 ans, mauvais pronostic
- Gdes cell. ± Immunoblastiques
- Profil non-GC (CD10-, BCL6+, MUM1++) et moléculaire ABC (*)
- Mutations *MYD88* et autres gènes de la voie du BCR (*CD79B*) ()
- Se développe dans un environnement particulier (“sanctuaires immunitaires”) qui favorise l’échappement tumoral (“immune evasion”) avec absence d’expression des MHC classe 1 et 2, et β2M,…
- “DLBCL” testicule ont tendance à rechuter dans le testicule controlatéral et SNC







(*) Utilisation préférentielle de IGHV4-34 ; C5/MCD/MYD88 signature

En 2022, que sont devenues les catégories « HGBL » de 2017 ?

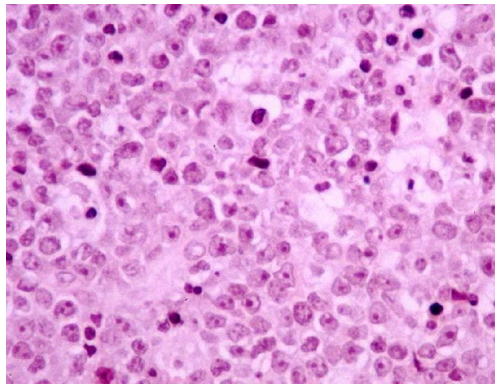
2017, OMS

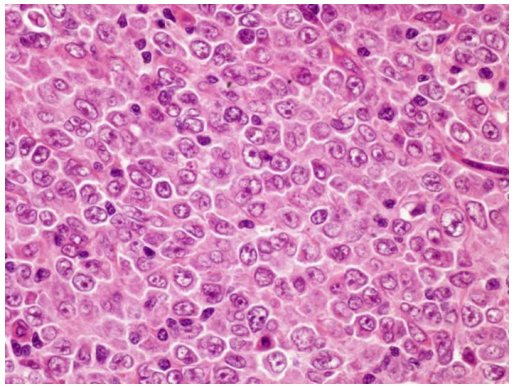
High grade B-cell lymphoma
« double hit »
With *MYC* and *BCL2* (or *BCL6*) R
(morphologie DLBCL or not)

Biologie différente

HGBL(DLBCL) MYC-BCL2
(WHO2022 & ICC)

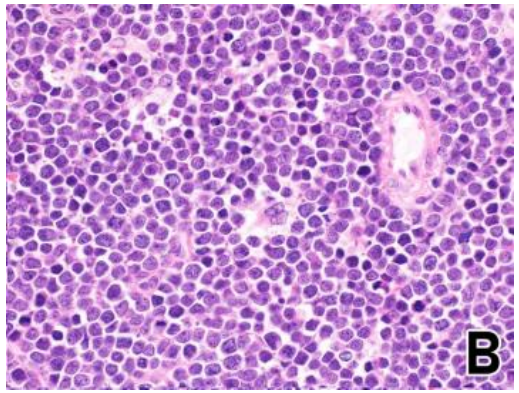
HGBL MYC-BCL6
(entité provisoire, ICC)
→ DLBCL ou HGBL selon WHO-HAEM5





High grade B-cell lymphoma
NOS

- ✓ Morphologie blastoïde ou équivoque avec Burkitt
- ✓ Groupe hétérogène
- ✓ MYC-R seul ~50%
- ✓ **Peu reproductible : diagnostic d'exclusion, à faire le moins possible !**
- ✓ Plus agressif que DLBCL?, Traitement ?



R King, E Hsi et al. Virchows Archiv 2022

High grade B-cell lymphomas with MYC and BCL2 rearrangements (both ICC and WHO-HAEM5)

- Morphology ranging from large cells to blastoid/intermediate → **WHO DLBCL/HGBL MYC6BCL2**

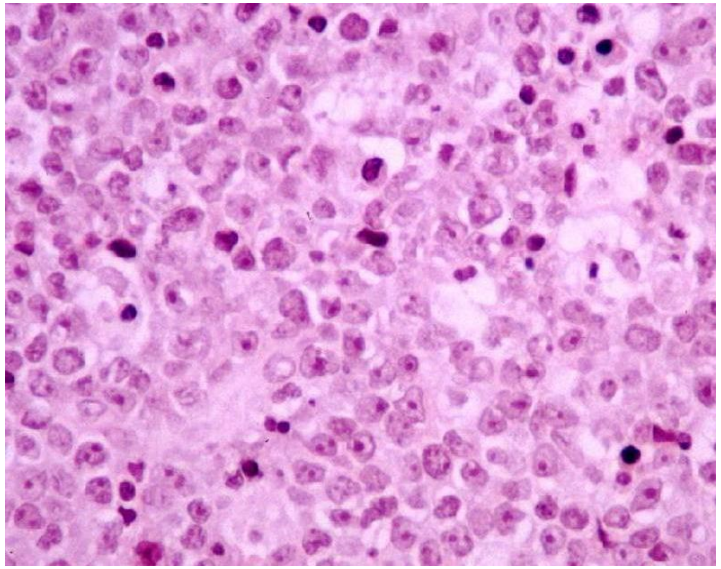
- Germinal center origin (100%)

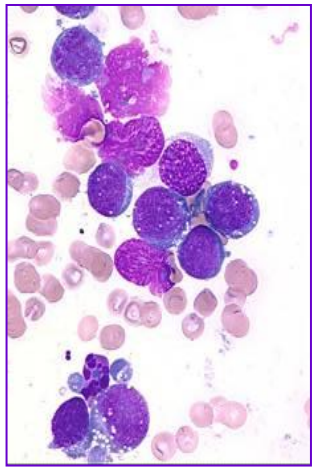
- GEP of centroblasts in the **germinal center dark zone**

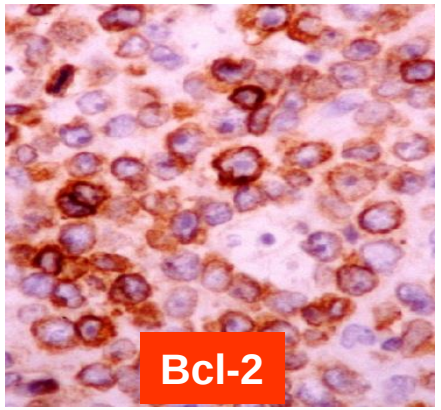
- **FISH break apart probes recommended but may miss up to 20% of cases (cryptic)**

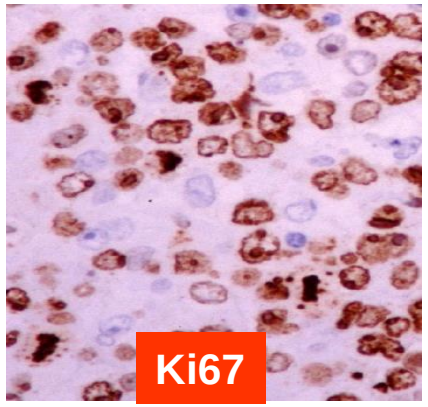
- Mutational profile similar to «aggressive» FL (*BCL2, KMTD2, CREBBP, TNRSF14, EZH2, FOXO1* but also *ID3, CCND3*)

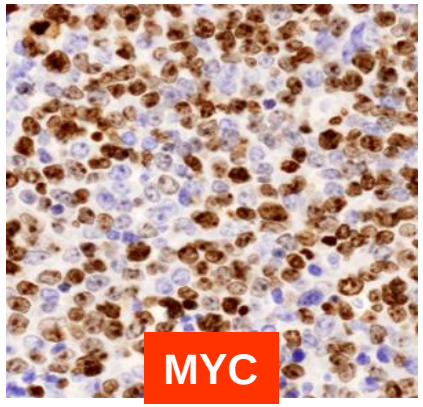
- **Exclude FL with *MYC* and *BCL2* and true LBL (TdT+, CD34-/+, CD20 weak) carrying *MYC* rearrangement**
- **Includes the TH *MYC-BCL2-BCL6***



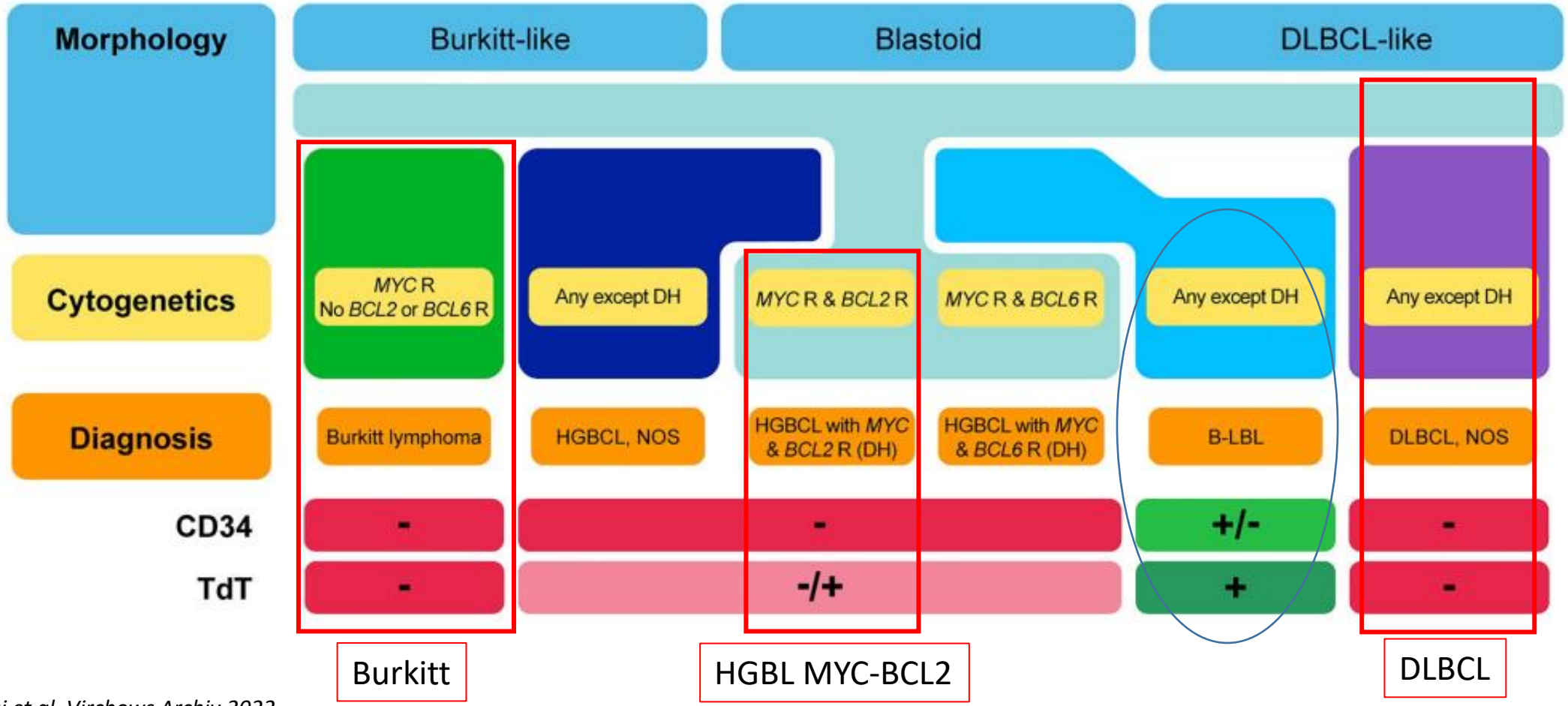








Approche des lymphomes B d'histologie agressive : du DLBCL au Burkitt



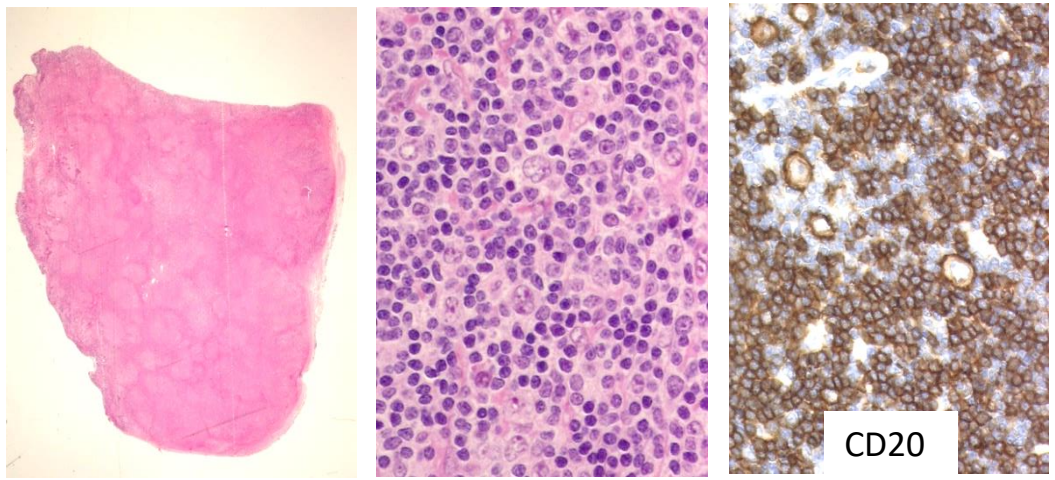
R King, E Hsi et al. Virchows Archiv 2022

Et quid du lymphome de Hodgkin ?

- **L de Hodgkin classique (LHC)** : inchangé

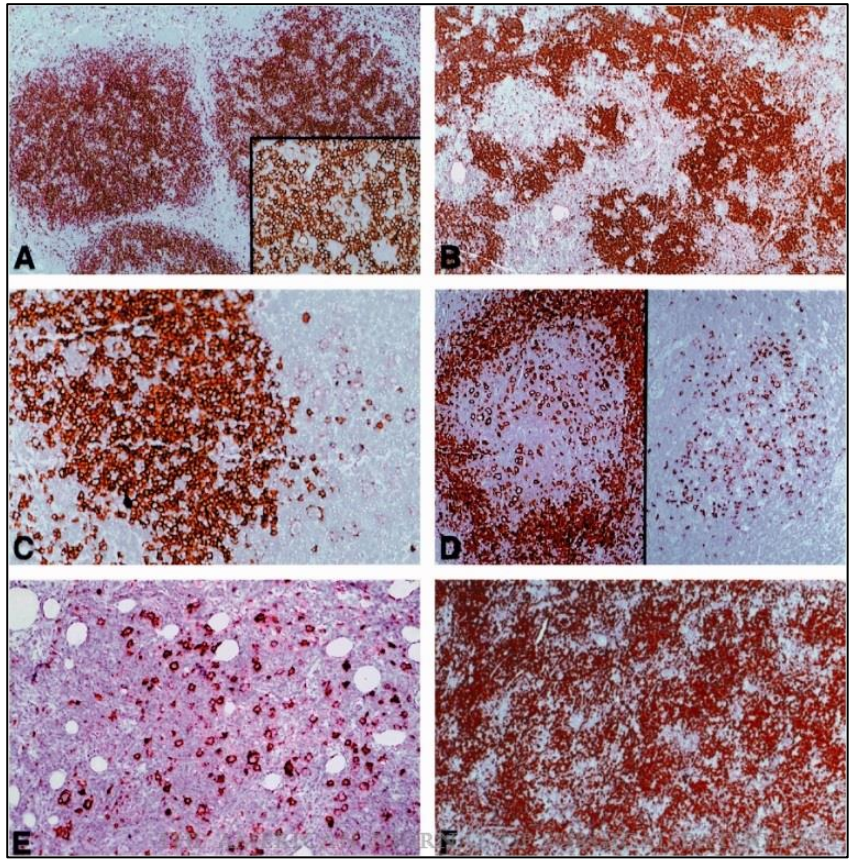
- **L de Hodgkin nodulaire à prédominance lymphocytaire (OMS 2017 et 2022)** devient **“Lymphome nodulaire à predominance lymphocytaire” (ICC):**
  - differences cliniques et biologiques
  - Relation avec les lymphomes B à grandes cellules riches en lymphocytes et en histiocytes
  - Variants histologiques (Fan) regroupés en 2 grades (1 & 2) selon la perte de architecture nodulaire et enrichissement en lymphocytes T/reduction en B
  - Grade 2: traitement plus agressif **selon** la clinique

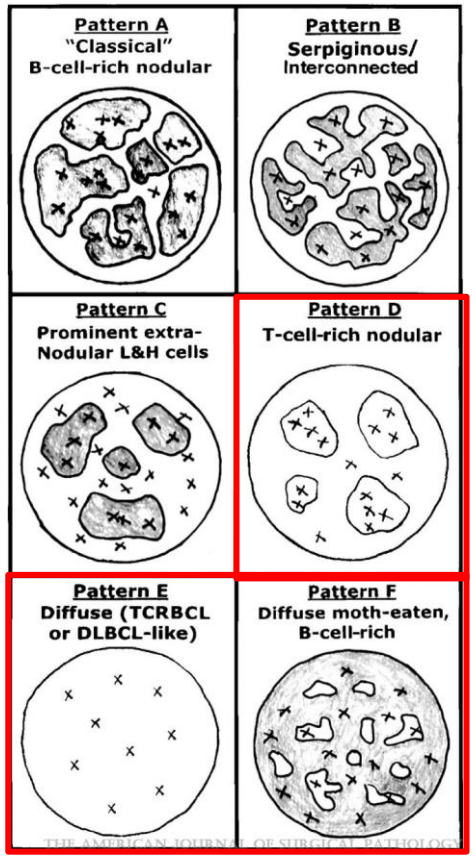
Ex « Poppema Lennert »), 10%



- souvent localisée
- absence symptomes B
- origine cellulaire B GC
- Programme B préservé
- Possibilité de transformation en DLBCL ou HTCRLBCL

Variants morphologiques du L (de Hodgkin) nodulaire à prédominance lymphocytaire





Grade 1
(pattern «classique»)

Grade 2
(patterns «variants»)

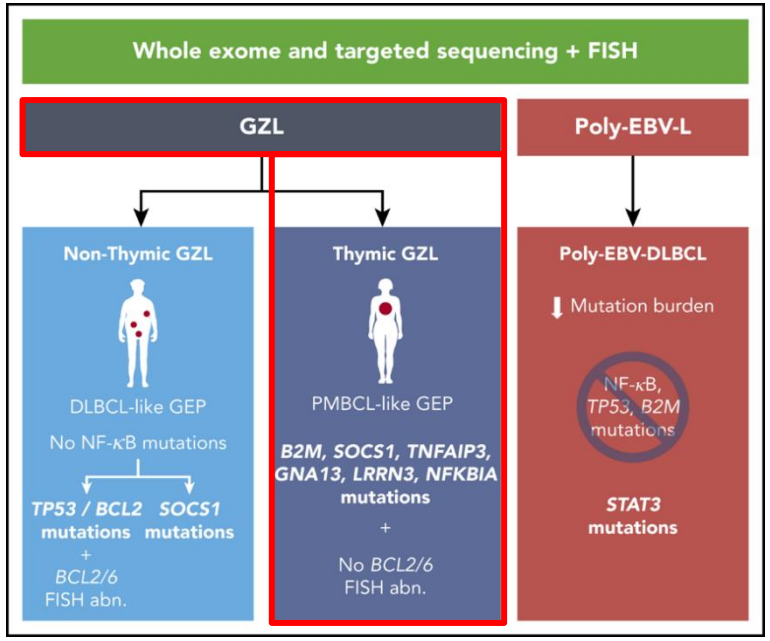
Tendency for:
°Advanced disease
°Higher relapse rate
° Response to R-CHOP

Attention à un tel diagnostic sur B à l'aiguille!

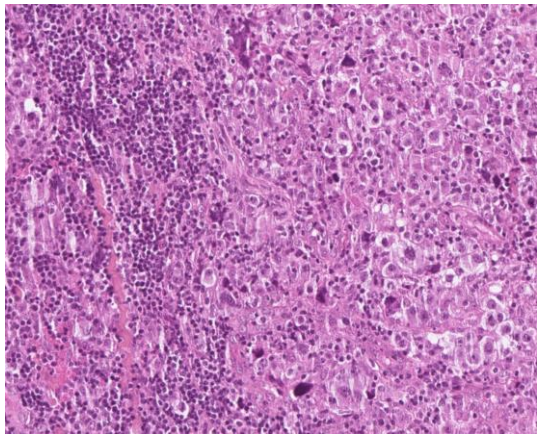
2022 (ICC & OMS): Mediastinal Gray Zone Lymphoma
(GZL in extra-mediastinal sites is a different entity related to DLBCL)

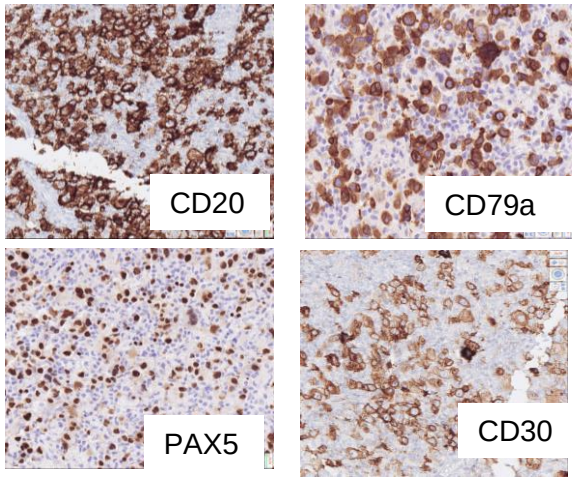
- ✓ Adultes jeunes, prédominance masculine
- ✓ Atteinte médiastinale souvent « bulky »
- ✓ Morphologie :
  - « LHc-like » ressemblant LHC scléro-nod (70%)
  - « PMBL-like », monomorphe, grandes cell.
- ✓ Expression uniforme (intense) **d'au moins 2 marqueurs B (CD20, CD79a, PAX5,…)**
- ✓ Génétique: similitudes avec LHc et PMBL (activation JAK/STAT et NF-kB, gains PD-L1/2, JAK2 et REL; mutations SOCS1, TNFAIP3, XPO1, B2M,… et perte expression des MHC-1 et MHC-2)

→ **Reflète le continuum entre LHc (SN) et PMBL et l'origine commune d'un lymphocyte B thymique**



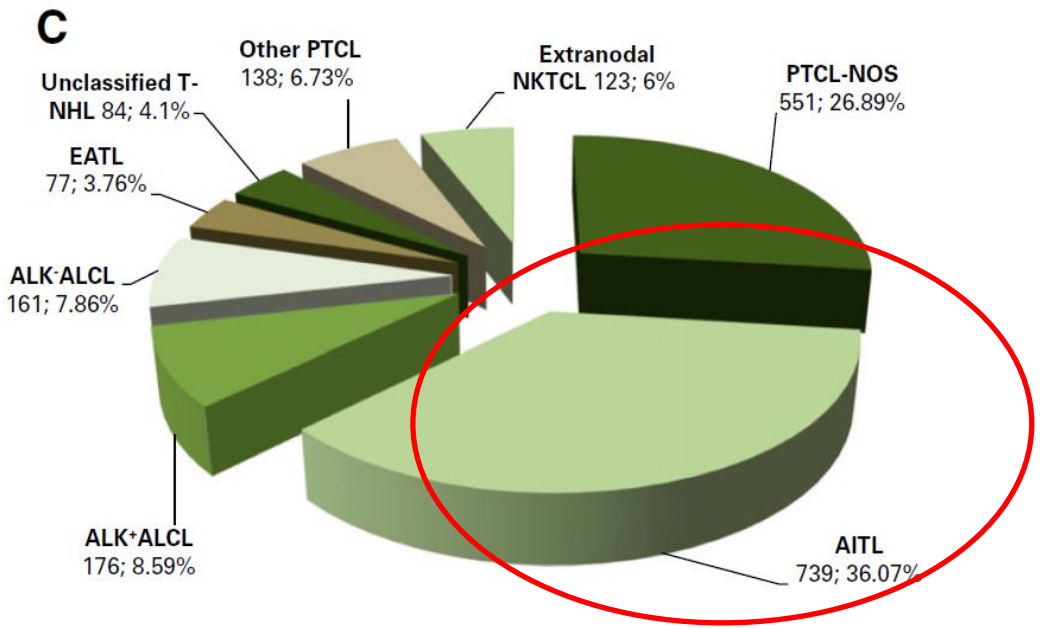
From Sarkozy C et al. Blood 2021





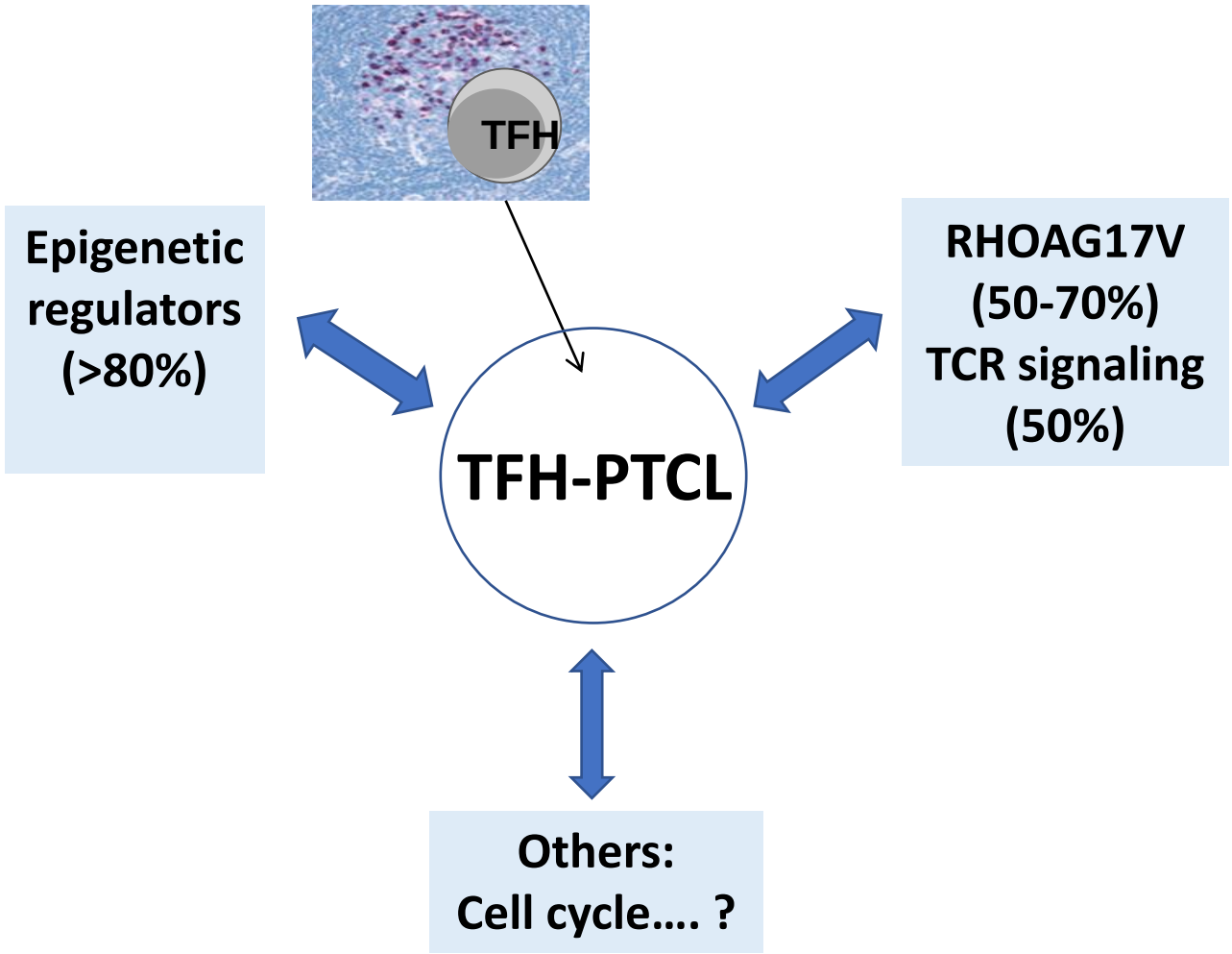
Sarkozy C et al. Blood 2021
Sarkozy C et al. Blood Adv 2020
Aussedat G. B J Haematol 2020
Sarkozy C et al. Am J Surg Pathol 2019

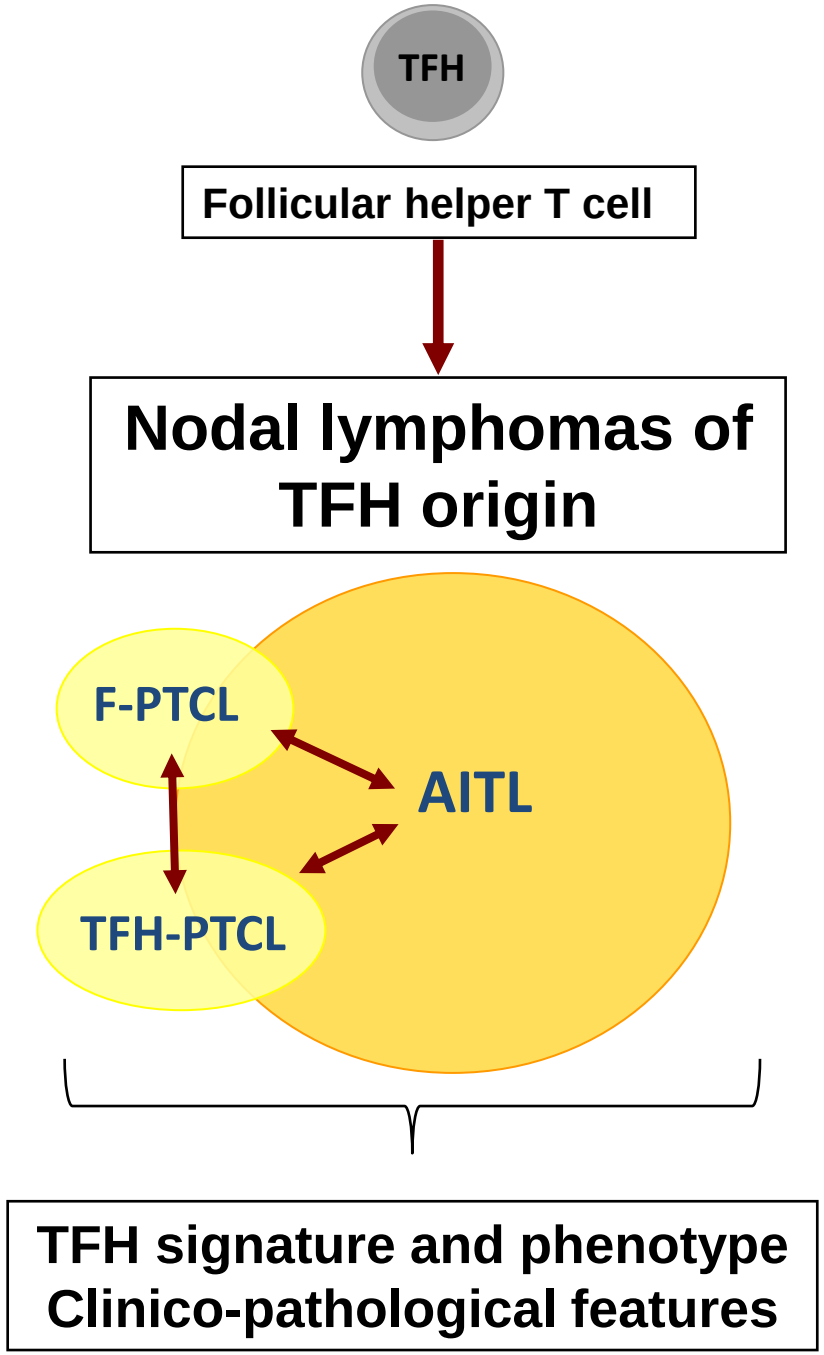
Et quoi de neuf dans les lymphomes T



C Laurent et al. J Clin Oncol 2017

Dans les lymphomes TFH ?

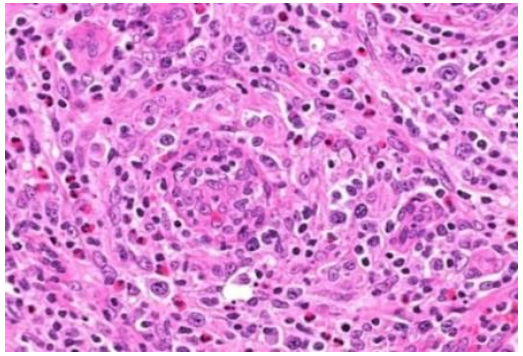


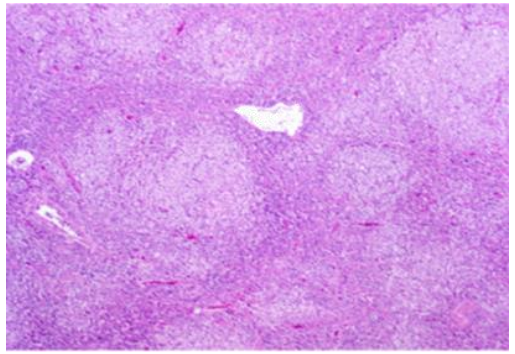


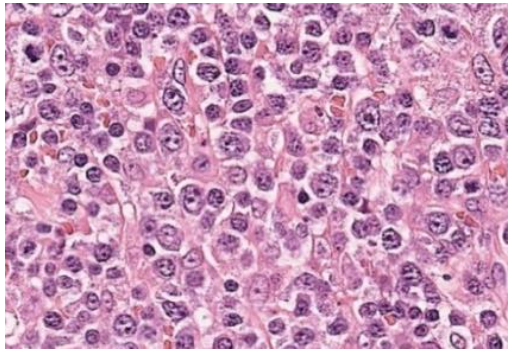
Streubel B et al. Leukemia 2006; Lemonnier et al Blood 2012; Cairns R*, Iqbal J*, Lemonnier F* et al. Blood 2012; Couronné L et al. NEJM 2012; Palomero T et al. Sakata M et al. Nature Genetics 2014; Rohr J et al. Leukemia 2016; Vallois D et al. Blood 2016; Dobay MP et al. Haematologica 2017; Lemonnier F et al. Haematologica 2017; Vallois D Dupuy A et al. Haematologica 2018; Moons CS Nat Cancer 2020; Debackere K Nat Communic 2021

TFH lymphoma: a new designation

Angioimmunoblastic-type	Follicular-type	Not otherwise specified (NOS)
Diffuse involvement and FDC expansion **Or** perifollicular without FDC expansion	Follicular lymphoma-like **Or** PTGC-like (with FDCs & IgD+ B cells)	Diffuse and no FDC expansion **Or** T-zone pattern
EBV +/- B-blasts	EBV +/- B-blasts -/+	EBV +/- B-blasts –/+
Increased vascularity (+)	Increased vascularity -/+	Increased vascularity (-)
Polymorphous environment	Polymorphous environment -/+	Polymorphous environment -





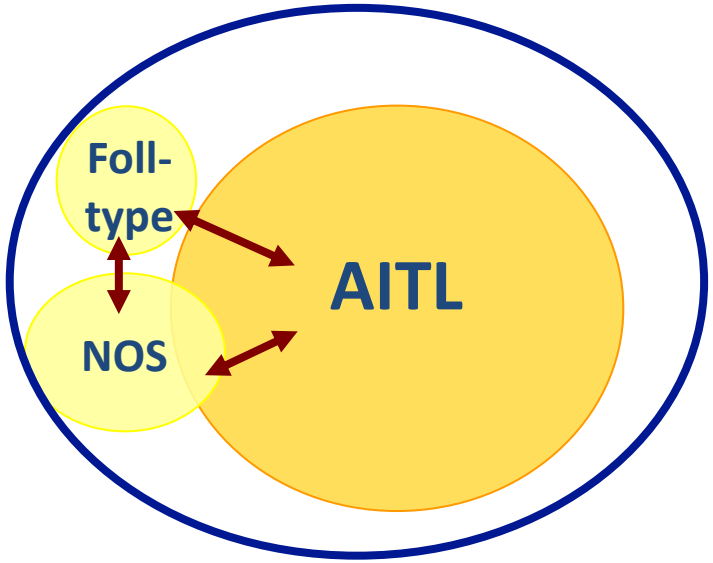


Single entity
Restricted to <u>nodal</u> systemic TFH lymphoma

Campo E et al. ICC Classification… . Blood 2022

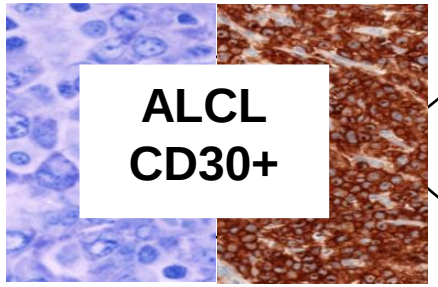
TFH LYMPHOMAS – Summary

- **The designation applies to CD4+ systemic cases**
- A large pathological spectrum and combinations of patterns
  - Overlapping features
  - FDC expansion is a key feature of AITL
  - Multiple patterns can be seen in individual patients
- Currently, no evidence that the distinction between AITL and other nodal TFH lymphomas has clinical or therapeutic importance, and a diagnosis of nodal TFH lymphoma is acceptable
- Use a five markers panel (CD10, PD1, BCL6, ICOS, CXCL13)
- Two (or three) should be convincingly positive on "neoplastic" cells
- Mutational analysis is helpful :
  - to aid a (challenging!) diagnosis
  - to support TFH derivation (RHOAG17V++, IDH2R172K)



Attygalle AD et al.AJSP 2007; Attygalle A et al. Histopathology 2014; Dobay MP et al Haematologica 2017
Iqbal et al. Blood 2010; Amador et al. J Clin Oncol 2022

Dans les lymphomes anaplasiques à grandes cellules (ALCL) ?



ALK+ → SYSTEMIC → sALCL ALK+

ALK- → SYSTEMIC → sALCL ALK- (*DUSP22* R)

ALK- → CUTANEOUS → cALCL

ALK- → BREAST IMPLANT-ASSOCIATED → BIA-ALCL

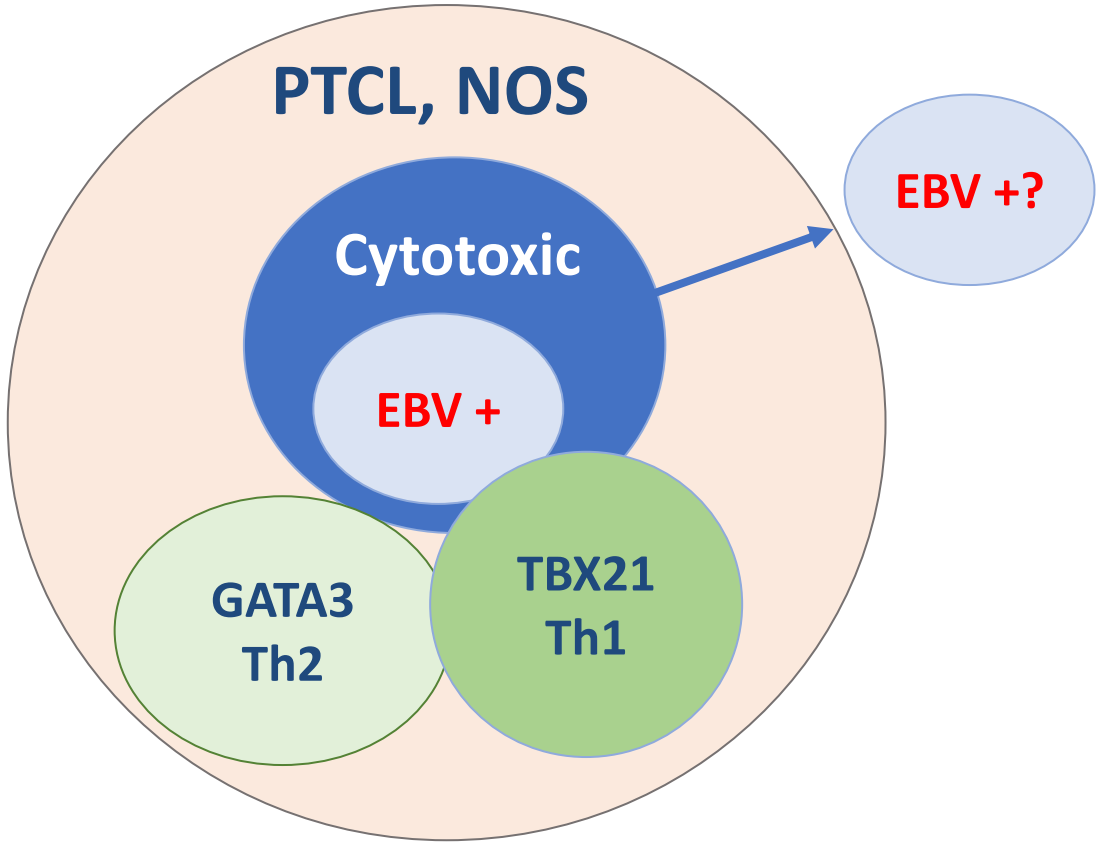
Overall diagnostic criteria unchanged

ICC: FISH testing for *DUSP22* *DUSP22-R* genetic subtype

BIA-ALCL
- **Upgraded to definite entity**
- **Encourage staging (TNM)**

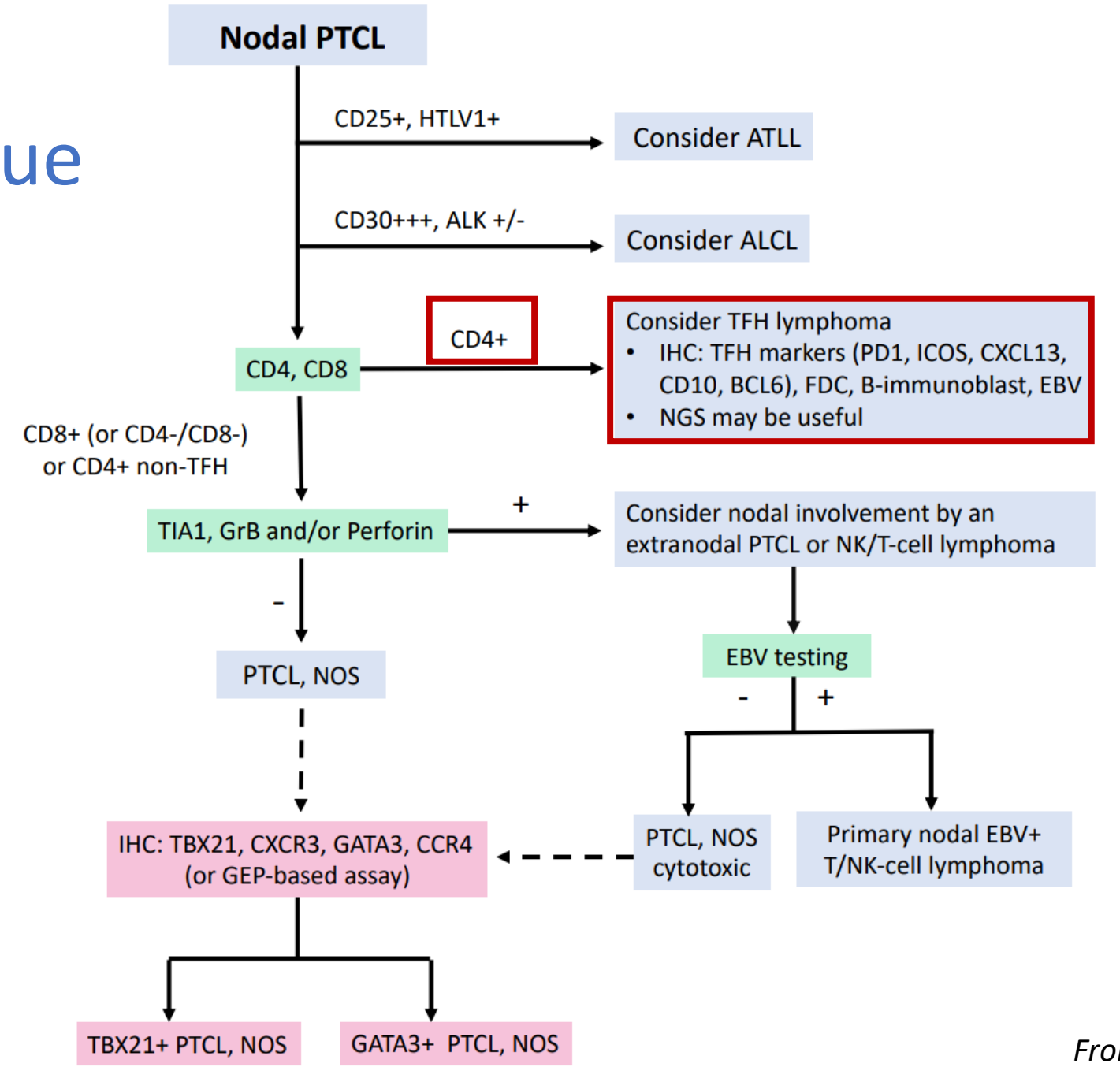
Et dans les PTCL, NOS ?

- PTCL, NOS is mainly a nodal lymphoma that remains a **diagnosis of exclusion**
- Two molecular subgroups, namely PTCL-TBX21 and PTCL-GATA3,
- Expression of cytotoxic molecules delineates a subgroup of aggressive PTCL, NOS which tend to occur in patients with impaired immunity and mostly cluster to PTCL-TBX21.
- **Designation of PTCL, NOS according to the molecular subgroups is not routinely incorporated into clinical diagnosis and requires further studies for clinical validation.**
- **Investigation for EBV NEEDED -→ Primary nodal EBV-positive T/NK cell lymphoma, a distinct entity (ICC, WHO)**



Iqbal et al. Blood 2010; Drieux et al. Haematologica 2020; Alinae et al. Modern Pathol 2022; Amador et al. J Clin Oncol 2022

En pratique



From Campo E et al.. Blood 2022

Et enfin… dans les lymphomes T(NK) extra-ganglionnaires ?

- **EATL and MEITL:** Novel immunophenotypic and genomic data reinforce their distinction
- **Type II refractory celiac disease** is a precursor of EATL and therefore has been added to the classification
- Two groups of indolent LPD of the gastrointestinal tract are recognized, according to their T-cell or NK-cell derivation:
  - **indolent <u>clonal</u> T-cell <u>LPD</u> of the GI tract**: the clonal nature of the T-cell cases, which variably express CD4 and/or CD8, is further supported by the finding of gene alterations in a subset of the cases.
  - **indolent NK cell LPD of the gastrointestinal tract (**formerly referred to as NK-cell enteropathy or lymphomatoid gastropathy).

Conclusions…..

- Classification de plus en plus basée sur des données moléculaires
- Alternatives pratiques à des tests moléculaires comme l'immunohistochimie (ALK, CCND1, BRAFV600E, …..) ?
- Traitements ciblés encore limités
- Besoin d'unifier les classifications afin de disposer – à nouveau - d'un langage commun et universel (patients, essais cliniques, publications,…)
- **Quelle classification choisir ?**
  - l'une ou l'autre
  - les 2 (WHO-5 et ICC) lorsque divergences ou selon…(?)
  - voire rester sur la WHO-2017?
  - **Importance d'une comprehension avec l'équipe Clinique ++**

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