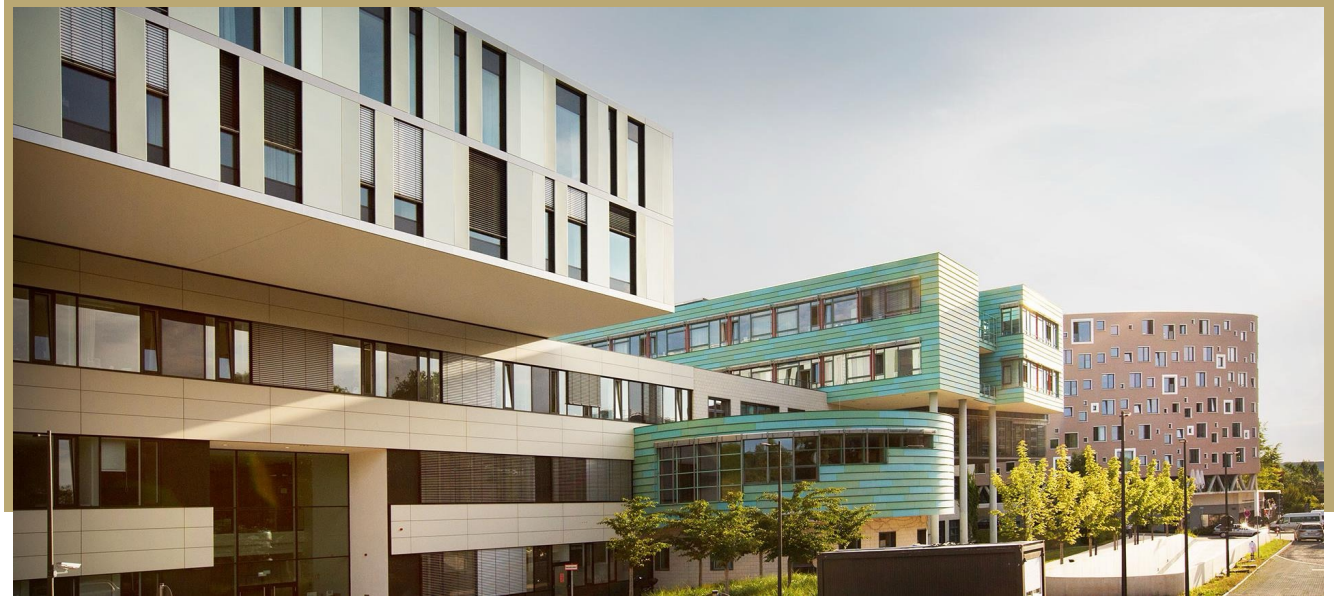
Diffuse large B-cell lymphomas. Challenges and controversies in the diagnosis



LYMPHOMA Forum of Ireland

20th lymphoma Forum of Ireland Plenary meeting

Leticia Quintanilla-Fend
Institute of Pathology

Universitätsklinikum Tübingen

Diffuse large B-cell lymphomas
Challenges and controversies

Objectives

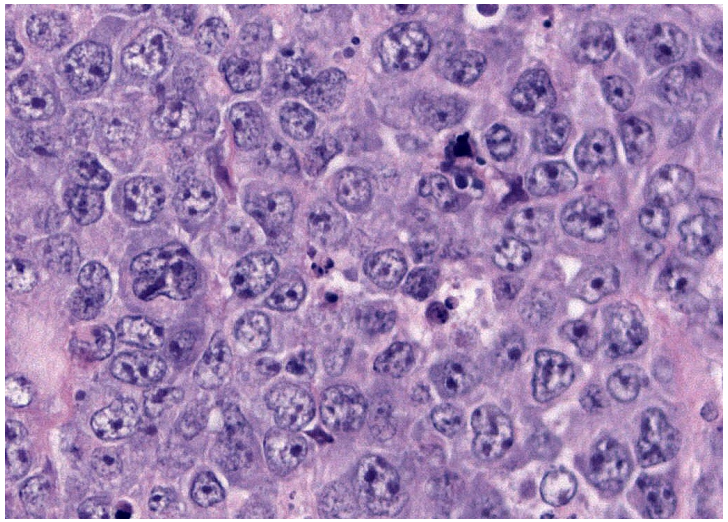
- Definition and classification
- Cell of origin
- Molecular classification of DLBCL
- *MYC* rearrangement
- Molecular high-grade signature/double-hit signature/ dark zone signature
- High grade B-cell lymphomas

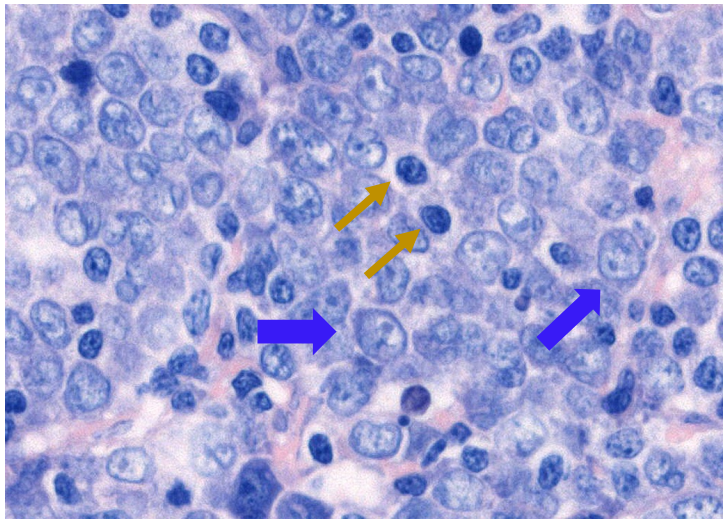
LYMPHOMA Forum of Ireland

Diffuse large B-cell lymphomas, NOS

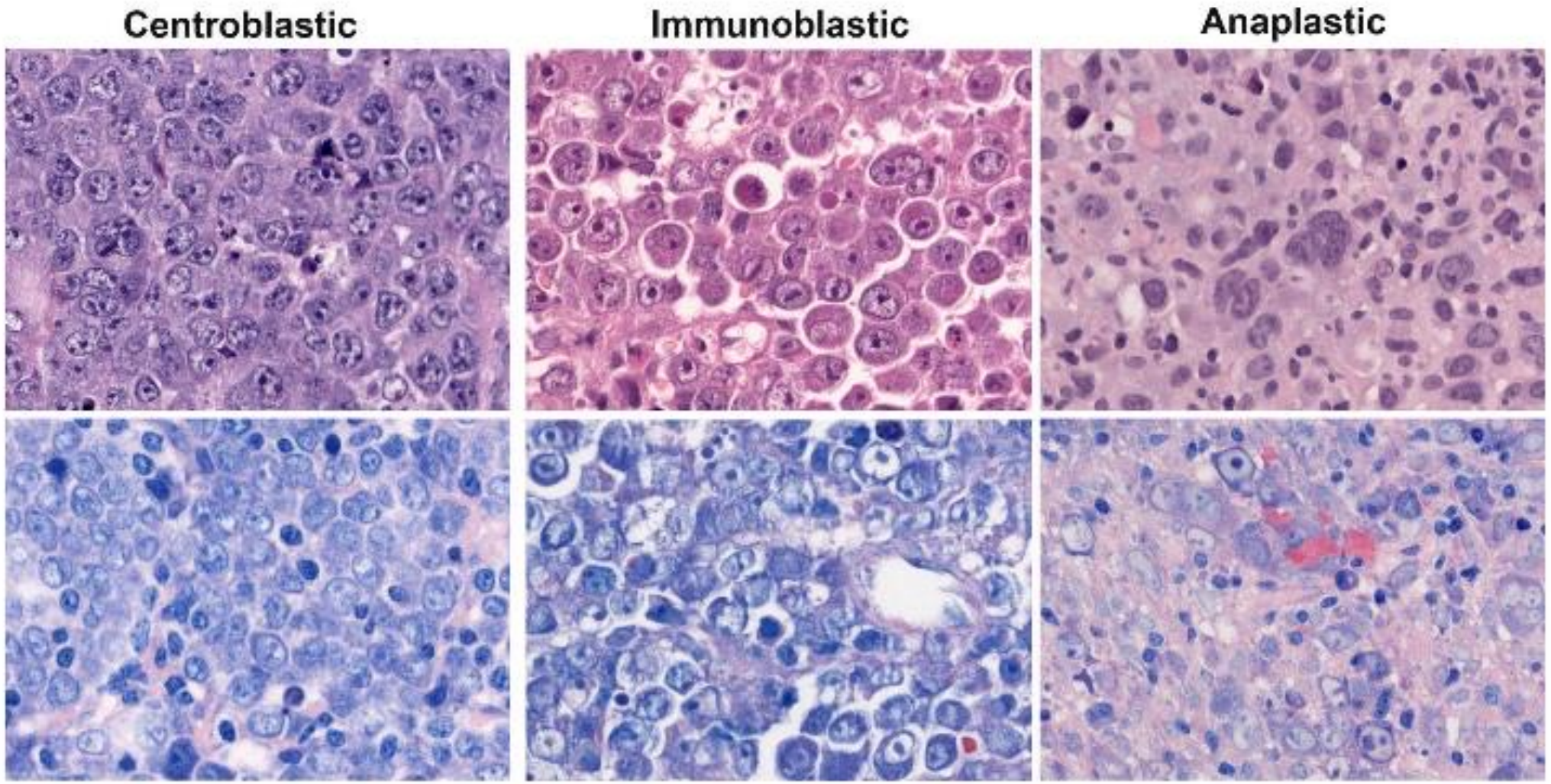
Definition: Diffuse large B-cell lymphoma is a neoplasm of large B lymphoid cells more than twice the size of a normal lymphocyte and with diffuse growth pattern.

➢DLBCL is clinically, morpholgically and biologically a heterogeneous disease reflected in the highly variable clinical course





Diffuse large B-cell lymphomas, NOS



Diffuse large B-cell lymphomas

International Consensus Classification

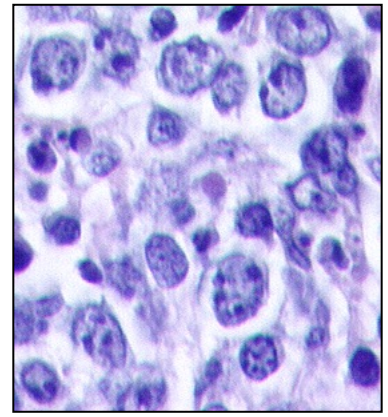
- Diffuse large B-cell lymphoma, NOS
  - Germinal center B-cell subtype
  - Activated B-cell subtype
- *Large B-cell lymphoma with 11q aberration**
- Nodular lymphocyte predominant B-cell lymphoma*
- T cell/histiocyte-rich large B-cell lymphoma
- Primary diffuse large B-cell lymphoma of the central nervous system
- Primary diffuse large B-cell lymphoma of the testis*
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Intravascular large B-cell lymphoma
- *HHV-8 and Epstein-Barr virus–negative primary effusion-based lymphoma**
- Epstein-Barr virus–positive mucocutaneous ulcer*
- Epstein-Barr virus–positive diffuse large B-cell lymphoma, NOS
- Diffuse large B-cell lymphoma associated with chronic inflammation
  - Fibrin-associated diffuse large B-cell lymphoma
- Lymphomatoid granulomatosis
- Epstein-Barr virus–positive polymorphic B-cell lymphoproliferative disorder, NOS*
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- HHV-8–associated lymphoproliferative disorders
  - Multicentric Castleman disease
  - HHV-8–positive germinotropic lymphoproliferative disorder
  - HHV-8–positive diffuse large B-cell lymphoma, NOS
  - Primary effusion lymphoma

Campo E. Blood 2022

5th Edition of the WHO

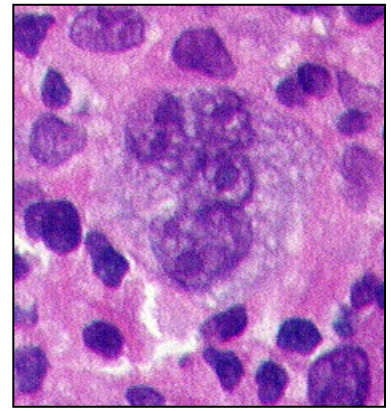
Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with *IRF4* rearrangement
High-grade B-cell lymphoma with 11q aberrations
Lymphomatoid granulomatosis
EBV-positive diffuse large B-cell lymphoma
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma
Fluid overload-associated large B-cell lymphoma
Plasmablastic lymphoma
Primary large B-cell lymphoma of immune-privileged sites
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Primary mediastinal large B-cell lymphoma
Mediastinal grey zone lymphoma

Alaggio R. Leukemia 2022

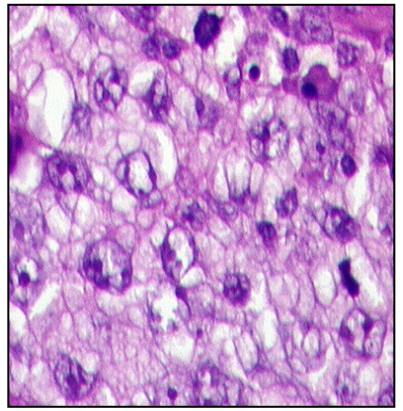


Centroblastic

Immunoblastic



T-cell rich

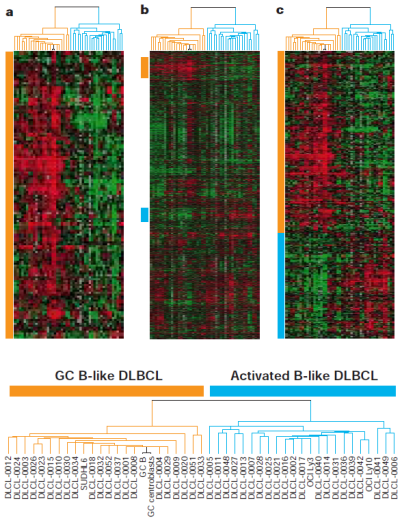


Mediastinal LBCL

DLBCL and the Cell of origin

2000

Molecular signature DLBCL Cell of origin

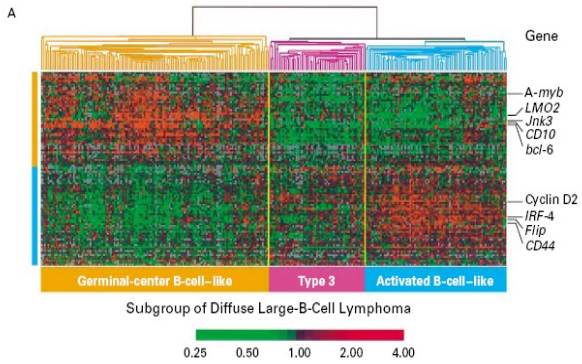


Alizadeh et al, Nature 2000

R-CHOP as treatment for DLBCL

2000

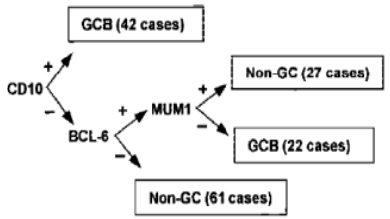
Molecular profiling to predict survival after chemotherapy



Rosenwald et al, NEJM 2002

2008

Hans Algorithm



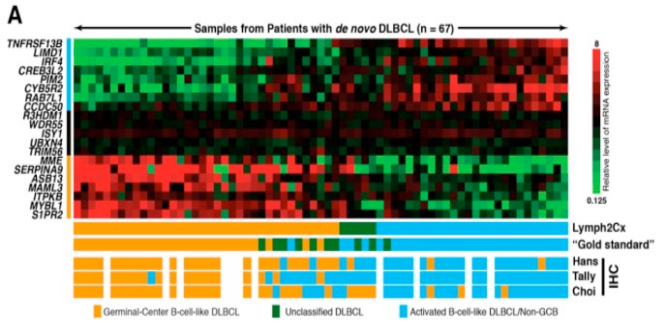
Hans et al, Blood 2004

COO introduced in the WHO classification

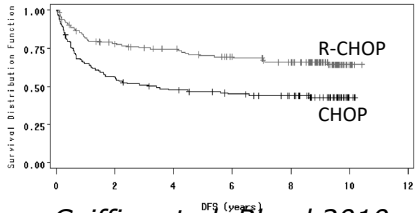
*Does not currently determine therapy

2010

Determining COO using GEP in FFPE



Scott et al, Blood 2014



Coiffier et al, Blood 2010

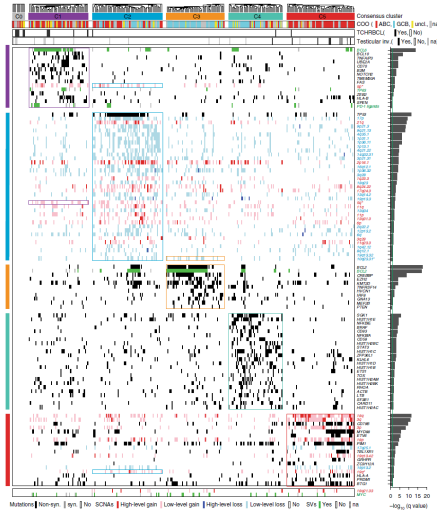
2017

COO required in the WHO classification

*Clinical trials showed a benefit of bortezomib to R-CHOP in the ABC subtype

2018

Molecular subtypes



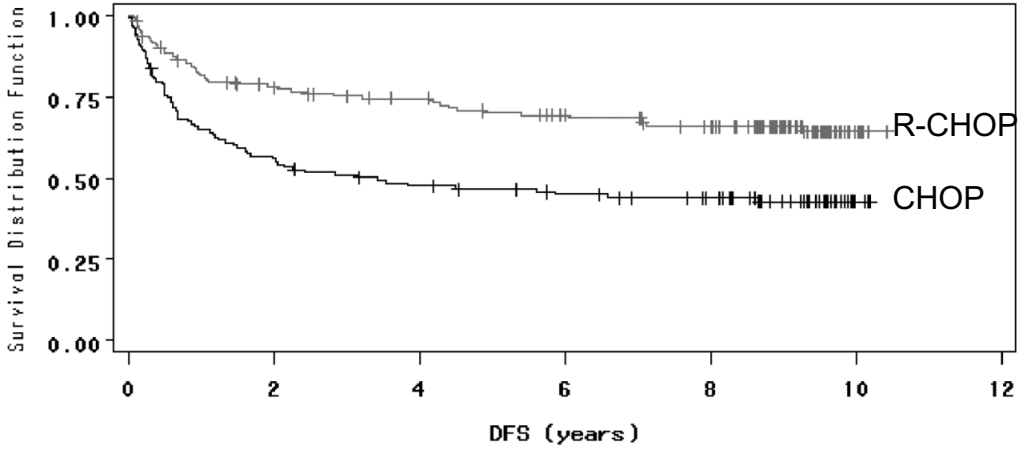
Chapuy et al, Nature Med 2018

2022

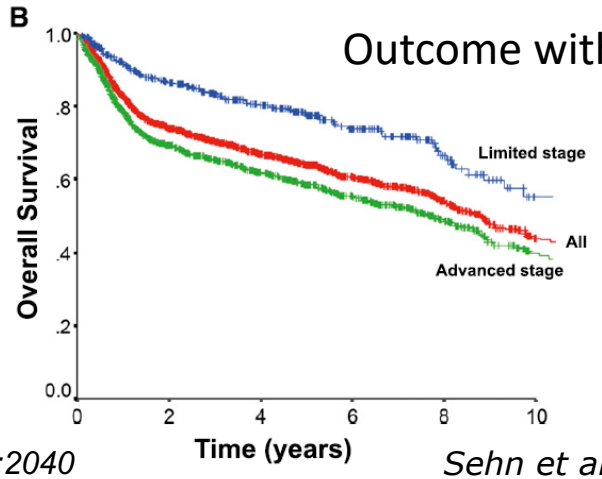
COO…? Molecular subgroups? WHO 5 ICC 2022

DLBCL and the Cell of origin

- COO GEP did not establish in routine diagnosis beyond IHC
  - Cost effectiveness
  - Available mainly in research centers
  - Limited to clinical trials
- Limited impact on the choice of frontline treatment
  - R-CHOP (70% success)
- Attempts to improve the outcome of specific subgroups had limited success

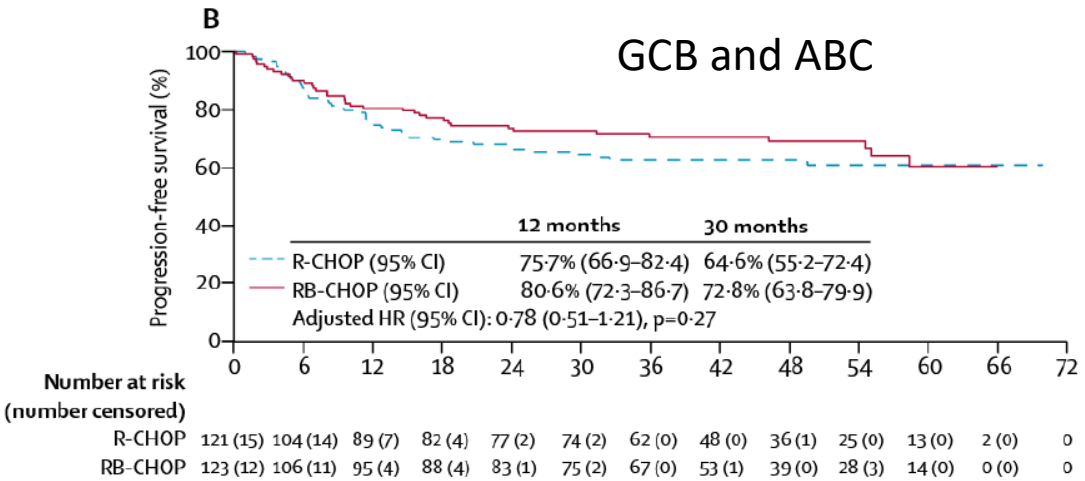


Coiffier et al, Blood 2010;116:2040



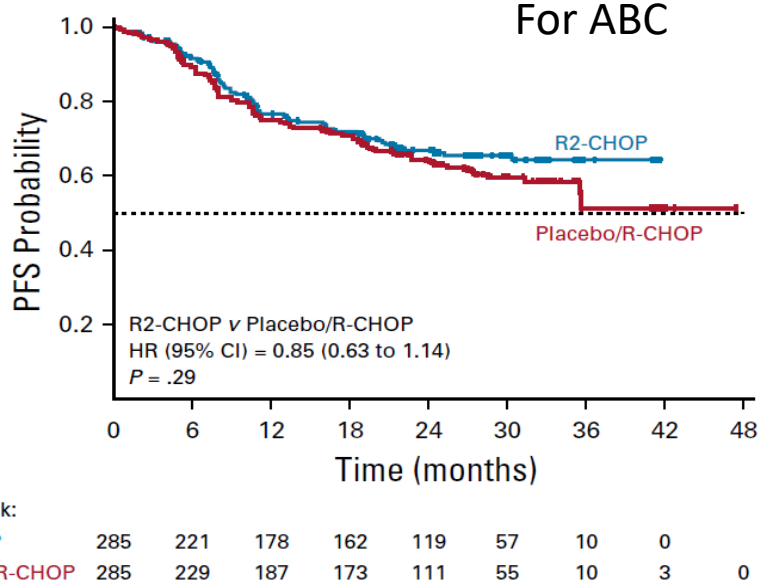
Sehn et al, Blood 2015;125:22

Attempts to improve the outcome of ABC subgroup has limited success

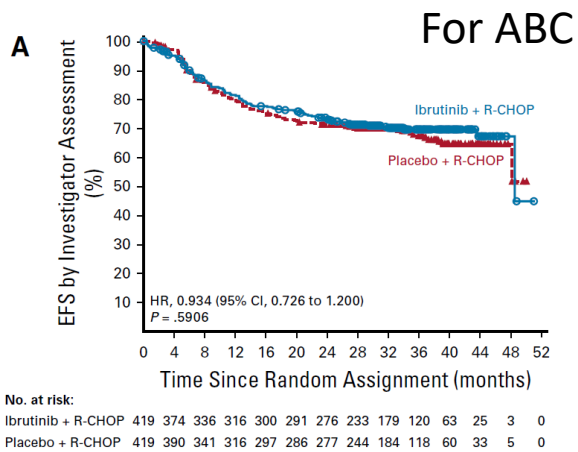


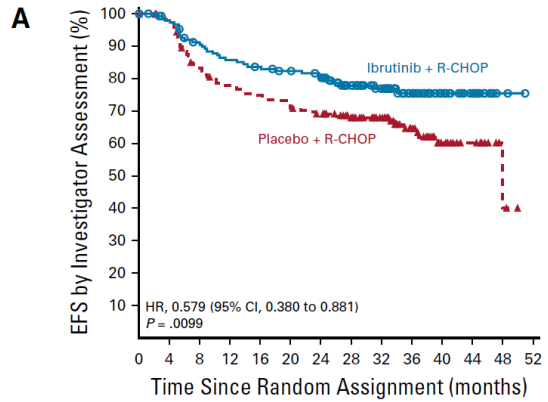
RMoDL-B
R-CHOP±bortezomib
Davies AJ et al Lancet Oncol 2019
COO by GEP
Results: no difference observed

ROBUST
R-CHOP ± Lenalidomide
Nowakowski GS, et al,
J Clin Oncol 2021
COO by GEP
Results: no difference observed



PHOENIX
R-CHOP±ibrutinib
Younes A, et al, J Clin Oncol 2019
COO by Hans algorithm
Results: in <60 years improved EFS, PFS and OS



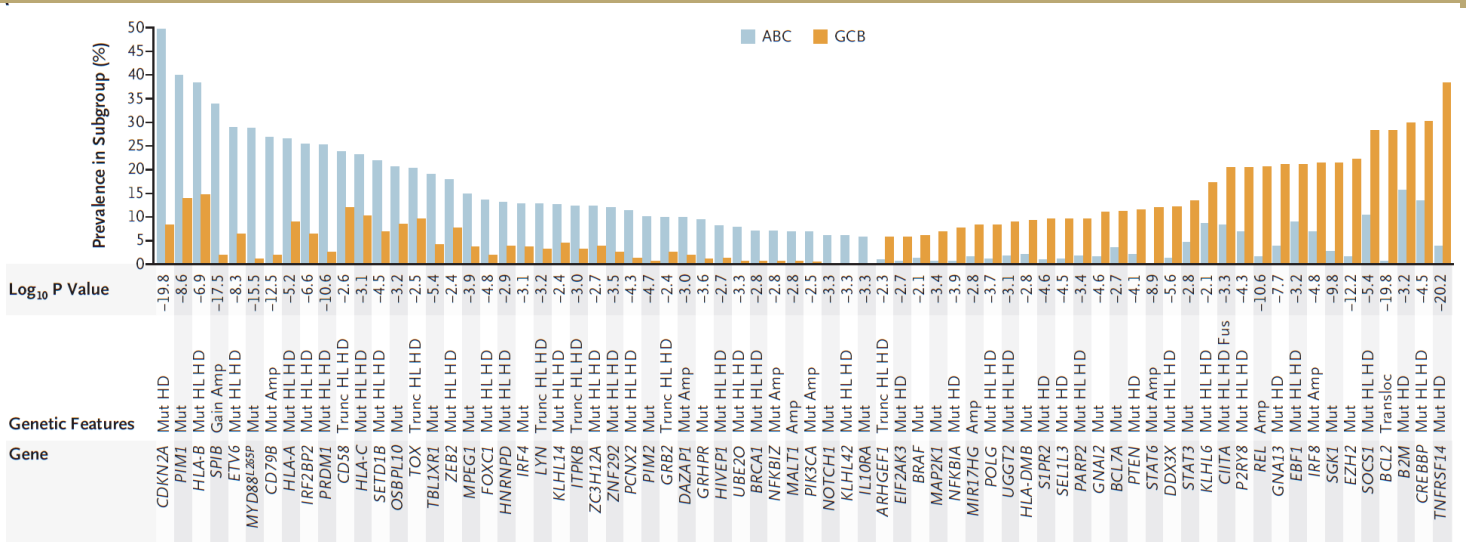


<60 years

Comprehensive Cancer Center

Eberhard Karls Universität Tübingen

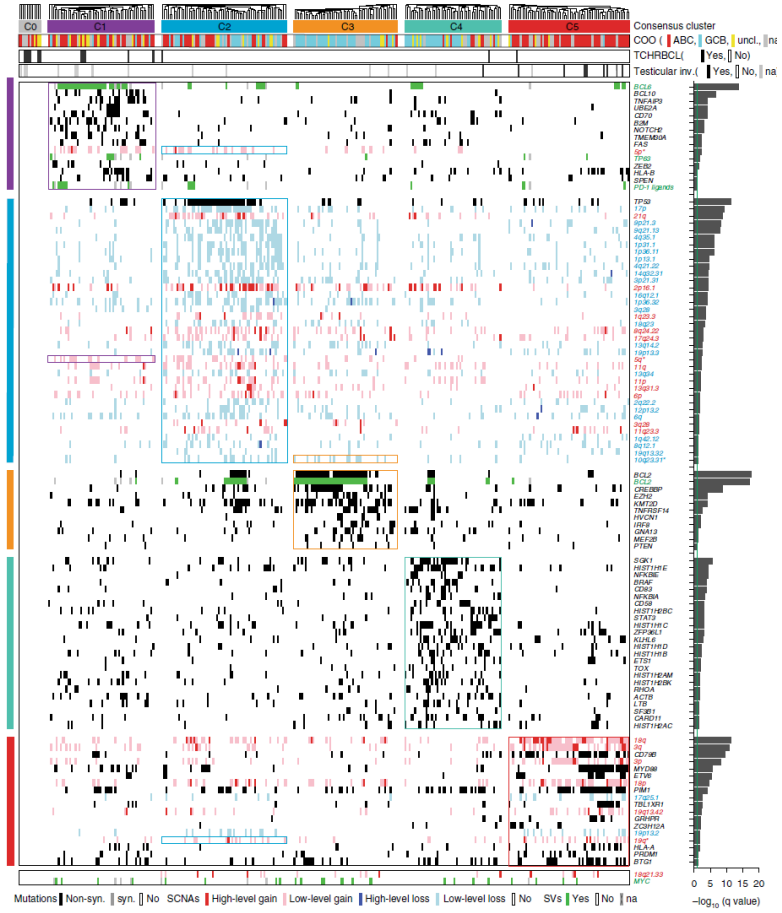
Cell of origin distinct biology



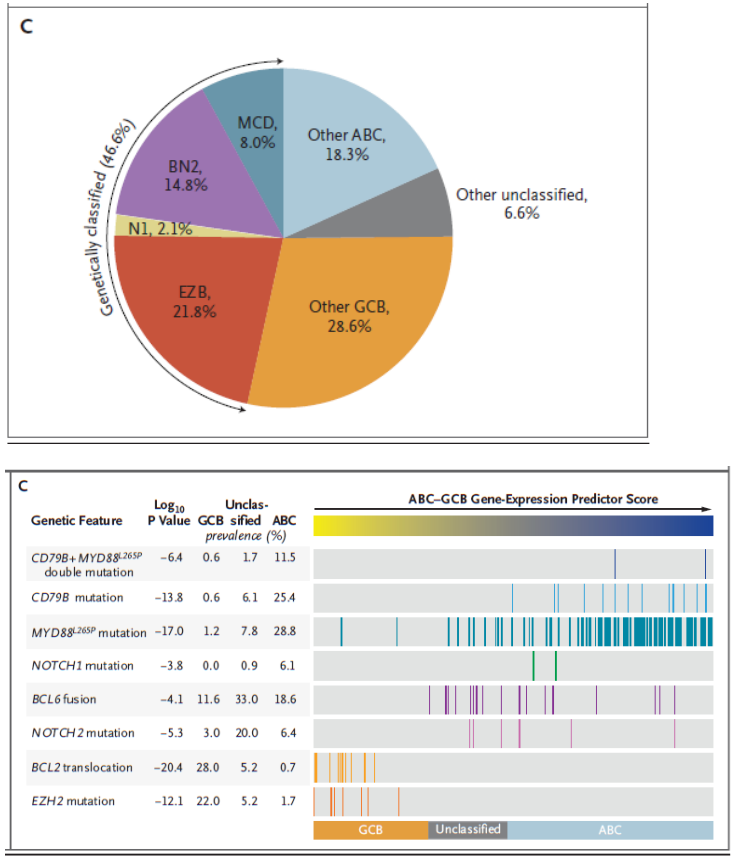
	ABC-DLBCL	GCB-DLBCL
Differentitation →	Up to plasmablastic stage - *BCL6, PRDM1*	Up to the light zone stage - Epigenetics
Proliferation →	Active BCR signaling	Tonogenic BCR signaling
Surivival →	*BCL2* amplification	*BCL2* rearrangement

DLBCL molecular classification

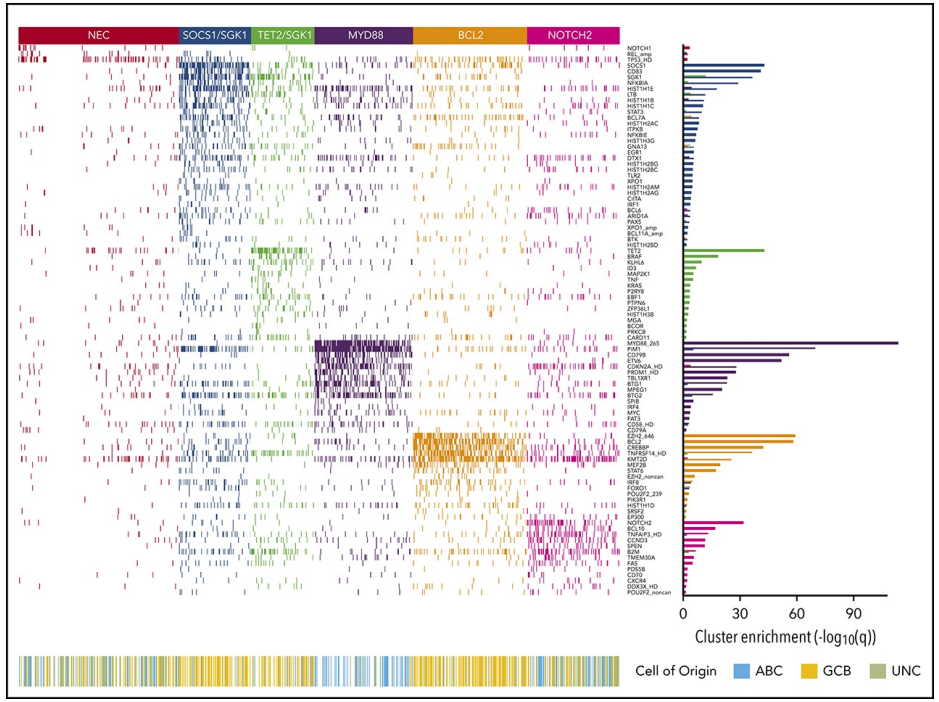
Biologic and molecular based classifications: Translocations, CNAs, mutations



Chapuy et al, Nature Med 2018

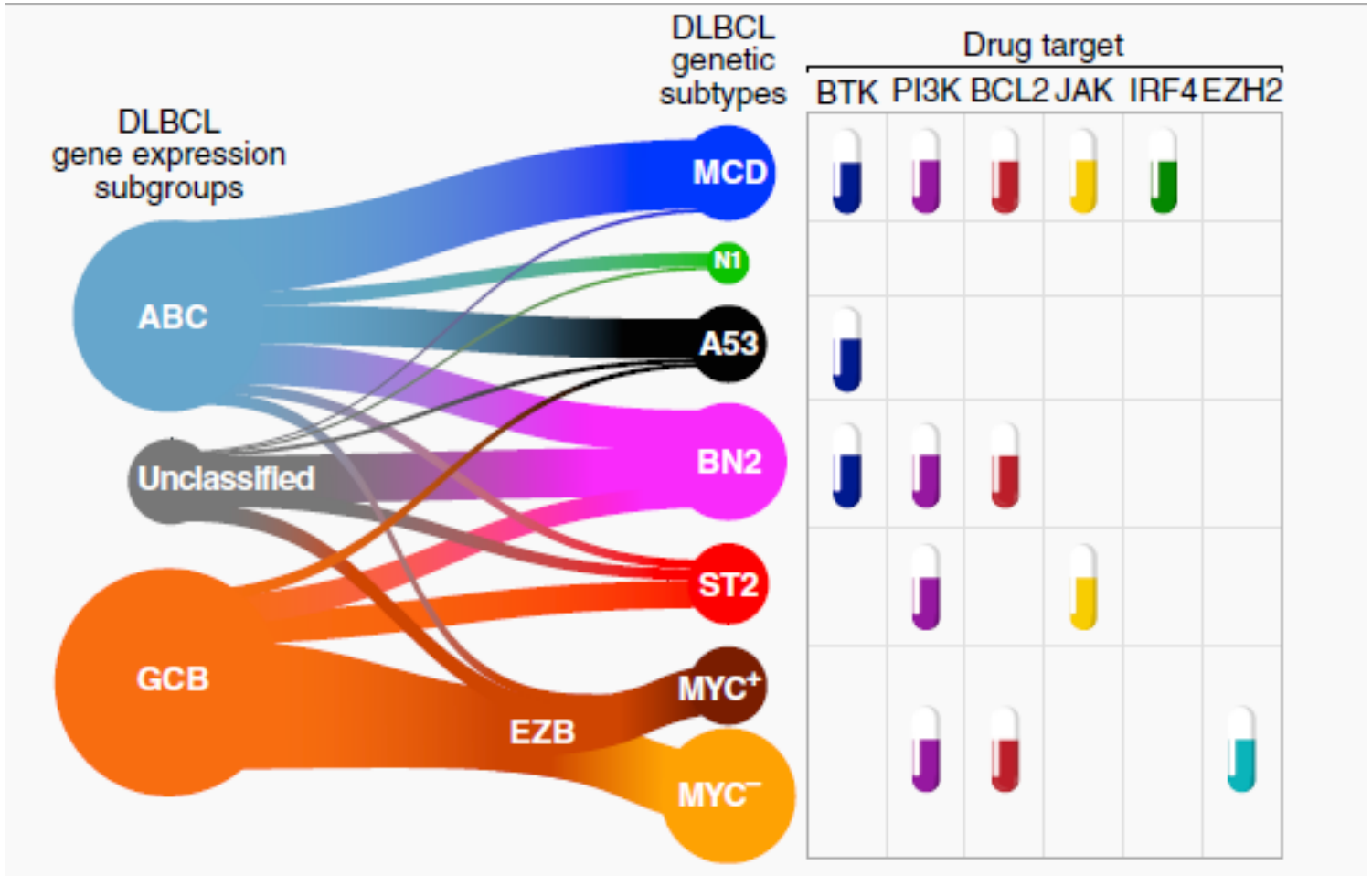


Schmitz et al, N Engl J Med 2018



Lacy et al, Blood 2020

DLBCL molecular classification



C5/MYD88 enriched in extranodal
DLBCL CNS/VRL/Testicular

C2 aneuploidy/*TP53*

C1/NOTCH2 marginal zone lymphoma

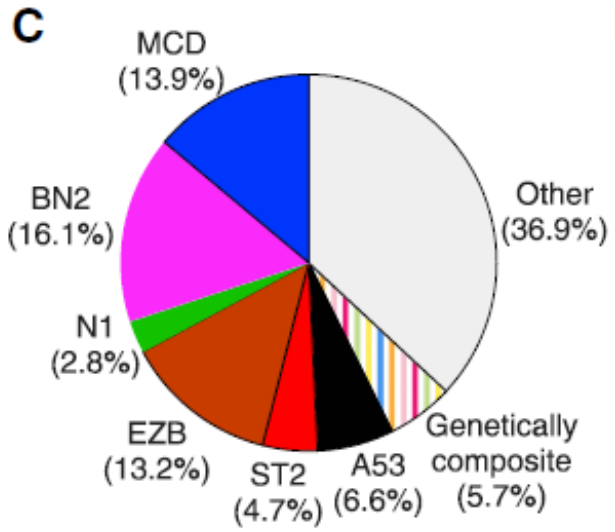
C4/ TET2/SGK1 NLPHL/THRLBCL

C3/EZB/BCL2 FL and tFL
Double hit signature +/-

Wright et al, Cancer Cell 2020

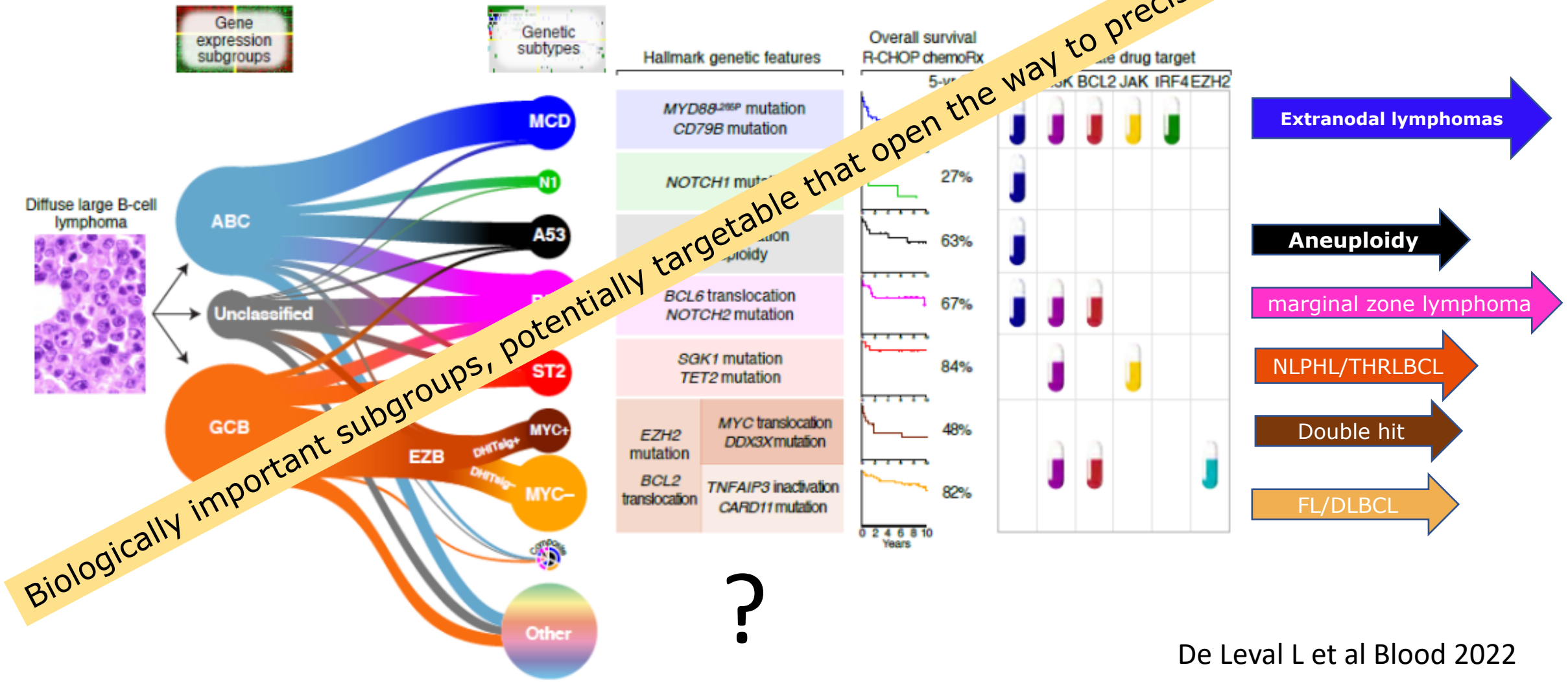
DLBCL molecular classification

Wright 2020	Chapuy 2018	Lacy 2020	Frequency
MCD	C5	MYD88	14-21%
BN2	C1	NOTCH2	16-19%
EZB-MYC-	C3	BCL2	13-18%
EZB-MYC+		Double hit	
A53	C2		7-21
ST2	C4	SOCS1/TET/SGK1	5-17
N1		NEC	3
Unclassifiable			37



Chapuy B et al Nat Med 2018; Wright GW et al Cancer Cell 2020; Lacy SE et al Blood 2020

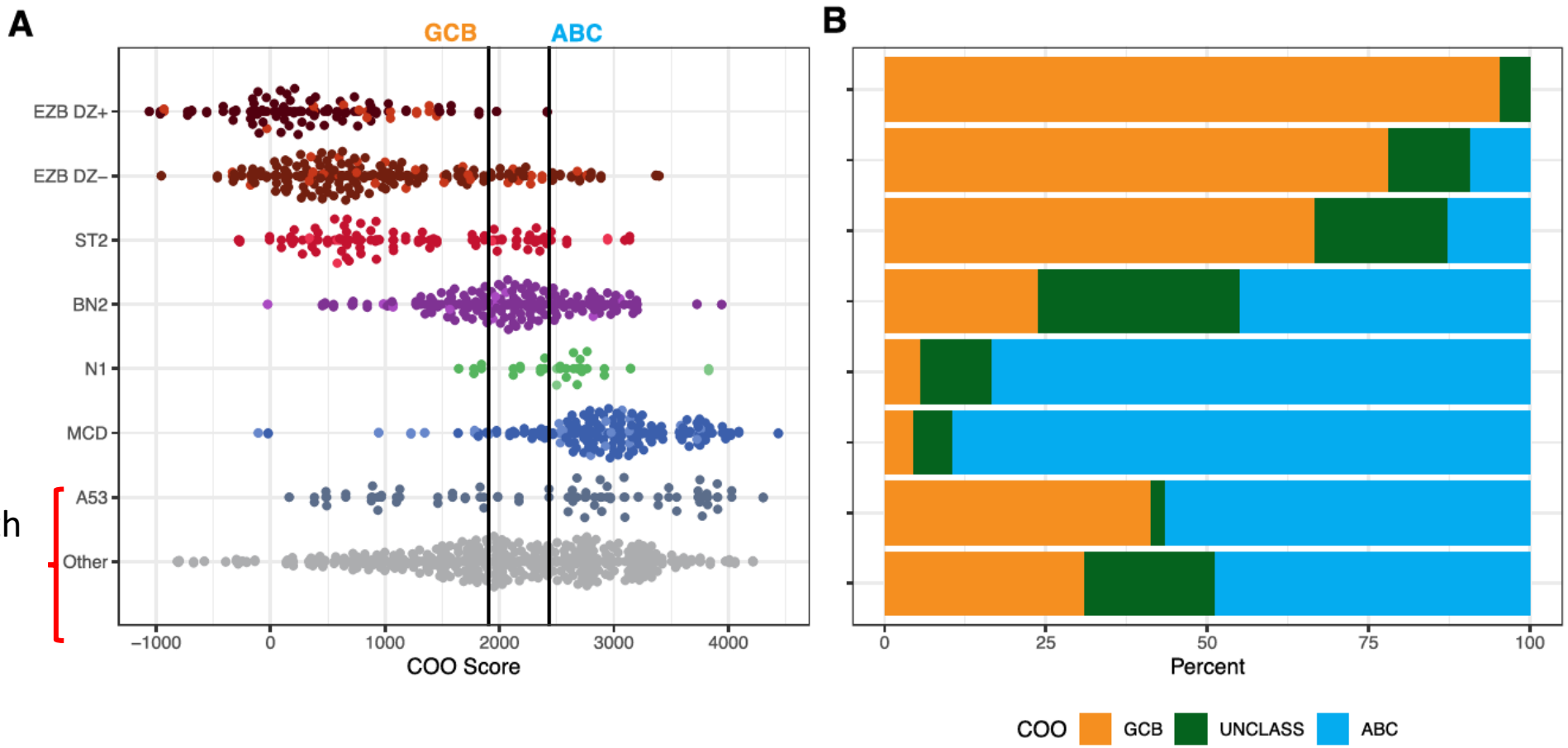
DLBCL molecular classification



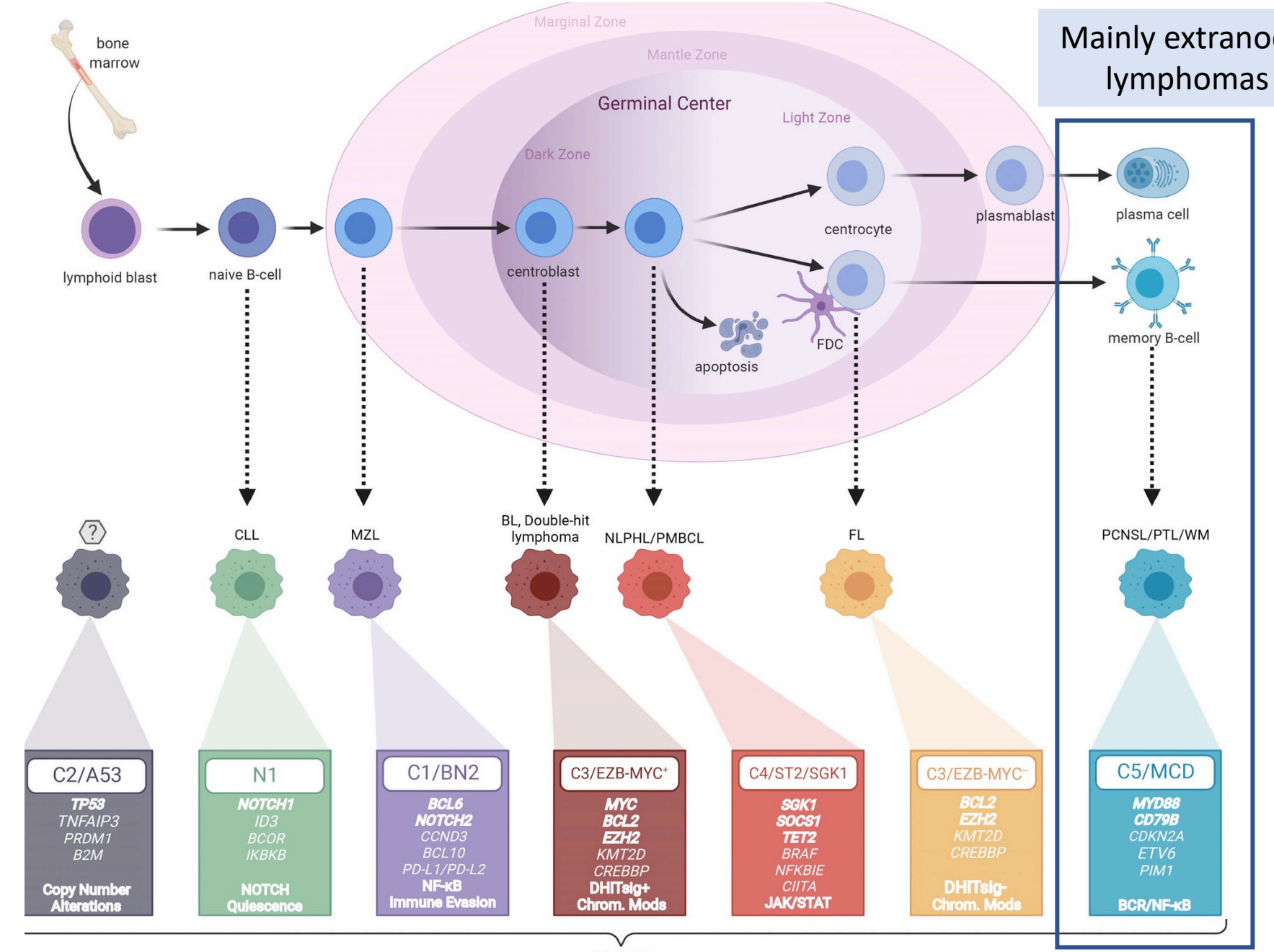
De Leval L et al Blood 2022

DLBCL molecular classification

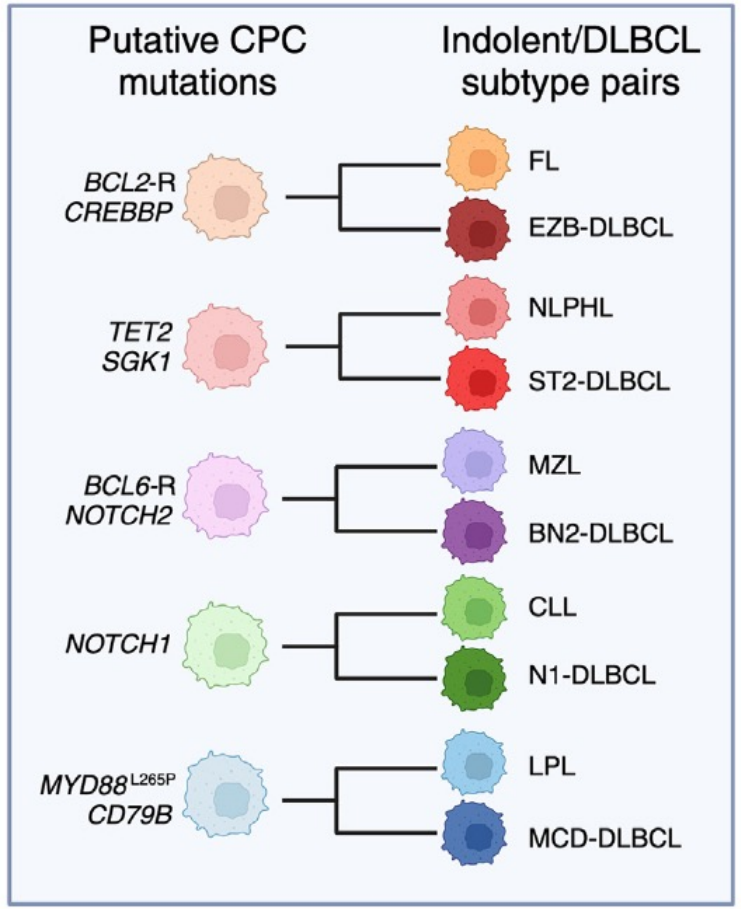
No association with either COO group



L.K. Hilton, D.W. Scott and R.D. Morin / Seminars in Hematology 60 (2023) 267–276



Mainly extranodal lymphomas

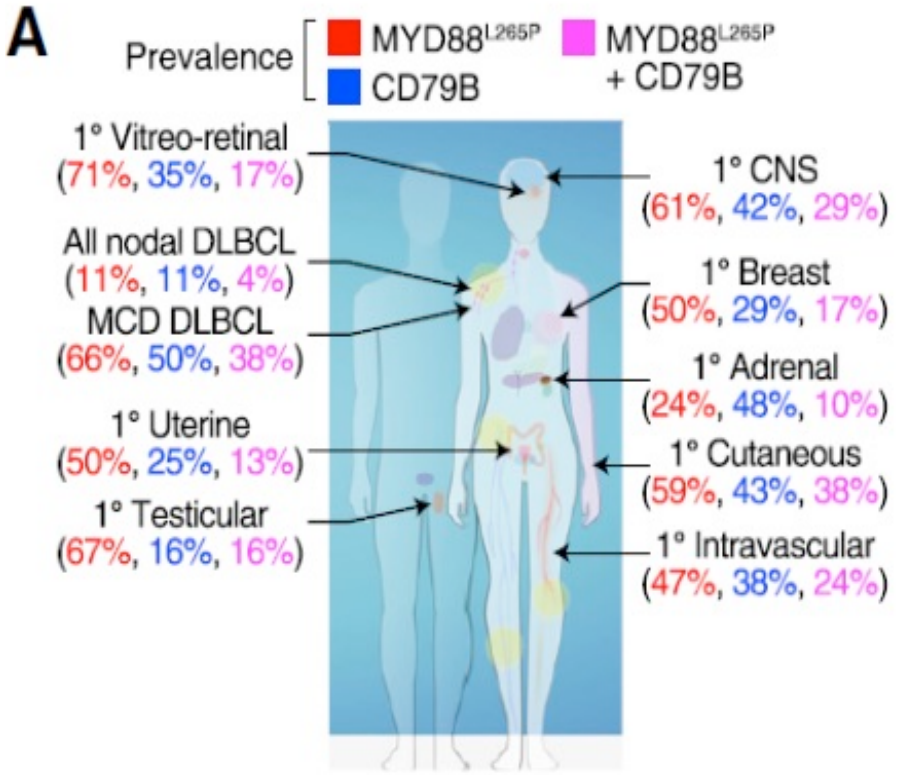


L.K. Hilton, D.W. Scott and R.D. Morin / Seminars in Hematology 60 (2023) 267–276

Morin RD, British Journal of Haematology, 2022, **196,** 814–829

Are extranodal DLBCL ABC-type an entity?

Still premature



Wright GW et al Cancer Cell 2020

- **Extranodal DLBCL, ABC, share biological features (MCD/C5)**
- **Close relationship of primary CNS and testicular DLBCL**
- **Some subtypes better defined by the topographic site (IVLBCL)**

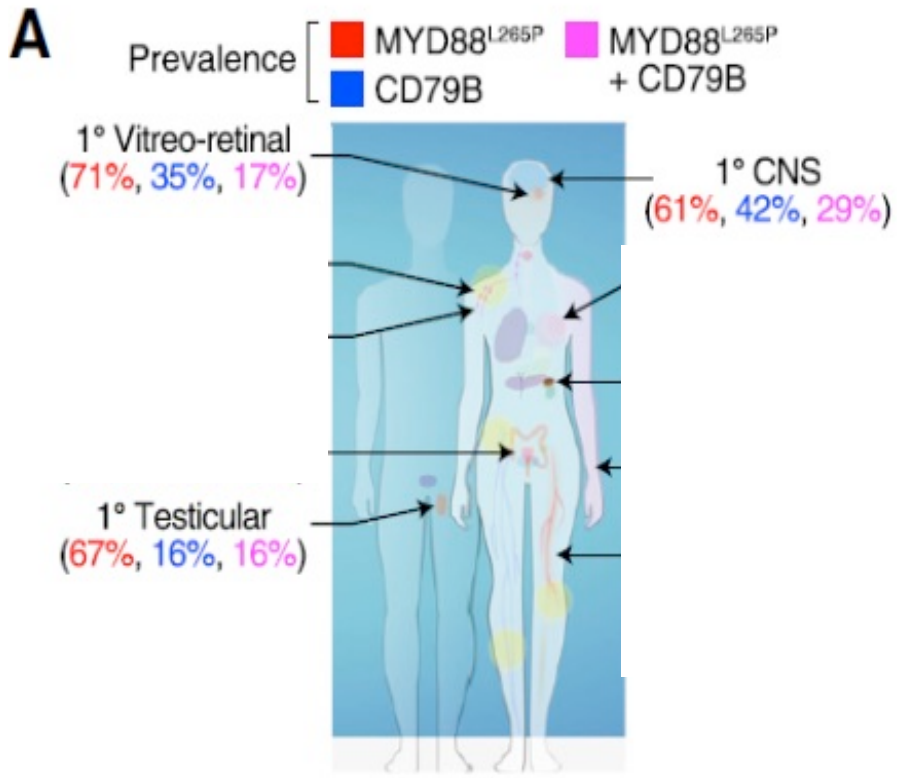
- **Not enough information on the relationship between tumors in different extranodal sites (e.g. Breast, Adrenal, Uterine)**
- **Difficult to define homogeneous clinical guidelines**

ICC Proposal

- **Maintain current defined entities**
- **Recognize this group of lymphomas as deserving more specific studies to clarify their relationship**

Campo E. Blood 2022

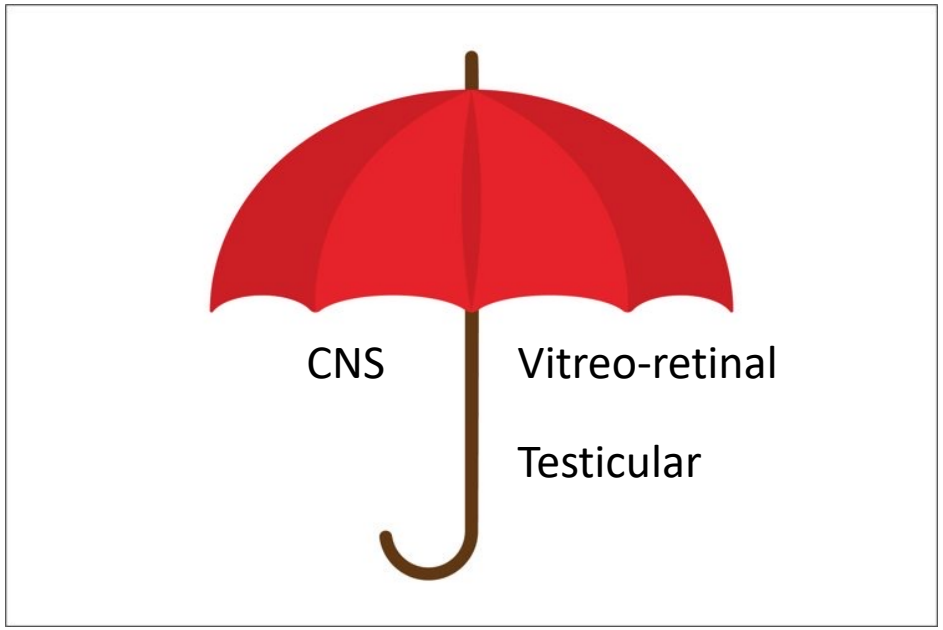
Are extranodal ABC-type an entity?



Modified from Wright GW et al Cancer Cell 2020

5th edition WHO approach

Primary large B-cell lymphomas of immune-privileged sites



Intravascular
Breast
Adrenal
Cutaneous
Uterine
Nodal

?

Alaggio R. Leukemia 2022

Is the CNS immune priviledge?

neuro-immune responses occur at the borders of the brain

Review

Brain borders at the central stage of neuroimmunology

https://doi.org/10.1038/s41586-022-05474-7

Received: 28 July 2022

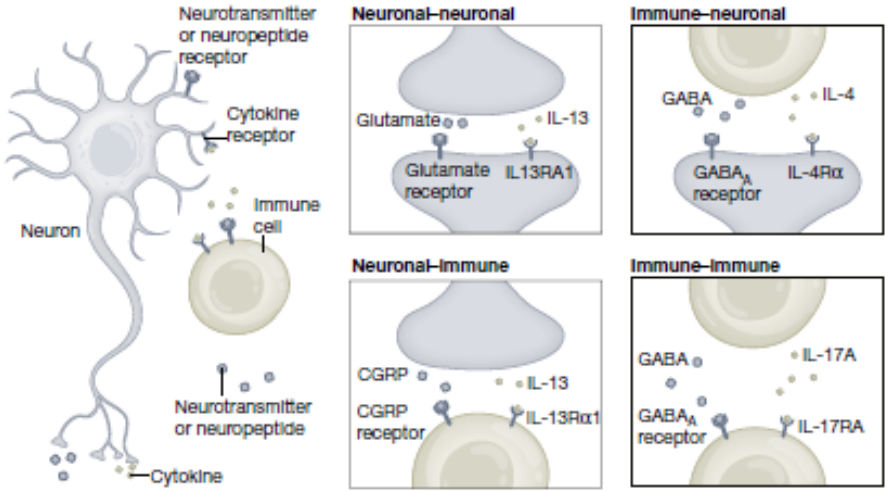
Accepted: 24 October 2022

Published online: 14 December 2022

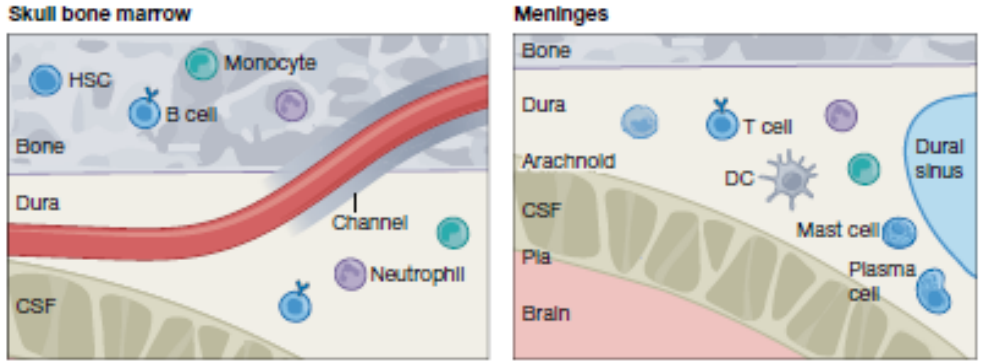
Check for updates

Justin Rustenhoven[1,2,3,4] & Jonathan Kipnis[1,2]

The concept of immune privilege suggests that the central nervous system is isolated from the immune system. However, recent studies have highlighted the borders of the central nervous system as central sites of neuro-immune interactions. Although the nervous and immune systems both function to maintain homeostasis, under rare circumstances, they can develop pathological interactions that lead to neurological or psychiatric diseases. Here we discuss recent findings that dissect the key anatomical, cellular and molecular mechanisms that enable neuro-immune responses at the borders of the brain and spinal cord and the implications of these interactions for diseases of the central nervous system.



Cells of the CNS and immune system communicate using numerous different signalling molecules



MYC

Double hit lymphomas

Double expressers

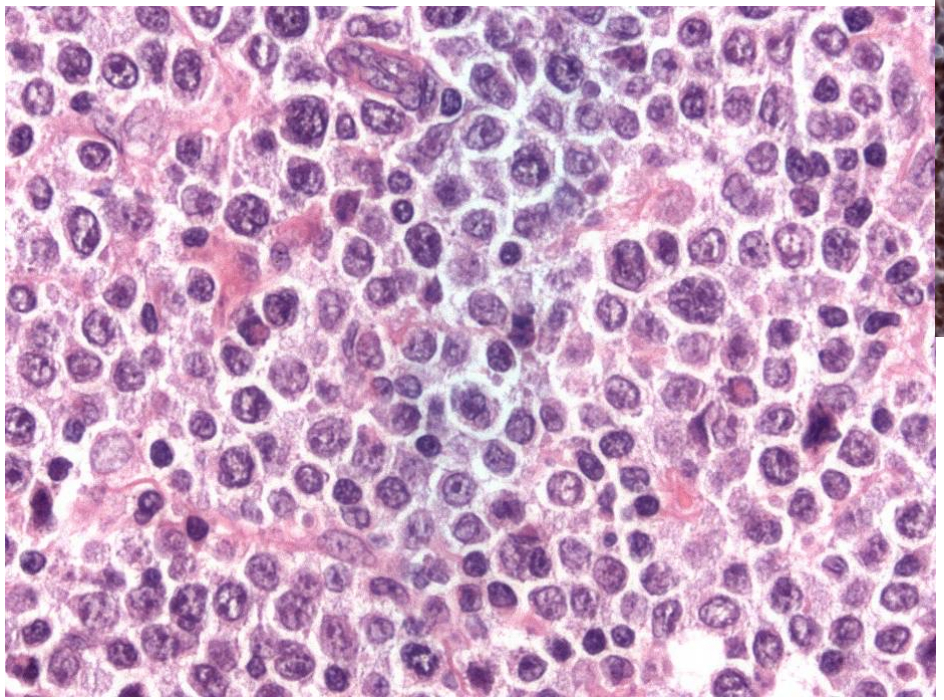
MYC

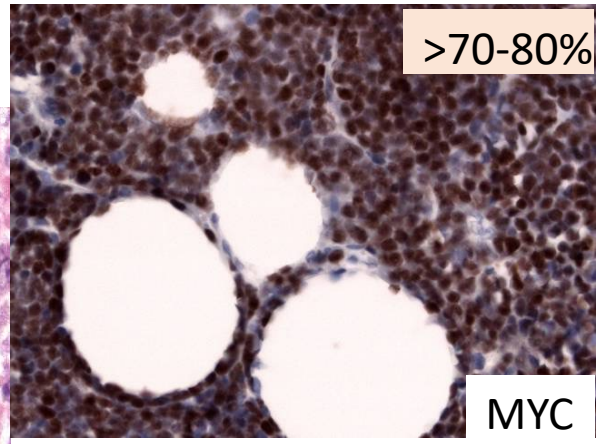
Double hit lymphomas

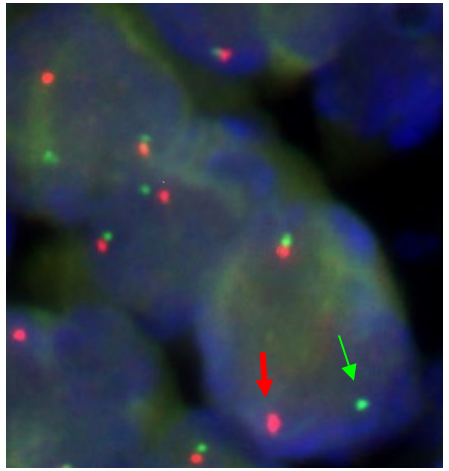
~~Double expressers~~

- Introduced in the 2017 WHO classification
- Deemphasized in the ICC and the 5th edition of the WHO, because may not be prognostically independent

MYC translocation in DLBCL







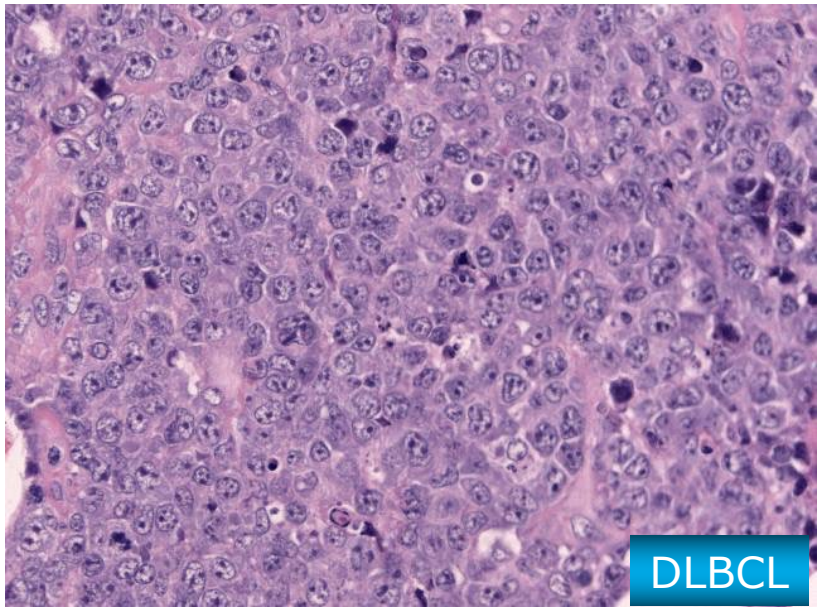
MYC break-apart probe

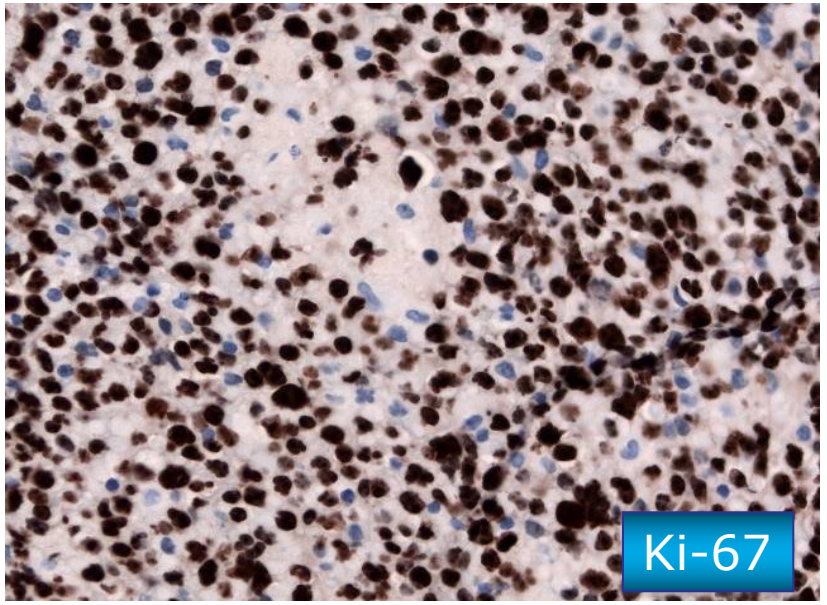
Selection of cases

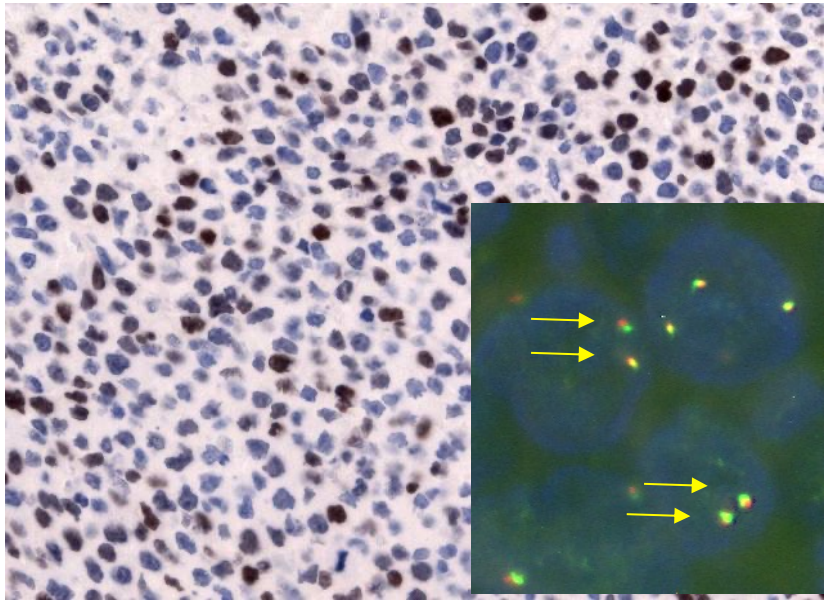
- Clinical presentation
  Extensive disease, CNS involvement, BM involvement and Leukemic presentation
- Morphology
  All BCL-U morphology
  All blastoid morphology
  ➢ DLBCL of GCB type
- FISH
  Start with break-apart probes for *MYC* followed for *BCL2* and *BCL6*.

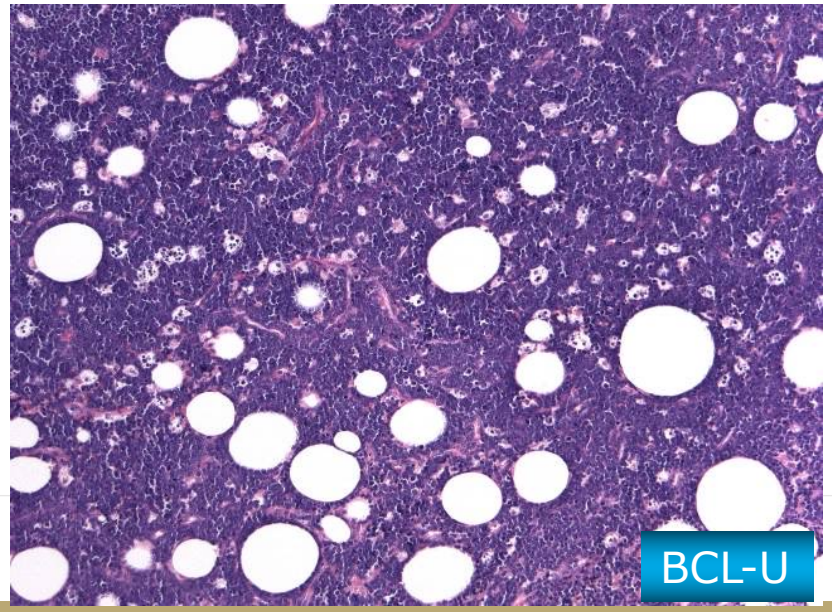
Ott et al, Blood 2013;122:3884-91
Karube K & Campo E, Semin Haematol 2015;52:97

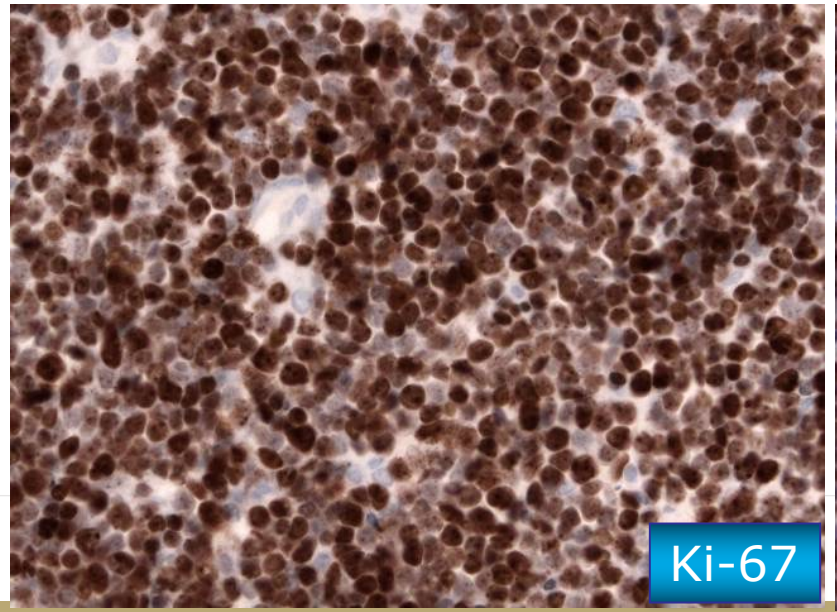
MYC translocation in DLBCL

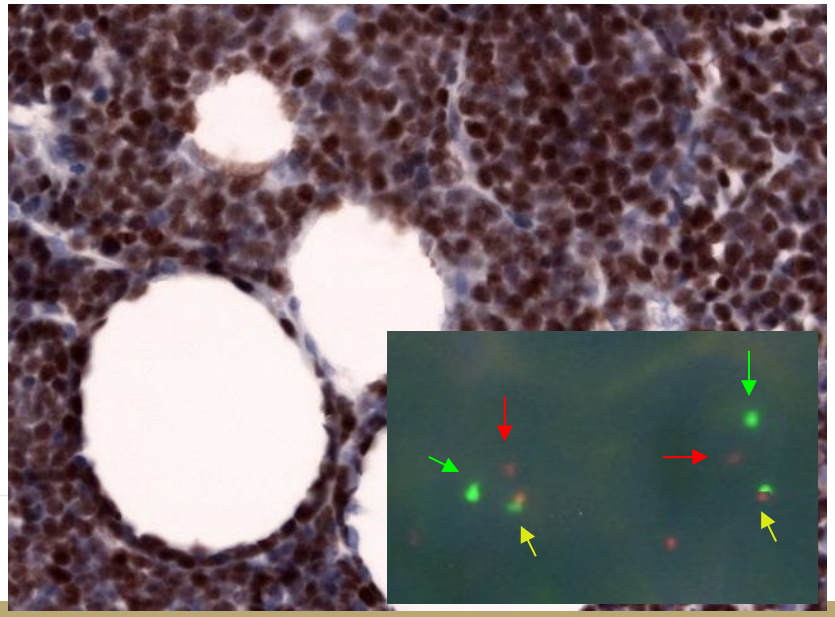




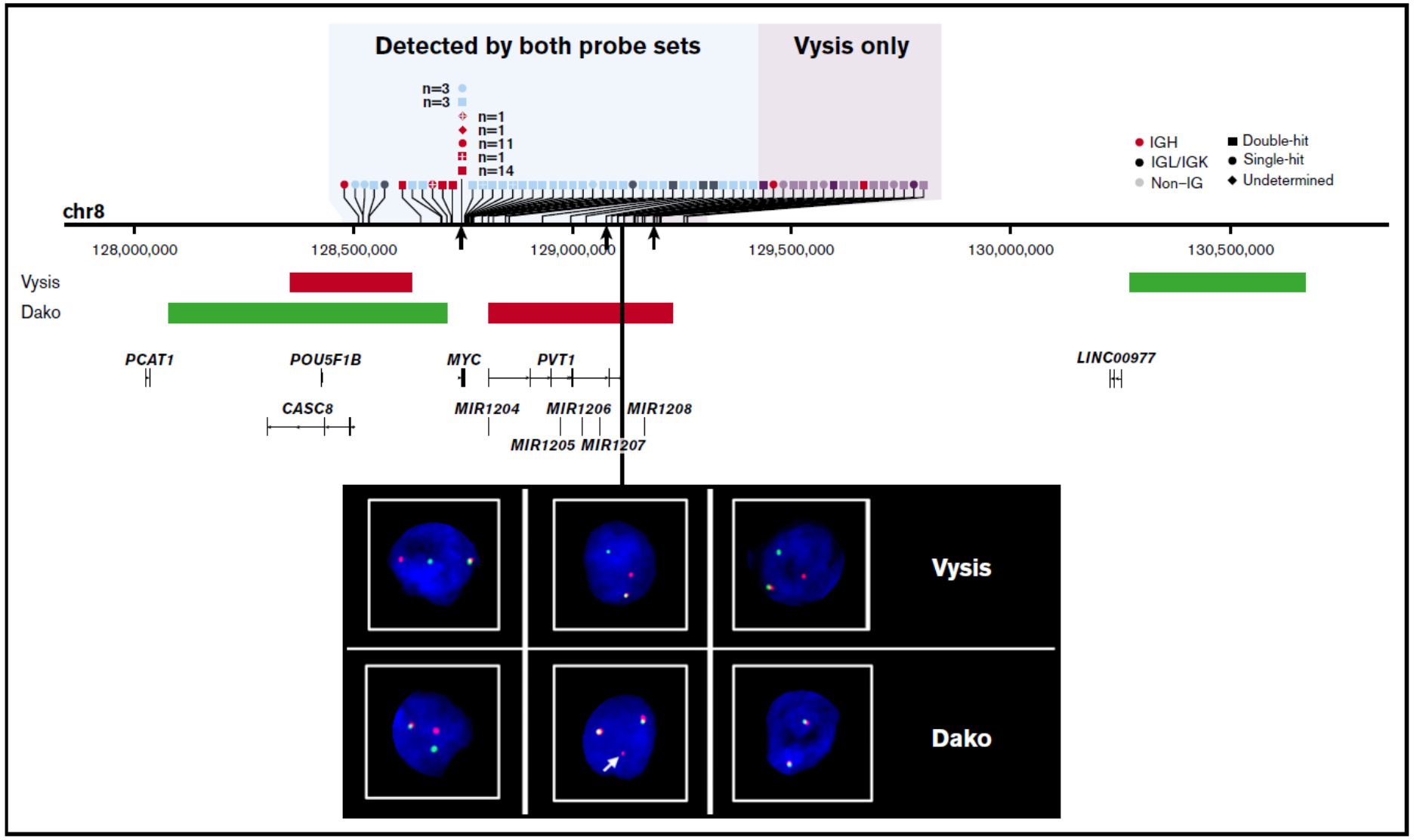






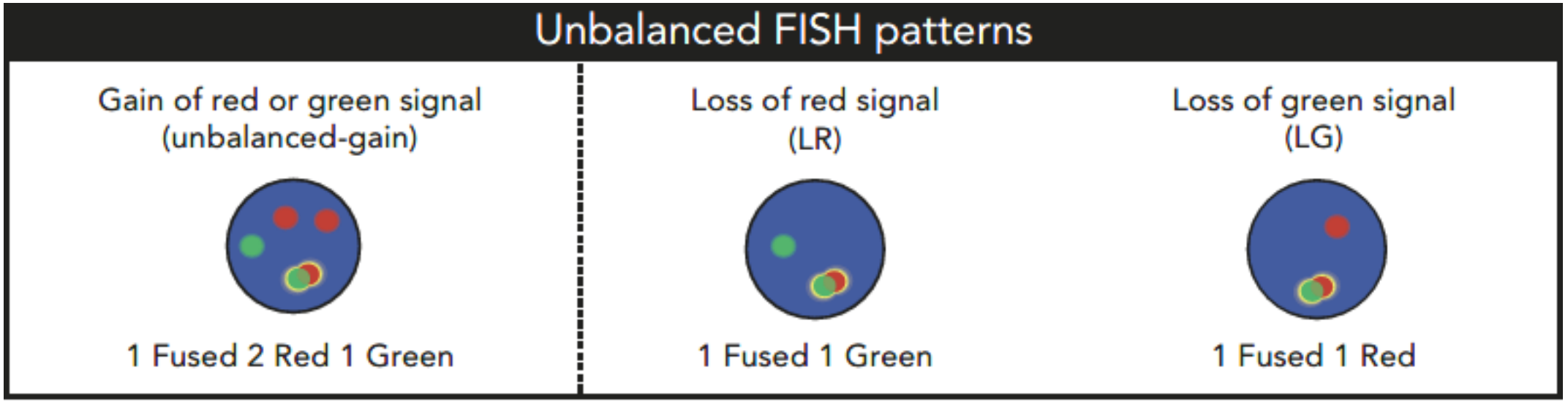


MYC translocation in DLBCL



- Comercially available FISH probes do not detect all the *MYC* rearrangements
- Break apart probes are more sensitive and therefore recommended in routine diagnosis
- Around 20% cryptic
- In negative cases with BAP fusion probes (IGH/*MYC*) are recommended.

MYC translocation in DLBCL



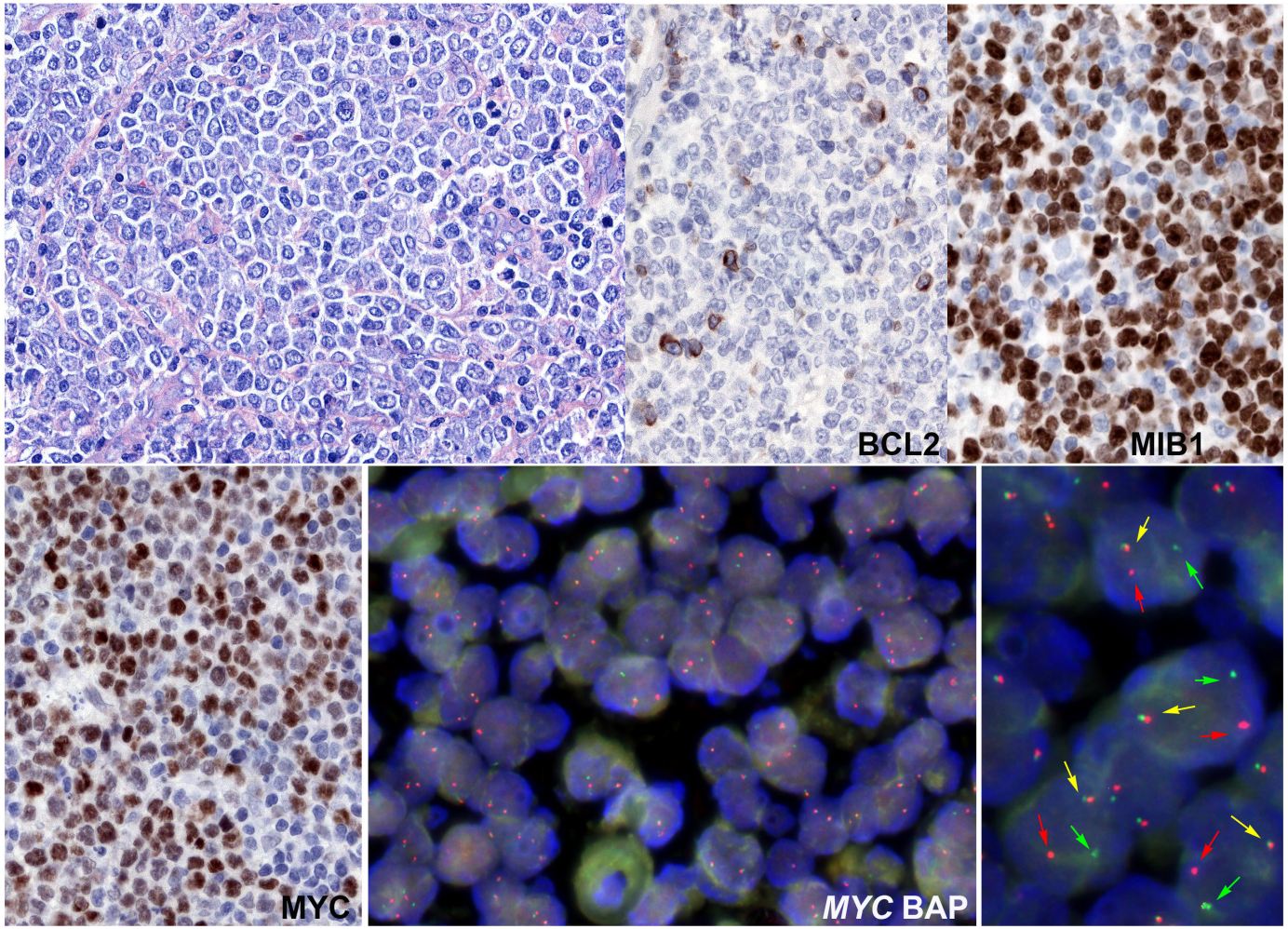
Balanced and unbalance *MYC* rearrangements have the same biological consequences and should be reported as positive for rearrangement

blood® 10 OCTOBER 2024 | VOLUME 144, NUMBER 15

MYC translocation in DLBCL

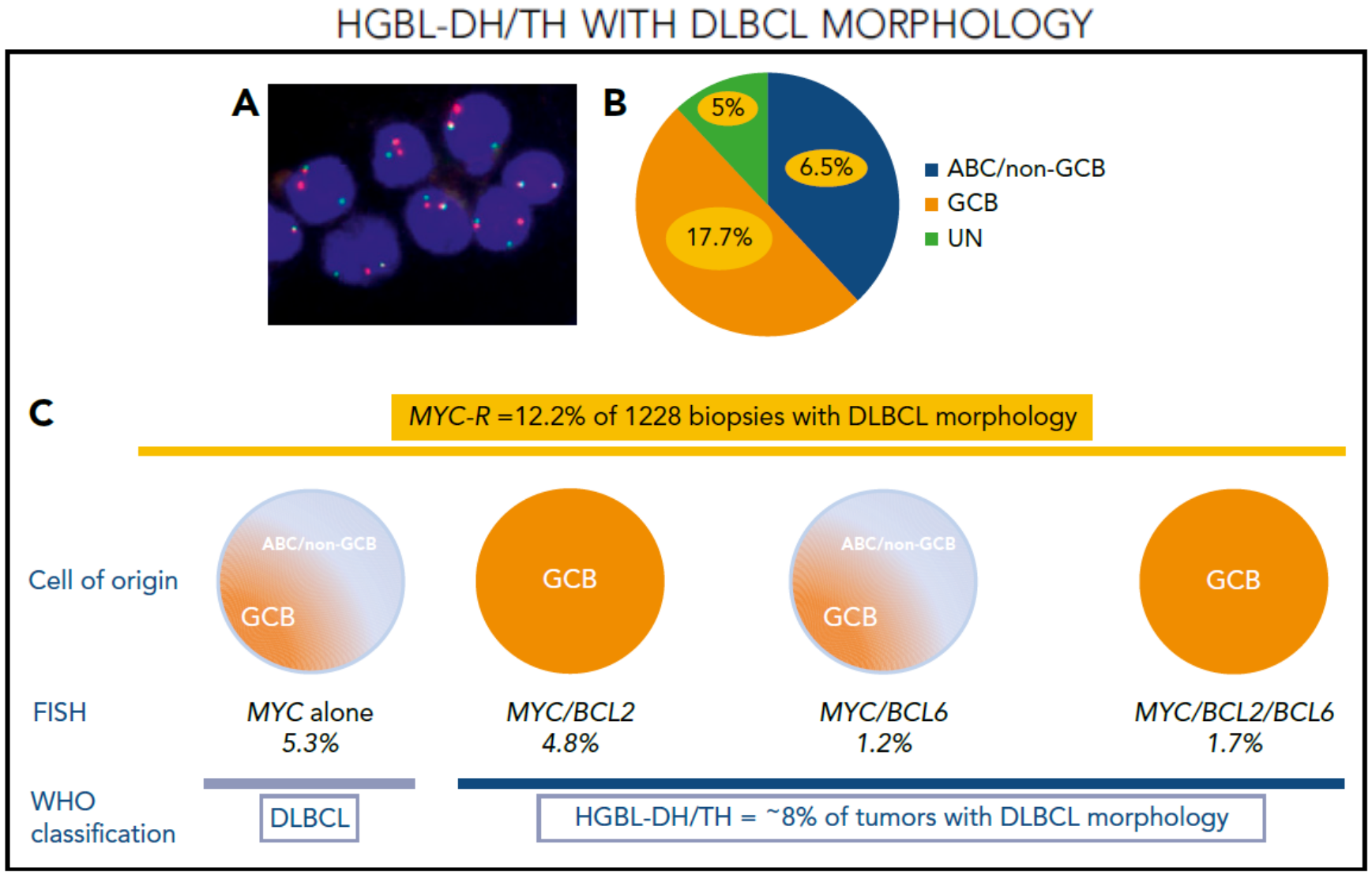
Prognostic Significance of *MYC* Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium

Andreas Rosenwald, MD[1]; Susanne Bens, MD[2]; Ranjana Advani, MD[3]; Sharon Barrans, PhD[4]; Christiane Copie-Bergman, PhD[5]; Mad-Helenie Elsensohn, PhD[6,7]; Yaso Natkunam, PhD[8]; Maria Calaminici, PhD[9]; Birgitta Sander, PhD[10,11]; Maryse Baia, MSc[5]; Alexandra Smith, PhD[12]; Daniel Painter, PhD[12]; Luu Pham, MD[3]; Shuchun Zhao, PhD[8]; Marita Ziepert, PhD[13]; Ekaterina S. Jordanova, PhD[14]; Thierry J. Molina, PhD[15]; Marie José Kersten, PhD[14,16]; Eva Kimby, PhD[10]; Wolfram Klapper, MD[17]; John Raemaekers, PhD[18]; Norbert Schmitz, MD[19]; Fabrice Jardin, PhD[20]; Wendy B.C. Stevens, MD[21]; Eva Hoster, PhD[22]; Anton Hagenbeek, MD[14,16]; John G. Gribben, MD[9]; Reiner Siebert, MD[2]; Randy D. Gascoyne, MD[23]; David W. Scott, PhD[23]; Philippe Gaulard, MD[5]; Gilles Salles, PhD[24]; Catherine Burton, MD[4]; Daphne de Jong, PhD[14,25]; Laurie H. Sehn, MD[23]; and Delphine Maucort-Boulch, PhD[6,7]



- 2383 patients with DLBCL (JCO, 2019):
- 264 (11.1%) with *MYC* rearrangement
- 40 (1.7%) with *MYC*-SH (IG)
- 17 (0.7%) with *MYC*-SH (non-IG)

MYC translocation in DLBCL



- HGBL *MYC/BCL2*
- GCB type 6.5%

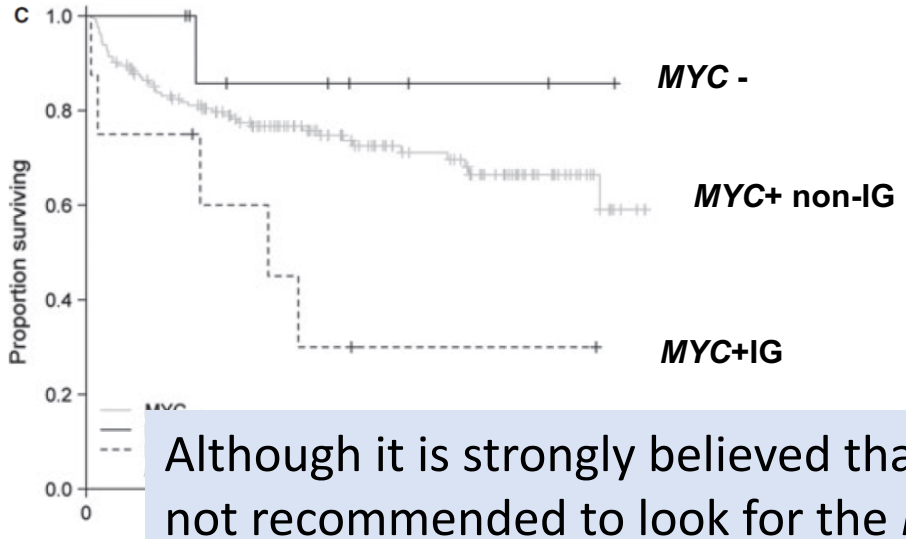
- HGBCL *MYC/BCL6*
- 1.2% of the cases
- 30% pseudo DH

KEY POINTS

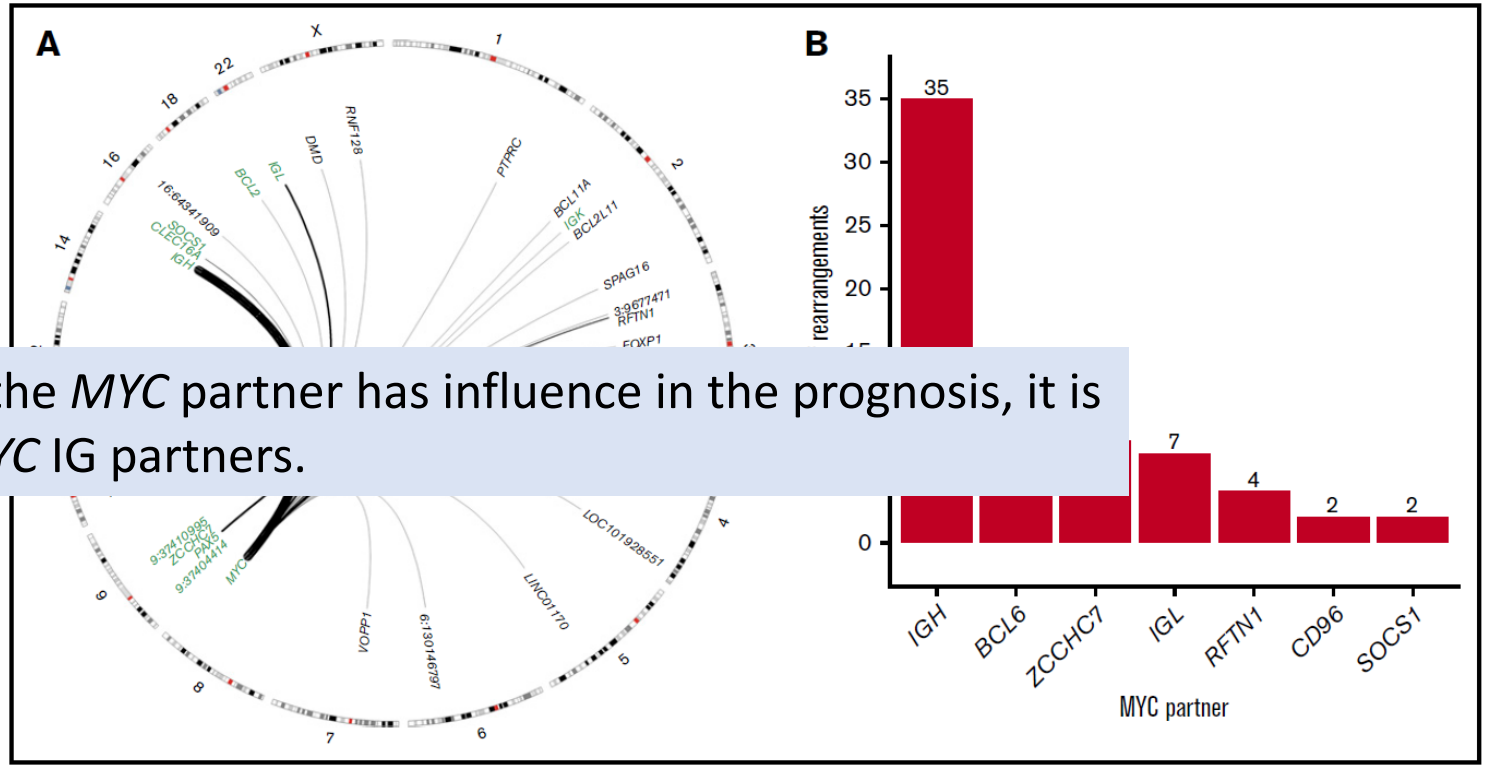
- **HGBL-DH/TH makes up 8% of de novo DLBCL, with HGBL-DH/TH with *BCL2* rearrangement being a GCB phenomenon.**
- **Restricting FISH testing to tumors with dual protein expression and GCB subtype results in testing <15% of tumors, but missing ~35% of HGBL-DH/TH.**

blood® 3 MAY 2018 | VOLUME 131, NUMBER 18

Not all *MYC* translocations are the same *MYC* partner matters? Ig vs non-IG



23 OCTOBER 2018 • VOLUME 2, NUMBER 20 blood advances

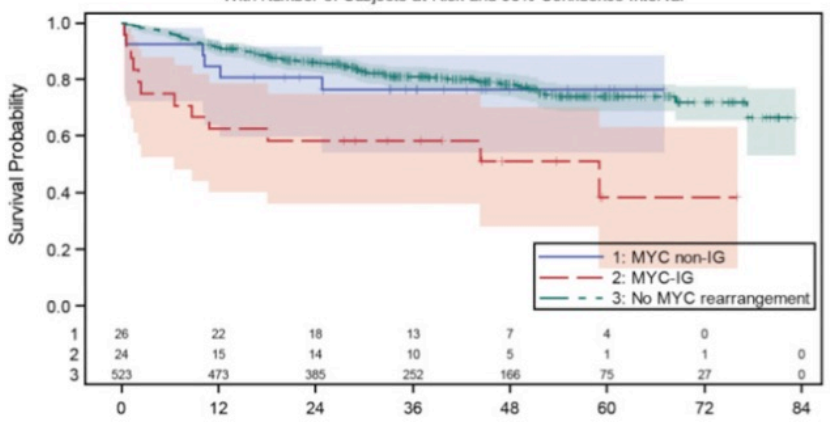


Although it is strongly believed that the *MYC* partner has influence in the prognosis, it is not recommended to look for the *MYC* IG partners.

MYC-IG

Overall survival according to MYC partner gene including patients with no MYC rearrangement

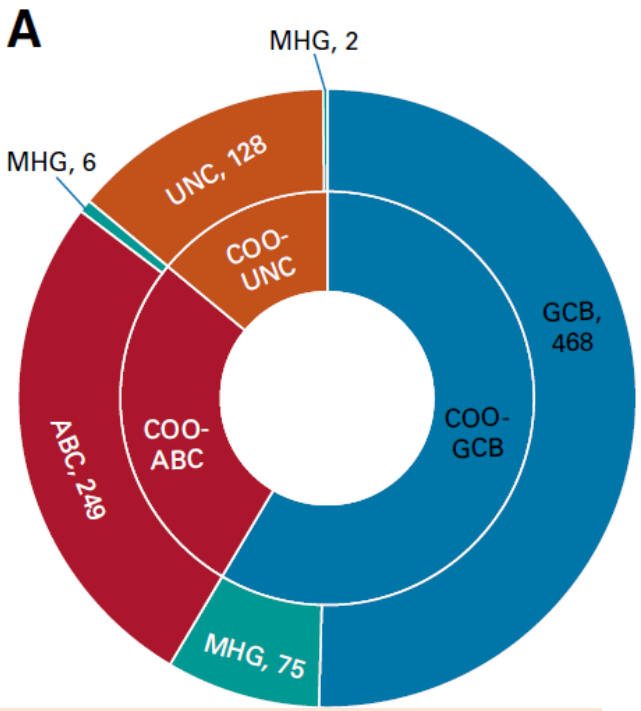
With Number of Subjects at Risk and 95% Confidence Interval



- *MYC::BCL6* occurs in 30% the cases „pseudo-DH“
- t(3;8)(q27;q24)

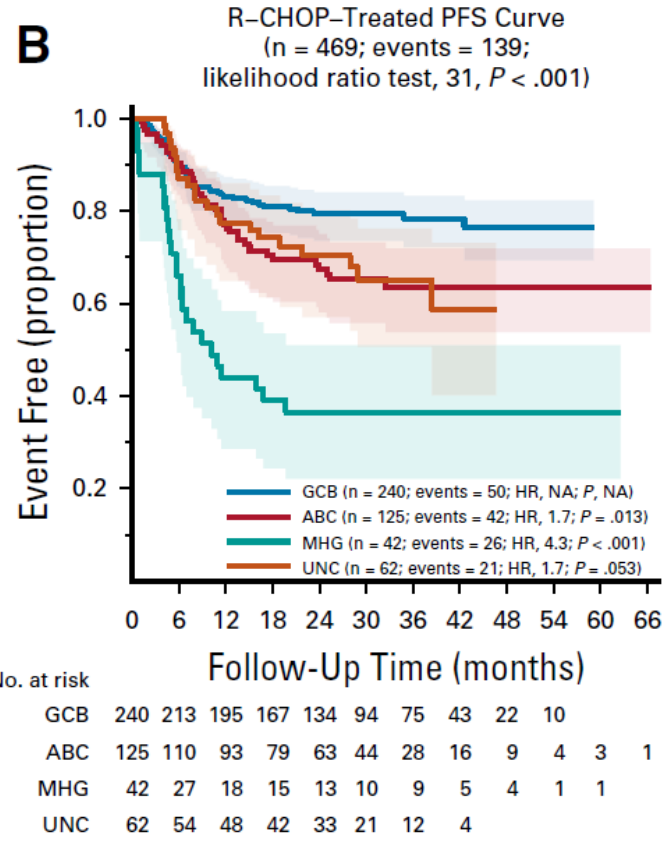
Pedersen et al, European J Haematol 2014;92-42-49
Copie-Bergman et al, Blood 2015

Molecular high grade signature DLBCL



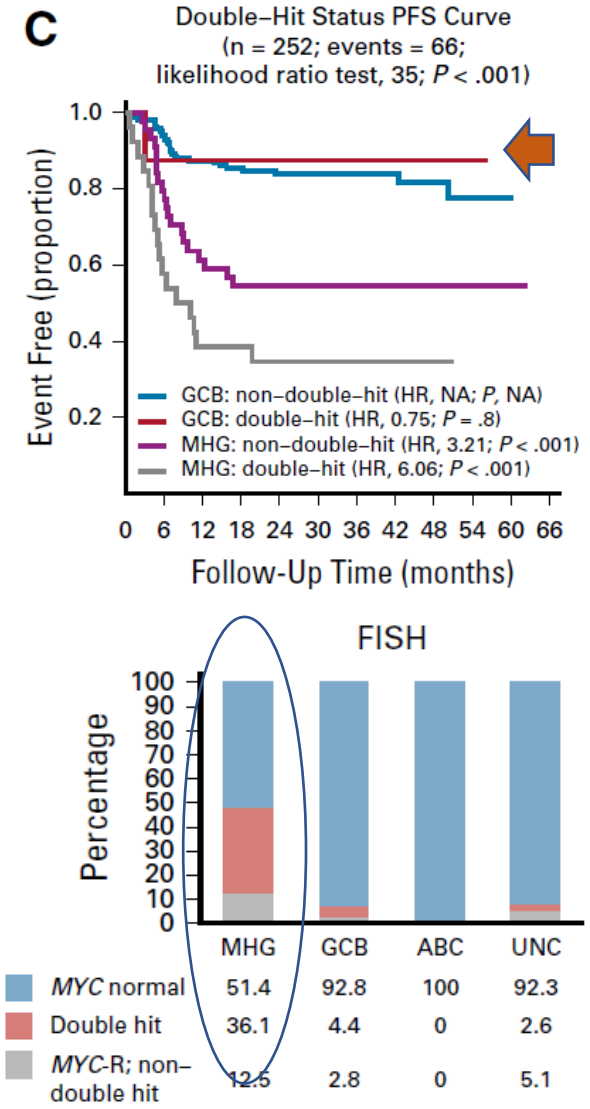
1

- 9% of all DLBCL
- Only 50% of the MHG signature carried DH
- The majority GCB (75/83)
- Some ABC



2

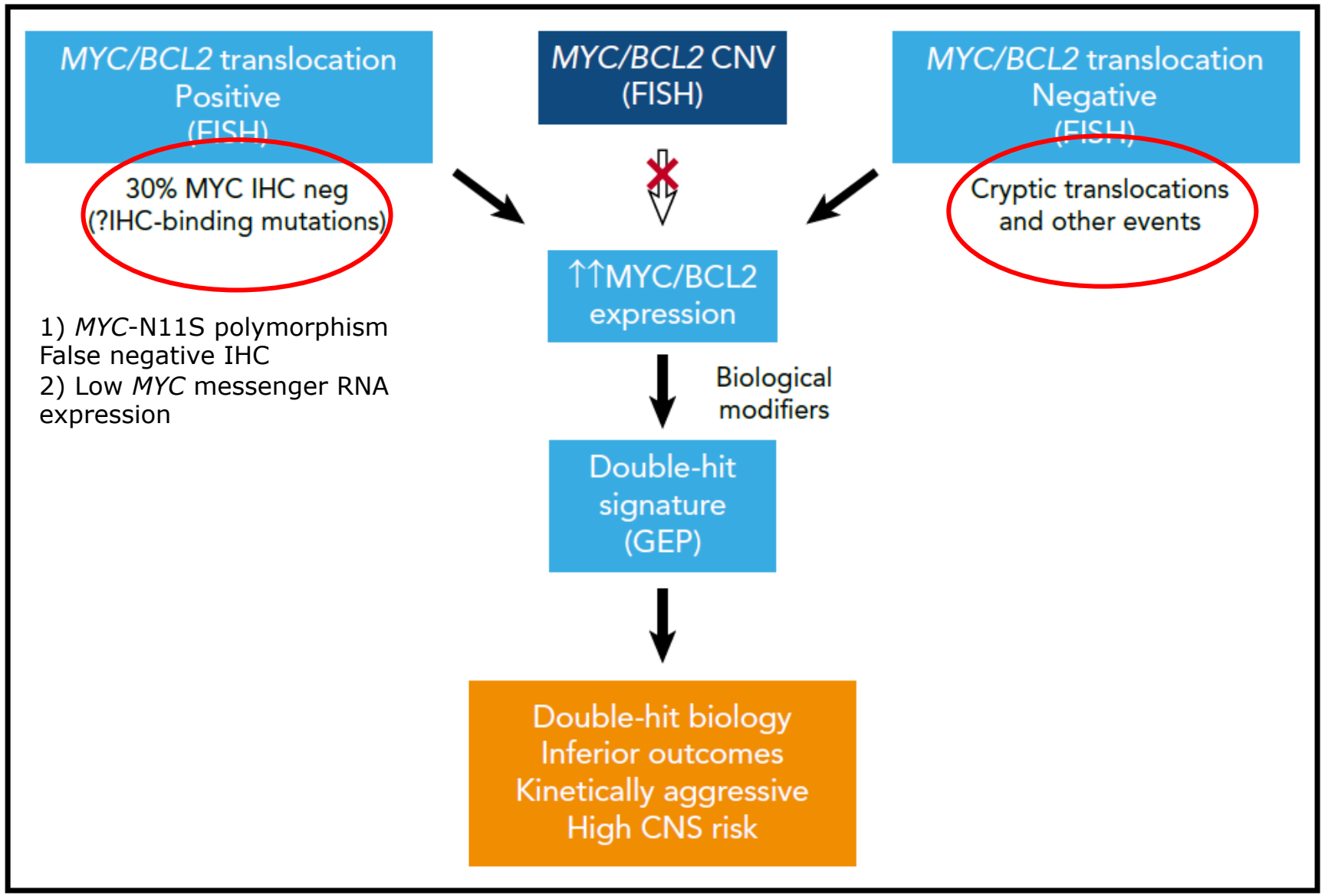
DH lymphomas without the MHG signature did not performed worse



Sha Ch et al, J Clin Oncol 37:202-212. © 2018 by American Society of Clinical Oncology

Are all *MYC* translocation the same?

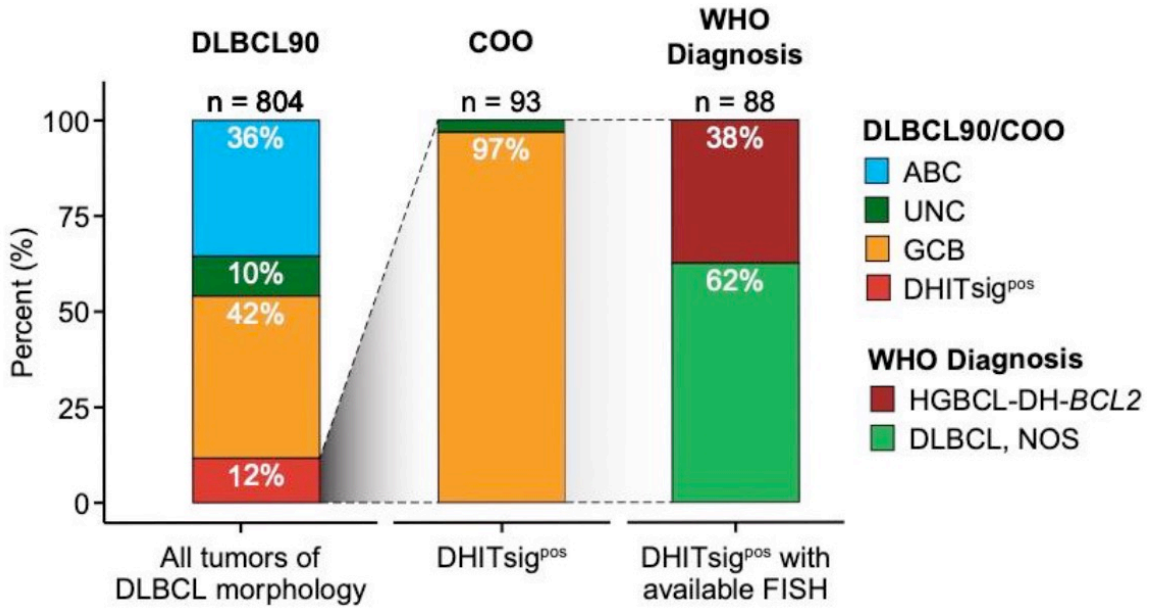
MYC and *BCL2* structural variants in DLBCL

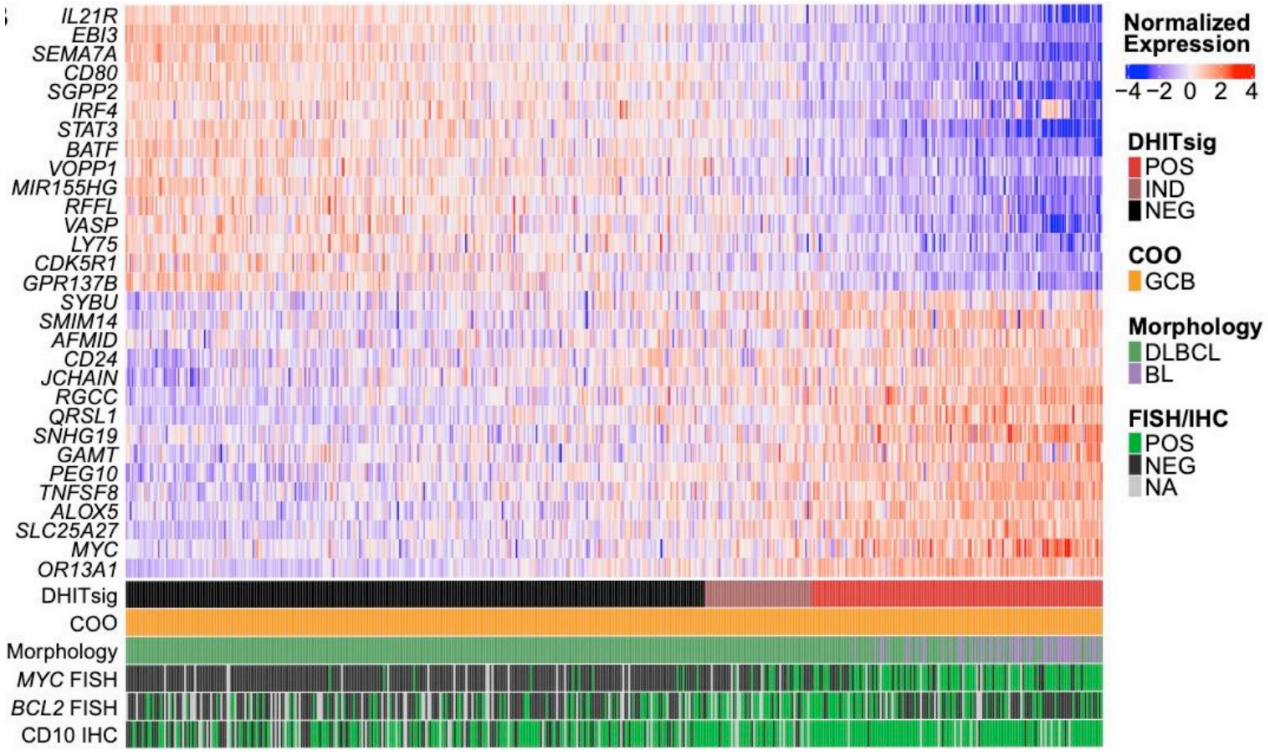


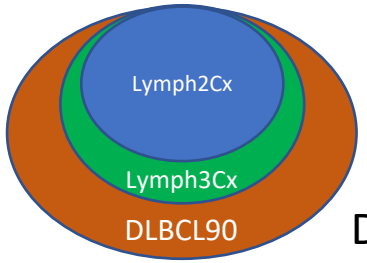
1) *MYC*-N11S polymorphism
False negative IHC
2) Low *MYC* messenger RNA expression

- Only 50% of the DHITsig harbor *MYC* and *BCL2* rearrangements
- GCB-DLBCL without the DHITsig have an overall survival of 90%
- MYC expression in GC is restricted to cells selected within the LZ for re-entry into the DZ.
- High incidence of mutations within chromatin modifier genes.
- High incidence of low MHC-I and MHC-II expression
- High oxidative phosphorylation

DHS is now renamed “dark zone signature”







DLBCL COO

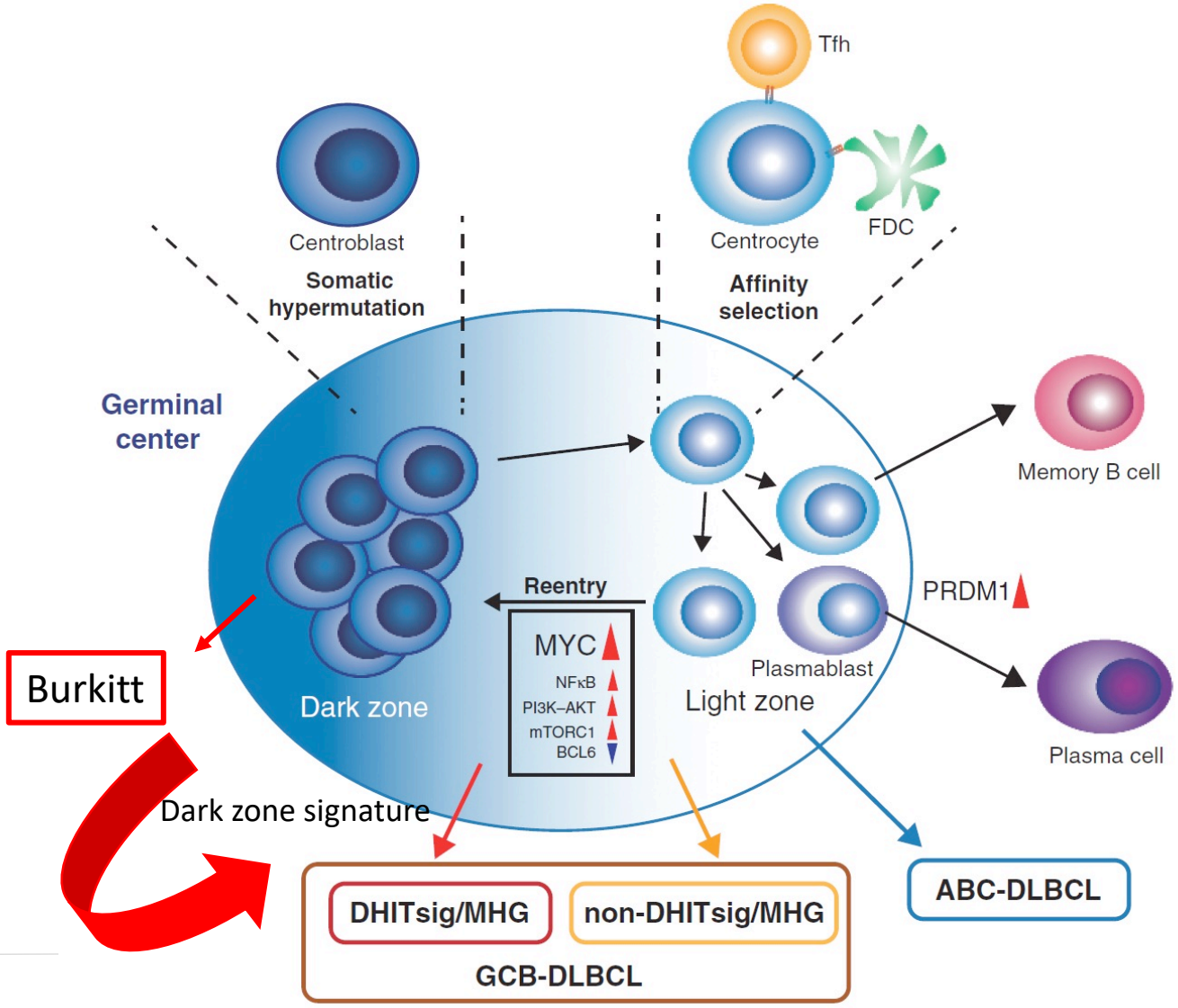
PMBL vs DLBCL

DZsig and *BCL2*

DZ signature refines the COO classification by identifying patients with GCB-DLBCL with inferior outcomes

Aduaij W, et al, Blood 2022 on line

Cell of origin and the dark zone signature



- In the dark zone GCB cells proliferate and undergo SHM
- The light zone is devoted to antigen-based affinity selection through GCB cells interaction with FDC´s and TFH
- GCB cells differentiate into memory B cells and plasma cells. Plasma cell differentiation and exit of the GC are controlled by PRDM1 (BLIMP1)

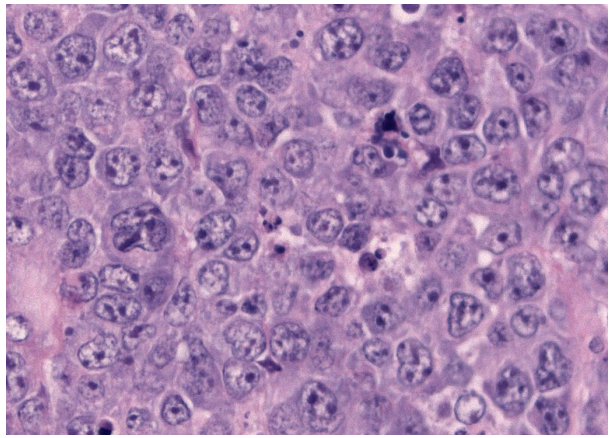
High-grade B-cell lymphomas

Biology or morphology?

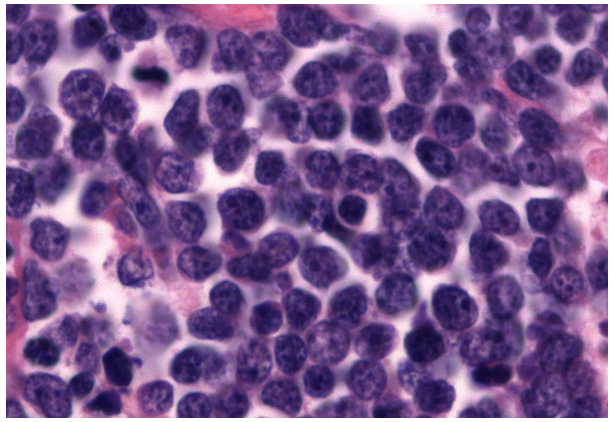
High-grade lymphomas

- WHO 4th edition 2008:
  - B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (BCLU)
    - Cases morphologically resembling BL but with morphological and phenotypical deviations
    - Includes but not limited to DHL.
- WHO 4th edition update 2017:
  - High grade B-cell lymphomas
    - High-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements (double or triple-hit)
      - Specifiy whether DLBCL, blastoid or BCLU morphology
      - Cases of FL or LBL with DH are not included!
    - High-grade B-cell lymphoma, NOS
      - Cases with BCLU or blastoid morphology or other high-grade features and no DH
- 2022 ICC
  - High grade B-cell lymphoma with *MYC* and *BCL2 (WHO and ICC)*
  - *High grade B-cell lymphoma with MYC and BCL6* (DLBCL in WHO)
  - High grade B-cell lymphoma, NOS

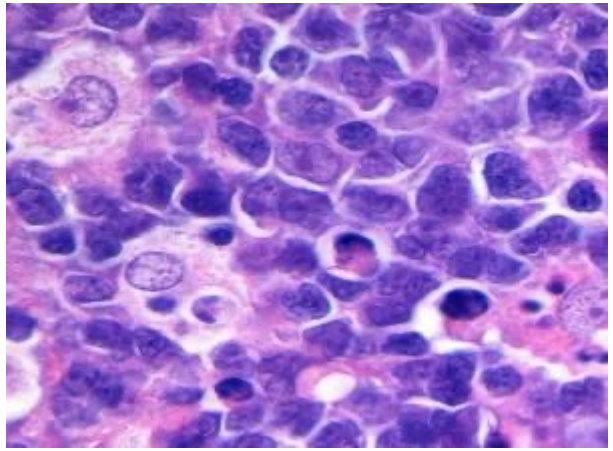
DLBCL



Blastoid



BCLU



The ICC approach to the HGBCL

ICC classification

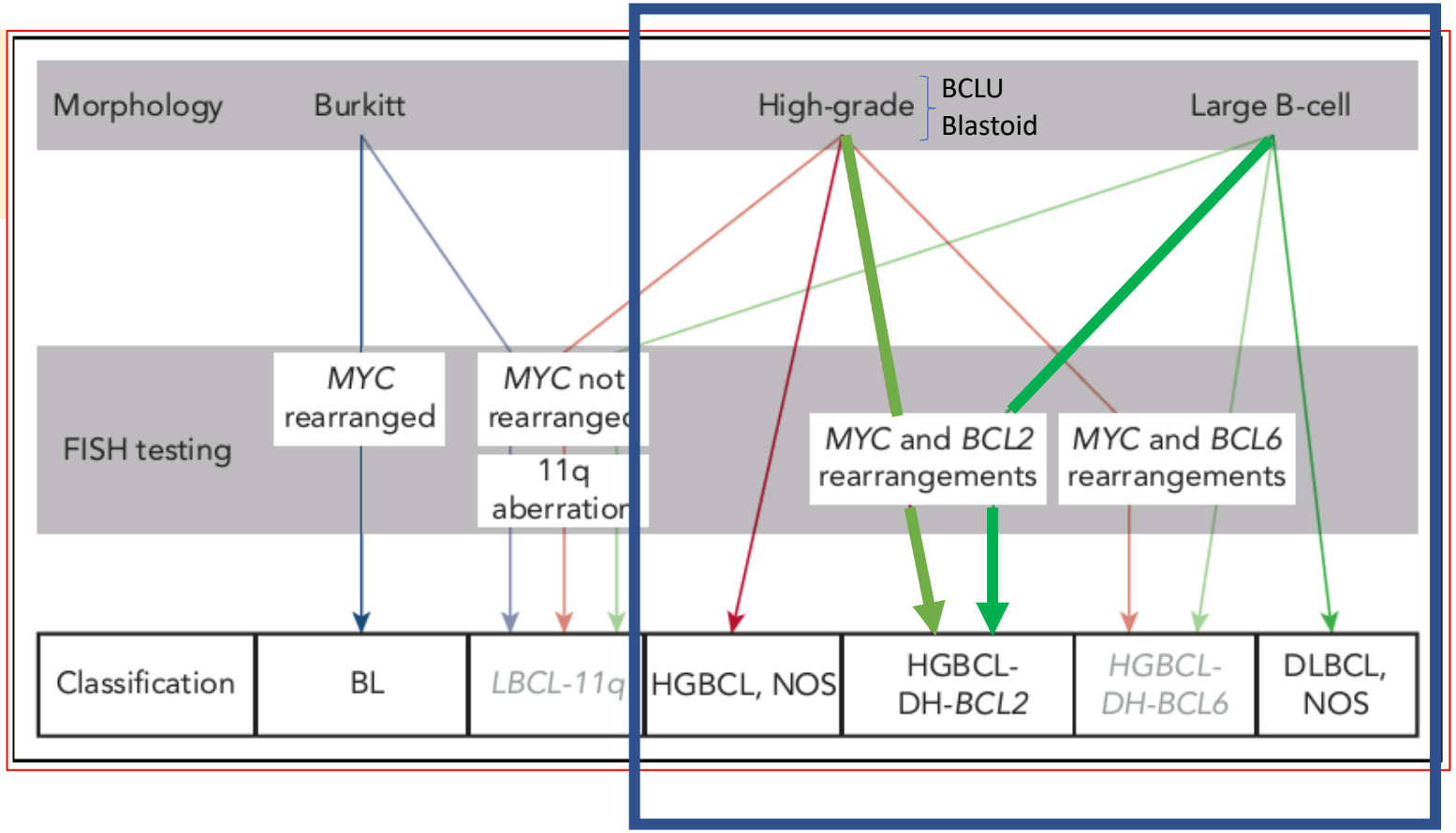
High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements*

*High-grade B-cell lymphoma with MYC and BCL6 rearrangements**

High-grade B-cell lymphoma, NOS

Campo E, Blood 2022

- The term is used to identify a group of tumors with very aggressive biological behaviour and poor response to current therapeutical strategies indepently of the specific morphology



The ICC proposal for HGBCL

- **High-grade B-cell lymphomas with *MYC* and *BCL2* rearrangements**
  - Specify whether DLBCL, blastoid or intermediate morphology
  - FISH break apart probes recommended but may miss up to 20% cases (cryptic)
    - IG or non-IG translocated partner inconclusive results and not required in daily practice
    - Do not consider CNA (amplification and copy numbers)
  - Germinal center origin
  - Gene expression signature of centroblast in the GC dark zone
  - Mutational profile similar to "aggressive" FL (*BCL2, **MYC**, KMT2D, CREBPP, TNFRS14, EZH2*)
- ***High-grade B-cell lymphoma with MYC and BCL6 rearragements***
  - Heterogeneous in cell of origin and mutational profile (less FL –type, *NOTCH2)*
  - 30% may be "pseudo double" hit
- **High-grade B-cell lymphoma, NOS**

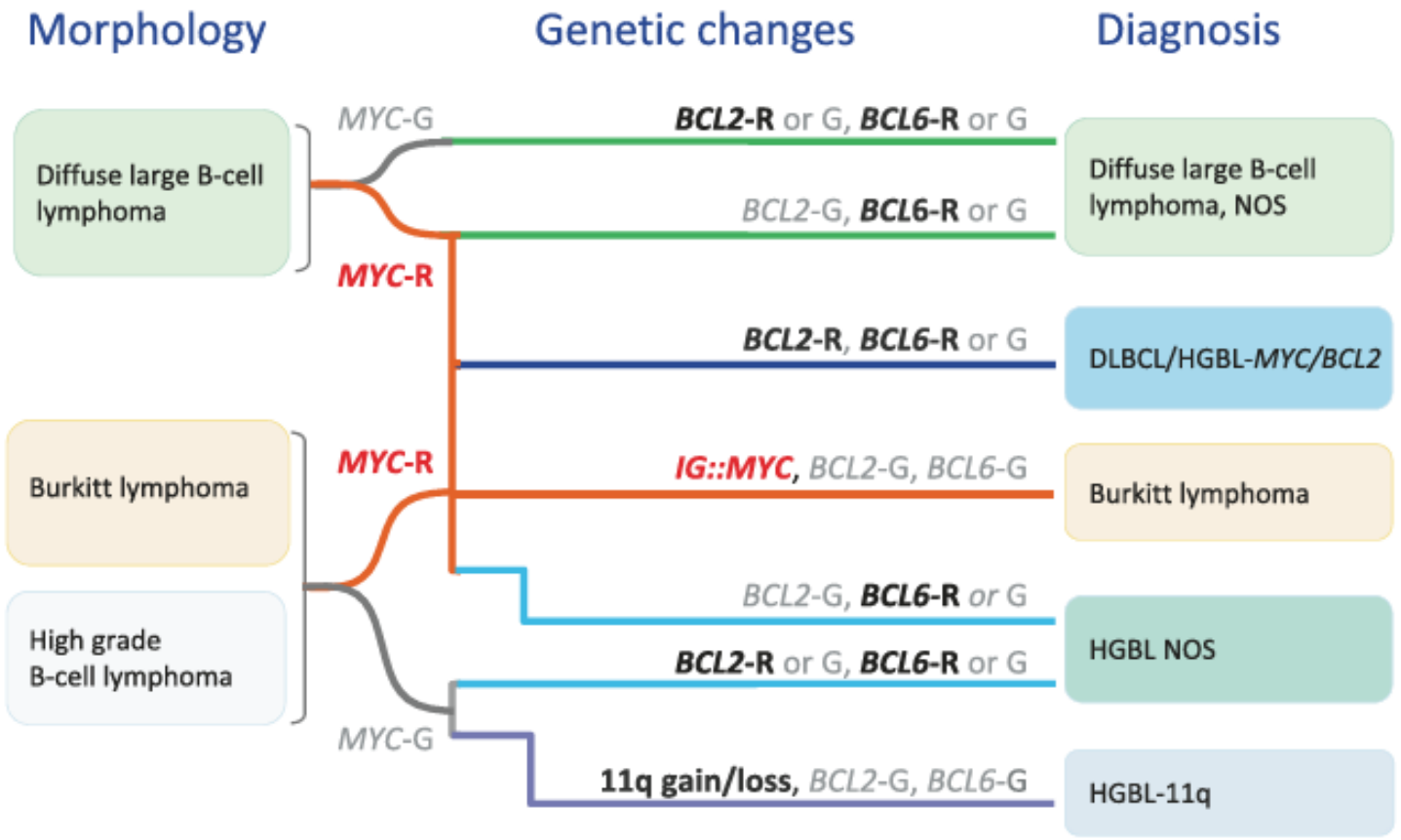
The 5th edition WHO approach to HGBCL

5th edition of the WHO

Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements

- The term „High-grade“ is used to name tumors based on their cytology, composed either blastoid or intermediate morphology between Burkitt lymphoma and DLBCL (BCLU)

- Double hit lymphomas *BCL6/MYC* are no longer recognized by the WHO. They are classified as DLBCL, NOS or HGBL, NOS



R. Alaggio et al. Leukemia (2022) 36:1720 – 1748

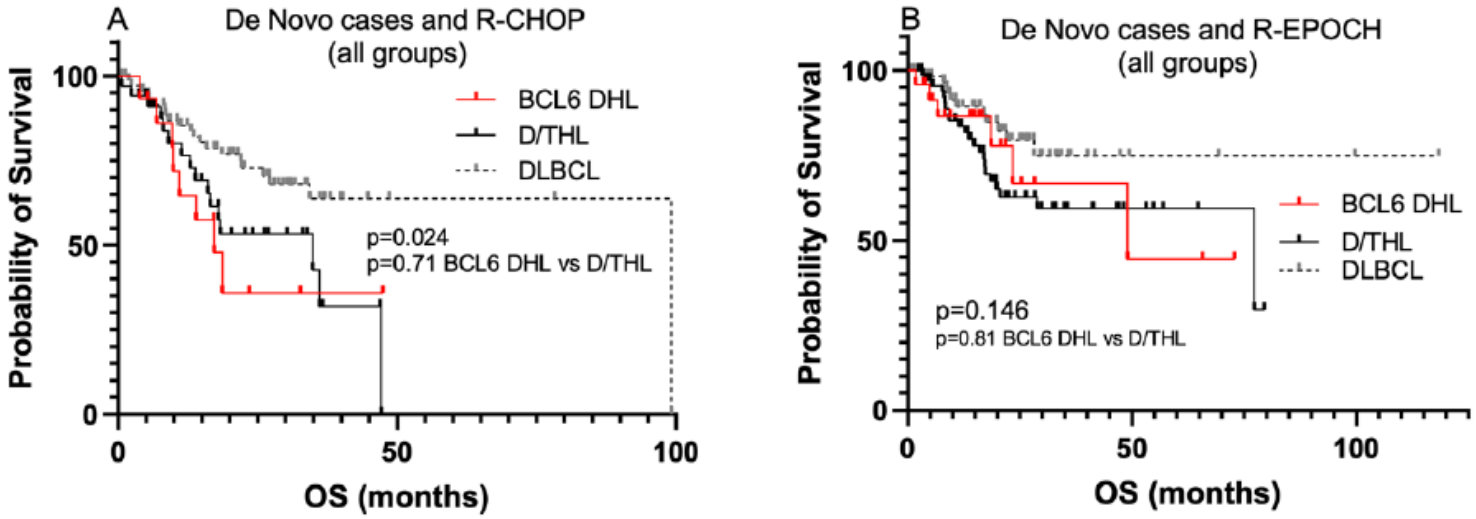
HGBCL with MYC/BCL6-R

1134 MYC and BCL6 Double Hit Lymphoma (DHL): A Clinicopathologic Study of 60 Cases in Comparison to BCL2-DHL and Diffuse Large B-cell Lymphoma (DLBCL)

Do Hwan Kim[1], Guilin Tang[1], Pei Lin[1], Jie Xu[1], Sa Wang[1], Lianqun Qiu[2], C. Cameron Yin[1], Wei Wang[1], L. Jeffrey Medeiros[1], Shaoying Li[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]University of Washington - Pathology, Houston, TX

Figure 1: Overall survival of *BCL6*-DHL patients vs *BCL2*-DHL and DLBCL-NOS patients.



Conclusions: *BCL6*-DHL patients show aggressive clinical characteristics similar to *BCL2*-DHL patients and more aggressive than DLBCL patients. The major difference between *BCL6*-DHL and *BCL2*-DHL was immunophenotype, with *BCL6*-DHL having less often MYC and BCL2 double expression and GCB type. R-EPOCH, but not R-CHOP, improved the survival of *BCL6*-DHL patients, similar to *BCL2*-DHL patients. These data suggest that *BCL6*-DHL needs a separate recognition other than DLBCL for optimal patient management.

MYC translocation in DLBCL

Title: *MYC/BCL6* double hit lymphoma negative for t(3;8) *BCL6::MYC* fusion is associated with inferior survival, in contrast with t(3;8) positive pseudo-double hit lymphoma

Author(s): B. D. Maybury [1] , L. James [2] , N. Chadderton [2] , J. Dowds [2] , I. Venkatadasari [3] , J. Riley [4] , I. Qureshi [5] , G. Talbot [6] , H. V. Giles [6] , N. J Phillips [6] , M. Vega Gonzalez [7] , P. Rakesh [8] , A. Haslam [4] , D. Davies [9] , S. Moosai [10] , S. A. Lane [11] , A. Shenouda [8] , G. V. Cherian [11] , P. K. Kaudlay [3] , J. Starczynski [2] , Z. Rudzki [2] , S. Chaganti [1]

[1] University Hospitals Birmingham NHS Foundation Trust, Department of Haematology, Birmingham, United Kingdom of Great Britain & Northern Ireland

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[3] The Royal Wolverhampton NHS Trust, Department of Haematology, Wolverhampton, United Kingdom of Great Britain & Northern Ireland

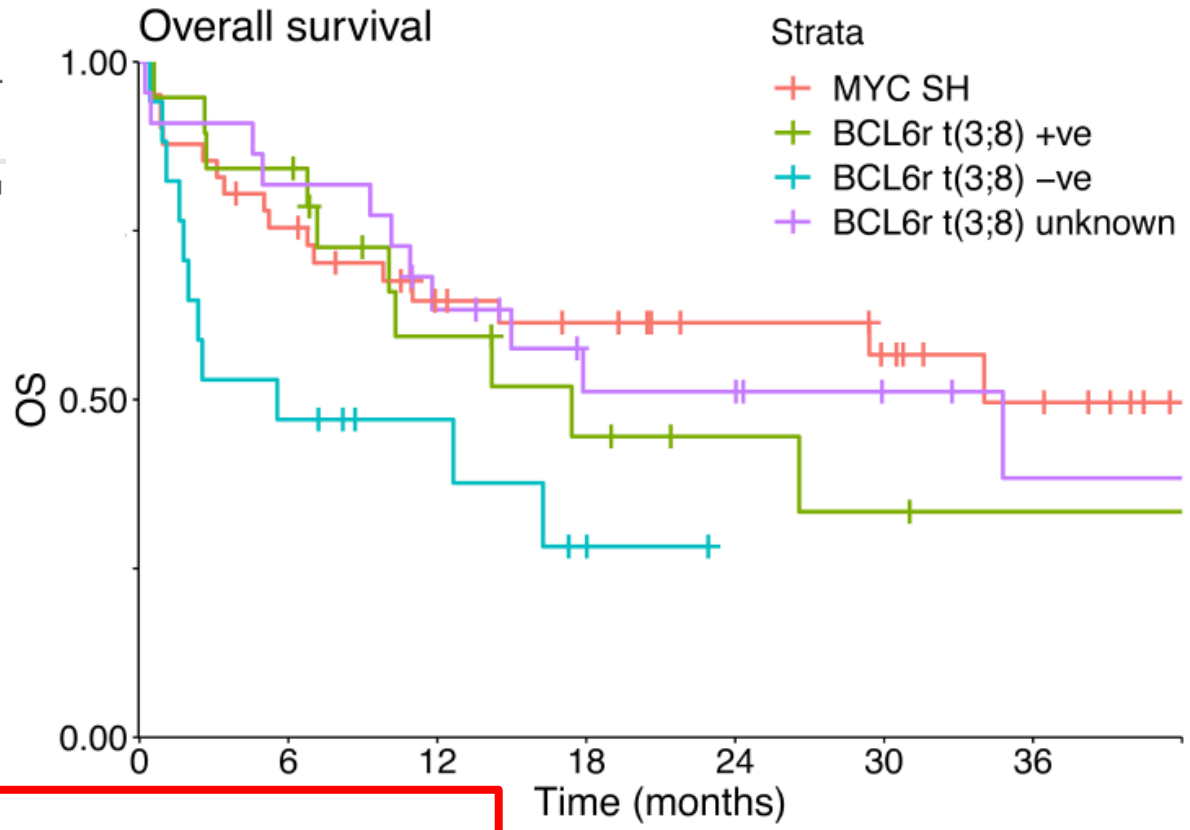
MYC and BCL6 re-arrangements (BCL6r) detected by FISH break-apart probes

↓

Tested for presence of t(3;8) *BCL6::MYC* by FISH fusion probe

↓

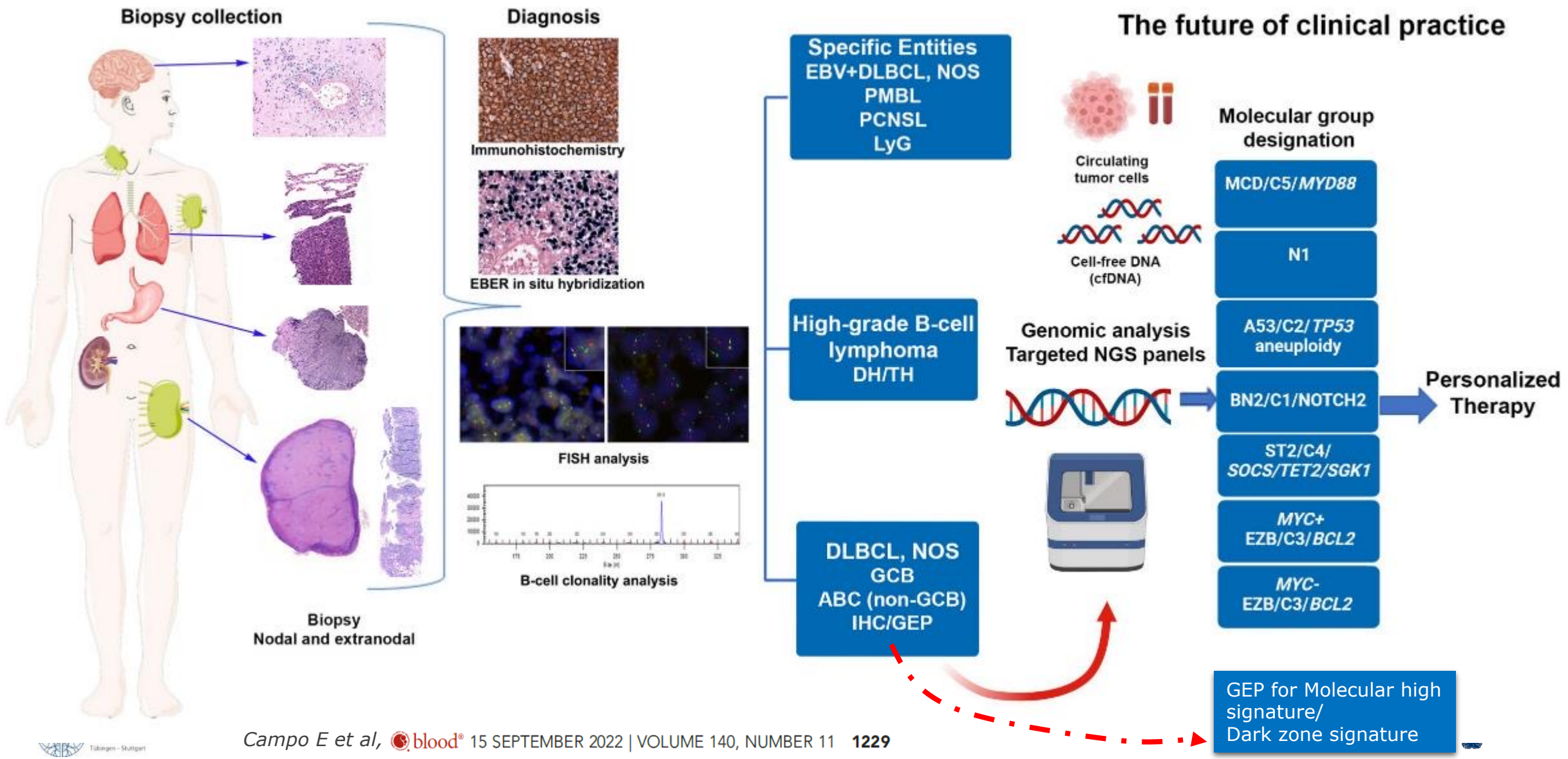
Regional retrospective cohort study studying the effect of t(3;8) status on survival



In high grade B cell lymphoma:

- the presence of t(3;8) is not associated with inferior survival.
- true MYC BCL6 double hit lymphomas, without t(3;8) have inferior survival.
- this association is independent of established prognostic risk factors.

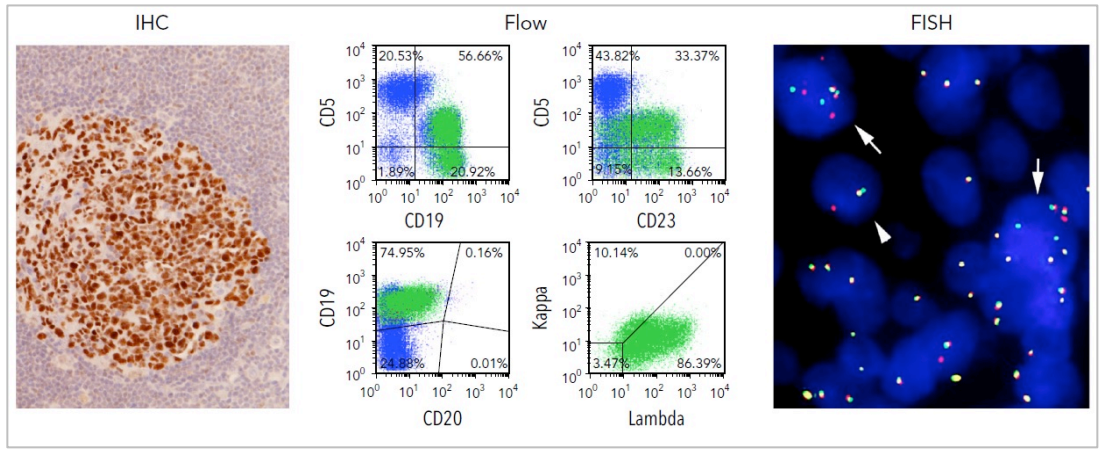
Current and future diagnostic approach to aggressive lymphomas



The rationale for molecular testing in aggressive B-cell lymphomas

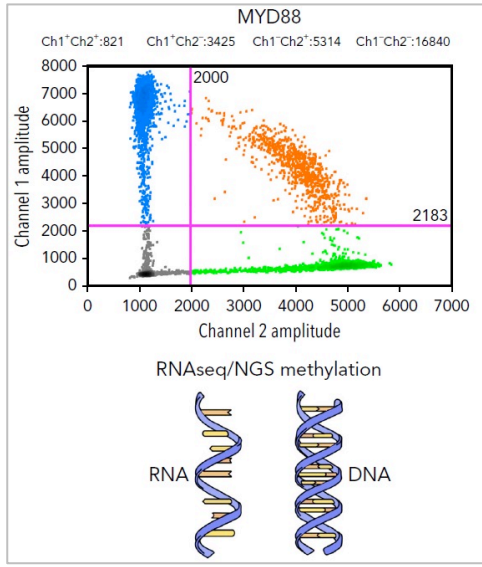
- There are still many challenges ahead in the diagnosis of DLBCL
  - COO IHC vs GEP (which method?)
  - Double hit lymphomas vs MHGsig/DZsig
    - FISH vs GEP
    - FISH all cases or only GCB? Cryptic translocations (20% of cases)
  - Molecular classification in DLBCL
    - NGS targeted analysis vs „one in all“ method. Whole exome/transcriptome analysis?

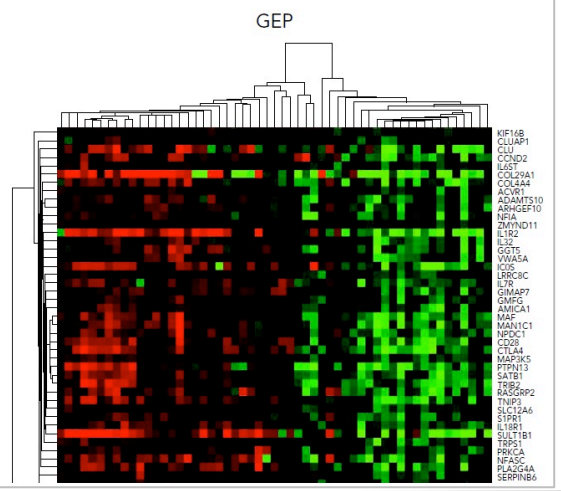
Traditional methods



Jaffe et al, Blood 2022;140:2526

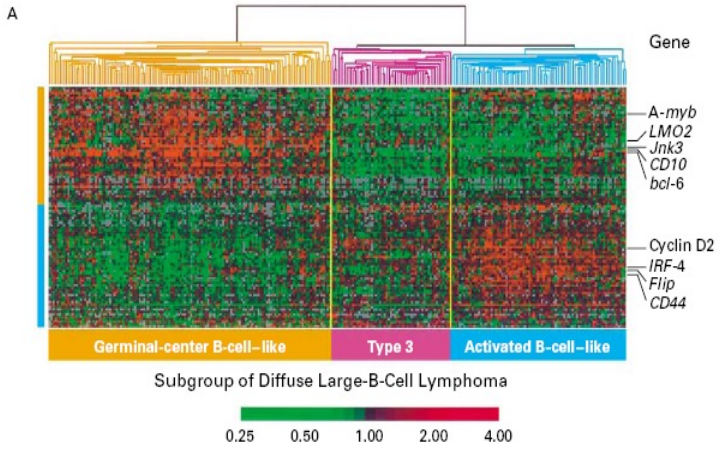
Molecular methods





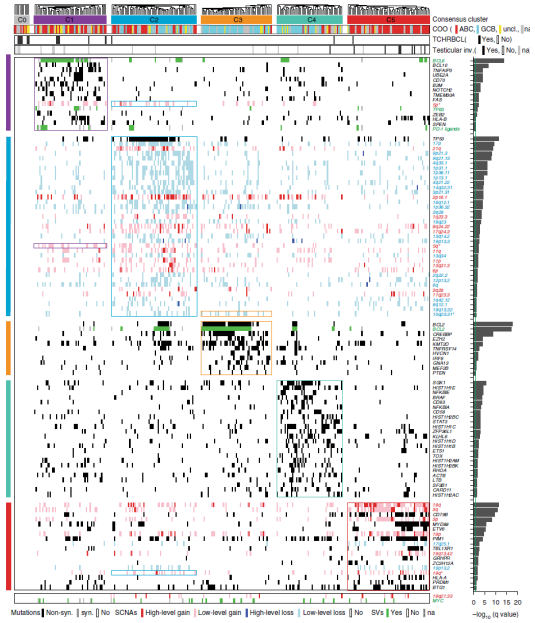
Molecular subtypes of DLBCL

- Cell-of-origin in DLBCL, NOS is mantained because it reflects a basic biological distinction
- It is recognized the limitation of this binary system to capture DLBCL complexity

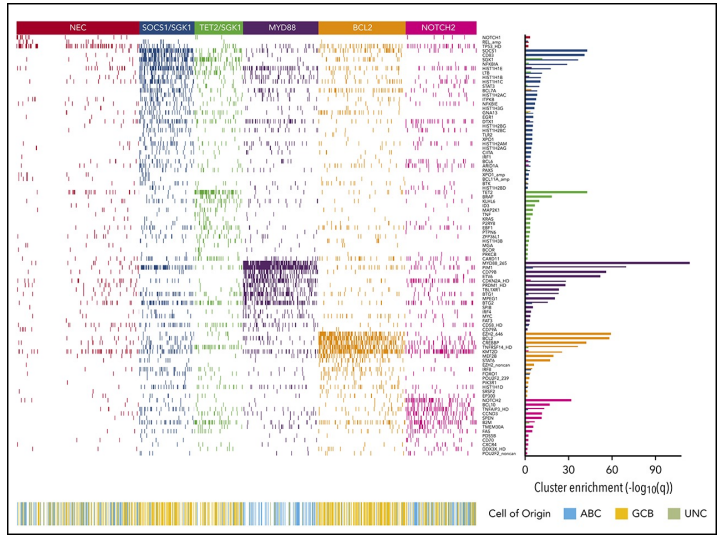


Rosenwald et al, NEJM 2002

- Genetic subgroups capture biological complexity but not ready for clinical use



Chapuy et al, Nature Med 2018



Lacy et al, Blood 2020

What needs to be improved?

Pathology

- Consensus and standardization of methods
  - ✓ Paraffin embedded
  - ✓ validated
  - ✓ harmonized minimal gene sets and bioinformatics
  - ✓ Affordable
  - ✓ Turn around time of 3-5 days
- Widely available

Clinical setting

- If this molecular classification will guide treatment choices
  - ✓ The treatment of choice should be available
  - ✓ Clinical studies should demonstrate the efficacy of the treatment
  - ✓ First line vs R/R treatment
  - ✓ Understanding of the biological and clinical implications of this knowledge

Thank you for your attention