# GIORNATE EMATOLOGICHE VICENTINE

**X edizione**

**12-13 Ottobre 2023**
Palazzo Bonin Longare - Vicenza

## Diagnosi molecolare dei linfomi ad alto grado: ready for prime time?

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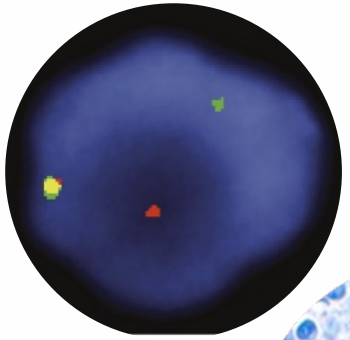
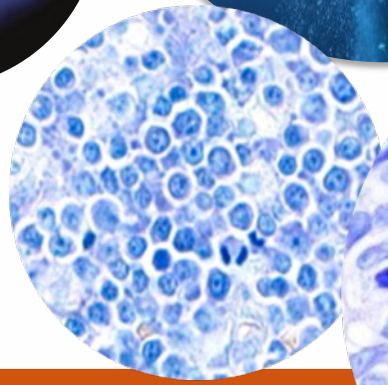
# Disclosures

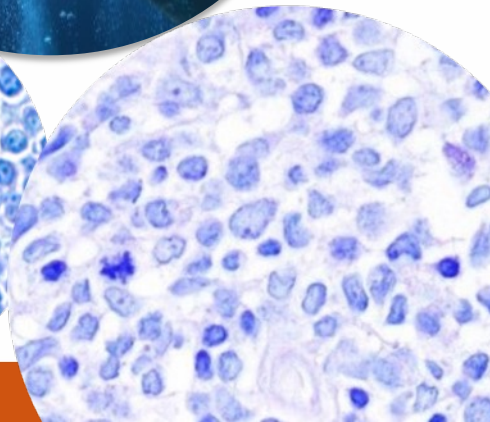
| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Sandoz | | | Non financial | | | | |

# High grade B-cell lymphoma

- Aggressive B-cell lymphoma
- Cytogenetics
- Morphology







# High grade B-cell lymphoma

**1988**

## Double hit

Gauwerky PNAS
De Jong NEJM

**1996**

## REAL

HGBL, Burkitt-like

**2008**

## WHO4

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (BCLU)

**2016**

## WHO4R

HGBL

- MYC and BCL2 and/or BCL6
- NOS

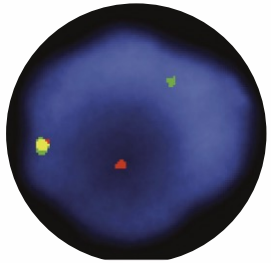
**2022**

## WHO5 / ICC

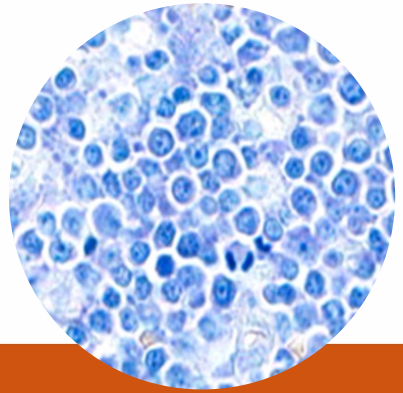
BCL6??

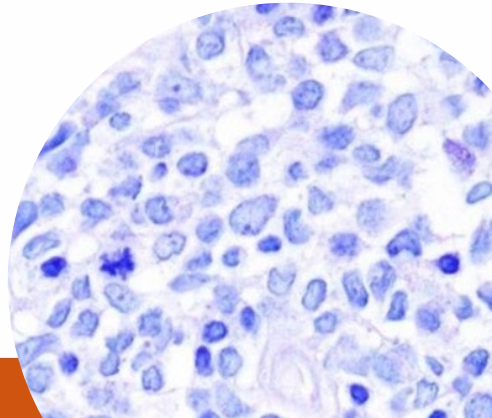
# HGBL – WHO 2016

- with *MYC* and *BCL2* and/or *BCL6* rearrangements
  - ❑ 80% *MYC/BCL2*
  - ❑ 20% *MYC/BCL6*
  - ❑ DLBCL, BL-like or blastoid morphology



- NOS
  - ❑ Burkitt-like
  - ❑ Blastoid





# International Consensus Classification (ICC)

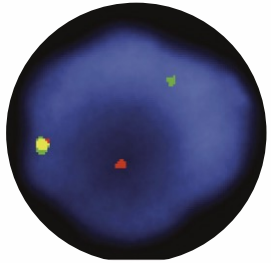
# 2022

# WHO-HAEM5

# HGBL - ICC 2022

- with *MYC* and *BCL2* rearrangements

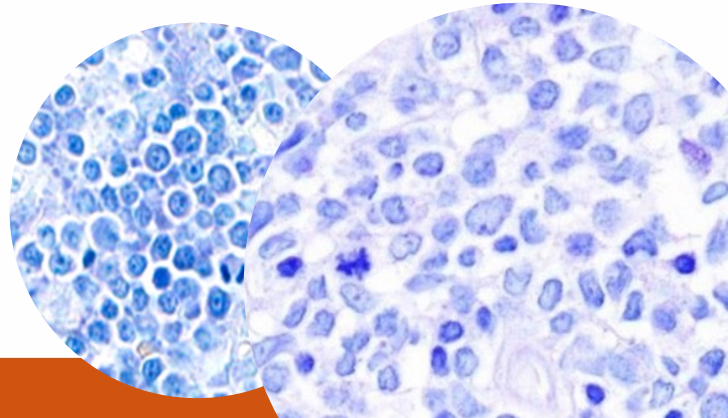
  (with or w/o *BCL6* rearrangement)



- with *MYC* and *BCL6* rearrangements

  (new provisional entity)

- NOS (Burkitt-like or blastoid morphology)

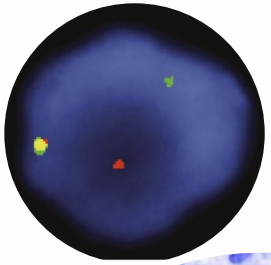


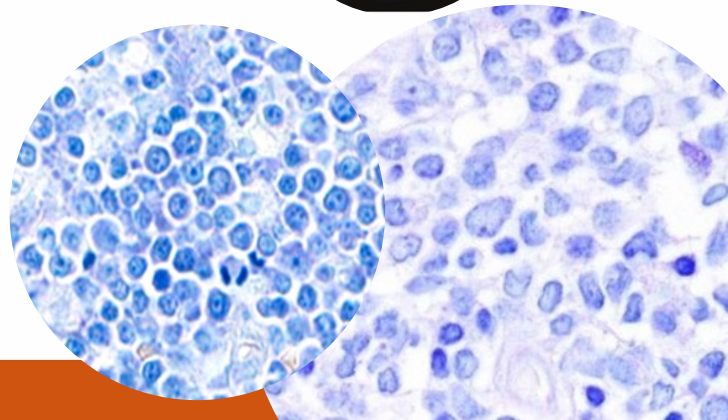
# HGBL - WHO-HAEM5

- DLBCL/HGBL with *MYC* and *BCL2* rearrangements

  (with or w/o BCL6 rearrangement)

- with ~~*MYC* and *BCL6* rearrangements~~





- HGBL, NOS

  (Burkitt-like or blastoid morphology)

# From molecular Burkitt to Dark Zone sig

**2006**

10% DLBCL and BCLUs

Up *MYC* targets
Low *MHC* & *NFkB* pathway gene expression

More CNAs, del 17p del and *MYC* ampl than “true” BL

## mBL

Dave NEJM
Hummel NEJM

**2019**

## mHG and DHITsig

Sha JCO
Ennishi JCO

**2023**

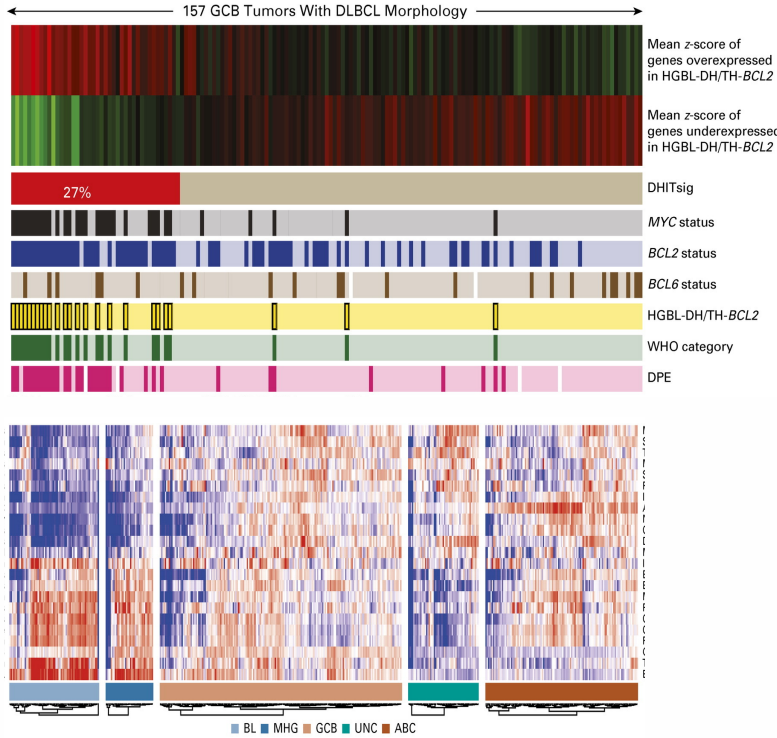
## DZsig

Aldujai Blood

# Molecular HG / DHIT signature

- GCB origin, double-expressors
- *60% MYC*-R
- 30% cryptic *MYC* and *BCL2* translocation

- *MYC*, *BCL2*, *DDX3X*, *TP53*, and *KMT2D* mutations



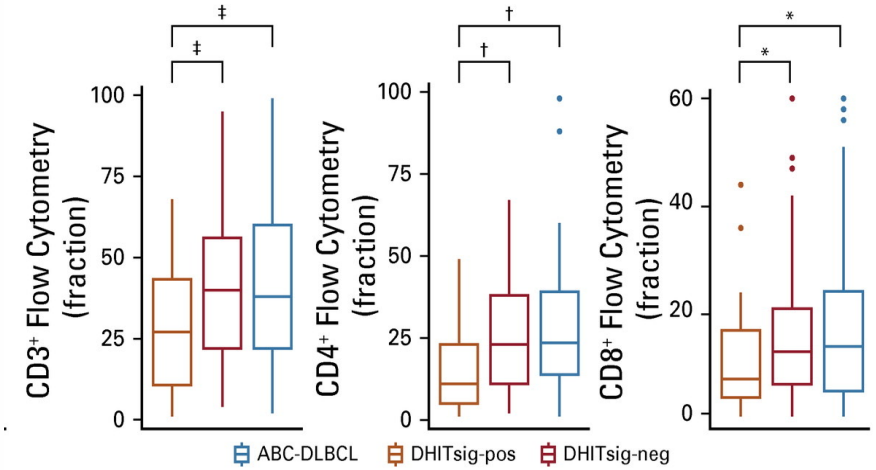



Sha et al, JCO 2019

Ennishi et al, JCO 2019

# Molecular HG / DHIT signature

- Low MHC-I gene expression
- Fewer tumor-infiltrating T-cells

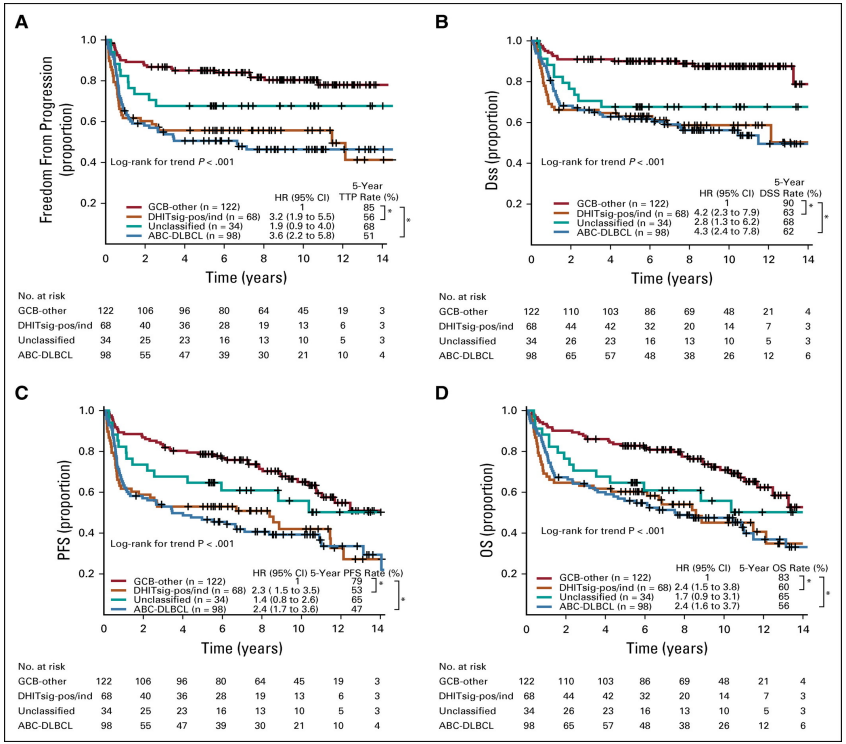





Sha et al, JCO 2019

Ennishi et al, JCO 2019

# Molecular HG / DHIT signature

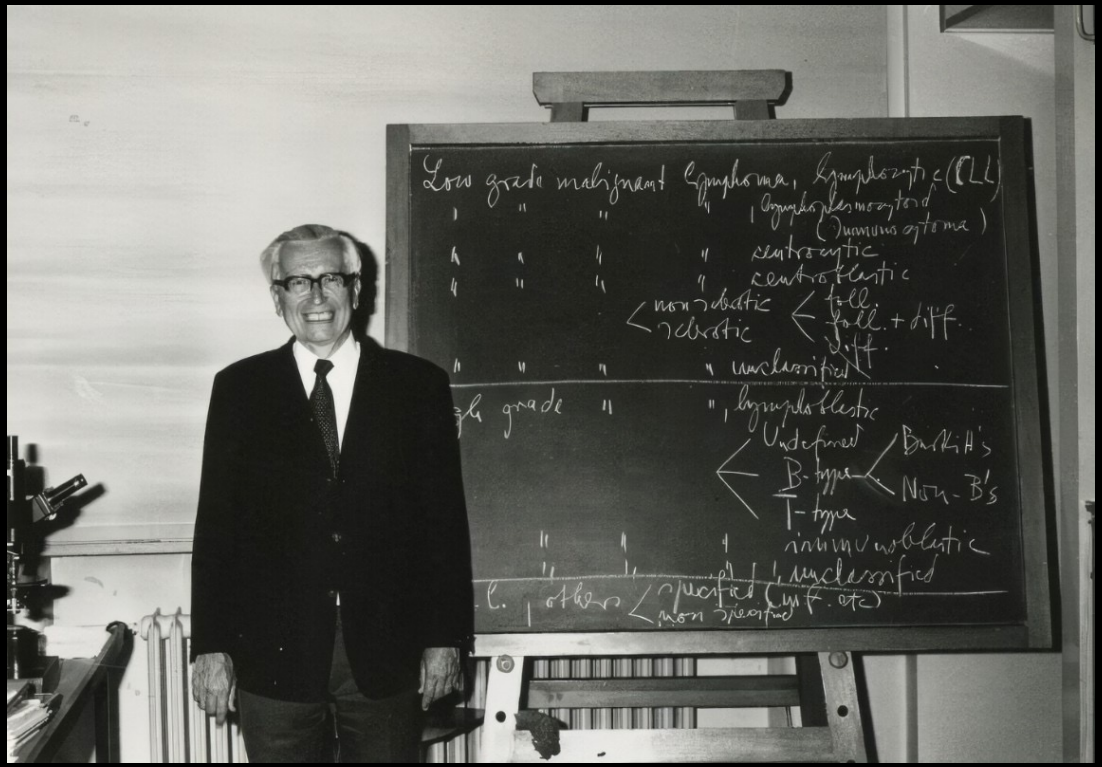





Sha et al, JCO 2019

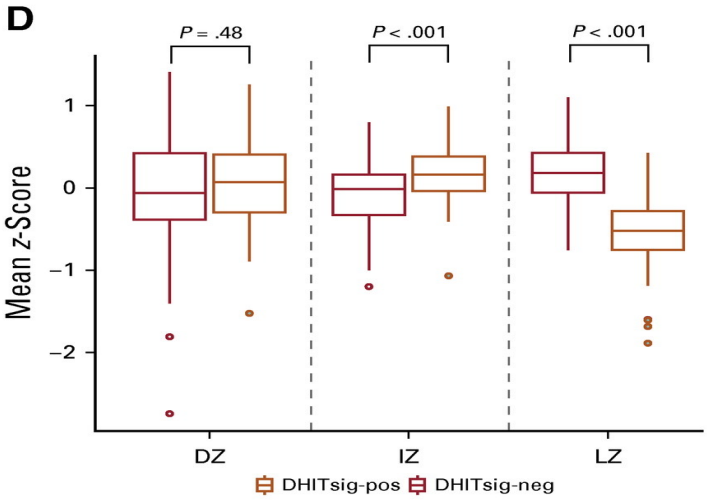
Ennishi et al, JCO 2019

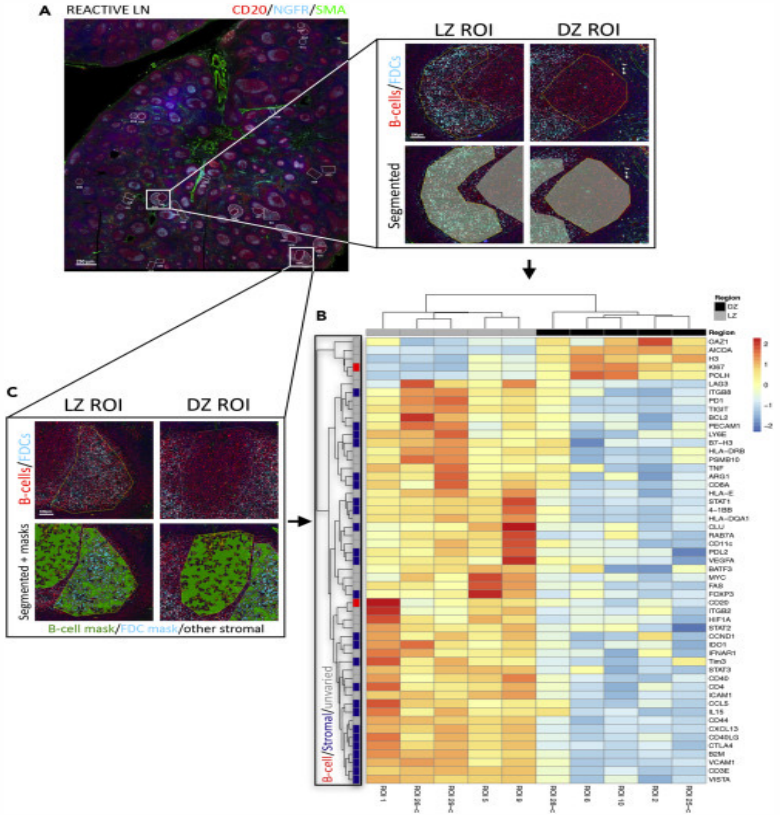
# «The normal counterpart model»



“B-cell neoplasms recapitulate stages of normal B-cell differentiation, so to some extent they can be classified according to the corresponding normal stage”

# Dark zone signature



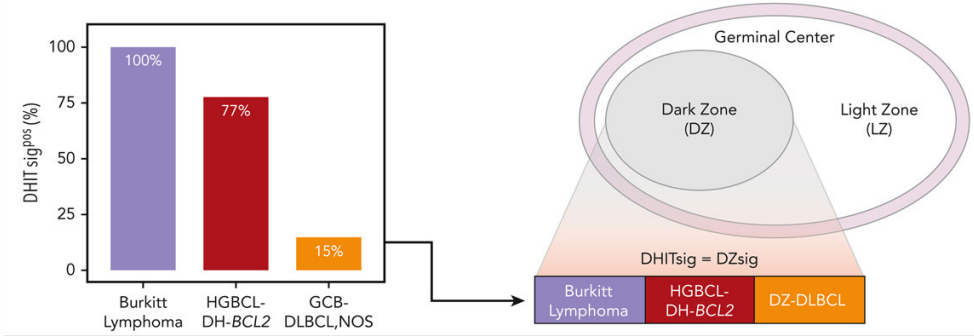





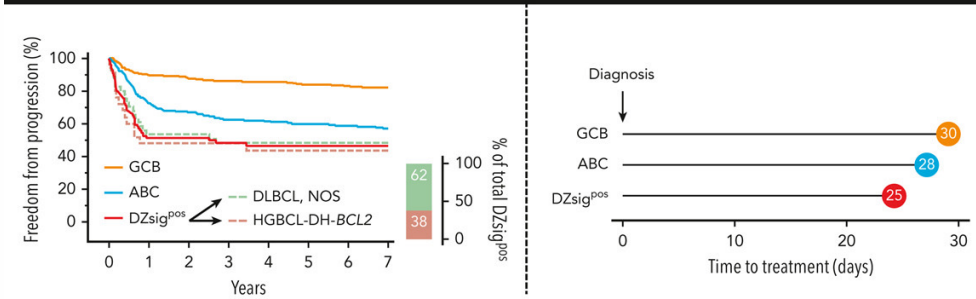

Ennishi et al, JCO 2019 Tripodo et al, iScience 2020

# Dark zone signature

1. DHITsig expression extends beyond HGBCL-DH-*BCL2* to identify dark zone lymphomas, and was thus renamed the "dark zone signature" (DZsig)



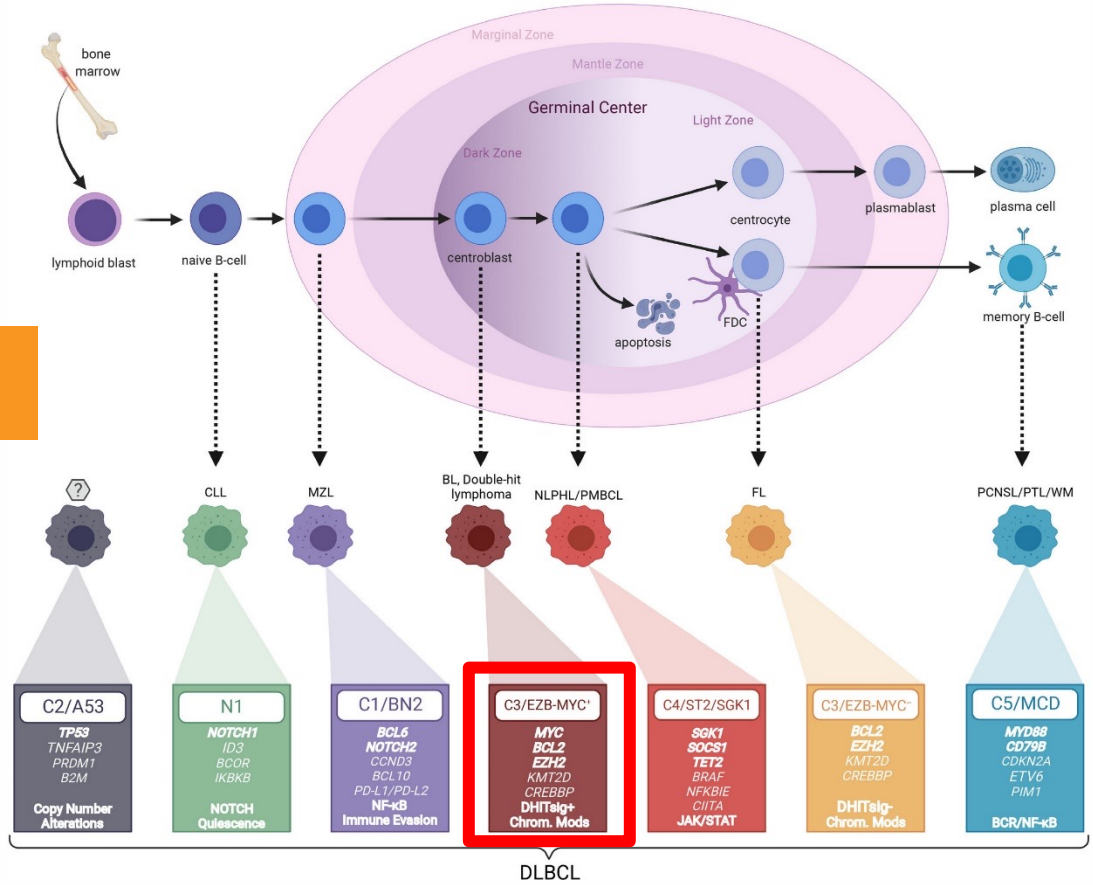

2. Among tumors of DLBCL morphology, gene expression profiling-defined molecular subgroups are associated with outcomes and diagnosis-to-treatment interval





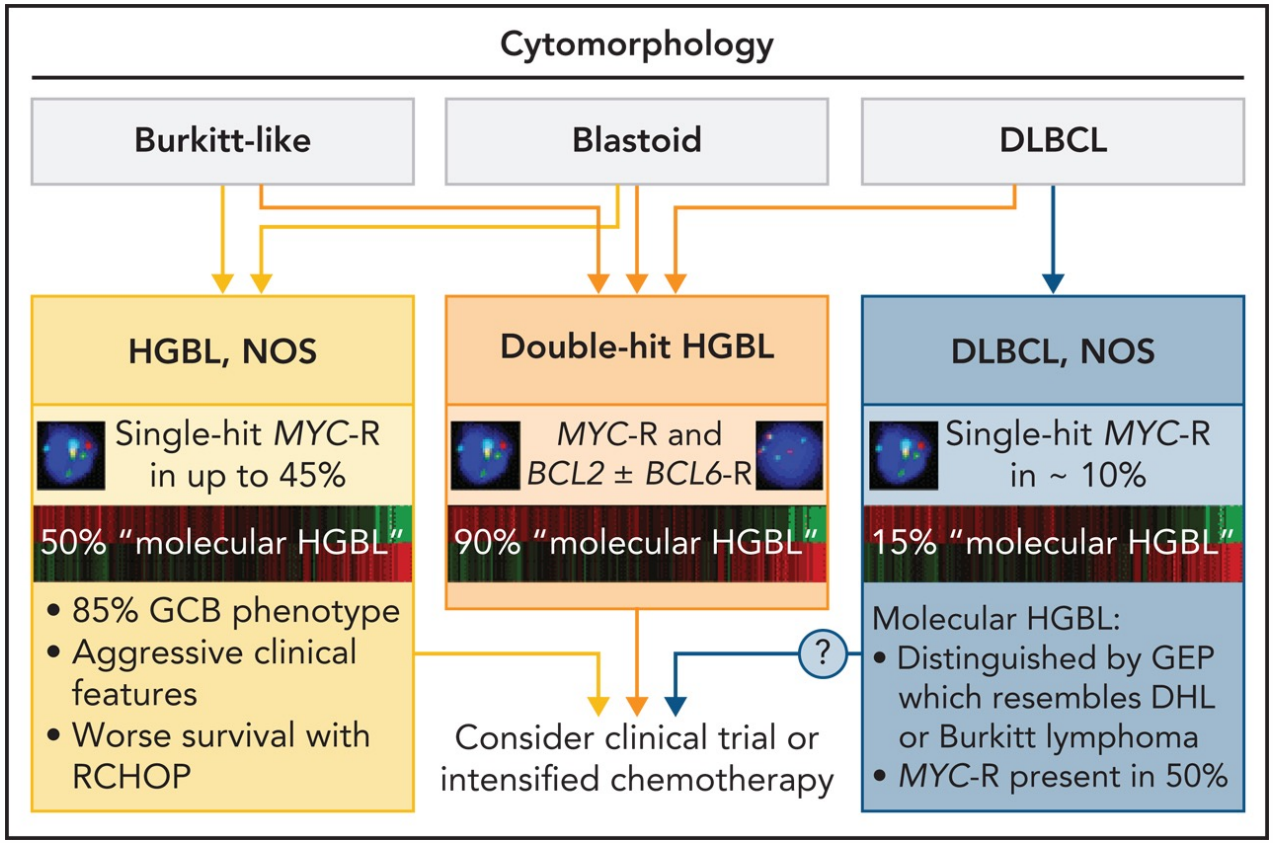

Alduaij et al, Blood 2023

**NCI –LymphGen**
**Harvard classification**






Adapted from Morin et al, BJH 2021






Olszewski et al, Blood, 2022

# Future perspectives

- DZsig distinguishes patients within GCB-DLBCL with poor outcomes.
- DZsig is undetectable by routine FISH testing
- GEP analysis may improve patient selection for intensified treatment
- Clinical trial design in DLBCL


«Biology-agnostic» therapies
Molecular classifications

# «Biology-agnostic» therapies

## (CAR-T, bispecific antibodies, etc)

- CD19-CART showed promising results, with ORR similar to DLBCL
- Downregulation of MHC genes and immune response pathways, low expression of PD-L1, and low macrophage content (!)
- Efficacy of other forms of immunotherapy in HGBL remains to be determined


Thank you