19th International Ultmann Chicago Lymphoma Symposium

LIVE Symposium

APRIL 29-30
2022

19TH ULTMANN

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

High-grade B-cell lymphoma, not otherwise specified (HGBCL, NOS): how to differentiate and what to do?

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19th Ultmann Chicago Lymphoma Symposium
30th April 2022

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Disclosures

Consulting: Abbvie, AstraZeneca, Incyte, Janssen

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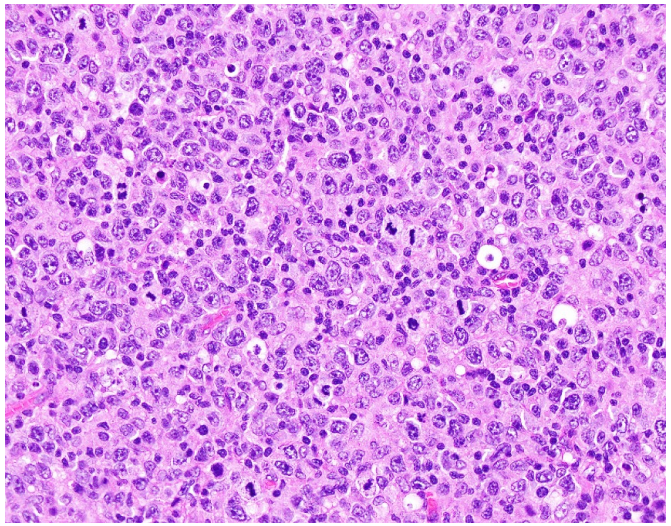
Patents: named inventor on patents related to using gene expression to identify subtypes of aggressive B-cell lymphomas – one of which is licensed to NanoString Technologies

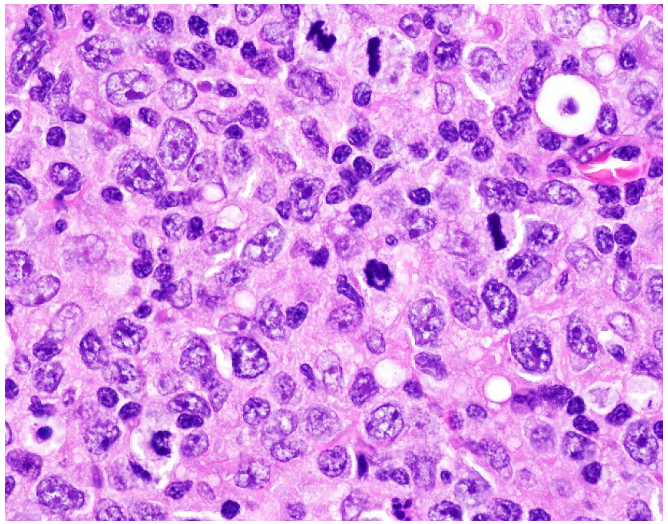
Off-label medications: discussion of targeted agents in the treatment of diffuse large B-cell lymphoma

Outline

- Evolving definitions – a brief history and where we are now
- Brief asides – genetics-based classification and dark zone signatures
- Mutational landscape of HGBCL, NOS – a true “waste basket”
- Treatment options
- Conclusions – where to from here?

First – a question





66-years old man with stage IVB B-cell lymphoma – drenching sweats.

IPI 4 with elevated LDH (750 with ULN 225).

Morphology of the lymph node biopsy: predominantly large cells with numerous mitotic figures, single cell necrosis. Ki67 is 100%

FISH: *MYC* rearrangement detected, negative for *BCL2* and *BCL6*.

The diagnosis is high-grade B-cell lymphoma, NOS:

a) True
b) False

Images courtesy of Dr. Steve Swerdlow from Campo *et al Blood In Review*

HGBCL – an evolving definition

- **First usage in the REAL classification (1994)**

II. Peripheral B-cell neoplasms

9. Diffuse Large B-cell lymphoma*
   Subtype: Primary mediastinal (thymic) B-cell lymphoma
10. Burkitt's lymphoma
11. Provisional entity: High-grade B-cell lymphoma, Burkitt-like*

Morphology. The participants in the meeting noted that several of the cases in the large cell lymphoma reproducibility study set appeared to have morphologic features intermediate between large cell lymphoma with centroblastic or immunoblastic features and typical Burkitt's lymphoma (Fig 8). All recalled many cases in their own practices in which distinction between large cell and Burkitt's lymphoma seemed impossible.

We believe that this is not a reproducible category, and probably not a single disease entity, but it appears to be necessary for cases that are borderline between large B-cell lymphoma and Burkitt's lymphoma.

Harris *et al Blood 1994*

HGBCL – an evolving definition

Table 10. Burkitt's Lymphoma, Morphologic Variants and Subtypes

Morphologic variants
Burkitt-like
With plasmacytoid differentiation (AIDS-associated)
Subtypes, clinical and genetic
Endemic
Sporadic
Immunodeficiency-associated

Thus, the definition of Burkitt-like lymphoma is a lymphoma that morphologically resembles Burkitt's lymphoma but has more pleomorphism or large cells than classical Burkitt's lymphoma and, in addition, has a proliferation fraction of greater than 99%.

- First usage in the REAL classification (1994)
- Adjusted in the WHO classification
  - Oncologists wanted it reserved for tumors that should be treated like Burkitt lymphoma

Harris *et al Blood 1994*

Harris *et al J Clin Oncol 1999*

HGBCL – an evolving definition

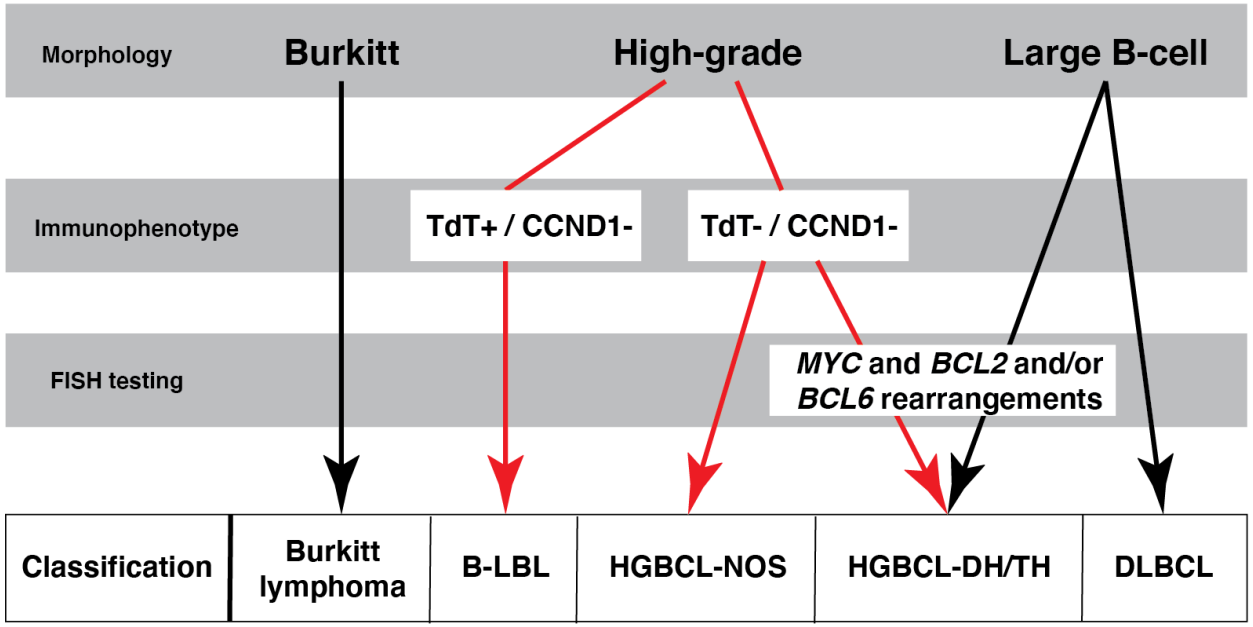
- First usage in the REAL classification (1994)
- Adjusted in the WHO classification
  - Oncologists wanted it reserved for tumors that should be treated like Burkitt lymphoma
- Evolving into BCLU* in the WHO 4th edition (2008)
- Definitions tightening up in the WHO 4th edition revised (2017), incorporating genetic features
- Lightly "retouched" in the 2022 updates (?)

Harris *et al Blood 1994* Harris *et al J Clin Oncol 1999* Swerdlow *et al Blood 2016* Campo *et al Blood In Review*

* B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma

HGBCL, NOS – current definitions

2017 WHO



HGBCL-NOS: high grade B-cell lymphoma, not otherwise specified
HGBCL-DH/TH: high grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements

Swerdlow *et al Blood 2016*

HGBCL, NOS – current definitions

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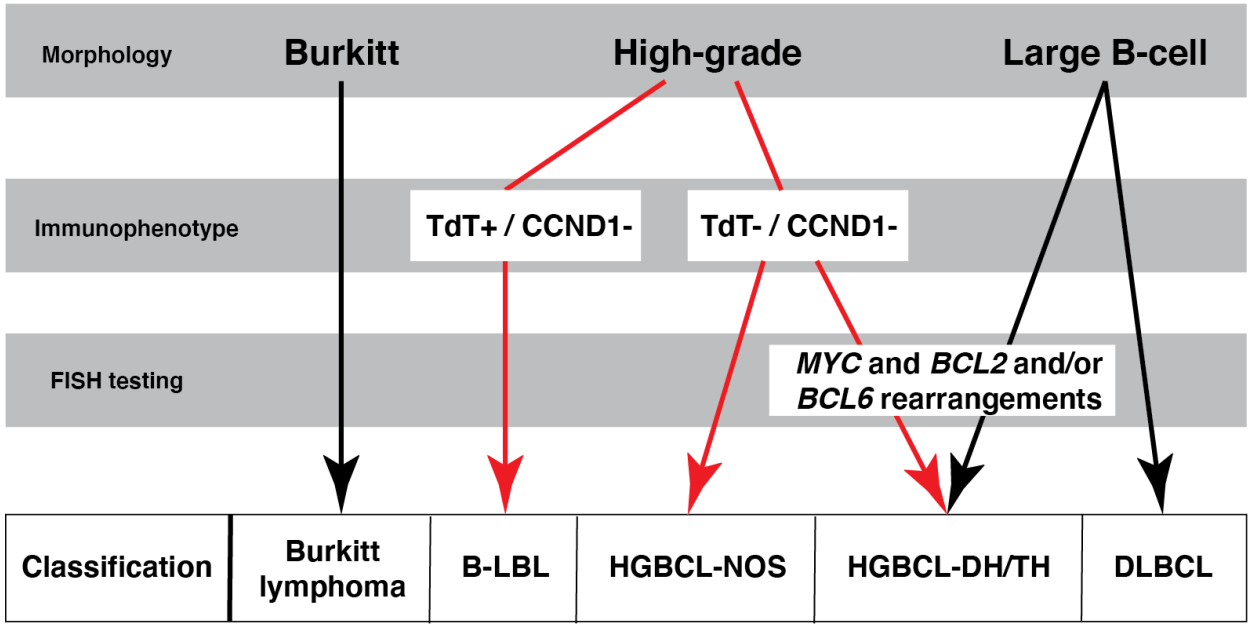
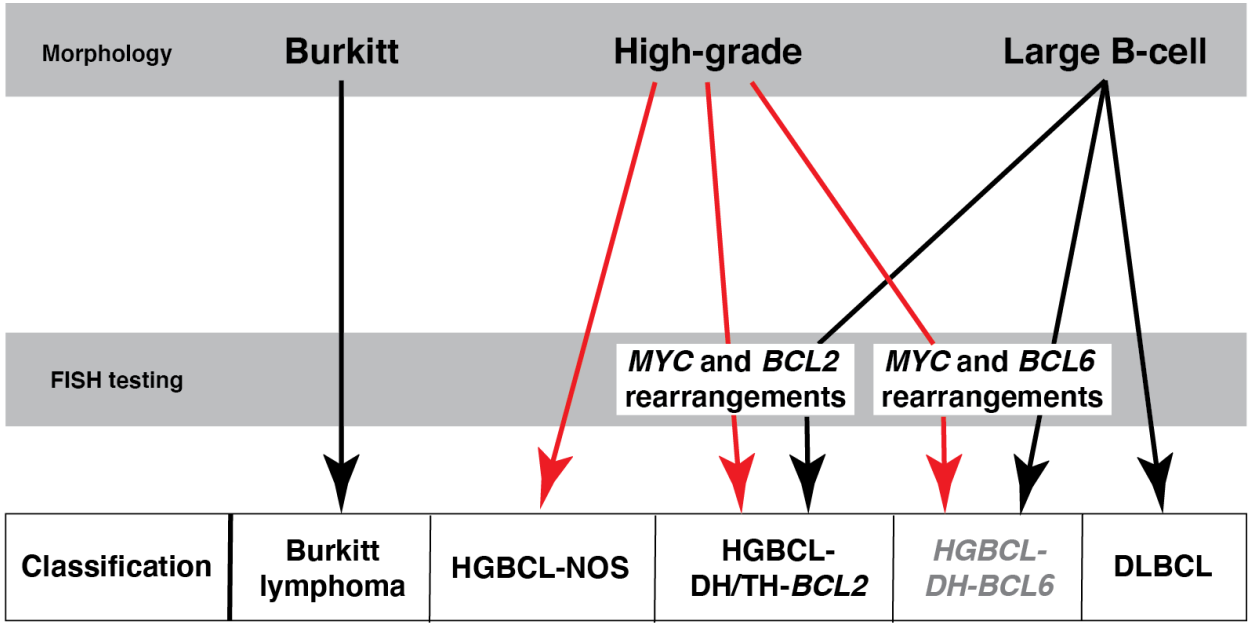


2022 ICC



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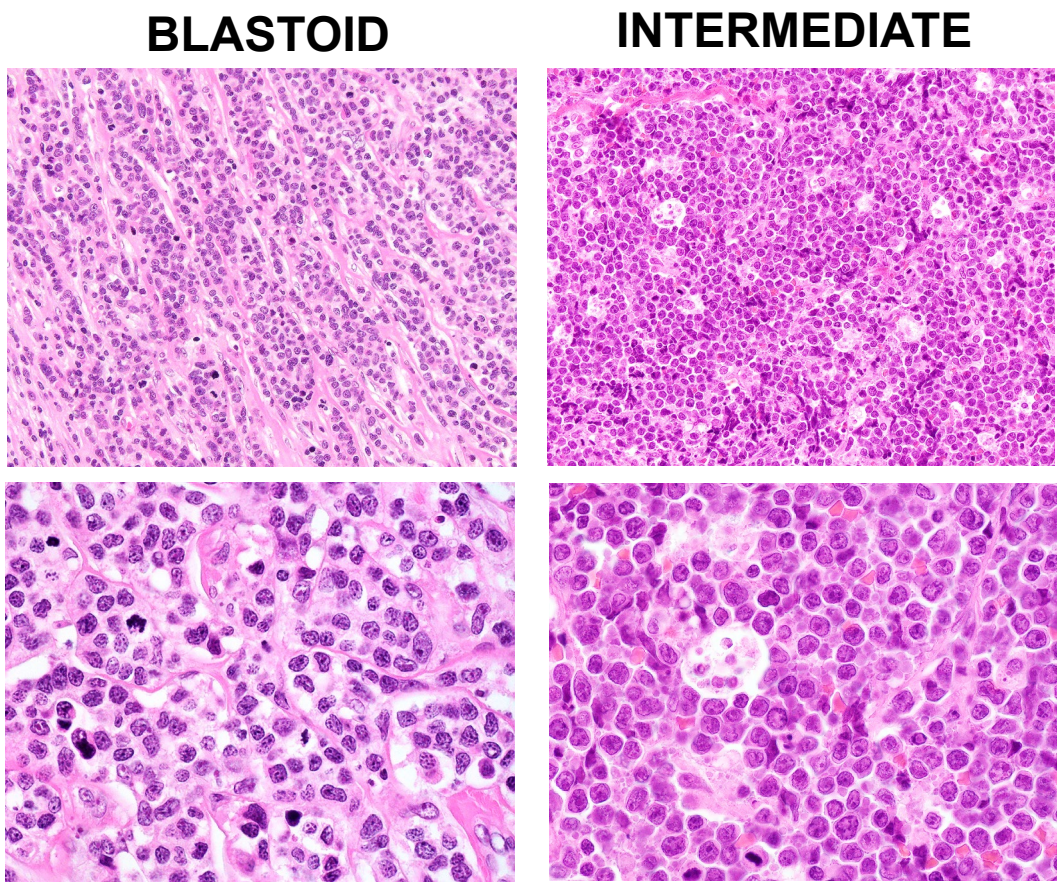
Swerdlow *et al Blood 2016*

Bhavsar *et al Am J Surg Pathol 2022*

Campo *et al Blood In Review*

Defining HGBCL, NOS



- Intermediate or blastoid morphology
- In a mature phenotype, TdT is allowed
- Should only be applied to well-preserved and well-fixed sections
- NOT large cell morphology with starry-sky appearance and/or high proliferation
- Exclude HGBCL-DH, *large B-cell lymphoma with 11q aberrations* and blastoid mantle cell lymphoma

Swerdlow *et al Blood 2016*

Images courtesy of Dr. Steve Swerdlow from Campo *et al Blood In Review*

Campo *et al Blood In Review*

Reproducibility - the problem with morphology

- LLMPP pathology panel reviewed 83 tumors submitted as HGBL, NOS
- ~50% were reclassified as DLBCL or Burkitt lymphoma
- Reclassification equally affected blastoid and intermediate tumors
- Many blastoid were reclassified to intermediate – very few the other way
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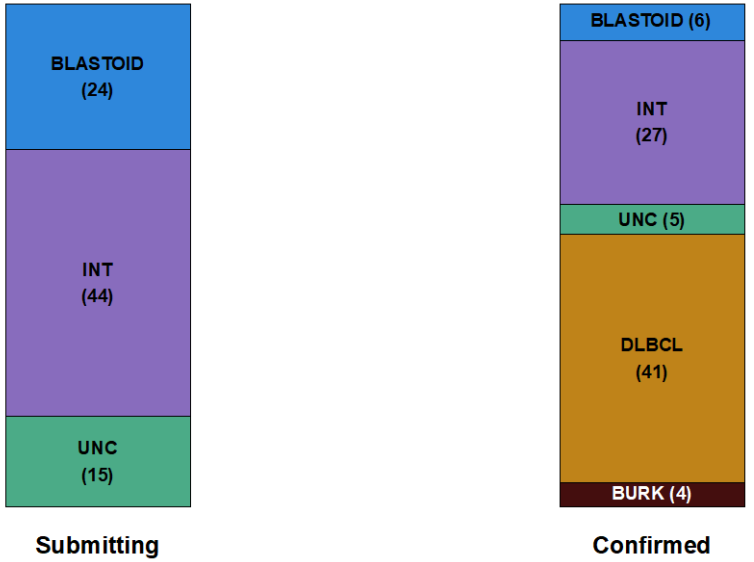

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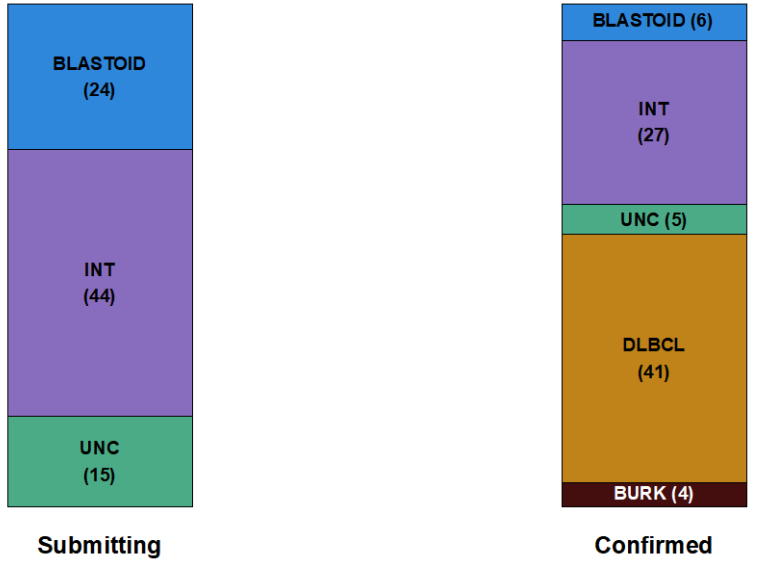
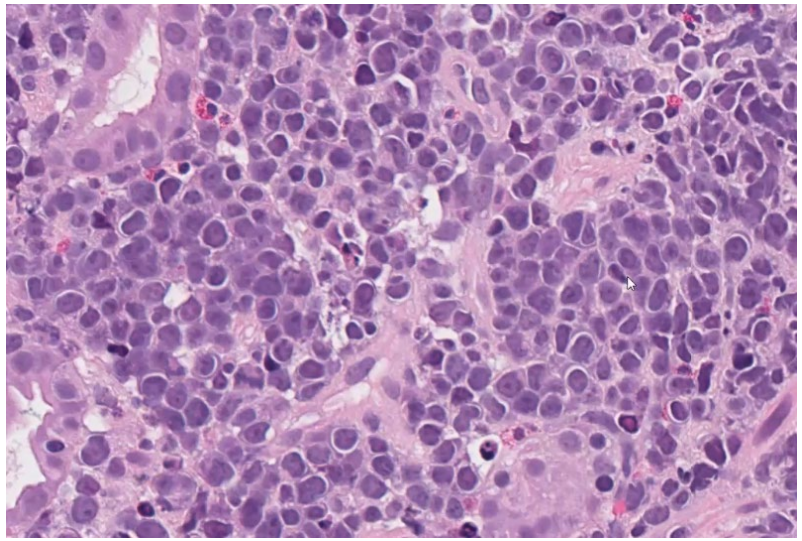
- A lot of lively debate
- Issues included section thickness and fixation artifacts





Submitted as Blastoid
Review = DLBLC

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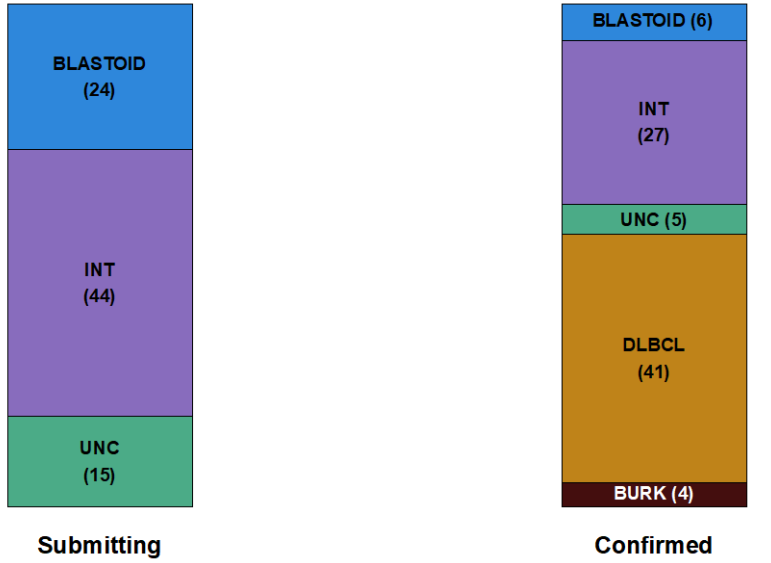

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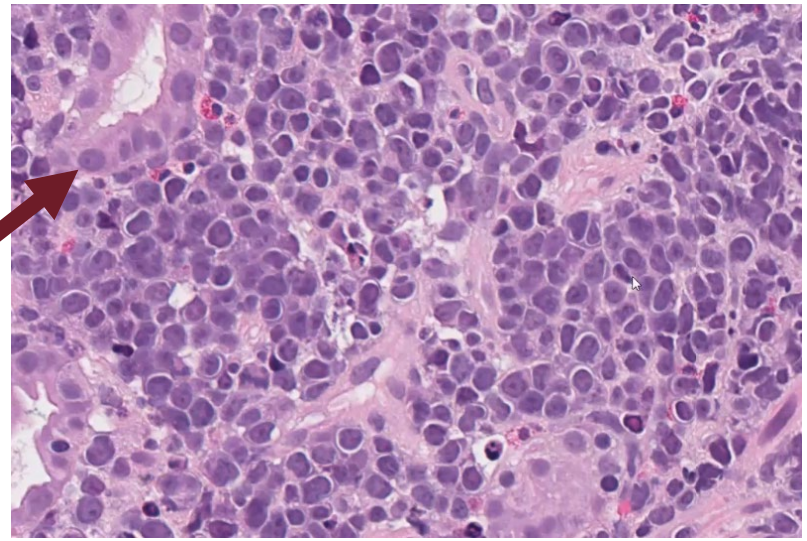
Fixation issue: epithelial cell nucleus appears blastoid



Submitted as Blastoid
Review = DLBCL

Brief asides:

Genetics-based classification and dark zone signatures

Genetics-based classification - LymphGen

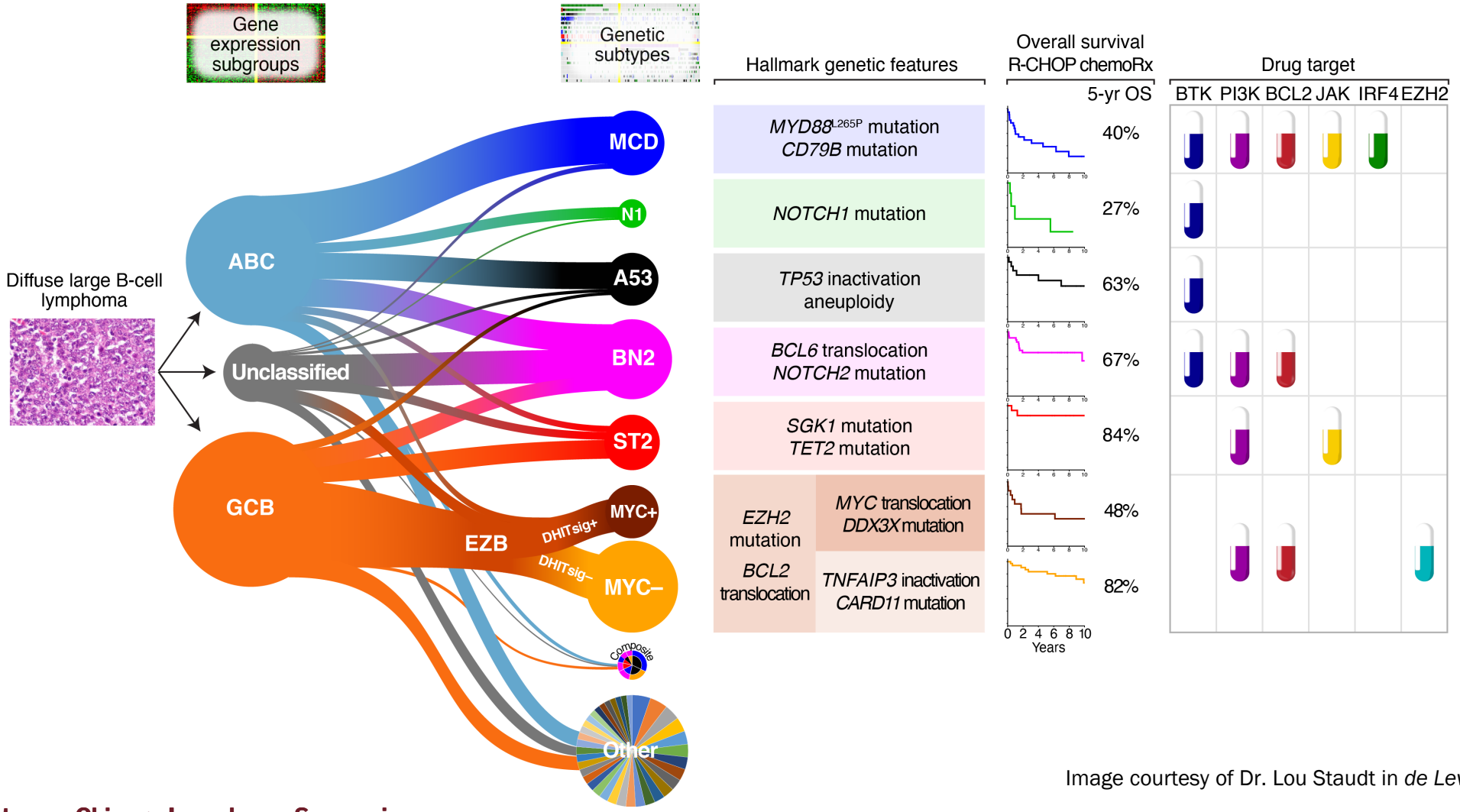
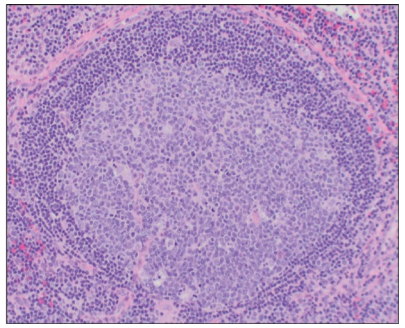


Image courtesy of Dr. Lou Staudt in *de Leval Blood In Review*

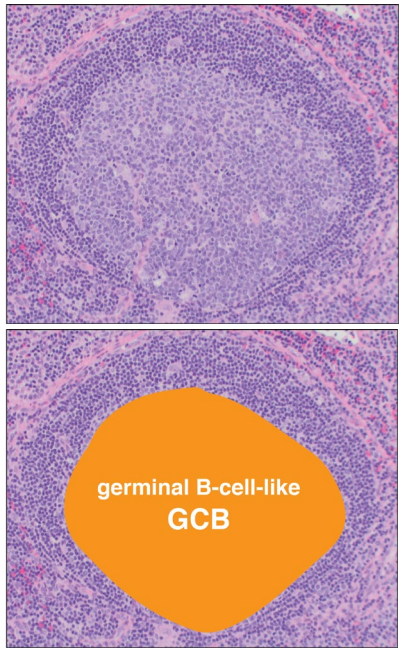
Dark zone gene expression signatures



- **“Cell-of-origin” is a binary gene expression classification: tumors with expression like germinal center B-cells (GCB) versus those that don’t (“ABC”)**

Alizadeh *et al Nature 2000*

Dark zone gene expression signatures



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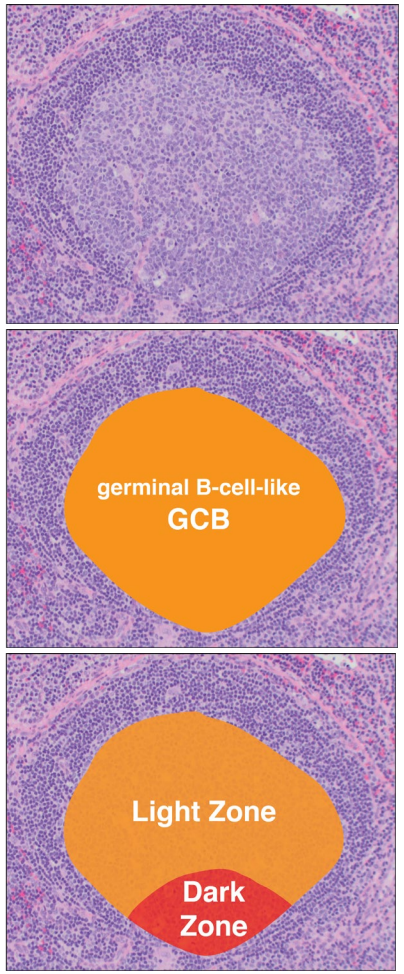

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  - Burkitt, HGBCL-DH-*BCL2* and GCB-DLBCL are all "GCB"

- Two signatures have been defined from different angles:
  - "Molecular high grade" (MHG) based on the "molecular Burkitt signatures"
  - "Double hit signature" (DHITsig) that distinguishes HGBCL-DH-*BCL2* from GCB-DLBCL

All Burkitt lymphomas are positive for DHITsig

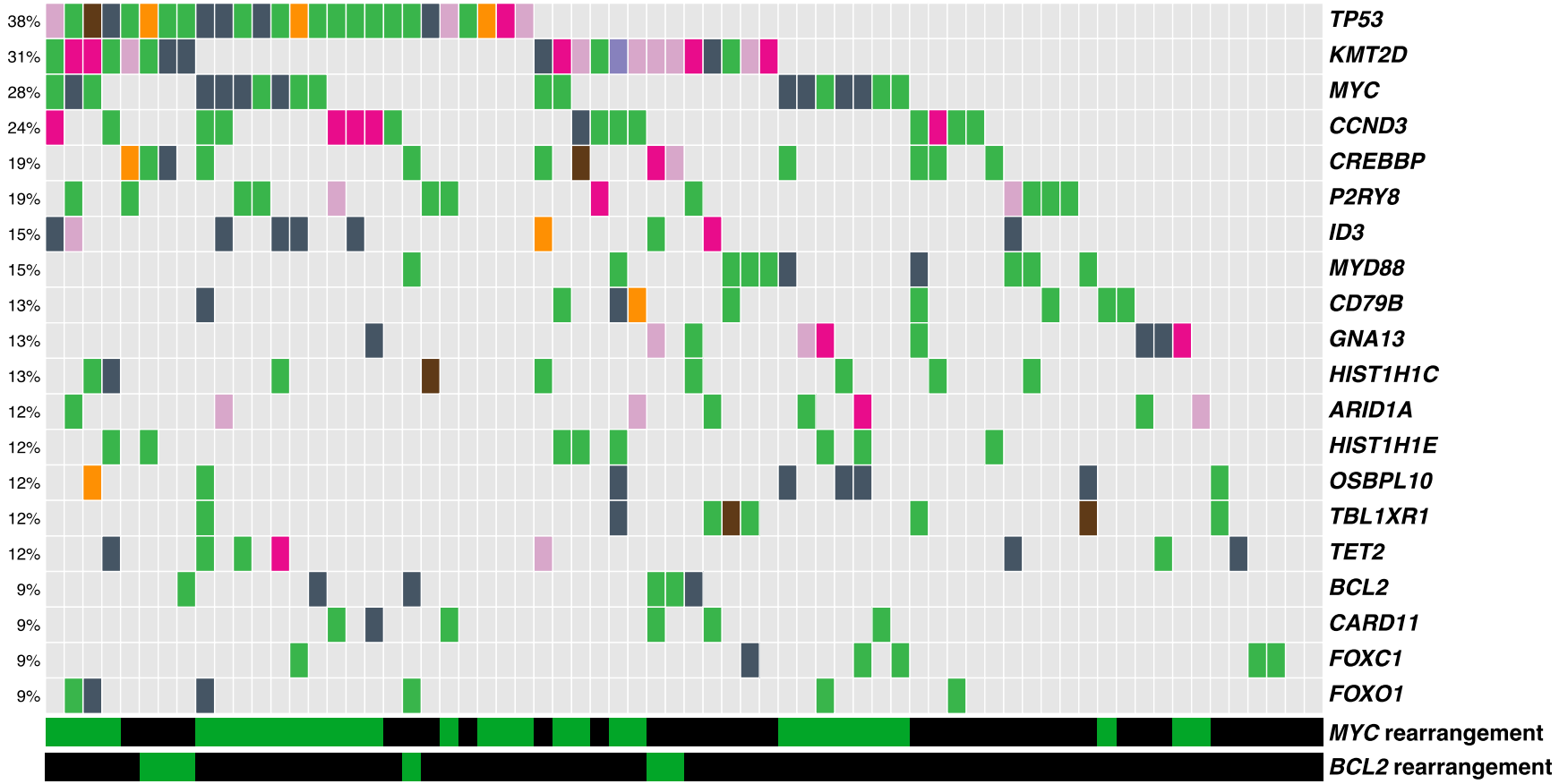
These signatures are actually signatures of the dark zone

Alizadeh *et al Nature 2000* Dave *et al N Engl J Med 2006* Hummel *et al N Engl J Med 2006* Sha *et al J Clin Oncol 2019* Ennishi *et al J Clin Oncol 2019*

Mutational Landscape of HGBCL, NOS

A true waste basket or, more generously, a “holding pen”

Rearrangements cryptic to FISH

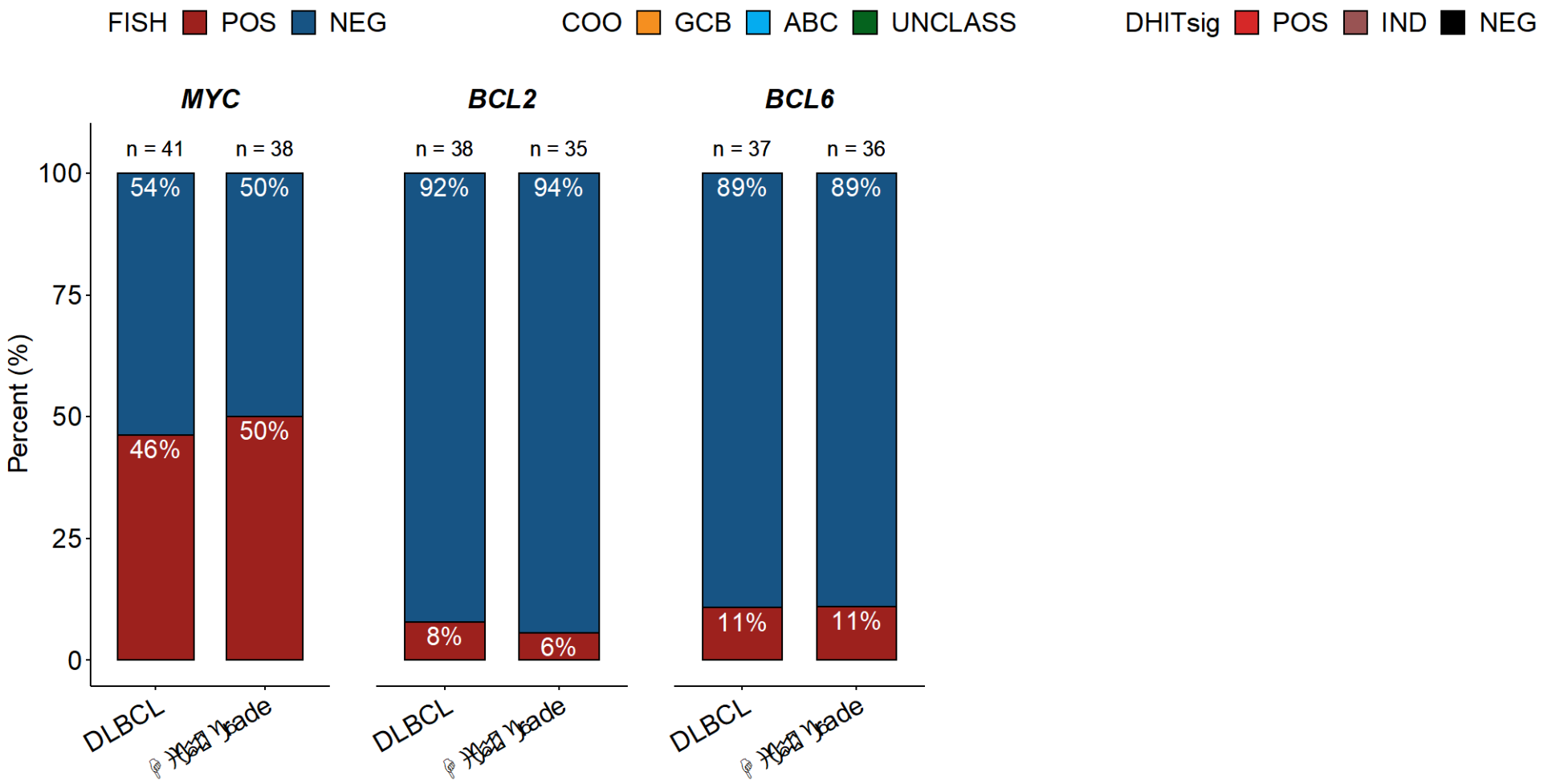


Rearrangements cryptic to FISH

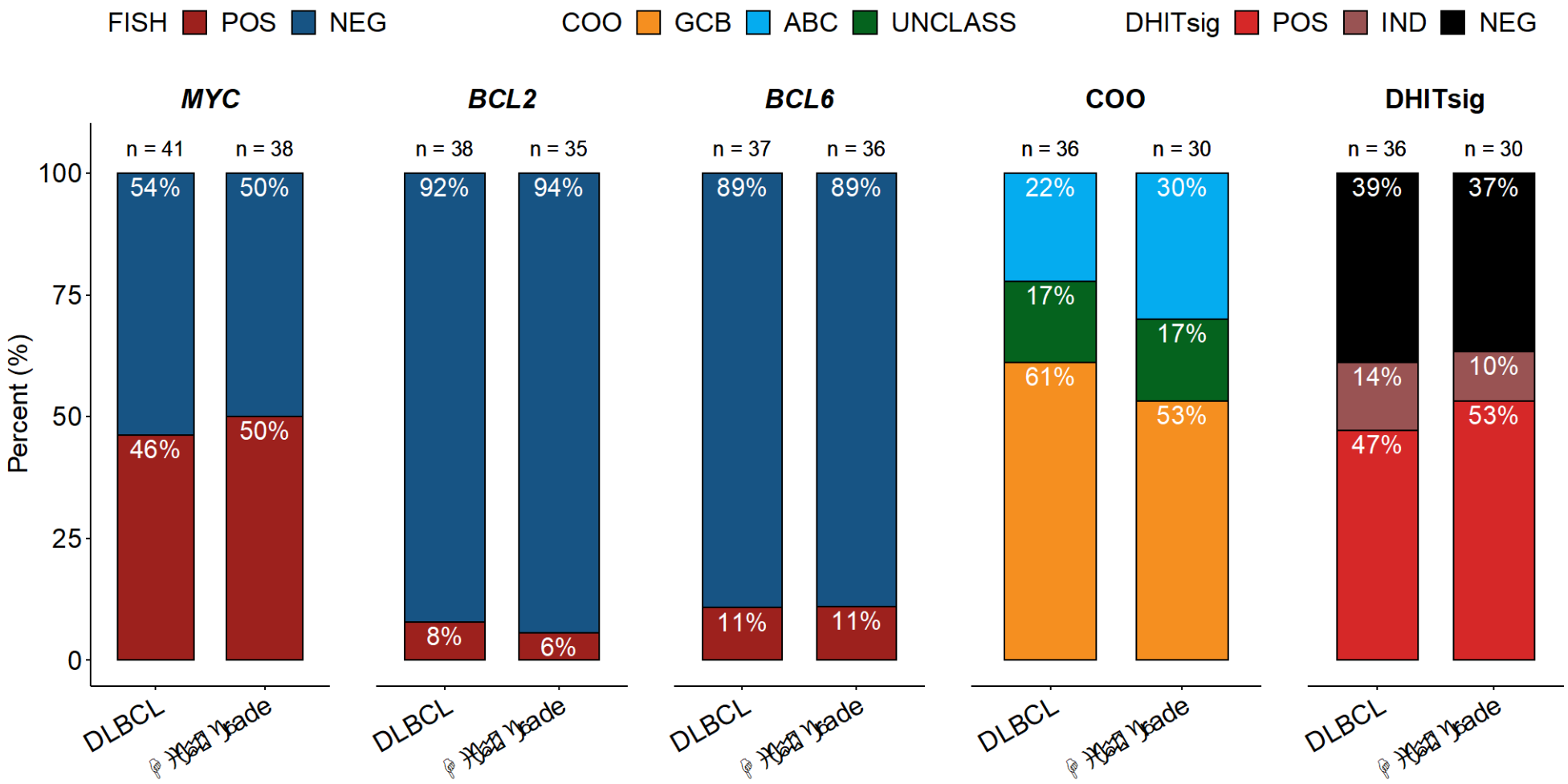
- Rearrangements that were not detected by break-apart FISH were detected in ~10% of these tumors
- A small number were reclassified as HGBCL-DH-*BCL2*

Hilton *et al Blood 2019*

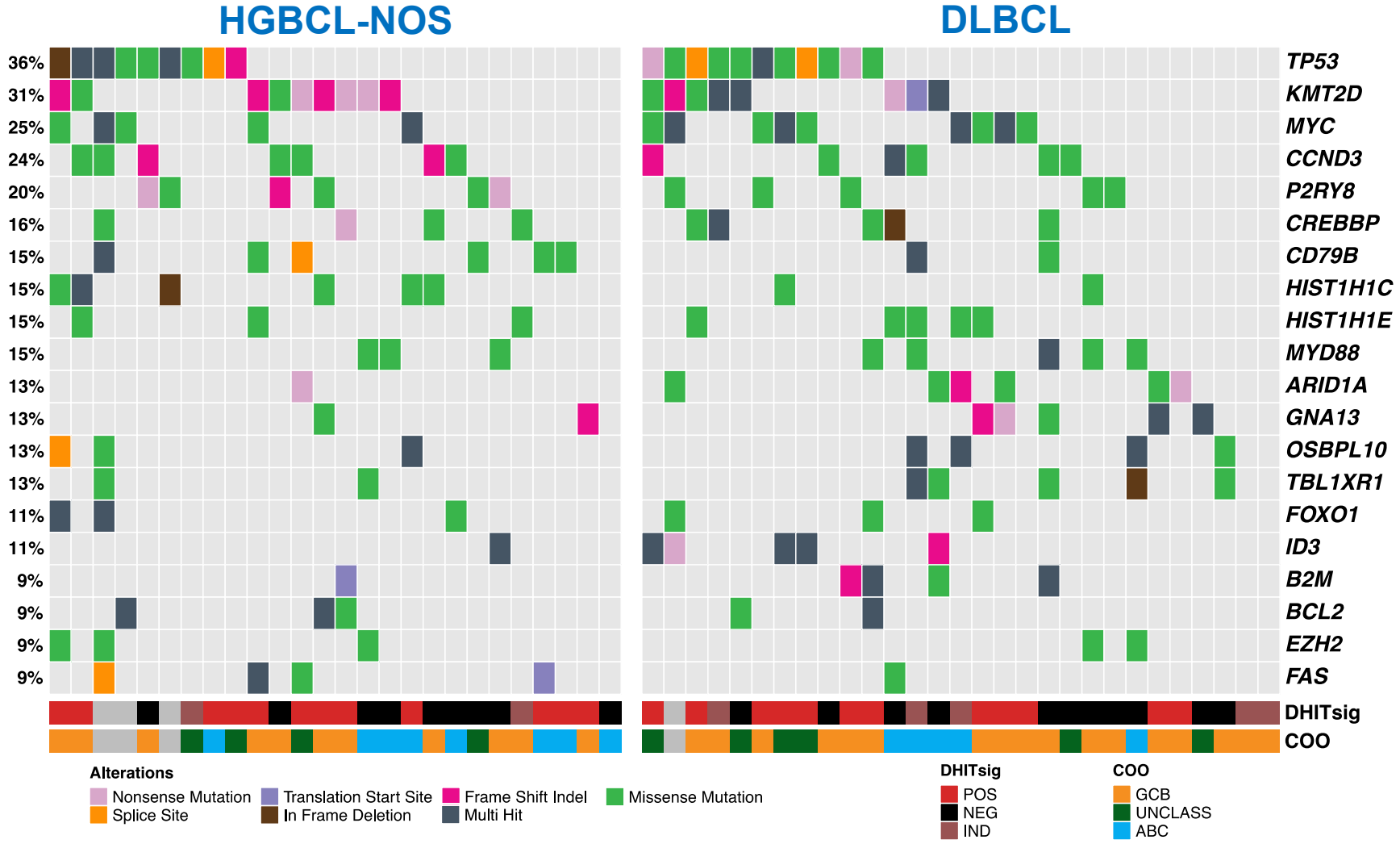
Rearrangements in HGBCL, NOS



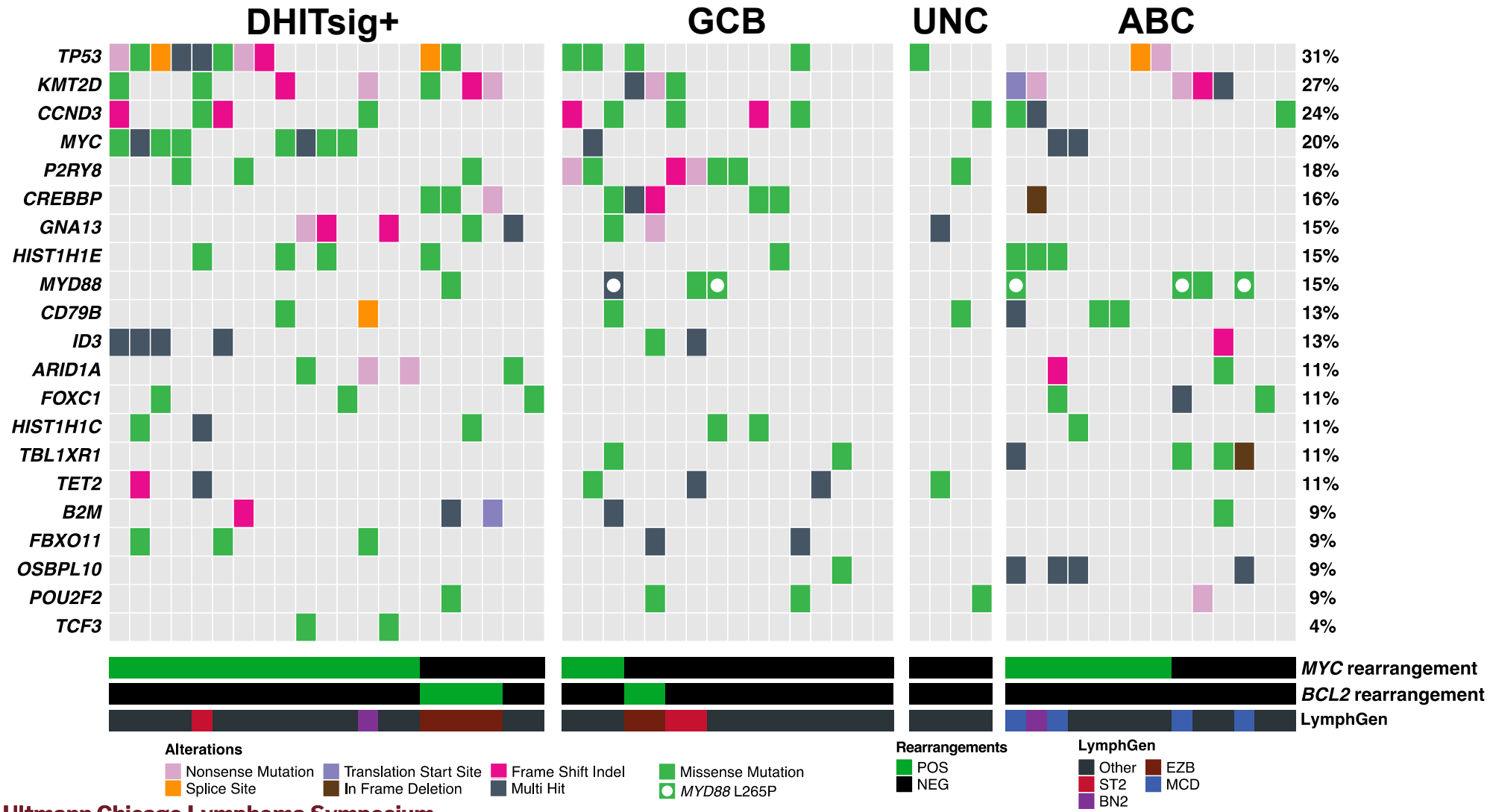
Gene expression groups in HGBCL, NOS



No differences in mutations between HGBCL, NOS and reclassified tumors



Arranging according to gene expression reveals biological patterns



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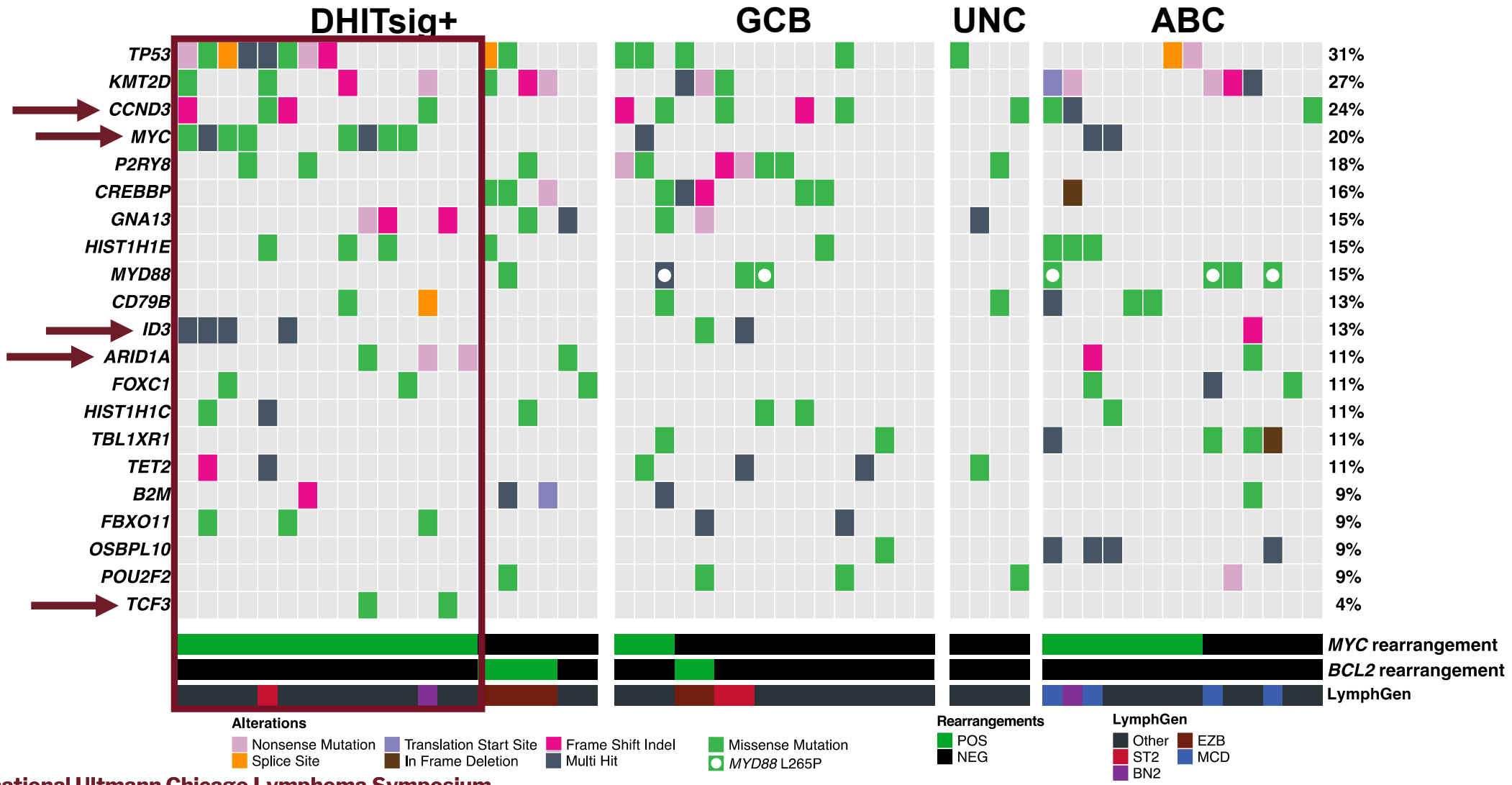

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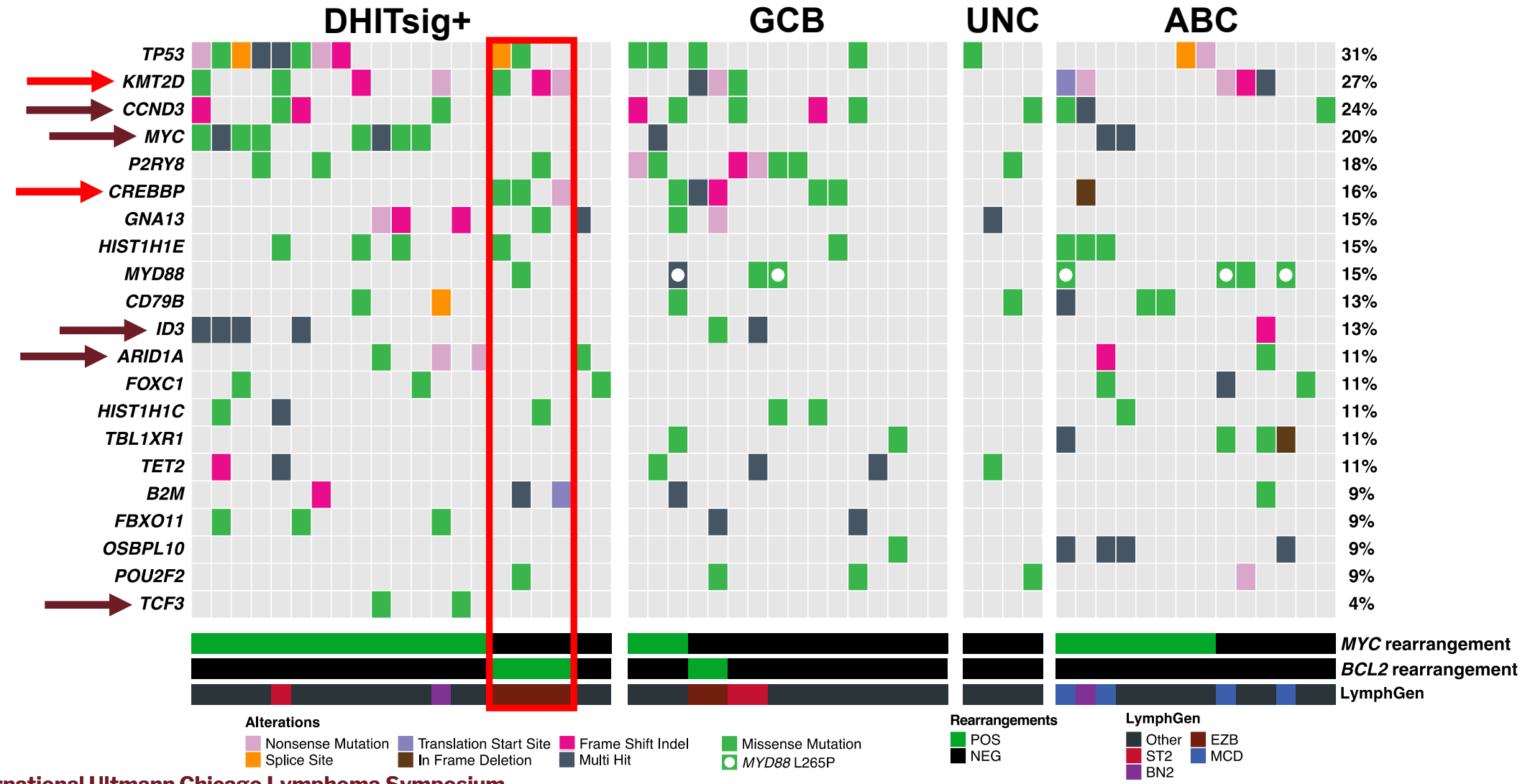

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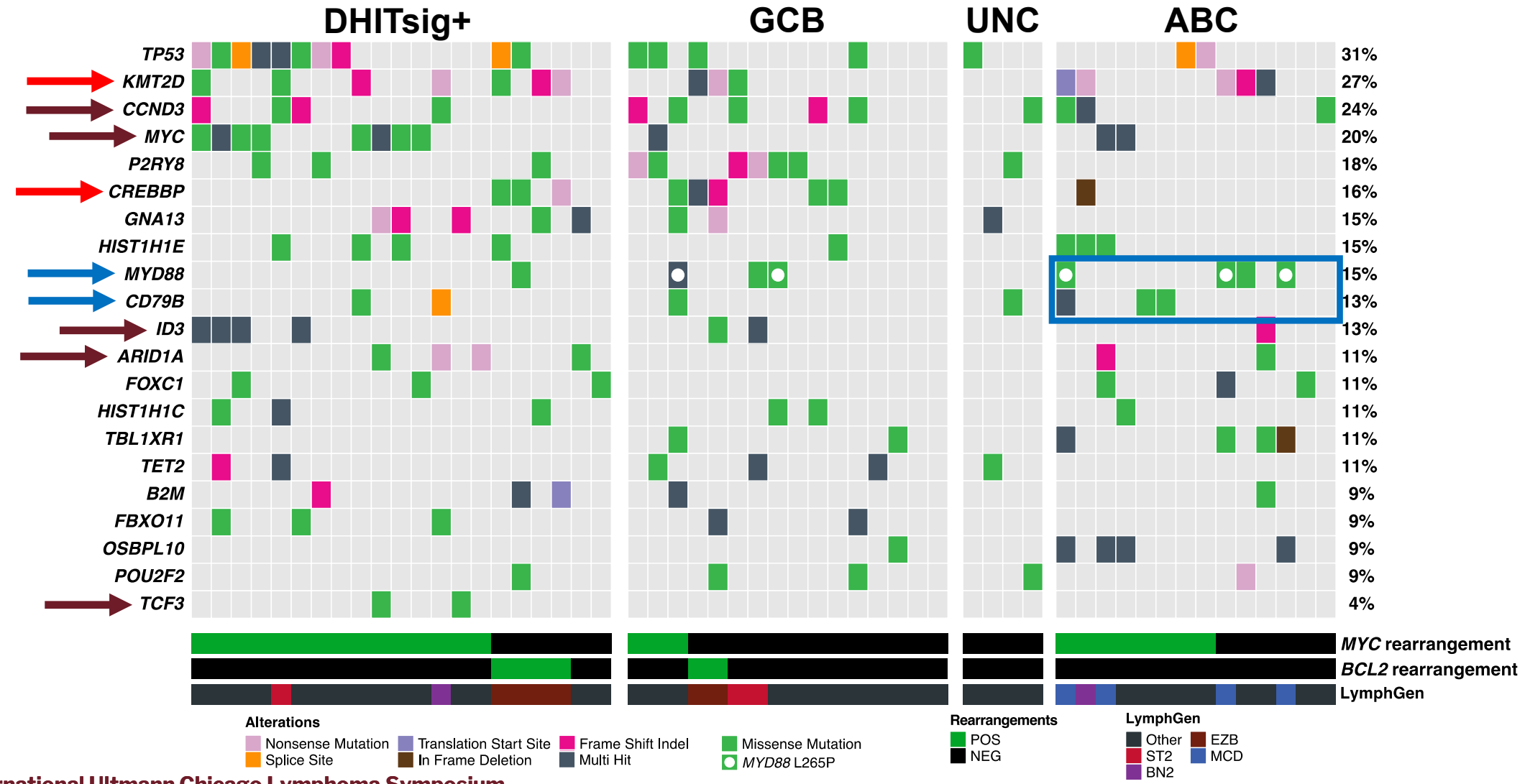


Treatment Options

Audience response question - treatment

54-years old woman with stage IVA HGBCL, NOS with no comorbidities. IPI 3 with LDH 600 (ULN 225). Adrenal involvement.

What would be your preferred treatment of the following options:

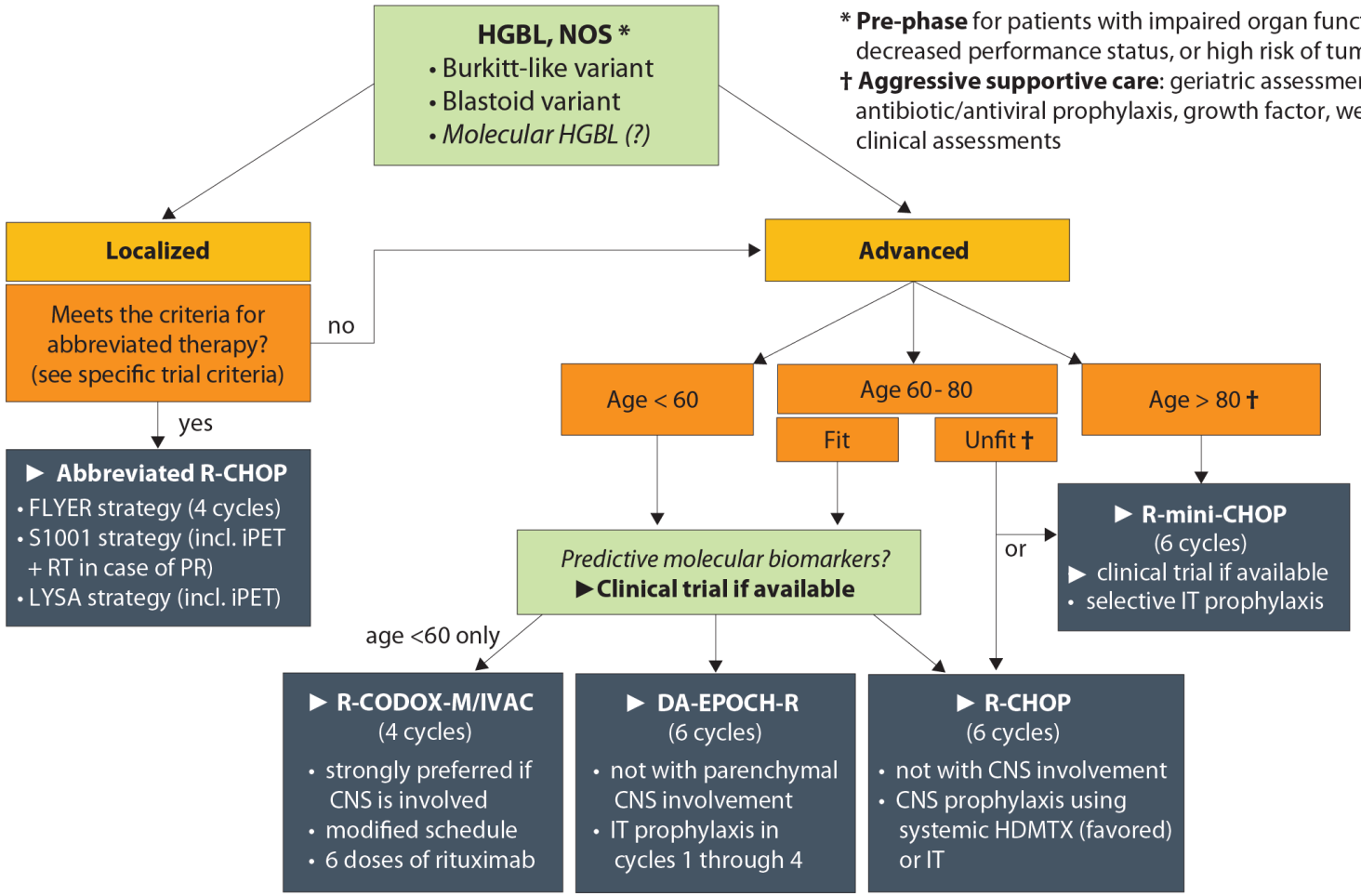
A) 6 cycles of R-CHOP

B) 6 cycles of DA-EPOCH-R with IT methotrexate

C) R-CODOX-M/IVAC

D) R-CODOX-M/IVAC plus autologous stem cell transplant

A treatment algorithm



Olszewski, Kurt and Evens *Blood In Press*

Schmitz *et al J Clin Oncol 2016*

- **Shifting definitions and problems with reproducibility mean that we do not have solid data to guide management decisions**
- **Concerns about very poor prognosis and CNS involvement at diagnosis and relapse**
- **Our preference is to intensify treatment where possible and use R-CODOX-M/IVAC +/- ASCT, especially where there is CNS involvement and in patients with high CNS-IPI**
- **Is this appropriate for tumors that are ABC?**

Conclusions

- HGBCL, NOS is defined on morphology, following exclusion of established entities – it is a “holding pen”
- It should be used sparingly and only on well preserved and fixed material
- Reproducibility of classification as HGBCL, NOS is poor
- The mutational landscape is heterogeneous with many tumors having patterns consistent with other entities, ranging from Burkitt lymphoma through to MCD-DLBCL
- A conclusion is that these tumors represent phenotypic extremes of these entities and may be best treated as such
- This is a group of tumors that would benefit from sequencing – the aim is to reallocate these tumors out of the “holding pen”

- A molecular taxonomy across the spectrum of aggressive B-cell lymphoma would likely reduce or even eliminate HGBCL, NOS

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