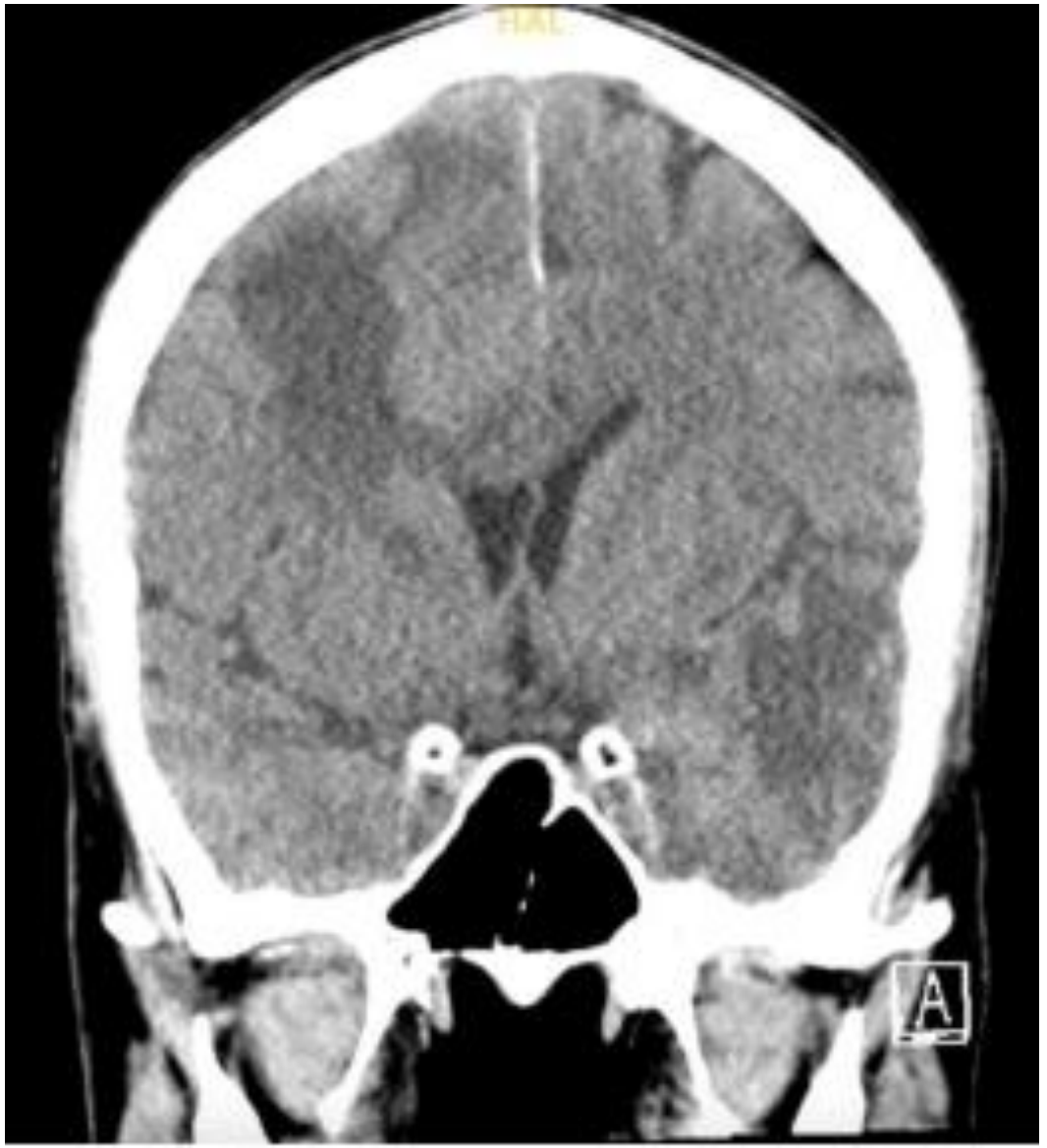
MIHCC

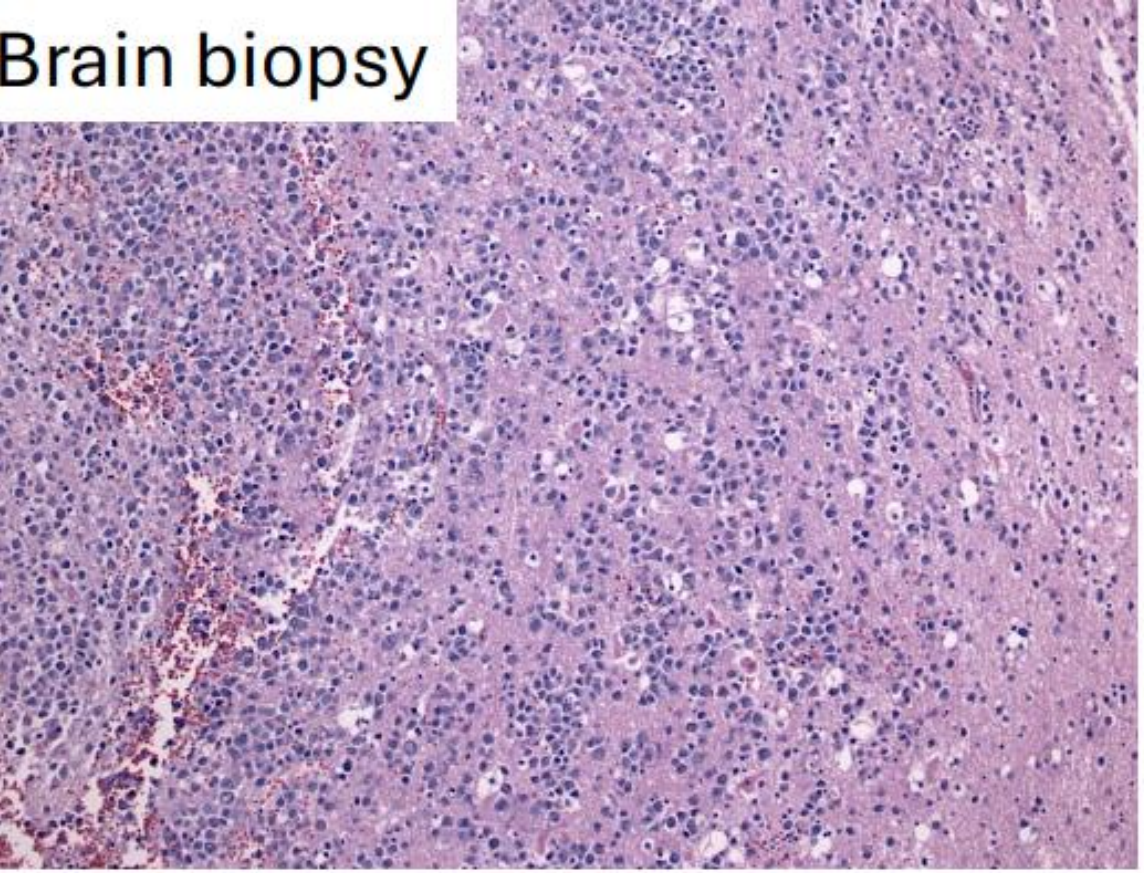
June 25, 2025

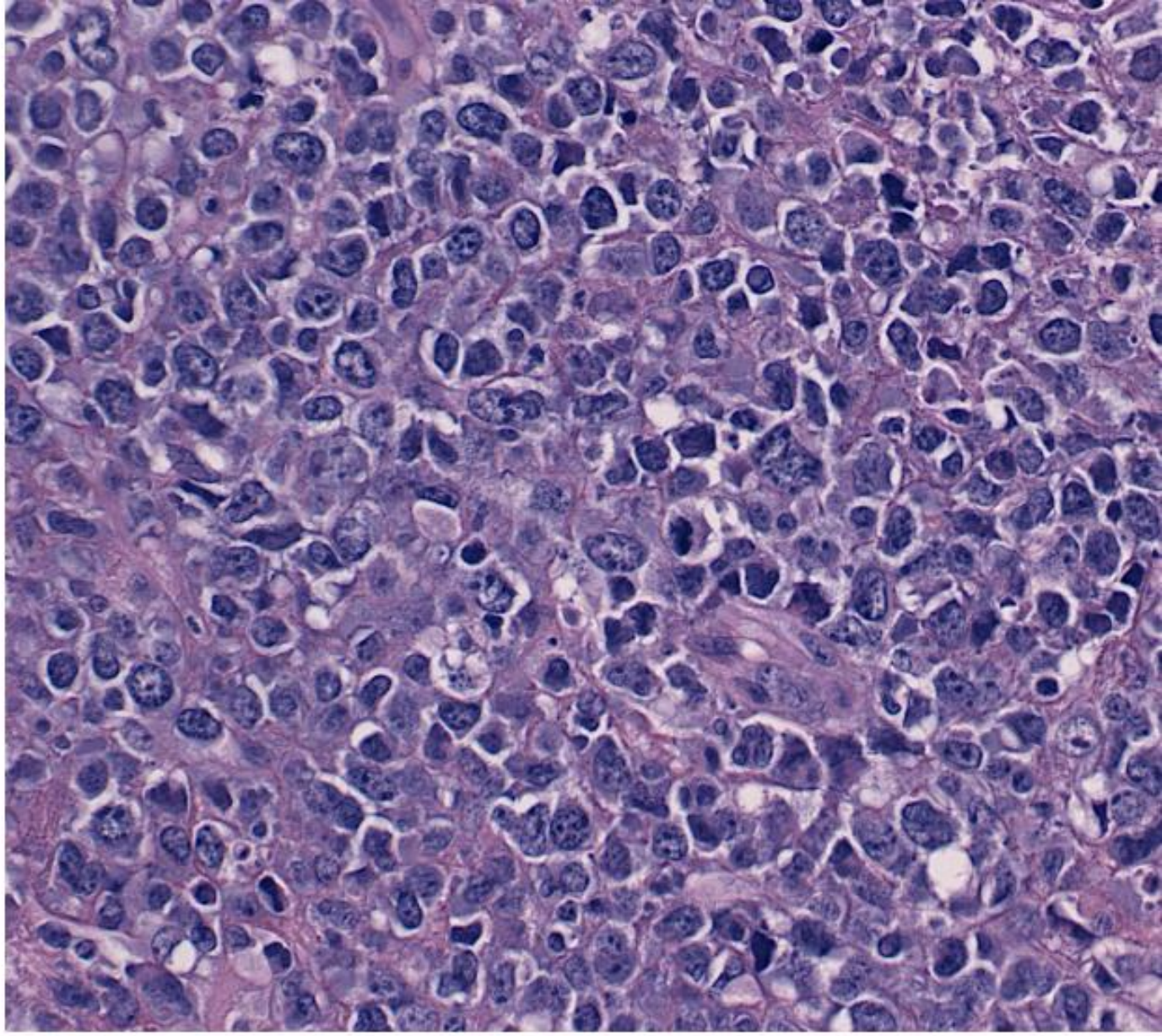
Case 3

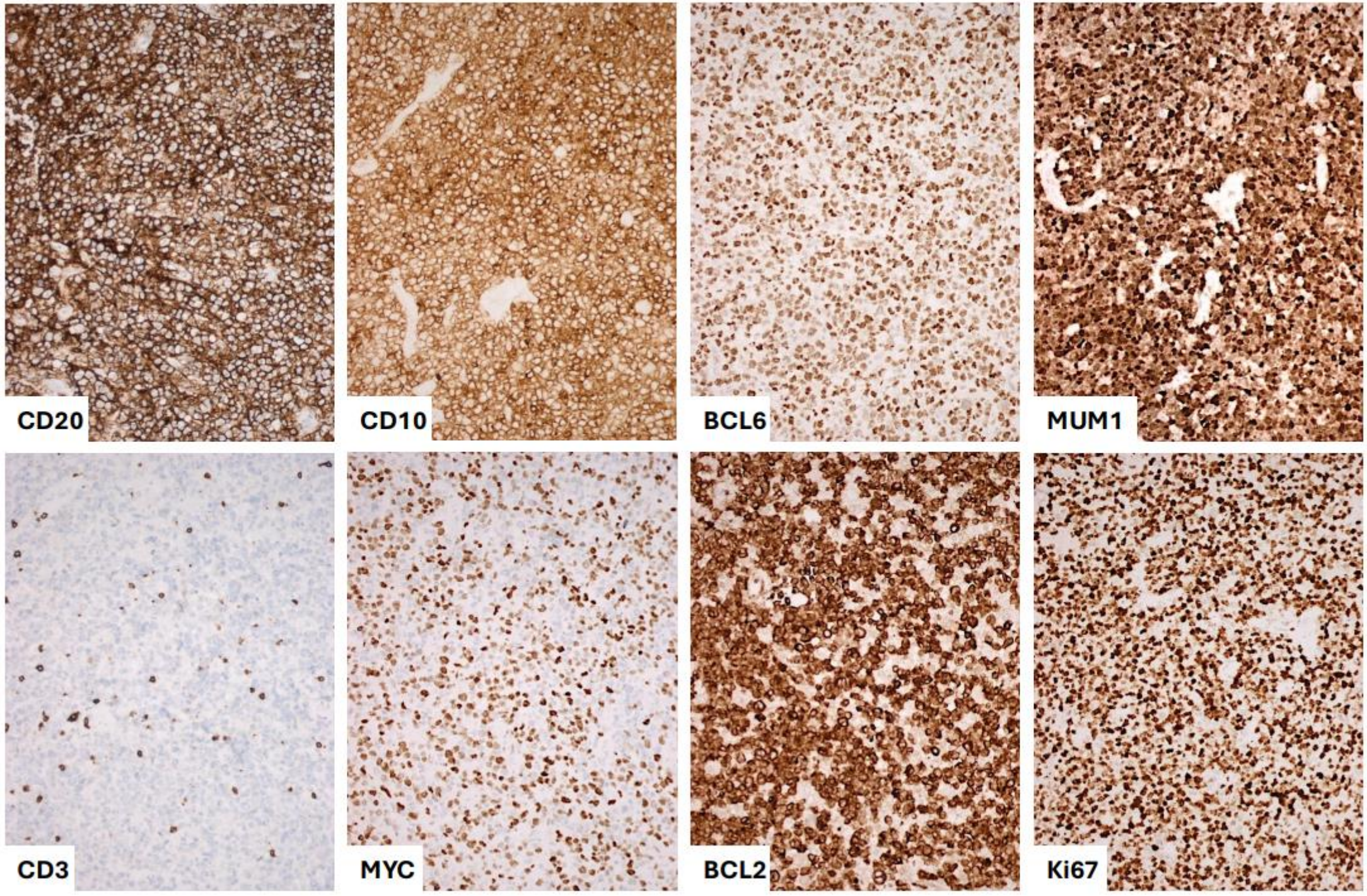
Clinical History

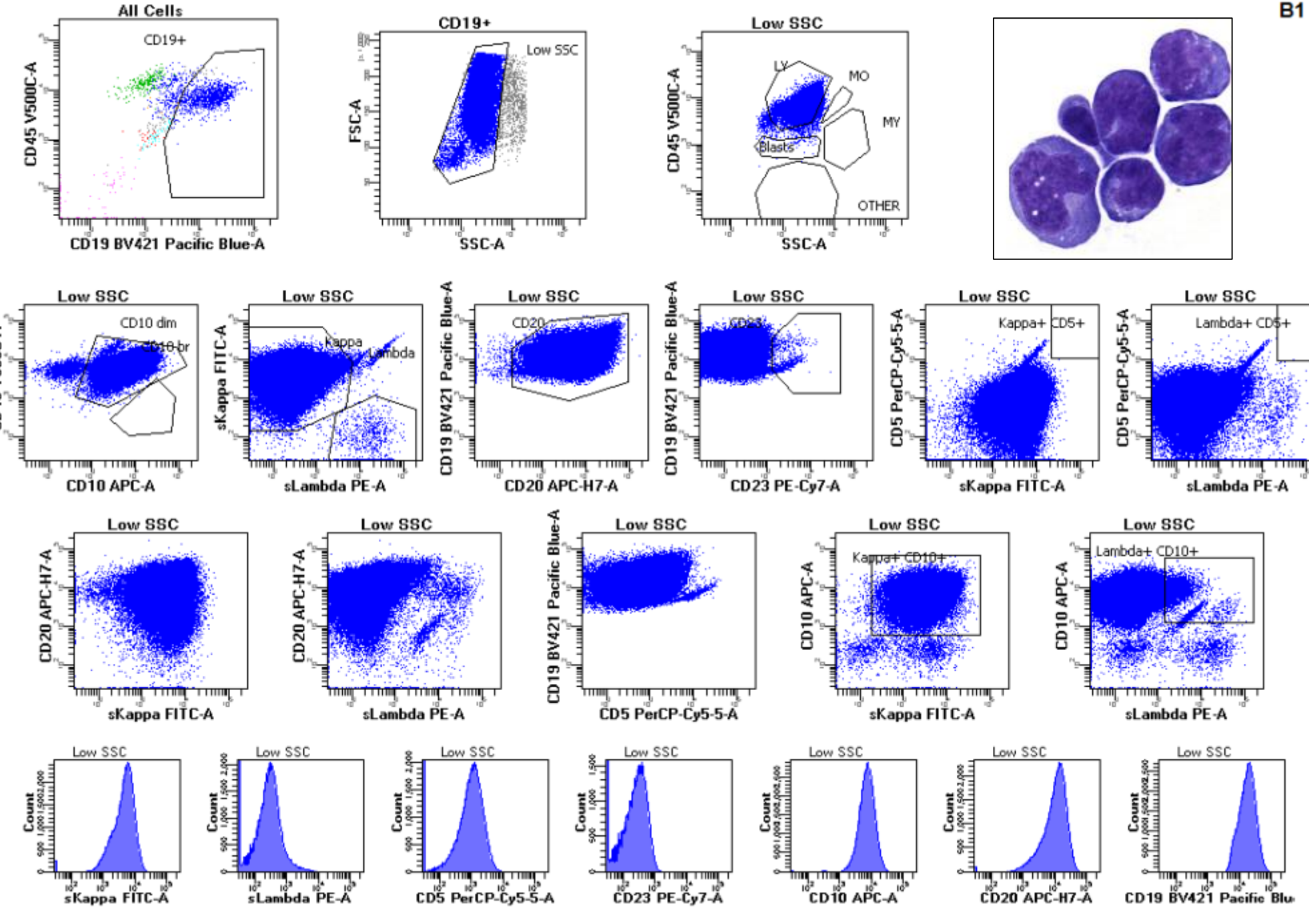
- June 2019: A 61-year-old man with a history of bipolar disorder and alcohol abuse presents with declining mental status over the past month.
- MRI showed multiple intracerebral lesions concerning for either metastatic disease or lymphoma.




Brain biopsy




CD20
CD10
BCL6
MUM1
CD3
MYC
BCL2
Ki67


B1
All Cells
CD19+
CD45 V500C-A
CD19 BV421 Pacific Blue-A
CD19+
Low SSC
FSC-A
SSC-A
Low SSC
LY
MO
MY
Blasts
OTHER
CD45 V500C-A
SSC-A
Low SSC
CD10 dim
CD10 br
CD45 V500C-A
CD10 APC-A
Low SSC
Kappa
Lambda
sKappa FITC-A
sLambda PE-A
Low SSC
CD20+
CD19 BV421 Pacific Blue-A
CD20 APC-H7-A
Low SSC
CD23+
CD19 BV421 Pacific Blue-A
CD23 PE-Cy7-A
Low SSC
Kappa+ CD5+
CD5 PerCP-Cy5-5-A
sKappa FITC-A
Low SSC
Lambda+ CD5+
CD5 PerCP-Cy5-5-A
sLambda PE-A
Low SSC
CD20 APC-H7-A
sKappa FITC-A
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CD20 APC-H7-A
sLambda PE-A
Low SSC
CD19 BV421 Pacific Blue-A
CD5 PerCP-Cy5-5-A
Low SSC
Kappa+ CD10+
CD10 APC-A
sKappa FITC-A
Low SSC
Lambda+ CD10+
CD10 APC-A
sLambda PE-A
Low SSC
Count
sKappa FITC-A
Low SSC
Count
sLambda PE-A
Low SSC
Count
CD5 PerCP-Cy5-5-A
Low SSC
Count
CD23 PE-Cy7-A
Low SSC
Count
CD10 APC-A
Low SSC
Count
CD20 APC-H7-A
Low SSC
Count
CD19 BV421 Pacific Blu

FISH Studies

nuc ish(**BCL6x3~4)[64/200],(MYCx3~4)[65/200]/(D8Z1x2~4,MYCx3~4,IGHx3~6)[165/200],**
(IGHx3~6,BCL2x2~4)[166/200]

Interphase FISH assays ruled out the presence of BCL6, MYC, MYC-IGH and IGH-BCL2 gene rearrangements in this sample.

FINAL DIAGNOSIS:

A & B. Brain tumor:

Diffuse large B-cell lymphoma, in brain. See note.

Note: The immunohistochemical profile of this DLBCL is consistent with a DLBCL of the germinal center B-cell subtype (BCL6+, CD10+, MUM1+, Hans' classifier). Differential diagnoses include a primary diffuse large B-cell lymphoma of the CNS versus CNS involvement by a systemic DLBCL. CD10 is expressed infrequently (<10%) by primary CNS DLBCL, but its expression is more frequent in systemic DLBCL. Thus, the strong CD10 positivity seen in this DLBCL raises the possibility of CNS dissemination by a systemic DLBCL. Therefore, clinical correlation, including thorough evaluation for a systemic DLBCL, is recommended.

June 2019: Work-up showed no other sites of disease

Treated with 6 cycles of R-MVP

(rituximab, methotrexate, procarbazine, vincristine)

Summer/Fall 2019: Interim/end of treatment MRIs showed decreased disease with improved mental status

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CSF flow cytometry: small population of kappa-restricted, CD10+ B cells

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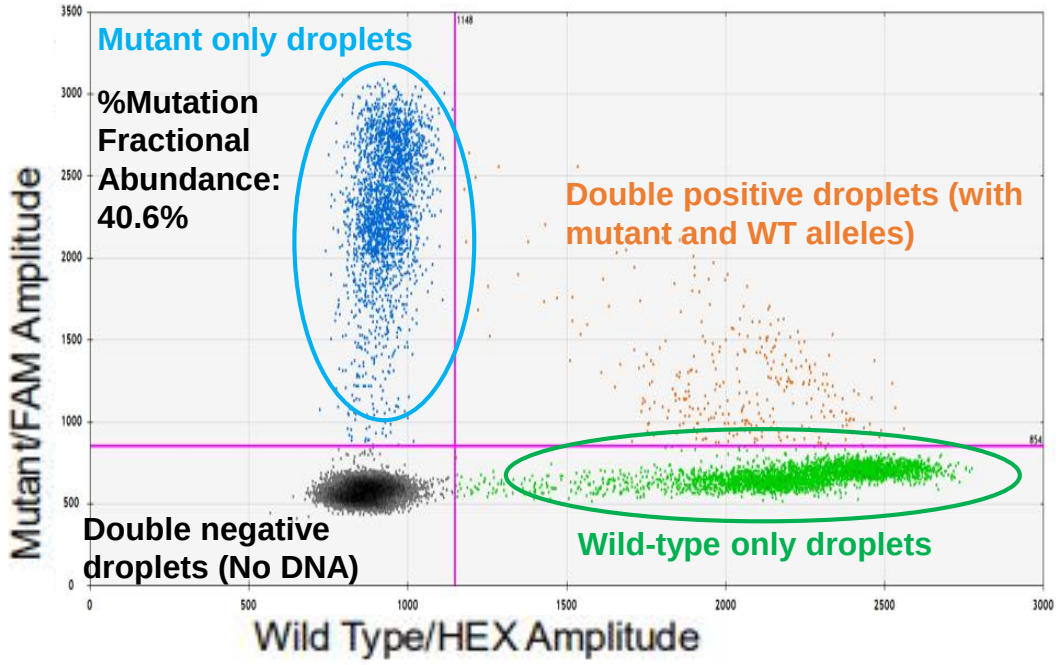
Molecular testing for *MYD88* mutation was done

MYD88 Testing

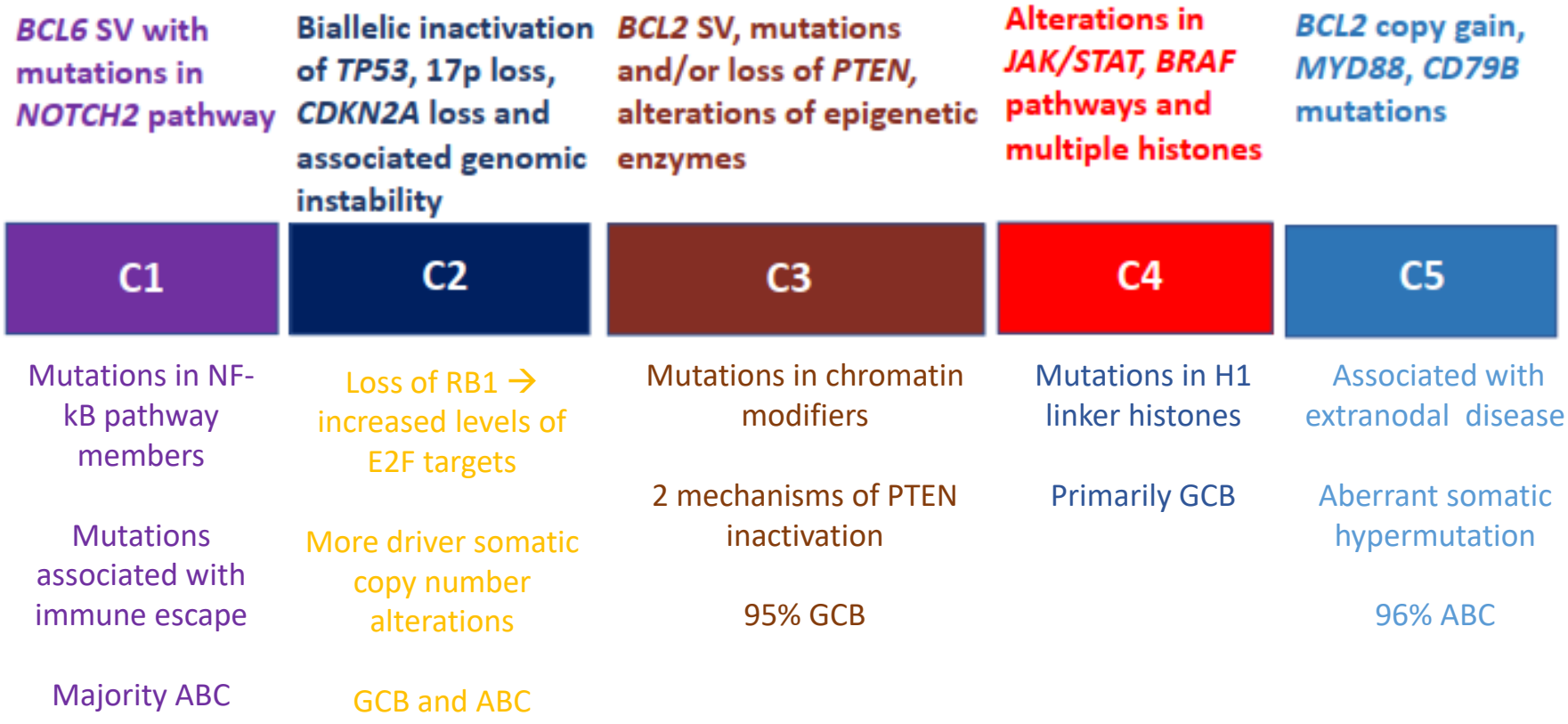
(Quantitative droplet digital PCR)



$$\text{\% Mutation Fractional Abundance} = \frac{\text{Mutant Droplets}}{\text{Mutant Droplets} + \text{Wild Type Droplets}} \times 100$$

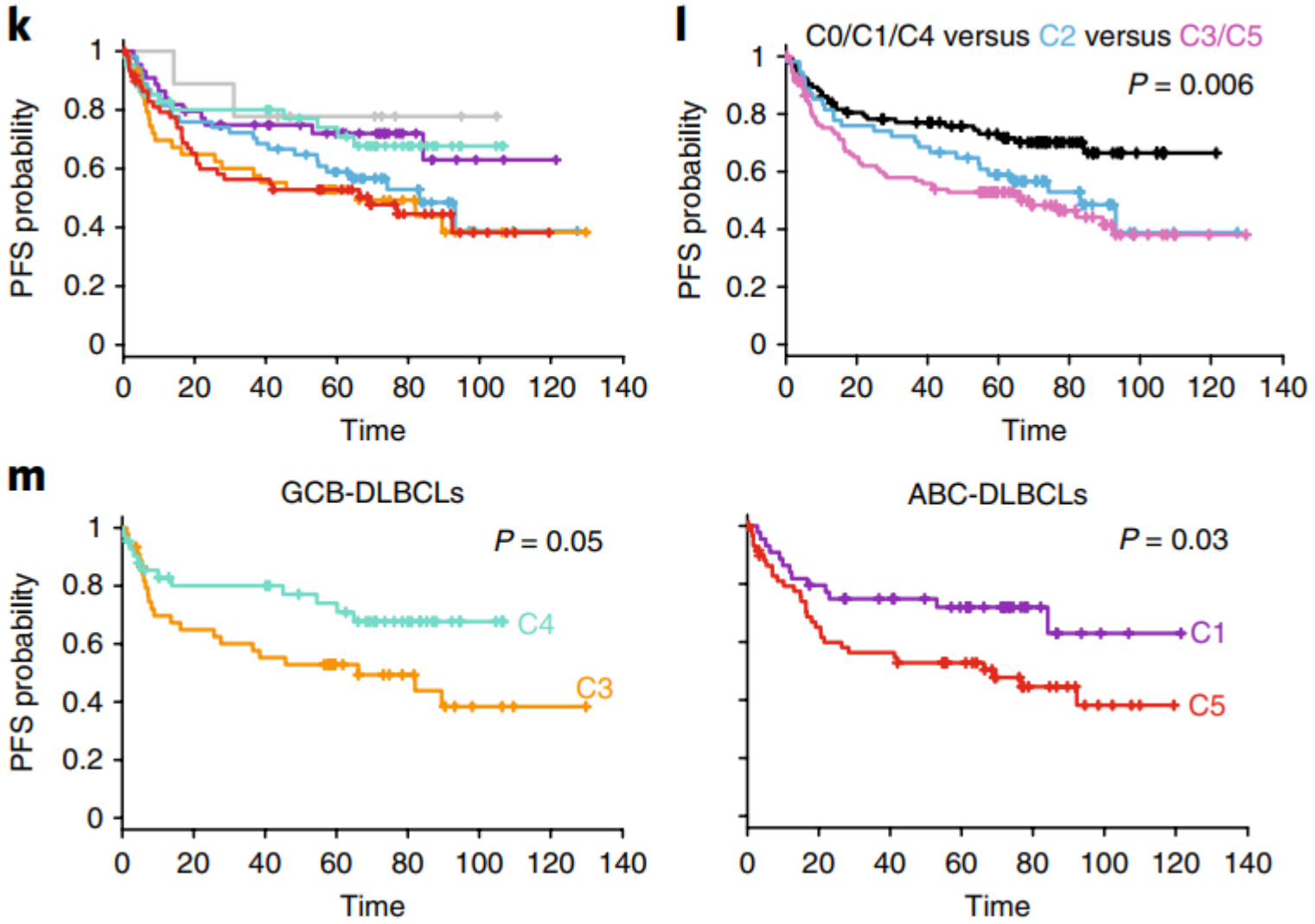
Harvard classification

Harvard study
- Retrospective
- WES, copy number changes and translocation
- R-CHOP like treatment



Graphic modified from Dr. Liu USCAP 2023 SC42 based on Chapuy et al. (2018), *Nat Med*

Genetic subtypes and outcome

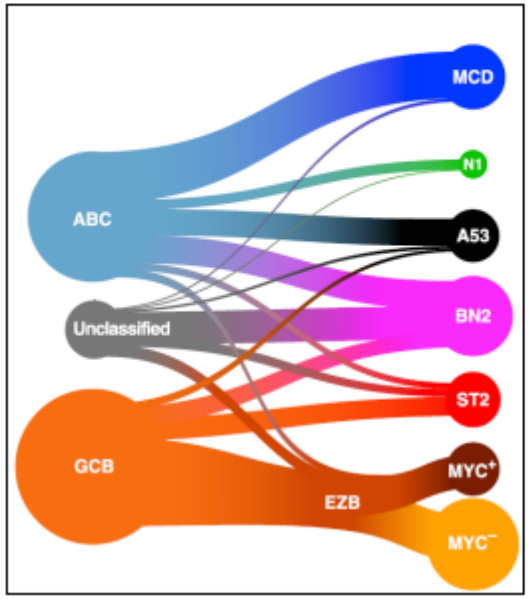


C1: ABC
C2: Both
C3: GCB
C4: GCB
C5 ABC

Chapuy et al. (2018), *Nat Med*

LymphGen

- 6 genetic subtypes of DLBCL were proposed:
  - MCD (*MYD88*L265P and *CD79B* mutations)
  - BN2 (*BCL6* translocations and *NOTCH2* mutations)
  - N1 (*NOTCH1* mutations)
  - EZB (*BCL2* translocations and *EZH2* mutations)
  - A53 (aneuploid with *TP53* inactivation)
  - ST2 (*SGK1* and *TET2* mutations)



Harvard classification

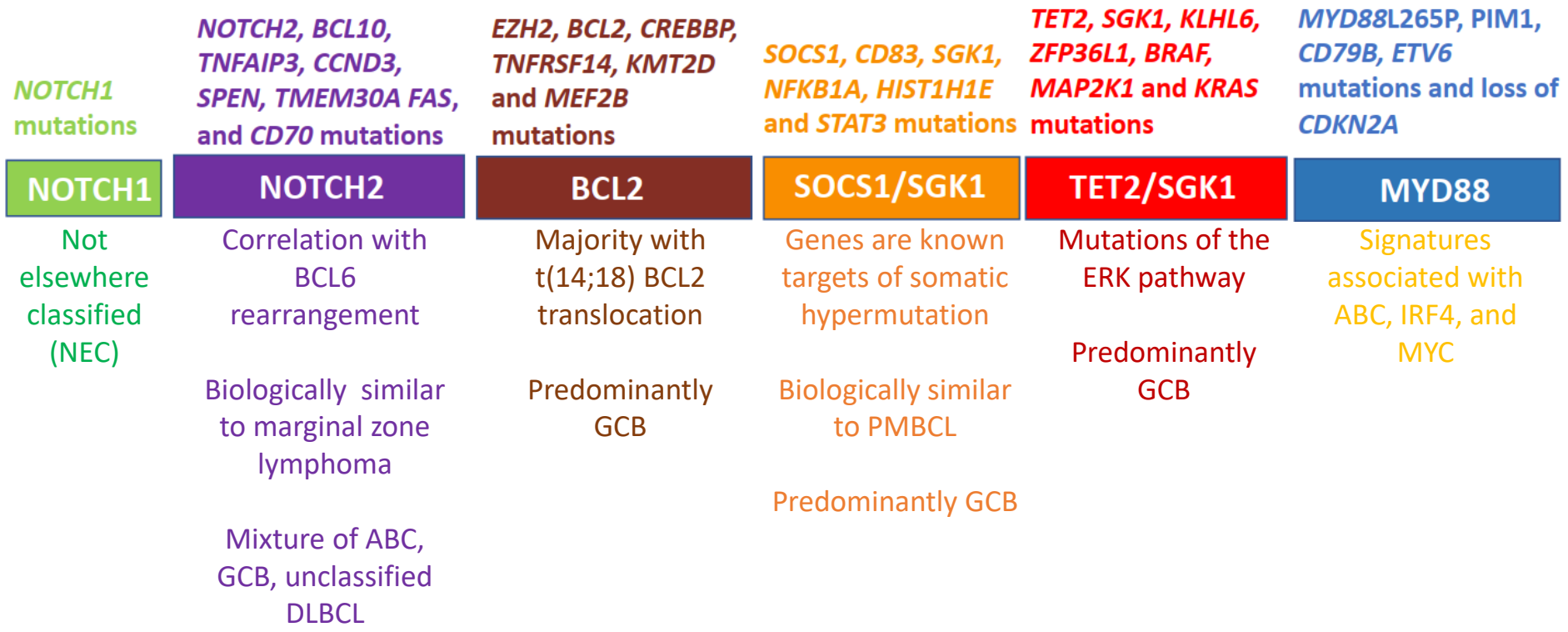
BCL6 SV with mutations in *NOTCH2* pathway	Biallelic inactivation of *TP53*, 17p loss, *CDKN2A* loss and associated genomic instability	*BCL2* SV, mutations and/or loss of *PTEN*, alterations of epigenetic enzymes	Alterations in *JAK/STAT, BRAF* pathways and multiple histones	*BCL2* copy gain, *MYD88, CD79B* mutations
C1	C2	C3	C4	C5

Cancer Cell. 2020 Apr 13;37(4):551-568.

UK Haematological Malignancy Research Network (HMRN) classification

UK HMRN classification

- Prospective
- Based predominantly on target panel mutation analysis; copy number changes are considered for a small number of genes-> **cannot reliably identify aneuploidy**
- Modified classification used the presence of *MYC* hotspot and *NOTCH1* PEST domain mutations
- Including a subset patients with R-CHOP full treatment



Graphic modified from Dr. Liu USCAP 2023 SC42 based on Lacy et al. (2020), *Blood*

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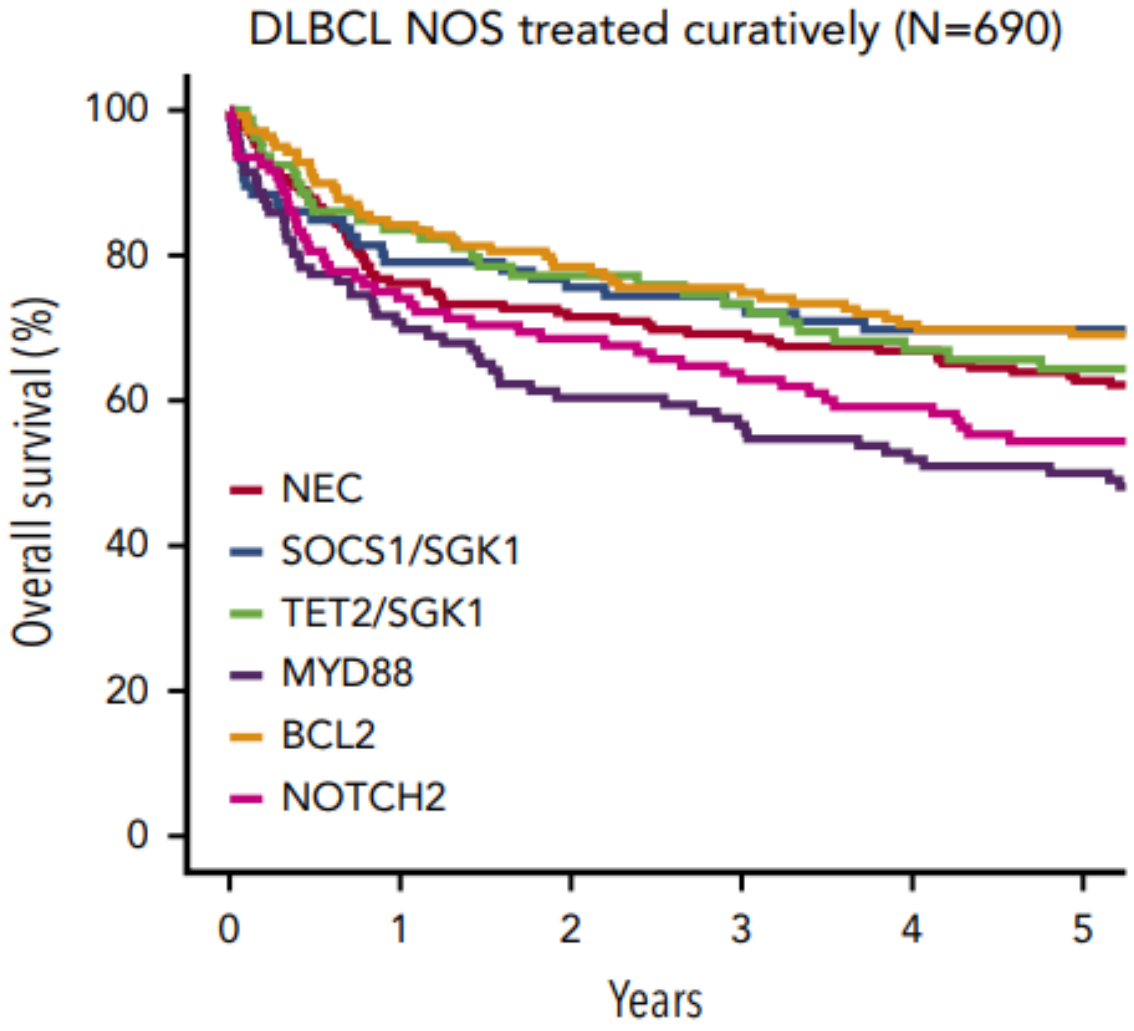
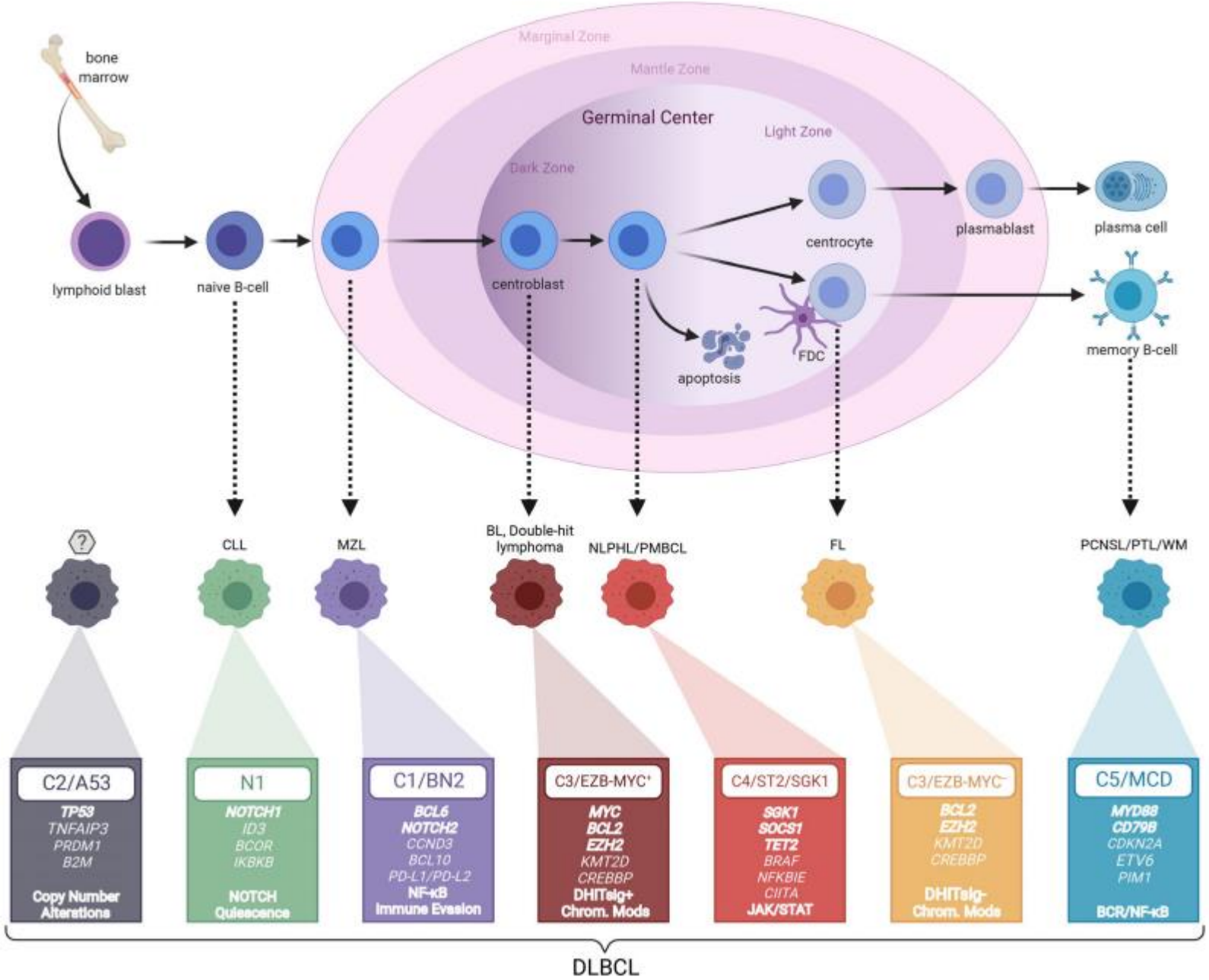


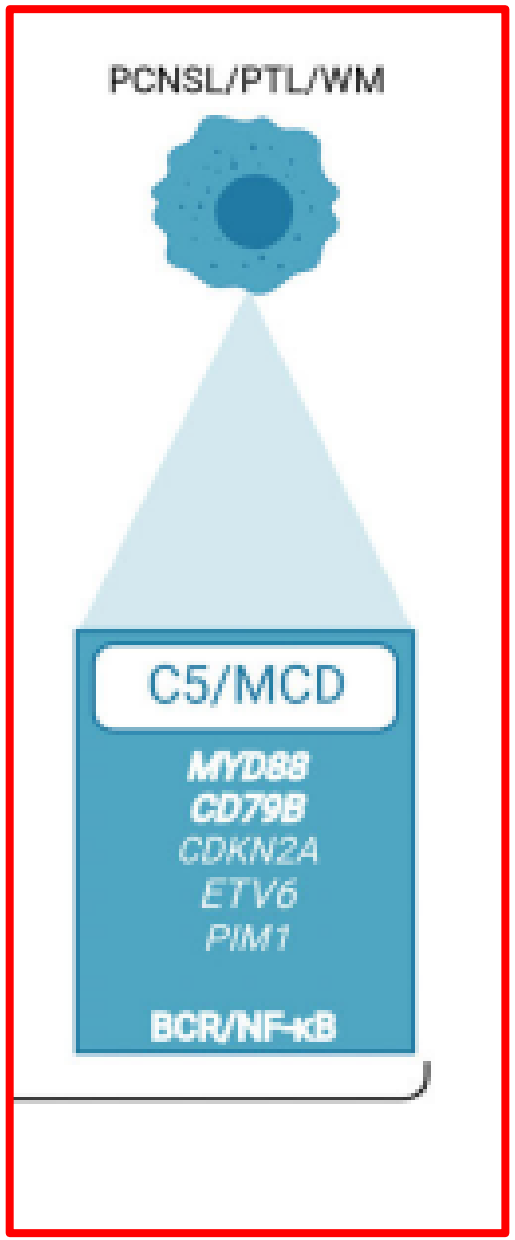
Better outcomes in SOCS1/SGK1, BCL2, and TET2/SGK1 clusters (**GCB**)

Intermediate survival for NEC and NOTCH2 clusters (**mix**)

Poor outcome in for MYD88 cluster (**ABC**)

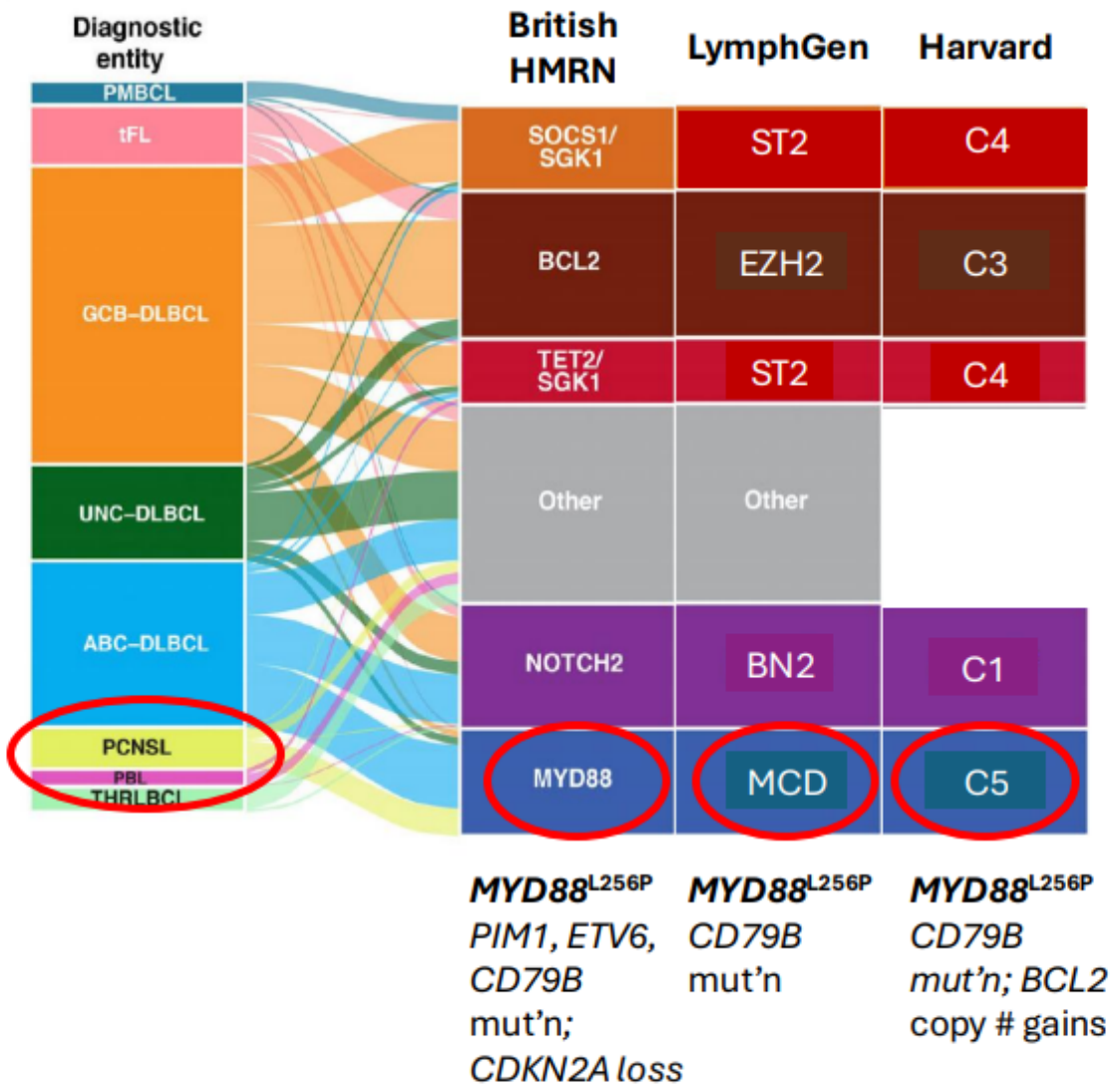
Lacy et al. (2020), *Blood*





Morin et al. (2022), *Br J Haematol*.

MYD88 Testing



***MYD88*^{L256P}** *PIM1, ETV6, CD79B* mut'n; *CDKN2A loss*

***MYD88*^{L256P}** *CD79B* mut'n

***MYD88*^{L256P}** *CD79B mut'n; BCL2* copy # gains

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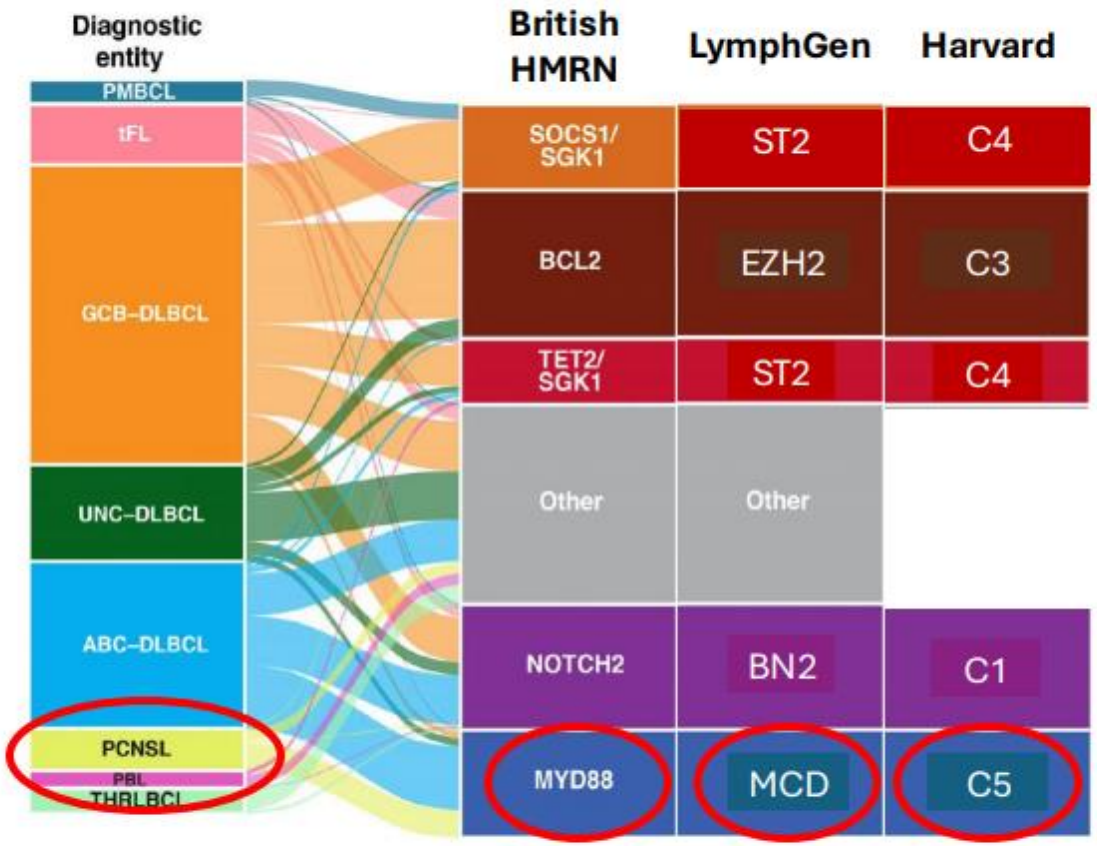

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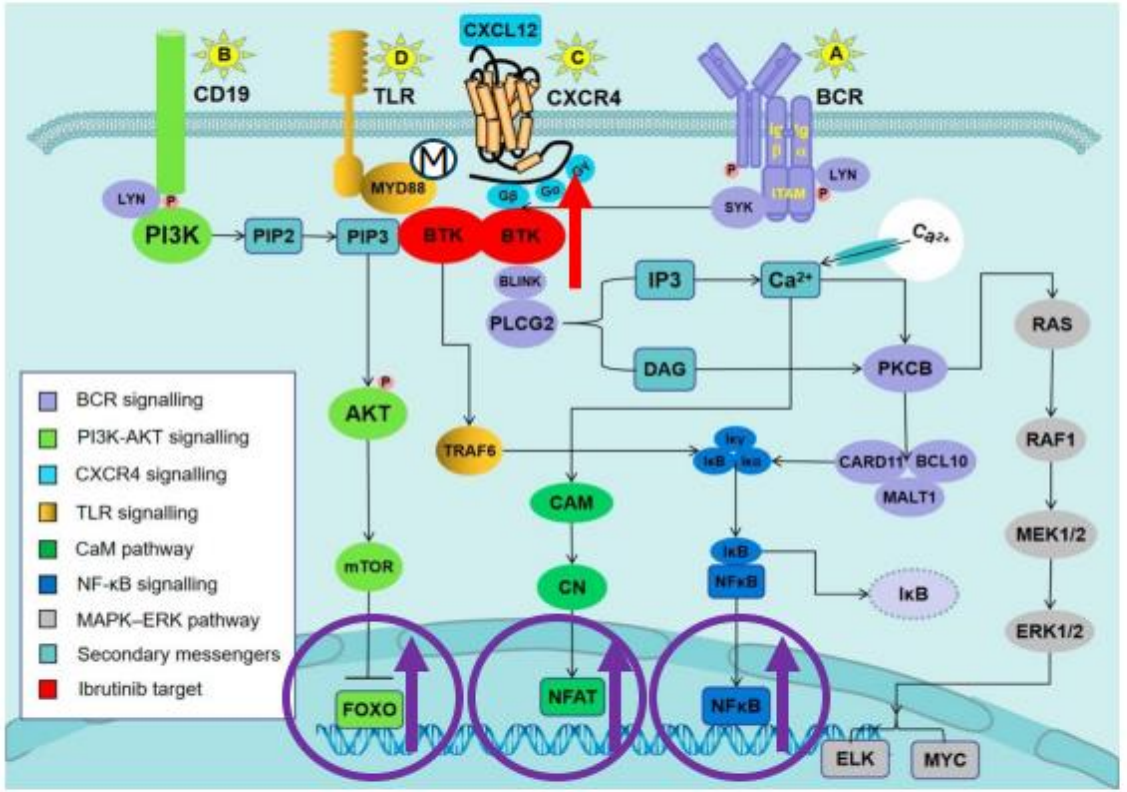

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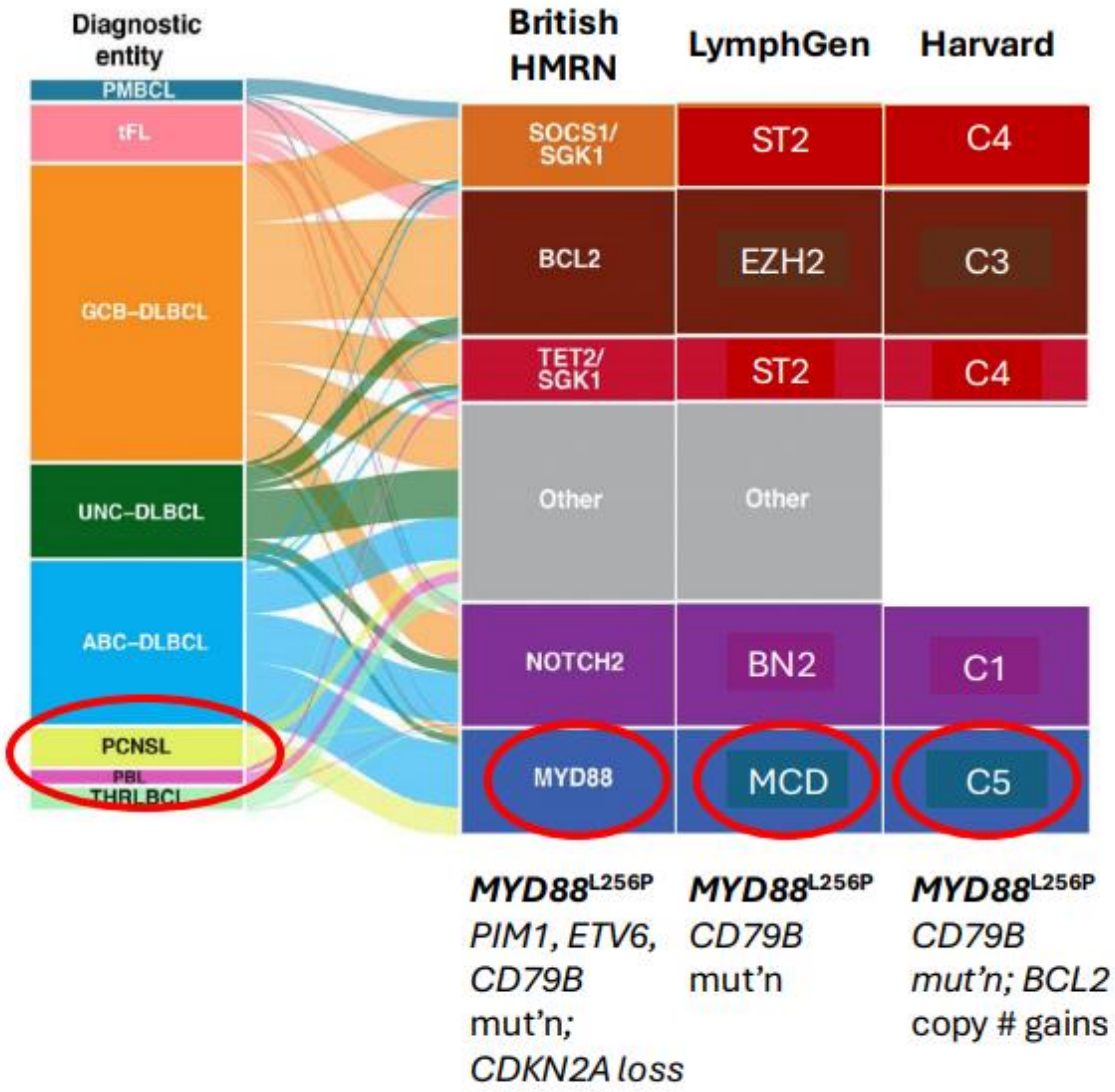

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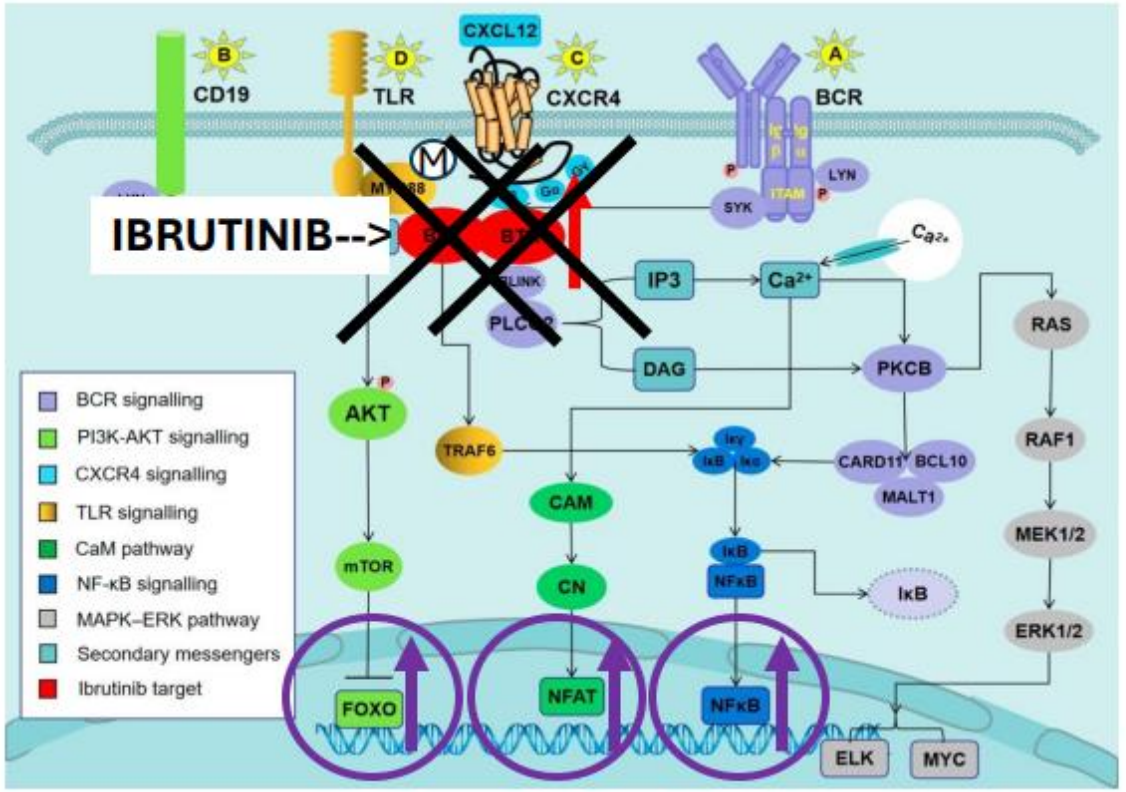

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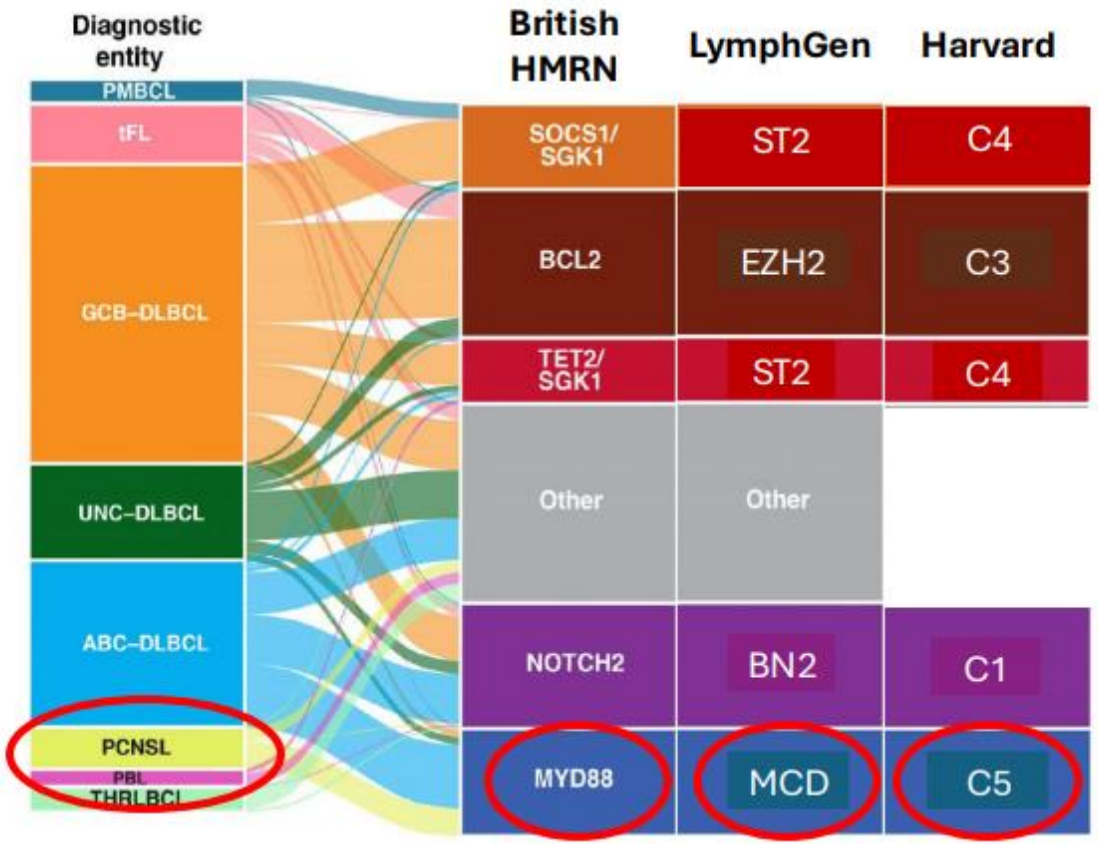

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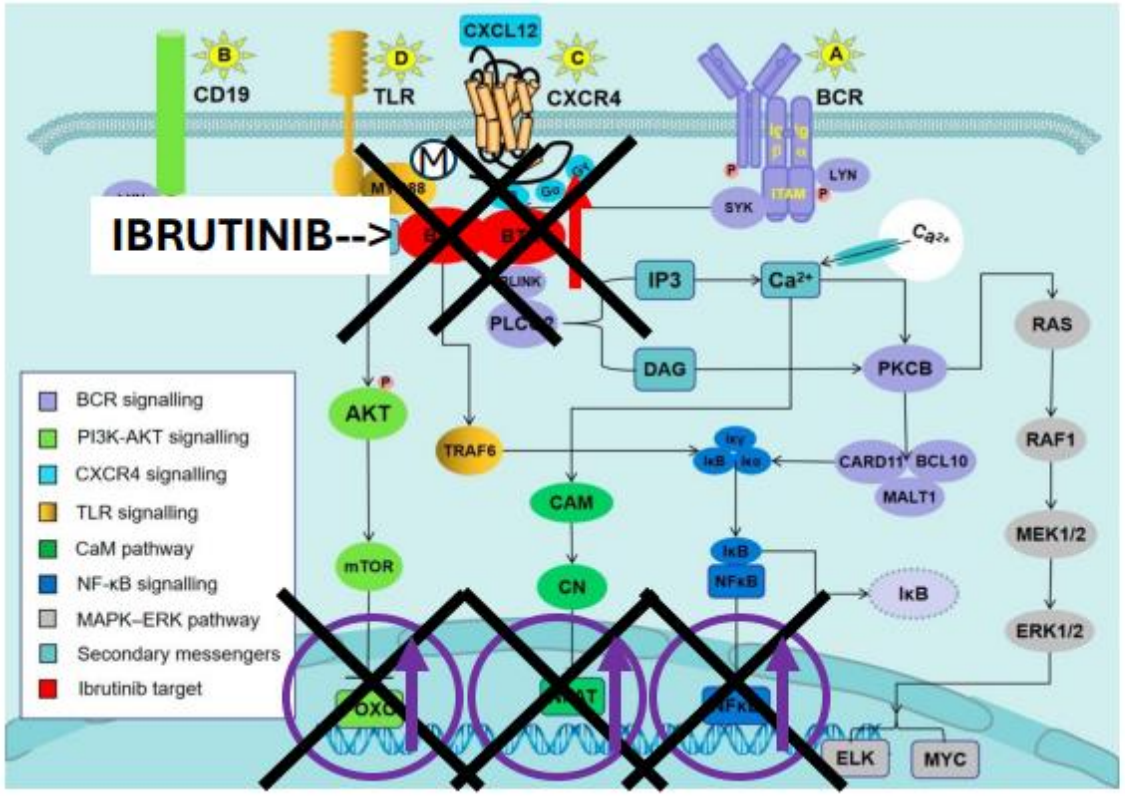

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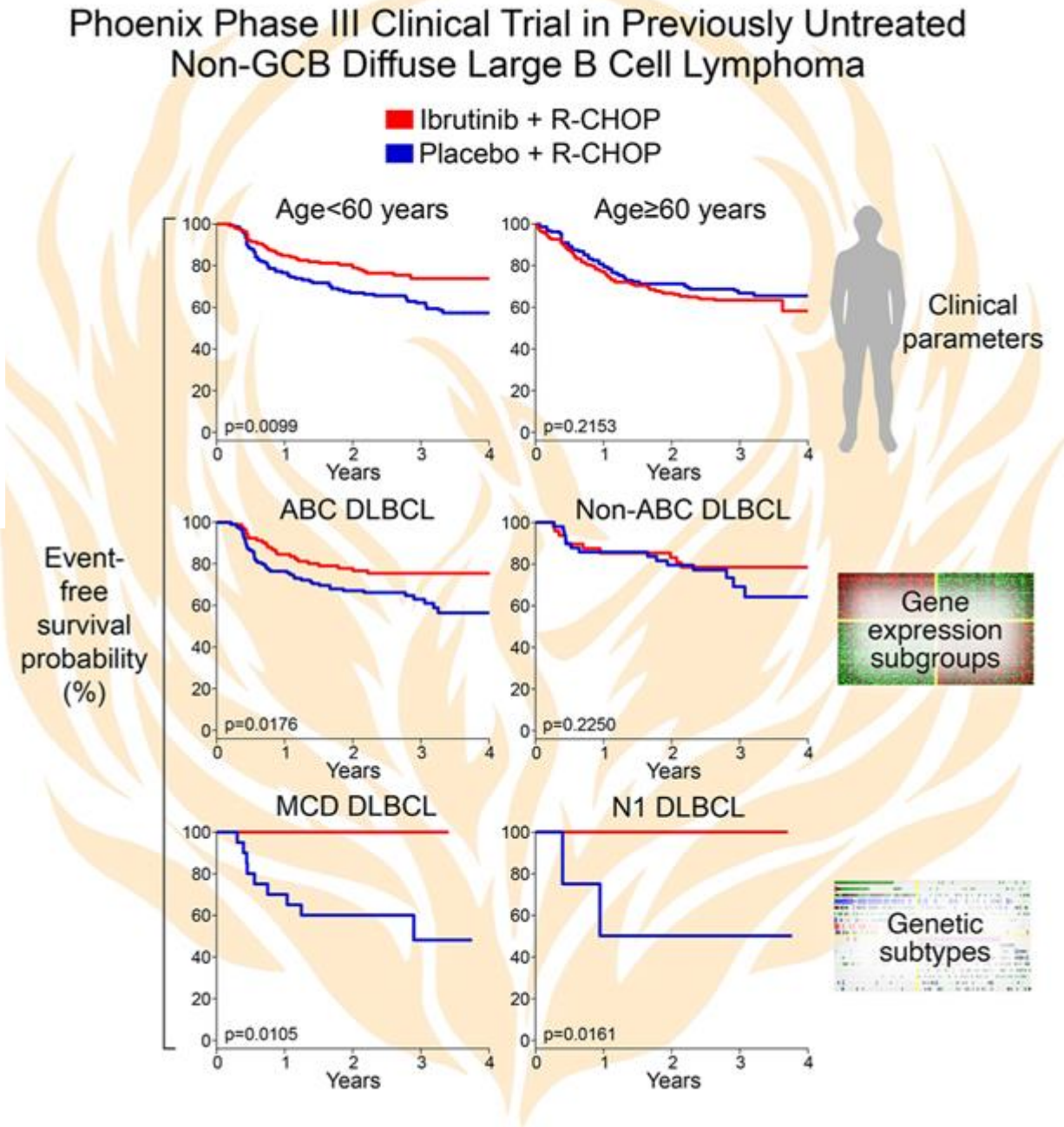
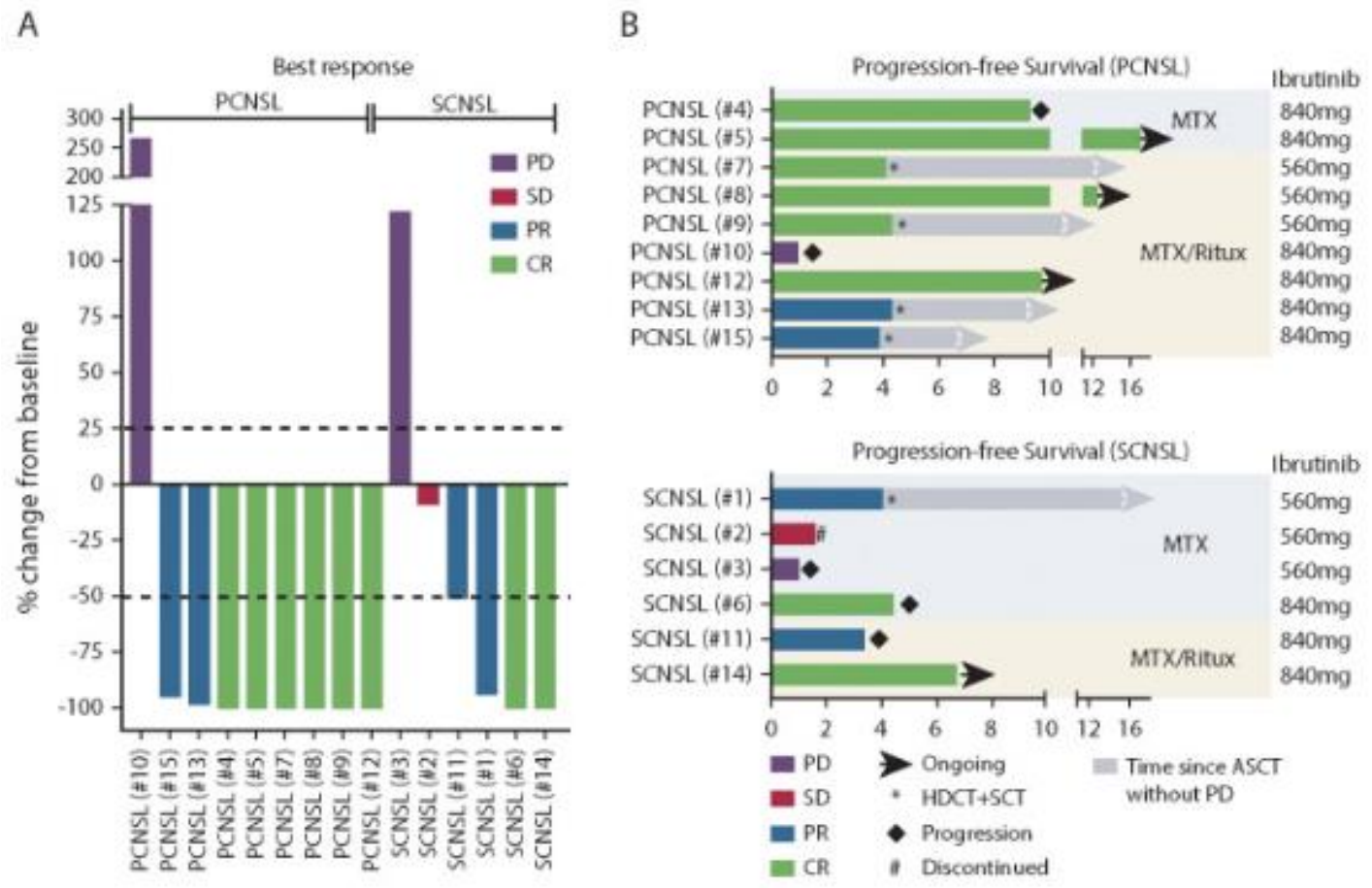
Two genetic subtypes of DLBCL – MCD and N1 – have 100% survival when treated with the BTK inhibitor ibrutinib plus R-CHOP chemotherapy but ≤50% survival when treated with R-CHOP alone.



Wilson et al. (2021), *Cancer Cell*.

Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma



- Explored the sequential combination of ibrutinib with high-dose methotrexate (HD-MTX) and rituximab in patients with R/R CNS lymphoma (both primary and secondary
- Eight of 9 (89%) primary CNS lymphoma patients and 4 of 6 (67%) secondary CNS lymphoma patients responded to ibrutinib-based combination therapy.

Grommes et al. (2019), *Blood*.

Patient started on TEDDI-R + brain XRT

(temozolomide, etoposide, doxorubicin, dexamethasone, ibrutinib, and rituximab)

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MRI showed no evidence of CNS lymphoma

PET-CT showed no evidence of extra-CNS disease

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Last follow-up: No evidence of disease

Thank you