10th POSTGRADUATE
Lymphoma
Conference

Capturing and targeting the molecular heterogeneity in DLBCL

David Scott

BC Cancer and University of British Columbia

Venice,
March 12-13, 2026

Hotel Monaco & Grand Canal

President:
P.L. Zinzani

Disclosures

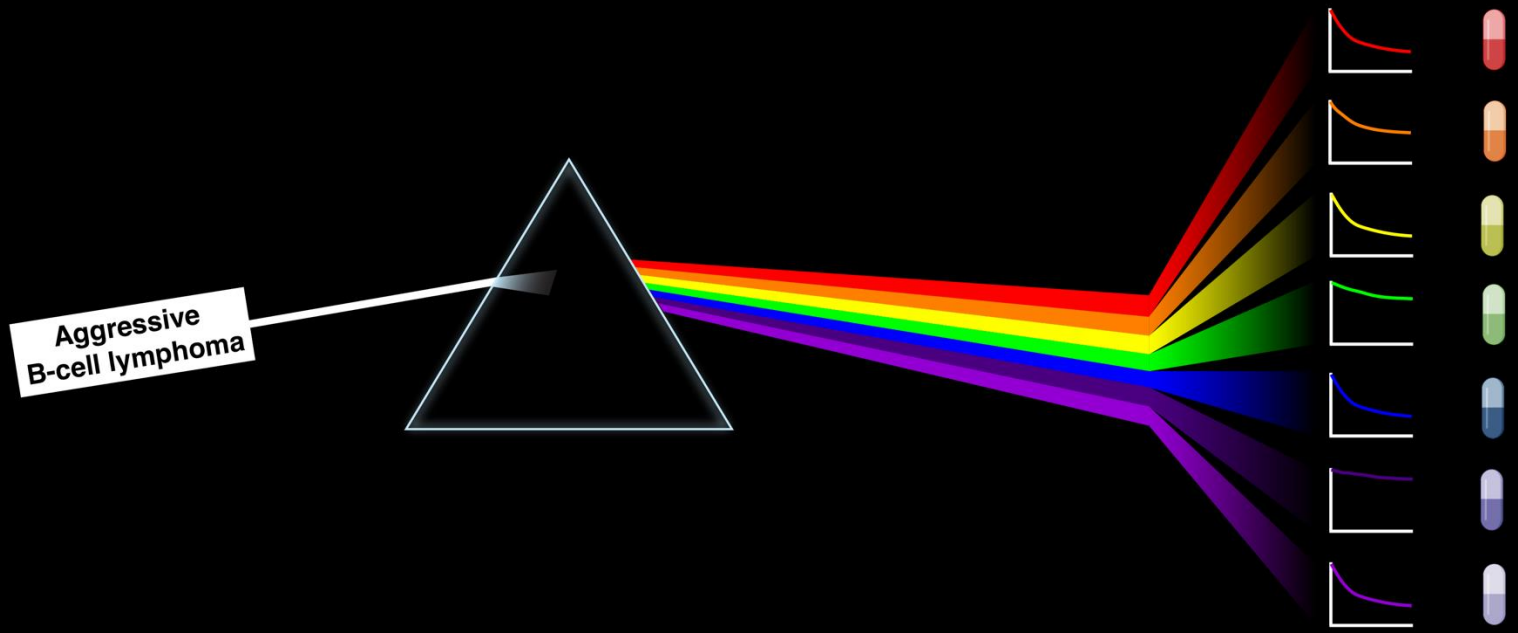
Disclosures of David Scott

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X				
AstraZeneca			X				
Chugai			X				
GenMab			X				
Lilly			X				
Kite/Gilead			X				
Roche/Genentech	X		X				
Veracyte			X				

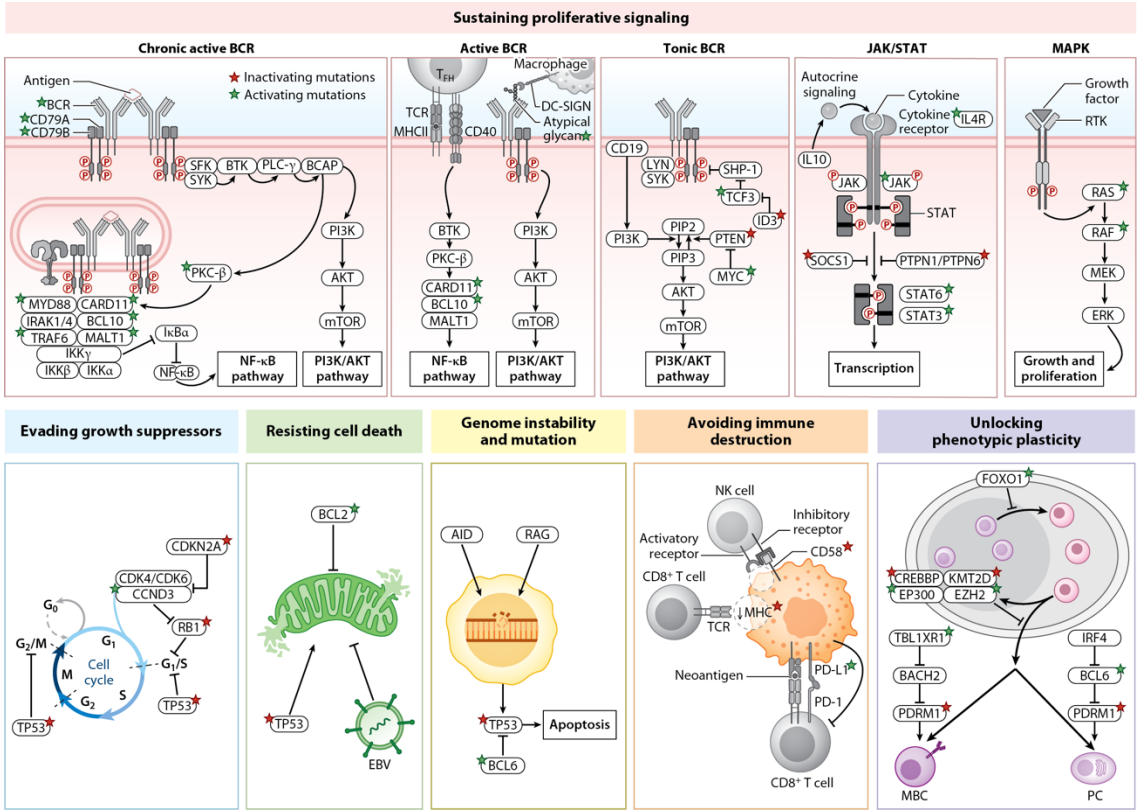
Named inventor on patents describing the use of gene expression profiling to subtype aggressive B-cell lymphomas, one of which is licensed to nanoString Technologies

Outline

- Organizing molecular heterogeneity
- Current pathology classifications
- Gene expression subtypes – refined cell-of-origin
- Genetic subtypes – foundation for precision approaches
- Tumour microenvironment subtypes


Aggressive
B-cell lymphoma

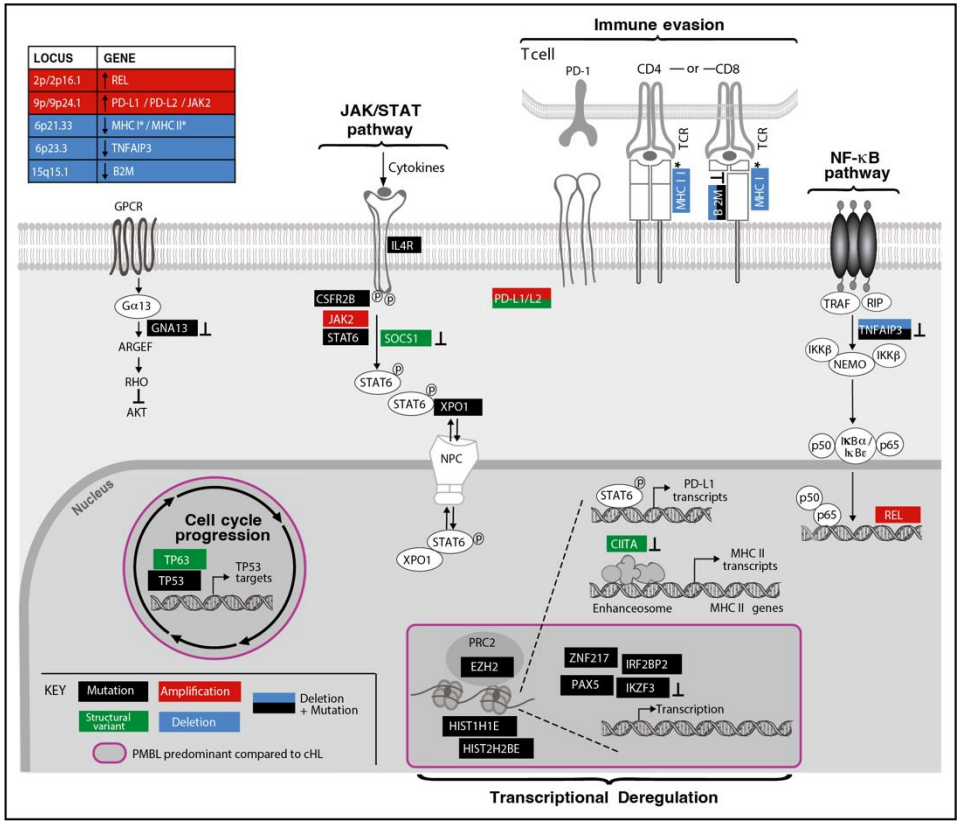
Organizing heterogeneity – maximizing utility



- **Linking biology to treatment**
- **Identifying how tumours attain lymphoma hallmarks**
- **Hijacking physiological B-cell programs and states**
  - **Direct effects – genetic aberrations**
  - **Indirect effects – differentiation blocks**
  - **Tumour-host interactions**

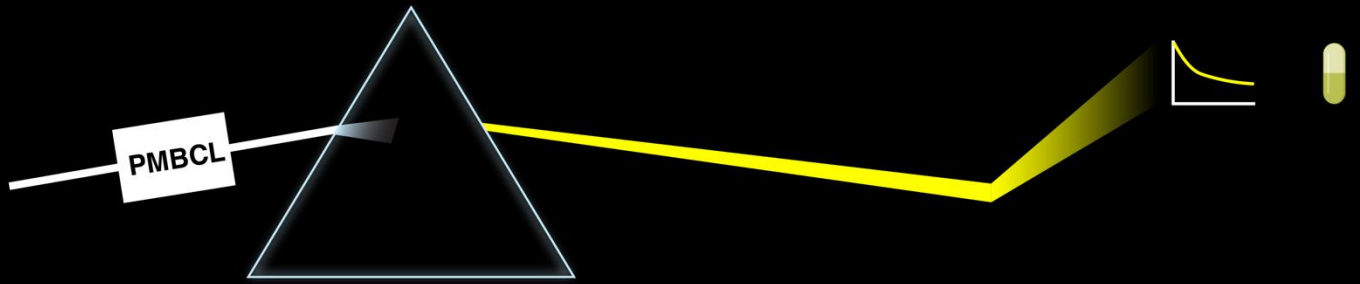
Hilton, Collinge, Scott Annu Rev Pathol 2026

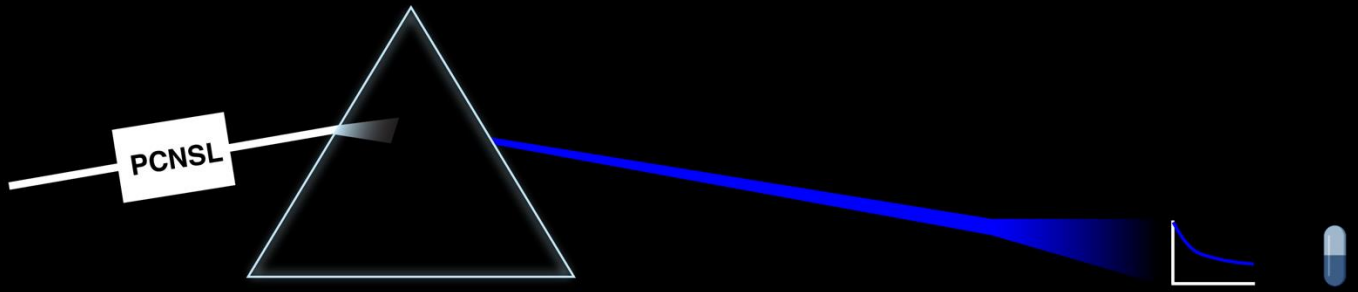
Primary mediastinal large B-cell lymphoma

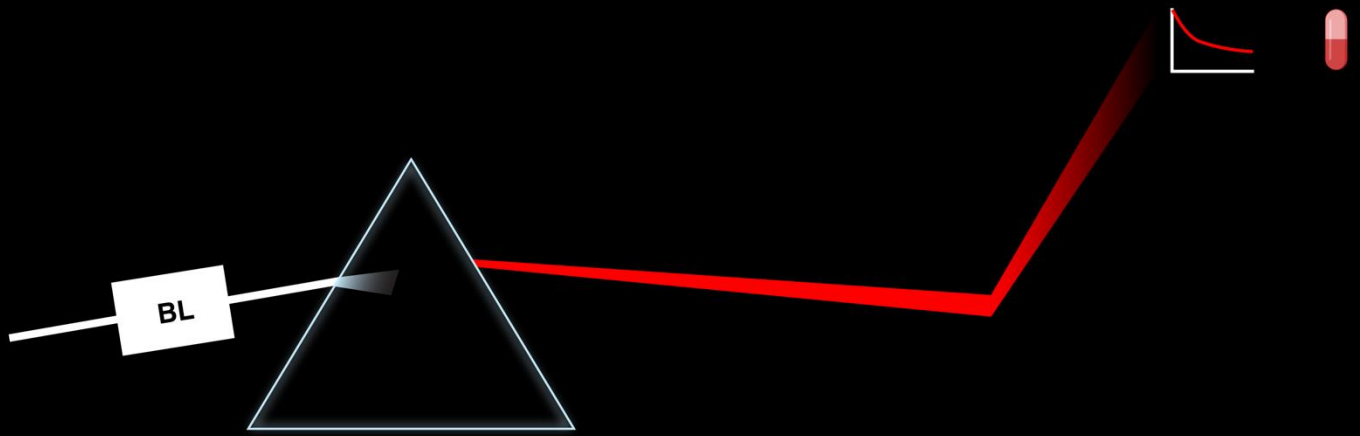


Mottok et al Blood 2019

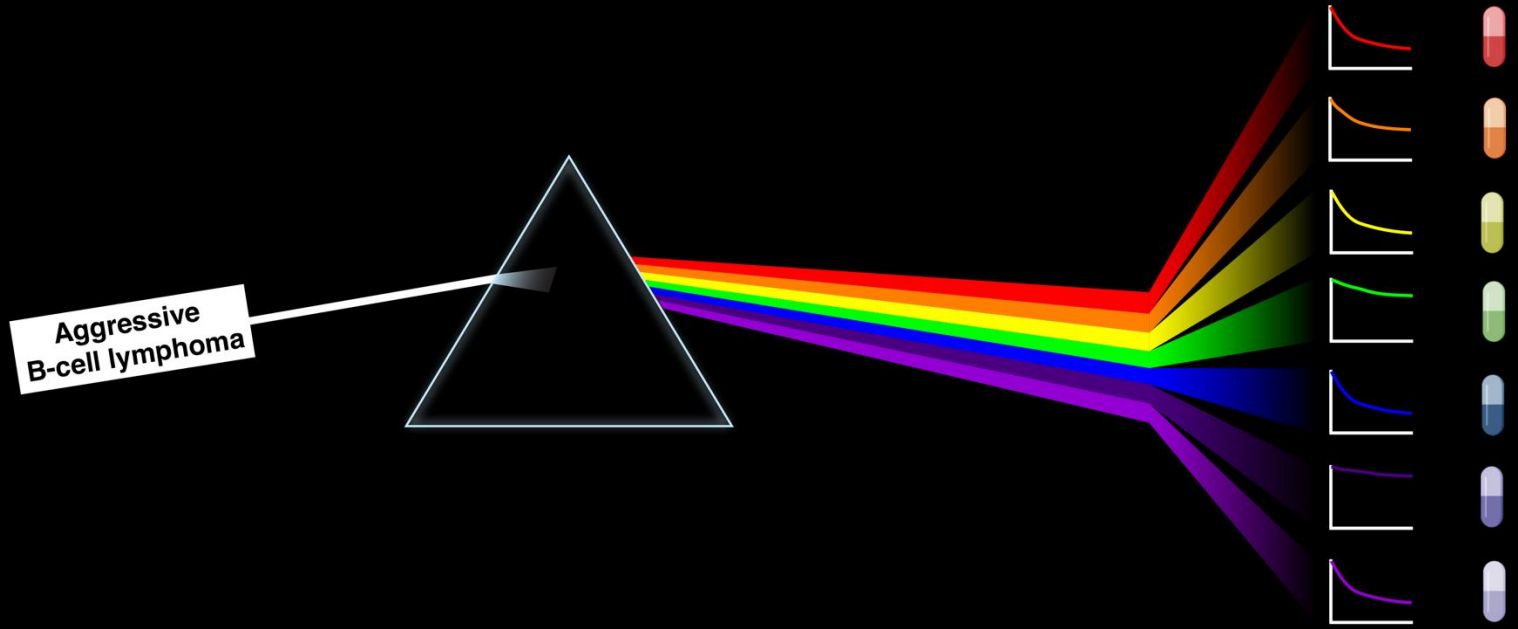
Chapuy et al Blood 2019


PMBCL


PCNSL


BL

In contrast to PMBCL and Burkitt lymphoma, the mutational landscape of diffuse large B-cell lymphoma is highly heterogeneous



In contrast to PMBCL and Burkitt lymphoma, the mutational landscape of diffuse large B-cell lymphoma is highly heterogeneous

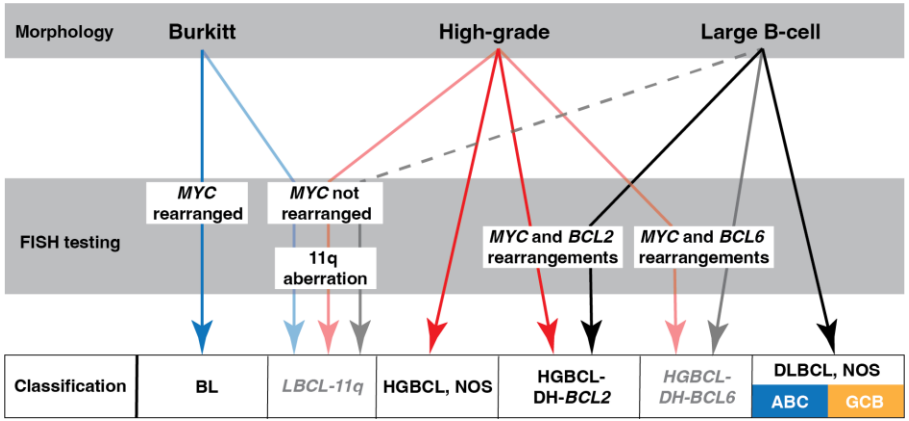
Do we improve outcomes in DLBCL by:

a) continuing to evolve the “one size fits all” approach

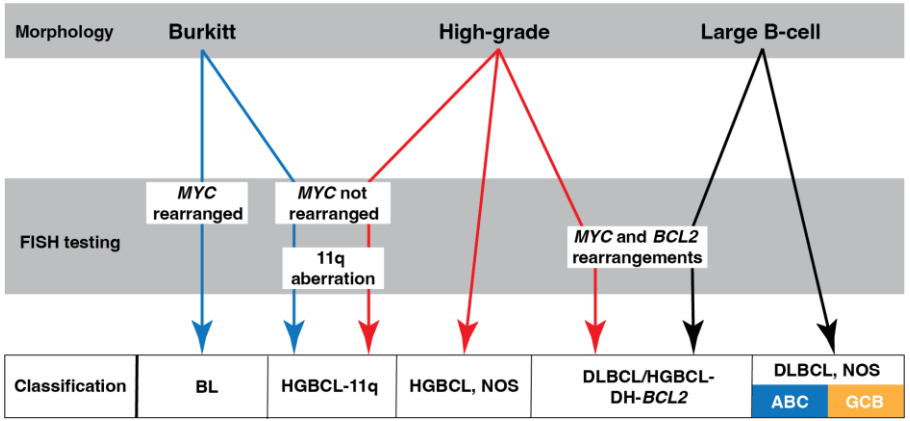
b) matching treatment to tumor biology - precision medicine

Aggressive B-cell lymphoma classification

International Consensus Classification



WHO HAEM5



Campo et al Blood 2022

Alaggio et al Leukemia 2022

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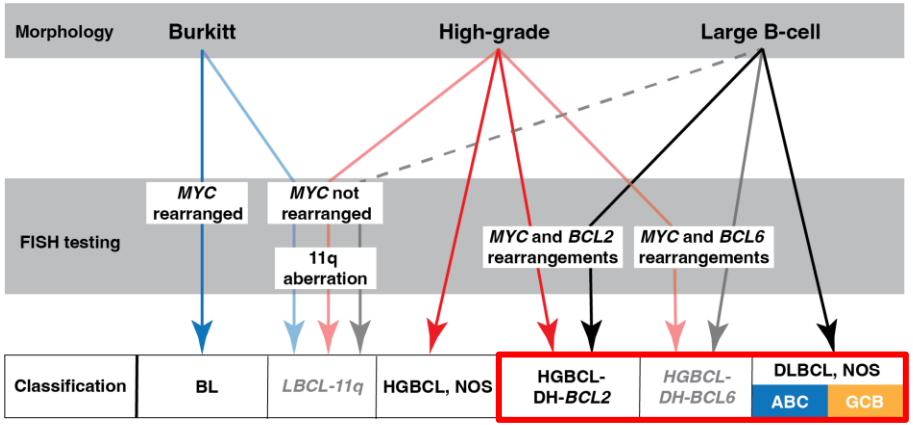

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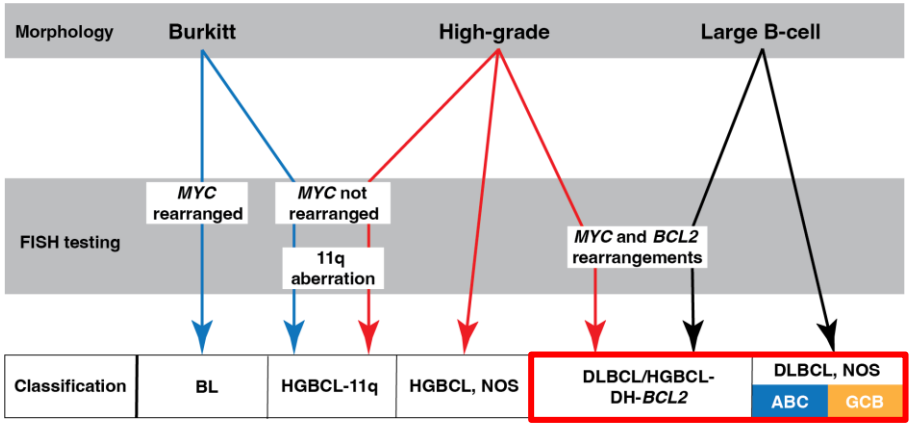
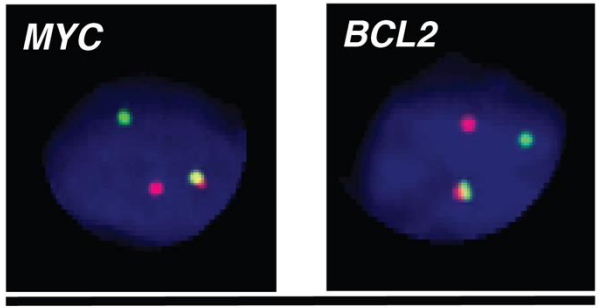


Campo et al Blood 2022

Alaggio et al Leukemia 2022

High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements – HGBCL–DH–*BCL2*



- Detected using FISH or (rarely) karyotype
- Translocations of both *MYC* and *BCL2*
- Can also harbor a *BCL6* rearrangement
- NOT copy number gains
- NOT dual protein expression of MYC and BCL2

Campo et al Blood 2022 *Alaggio et al Leukemia 2022* *Collinge et al Blood 2022*

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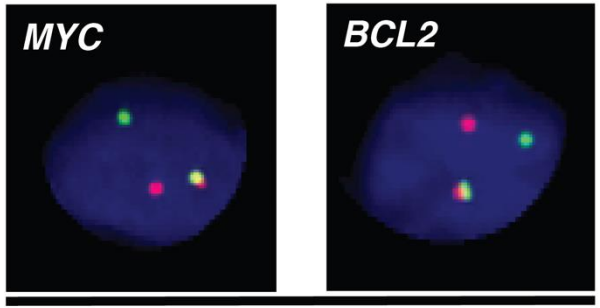

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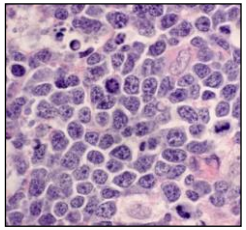
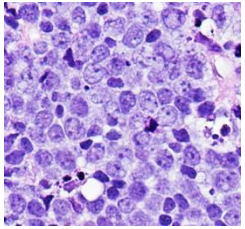
MORPHOLOGY – "High-grade"

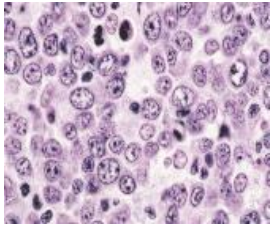
High-grade

Blastoid





Intermediate between DLBCL and Burkitt "BCLU"

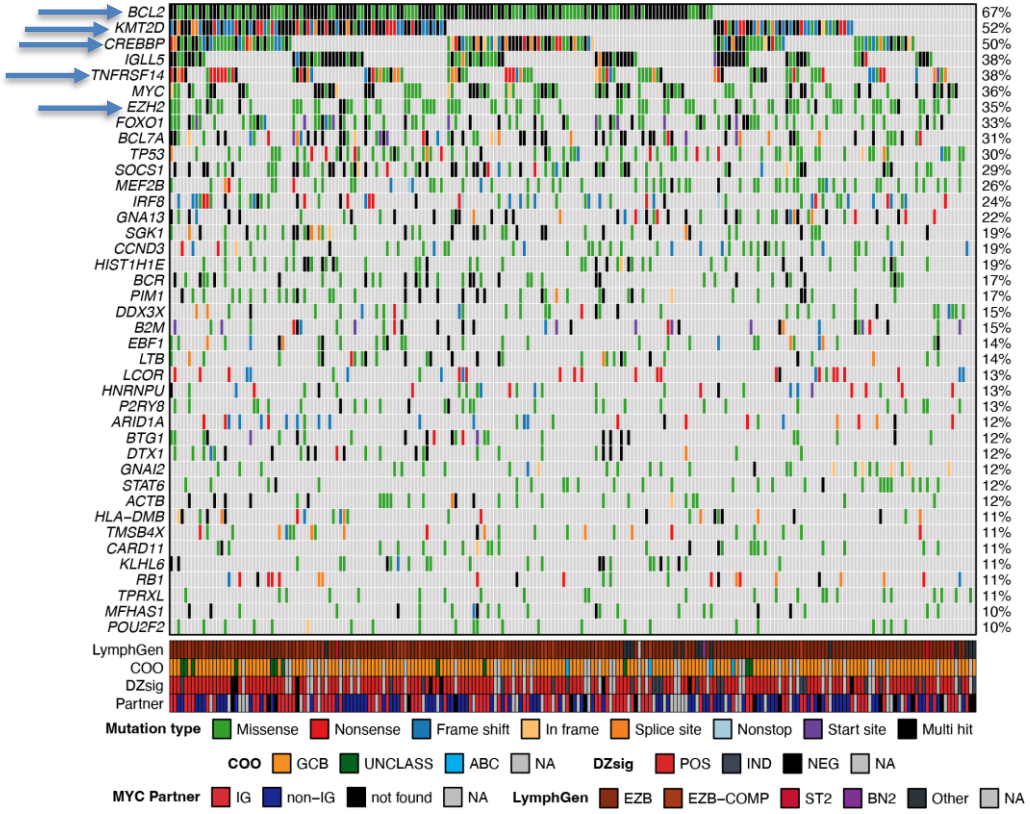


Diffuse large B-cell lymphoma

NOT follicular lymphoma

Campo et al Blood 2022 *Alaggio et al Leukemia 2022* *Collinge et al Blood 2022*

HGBCL-DH-*BCL2*: mutational landscape



- **Most recurrently mutated genes are shared with follicular lymphoma suggesting a common precursor cell population**

Fong, Collinge et al In preparation

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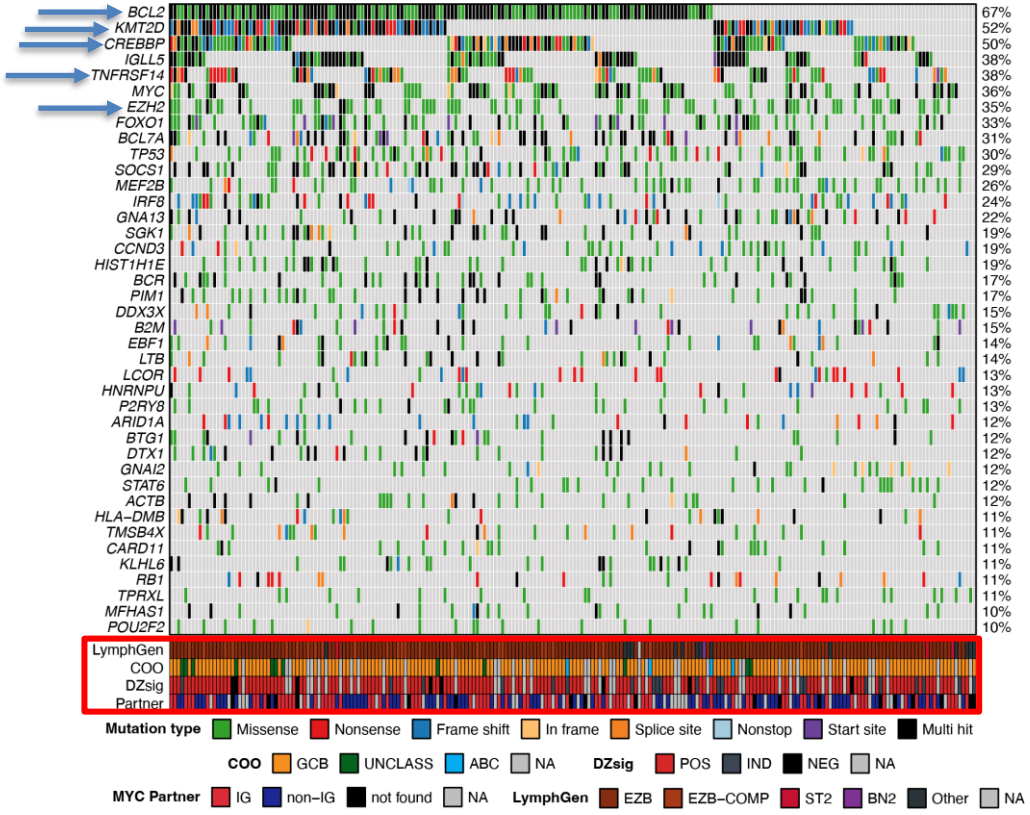

- **Most recurrently mutated genes are shared with follicular lymphoma suggesting a common precursor cell population**
- **Almost all are GCB, express the "dark zone" signature and are EZB genetic subgroup**

Fong, Collinge et al In preparation

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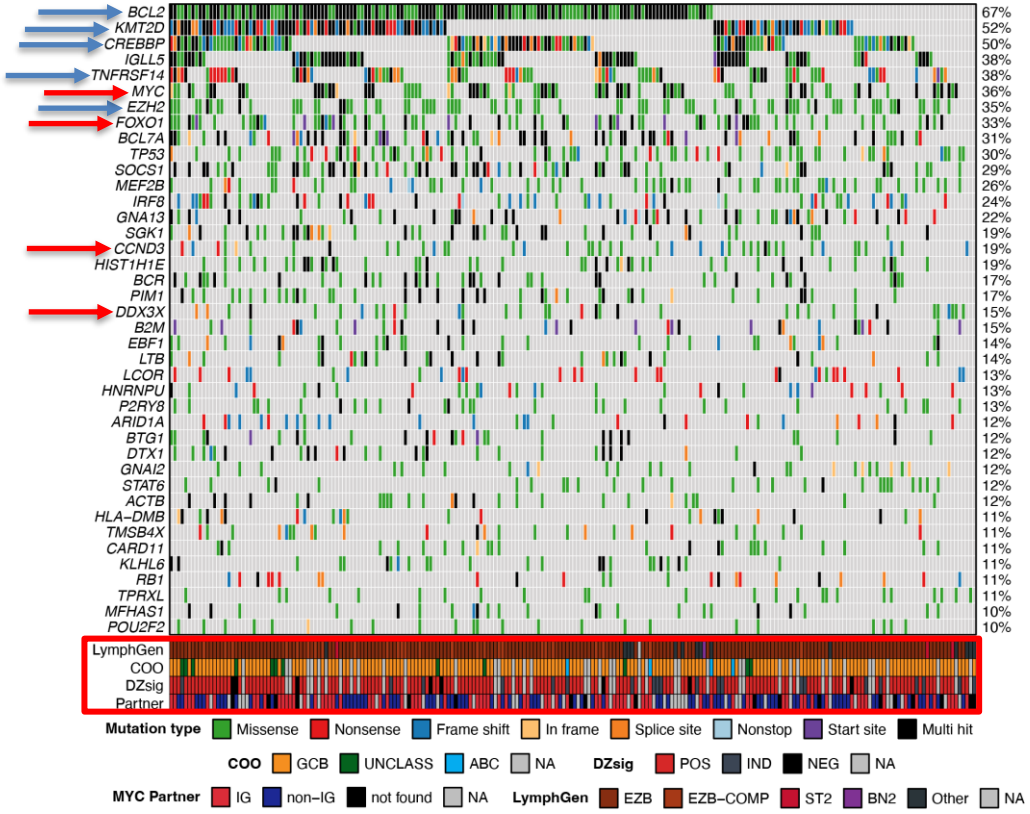
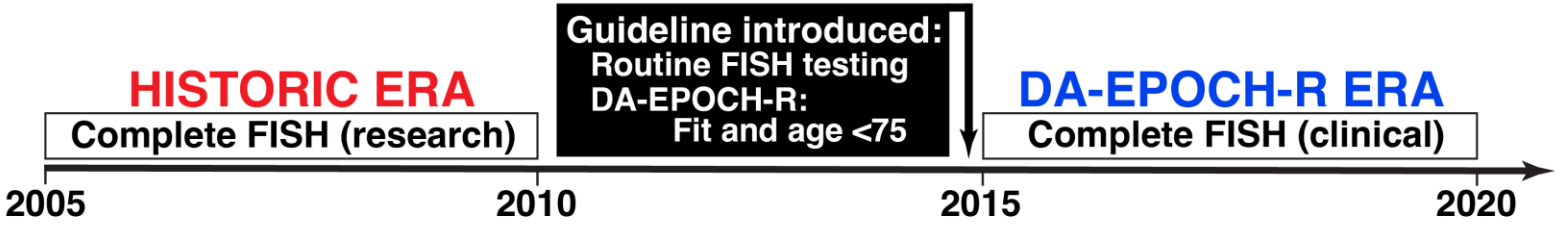
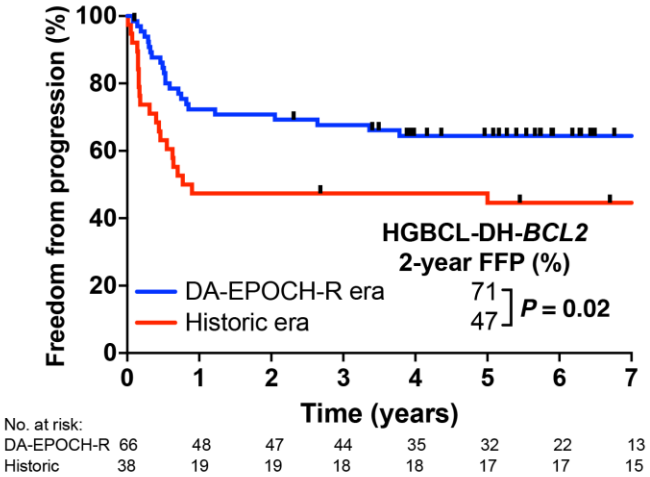


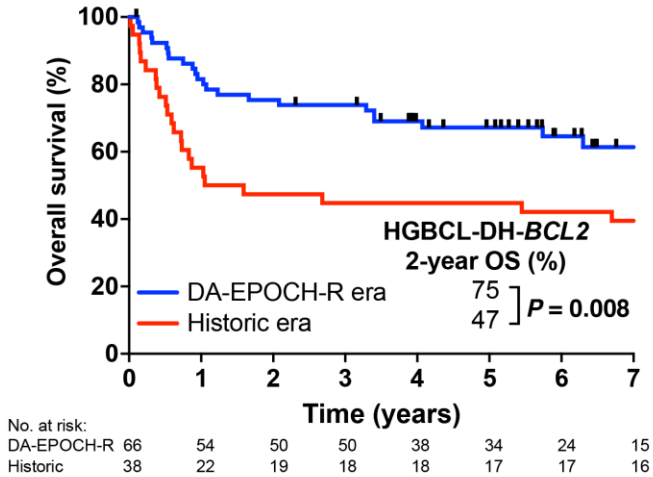
- **Most recurrently mutated genes are shared with follicular lymphoma suggesting a common precursor cell population**
- **Almost all are GCB, express the "dark zone" signature and are EZB genetic subgroup**
- **Shared mutations with Burkitt lymphoma – genes that regulate the dark zone of the germinal centre**

Fong, Collinge et al In preparation

Intensification is associated with better outcomes

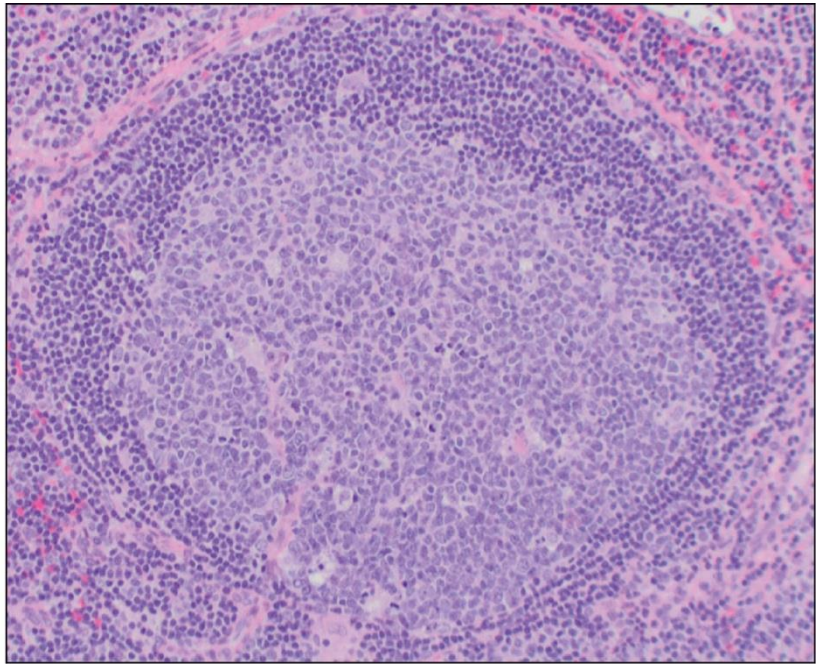






Alduaij et al
Blood Adv 2026

Gene expression - Cell-of-Origin classification



- Comparison of gene expression of tumors with B cells at different stages of differentiation
- Clustering approach producing binary groups – tumours that "look like" (phenocopy) germinal center B cells (GCB) vs those that don't (ABC)

Alizadeh et al Nature 2000 *Rosenwald et al N Eng J Med 2002* *Lenz et al N Eng J Med 2008*

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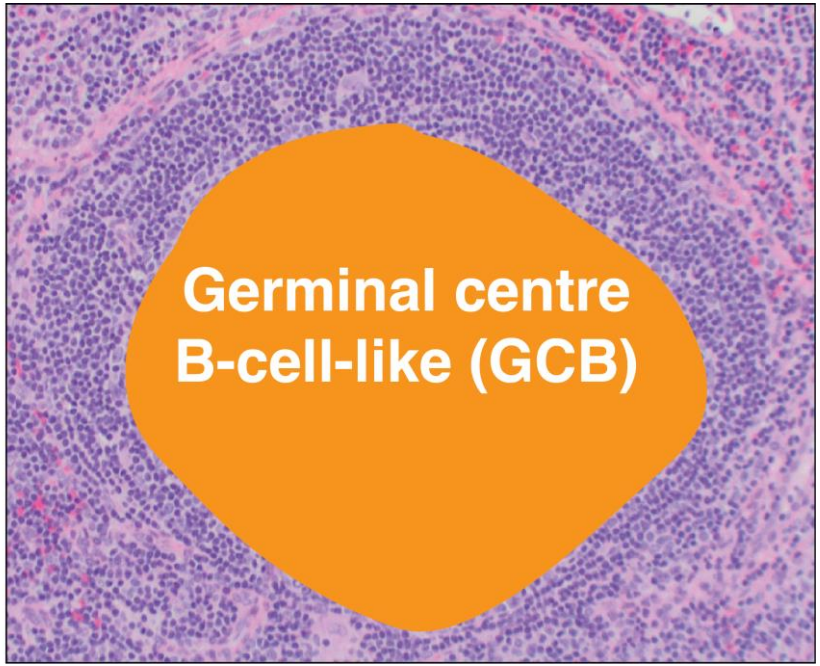

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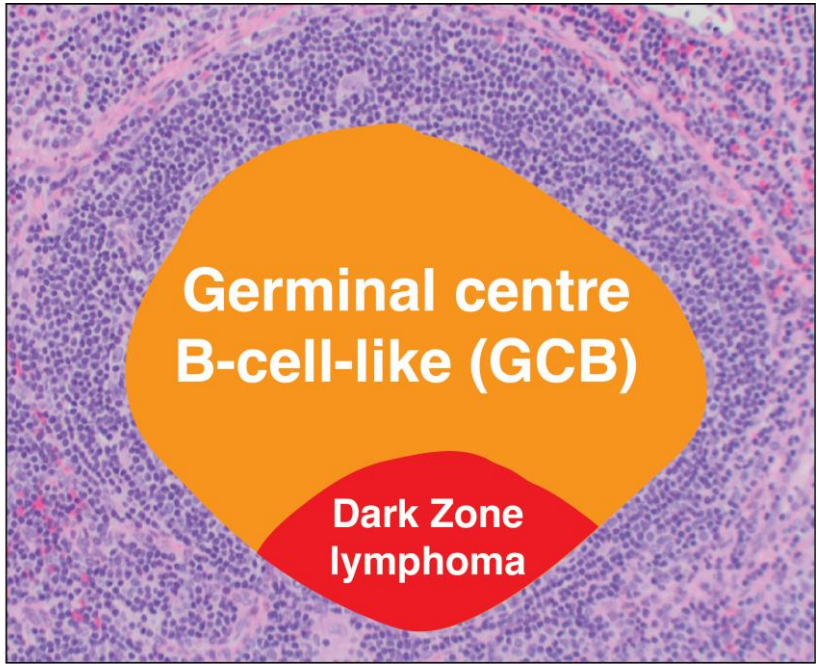

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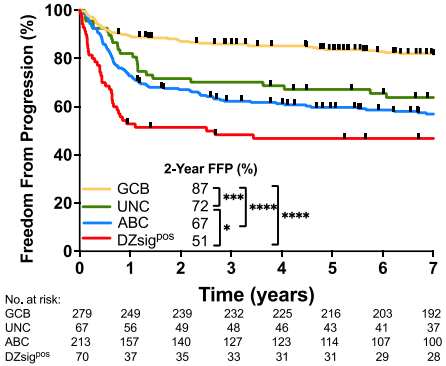

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- Distinct outcomes following R-CHOP

Alduaij, Collinge et al Blood 2023
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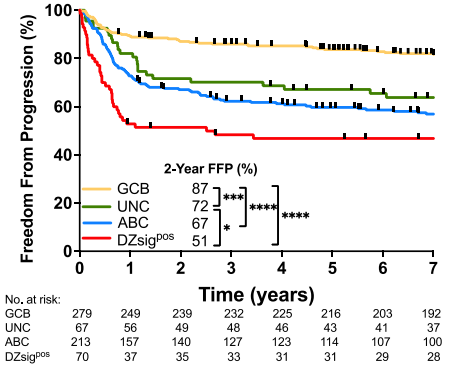
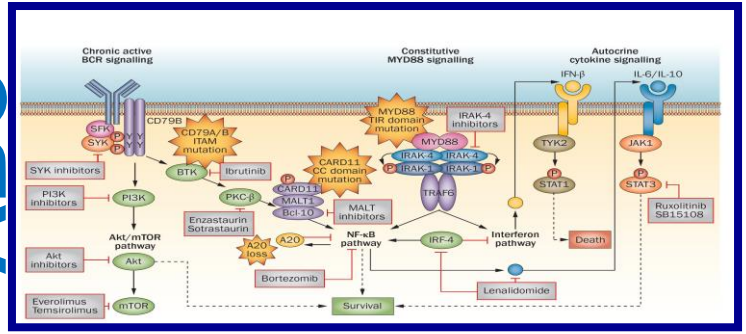


ABC



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- GCB has been further resolved into Dark zone lymphoma and GCB – "refined cell-of-origin"
- Distinct outcomes following R-CHOP
- Distinct mutational landscape and underlying biology

Alduaij, Collinge et al Blood 2023
Alizadeh et al Nature 2000
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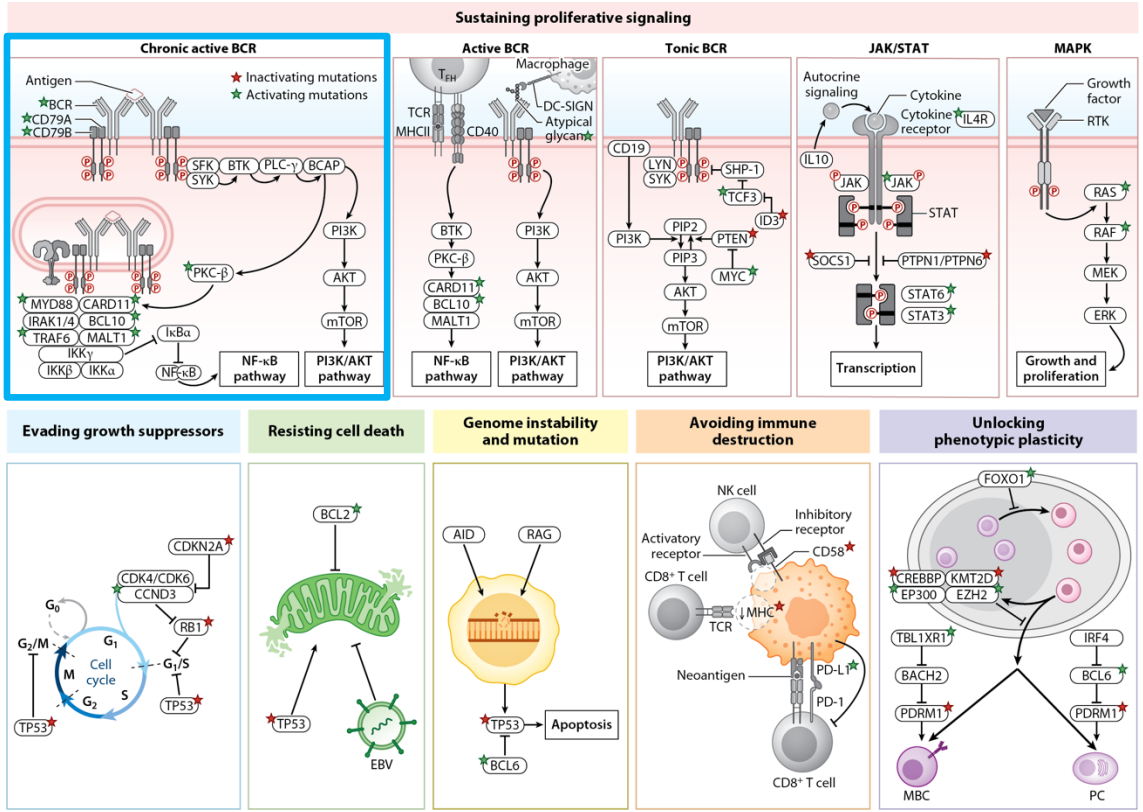
Differential hijacking of BCR signaling



ABC

Hilton, Collinge, Scott
Annu Rev Pathol 2026

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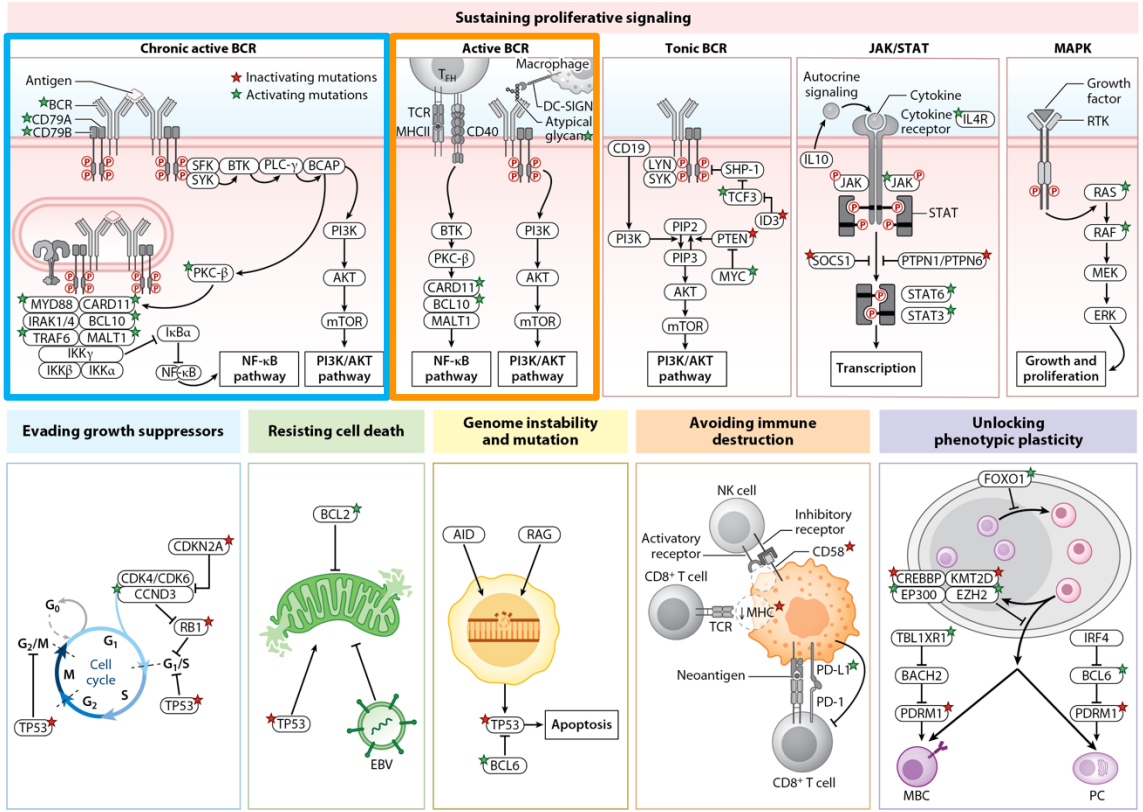

ABC

GCB

Hilton, Collinge, Scott
Annu Rev Pathol 2026

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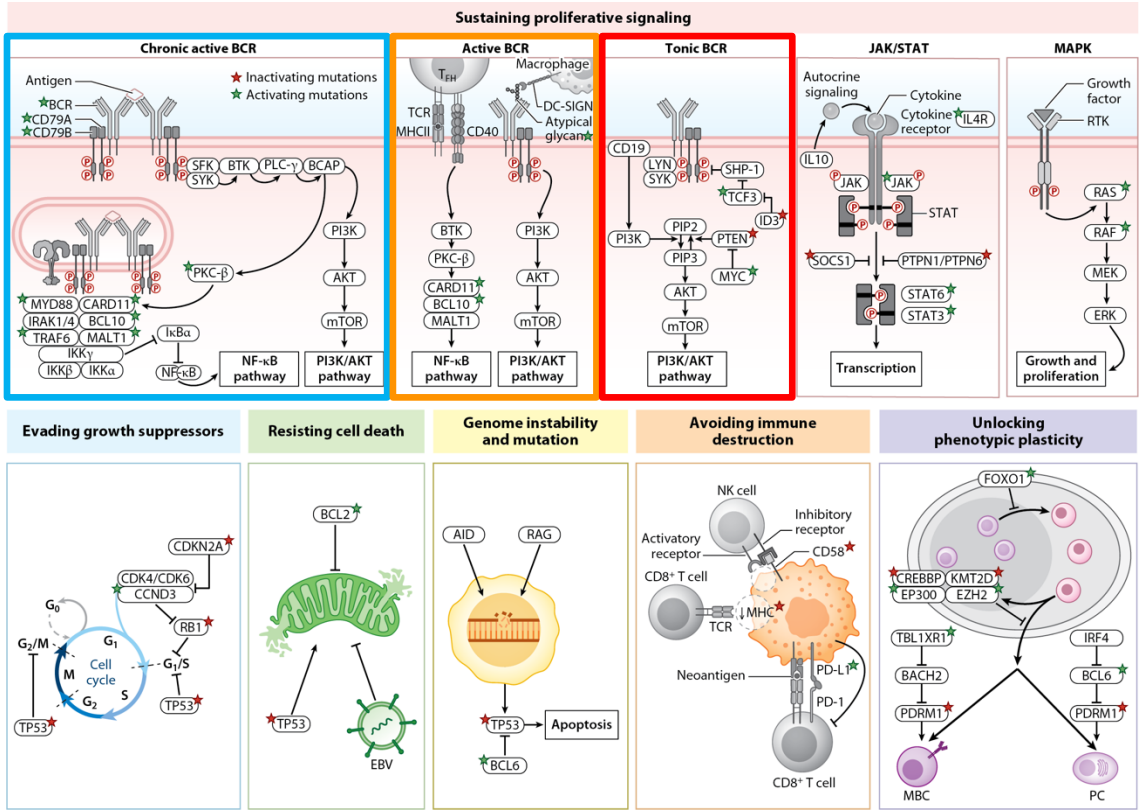


ABC

GCB

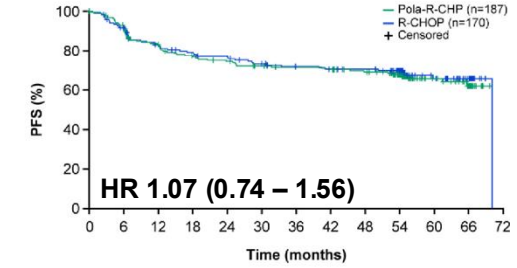
Dark Zone

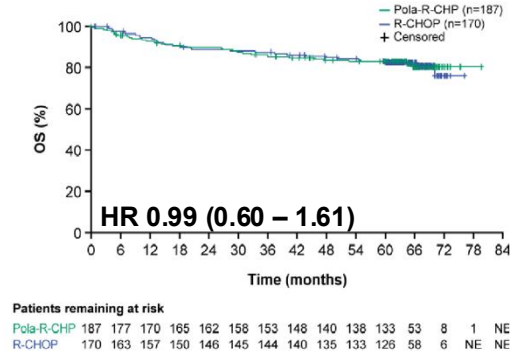
Hilton, Collinge, Scott
Annu Rev Pathol 2026

Is Cell-of-Origin now a historic footnote?

POLARIX: polatuzumab vedotin-R-CHP vs R-CHOP

GCB





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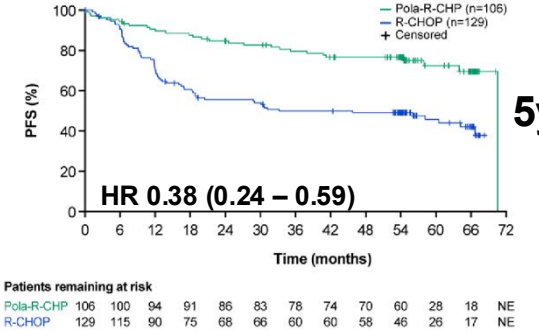
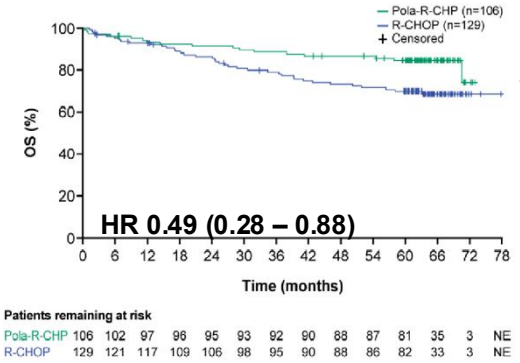


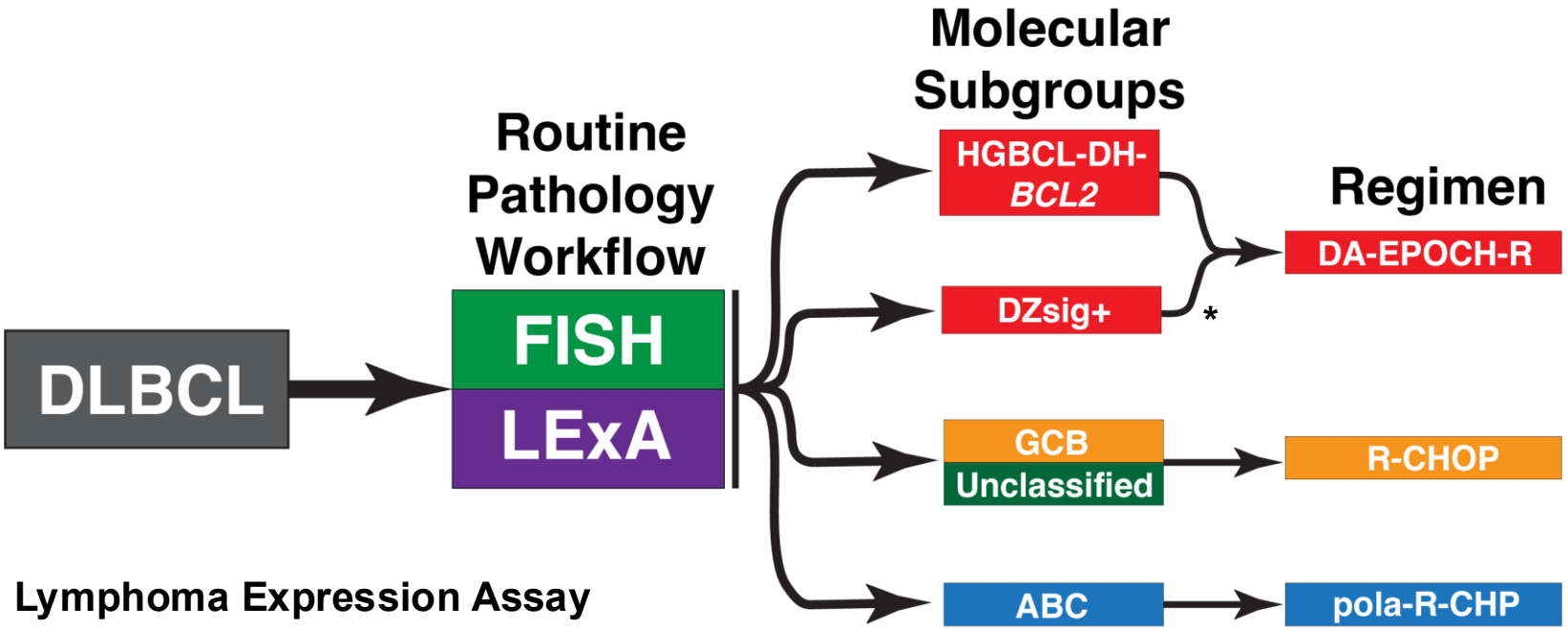
5y PFS Δ 26.7%



5y OS Δ 14.7%

Morschhauser et al J Clin Oncol 2025

BC Cancer's treatment selection algorithm

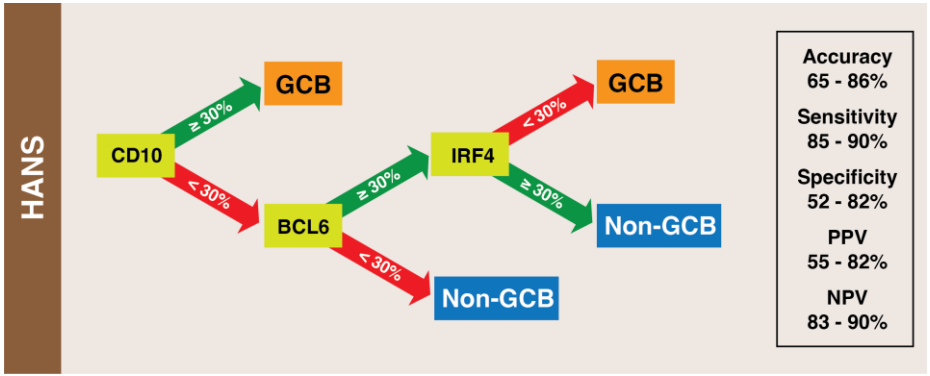


LExA: Lymphoma Expression Assay
Routine since October 2023
Turn-around-time = FISH

*Awaiting funding decision

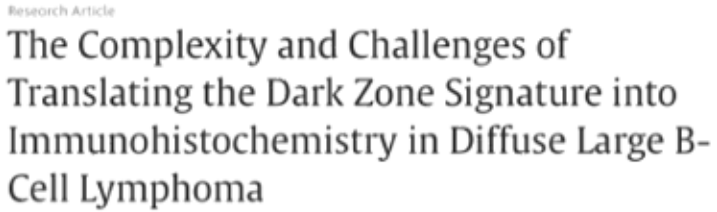
Identifying Cell-of-Origin: IHC

ABC vs GCB



- Widely used surrogate
- Variable accuracy
  - Technical
  - Inter-observer

Dark Zone lymphoma


Research Article

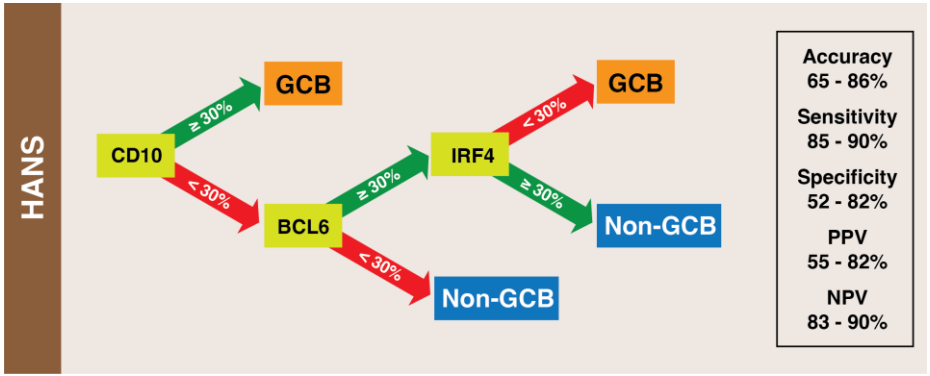
The Complexity and Challenges of Translating the Dark Zone Signature into Immunohistochemistry in Diffuse Large B-Cell Lymphoma

- Not quite ready for prime time
- Issue with low positive predictive values

Momose et al Mod Pathol 2026
Zhao et al Am J Clin Pathol 2025

Identifying Cell-of-Origin: IHC

ABC vs GCB



- Widely used surrogate
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Dark Zone lymphoma

76%
96%
59%
98%

Research Article

The Complexity and Challenges of Translating the Dark Zone Signature into Immunohistochemistry in Diffuse Large B-Cell Lymphoma

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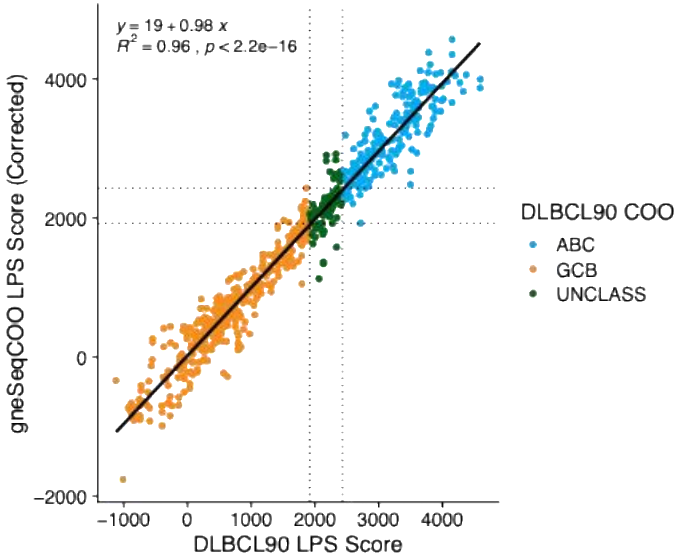
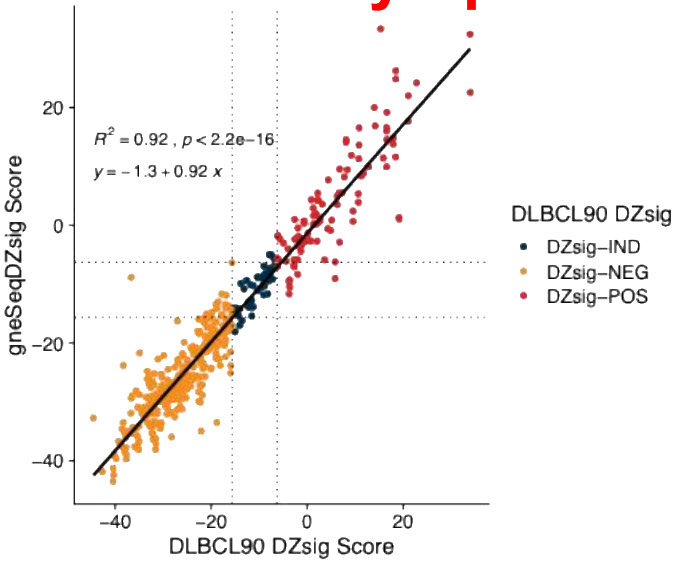
Momose et al Mod Pathol 2026
Zhao et al Am J Clin Pathol 2025

Identifying Cell-of-Origin: RNA-seq

ABC vs GCB



Dark Zone lymphoma

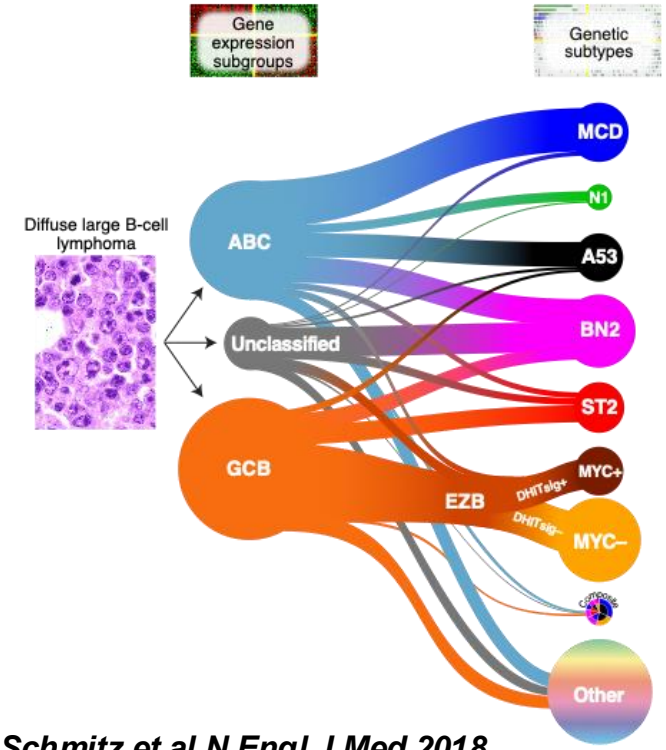


Use of one algorithm for refined COO assignment would provide uniform identification of patients and treatment effects

gneSeqCOO: *Harris et al Leuk Lymphoma 2025*

Akkad, Hilton et al Under review

Genetics-based subtypes of DLBCL



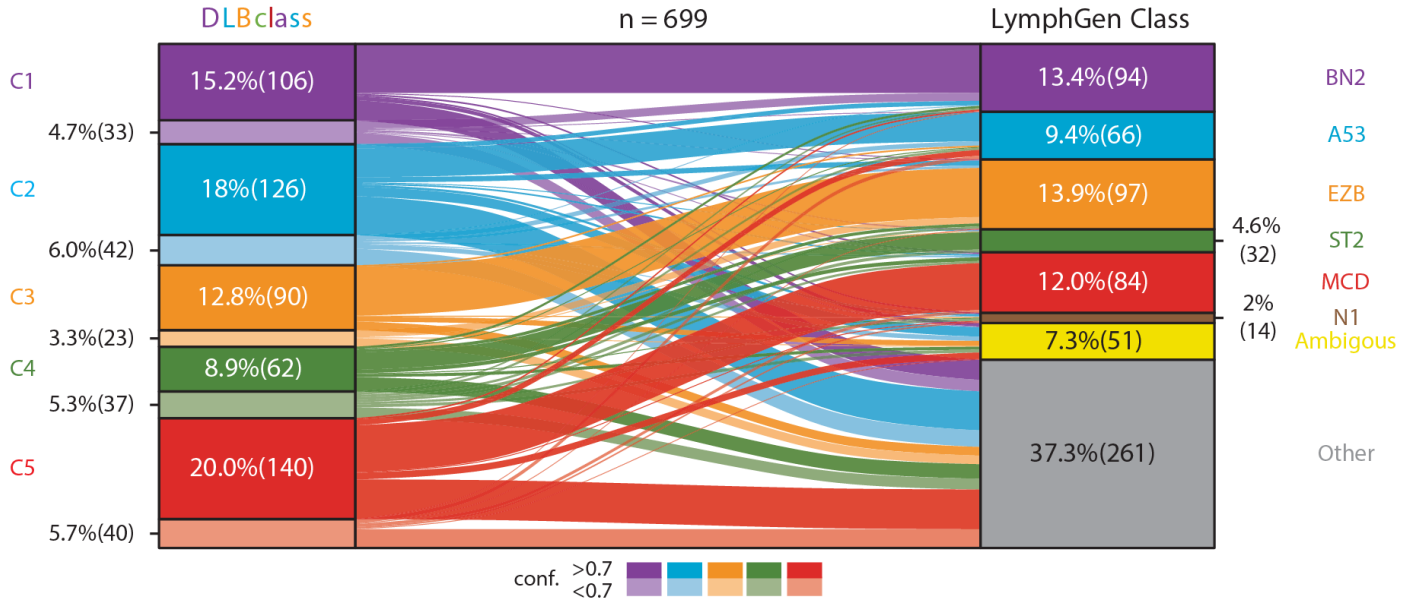
- Three groups have described similar (but not identical) groupings based on co-occurrence of selected genetic features
- Variable requirements for mutation, copy number and rearrangement data
- LymphGen and DLBclass have been developed to allow biopsy-by-biopsy assignment

Schmitz et al N Engl J Med 2018
Chapuy et al Nat Med 2018

Lacy et al Blood 2020

Wright et al Cancer Cell 2020
Chapuy et al Blood 2025

Comparing DLBclass and LymphGen



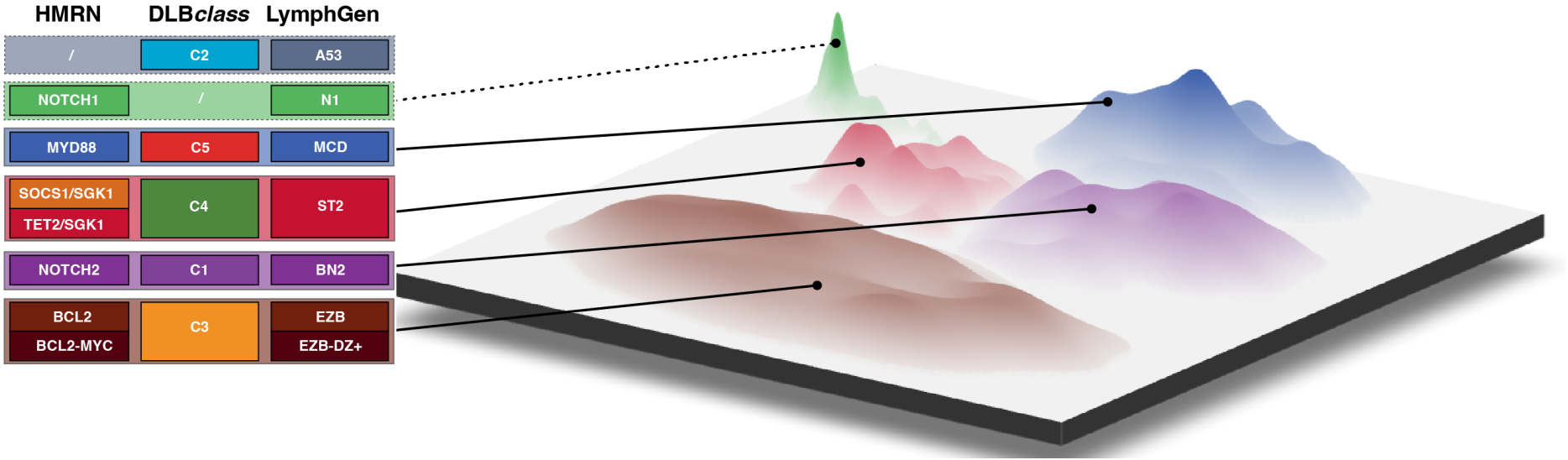
DLBclass: “every tumour finds a home”

LymphGen: “membership is earned”

Chapuy et al Blood 2025

Wright et al Cancer Cell 2020

Converging on groups but not perfect agreement



Broad agreement on what the peaks are and the tumours at the top
Are there more smaller peaks to discover?
Should some tumours not be classified?

Shipp et al Blood Cancer Discov In Press

Hallmarks to predicted vulnerabilities

Hallmark	Pathway	EZB-DLBCL	ST2-DLBCL	BN2-DLBCL	MCD-DLBCL
Sustaining proliferative signaling	Chronic active BCR signaling	–	–	?	+++
	Active BCR signaling	+++	++	++	–
	Tonic BCR signaling	–	–	–	–
	JAK/STAT	+	+++	?	++
	MAPK	–	?	–	–
Evading growth suppressors	Cell cycle checkpoint LOF	+	+	++	+++
Resisting cell death	BCL2	+++	–	+++	+++
	TP53	+	+	+	+
	EBV	–	–	–	–
Genomic instability and mutation	Drivers	+++	+++	++	++
	Sensors	+++	+++	+++	+++
Avoiding immune destruction	Genetic	+	+++	+++	+++
	Differentiation	–	–	–	++
	Immunosuppression	–	–	–	–
Unlocking phenotypic plasticity	Differentiation skew	++	++	++	+++
	Differentiation block	+++	+++	+++	+++

Relative activity: Least – + ++ +++ Most ? Uncertain

- **Modes of achieving hallmarks can be inferred from patterns of genetic aberrations and targeting has been tested in cell lines**
- **Whether these vulnerabilities can be exploited needs to be tested**
  - **retrospective analyses**
  - **prospective trials**

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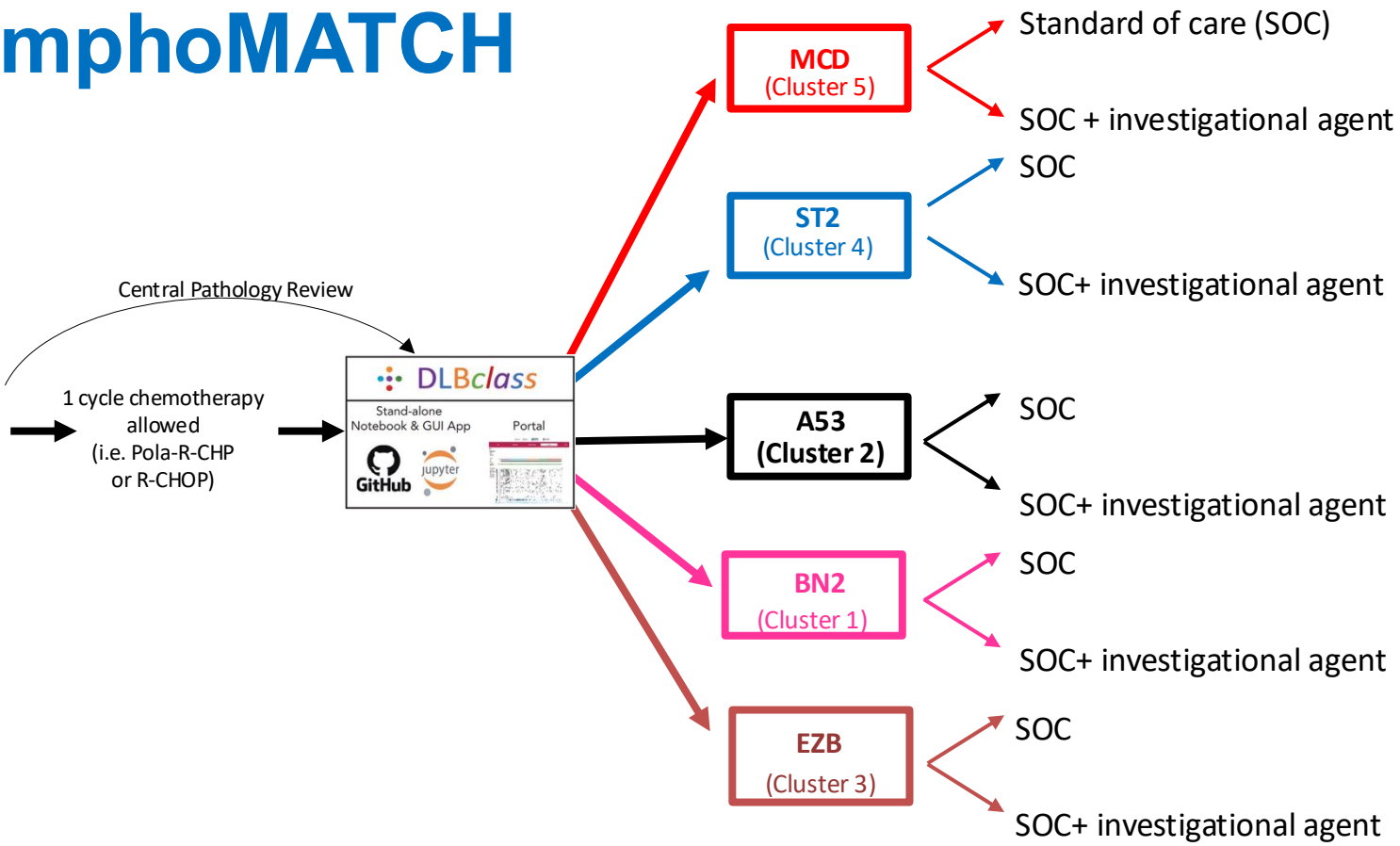
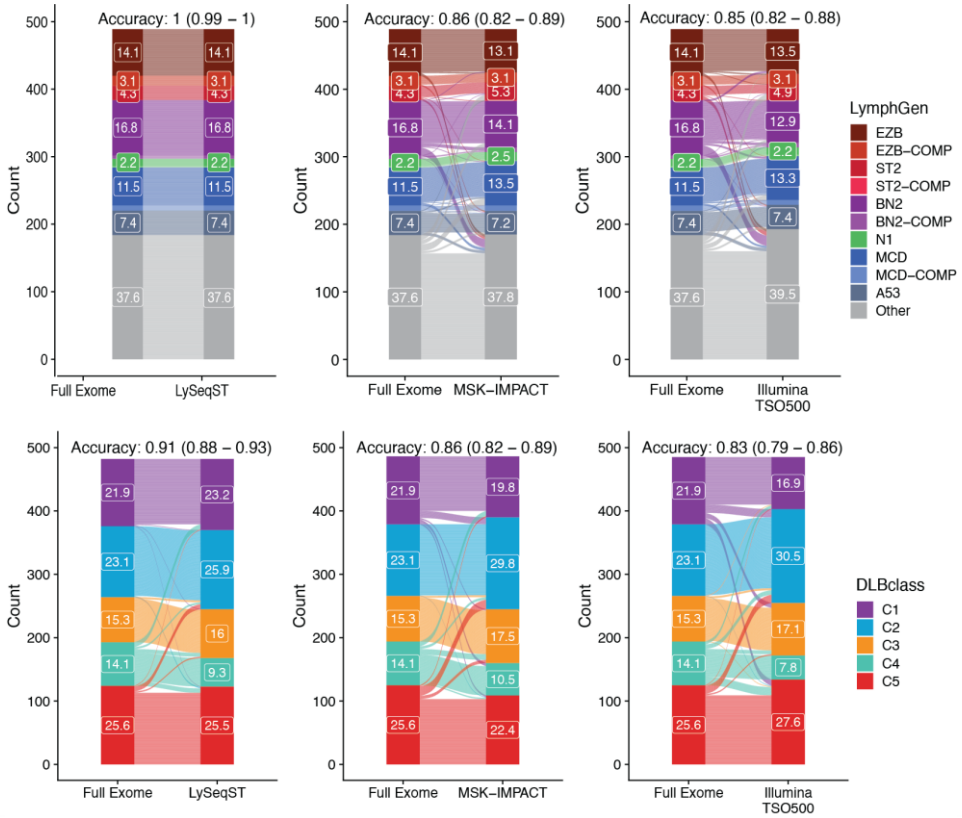
LymphoMATCH



Identifying genetic subtypes



- **Whole exome sequencing (plus spike-in) is the gold standard**
- **Panel sequencing is widely used and (correctly designed) can provide accurate assignments**
- **Are FISH results and germline needed?**
- **In clinical trials, whole exome and transcriptome sequencing should be encouraged**

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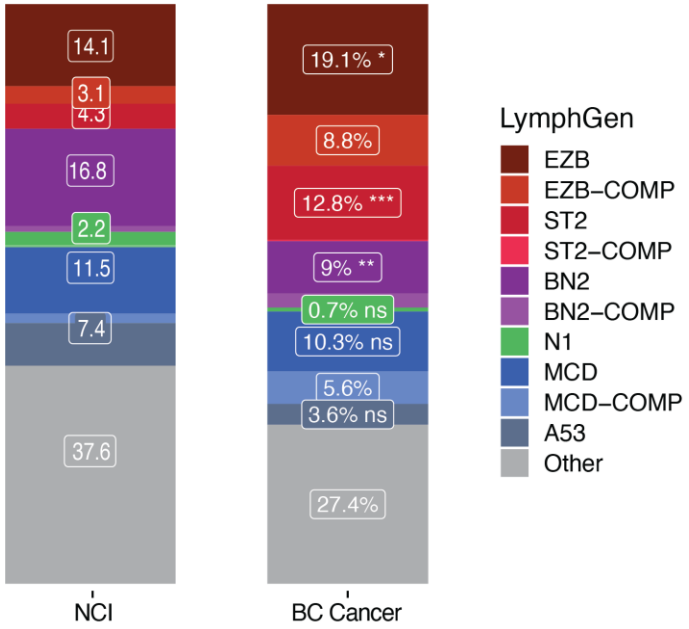
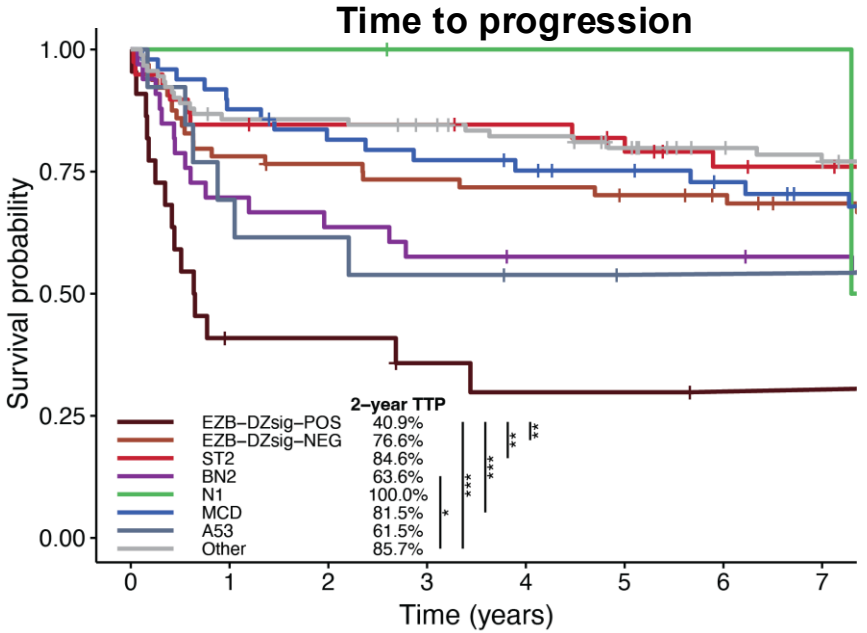
Considerations for trial design

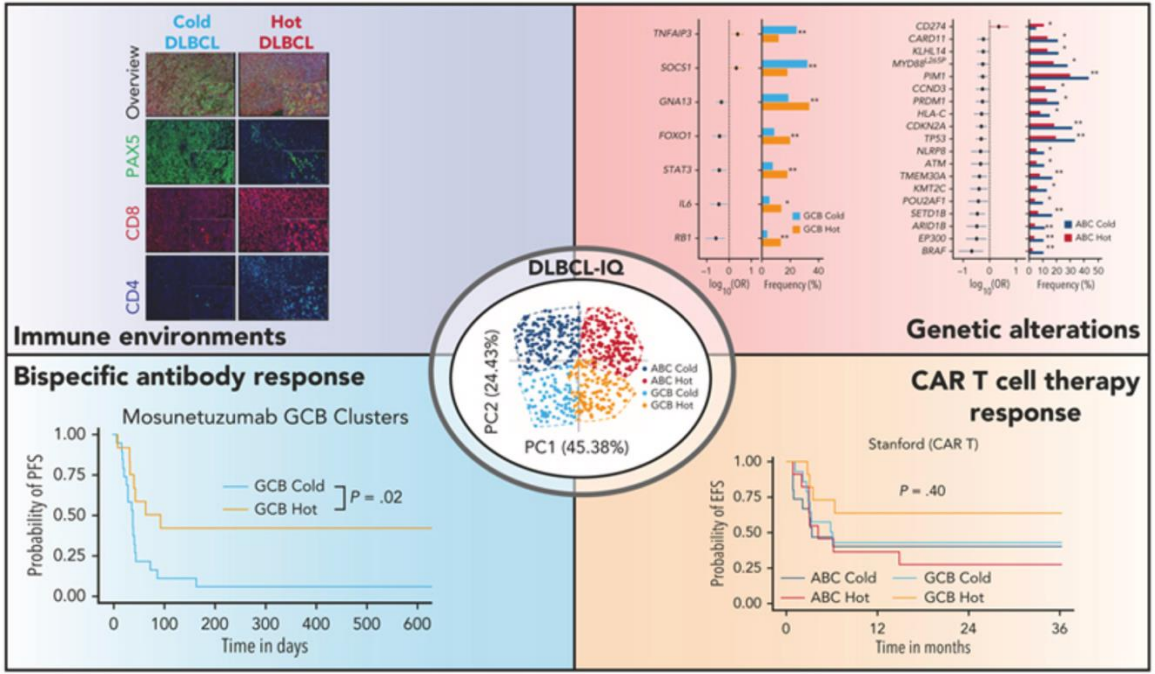




Proportions of the genetic subtypes in the real world may deviate from the original publications and the outcomes may be different

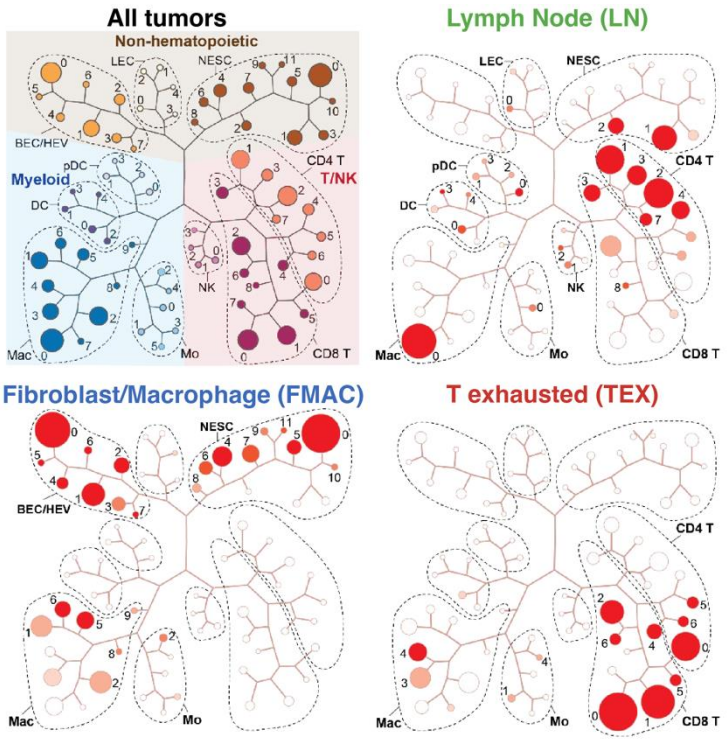
Runge et al Br J Haematol 2022 *Hilton et al In revision*

Tumour microenvironment impacts response to bispecific antibodies



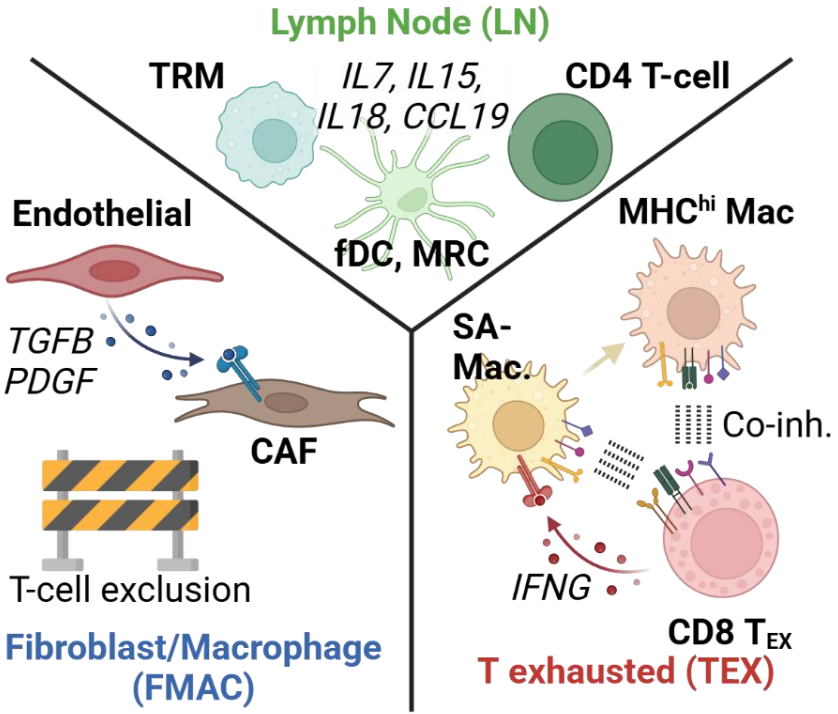
Tumuluru et al Blood 2025

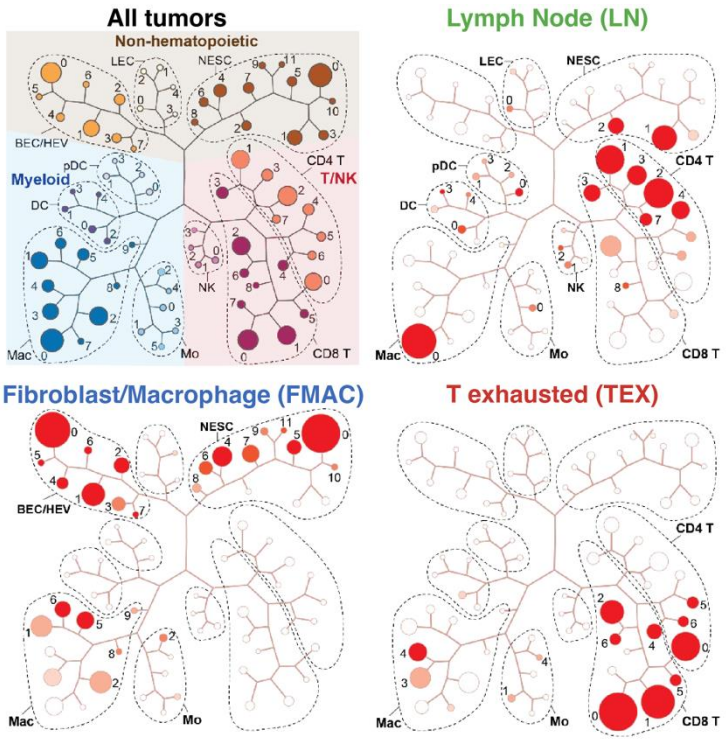
Tumour microenvironments - LymphoMAPs



Li et al Cancer Cell 2025

Tumour microenvironments - LymphoMAPs





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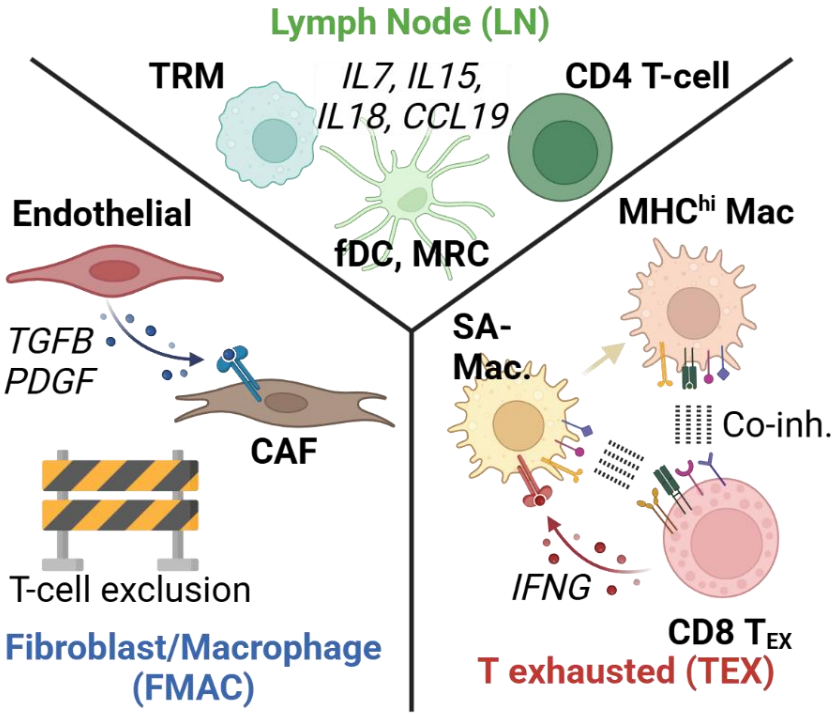
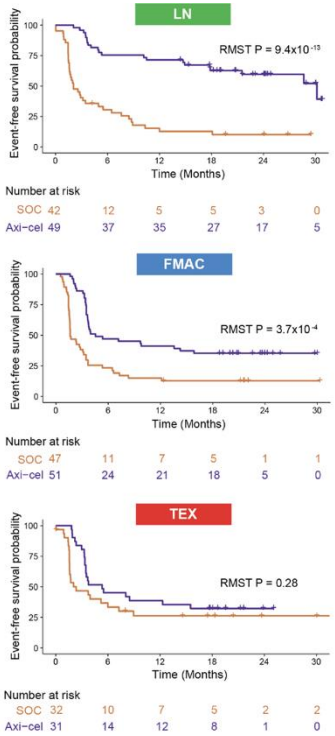
LymphoMAPs – impact on CAR-T outcomes





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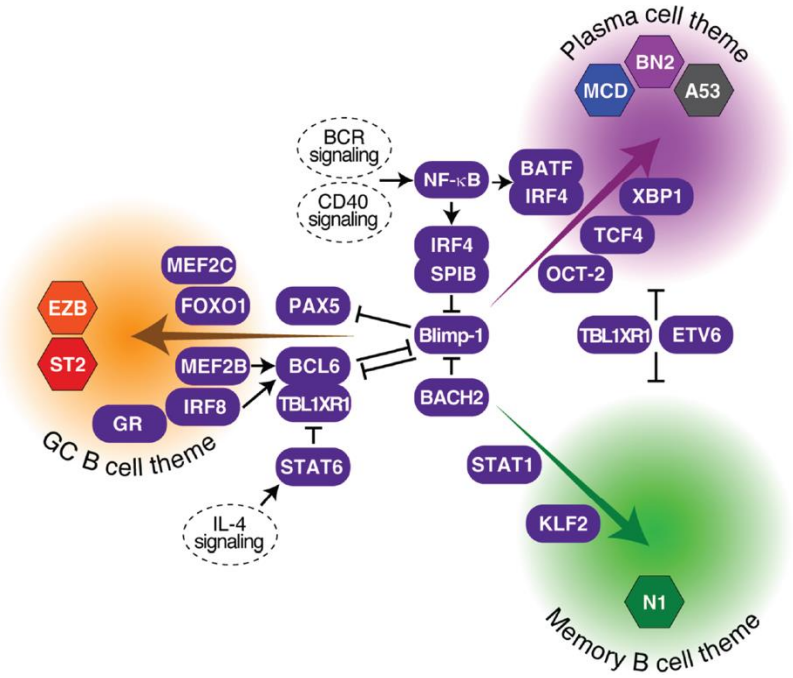
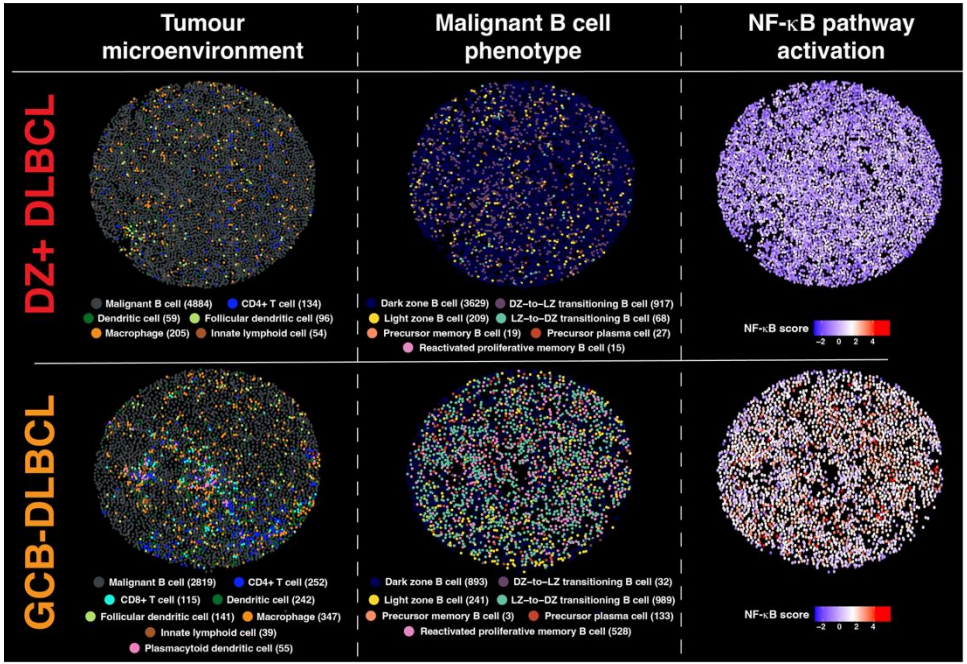
Insights from single cell analyses

Disaggregated single cell multiome



In situ single cell transcriptomics



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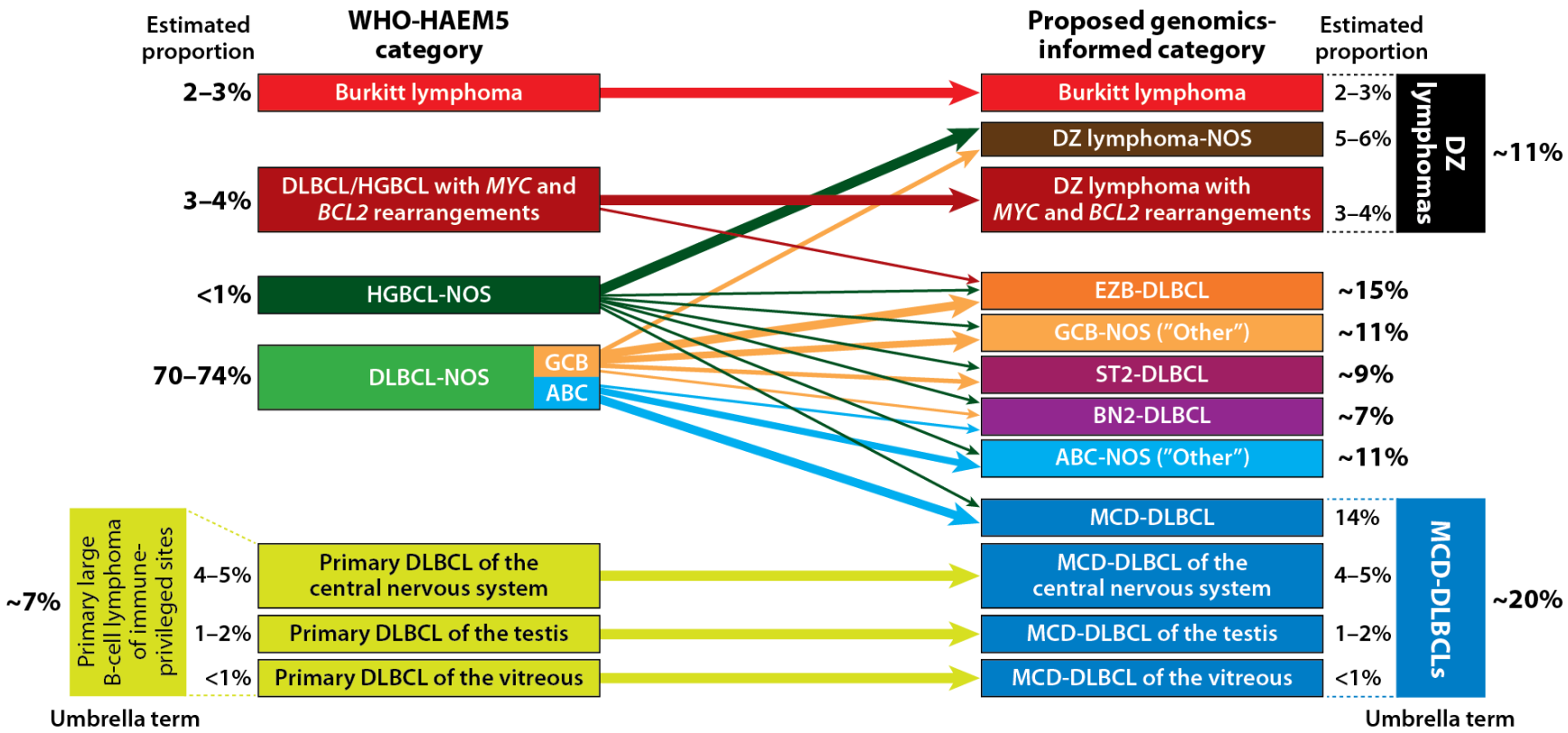
Concluding comments

- DLBCL makes up 70-75% of aggressive B-cell lymphoma and is highly heterogeneous
- Molecular subgroups can be identified using structural variants, gene expression profiling, patterns of genetic aberrations and tumour microenvironment composition
- The relationships between these layers are crystalizing, with the exception of tumour microenvironment – work is ongoing
- Treatment is shifting from the one-size-fits-all approach in defined molecular subgroups – ABC-DLBCL and HGBCL-DH-*BCL2*
- Targetable biology can be inferred in the genetic subtypes and now needs to be tested in prospective trials



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