9th POSTGRADUATE
Lymphoma
Conference

The use of molecular profiling for patient selection

David Scott

BC Cancer and University of British Columbia

Florence,
March 20-21, 2025

Hotel Brunelleschi

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				
GenMab			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

- **Current classifications of aggressive B-cell lymphoma**

Treatment selection "today": **(what we do at BC Cancer)**

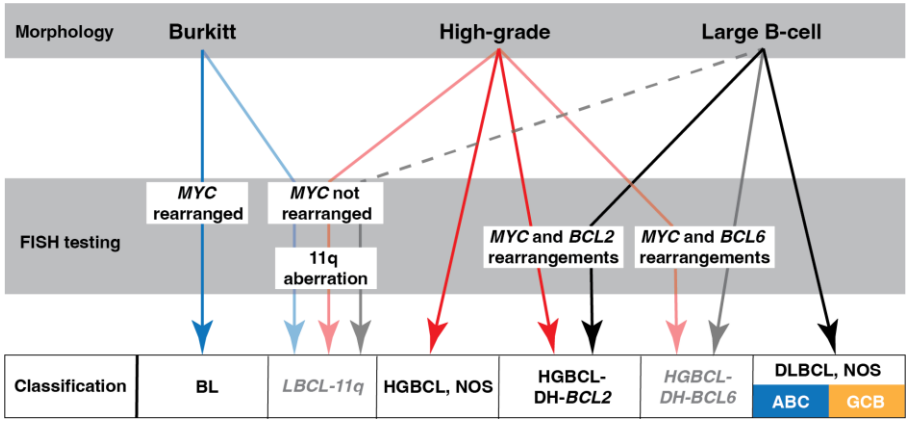
- **High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement**
- **Cell-of-origin**
- **Dark zone lymphoma**

Molecular profiling for patient selection for clinical trials:

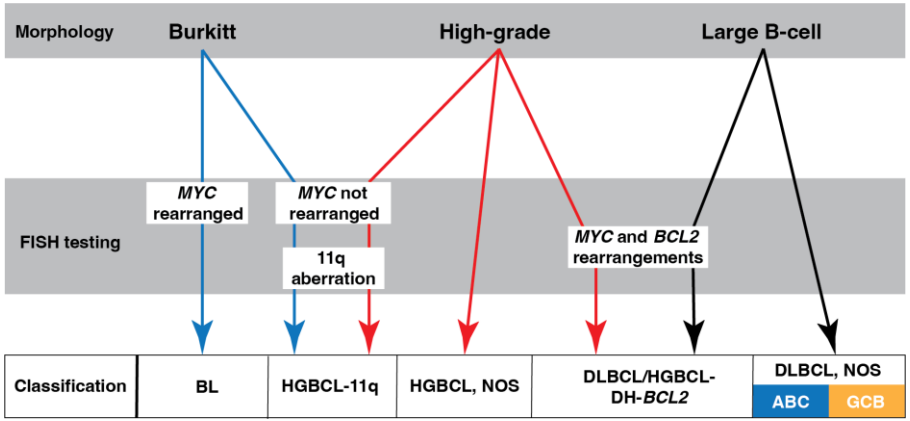
- **Genetics-based subtypes**
- **Opportunities and challenges**

Aggressive B-cell lymphoma classification

International Consensus Classification



WHO HAEM5



Campo et al Blood 2022

Alaggio et al Leukemia 2022

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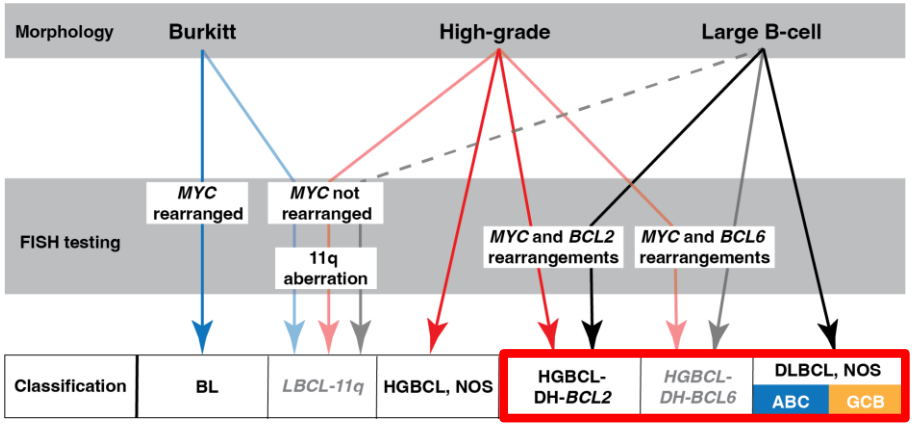

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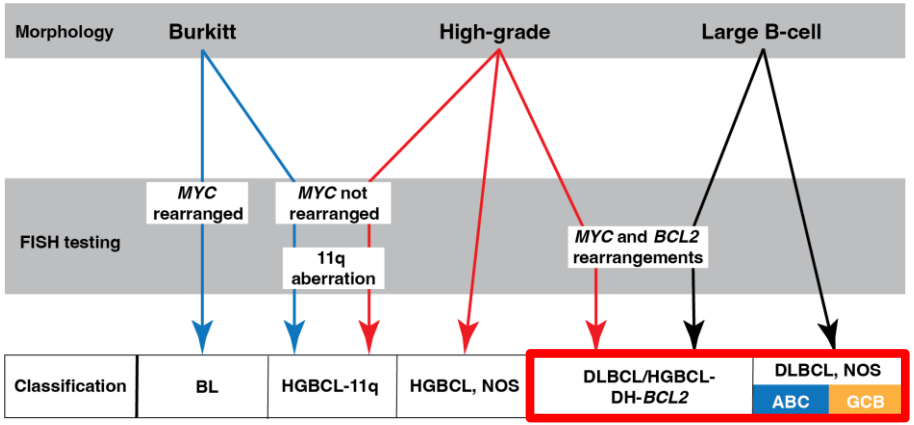

Classifications are largely concordant with the exception of aggressive tumors with *MYC* and *BCL6* rearrangements

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

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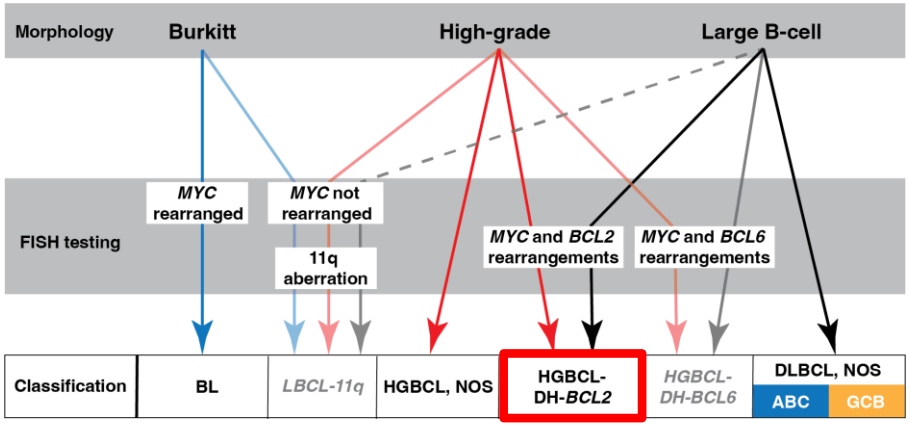

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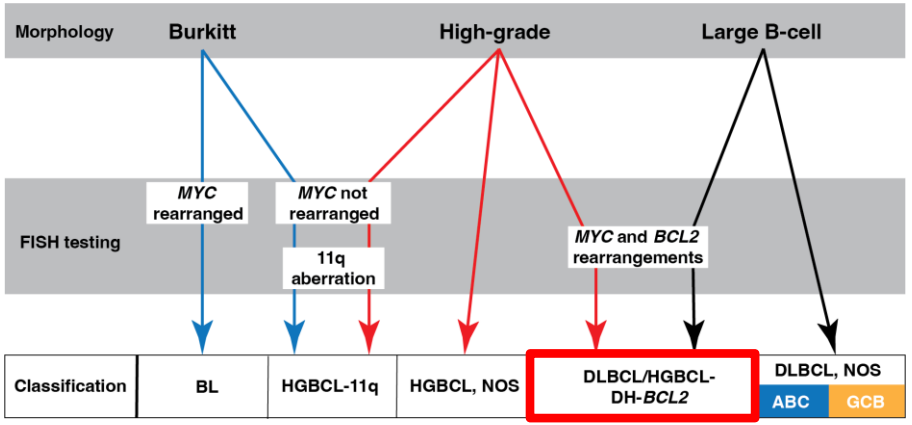
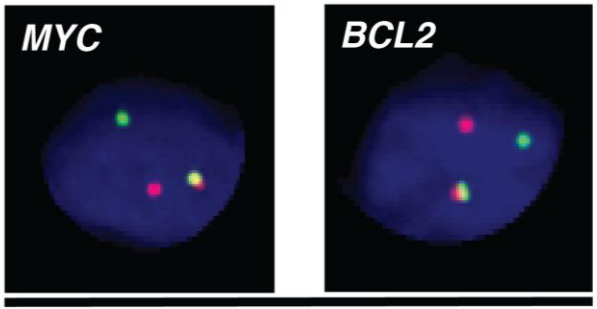


Classifications are largely concordant with the exception of aggressive tumours with *MYC* and *BCL6* rearrangements

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

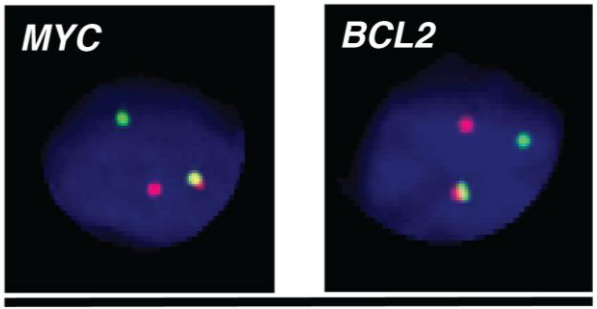
High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements – HGBCL–DH–*BCL2*



- **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

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



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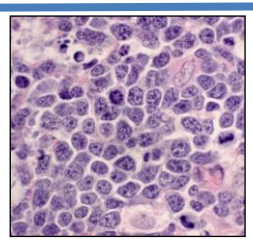
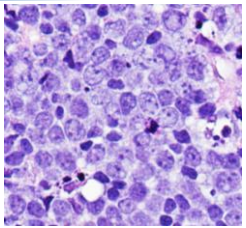
MORPHOLOGY – "High-grade"

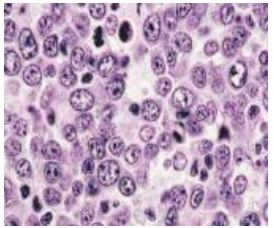
High-grade

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

Cucco et al Leukemia 2020
Collinge et al ICML 2021

HGBCL-DH-*BCL2*: mutational landscape

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

Cucco et al Leukemia 2020
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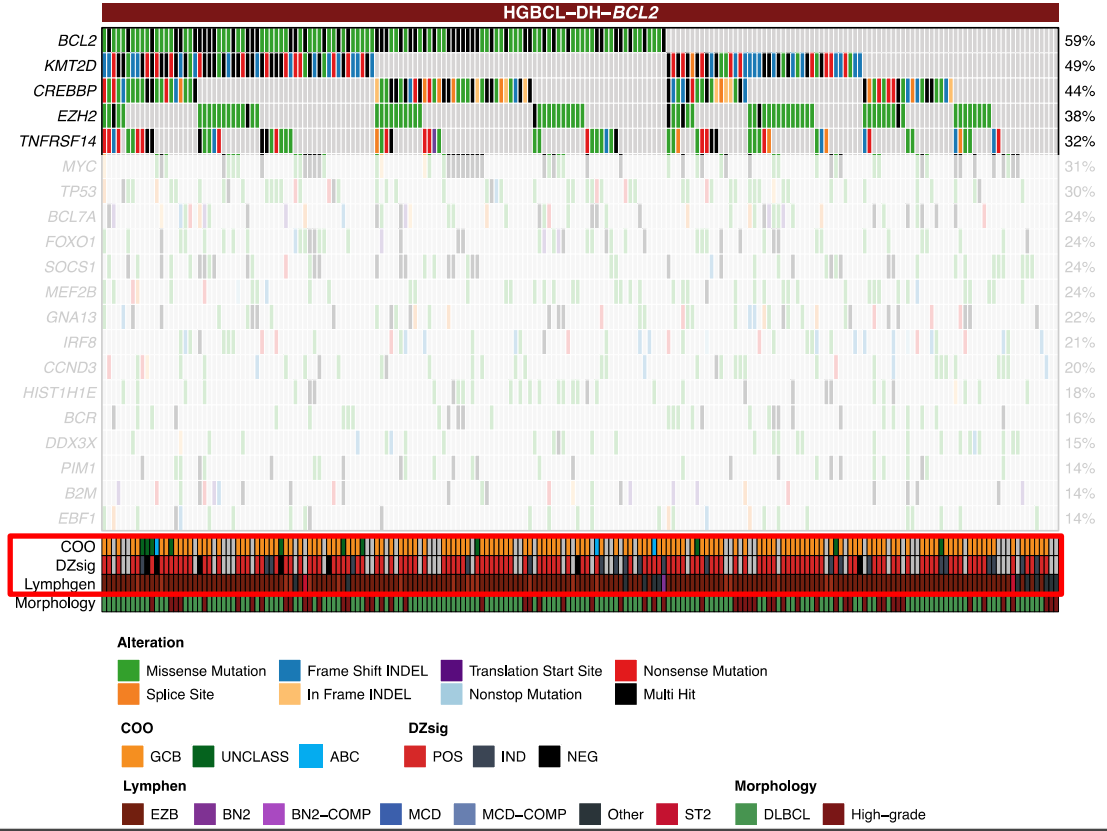
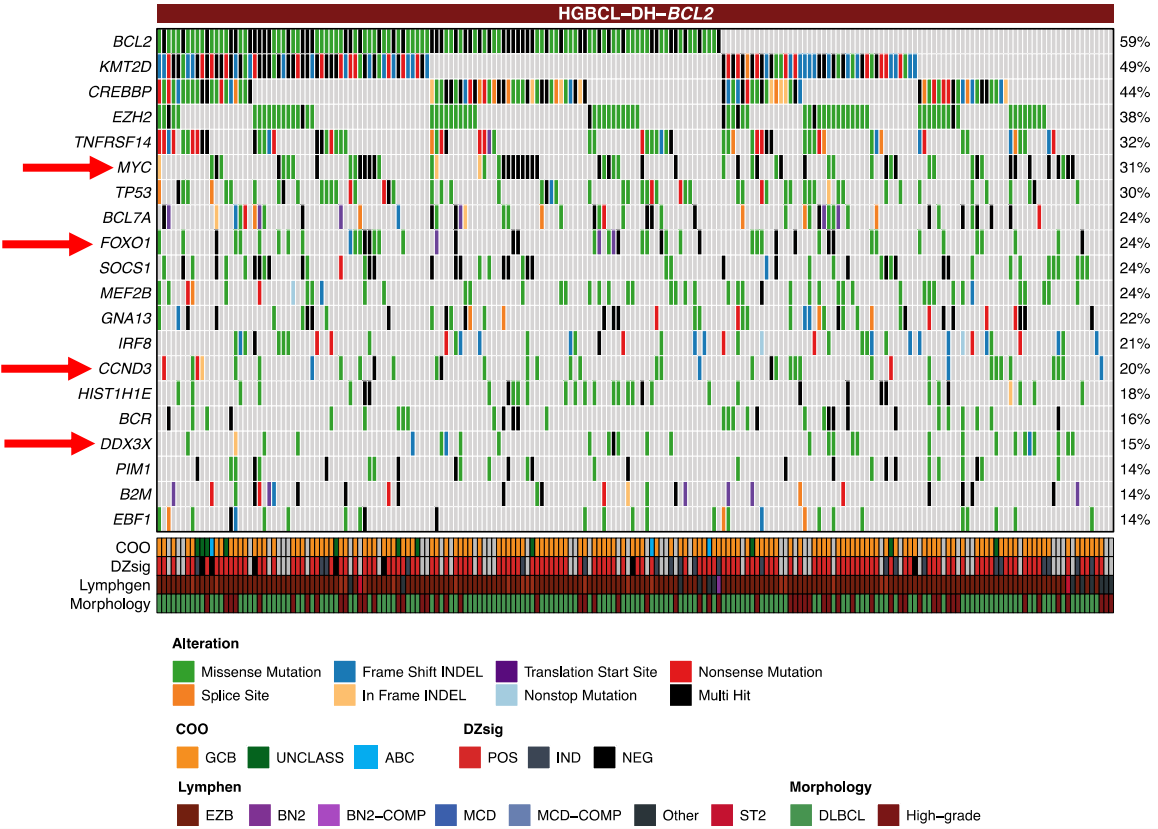


- **Most recurrently mutated genes are shared with follicular lymphoma suggesting a common precursor cell population**
- **Almost all are GCB, express the “dark zone” signature and are EZB genetic subgroup**

Cucco et al Leukemia 2020
Collinge et al ICML 2021

HGBCL-DH-*BCL2*: mutational landscape



- **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**

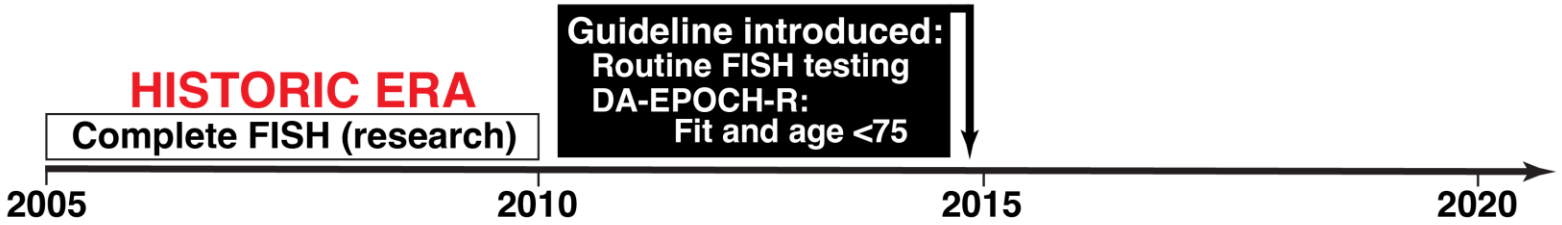
Cucco et al Leukemia 2020
Collinge et al ICML 2021

HGBCL-DH-*BCL2* – why does it matter? Intensification is associated with better outcomes

Petrich et al Blood 2014

Goyal et al Haematologica 2023

HGBCL-DH-*BCL2* – why does it matter?
Intensification is associated with better outcomes



Alduaij et al
In preparation

HGBCL-DH-*BCL2* – why does it matter?
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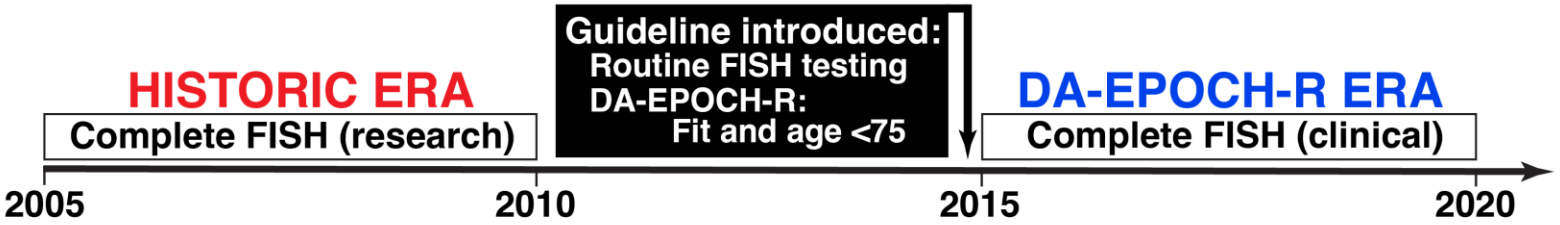

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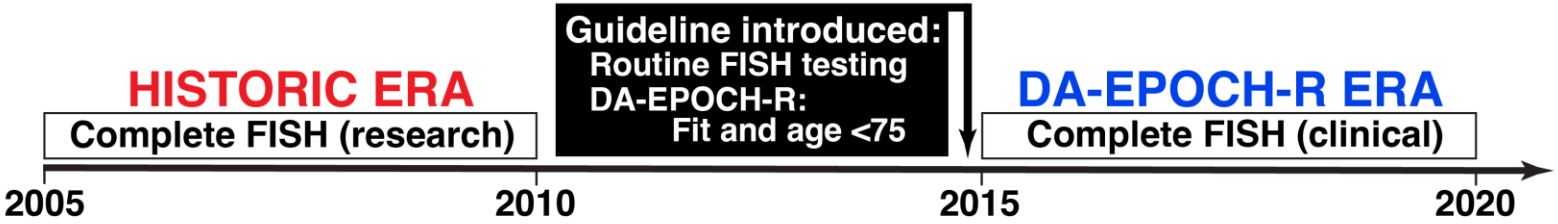

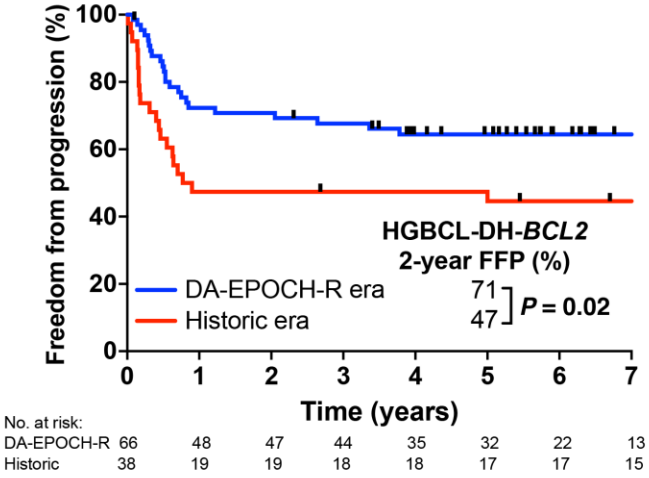

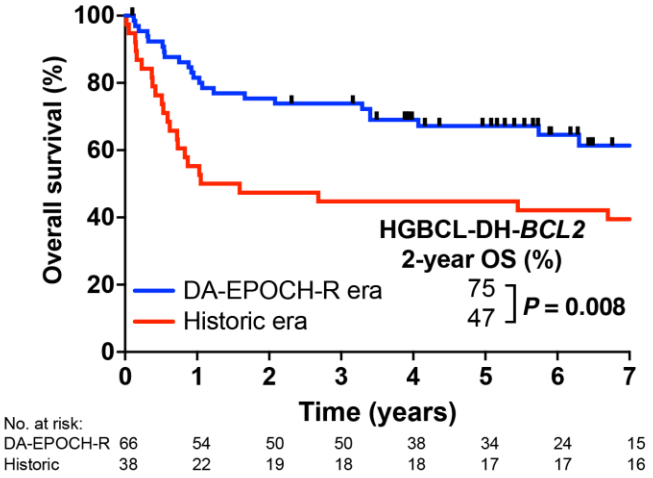

Alduaij et al
In preparation

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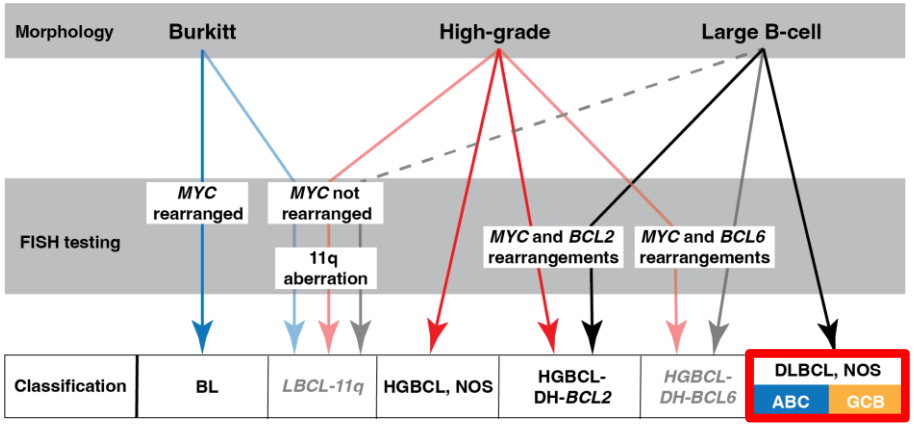

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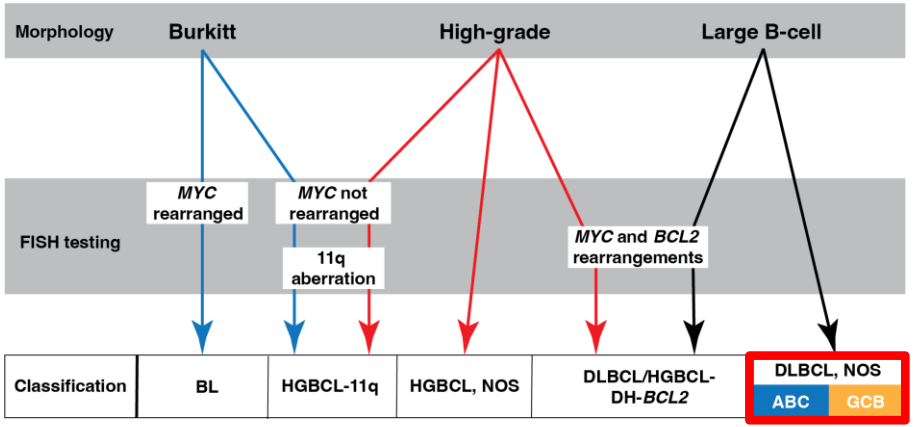

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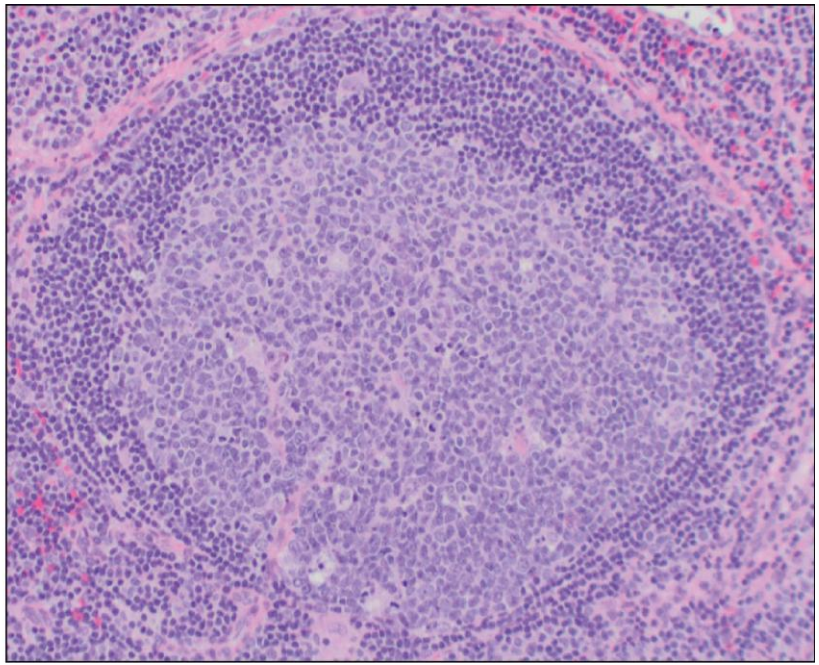
Campo et al Blood 2022 *Alaggio et al Leukemia 2022*

Cell-of-Origin classification



- **Comparison of gene expression of tumors with B cells at different stages of differentiation**

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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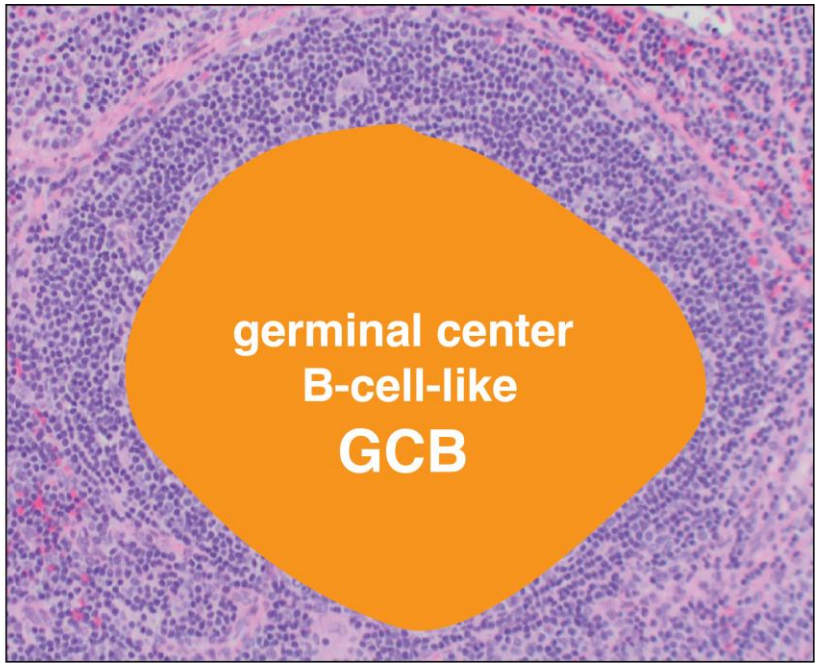

- Comparison of gene expression of tumors with B cells at different stages of differentiation
- Clustering approach producing binary groups – tumors that “look like” (phenocopy) germinal center B cells (GCB) vs those that don’t (ABC)

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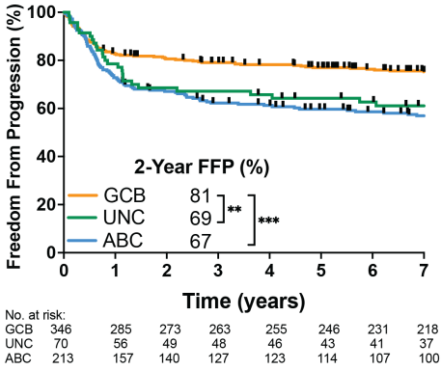

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- Different outcomes following R-CHOP

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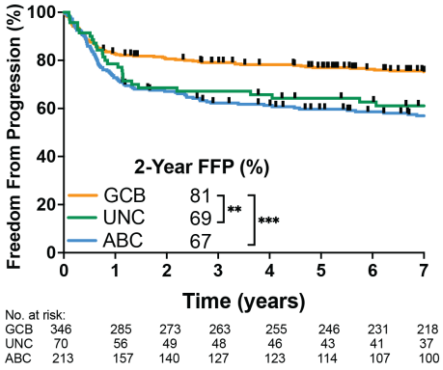
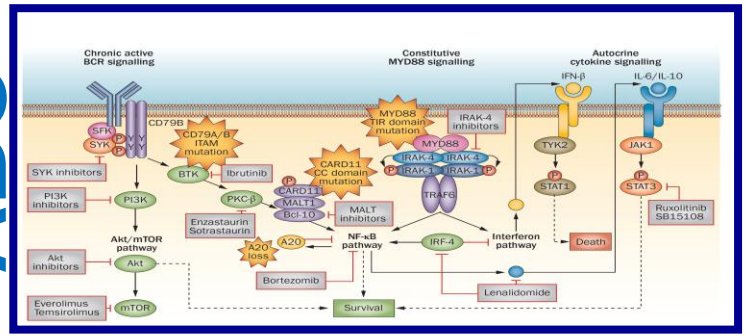


ABC



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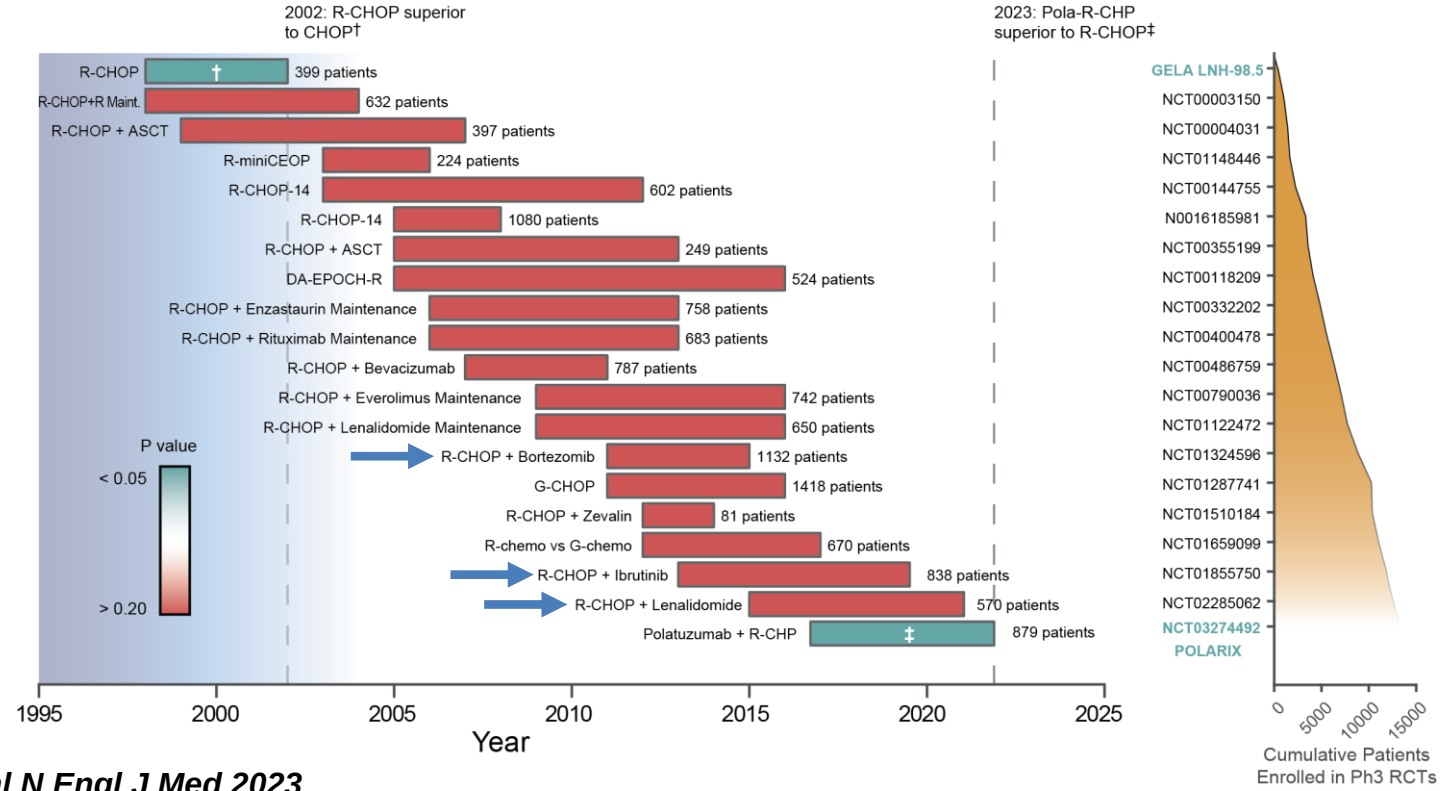
- Clustering approach producing binary groups – tumors that "look like" (phenocopy) germinal center B cells (GCB) vs those that don't (ABC)
- Different outcomes following R-CHOP
- Distinct mutational landscapes and underlying biology

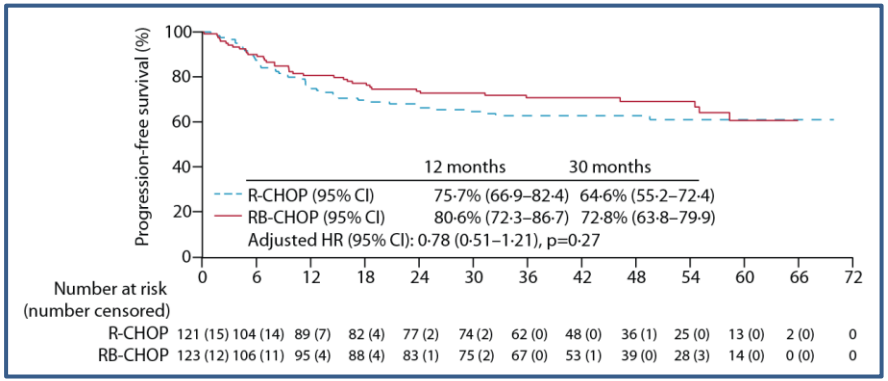
Alduaij, Collinge et al Blood 2023
Alizadeh et al Nature 2000
Rosenwald et al N Eng J Med 2002
Roschewski et al Nat Rev Clin Oncol 2014
Lenz et al N Eng J Med 2008

Phase III RCTs moving beyond R-CHOP

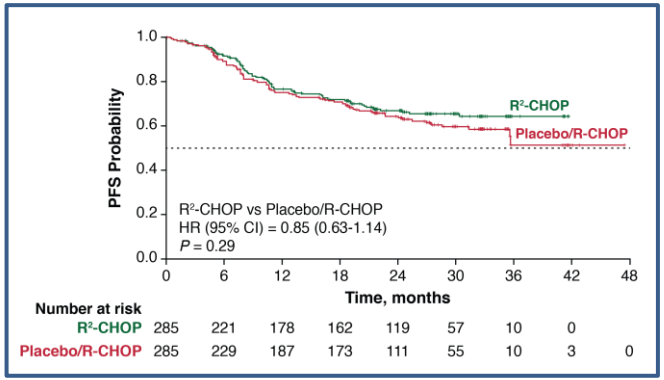


Palmer et al N Engl J Med 2023

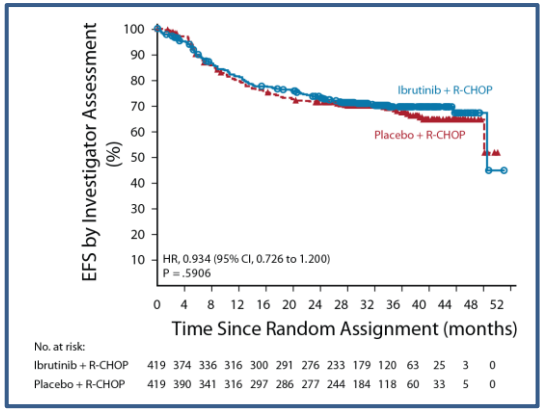
Is cell-of-origin now a historic footnote?



RMoDL-B:
R-CHOP ± bortezomib
Davies et al Lancet Oncol 2019
COO by gene expression



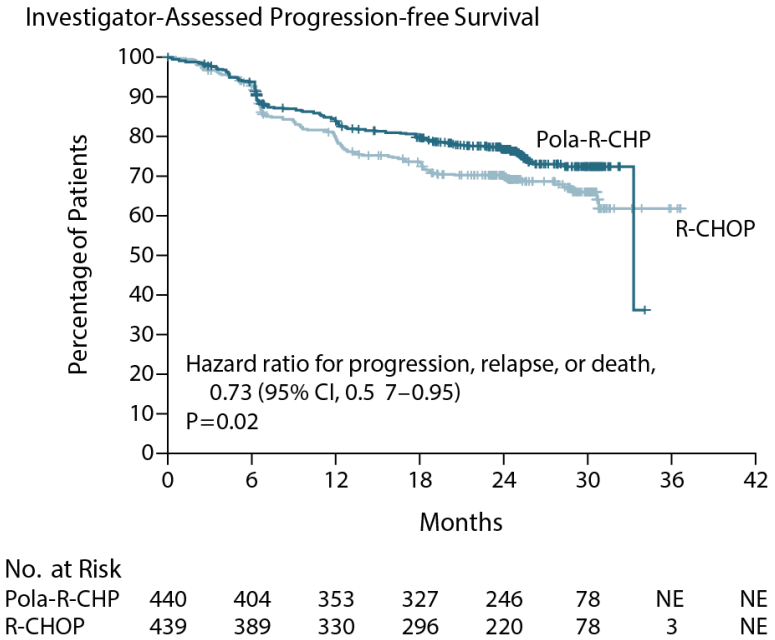
ROBUST:
R-CHOP ± lenalidomide
Vitolo et al ICML 2019
COO by gene expression

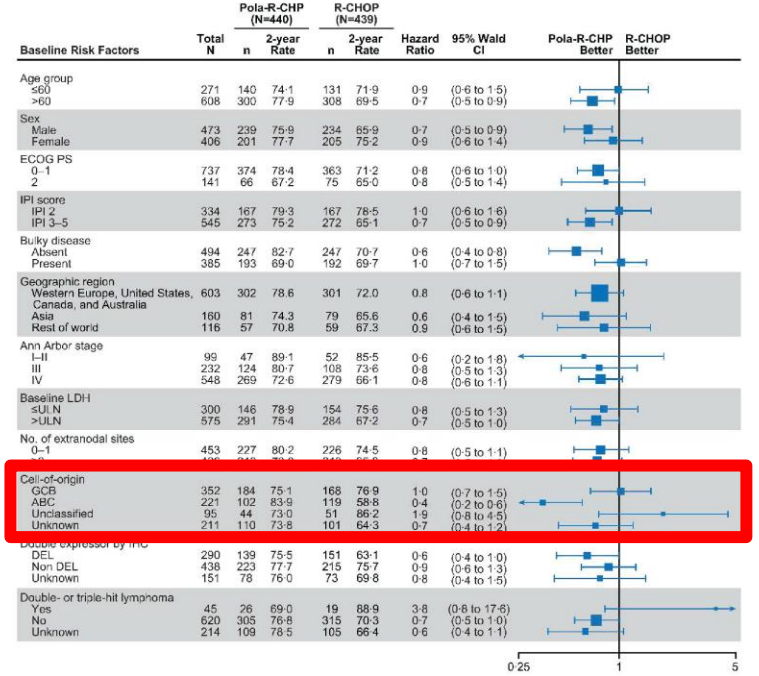


PHOENIX:
R-CHOP ± ibrutinib
Younes et al J Clin Oncol 2019
COO by Hans IHC

Is cell-of-origin now a historic footnote?

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





Tilly et al N Engl J Med 2022

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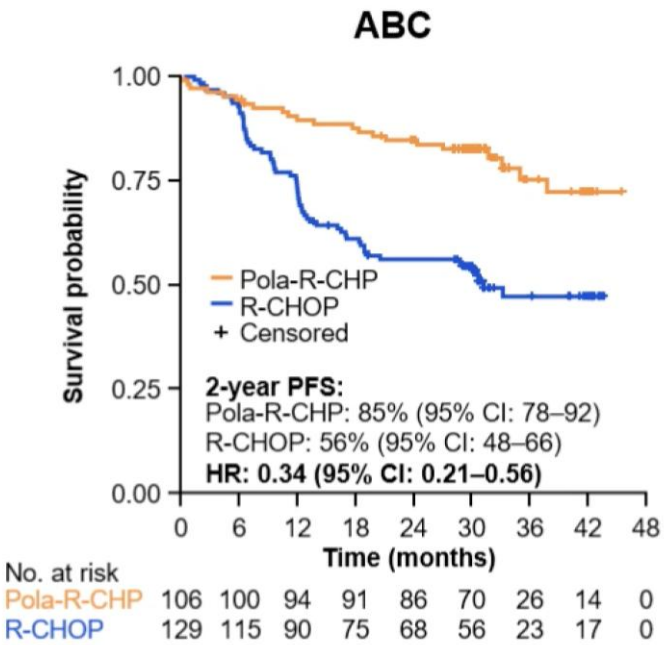
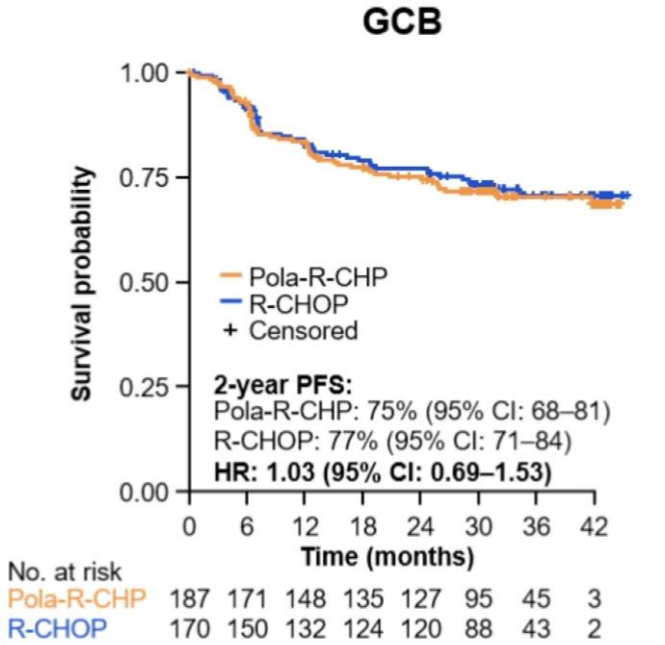




Morschhauser et al ASH Annual Meeting 2023

Is cell-of-origin now a historic footnote?

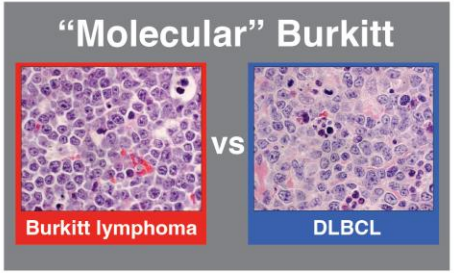
POLARIX: polatuzumab vedotin-R-CHP vs R-CHOP

Baseline risk factors		PFS								OS							
		Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI	Pola-R-CHP better	R-CHOP better	Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI	Pola-R-CHP better	R-CHOP better
		n	60-month (%)	n	60-month (%)					n	60-month (%)	n	60-month (%)				
All patients		440	64.9	439	59.1	**0.78**	0.62–0.97			440	82.3	439	79.5	**0.85**	0.63–1.16		
Age group	≤65	225	69.6	219	64.3	**0.80**	0.57–1.11			225	89.1	219	84.7	**0.73**	0.44–1.21		
	>65	215	60.0	220	54.5	**0.78**	0.58–1.06			215	75.3	220	74.5	**0.95**	0.65–1.38		
Stratification – IPI score	2	167	67.2	167	68.3	**0.91**	0.61–1.36			167	87.6	167	87.4	**0.96**	0.53–1.75		
	3–5	273	63.2	272	53.5	**0.72**	0.55–0.94			273	79.2	272	74.7	**0.81**	0.57–1.15		
Stratification – bulky disease (≥ 7cm)	Absent	247	69.9	247	60.0	**0.61**	0.44–0.83			247	83.9	247	80.9	**0.79**	0.52–1.20		
	Present	193	58.5	192	57.9	**1.02**	0.73–1.41			193	80.3	192	77.9	**0.92**	0.60–1.43		
Baseline LDH	≤1xULN	146	65.3	154	64.8	**0.83**	0.55–1.23			146	88.7	154	87.9	**0.85**	0.45–1.61		
	>1xULN	291	64.3	284	55.7	**0.77**	0.59–1.01			291	79.0	284	74.9	**0.85**	0.60–1.19		
No. of extranodal sites	0–1	227	68.1	226	64.2	**0.78**	0.56–1.09			227	83.7	226	81.9	**0.86**	0.56–1.34		
	≥2	213	61.2	213	53.8	**0.78**	0.58–1.06			213	80.9	213	77.1	**0.85**	0.56–1.28		
NHL subtype	DLBCL	373	65.7	367	58.8	**0.75**	0.59–0.95			373	81.9	367	79.8	**0.89**	0.64–1.23		
	HGBL, DHL/THL	43	66.0	50	57.6	**0.67**	0.33–1.37			43	85.4	50	72.4	**0.46**	0.18–1.22		
	Other LBCL	24	49.7	22	70.3	**1.86**	0.69–5.04			24	83.3	22	90.9	**1.93**	0.35–10.52		
NanoString COO	NanoString GCB	187	65.9	170	65.8	**1.07**	0.74–1.56			187	82.9	170	82.3	**0.99**	0.60–1.61		
	NanoString ABC	106	72.5	129	45.8	**0.38**	0.24–0.59			106	84.6	129	69.9	**0.49**	0.28–0.88		
	NanoString UNC	44	55.2	53	70.8	**1.60**	0.79–3.25			44	76.9	53	94.2	**4.46**	1.23–16.21		
	Unknown	103	60.2	87	59.7	**0.83**	0.51–1.33			103	81.3	87	79.0	**0.80**	0.42–1.51		
Double expressor by IHC	DEL	139	63.1	151	50.0	**0.65**	0.45–0.94			139	76.4	151	73.0	**0.84**	0.53–1.33		
	Non DEL	223	66.6	215	64.7	**0.89**	0.64–1.24			223	86.3	215	82.8	**0.81**	0.51–1.30		
	Unknown	78	63.7	73	63.5	**0.84**	0.48–1.47			78	81.6	73	84.1	**1.18**	0.53–2.59		

- **Note that these are subgroup analyses**

Salles et al ASH Annual Meeting 2024

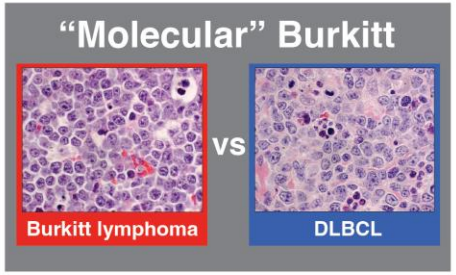
Dark zone lymphomas: converging evidence

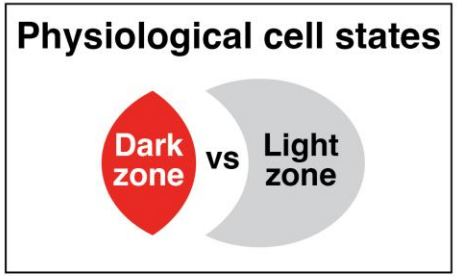


Dave et al N Engl J Med 2006
Hummel et al N Engl J Med 2006
Sha et al J Clin Oncol 2019

"Molecular high-grade" signature

Dark zone lymphomas: converging evidence



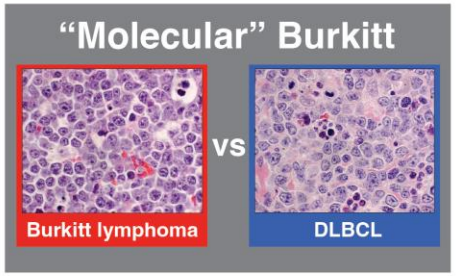


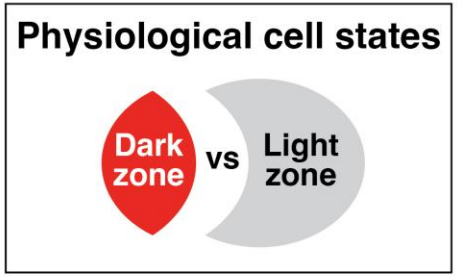
Dave et al N Engl J Med 2006
Hummel et al N Engl J Med 2006
Sha et al J Clin Oncol 2019

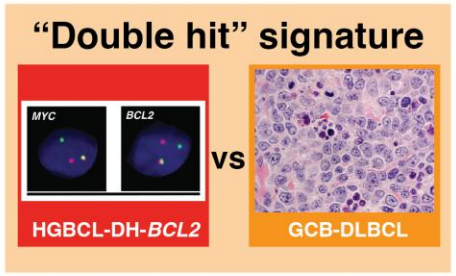
Victora et al Blood 2012
Dybkær et al J Clin Oncol 2015
Holmes et al J Exp Med 2020

"Molecular high-grade" signature

Dark zone lymphomas: converging evidence







Dave et al N Engl J Med 2006
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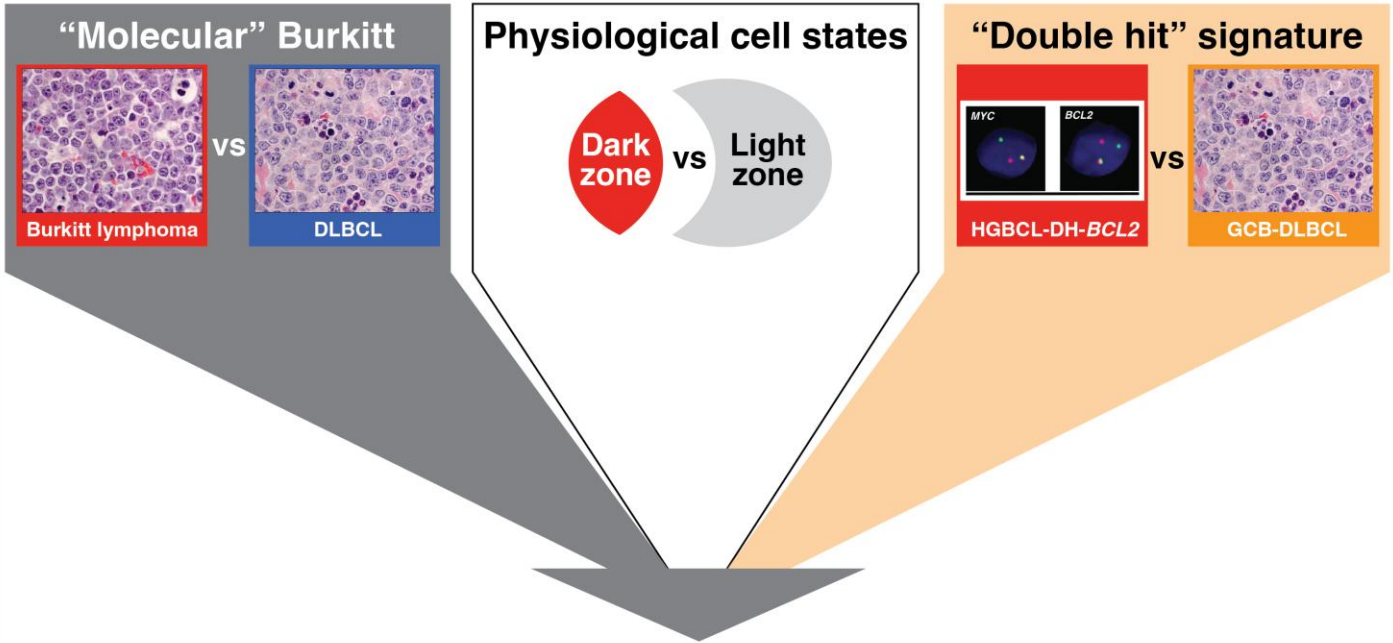
Victora et al Blood 2012
Dybkær et al J Clin Oncol 2015
Holmes et al J Exp Med 2020

Ennishi et al J Clin Oncol 2019
Alduaij et al Blood 2023

"Molecular high-grade" signature

"Dark zone" signature (DZsig)

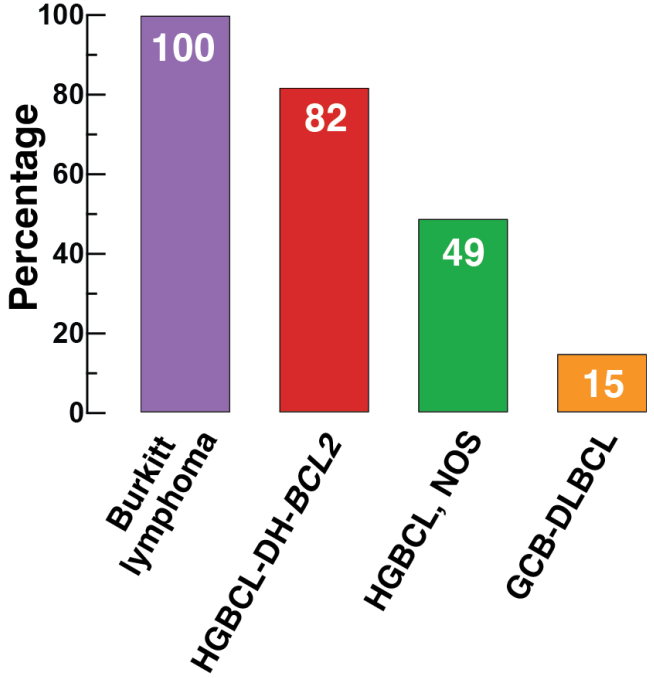
Dark zone lymphomas: converging evidence



Dark zone lymphoma

An umbrella term encompassing lymphomas that phenocopy B cells from the germinal center dark zone

Dark zone lymphomas



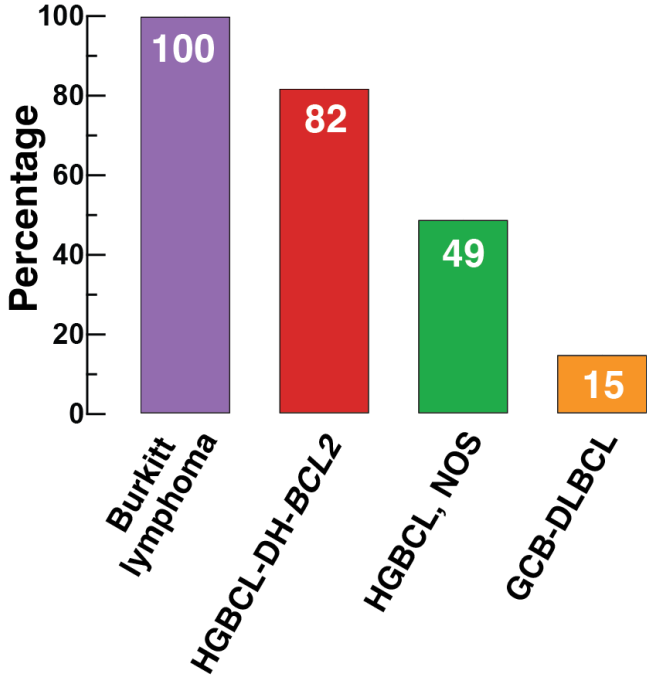
Defined ICC/WHO entities:

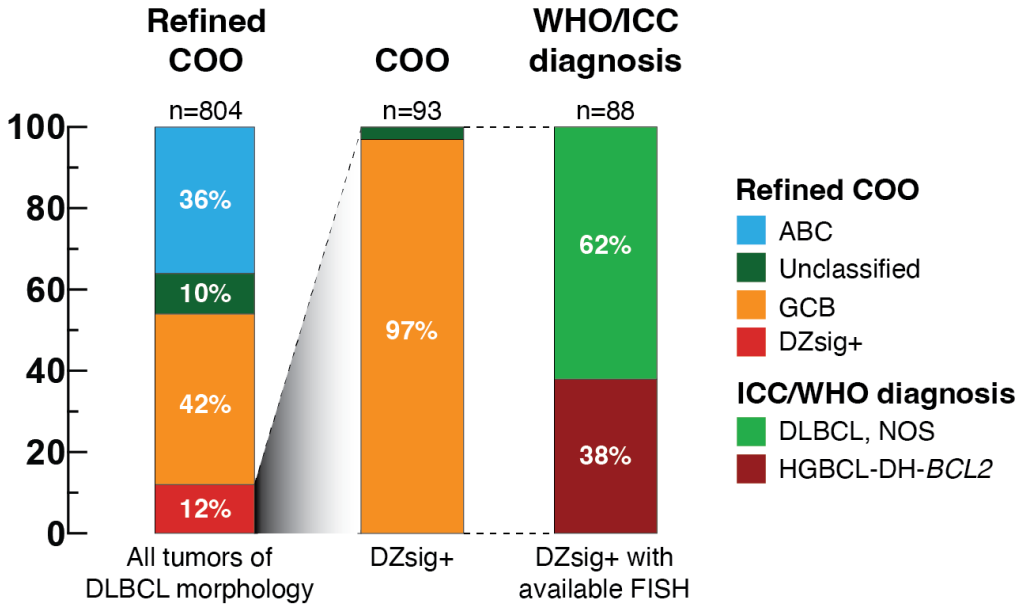
- **All Burkitt lymphoma**
- **Most HGBCL-DH-*BCL2* (“double hit”)**

Not otherwise specified groups:

- **Half of high-grade B-cell lymphoma, NOS**
- **15% of GCB-DLBCL, NOS**

Dark zone lymphomas





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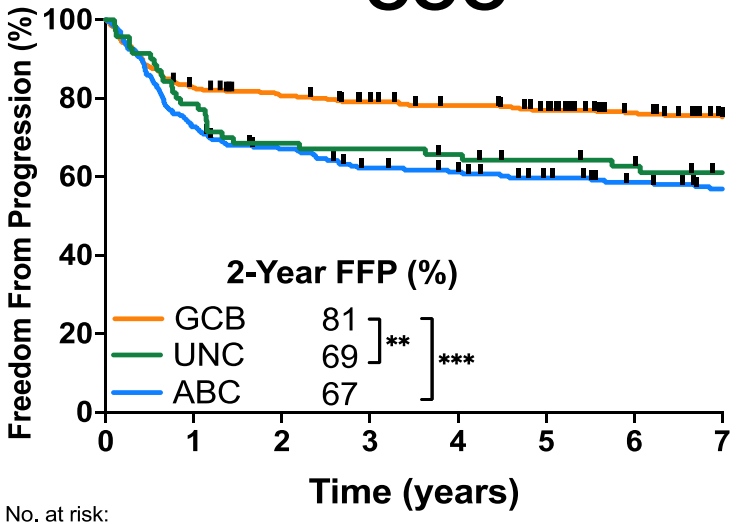
Dark zone lymphomas: outcomes

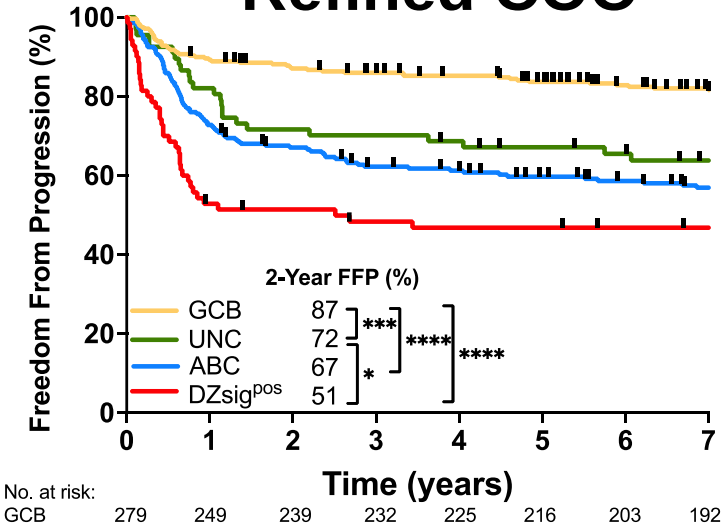
COO



No. at risk:

GCB	346	285	273	263	255	246	231	218
UNC	70	56	49	48	46	43	41	37
ABC	213	157	140	127	123	114	107	100

Refined COO



No. at risk:

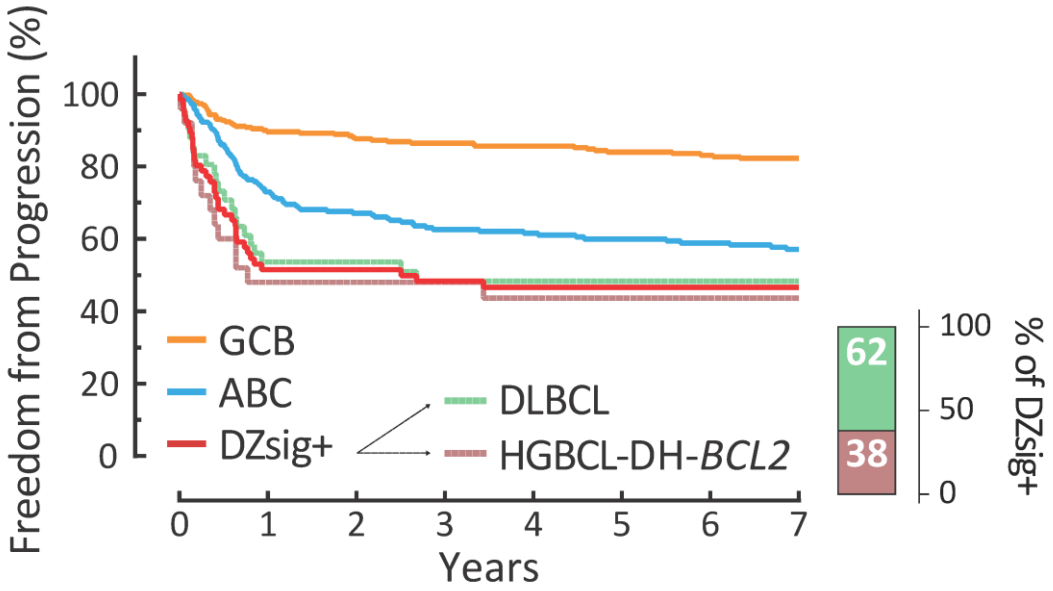
GCB	279	249	239	232	225	216	203	192
UNC	67	56	49	48	46	43	41	37
ABC	213	157	140	127	123	114	107	100
DZsig^{pos}	70	37	35	33	31	31	29	28

DZsig+ identifies the poorest prognosis group

Removing these tumors from GCB-DLBCL leaves a patient group with excellent outcomes following R-CHOP

Alduaij, Collinge et al Blood 2023

Dark zone lymphomas: poor outcomes whether HGBCL-DH-*BCL2* or not



DZsig+ identifies the poorest prognosis group

Removing these tumors from GCB-DLBCL leaves a patient group with excellent outcomes following R-CHOP

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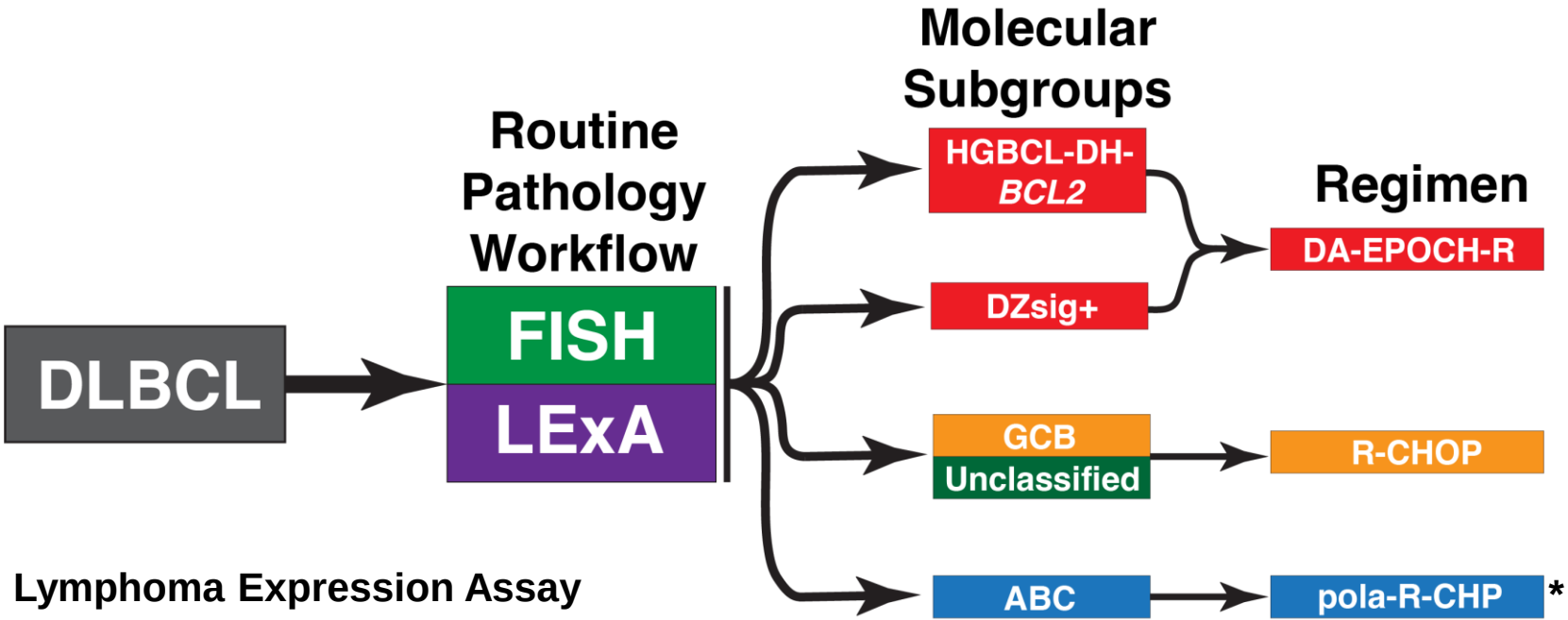
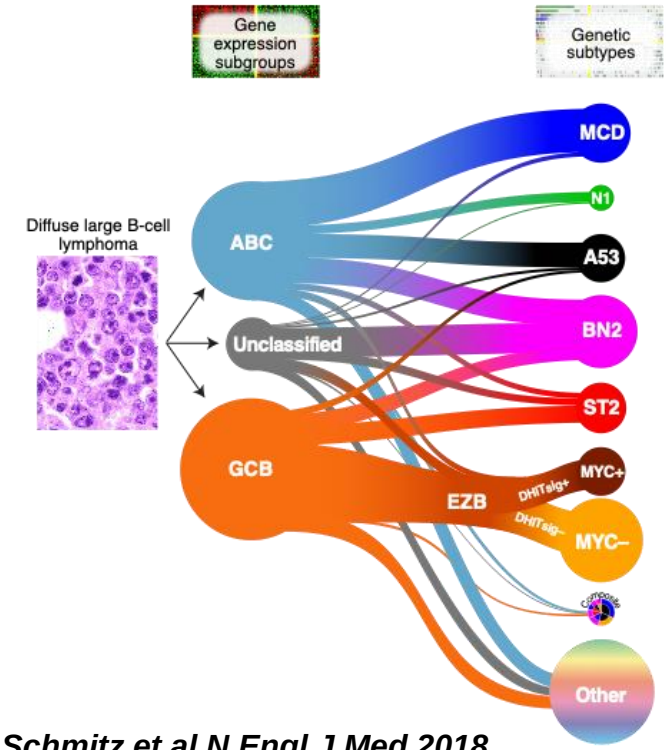
BC Cancer's treatment selection algorithm



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

***Awaiting Canadian funding decision**

Genetics-based subtypes of DLBCL



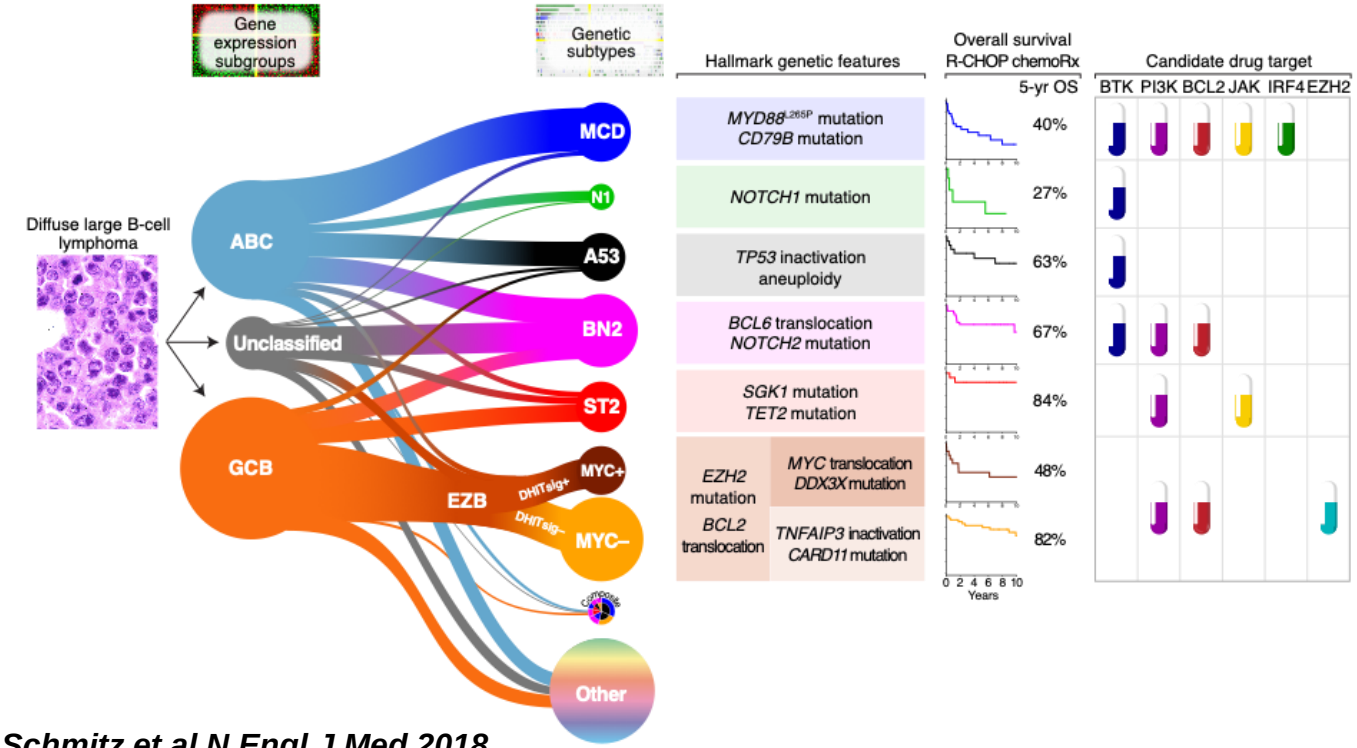
- **Three groups have described similar (but not identical) groupings based on co-occurrence of selected genetic features**
- **Variable requirements for mutation, copy number and rearrangement data**
- **LymphGen was the only algorithm that could be applied on a biopsy-by-biopsy basis**
  - **~35% of tumors that can not be assigned to a group (“Other”)**
- **DLBclass has just been released (December 2024)**
  - **All tumors are assigned to a group (25% at low confidence)**
  - **Optimal performance needs copy number data**

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

Genetics-based subtypes of DLBCL



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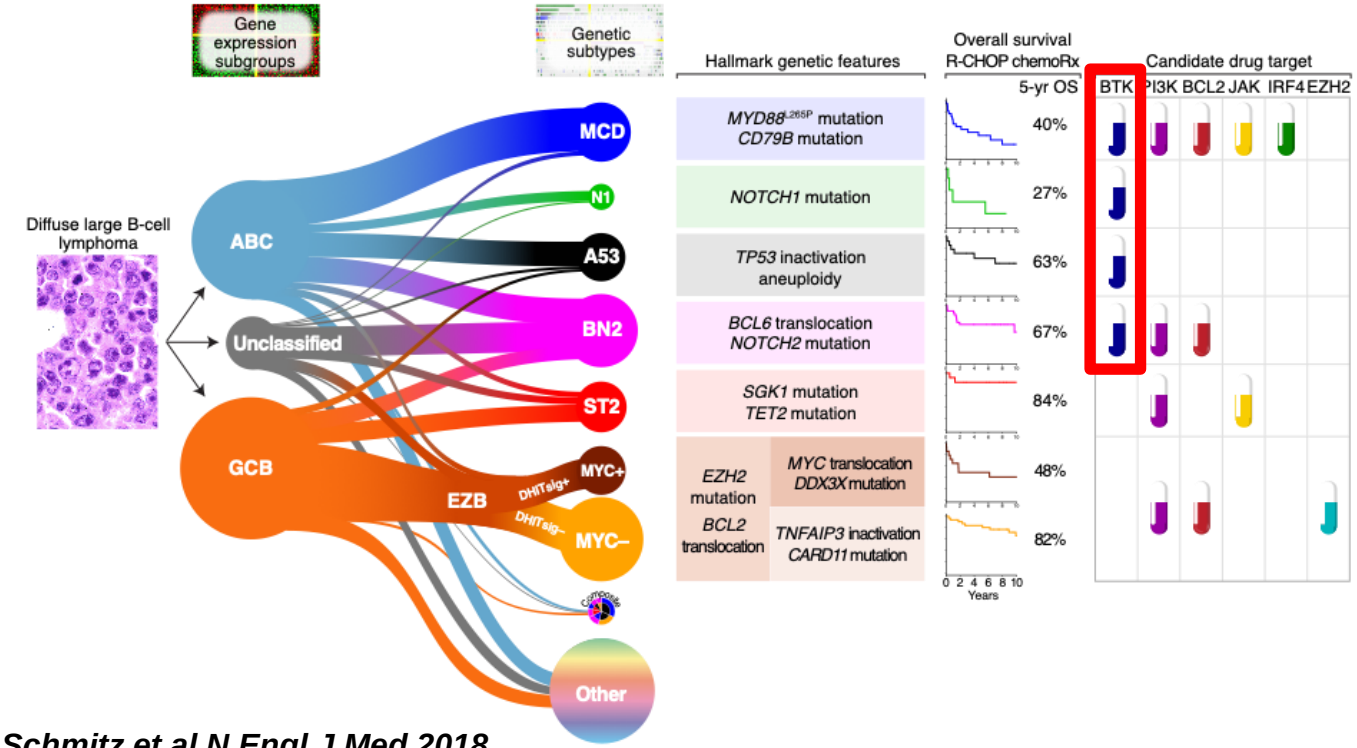
Genetics-based subtypes of DLBCL



Schmitz et al N Engl J Med 2018
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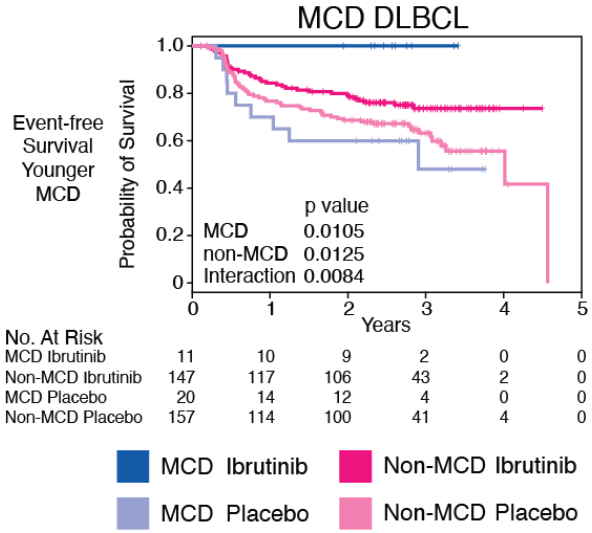
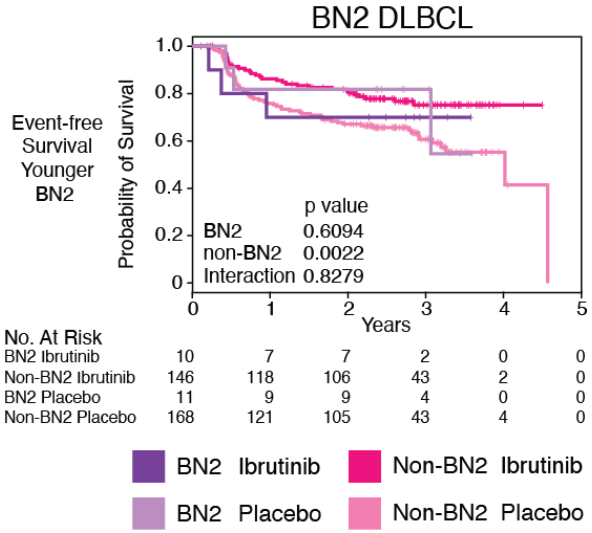
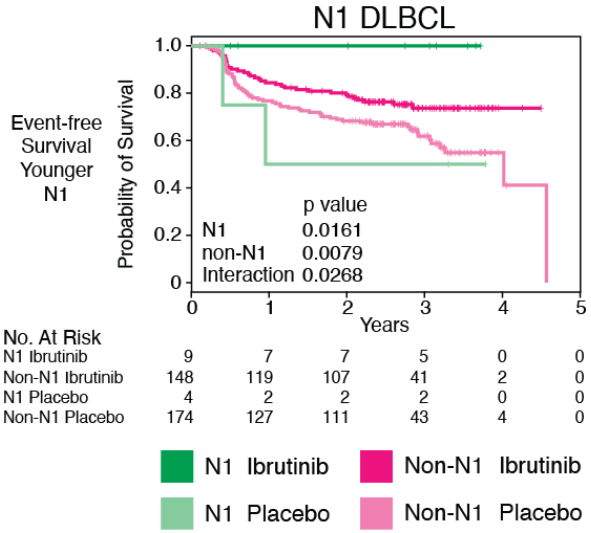
Genetics-based subtypes as a predictive biomarker – retrospective genomic analysis of the PHOENIX trial

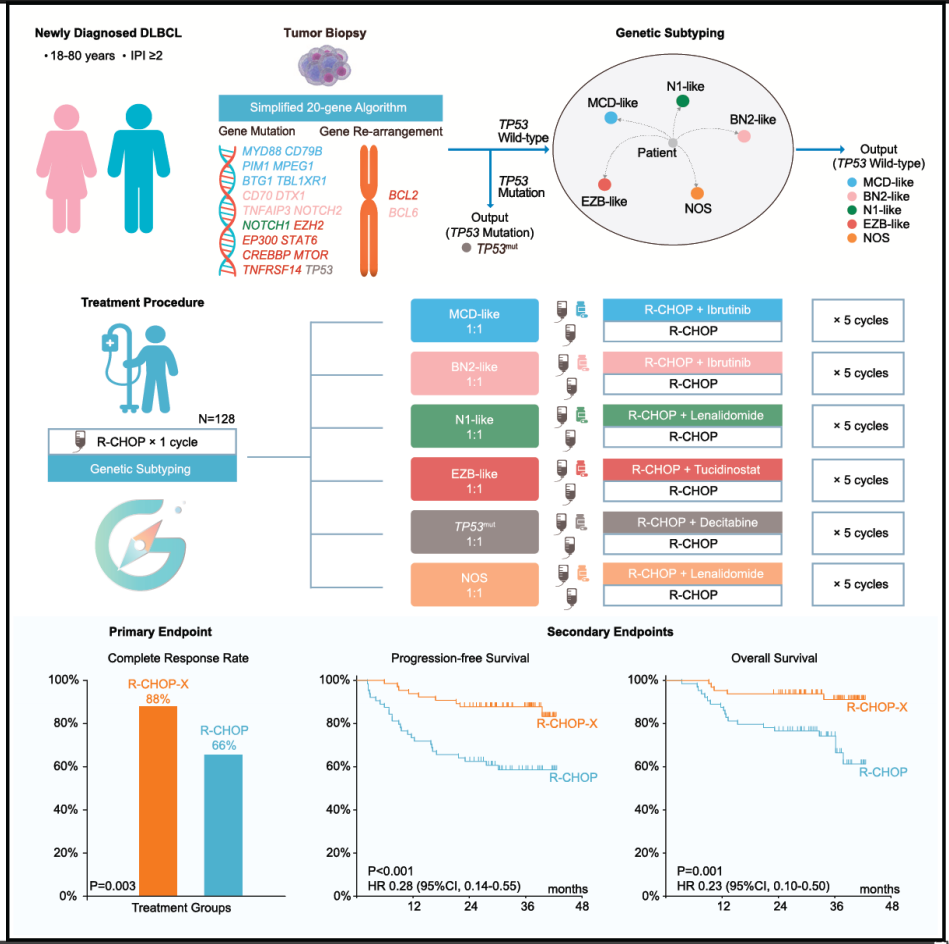






Wilson et al Cancer Cell 2021

Guidance 1 – a model for trials of precision medicine based on genetics-based subtypes



Zhang et al Cancer Cell 2023

Challenges to implementing refined classifications

- **Harmonization of the genetics-based classifications**
- **Settling on (and validating) an appropriate assay**
- **Turn-around-time**

Maurer et al J Clin Oncol 2014

Alduaij, Collinge et al Blood 2023

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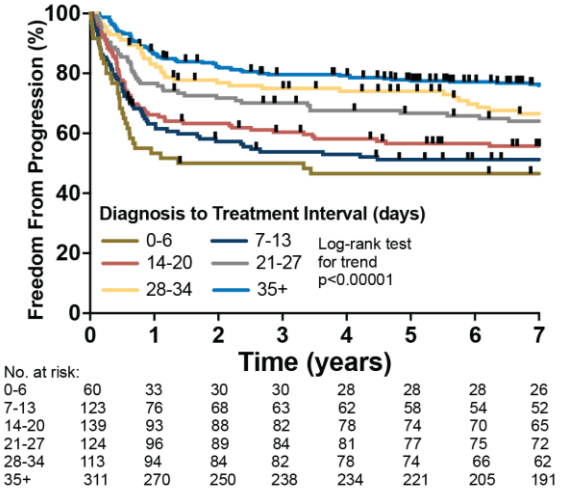
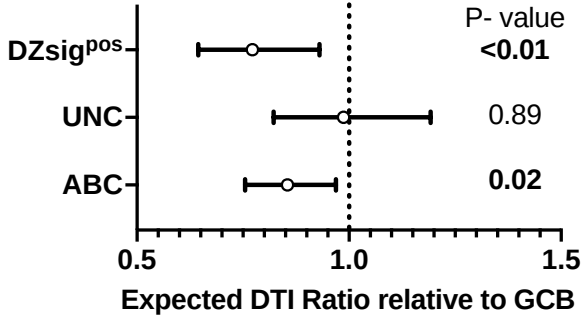


Maurer et al J Clin Oncol 2014

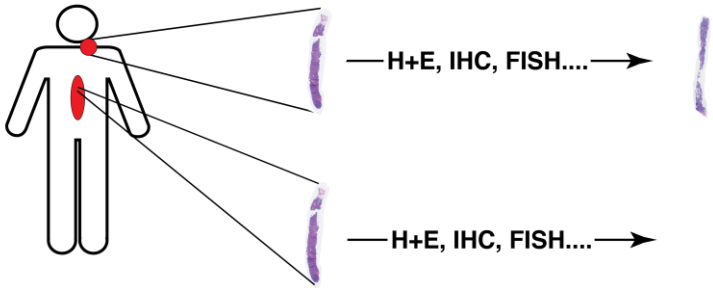


Impact of the genetics-based subtypes is not known

Alduaij, Collinge et al Blood 2023

Challenges to implementing refined classifications

- Harmonization of the genetics-based classifications
- Settling on (and validating) an appropriate assay
- Turn-around-time
- Availability of tissue – small biopsies, bone marrow



- FFPE core needle biopsies are now the norm
- They are a suitable substrate for genomics assays if they are not "exhausted"
- Are we adequately sampling the tumor? This impacts our ability to detect mutational subclones

Maurer et al J Clin Oncol 2014

Alduaij, Collinge et al Blood 2023

Challenges to implementing refined classifications

- Harmonization of the genetics-based classifications
- Settling on (and validating) an appropriate assay
- Turn-around-time
- Availability of tissue – small biopsies, bone marrow
  - Patients diagnosed with core needle biopsies have worse prognosis and are more likely to have inadequate tissue for molecular analyses
  - Patients where molecular analyses were not possible had shorter diagnosis-to-treatment interval
  - Characterization at relapse (particularly ”late”) is important as these can be *de novo* from a common precursor cell population
  - Circulating tumor DNA may be able to fill this gap
- US Intergroup trial based on genetics-based subtypes is in the late planning stage

Maurer et al J Clin Oncol 2014

Desai et al Blood Adv 2022

Hilton et al J Clin Onocl 2023
Alduaij, Collinge et al Blood 2023