L’ottimizzazione diagnostica del DLBCL

Stefano A. Pileri

Istituto Europeo di Oncologia

MONDO LINFOMI:
UN’INCREDIBILE DINAMICITÀ

4 OTTOBRE 2023
Unahotels Decò

Roma

Predominantly nodal

Diffuse large B-cell lymphoma, NOS

Germinal center B-cell subtype

Activated B-cell subtype

Large B-cell lymphoma with 11q aberration*

T cell/histiocyte-rich large B-cell lymphoma

Extranodal

Primary diffuse large B-cell lymphoma of the central nervous system

Primary diffuse large B-cell lymphoma of the testis*

Primary cutaneous diffuse large B-cell lymphoma, leg type

Intravascular large B-cell lymphoma

*HHV-8 and Epstein-Barr virus–negative primary effusion-based lymphoma**

Primary mediastinal large B-cell lymphoma

Mediastinal gray-zone lymphoma*

Epstein-Barr virus related

Epstein-Barr virus–positive diffuse large B-cell lymphoma, NOS

Diffuse large B-cell lymphoma associated with chronic inflammation

Fibrin-associated diffuse large B-cell lymphoma

Large cell lymphoma with terminal B-cell differentiation

ALK-positive large B-cell lymphoma

Plasmablastic lymphoma

HHV-8–positive diffuse large B-cell lymphoma, NOS

Primary effusion lymphoma

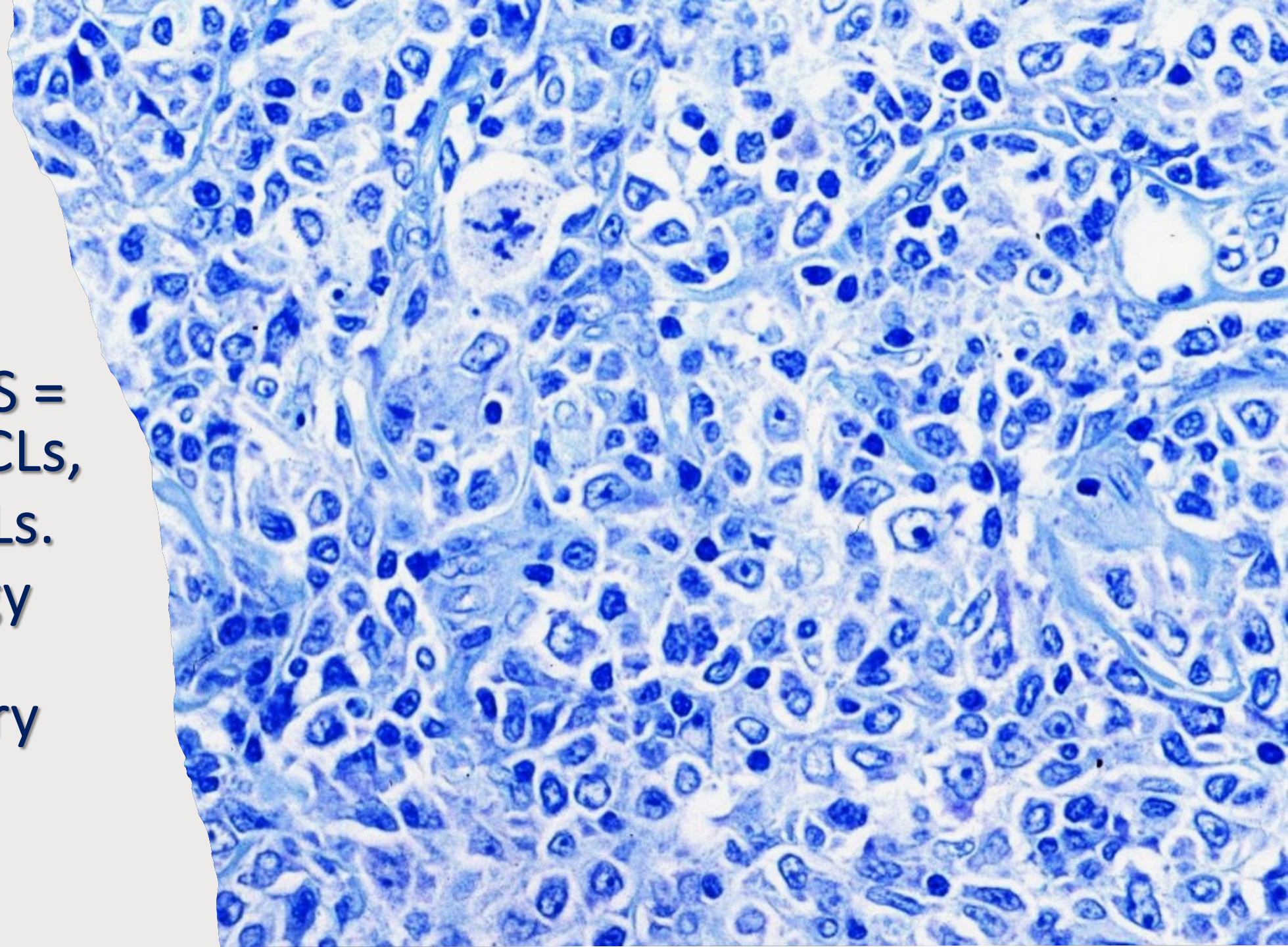
High grade B-cell lymphomas¶

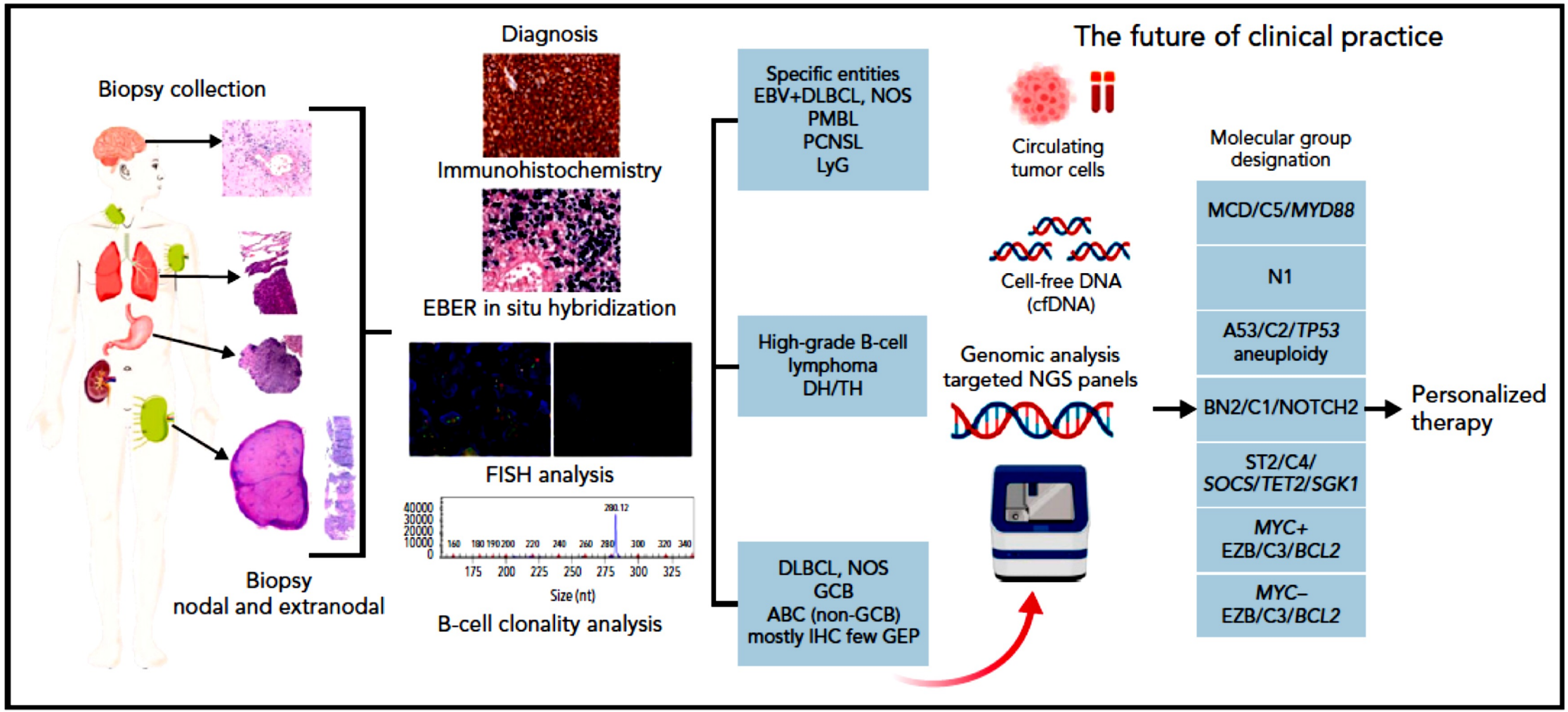
High-grade B-cell lymphoma, with MYC and BCL2 rearrangements*

*High-grade B-cell lymphoma with MYC and BCL6 rearrangements**

DLBCL, NOS = 80% of DBCLs, 40% of NHLs.

Morphology not contributory

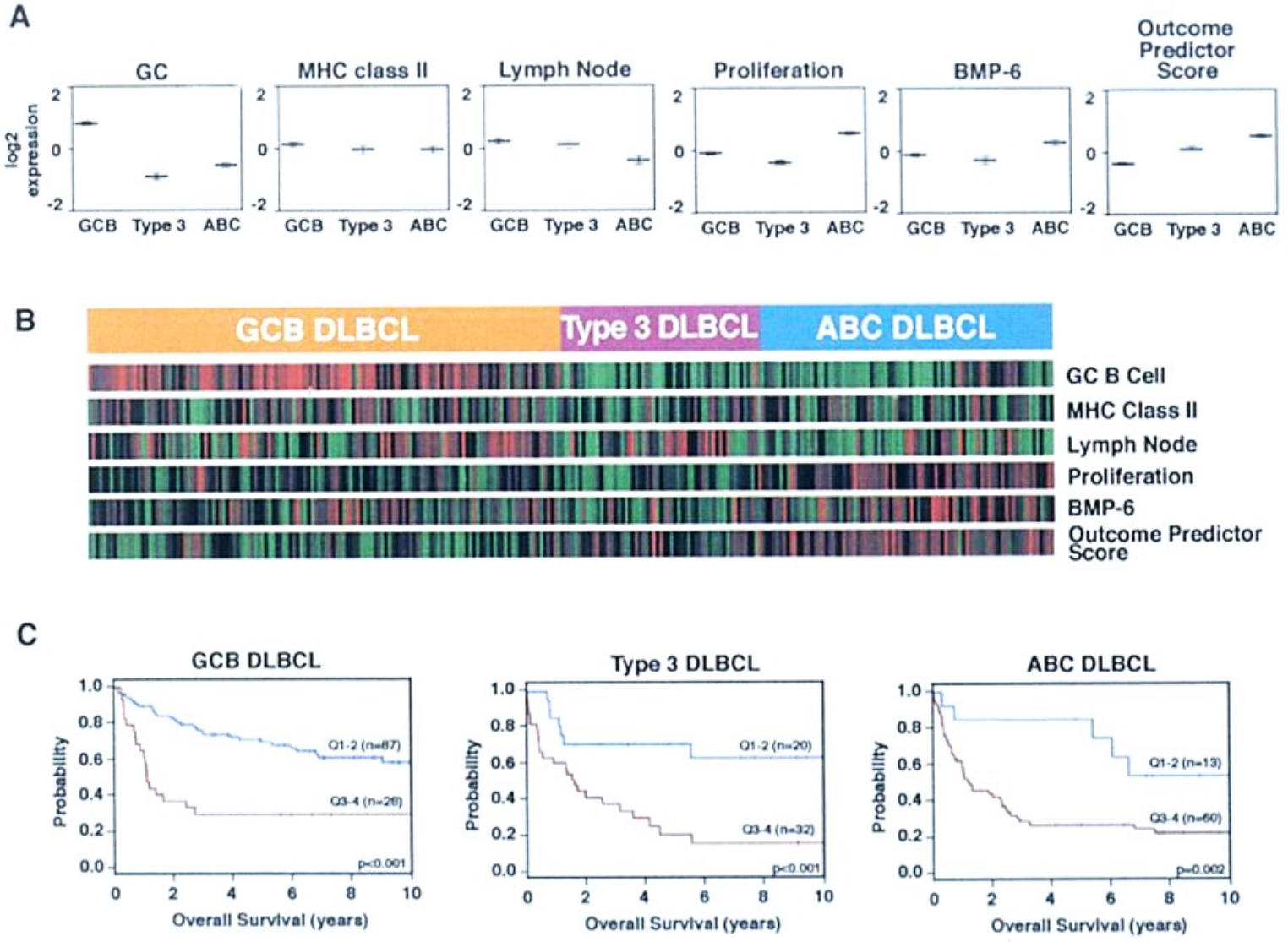




International Consensus Classification, Blood, 2022

Cell of Origin (COO)

Rosenwald A et al. NEJM, 346:1937-47, 2002. Wright G et al. PNAS, 100:9991-6, 2003.



Targeted Digital Gene expression profiling

Smaller samples

FFPE tissue, Blood, Cell Lines, Etc.

Input
Lyse and Go Protocols

More biology

Proteins

- **Aβ**
- **APOE**
- **Iba1**
- **HLA-DR**

Genes

- Apoe
- Atm
- Akt1
- Bcl2
- Crip1
- Abcc3
- Akt2
- Cx3cr1
- Ago4
- Snca
- Pik3r1
- Mapk10
- Casp3
- Gria2
- Atp6v0e
- Bid
- Il1r1
- Anxa1
- Atg9a
- Bin1
- Ptgs2
- Grin2a
- Pik3ca
- Anapc15
- Pik3cb
- C3
- Bax
- Ngfr
- Bcas1
- Casp7
- Agt
- Creb1
- Csf1r
- Bmi1
- Pten
- Fas
- Cd33
- Pla2g4a
- Casp8
- Atp6v1a
- Birc2
- Cd69
- Mdm2
- Bad
- Cldn5
- Jun

blood® 28 SEPTEMBER 2023 | VOLUME 142, NUMBER 13 1143

BRD4 inhibition sensitizes diffuse large B-cell lymphoma cells to ferroptosis

Anja Schmitt,[1] Melanie Grimm,[2] Nina Kreienkamp,[1] Hannah Junge,[1] Jan Labisch,[1] Laurentz Schuhknecht,[3] Caroline Schönfeld,[2] Elsa Görsch,[4] Alessia Tibello,[5] Kerstin Menck,[1] Annalen Bleckmann,[1] Claudia Lengerke,[4] Frank Rosenbauer,[5] Michael Grau,[1] Mattia Zampieri,[3] Klaus Schulze-Osthoff,[2,6,7] Pavel Klener,[8,9] Alexandra Dolnikova,[8] Georg Lenz,[1] and Stephan Hailfinger[1]

[1]Department of Medicine A, Hematology, Oncology and Pneumology, University Hospital Münster, Münster, Germany; [2]Department of Molecular Medicine, Interfaculty Institute of Biochemistry, University of Tübingen, Tübingen, Germany; [3]Department of Biomedicine, University of Basel, Basel, Switzerland; [4]Department for Internal Medicine, Internal Medicine II, Hematology, Oncology, Clinical Immunology and Rheumatology, University Hospital Tübingen, Tübingen, Germany; [5]Institute of Molecular Tumor Biology, Faculty of Medicine, University of Münster, Münster, Germany; [6]German Cancer Consortium (Deutsches Konsortium für Translationale Krebsforschung) and German Cancer Research Center (Deutsches Krebsforschungszentrum), Heidelberg, Germany; [7]Cluster of Excellence iFIT (EXC 2180) "Image-Guided and Functionally Instructed Tumor Therapies," University of Tübingen, Tübingen, Germany; [8]Institute of Pathological Physiology, First Faculty of Medicine; and [9]First Department of Medicine, Hematology, University General Hospital and First Faculty of Medicine, Charles University Prague, Prague, Czech Republic

KEY POINTS

- **BRD4 protects DLBCL cells from ferroptosis by positively regulating the expression of FSP1.**
- **BET inhibitors increase the susceptibility of GCB-DLBCL cells to ferroptosis and thus promote the toxicity of DMF both in vitro and in vivo.**

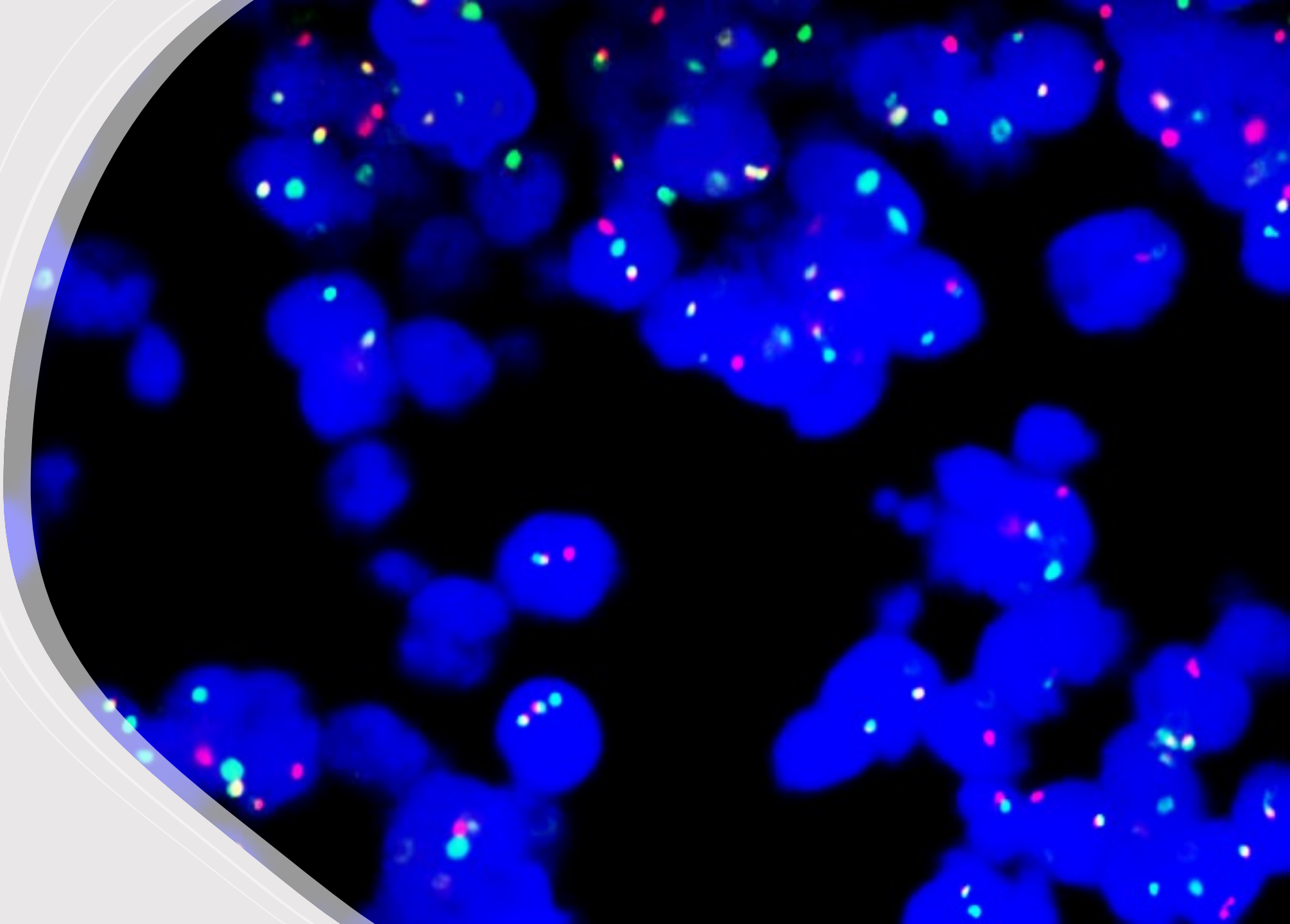
Diffuse large B-cell lymphoma (DLBCL), the most common form of non-Hodgkin lymphoma, is characterized by an aggressive clinical course. In approximately one-third of patients with DLBCL, first-line multiagent immunochemotherapy fails to produce a durable response. Molecular heterogeneity and apoptosis resistance pose major therapeutic challenges in DLBCL treatment. To circumvent apoptosis resistance, the induction of ferroptosis might represent a promising strategy for lymphoma therapy. In this study, a compound library, targeting epigenetic modulators, was screened to identify ferroptosis-sensitizing drugs. Strikingly, bromodomain and extra-terminal domain (BET) inhibitors sensitized cells of the germinal center B-cell–like (GCB) subtype of DLBCL to ferroptosis induction and the combination of BET inhibitors with ferroptosis inducers, such as dimethyl fumarate or RSL3, synergized in the killing of DLBCL cells in vitro and in vivo. On the molecular level, the BET protein BRD4 was found to be an essential regulator of ferroptosis suppressor protein 1 expression and thus to protect GCB-DLBCL cells from ferroptosis. Collectively, we identified and characterized BRD4 as an important player in ferroptosis suppression in GCB-DLBCL and provide a rationale for the combination of BET inhibitors with ferroptosis-inducing agents as a novel therapeutic approach for DLBCL treatment.

FISH

MYC
BCL2
BCL6
IRF4
11q

EBER ISH

HHV8



Virchows Archiv (2023) 483:281–298
https://doi.org/10.1007/s00428-023-03590-x

REVIEW AND PERSPECTIVES

Emerging entities: high-grade/large B-cell lymphoma with 11q aberration, large B-cell lymphoma with *IRF4* rearrangement, and new molecular subgroups in large B-cell lymphomas. A report of the 2022 EA4HP/SH lymphoma workshop

Leticia Quintanilla-Martinez[1,2] · Camille Laurent[3] · Lorinda Soma[4] · Siok-Bian Ng[5,6] · Fina Climent[7] · Sarah L. Ondrejka[8] · Alberto Zamo[9] · Andrew Wotherspoon[10] · Laurence de Leval[11] · Stefan Dirnhofer[12] · Lorenzo Leoncini[13]

Virchows Archiv (2023) 483:299–316
https://doi.org/10.1007/s00428-023-03599-2

REVIEW AND PERSPECTIVES

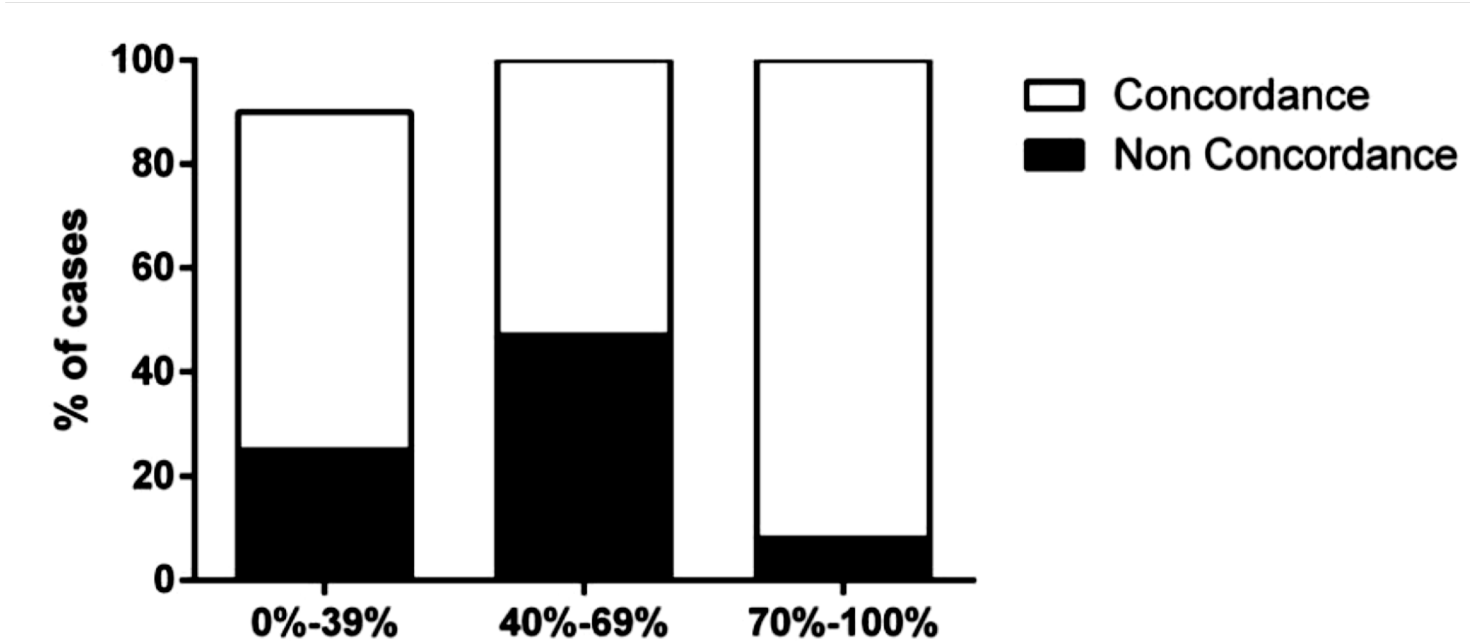
Cavity-based lymphomas: challenges and novel concepts. A report of the 2022 EA4HP/SH lymphoma workshop

Arianna Di Napoli[1] · Lori Soma[2] · Leticia Quintanilla-Martinez[3] · Laurence de Leval[4] · Lorenzo Leoncini[5] · Alberto Zamò[6] · Siok-Bian Ng[7] · Sarah L. Ondrejka[8] · Fina Climent[9] · Andrew Wotherspoon[10] · Stefan Dirnhofer[11]

MYC protein expression scoring and its impact on the prognosis of aggressive B-cell lymphoma patients

by Maria R. Ambrosio, Stefano Lazzi, Giuseppe Lo Bello, Raffaella Santi, Leonardo Del Porro, Maria M. de Santi, Raffaella Guazzo, Lucia Mundo, Luigi Rigacci, Sofia Kovalchuck, Noel Onyango, Alberto Fabbri, Emanuele Cencini, Pier Luigi Zinzani, Francesco Zaja, Francesco Angrilli, Caterina Stelitano, Maria G. Cabras, Giuseppe Spataro, Roshanak Bob, Thomas Menter, Massimo Granai, Gabriele Cevenini, Kikkeri N. Naresh, Harald Stein, Elena Sabattini, and Lorenzo Leoncini

Haematologica 2018 [Epub ahead of print]



editorial

Using Gene Expression Profiling to Move Beyond *MYC/BCL2* Rearrangements in High-Grade Lymphoma

Wing C. Chan, MD[1]

rapid communication

Double-Hit Gene Expression Signature Defines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma

Daisuke Ennishi, PhD[1]; Aixiang Jiang, MSc[1,2]; Merrill Boyle, BSc[1]; Brett Collinge, BSc[1]; Bruno M. Grande, BSc[2]; Susana Ben-Neriah, MSc[1]; Christopher Rushton, BSc[2]; Jeffrey Tang, BSc[2]; Nicole Thomas, BSc[2]; Graham W. Slack, MD[1]; Pedro Farinha, PhD[1]; Katsuyoshi Takata, MD[1]; Tomoko Miyata-Takata, MD[1]; Jeffrey Craig, PhD[1]; Anja Mottok, PhD[3]; Barbara Meissner, PhD[1]; Saeed Saberi, PhD[4]; Ali Bashashati, PhD[4]; Diego Villa, MD[1]; Kerry J. Savage, MD[1]; Laurie H. Sehn, MD[1]; Robert Kridel, PhD[5]; Andrew J. Mungall, PhD[6]; Marco A. Marra, PhD[6]; Sohrab P. Shah, PhD[4]; Christian Steidl, MD[1]; Joseph M. Connors, MD[1]; Randy D. Gascoyne, MD[1]; Ryan D. Morin, PhD[2]; and David W. Scott, PhD[1]

original report

Molecular High-Grade B-Cell Lymphoma: Defining a Poor-Risk Group That Requires Different Approaches to Therapy

Chulin Sha, PhD[1]; Sharon Barrans, PhD[2]; Francesco Cucco, PhD[3]; Michael A. Bentley, DPhil[1]; Matthew A. Care, PhD[1]; Thomas Cummin, MD[4]; Hannah Kennedy, PhD[3]; Joe S. Thompson, MPhil[3]; Rahman Uddin, MSc[1]; Lisa Worrillow, PhD[2]; Rebecca Chalkley, MPhil[2]; Moniek van Hoppe, MSc[2]; Sophia Ahmed, PhD[1]; Tom Maishman, PhD[4]; Josh Caddy, BSc[4]; Anna Schuh, MD[5]; Christoph Mamot, MD[6]; Catherine Burton, MD[2]; Reuben Tooze, PhD[1]; Andrew Davies, PhD[4]; Ming-Qing Du, PhD[3]; Peter W.M. Johnson, MD[4]; and David R. Westhead, DPhil[1]

A 3-gene signature based on MYC, BCL-2 and NFKBIA improves risk stratification in diffuse large B-cell lymphoma

by Enrico Derenzini, Saveria Mazzara, Federica Melle, Giovanna Motta, Marco Fabbri, Riccardo Bruna, Claudio Agostinelli, Alessandra Cesano, Chiara Antonia Corsini, Ning Chen, Simona Righi, Elena Sabattini, Annalisa Chiappella, Angelica Calleri, Stefano Fiori, Valentina Tabanelli, Antonello Cabras, Giancarlo Pruneri, Umberto Vitolo, Alessandro Massimo Gianni, Alessandro Rambaldi, Paolo Corradini, Pier Luigi Zinzani, Corrado Tarella, and Stefano Pileri

Haematologica 2020 [Epub ahead of print]

Targeted Digital Gene Expression Profiling

RefSeq NCBI	Gene	Length NCBI	Protein aa	
NM_002467.4	MYC	2379	454	
NM_000633.2	BCL2	6492	239	
NM_012452.2	TNFRSF13B	1377	293	
NM_014240.2	LIMD1	6284	676	
NM_001195286.1	IRF4	5329	451	*
NM_194071.3	CREB3L2	7471	520	*
NM_006875.3	PIM2	2234	311	
NM_001302826.1	CYB5R	1713	276	
NM_003929.2	RAB7L1	3324	203	
NM_174908.3	CCDC50	8421	306	
NM_015361.3	R3HDM1	4722	1099	
NM_017706.4	WDR55	2580	383	
NM_020701.3	ISY1	3778	285	
NM_014607.3	UBXN4	4018	508	
NM_030961.2	TRIM56	4723	755	
NM_000902.3	MME	5643	750	
NM_001284275.1	SERPINA9	1661	435	*
NM_024701.3	ASB13	2736	278	
NM_018717.4	MAML3	7086	1138	
NM_002221.3	ITPKB	6162	946	
NM_001080416.3	MYBL1	5192	752	
NM_004230.3	S1PR2	3589	353	
NM_020529.2	NFKBIA	1579	371	
NM_139276.2	STAT3	4978	770	
NM_000314.6	PTEN	8718	403	*
NM_006218.2	PKI3CA	3724	1068	

26-gene-panel for COO & key-genes Haematologica, 2020

224 DLBCL patients
FFPE specimens

DLCL04 (n = 130)
R-HDS (n = 94)

NanoString
insufficient mRNA n = 17

207 DLBCL patients

IHC
non-NOS n = 21

186 DLBCL patients

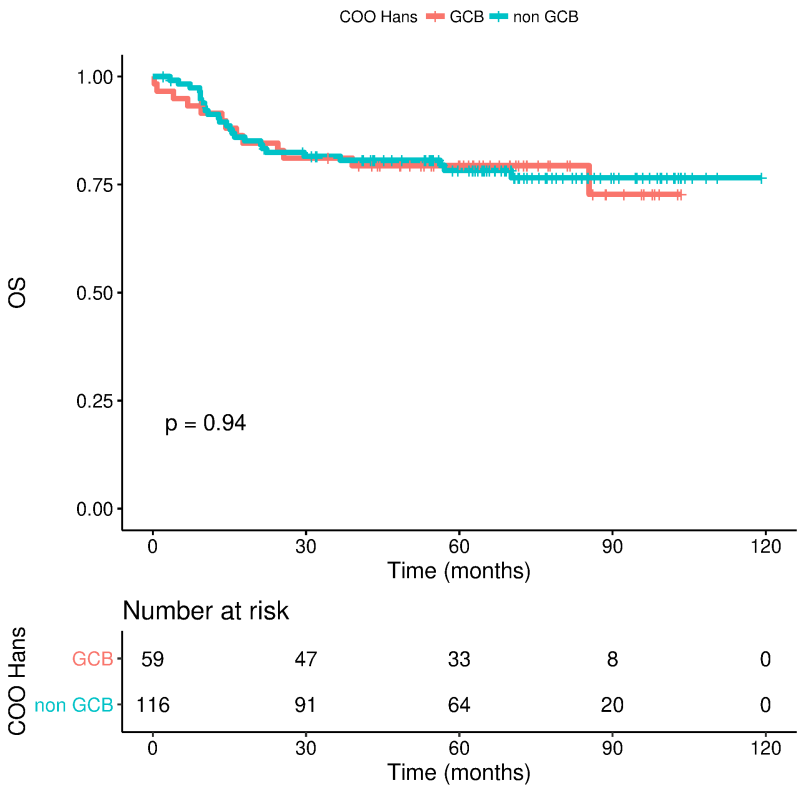
DLCL04 (n = 99)
R-HDS (n = 87)

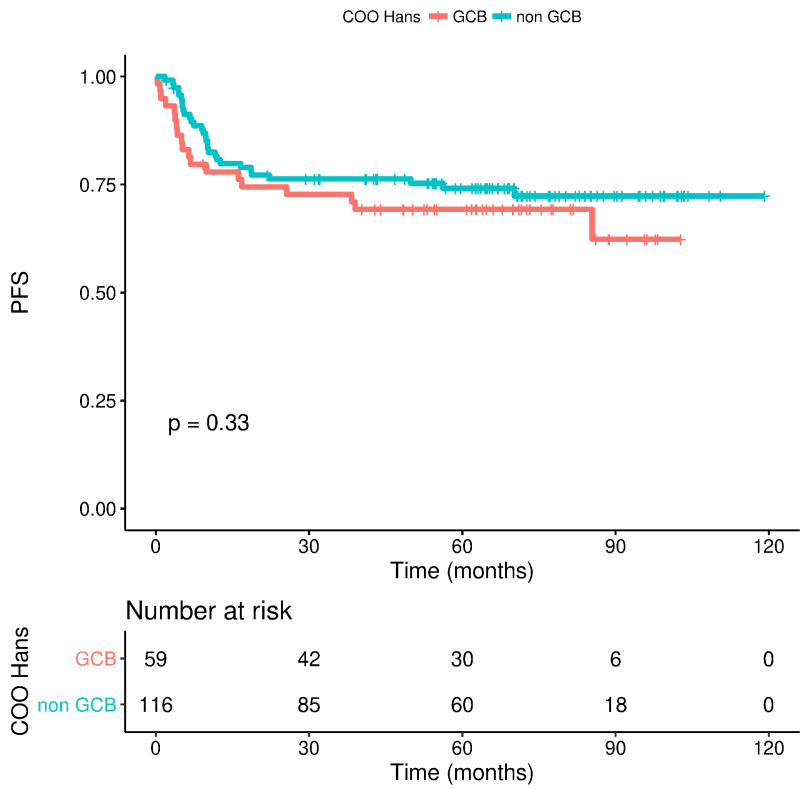
In both trials, only patients staged III-IV were enrolled, all treated with R-CHOP or R-CHOP-like therapies followed or not by Auto-SCT.

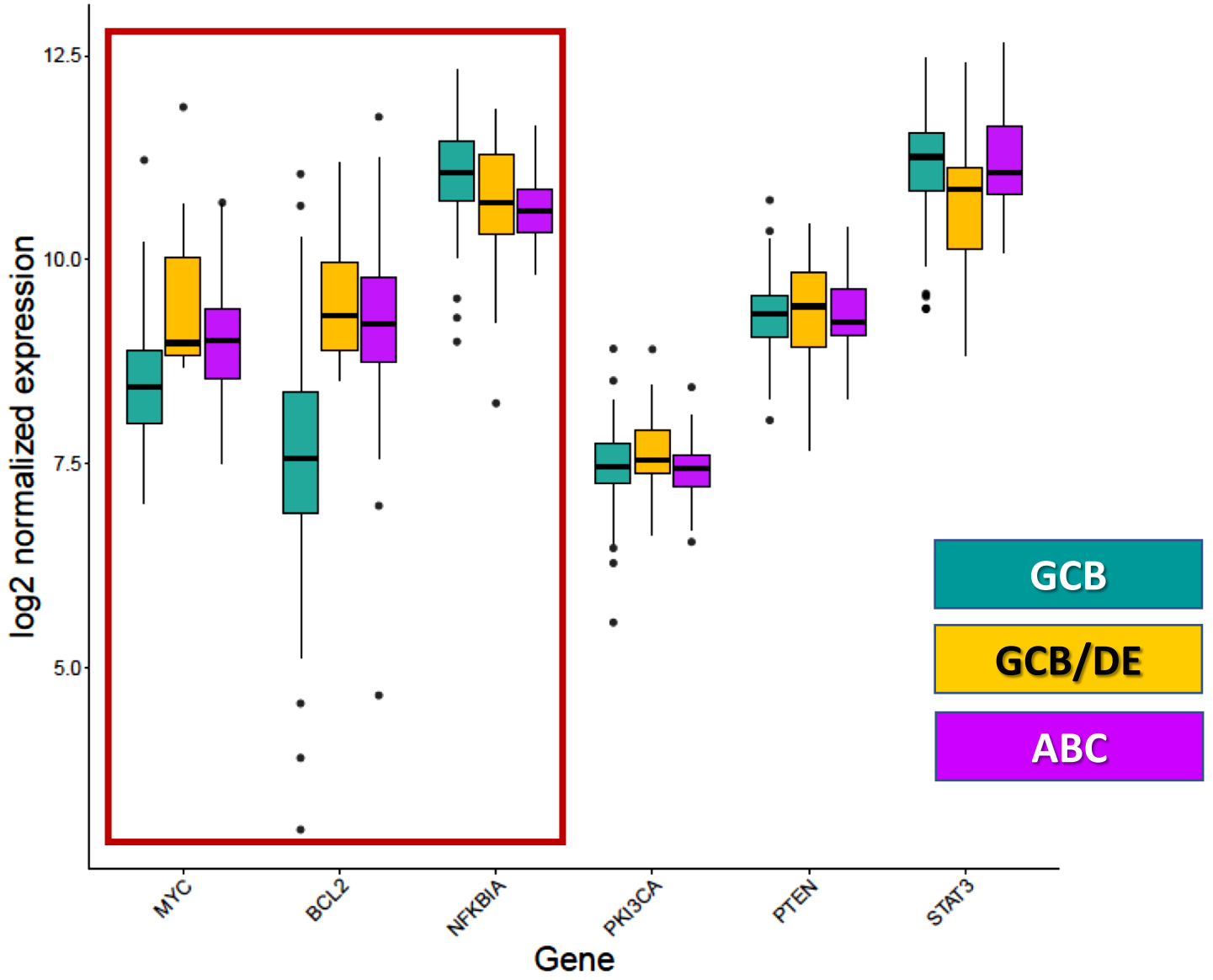
The mean age was 52 yr.s (18 – 65)

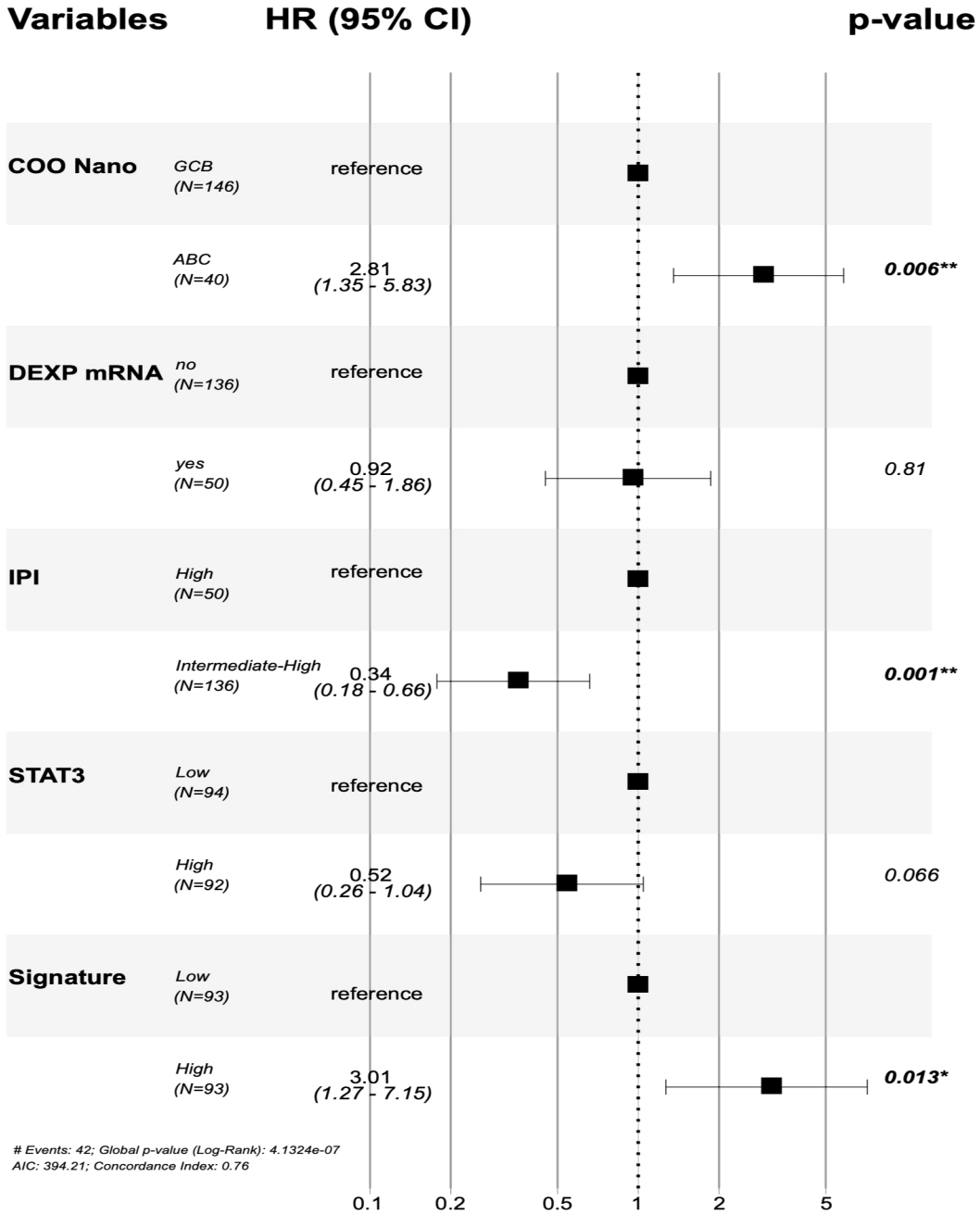
All the cases were studied by immunohistochemistry, targeted GEP and FISH (*BCL2*, *MYC* and *BCL6*).

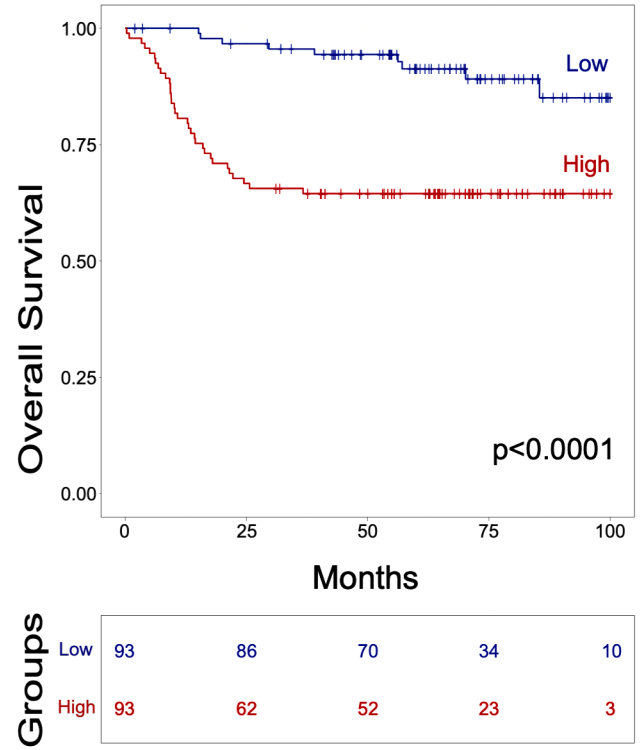
COO according to Hans' classifier





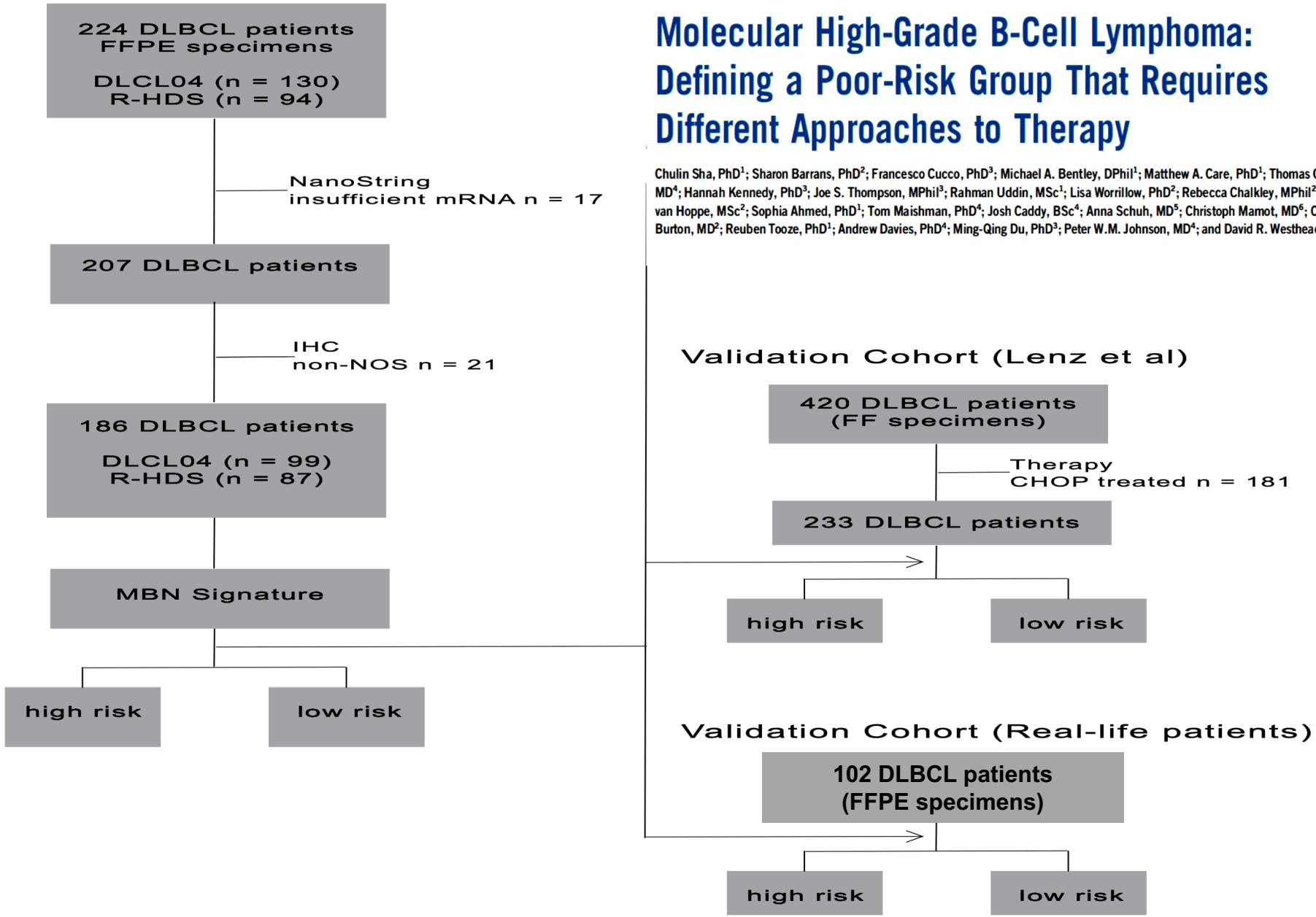

log2 normalized expression
12.5
10.0
7.5
5.0
MYC
BCL2
NFKBIA
PIK3CA
PTEN
STAT3
Gene
GCB
GCB/DE
ABC


Variables
HR (95% CI)
p-value
COO Nano
GCB (N=146)
reference
ABC (N=40)
2.81 (1.35 - 5.83)
0.006**
DEXP mRNA
no (N=136)
reference
yes (N=50)
0.92 (0.45 - 1.86)
0.81
IPI
High (N=50)
reference
Intermediate-High (N=136)
0.34 (0.18 - 0.66)
0.001**
STAT3
Low (N=94)
reference
High (N=92)
0.52 (0.26 - 1.04)
0.066
Signature
Low (N=93)
reference
High (N=93)
3.01 (1.27 - 7.15)
0.013*
Events: 42; Global p-value (Log-Rank): 4.1324e-07
AIC: 394.21; Concordance Index: 0.76
0.1
0.2
0.5
1
2
5

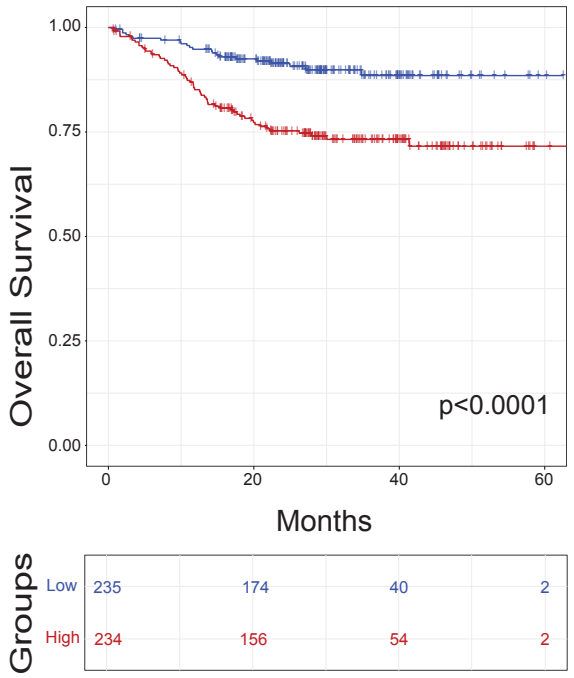

Overall Survival
1.00
0.75
0.50
0.25
0.00
Low
High
p<0.0001
0
25
50
75
100
Months
Groups
Low 93 86 70 34 10
High 93 62 52 23 3

Molecular High-Grade B-Cell Lymphoma: Defining a Poor-Risk Group That Requires Different Approaches to Therapy

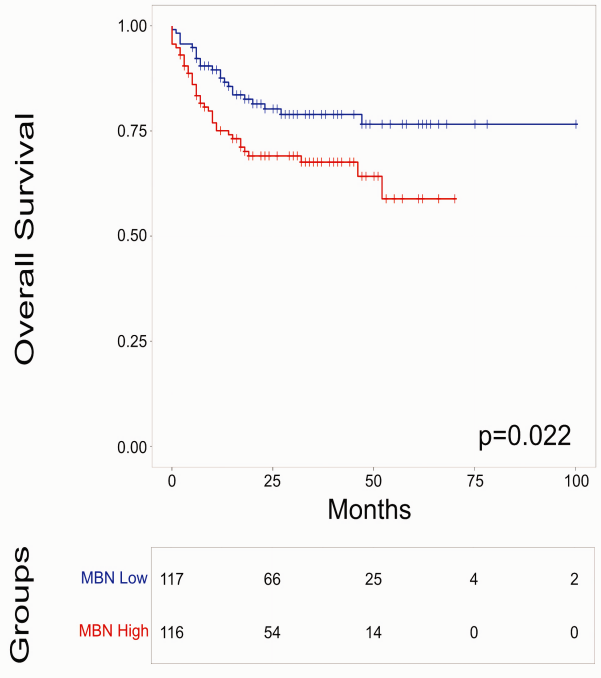
Chulin Sha, PhD[1]; Sharon Barrans, PhD[2]; Francesco Cucco, PhD[3]; Michael A. Bentley, DPhil[1]; Matthew A. Care, PhD[1]; Thomas Cummin, MD[4]; Hannah Kennedy, PhD[3]; Joe S. Thompson, MPhil[3]; Rahman Uddin, MSc[1]; Lisa Worrillow, PhD[2]; Rebecca Chalkley, MPhil[2]; Moniek van Hoppe, MSc[2]; Sophia Ahmed, PhD[1]; Tom Maishman, PhD[4]; Josh Caddy, BSc[4]; Anna Schuh, MD[5]; Christoph Mamot, MD[6]; Catherine Burton, MD[2]; Reuben Tooze, PhD[1]; Andrew Davies, PhD[4]; Ming-Qing Du, PhD[3]; Peter W.M. Johnson, MD[4]; and David R. Westhead, DPhil[1]



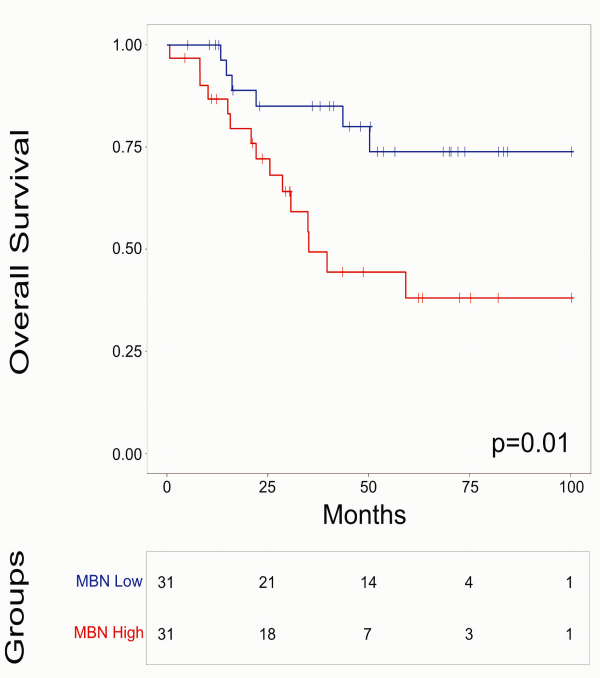
Sha's



Lenz's

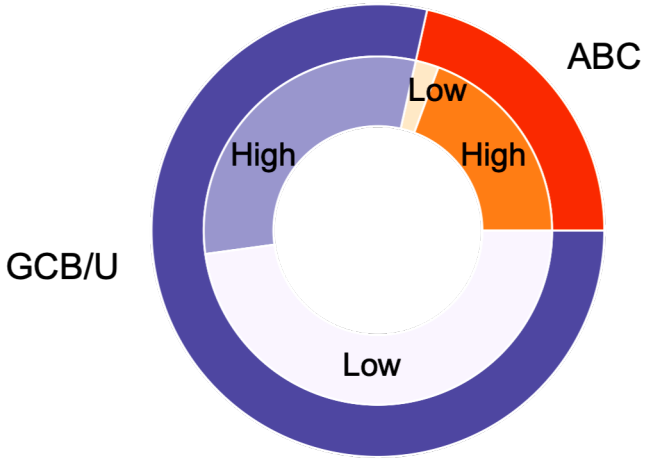


Real-life

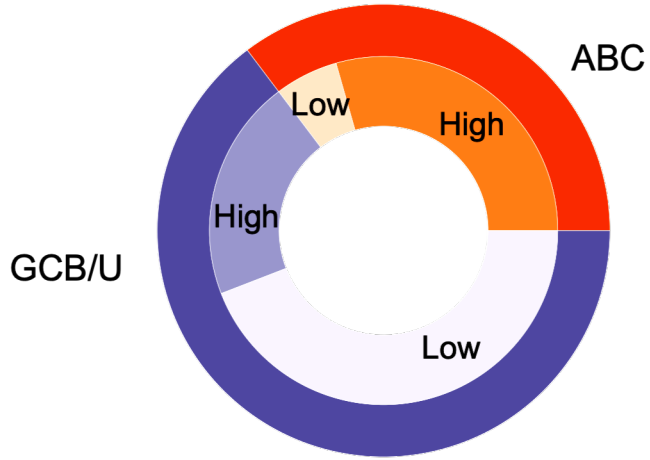


R-CHOP

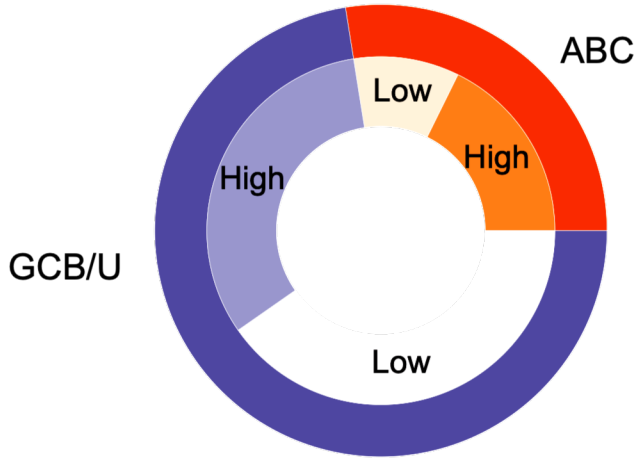
TRIALS n = 186

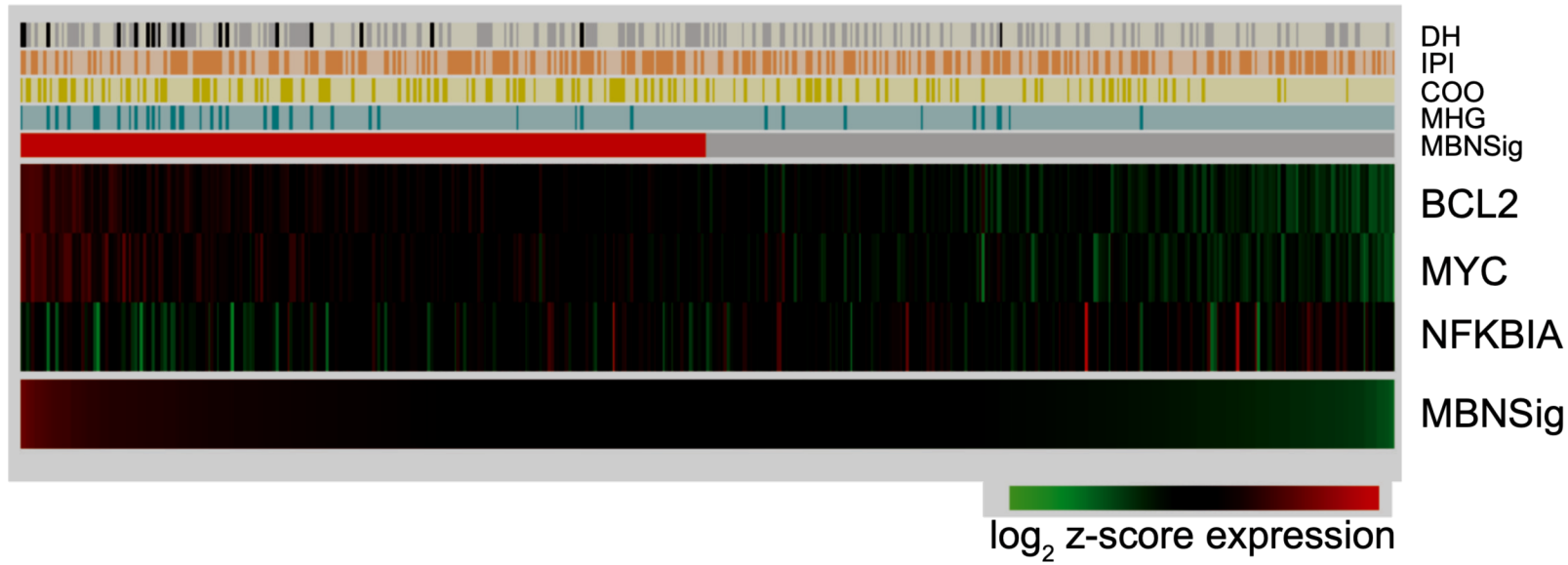


REAL-LIFE n = 102



SHA COHORT n = 469





MBNSig	Positive	Negative	
MHG	MHG	Not MHG	
COO	ABC	Not ABC	
IPI	High	Low	
DH	Positive	Negative	NA

Longitudinal expression profiling identifies a poor risk subset of patients with ABC-type diffuse large B-cell lymphoma

Submitted 18 March 2022; accepted 25 July 2022; prepublished online on *Blood Advances* First Edition 10 August 2022; final version published online 6 March 2023.

Findlay Bewicke-Copley,[1] Koorosh Korfi,[1] Shamzah Araf,[1] Brendan Hodkinson,[2] Emil Kumar,[1] Thomas Cummin,[3] Margaret Ashton-Key,[4] Sharon Barrans,[5] Suzan van Hoppe,[5] Cathy Burton,[5] Mohamed Elshiekh,[6] Simon Rule,[7] Nicola Crosbie,[8] Andrew Clear,[9] Maria Calaminici,[9] Hendrik Runge,[10] Robert K. Hills,[11] David W. Scott,[12] Lisa M. Rimsza,[13] Geetha Menon,[14] Chulin Sha,[15] John R. Davies,[15] Ai Nagano,[1] Andrew Davies,[3] Daniel Painter,[16] Alexandra Smith,[16] John Gribben,[9] Kikkeri N. Naresh,[6] David R. Westhead,[15] Jessica Okosun,[9] Andrew Steele,[17] Daniel J. Hodson,[10] Sriram Balasubramanian,[17] Peter Johnson,[3] Jun Wang,[1,*] and Jude Fitzgibbon[1,*]

Microenvironment (ME)

ACCEPTED MANUSCRIPT

Dissection of DLBCL Microenvironment Provides a Gene Expression-Based Predictor of Survival Applicable to Formalin-Fixed Paraffin-Embedded Tissue

S Ciavarella, M C Vegliante, M Fabbri, S De Summa, F Melle, G Motta, V De Iuliis, G Opinto, A Enjuanes, S Rega, A Gulino, C Agostinelli, A Scattone, S Tommasi, A Mangia, F Mele, G Simone, A F Zito, G Ingravallo, U Vitolo, A Chiappella, C Tarella, A M Gianni, A Rambaldi, P L Zinzani, B Casadei, E Derenzini, G Loseto, A Pileri, V Tabanelli, S Fiori, A Rivas-Delgado, A López-Guillermo, T Venesio, A Sapino, E Campo, C Tripodo, A Guarini, S A Pileri ✉

Annals of Oncology, mdy450, https://doi.org/10.1093/annonc/mdy450

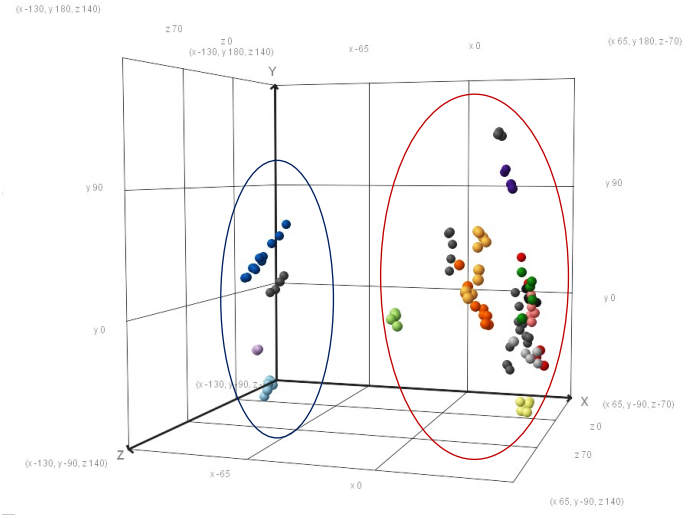
Published: 11 October 2018

CIBERSORT analysis and selection of prognostic genes

A customized signature including 1,028 genes was generated to distinguish 17 cell types of both stromal and immune origin.

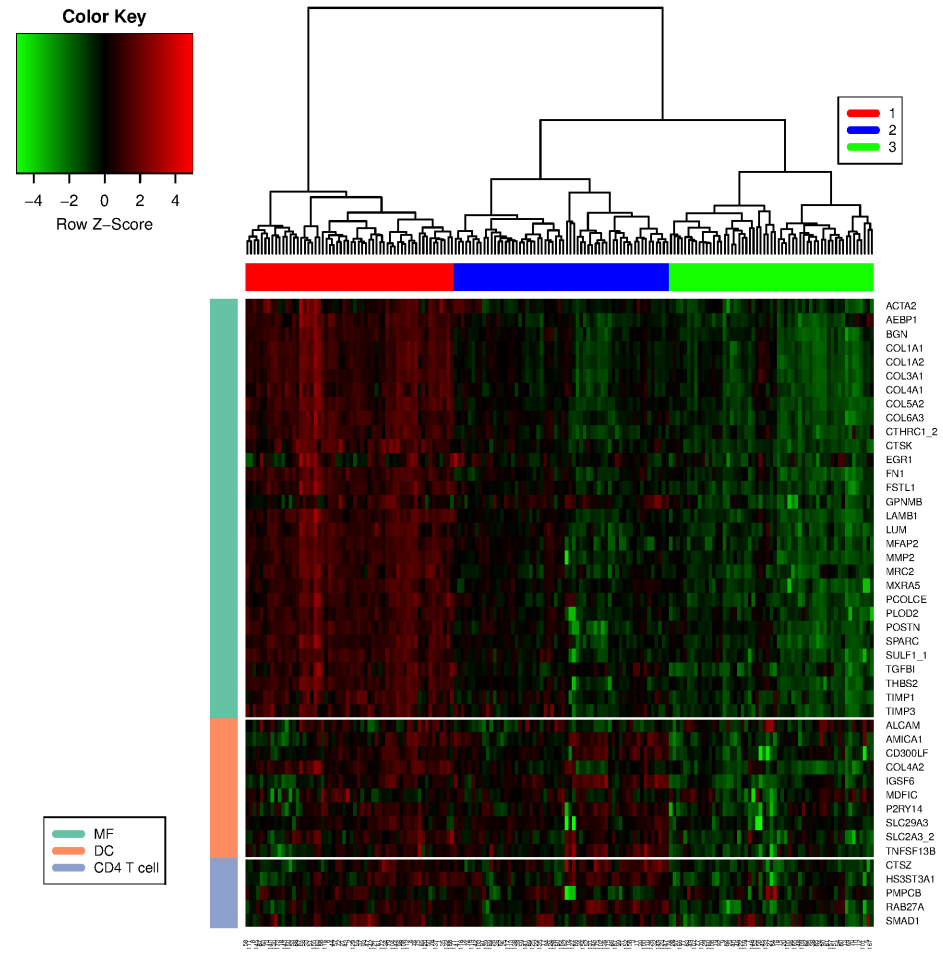
- Adipocites
- CD4-T cells
- CD8-T cells
- Dendritic cells
- Eosinophils
- Lymphatic endothelial cells
- Macrophages M2
- Memory_B_cells
- Monocytes
- Myofibroblasts
- NK_activated
- NK_resting
- Naive_B
- Neutrophils
- Pericytes
- Plasmacells
- Tgamma-delta

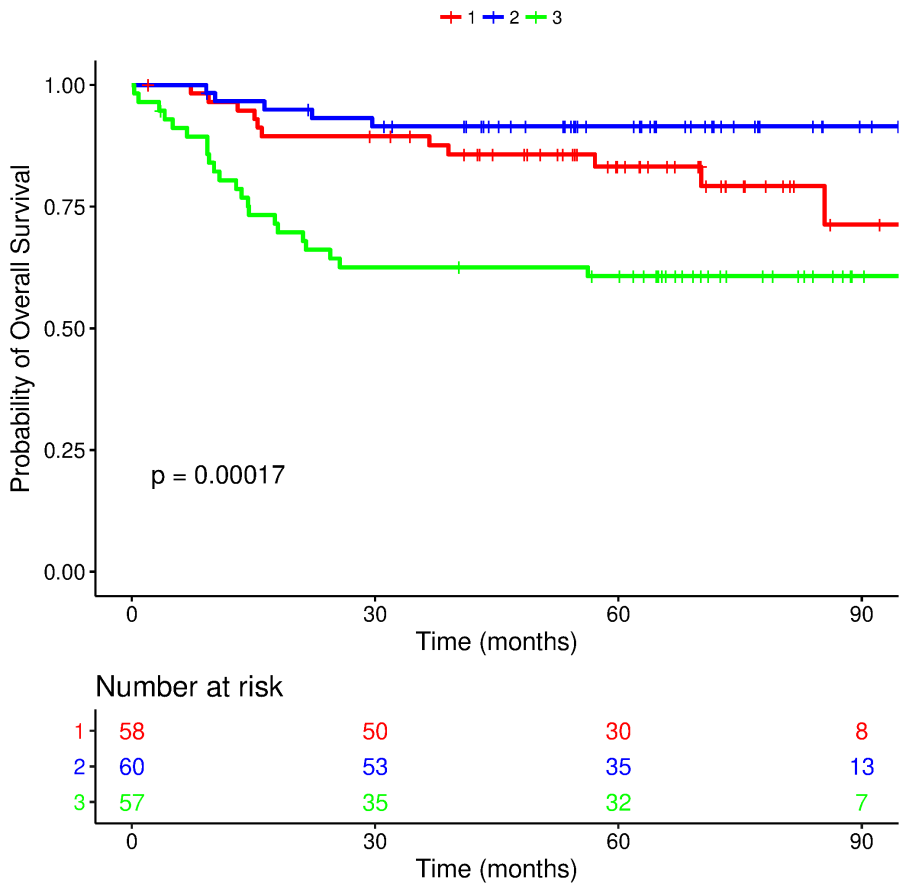
PCA



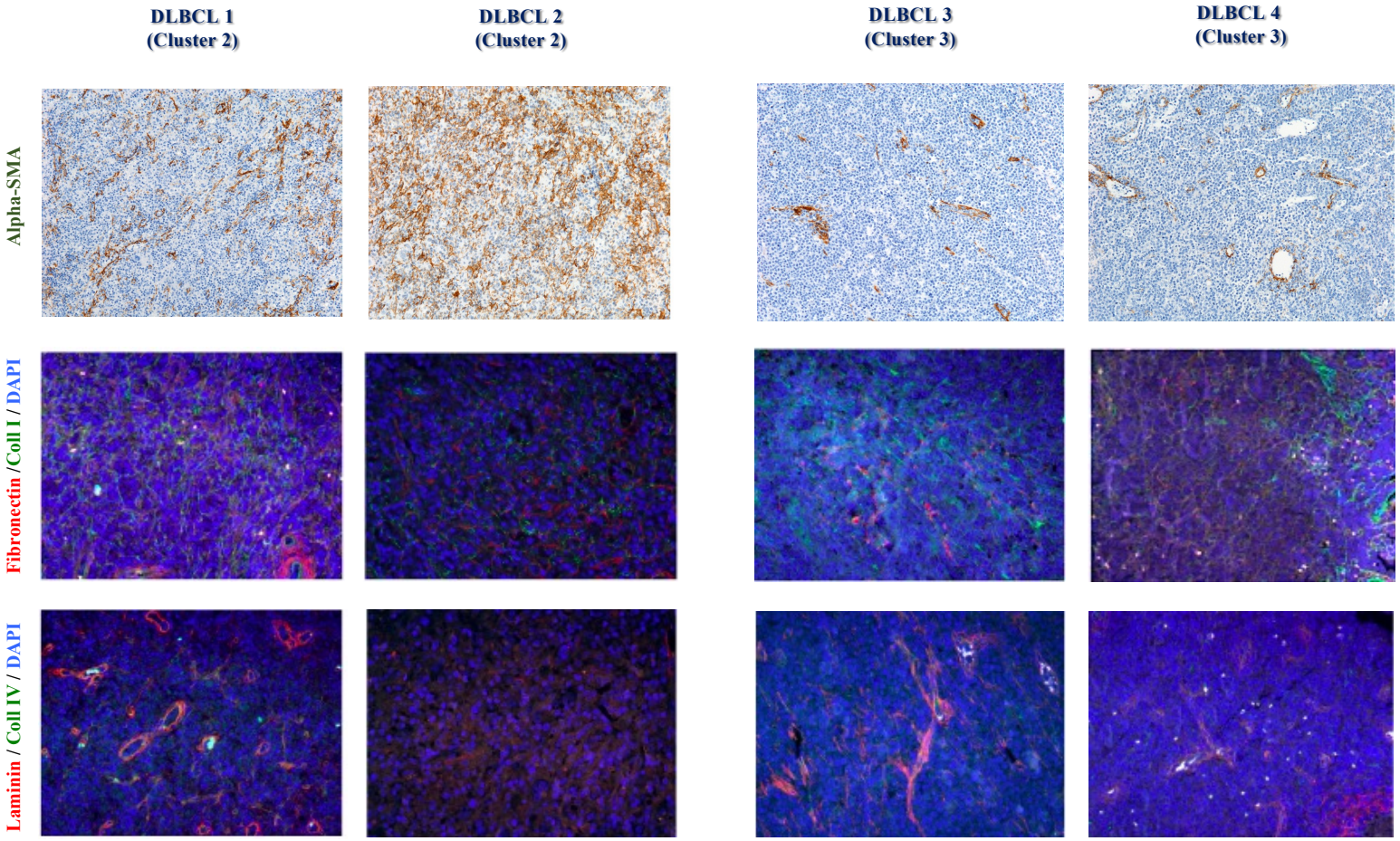
MF-related genes	*ACTA2*	Actin, alpha 2, smooth muscle
	AEBP1	AE binding protein 1
	BGN	Biglycan
	COL1A1	Collagen type I alpha 1
	COL1A2	Collagen type I alpha 2
	COL3A1	Collagen type III alpha 1
	COL4A1	Collagen type IV alpha 1
	COL5A2	Collagen type V alpha 2
	COL6A3	Collagen type VI alpha 3
	CTHRC1	Collagen triple helix repeat containing 1
	CTSK	Cathepsin K
	EGR1	Early growth response 1
	FN1	Fibronectin 1
	FSTL1	Follistatin like 1
	GPNMB	Glycoprotein nmb
	LAMB1	Laminin subunit beta 1
	LUM	Lumican
	MFAP2	Microfibrillar associated protein 2
	MMP2	Matrix metallopeptidase 2
	MRC2	Mannose receptor, C type 2
	MXRA5	Matrix-Remodelling Associated 5
	PCOLCE	Procollagen C-endopeptidase enhancer
	PLOD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2
	POSTN	Periostin, osteoblast specific factor
	SPARC	Secreted protein acidic and cysteine rich
	SULF1	Sulfatase 1
	TGFBI	Transforming growth factor beta induced
DC-related genes	*ALCAM*	Activated leukocyte cell adhesion molecule
	AMICA1	Adhesion molecule, interacts with CXADR antigen 1
	CD300LF	CD300 molecule-like family member F
	COL4A2	Collagen, type IV, alpha 2
	IGSF6	Immunoglobulin superfamily, member 6
	MDFIC	MyoD Family Inhibitor Domain Containing
	P2RY14	Purinergic receptor P2Y, G-protein coupled, 14
	SLC29A3	Solute carrier family 29 (nucleoside transporters), member 3;
	SLC2A3	Solute carrier family 2 (facilitated glucose transporter),
$CD4^+$ T cell-related genes	*CTSZ*	Cathepsin Z
	HS3ST3A1	Heparan Sulfate-Glucosamine 3-Sulfotransferase 3A1
	PMPCB	Peptidase, Mitochondrial Processing Beta Subunit
	RAB27A	RAB27A, Member RAS Oncogene Family
	SMAD1	SMAD Family Member 1

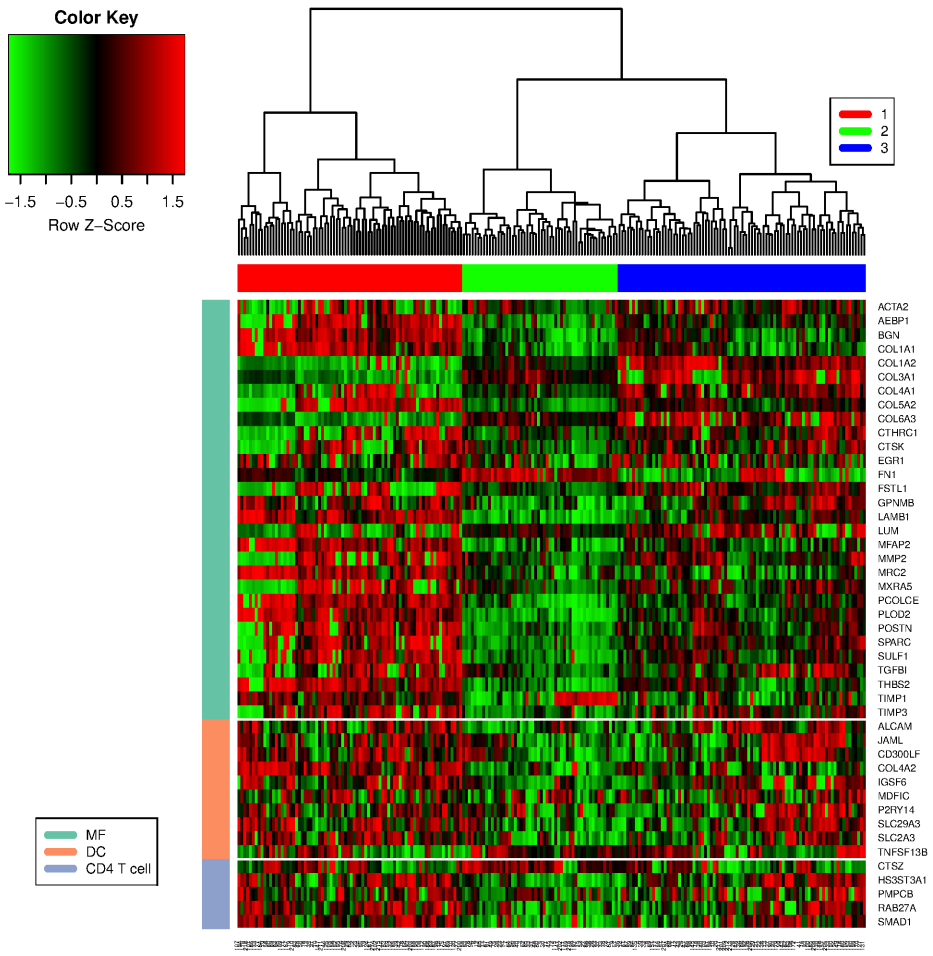
DLCL04 and R-HDS0305



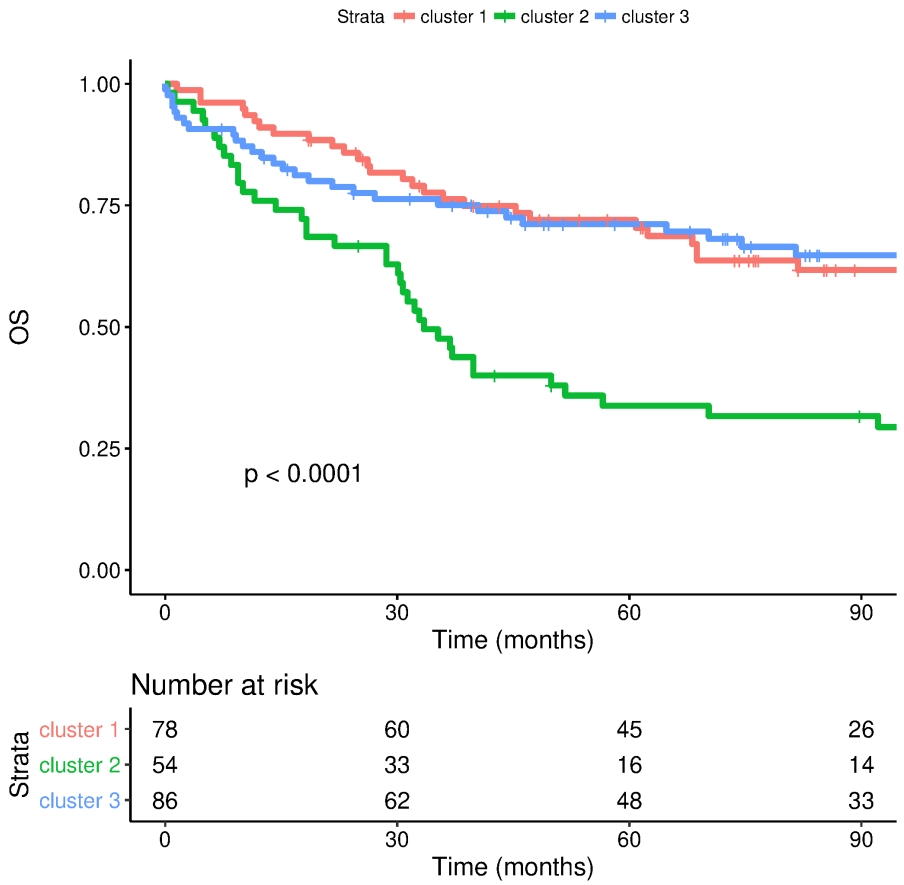


By *in situ* immunostaining we analyzed the expression of ECM proteins encoded by four of the fronting genes of the MF signature, namely Fibronectin, Collagen-I, Laminin, and Collagen-IV. However, the expression variability of these proteins does not support the use of immunohistochemistry as a reliable assay to provide insight on the prognostic gene expression patterns of DLBCL microenvironment determinants.

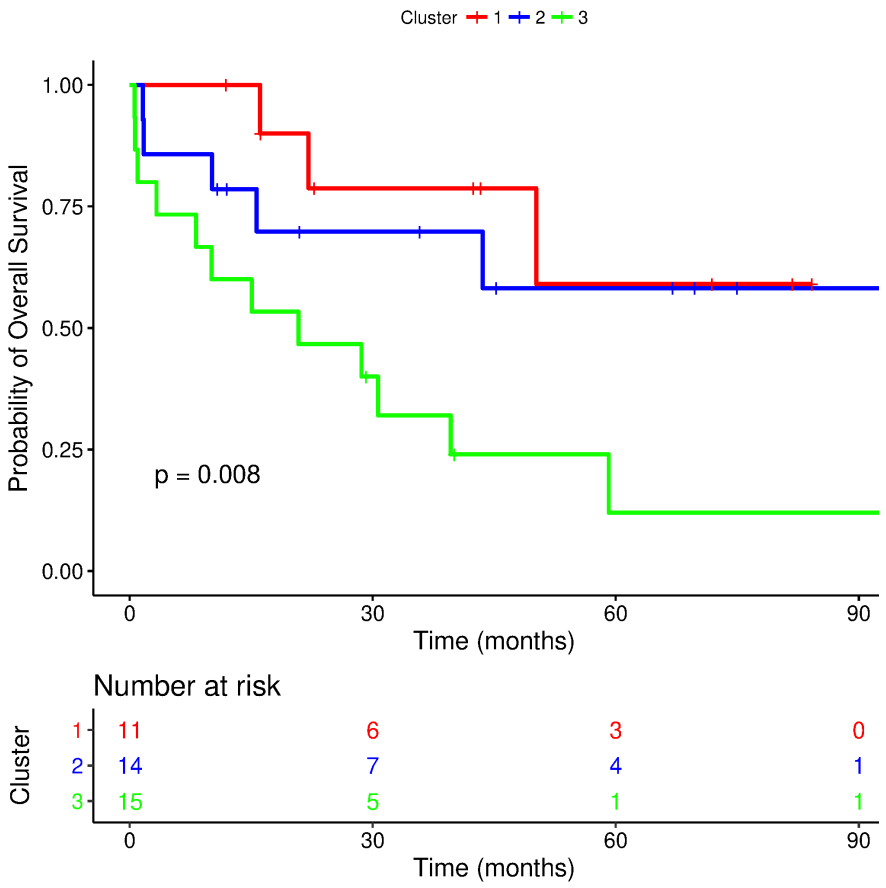


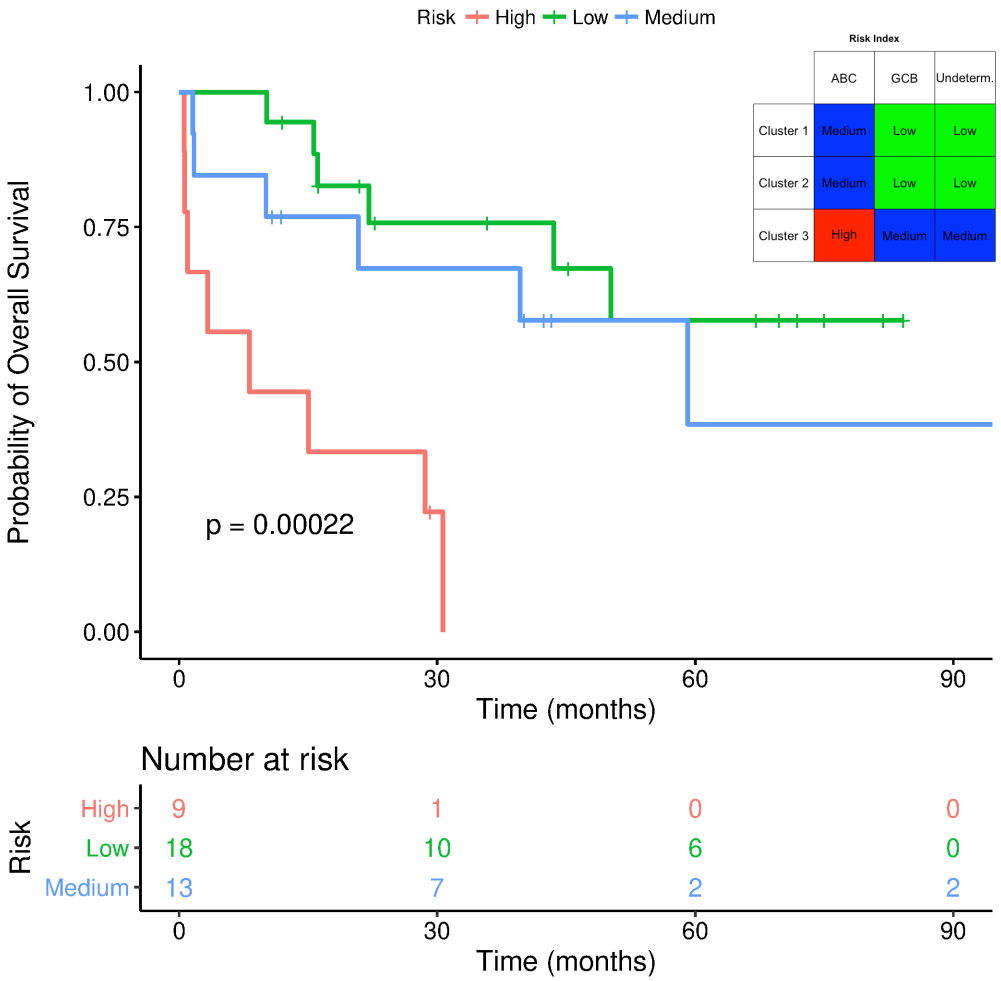

Color Key
−1.5 −0.5 0.5 1.5
Row Z−Score
1
2
3
ACTA2
AEBP1
BGN
COL1A1
COL1A2
COL3A1
COL4A1
COL5A2
COL6A3
CTHRC1
CTSK
EGR1
FN1
FSTL1
GPNMB
LAMB1
LUM
MFAP2
MMP2
MRC2
MXRA5
PCOLCE
PLOD2
POSTN
SPARC
SULF1
TGFBI
THBS2
TIMP1
TIMP3
ALCAM
JAML
CD300LF
COL4A2
IGSF6
MDFIC
P2RY14
SLC29A3
SLC2A3
TNFSF13B
CTSZ
HS3ST3A1
PMPCB
RAB27A
SMAD1
MF
DC
CD4 T cell

Lenz' series


Strata cluster 1 cluster 2 cluster 3
OS
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
30
60
90
Time (months)
Number at risk
Strata
cluster 1 78 60 45 26
cluster 2 54 33 16 14
cluster 3 86 62 48 33
0
30
60
90
Time (months)

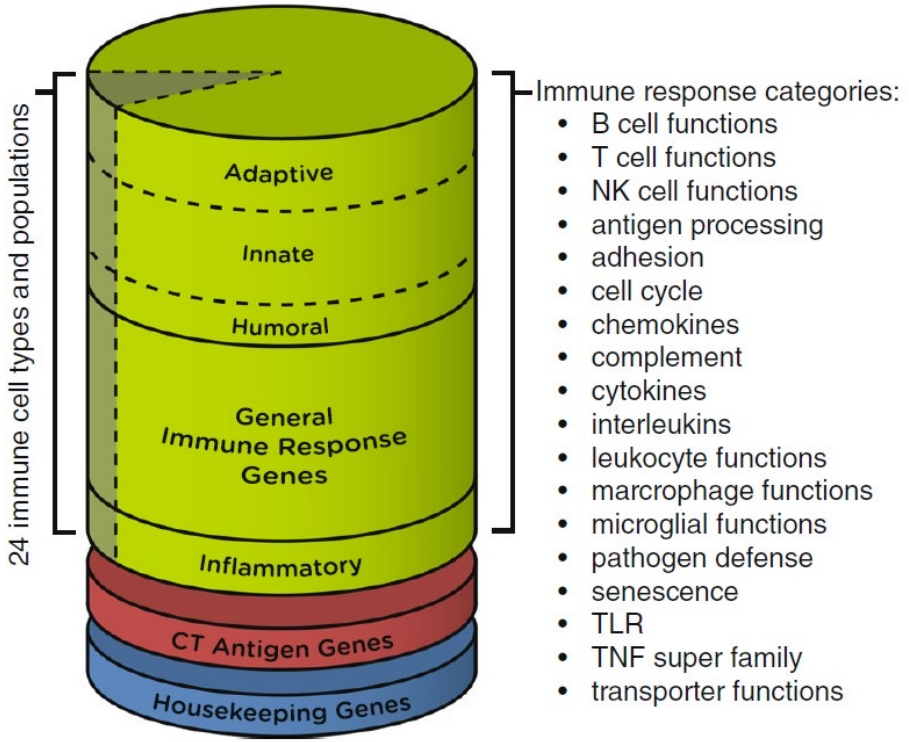
Real-life

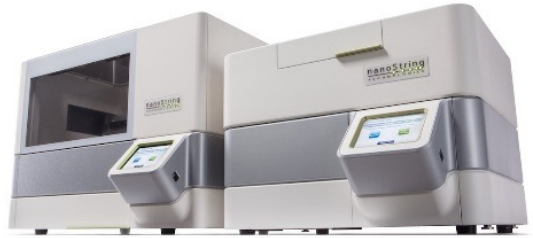

Cluster 1 2 3
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
p = 0.008
0
30
60
90
Time (months)
Number at risk
Cluster
1 11 6 3 0
2 14 7 4 1
3 15 5 1 1
0
30
60
90
Time (months)


Risk High Low Medium
Risk Index
ABC GCB Undeterm.
Cluster 1 Medium Low Low
Cluster 2 Medium Low Low
Cluster 3 High Medium Medium
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
p = 0.00022
0
30
60
90
Time (months)
Number at risk
Risk
High 9 1 0 0
Low 18 10 6 0
Medium 13 7 2 2
0
30
60
90
Time (months)

PanCancer Immune Profiling Panel (PCIP)

- A multiplexed gene expression approach to profiling cancer immunology
  - Quantify infiltrating immune cells in a tumor microenvironment
  - Assess immunological activity and response to therapeutic intervention
  - Identify tumor-specific antigens





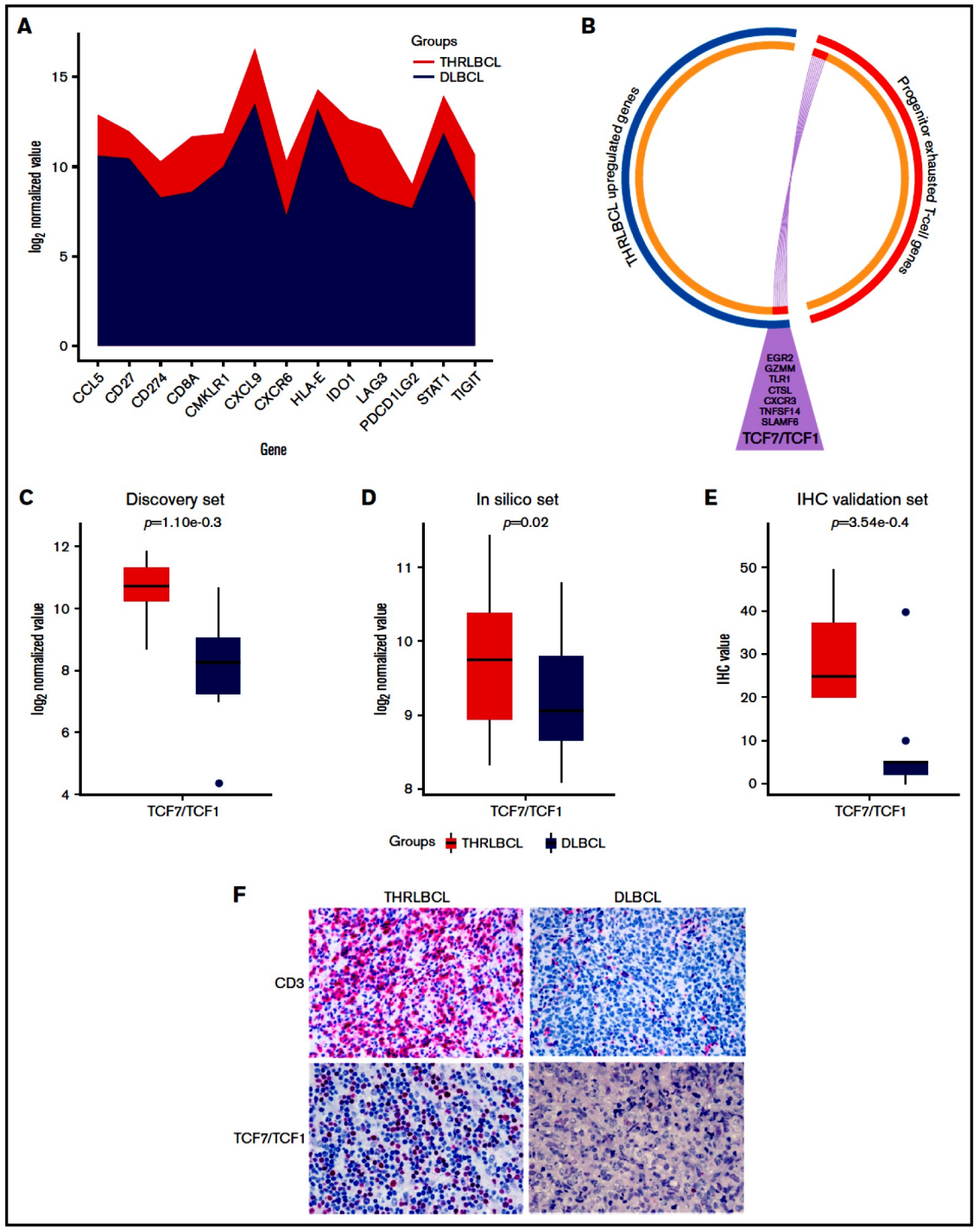
Discovery set: 12 THRBCLs vs. 10 DLBCLs, NOS

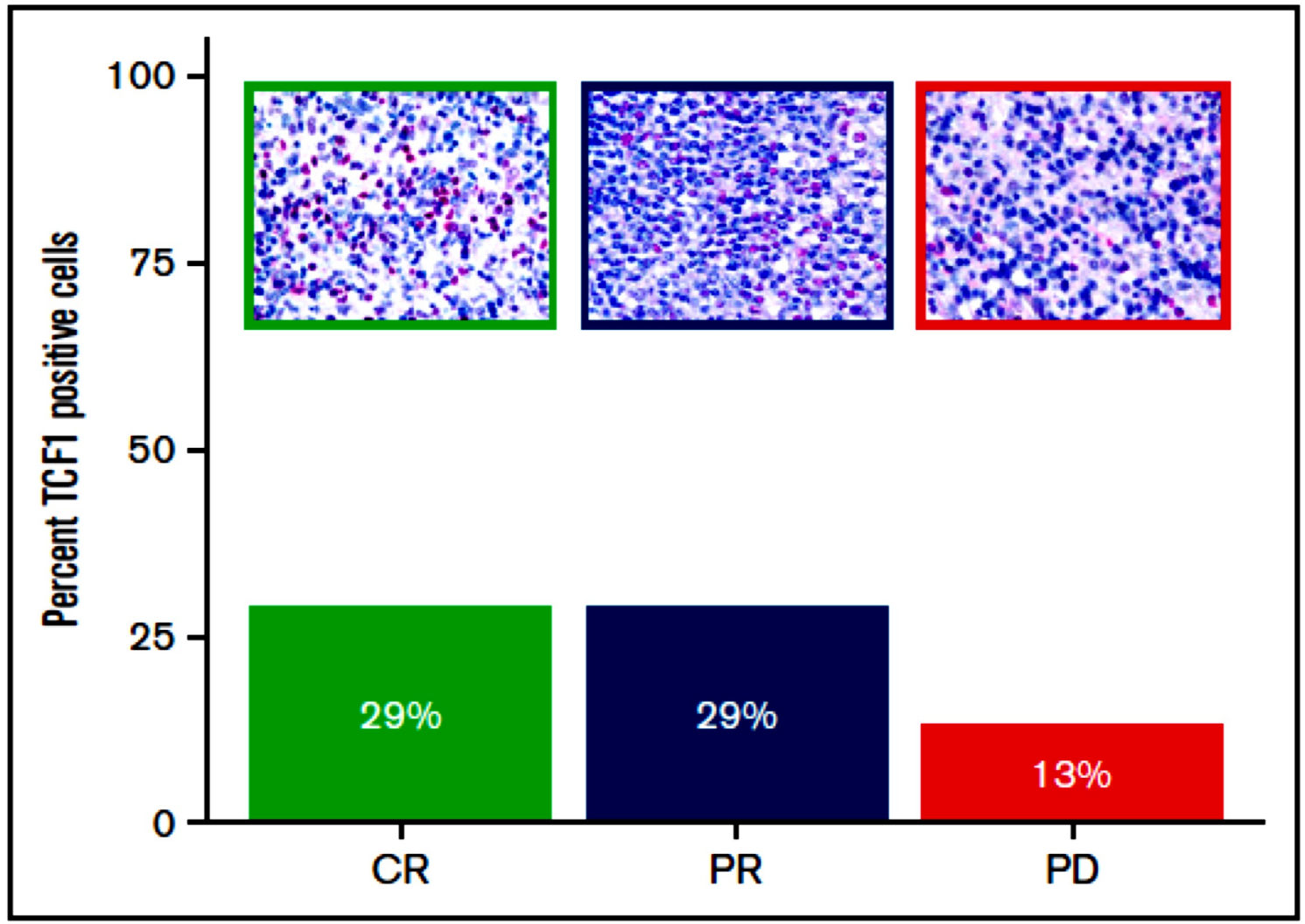
Key Points

- The interferon–driven inflammatory response and the PD-1 signaling were the most relevant modulators of the THRLBCL immune response.
- THRLBCL cases may be enriched in TCF1^{+} T cells, a subset of progenitor exhausted T cells associated with good response to immunotherapy.

***In silico*: 31 THRBCLs vs. 473 DLBCLs, NOS**

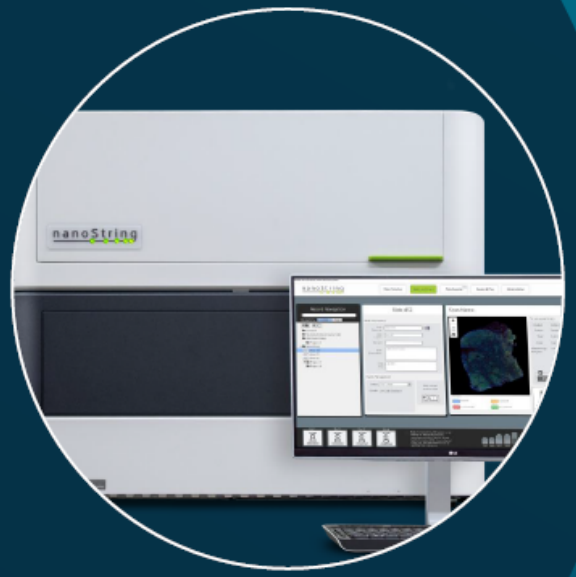
IHC: 15 THRBCLs vs. 26 DLBCLs, NOS




Percent TCF1 positive cells
100
75
50
25
0
29%
29%
13%
CR
PR
PD

Spatial-omics for Every Spatial-scale

RNA and Protein



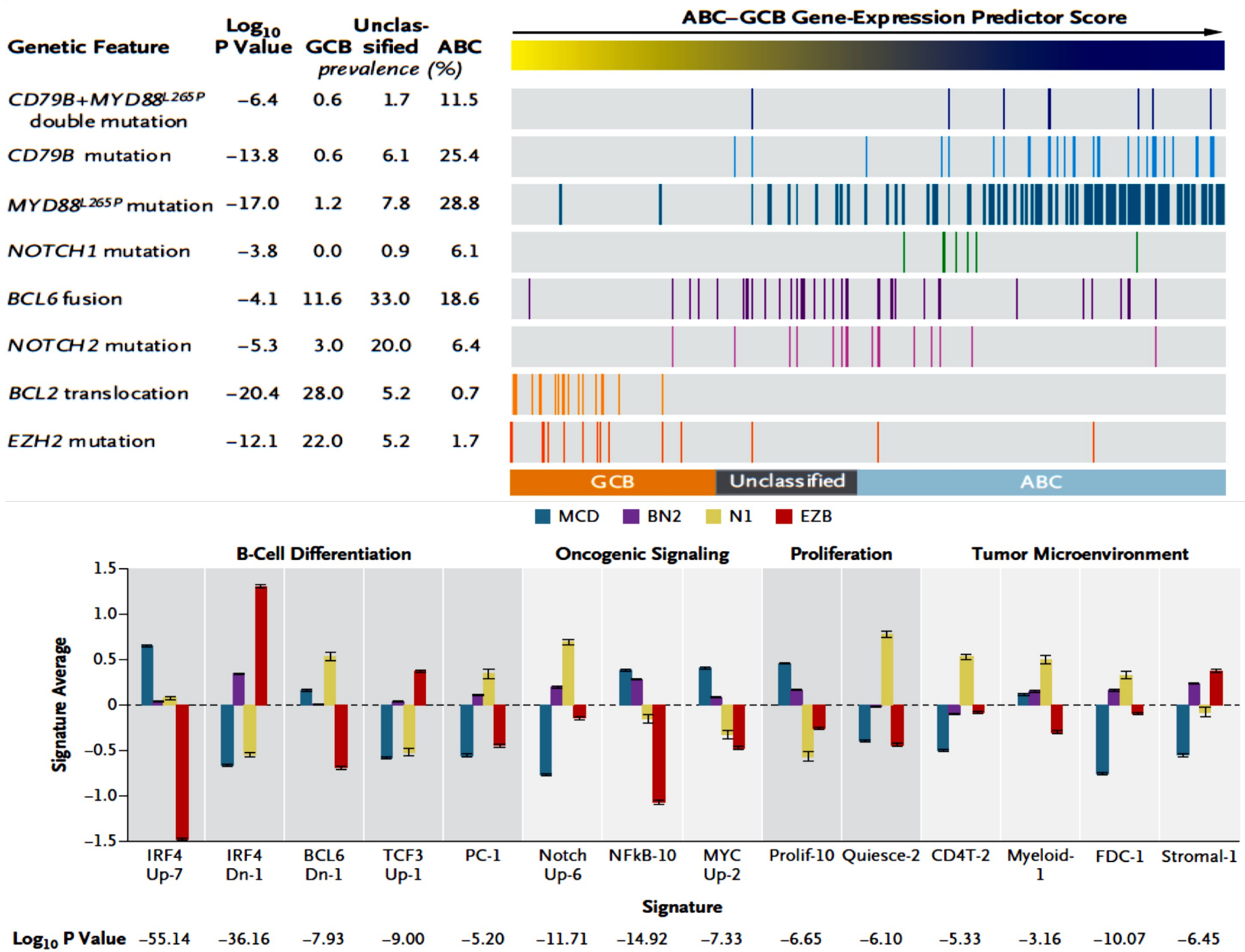
GeoMx DSP

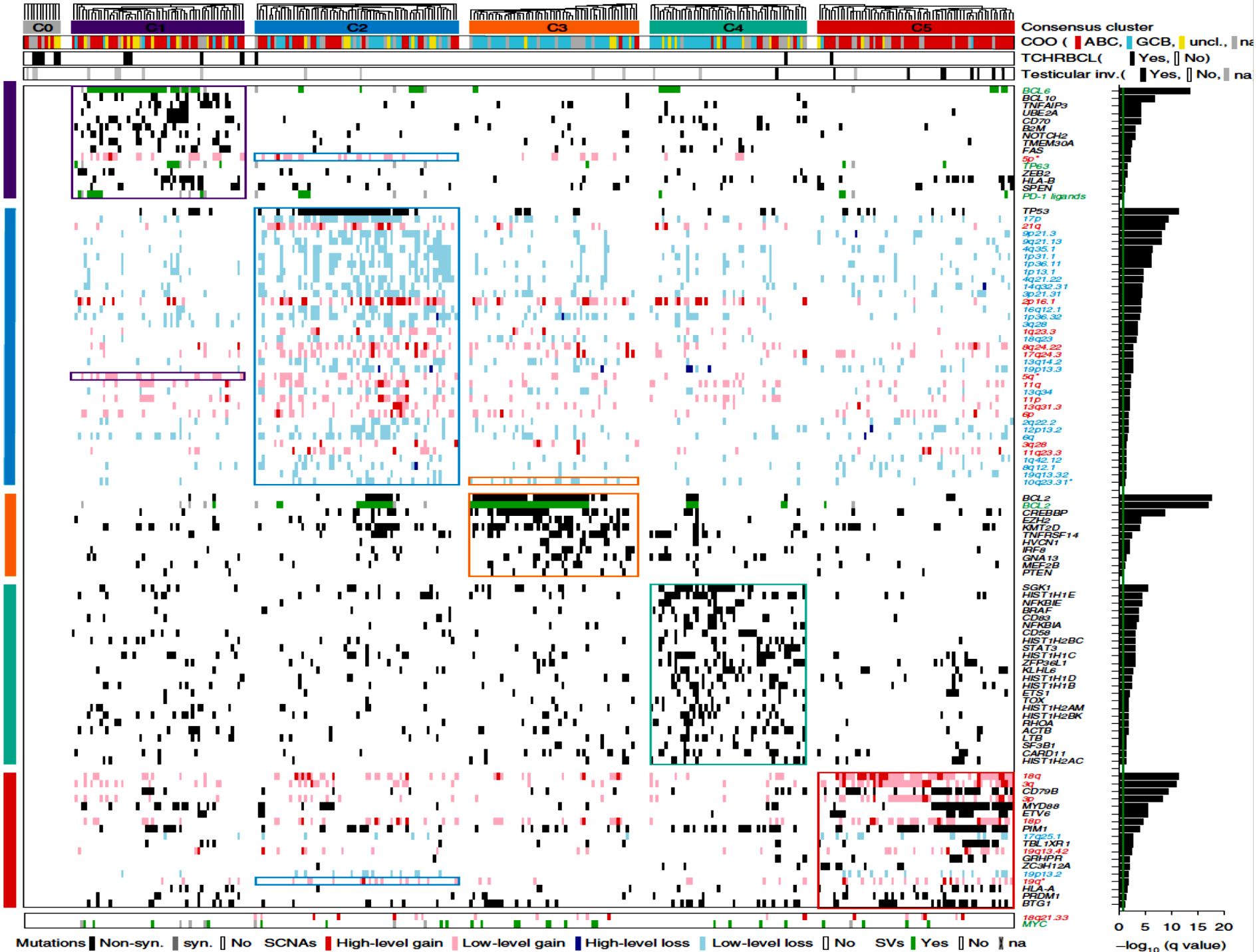
- Whole Transcriptome
- High Throughput
- Single Phenotype
- Unbiased Molecular Profile
- Difference Between Samples

- Single-Cell Resolution
- Entire Tissue Section
- High Multiplexing
- Comprehensive Cell Type Map
- Difference Between Cell Type and Cell State

CosMx SMI

Next generation sequencing (NGS)


Genetic Feature
Log10 P Value
Unclas-
GCB sified ABC
prevalence (%)
CD79B+MYD88L265P double mutation
−6.4 0.6 1.7 11.5
CD79B mutation
−13.8 0.6 6.1 25.4
MYD88L265P mutation
−17.0 1.2 7.8 28.8
NOTCH1 mutation
−3.8 0.0 0.9 6.1
BCL6 fusion
−4.1 11.6 33.0 18.6
NOTCH2 mutation
−5.3 3.0 20.0 6.4
BCL2 translocation
−20.4 28.0 5.2 0.7
EZH2 mutation
−12.1 22.0 5.2 1.7
ABC–GCB Gene-Expression Predictor Score
GCB
Unclassified
ABC
MCD
BN2
N1
EZB
B-Cell Differentiation
Oncogenic Signaling
Proliferation
Tumor Microenvironment
Signature Average
1.5
1.0
0.5
0
−0.5
−1.0
−1.5
IRF4 Up-7
IRF4 Dn-1
BCL6 Dn-1
TCF3 Up-1
PC-1
Notch Up-6
NFkB-10
MYC Up-2
Prolif-10
Quiesce-2
CD4T-2
Myeloid-1
FDC-1
Stromal-1
Signature
Log10 P Value
−55.14 −36.16 −7.93 −9.00 −5.20 −11.71 −14.92 −7.33 −6.65 −6.10 −5.33 −3.16 −10.07 −6.45


C0
C1
C2
C3
C4
C5
Consensus cluster
COO (ABC, GCB, uncl., na
TCHRBCL(Yes, No)
Testicular inv.(Yes, No, na
BCL6
BCL10
TNFAIP3
UBE2A
CD70
B2M
NOTCH2
TMEM30A
FAS
5p*
TP63
ZEB2
HLA-B
SPEN
PD-1 ligands
TP53
17p
21q
9p21.3
9q21.13
4q35.1
1p31.1
1p36.11
1p13.1
4q21.22
14q32.31
3p21.31
2p16.1
16q12.1
1p36.32
3q28
1q23.3
18q23
9q24.22
17q24.3
13q14.2
19p13.3
5q*
11q
13q34
11p
13q31.3
6p
2q22.2
12p13.2
6q
3q28
11q23.3
1q42.12
8q12.1
19q13.32
10q23.31*
BCL2
BCL2
CREBBP
EZH2
KMT2D
TNFRSF14
HVCN1
IRF8
GNA13
MEF2B
PTEN
SGK1
HIST1H1E
NFKBIE
BRAF
CD83
NFKBIA
CD58
HIST1H2BC
STAT3
HIST1H1C
ZFP36L1
KLHL6
HIST1H1D
HIST1H1B
ETS1
TOX
HIST1H2AM
HIST1H2BK
RHOA
ACTB
LTB
SF3B1
CARD11
HIST1H2AC
18q
3q
CD79B
3p
MYD88
ETV6
18p
PIM1
17q25.1
TBL1XR1
19q13.42
GRHPR
ZC3H12A
19p13.2
19q*
HLA-A
PRDM1
BTG1
18q21.33
MYC
0
5
10
15
20
−log10 (q value)
Mutations Non-syn. syn. No SCNAs High-level gain Low-level gain High-level loss Low-level loss No SVs Yes No na

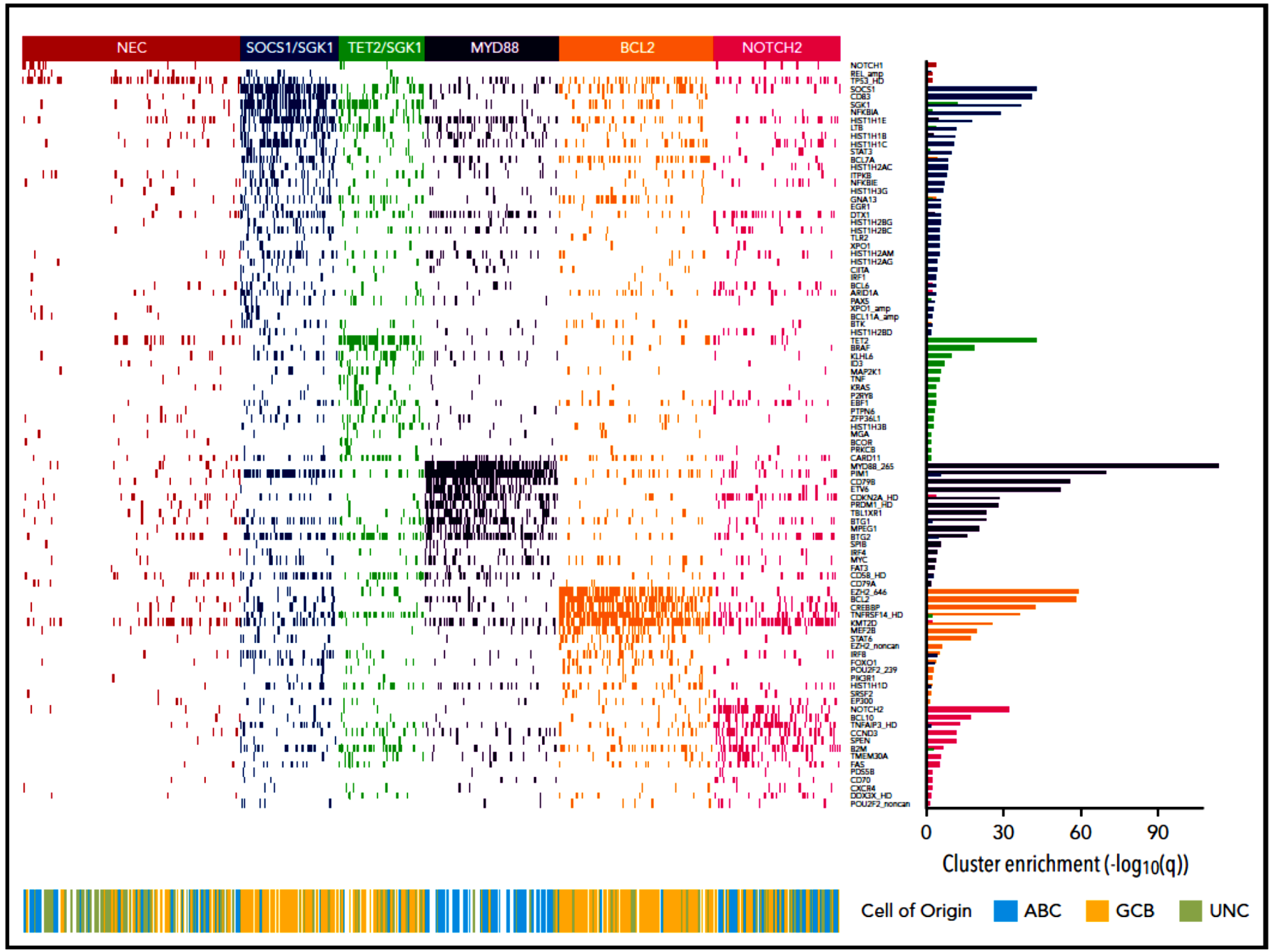

NEC
SOCS1/SGK1
TET2/SGK1
MYD88
BCL2
NOTCH2
NOTCH1
REL_amp
TP53_HD
SOCS1
CD83
SGK1
NFKBIA
HIST1H1E
LTB
HIST1H1B
HIST1H1C
STAT3
BCL7A
HIST1H2AC
ITPKB
NFKBIE
HIST1H3G
GNA13
EGR1
DTX1
HIST1H2BG
HIST1H2BC
TLR2
XPO1
HIST1H2AM
HIST1H2AG
CIITA
IRF1
BCL6
ARID1A
PAX5
XPO1_amp
BCL11A_amp
BTK
HIST1H2BD
TET2
BRAF
KLHL6
ID3
MAP2K1
TNF
KRAS
P2RY8
EBF1
PTPN6
ZFP36L1
HIST1H3B
MGA
BCOR
PRKCB
CARD11
MYD88_265
PIM1
CD79B
ETV6
CDKN2A_HD
PRDM1_HD
TBL1XR1
BTG1
MPEG1
BTG2
SPIB
IRF4
MYC
FAT3
CD58_HD
CD79A
EZH2_646
BCL2
CREBBP
TNFRSF14_HD
KMT2D
MEF2B
STAT6
EZH2_noncan
IRF8
FOXO1
POU2F2_239
PIK3R1
HIST1H1D
SRSF2
EP300
NOTCH2
BCL10
TNFAIP3_HD
CCND3
SPEN
B2M
TMEM30A
FAS
PDSSB
CD70
CXCR4
DDX3X_HD
POU2F2_noncan
0
30
60
90
Cluster enrichment (-log10(q))
Cell of Origin
ABC
GCB
UNC

Table 2: Genomic subtypes of DLBCL

Wright 2020[30]	Chapuy 2018[29]	Lacy 2020[31]	Hallmark drivers	COO	% of cases	Outcome 5 yr OS (%)	Putative related small cell lymphoma
MCD	C5	MYD88	MYD88/CD79B	ABC	9-14-21	40-42	
BN2	C1	NOTCH2	tBCL6/ NOTCH2	GCB/ABC Unclassified	16-19	48-67	MZL
EZB-MYC-	C3	BCL2	EZH2 tBCL2	GCB	13-18	63-82	FL
EZB-MYC+			EZH2/tMYC	GCB/DZ	6	48	
A53	C2		TP53 Aneuploidy	All	7-21	63	
ST2	C4	SOCS1/SGK1 TET/SGK1	SOCS1/TET/ SGK1	GCB	5-17	65-84	NLPBL
N1			NOTCH1	ABC	2	27	CLL
UNCLASS		UNCLASS		Unclass, GCB,ABC	27-37	66	

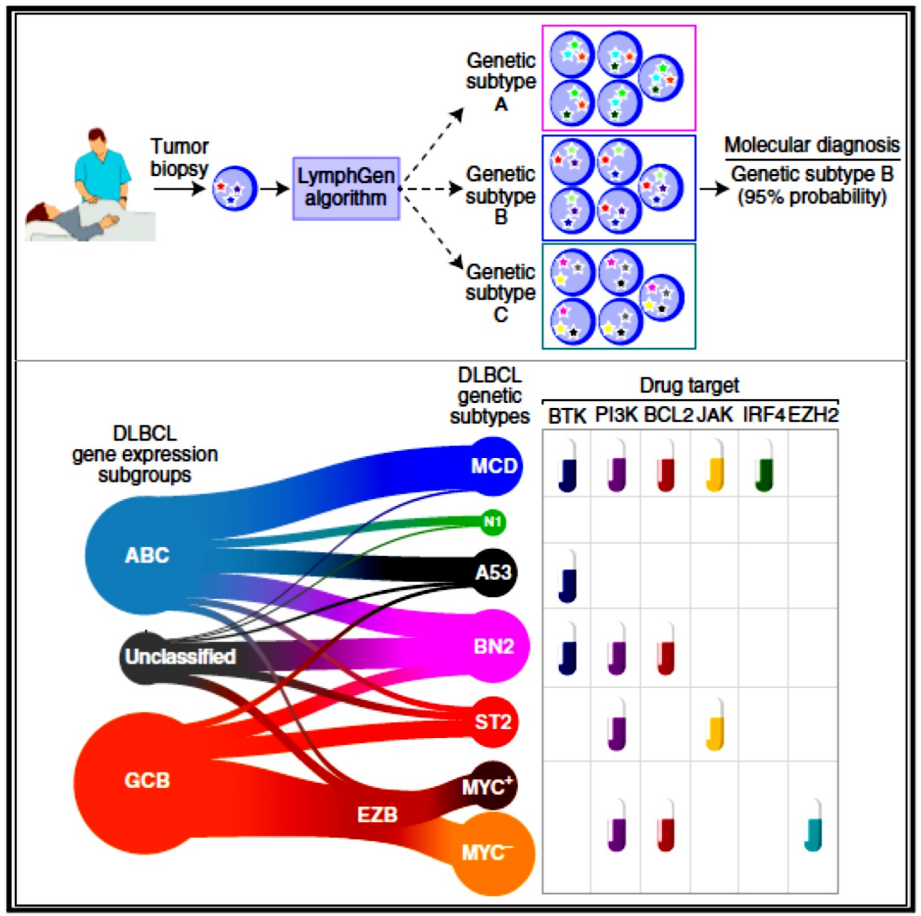
ABC: Activated B-cell type; GCB: Germinal center B-cell type;
DZ: Dark zone signature; CLL: Chronic lymphocytic leukemia;
FL: Follicular lymphoma, MZL: Marginal zone lymphoma;
NLPBL: Nodular lymphocyte predominant B-cell lymphomat;
t: Translocation

Article

Cancer Cell

A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications

Graphical Abstract



Authors

George W. Wright, Da Wei Huang, James D. Phelan, ..., Wyndham H. Wilson, David W. Scott, Louis M. Staudt

Correspondence

lstaudt@mail.nih.gov

In Brief

Wright et al. identify seven genetic subtypes of diffuse large B cell lymphoma (DLBCL) with distinct outcomes and therapeutic vulnerabilities. The LymphGen probabilistic classification tool that can classify a DLBCL biopsy into the genetic subtypes is developed, which could be used for precision medicine trials.

blood

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

DLBCL associated NOTCH2 mutations escape ubiquitin-dependent degradation and promote chemo-resistance

Tracking no: BLD-2022-018752R1

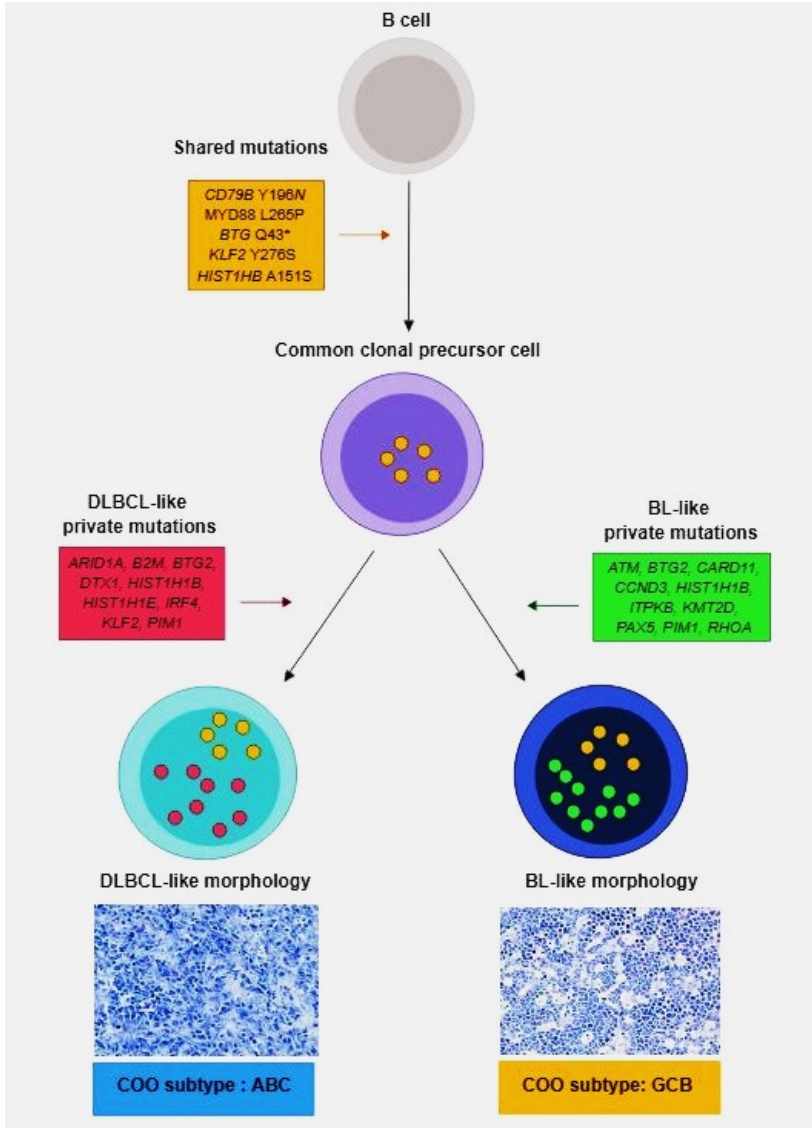
Nan Zhou (University of Pennsylvania, United States) Jaewoo Choi (University of Pennsylvania, United States) Grant Grothusen (University of Pennsylvania, United States) Bang-Jin Kim (University of Pennsylvania, United States) Diqiu Ren (University of Pennsylvania, United States) Zhendong Cao (University of Pennsylvania, United States) Qinglan Li (University of Pennsylvania, United States) Yiman Liu (University of Pennsylvania, United States) Arati Inamdar (University of Pennsylvania, United States) Thomas Beer (The Wistar Institute, United States) Hsin-Yao Tang (The Wistar Institute, United States) Eric Perkey (University of Pennsylvania, United States) Ivan Maillard (University of Pennsylvania, United States) Roberto Bonasio (University of Pennsylvania, United States) Junwei Shi (University of Pennsylvania, United States) Marco Ruella (University of Pennsylvania, United States) Liling Wan (University of Pennsylvania, United States) Luca Busino (University of Pennsylvania, United States)

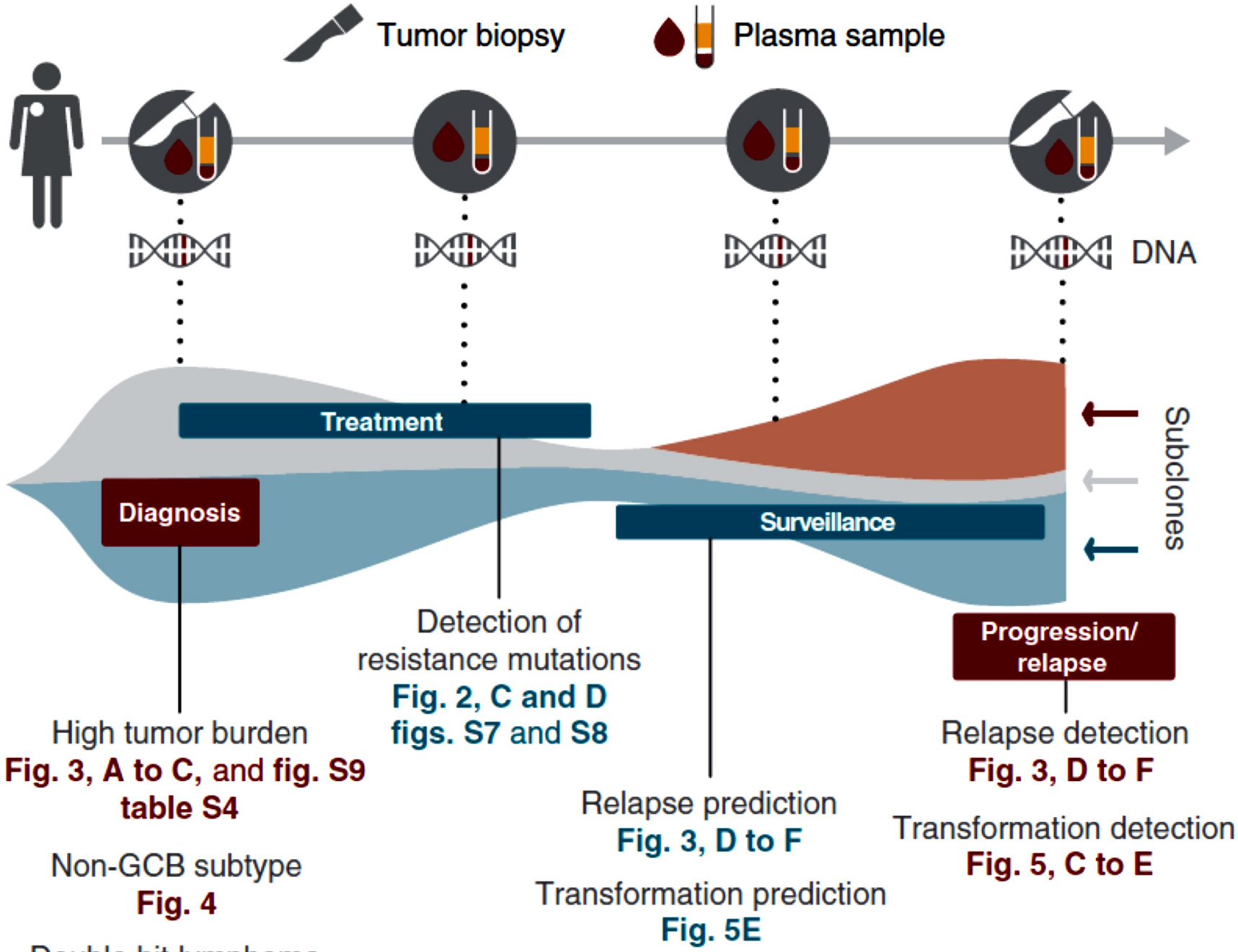

Covaris
HOME
HISTORY
ABOUT
Run
Pause
Covaris

Evolutionary crossroads: morphological heterogeneity reflects divergent intra-clonal evolution in a case of high-grade B-cell lymphoma

by Valentina Tabanelli, Federica Melle, Giovanna Motta, Saveria Mazzara, Marco Fabbri, Chiara Corsini, Elvira Gerbino, Angelica Calleri, Maria Rosaria Sapienza, Ignazio Abbene, Viviana Stufano, Massimo Barberis, and Stefano A. Pileri

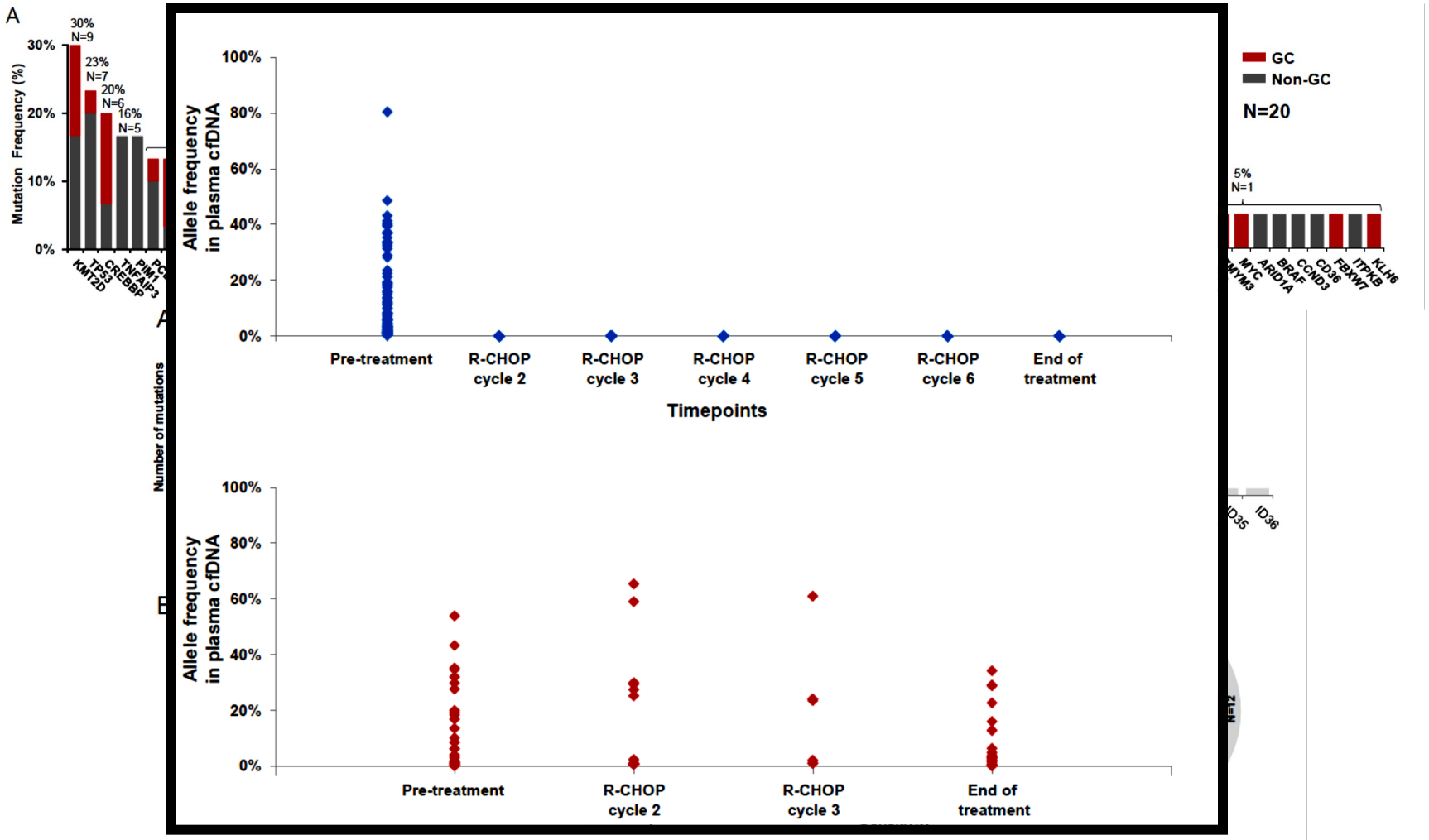
Haematologica 2020 [Epub ahead of print]




Tumor biopsy
Plasma sample
DNA
Treatment
Diagnosis
Surveillance
Subclones
Progression/ relapse
High tumor burden
Fig. 3, A to C, and fig. S9
table S4
Non-GCB subtype
Fig. 4
Double hit lymphoma
fig. S4A
Detection of resistance mutations
Fig. 2, C and D
figs. S7 and S8
Relapse prediction
Fig. 3, D to F
Transformation prediction
Fig. 5E
Relapse detection
Fig. 3, D to F
Transformation detection
Fig. 5, C to E

Rossi et al, Blood 2017

DIFFUSE LARGE B-CELL LYMPHOMA GENOTYPING ON THE LIQUID BIOPSY




thank you
gracias
merci
obrigado
danke
謝謝
ngiyabonga
teşekkür ederim
go raibh maith agat
mochchakkeram
dziękuję
bedankt
sukriya
kop khun krap
terima kasih
grazie
arigatô
takk
dakujem
спасибо
рахмат
Баярлалаа
dank je
tapadh leat
sagolun
mauruuru
hvala
감사합니다
ありがとう
ευχαριστώ
мерси
хвала
дякую
спасибі
mersi
kia ora
barka
welalin
tack
spas
mahalo
paldies
grazzi
misaotra
matondo
blagodaram
vinaka
faafetai lava
kiitos
dankie
nanni
nandri
dhanyavad
bayarlalaa
gracie
koszonom
enkosi
aciu
dankon
akun
djiere dieuf
tau
asante
manana
obrigada
tenki
murakoze
mamnun
chokrane
chnorakaloutioun
grafias ago
gràcies
sulpay
taiku
sobodi
dekuji
mesi
madloba
didi
kam sah hamnida
najis tuke
rahmat
tanemirt
rahmet
diolch
dhanyavadagalu
shukriya
merce
trugarez
xiexie