

SANT'ORSOLA

ER STUDIORUM FA DI BOLOGNA TIMENTO DI CHE E CHIRURGICHE SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA Azienda Ospedaliero - Universitaria di Bologn

# Aggressive Lymphoma Workshop

Bologna, Royal Hotel Carlton May 8-9, 2023

## Genomic classification of DLBCL Roland Schmitz, Ph.D. Justus Liebig University Giessen

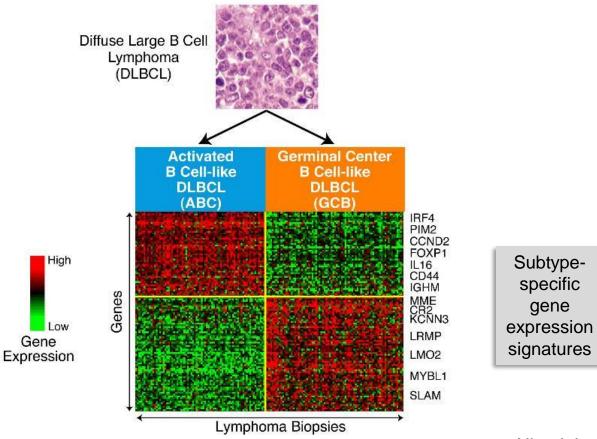
President: Pier Luigi Zinzani

#### **Disclosures**

#### **Disclosures of Name Surname**

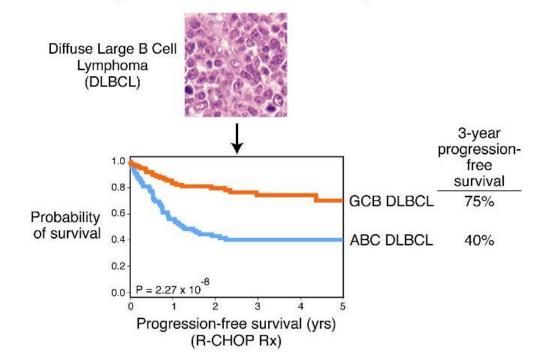
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NONE	-	-	-	-	-	-	-

#### Dissecting Cancer Into Molecularly and Clinically Distinct Subtypes by Gene Expression Profiling



#### Alizadeh et al. Nature 2000

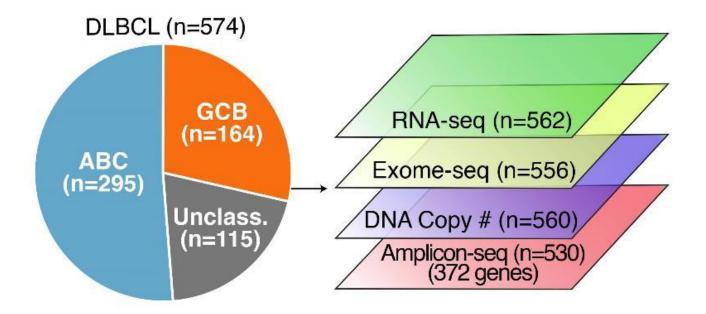
#### Dissecting Cancer Into Molecularly and Clinically Distinct Subtypes by Gene Expression Profiling



Subtype-specific response To chemotherapy

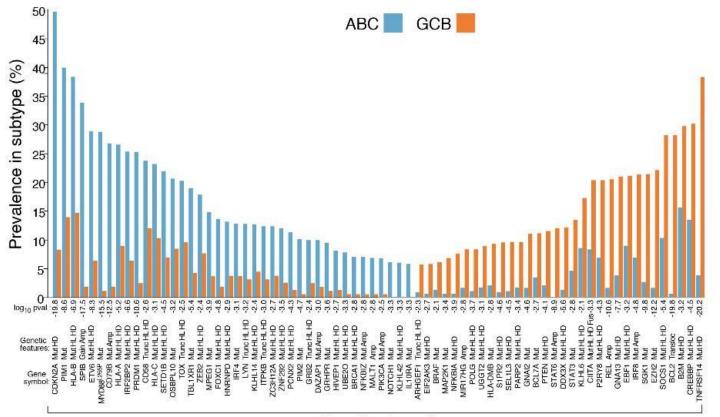
Alizadeh et al. Nature 2000

## Building a Genetic Classification of DLBCL

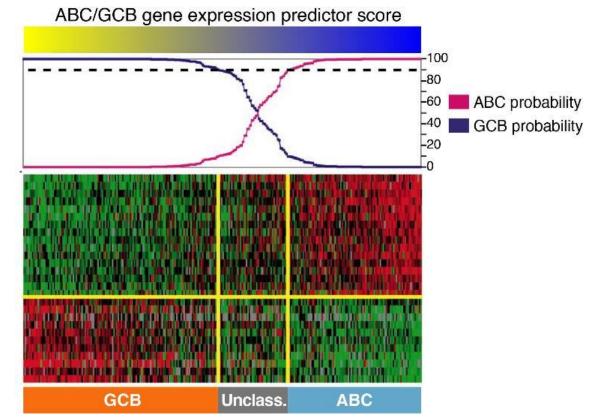


Schmitz et al. NEJM 2018

#### Extensive Genetic Differences Between ABC and GCB DLBCL

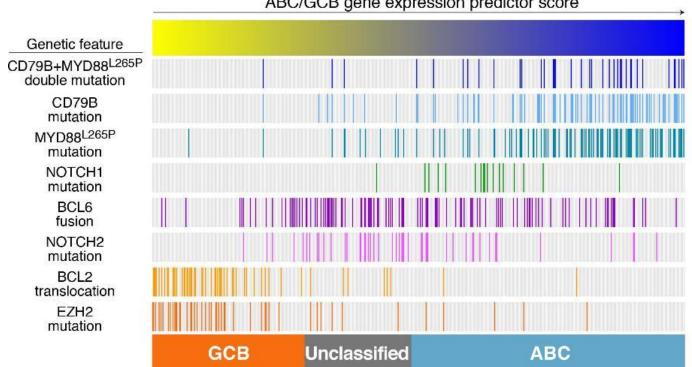


# Defining ABC, GCB and Unclassified DLBCL Based on the ABC/GCB predictor score



#### Schmitz et al. NEJM 2018

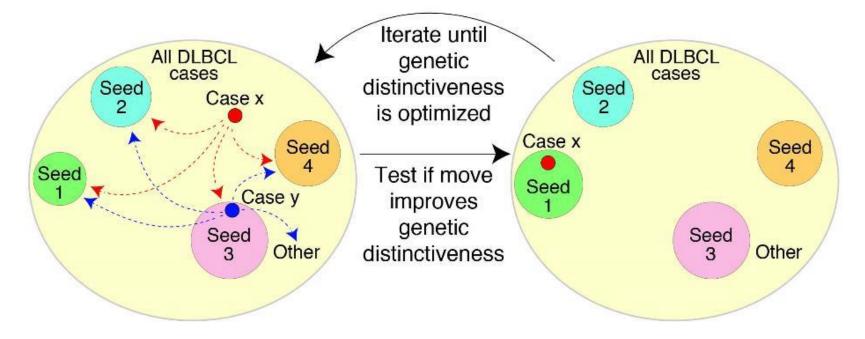
#### Heterogeneity of Genetic Aberrations Within DLBCL Gene Expression Subgroups



ABC/GCB gene expression predictor score

Schmitz et al. NEJM 2018

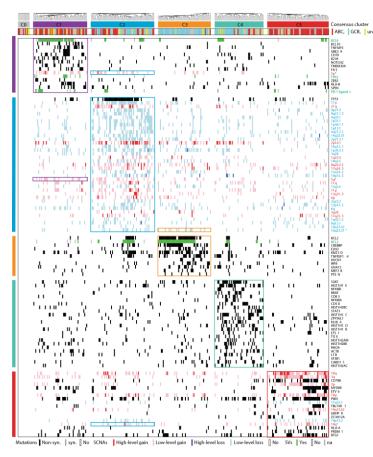
## Building a Genetic Classification of DLBCL

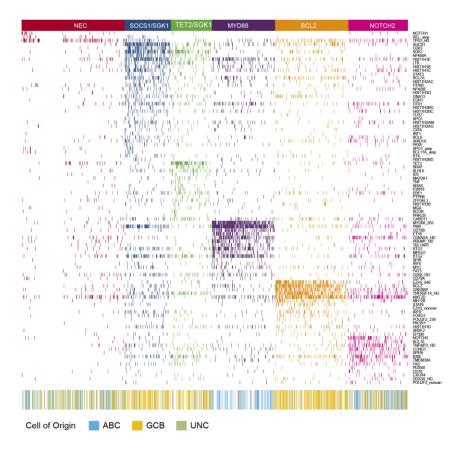


Schmitz et al. NEJM 2018

CVD88     CVD788     CVD788 </th <th></th> <th>Oncogene Tumor suppressor Unknown Genetic alteration</th>		Oncogene Tumor suppressor Unknown Genetic alteration
Checkboo   SPIB     SPIB   SPID     SPID   SPID     TOX   SPID     HLAA   SPID     SETUD   SPID </td <td></td> <td>suppressor Unknown</td>		suppressor Unknown
SPIB   Image: SPIB     TULAA     BEGRIN     HLAC     MELGRAN	(-)	
BTG1 B   State   State <t< td=""><td></td><td>Genetic alteration</td></t<>		Genetic alteration
HLA-C TELIXRI TELIX	1.11	
CDSS PROMI WHP1 BGL17A CCF070 PPPFIRBB H16 BC17A CCF070 BC2A TWFAPS BGL10 BE2A TWFAPS BGL10 BC10 BC10 BC10 BC10 BC10 BC10 BC10 BC		Missense
CDSS CDSS File File File File   VMP1 VMP1 File File File   VMP1 VMP1 File File File   SC11A CCT00 File File File   VMP1 File File File File   VMP1 File File File File   SC11A File File File File   VMP1 File File File File   VMP1 File File File File   SC10 File File File File   VMP2	S	Truncation
PDSS PROMI VMP1 PROMI VMP1 PROMI VMP1 PROMI VMP1 PROMI PROMI VMP1 PROMI		Fusion
PIN2 WEETA WEETA ARIDSB HASPIN LEP RB RB HNFIB BCL6 NOTCH2 CUTO, LP2 CUTO, L	•	Amplification
CHST2 ALAGER HASER HASER HASER HNF18 BCL6 NOTO12 OTX1 BCL6 EXCL0 DTX1 BCL10 UBE2A A	•	Gain-of-function
	1 I I.	Homozygous deletion
		Heterozygous
		deletion
	1 11 1	
	1.12 . 100	
	ation de caix	
VP33 SPEN ETSI NOI9		
KINUS TRRAP CXCR5 VPS188		
		(
		1
		1
MEFEZB STATE GNAT3 ARIDTA	1	
DDX3X		1
S1PR2 BCL7A HLA.DMB		
HLA.DMB NFKBIA NFKBIA		1 400
	( , ( <sup>2</sup> 1)	ABC GCB

chmitz et al. NEJM 2018





Chapuy et al. Nat. Med. 2018

Lacy et al. Blood 2020

Gene TP53

Chrom. 6g Chrom. 17p

Chrom. 8p Chrom. 7p Chrom. 3q

Chrom. 1p Chrom. 7q

Chrom. 24p

B2M Chrom. 24q 

Chrom. 2q Chrom. 4p

Chrom. 11q

Chrom. 15q Chrom. 16q T

TP53BP1 111

Chrom. 2p Chrom. 4g

Chrom. 22q CNPY3 

Chrom. 8q Chrom. 19p Chrom. 20p Chrom. 6p Chrom. 9q Chrom. 12p Chrom. 3p Chrom. 11p Chrom. 12a Chrom. 14q Chrom. 21p ING1 NFKBIZ

Chrom. 21q TP73 Chrom. 16p Chrom. 18a Chrom. 20q Chrom. 23p Chrom. 19q 

Gene NOTCH1 IRF2BP2 .....

BCOR EPB41

**IKBKB** ALDH18A1

Chrom. 4p ID3 ....

Chrom. 1q Chrom. 9p Chrom. 10p Chrom. 10q Chrom. 13q

Gene	MCD
MYD88 1265P	
CD79B	
PIM1 HLA-B	
BTG1	
DKN2A	
TV6	
PIB	
SBPL10 DX	
CL2	
TG2	
1PEG1	
ILA-A	
ILA-C ETD1B	
LHL14	
BL1XR1	
SRHPR	
RDM1	
D58 AP1	
PIM2	
OXC1	
RF4	
MP1	
SLC1A5 DAZAP1	• • • •
BCL11A	
PP1R9B	
L10RA	
L10RA L16	
L10RA L16 IHST2	•
_10RA _16 :HST2 :RID5B DCD1LG2	
L10RA L16 CHST2 ARID5B PDCD1LG2 WEE1	
L10RA L16 CHST2 ARID5B 20CD1LG2 WEE1 KLHL42	
IL10RA IL16 CHST2 ARID5B PDCD1LG2 WEE1 KLHL42	
IL10RA IL16 CHST2 ARID5B PDCD1LG2 WEE1 KLHL42	
IL10RA IL16 CHST2 ARID5B PDCD1LG2 WEE1 KLHL42	
ILTORA ILTO CHST2 ARID5B PDCD1LG2 WEE1 KLHL42 TNRC18 Gene	
L10RA L16 CHST2 ARID5B POCD1LG2 WEE1 KLHL42 INRC18 Gene BCL2	
L10RA L16 CHST2 ARID5B DCD1LG2 WEE1 KLHL42 FNRC18 Gene BCL2 EZH2	EZB
L10RA L16 CHST2 ARID5B 7DCD1LG2 WEE1 KLHL42 TNRC18 Gene BCL2 BCL2 EZH2 TNFRSF14	
LL10RA L16 CHST2 ARID5B DOCDILG2 WEE1 KLHL42 TNRC18 Gene BCL2 EZH2 TNFRSF14 KMT2D	EZB
L10RA L16 CHST2 ARID5B POCD1LG2 WEE1 KLHL42 TNRC18 BCL2 EZH2 EZH2 EZH2 CREBBP DC	EZB
L10RA L16 CHST2 ARID5B POCDILG2 WEE1 (LHL42 KLHL42 TNRC18 BCL2 ZH2 TNFRSF14 (MT2D CREBBP REL CREBBP REL FAS	
L10RA L16 CHST2 ARID5B MCD1LG2 MEE1 (LHL42 INRC18 Gene BCL2 ZH2 CREBBP REL ASS RF8	EZB
L10RA L16 HST2 RRID5B VDCDILG2 VEE1 LLHL42 NRC18 SGL2 ZZH2 SZH2 SZH2 SZH2 SZH2 SZH2 SZH2 SZH	
L10RA L16 CHST2 ARID5B DODILG2 MEE1 LLHL42 INRC18 Gene BCL2 ZH2 CHFAS REBBP REL CREBBP REL RF85 RF8 P300 Chrom. 12p	EZB
L10RA L16 HST2 RRID5B DCD1LG2 WEE1 LHL42 NRC18 SGL2 ZH2 ZH2 ZH2 ZH2 ZH2 ZH2 ZH2 ZH2 ZH2 ZH	EZB
L10RA L16 CHST2 ARID5B DODLG2 WEE1 LLHL42 TNRC18 Gene 3CL2 CH2 TNRFSF14 KMT2D CREBBP REB RF8 EP300 Chrom.12F WEF2B SUF2B Chrom.12F ARID1A ARID1A	EZB
L10RA L16 HST2 ARID5B DODILG2 WEE1 (LHL42 TNRC18 BGCL2 EZH2 EZH2 EZH2 CREBBP REL RF8 BP300 Chrom.12F WEF2B F730 Chrom.12F MEF2B MEF2B ARD1A SNA13	EZB
L10RA L16 CHST2 ARID58 POCDLG2 WEE1 KLHL42 TNRC18 BCL2 EZH2 BCL2 EZH2 REL FAS IRFRS REL FAS IRFRS FAS IRFRS RES RES RES RES RES RES RES RES RES R	EZB
L10RA L16 HST2 ARID5B DCDILG2 WEE1 (LHL42 TNRC18 BCL2 ZH2 ZH2 ZH2 ZH2 ZH2 CREBBP RF8 EP300 CREBBP RF8 EP300 CREBBP TAS FATS FATS FATS FATS FATS FATS FATS	EZB
L10RA L16 HST2 ARID5B DCDILG2 WEE1 CLHL42 TNRC18 BCL2 ZH2 TNFR5F14 KMT2D CREBBP REB RF8 EP300 Chrom.12F MEF2B SNA13 STAT6 PTEN Chrom.21 EbF1	
LIORA LIG HST2 KRID5B VCDILG2 VEE1 LLHL42 NRC18 Gene 3GL2 CL2 KIT2D CL2 KIT2	
LIORA LIGA HST2 KRID5B DODILG2 WEE1 LHL42 NRC18 SCH2 SCH2 SCH2 SCH2 SCH2 SCH2 SCH2 SCH2	
L10RA L16 HSTD2 KRID5B KRID5B CDEDILG2 (L12 KRID5B CDEDILG2 KRID5B SOL2 ZZH2 ZZH2 KRFRSF14 KMT2D SREBBP SOL0 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH	
L10RA L16 SHSTD AND5B AND5B AND5B AND51 SHSTD AND5 SHSTD SHS	
LIORA LIG HSTD HSTD MEND5B MEDILG2 (LIC) CHLG2 C	
LIORA LIG HSTD HSTD ARID5B MCDLIG2 WEH LLHUZ HTRC18 Gene SGL2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZ	
LIORA LIG HSTD HSTD ARID5B MCDLIG2 WEH LLHUZ HTRC18 Gene SGL2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZH2 ZZ	

Gene BCL6 NOTCH2 TWFAIP3 DTX1 CD70 BCL10A WEM300A KEPA SPEN CCND3 NOL9 TP63 ETS1 HIST1H1D PRKCB HIST1H2BK 1 TRIAP2 KIH123 TRIAP3 PABPC1
Gene ST2

Genetic alteration					
Missense mutation					
■ Truncating mutation					
Inframe mutation					
Fusion					
Amplification					
Gain					
Homozygous deletion					
Heterozygous deletion					
Gene expression subgroup					
ABC					
GCB					

Unclassified

BN2

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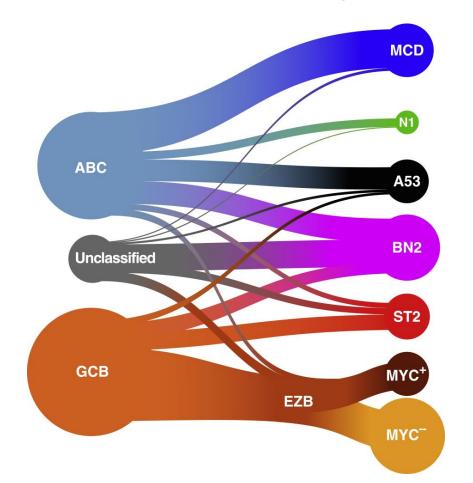
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Wright et al. Cancer Cell 2020

#### Relationship between DLBCL COO Subgroups and Genetic Subtypes

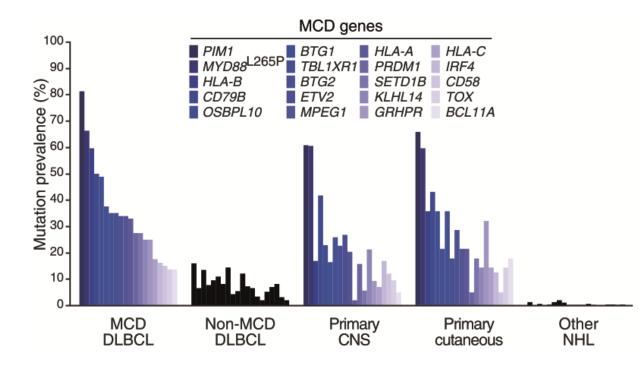


Wright et al. Cancer Cell 2020

#### The MCD Genetic Subtype of DLBCL

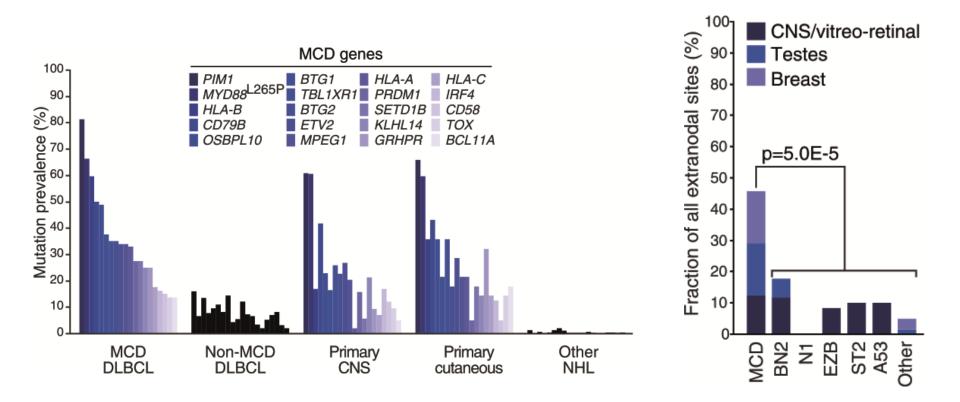
Gene	MCD
MYD88 L265P CD79B	
PIM1 HLA-B	
BTG1	
CDKN2A ETV6	
SPIB	
OSBPL10 TOX	
BCL2	
BTG2 MPEG1	
HLA-A	
HLA-C SETD1B	
KLHL14	· · · · · · · · · · · · · · · · · · ·
TBL1XR1 GRHPR	
PRDM1	
CD58 TAP1	
PIM2 FOXC1	
IRF4	
VMP1 SLC1A5	
DAZAP1	
BCL11A PPP1R9B	
IL10RA	
IL16 CHST2	······································
ARID5B	
PDCD1LG2 WEE1	
KLHL42	
TNRC18	

#### Similarities of MCD DLBCL to Extranodal DLBCL



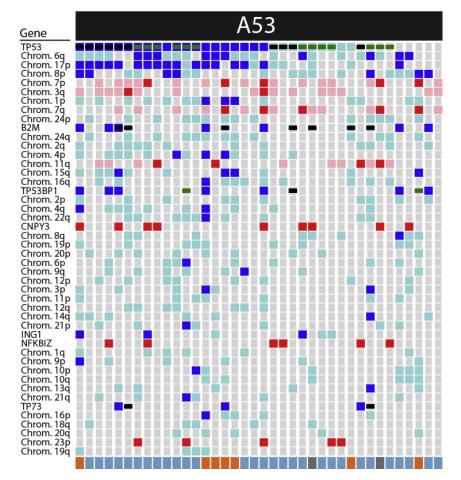
Wright et al. Cancer Cell 2020

#### Similarities of MCD DLBCL to Extranodal DLBCL



Wright et al. Cancer Cell 2020

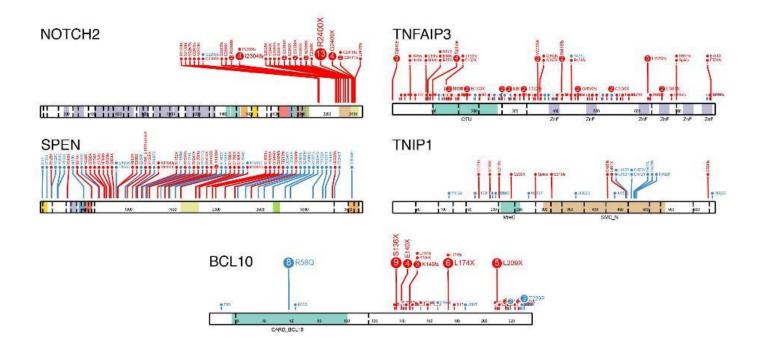
#### The A53 Genetic Subtype of DLBCL



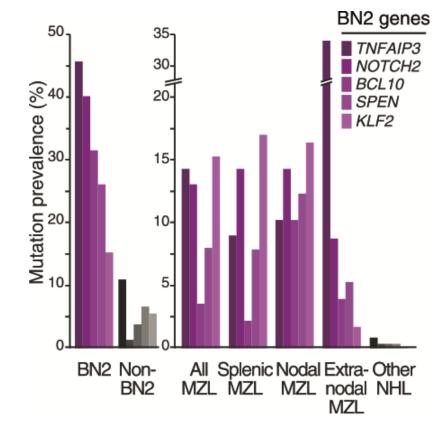
#### The BN2 Genetic Subtype of DLBCL

Gene							В	Ν	2							
BCL6																
NOTCH2												 				
TNFAIP3 DTX1			-													
CD70				•								11				
BCL10													i ti t			
UBE2A		•					_			•		 Ш				
TMEM30A			••			••		•			••	 				
KLF2 SPEN	•											 H				
CCND3								Π.		••						
NOL9					ш					•			•			
TP63										-						
ETS1 HIST1H1D						•										
PRKCB												ш			11	
HIST1H2BK															ш	
TRIP12			•	• •												
KLHL21									••							
TRRAP PABPC1												₩				
FADPCT						-										

#### Genetic Relationship Between BN2 DLBCL and Marginal Zone Lymphomas

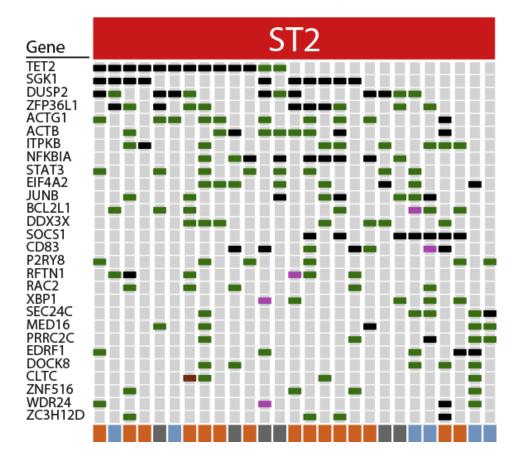


## Genetic Relationship Between BN2 DLBCL and Marginal Zone Lymphomas

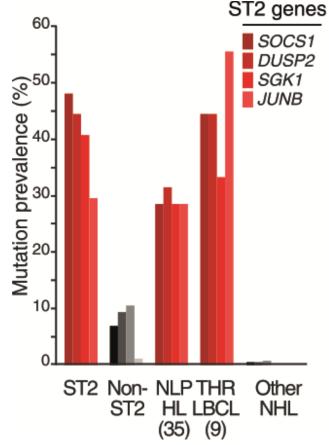


Wright et al. Cancer Cell 2020

#### The ST2 Genetic Subtype of DLBCL

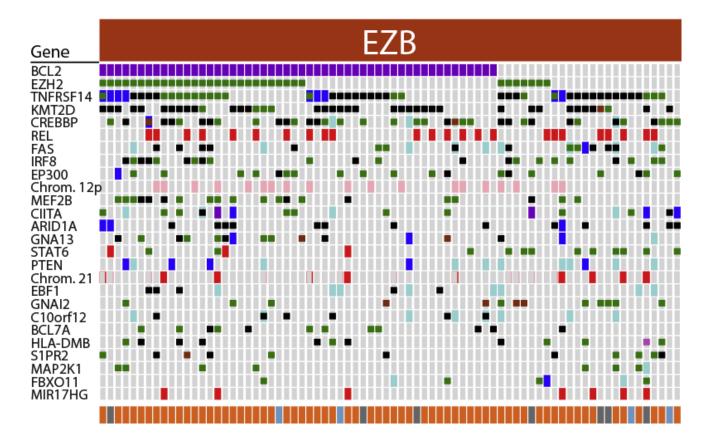


## Genetic Relationship Between ST2 DLBCL and T cell/histiocyte-rich large B cell lymphoma / Hodgkin Lymphoma

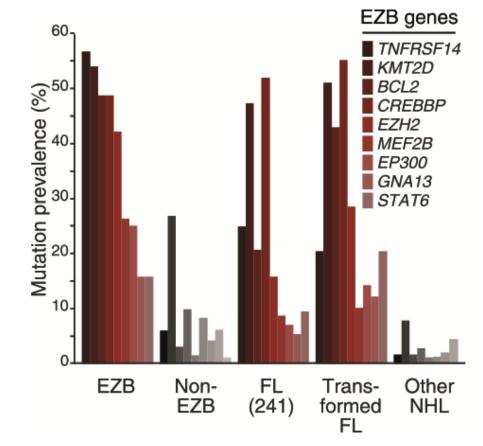


Wright et al. Cancer Cell 2020

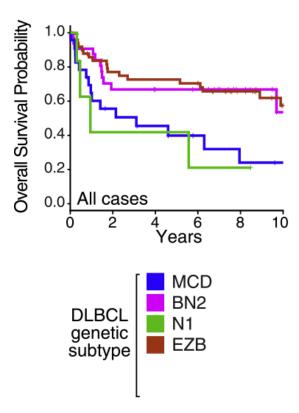
#### The EZB Genetic Subtype of DLBCL



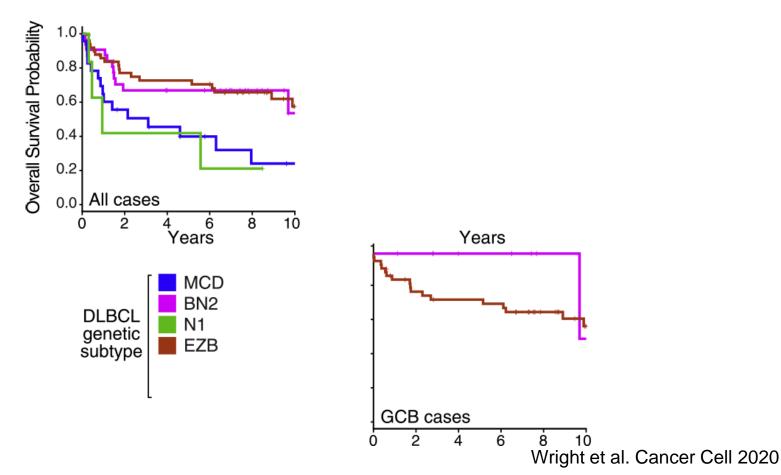
# Genetic Relationship Between EZB DLBCL and Follicular Lymphomas

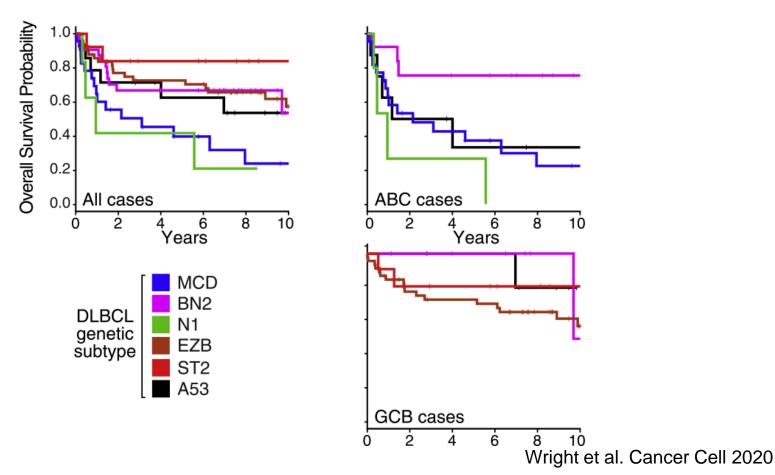


Wright et al. Cancer Cell 2020



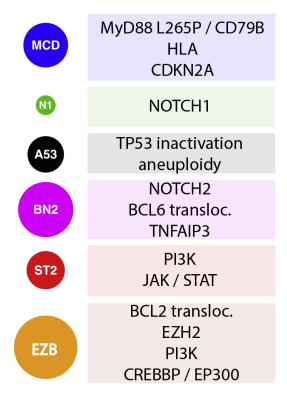
Wright et al. Cancer Cell 2020



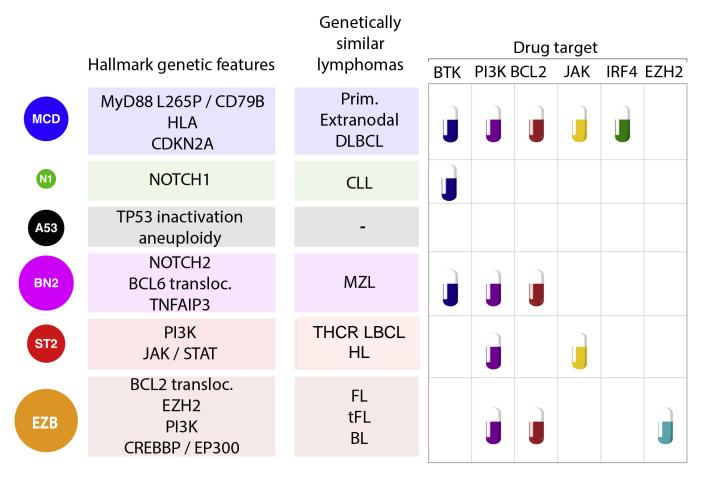




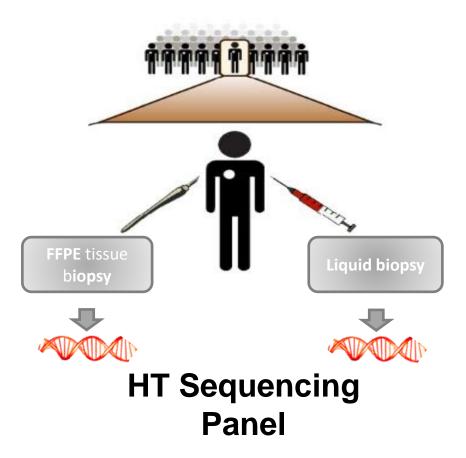
Hallmark genetic features



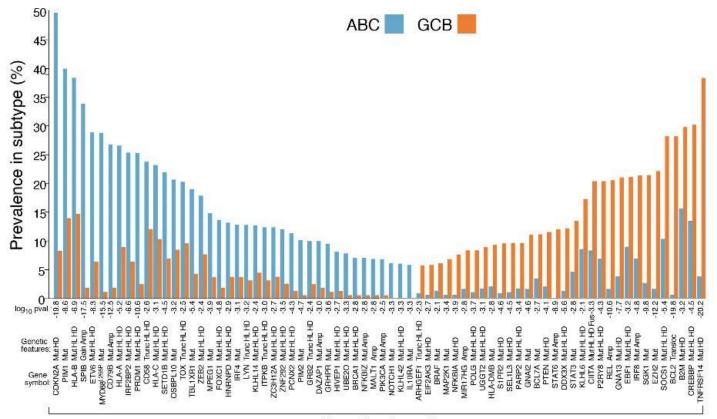
	Hallmark genetic features	Genetically similar lymphomas
MCD	MyD88 L265P / CD79B HLA CDKN2A	Prim. Extranodal DLBCL
N1	NOTCH1	CLL
A53	TP53 inactivation aneuploidy	-
BN2	NOTCH2 BCL6 transloc. TNFAIP3	MZL
ST2	PI3K JAK / STAT	THCR LBCL HL
EZB	BCL2 transloc. EZH2 PI3K CREBBP / EP300	FL tFL BL



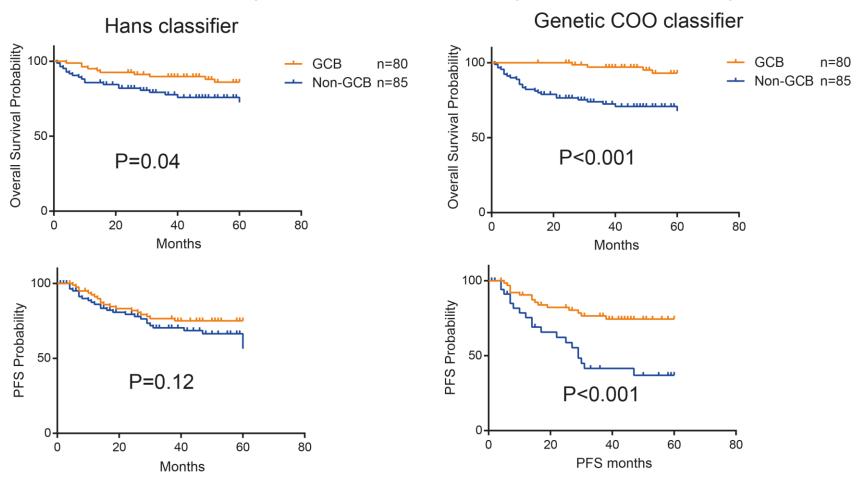
#### Genetic Subclassification in a "Real-World" Analysis



#### Cell of Origin Classification Using Mutation Profiling

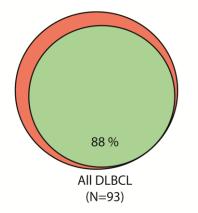


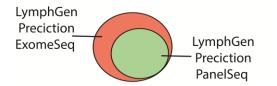
Genetic aberrations



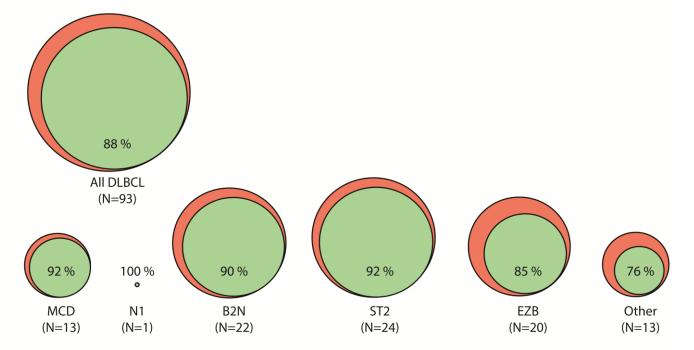
#### Cell of Origin Classification Using Mutation Profiling

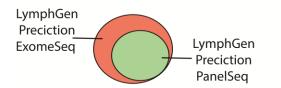
### Genetic Subgroups using Whole Exome Seq and Panel Seq



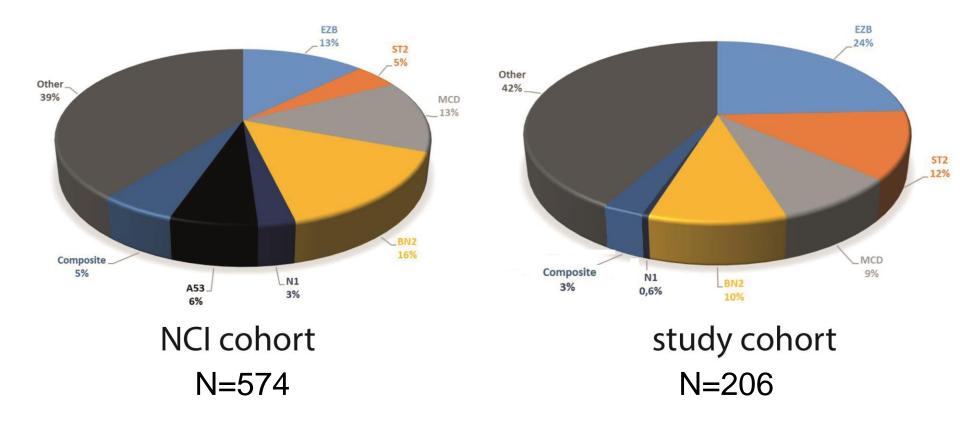


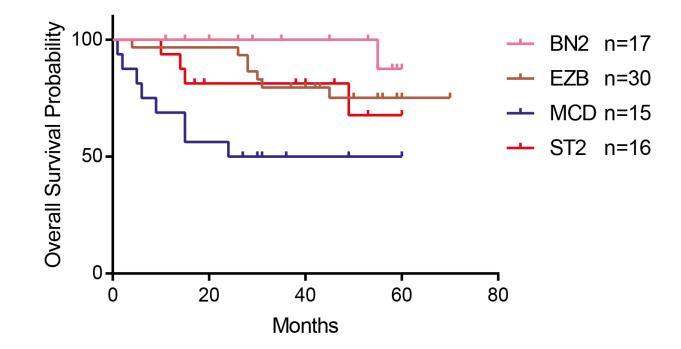
### Genetic Subgroups using Whole Exome Seq and Panel Seq





#### Similar Composition of DLBCL Cohorts





1. DLBCL is genetically very heterogeneous

MCD

**N1** 

A53

BN2

ST2

EZB

- 2. Comprehensive, multi-platform genomic analysis reveals at least 6 genetic subtypes of DLBCL
- 3. DLBCL genetic subtypes reveal genetic relationships with other lymphoma types point towards an origin from occult indolent lymphomas
- 4. The response to R-CHOP therapy is influenced by the DLBCL genetic subtype distinction
- 5. Precision medicine approaches should take into account both the DLBCL genetic subtypes AND genetic aberrations in oncogenic pathways

## Acknowledgements

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Members of the LLMPP Consortium

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Andreas Bräuninger Stefan Gattenlöhner

Hematology Department University of Giessen

> Tobias Arnold Felix Schell

Mathias Rummel