Eppur si muove...

La terapia nel MONDO LINFOMI

IL RAZIONALE BIOLOGICO DELLE COMBINAZIONI NEL PAZIENTE CON DLBCL R/R

BOLOGNA, 8 MARZO 2022

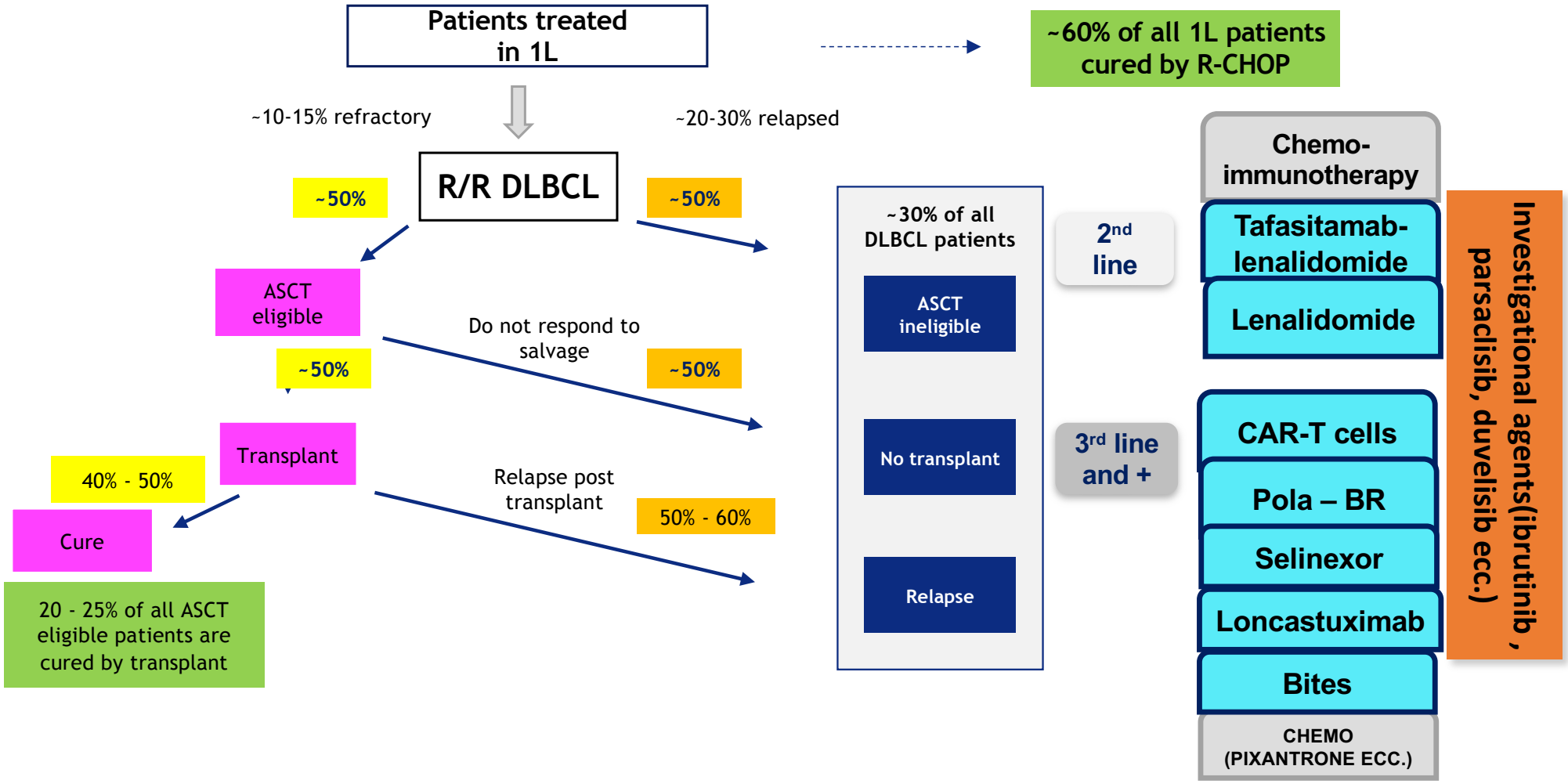
Gerardo Musuraca
IRST IRCCS "Dino Amadori" Meldola

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

DISCLOSURE

- JANSSEN: Advisory, consultant
- ROCHE: Advisory, consultant
- INCYTE: Advisory, consultant

Relapsed and refractory DLBCL

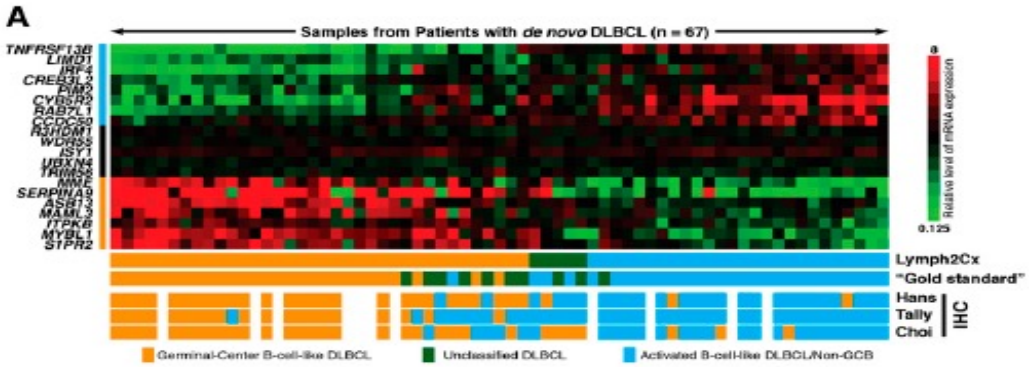


DLBCL

EXCEPT CAR T:

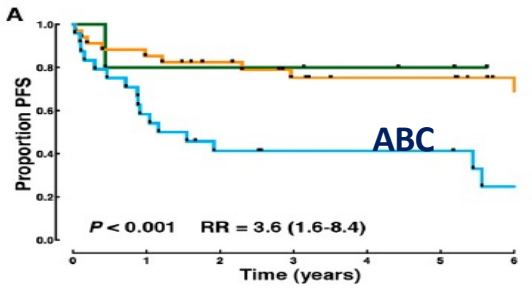
HOW WE CAN CHOICE THE NEW DRUGS IN R/R ?

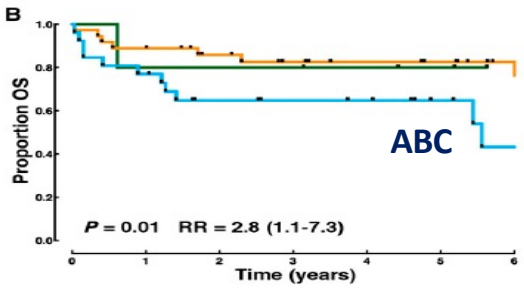
DLBCL: COO profile subgroups



Nanostring test

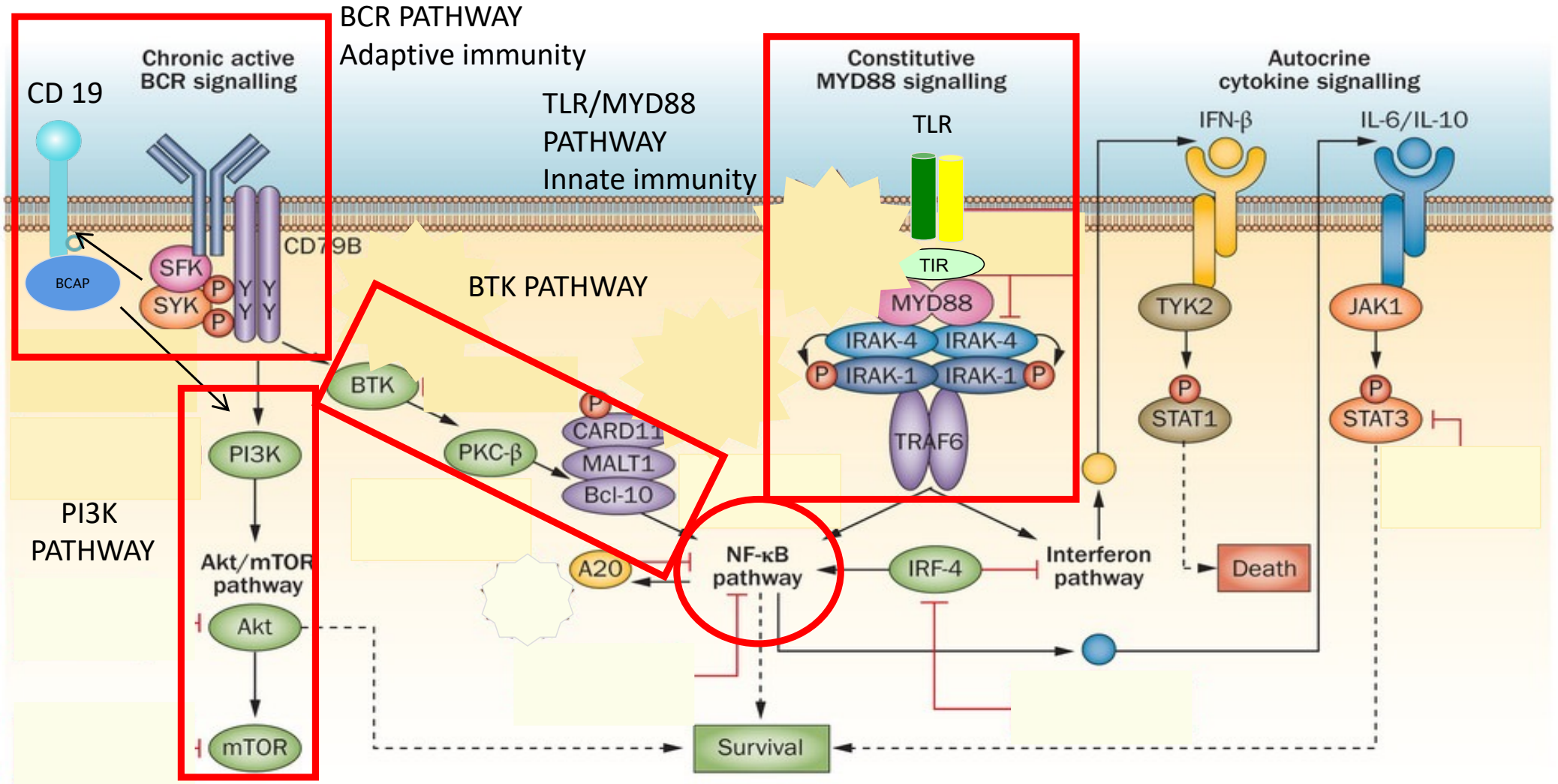
Lymph 2Cx assay
20 gene assay

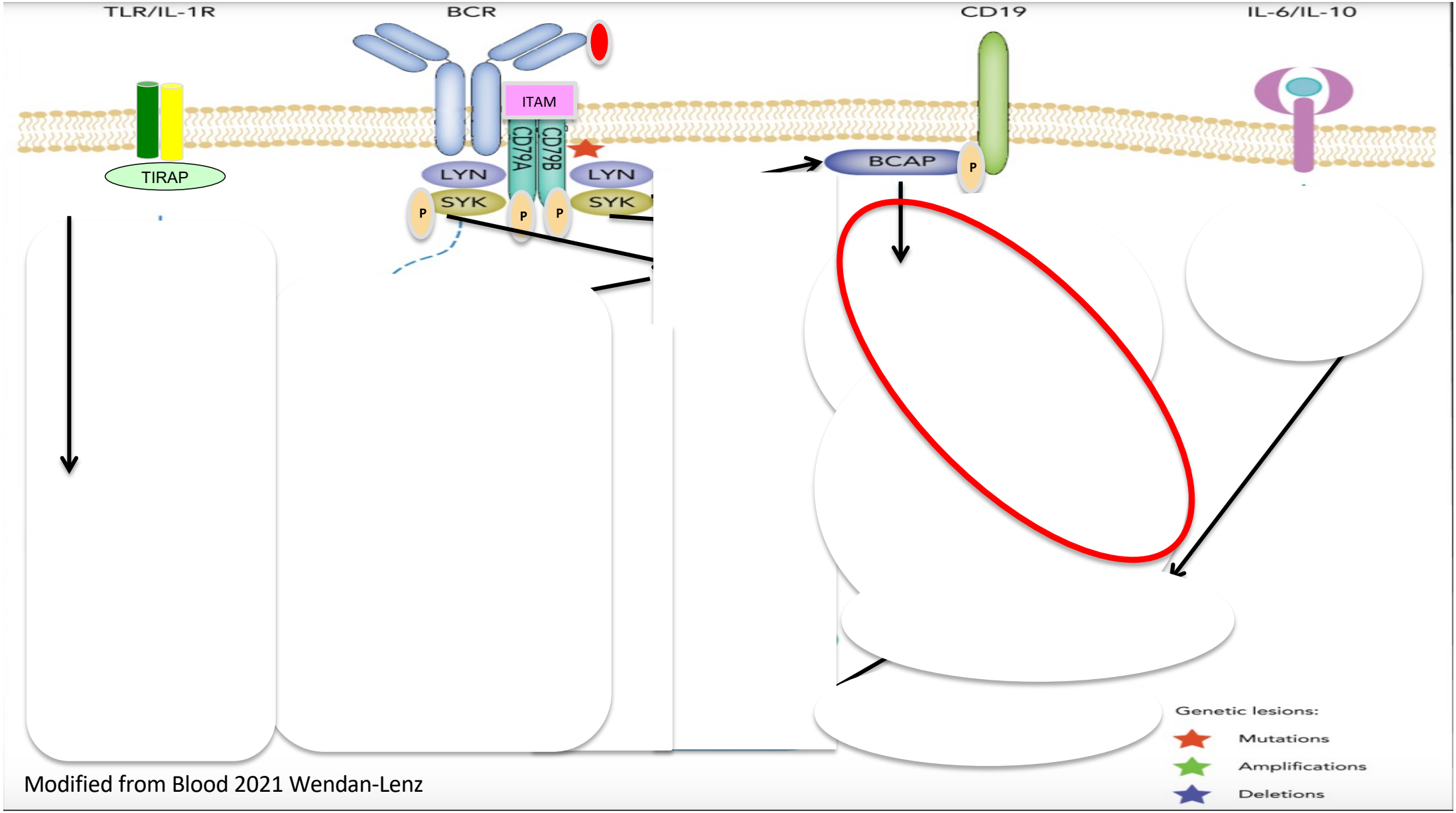




Molecular Aberration	GC	ABC
BCL2 translocation	++	-
c-rel amplification	++	-
EZ2H mutation	++	-
MYD88 mutation	+	+++
CD79A, CD79B mutation		++
BCL6 translocation	+	++
BCL6 pathway	+++	++
MYC pathway	+	+++
NF-κB pathway	-	+++
BCR pathway		++
IRF4 pathway	-	+++

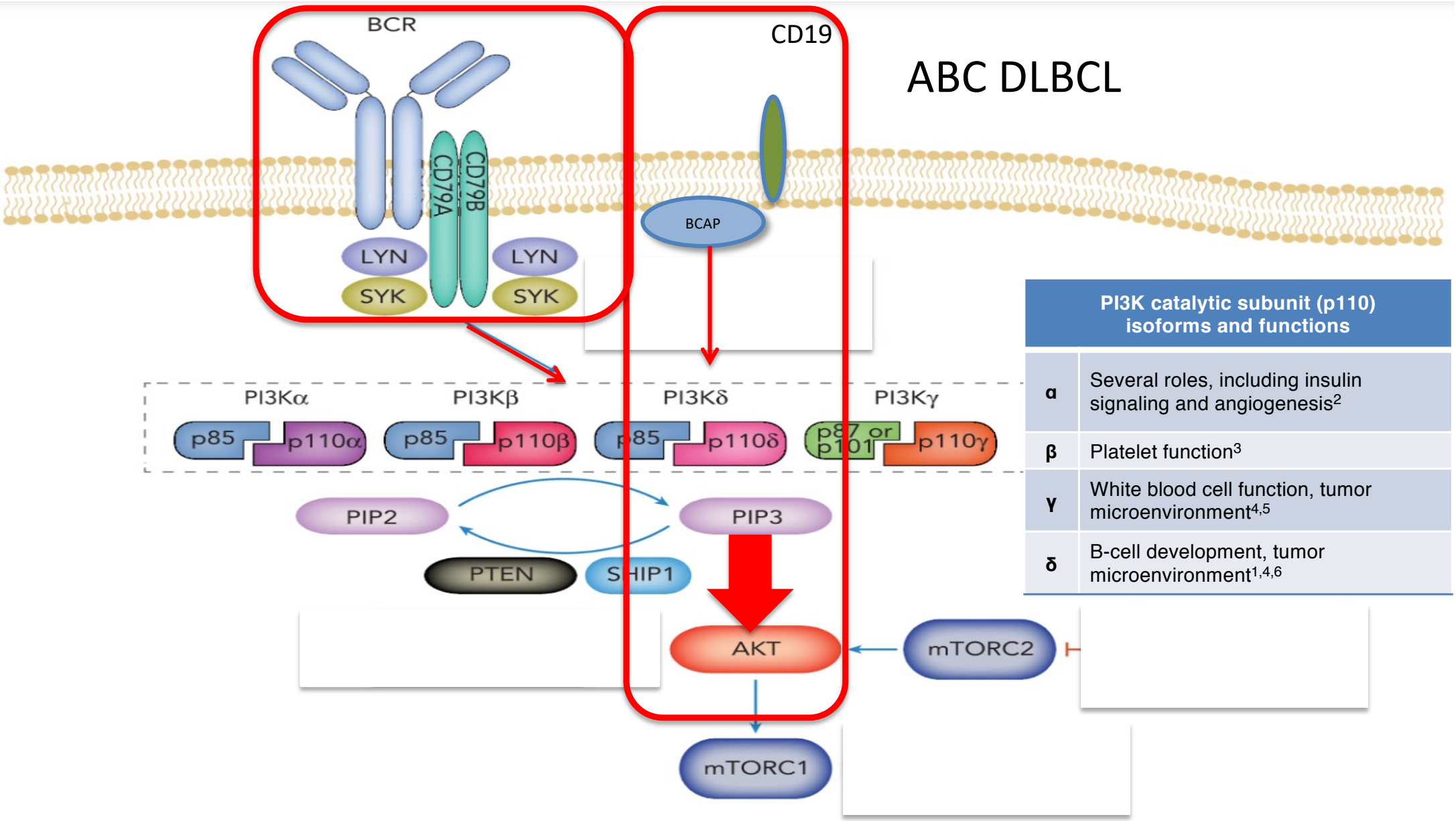
Survival pathways with therapeutic potential in DLBCL



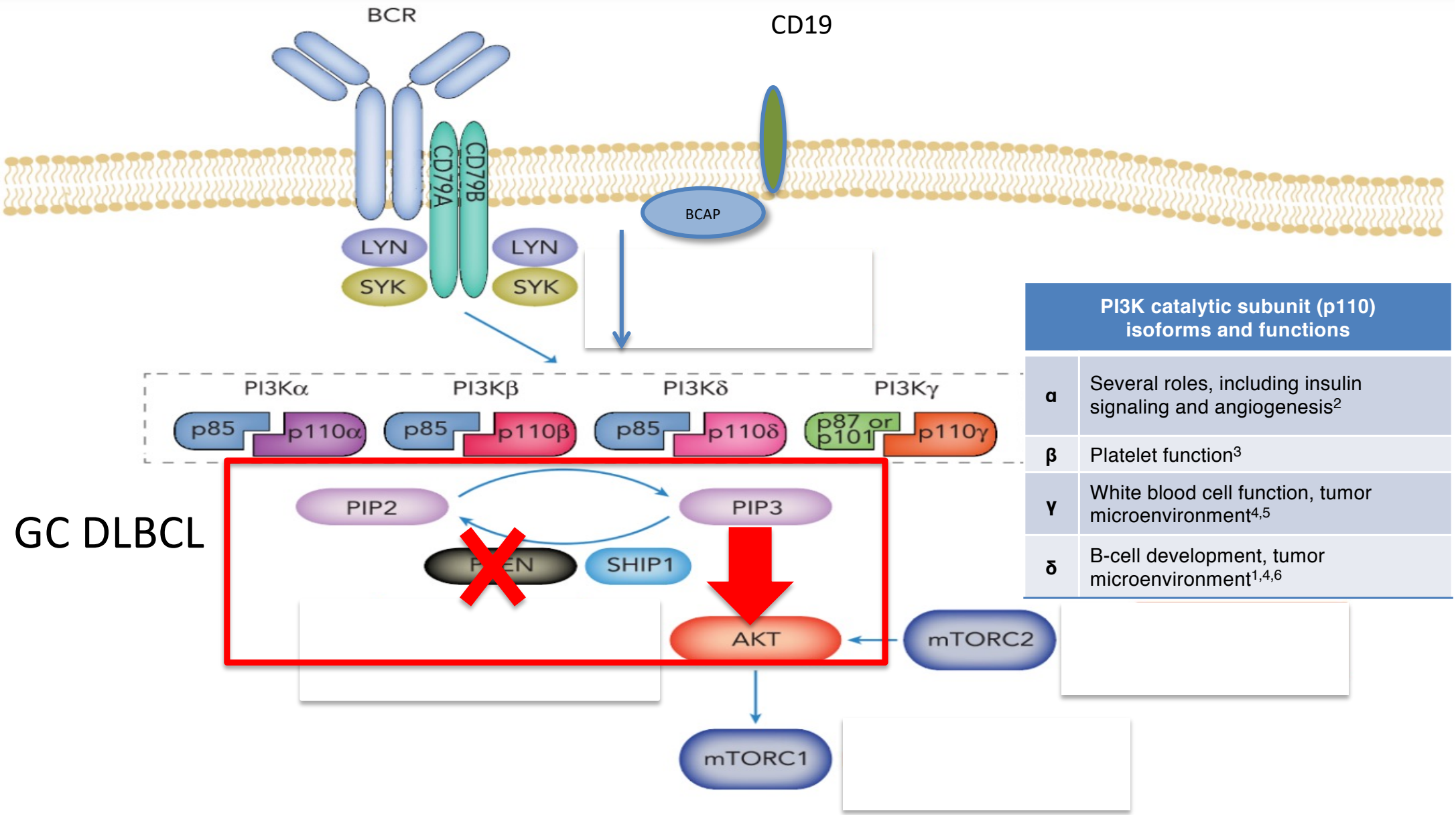


Modified from Blood 2021 Wendan-Lenz

ABC DLBCL



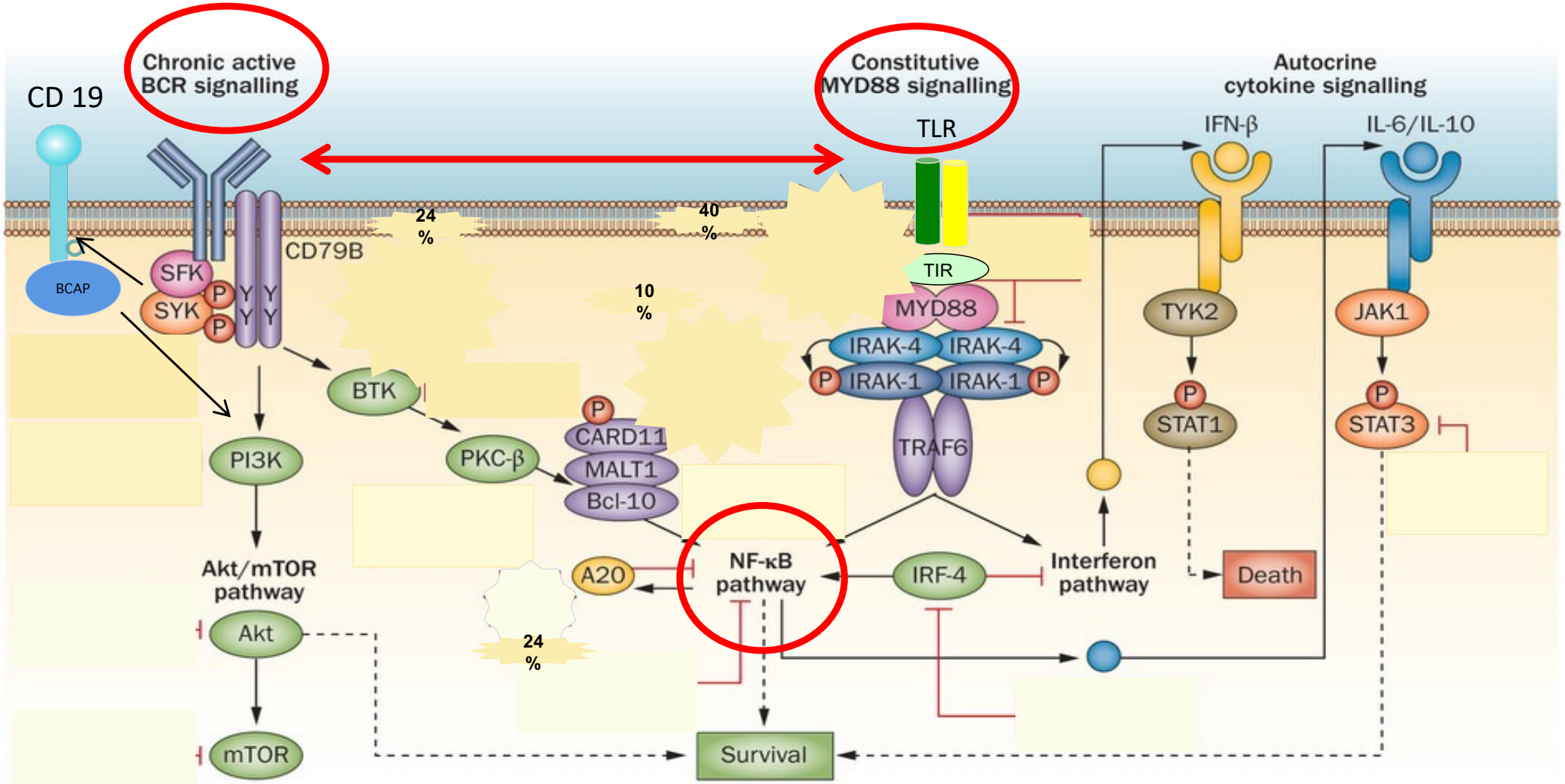
PI3K catalytic subunit (p110) isoforms and functions	
α	Several roles, including insulin signaling and angiogenesis[2]
β	Platelet function[3]
γ	White blood cell function, tumor microenvironment[4,5]
δ	B-cell development, tumor microenvironment[1,4,6]

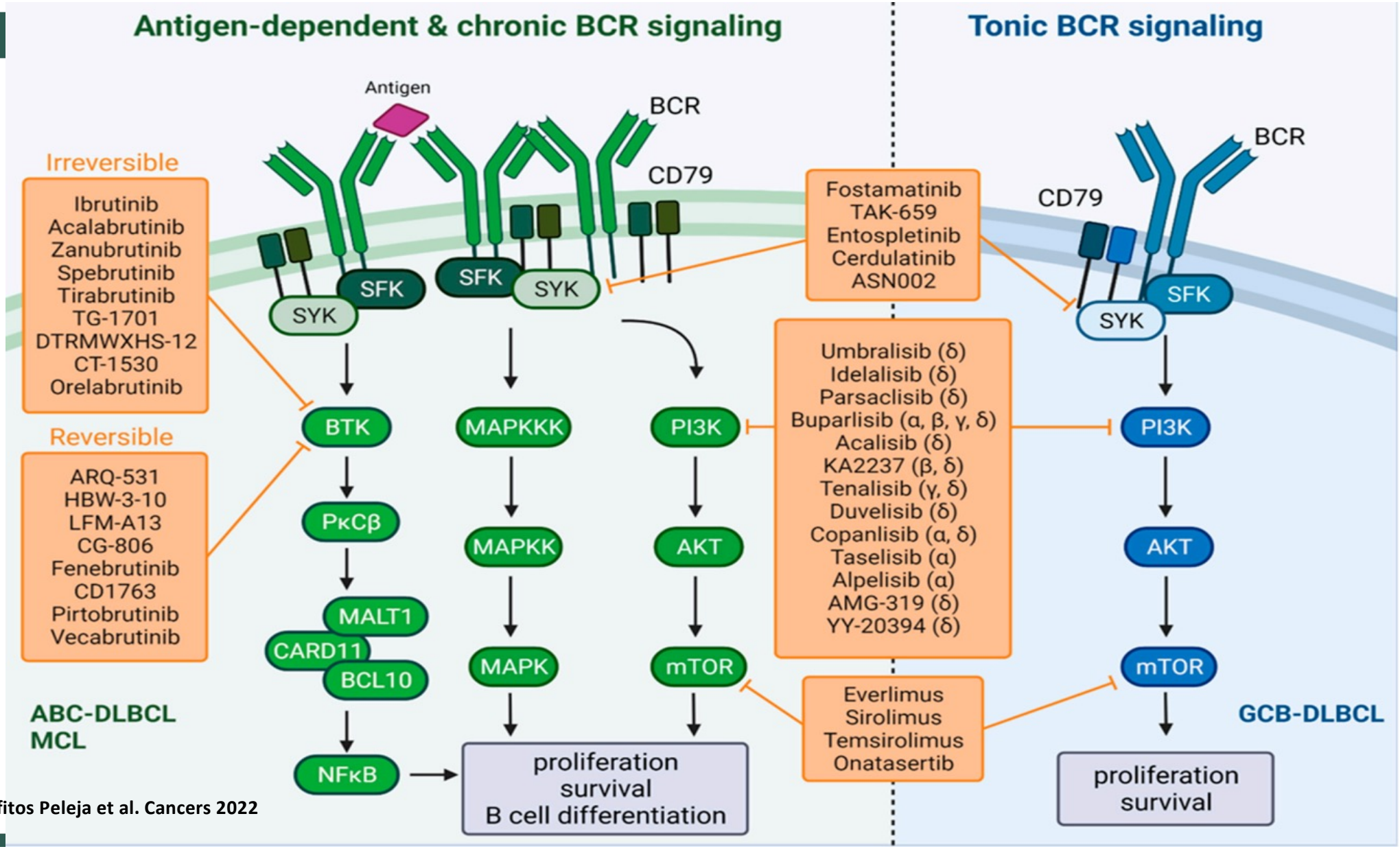


GC DLBCL

PI3K catalytic subunit (p110) isoforms and functions	
α	Several roles, including insulin signaling and angiogenesis[2]
β	Platelet function[3]
γ	White blood cell function, tumor microenvironment[4,5]
δ	B-cell development, tumor microenvironment[1,4,6]

Survival pathways with therapeutic potential in DLBCL





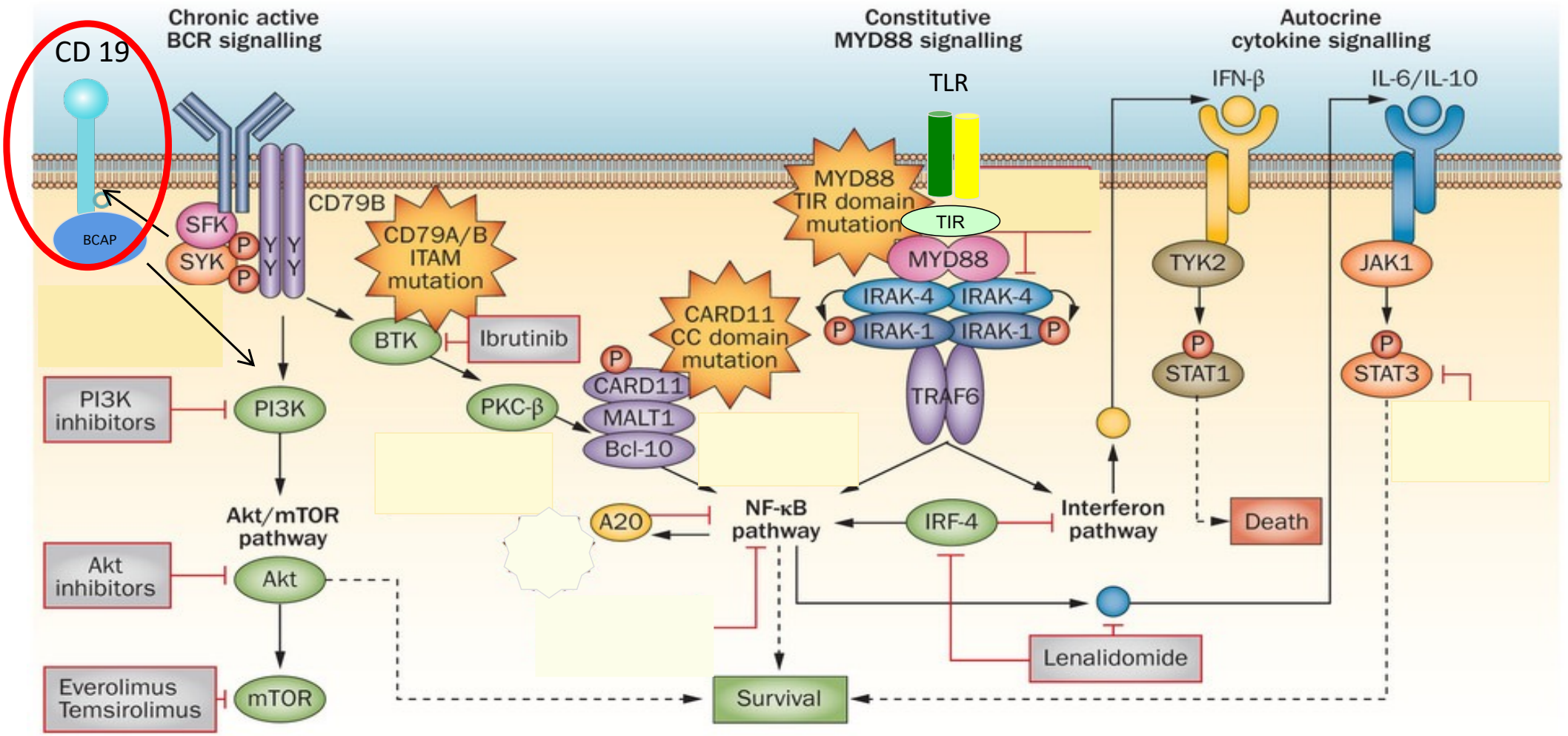
Profitos Peleja et al. Cancers 2022

Drug	Targets	n	Treatment	ORR, %	Reference
Buparlisib	Pan-class I PI3K	26	Monotherapy	11.5	93
Copanlisib	Pan-PI3K, with preferential inhibition of PI3Kα and PI3Kδ	15	Monotherapy	6.7	110
Copanlisib	Pan-PI3K, with preferential inhibition of PI3Kα and PI3Kδ	67	Monotherapy	19.4 (31.6 in ABC, 13.3 in GCB)	90
CUDC-907	PI3Kα, β, and δ, histone deacetylase	37	Monotherapy or combined with rituximab	37	97
Umbralisib	PI3Kδ	26	Combined with ublituximab	23	102
Parsaclisib	PI3Kδ	60	Monotherapy	25.5	94

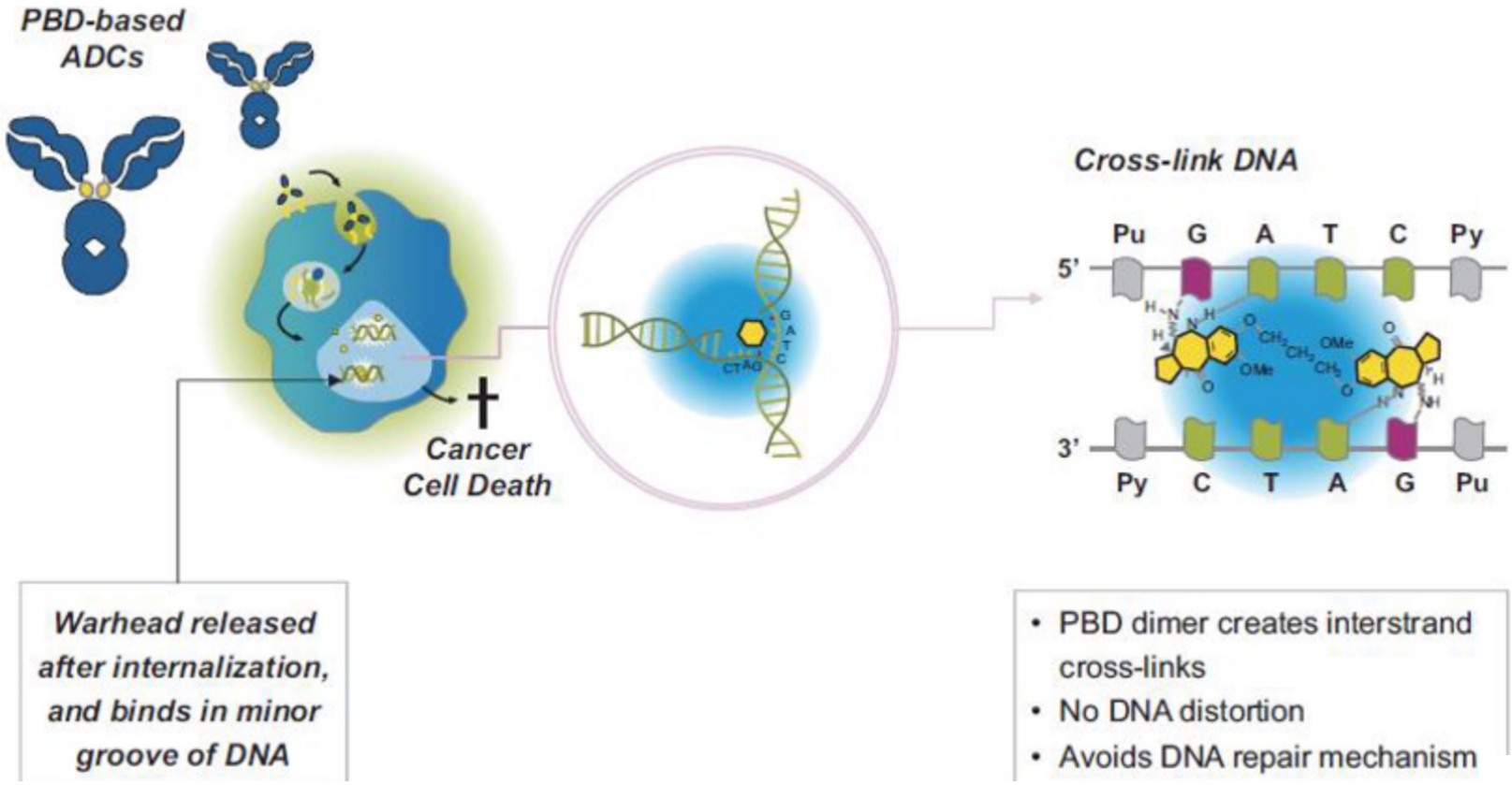
Wendan et al. Blood 2021

Targets	Drug/Regimen	Clinical Trial	Phase	Nb Pts	Status	Conditions	Response Data	References
BTK CD20	Ibrutinib + Rituximab + Bendamustine	NCT01479842	1	48	Active	MZL, FL, MCL, WM	OR 94% in MCL and 37% in DLBCL CR 76% in MCL and 31% in DLBCL	[160]
BTK	Ibrutinib + Rituximab + Lenalidomide	NCT02636322	2	60	Active	DLBCL	ORR 65% DOR 15.9 months	[161]
BTK CD20	Ibrutinib + Rituximab + Lenalidomide	NCT02077166	1 & 2	134	Completed	R/R DLBCL	ORR 47% CR 28% PFS 21 months AEs grade > 3 in less 30% patients	[162]
BTK CD20	Ibrutinib + Rituximab + Venetoclax	NCT03136497	1	10	Active	R/R DLBCL	NA	NA
BTK	Spebrutinib	NCT01351935	1	113	Completed	B-cell Lymphomas	ORR 53%	[163]
BTK	Spebrutinib + Lenalidomide	NCT01766583	1	18	Completed	R/R B-cell Lymphomas	NA	NA
BTK CD20	Zanubrutinib + Rituximab	NCT03520920	2	41	Completed	MZL, FL, DLBCL	ORR 35% PFS 3.38 months	[164]
BTK mTOR	DTRMWXHS-12 + Everolimus + Pomalidomide	NCT02900716	1	48	Completed	B-cell Lymphomas	Well-tolerated and no DLT achieved	[131]
BTK PI3K	Ibrutinib + Umbralisib	NCT02874404	2	13	Completed	R/R DLBCL	ORR 31% PFS 3 months	[165]
BTK PI3K CD20	Ibrutinib + Parsaclisib+ Rituximab+ Bendamustine	NCT03424122	1	50	Active	B-cell Lymphomas	NA	NA
BTK PI3K	Ibrutinib + Umbralisib	NCT02268851	1	45	Active	CLL, SLL, MCL	ORR 67% CR 19% PR 48% AEs grade >3 in less than 10%	[166]
BTK PI3K CD20	Ibrutinib + Umbralisib + Ublituximab + Bendamustine	NCT02006485	1	160	Completed	B-cell Lymphomas	DOR 20 months	[167]
mTOR	Everolimus + Lenalidomide	NCT01075321	1 & 2	58	Completed	MZL, FL, MCL, WM	ORR 27%	[168]

Survival pathways with therapeutic potential in DLBCL



LONCASTUXIMAB TESIRINE MoAb CD19 drug conjugated



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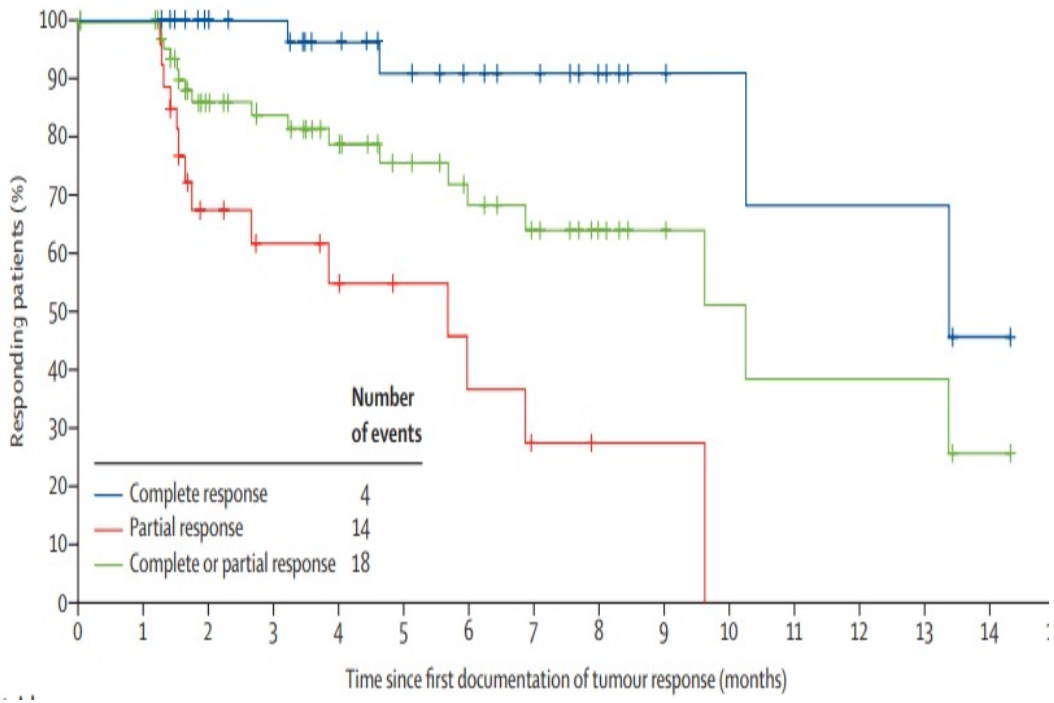
Loncastuximab: duration of response



	As-treated population (n=145)
Overall response rate (complete or partial response)	70 (48·3% [39·9–56·7])
Complete response rate	35 (24·1% [17·4–31·9])
Complete response	35 (24%)
Partial response	35 (24%)
Stable disease	22 (15%)
Progressive disease	30 (21%)
Not evaluable*	23 (16%)

Data are n (% [95% CI]) or n (%). Response was assessed by central independent review. A best overall response of stable disease could only be achieved after the patient was on the study for a minimum of 35 days following the first dose of loncastuximab tesirine. Any disease assessment indicating stable disease before this timepoint was considered not evaluable for response if no assessment after this timepoint was available. *Patients without any scan available to the independent reviewer or patients whose scan was determined to be not evaluable by the independent reviewer.

Table 2: Best overall responses and overall response rate

Median DOR for the whole population 10.3 months
Median DOR for CR patients 13.4 months

Caimi et al. Lancet Oncology 2021

2099 Interim Results of Loncastuximab Tesirine Combined with Ibrutinib in Diffuse Large B–Cell Lymphoma or Mantle Cell Lymphoma (LOTIS–3)

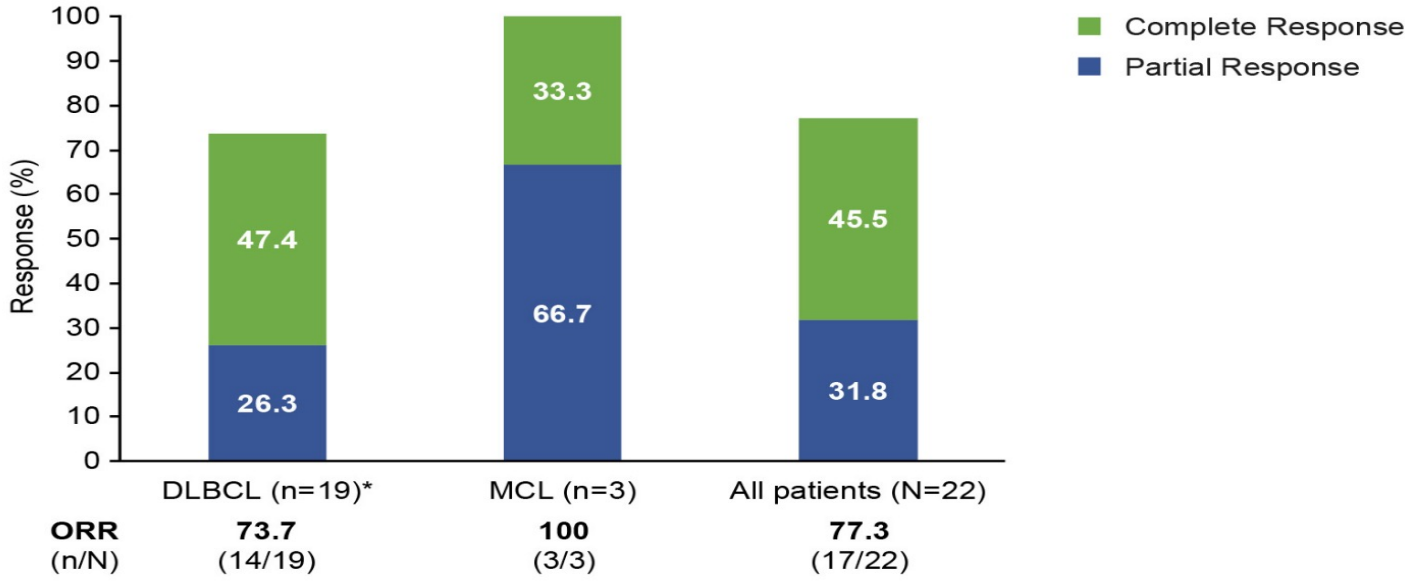
Program: Oral and Poster Abstracts
Session: 626. Aggressive Lymphoma (Diffuse Large B–Cell and Other Aggressive B–Cell Non–Hodgkin Lymphomas)—Results from Prospective Clinical Trials: Poster II
Hematology Disease Topics & Pathways:
Diseases, Therapies, Combinations, Lymphoid Malignancies

Sunday, December 6, 2020, 7:00 AM-3:30 PM

Julien Depaus[1], Nina D. Wagner–Johnston[2], Pier Luigi Zinzani, MD[3], Tycel J. Phillips, MD[4*], Joseph Maly, MD[5], Silvia Ferrari, MD[6*], Emmanuel Bachy, MD, PhD[7*], Locke J. Bryan[8], Vincent Delwail[9*], Murali Janakiram[10*], Sophie de Guibert[11*], Monica Tani, MD[12*], Jennifer Adeleye[13*], Xiaoyan Zhang[13*], Luqiang Wang[13*], Annette Ervin–Haynes[13*] and Carmelo Carlo–Stella, MD[14]*

LOTIS 3: LONCA+ IBRUTINIB

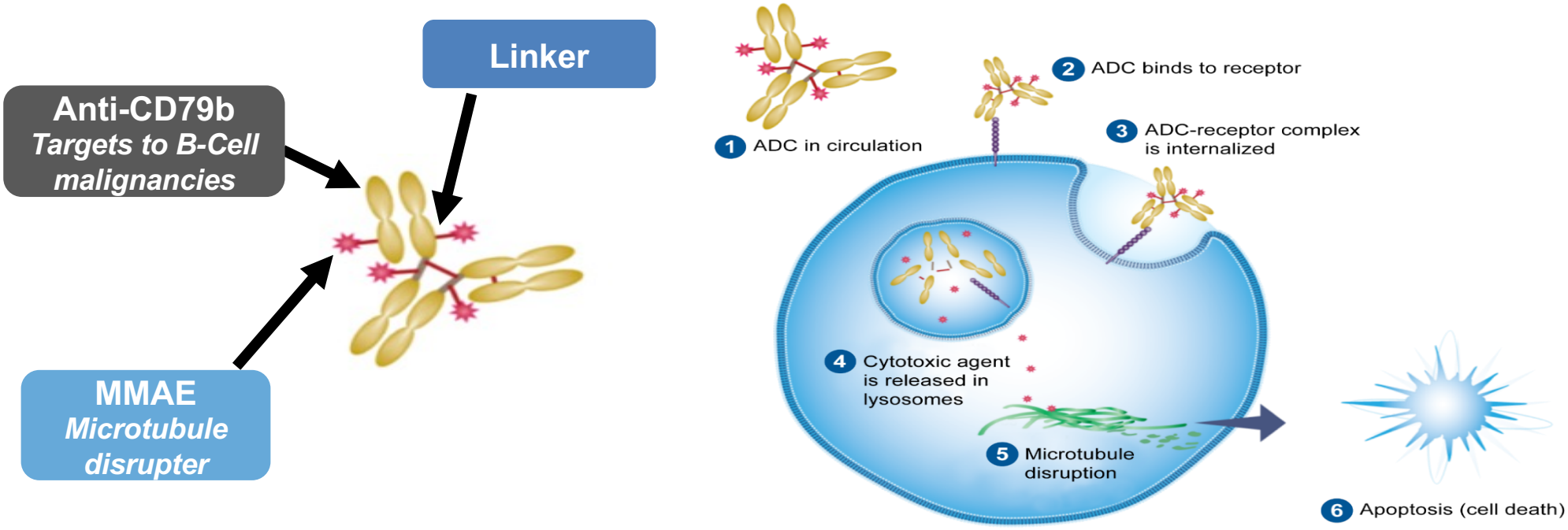
Figure 1. Response in patients receiving Lonca 60 µg/kg and ibrutinib 560 mg



*Only 1 pt with GCB DLBCL was evaluable and had a partial response.

Polatuzumab Vedotin (CD79b-ADC)

- ADC comprising potent microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



ADC, antibody drug conjugate; MMAE, monomethyl auristatin E

Polson AG et al. Expert Opin Investig Drugs 2011;20(1):75–85; Dornan D et al. Blood 2009;114:2721–2729.

2273 Combination of Loncastuximab Tesirine and Polatuzumab Vedotin Shows Increased Anti-Tumor Activity in Pre-Clinical Models of Non-Hodgkin Lymphoma

Program: Oral and Poster Abstracts
Session: 605. Molecular Pharmacology and Drug Resistance: Lymphoid Neoplasms: Poster II
Hematology Disease Topics & Pathways:
Translational Research

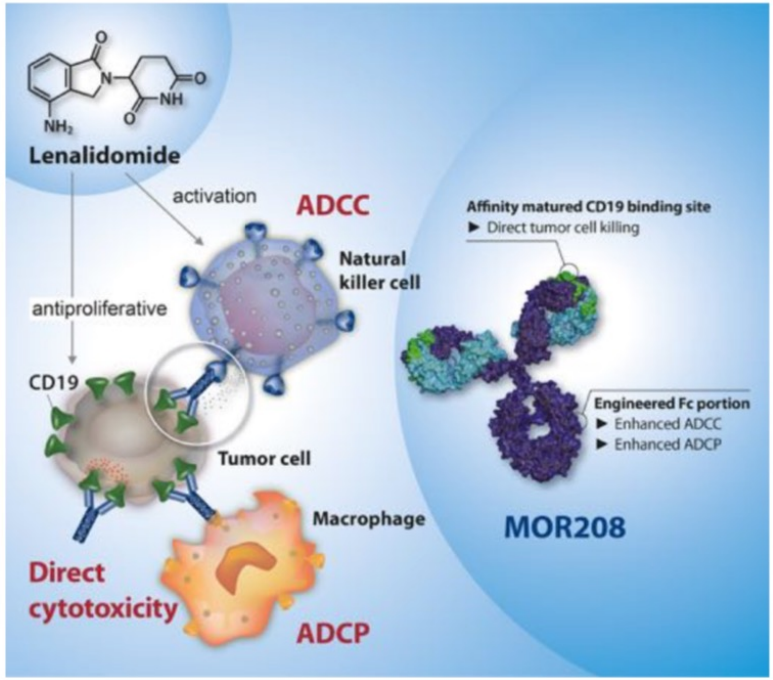
Sunday, December 12, 2021, 6:00 PM-8:00 PM

Nikoleta Sachini, PhD, Asma Jabeen, PhD*, Patrick H van Berkel, PhD* and Francesca Zammarchi, PhD**

MOR208 + Lenalidomide: novel immunological combination

MOR208

- ↑ADCC
- ↑ADCP
- Direct Cell Death
- Encouraging single agent activity in R/R DLBCL & iNHL patients



Lenalidomide

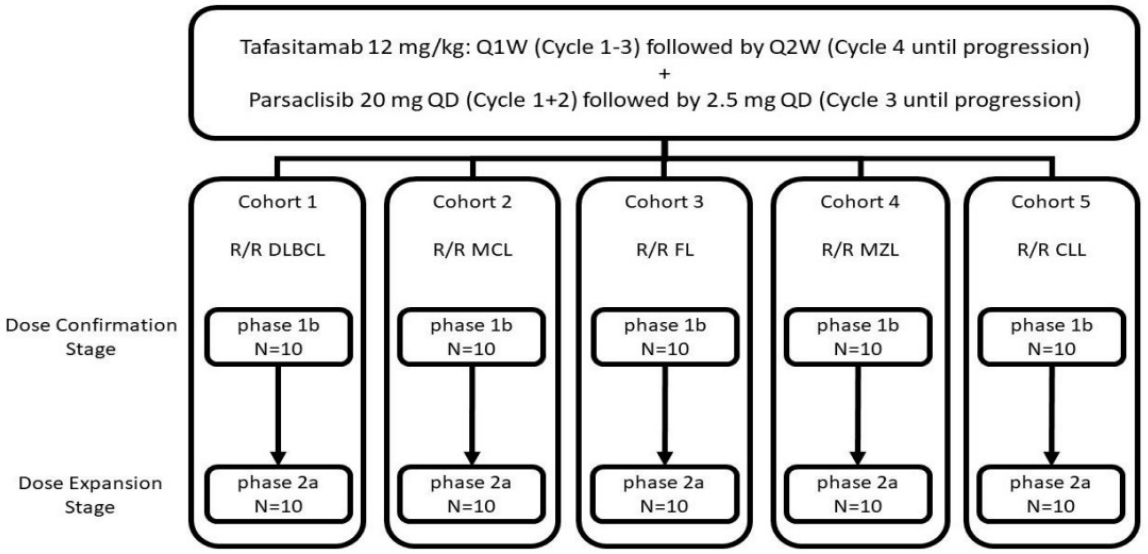
- T and NK Cell Activation/ Expansion
- Direct Cell Death
- Has been well studied as an anti-lymphoma agent, alone or in combination

Horton et al., 2008; Awan et al., 2010; Richter et al., 2013; MorphoSys data on file; Wu et al., 2008; Lapalombella et al., 2008; Zhang et al., 2013, Wiernik et al., 2008; Witzig et al., 2011; Czuczman et al., 2017; Jurczak et al, 2018

TAFASITAMAB+ PARSACLISIB IN LNH

Number of Participants	Approx. 100 - 50 in the Dose Confirmation Part - 50 in the Dose Expansion Part
Targeted Population	Male and female participants at least 18 years of age who have relapsed or refractory B-cell malignancies including R/R DLBCL, R/R MCL, R/R FL, R/R MZL, and R/R CLL/SLL.

- **Approx. 100 subjects**
- **Approx. 30 sites, feasibility currently ongoing.**
- **5 countries (US, France, Spain, Italy – 8 sites, Germany)**



- Participants must have received at least 3 of 4 doses of tafasitamab and 21 days of treatment with parsaclisib 20 mg QD during the first cycle (28 days) or have experienced a DLT to be considered evaluable for the dose confirmation period.
- An iDSMB will review data from each of the disease-specific cohorts after the 10th evaluable participant in each cohort completes Day 28 of the first cycle.

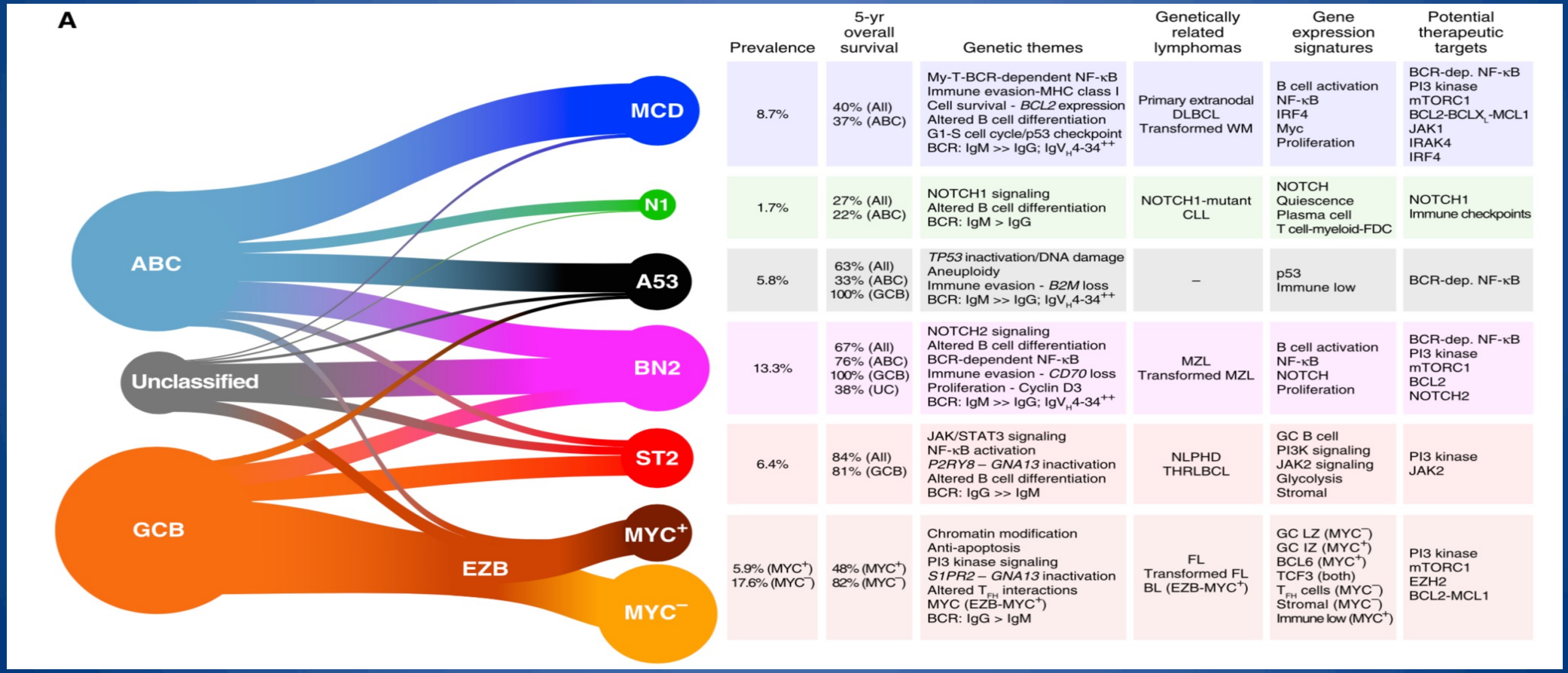
CONCLUSION

The knowledge of the BCR processes has allowed us a substantial step forward in the therapeutic possibilities of patients with Lymphoma.

However, the poor results with single target agents still delineate a complexity not fully understood and suggest a multi-shot approach in order to target various metabolic pathways reducing toxicity and synergizing the results.

The broad spectrum genetic analyzes currently possible will lead to a further improvement of the pharmacological strategies to be adopted

A Probabilistic Classification Tool for Genetic Subtypes of DLBCL with Therapeutic Implications



	Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
MCD	8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF-κB Immune evasion-MHC class I Cell survival - *BCL2* expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	Primary extranodal DLBCL Transformed WM	B cell activation NF-κB IRF4 Myc Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2-$BCLX_L$-MCL1 JAK1 IRAK4 IRF4
N1	1.7%	27% (All) 22% (ABC)	NOTCH1 signaling Altered B cell differentiation BCR: IgM > IgG	NOTCH1-mutant CLL	NOTCH Quiescence Plasma cell T cell-myeloid-FDC	NOTCH1 Immune checkpoints
A53	5.8%	63% (All) 33% (ABC) 100% (GCB)	*TP53* inactivation/DNA damage Aneuploidy Immune evasion - *B2M* loss BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	–	p53 Immune low	BCR-dep. NF-κB
BN2	13.3%	67% (All) 76% (ABC) 100% (GCB) 38% (UC)	NOTCH2 signaling Altered B cell differentiation BCR-dependent NF-κB Immune evasion - *CD70* loss Proliferation - Cyclin D3 BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	MZL Transformed MZL	B cell activation NF-κB NOTCH Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2 NOTCH2
ST2	6.4%	84% (All) 81% (GCB)	JAK/STAT3 signaling NF-κB activation *P2RY8 – GNA13* inactivation Altered B cell differentiation BCR: IgG >> IgM	NLPHD THRLBCL	GC B cell PI3K signaling JAK2 signaling Glycolysis Stromal	PI3 kinase JAK2
EZB	5.9% (MYC^+) 17.6% (MYC^-)	48% (MYC^+) 82% (MYC^-)	Chromatin modification Anti-apoptosis PI3 kinase signaling *S1PR2 – GNA13* inactivation Altered T_{FH} interactions MYC (EZB-MYC^+) BCR: IgG > IgM	FL Transformed FL BL (EZB-MYC^+)	GC LZ (MYC^-) GC IZ (MYC^+) BCL6 (MYC^+) TCF3 (both) T_{FH} cells (MYC^-) Stromal (MYC^-) Immune low (MYC^+)	PI3 kinase mTORC1 EZH2 BCL2-MCL1

Wright et al Canc cell 2020

IL PROBLEMA NON E' AVERE I PEZZI

E' SAPERLI ORDINARE

THANKS