Eppur si muove...

La terapia nel MONDO LINFOMI

Il razionale biologico delle combinazioni nei linfomi non Hodgkin

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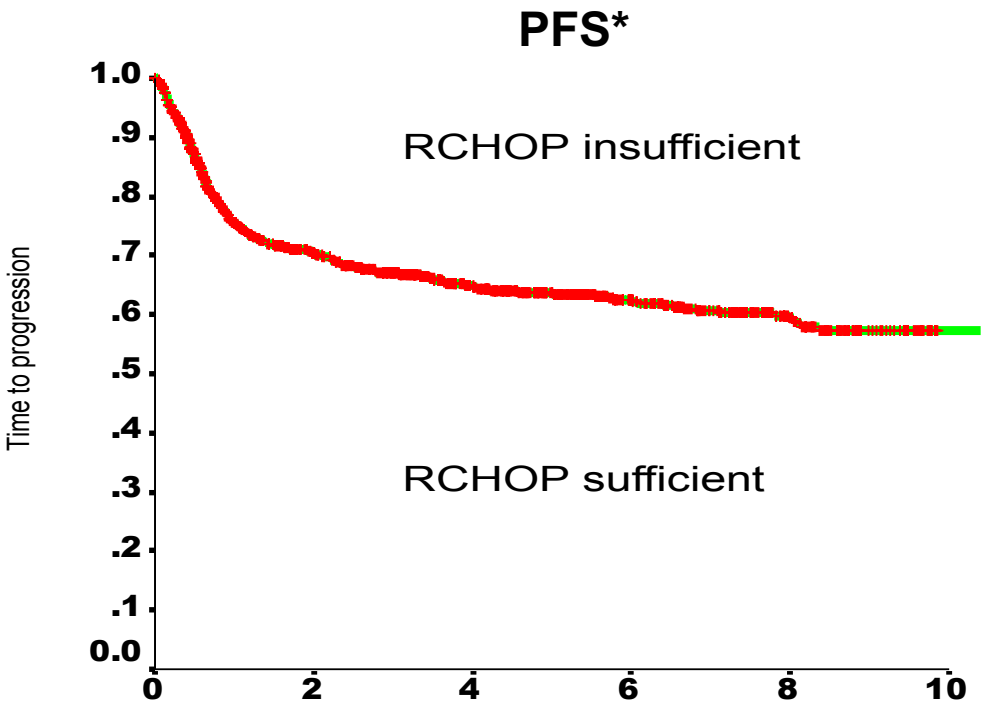
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X		
Bayer					X	X	
Constellation						X	
Genmab						X	
Gilead					X	X	
Incyte					X	X	
Janssen					X	X	
Morphosys	X					X	
Novartis					X		
Regeneron						X	

Heterogeneity of Outcomes in DLBCL

- Clinical factors
  - IPI (R-IPI)
- Interim PET scan
- GEP
  - ABC vs GCB
- Protein expression
  - MYC and BCL2
- Chromosomal alterations
  - MYC, BCL2, BCL6
- Deep sequencing mutation/combined expression analysis



Two broad strategies:

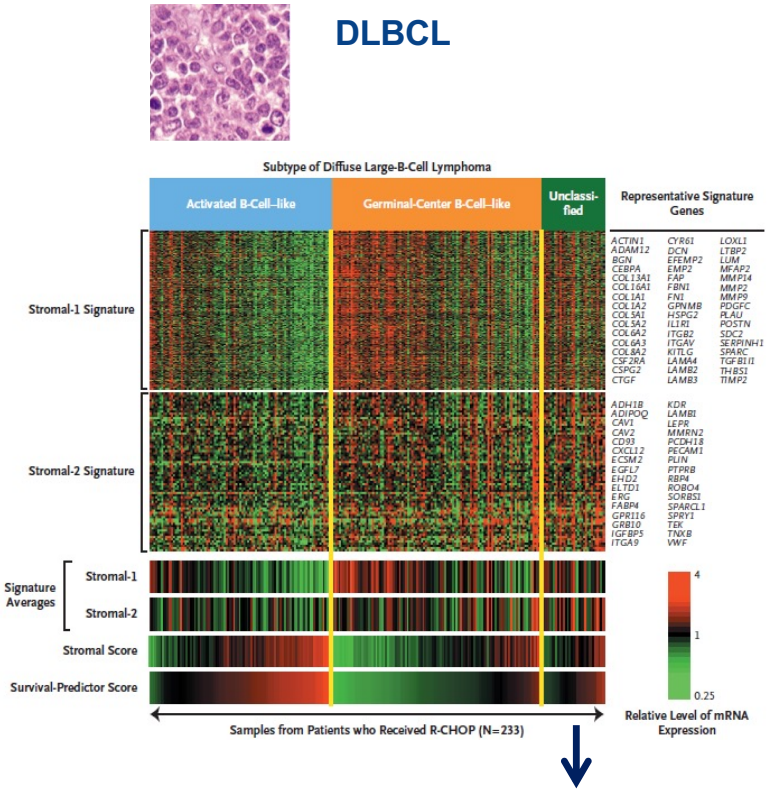
- Target both subgroups
  - Possibly overtreating RCHOP “sufficient group”
- Target RCHOP “insufficient” group provided
  - It can be identified
  - It can be targeted

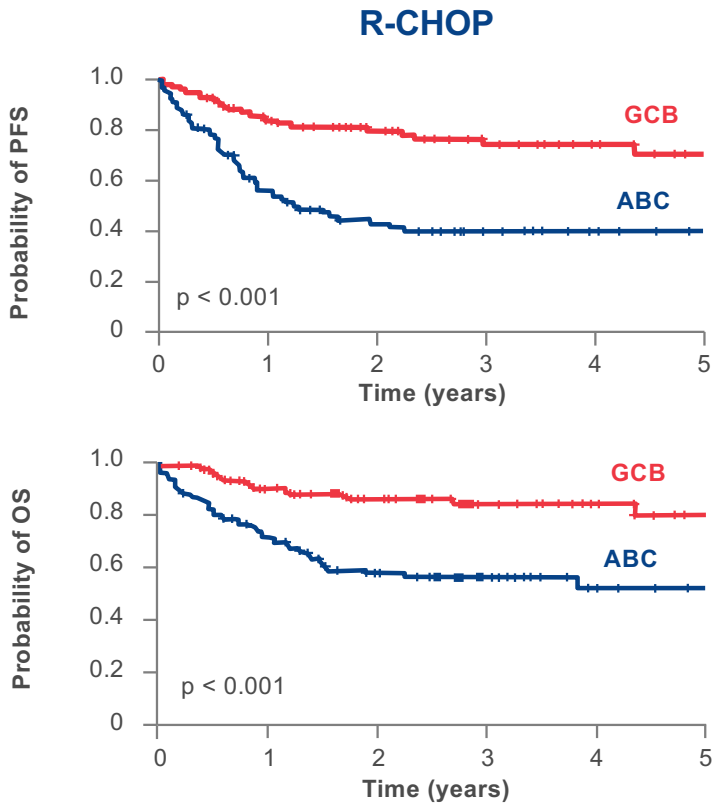
*Patients with DLBCL treated with R-CHOP-21 at BCCA (n = 1,476).

Sehn LH. ASH Education Book. 2012;1:402-9.

Targeting “Insufficient” R-CHOP Group

Evaluation of unfavourable DLBCL subsets: Cell of Origin profile subgroups by GEP



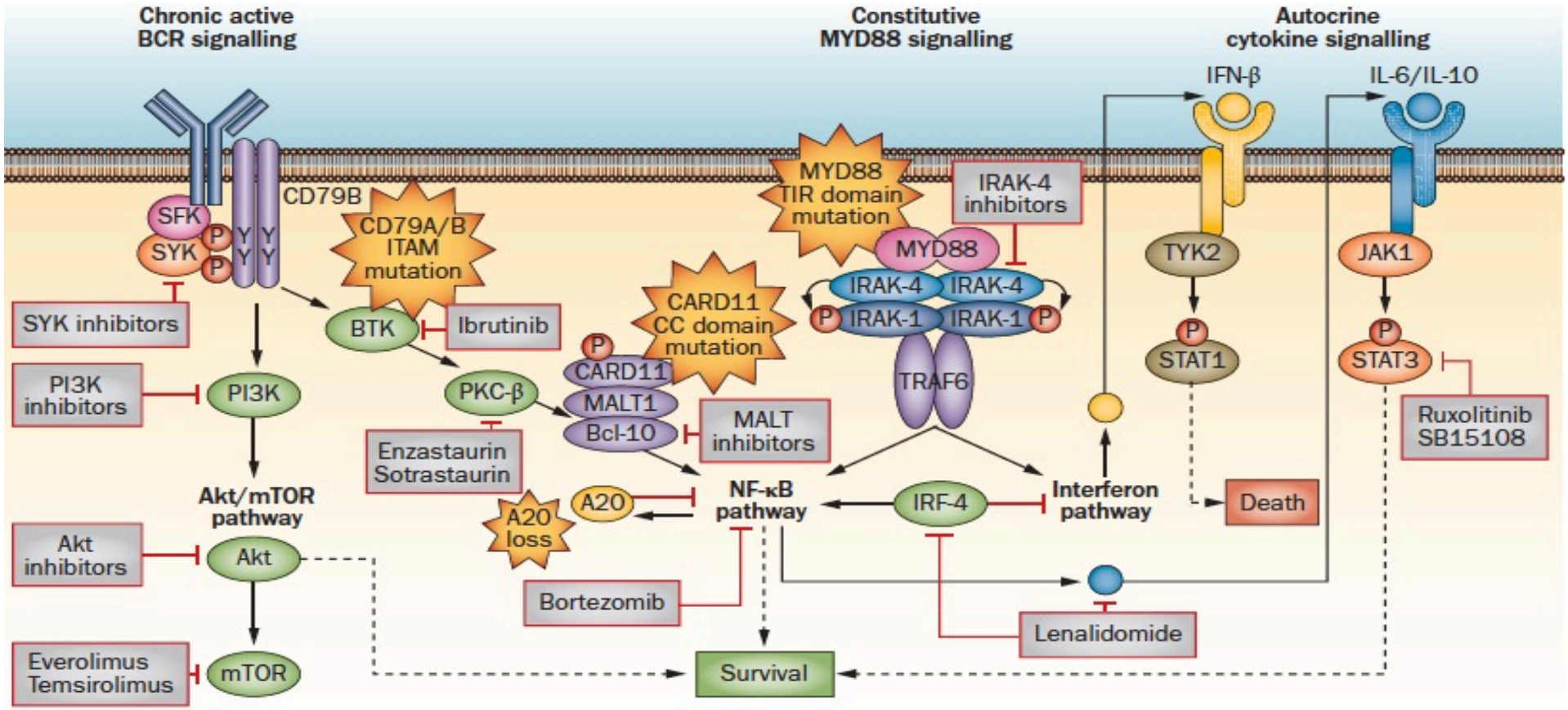


The GEP classification is not available in daily clinical practice

GEP, gene expression profiling; OS, overall survival.

Lenz G, et al. *N Engl J Med*. 2008;359:2313-23.

The key signalling pathways implicated in ABC DLBCL



Roschewski M, Staudt LM, Wilson WH, Nat. Rev. Clin. Oncol. 2013.

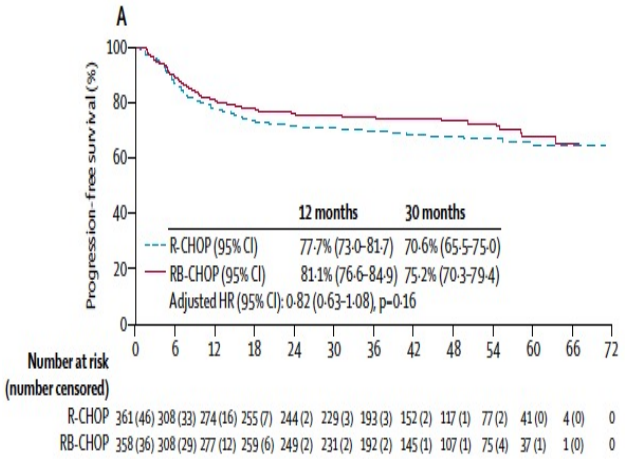
Attempt to improve the outcome with the addition of novel drugs with or after R-CHOP: overall no significative advantage

Drug	Regimen	Subtype or not	Study	Results
R-CHOP + X as induction				
Bevacizumab[1]	RA-CHOP	DLBCL	Main	No advantage (PFS and OS)
Bortezomib[2]	BorR-CHOP	DLBCL	ReMoDL-B	No PFS advantage
Ibrutinib[3]	IR-CHOP	Non-GCB DLBCL	Phoenix	No EFS advantage
Lenalidomide[4]	R^2-CHOP	ABC-DLBCL	Robust	No PFS advantage
Venetoclax[5]	VR-CHOP	DLBCL	Cavalli	Promising results
R-CHOP + X as maintenance				
Rituximab[6]	Rituximab	DLBCL	NHL-13	No EFS advantage 3-yr
Enzanstaurin[7]	Enzanstaurin	DLBCL	Prelude	No DFS advantage 4yr
Everolimus[8]	Everolimus	DLBCL	Pillar-2	No DFS advantage 2yr
Lenalidomide[9]	Lenalidomide	Elderly DLBCL	Remarc	PFS advantage, no OS

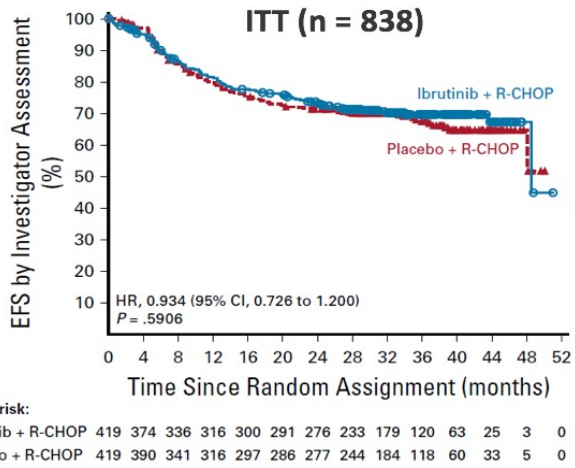
1. Seymour JF et al, Haematologica 2014; 2. Davies A et al, Lancet Oncol 2019; 3. Younes A et al, J Clin Oncol 2019; 4. Vitolo U et al, Hematol Oncol 2019; 5. Morschhauser F at al, Blood 2021; 6. Jagger U et al, Haematologica 2013; 7. Crump M et al, J Clin Oncol 2016; 8. Witzig T et al, Ann Oncol 2018; 9. Thieblemont C et al, J Clin Oncol 2019.

Moving beyond R-CHOP… targeting ABC DLBCL

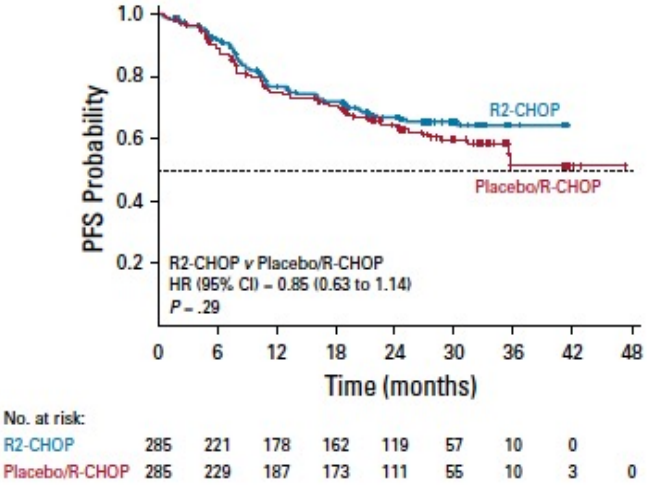
R-CHOP + Bortezomib



R-CHOP + iBTK



R-CHOP + Lenalidomide



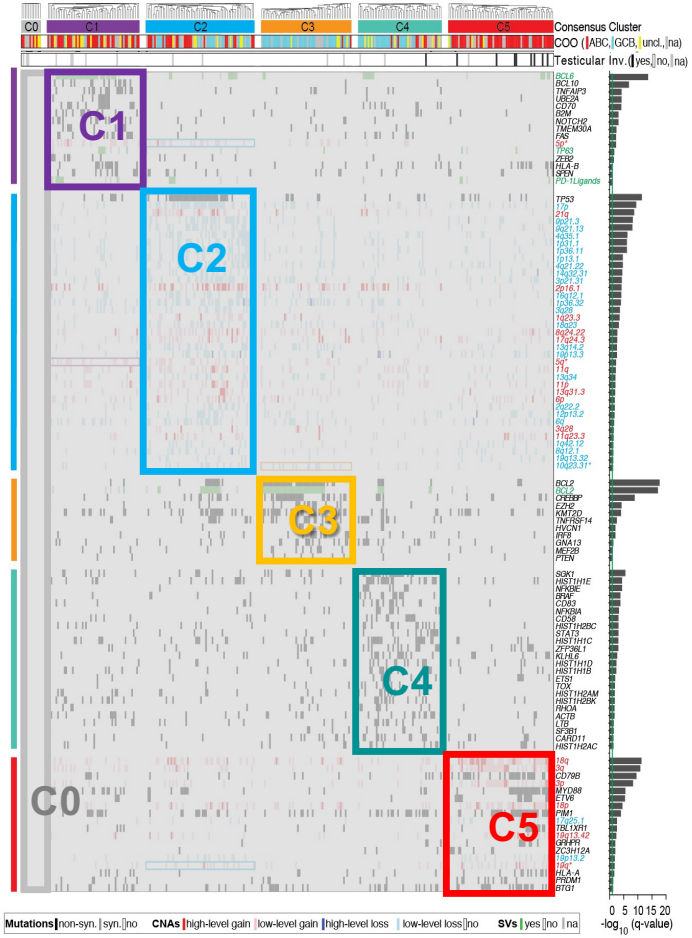
Davies A, et al. Lancet Oncol 2019; Younes A, et al. J Clin Oncol 2019; Nowakowski G, et al. J Clin Oncol 2021.

Should We Still Care About COO?

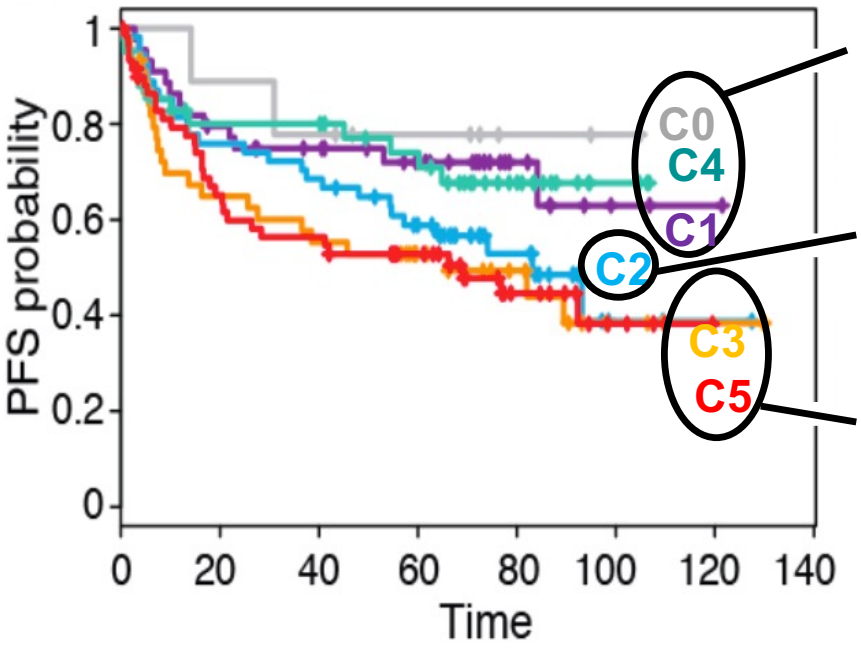
- Yes: the prognosis of ABC is still unsatisfactory
- Yes: subgroups of ABC patients benefit from the addition of specific drugs as ibrutinib in young and lenalidomide in high risk
- No: ABC *alone* is not the best target; DLBCLs are more heterogenous, mutational alterations, etc
- Maybe: ibrutinib or lenalidomide are not the best drugs, we need better drugs, novel-novel combinations

Genetically-distinct DLBCL Subsets are Predictive for Outcome

Genetically-distinct DLBCLs



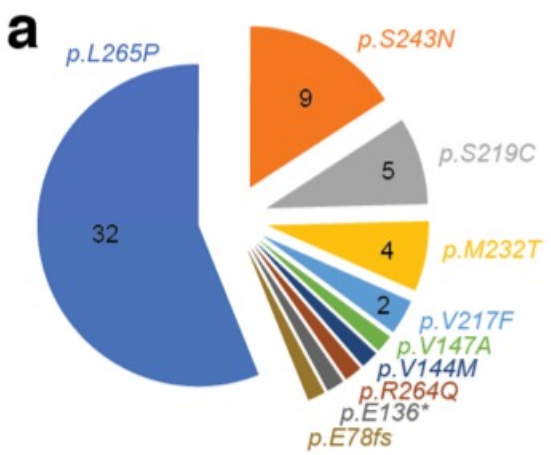
Predictive for Outcome

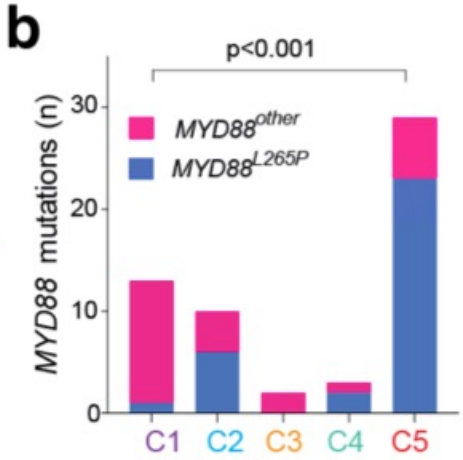


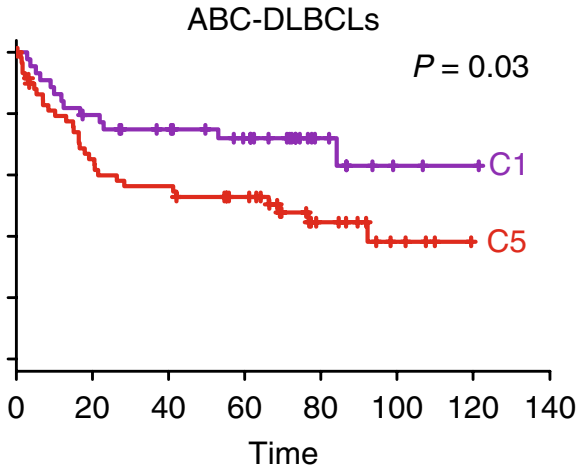
- **Genetic signatures comprised of**
  - Mutations
  - Somatic copy number alterations (SCNAs)
  - Structural Variants (SVs)

Chapuy B, et al. *Nat Med;* 2018; 24(5):679-690.

C1 vs. C5 DLBCLs – Two Genetically Distinct ABC-DLBCLs







c	C1 DLBCLs	C5 DLBCLs
MYD88 mutations	23%(13/56)	44%[28/64]
Type of *MYD88* mutations	non-L265P	L265P
Concordant *CD79B* mutations	no	frequent

C5 DLBCLs - highest cAID activity
- tumors passaged through the GC

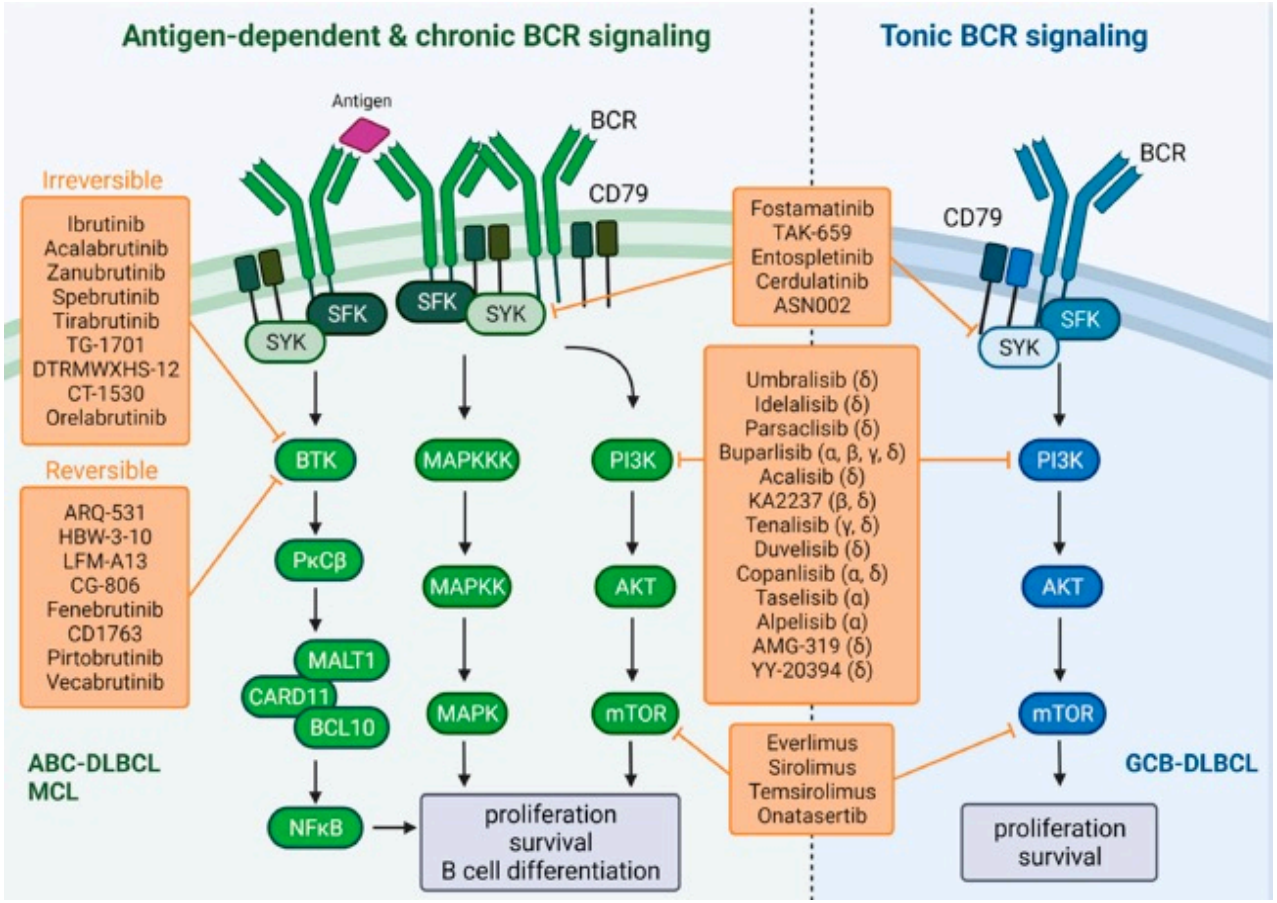
C1 DLBCLs - low to absent cAID activity
- suggestive of extrafollicular origin

- Different types and incidences of *MYD88* mutations

➔ C1 and C5 ABC-type DLBCLs arise by distinct pathogenetic mechanisms.

Chapuy B, et al. *Nat Med;* 2018; 24(5):679-690.

Regulation of BCR signaling and the therapeutic inhibition of BTK and PI3K in DLBCL



- ✓ ABC-DLBCL displays chronic active BCR signaling resulting in constitutive NF-kB activity
- ✓ In contrast to antigen and chronic active BCR signaling, the antigen-independent signal, termed 'tonic BCR signaling', is mediated by PI3K + PI3K /AKT/mTOR, but not the NF-kB pathway, to promote the proliferation and survival of malignant B cells. Genomic data have shown that GCB-DLBCL lines exclusively use tonic BCR signaling.

Profitos Peleja et al. Cancers 2022.

Evolving Strategies in the Treatment of DLBCL

Targeting all comers

Vs

Single gene/single drug model

Vs

Combination of genes/combination of drugs?

Drugs by Molecular Classification Subgroups

Genetically defined category	Drugs
MCD/C5	ibrutinib, acalabrutinib, venetoclax
BN2/C1	ibrutinib, bortezomib, carfilzomib
EZB/C3	venetoclax, tazemetostat, idelalisib, copanlisib, duvelisib, umbralisib
C4	idelalisib, copanlisib, duvelisib, borezomib, carfilzomib, ruxolitinib

MCD: MYD88^{L265P} and CD79B mutations **/ C5**
predominantly ABC

BN2 : BCL6 fusions and NOTCH2 mutations **/ C1**
both ABC and GCB

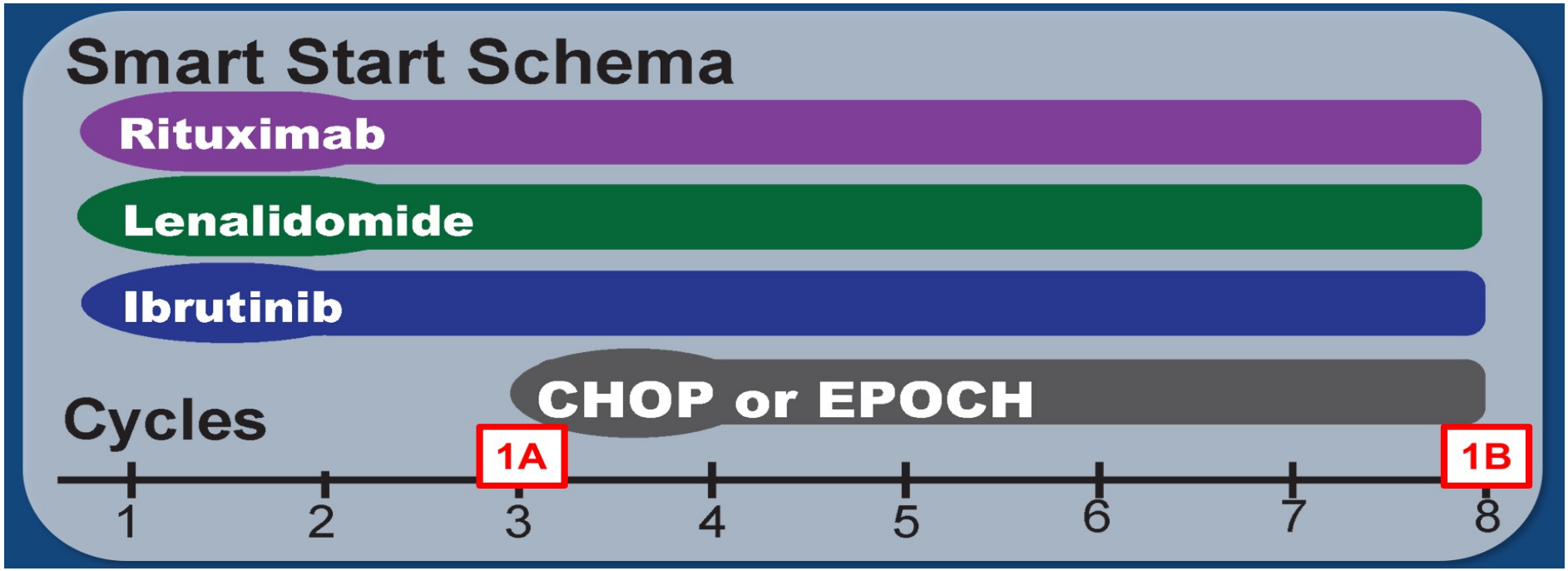
N1 : NOTCH1 mutations
predominantly ABC

EZB : EZH2 and BCL2 mutations **/ C3**
predominantly GCB

Chapuy B et al, Nature Medicine 2018, 24: 679-690
Schmitz R et al: N Engl J Med 2018;378:1396-407

Courtesy of M. Trneny

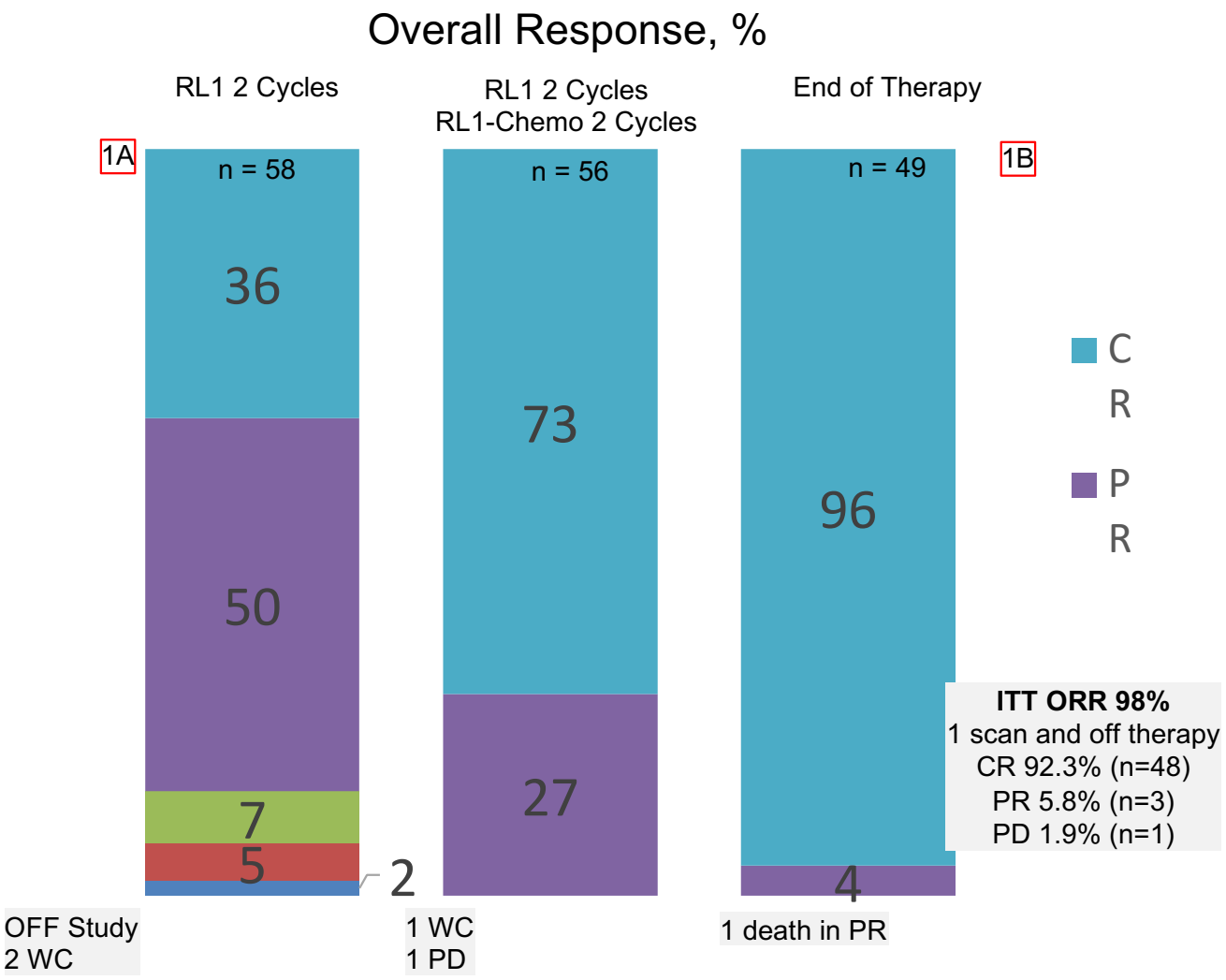
Smart Start: R+Len+Ibrutinib Lead-in Prior to Addition of Chemotherapy for Newly Diagnosed DLBCL



- Primary Objectives
  - 1A: To determine the ORR at the end of 2 cycles of RLI alone
  - 1B: To determine the CR rate at the end of RLI x 2 + RLI combined

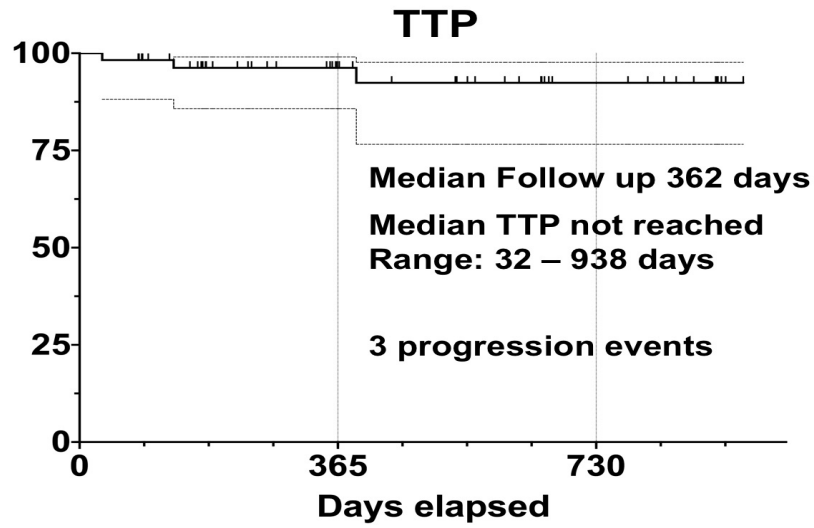
Westin J, ICML 2019.

Smart Start: Responses



1B

ITT ORR 98%
1 scan and off therapy
CR 92.3% (n=48)
PR 5.8% (n=3)
PD 1.9% (n=1)



Genetic Subtype Guided Rituximab-based Immunochemotherapy Improves Outcome in Newly Diagnosed Diffuse Large B-cell Lymphoma: First Report of a Randomized Phase 2 Study

Subtype	Drug X
MCD, BN2	ibrutinib
N1, NOS	lenalidomide
EZB	tucidinostat (HDAC) inhibitor
TP53	decitabine

- 128 patients:

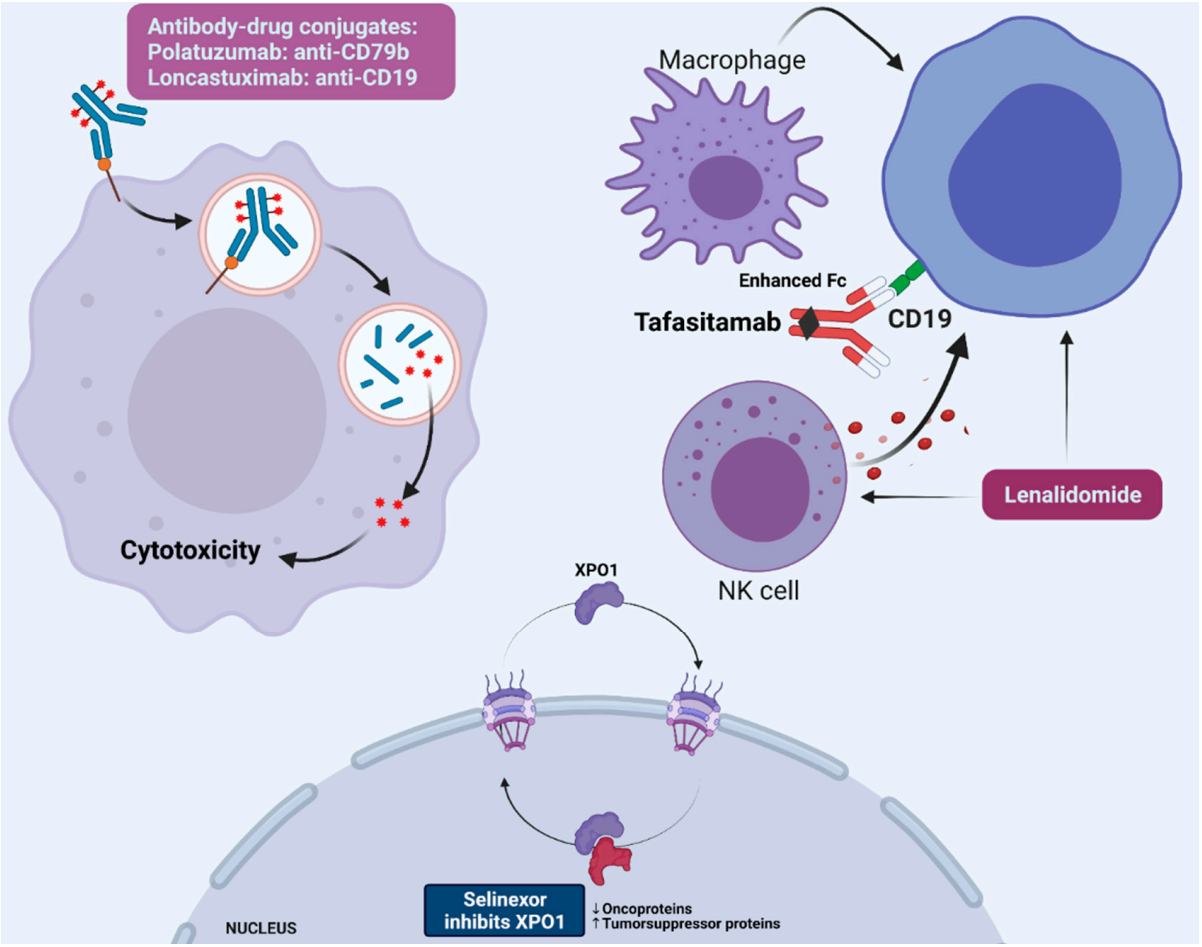
NOS – 50	TP-53 – 21
MCD – 26	EZB – 3
BN2 – 23	N1 - 3

- Outcome:

	CHOP-R	CHOP-R-X
CR	65%	85%
1 yr. PFS	79%	96%

Zhang M, ICML 2021.

Mechanisms of Action for recent approved novel therapy in R/R DLBCL



Sawalha Y, J Pers Med 2021.

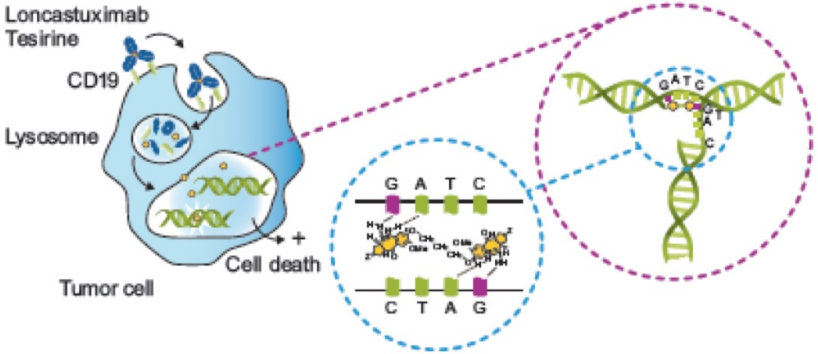
Select ongoing or planned clinical trials of novel agents in relapsed/refractory DLBCL

Agent/Combination	Phase	Identifier (Trial Name)
R-GemOx +/− polatuzumab	III	NCT04182204 (POLARGO)
Polatuzumab, lenalidomide, rituximab	Ib/II	NCT02600897
Selinexor plus R-ICE	I	NCT02471911
Selinexor plus R-DHAX or R-GDP	Ib	NCT02741388 (SELINDA)
Selinexor and ibrutinib	I	NCT02303392
Selinexor and venetoclax	Ib	NCT03955783
Tafasitamab plus bendamustine vs. BR	II/III	NCT02763319 (B-MIND)
Loncastuximab plus ibrutinib	I/II	NCT03684694
Loncastuximab plus venetoclax	I	NCT05053659
Loncastuximab plus rituximab vs. R-GemOx	III	NCT04384484 (LOTIS-5)
Glofitamab, RO7227166, and obinutuzumab	I/II	NCT04077723
Glofitamab or mosunetuzumab plus GemOx	Ib	NCT04313608
Glofitamab plus atezolizumab or polatuzumab	Ib/II	NCT03533283
Glofitamab plus GemOx vs. R-GemOx	III	NCT04408638 (STARGLO)
Epcoritamab vs. investigator's choice chemotherapy	III	NCT04628494 (GCT3013-05)
Epcoritamab plus R-DHAX/C or R-GemOx	Ib/II	NCT04663347
Mosunetuzumab and polatuzumab	Ib/II	NCT03671018
Mosunetuzumab and atezolizumab	I/II	NCT02500407
Venetoclax, ibrutinib, and rituximab	I	NCT03136497
Venetoclax, lenalidomide, and obinutuzumab	I	NCT02992522
Venetoclax plus R-ICE	I/II	NCT03064867
Magrolimab plus rituximab or R-GemOx	Ib/II	NCT02953509
Abexinostat and ibrutinib	I	NCT03939182

Sawalha Y, J Pers Med 2021.

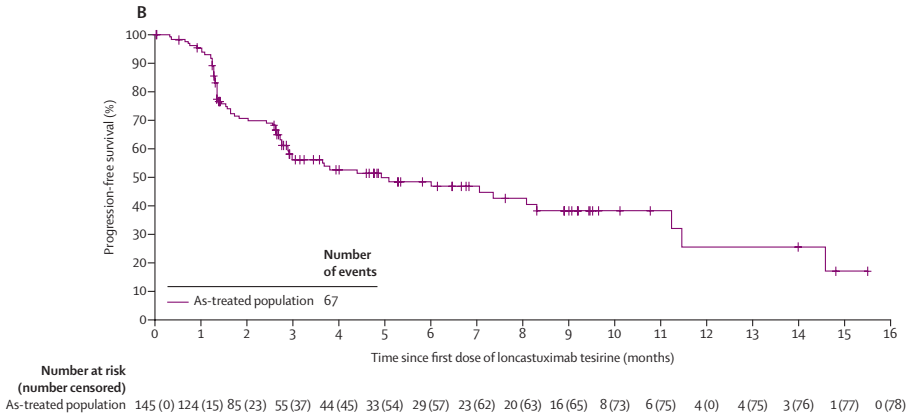
Loncastuximab Tesirine in R/R DLBCL: a multicentre, open-label, single-arm, phase 2 trial

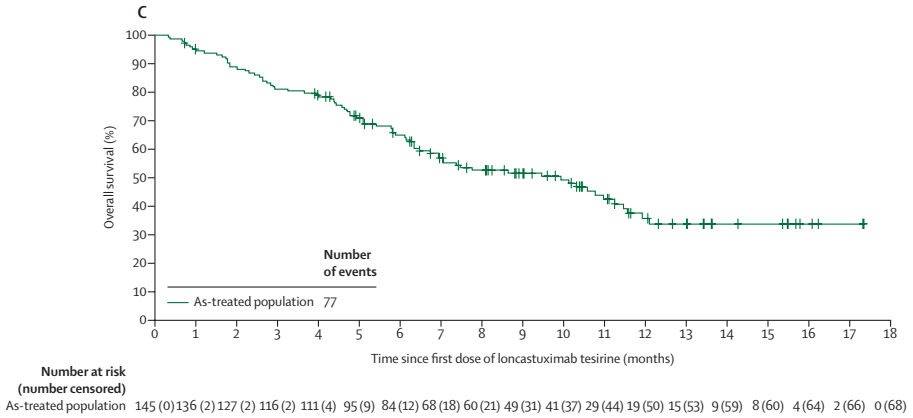
Mechanism of action of Lonca



- humanized anti-CD19 antibody, stochastically conjugated through a cathepsin-cleavable valine-alanine linker to a pyrrolobenzodiazepine (PBD) dimer toxin causing DNA crosslinking

	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%)





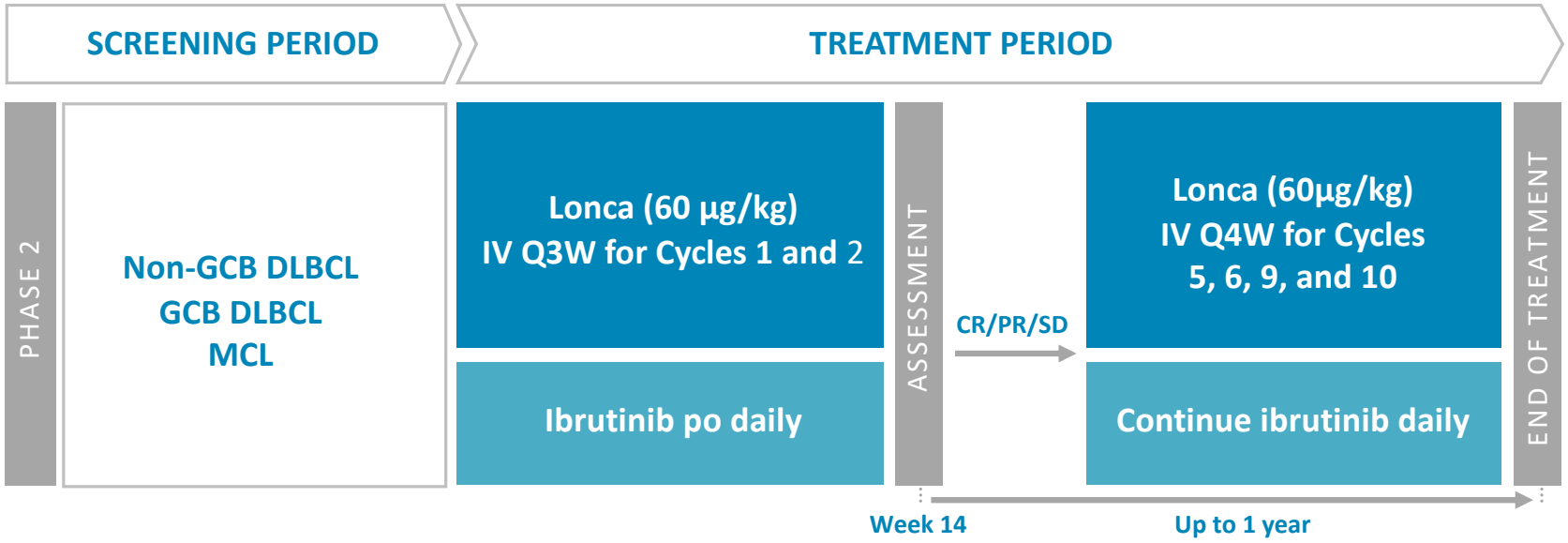
Caimi PF et al, Lancet Oncol 2021, 22:790-800.

Phase 2 Study of Loncastuximab Tesirine Plus Ibrutinib in RR-DLBCL (LOTIS-3)

Primary phase 2 study objective:
- CRR assessed by central review in R/R non-GCB DLBCL (investigator-determined COO)

Planned interim analysis objective:
- To determine if CRR in the non-GCB DLBCL cohort warranted the continuation of patient enrollment for study completion[a]

KEY INCLUSION CRITERIA:
- R/R DLBCL, measurable disease (2014 Lugano)
- ECOG PS 0–2



As of Aug 30, 2021, **35 patients with R/R DLBCL** received Lonca 60 µg/kg plus ibrutinib 560 mg

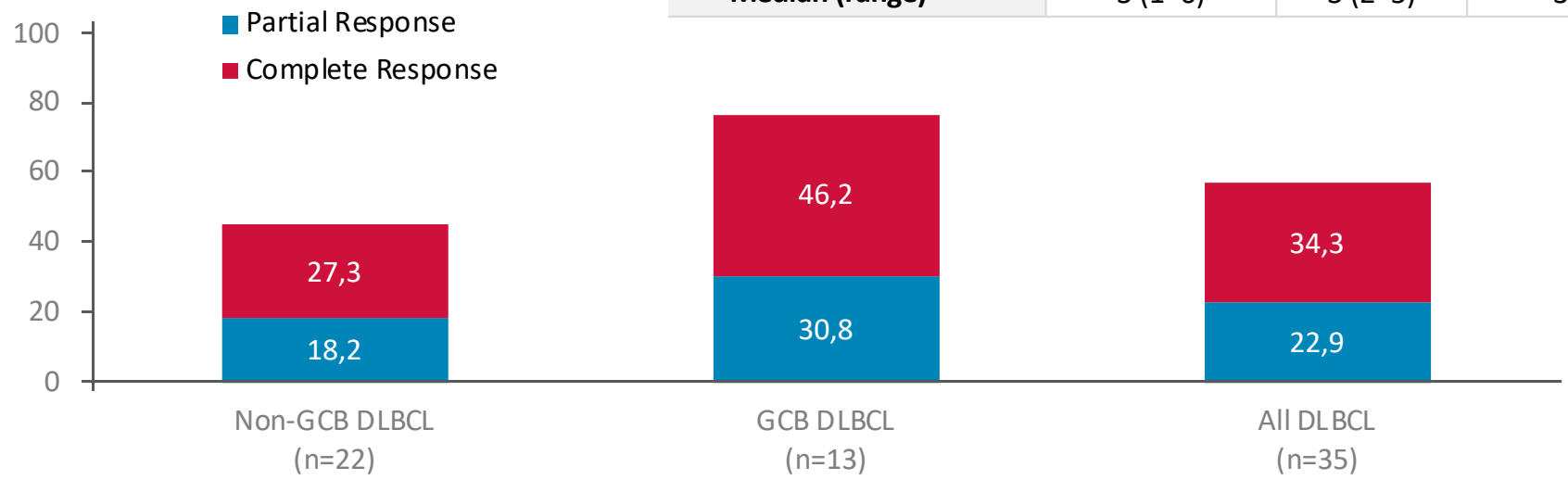
Carlo-Stella C, Abs#0054, ASH 2021

Phase 2 Study of Loncastuximab Tesirine Plus Ibrutinib in RR-DLBCL (LOTIS-3)

Median Lonca cycles: 2 (range: 1–6)

Median ibrutinib cycles: 3.5 (range: 1–15)

Characteristic	Non-GCB (n=22)	GCB (n=13)	All patients (n=35)
Age, yrs, median (range)	72 (19–82)	66 (53–82)	72 (19–82)
Prior systemic therapies, n Median (range)	3 (1–6)	3 (2–5)	3 (1–6)



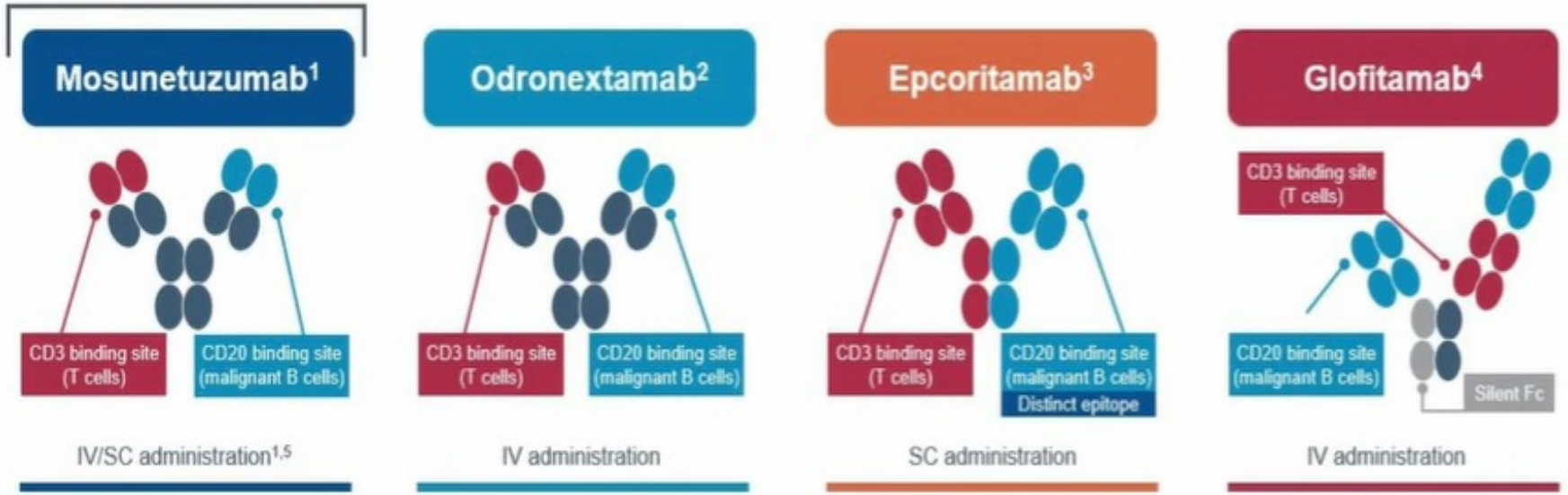
ORR (n/N) (95% CI)[b]	**45.5%** (10/22) (24.4, 67.8)	**76.9%** (10/13) (46.2, 95.0)	**57.1%** (20/35) (39.4, 73.7)

Carlo-Stella C, Abs#0054, ASH 2021

Emerging therapies: Bispecific Antibodies

Investigational CD20×CD3 bispecific antibodies for B-cell lymphomas:

FDA BTD for R/R FL (2020)



MOA: Simultaneously bind CD20 on malignant B cells and CD3 on cytotoxic T cells, resulting in T-cell activation, and T-cell–mediated apoptosis of malignant B cells

CD20xCD3 bispecific antibodies + SoC

Rational combinations of targeted therapies

Mosunetuzumab/glofitamab (+obi) + lenalidomide
Phase 1, R/R FL
NCT04246086 (est. completion Aug 2022)

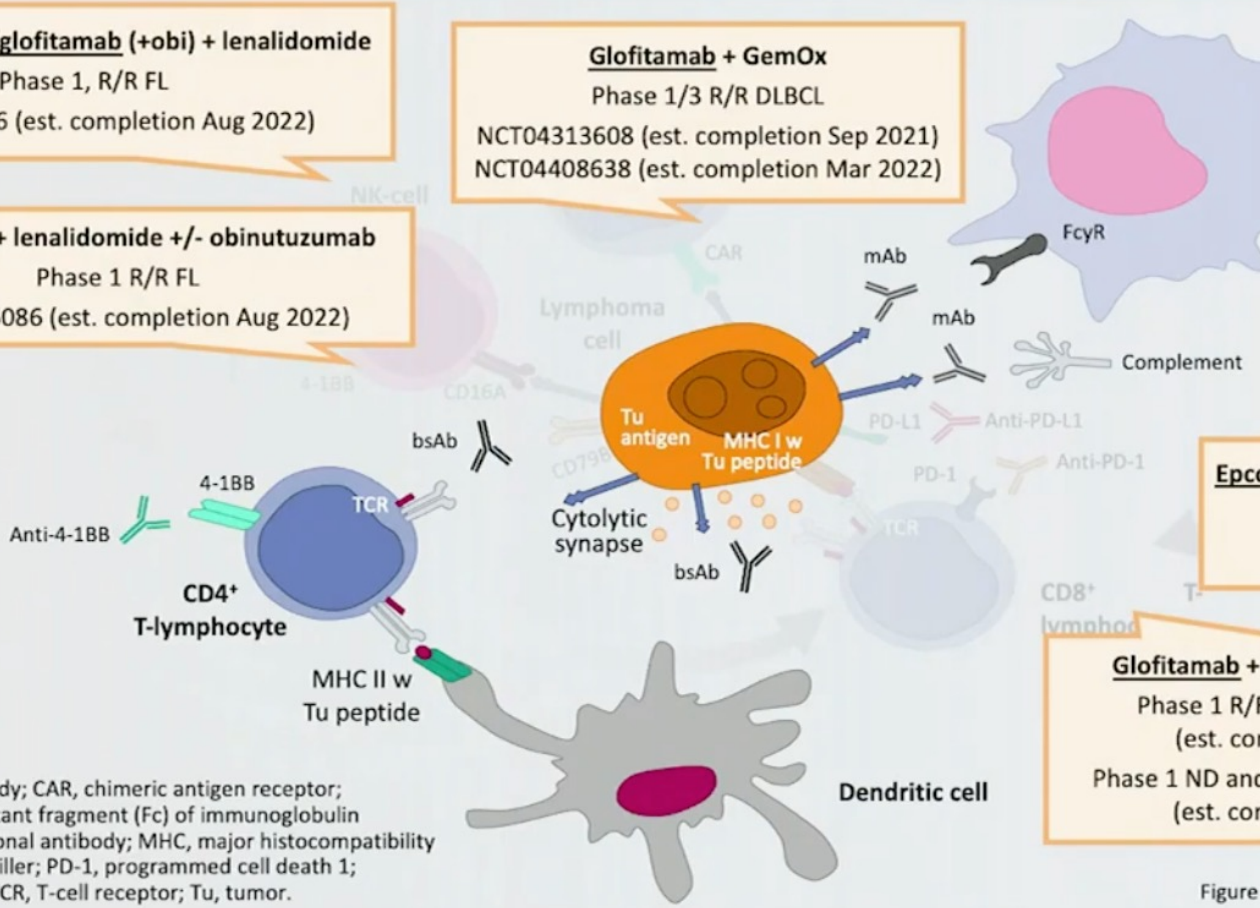
Glofitamab + GemOx
Phase 1/3 R/R DLBCL
NCT04313608 (est. completion Sep 2021)
NCT04408638 (est. completion Mar 2022)

Glofitamab + lenalidomide +/- obinutuzumab
Phase 1 R/R FL
NCT04246086 (est. completion Aug 2022)

Epcoritamab + SoC
Phase 1b/2 ND or R/R DLBCL, ND or R/R FL
NCT04663347 (est. completion Jan 2022)

Epcoritamab + investigator's choice chemotherapy
Phase 3 R/R DLBCL
NCT04628494 (est. completion Jun 2023)

Glofitamab + obi ± obi pre-treatment
Phase 1 R/R B-NHL NCT03075696
(est. completion Jun 2023)
Phase 1 ND and R/R B-NHL NCT03467373
(est. completion Dec 2023)



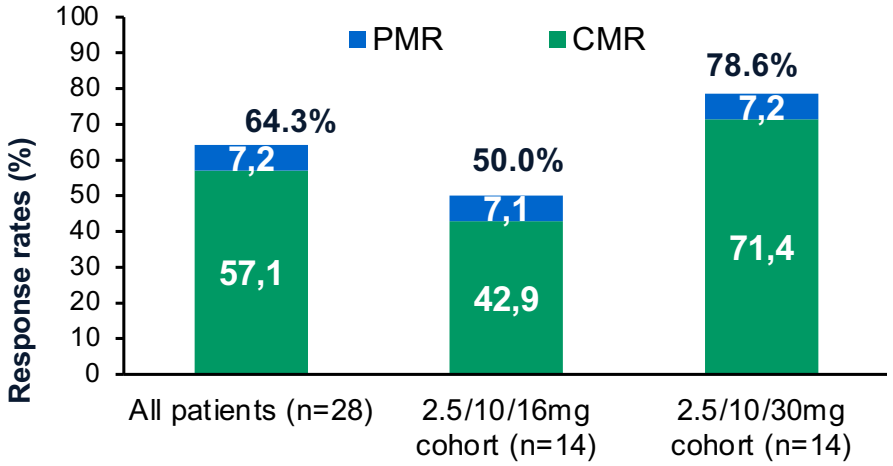
bsAb, bispecific antibody; CAR, chimeric antigen receptor; FcR, receptor for constant fragment (Fc) of immunoglobulin gamma; mAb, monoclonal antibody; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death 1; PD-L1, PD-1 ligand 1; TCR, T-cell receptor; Tu, tumor.

Figure adapted from: Pytlik R, *et al. Vaccines (Basel)* 2020; **8**:708.

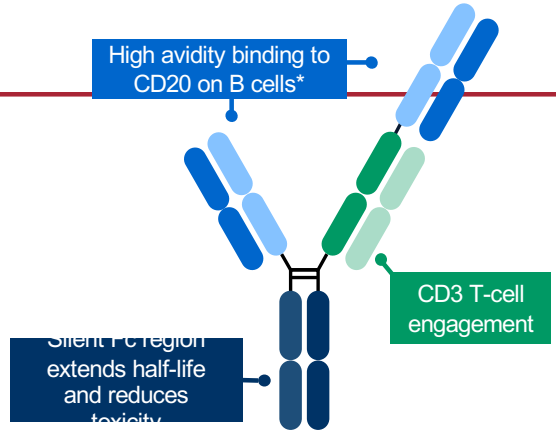
By courtesy of Salles G, ICML 2021

Glofitamab in R/R B-cell lymphoma patients. CRS 67%, Grade 3-4 6%

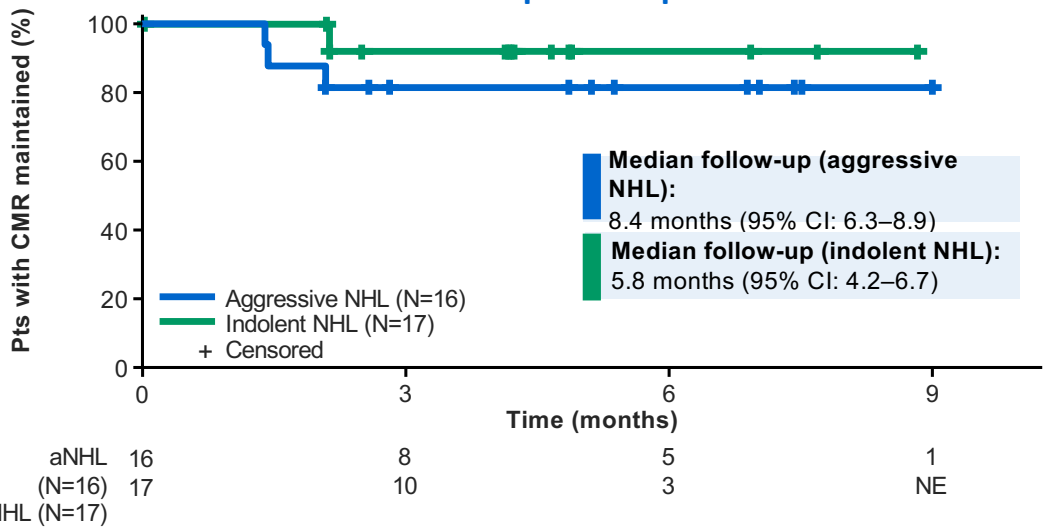
Response rate: Aggressive and Indolent NHL



For aggressive NHL, a trend of improved response was observed at the RP2D (2.5/10/30mg; N=14), with a **CMR rate of 71.4%**



Duration of Complete Response



- The median duration of response for complete responders have not been reached
- **Aggressive NHL**: 13/16 CMRs are ongoing, 8 CMRs lasting >3 months; 5 CMRs lasting >6 months
- **Indolent NHL**: 16/17 CMRs are ongoing, 10 CMRs lasting >3 months; 3 CMRs lasting >6 months

Hutchings M et al, JCO 2021, Carlo-Stella, ICML-16.

Glofitamab in Combination with Polatuzumab Vedotin: Phase Ib/II in 59 pts with R/R Diffuse Large B-Cell Lymphoma (DLBCL)

- Glofit + Pola arm: study design in R/R DLBCL

Key inclusion criteria (DLBCL arm)

- Age ≥18 years
- R/R DLBCL (including trFL and HGBCL)
- ECOG performance status 0–2

Objectives

Primary:

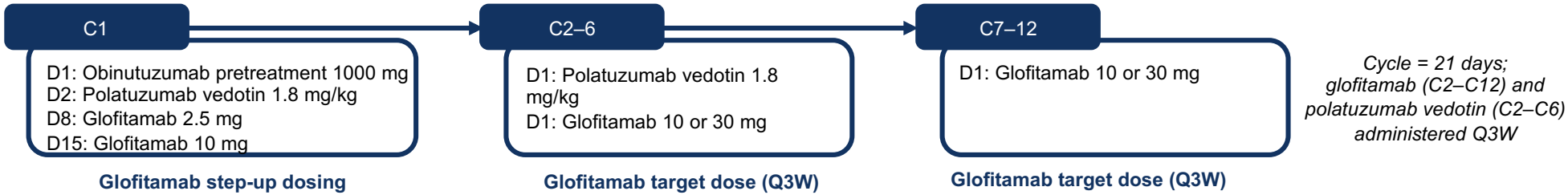
- DLTs
- Determine MTD and/or RP2D for Glofit + Pola (including obinutuzumab pretreatment)

Secondary:

- Safety and tolerability
- Efficacy (CR rate and BORR per Lugano 2014[1])

Glofit + Pola administration in R/R DLBCL

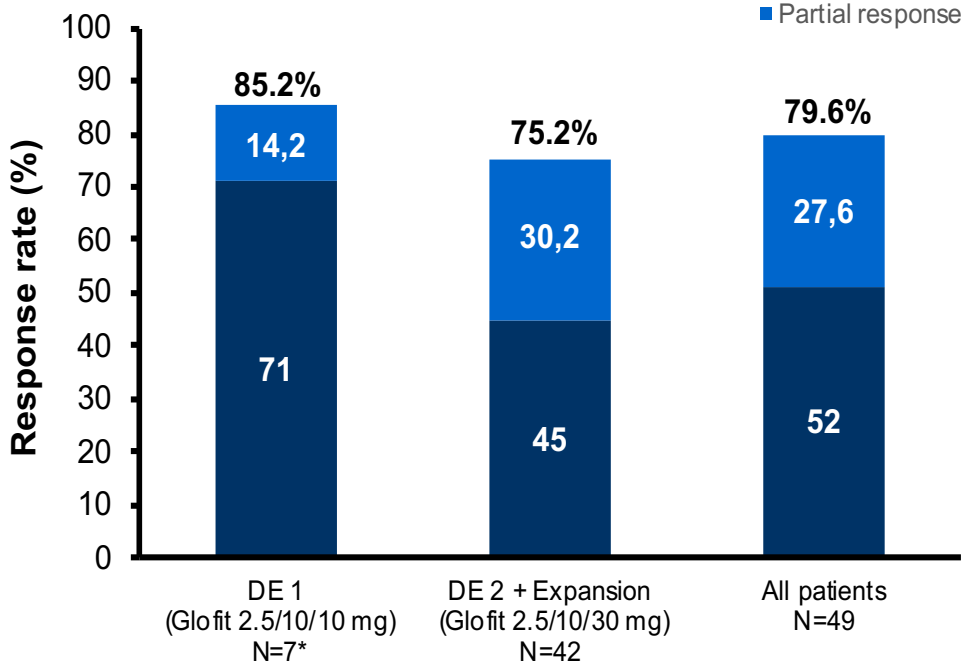
- Target enrollment ~90 patients
- CRS mitigation: obinutuzumab IV 1000 mg 7 days prior to glofitamab administration (step-up dosing)
- Efficacy assessments with PET-CT C3D1, C6D1 C8D15, EOT and Q3M

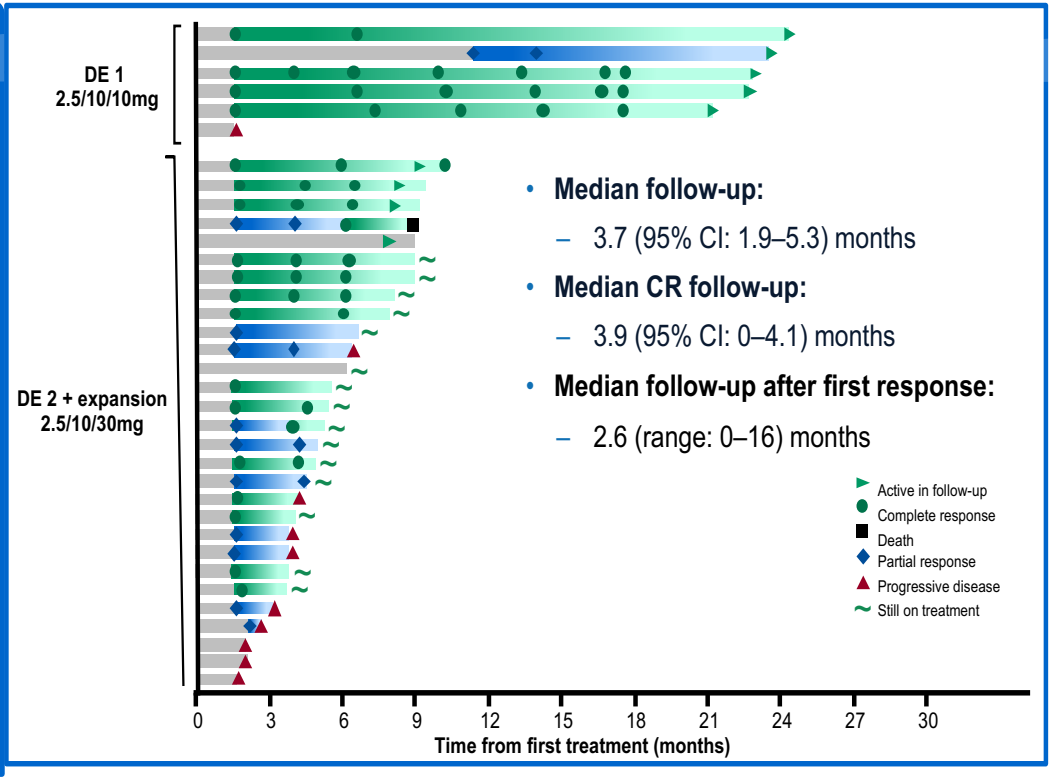


Hutchings M et al. Abs#525, ASH 2021.

Glofitamab in Combination with Polatuzumab Vedotin: response rate and adverse events

Response rate by Glofit + Pola dosing cohort





Hutchings M et al. Abs#525, ASH 2021.

topMIND

topMIND: PHASE 1B/2A BASKET STUDY TO EVALUATE TAFASITAMAB[a] AND THE PI3Kδ INHIBITOR PARSACLISIB IN RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA OR CHRONIC LYMPHOCYTIC LEUKAEMIA[1]

Adult patients with R/R B-cell malignancies, including DLBCL, MCL, FL, MZL and CLL/SLL, with ECOG PS 0–2 and ≥2 prior systemic antilymphoma/antileukemia therapies (N=100)

→

Tafasitamab 12 mg/kg IV QW (Cycles 1–3) then Q2W (Cycle 4 onward), plus parsaclisib 20 mg QD (Cycles 1–2) then 2.5 mg QD (Cycle 3 onward)

	R/R DLBCL	R/R MCL	R/R FL	R/R MZL	R/R CLL/SLL
Phase 1b	n=10	n=10	n=10	n=10	n=10
Phase 2a	n=10	n=10	n=10	n=10	n=10

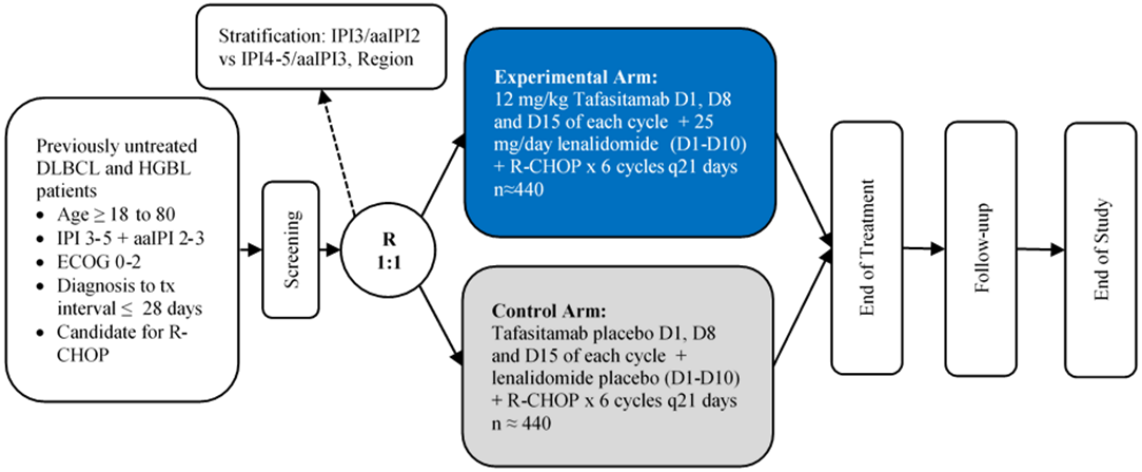
Primary Endpoint:[b]

- Phase 1b: incidence and severity of TEAEs and incidence of DLTs
- Phase 2a: ORR

Key Secondary/Exploratory Endpoints:[b]

- PK parameters of tafasitamab in combination with parsaclisib
- PK parameters of parsaclisib in combination with tafasitamab
- CRR, DOR, PFS, OS, MRD
- Immunogenicity of tafasitamab
- Cytokine, immune cell and tumour microenvironment response to tafasitamab plus parsaclisib
- Molecular markers for response or resistance

A Phase 3, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of **Tafasitamab** plus **Lenalidomide** in addition to **R-CHOP** versus **R-CHOP** in previously untreated, high-intermediate and high-risk patients with newly diagnosed Diffuse Large B-Cell Lymphoma



Primary endpoint	Secondary endpoints	Exploratory endpoints
■ PFS* by INV, event driven ■ Primary analysis: 274 events ■ Interim analysis (futility): 100 events **Sample size** ■ N= 880 incl. drop outs ■ Assumptions ■ Projected PFS increase @36 months from~57% (control) to ~68% ■ HR = 0.70, Power: 83% ■ Accrual: 21 months (350 sites) ■ Annual Drop-out: 15%	Key secondary ■ EFS by INV, OS (to be tested hierarchically) Other secondary endpoints ■ Efficacy: PET-CR at EOT by INV and IRC, PFS by IRC, DoR ■ Safety ■ Key efficacy by COO subtype ■ ctDNA analysis (MRD assessment) ■ Incidence of CNS relapse ■ PRO/QoL ■ PK & immunogenicity of tafa	■ Key efficacy parameters by: NK cell count in peripheral blood and tumor tissue; Quantitative and semiquantitative CD19 and CD20 expression on tumor cells ■ Selected genetic mutations and genetic subtypes of DLBCL ■ Other biomarkers

***defined as the time from randomization to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier**

Study team

International Steering Committee Members

- John Burke
- Annalisa Chiappella
- Christopher Fox
- Georg Lenz
- Grzegorz Nowakowski
- Marek Trneny
- Umberto Vitolo

FIL Clinical team

- Monica Balzarotti
- Annalisa Chiappella
- Maurizio Martelli
- Umberto Vitolo

MorphoSys

- Alok Pachori
- Maeve Waldron-Lynch
- Nira Hadar
- Aizza Hassan
- Johannes Weirather
- Silvia Stingele
- Fausto Loberiza
- Mikhail Akimov
- Oliver Manzke (Incyte)

FONDAZIONE ITALIANA LINFOMI

Pathology and Molecular biology team

- Bjorn Chupey
- Ilaria Del Giudice
- Simone Ferrero
- Gianluca Gaidano
- Marco Ladetto
- Georg Lenz
- Stefano Pileri
- Maurillo Ponzoni
- Andreas Rosenwald

GLA German Lymphoma Alliance

ENROLLMENT IN ITALY

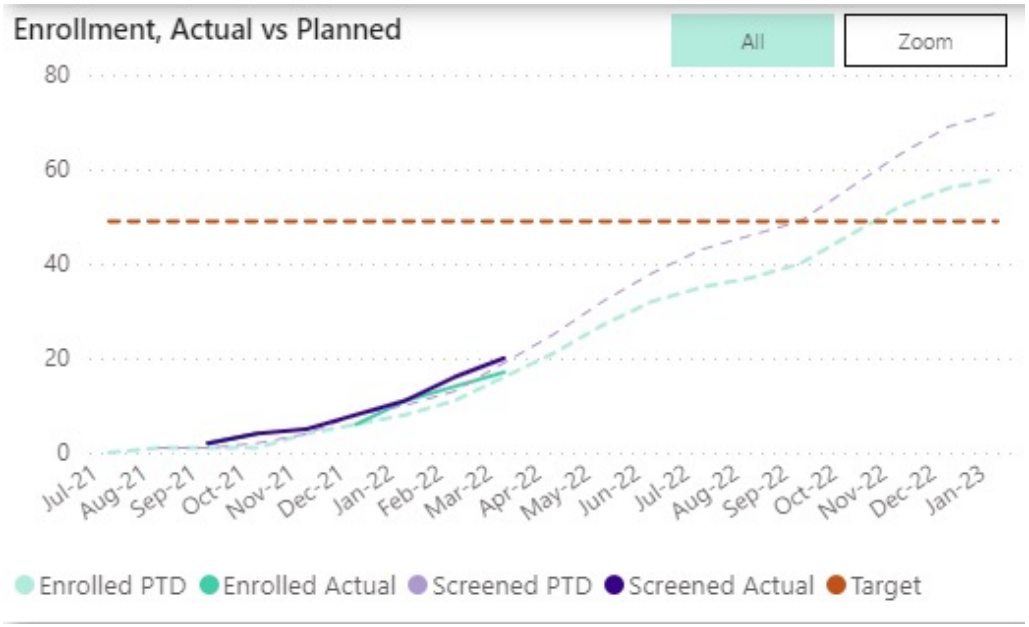
Subjects Screened	22
In Screening	4
Screened Out	1

5% screenout rate (vs 19% planned)

Subjects Enrolled

17

IXRS Updates:
19 enrolled patients
3 patients in screening



Site activation to first subject screened (average days): 79.9

Last Subject screened: **21-Mar-2022 51011/Tucci, Alessandra/Italy**

Site activation to FPI (average days): 65.6

Last Subject enrolled: **21-Mar-2022 51061/Zaja, Francesco/Italy**

Conclusions

- R-CHOP is still the standard of care in DLBCL but we need to move forward to improve the outcome of our patients.
- COO is predictive of the outcome with ABC subtype having a worst prognosis in terms of systemic and also CNS progression but we cannot based anymore on this simple subgrouping
- A single target approach have failed underlining the molecular complexity of DLBCL
- A more accurate recognition of unfavourable DLBCL subsets is recommended to better tailor the treatment
- New study designs potentially focused on mutational alterations with combination of multiple novel drugs may have a greater chance of success.
- Novel-novel combinations as anti-CD19 and immunomodulators, or bispecific antibodies + different novel biological drugs or chemoimmunotherapy represent a step forward the cure of all DLBCL