Eppur si muove...

La terapia nel MONDO LINFOMI

Il razionale biologico delle combinazioni nei linfomi non Hodgkin

ROMA, 26 MAGGIO 2022

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AO San Camillo
Roma

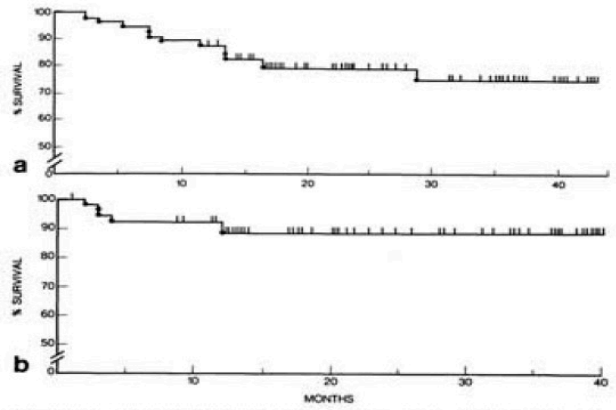
Disclosures, Luigi Rigacci

Company name	Advisory board	Educational activities/Lecture fees
Astra Zeneca		x
Gilead-Sciences	x	x
Incyte		x
Janssen-Cilag	x	x
Novartis	x	
Roche	x	x
Gentili		x
Takeda	x	x
Abbvie	x	x
Sandoz		x

Once upon a time……

MACOP-B

alterning weekly myelotoxic drugs with non-myelotoxic drugs!

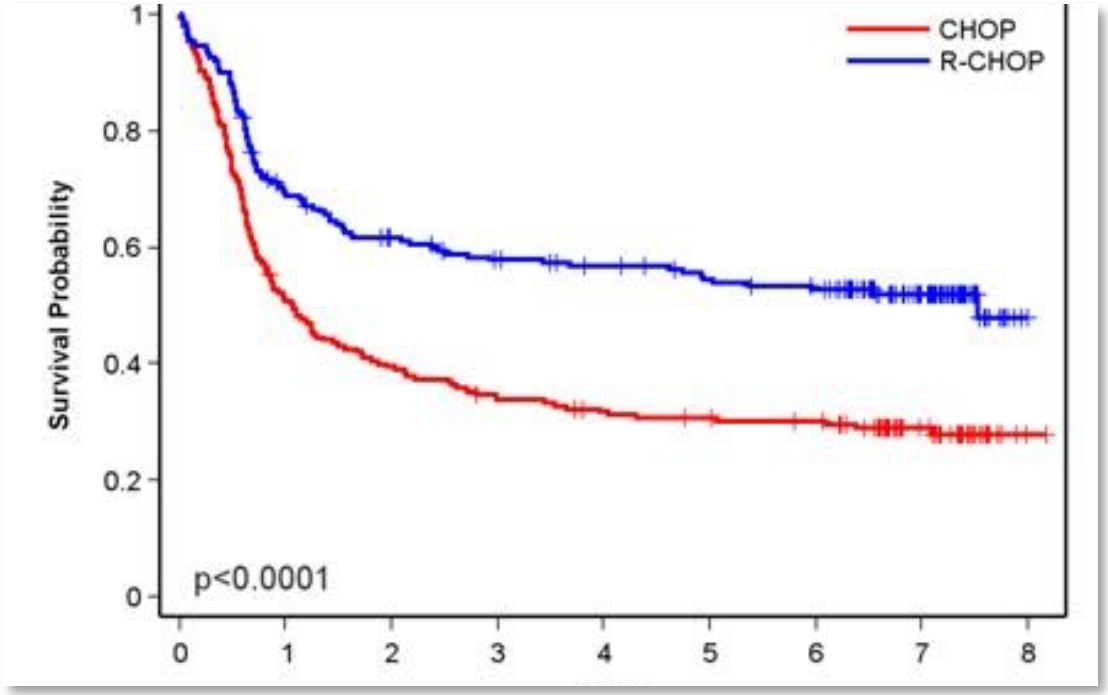


MACOP-B Chemotherapy for the Treatment of Diffuse Large-Cell Lymphoma

PAUL KLIMO, M.D.; and JOSEPH M. CONNORS, M.D.; Vancouver, British Columbia, Canada

Annals of Internal Medicine. 1985;102:596-602.

Ours are coming!

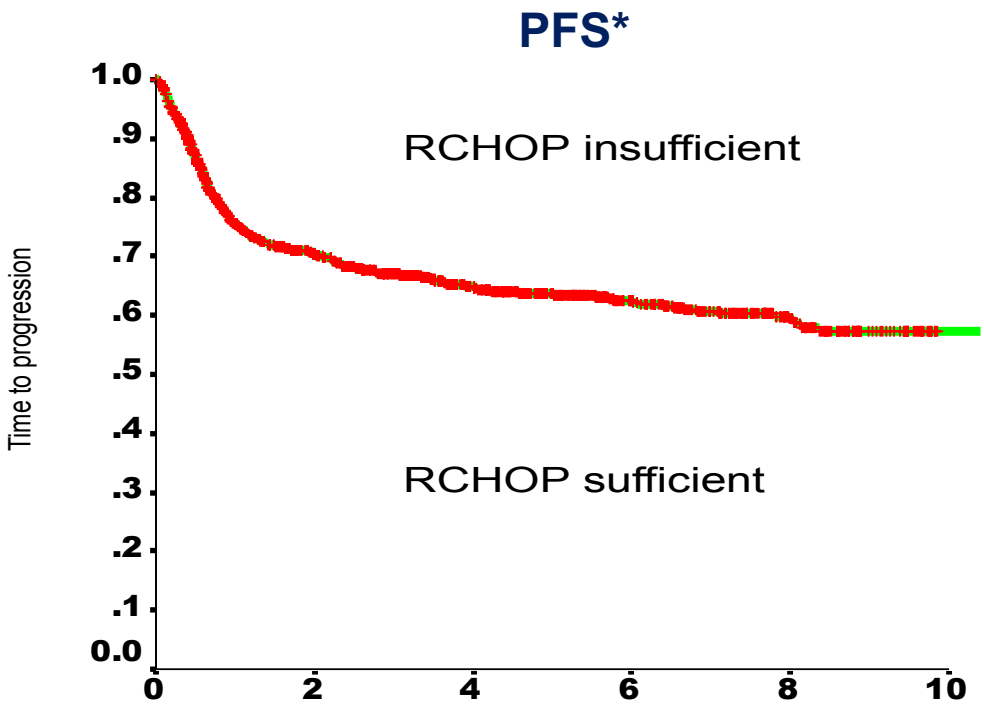


Coiffier, NEJM 2002

immunotherapy added a great benefit

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:

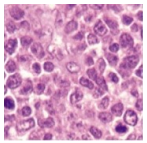
- Target both subgroups
  - Possibly overtreating RCHOP “sufficient group”
- Target RCHOP “insufficient” group provided
  - It can be identified
  - It can be targeted

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

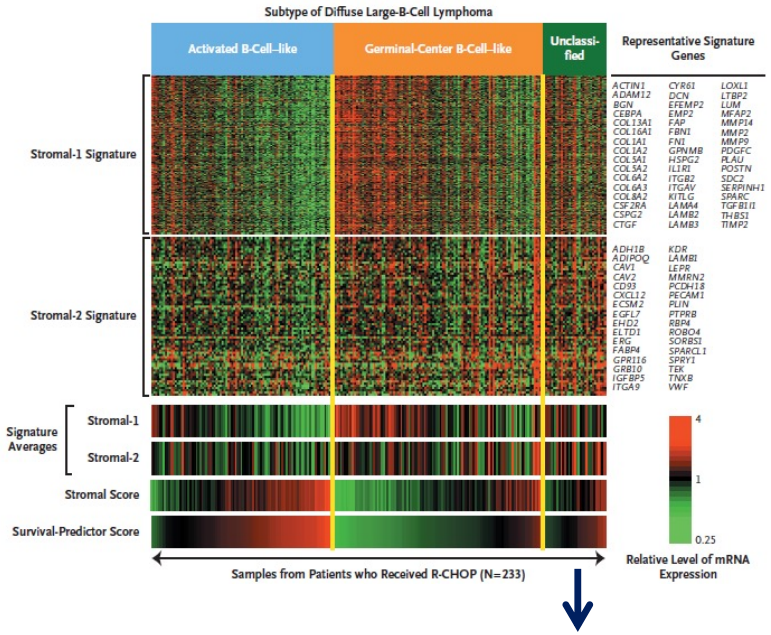
Sehn LH. ASH Education Book. 2012;1:402-9.

Targeting "Insufficient" R-CHOP Group

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

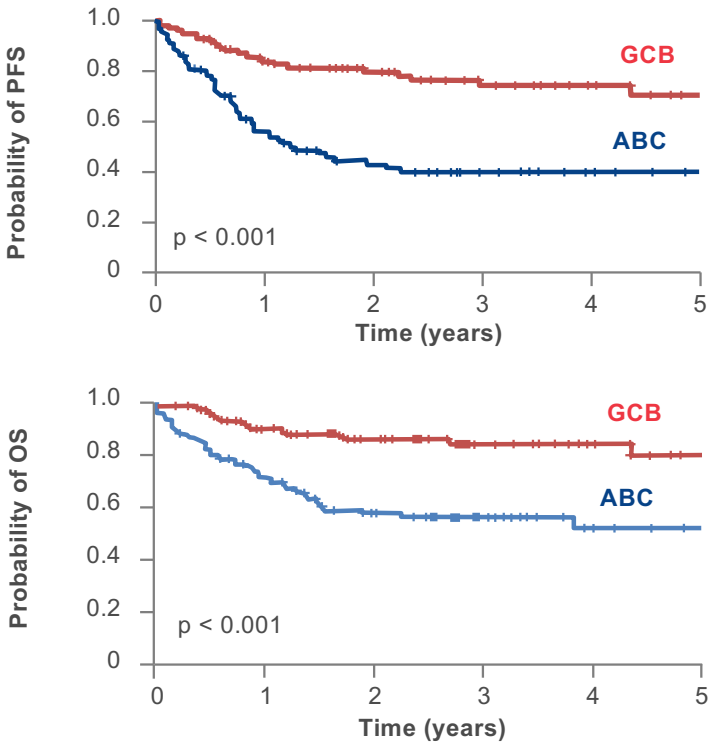


DLBCL



15% Unclassifiable

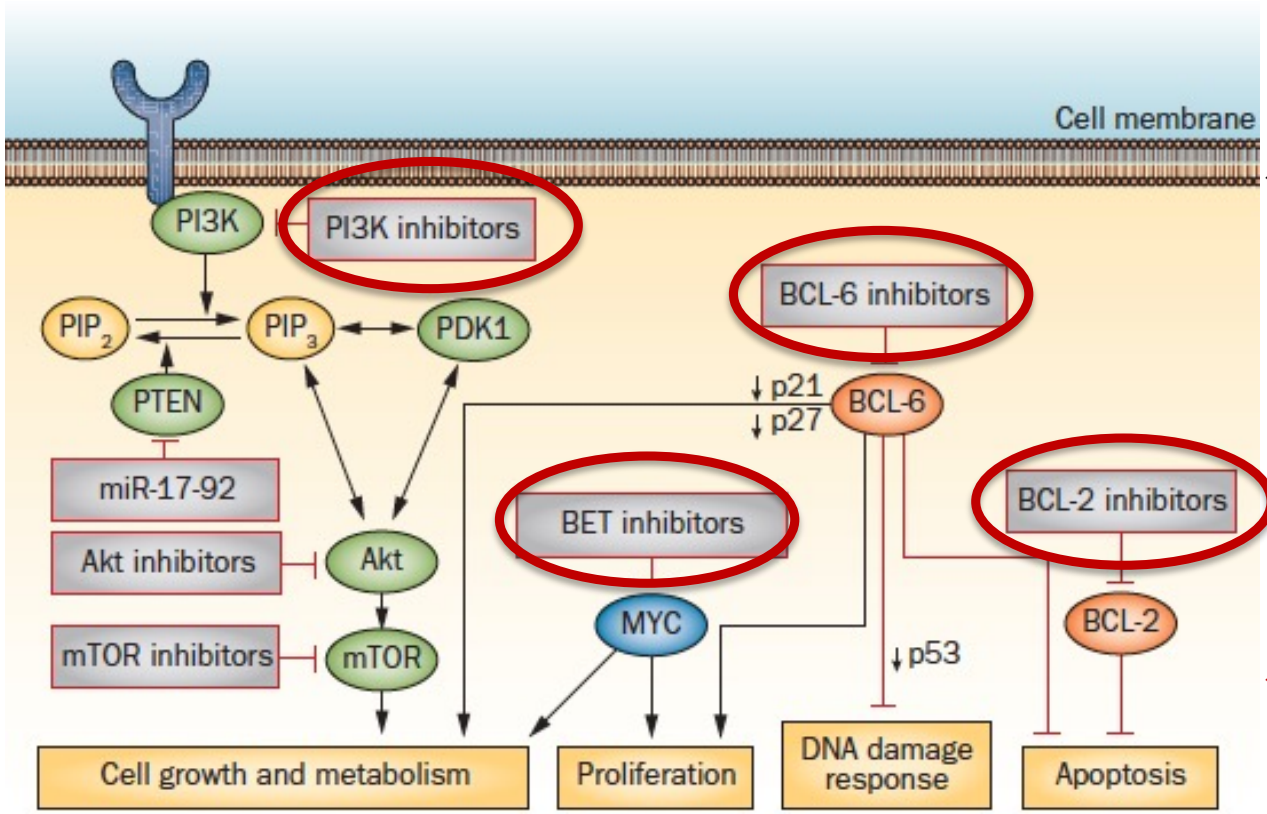
R-CHOP



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.*

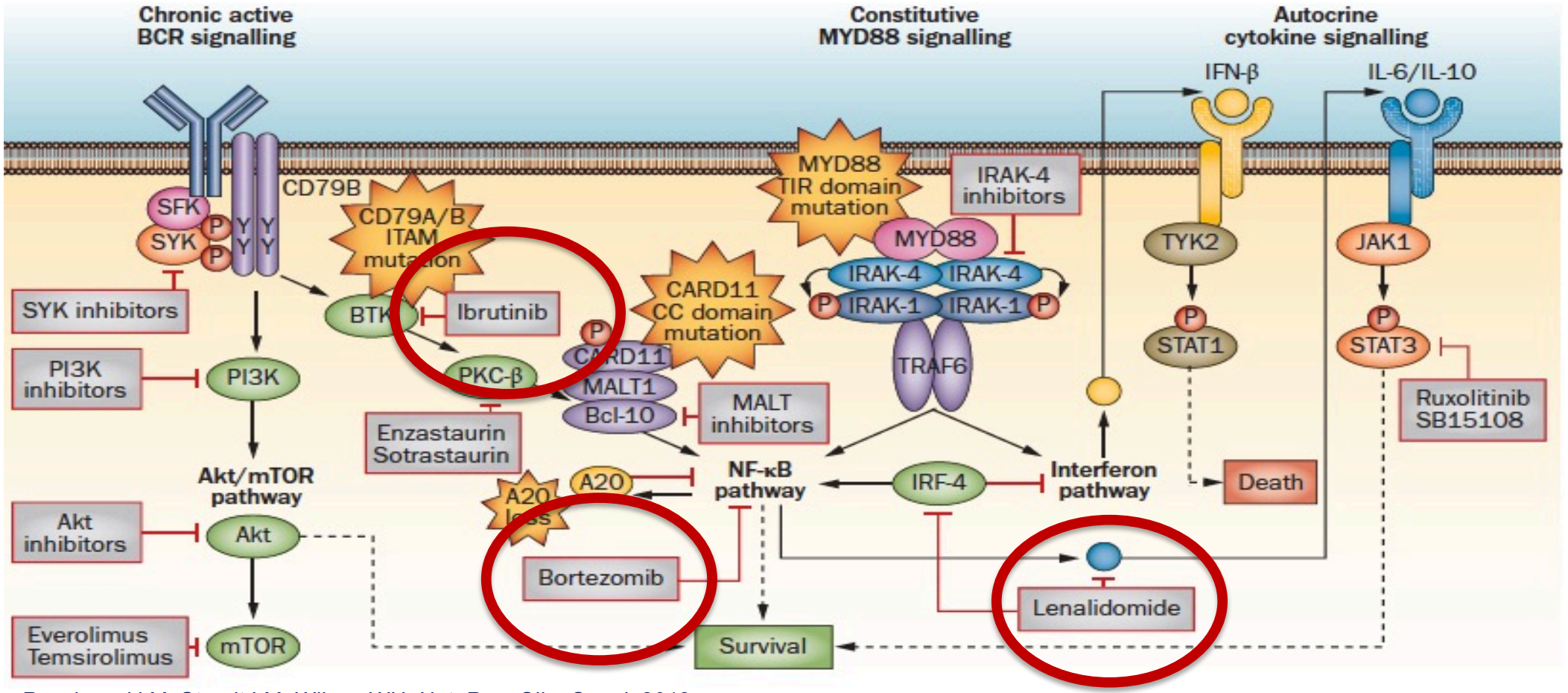
The key signalling pathways implicated in GCB DLBCL



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

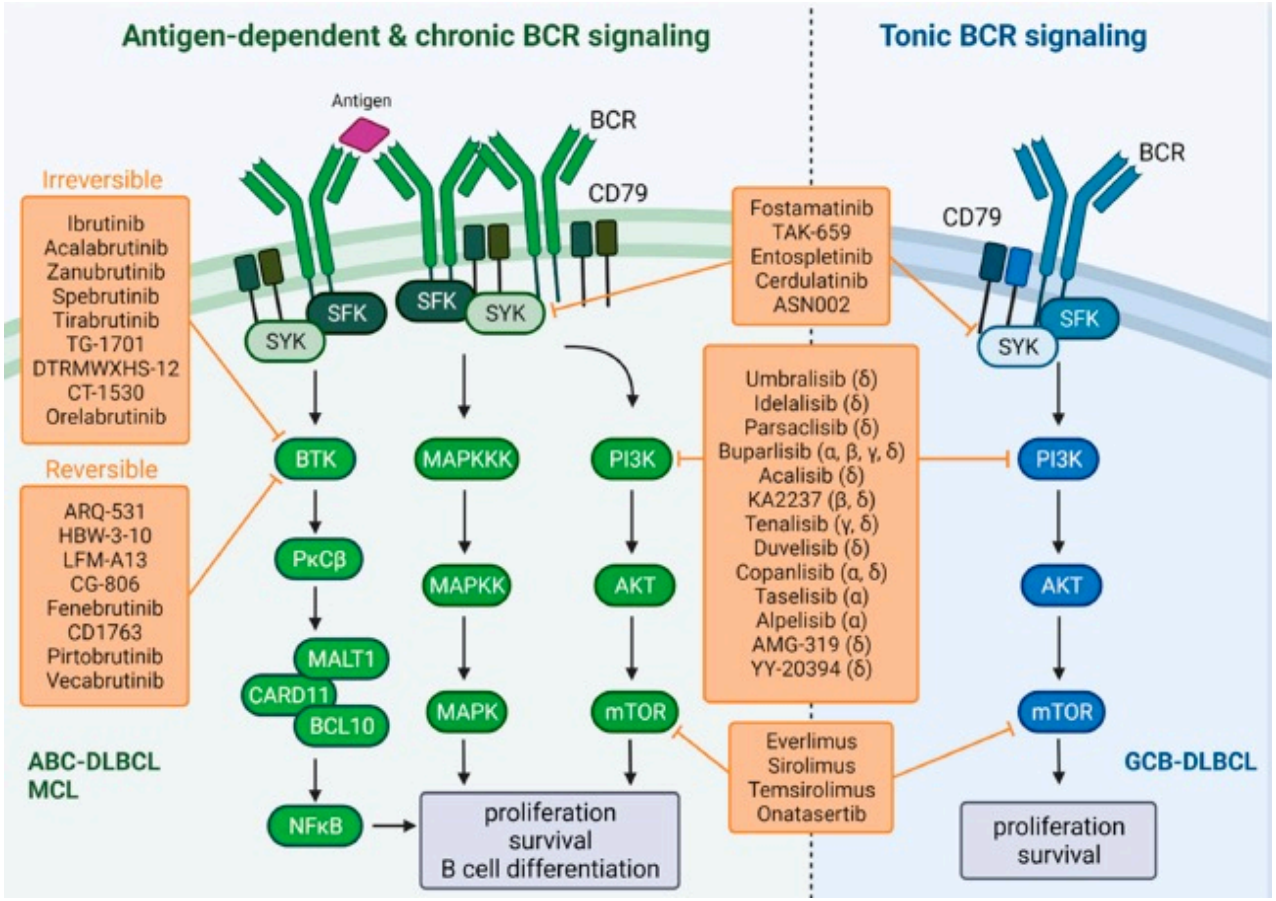
- ✓ Loss of PTEN (Phosphatase and tensin homologue) expression in 55% of cases → activation of PI3K/Akt/mTOR signalling pathway; → **small-molecule inhibitors can be effective in GCB with decreased PTEN expression.**
- ✓ BCL-6 is frequently activated in GCB DLBCL; BCL6 deregulation results in enhanced tumour proliferation via decreased expression of the cell-cycle checkpoint proteins p21 and p27, impaired DNA damage response through decreased p53 expression, impaired cellular metabolism and resistance to apoptosis. → **inhibitors that target key co-repressor proteins of BCL-6.** In normal B cells, BCL-6 suppresses transcription of the MYC oncogene.
- ✓ **BET bromodomain inhibitors** represent a novel strategy of epigenetic regulation of MYC-driven tumours.
- ✓ BCL2 translocations are observed in up to 35% of GCB DLBCL cases, resulting in inhibition of apoptosis → **Inhibitors of BCL-2.**

The key signalling pathways implicated in ABC DLBCL



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

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.

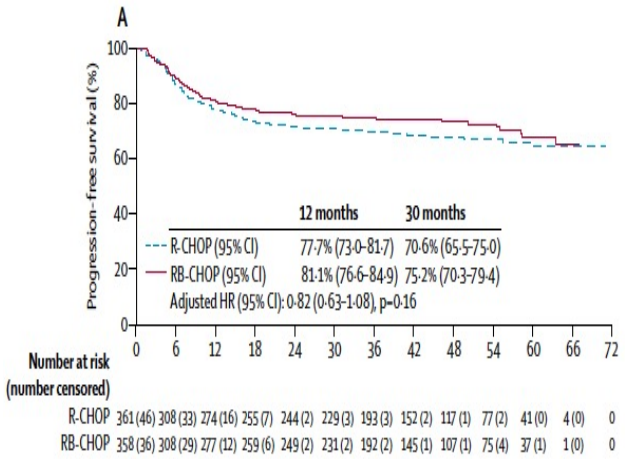
Attempt to improve the outcome with the addition of novel drugs with or after R-CHOP: overall no significative advantage

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

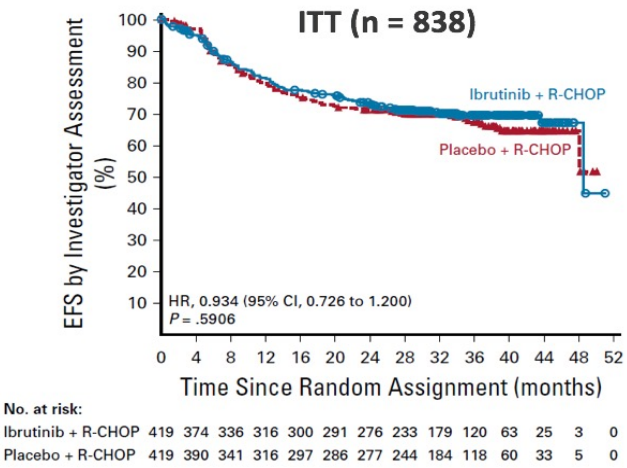
1. Seymour JF et al, Haematologica 2014; 2. Davies A et al, Lancet Oncol 2019; 3. Younes A et al, J Clin Oncol 2019; 4. Vitolo U et al, Hematol Oncol 2019; 5. Morschhauser F at al, Blood 2021; 6. Jagger U et al, Haematologica 2013; 7. Crump M et al, J Clin Oncol 2016; 8. Witzig T et al, Ann Oncol 2018;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

Moving beyond R-CHOP… targeting ABC DLBCL

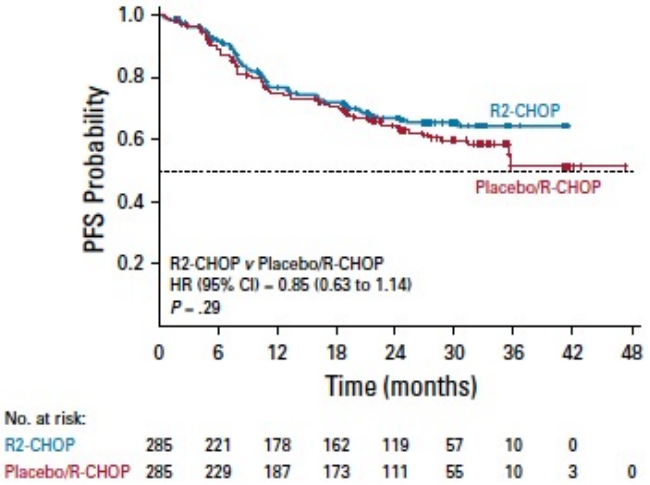
R-CHOP + Bortezomib



R-CHOP + iBTK



R-CHOP + Lenalidomide



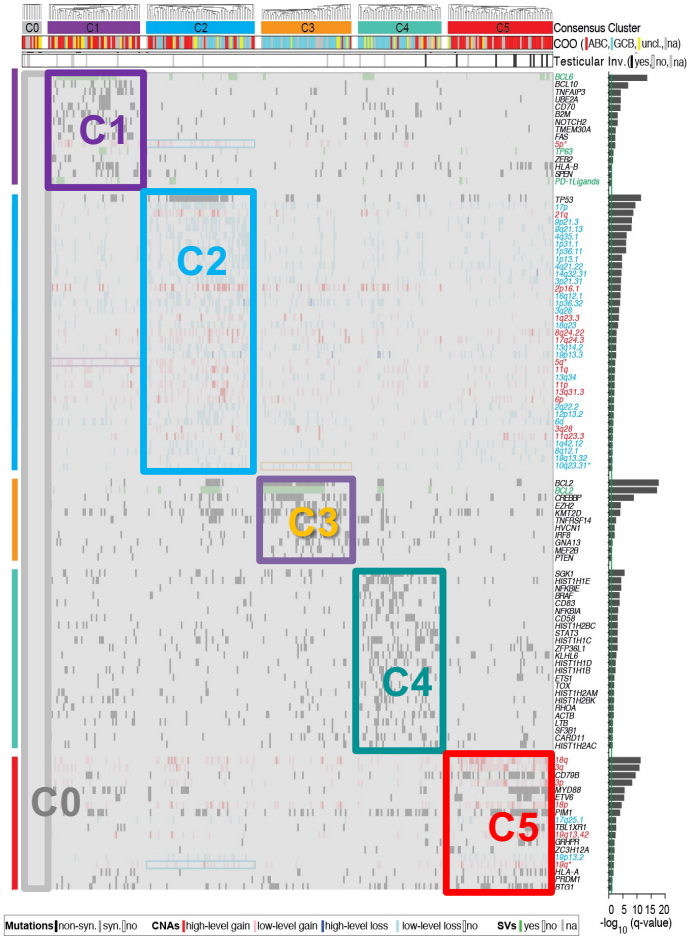
Davies A, et al. Lancet Oncol 2019; Younes A, et al. J Clin Oncol 2019; Nowakowski G, et al. J Clin Oncol 2021.

Where are we wrong? Should we still care about COO?

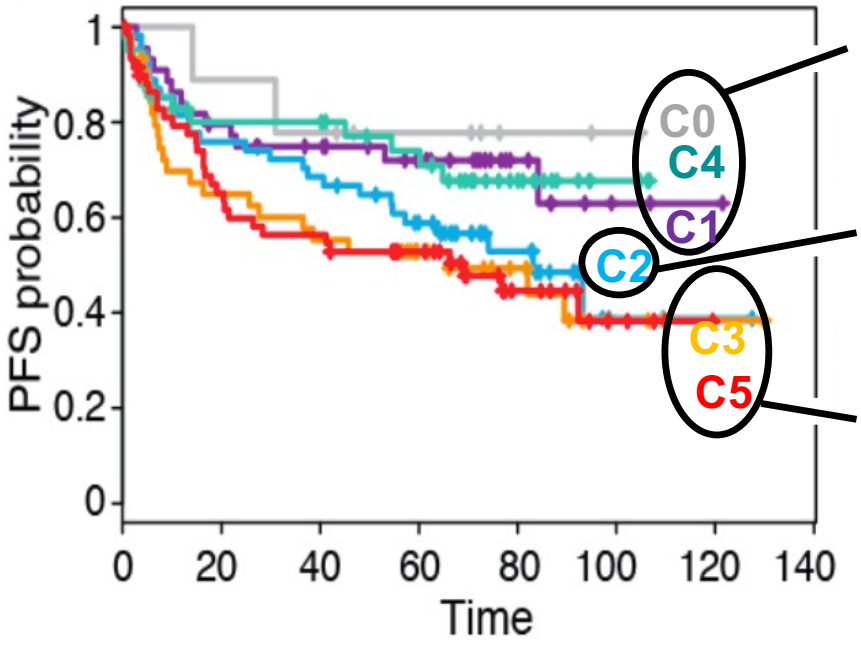
- Yes: the prognosis of ABC is still unsatisfactory
- Yes: subgroups of ABC patients benefit from the addition of specific drugs as ibrutinib in young and lenalidomide in high risk
- No: ABC *alone* is not the best target; DLBCLs are more heterogenous, mutational alterations, etc
- Maybe: ibrutinib or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

Genetically-distinct DLBCL Subsets are Predictive for Outcome

Genetically-distinct DLBCLs



Predictive for Outcome



C0/C1/C4 favorable

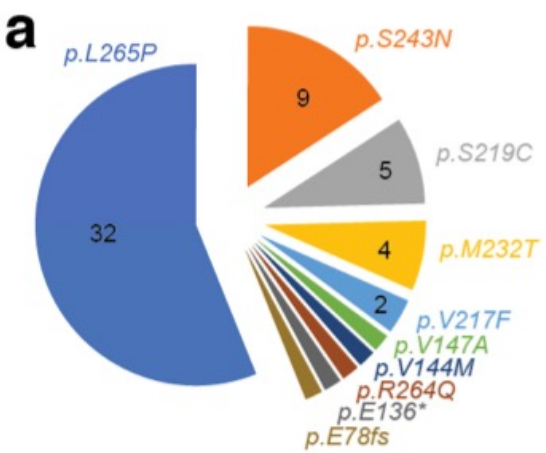
C2 distinct trajectory

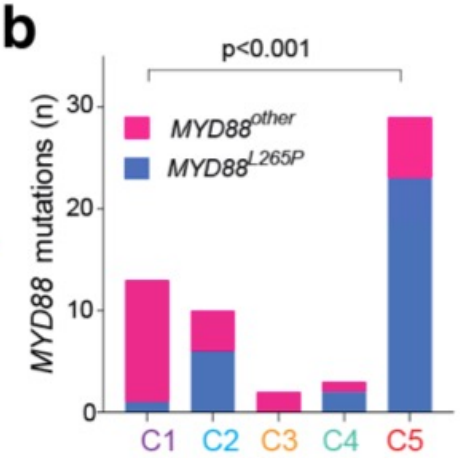
C3/C5 unfavorable

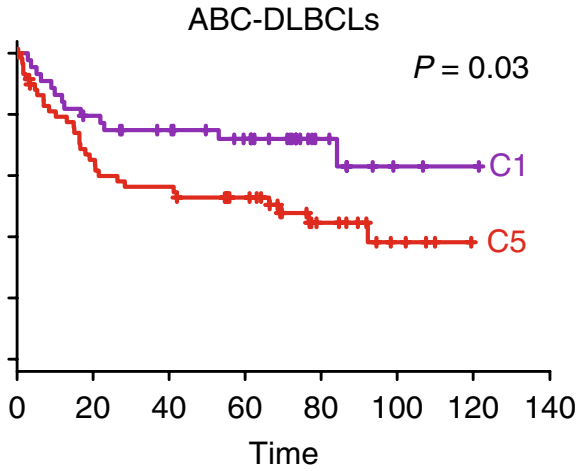
- **Genetic signatures comprised of**
  - Mutations
  - Somatic copy number alterations (SCNAs)
  - Structural Variants (SVs)

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.

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, bortezomib, 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

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

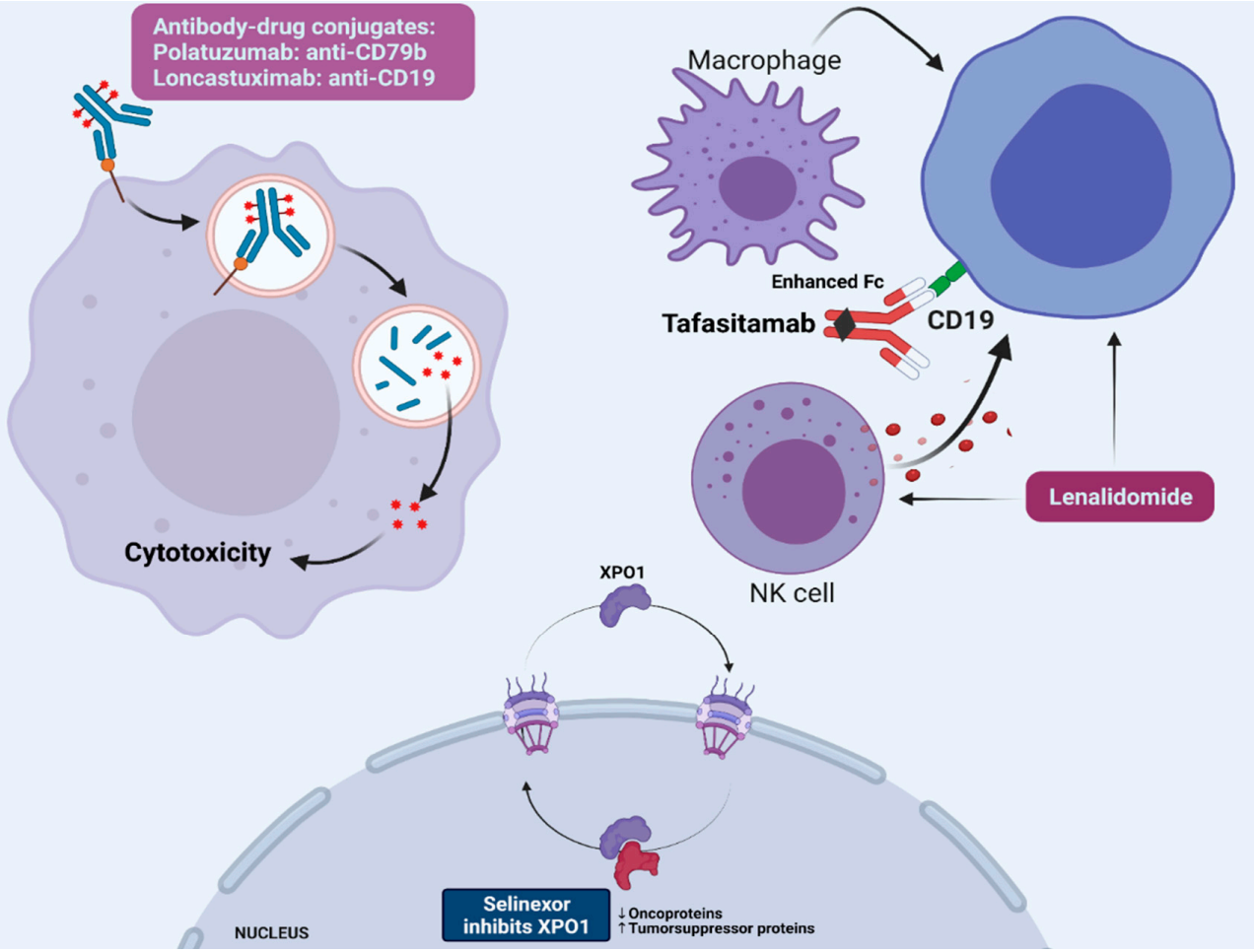
  BN2 – 23 N1 - 3

- 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.

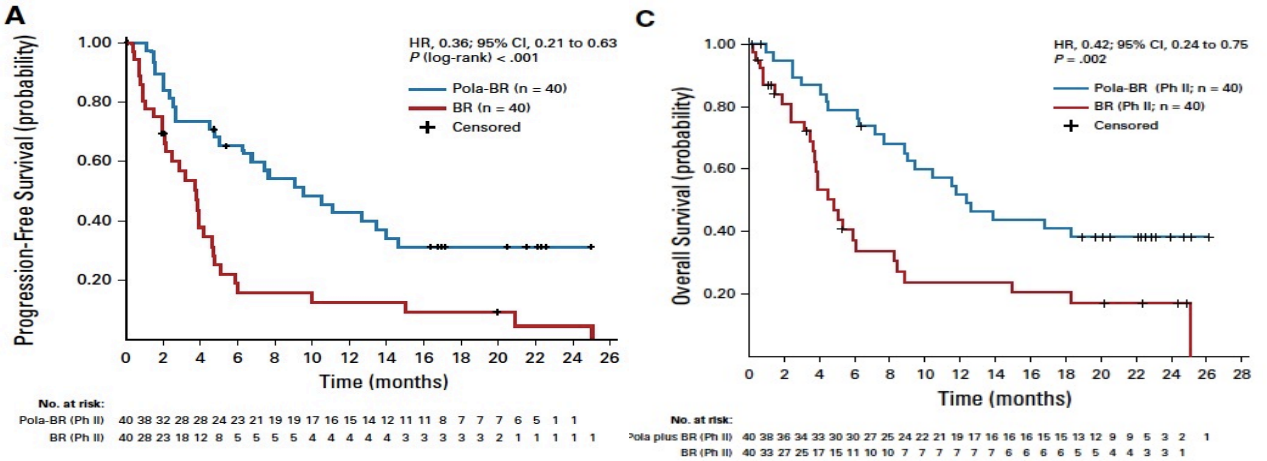
ADC + R-chemotherapy

R/R

Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, MD, MPH[1]; Alex F. Herrera, MD[2]; Christopher R. Flowers, MD, MSc[3]; Manali K. Kamdar, MD, MBBS[4]; Andrew McMillan, PhD[5]; Mark Hertzberg, MBBS, PhD[6]; Sarit Assouline, MDCM, MSc[7]; Tae Min Kim, MD[8]; Won Seog Kim, MD, PhD[9]; Muhit Ozcan, MD[10]; Jamie Hirata, PharmD[11]; Elicia Penuel, PhD[11]; Joseph N. Paulson, PhD[11]; Ji Cheng, PhD[12]; Grace Ku, MD[11]; and Matthew J. Matasar, MD[13]

J Clin Oncol 38:155-165. © 2019



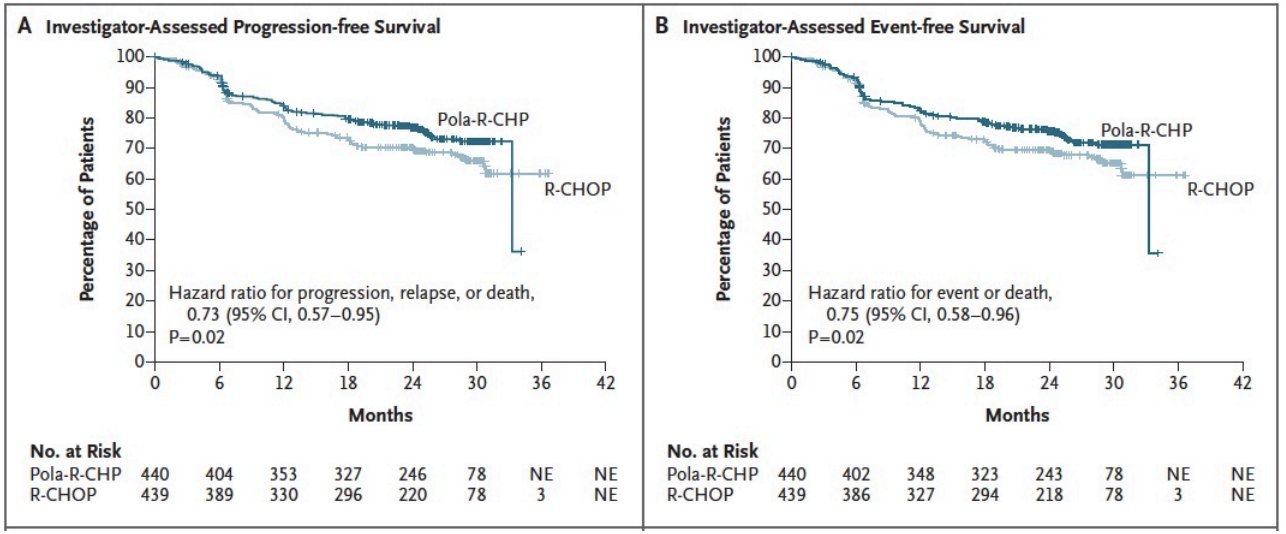
FIRST LINE

ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

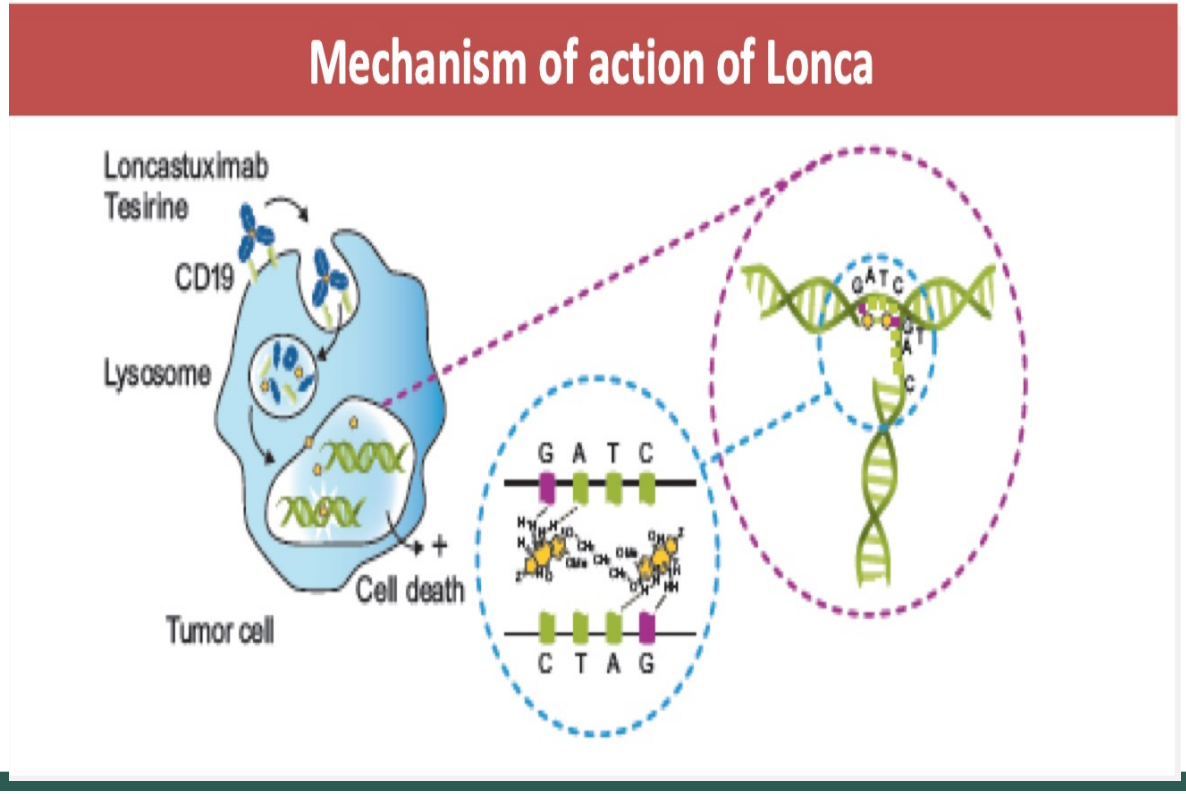
H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trněný, J.P. Sharman, C. Herbaux, J.M. Burke, M. Matasar, S. Rai, K. Izutsu, N. Mehta-Shah, L. Oberic, A. Chauchet, W. Jurczak, Y. Song, R. Greil, L. Mykhalska, J.M. Bergua-Burgués, M.C. Cheung, A. Pinto, H.-J. Shin, G. Hapgood, E. Munhoz, P. Abrisqueta, J.-P. Gau, J. Hirata, Y. Jiang, M. Yan, C. Lee, C.R. Flowers, and G. Salles

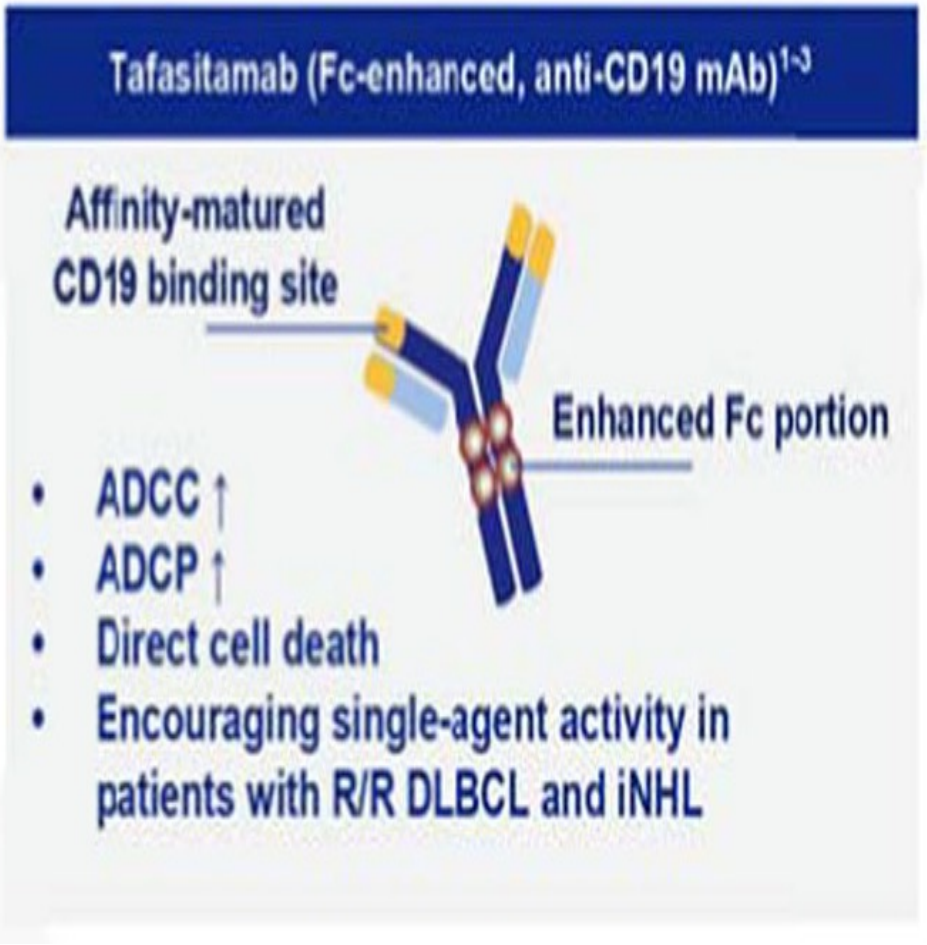
N Engl J Med 2022;386:351-63.



…adding mAb antiCD19?

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

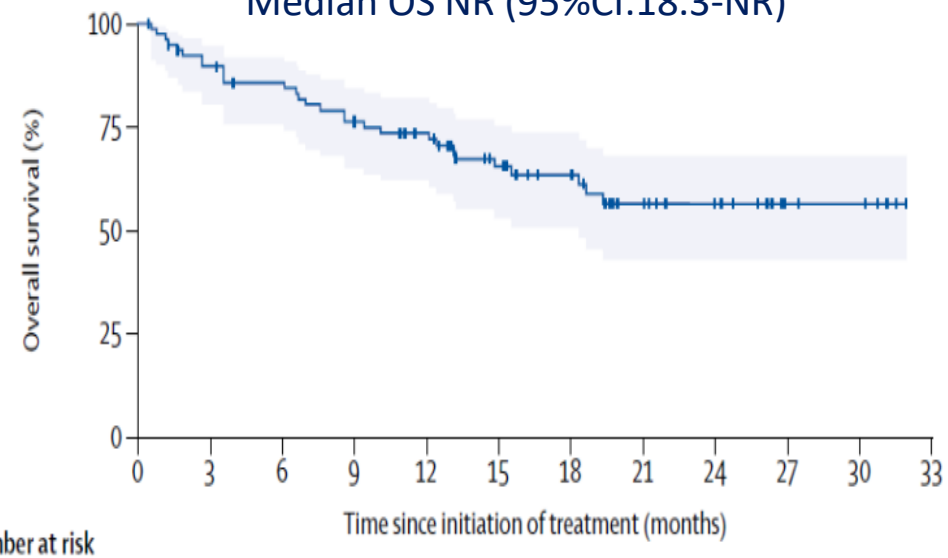




Tafasitamab + lenalidomide in R/R DLBCL

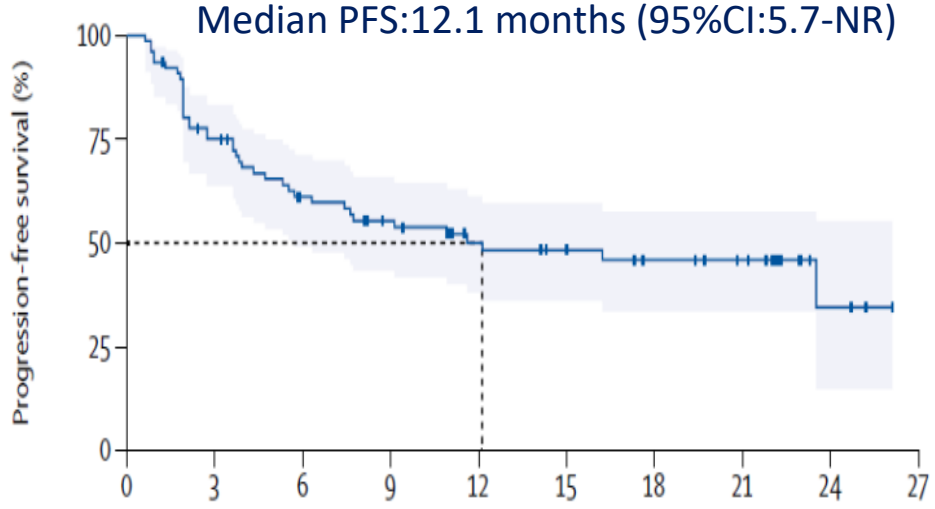
Single arm phase II study L-Mind

Median OS NR (95%CI:18.3-NR)



Number at risk (number censored)												
All treated patients	80 (0)	69 (3)	64 (5)	57 (6)	50 (10)	35 (20)	29 (26)	20 (32)	14 (37)	6 (45)	5 (46)	0 (51)

Median PFS:12.1 months (95%CI:5.7-NR)



Number at risk (number censored)										
All treated patients	80 (3)	56 (5)	42 (9)	35 (12)	26 (18)	22 (23)	17 (25)	13 (29)	3 (38)	0 (41)

Median follow-up:19.6 months

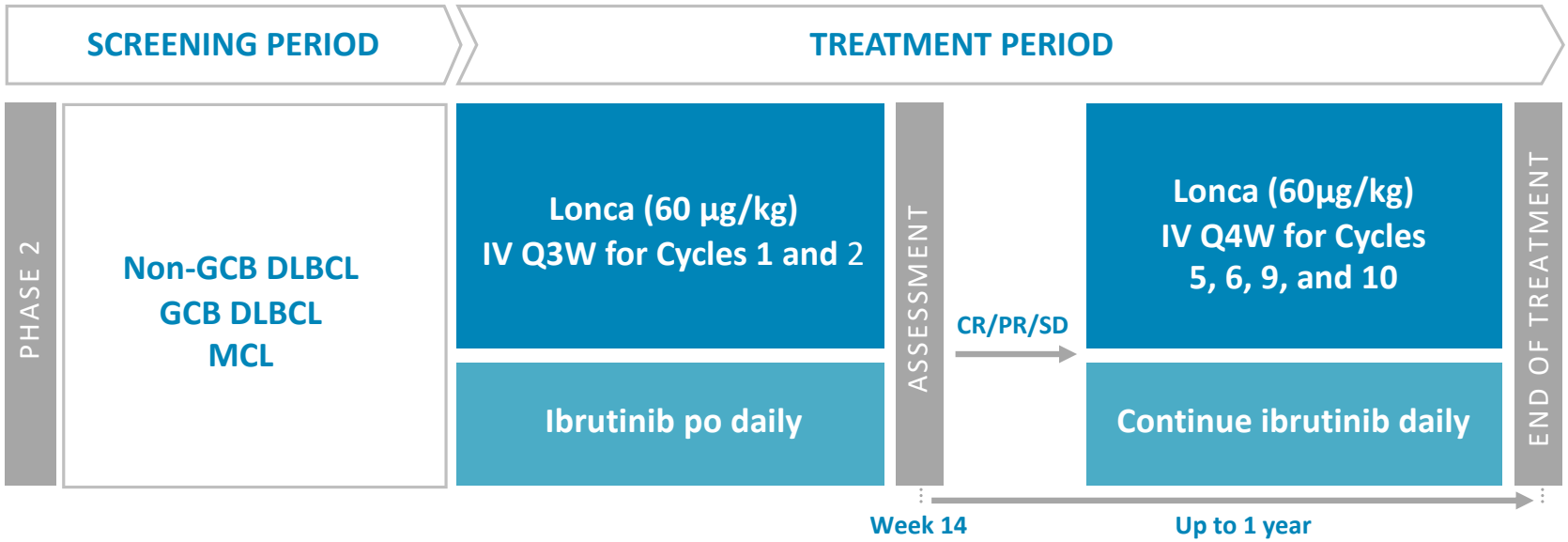
Salles G et al. Lancet Oncology 2020

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

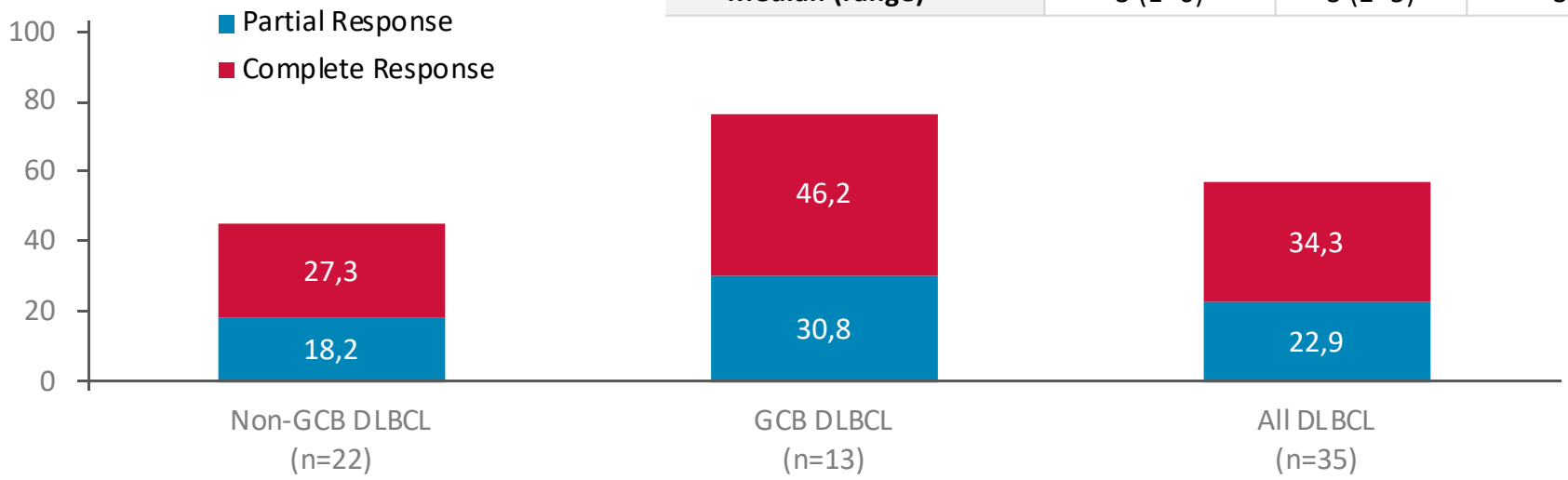
Carlo-Stella C, Abs#0054, ASH 2021

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)

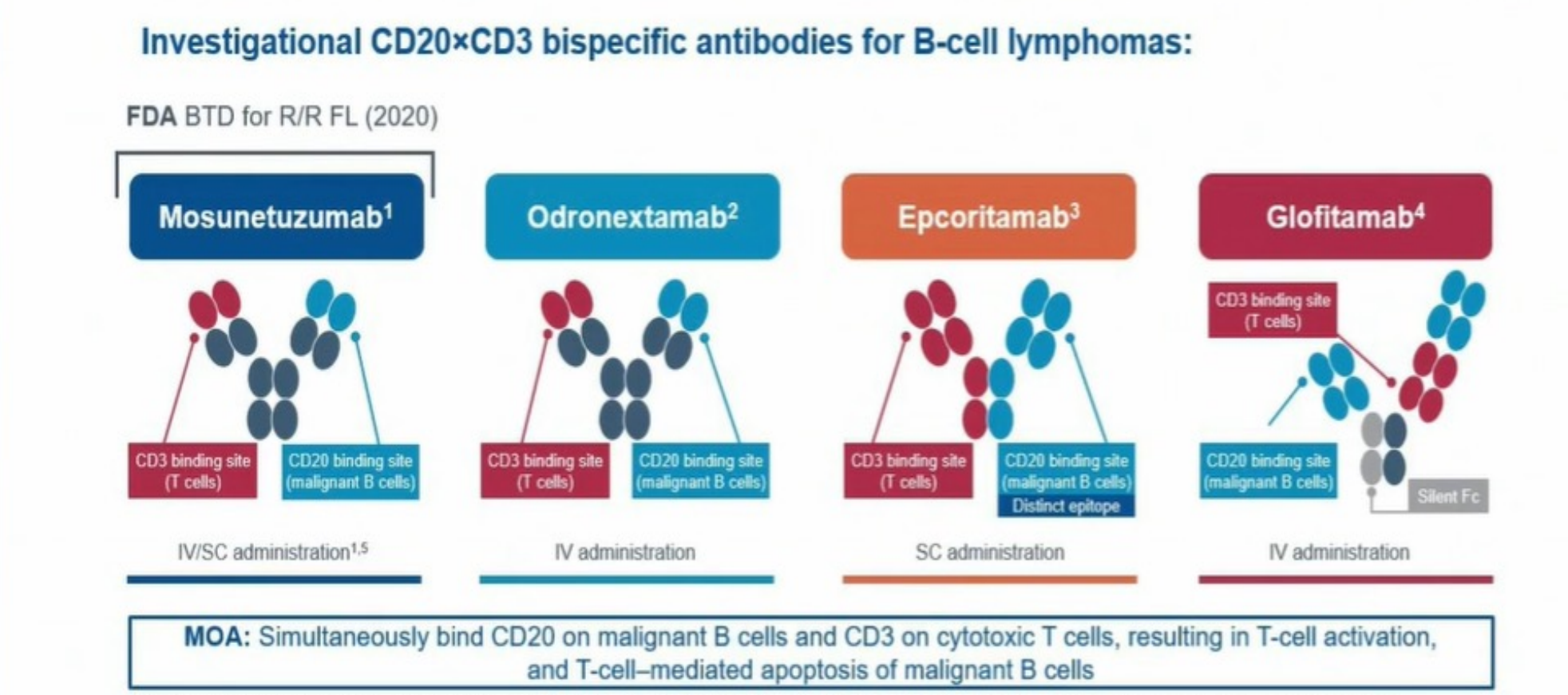
Characteristic	Non-GCB (n=22)	GCB (n=13)	All patients (n=35)
Age, yrs, median (range)	72 (19–82)	66 (53–82)	72 (19–82)
Prior systemic therapies, n Median (range)	3 (1–6)	3 (2–5)	3 (1–6)



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



CD20xCD3 bispecific antibodies + SoC

Rational combinations of targeted therapies

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

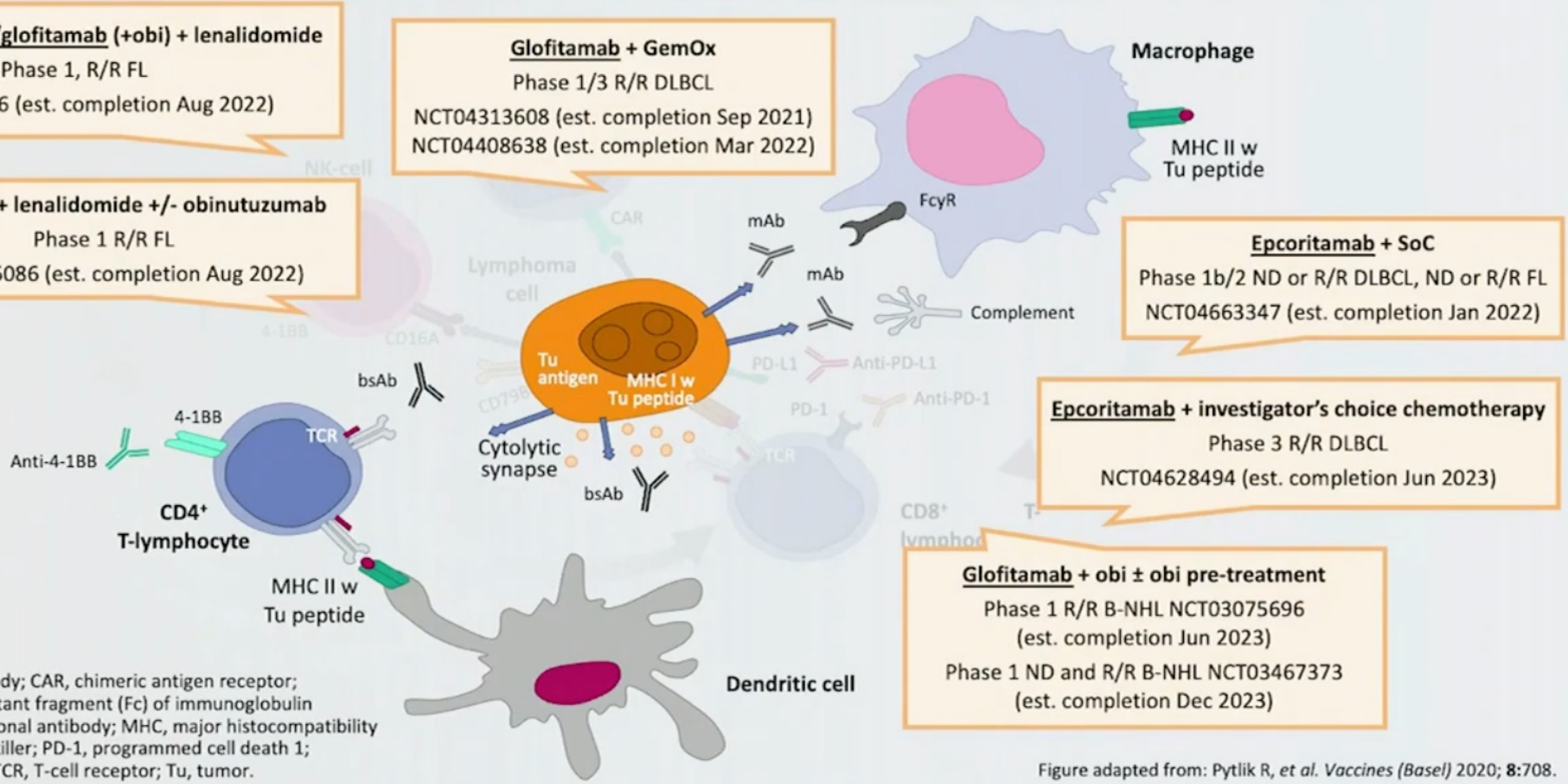
Glofitamab + lenalidomide +/- obinutuzumab
Phase 1 R/R FL
NCT04246086 (est. completion Aug 2022)

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

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)

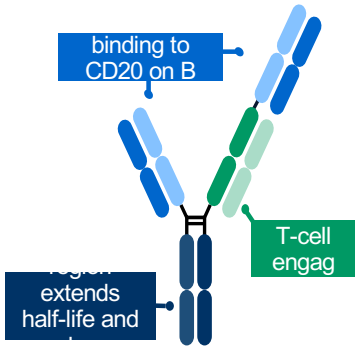


bsAb, bispecific antibody; CAR, chimeric antigen receptor; FcR, receptor for constant fragment (Fc) of immunoglobulin gamma; mAb, monoclonal antibody; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death 1; PD-L1, PD-1 ligand 1; TCR, T-cell receptor; Tu, tumor.

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

By courtesy of Salles G, ICML 2021

Glofitamab in 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

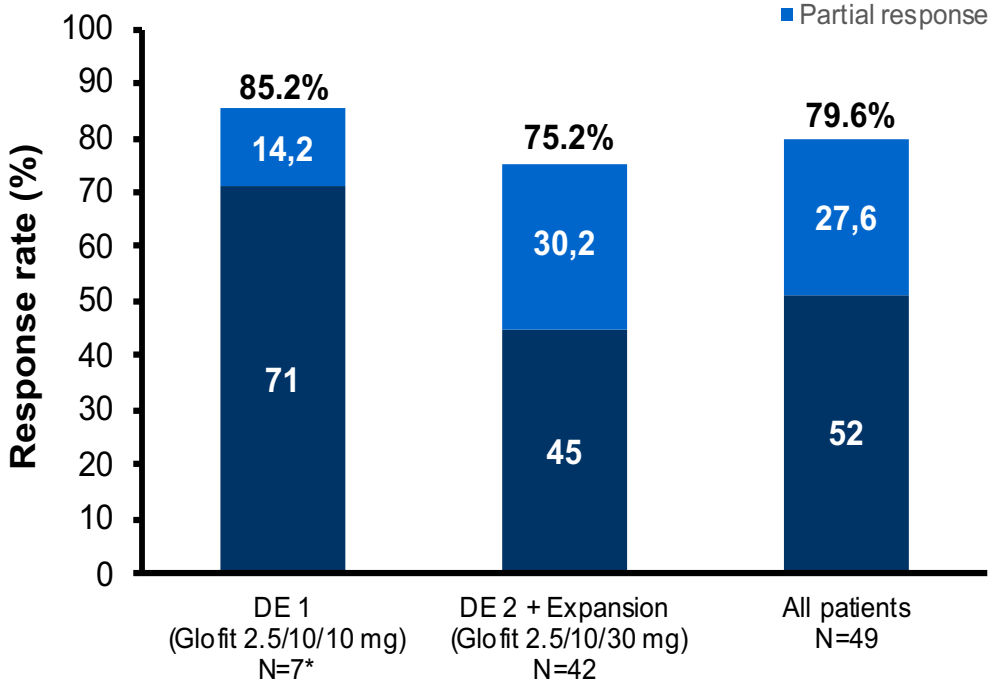
C1	C2–6	C7–12
D1: Obinutuzumab pretreatment 1000 mg D2: Polatuzumab vedotin 1.8 mg/kg D8: Glofitamab 2.5 mg D15: Glofitamab 10 mg	D1: Polatuzumab vedotin 1.8 mg/kg D1: Glofitamab 10 or 30 mg	D1: Glofitamab 10 or 30 mg
Glofitamab step-up dosing	**Glofitamab target dose (Q3W)**	**Glofitamab target dose (Q3W)**

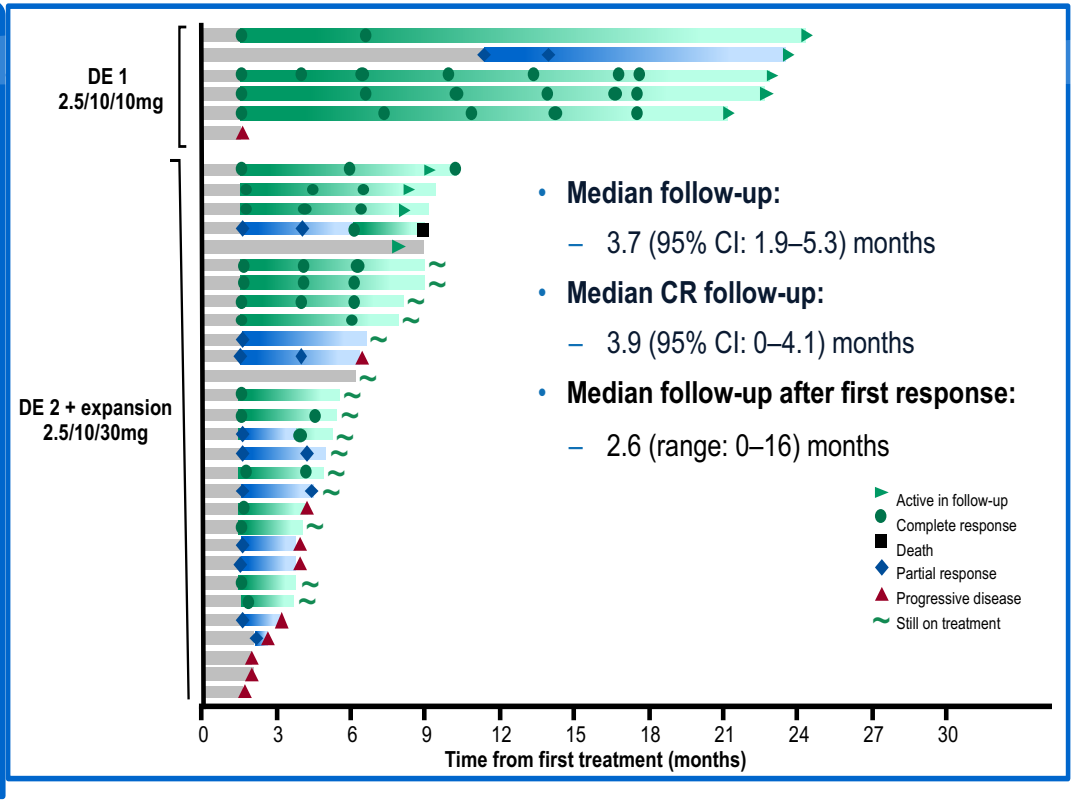
Cycle = 21 days; glofitamab (C2–C12) and polatuzumab vedotin (C2–C6) administered Q3W

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]

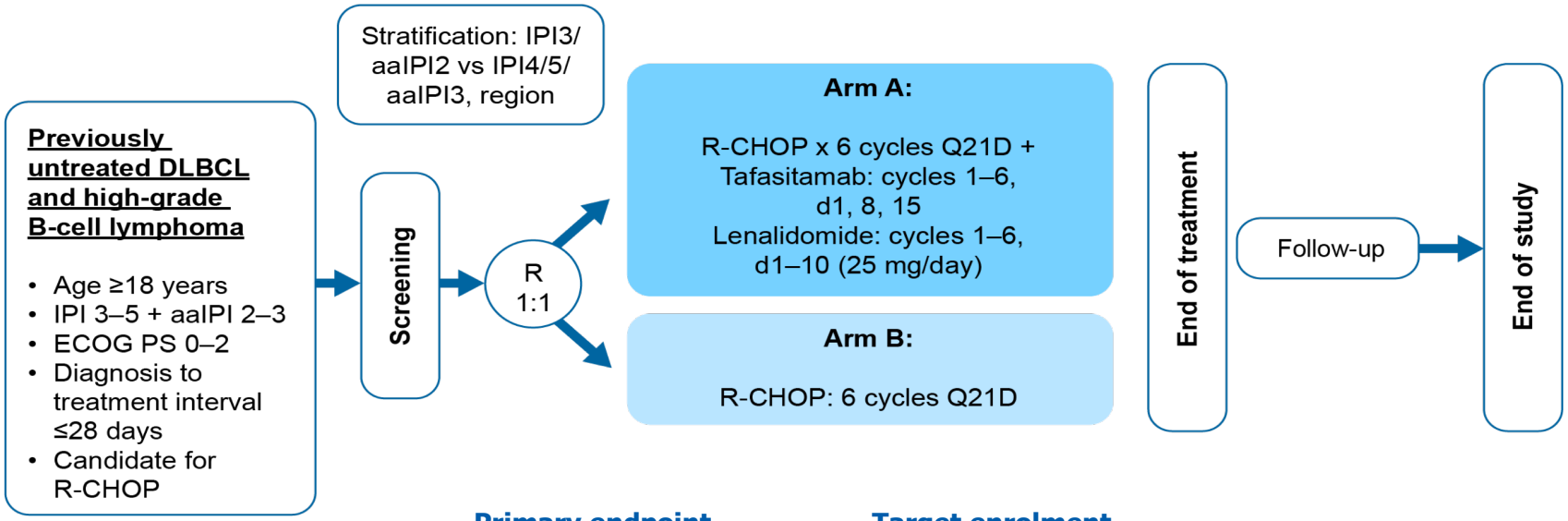
- Phase 1b: incidence and severity of TEAEs and incidence of DLTs
- Phase 2a: ORR

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

frontMIND: STUDY DESIGN (MORPHOSYS TRIAL)

INTERNATIONAL, PROSPECTIVE, OPEN-LABEL PHASE 3 STUDY IN 1L DLBCL AND HIGH-GRADE B-CELL LYMPHOMA



Primary endpoint
- EFS

Target enrolment
- N=450

1L, first-line; aaIPI, age-adjusted International Prognostic Index; d, day(s); DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IPI, International Prognostic Index; Q21D, every 21 days; R, randomisation; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone.

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

GRAZIE