Eppur si muove...

La terapia nel MONDO LINFOMI

Il razionale biologico delle combinazioni nei linfomi non Hodgkin

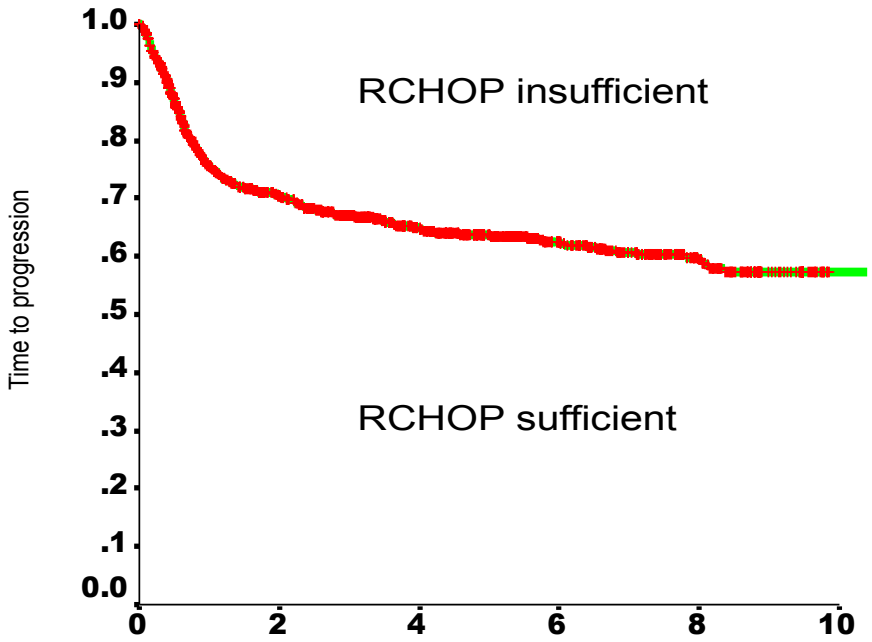
Annalisa Chiappella
Ematologia,
Fondazione IRCCS Istituto Nazionale dei Tumori
Milano

MILANO, 4 APRILE 2022

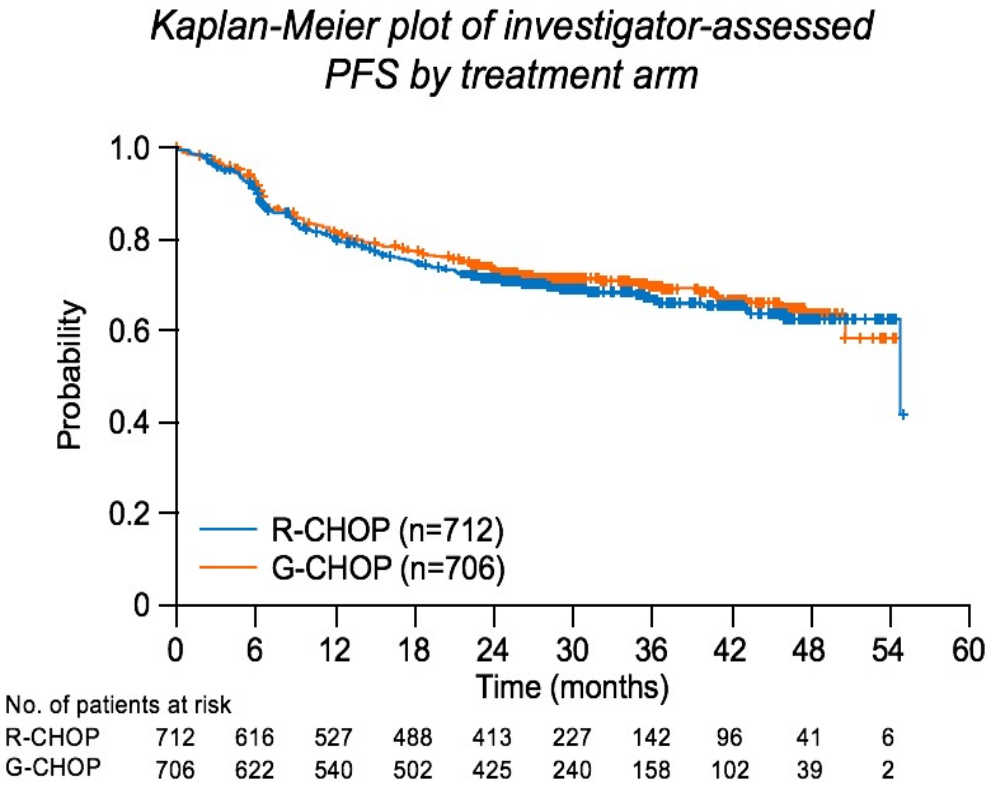
Disclosures, Annalisa Chiappella

Company name	Advisory board	Educational activities/Lecture fees
Astrazeneca		x
Celgene-BMS	x	x
Clinigen	x	x
Gilead-Sciences	x	x
Incyte		x
Janssen-Cilag	x	x
Novartis		x
Roche	x	x
SecuraBIO	x	
Takeda	x	x

DLBCL: R-CHOP fit in all aggressive lymphomas?



Moving beyond R-CHOP… targeting all DLBCL



Coiffier B, et al. Blood. 2010;116:2040-5; Sehn LH. ASH Education Book. 2012;1:402-9; Vitolo U, et al. J Clin Oncol 2017.

The NEW ENGLAND JOURNAL of MEDICINE

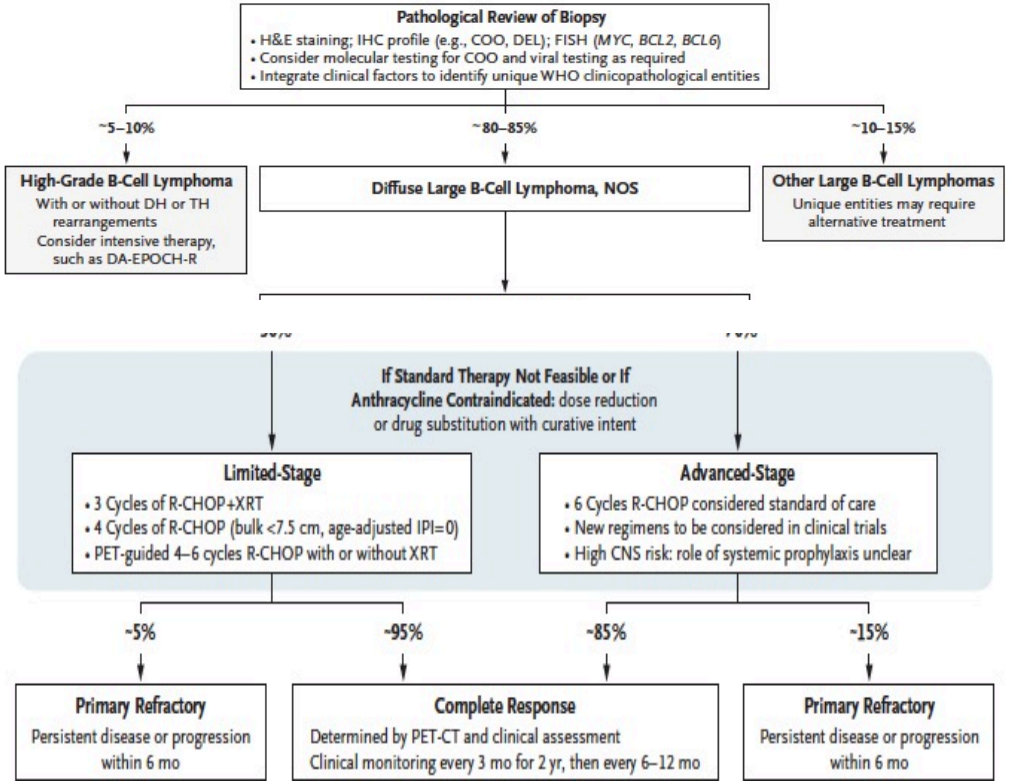
REVIEW ARTICLE

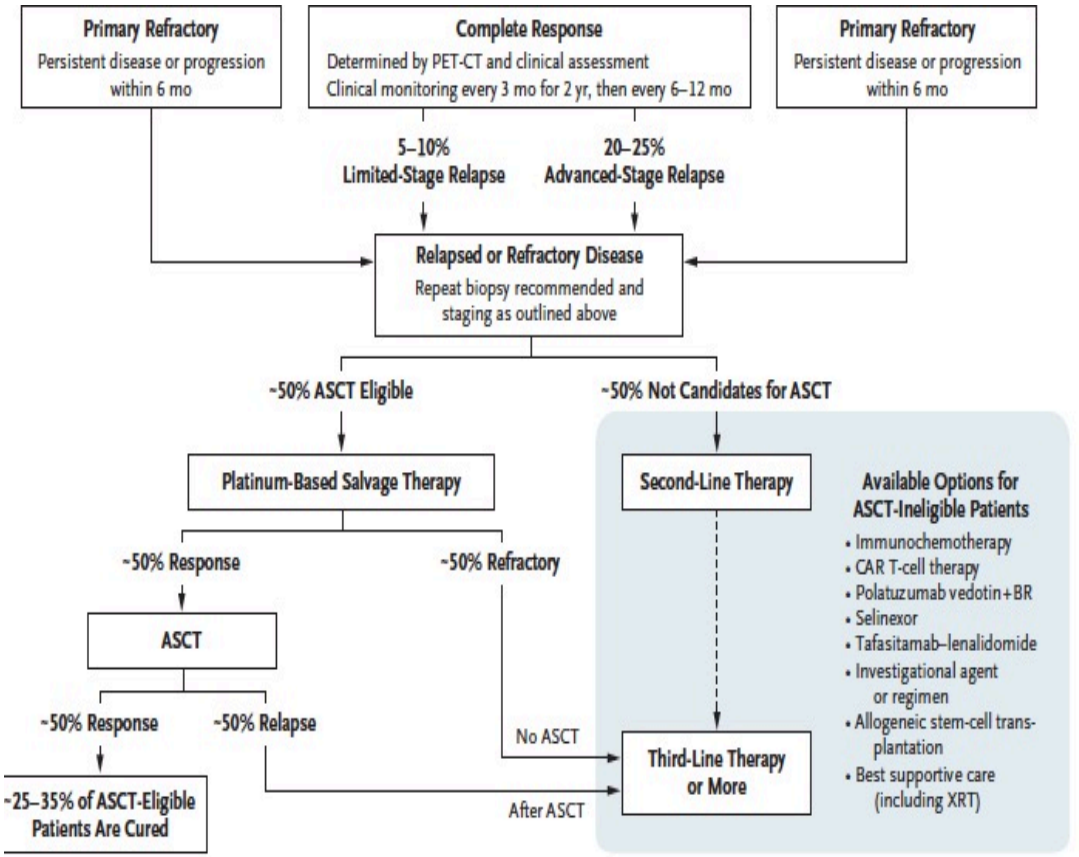
N Engl J Med 2021;384:842-58.
DOI: 10.1056/NEJMra2027612

Dan L. Longo, M.D., *Editor*

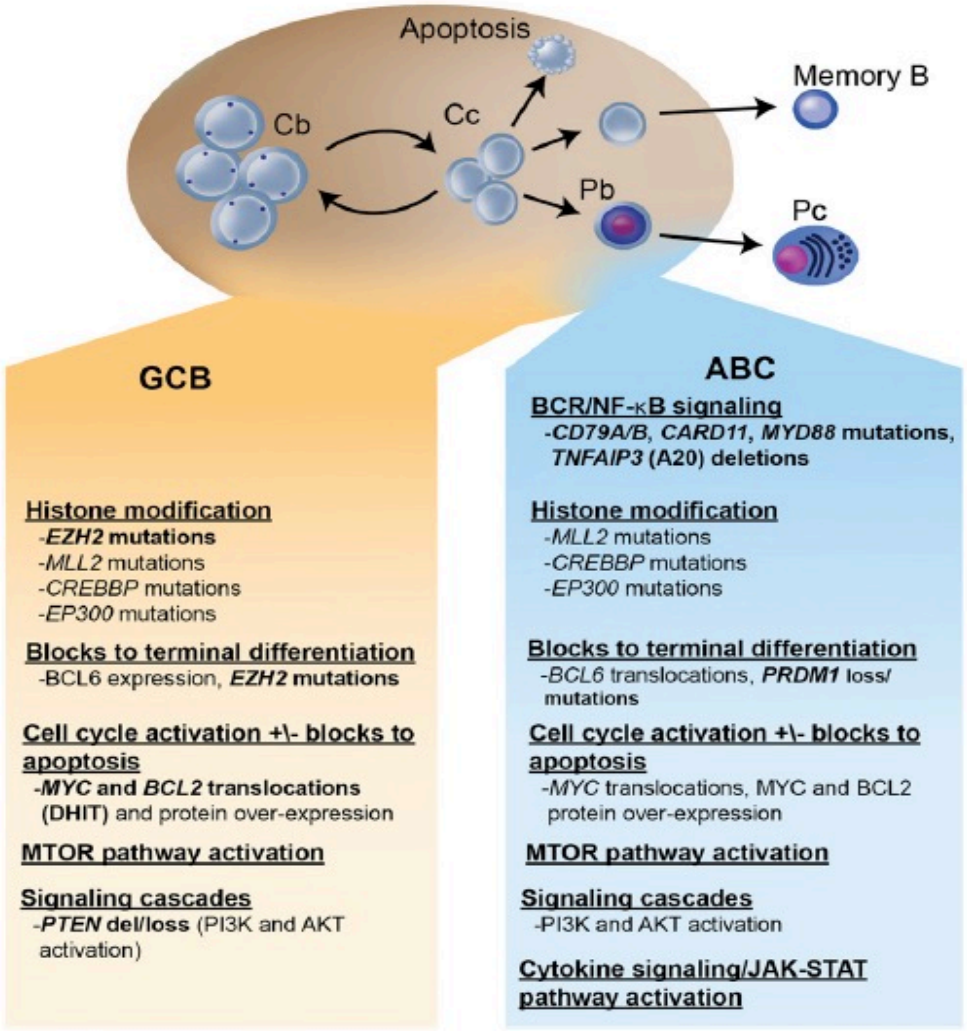
Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, M.D., M.P.H., and Gilles Salles, M.D., Ph.D.





What is the rationale of adding novel drugs to standard chemo in 1st line, or chemo-free regimens in R/R setting?



Sehn LH, Gascoyne RD, Blood 2015.

Key oncogenic pathways in DLBCL.

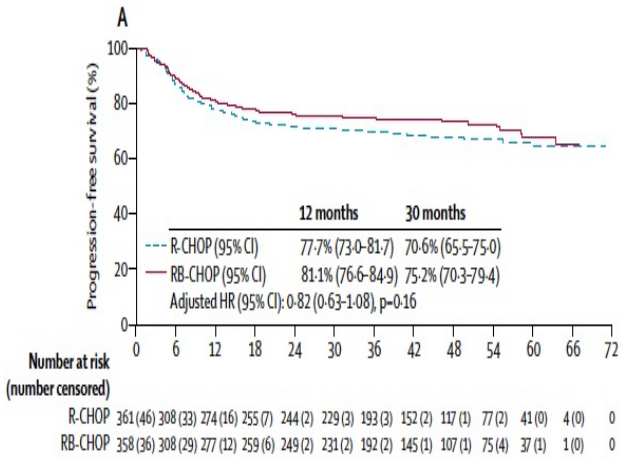
The GCB subtype arises from centroblasts, whereas the ABC subtype arises from a plasmablastic cell just prior to germinal center exit.

- main oncogenic pathways
- recurrent mutations, gains and losses of genetic material, characteristic translocations that underlie these pathway perturbations.

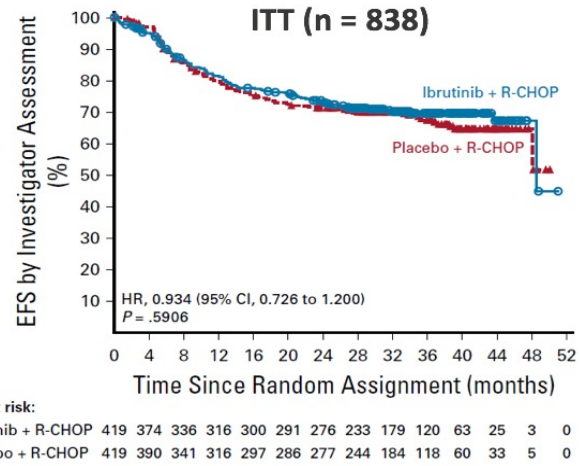
Agent	Target	Molecular subgroup
Bortezomib	NF-κB	ABC
Fostamatinib	SYK	ABC
Ibrutinib	BTK	ABC
Enzastaurin	PKCβ	ABC
Idelalisib	PI3K	(?) GCB
ABT-199	BCL2	(?) GCB, dual expressers
EZH2 inhibitors	EZH2	GCB
BCL6 inhibitors	BCL6	GCB
Lenalidomide	Microenvironment, NF-κB	ABC
Obinutuzumab	CD20	All
Ofatumomab	CD20	All
Polatuzumab vedotin	CD79b	All

Moving beyond R-CHOP… targeting ABC DLBCL

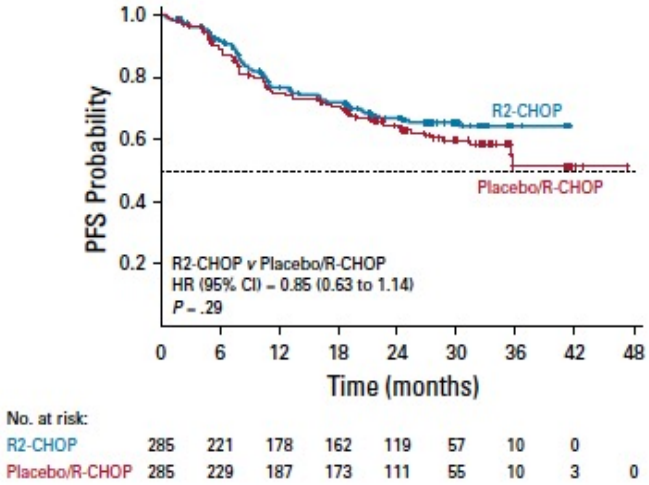
R-CHOP + Bortezomib



R-CHOP + iBTK

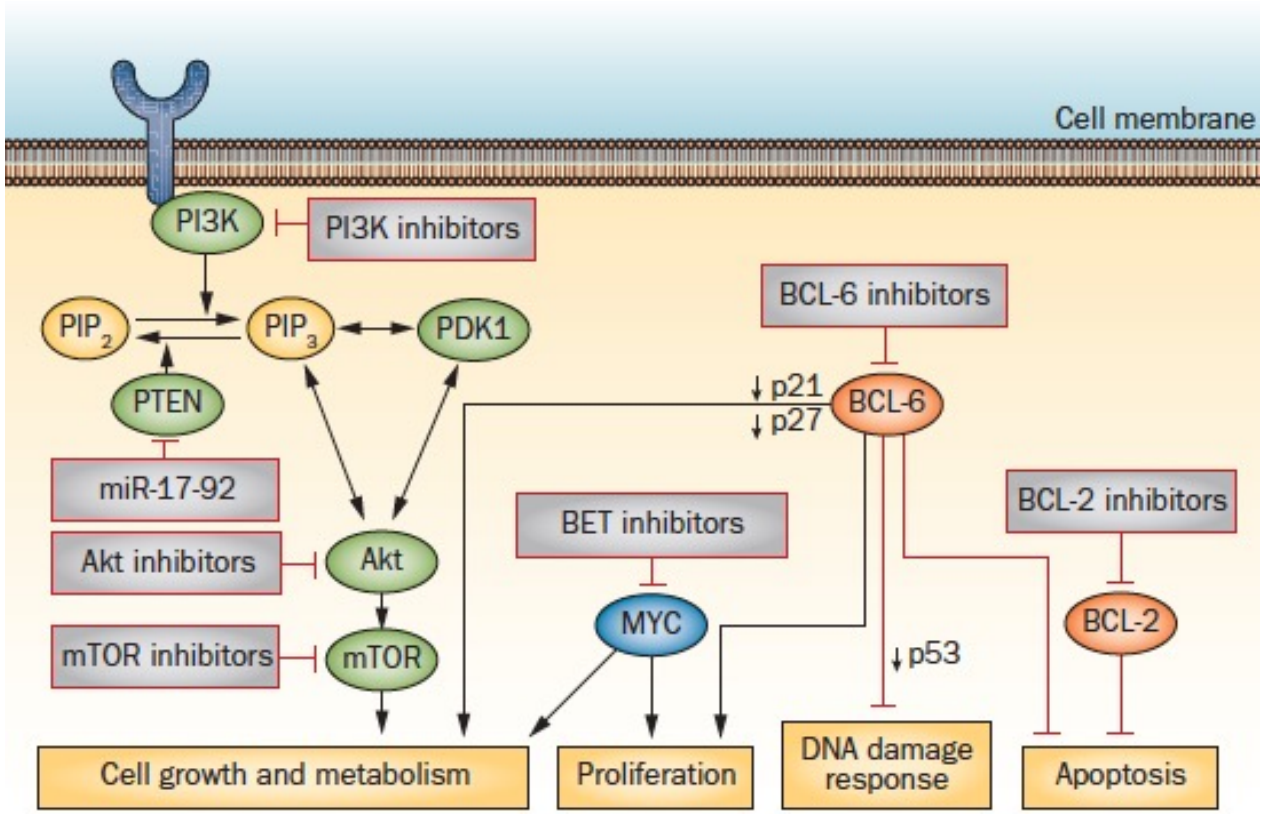


R-CHOP + Lenalidomide



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

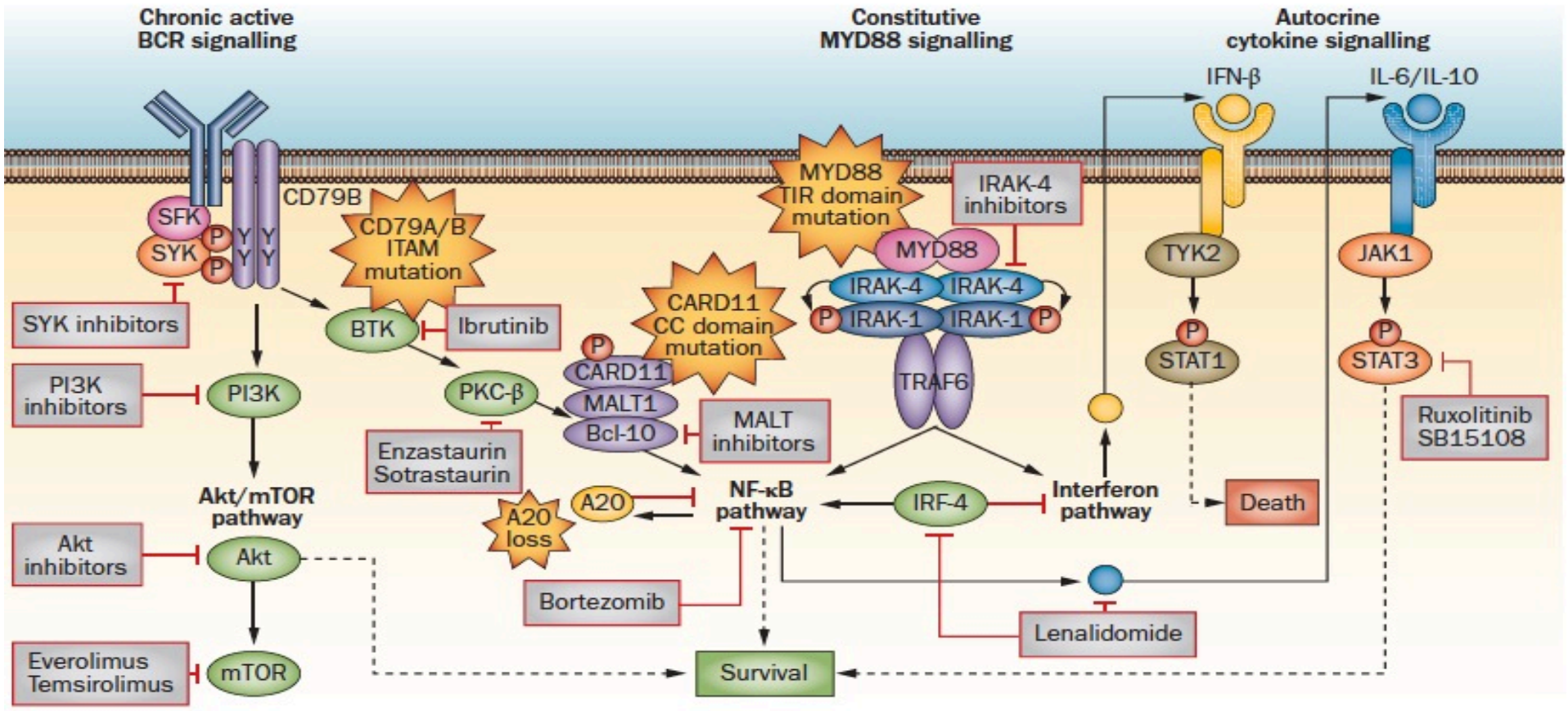
The key signalling pathways implicated in GCB DLBCL



- ✓ Loss of PTEN 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.**

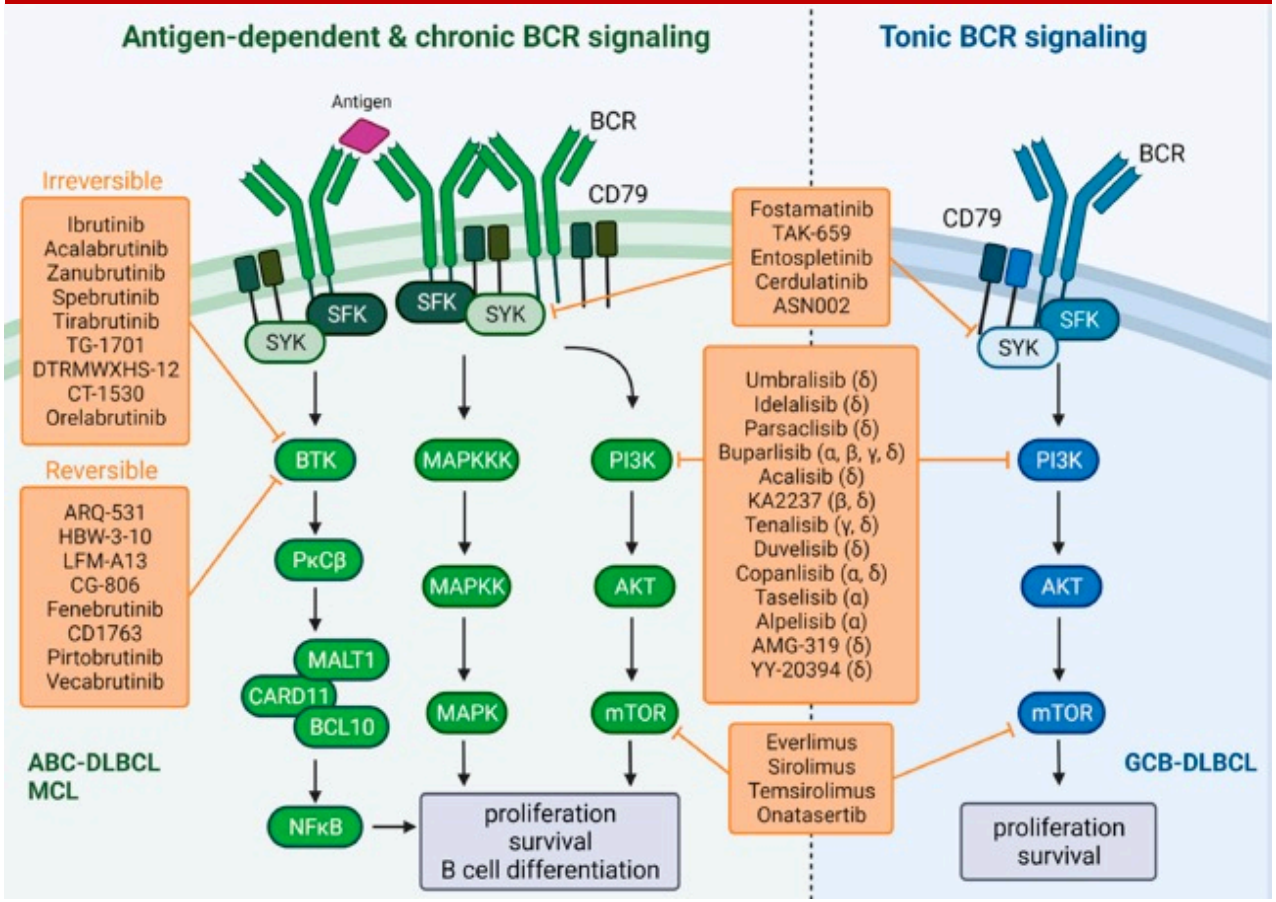
Roschewski M, Staudt LM, Wilson WH, Nat. Rev. Clin. Oncol. 2013.

The key signalling pathways implicated in ABC DLBCL



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

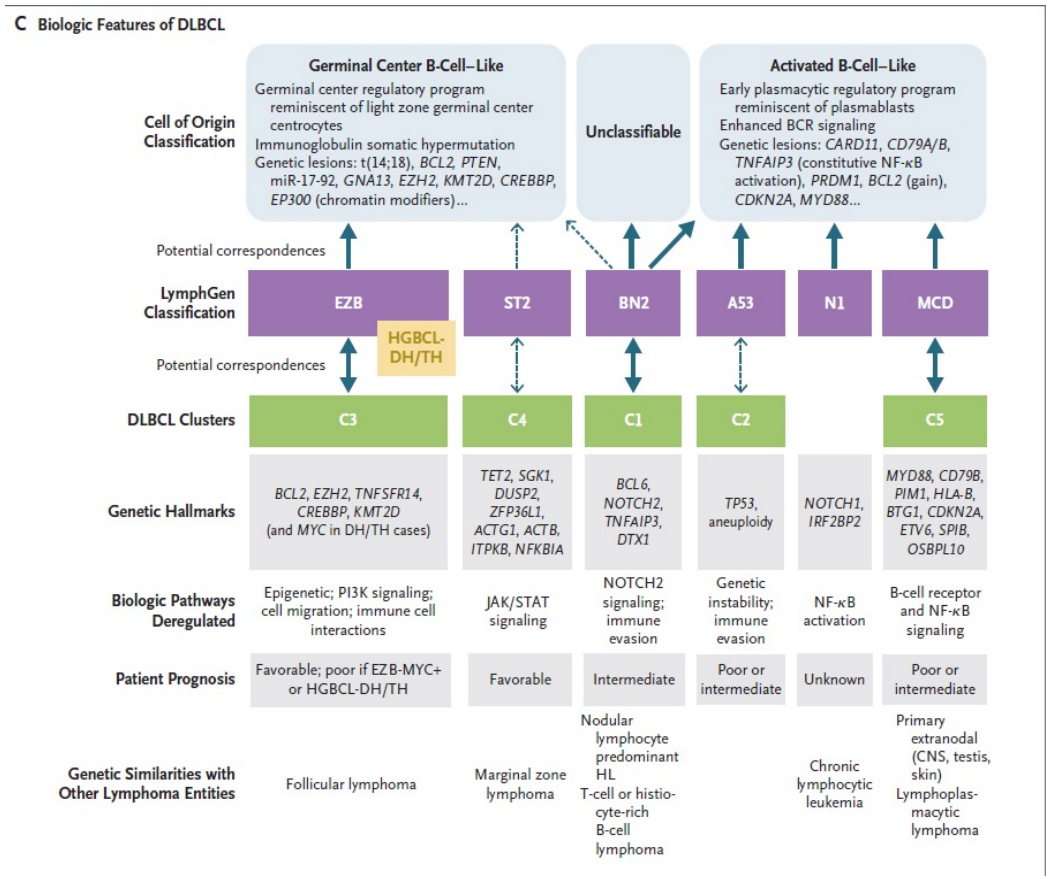
Regulation of BCR signaling and the therapeutic inhibition of BTK and PI3K in DLBCL



- ✓ 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.

…Targeting 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

Future directions: "X-Y-Z" +/- R-chemo

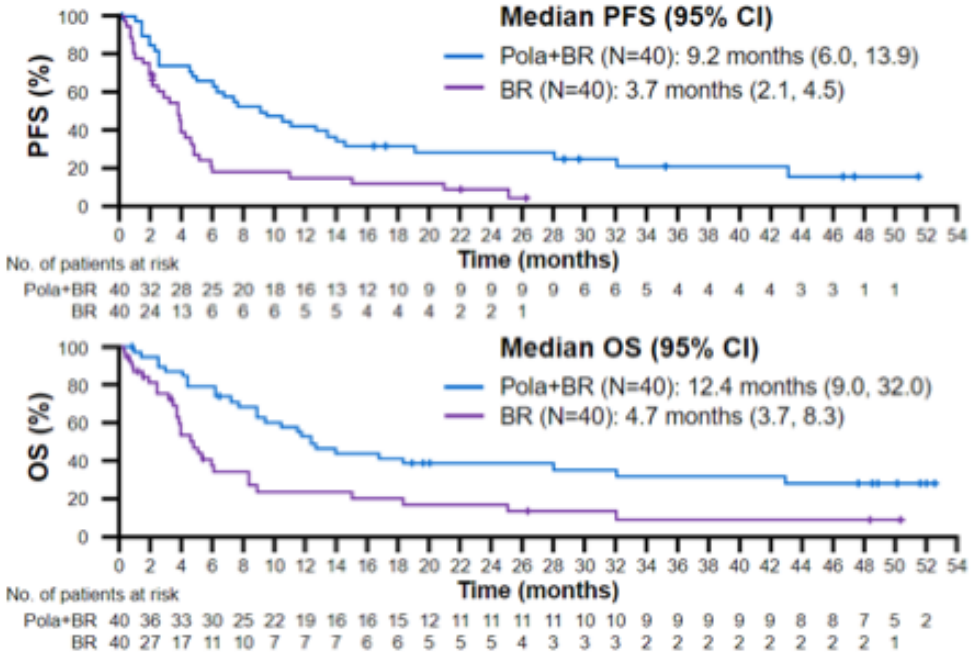
- Bispecific Antibodies
- Antibody-Drug Conjugated
- IMIDs, iBTK, iPI3K…
- Monoclonal Antibodies

Sehn LH, Salles G. N Engl J Med. 2021; Chapuy B et al, Nature Medicine 2018.

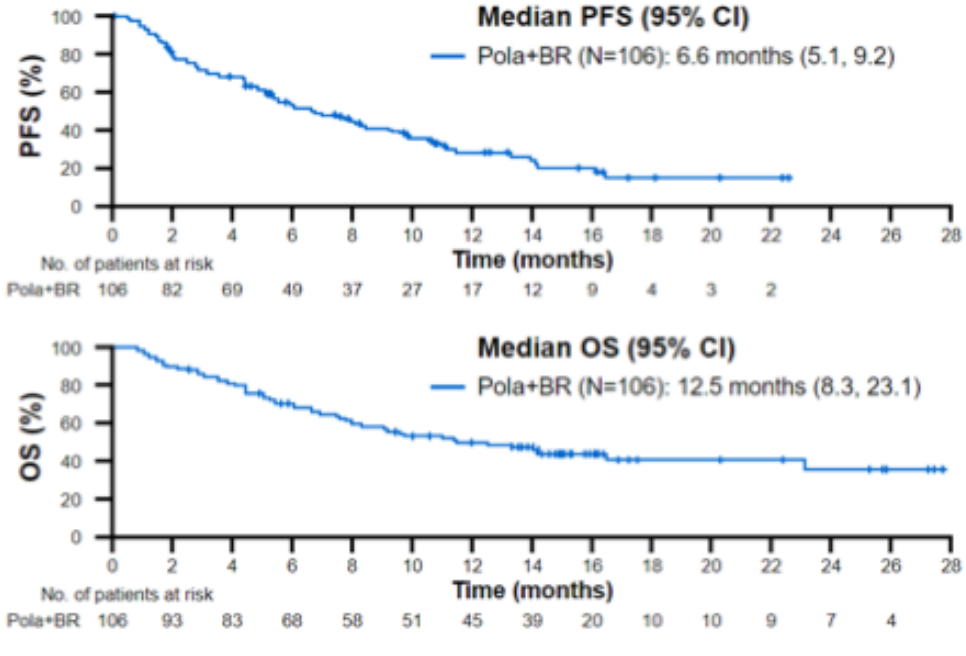
ADC + R-chemotherapy

Rituximab + Bendamustine +/- Polatuzumab Vedotin in R/R DLBCL

Randomized



Extension cohort



- The significant survival benefit with Pola+BR persists with longer follow-up
- The 2-year PFS probability was 28.4% and the 2-year OS probability was 38.2% for patients in the randomized Pola+BR cohort

Sehn LH et al, J Clin Oncol 2020; Sehn LH et al. Blood Adv 2021.

CD20xCD3 bispecific antibodies + SoC

Rational combinations of targeted therapies

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

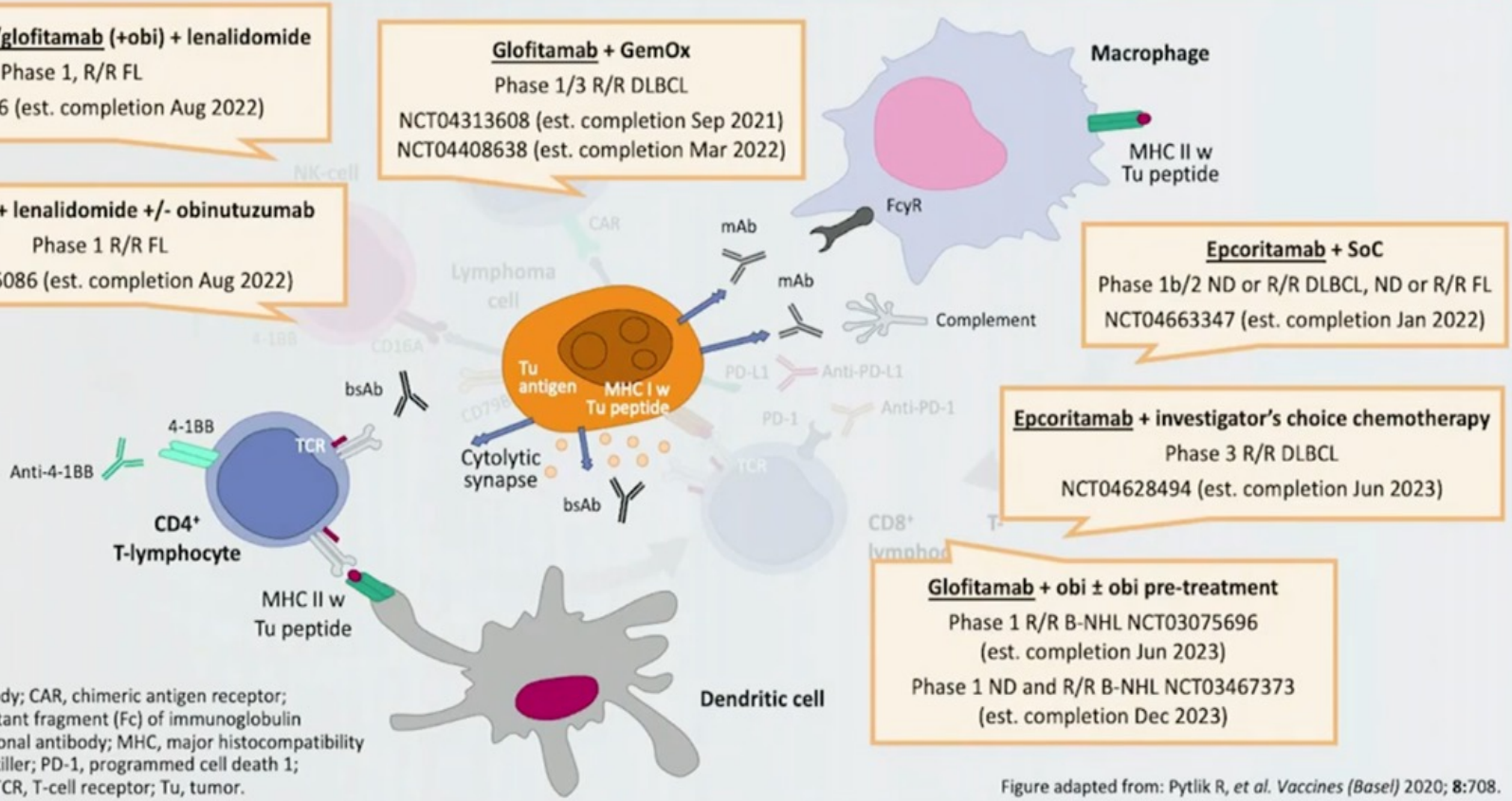
Glofitamab + GemOx
Phase 1/3 R/R DLBCL
NCT04313608 (est. completion Sep 2021)
NCT04408638 (est. completion Mar 2022)

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 Combination with Polatuzumab Vedotin: Phase Ib/IIb in R/R 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:

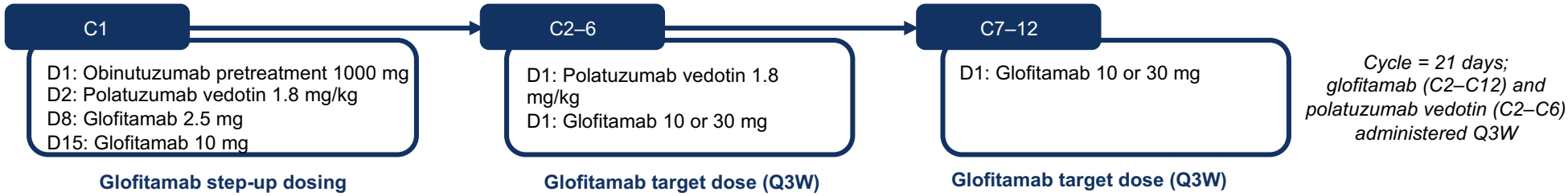
- DLTs
- Determine MTD and/or RP2D for Glofit + Pola (including obinutuzumab pretreatment)

Secondary:

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

Glofit + Pola administration in R/R DLBCL

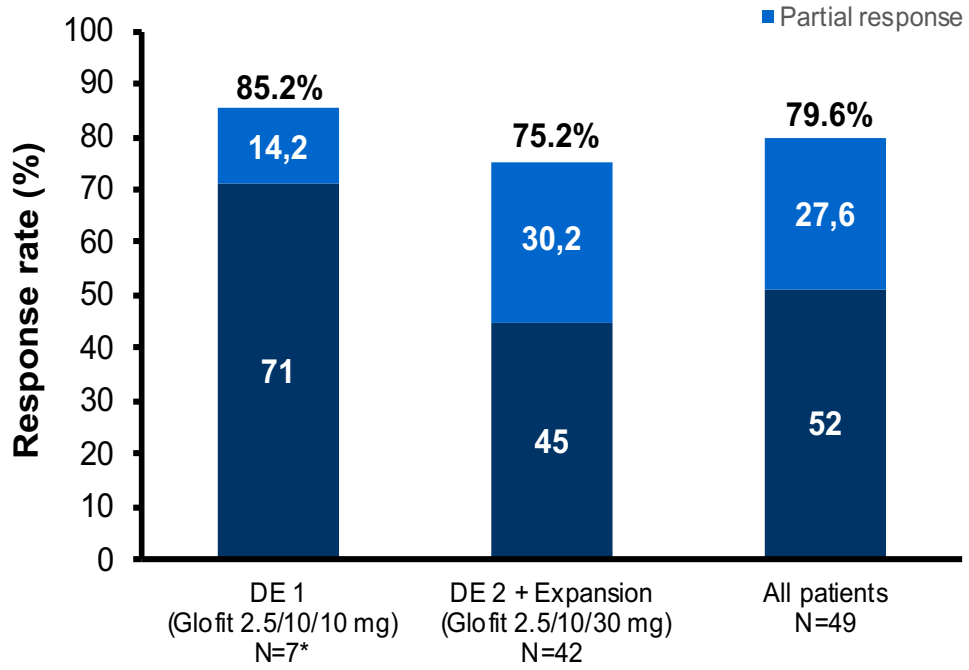
- Target enrollment ~90 patients
- CRS mitigation: obinutuzumab IV 1000 mg 7 days prior to glofitamab administration (step-up dosing)
- Efficacy assessments with PET-CT C3D1, C6D1 C8D15, EOT and Q3M

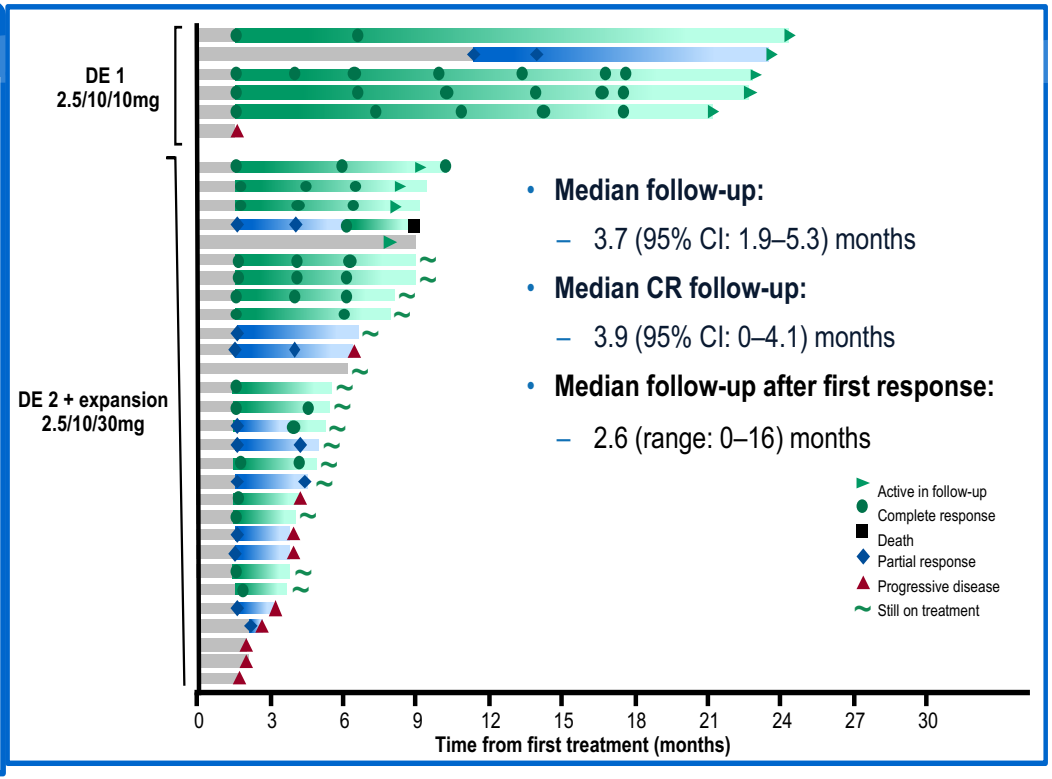


Hutchings M et al. Abs#525, ASH 2021.

Glofitamab in Combination with Polatuzumab Vedotin: Phase Ib/IIb in R/R DLBCL

Response rate by Glofit + Pola dosing cohort





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

Clinical trials with targeted BCR inhibition in combination

Targets	Drug/Regimen	Clinical Trial	Phase	Nb Pts	Status	Conditions	Response Data	References
BTK PD1	Acalabrutinib + Pembrolizumab	NCT02362035	1 & 2	161	Active	R/R DLBCL	ORR 26% Discontinuation was due to PD (62%) and AEs (26%)	[153]
BTK	Acalabrutinib + R-CHOP	NCT03571308	1 & 2	39	Active	nHL	NA	NA
BTK	Ibrutinib + R-CHOP	NCT01855750	3	838	Completed	B-cell Lymphomas	ORR 93.6%	[154]
BTK	Ibrutinib + R-ICE	NCT02219737	1	26	Completed	DLBCL	ORR 90%	[155]
BTK	Ibrutinib + CAR-T cell	NCT05020392	3	24	Active	DLBCL, MCL, CLL, SLL, BL	ORR 83%	[156]
BTK PDL1 4-1BB CD20	Ibrutinib + Avelumab + Utomilumab + Rituximab	NCT03440567	1	16	Active	R/R DLBCL, R/R MCL, Transformed FL	NA	NA
BTK	Ibrutinib + Immuno-chemotherapy	NCT02055924	1	85	Terminated	B-cell Lymphomas	CR 42% PR 25% Terminated due to due to veno occlusive disease	[157]
BTK JAK1	Ibrutinib + Itacitinib	NCT02760485	1 & 2	33	Active	B-cell Lymphomas	ORR 24%	[158]
BTK	Ibrutinib + Lenalidomide	NCT01955499	1	34	Active	R/R DLBCL, R/R FL, R/R MZL, R/R MCL	NA	NA
BTK CD20	Ibrutinib + Rituximab	NCT01980654	2	80	Completed	B-cell Lymphomas	ORR 85–75%	[159]

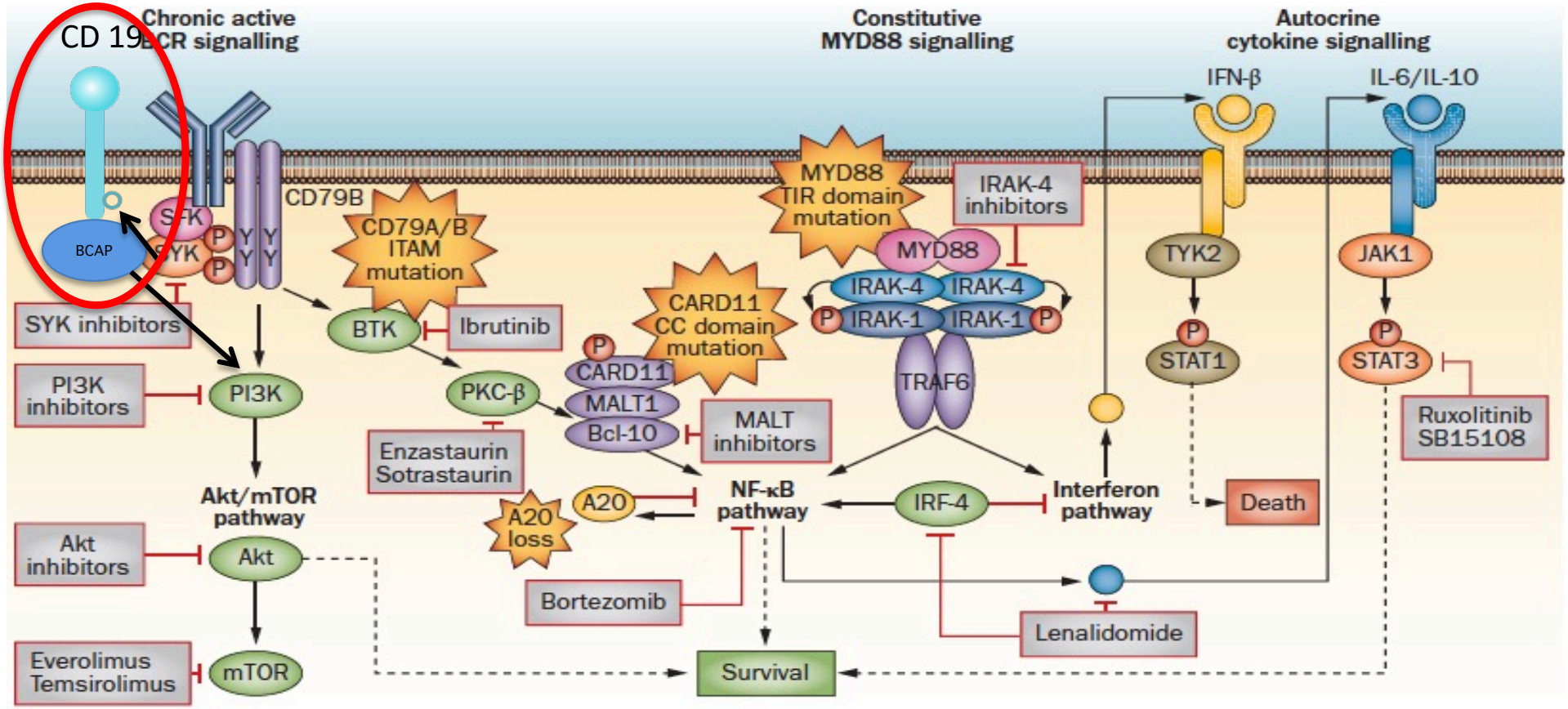
Profitos Peleja et al. Cancers 2022.

Clinical trials with targeted BCR inhibition in combination

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]

Profitos Peleja et al. Cancers 2022.

…adding mAb antiCD19?

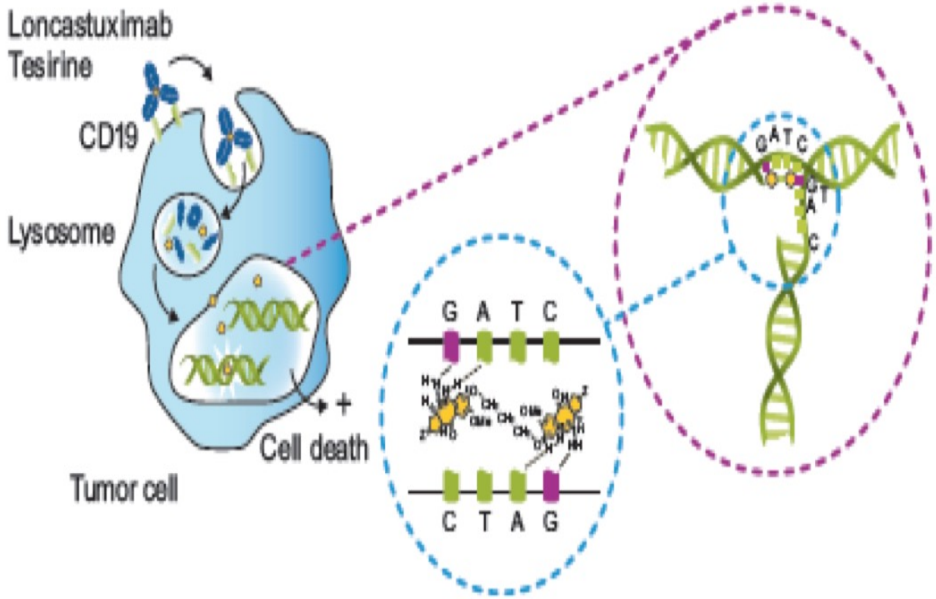


Roschewski M, Staudt LM, Wilson WH, Nat. Rev. Clin. Oncol. 2013.

…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.

Mechanism of action of Lonca



Tafasitamab (Fc-enhanced, anti-CD19 mAb)[1-3]

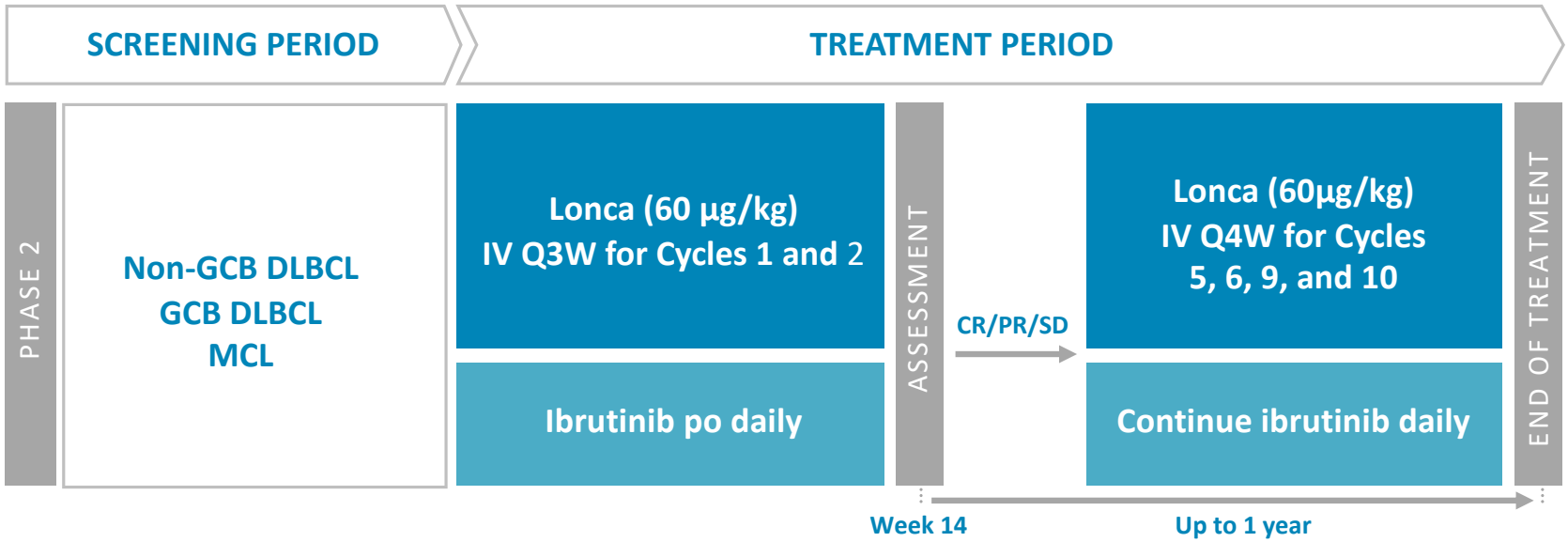
- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single-agent activity in patients with R/R DLBCL and iNHL

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

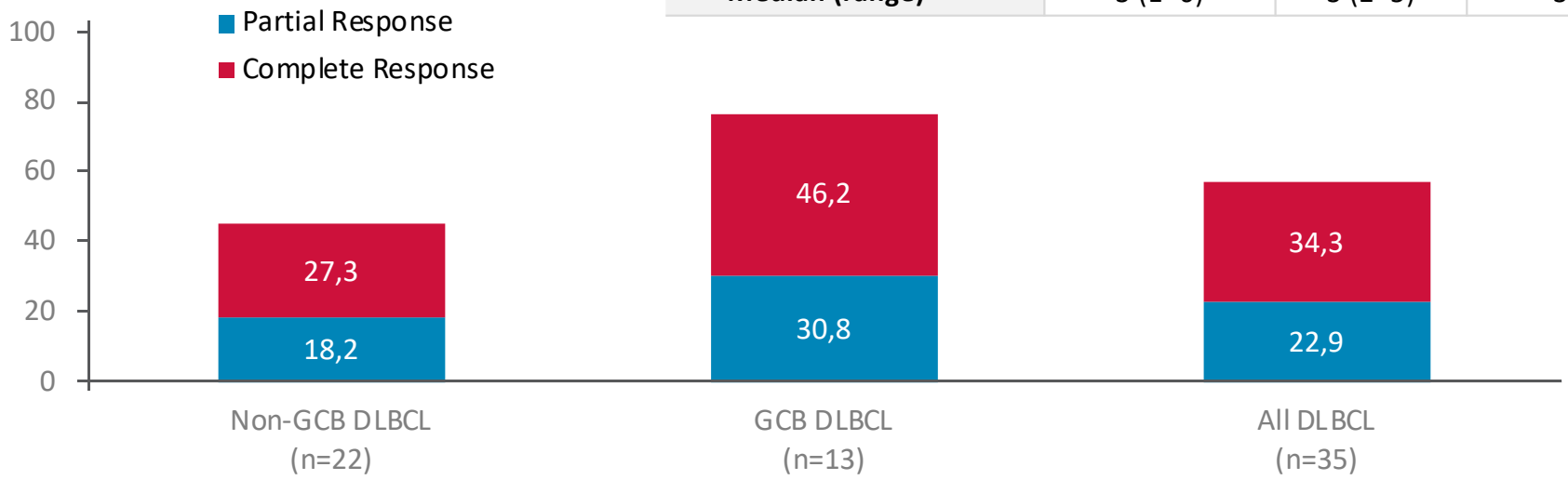
Carlo-Stella C, Abs#0054, ASH 2021

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)

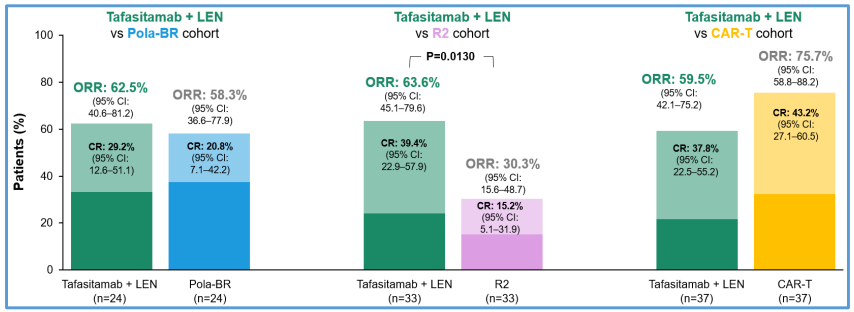


ORR (n/N) (95% CI)[b]	**45.5%** (10/22) (24.4, 67.8)	**76.9%** (10/13) (46.2, 95.0)	**57.1%** (20/35) (39.4, 73.7)

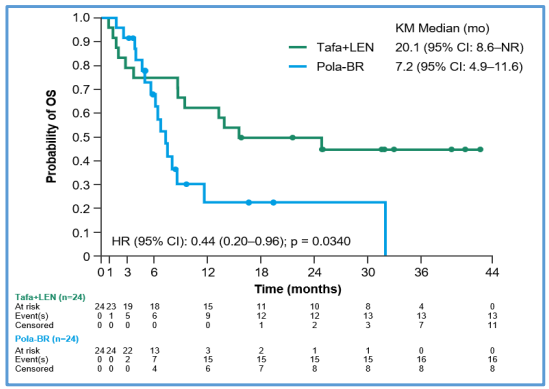
Carlo-Stella C, Abs#0054, ASH 2021

RE-MIND2: Tafa-Len vs. Pola-BR, R2, and CAR T in RR-DLBCL

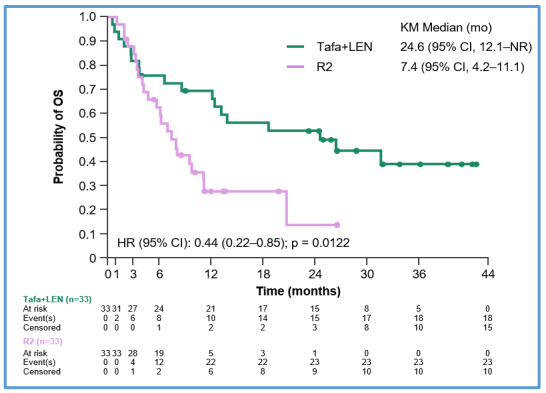
Observational, Retrospective Cohort Study in RR-DLBCL



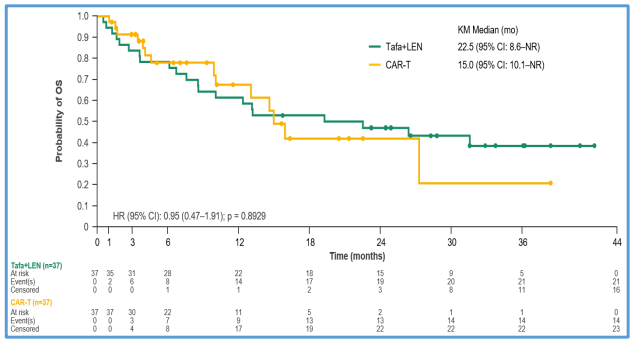
Tafa +Len vs Pola BR



Tafa +Len vs R2



Tafa +Len vs CART



- ORR: **62.5% for taf + LEN vs 58.3% for pola-BR, 63.6% vs 30.3% for R2,** and **59.5% vs 75.7% for CAR-T**
- OS: significant benefit was associated with taf + LEN vs pola-BR and vs R2 (HR: 0.44 in both matched comparisons)
  - There was no significant difference in OS benefit between taf + LEN vs CAR-T (HR: 0.95)

Nowakowski G, Abs#183, ASH 2021

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]

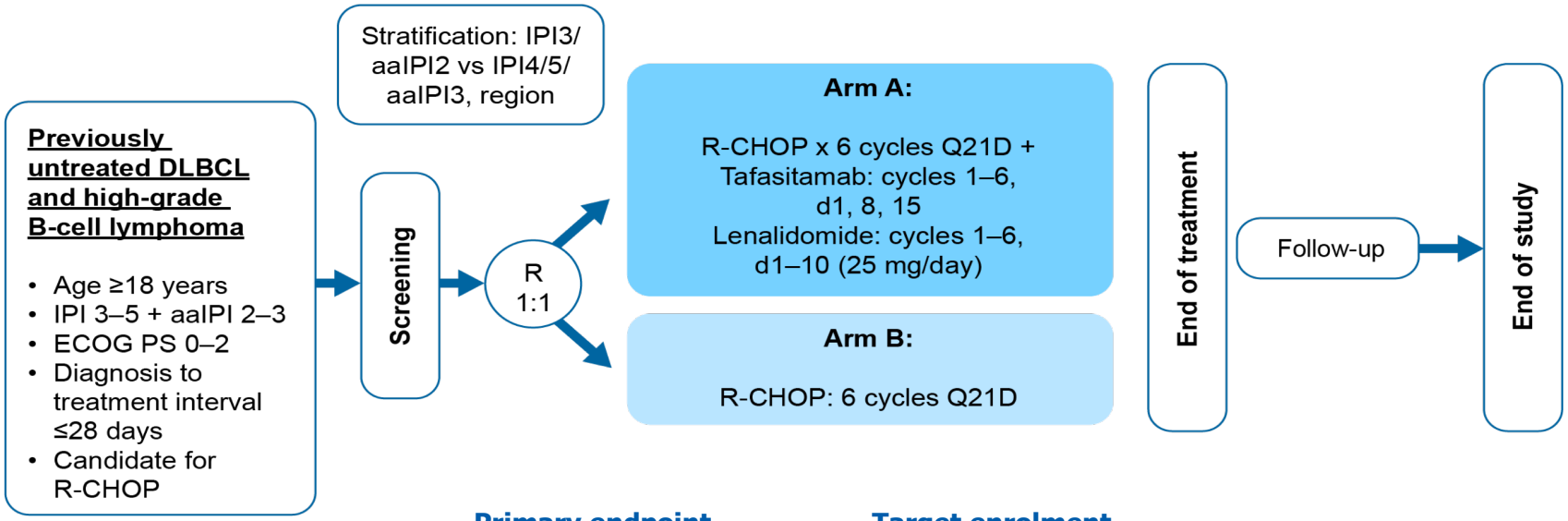
- Phase 1b: incidence and severity of TEAEs and incidence of DLTs
- Phase 2a: ORR

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

- ✓ DLBCL is a heterogenous disease, and a more accurate recognition of unfavourable DLBCL subsets is recommended to better tailor the treatment
- ✓ R-chemotherapy is the backbone of treatments with novel drugs, but randomized trials with «X» + R-CHOP have failed.
- ✓ New study designs potentially focused on mutational alterations with combination of multiple novel drugs may have a greater chance of success.
- ✓ The addition of mAb anti-CD19 could represent the keystone in the treatment of DLBCL.

Aknowledgments

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