9th POSTGRADUATE
Lymphoma
Conference

Frontline Treatments in DLBCL: Current scenario, ongoing trails speculations and potential future vision

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Mayo Clinic

Florence,
March 20-21, 2025

Hotel Brunelleschi

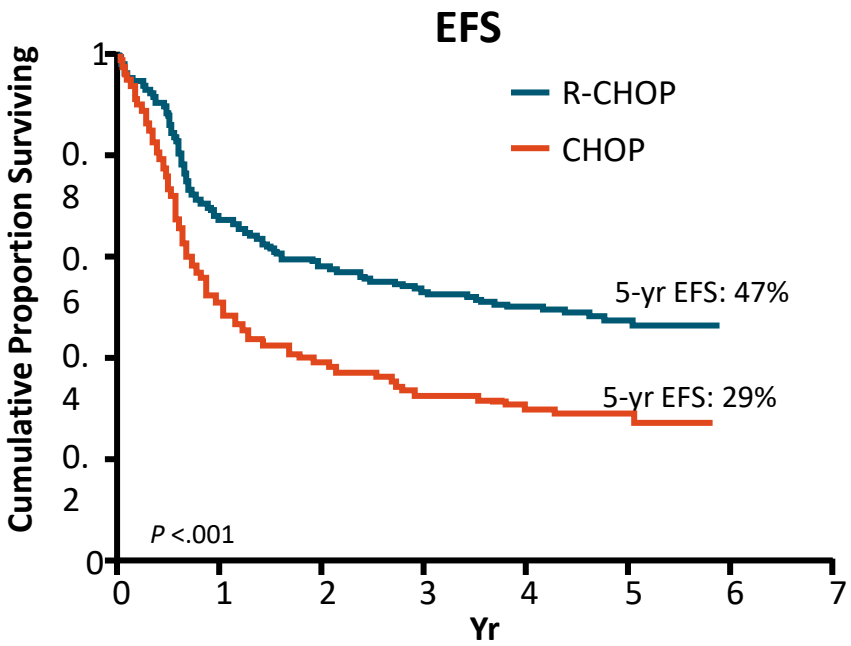
President:
P.L. Zinzani

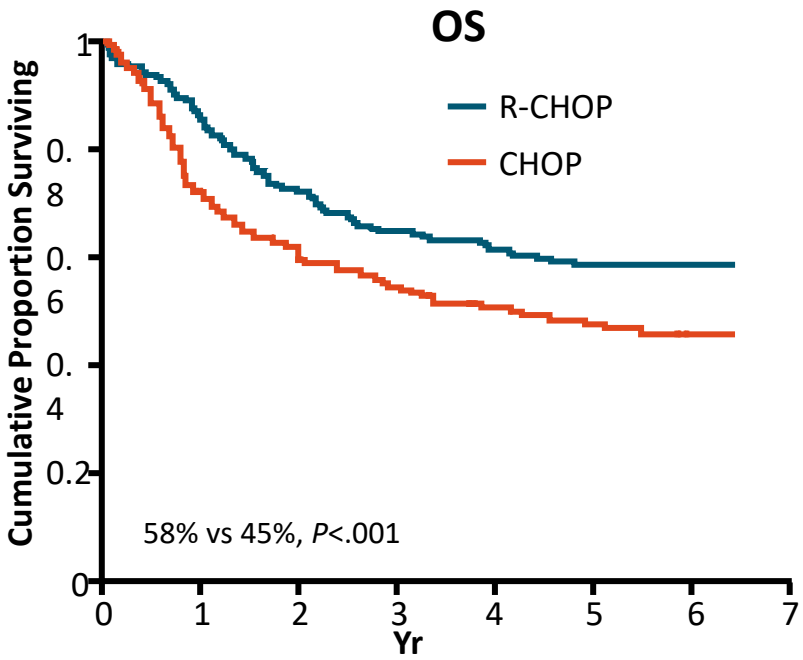
Disclosures of Grzegorz S. Nowakowski

Employment: None
Consultancy: AbbVie, ADC Therapeutics, Bantam Pharmaceutical LLC, Blueprint Medicines, Bristol-Myers Squibb, Celgene Corporation, Curis, Debiopharm, F Hoffmann-La Roche Limited, Fate Therapeutics, Genentech, Genmab, Incyte, Karyopharm Therapeutics, Kite Pharma, Kymera Therapeutics, MEI Pharma, MorphoSys AG, Regeneron, Roche, Ryvu Therapeutics, Seagen, Selvita Inc, TG Therapeutics, and Zai Lab Limited
Equity Ownership: None
Research Funding: None
Honoraria: None
Patents & Royalties: None
Speakers Bureau: None
Membership on an entity's Board of Directors or standing advisory committees:, Ryvu Therapeutics, Fate Therapeutics, Bristol-Myers Squibb, Genmab, Genetech, AbbVie, Regeneron, Novou Therapeutics

R-CHOP Has Been the Standard Initial Therapy for DLBCL for >20 Yr

- Long-term outcomes from randomized study of 399 previously untreated patients with DLBCL





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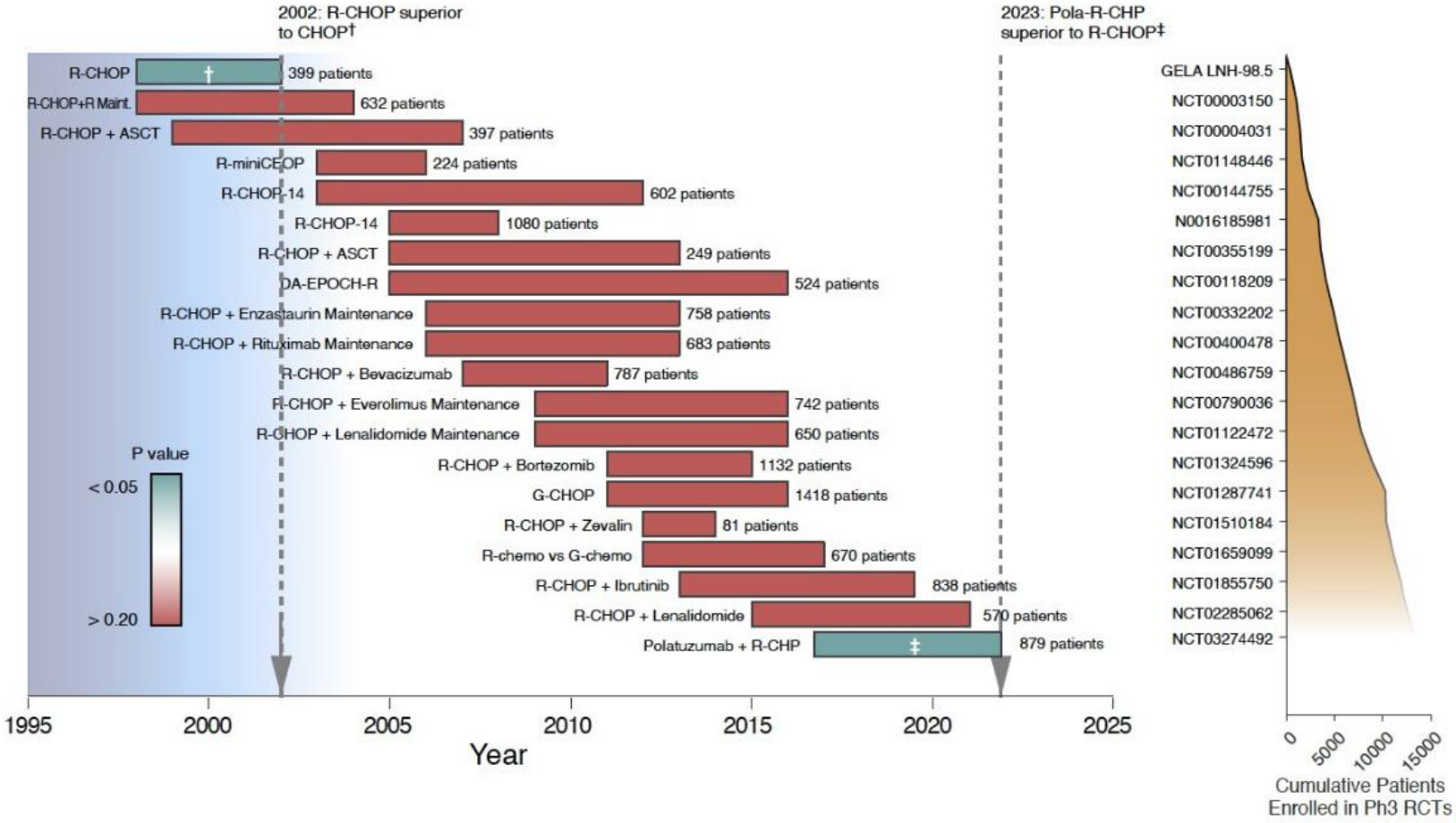
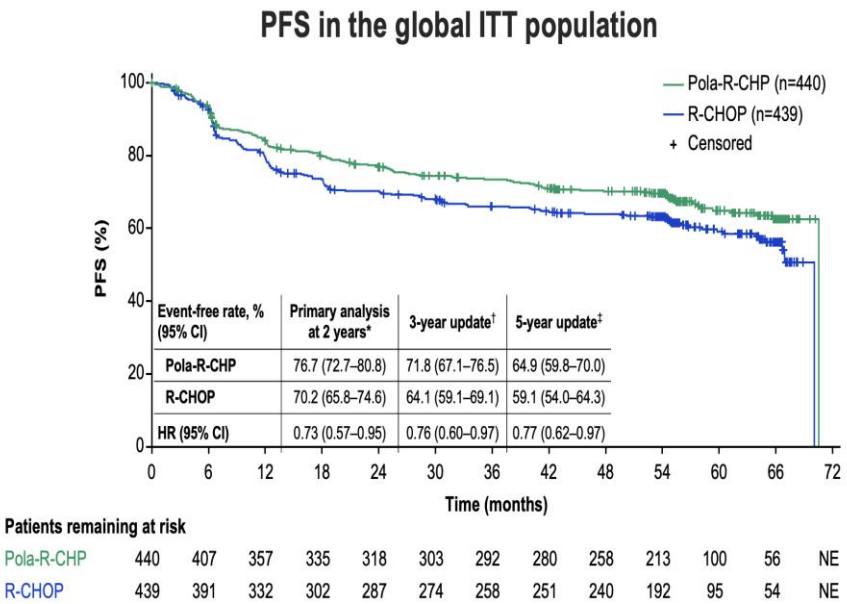
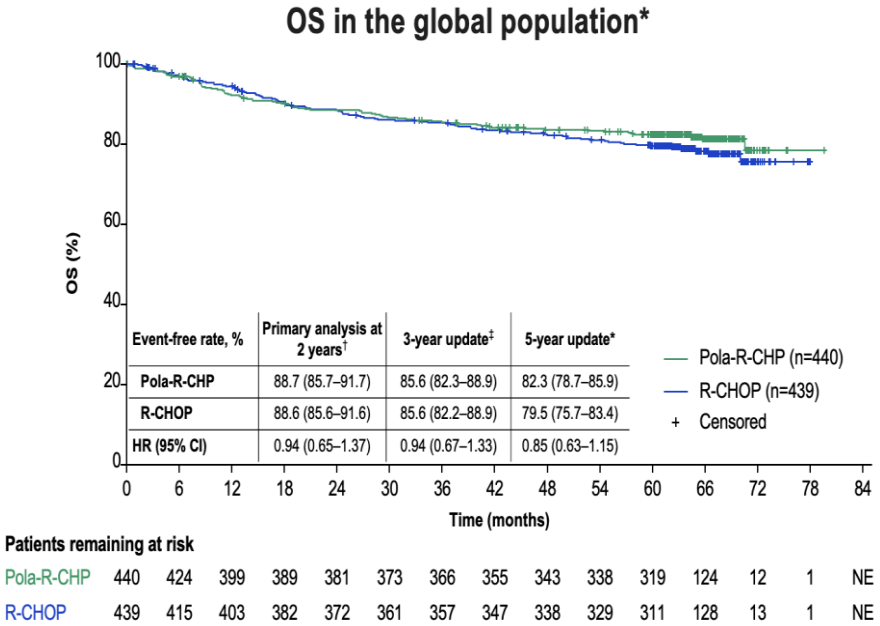


After Alizadeh and Kurtz; NEJM 2023

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP

5-year follow up





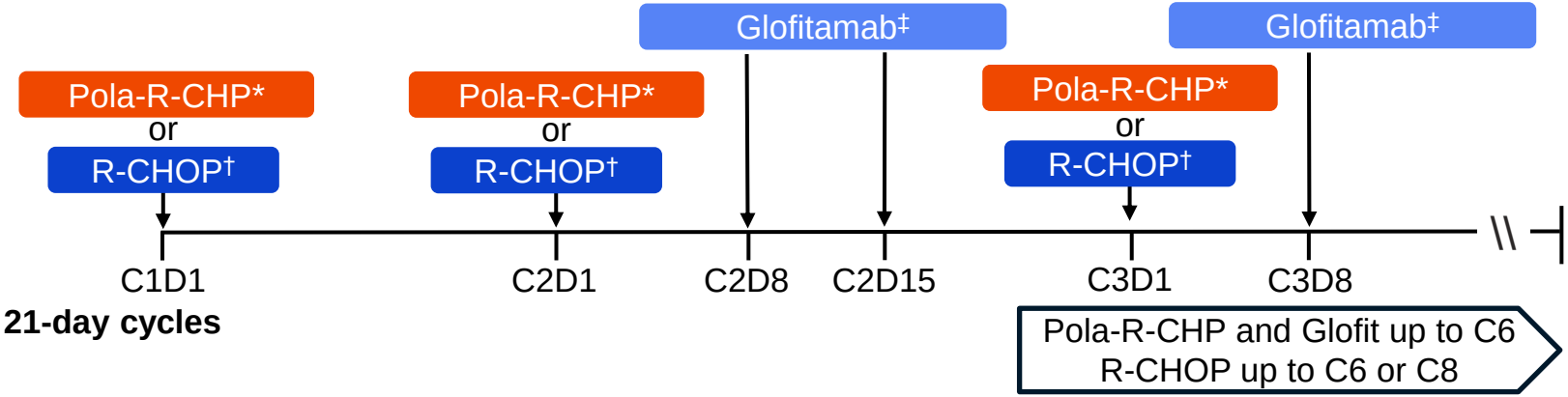
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351, Salles ASH2024.

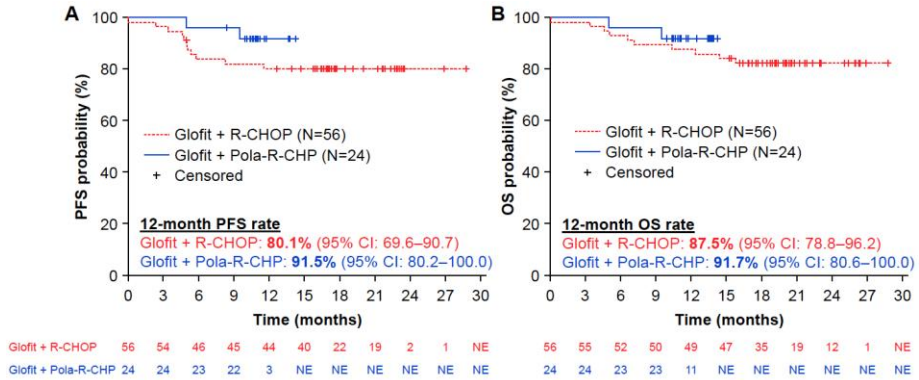
Chemoimmunotherapy backbone in clinical trails

RCHOP vs Pola RCHP

Glofit + R-CHOP and Glofit + Pola-R-CHP in 1L DLBCL

Glofit + R-CHOP and Glofit + Pola-R-CHP administration



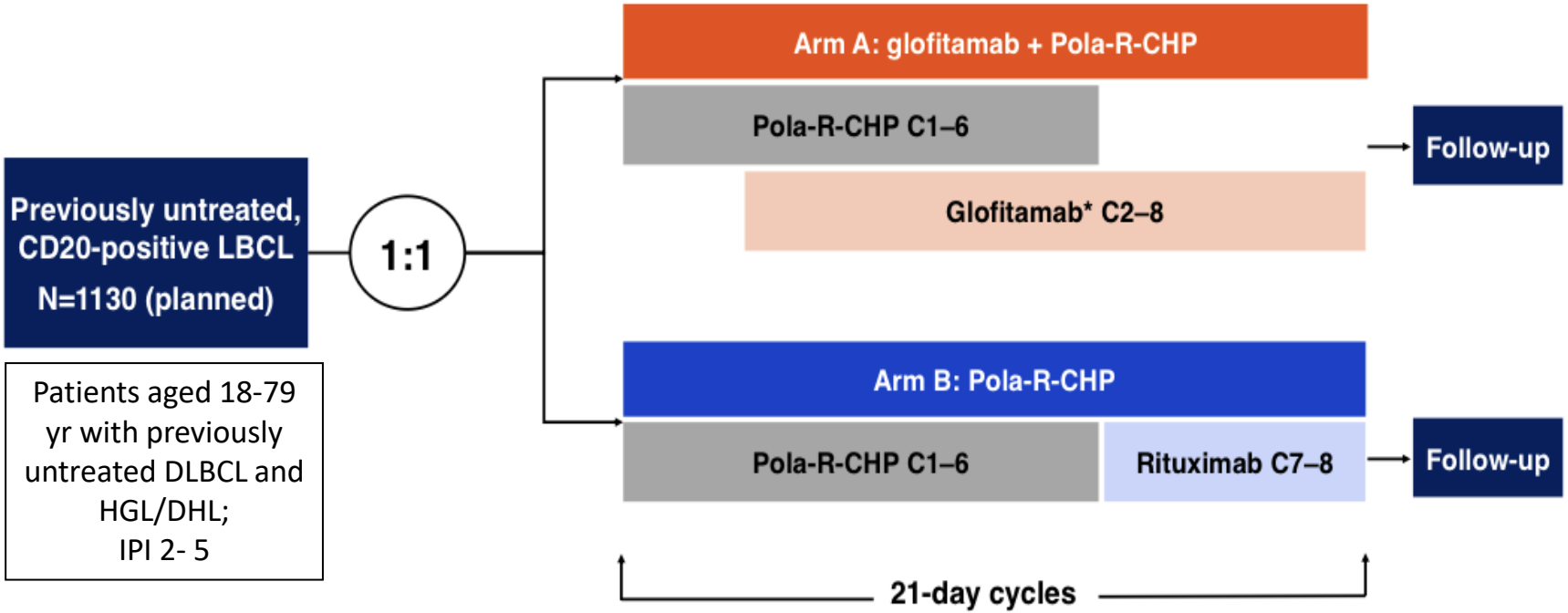


NCT03467373

1. Topp MS, et al. Blood 2022;140:1775–7;
2. Dickinson MJ, et al. J Clin Oncol 2023:7549.

SKYGLO (NCT06047080) is a Phase III, multicenter, randomized, open-label trial of Pola-R-CHP with or without glofitamab in 1L LBCL.

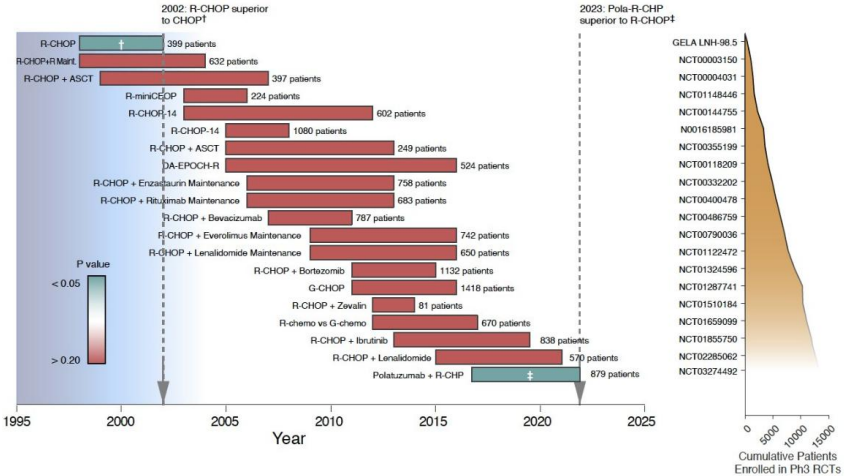
Study design



Patients aged 18-79 yr with previously untreated DLBCL and HGL/DHL;
IPI 2- 5

*Administered with step-up dosing. C, cycle.

Beyond RCHOP – RCHOP Backbone Dominates in RP3



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R-CHOP+ Acala — 600 patients

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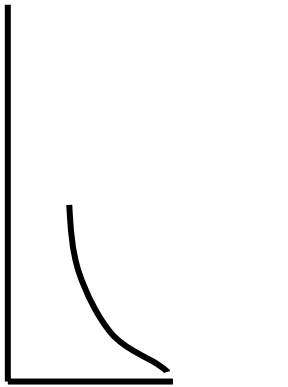


RCHP Backbone

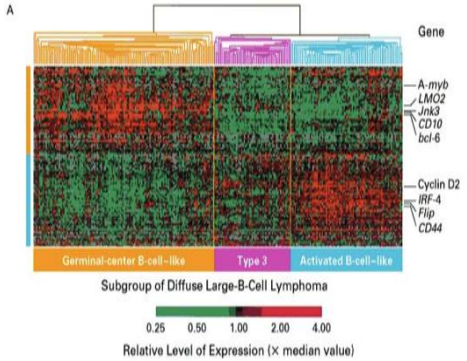
RCHOP vs Pola V-RCHP in ongoing studies

- RCHOP acceptable control arm
  - Studies are complicated depending on region and Pola-V approval status
- Pola-V activity in ABC DLBCL could affect control arm PFS in studies focusing on non-GCB/ABC subtypes

Patient selection:

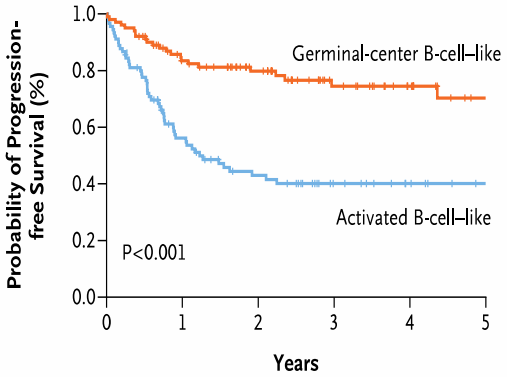
IPI and molecularly driven patient selection

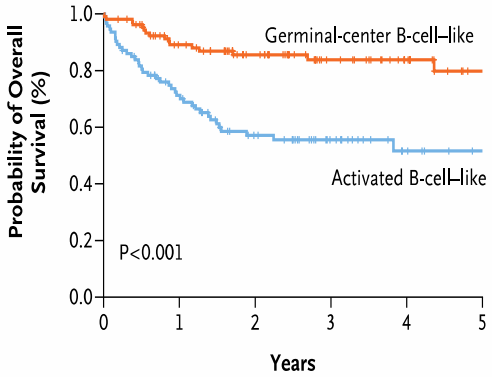
Cell of Origin Subtypes in DLBCL – Over 25 Years in Making



Two major molecular subtypes:

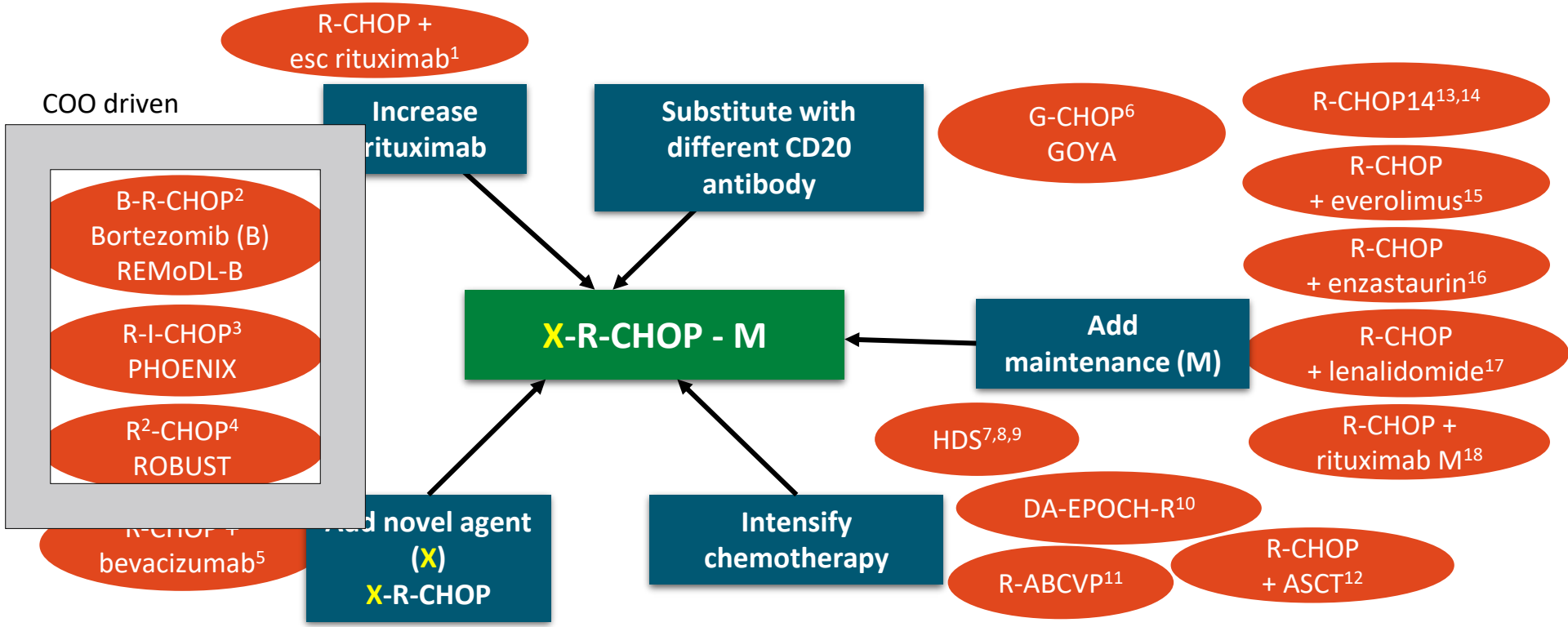
- Activated B-cell like (ABC)
  - B-cell receptor driven
- Germinal center B-cell like (GCB)





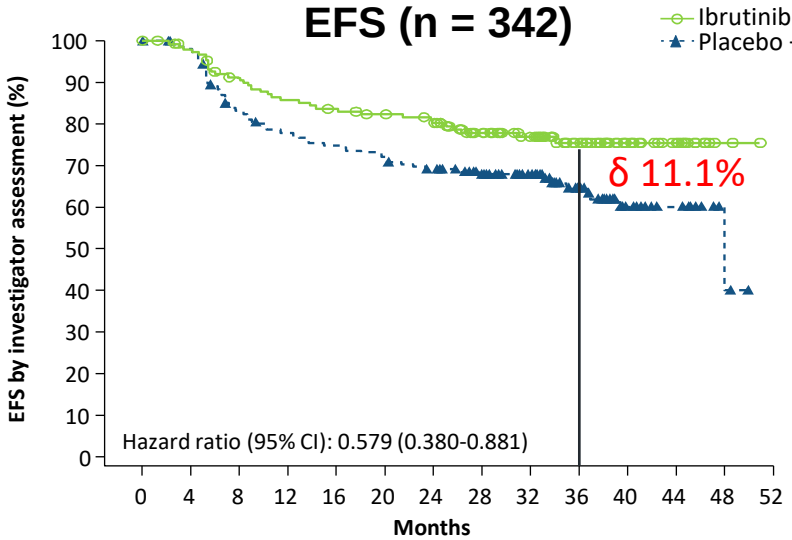
Lenz et al. N Engl J Med 2008;359:2313–2323.

Improving on R-CHOP in DLBCL



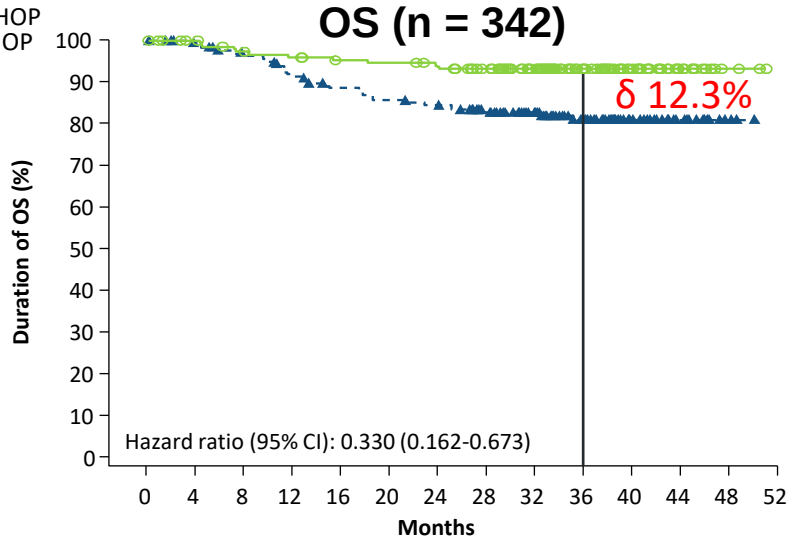
1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 10. Wilson. Blood. 2016;128:469. 11. Casasnovas. Blood. 2017;130:1315. 12. Stiff. NEJM. 2013;369:1681. 13. Delarue. Lancet Oncol. 2013;14:525. 14. Cunningham. Lancet. 2013;381:1817. 15. Witzig. Ann Oncol. 2018;29:707. 16. Crump. JCO. 2016;34:2484. 17. Thieblemont. JCO. 2017;35:2473. 18. Jaeger. Haematologica 2015;100:955.

EFS and OS in Patients < 60 Years



Patients at risk

Ibrutinib + R-CHOP	156	146	133	125	121	117	113	93	72	44	27	13	2	0
Placebo + R-CHOP	186	177	148	137	132	127	120	104	78	52	24	16	3	0

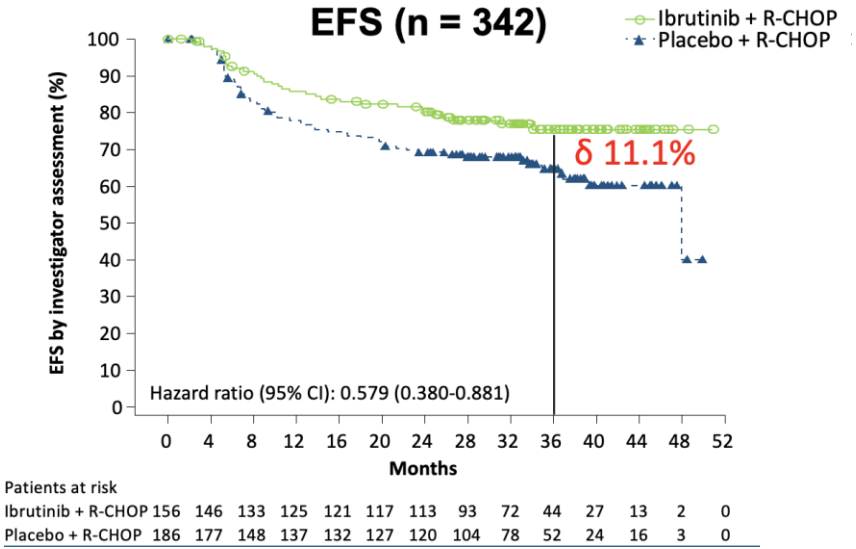


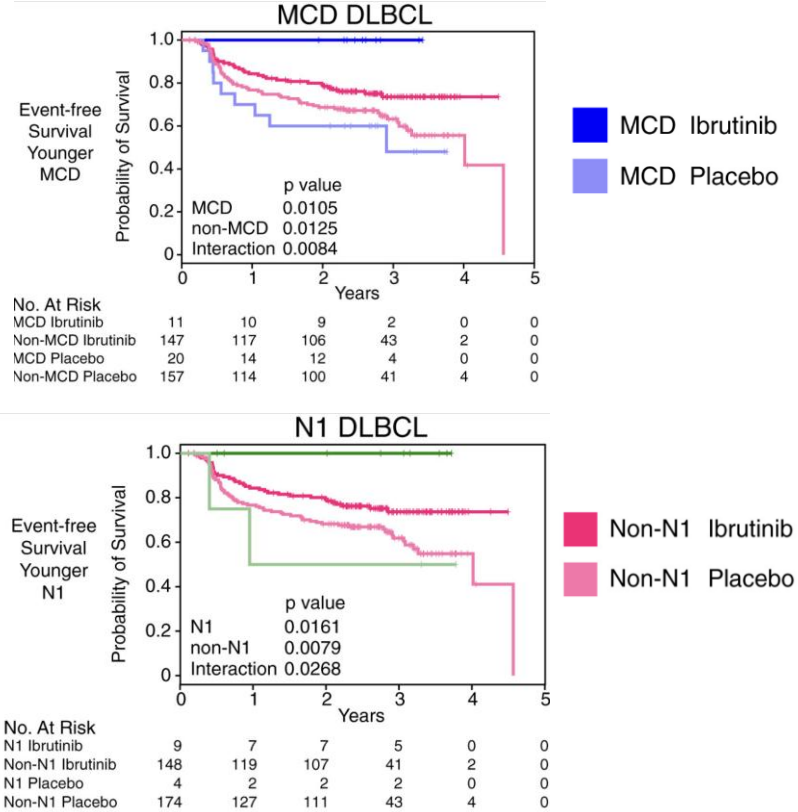
Patients at risk

Ibrutinib + R-CHOP	156	151	145	142	138	137	134	125	96	62	39	18	3	0
Placebo + R-CHOP	186	181	173	161	153	148	145	130	101	70	38	21	5	0

Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

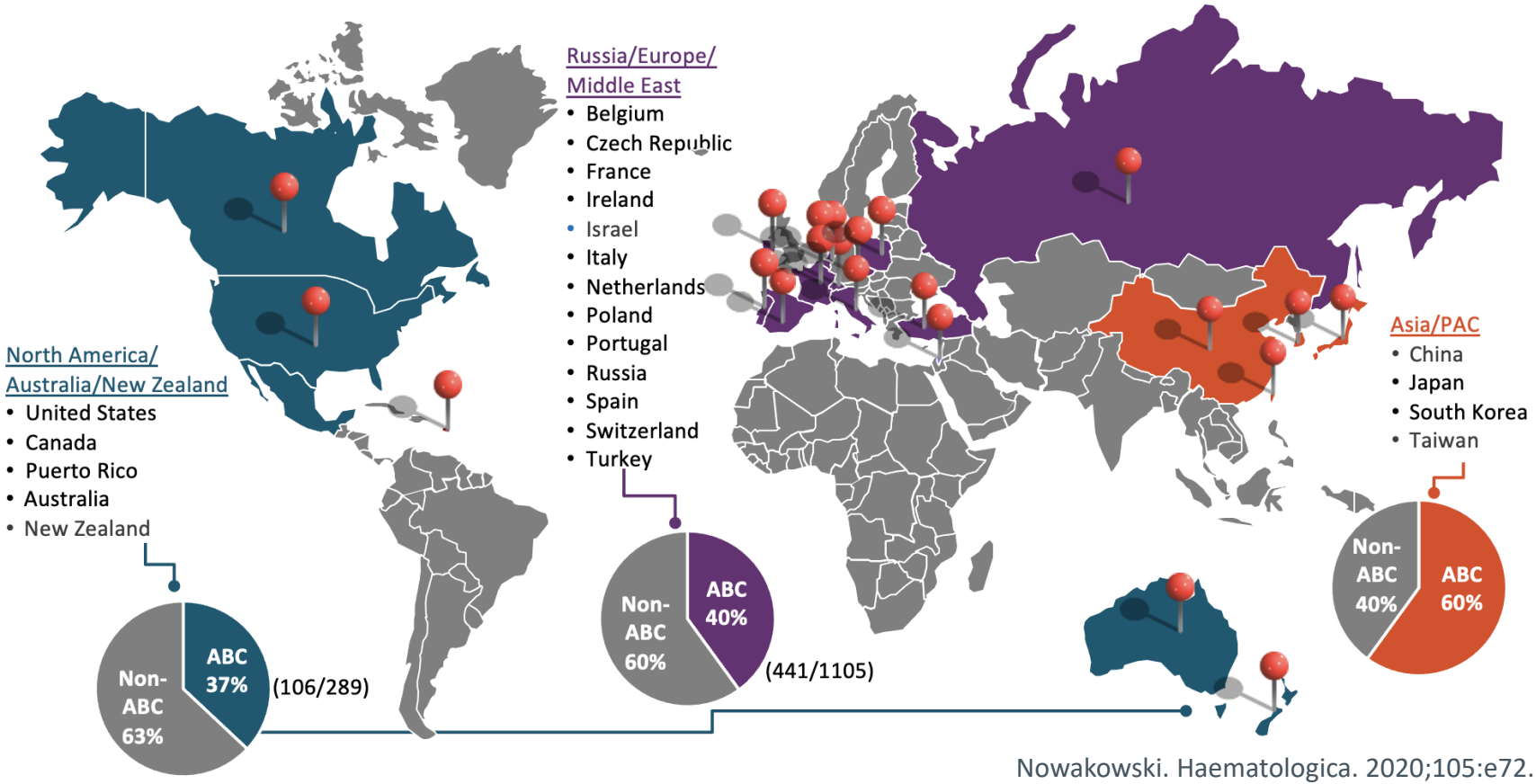
Ibrutinib plus RCHOP in Patients < 60 Years and MCD/N1





Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

ROBUST Trial: Geographical Distribution of Cell of Origin in DLBCL



Nowakowski. Haematologica. 2020;105:e72.

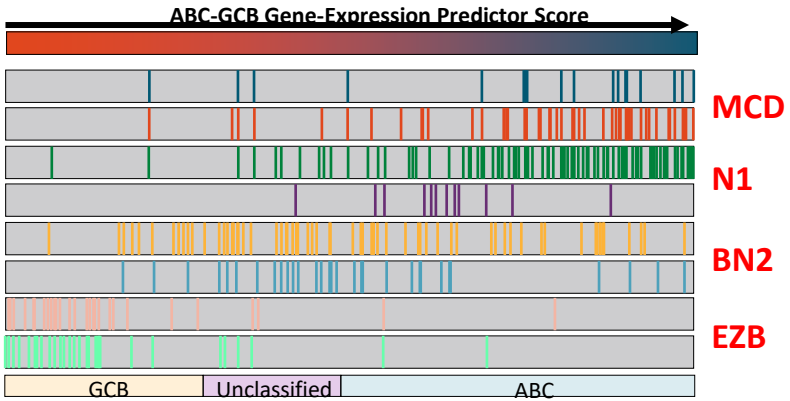
BTK inhibitors plus RCHOP approaches

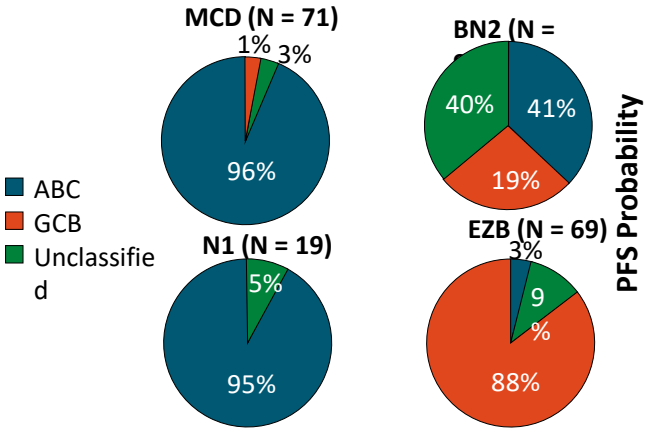
- **Younger patients**
  - Phase 3 study**, <65 (now 70) yo, non-GCB** : Acalabrutinib (A)R-CHOP vs RCHOP (Escalade)

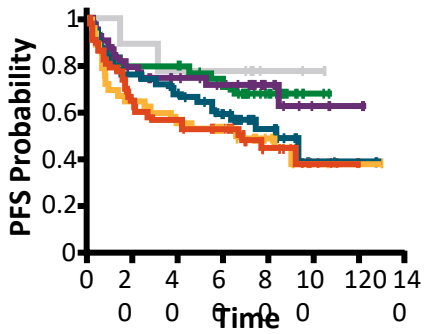
- **Deeper molecular profiling**
  - Phase 3 Orlelabrutinib plus RCHOP vs RCHOP in **MCD subtype** of DLBCL (Belive 01) (NCT05234684) – stopped
  - Guidance 2 – one of the arms

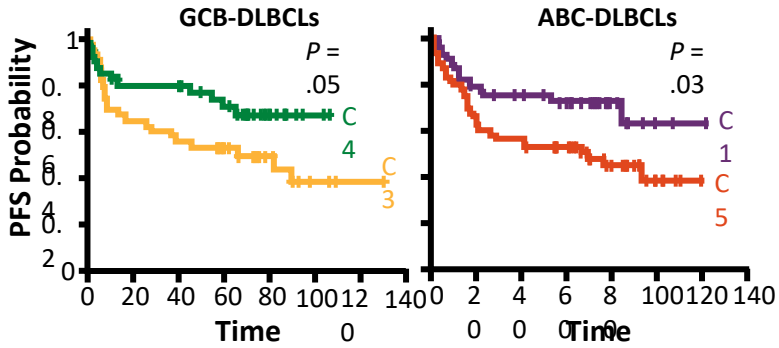
Integrated Genomic Analyses Identify Subgroups Within and Distinct From Cell of Origin

Genetic Feature	Log_{10} *P* Value	GCB	Unclassified	ABC
		Prevalence (%)		
CD79B+MYD88^{L265P} double mutation	-0.4	0.6	1.7	11.5
CD79B mutation	-13.8	0.6	6.1	25.4
MYD88^{L265P} mutation	-17.0	1.2	7.8	28.8
NOTCH1 mutation	-3.8	0.0	0.9	6.1
BCL6 fusion	-4.1	11.6	33.0	18.6
NOTCH2 mutation	-5.3	3.0	20.0	6.4
BCL2 translocation	-20.4	28.0	5.2	0.7
EZH2 mutation	-12.1	22.0	5.2	1.7





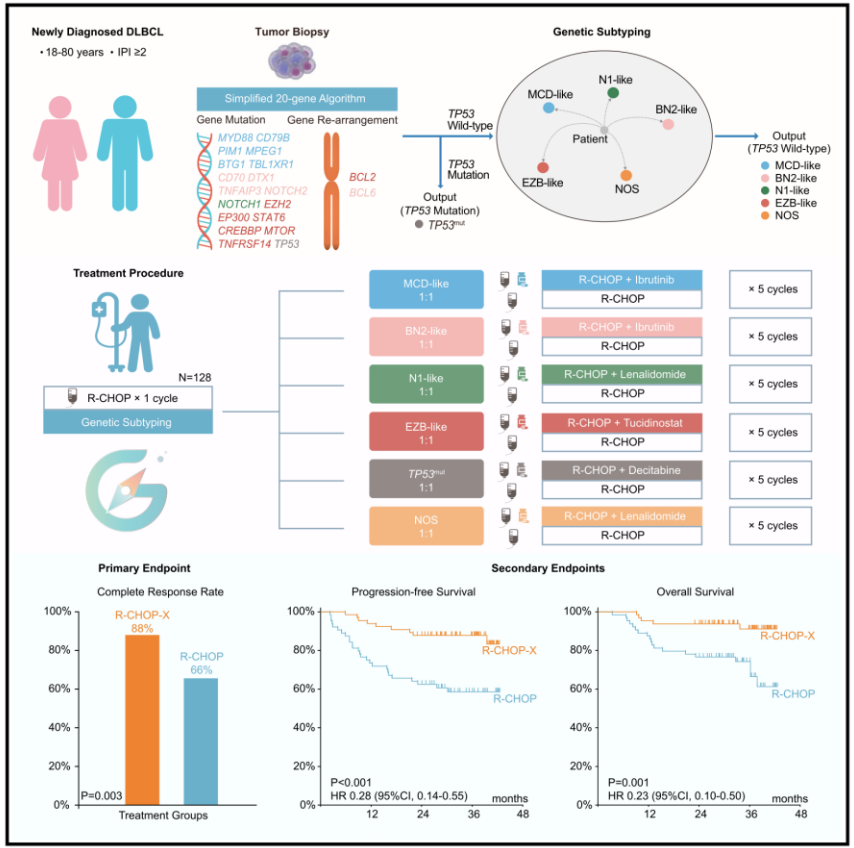




Chapuy. Nat Med. 2018;24:679. Schmitz. NEJM. 2018;378:1396.

RCHOP vs RCHOP + Molecularly Selected X

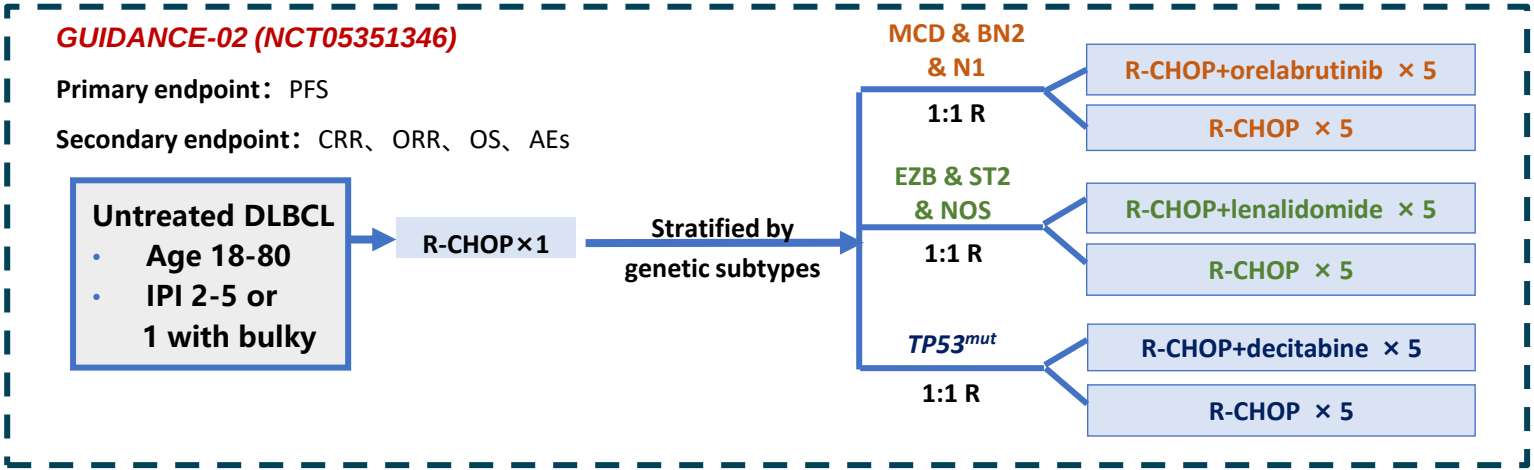
Guidance-01



- ECOG-ACRIN working on molecularly targeted design with each arm independently powered
- Major limitation feasibility of molecular assessment
  - Looking into liquid bx vs tissue-based classifier

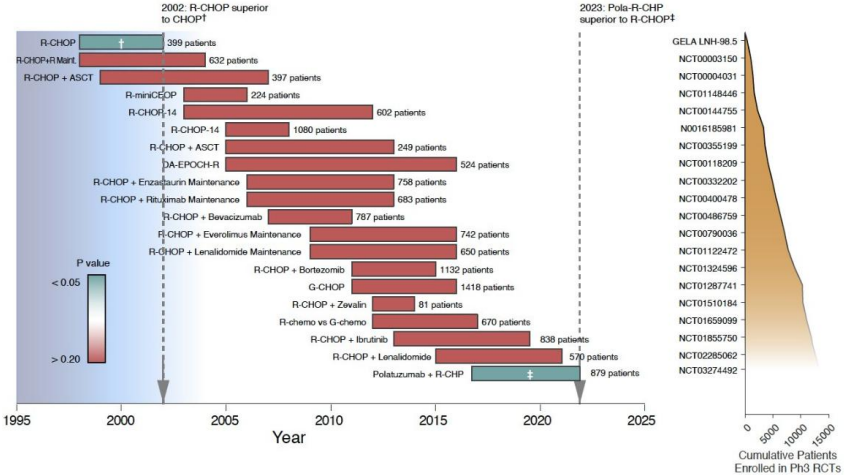
Zhang et al., 2023, Cancer Cell 41, 1705–1716

Ongoing multicenter trials: The *GUIDANCE-02* study



Thanks to Peng P and Zhao WL \

Beyond RCHOP – Subtype Driven vs Agnostic



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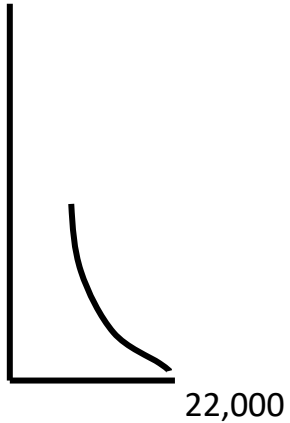
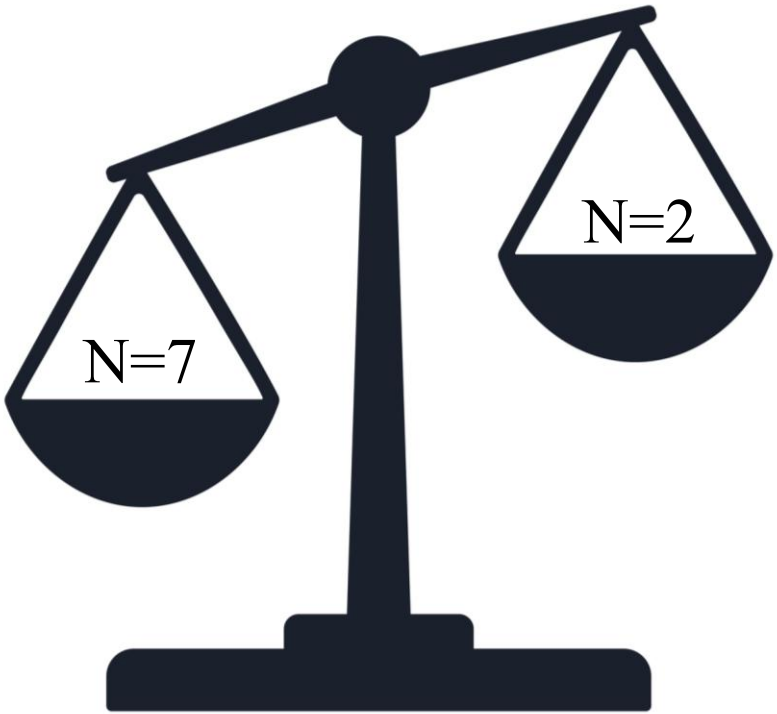


RCHP Molecularly driven

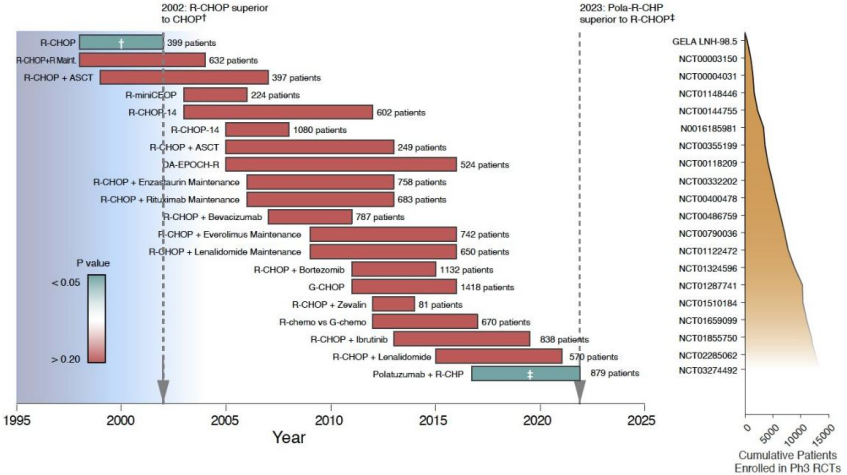
Front Line Subtype Driven vs Agnostic



Biological subtype specific

Biological subtype agnostic

Beyond RCHOP – IPI



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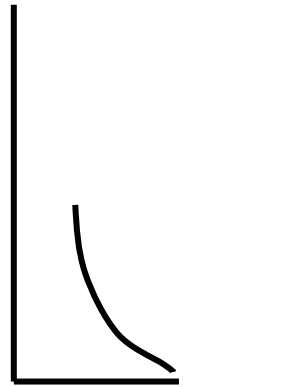


IPI 1*-5

IPI 2-5

IPI 3-5

IPI 4-5

* High risk IPI 1 and 2

High Risk Low IPI in Golcadomide plus RCHOP vs RCHOP Trial

GOLSEEK-1 trial design

Key eligibility criteria
- Previously untreated LBCL (WHO 2022 classification[a])
- IPI 1-2 HR or 3-5
- Age 18-80 years
- ECOG performance status 0-2
- Measurable disease per Lugano response criteria

R 1:1

Stratification factors
- IPI 1-2 HR and 3 vs 4-5
- Bulky disease > 7 cm vs ≤ 7 cm

Golcadomide (0.4 mg) + R-CHOP (6 cycles)

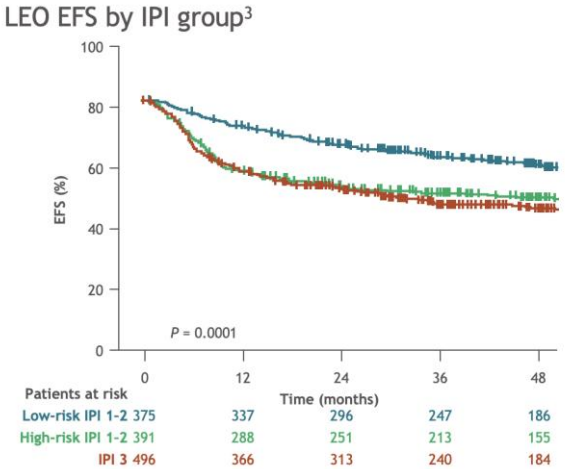
Placebo + R-CHOP (6 cycles)

Primary endpoint
- PFS by investigator

Key secondary endpoints
- OS
- EFS by investigator
- CMR by IRAC
- uMRD at EOT

Vassilakopoulos T, Nowakowski GS. EHA Abstract PB3076.

The presence of bulky disease and/or very high LDH defines a high-risk subset of IPI 1-2 for eligibility in clinical trials of newly diagnosed aggressive B-cell lymphoma.



Maurer MJ et al, *Blood* 2023;142(suppl 1):4512-4514

Dose optimization in front like studies – totality of evidence or gut feeling

Project Optimus

eforming the dose optimization and dose selection paradigm in oncology

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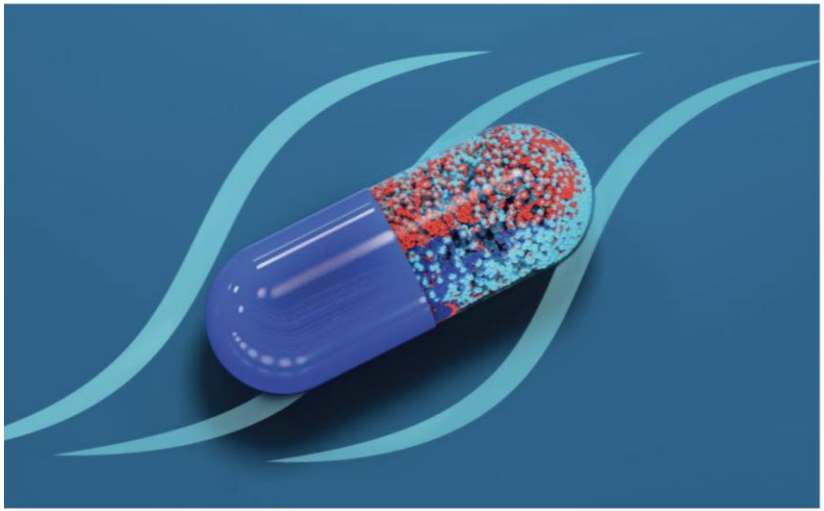
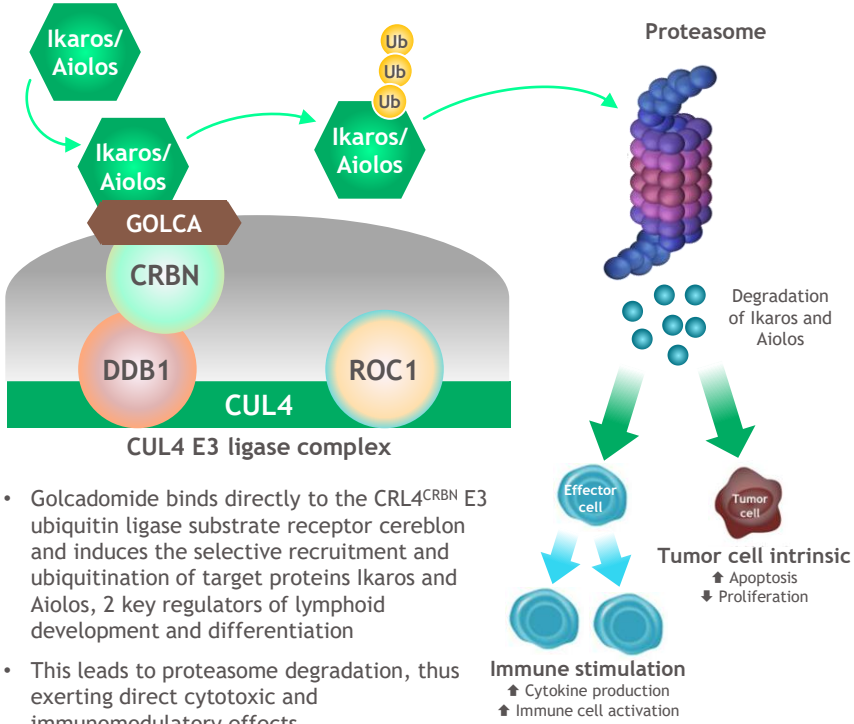


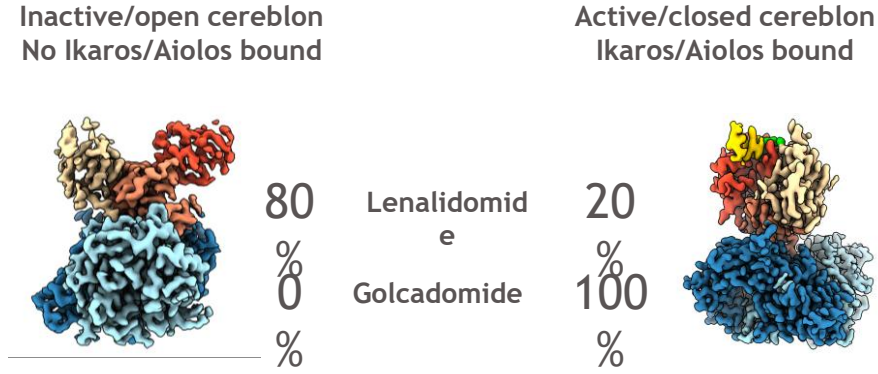
Golcadomide as a potential first-in-class oral CELMoD™ agent for NHL

Mechanism of action[1]



- Golcadomide binds directly to the CRL4^{CRBN} E3 ubiquitin ligase substrate receptor cereblon and induces the selective recruitment and ubiquitination of target proteins Ikaros and Aiolos, 2 key regulators of lymphoid development and differentiation
- This leads to proteasome degradation, thus exerting direct cytotoxic and immunomodulatory effects

Allosteric regulation of cereblon[1]



- Recent cryo-EM data indicate that the cereblon complex has both an ***open, inactive state*** and a ***closed, active state***[1]
- Due to the unique binding modes of golcadomide, it is significantly more efficient than lenalidomide at driving the closed conformation,[1] leading to deeper and more rapid degradation of Ikaros/Aiolos

CELMoD, cereblon E3 ligase modulator; CRBN, cereblon; CRL4^{CRBN}, CRL4 E3 ubiquitin ligase complex; CUL, cullin; cryo-EM, cryo-electron microscopy; DDB, DNA damage-binding protein; GOLCA, golcadomide; ROC, regulator of cullins; Ub, ubiquitin.

1. Bristol Myers Squibb. Data on file - study report 06C74.

Example of small molecule optimization – Golcadomide (CC282)

Screening period

Key eligibility criteria

- Age ≥ 18 years
- Diagnosis of a-BCL
- Measurable lesion ≥ 1.5 cm (CT/MRI)
- Previously untreated
- ECOG PS 0-2
- IPI score
  - Part 1: 0-5
  - Part 2: 2-5

Primary endpoints

- Part 1: MTD, RP2D
- Part 2: Safety and tolerability at RP2D

Secondary efficacy endpoints

- Best ORR, CMRR, DOR, PFS, OS

Treatment period

Dose escalation (Part 1) | Dose expansion (Part 2)

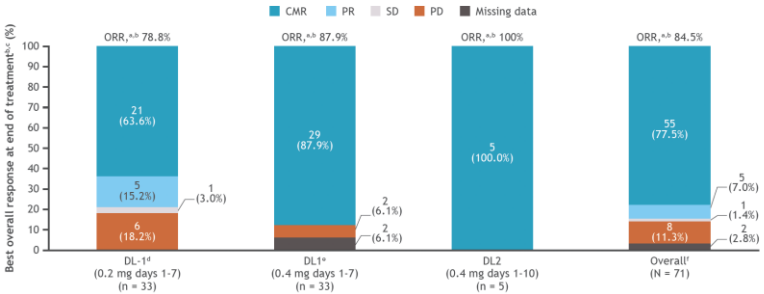
GOLCA + R-CHOP-21 (n = 78)

GOLCA dose levels
DL-1: 0.2 mg days 1-7
DL1: 0.4 mg days 1-7
DL2: 0.4 mg days 1-10

R[a]

GOLCA + R-CHOP-21 at RP2D-1

GOLCA + R-CHOP-21 at RP2D[b]



	GOLCA		Cyclophosphamide		Doxorubicin		Vincristine	
	DL-1[a] (n = 35)	DL1[b] (n = 37)	DL-1[a] (n = 35)	DL1[b] (n = 37)	DL-1[a] (n = 35)	DL1[b] (n = 37)	DL-1[a] (n = 35)	DL1[b] (n = 37)
Median relative dose intensity, %	98.4	97.1	98.4	98.9	99.4	99.1	92.8	99.2
Proportion of patients with relative dose intensity ≥ 85%, n (%)	32 (91.4)	31 (83.8)	32 (91.4)	33 (89.2)	31 (88.6)	35 (94.6)	23 (65.7)	32 (86.5)

a-BCL defined according to World Health Organization 2016 classification, including: DLBCL, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, primary mediastinal BCL, primary cutaneous DLBCL-leg type, ALK-positive large BCL, EBV-positive DLBCL, and grade 3b FL.

[a]Randomization for the purpose of dose optimization; [b]The safety review committee may reconsider the RP2D in regard to emergent AEs experienced from cycle 1 day 1 through completion of cycle 6.

a-BCL, aggressive B-cell lymphoma; AE, adverse event; ALK, anaplastic lymphoma kinase; BCL, B-cell lymphoma; CMRR, complete metabolic response rate; DL, dose level; DOR, duration of response; EBV, Epstein-Barr virus; FL, follicular lymphoma; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; R, randomization; R-CHOP-21, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in 21-day cycles; RP2D, recommended phase 2 dose; RP2D-1, 1 step below recommended phase 2 dose.

Westin, SOHO 2024

Golcadomide (CC282) plus RCHOP vs RCHOP in Newly Diagnosed LBCL

GOLSEEK-1 trial design

Key eligibility criteria
- Previously untreated LBCL (WHO 2022 classification[a])
- IPI 1-2 HR or 3-5
- Age 18-80 years
- ECOG performance status 0-2
- Measurable disease per Lugano response criteria

R 1:1

Stratification factors
- IPI 1-2 HR and 3 vs 4-5
- Bulky disease > 7 cm vs ≤ 7 cm

Golcadomide (0.4 mg) + R-CHOP (6 cycles)

Placebo + R-CHOP (6 cycles)

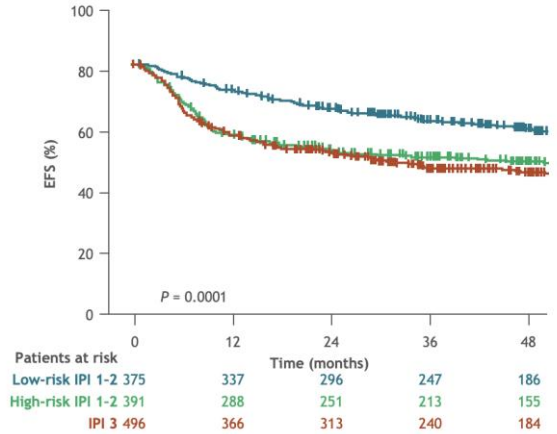
Primary endpoint
- PFS by investigator

Key secondary endpoints
- OS
- EFS by investigator
- CMR by IRAC
- uMRD at EOT

Vassilakopoulos T, Nowakowski GS. EHA Abstract PB3076.

The presence of bulky disease and/or very high LDH defines a high-risk subset of IPI 1-2 for eligibility in clinical trials of newly diagnosed aggressive B-cell lymphoma.

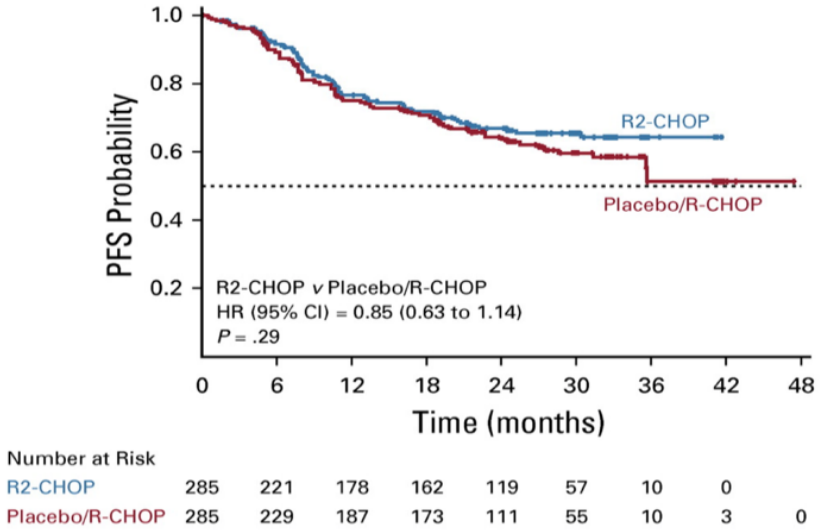
LEO EFS by IPI group[3]



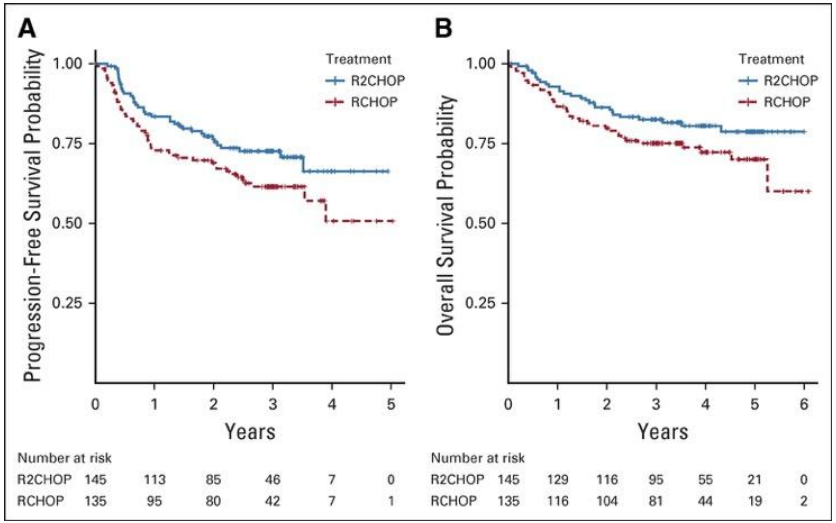
Maurer MJ et al, *Blood* 2023;142(suppl 1):4512-4514

Results of Randomized Studies of Lenalidomide Plus RCHOP (R2CHOP) vs. RCHOP

Robust



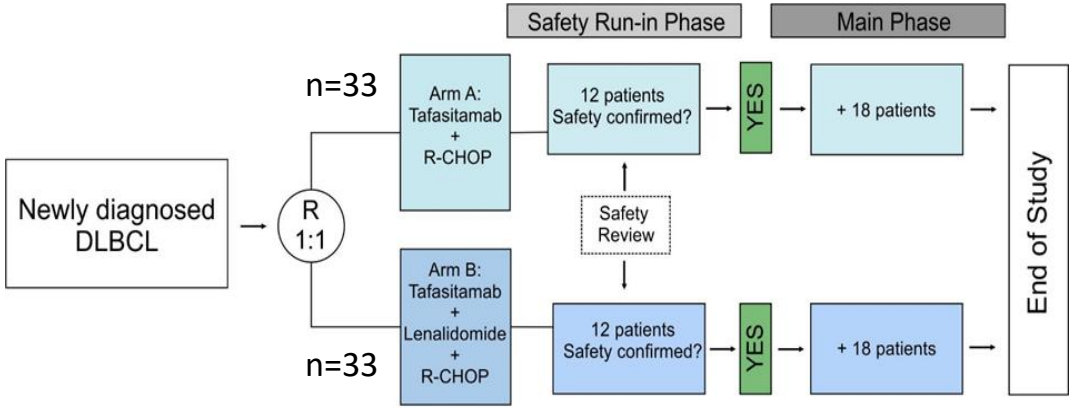
E1412

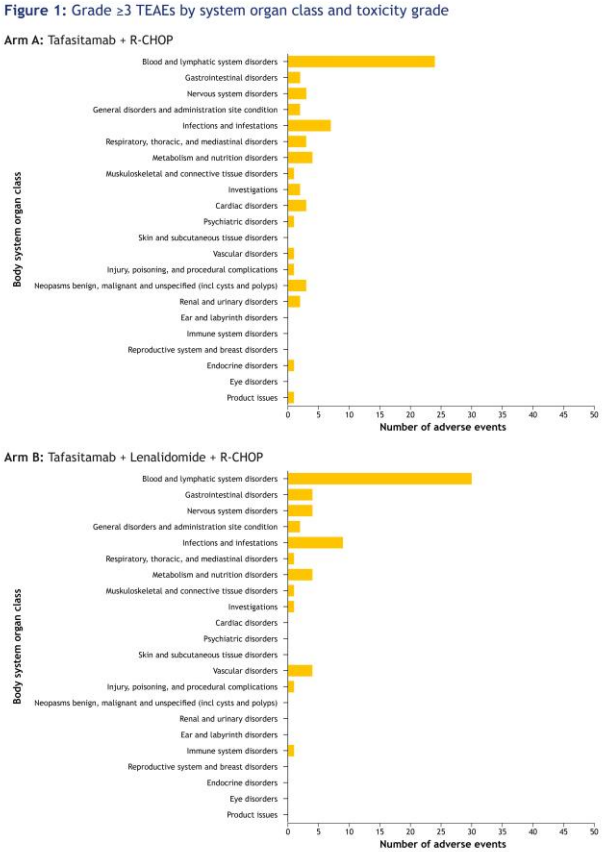


Nowakowski GS et al. *J Clin Oncol.* 2021Feb23;JCO2001366.

Nowakowski GS et al. *J Clin Oncol*. 2021 Feb 8:JCO2001375

Example of Doublet Optimization: First-MIND Trial – RCHOP/R2CHOP (E1412 Dose) Plus Tafasitamab

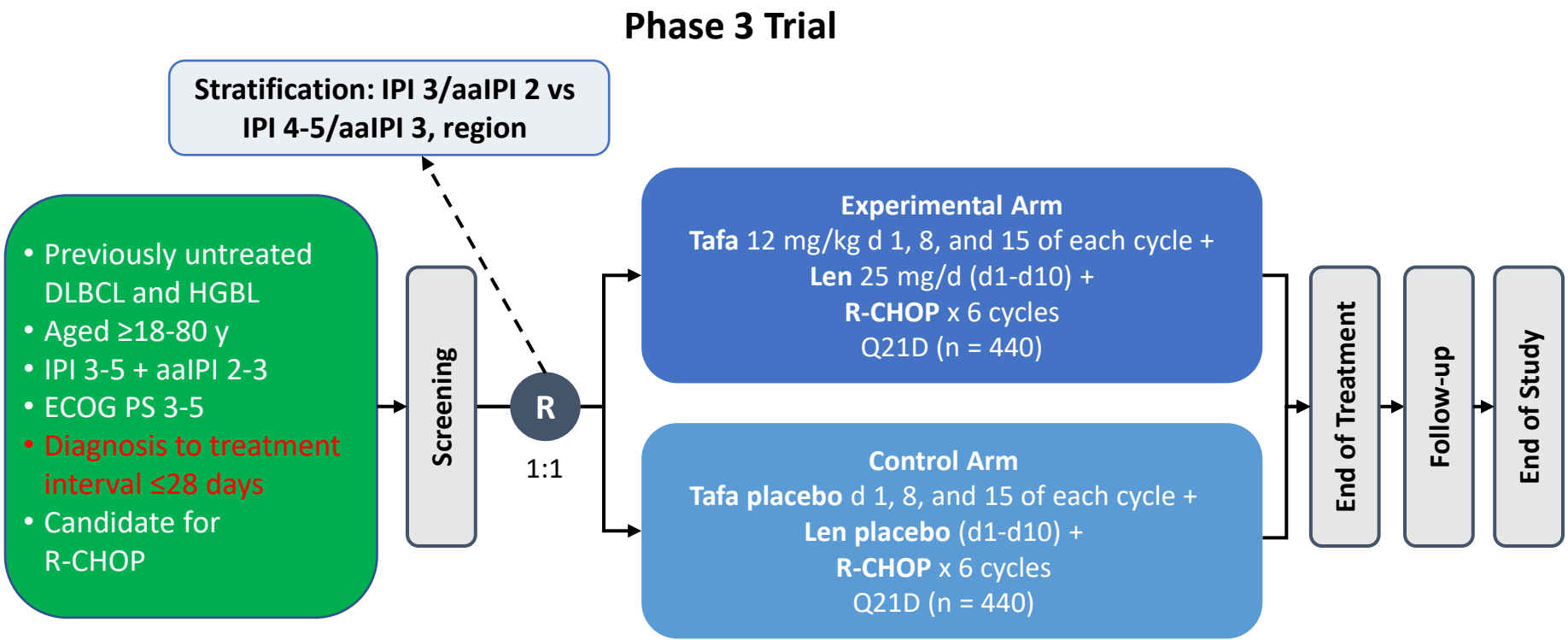




- Neutropenia and thrombocytopenia more common in arm B but no increase in neutropenic fever/infections
- Discontinuations due to AEs rare and not different average relative dose intensity of R-CHOP
- ORR at EOT was 75.8% (arm a) vs 81.8% (arm B)

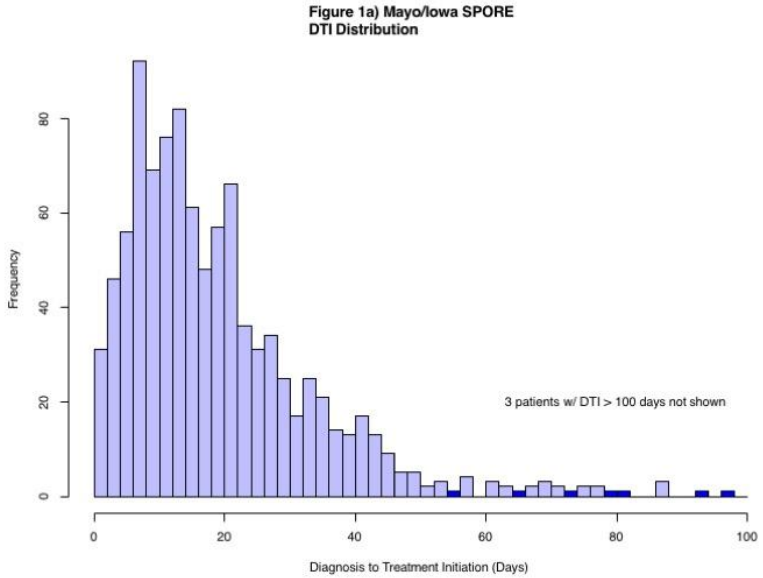
Nowakowski et al. ASH 2022, Beleda et al.. Blood 2023.

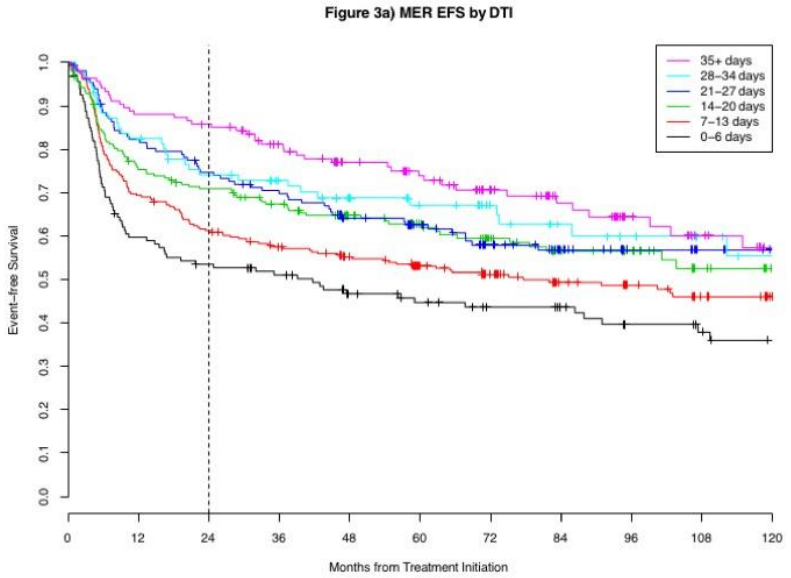
Front-MIND Newly Diagnosed DLBCL



NCT04824092

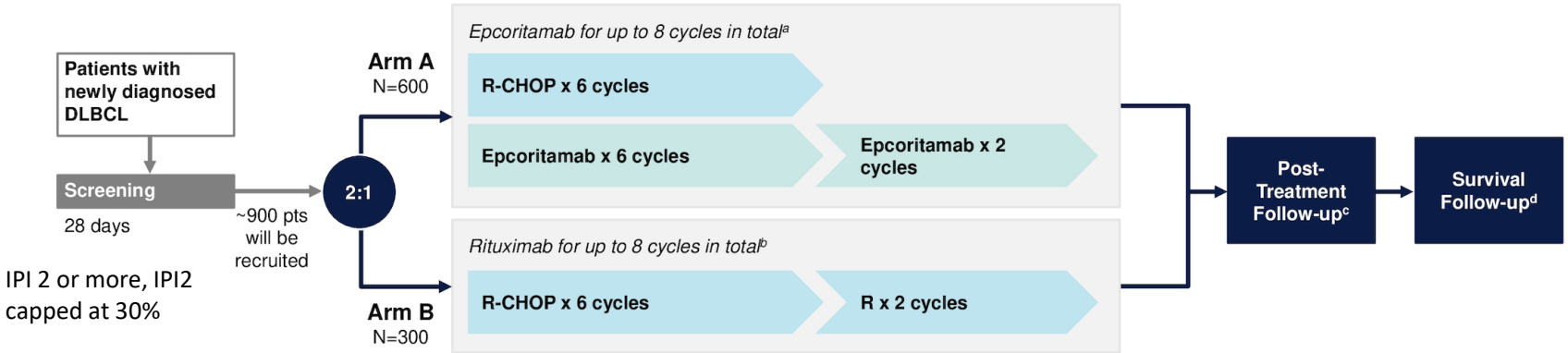
Time from Diagnosis to Therapy and Outcome in DLBCL



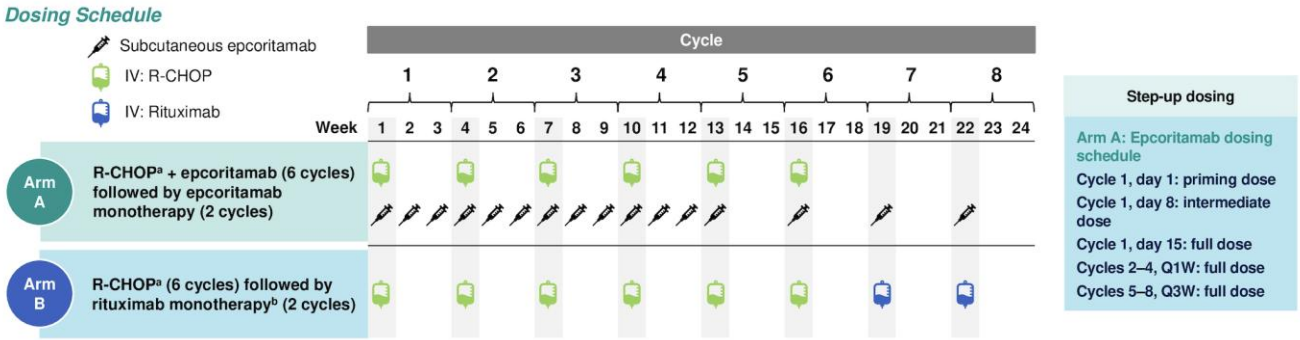


Maurer & Nowakowski J Clin Oncol. 2018 Jun 1;36(16):1603-1610.

Epcoritamab in Combination With R-CHOP vs R-CHOP in Newly Diagnosed DLBCL



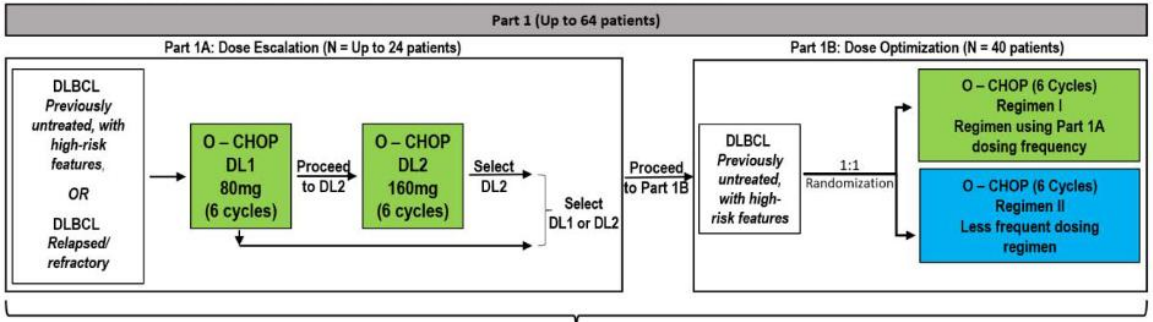
IPI 2 or more, IPI2 capped at 30%



NCT05578976, Sehn et al. TiP ASCO 2023

OLYMPIA-3: Odronextamab + CHOP in 1L DLBCL

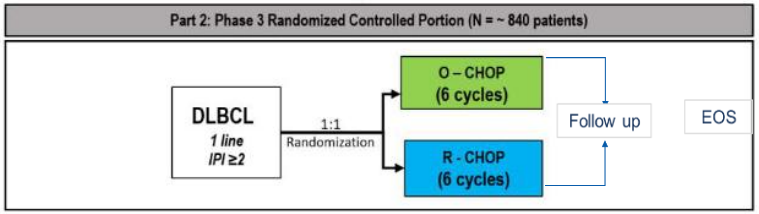
Part 1 – Safety Lead-in



Primary endpoint: DLT and incidence TEAEs.
Secondary endpoint: Efficacy: BOR, CR,DOR

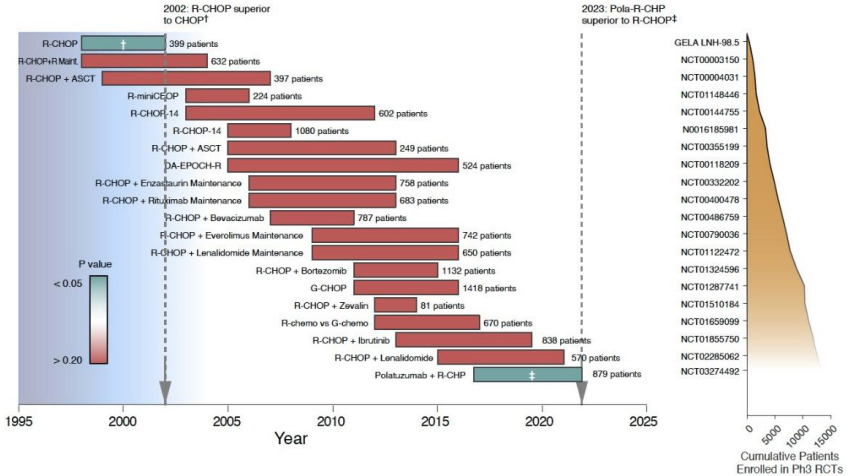
Part 2 – RCT

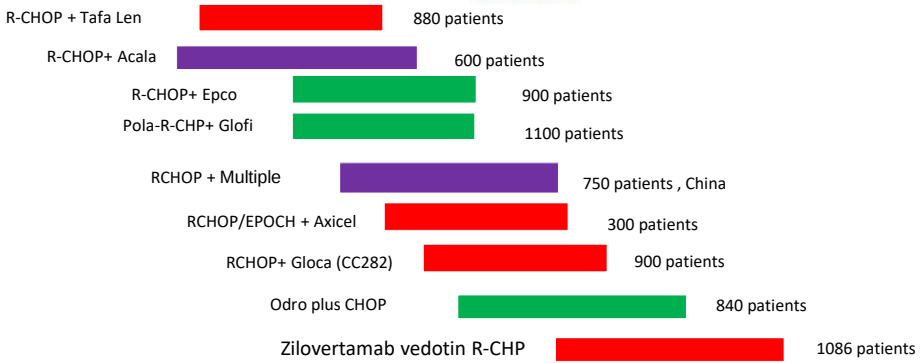
Proceed to Part 2



- *CHOP treatment starts on Cycle 1 Day 1*
- *Odronextamab treatment begins on Cycle 1 Day 8;*
- *Ph3 Randomization Stratified by:*
  - *Age (<65 vs >= 65)*
  - *IPI Score (2 vs 3 vs 4 to 5)*
- **Primary endpoint: PFS by ICR**
- **Secondary endpoint: EFS,CR by ICR**

Beyond RCHOP – Subtype Driven vs Agnostic

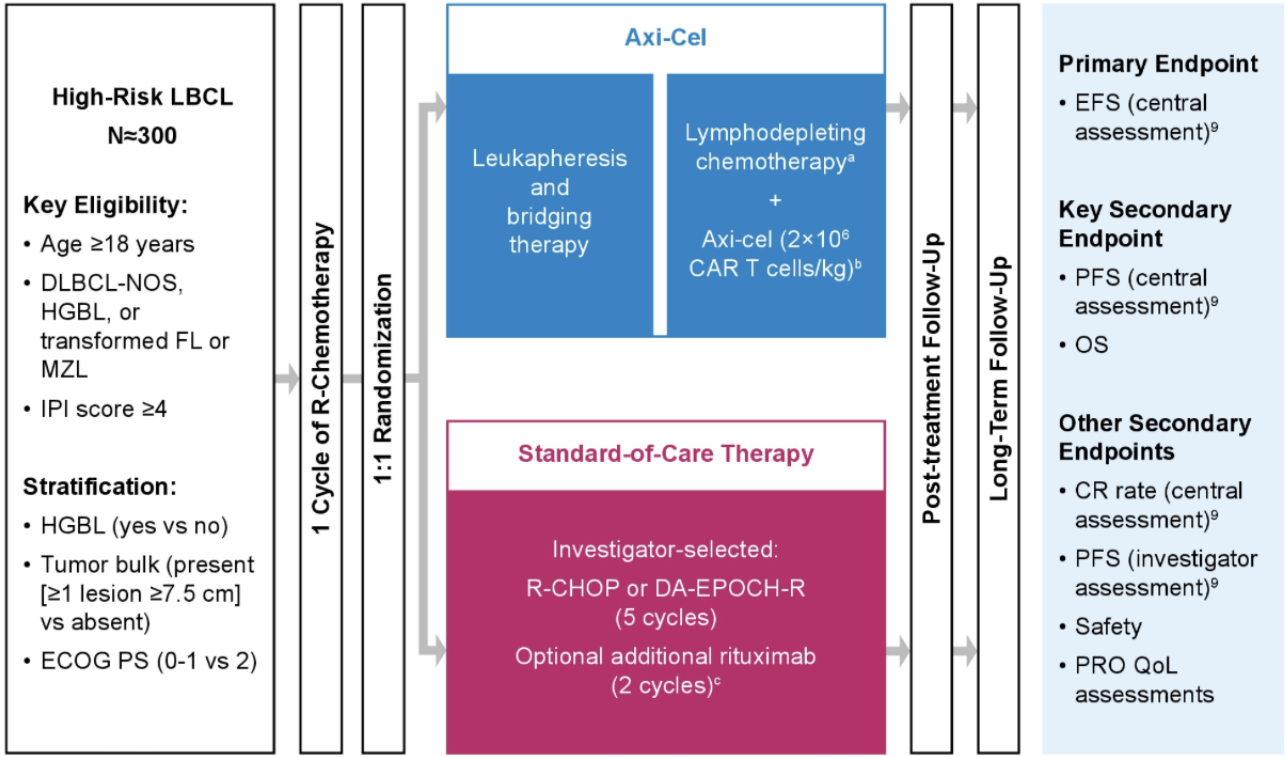




22,000

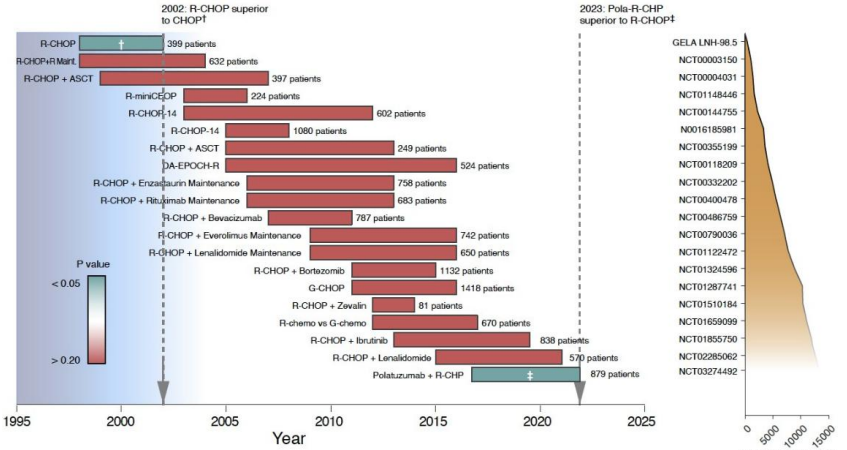
Bispecific antibody

Axicabtagene Ciloleucel vs CIT as First-line Treatment in Participants With High-risk Large B-cell Lymphoma (ZUMA-23)



NCT05605899

Beyond RCHOP – Subtype Driven vs Agnostic



R-CHOP + Tafa Len — 880 patients

R-CHOP+ Acala — 600 patients

R-CHOP+ Epco — 900 patients

Pola-R-CHP+ Glofi — 1100 patients

RCHOP + Multiple — 750 patients , China

RCHOP/EPOCH + Axicel — 300 patients

RCHOP+ Gloca (CC282) — 900 patients

Odro plus CHOP — 840 patients

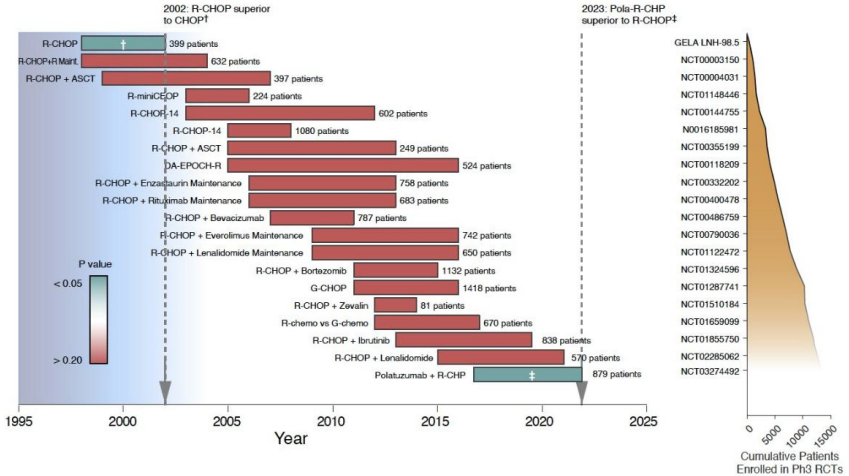
Zilovertamab vedotin R-CHP — 1086 patients

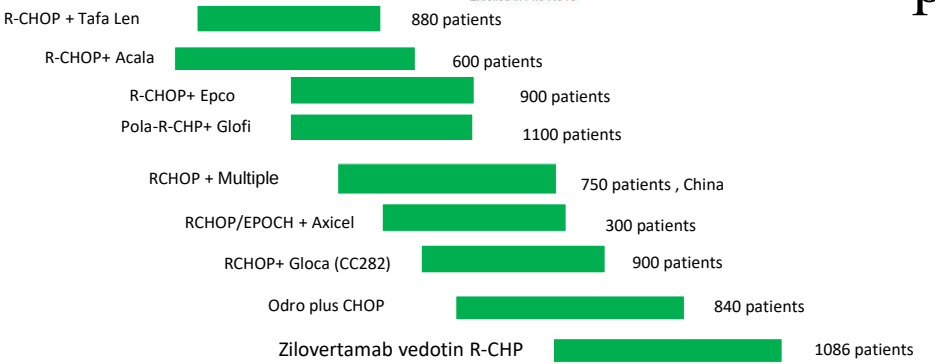
5 phase 3 studies in development…I know about

30,000

Ongoing

Beyond RCHOP – Subtype Driven vs Agnostic





Likely several positive

5 phase 3 studies in development…I know about

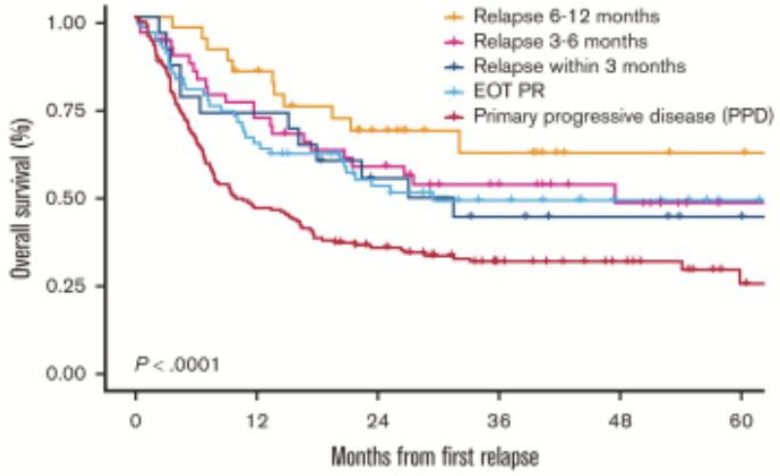
30,000

Ongoing

How do we choose if multiple trials positive

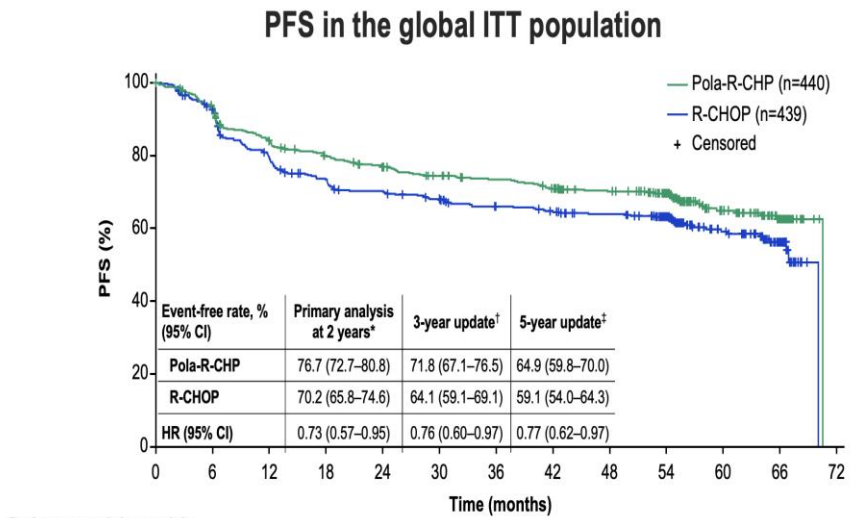
- OS advantage
- Degree of PFS advantage
  - Early separation of PFS curves e.i. reduction in primary progressive and refractory disease
  - Higher rate of MRD negativity
- If no OS but PFS in subset – may consider for subset
- Complexity/cost/logistics

Impact of primary progressive disease on OS



Number at risk						
6-12 Months	31	25	15	9	3	2
3-6 Months	44	32	22	15	9	2
Within 3 Months	21	15	9	6	4	2
EOT PR	66	39	25	13	7	2
PPD	145	62	41	27	15	6

Bock et al. Blood Adv 2024

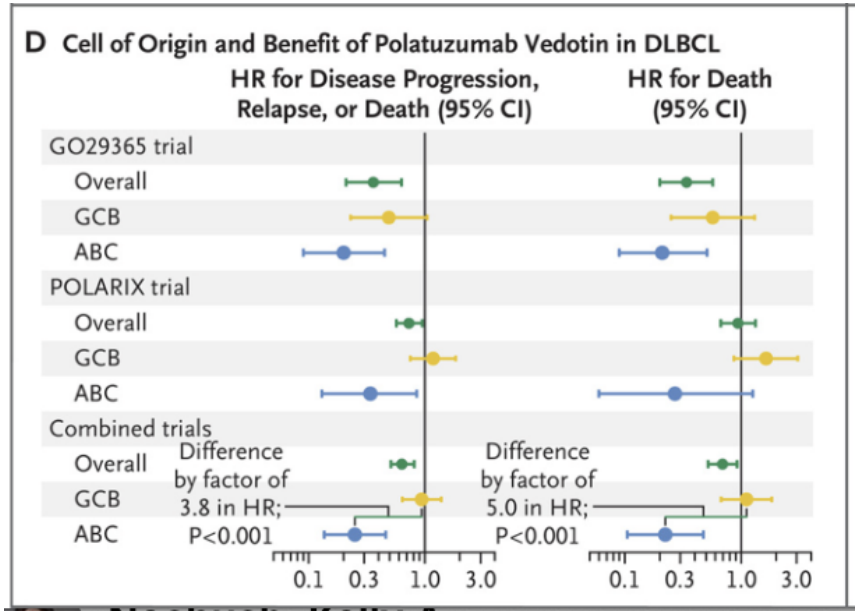


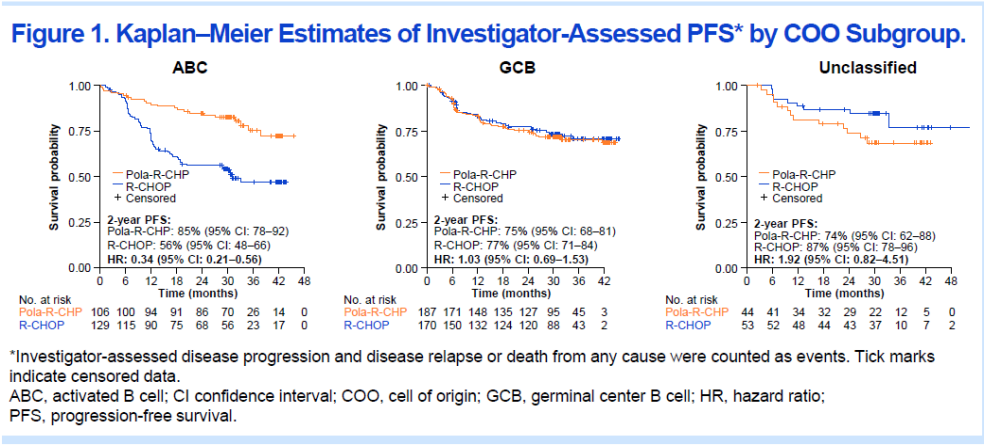
Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update‡
Pola-R-CHP	76.7 (72.7–80.8)	71.8 (67.1–76.5)	64.9 (59.8–70.0)
R-CHOP	70.2 (65.8–74.6)	64.1 (59.1–69.1)	59.1 (54.0–64.3)
HR (95% CI)	0.73 (0.57–0.95)	0.76 (0.60–0.97)	0.77 (0.62–0.97)

Patients remaining at risk													
Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351, Salles ASH2024.

COO and Benefit of Polatuzumab Vedotin





Palmer, A. N Engl J Med 2023; 389:764-766; Morchhauser et al ASH2023

Conclusions

- RCHOP remains a valid control arm and a valid backbone
- Pola RCHP alternative
- Optimization important
- Most trails focus on high-risk patients:
  - IPI
  - Short time from dx to rx
  - High molecular risk
- Molecularly driven or MRD driven trials difficult – lack of companion diagnostics; prolongs time to rx
  - Best option might be targeting MRD positive patients at the end of therapy
- Chemo free interesting but might be challenging as randomized study

Thank You

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