Indian Society of Hematology & Blood Transfusion

EHA EUROPEAN HEMATOLOGY ASSOCIATION

5th ISHBT-EHA Tutorial

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Large B-cell lymphoma: Diagnosis and treatment

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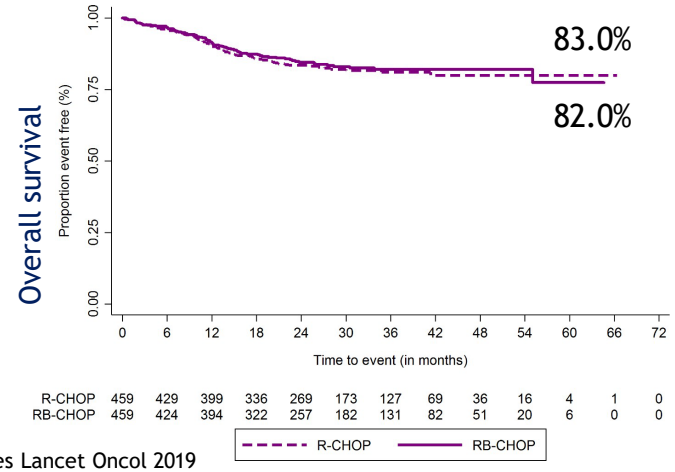
Disclosures

Celgene, a Bristol Myers Squibb Company	Research funding, advisory board, honorarium, travel to scientific conferences
Roche	Advisory boards, honorarium, research support, travel to scientific conferences
Kite, a Gilead company	Advisory boards, honorarium, research support
Abbvie	Advisory Boards, honorarium
Genmab	Advisory Boards
Janssen	Honorarium, research support
MSD	Research support
Acerta Pharma/AstraZeneca	Research support, honorarium
Prelude	Advisory Board
Incyte	Advisory board
Sobi	Advisory Board

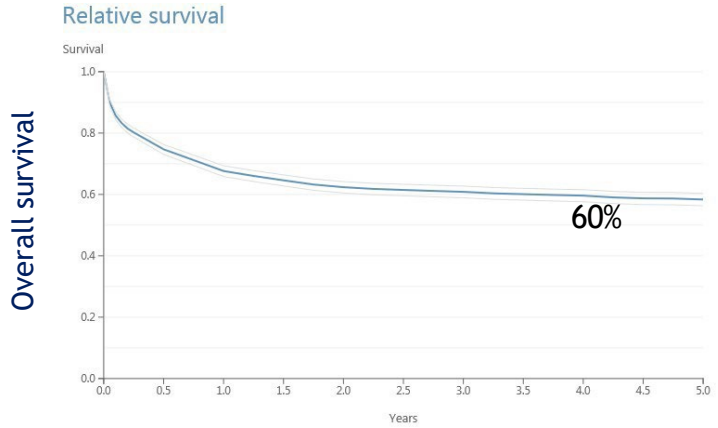
Aims

- To understand molecular heterogeneity in the large B-cell lymphomas and how this might impact upon prognosis and therapeutic pathways
- To discuss the changing landscape of therapy in the first line management of large B-cell lymphoma
- To review new approaches to relapsed disease and how we might sequence therapies to maximise their benefit.

DLBCL is a curable disease…but many patients are failed by our current therapies

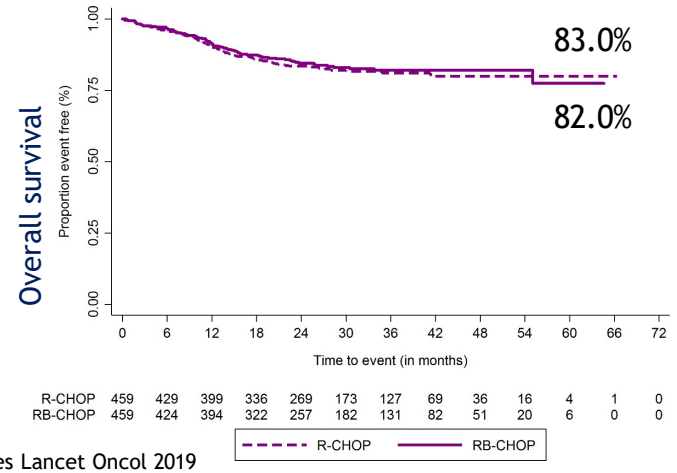


Davies Lancet Oncol 2019

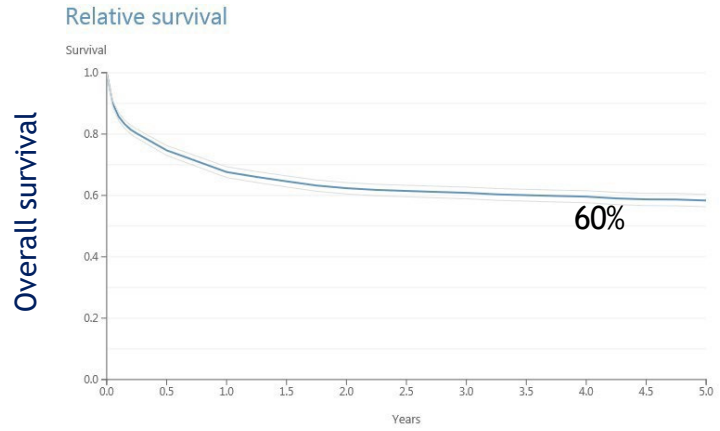


Haematological Malignancies research Network 2017

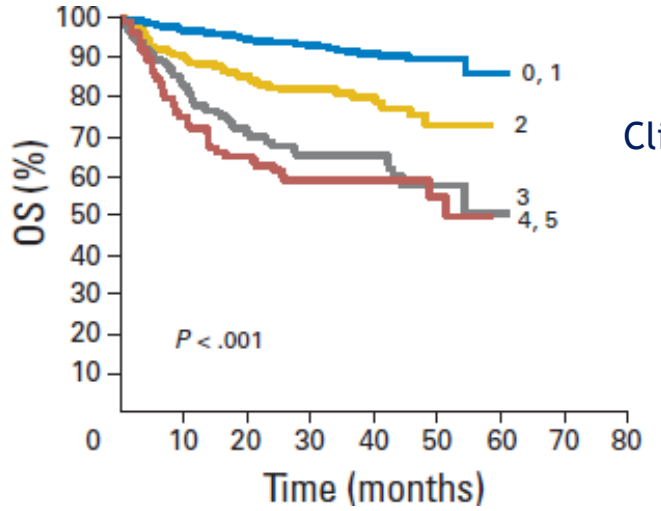
DLBCL is a curable disease…but many patients are failed by our current therapies



Davies Lancet Oncol 2019

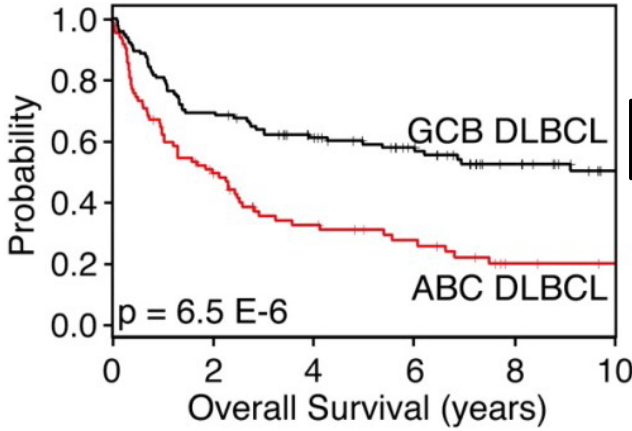


Haematological Malignancies research Network 2017



Clinical stratification

Ziepert at al. J Clin Oncol 28:2373-2380.

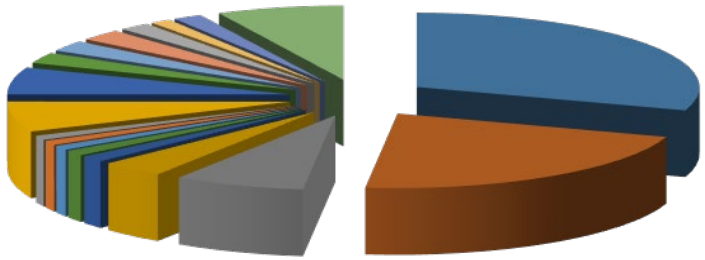


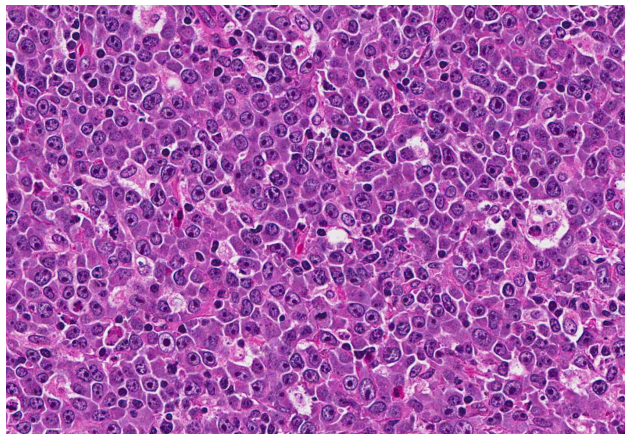
Biological stratification

DHL/THL
DEL

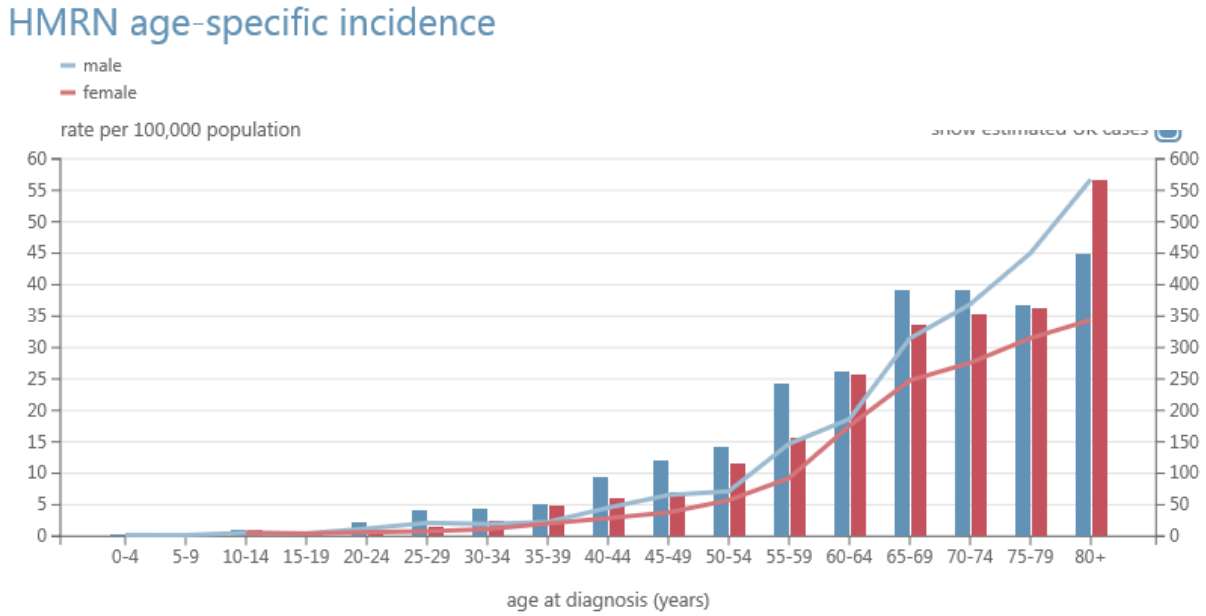
Wright, George et al. (2003) Proc. Natl. Acad. Sci. USA 100, 9991-9996

DLBCL



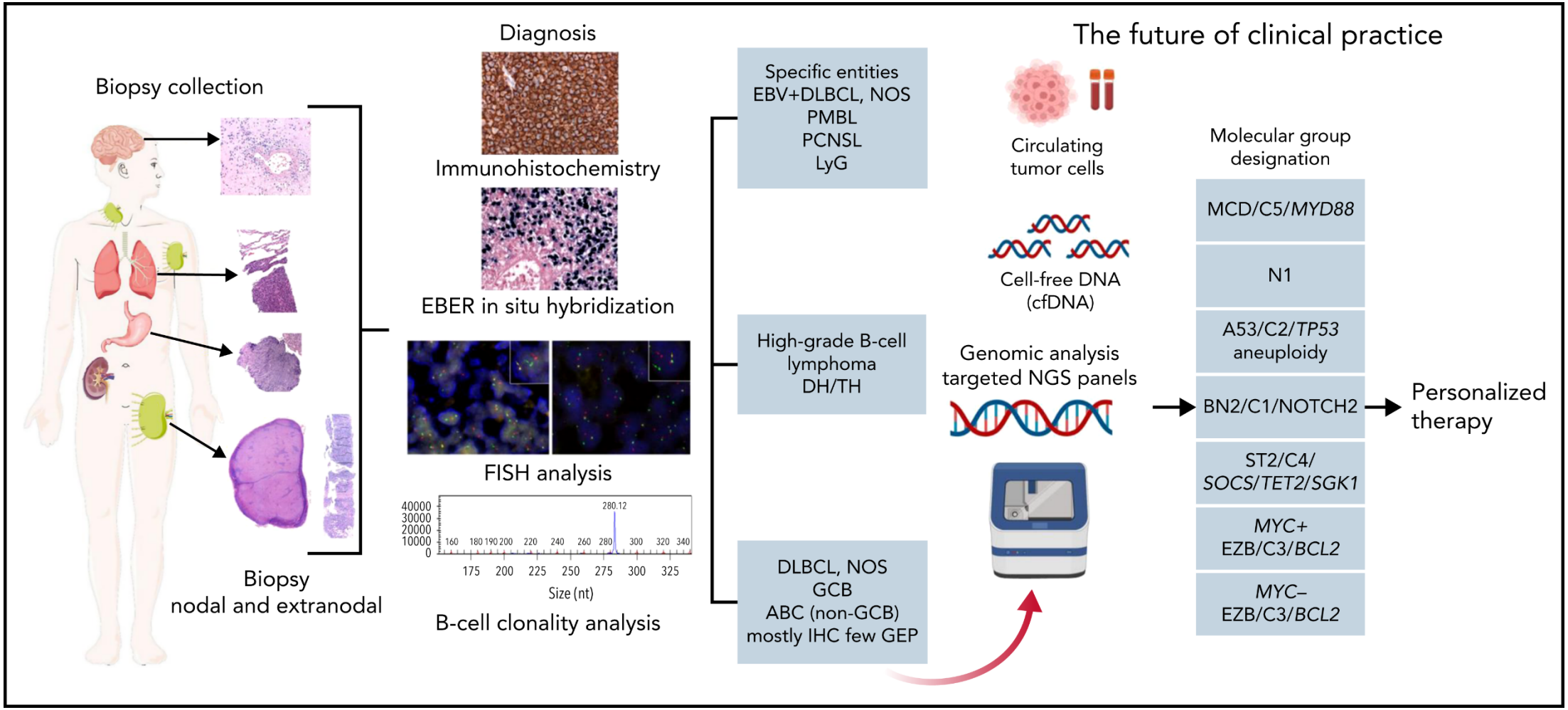


- LBLC
- FOLLICULAR
- EXTRA NODAL MARGINAL ZONE
- PERIPHERAL T NOS
- NASAL NK/T
- ANCIOIMMUNOBLASTIC
- ENTEROPATHY ASSOCIATED
- HEPATOSPLENIC
- ATLL
- CLL
- MANTLE CELL
- MEDIASTINAL LARGE B CELL
- ANAPLASTIC LARGE CELL



Haematological Malignancies Research Network 2019

The evolving diagnostic work-up in aggressive B-cell lymphoma



Campo *et al*. 2022

International Consensus Classification

- The definition of most entities remains unchanged, but criteria for diagnosis and recommended ancillary studies have been extensively refined.
- Some categories considered provisional in 2017 have now been upgraded to definite entities.
- Terminology for some diseases has been revised to adapt nomenclature to the current knowledge of their biology.

blood Special Report

Check for updates

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

Elias Campo,[1] Elaine S. Jaffe,[2] James R. Cook,[3] Leticia Quintanilla-Martinez,[4] Steven H. Swerdlow,[5] Kenneth C. Anderson,[6] Pierre Brousset,[7] Lorenzo Cerroni,[8] Laurence de Leval,[9] Stefan Dirnhofer,[10] Ahmet Dogan,[11] Andrew L. Feldman,[12] Falko Fend,[4] Jonathan W. Friedberg,[13] Philippe Gaulard,[14,15] Paolo Ghia,[16] Steven M. Horwitz,[17] Rebecca L. King,[12] Gilles Salles,[17] Jesus San-Miguel,[18] John F. Seymour,[19] Steven P. Treon,[6] Julie M. Vose,[20] Emanuele Zucca,[21] Ranjana Advani,[22] Stephen Ansell,[23] Wing-Yan Au,[24] Carlos Barrionuevo,[25] Leif Bergsagel,[26] Wing C. Chan,[27] Jeffrey I. Cohen,[28] Francesco d'Amore,[29] Andrew Davies,[30] Brunangelo Falini,[31] Irene M. Ghobrial,[6,32] John R. Goodlad,[33] John G. Gribben,[34] Eric D. Hsi,[35] Brad S. Kahl,[36] Won-Seog Kim,[37] Shaji Kumar,[23] Ann S. LaCasce,[6] Camille Laurent,[7] Georg Lenz,[38] John P. Leonard,[39] Michael P. Link,[40] Armando Lopez-Guillermo,[41] Maria Victoria Mateos,[42] Elizabeth Macintyre,[43] Ari M. Melnick,[44] Franck Morschhauser,[45] Shigeo Nakamura,[46] Marina Narbaitz,[47] Astrid Pavlovsky,[48] Stefano A. Pileri,[49] Miguel Piris,[50] Barbara Pro,[51] Vincent Rajkumar,[12] Steven T. Rosen,[52] Birgitta Sander,[53] Laurie Sehn,[54] Margaret A. Shipp,[6] Sonali M. Smith,[55] Louis M. Staudt,[56] Catherine Thieblemont,[57,58] Thomas Tousseyn,[59] Wyndham H. Wilson,[56] Tadashi Yoshino,[60] Pier-Luigi Zinzani,[61] Martin Dreyling,[62] David W. Scott,[54] Jane N. Winter,[63] and Andrew D. Zelenetz[17,64]

WHO HAEM 5

Systematic evolution: Restructuring of entities into a hierarchical system, updates to nomenclature, revision of diagnostic criteria or subtypes, deletion of certain entities, and introduction of new entities

REVIEW ARTICLE OPEN

Check for updates

LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20]✉, Kojo S. Elenitoba-Johnson[21], Judith Ferry[22]✉, Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51]✉, Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62]✉, Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

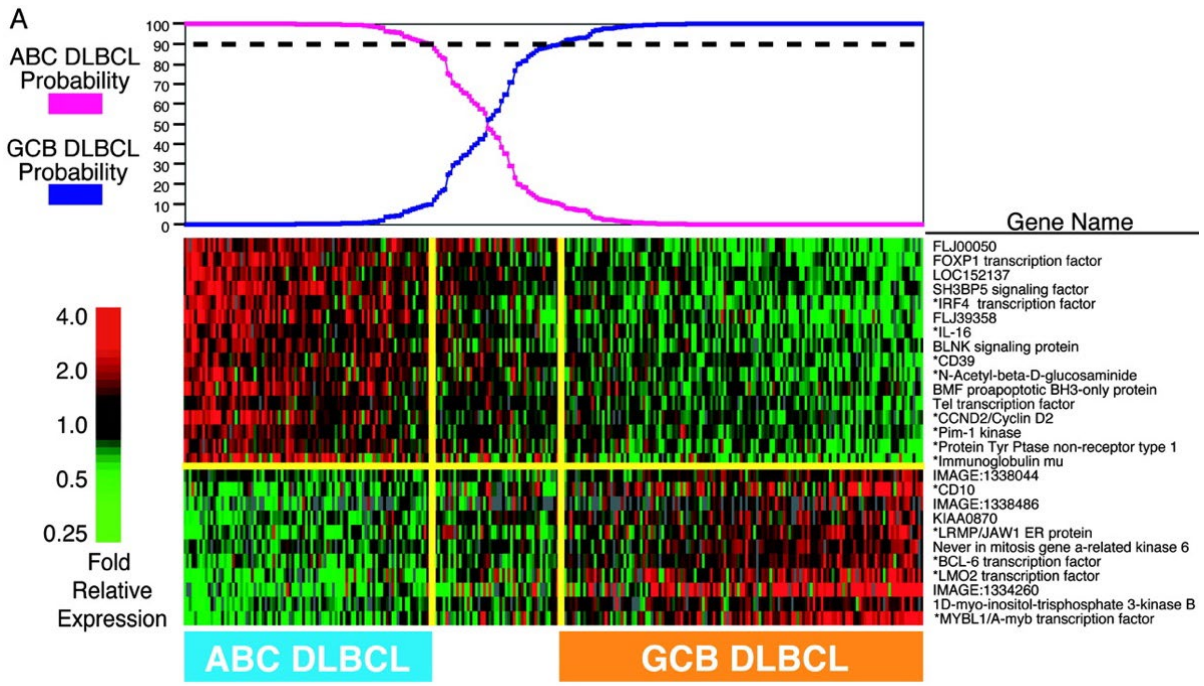
Large B-cell lymphoma is not just one disease

- 5th WHO Classification of Lymphoid tumours 2022

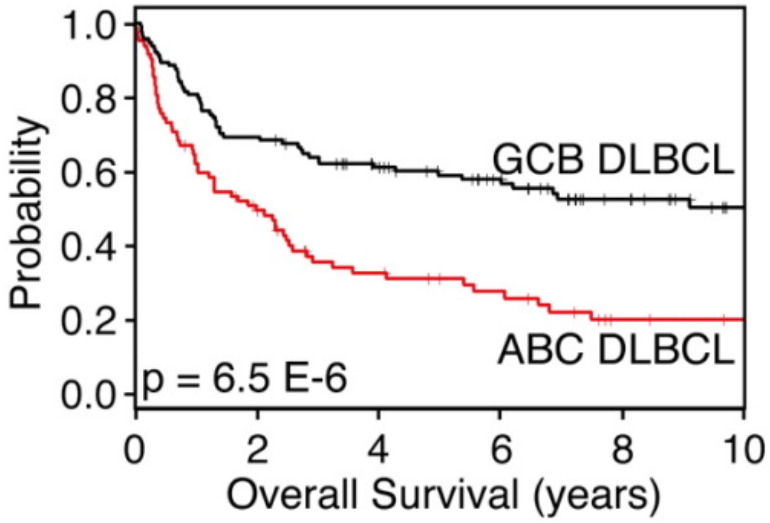
- Morphological variants have been de-emphasised

Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with *IRF4* rearrangement
High-grade B-cell lymphoma with 11q aberrations
Lymphomatoid granulomatosis
EBV-positive diffuse large B-cell lymphoma
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma
Fluid overload-associated large B-cell lymphoma
Plasmablastic lymphoma
Primary large B-cell lymphoma of immune-privileged sites
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Primary mediastinal large B-cell lymphoma
Mediastinal grey zone lymphoma
High-grade B-cell lymphoma, NOS

Not a single disease: complex models of biological heterogeneity



Wright et al., PNAS, 2003



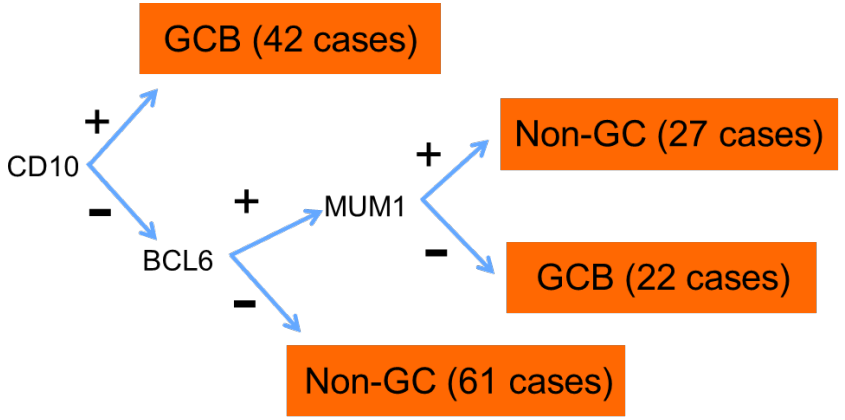
Wright et al. 2003

Failed to translate into diagnostic laboratories

Why? No effective therapeutic intervention

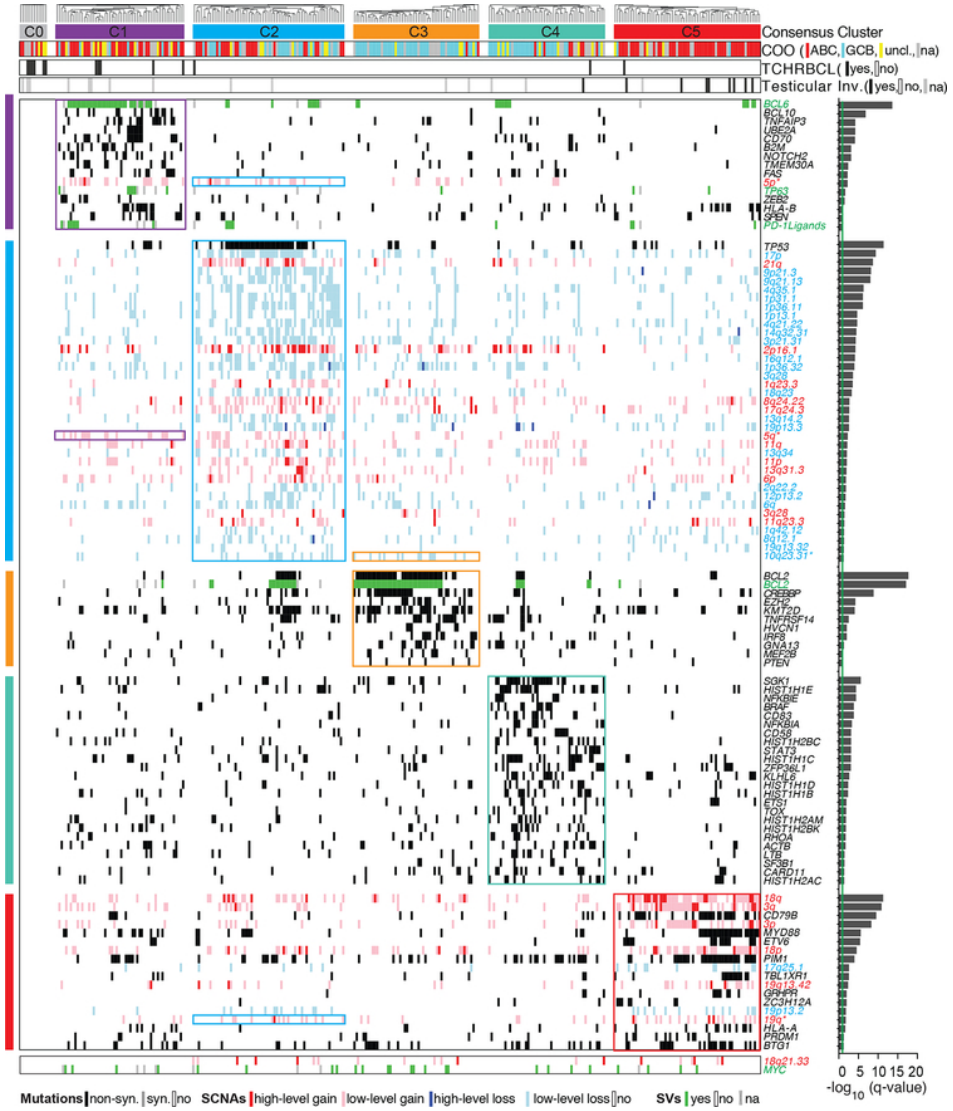
Ineffective proxies

Never the less incorporated into WHO HAEM 4 and retained



Hans et al., Blood, 2004

Further complex models of biological heterogeneity



Integration of multiple platforms.

Classes differ with respect to pathogenesis, phenotypic properties, oncogenic survival path-ways, and responses to therapy

Patients may do not fall within genetic sub-group

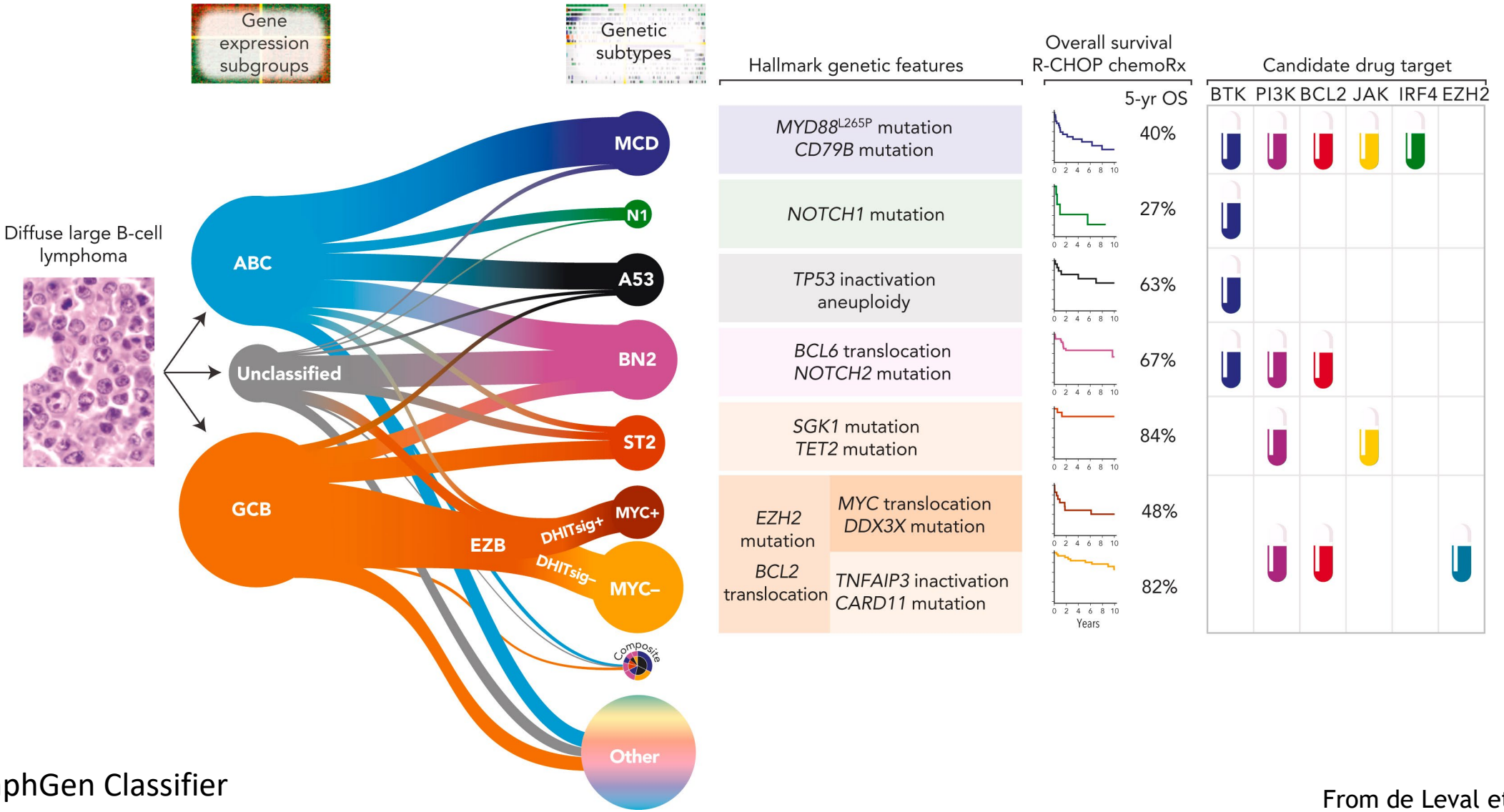
Ability to deliver per patient classification in clinically meaningful timeframes.

Appropriate therapeutic to target vulnerabilities

Complexities of trial design.

Chapuy et al. Nat Med. 2018

Genomic classification: What does this add?



LymphGen Classifier

From de Leval et al.2022

Before the chemotherapy…

- **Staging** : PET scan/CT

- **Prognostic score**:

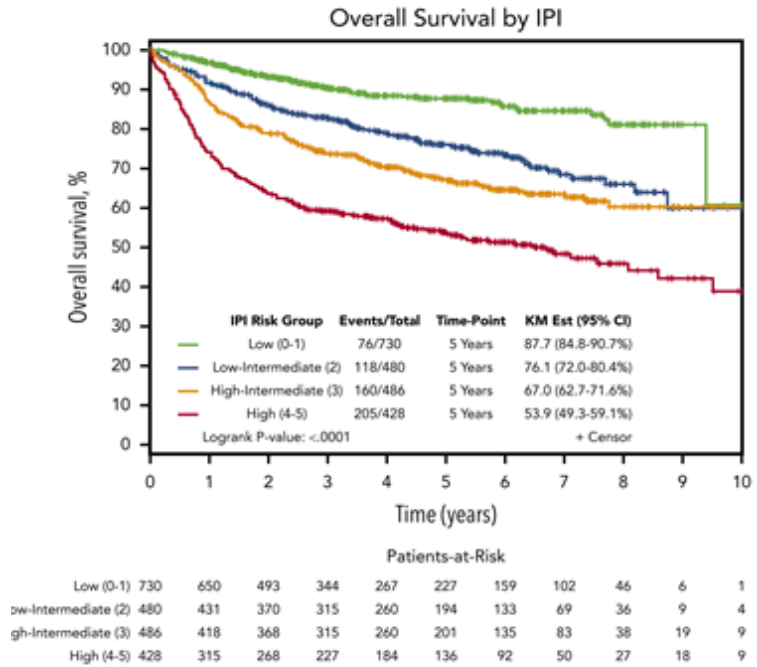
IPI (APLES Age >60, PS 2-4 , LDH, EN sites>1, Stage III,IV,,) [1]

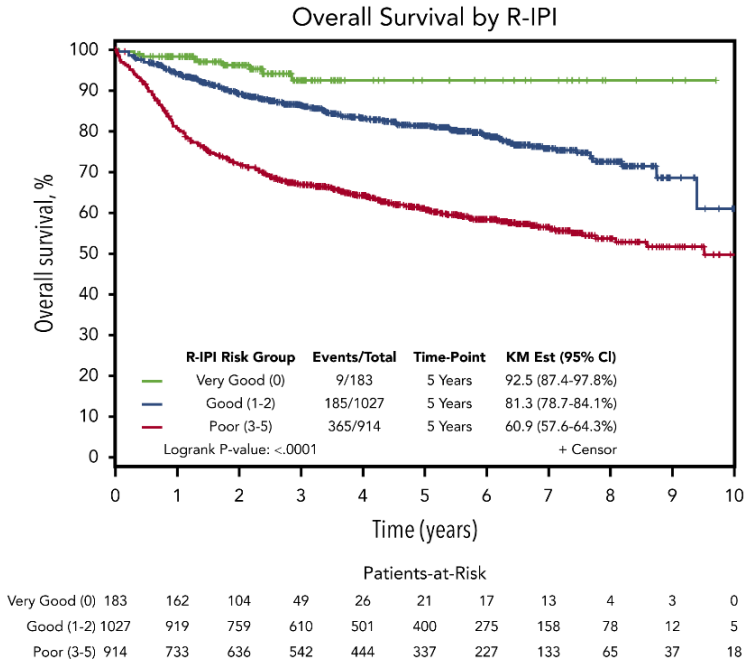
The revised IPI [2] confirms the prognostic significance of IPI in the R-CHOP era

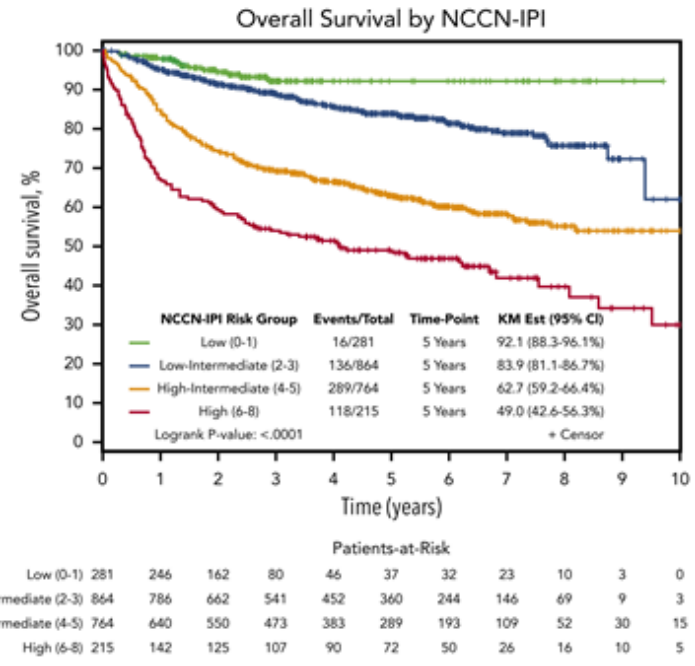
NCCN-IPI [3], superior at discriminating low and high-risk groups.

International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI

- NCCN-IPI had the greatest absolute difference in OS estimates between the highest- and lowest-risk
- NCCN best discriminator for PFS and OS endpoints
- Low-risk NCCN-IPI had favourable survival outcomes with little room for further improvement.
- None of the clinical risk scores identified a patient subgroup with long-term survival clearly <50%.







Amy S. Ruppert, et al. Blood, 2020.

Before the chemotherapy…

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- The revised IPI [2] confirms the prognostic significance of IPI in the R-CHOP era
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- **Cardiac function**

- **Bloods**: Viral screen including hepatitis B/C /HIV and LDH

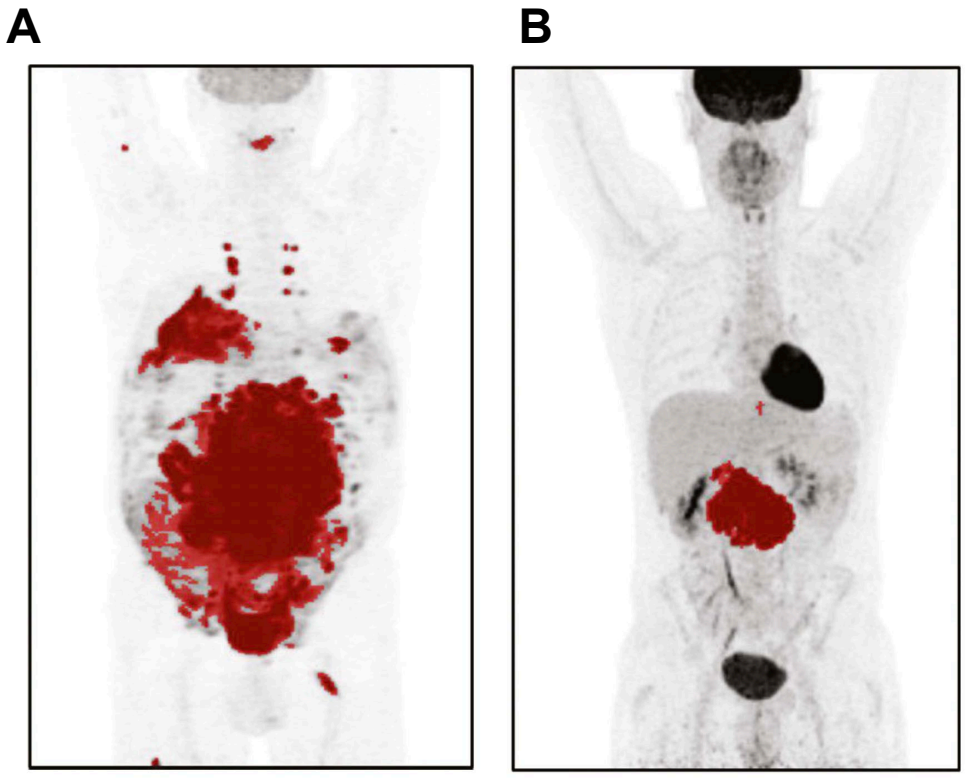
- **Fertility** preservation

- **Specialist nurse** and contact details

- **MDT discussion**

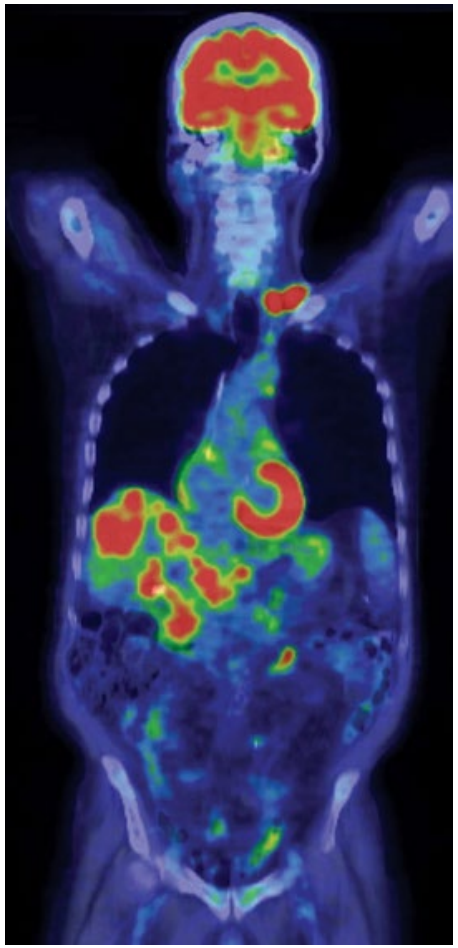
Adding PET imaging to prognosis prediction

International Metabolic Prognostic Index



- Adding PET-based metabolic measurements, i.e. in the form of TMTV to IPI improves prognosis prediction.

7 first line treatment decisions in Large B-cell Lymphoma



CNS prophylaxis, who and how?

How should we treat early-stage disease?

Can we improve on RCHOP21?

Should we ever intensify first line chemotherapy?

Radiotherapy use in advanced disease?

How should we treat older patients?

PMBCL, how is the treatment different?

Early stage DLBCL

25-30% of DLBCL presents as limited stage I-II

Limited stage DLBCL usually implies the disease can be encompassed within a reasonable radiotherapy field

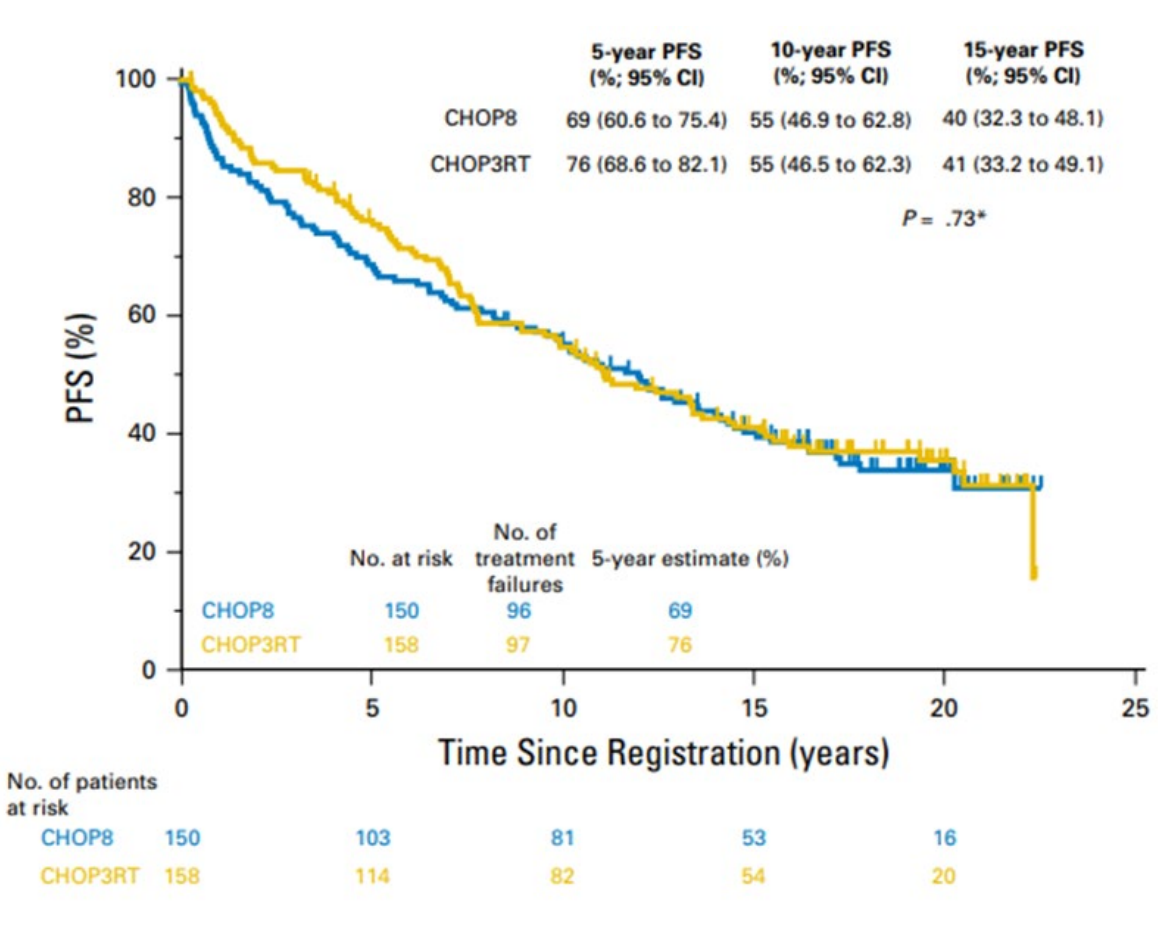
Stage II patients with bulk were usually excluded from early-stage studies and patients treated as advanced stage

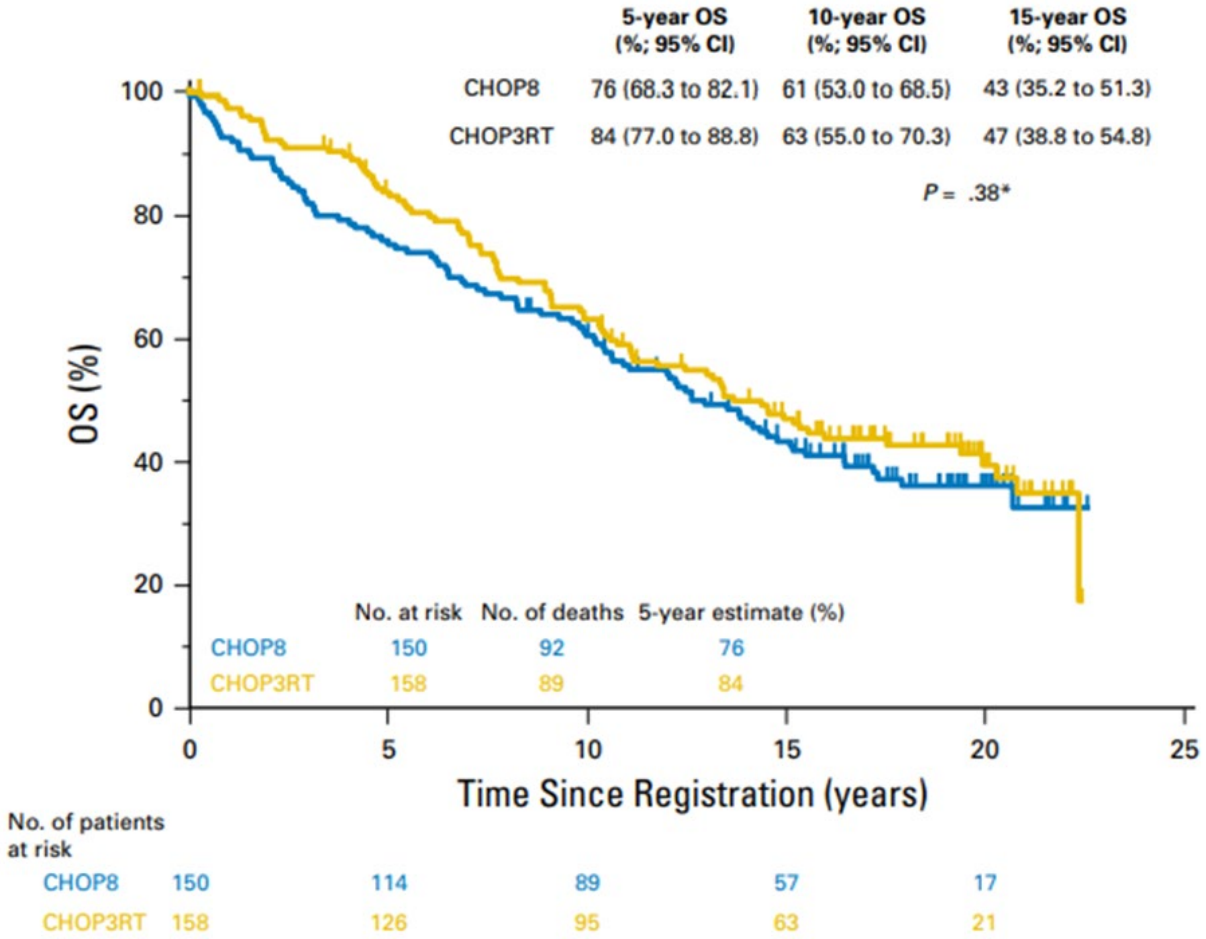
Age >60 years
ECOG performance status 2 or more
Stage II
Elevated LDH

5 year PFS
smIPI 0 = 97%
smIPI 1-2 = 86%
smIPI 3-4 = 30%

Stephens et al JCO 2016;34 (25) 2997-3004

A continuous pattern of relapse beyond 5 years in patients with early-stage disease treated with CMT





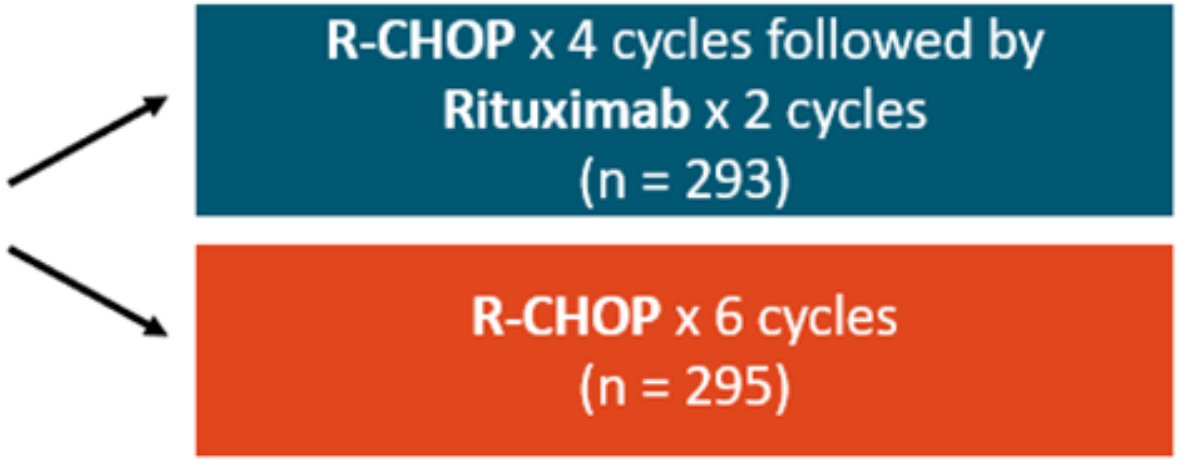
Biological reason for the different relapse pattern compared to advanced stage DLBCL is not clear

2) Stephens et al JCO 2016;34:2997-3004

FLYER study, is 4 X RCHOP adequate for low-risk early stage disease?

International, randomized phase III noninferiority trial

Patients with untreated aggressive B-cell lymphoma, aged 18-60 yrs, stage I/II disease, age-adjusted IPI = 0, no bulky disease (maximum diameter < 7.5 cm) (N = 588)



Primary endpoint: PFS, 3-yr PFS rate

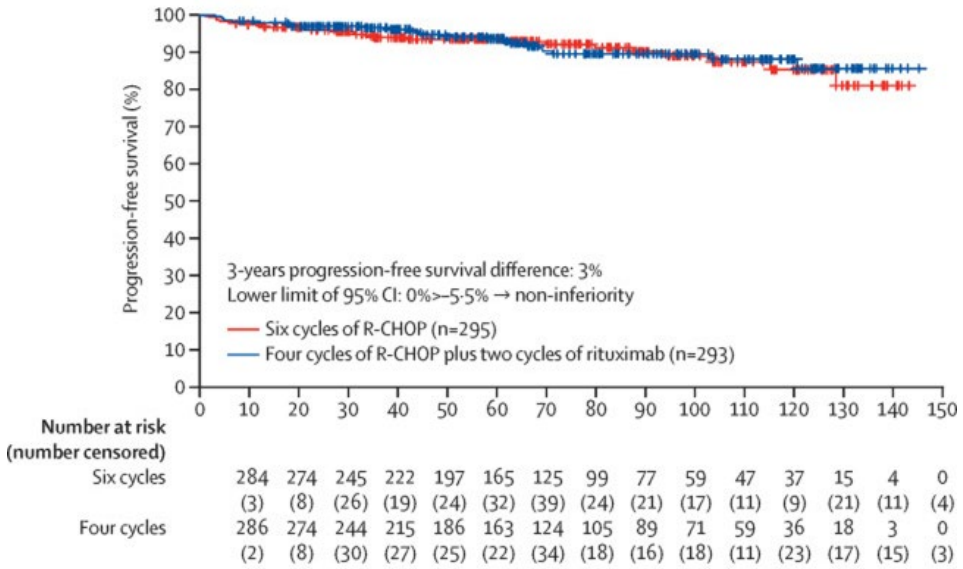
Poeschel et al Lancet 2019 ; 394 (10216): 2271-81

Early stage DLBCL

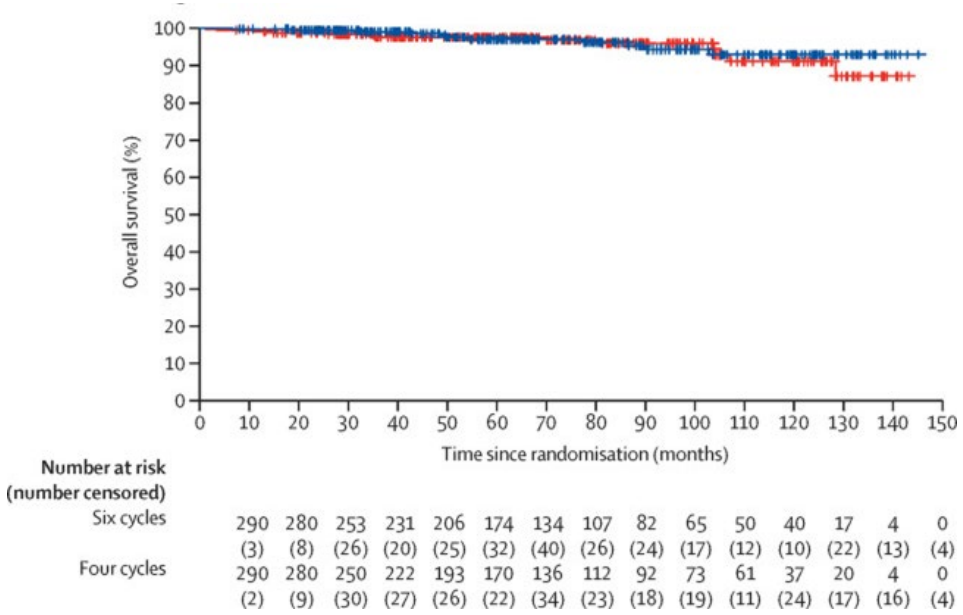
- **The FLYER study** **Poeschel *et al* Lancet 2019; 394: 2271-81**
  - Phase 3 non-inferiority (margin −5·5%) RCT in ≤60 years with no IPI risk factors or bulk
    - **RCHOPx4 (+2R) *versus* RCHOPx6**
    - 33% of patients had extra-nodal disease
    - No RT planned (except for testicular)
  - n=588 patients in the intention-to-treat analysis.
  - 3-year PFS with R-CHOPx4 (+2R) = 96% (95% CI 94–99)
    - 3% better than six cycles of R-CHOP
    - Lower limit of the one-sided 95% CI was 0%

RCHOPx4 (+2R) is non-inferior to RCHOPx6 for IPI 0, non-bulky DLBCL

Progression-free survival



Overall survival

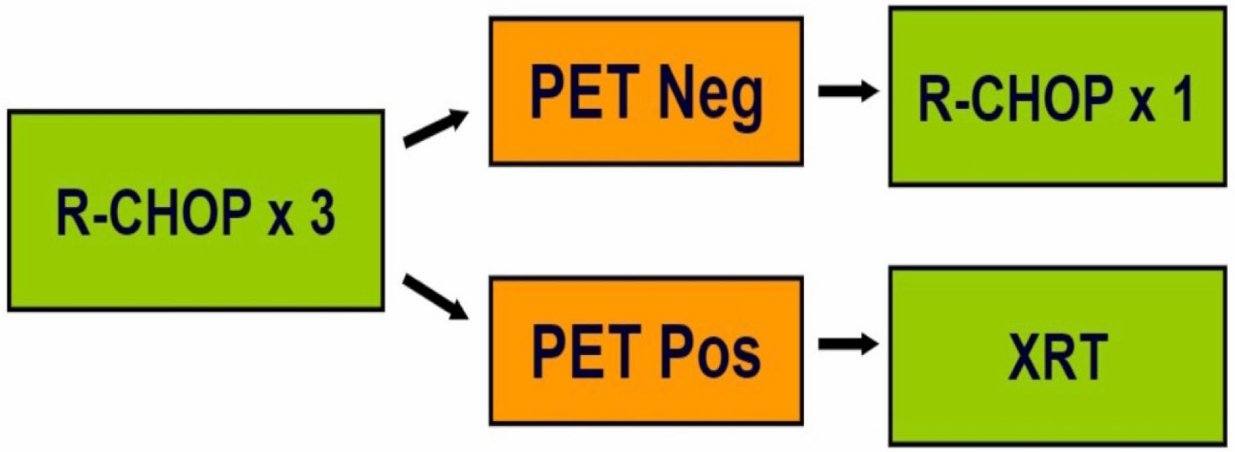


Canadian Retrospective data has shown that we can use a PET adapted approach in higher risk patients

Limited stage (Stage I/II, non-bulky <10cm, no B-symptoms, radiation encompassable)

PET after 3 cycles R-CHOP

PET-Guided Treatment Algorithm for Limited Stage DLBCL in BC



DS 3-5 considered positive, 18% positive

Sehn *et al* ASH 2019 abstract no. 401 ASH 2019

Higher risk patients than were in the FLYER study

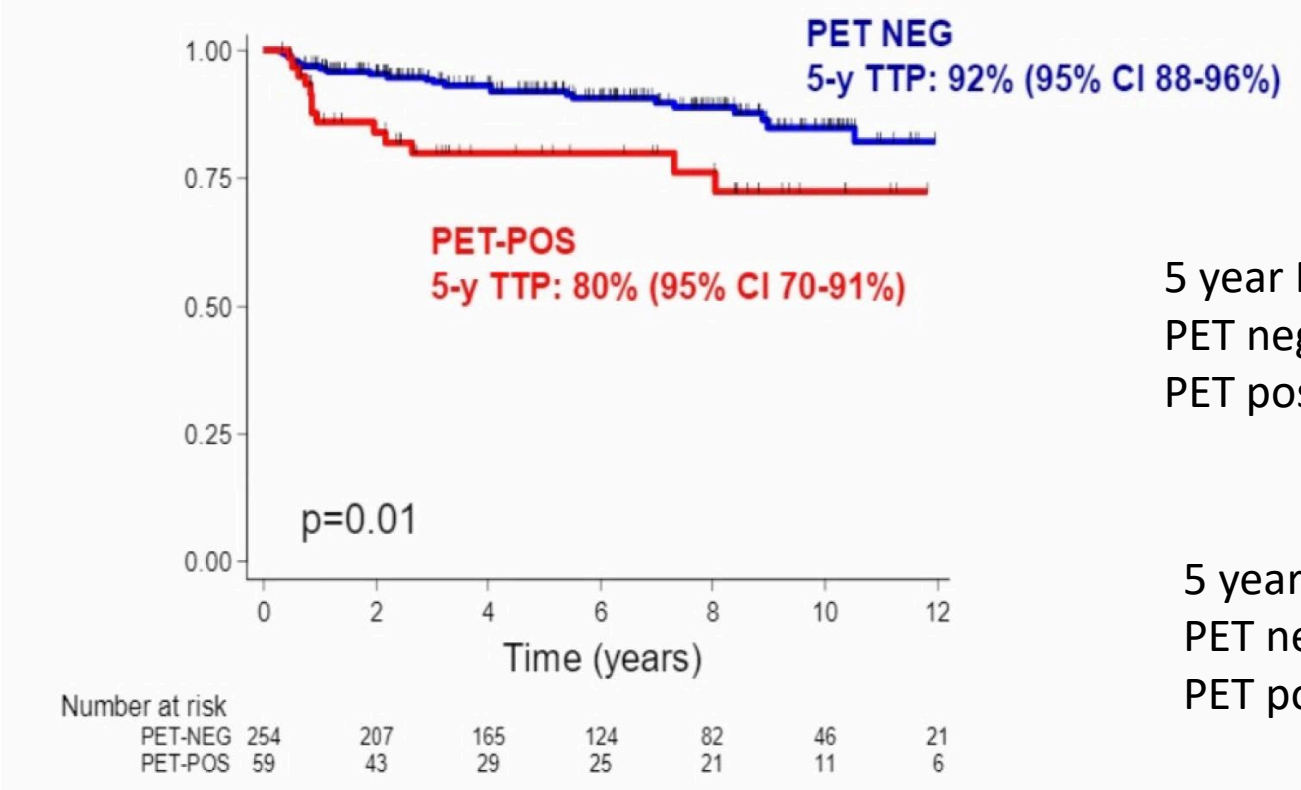
(n=319)

Characteristic	n	%*
Median Age, yrs (range)	68 (19-92)	-
Male Gender	152	48
Ann Arbor Stage		
I	189	59
II	130	41
PS >1	25	8
Elevated LDH	38	13
Extranodal involvement	166	52
Median mass size (range)	4 (1-9)	-
Stage-modified IPI		
0	55	19
1	131	45
2	82	27
3-4	27	9

Sehn et al abstract no. 401. ASH 2019

If patients are PET negative after 3 X RCHOP then can proceed to 4th RCHOP instead of RT

Time to progression according to PET status



5 year PFS:
PET neg 88%
PET pos 75%

5 year OS
PET neg 90%
PET pos 77%

Outcomes if PET positive are disappointing even though patients proceeded to radiotherapy

Sehn et al abstract no. 401

Small subgroups of all the different extranodal sites make it difficult to interpret data for individual sites

- Retrospective data stage I DLBCL - inferior outcome in patients with extranodal sites [1]
- 10 year OS 70% vs 89%, difference was observed despite similar clinical characteristics and use of RT between groups and more patients with EN disease receiving 6 cycles of RCHOP
- Other smaller studies have shown a similar outcome between nodal and extranodal sites [2,3]
- 3 prospective SWOG trials, no difference but small numbers of each EN site [4]

1)Bobillo et al Blood 2021;137(1):39-48, 2) Nijland et al Hem Onc 2018;36(2):416-421, 3) Hui et al Leuk Lymph 2010;51(9);1658-1667 4)Stephens et al Haematologica Nov 2022

Management of specific extranodal sites

- **Testicular**: 6 X RCHOP, CNS prophylaxis and radiotherapy to contralateral testis
- **Primary gastric**: In one study [1] of 50 patients with H Pylori positive DLBCL, eradication of H Pylori alone achieved (CR 69% (56% if transformed from MALT) with no relapses at 8 year FU. This approach is only practised in a few centres and if done but be done with regular monitoring. Most centres use CMT or 6 cycles RCHOP
- **Primary bone**: Ltd data, CMT or 6 X RCHOP +/- RT
- **Primary breast**: IELSG and SEER data [2,3] suggest inferior outcomes if less chemotherapy and radiotherapy, therefore 6 x RCHOP, radiotherapy and CNS prophylaxis is recommended

1)Kuo et al Blood 2012;119(21):4838-44, 2) Ryan et al Ann Oncol 2008;19(2):233-41 3)Liu et al Cancer Med 2018;7(5): 1845-51 3)Bobillo et al Blood 2021;137(1):39-48

Considerations in MDT for early stage disease

Is the patient favourable risk?

- Not bulky
- Stage modified IPI 0-2
- No extranodal disease (except Waldeyers ring)
- Can tolerate full dose RCHOP

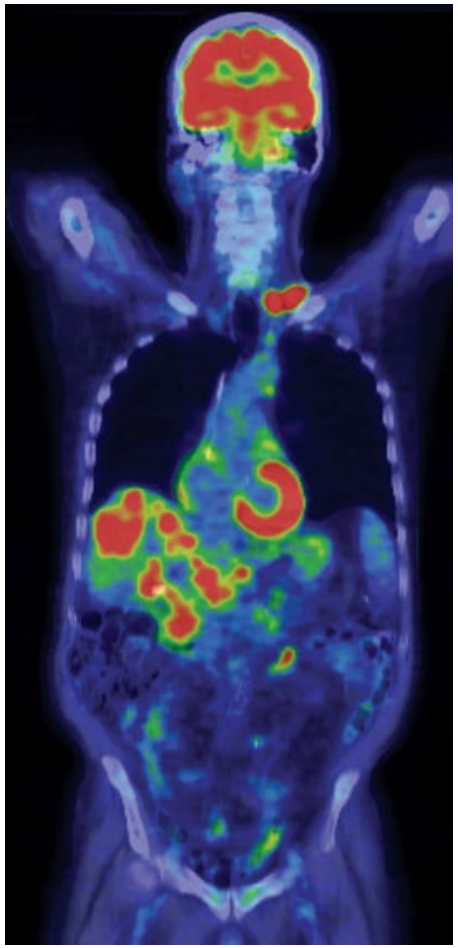
Which will have more toxicity concerns for the patient?

- 1 further cycle RCHOP or radiotherapy?

Depending on risk : RCHOP X 3 + RT

- PET guided approach, aiming 4 cycles RCHOP
- If considered high-risk then for 6 cycles RCHOP +/- RT

7 first line treatment decisions in Large B-cell Lymphoma



CNS prophylaxis, who and how?

How should we treat early-stage disease?

Can we improve on RCHOP21?

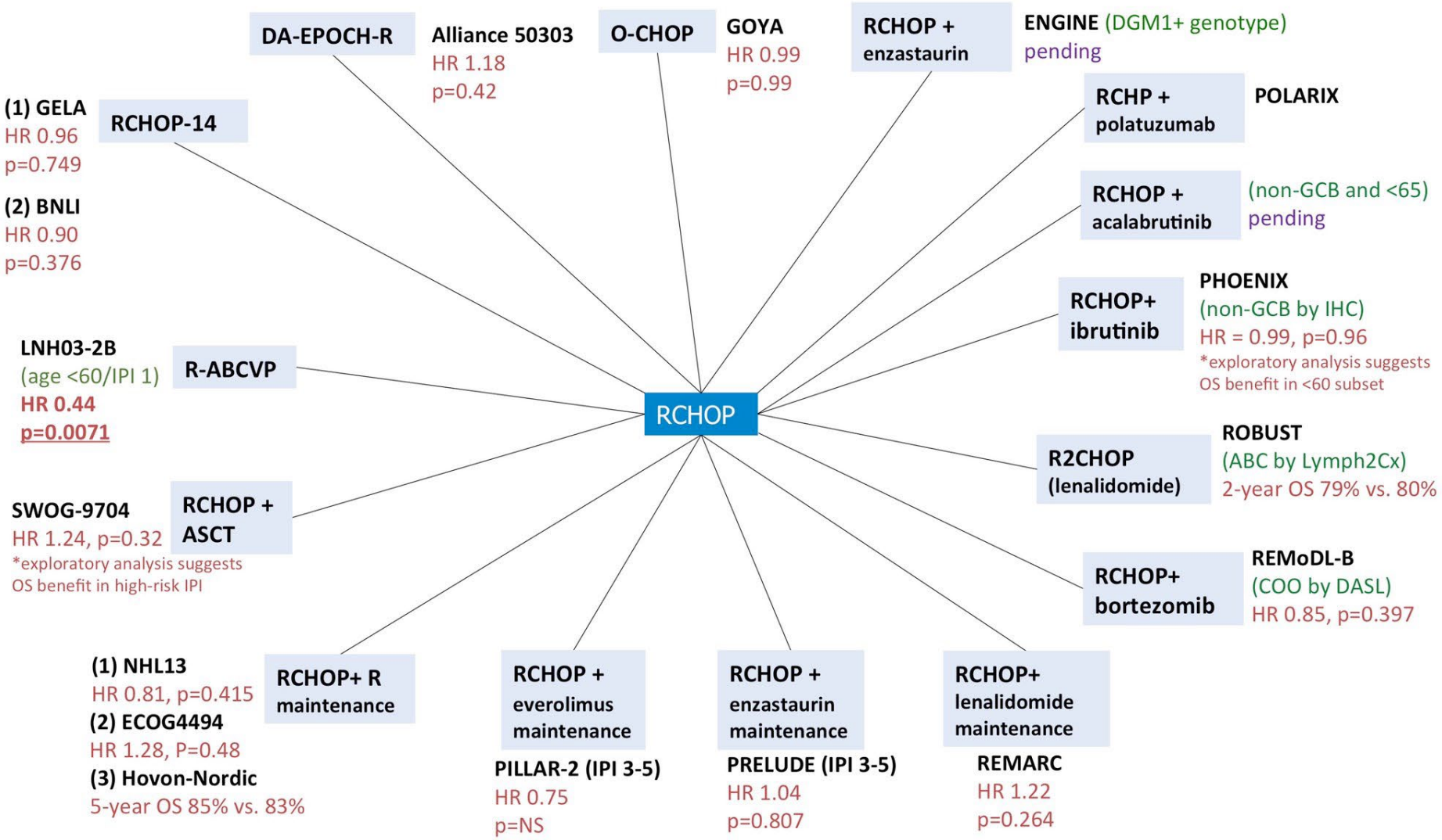
Should we ever intensify first line chemotherapy?

Radiotherapy use in advanced disease?

How should we treat older patients?

PMBCL, how is the treatment different?

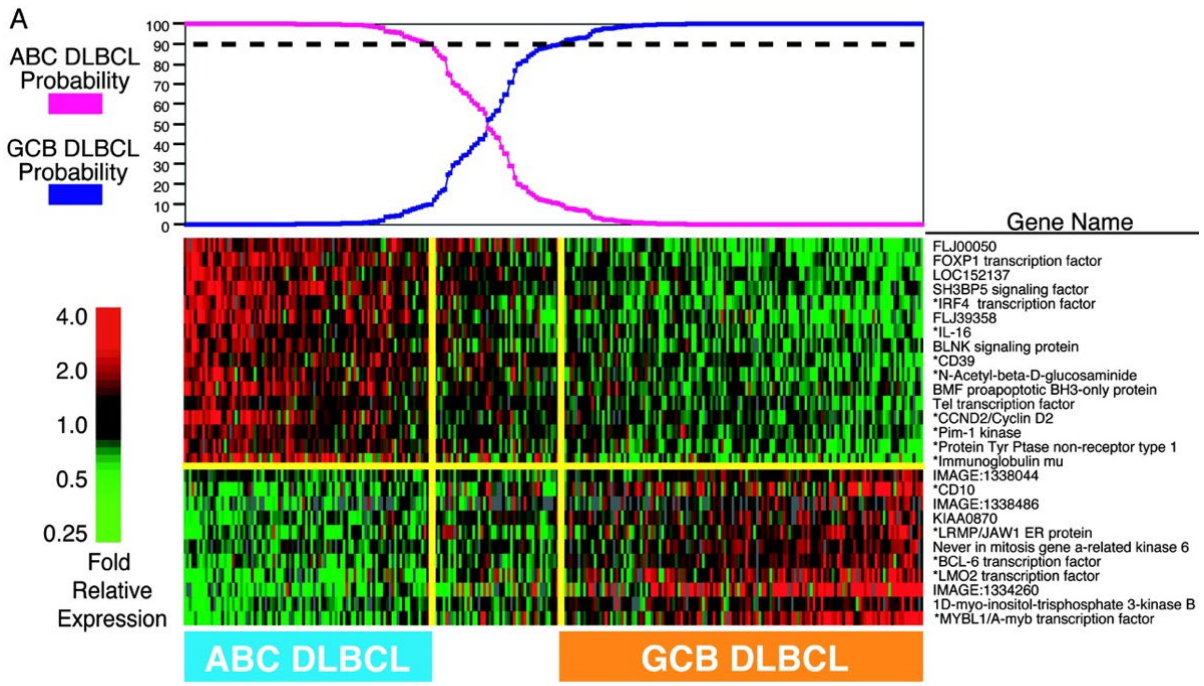
Some great trials….apart from the results



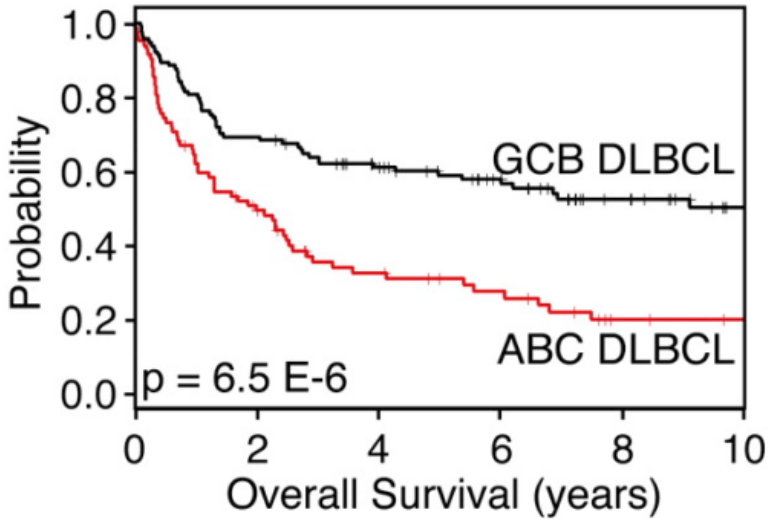
Competing schools of thought:

- Targeted therapy based on molecular phenotype
  - Gene expression/genomic typing
  - Small molecule inhibitors
- Better ways to use the cell surface markers
  - Antibodies with benefits
  - T-cell recruitment/expansion

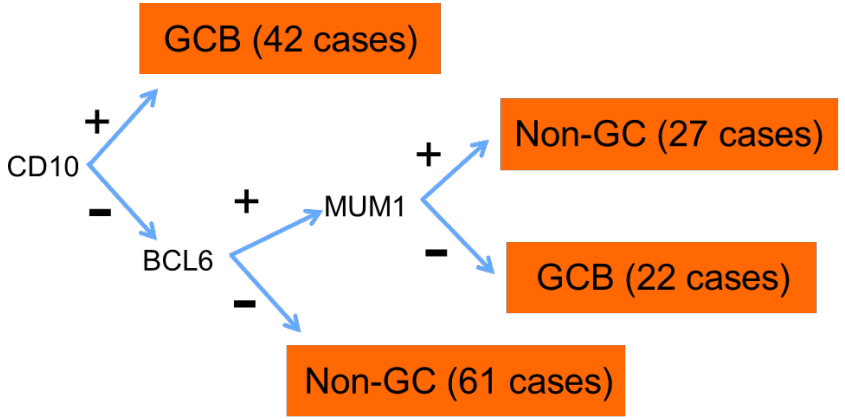
Not a single disease: complex models of biological heterogeneity



Wright et al., PNAS, 2003



Wright et al. 2003



Hans et al., Blood, 2004

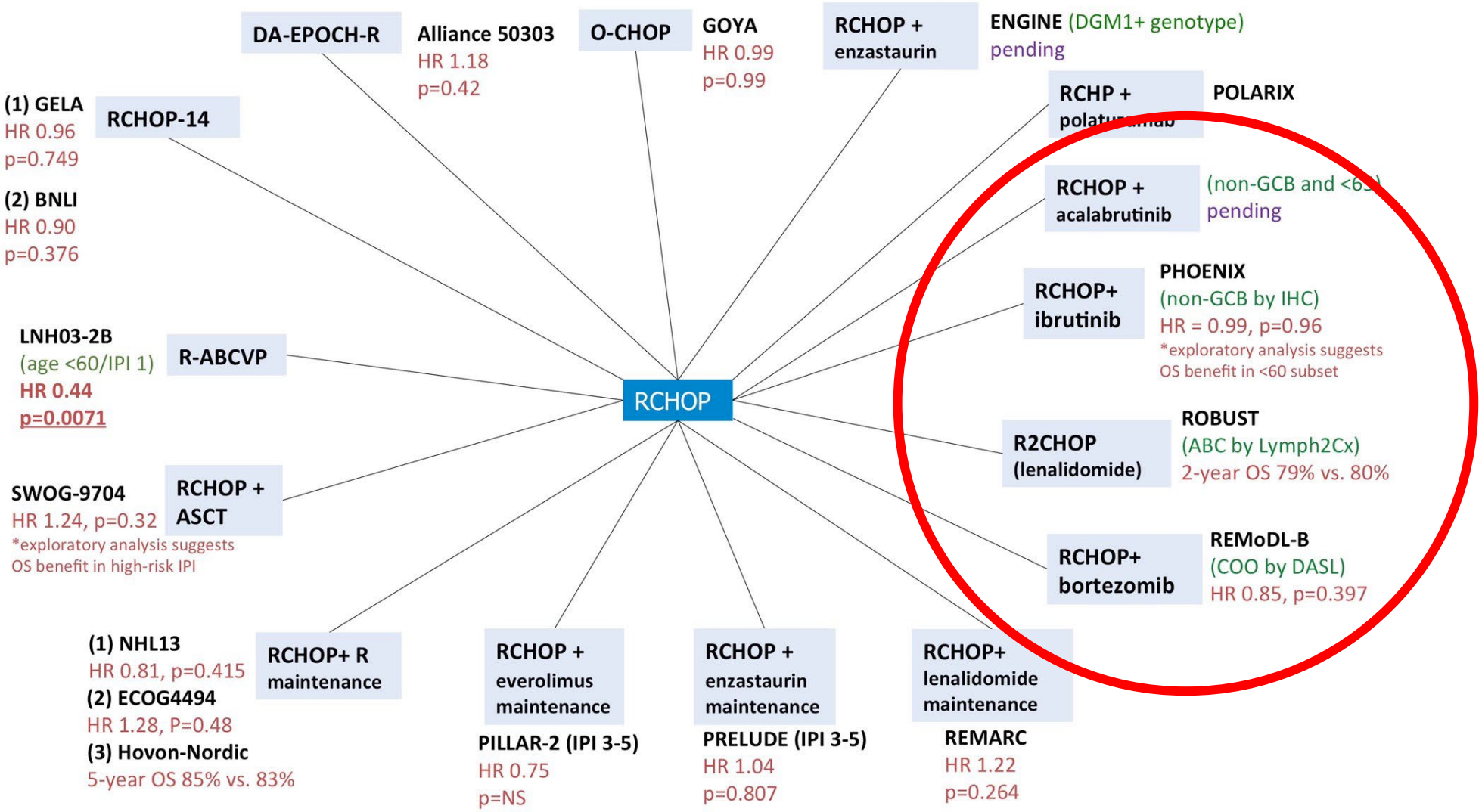
Failed to translate into diagnostic laboratories

Why? No effective therapeutic intervention

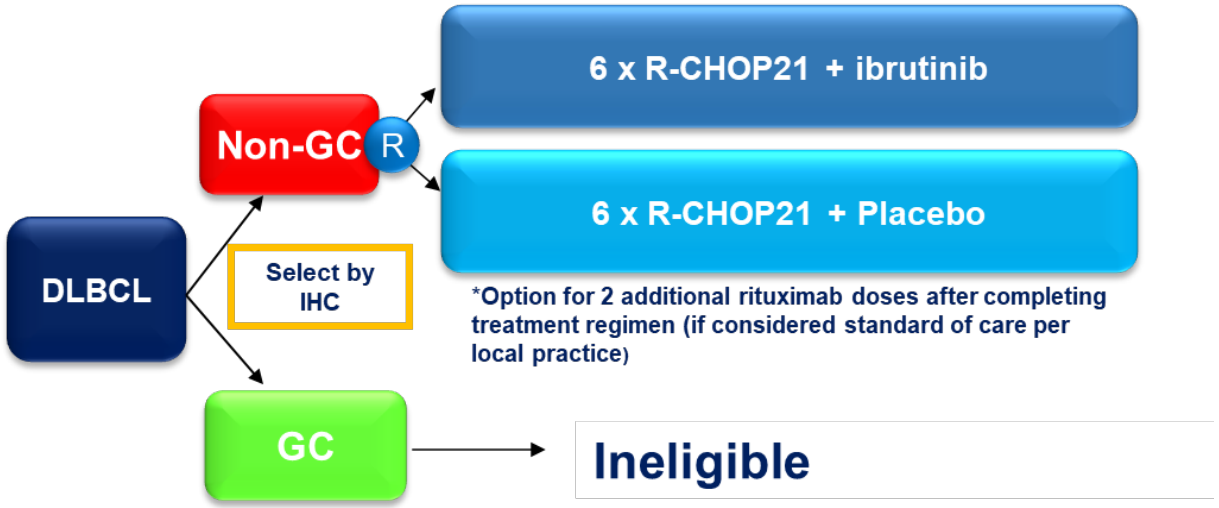
Ineffective proxies

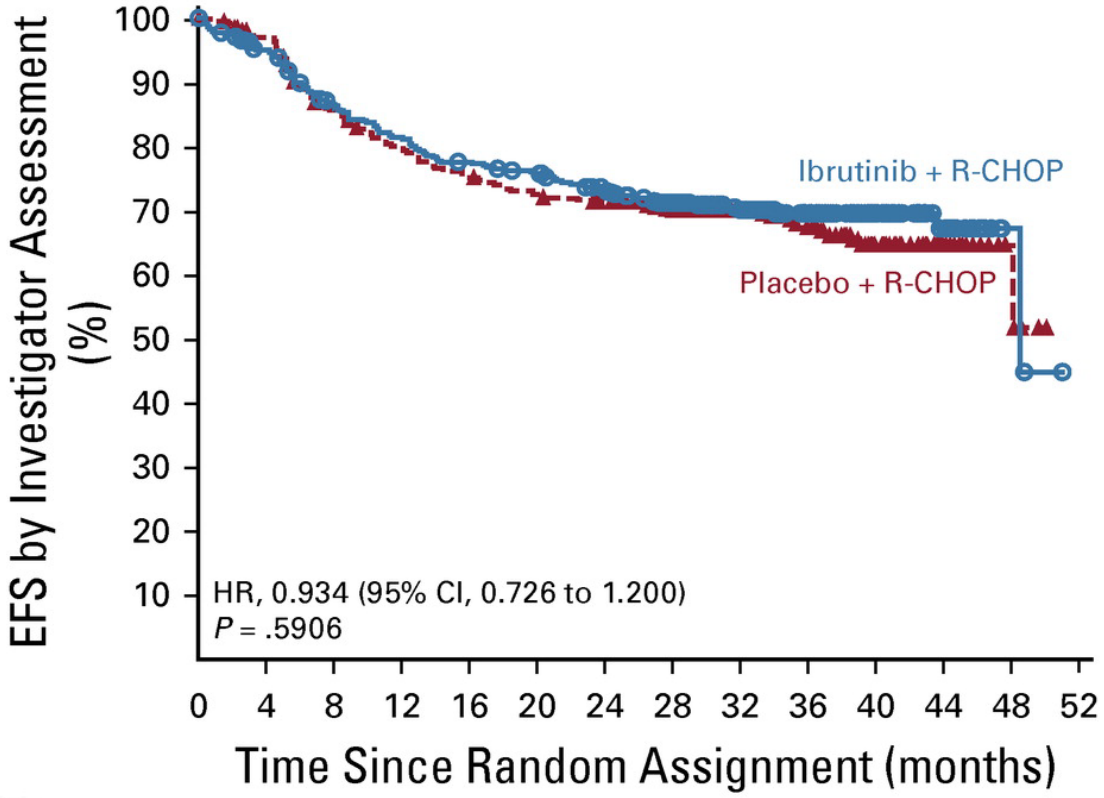
Never the less incorporated into WHO HAEM 4 and retained

Strategies to capitalise on the biology?



PHOENIX: Phase III double blind study of ibrutinib



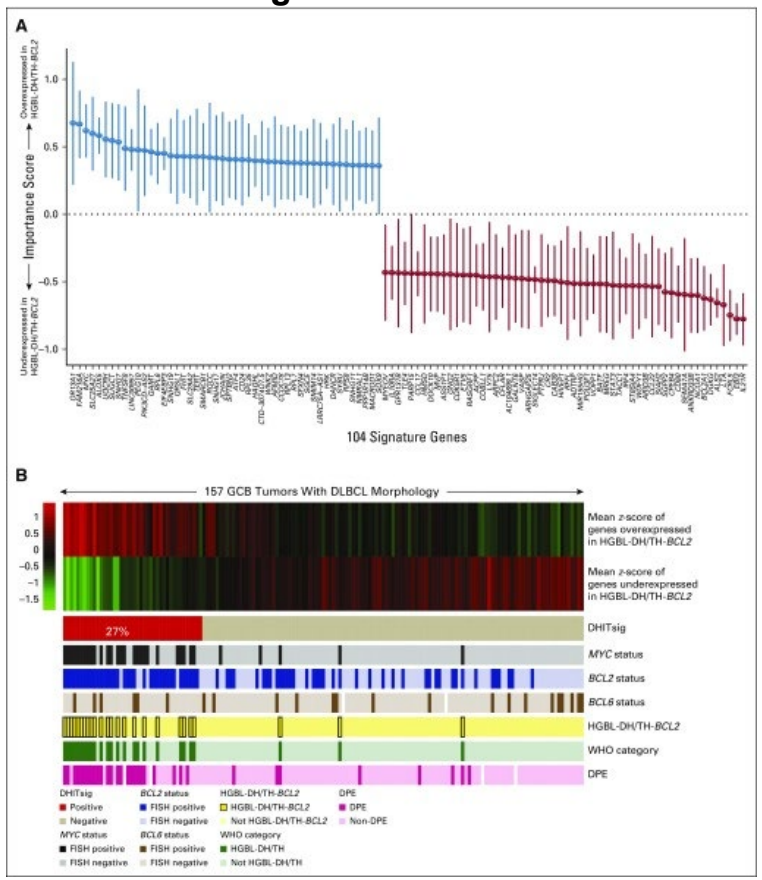


- Newly diagnosed DLBCL of non-GC
- ECOG PS ≤ 2; Age 18-80
- Primary Endpoint = EFS
- N = 800

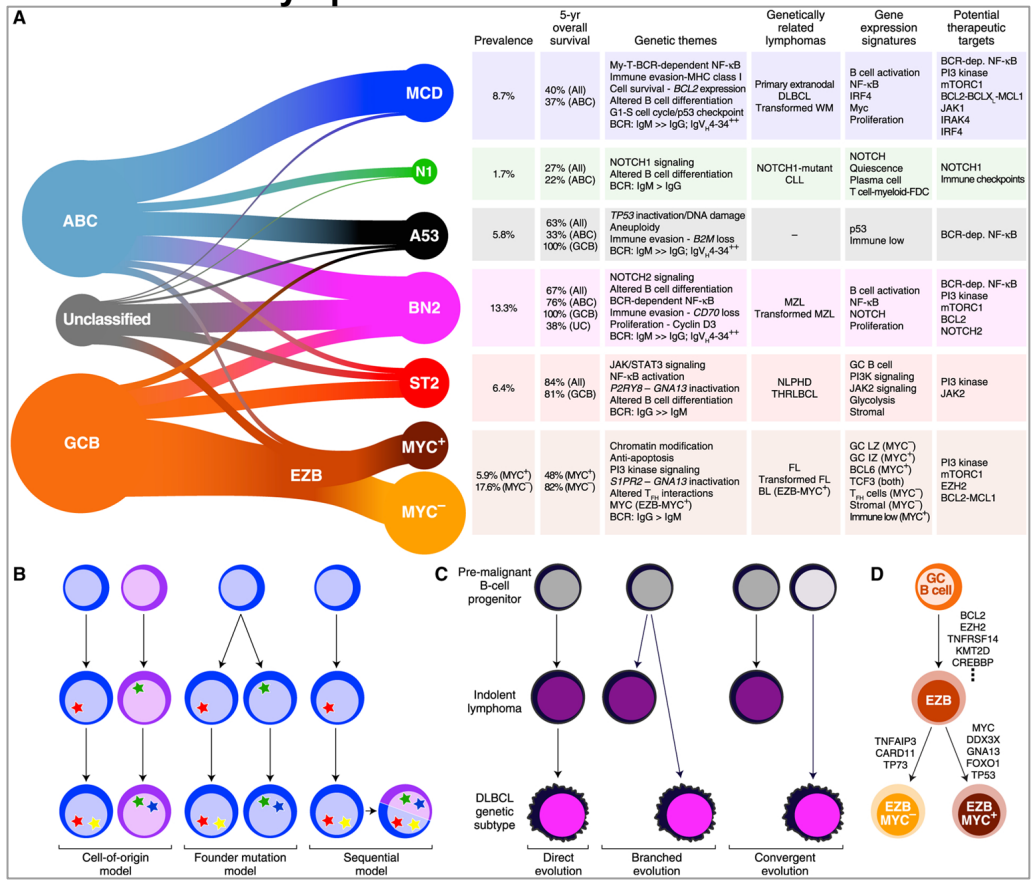
A Younes et al., ; J Clin Oncol 2019; 37:1285-1295.

DZsig and LymphGen classification

DZsig classification[1]



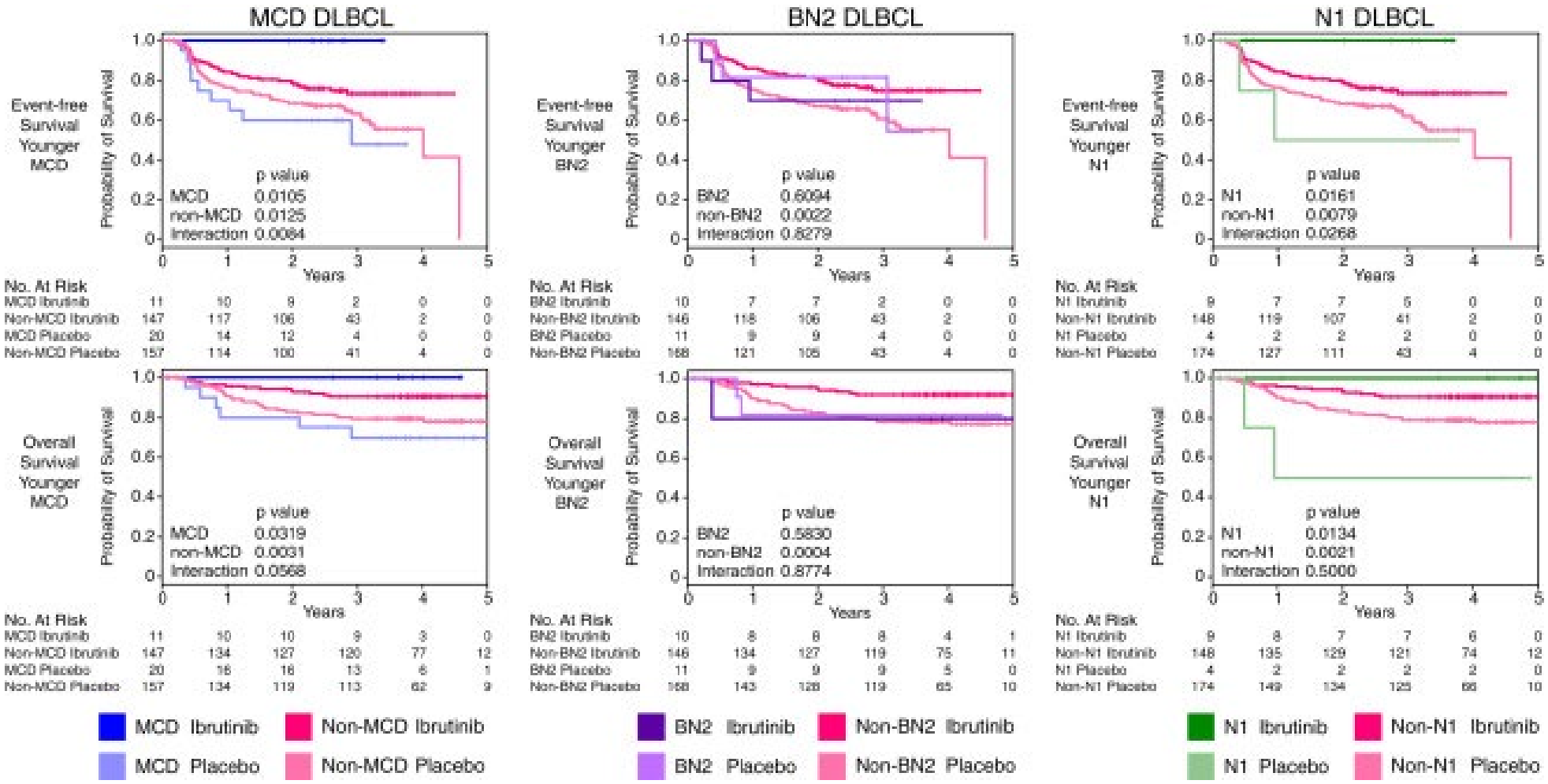
LymphGen classification[2]



- DZsig classification analyzes RNA sequencing data to define a gene expression signature that distinguishes HGBL-DH/TH-BCL2, a type of DLBCL associated with poor prognosis, from other GCB-DLBCL subtypes[1]
- The LymphGen algorithm provides a probabilistic classification of a tumor from an individual patient into a genetic subtype, defined as a group of tumors that is enriched for genetic aberrations (e.g., mutations, copy-number alterations, or fusions)[2]

1. Ennishi D, et al. J Clin Oncol 2019;37:190–201; 2. Wright GW, et al. Cancer Cell 2020;37:551–568.

Perhaps outcomes to target therapies by genomic class



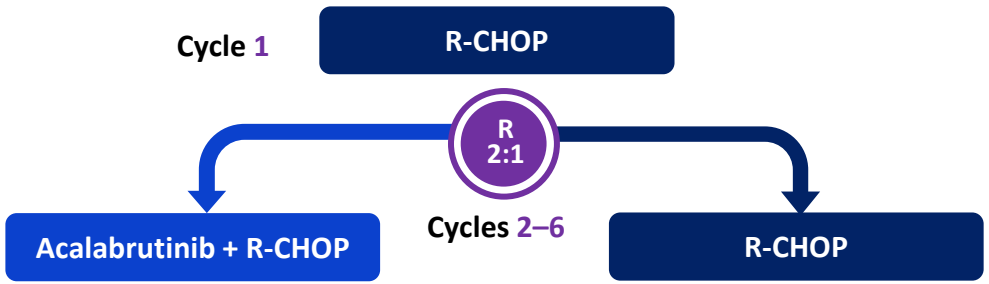
Wilson et al. 2021 Cancer Cell

Selected ongoing molecularly informed studies of acalabrutinib + R-CHOP in DLBCL: REMoDL-A and ESCALADE

REMoDL-A[1]
A Phase 2, open-label, randomized study

Patients (estimated enrollment N=453)

- ✓ Previously untreated CD20+ DLBCL
- ✓ Age ≥16 years
- ✓ ECOG PS 0–2*

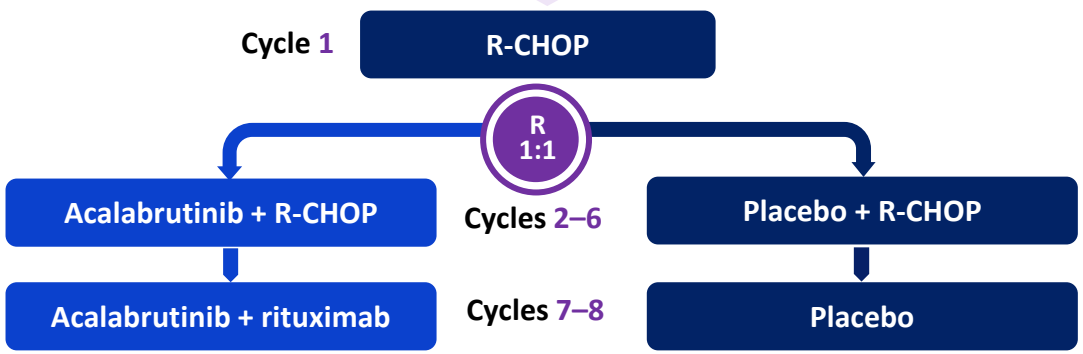


Primary endpoint: PFS
Secondary endpoints: PFS by COO subgroup, OS, EFS, DFS, DoR, ORR, safety

ESCALADE[2]
A Phase 3, double-blind, randomized study

Patients (estimated enrollment N=600)

- ✓ Previously untreated non-GCB DLBCL
- ✓ Age 18–65 years
- ✓ Ann Arbor Stage II–IV[3]
- ✓ R-IPI score 2–5

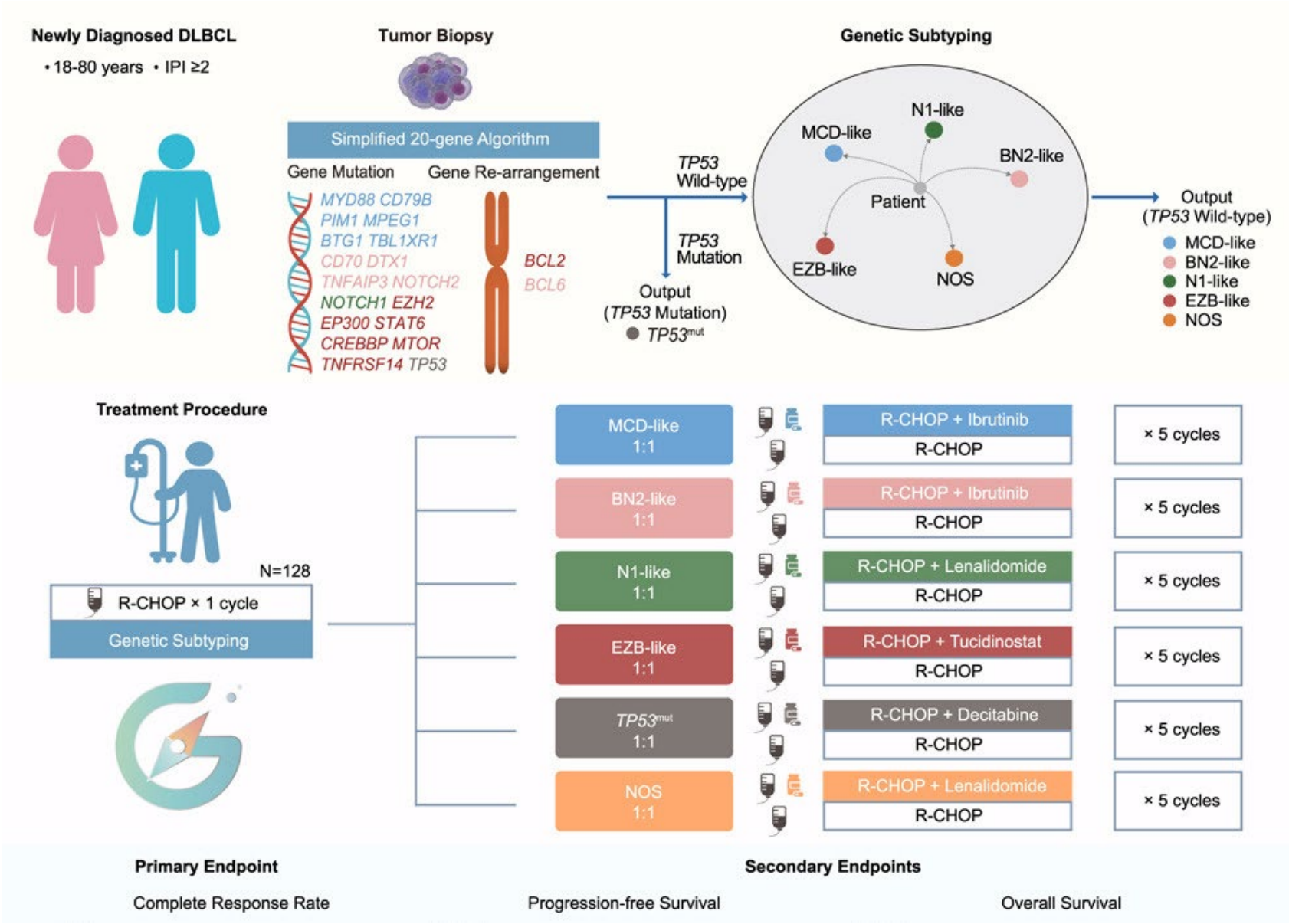


Primary endpoint: PFS
Secondary endpoints: EFS, CR, OS, PK, safety

*ECOG PS 3 if it is directly attributable to lymphoma.
R-IPI, Revised-International Prognostic Index.

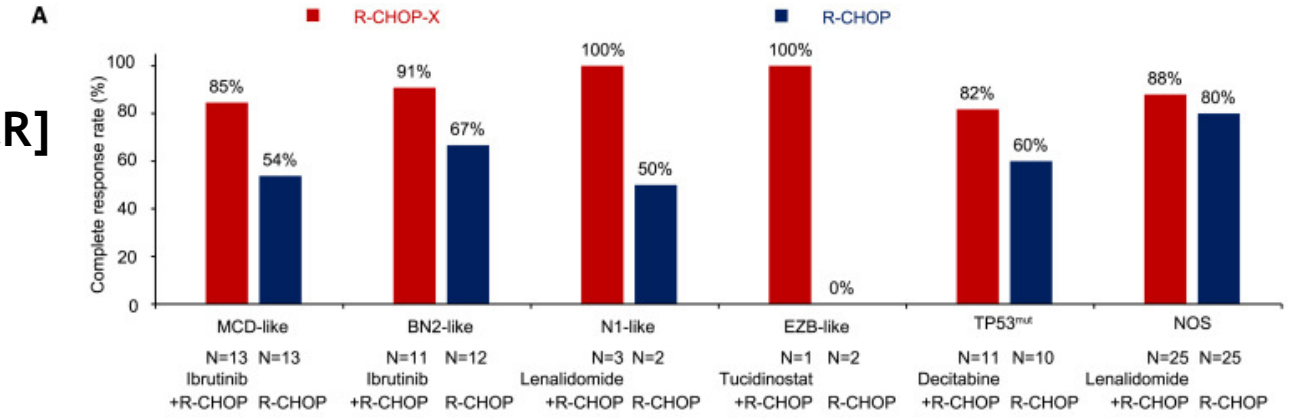
1. NCT04546620. Available at: https://clinicaltrials.gov/ct2/show/NCT04546620 [Accessed 03.03.2023]; 2. Sehn et al. JCO 2021;TPS7572; 3. NCT04529772. Available at: https://clinicaltrials.gov/ct2/show/NCT04529772 [Accessed 10.03.2023].

GUIDANCE-01 (Zhang et al. Cancer Cell 2023) n=128

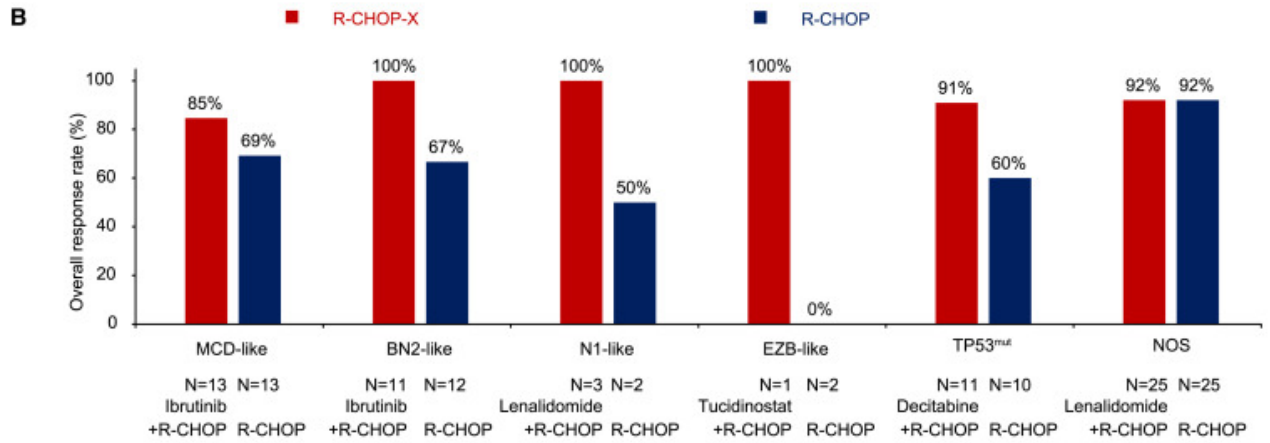


Primary endpoint [CR]
88% R-CHOP-X arm
66% (R-CHOP arm
(p = 0.003)

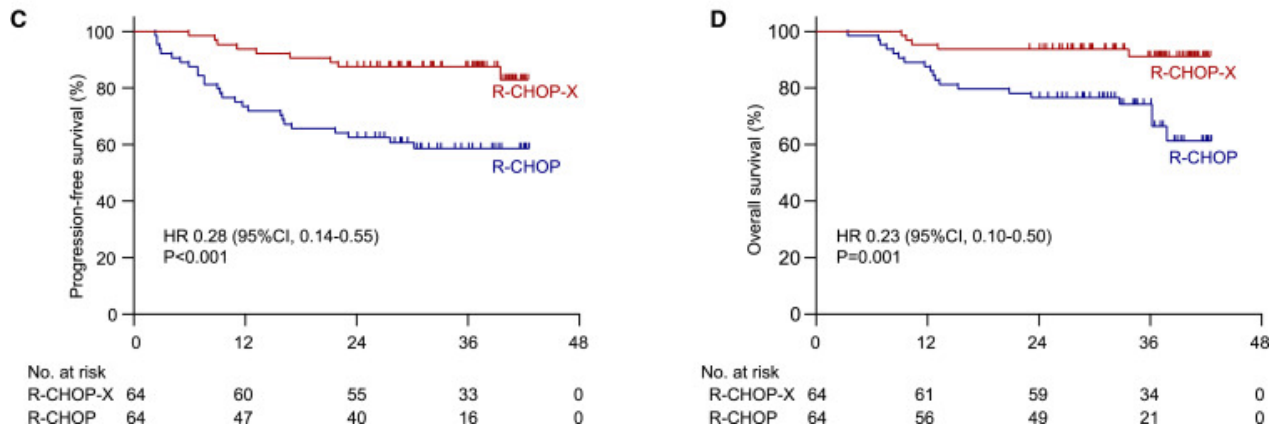
Toxicity: cytopenias
Intensity maintained



CR



ORR



Improvement in OS

Zhang et al. Cancer Cell 2023

Better ways of exploiting widely expressed cell surface antigens

Polatuzumab Vedotin : Mechanism of Action

- Polatuzumab vedotin is an antibody drug conjugate (ADC) consisting of a potent microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker

CD79b

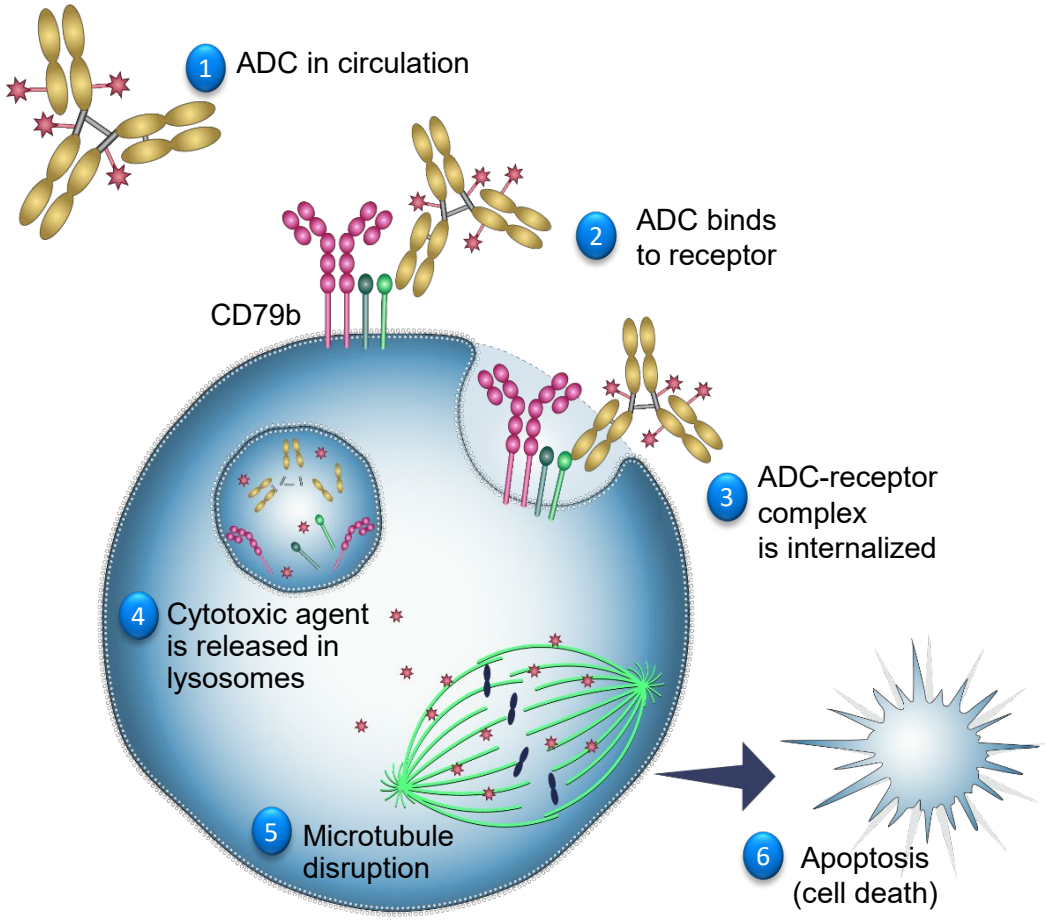
- Signaling component of the B-cell receptor
- Restricted to mature B cells (except plasma cells); expressed by most B-cell hematologic malignancies
- Expressed in >95% of DLBCL[1,2]

Linker

- Cathepsin-B-sensitive vc linker

Payload

- MMAE – tubulin inhibitor x100-1000 more potent that vincristine



[1]Dornan Blood 2009; [2]Pfeifer Leukemia 2015

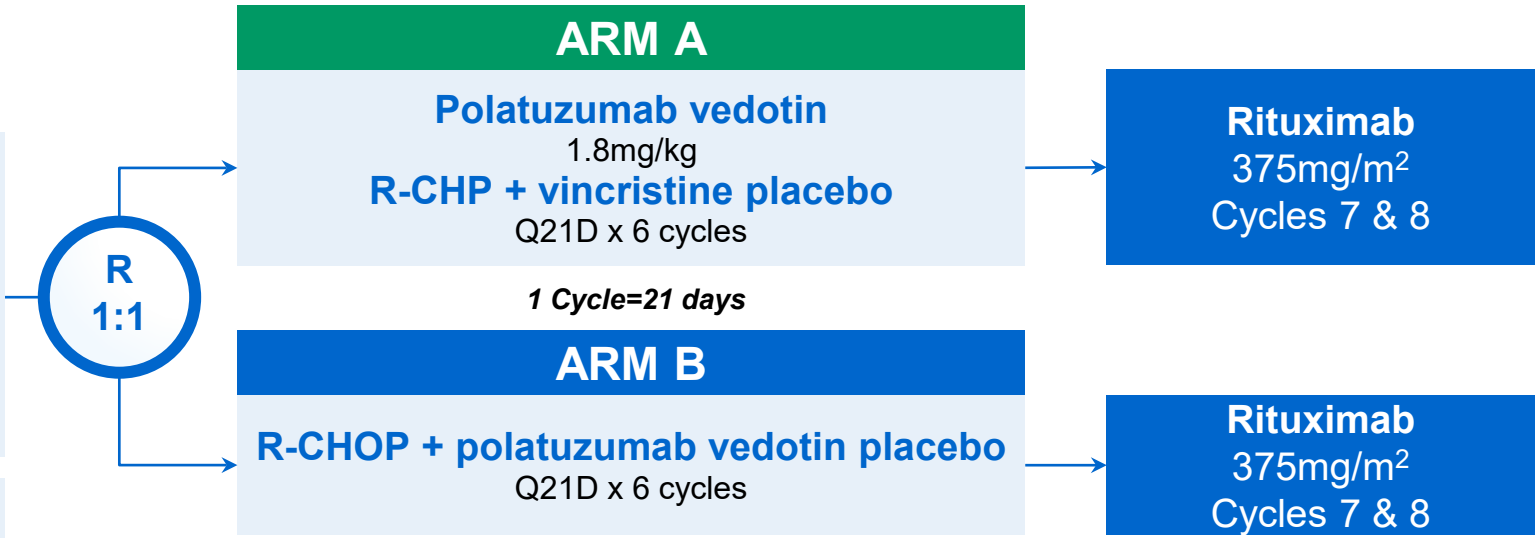
Study design overview

- **Double-blind, randomized controlled**
- Collaboration with LYSA
- NCT03274492

Patients
- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

N=879

Stratification factors
- IPI score (2 vs 3–5)
- Bulky disease (≥7.5cm vs absence)
- Geographic region*

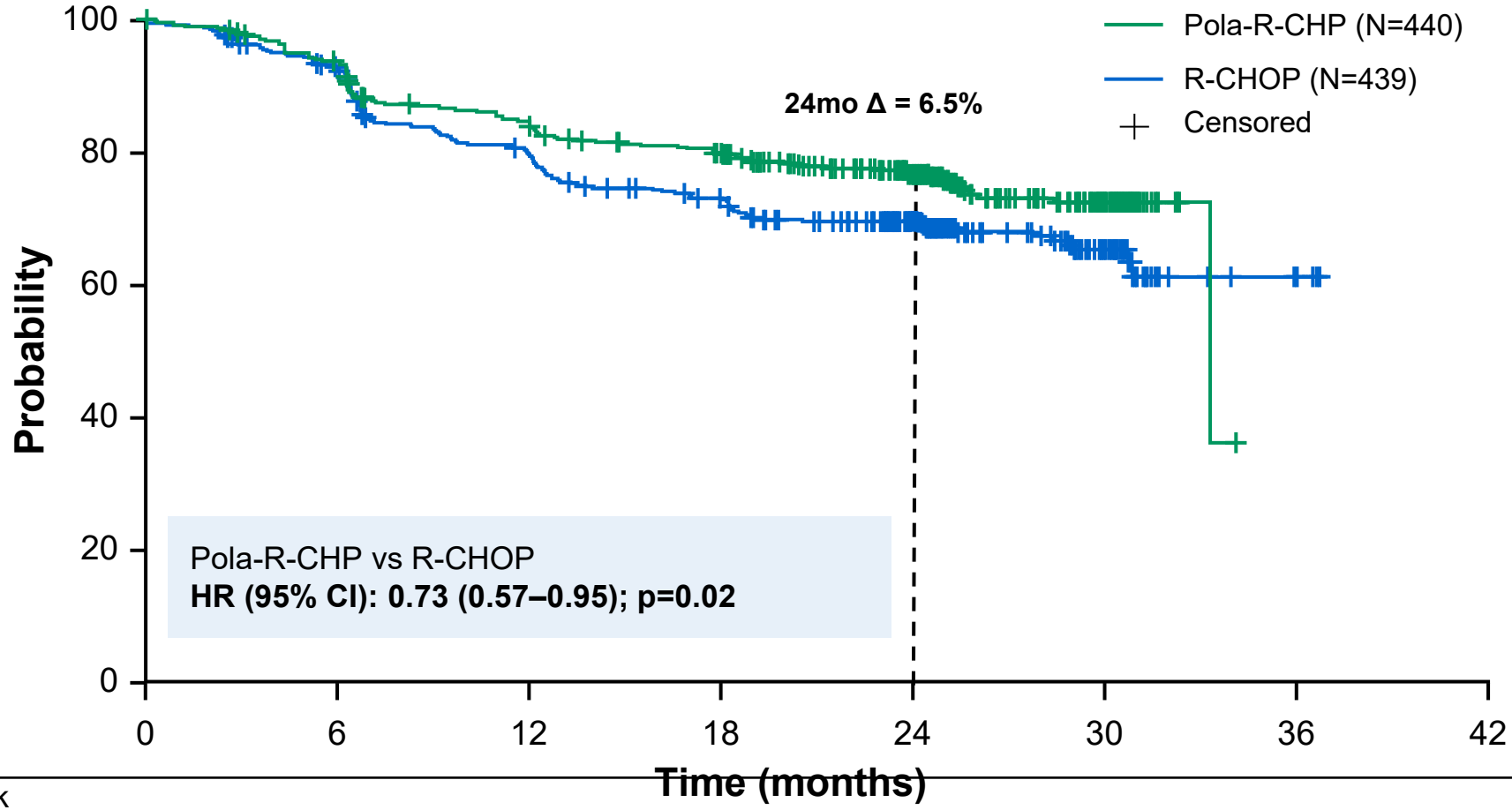


Primary endpoint	PFS by INV
Key secondary endpoints	EFS efficacy by INV, PET CR at EOT by BICR, OS, and safety

*Western Europe, United States, Canada and Australia vs Asia vs Rest of World. BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS efficacy, event-free survival for efficacy causes (time from randomization to the earliest occurrence of disease progression/relapse, death due to any cause, initiation of any non-protocol specified anti-lymphoma treatment, or biopsy-confirmed residual disease after treatment completion); EOT, end of treatment; INV, investigator; IPI, International Prognostic Index; LYSA, Lymphoma Study Association; PET, positron emission tomography; Q21D, every 21 days; R, randomization; R-CHP, rituximab plus cyclophosphamide, doxorubicin, prednisone.

Tilly H, et al. New Engl J Med 2022;386:351–63.

Investigator-assessed PFS



Number at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

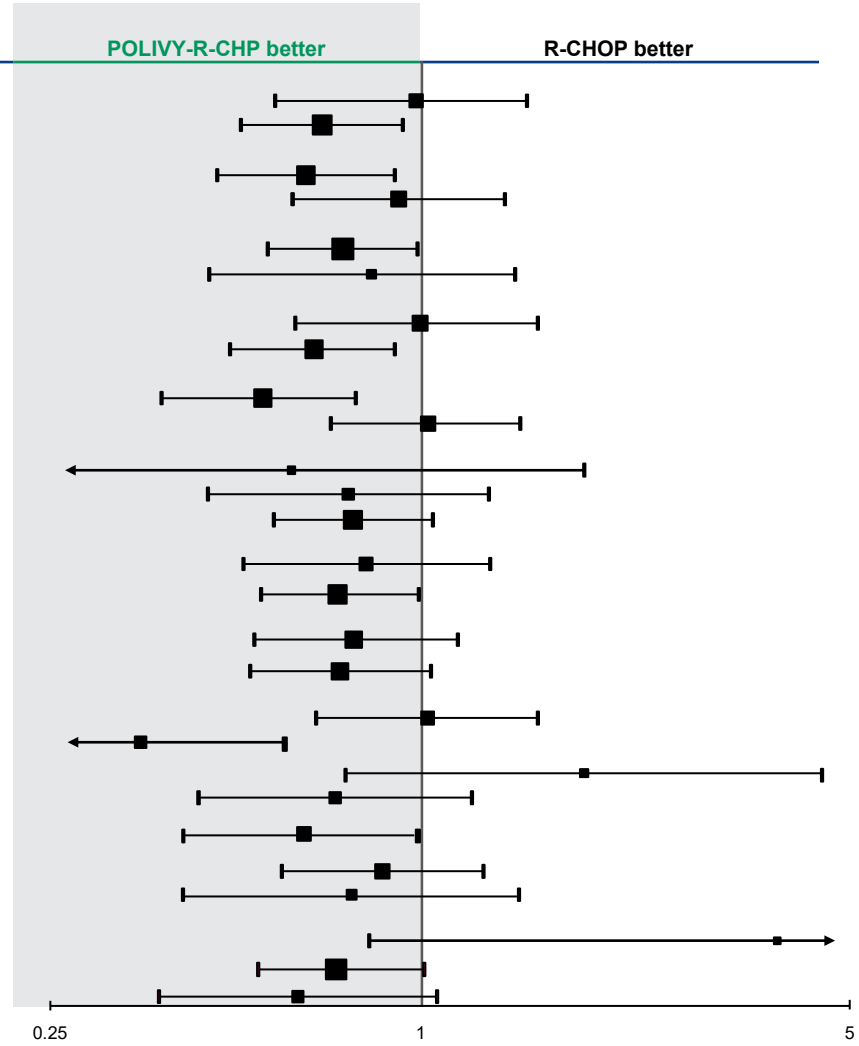
mo, months; NE, not evaluable.

Tilly H, et al. New Engl J Med 2022;386:351–63.

Investigator-assessed PFS by subgroup (unstratified)

Exploratory subgroup analyses are signal seeking and hypothesis generating; event numbers and sample size are limited

Baseline risk factors	Total N	n	2-year rate	n	2-year rate	HR	95% Wald CI
Age group							
≤60	271	140	74.1	131	71.9	0.9	(0.6 to 1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5 to 0.9)
Sex							
Male	473	239	75.9	234	65.9	0.7	(0.5 to 0.9)
Female	406	201	77.7	205	75.2	0.9	(0.6 to 1.4)
ECOG PS							
0–1	737	374	78.4	363	71.2	0.8	(0.6 to 1.0)
2	141	66	67.2	75	65.0	0.8	(0.5 to 1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6 to 1.6)
IPI 3–5	545	273	75.2	272	65.1	0.7	(0.5 to 0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4 to 0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7 to 1.5)
Ann Arbor stage							
I–II	99	47	89.1	52	85.5	0.6	(0.2 to 1.8)
III	232	124	80.7	108	73.6	0.8	(0.5 to 1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6 to 1.1)
Baseline LDH							
≤ULN	300	146	78.9	154	75.6	0.8	(0.5 to 1.3)
>ULN	575	291	75.4	284	67.2	0.7	(0.5 to 1.0)
No. of extranodal sites							
0–1	453	227	80.2	226	74.5	0.8	(0.5 to 1.1)
≥2	426	213	73.0	213	65.8	0.7	(0.5 to 1.0)
Cell-of-origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7 to 1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2 to 0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8 to 4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4 to 1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4 to 1.0)
Non-DEL	438	223	77.7	215	75.7	0.9	(0.6 to 1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4 to 1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8 to 17.6)
No	620	305	76.8	315	70.3	0.7	(0.5 to 1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4 to 1.1)

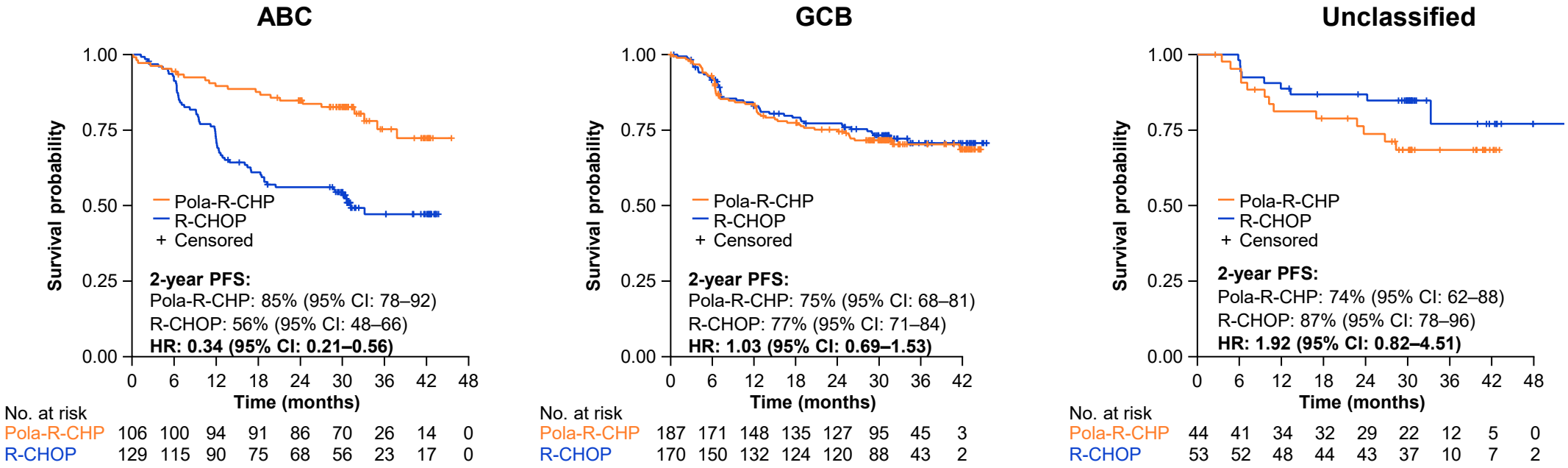


ABC, activated B-cell type; CI, confidence interval; DEL, double-expressor lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCB, germinal centre B-cell type; HR, hazard ratio; IHC, immunochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PFS, progression-free survival; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper limit normal.

Tilly H, *et al. N Engl J Med*. 2022;386:351–363 (supplementary appendix).

Investigator-Assessed PFS* by COO Subgroup

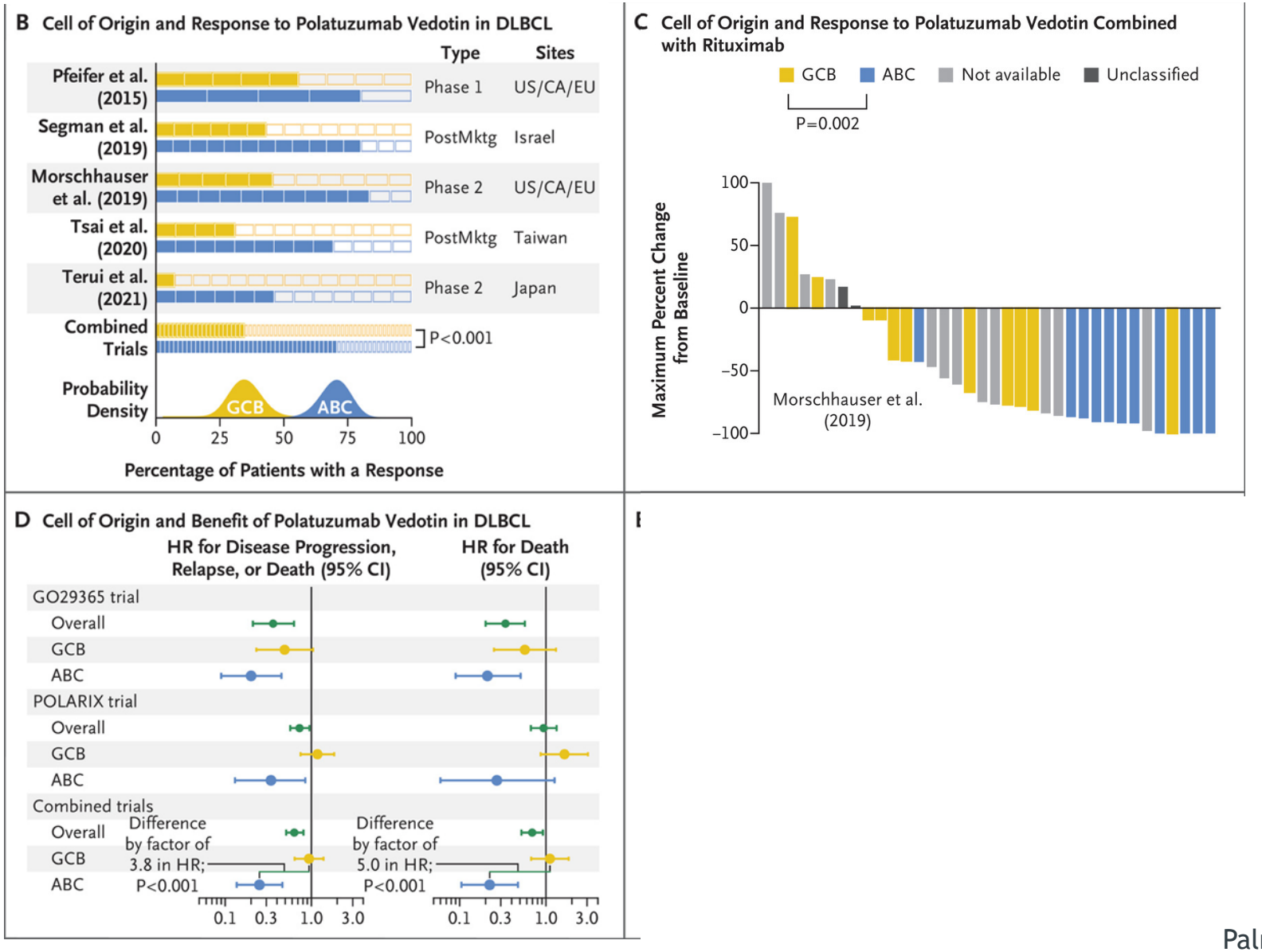
- COO status was determined in 689 patients in POLARIX (ABC, n=235; GCB, n=357; unclassified, n=97)
- Based on a data cutoff of June 15, 2022, with a median follow-up of 39.7 months, a **PFS difference between treatment groups** was observed in ABC-DLBCL, but not in GCB or the unclassified subgroups



*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events. Tick marks indicate censored data.

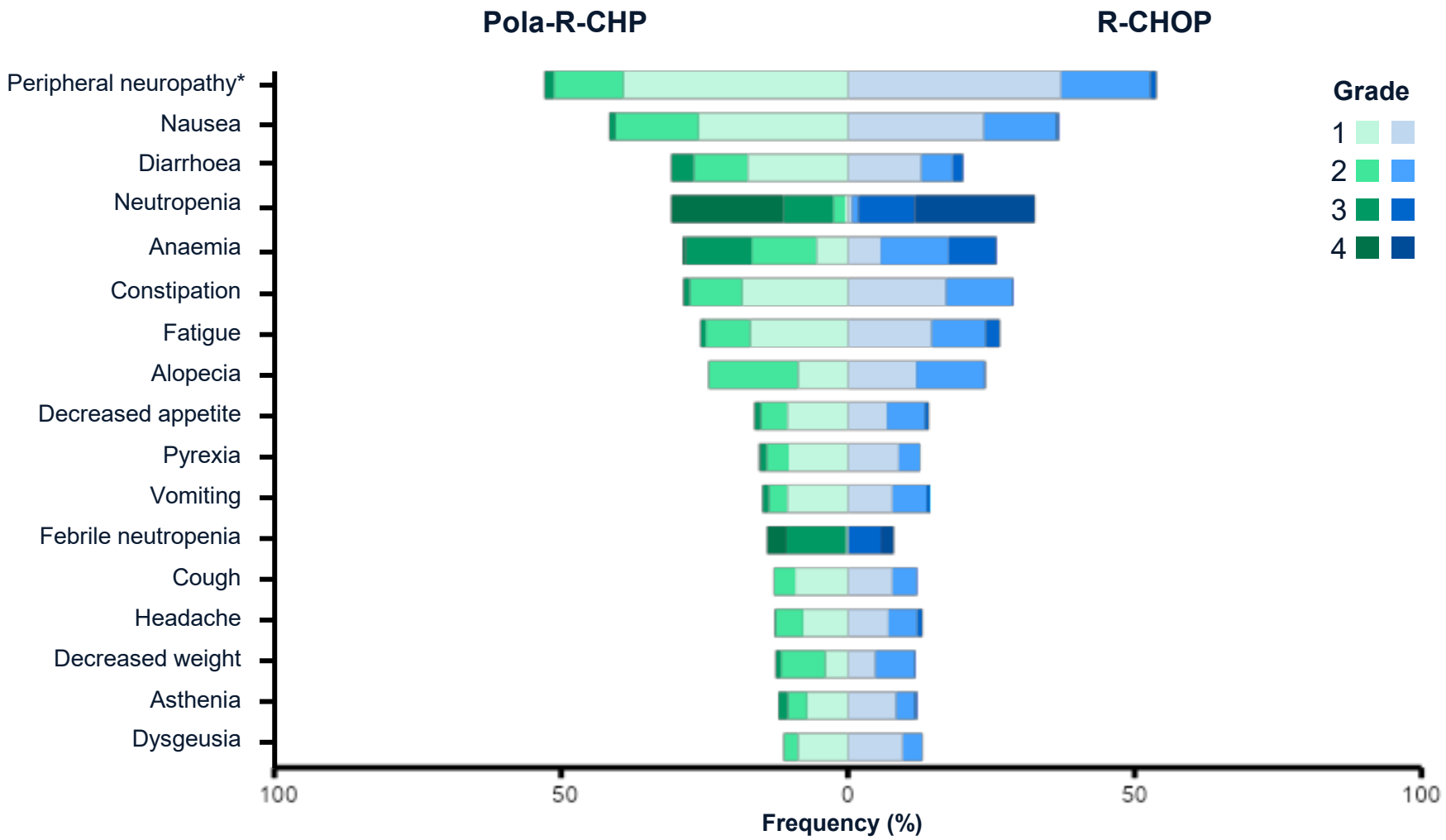
Morschhauser F, et al. ASH 2023. Poster 3000.

Cell of origin and benefit from polatuzumab



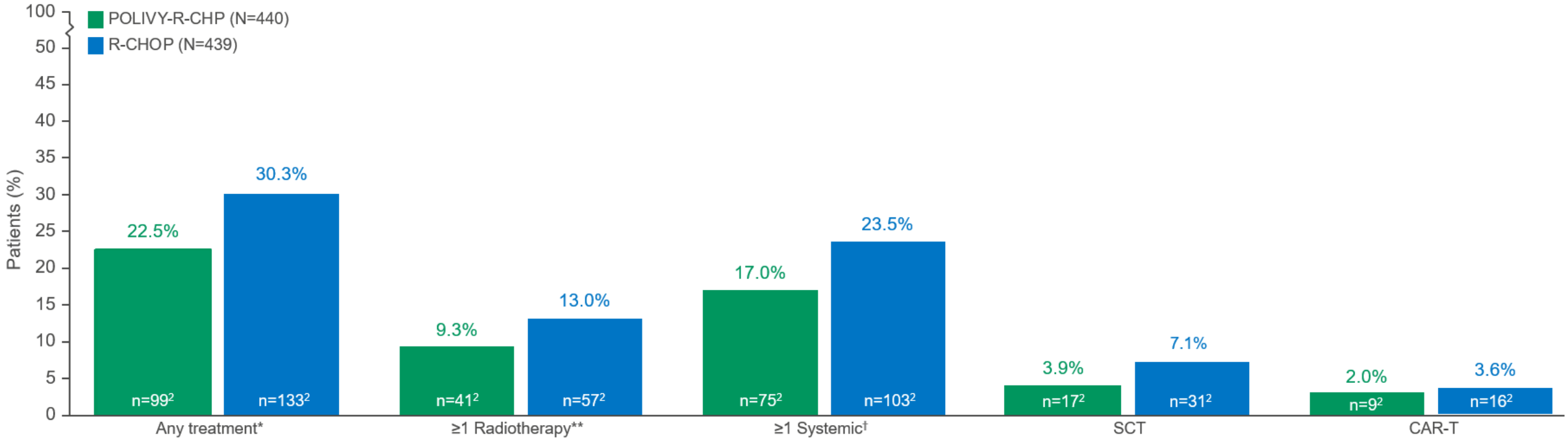
Palmer et al. NEJM 2023

Common adverse events



Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

Subsequent lines of therapies received by patients

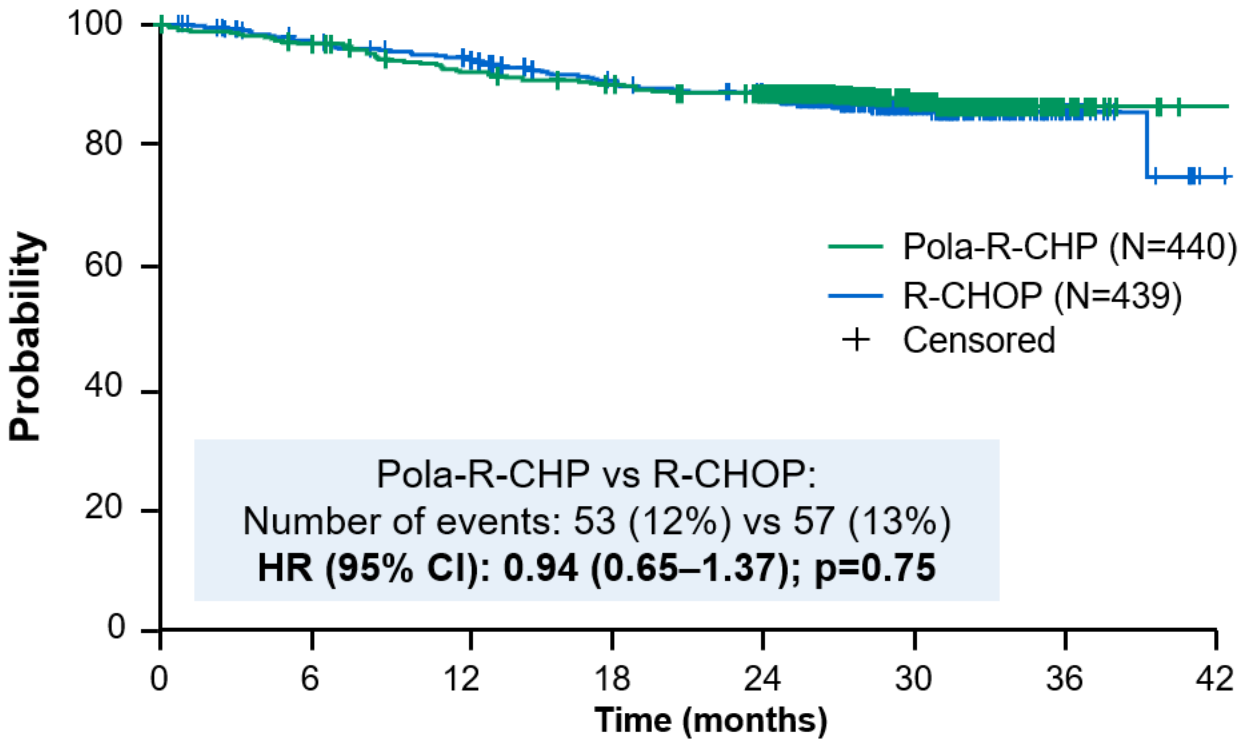


*≥1 Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy and does not include intrathecal central nervous system disease prophylaxis as part of treatment; **Includes preplanned and unplanned radiotherapy; †Includes any monotherapy, multi-drug, or cell-based regimen[2]

1L, first-line; CAR-T, chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; R-CHP, rituximab cyclophosphamide, doxorubicin, prednisone; R-CHOP, rituximab, cyclophosphamide, vincristine, prednisone; R/R, relapsed/refractory; SCT, stem cell transplant.

1. Tilly H, *et al. N Engl J Med.* 2022;386:351–363;
2. Tilly H, *et al. N Engl J Med.* 2022;386:351–363 (supplementary appendix).

There is no OS difference between the arms



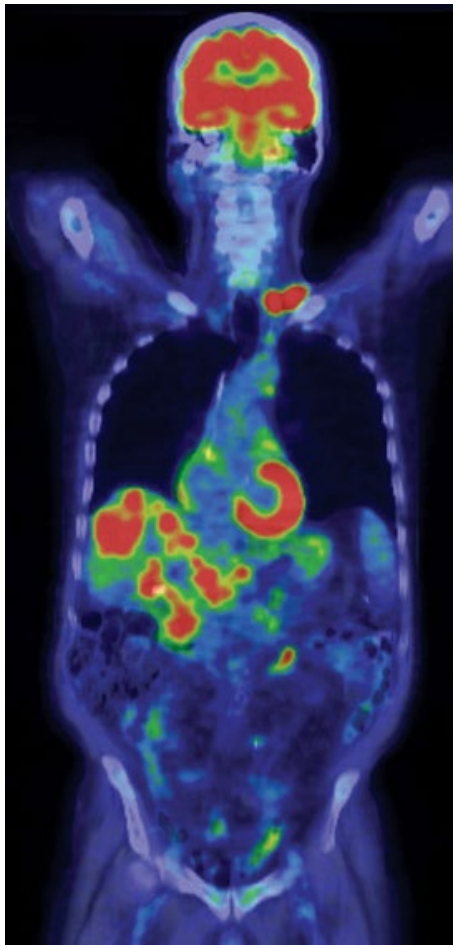
Number at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

	Pola-R-CHP (N=440)	R-CHOP (N=439)
No. of events, n (%)	**53 (12.0)**	**57 (13.0)**
Earliest contributing event, n		
Death	53	57
Stratified analysis*		
p-value (Log-rank)	0.75	
Hazard ratio (95% CI)	0.94 (0.65–1.37)	
24 months OS rate† (95% CI)	88.7 (85.7–91.6)	88.6 (85.6–91.6)

The final OS analysis will be performed (two-sided alpha boundary = 0.04) in the 2nd half of 2022.
*Stratified for IPI score (IPI 2 vs IPI 3–5), bulky disease (present vs absent), and geographical region (Western Europe, United States, Canada and Australia vs Asia vs Rest of World [remaining countries]); †Kaplan–Meier estimate.

Tilly H, et al. New Engl J Med 2022;386:351–63.

7 first line treatment decisions in Large B-cell Lymphoma



CNS prophylaxis, who and how?

How should we treat early-stage disease?

Can we improve on RCHOP21?

Should we ever intensify first line chemotherapy?

Radiotherapy use in advanced disease?

How should we treat older patients?

PMBCL, how is the treatment different?

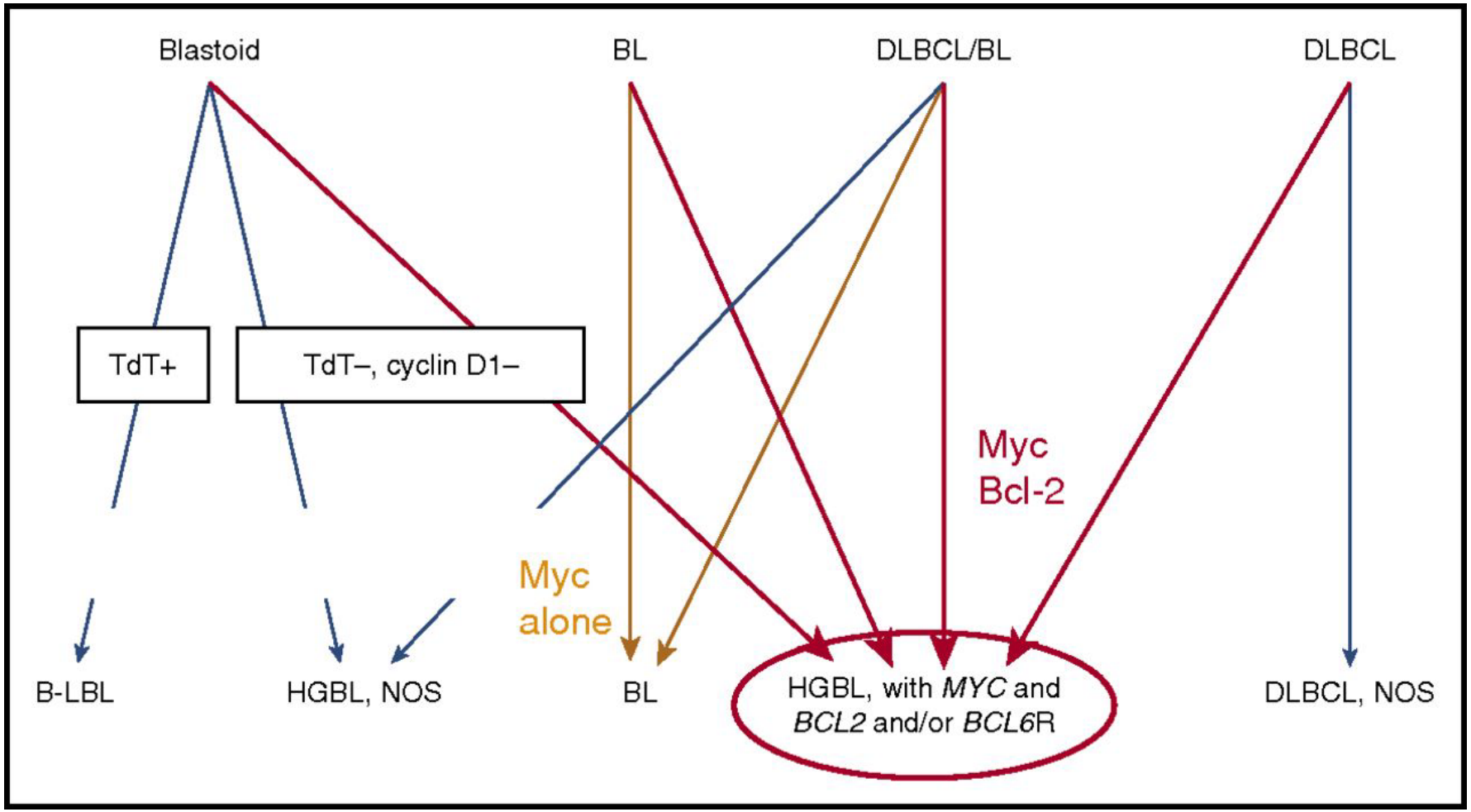
Diagnostic algorithm: Keep reporting morphology

Morphology

immuno

FISH

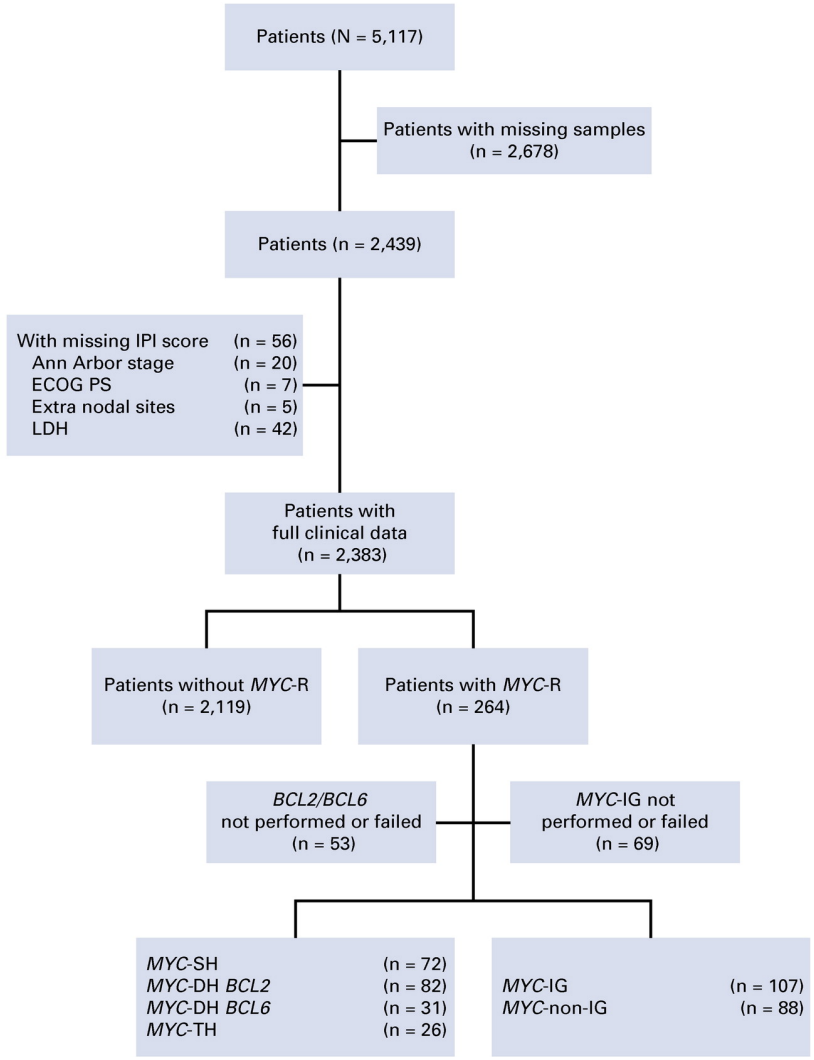
WHO



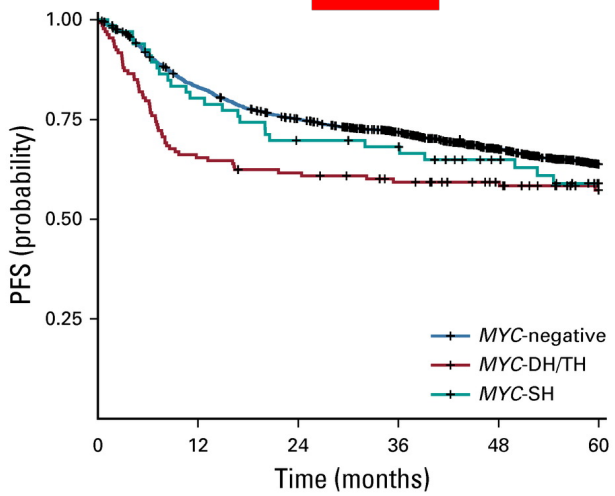
Jonathan W. Friedberg Blood 2017;130:590-596

Double and triple-hit lymphomas can show a morphological spectrum of findings, but are united by the presence of rearrangements involving MYC, with either BCL2 or BCL6 or both

FISH and DLBCL prognosis



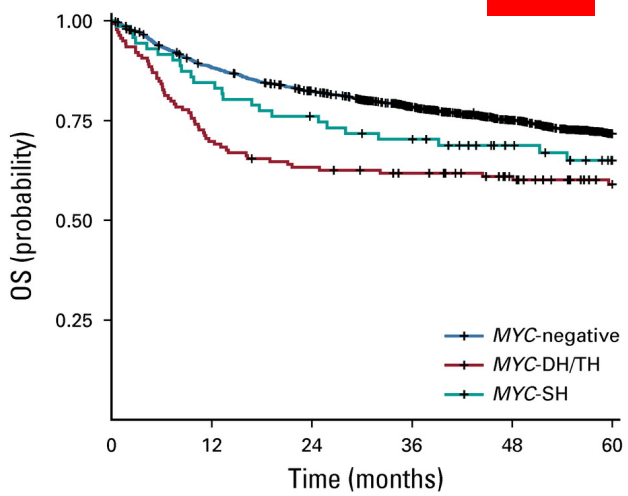
PFS



No. at risk:

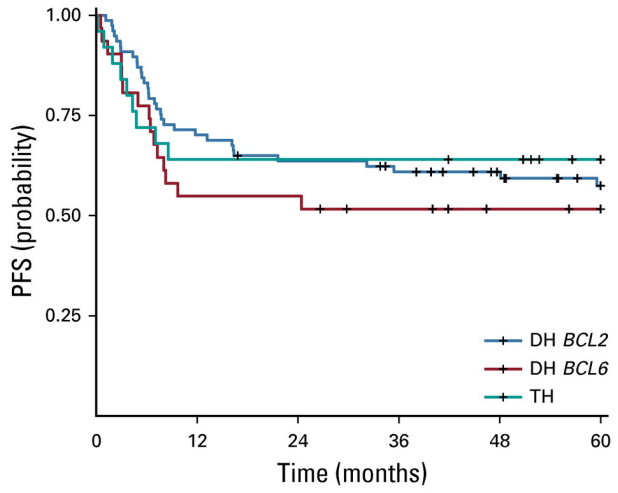
MYC-negative	2,049	1,687	1,508	1,371	1,173	949
MYC-DH/TH	133	87	81	74	64	52
MYC-SH	67	53	45	43	34	25

OS



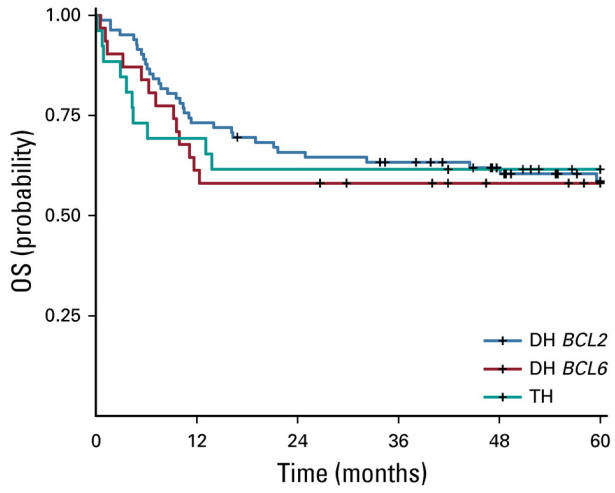
No. at risk:

MYC-negative	2,119	1,858	1,716	1,556	1,353	1,106
MYC-DH/TH	139	97	87	81	69	54
MYC-SH	72	60	53	48	38	29



No. at risk:

DH *BCL2*	77	54	48	44	38	31
DH *BCL6*	31	17	17	14	11	10
TH	25	16	16	16	15	11



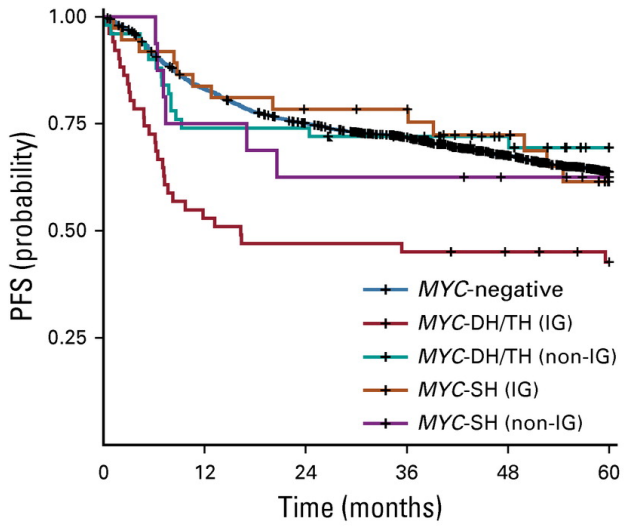
No. at risk:

DH *BCL2*	82	60	53	49	41	32
DH *BCL6*	31	19	18	16	13	11
TH	26	18	16	16	15	11

Rosenwald et al JCO 2019 on behalf of the LLBC

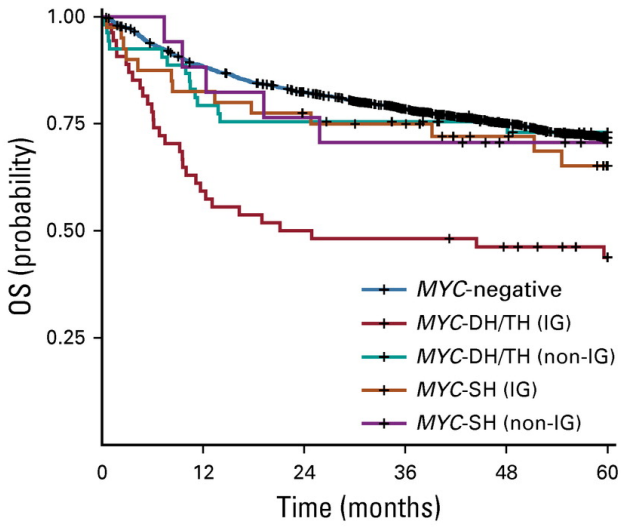
Impact of *MYC*-R partner

PFS



No. at risk:						
MYC-negative	2,049	1,687	1,508	1,371	1,173	949
MYC-DH/TH (IG)	51	27	24	23	21	18
MYC-DH/TH (non-IG)	50	37	37	34	28	21
MYC-SH (IG)	37	31	28	27	21	14
MYC-SH (non-IG)	16	12	10	10	8	6

OS



No. at risk:						
MYC-negative	2,119	1,858	1,716	1,556	1,353	1,106
MYC-DH/TH (IG)	54	32	27	26	23	18
MYC-DH/TH (non-IG)	53	42	40	38	31	23
MYC-SH (IG)	40	33	30	28	22	16
MYC-SH (non-IG)	17	15	13	12	9	7

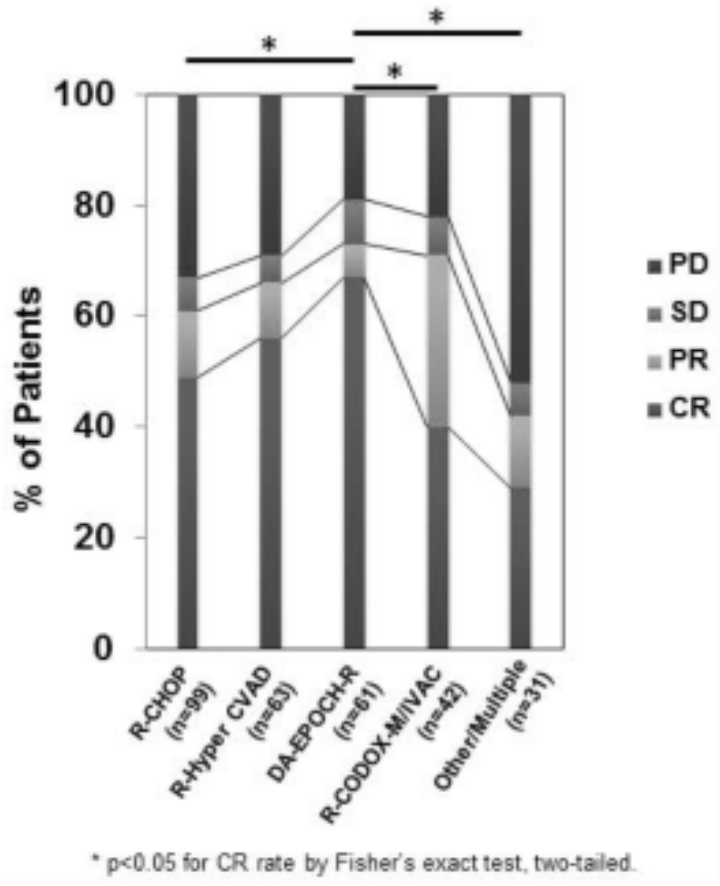
- Patients with DLBCL in which MYC is rearranged to a non-IG partner do not differ in outcomes from those with DLBCL without MYC-R.
- Include the IG light-chain loci in FISH strategy.
- risk-adjusted therapeutic approaches needed only for MYC-DH/TH cases in which *MYC*-R is to an IG partner.

Rosenwald et al JCO 2019 on behalf of the LLBC

A role for intensified therapies?

Retrospective 23 US centres (n=311)

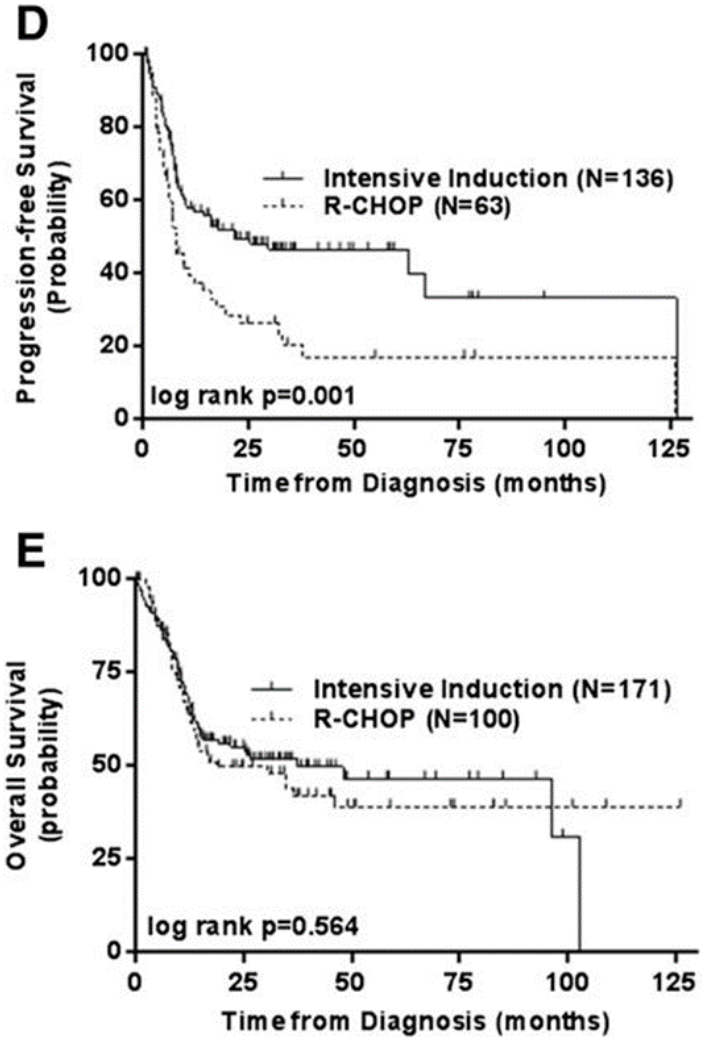
Higher CR rates with DA-EPOCH-R



Petrich at al Blood 2014

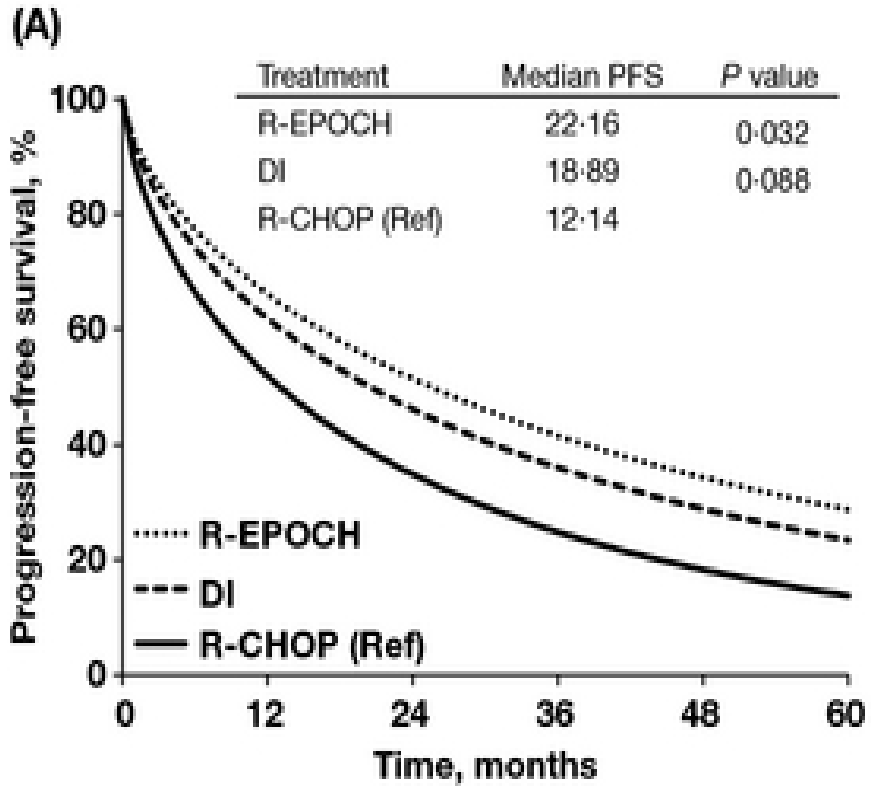
Inferior PFS with R-CHOP compared to composite of more intensive induction regimens

No difference in OS

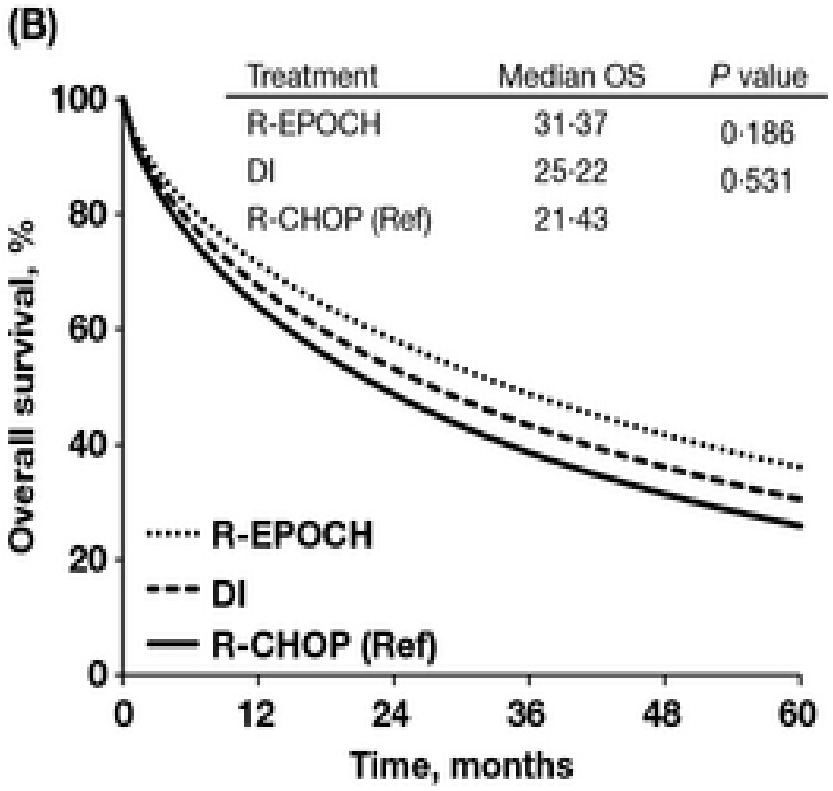


Meta-analysis (Howlett et al. BJH 2015)

394 patients (11 studies)
R-CHOP =180; DA-EPOC-R=91; DI=123



PFS



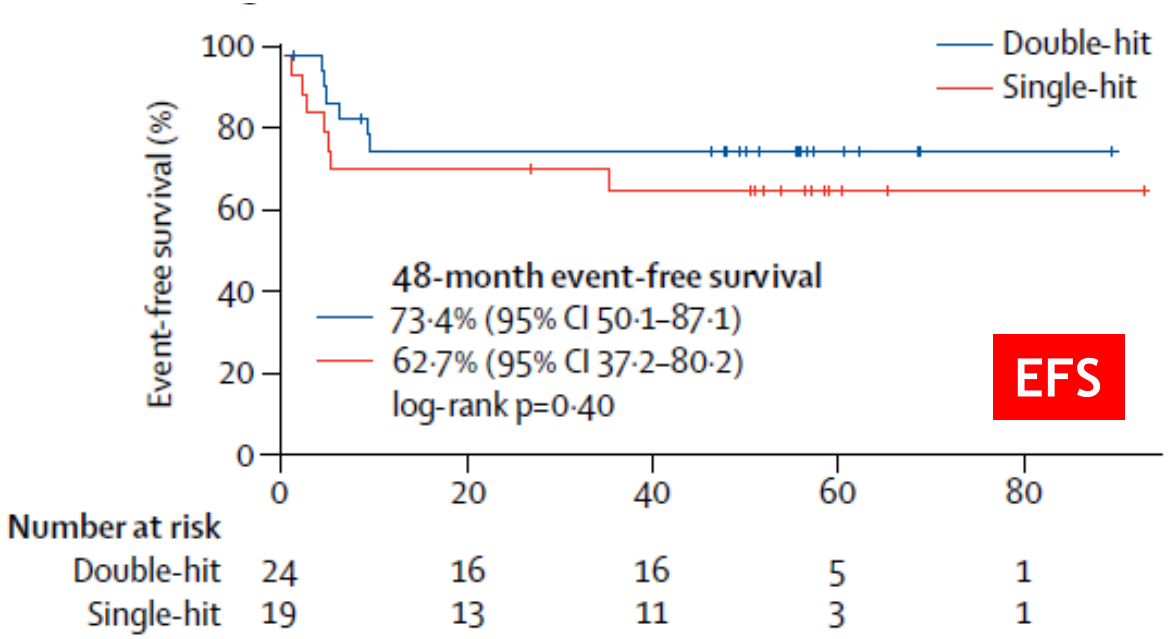
OS

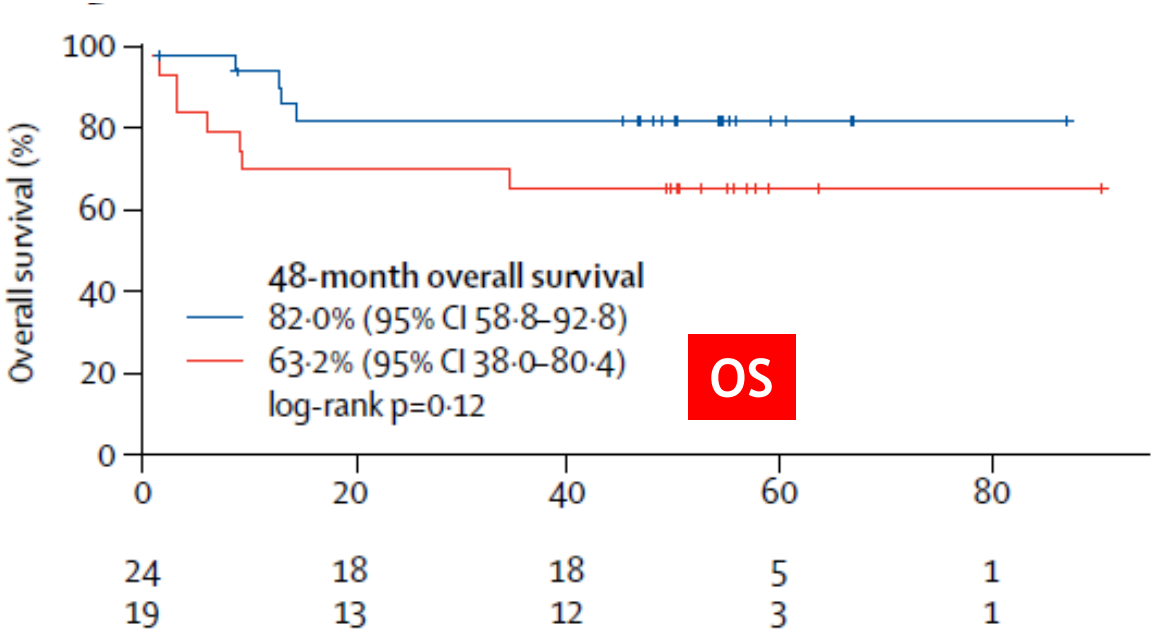
- Only 2 of 11 studies provided IPD
- No clarity in baseline prognostic variables
- 40% of data from congress reports with no formal publication
- No stratification according to transplantation consolidation

DA-EPOCH-R…at last a prospective study

n=53 *MYC* rearranged
(42% *BCL2* ; 16% *BCL6* rearranged)
46% of double hits high IPI

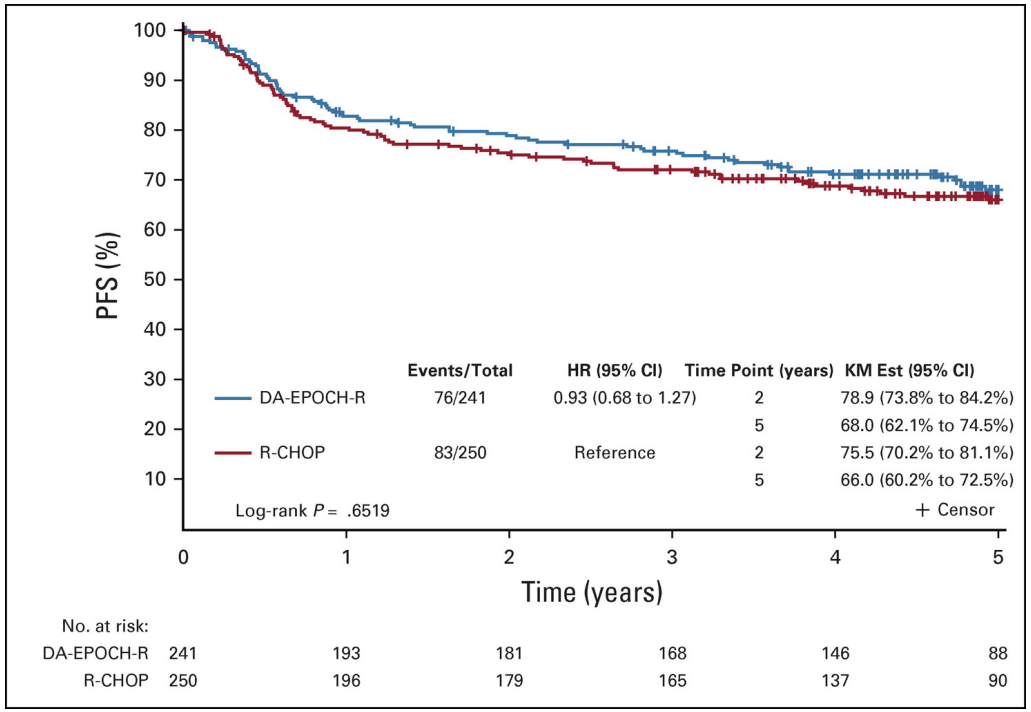
DHL 48 month EFS 73%
Low IPI= 92%
High IPI=55%
No difference with age



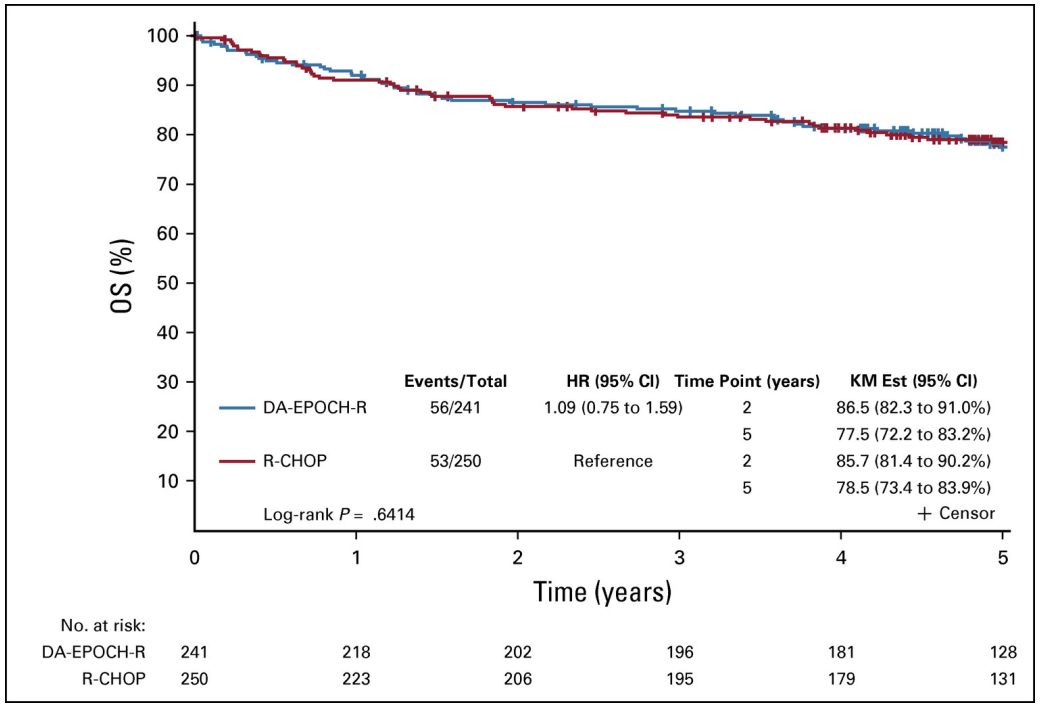


Dunleavy et al. Lancet Haem 2018

What about CALGB/Alliance 50303 DA-EPOCH vc R-CHOP (n=524) in DLBCL?



Event Free Survival



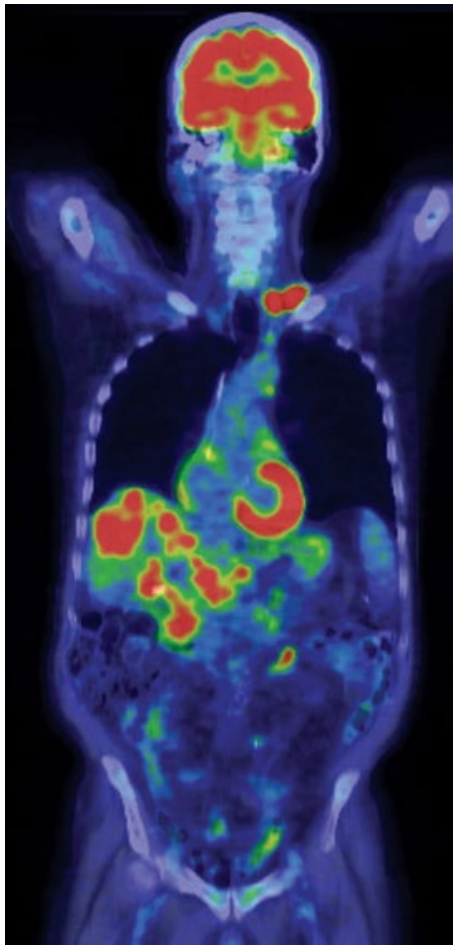
Overall survival

Only 13 patient documented to have *MYC* arrangements and 3 of these *MYC* and *BCL2/BCL6..no conclusions*

Bartlett et al. JCO 2019

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

7 first line treatment decisions in Large B-cell Lymphoma



CNS prophylaxis, who and how?

How should we treat early-stage disease?

Can we improve on RCHOP21?

Should we ever intensify first line chemotherapy?

Radiotherapy use in advanced disease?

How should we treat older patients?

PMBCL, how is the treatment different?

Consolidation to bulk, no randomised data but can consider not consolidating bulk if PET negative after 6 X RCHOP

Unfolder:

Patients with bulk >7.5cm were randomised to 36Gy IFRT or no further treatment. Radiotherapy benefit.

RICOVER-60: (pts 61-80 comparing 6 vs 8 RCHOP)

Benefit in addition of 36Gy IFRT to bulk >7.5 cm and extra nodal [2]

OPTIMAL >60: Radiotherapy can be spared in elderly (aged 61 to 80) if negative PET after immunochemotherapy [3]

2021 meta-analysis no benefit of RT if bulk [4]

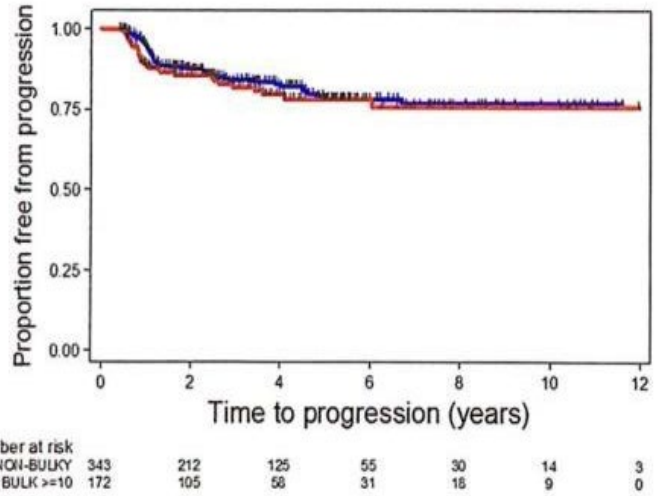
1) Lowry et al 2011 rad and onc 100,86-92 2) Held et al 2014 JCO 32, 1112-1118 3) Pfreundschuh et al abstract 120 4) Berger et al Haematologica 2021 Volume 106(7):1923-1931

Canadian retrospective data

Radiotherapy not required if PET negative

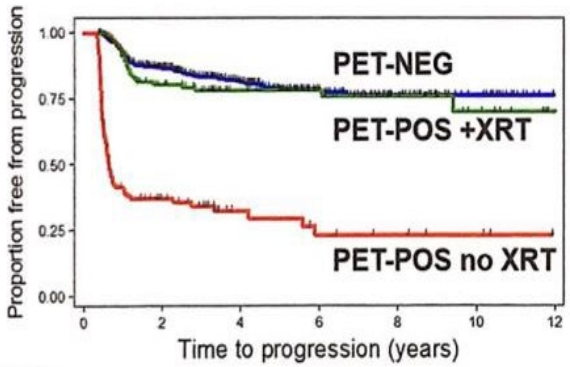
Benefit of radiotherapy consolidation if residual PET positive sites of disease

Impact of Bulky Disease ≥10cm in PET-NEG



	Non-Bulky Disease	Bulky Disease ≥10cm
N	343	172
3-year TTP	84%	82%

Time-to-Progression According to EOT-PET and XRT



3-year TTP

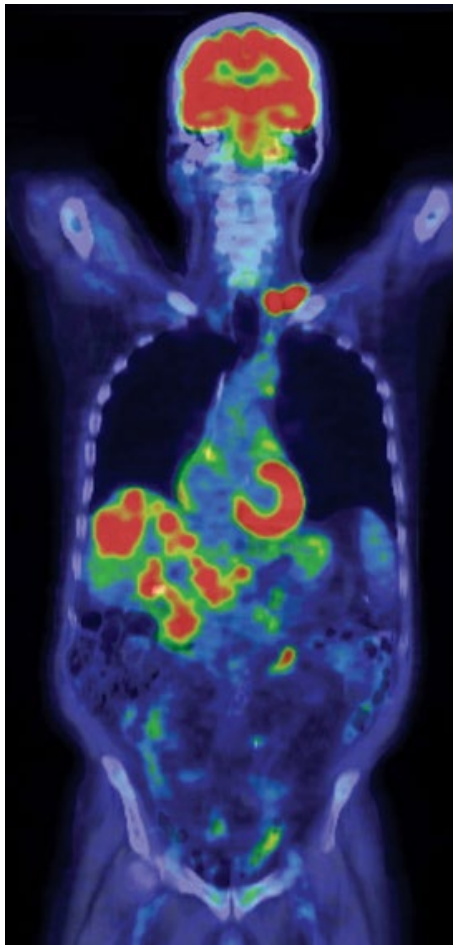
83% (95% CI 79-87%)

78% (95% CI 68-85%)

34% (95% CI 24-43%)

Freeman et al Blood 2021;137(7)929-938

7 first line treatment decisions in Large B-cell Lymphoma



CNS prophylaxis, who and how?

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PMBCL, how is the treatment different?

Older or less fit patients

Functional assessment: CGA[1], Charlson Comorbidity Index [2], Cumulative Illness Rating Scale(CIRS)

Steroid pre-phase if PS >2 [5]

PolaR CHOP/RCHOP or

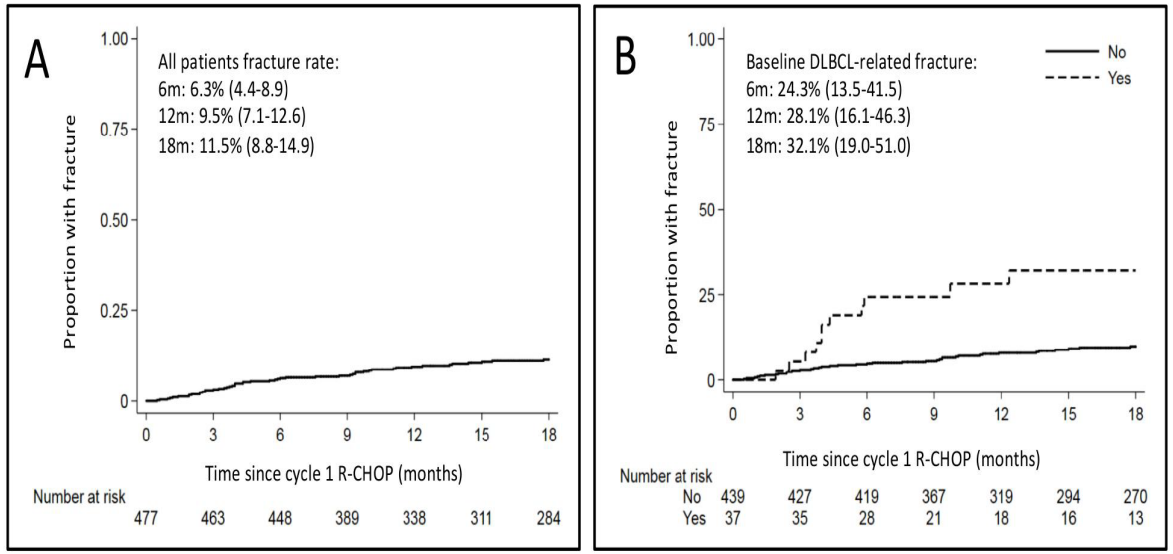
R-mini CHOP [3]

RCGVP if cardiac compromise [4]

Bone protection and GCSF prophylaxis[6]

1) Olivieri et al 2012, the Onc 17, 663-672 2) Kobayashi et al 2011 J Ca Res Clin Onc 137, 1079-1084, 3) Peyrade et al 2011 Lancet Onc 12, 460-468 4)Fields et al 2014 JCO 32, 282-287 5) Pfreundschuh et al 2010 Blood 116, 5103-5110 6) Repetto et al 2003 Eur Journ Canc 39, 2264-2272

Data on consecutive DLBCL patients ≥70 years treated with 1-9 cycles of full or attenuated R-CHOP
(excluded if PD or died within 6 months of course 1)

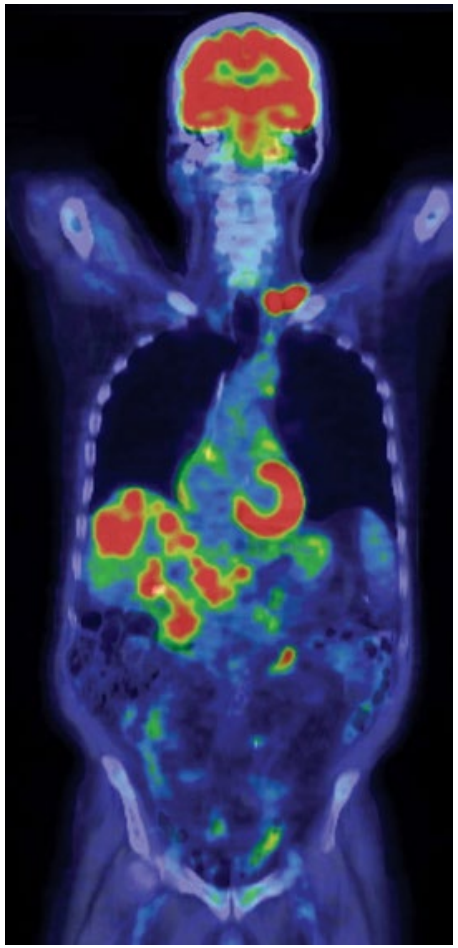


The cumulative fracture incidence: 6.3% at 6 months; 9.5% at 12 months and **11.5% at 18 months**

50 fractures in 18 months of follow up, predominantly vertebral

Booth et al ASH 2019

7 first line treatment decisions in Large B-cell Lymphoma



CNS prophylaxis, who and how?

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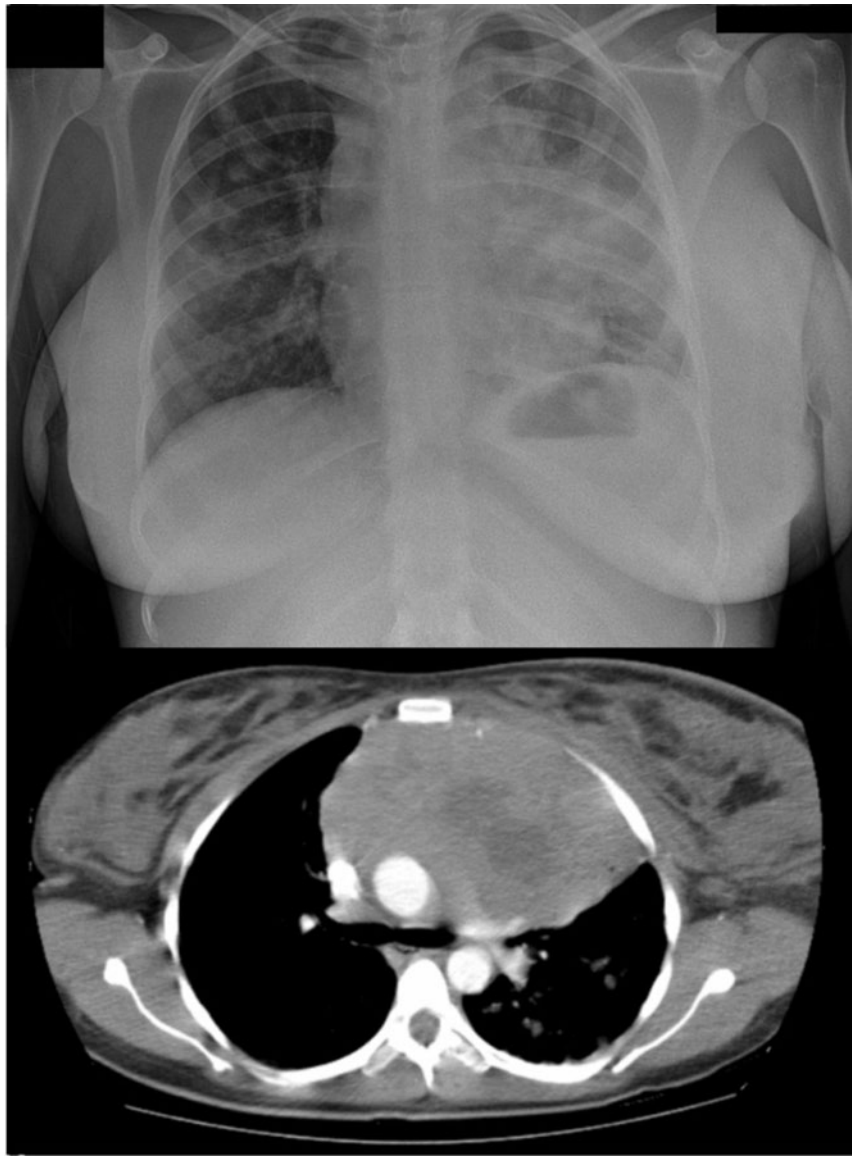
Radiotherapy use in advanced disease?

How should we treat older patients?

PMBCL, how is the treatment different?

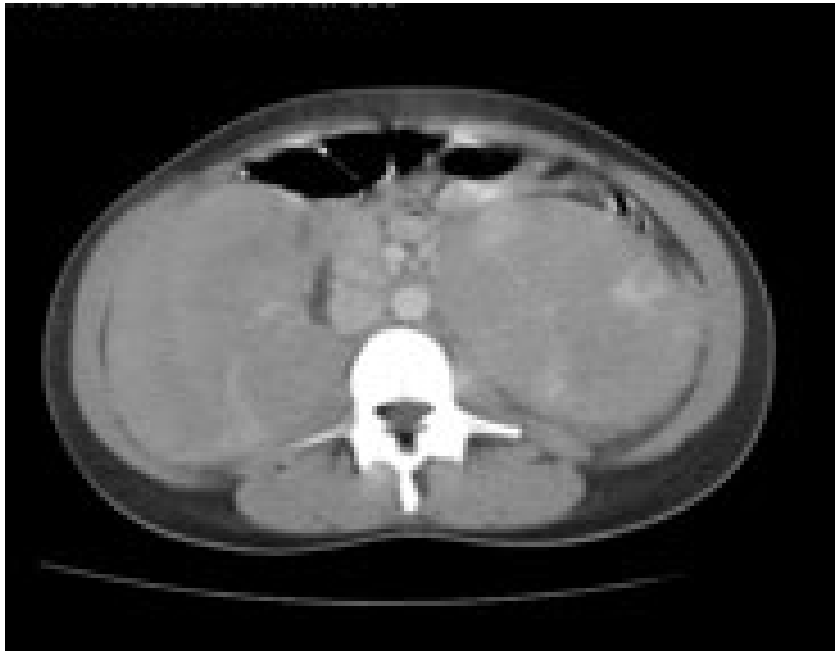
Clinical Features

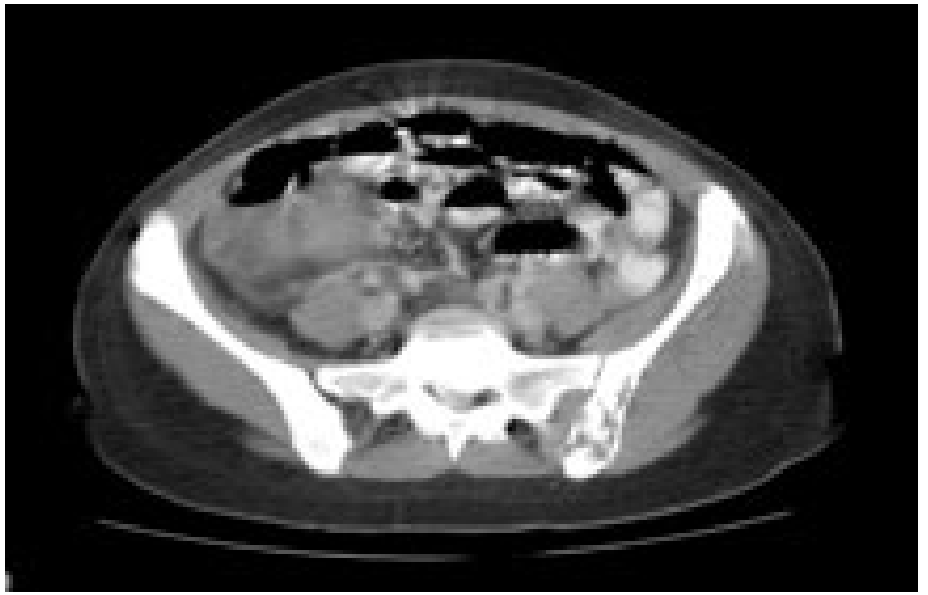
- Rapidly growing mass of anterior mediastinum. Frequent emergency presentation
- Bulk common
- Young patient population (median age 35)..many TYA
- Female predominance (2:1)
- Diagnosed as a result of symptoms compressing mediastinal structures. SVCO present in 40%
- Recurrent laryngeal nerve palsy with hoarse voice
- Breast swelling
- Cough/chest pain/dyspnoea/dysphagia



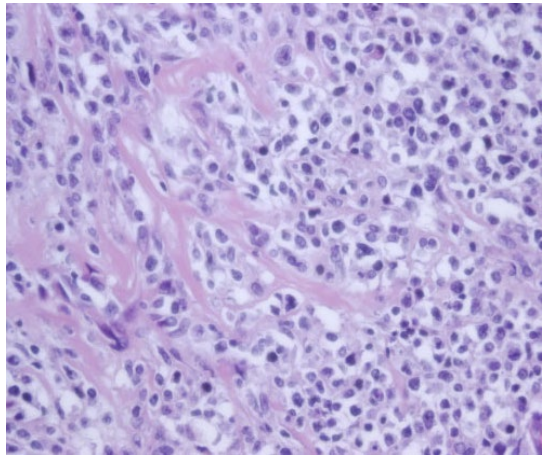
Clinical Features

- Frequent invasion of local structures including pleura, pericardium and chest wall. Effusions common
- Involvement of bone marrow or extra-thoracic structures uncommon [no need for bone marrow]
- Usually stage I/II at presentation
- Recurrence often at extranodal sites including kidney, adrenals, ovaries and CNS





Pathology



Cytologically resembles many other large B cell lymphomas

Large transformed cells resembling centroblasts

Abundant pale cytoplasm

Diffuse involvement

Areas of fine compartmentalising sclerosis

Expression of B-cell antigens: CD20 and CD79a positive, but lack sIg

Evidence of somatic hypermutation

CD30 often present (>80%), typically weak

CD23: Frequent (73%)

BCL2: variable (50-80%, no t(14;18))

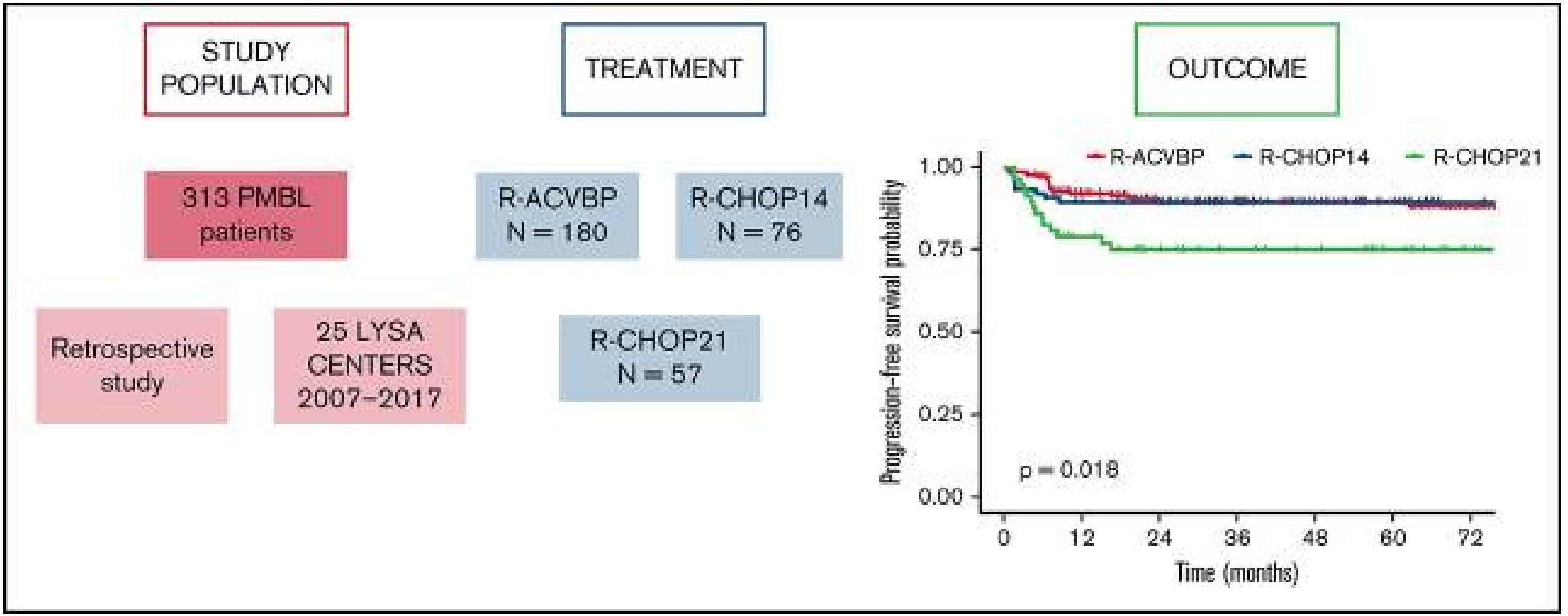
BCL6: variable (45-100%)

CD10: less common (8-30%)

CD15: almost always negative

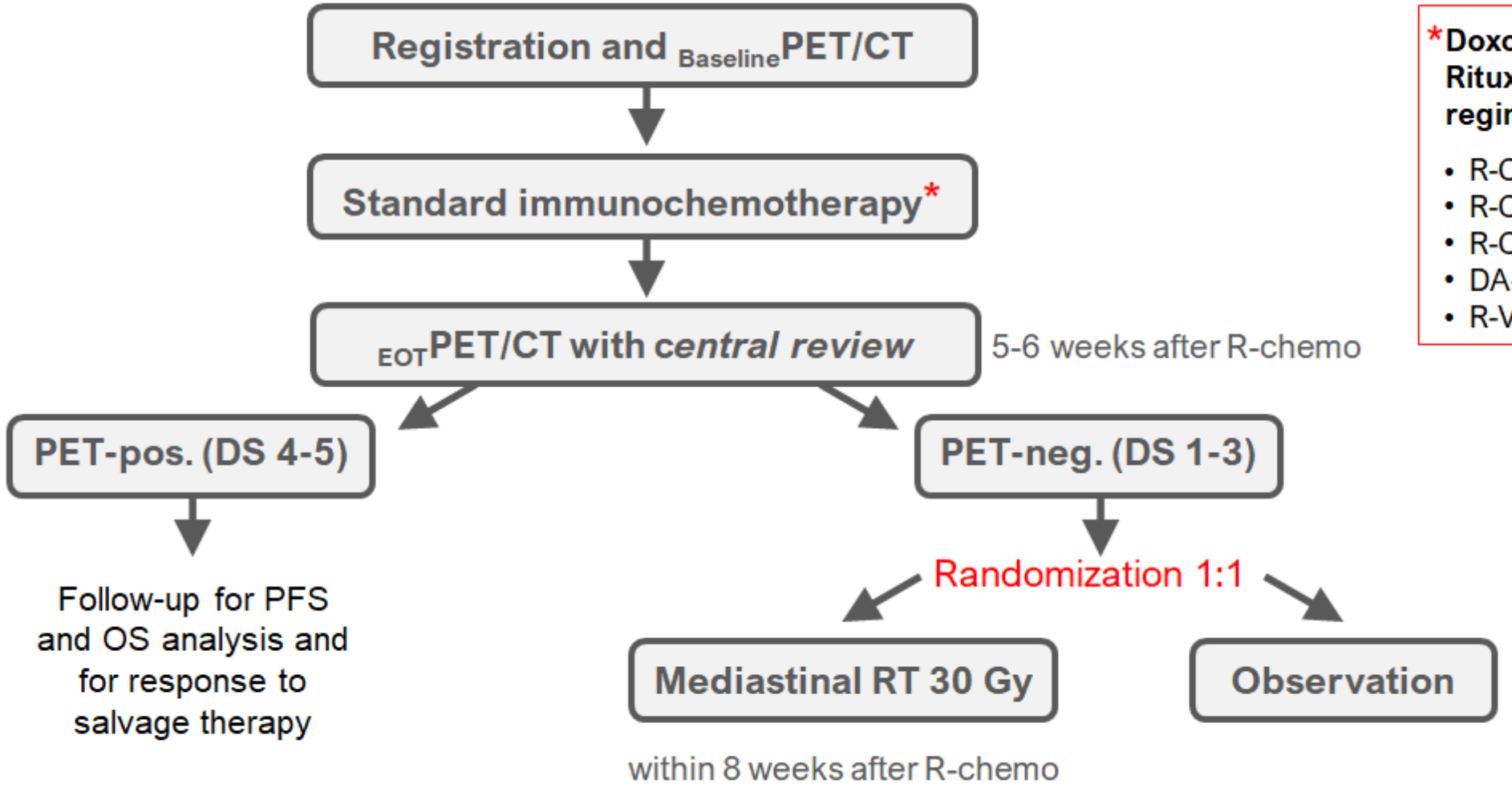
MAL (70%) – normal expression in thymic medullary cells, CD54, CD95, nuclear REL, TRAF

LYSA: Further evidence of dose density



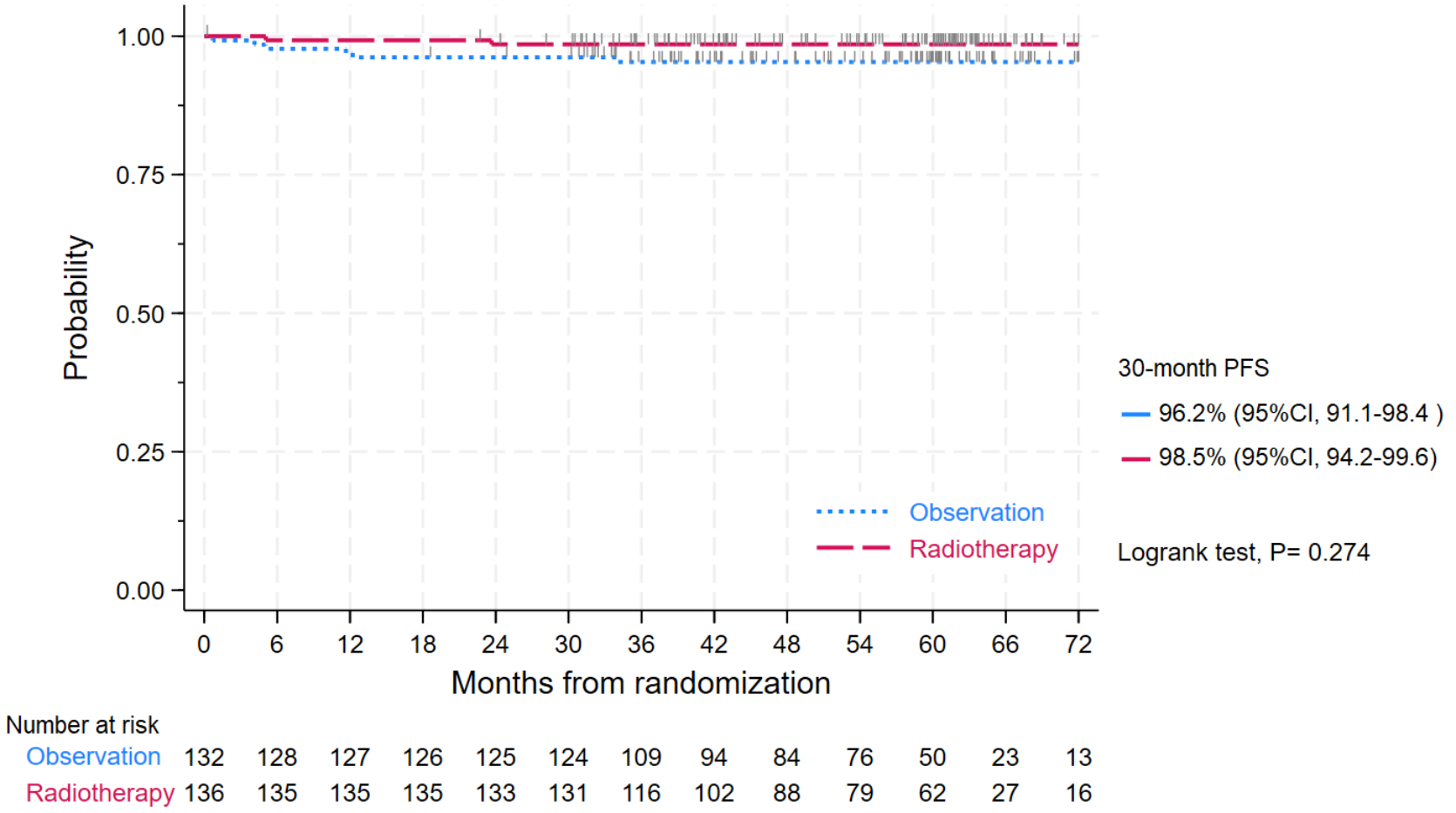
Camus et al. Blood Adv 2021

Randomised non-inferiority trial design

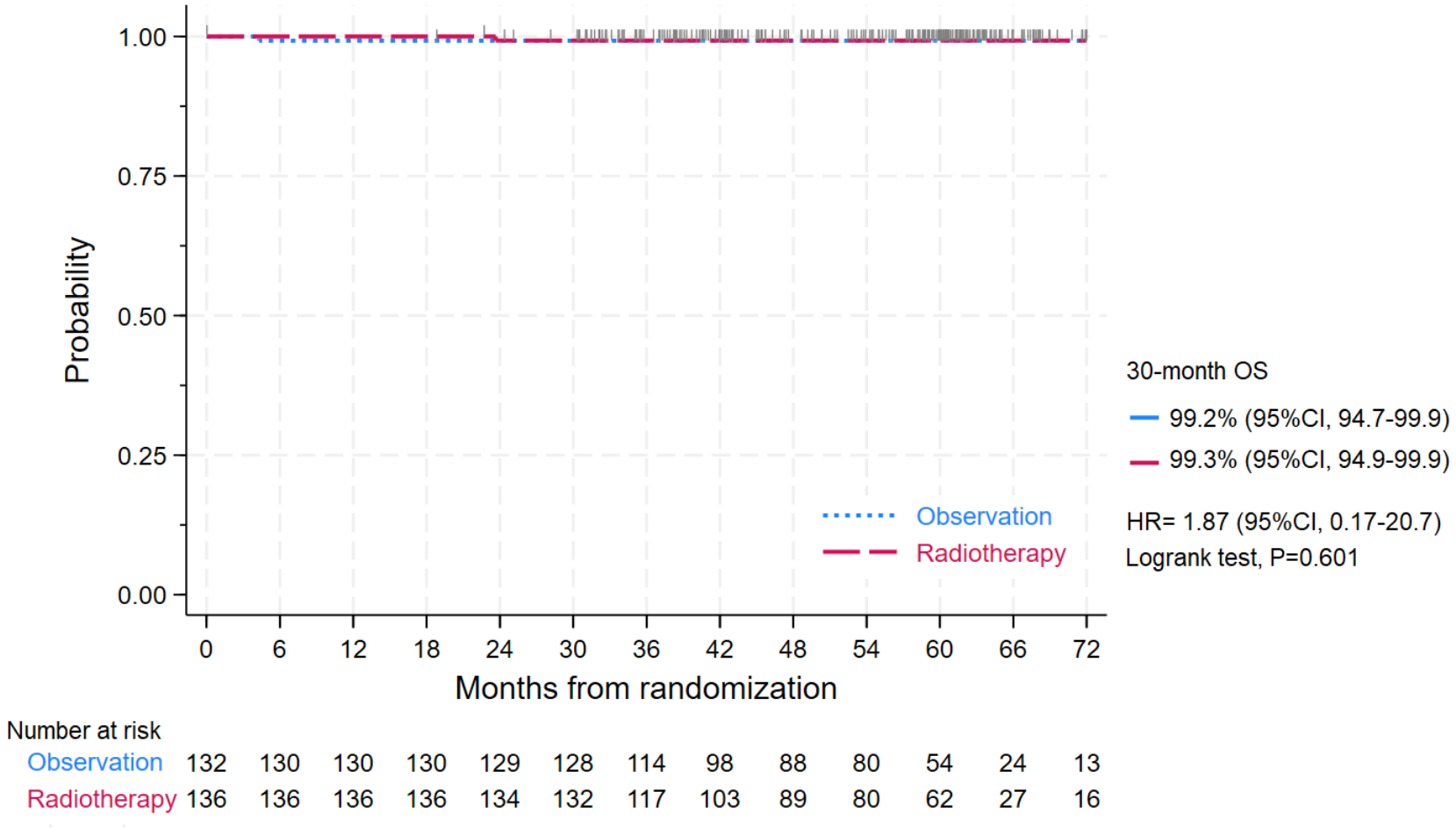


Davies ICML 2023, Martelli EHA 2023, Zucca ASCO 2023

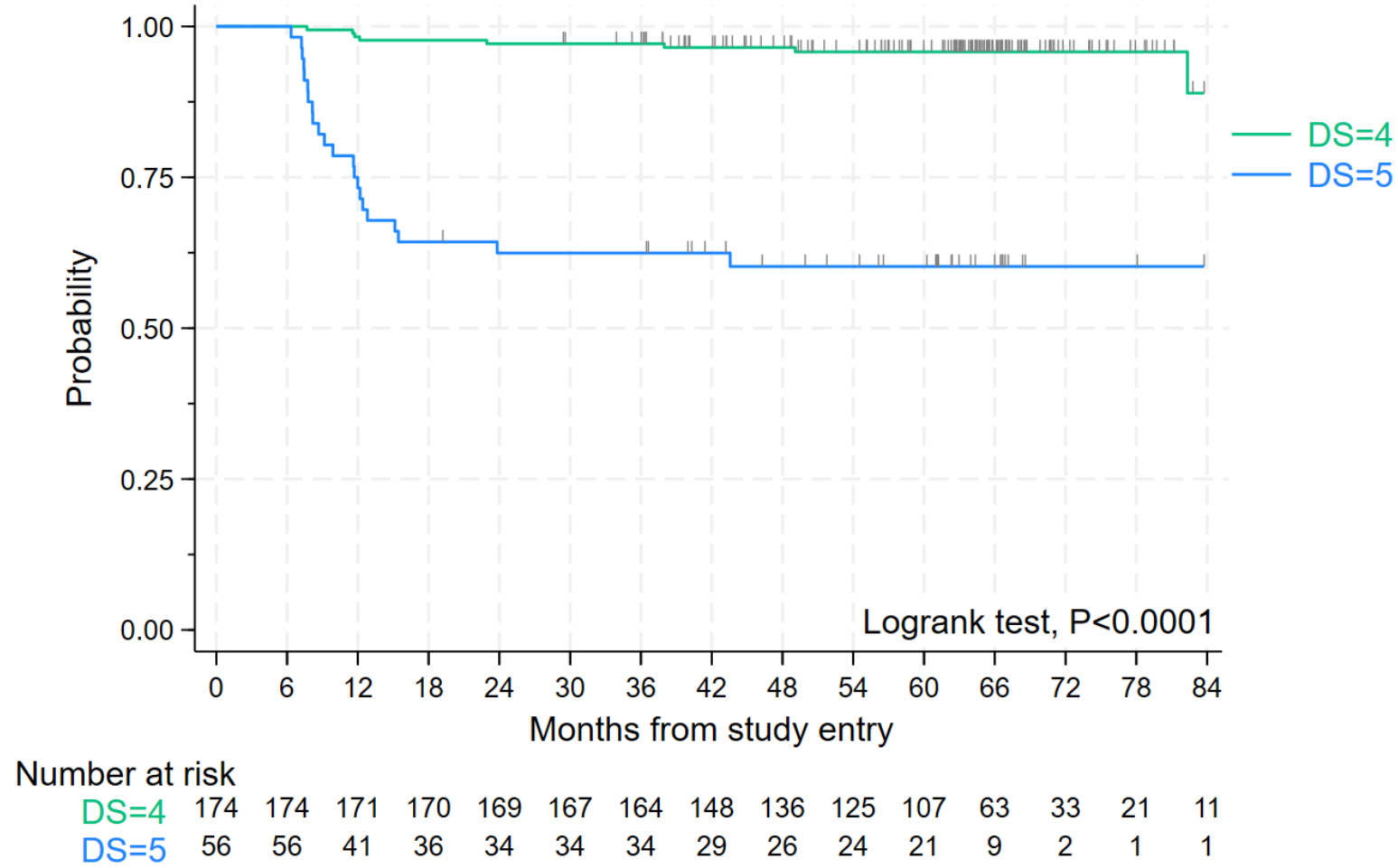
Progression-free survival



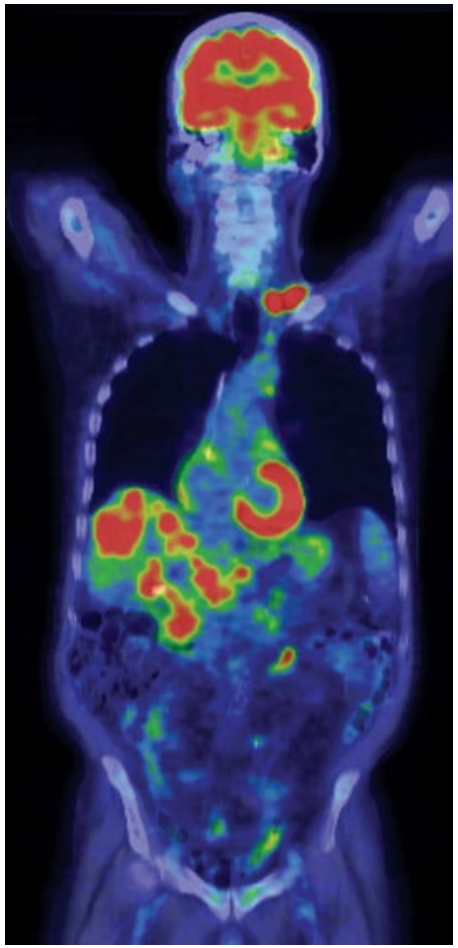
Overall survival



PFS of non-randomised patients



7 first line treatment decisions in Large B-cell Lymphoma



CNS prophylaxis, who and how?

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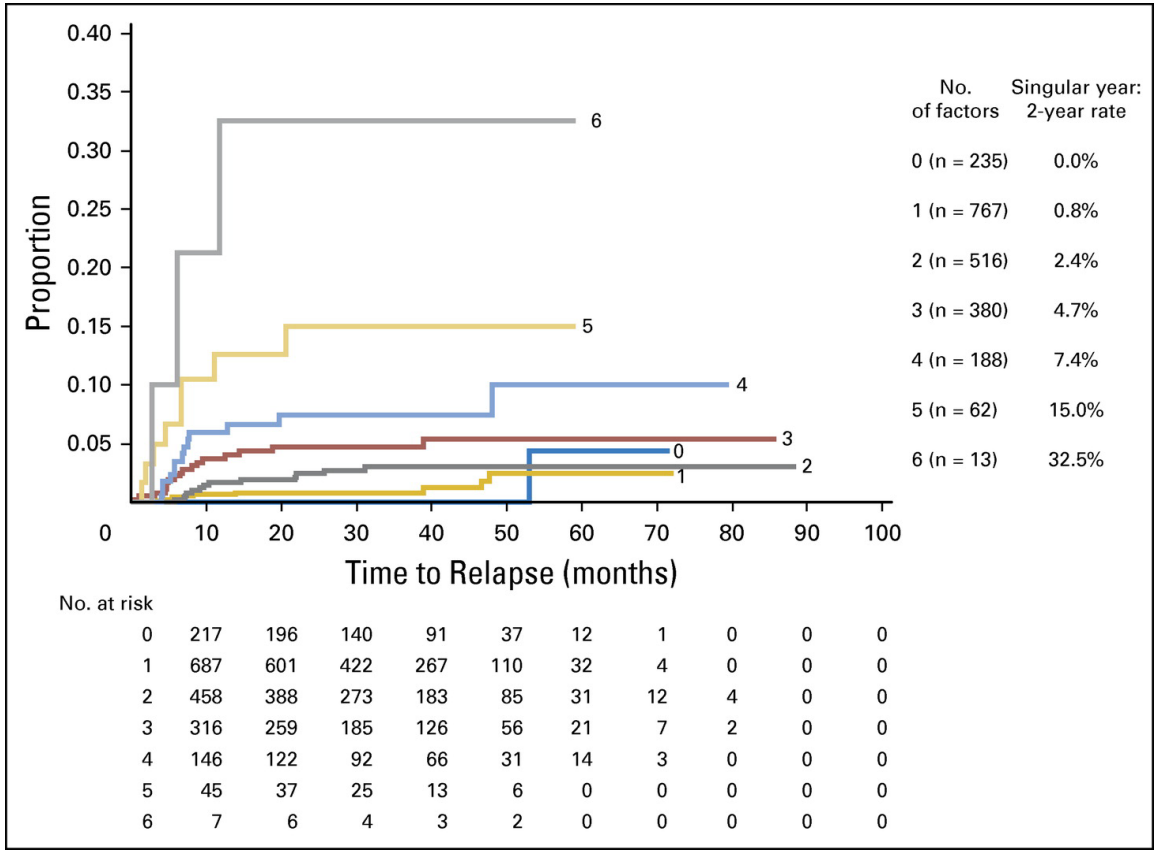
PMBCL, how is the treatment different?

CNS IPI (IPI plus renal/adrenal)

We know who is at risk of CNS relapse



32.5% 2-year rate of CNS relapse if CNS IPI 6

15% if CNS IPI 5

Schmitz; *Journal of Clinical Oncology* 2016 343150-3156.
DOI: 10.1200/JCO.2015.65.6520

BSH Good Practice Paper 2020

High-dose intravenous methotrexate is preferred

CNS prophylaxis should be offered to patients with any of these factors

- High (4–6) CNS-IPI
- Involvement of three or more extranodal sites irrespective of CNS-IPI
- Anatomical sites: testicular, renal/adrenal, intravascular
- (consider if breast,uterus)

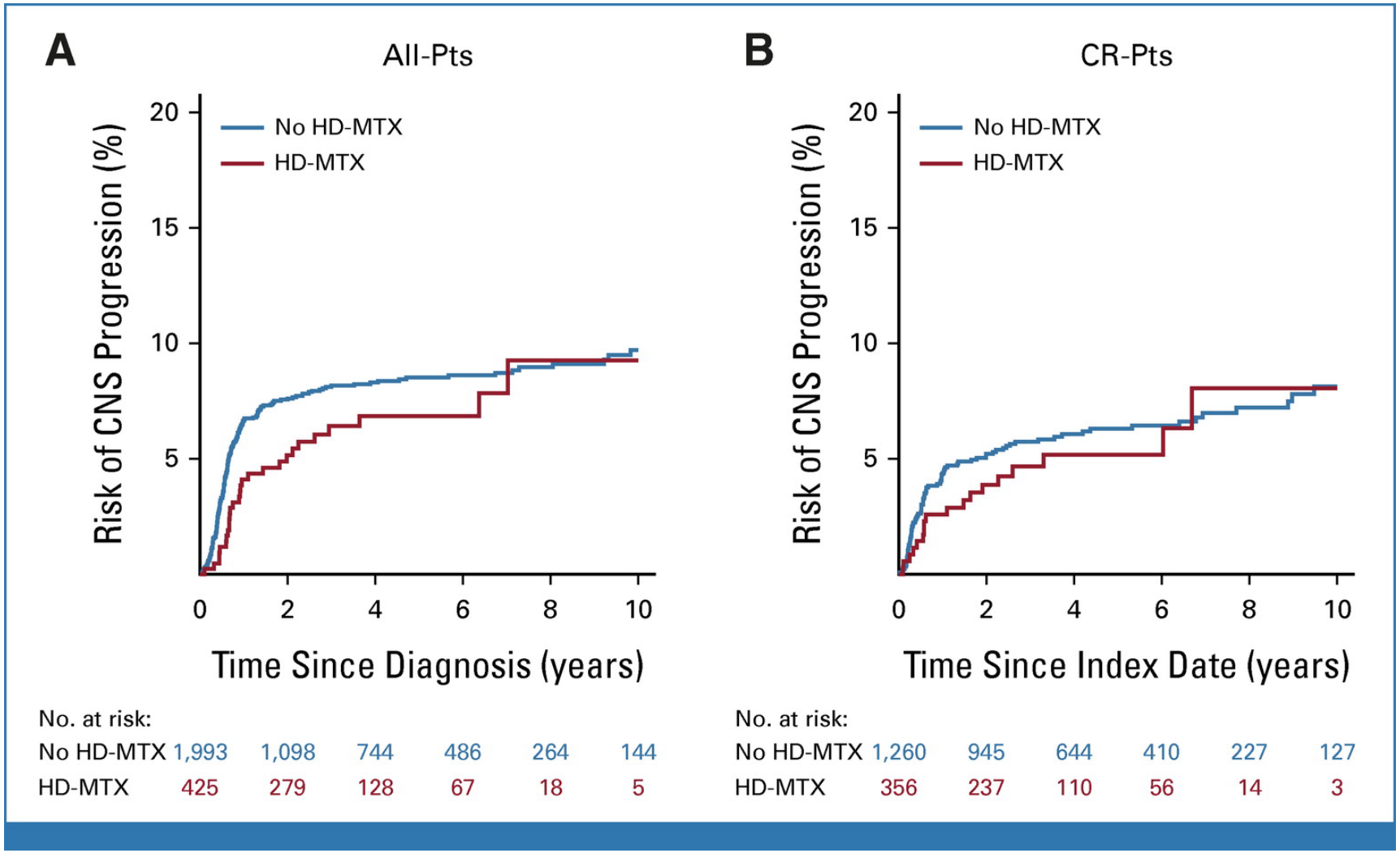
- Patients with testicular lymphoma should be considered for IT as well as systemic prophylaxis

McKay P, Br J Haematol, 2020

* El-Galaly TC, Eur J Cancer 2017

Large retrospective cohort: Anthracycline/rituximab(n>2500; 1600 in CR)

5-year cumulative CNS progression risk was 7.4% (95% CI, 5.9 to 8.9)



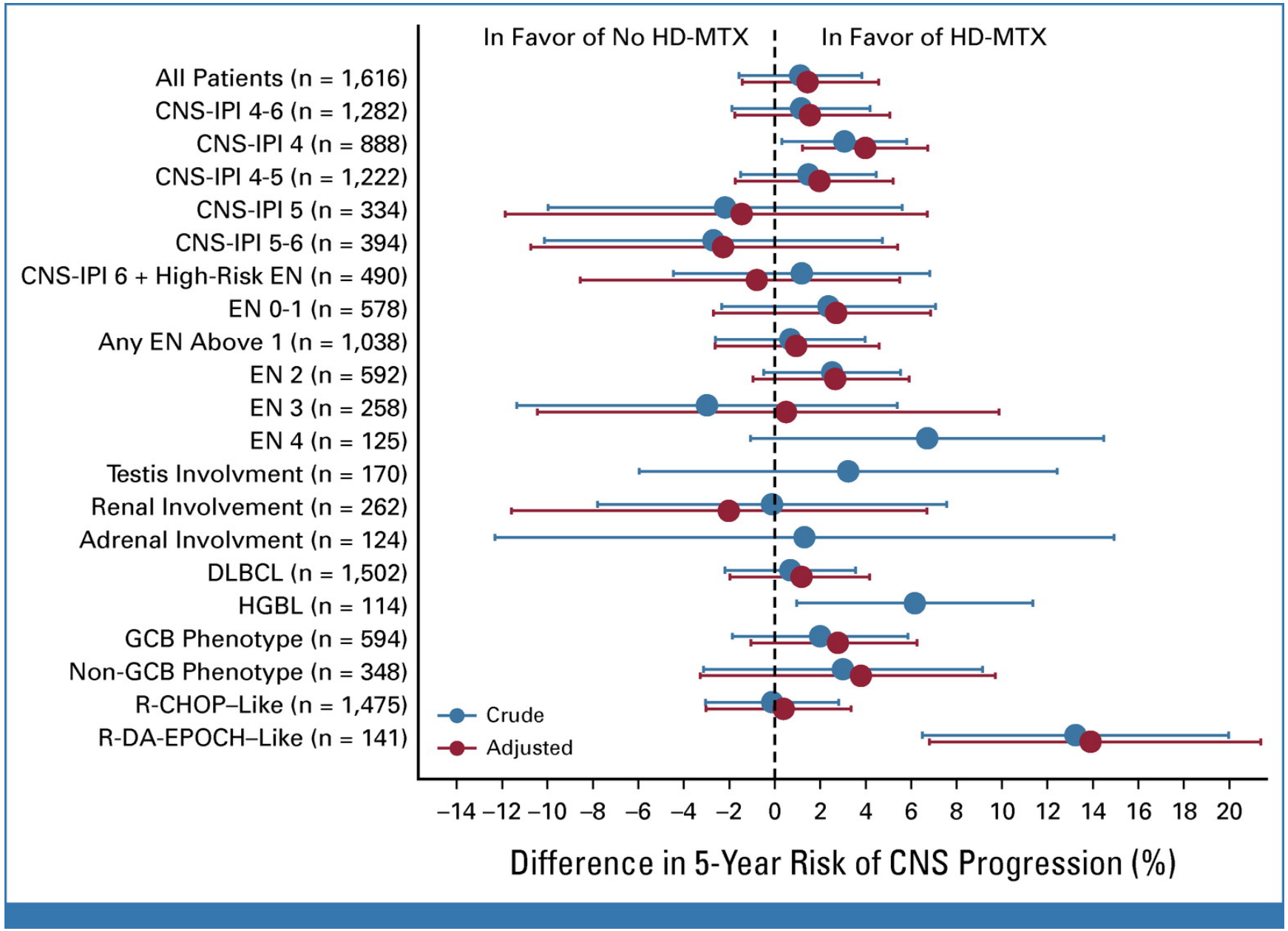
- no difference

in 5-year adjusted risk of CNS progression between HD-MTX and no HD-MTX groups; 5.0% versus 6.5% (adjusted risk difference, 1.4% [95% CI, –1.5 to 4.1]

- absolute risk reduction of 1.6% with HD-MTX,

63 patients would need to be treated to prevent one CNS progression event over 5 years

Lewis et al. JCO 2023



No significant impact of HD-MTX observed in high-risk subgroups. All underpowered to draw definitive conclusions regarding the efficacy of HD-MTX in specific high-risk clinical scenarios

Lewis et al. JCO 2023

Newer retrospective data has suggested CNS prophylaxis is not effective

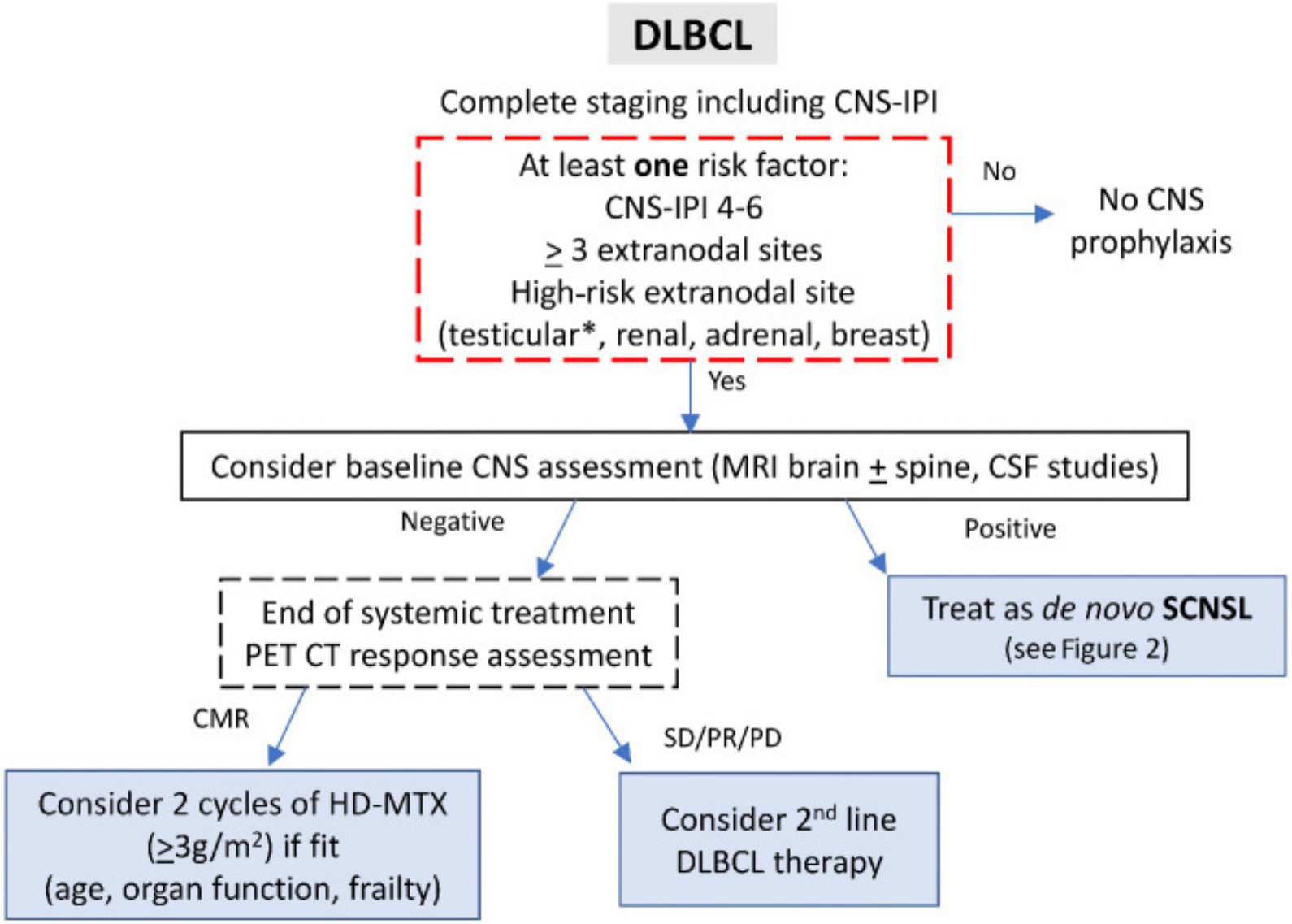
We have to be cautious with retrospective data analysis which is underpowered

We continue prophylaxis in the UK in most centres

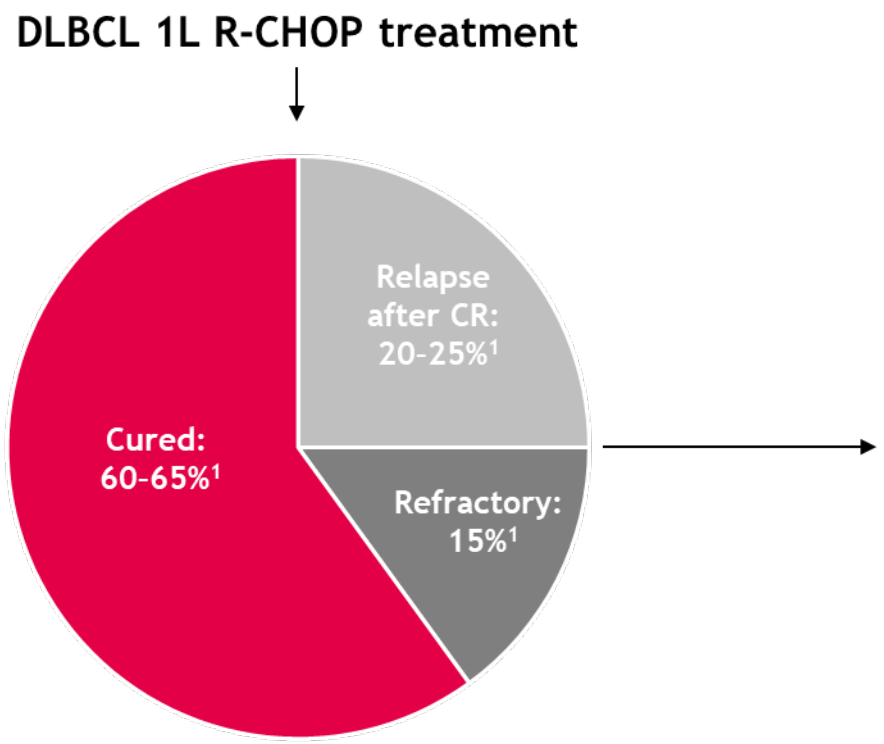
Since these retrospective data lower threshold for not delivering IV MTX if patient has comorbidities or is older and no longer give for CNS IPI 4

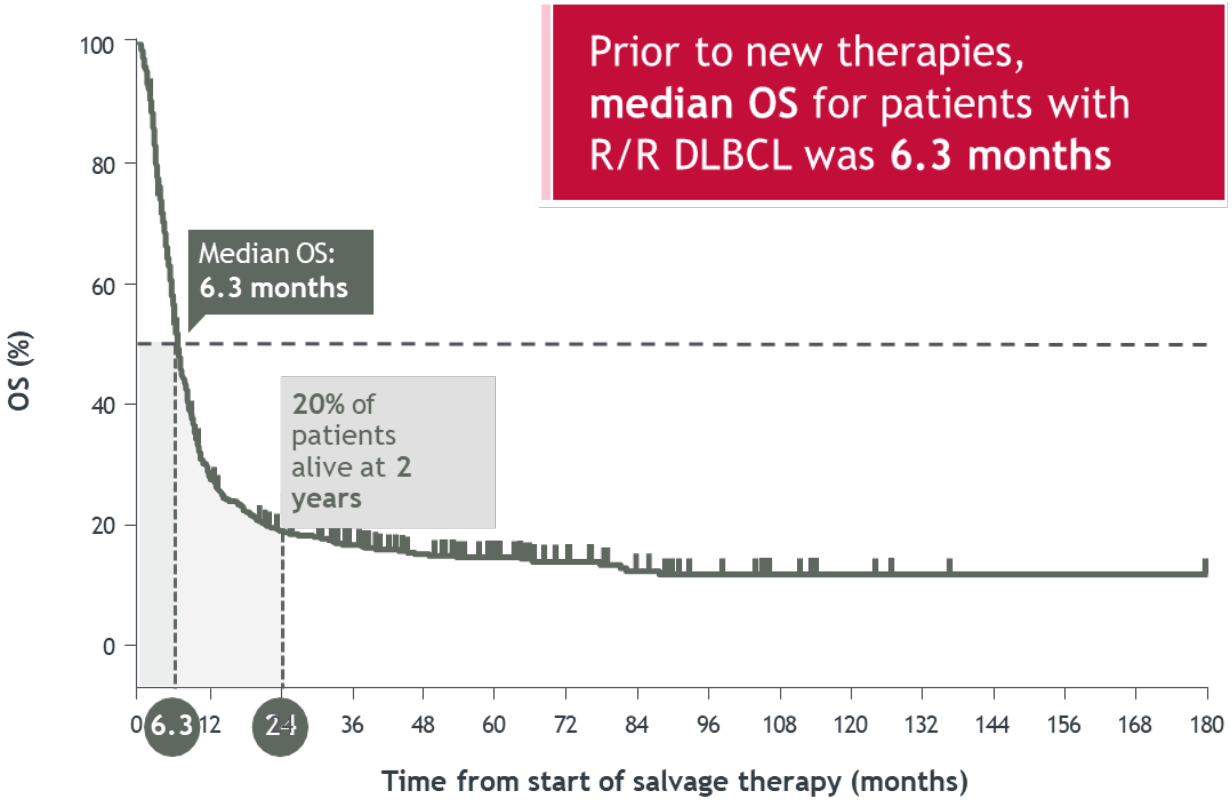
If given, IV MTX should be delivered post RCHOP

Our approach to preventing CNS disease

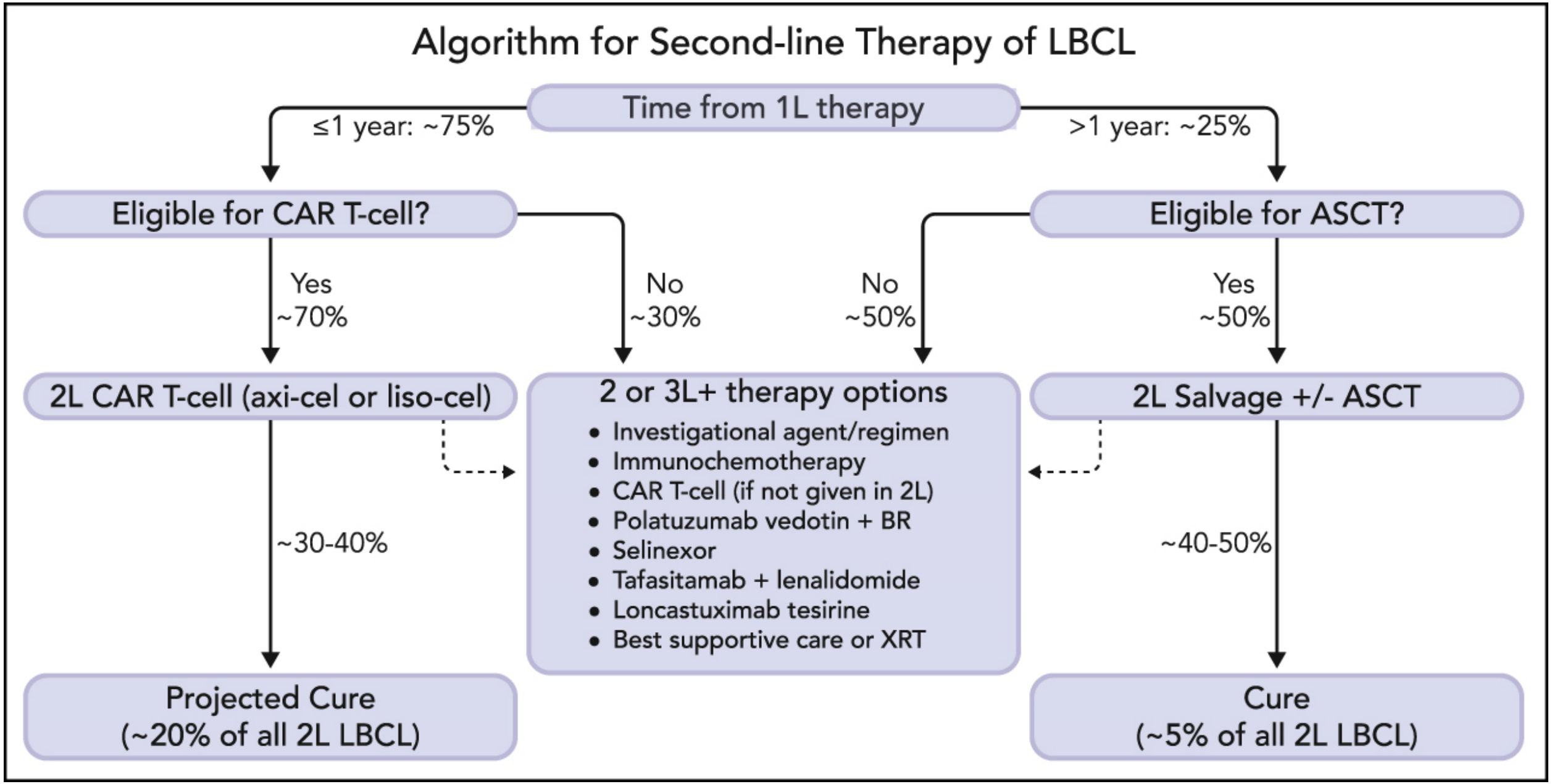


Outcomes are poor for patients who are refractory to or relapse following 1L therapy

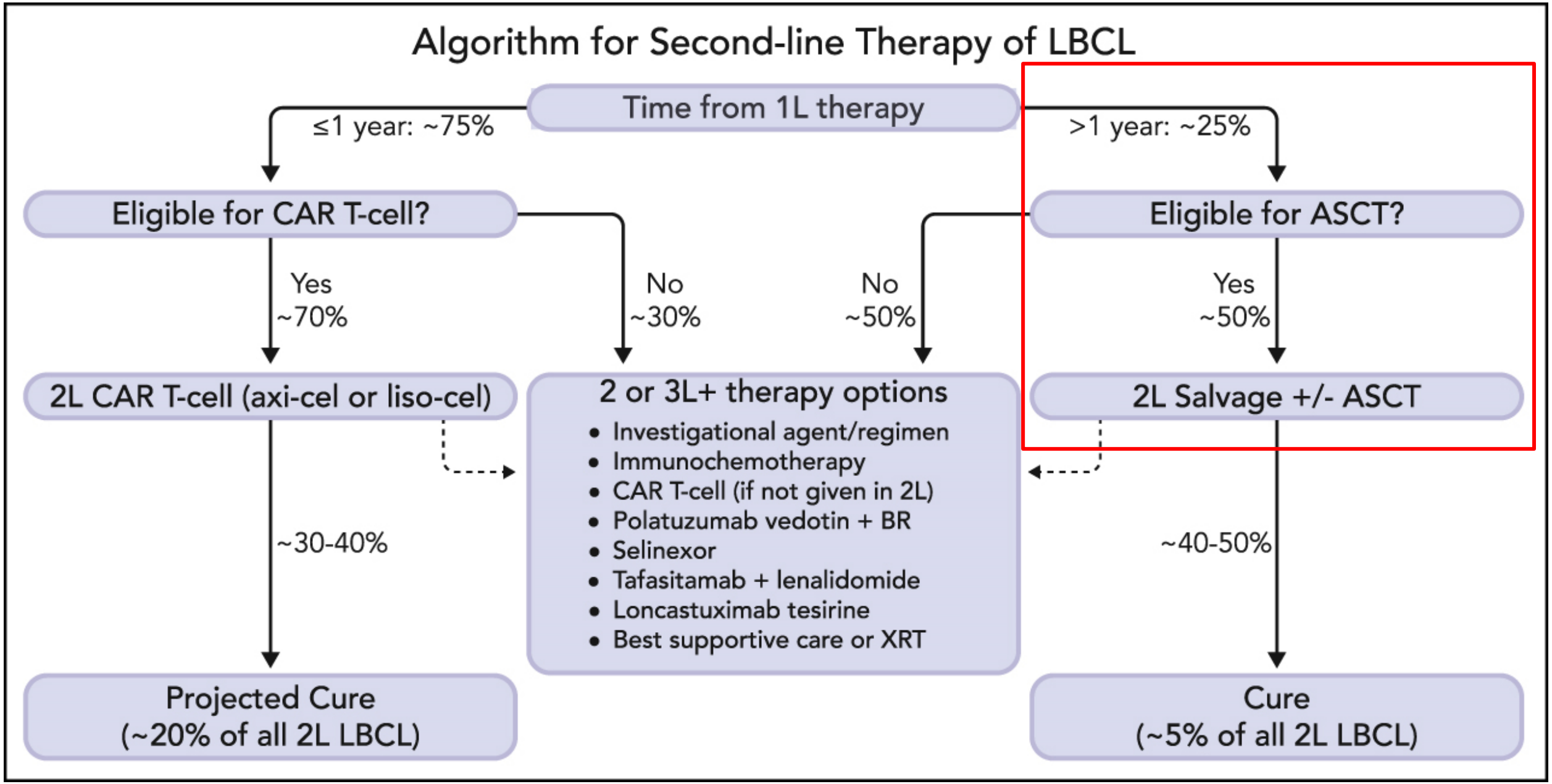




1L, first line; 2L, second line; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone



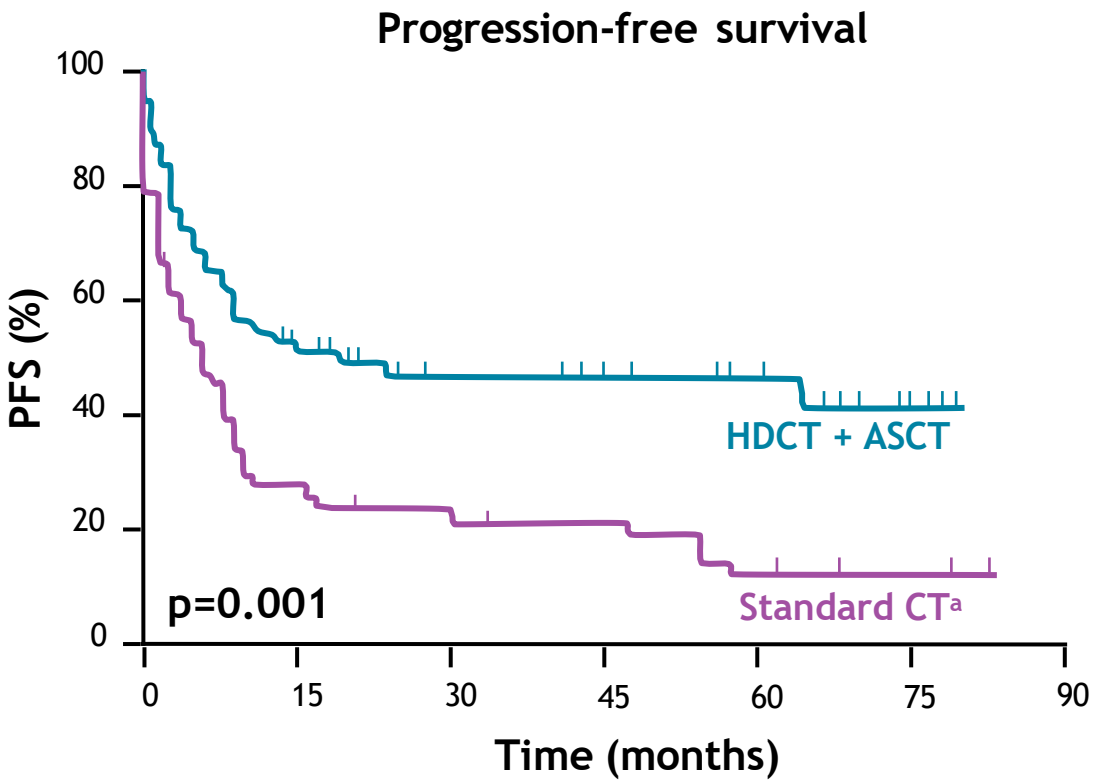
Westin and Sehn 2022

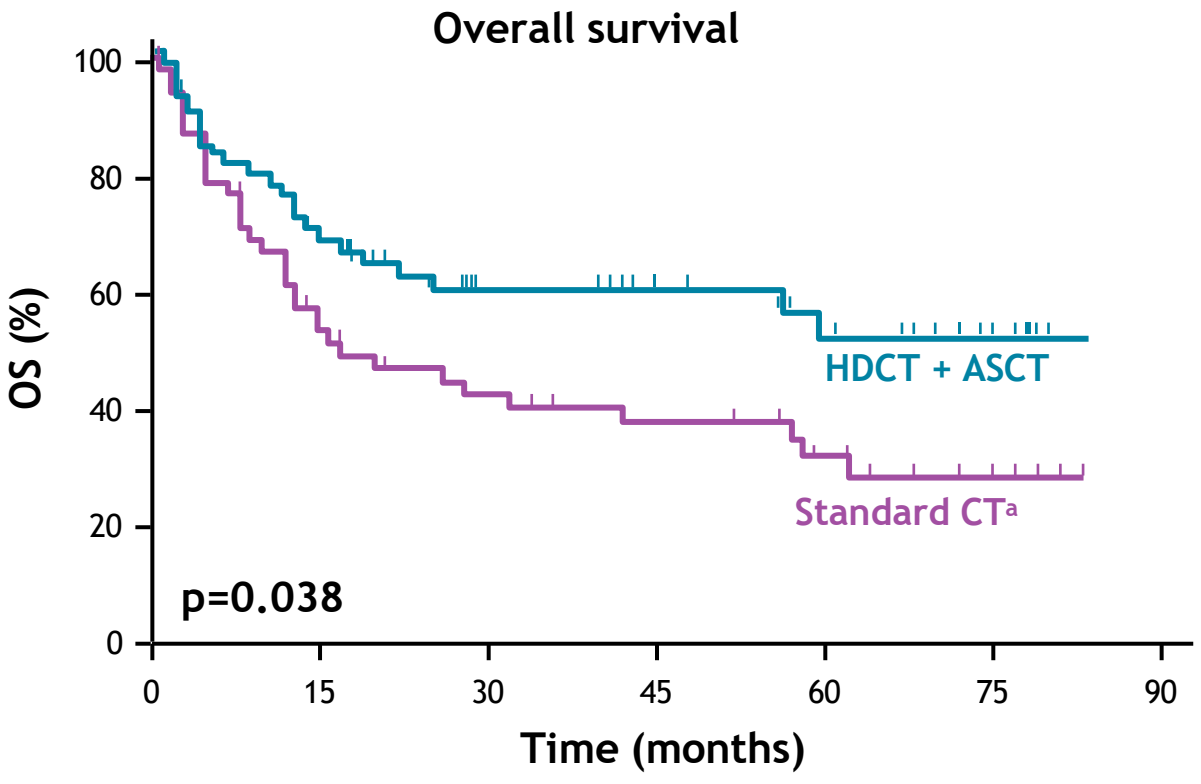


Westin and Sehn 2022

The Parma trial for relapsed aggressive NHL: HDCT + ASCT better than standard chemotherapy

Randomised study of HDCT + ASCT vs. standard chemotherapy in patients with relapsed chemo-sensitive aNHL (N=109)



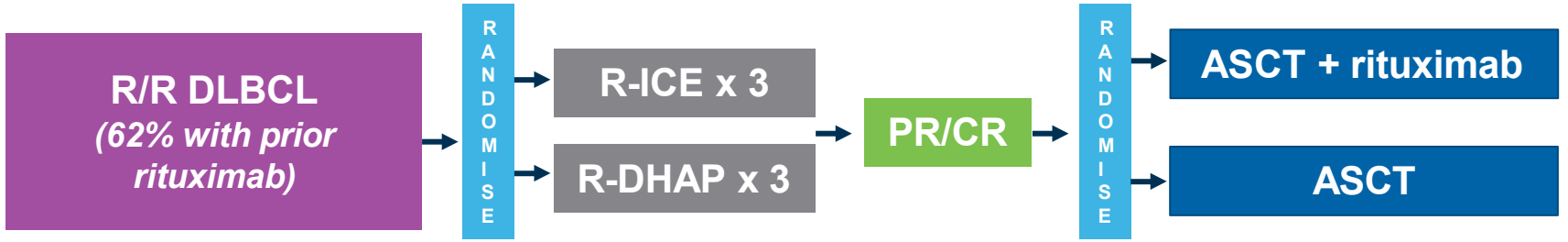


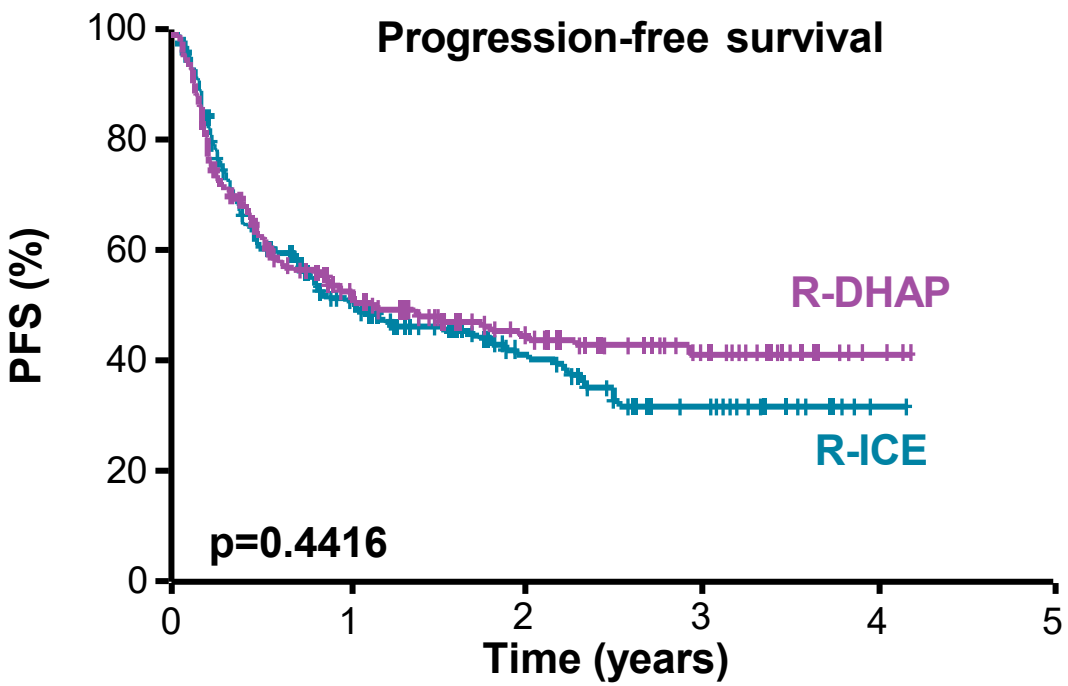
[a] Four courses of DHAP every 3–4 weeks followed, if no progression, by radiotherapy of the involved field
aNHL: aggressive non-Hodgkin lymphoma; CT: chemotherapy; DHAP: dexamethasone, cytarabine, cisplatin

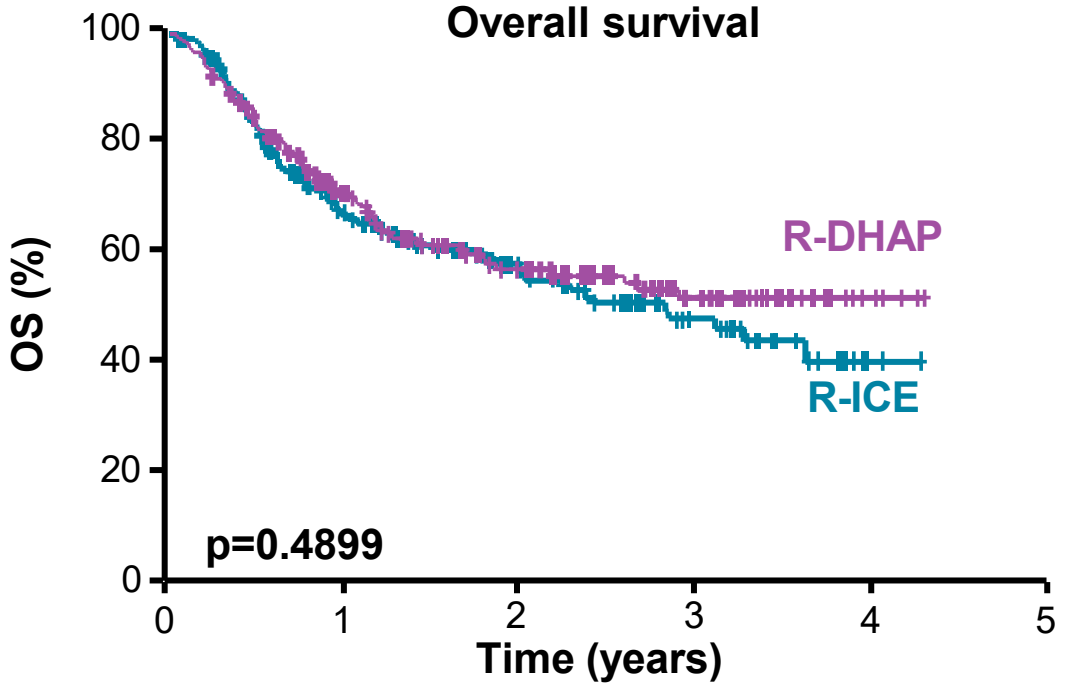
Philip T, et al. N Engl J Med 1995; 333:1540–1545.

Is there a better second line regimen?

CORAL: Randomised study of R-ICE vs. R-DHAP in patients with R/R DLBCL after 1L R-CHOP (N=396)





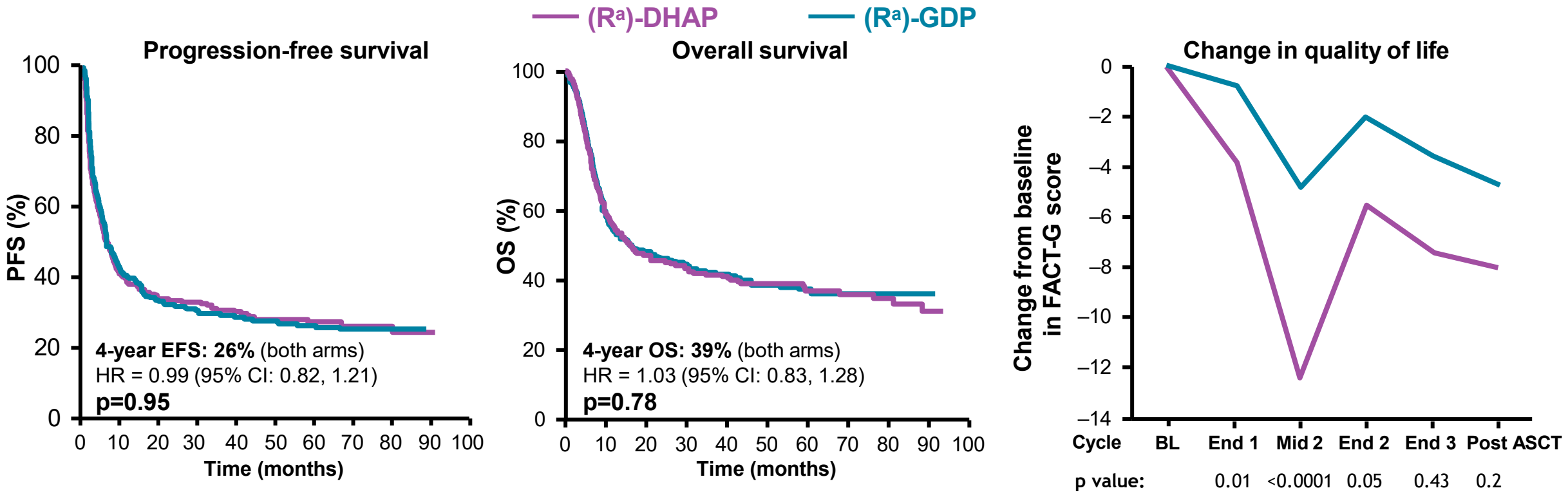


ICE: ifosfamide, carboplatin, cisplatin; PR: partial response

Gisselbrecht C, *et al. J Clin Oncol* 2010; 28:4184–4190.

Canadian study: GDP vs. DHAP therapy

NCIC-CTG LY.12: Randomised Phase III study of outpatient GDP vs. standard DHAP[a] prior to ASCT in R/R aNHL (N=619)



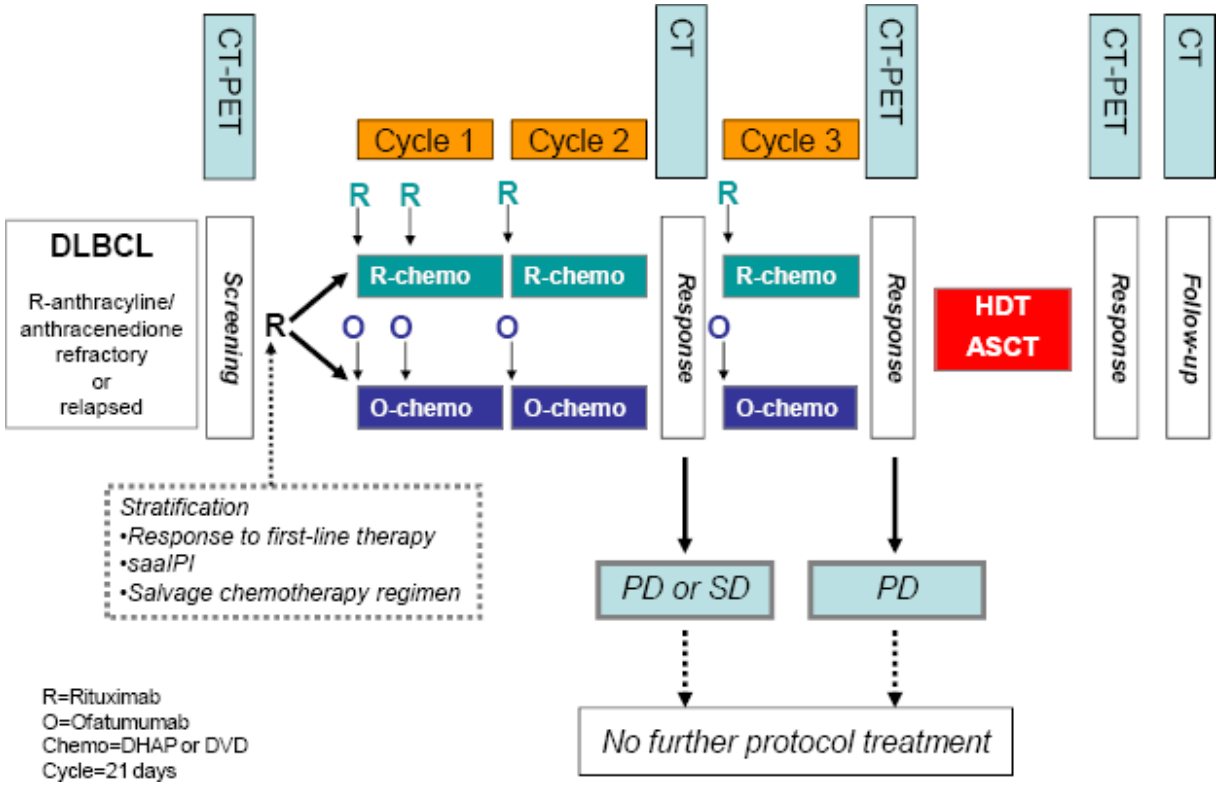
GDP RESULTED IN SIMILAR RATES OF TRANSPLANTATION, EFS AND OS TO STANDARD DHAP, WITH LESS TOXICITY, IMPAIRMENT OF QOL AND NEED FOR HOSPITALISATION

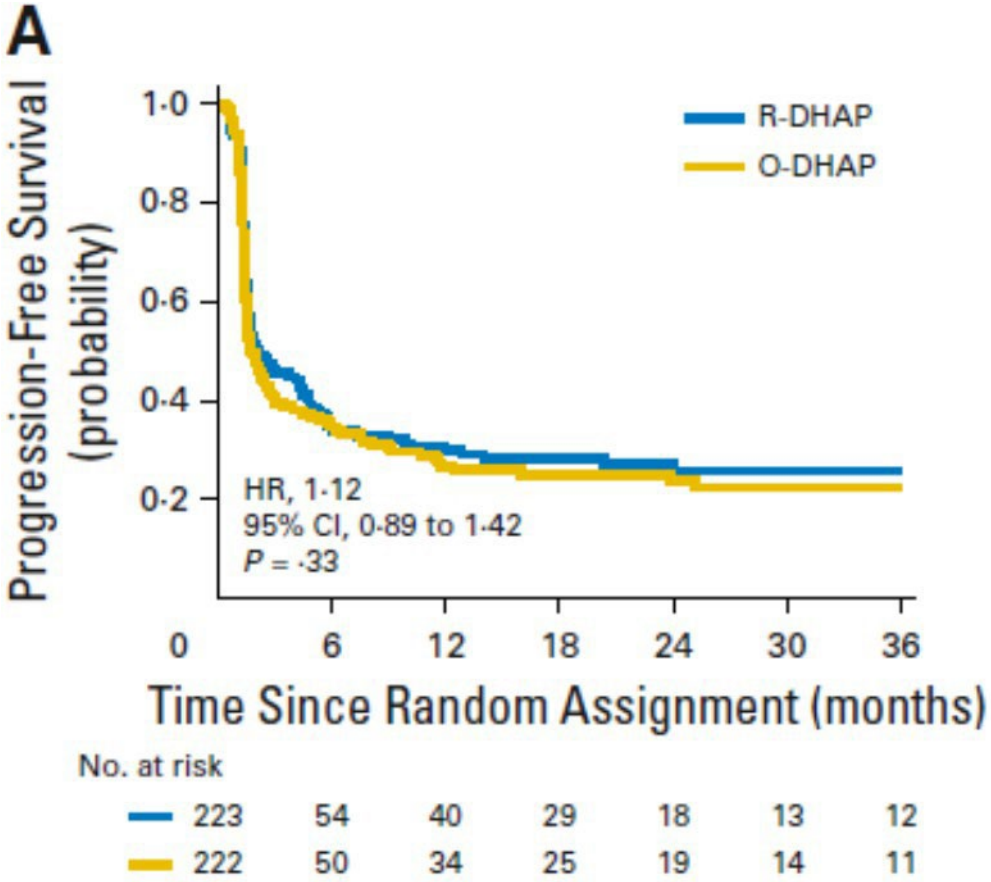
[a] Study regimens amended to include rituximab for pts with CD20+ disease from November 2005

BL: baseline; FACT-G: Functional Assessment of Cancer Therapy – General; GDP: gemcitabine, dexamethasone, cisplatin; NCIC-CTG: National Cancer Institute of Canada Clinical Trials Group; QOL: quality of life

Crump M, *et al. J Clin Oncol* 2014; 32:3490–3496.

ORCHARRD: An alternative anti-CD20

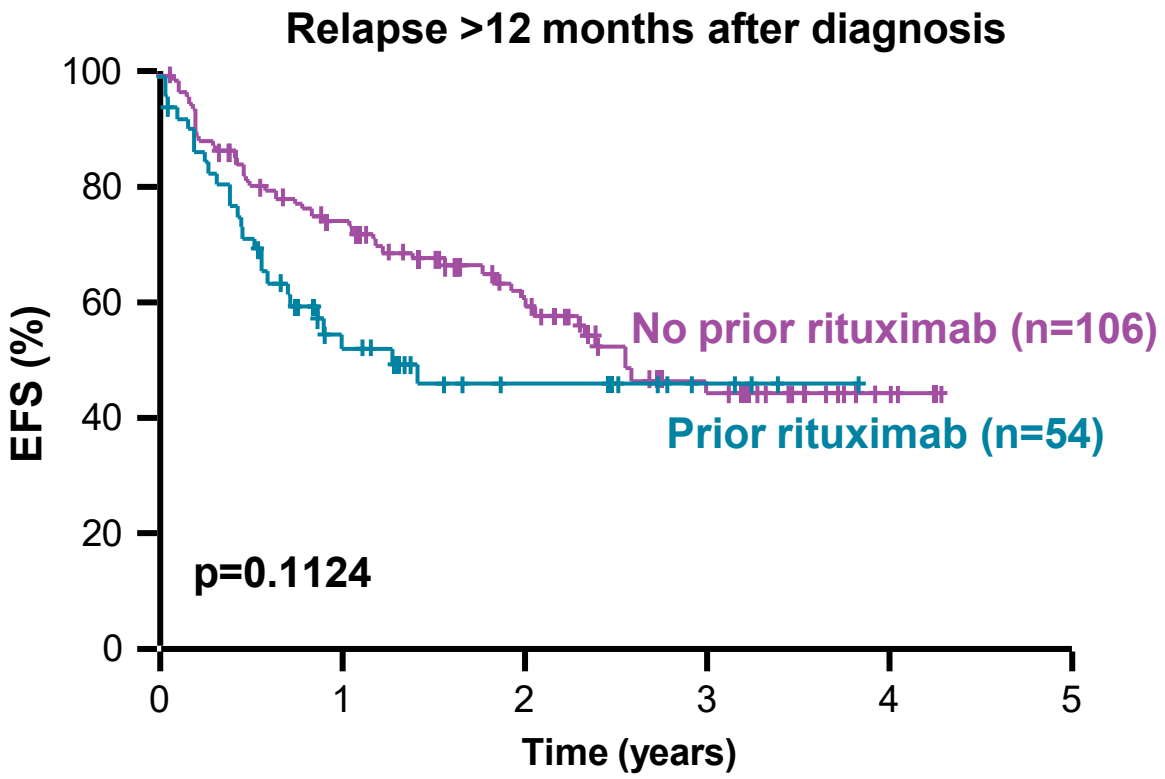


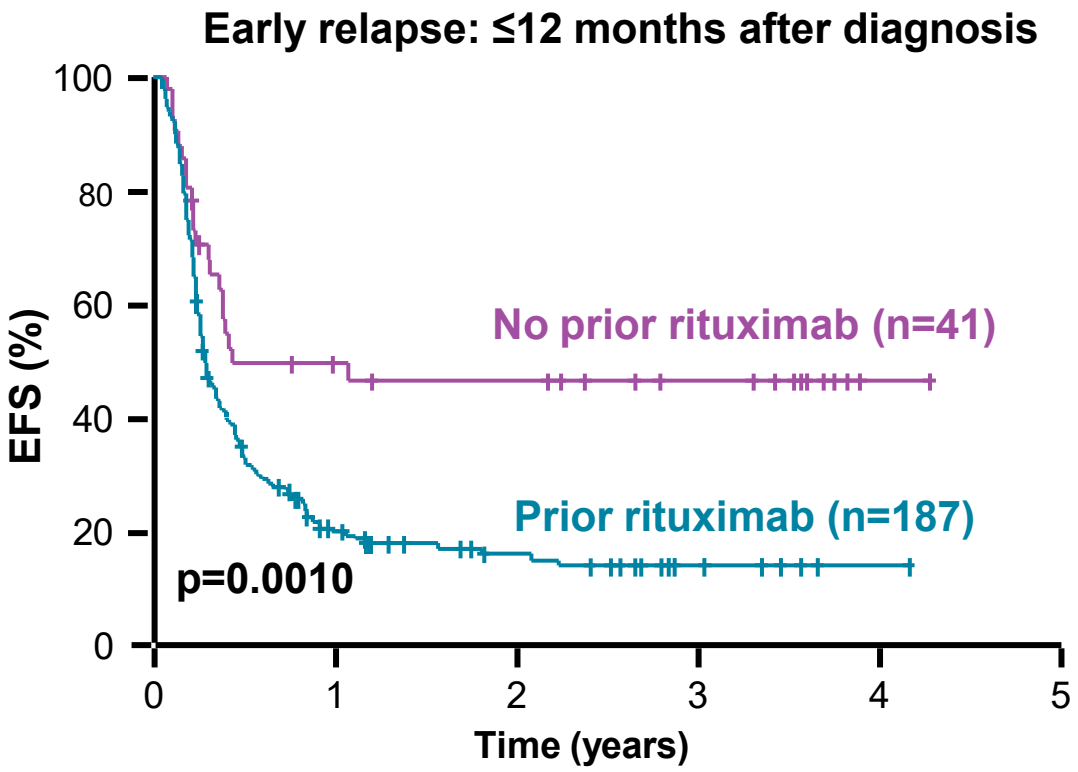


Van Imhoff et al JCO 2016

CORAL study: Standard regimens do not overcome poor prognosis of early relapse

CORAL: Randomised study of R-ICE vs. R-DHAP in patients with R/R DLBCL after 1L R-CHOP (N=396)



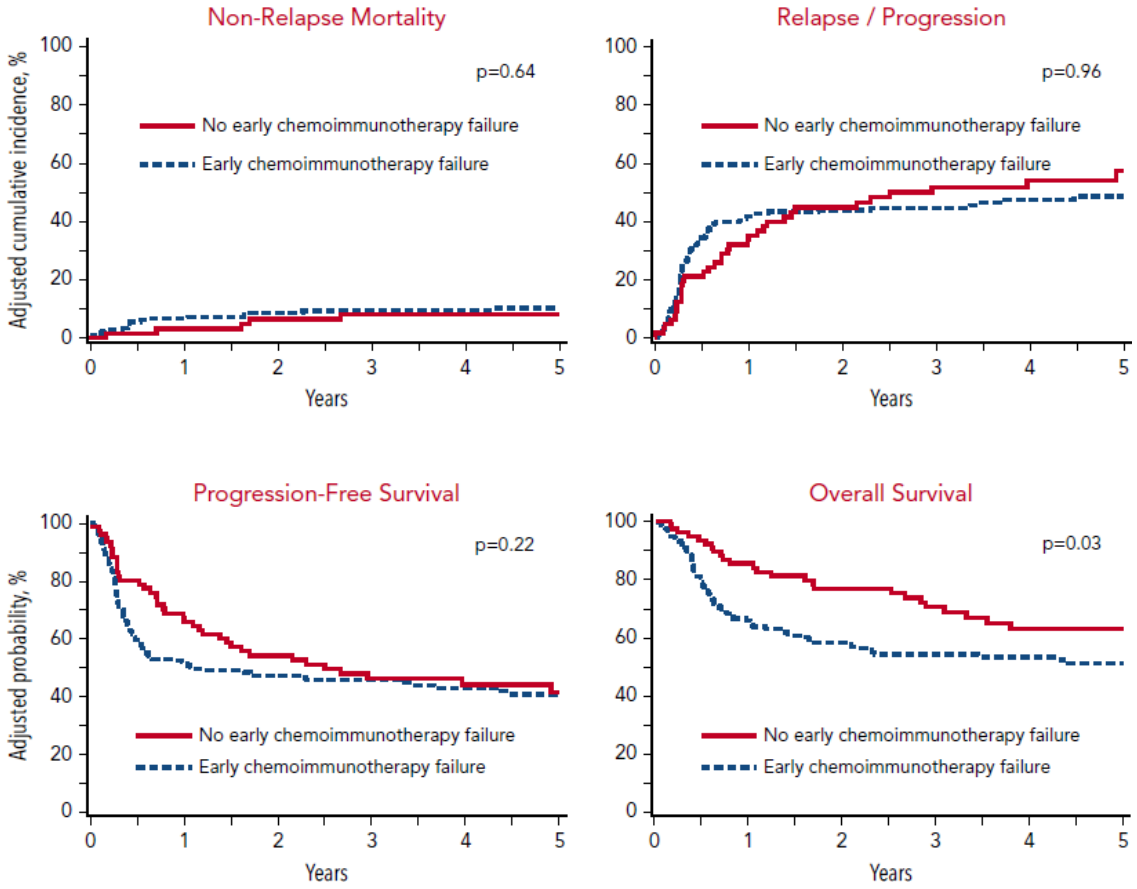


EARLY RELAPSE AND PRIOR RITUXIMAB TREATMENT DEFINED A POPULATION WITH A POOR RESPONSE RATE TO STANDARD SALVAGE TREATMENT

CORAL: Collaborative Trial in Relapsed Aggressive Lymphoma

Gisselbrecht C, *et al. J Clin Oncol* 2010; 28:4184–4190.

Should ASCT be offered to patients in PET+ PR?[1,2]



- CIBMTR (n = 249) relapsed DLBCL PET+ PR
- Included early chemotherapy failures (relapse within 12 months; n = 182)
  - 79% were primary refractory

5-year

PFS	41%
OS	51%

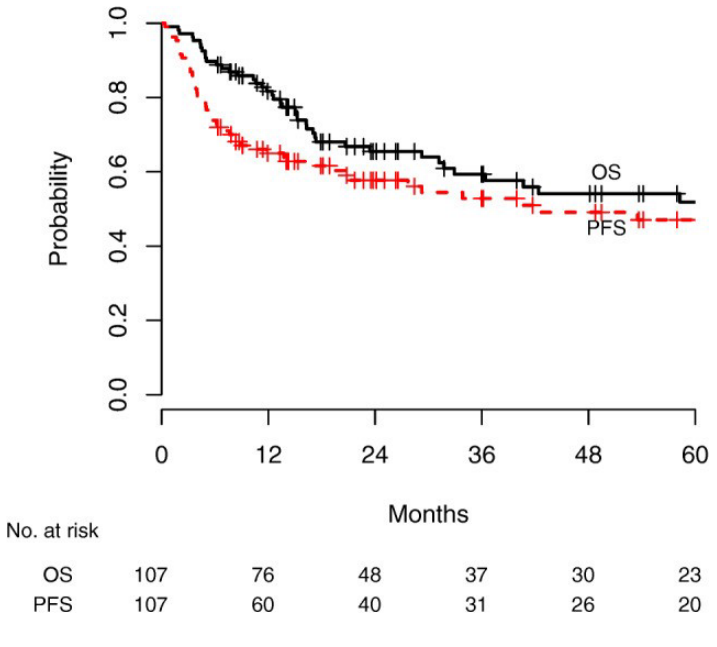
- Cures with low NRM/modest cost

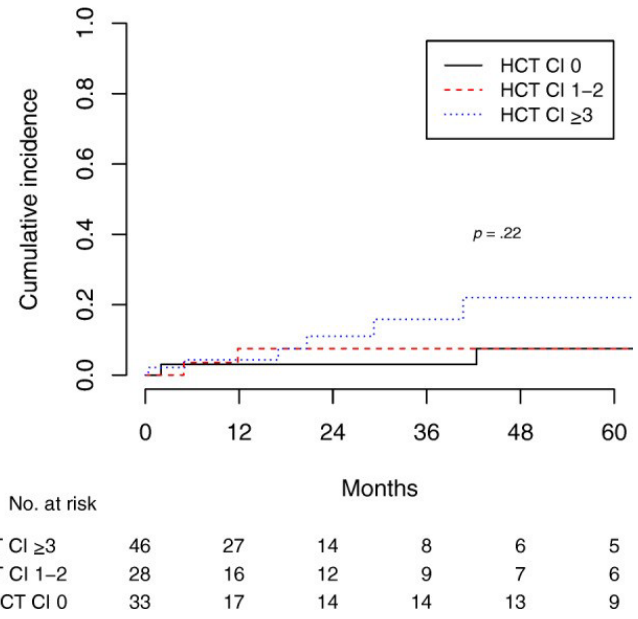
ASCT, autologous stem cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; DLBCL, diffuse large B-cell lymphoma; NRM, non-relapse mortality; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SD, stable disease.

1. Shah N, et al. *Blood.* 2021;137(10):1416-1423. **2.** *Oncologist*. 2020;25(Suppl 1):S10-S11.

Should we challenge the assumption that ASCT is too toxic in the elderly?

- Outcomes for patients aged >70 receiving ASCT (DLBCL n = 63; 59%)





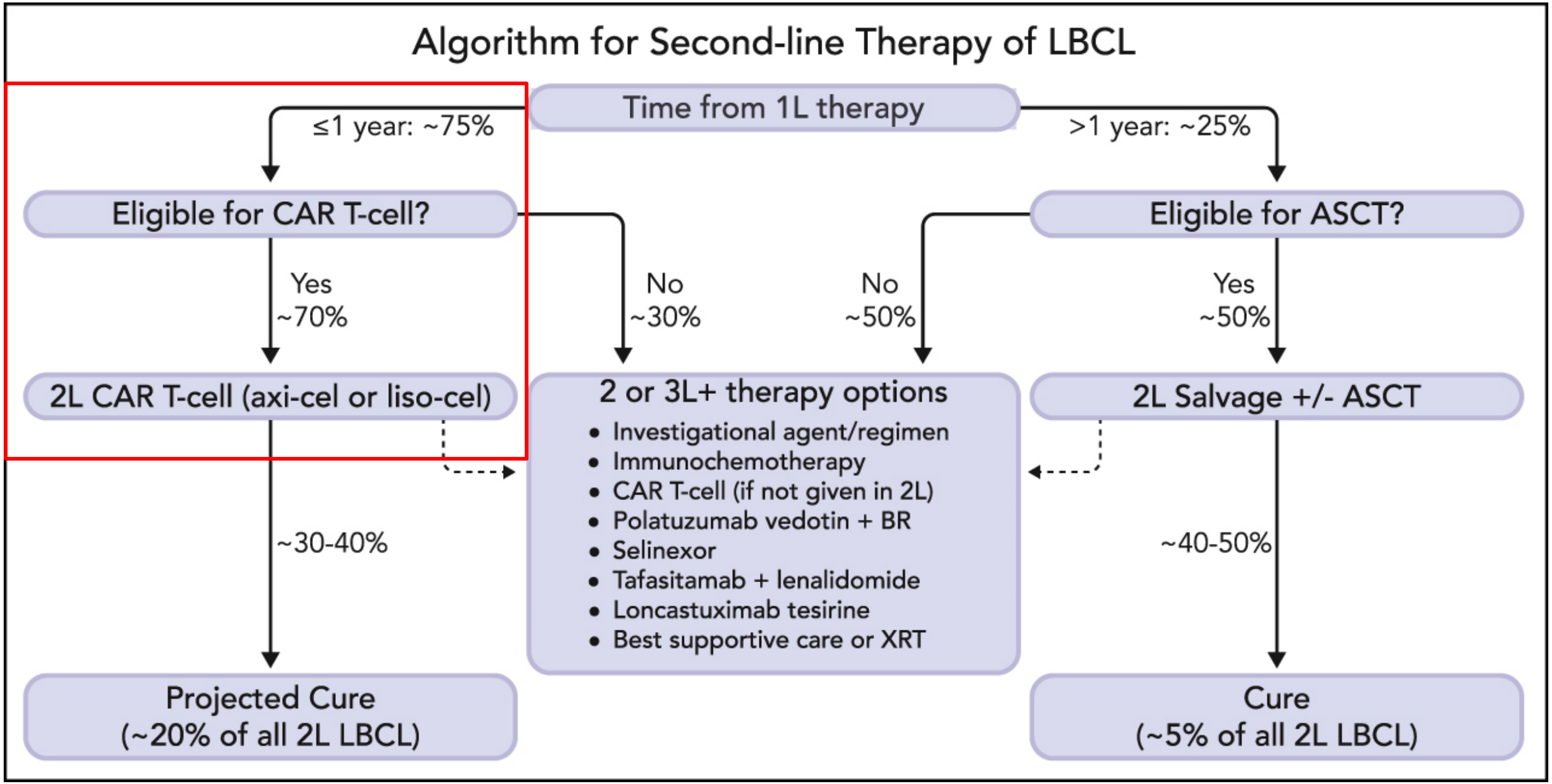
2-year PFS 58% (95% CI, 48–67)
OS 65% (95% CI, 55–74)

NRM 7% (95% CI, 3–14)

- Patient selection
- Optimising supportive care
- Use of comprehensive geriatric assessment methodologies
- Trajectory of functional recovery
- Individualised choices/shared decisions

ASCT, autologous stem cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; DLBCL, diffuse large B-cell lymphoma; HCT CI, hematopoietic cell transplantation-specific comorbidity index; NRM, non-relapse mortality; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

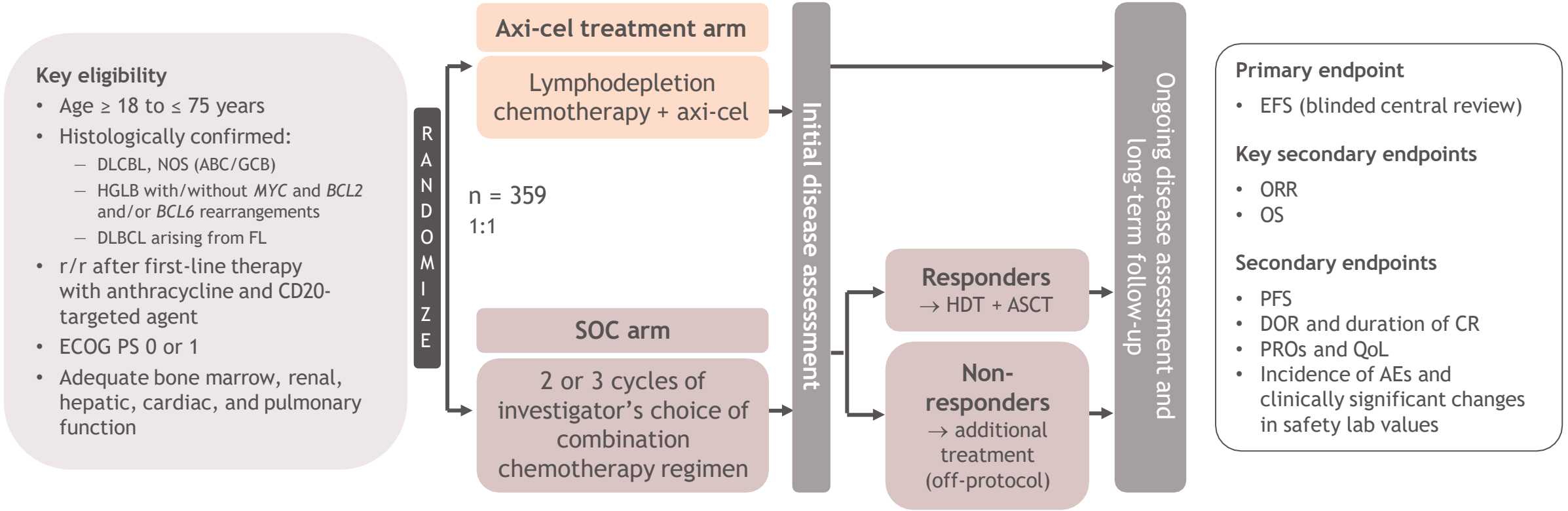
Sun L, et al. *Oncologist*. 2018;23(5):624-630.



Westin and Sehn 2022

Progression to the second line of therapy?

ZUMA-7, a randomized, open label, phase 3 trial of second-line axicabtagene ciloleucel versus standard of care in adult patients with r/r DLBCL

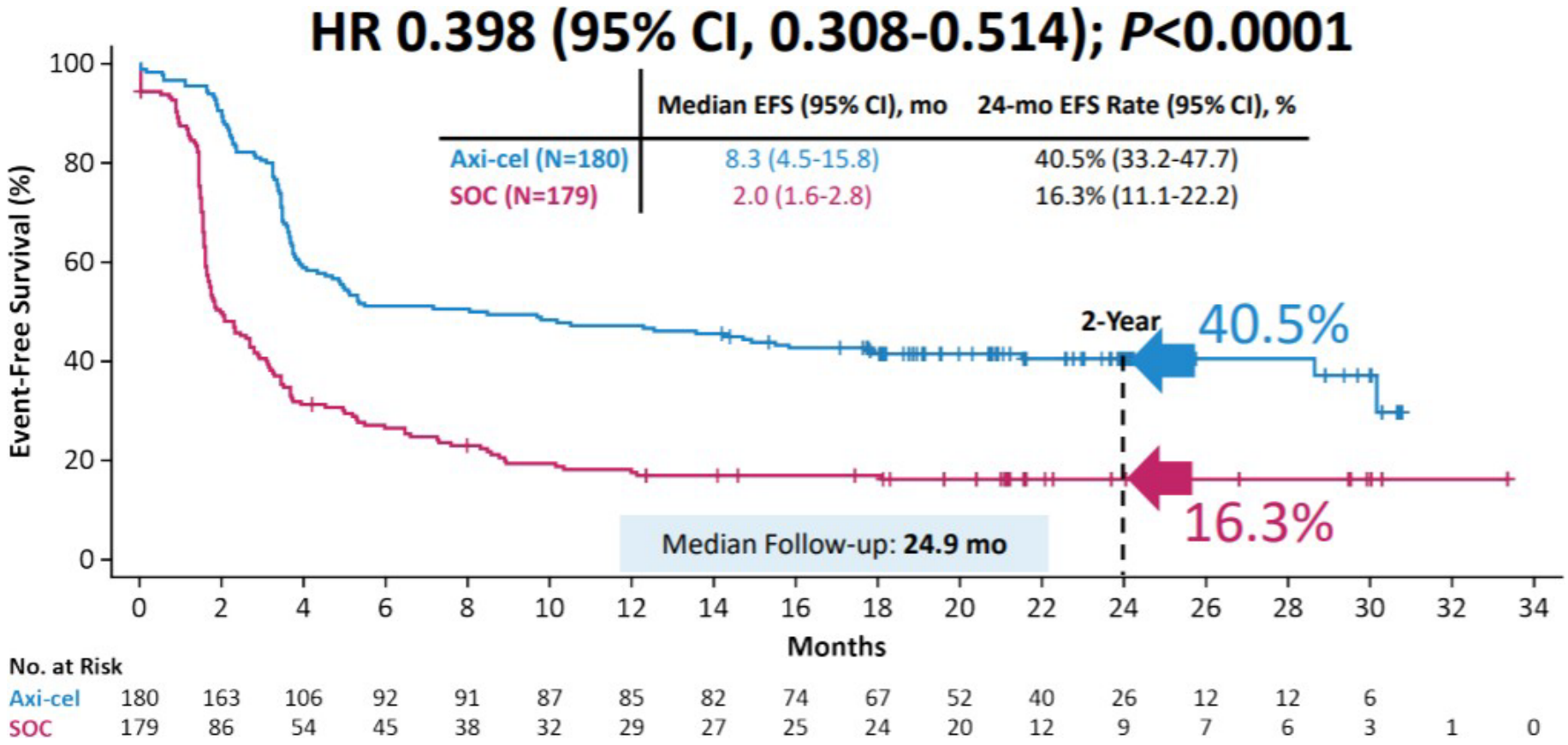


Axi-cel, axicabtagene ciloleucel; HDT, high-dose therapy; NOS, not otherwise specified; PRO, patient-reported outcome; QoL, quality of life; SOC, standard of care.

NCT03391466. Available from: https://clinicaltrials.gov/ct2/show/NCT03391466. Accessed October 2020.

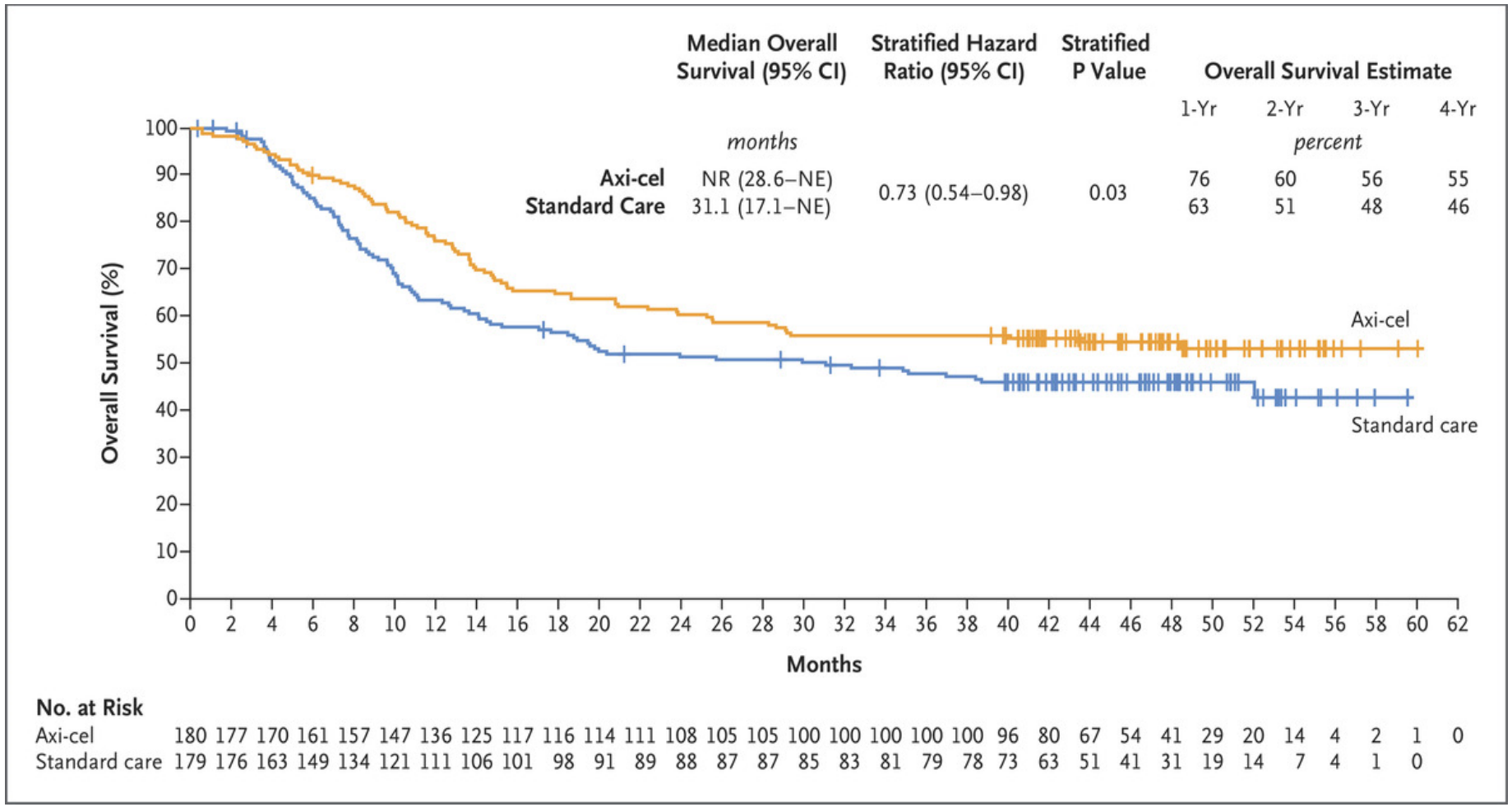
TRANSFORM (**lisocabtagene maraleucel**) and BELINDA (tisagenlecleucel)

Zuma-7 Primary endpoint: Event-Free Survival



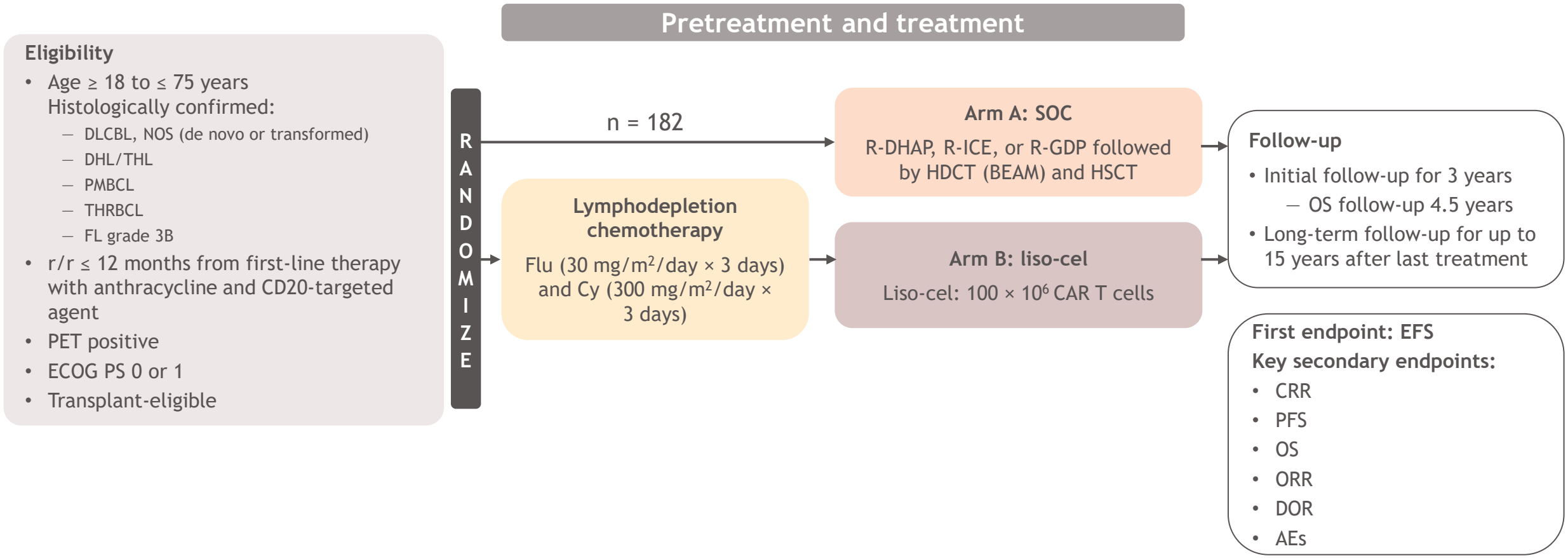
Locke et al ASH 2021

Overall Survival advantage.



JR Westin et al. N Engl J Med 2023;389:148-157.

TRANSFORM: lisocabtagene maraleucel compared to standard of care second-line therapy in r/r aggressive B-cell NHL

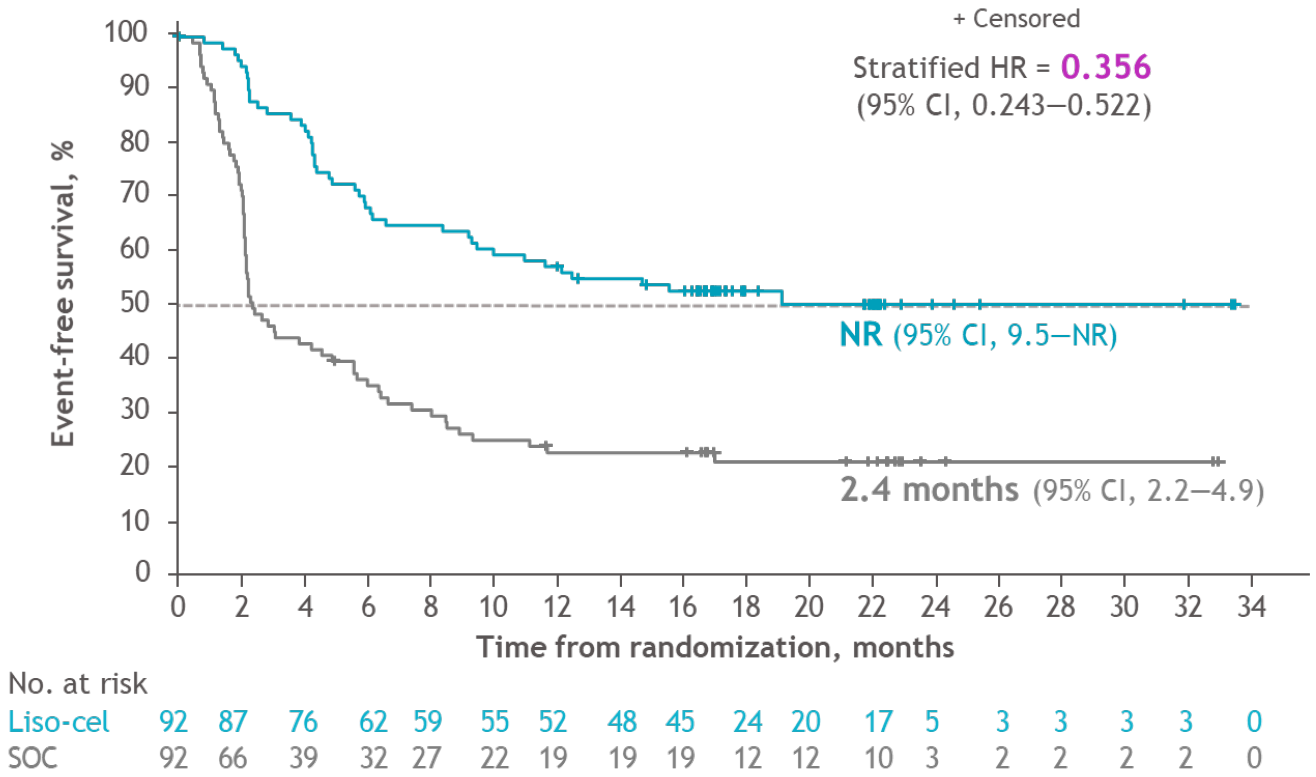


Lisocabtagene maraleucel is not approved by any regulatory agency.

BEAM, carmustine, etoposide, cytarabine, melphalan; CR, complete response; HRQoL, health-related quality of life; HDCT, high-dose chemotherapy; ORR, overall response rate; PFS-2, progression after the next line of therapy.

NCT03575351. Available from: https://clinicaltrials.gov/ct2/show/NCT03575351. Accessed October 2020.

TRANSFORM: EFS per IRC (ITT set; primary endpoint)



No. at risk

Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0
SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	2	0

18-month EFS rate	
Liso-cel	SOC
52.6%	**20.8%**
(95% CI, 42.3–62.9)	(95% CI, 12.2–29.5)

Median follow-up: 17.5 months

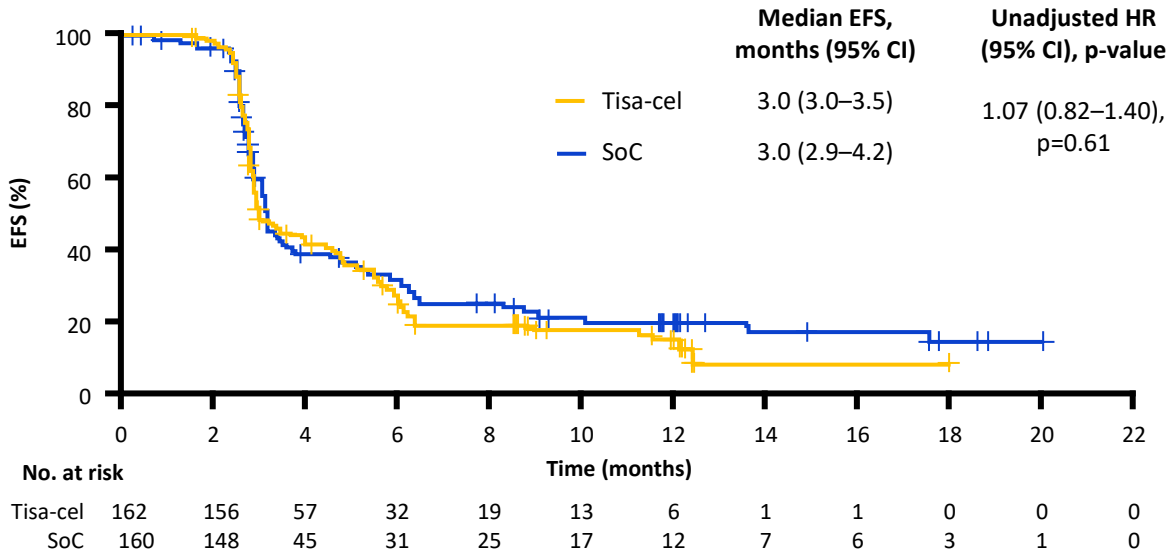
EFS was defined as the time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomisation, or start of a new antineoplastic therapy due to efficacy concerns, whichever occurred first. This endpoint was not statistically retested for the primary analysis.
EFS, event free survival; IRC, independent review committee; ITT, intent-to-treat; NR, not reached.

Abramson JA et al, Oral 655, ASH 2022

Abramson JA et al, Oral 655, ASH 2022

BELINDA: Tisa-cel failed to show improved efficacy vs SoC in 2L R/R aggressive B-cell lymphoma

EFS with tisa-cel vs SoC



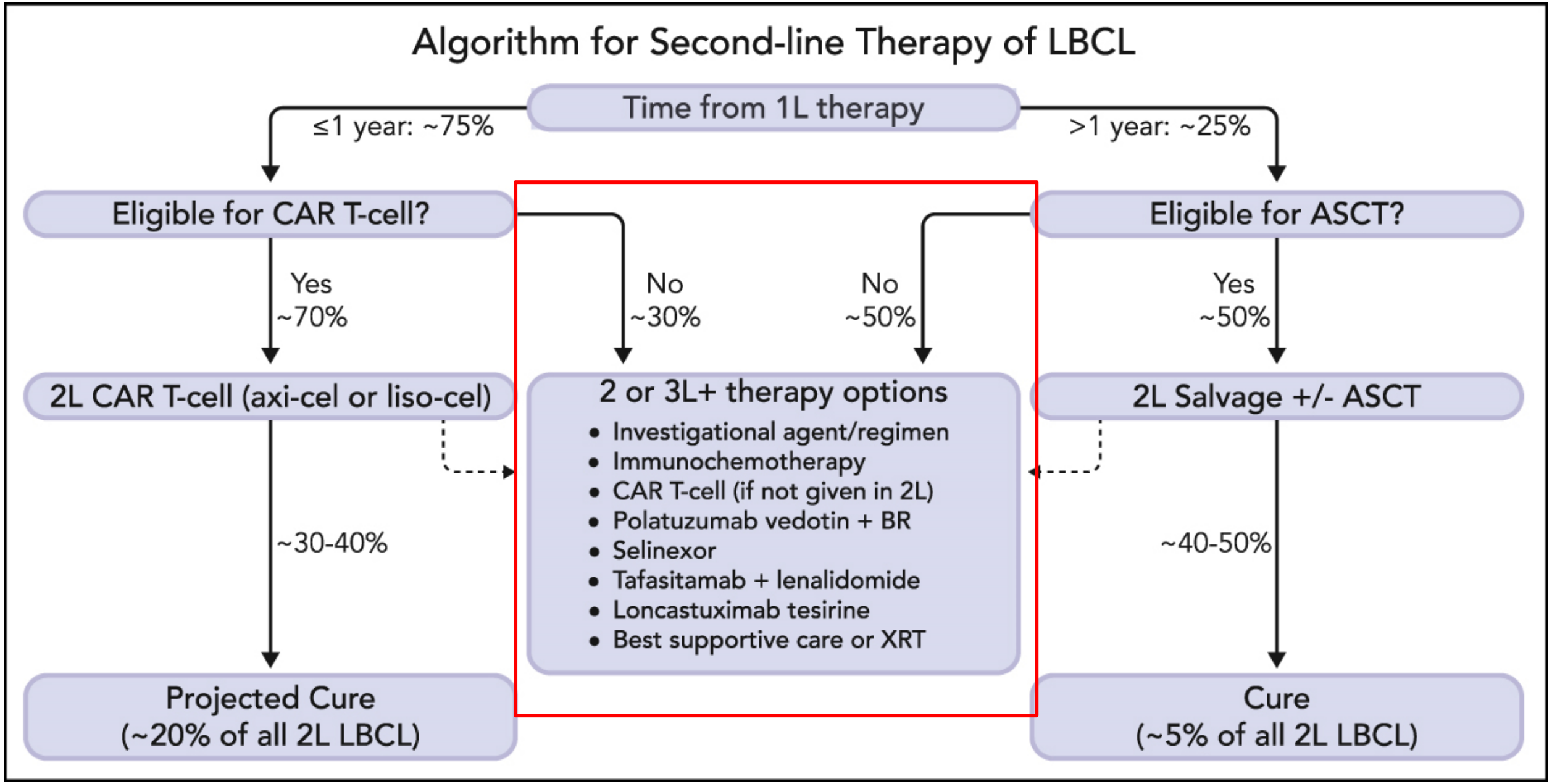
Response rates

- **At week 6**, 38.3% of patients receiving tisa-cel and 53.8% of those receiving SoC had a response
- **From week 12**, a response occurred in 46.3% of patients receiving tisa-cel and 42.5% receiving SoC

Safety, n (%)	Tisa-cel (n=162)	SoC (n=160)
Grade ≥3 AEs	136 (84.0)	144 (90.0)
Treatment-related Grade ≥3 AEs	121 (74.7)	137 (85.6)
Grade ≥3 CRS*	8 (5.2)	NA
Grade ≥3 neurologic events*	3 (1.9)	NA
Fatal AEs	10 (6.2)	13 (8.1)

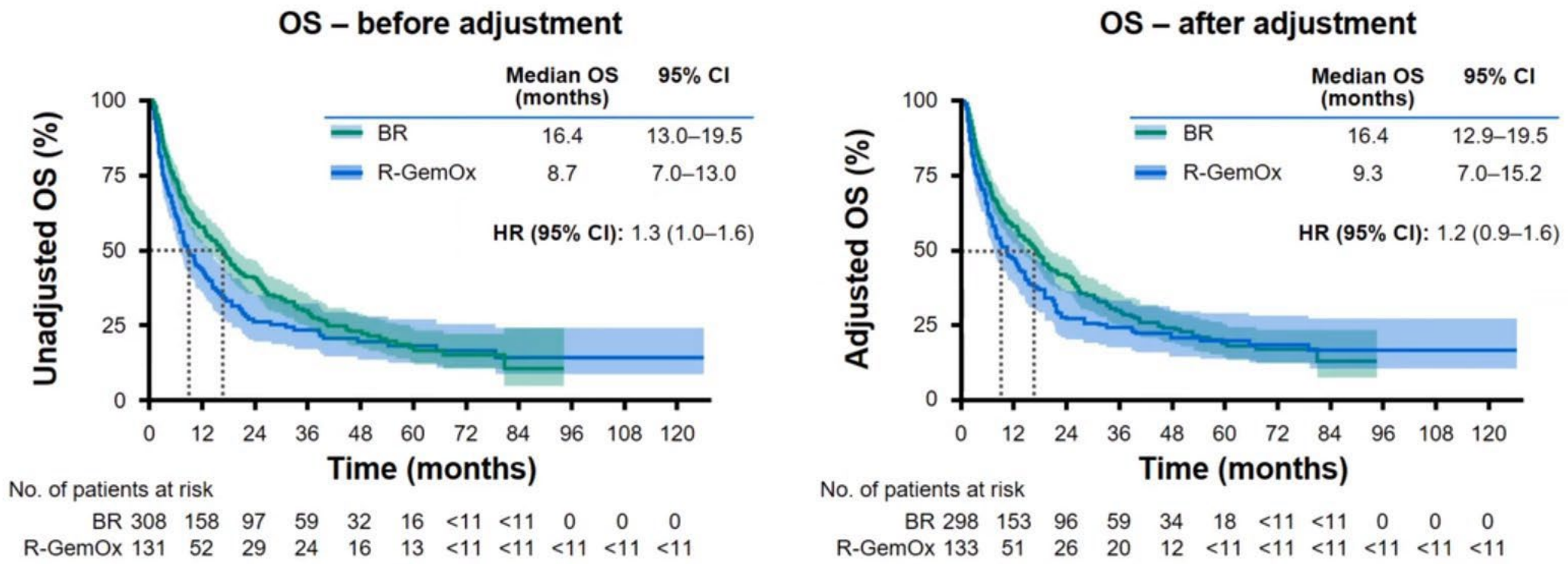
*A total of 155 patients from the tisa-cel arm were evaluable for CRS and neurologic events.

Bishop MR, et al. N Engl J Med 2022;386:629-39.



Westin and Sehn 2022

SEER Database review: No significant difference in outcomes between combinations (Second line)

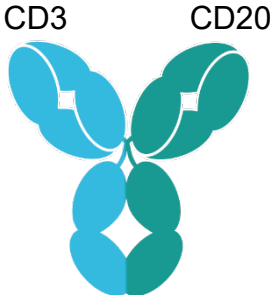


Adjusted KM curves show no significant difference in median OS for BR and R-GemOx in 2L after balancing with propensity score methods

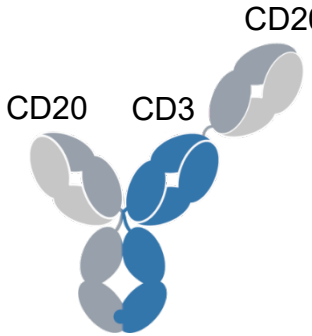
Propensity score analysis

Castro et al. ASH 2020

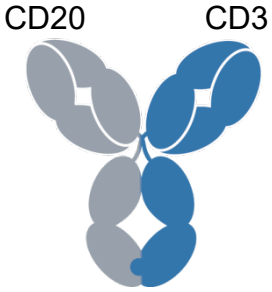
CD20xCD3 bispecific antibodies of various formats are in early clinical development for NHL[1-3]



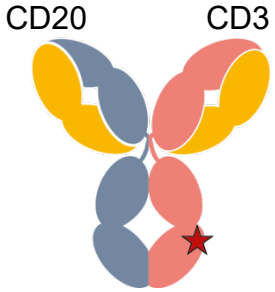
Epcoritamab
DuoBody-CD3×CD20
IgG1



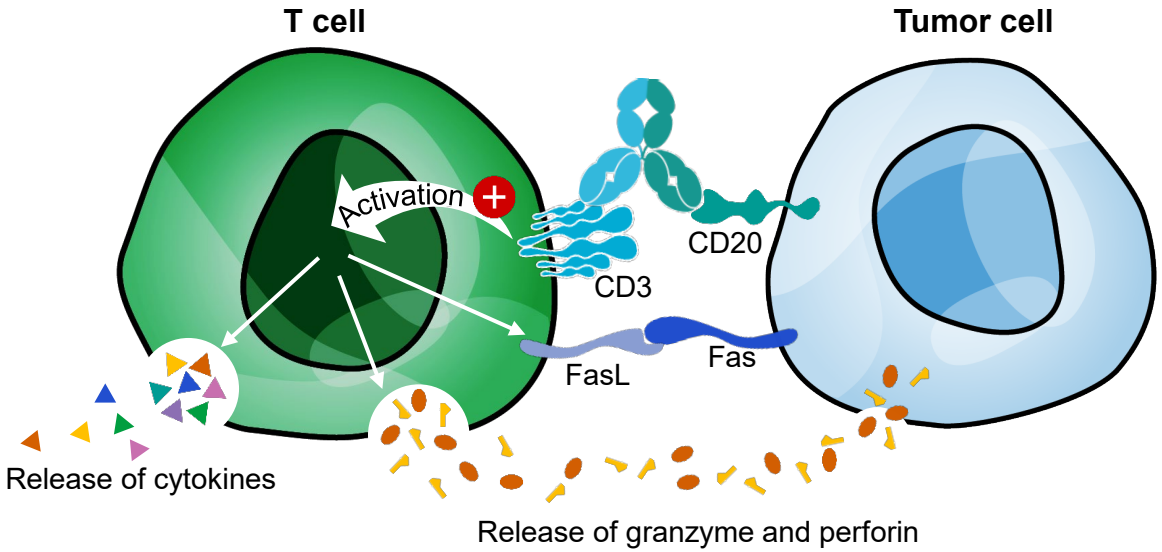
Glofitamab
2+1 CrossMab
IgG1



Mosunetuzumab
Knob-in-hole
IgG1



Odronextamab
VELOCI-Bi
IgG4



- CD3 ×CD20 bsAbs bring together T cells and CD20+ tumor cells to induce T cell-mediated killing of the tumor cell[2]
- Able to induce effector T cell binding without requiring MHC-mediated antigen presentation[2]

B-NHL, B-cell non-Hodgkin lymphoma; bsAb, bispecific antibody; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625. 2. Schuster SJ. *Hematological Oncology*. 2021;39(S1):113–116. 3. You G, et al. *Vaccines*. 2021;9:724.

Delivery

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	29	21	22	23	24	25	26	27	28	29	30
Epcoritamab																														
Glofitamab																														

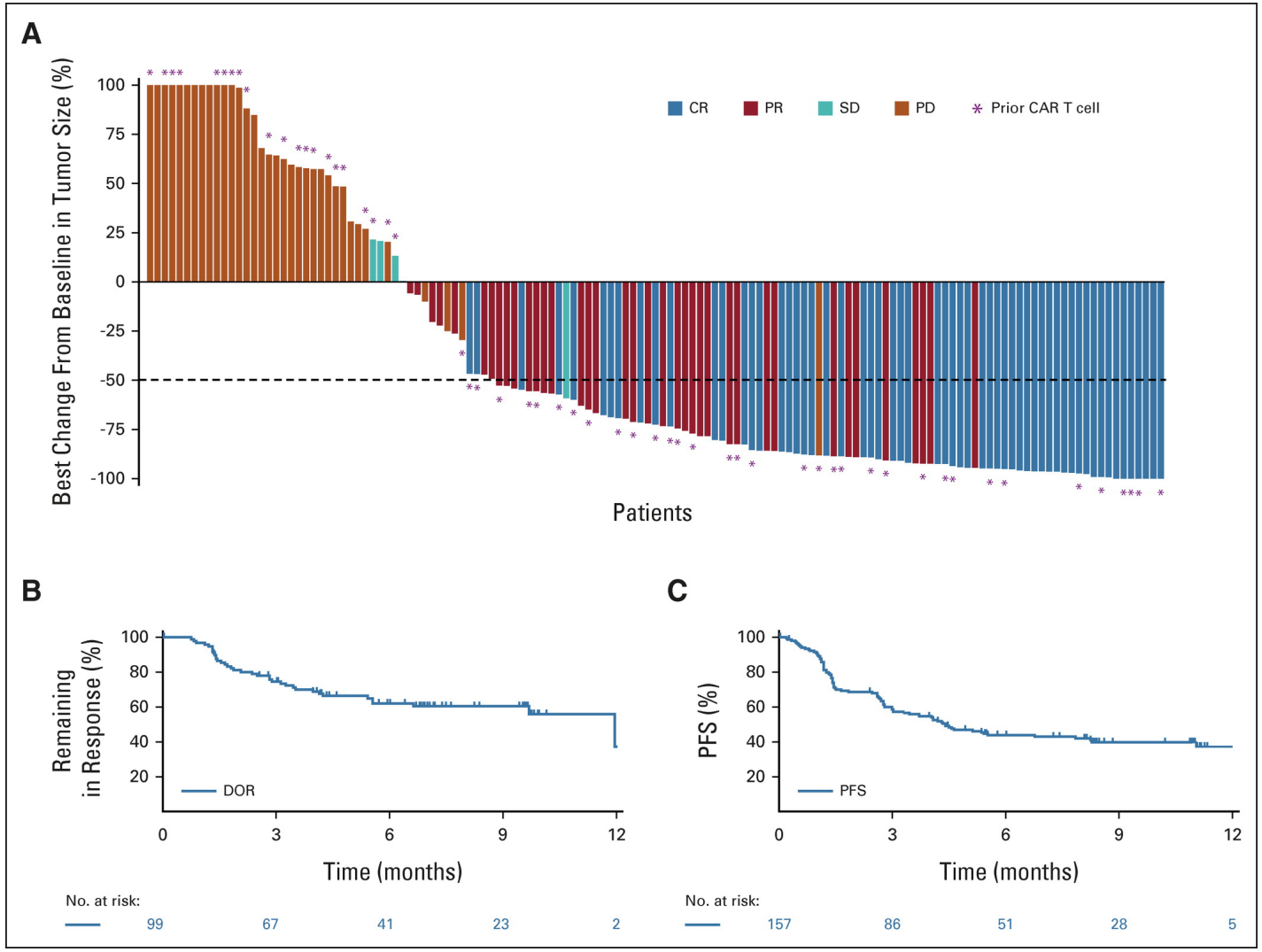
Week	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Epcoritamab																														
Glofitamab																															

Week	61	62	63	64	65	66	67	68	68	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
Epcoritamab																														
Glofitamab																														

Thieblemont et al. JCO 2022 Dickinson *et al*. NEJM 2022

Epcoritamab: responses in relapsed/refractory DLBCL

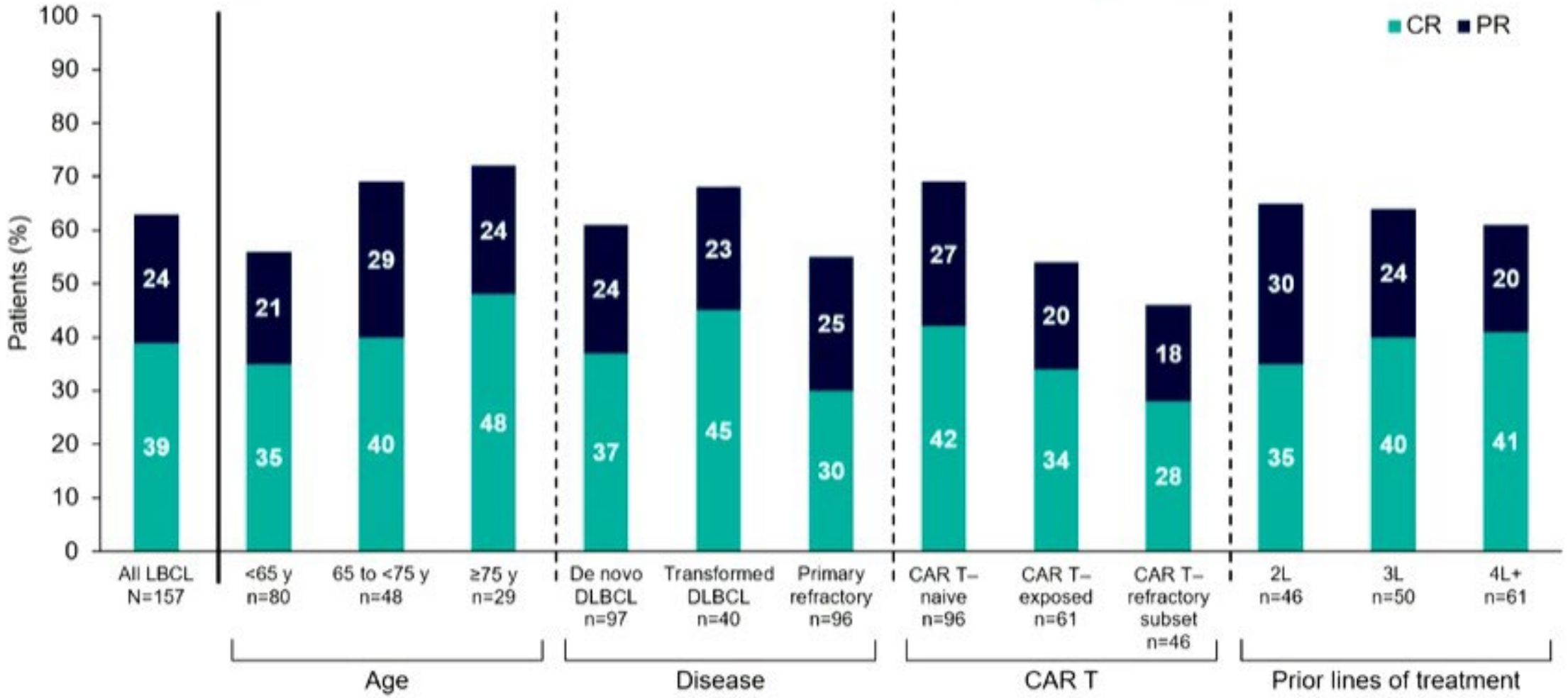
- 157 patients ≥2 lines of therapy
- 61 prior CAR-T therapy
- 0.16 →0.8 →48mg SC
- Overall response rate 63% (55.0 to 70.6)
- CR 39% (31.2 to 46.9).
- Median duration of response 12.0 months
- 50% CRS, 2.5% grade 3



Thieblemont C et al., J Clin Oncol 2022

Epcoritamab: SC delivery

Deep Responses Consistent Across Key Subgroups



Based on IRC assessment and Lugano criteria.

155 patients ≥ 2 lines of therapy

52 prior CAR-T therapy

Obinutuzumab pre-dose

Glofitamab 2.5 →10 → 30 mg IV

Up to 12 doses (median 5 given)

39% CR rate 52% ORR (35% among CAR-T group)

CRS in 63%, ≥grade 3 in 4%

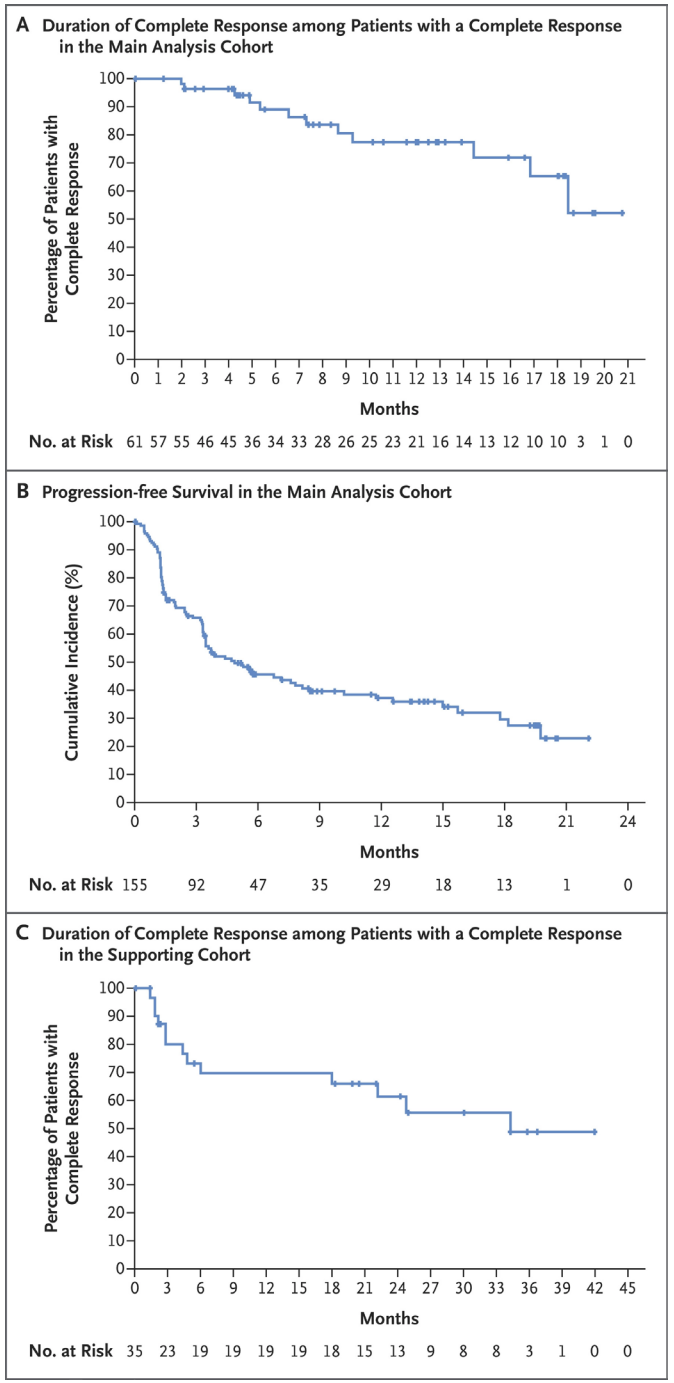
Median follow-up: 12.6 months (range, 0.1 to 22.1)

6-month progression-free survival was 46% (95% CI, 37 to 54)

12-month progression-free survival was 37% (95% CI, 28 to 46).

12-month OS 50% (95% CI, 41 to 58)

Dickinson *et al.* NEJM 2022

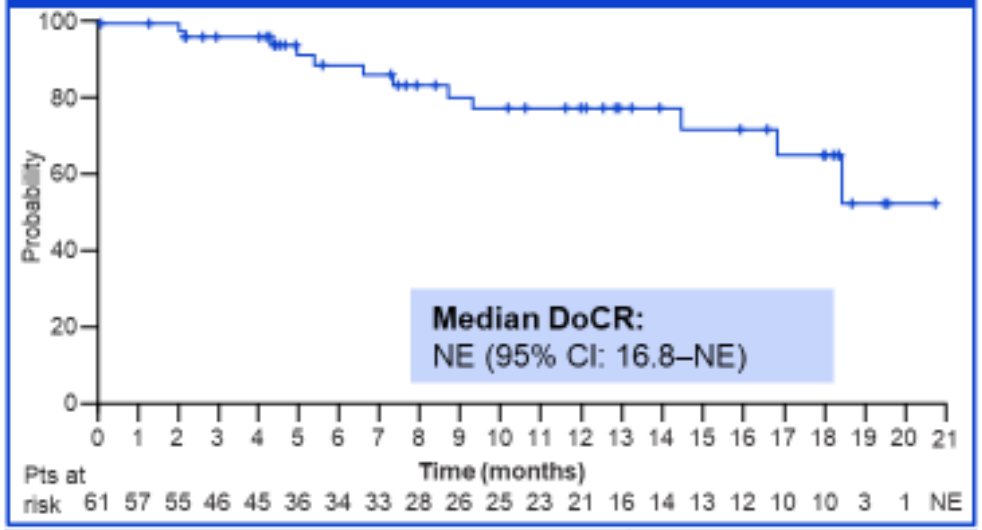


Background: Glofitamab monotherapy at RP2D induces durable complete responses

Pivotal Phase II results presented at ASCO 2022

- DLBCL NOS, HGBCL, trFL or PMBCL; ≥2 prior therapies
- Glofitamab 2.5/10/30mg (**N=155**)
- Efficacy
  - **CR rate: 39.4%** (61/155)
  - **ORR: 51.6%** (80/155)
- Safety
  - Glofitamab was well tolerated with a low rate of discontinuation
  - CRS was mostly low grade

Pivotal Phase II cohort (ASCO 2022) – DoCR* by IRC



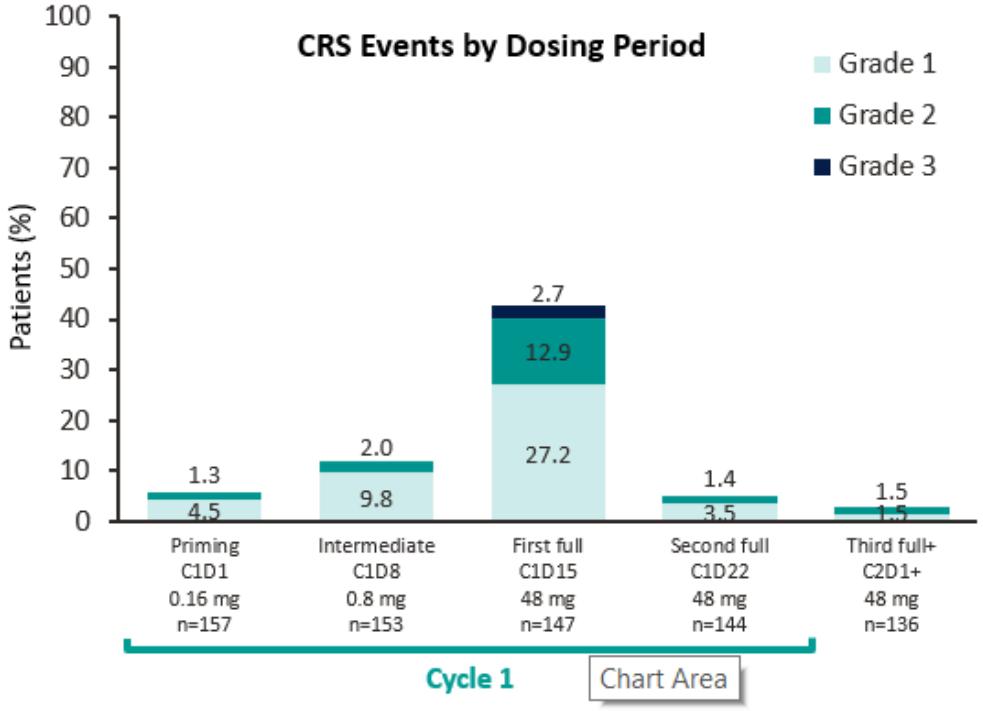
	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3–90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

Clinical cut-off date: March 14, 2022. *Time from the initial occurrence of a CR until PD or death due to any cause, whichever occurs first.
CRS, cytokine release syndrome; DoCR, duration of complete response; IRC, Independent Review Committee; PD, progressive disease.

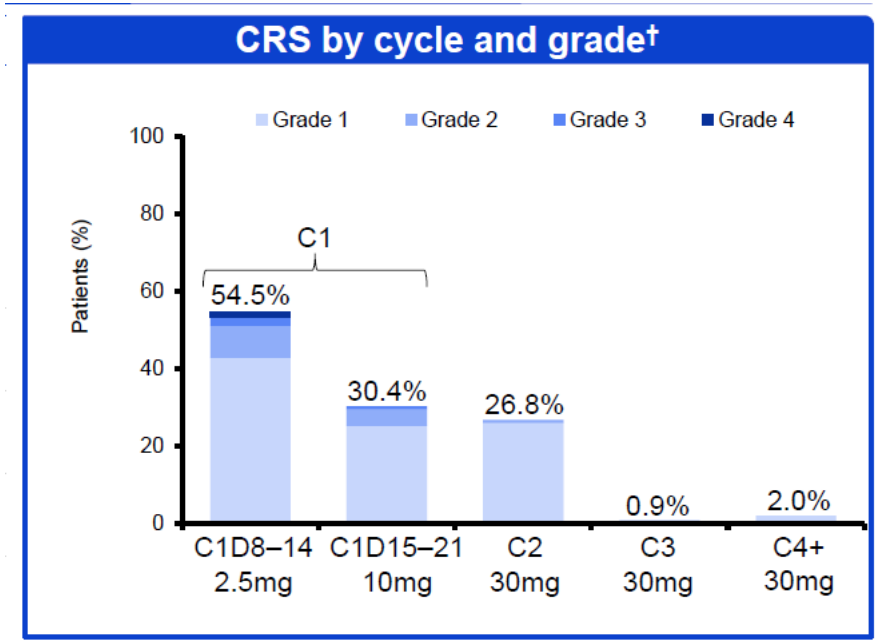
Dickinson M, et al. ASCO 2022:7500.

Despite step-up dosing, CRS still occurs in 50% of patients receiving bispecifcs:

Are we ready to deal with this?

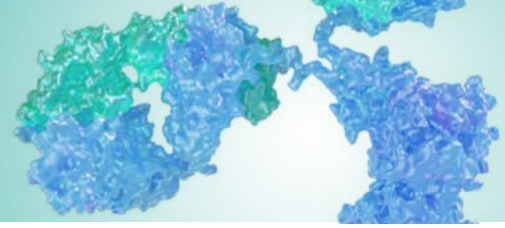


Thieblemont et al. EHA 2022 and JCO 2022



Dickinson et al. EHA 2022 and NEJM 2022

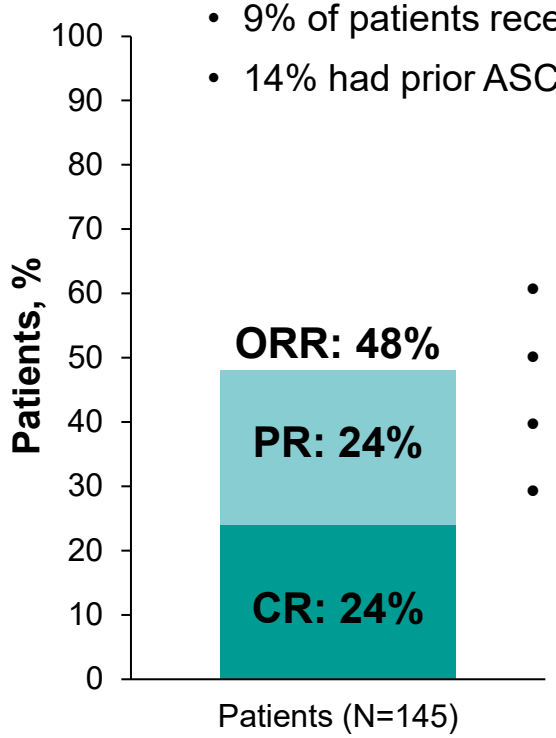
LOTIS-2 Phase 2 Trial
Loncastuximab Teserine in 3L+ DLBCL



Eligibility
- Aged ≥18 years
- R/R DLBCL
- ≥2 prior regimens
- Prior CAR T permitted (persistent CD19 expression required)

Lonca IV as 30-min infusion
In 21-d cycles
C1-2: 150 µg/kg Q3W
C3+: 75 µg/kg Q3W for up to 1 year or PD/unacceptable toxicity

- 9% of patients received prior CAR T
- 14% had prior ASCT



- Median DOR: 10.3 mo
- 9-month DOR: 64%
- Median PFS: 4.9 mo
- Median OS: 9.9 mo

Most Common TEAEs (≥20% Any Grade or ≥5% Grade ≥3)

Patients, %	Patients (N=145)	
	Grade 1-2	Grade 3-4
Neutropenia	14	26
GGT increased	24	16
Thrombocytopenia	15	18
Anemia	16	10
Fatigue	26	1
Nausea	23	0
Cough	21	1
Peripheral edema	19	1
Blood alkaline phosphatase increased	19	1
Hypophosphatemia	10	6
Leukopenia	6	9
Lymphopenia	2	6

Median treatment duration was 45 days.
3L, third-line; ASCT, autologous stem cell transplant; C, cycle; CAR T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; GGT, gamma-glutamyl transferase; Lonca, loncastuximab teserine; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
Caimi P, et al. *Lancet Oncol*. 2021;22:790-800.

Relapsed/Refractory disease: Conclusions

- Results from conventional chemotherapeutic approaches are disappointing in R/R DLBCL
- Our treatment paradigms are changing. More options for patients
- Demonstration of success of cellular therapies..moving earlier up the treatment lines
- ADC combine high specificity of a mAb with potent cytotoxic
- Promise from the bispecific antibodies
- Much still to be understood regarding sequencing, bridging…