VCC VIRTUAL Challenging Case Clinic

B-Cell Lymphomas SERIES

Diffuse Large B-Cell Lymphoma

December 14, 2022

University of Nebraska Medical Center

Bio Ascend™

Introductions

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Abbvie Inc., AstraZeneca, Genmab, Lilly, and Merck & Co. Inc.

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Disclosures

John Leonard, MD

Consulting Fees: Abbvie, Astellas, Beigene, Calithera, Celgene/BMS, Constellation, Eisai, Epizyme, Genmab, Grail, Incyte, Janssen, Karyopharm, Lilly, Merck, Mustang Bio, Pfizer, Roche/Genentech, Second Genome, Sutro

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Research/Consulting: AbbVie, AstraZeneca, BMS, Daiichi Sankyo, Genentech, Janssen, Johnson & Johnson, Lilly, MEI Pharma, Pharmacyclics

Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP
Bio Ascend: Patti Bunyasaranand, MS; Dru Dace, PhD; Kraig Steubing

Learning Objectives

- ✓ Evaluate best available evidence regarding the treatment of indolent and aggressive subtypes of B-cell lymphoma
- ✓ Assess the implications of emerging clinical trial data regarding B-cell lymphoma therapeutic approaches
- ✓ Develop strategies to optimize the outcomes of complicated B-cell lymphoma cases

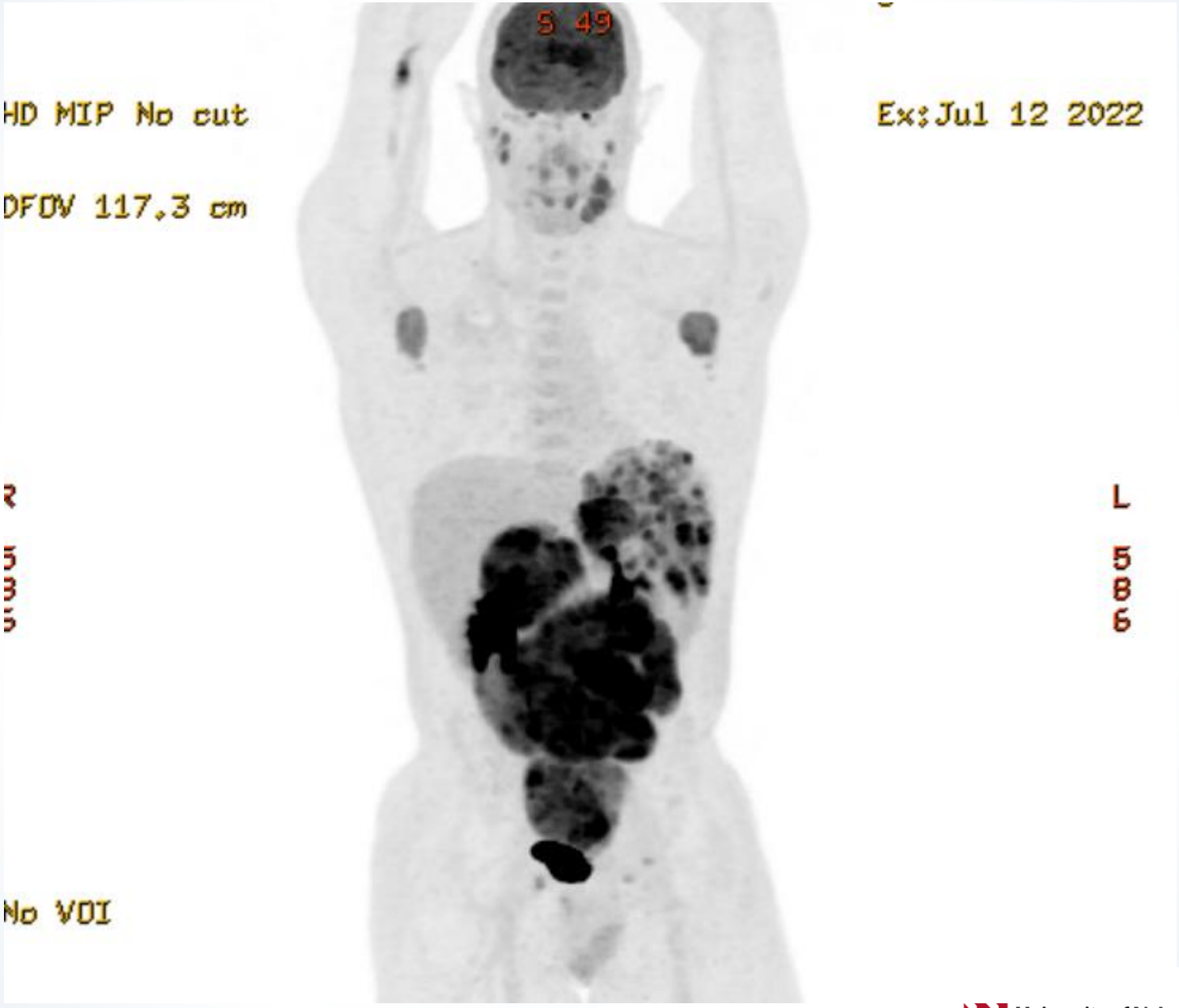
Reminders!

- ✓ Visit www.OncologyCaseClinic.com to register for upcoming webinars and view past webinars

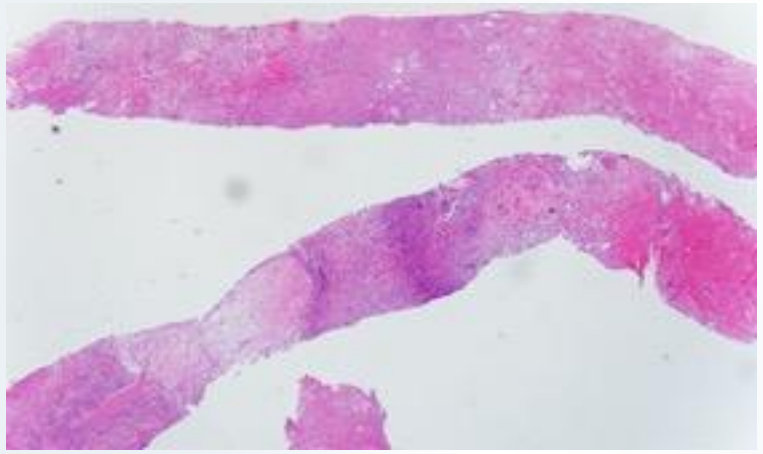
“Standard” DBLCL – Case Example

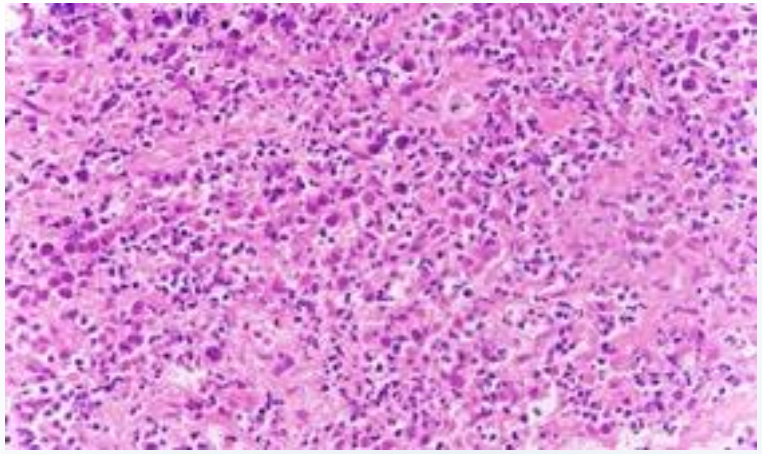
- 31 y/o with some “fullness” in his abdomen for a few months
- New lymph nodes enlarging in his neck – biopsies DLBCL, non- GCB subtype and FISH neg for c-Myc and bcl-2/bcl-6
- Otherwise healthy, farmer with herbicide exposures long term

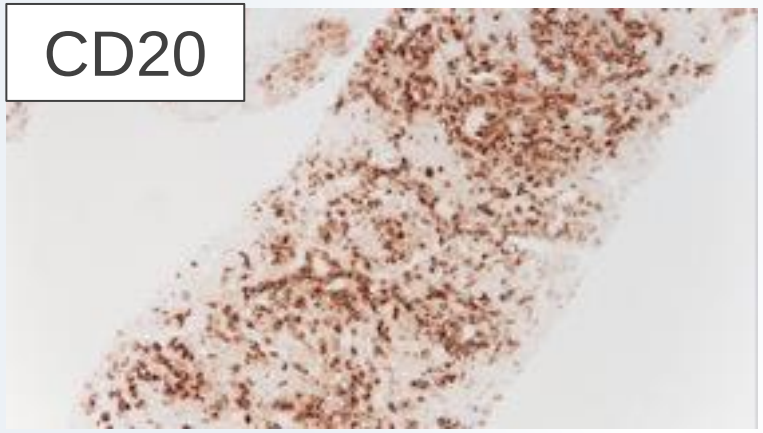
PET at Baseline

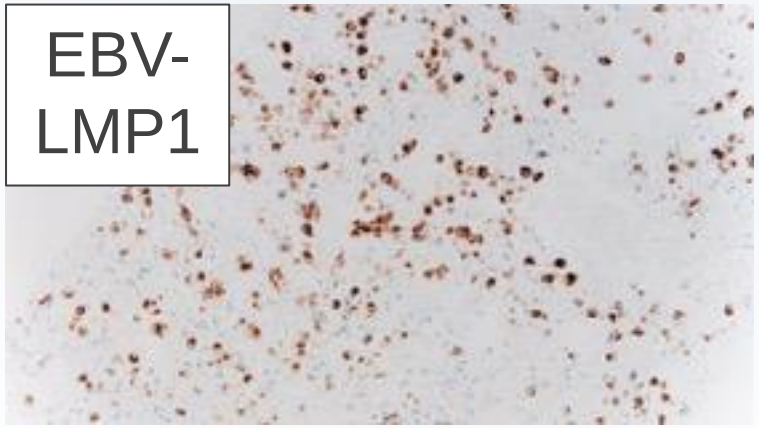


Pathology CT-Guided Core Biopsy









Positive: CD20, PAX5, EBV-LMP1, EBER (in intact viable cells), MUM1 (>30%).
Negative: CD10 (<30%), BCL6 (<30%), BCL2, BCL6 (<50%), and MYC (<40%), CD30.
Non-GCB by Hans
FISH: MYC-/BCL2-

Case Summary

31 yo with non-GCB subtype DLBCL
Stage IVB (+ BM involvement, spleen)
IPI 3 (stage IV, extranodal sites, elevated LDH)
CNS IPI 3 (> 1 extranodal, elevated LDH, stage IV)

How would you treat this patient?

1. DA-EPOCH-R
2. R-CHOP
3. Ibrutinib-RCHOP
4. Lenalidomide + R-CHOP (R^2CHOP)
5. CODOX-M/IVAC/R

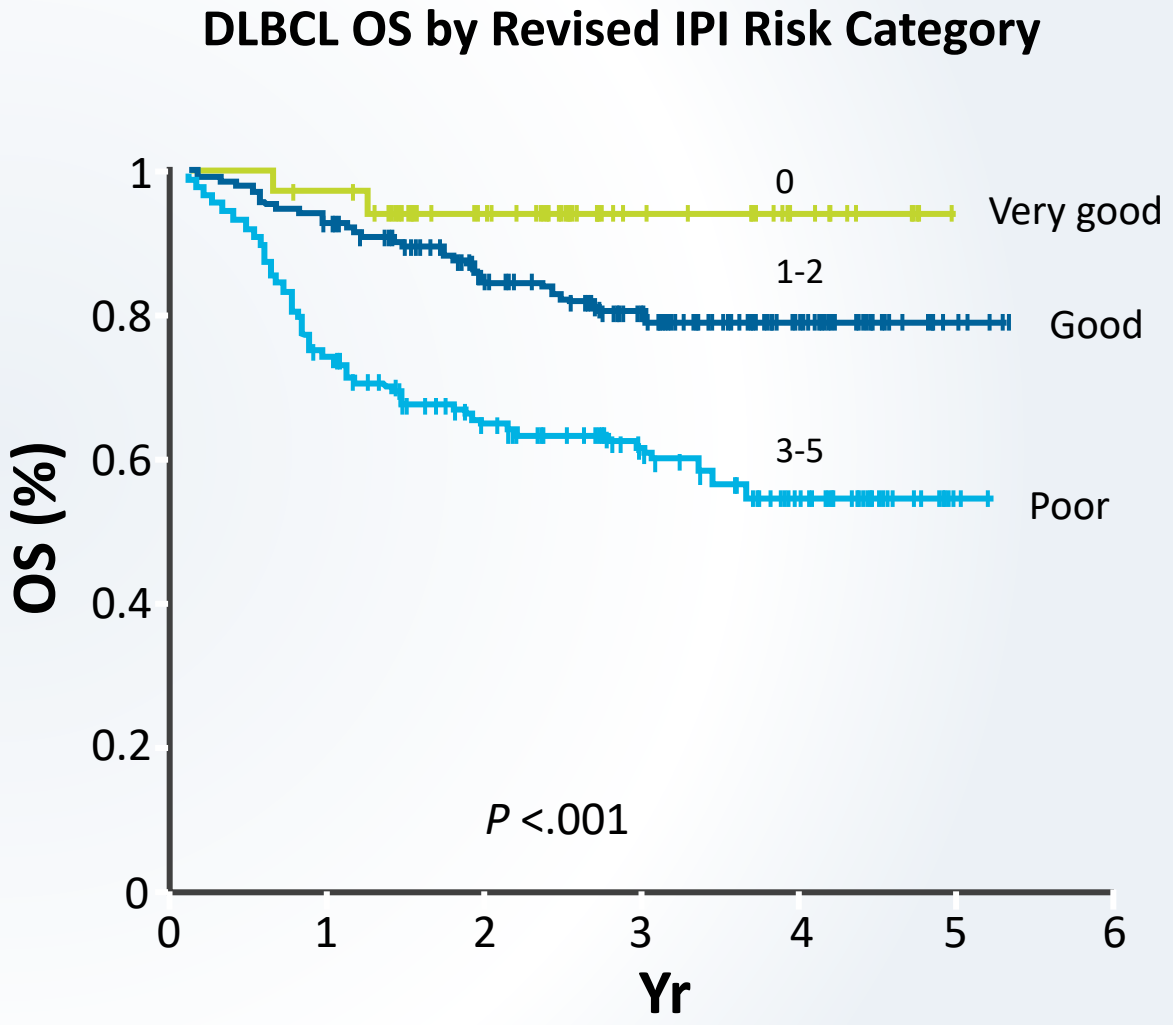
Types of Diffuse Large B-Cell Lymphomas (WHO 4th Edition Update)

- DLBCL, NOS
  - GCB/ABC subtypes
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary CNS DLBCL
- Primary cutaneous DLBCL ("leg type")
- EBV+ DLBCL NOS
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Intravascular large B-cell lymphoma
- *ALK*+ large B-cell lymphoma
- Primary mediastinal (thymic) large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8+ DLBCL NOS

Ott. *Br J Haematol*. 2017;178:871.

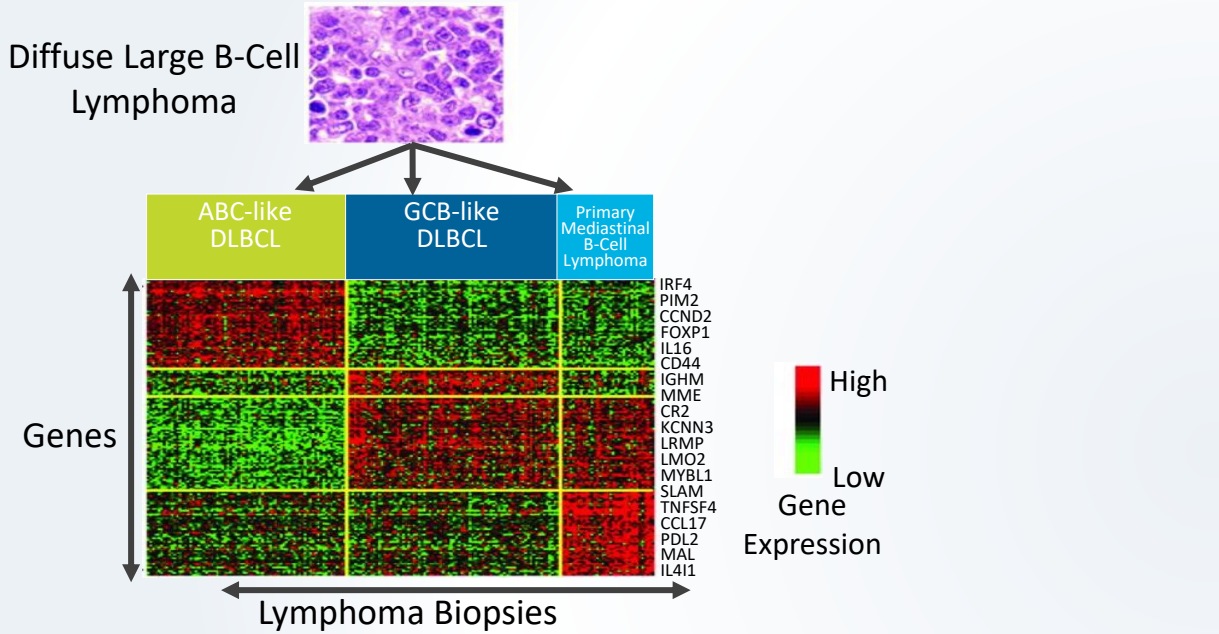
International Prognostic Index

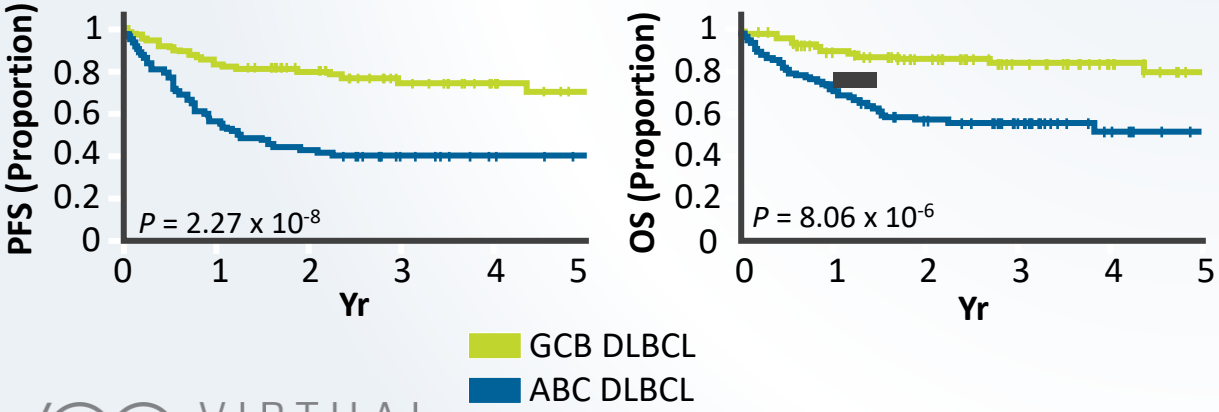
- Independent predictors of adverse outcome at diagnosis
  - Age >60 yr
  - Poor performance status (2-4)
  - Elevated LDH
  - Advanced Ann Arbor stage (III/IV)
  - Multiple extranodal sites
- Risk groups
  - Low (0-1)
  - Low-intermediate (2)
  - High-intermediate (3)
  - High (4-5)

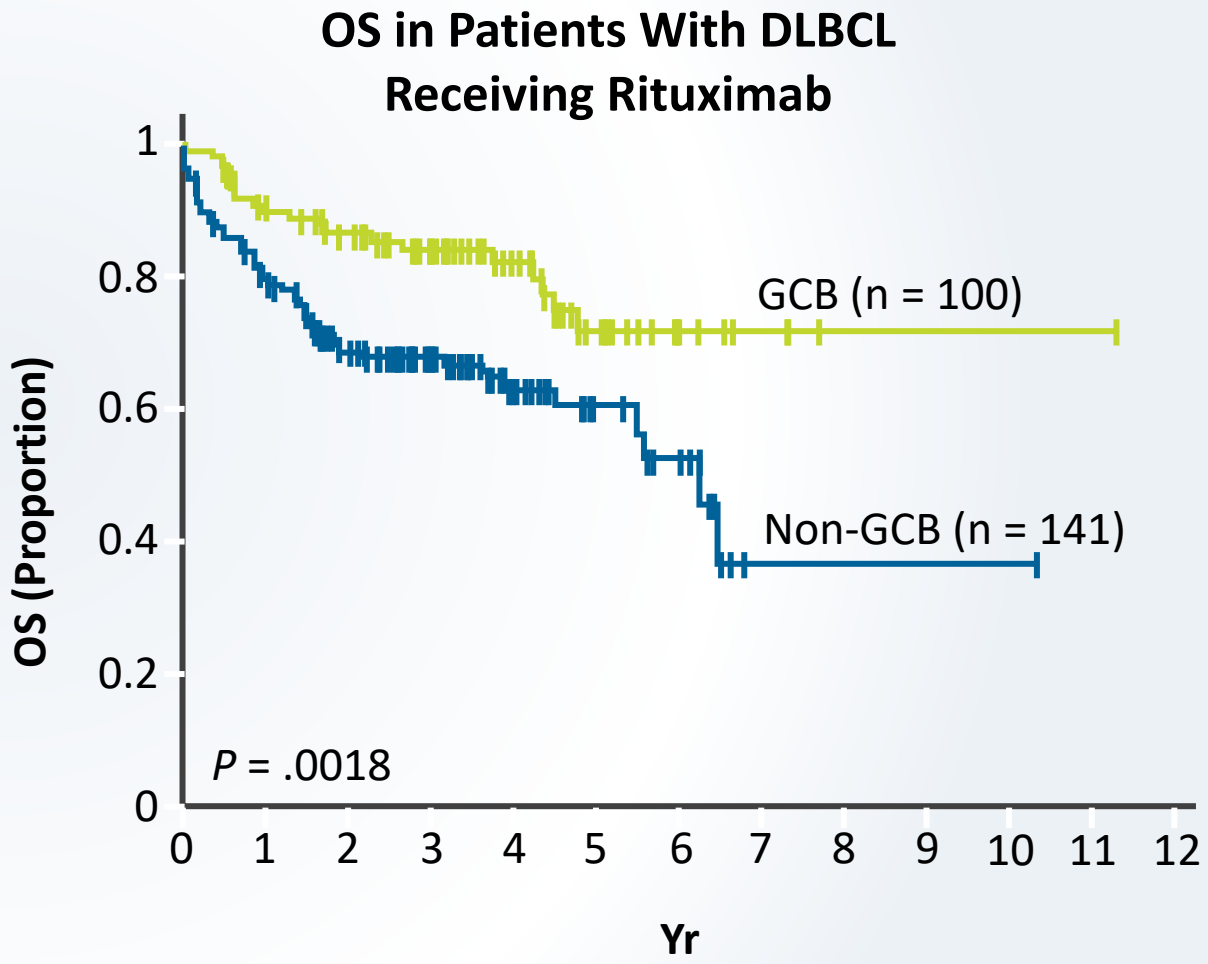


INHLPFP. *N Engl J Med*. 1993;329:987. Sehn. *Blood*. 2007;109:1857.

Cell of Origin in DLBCL NOS

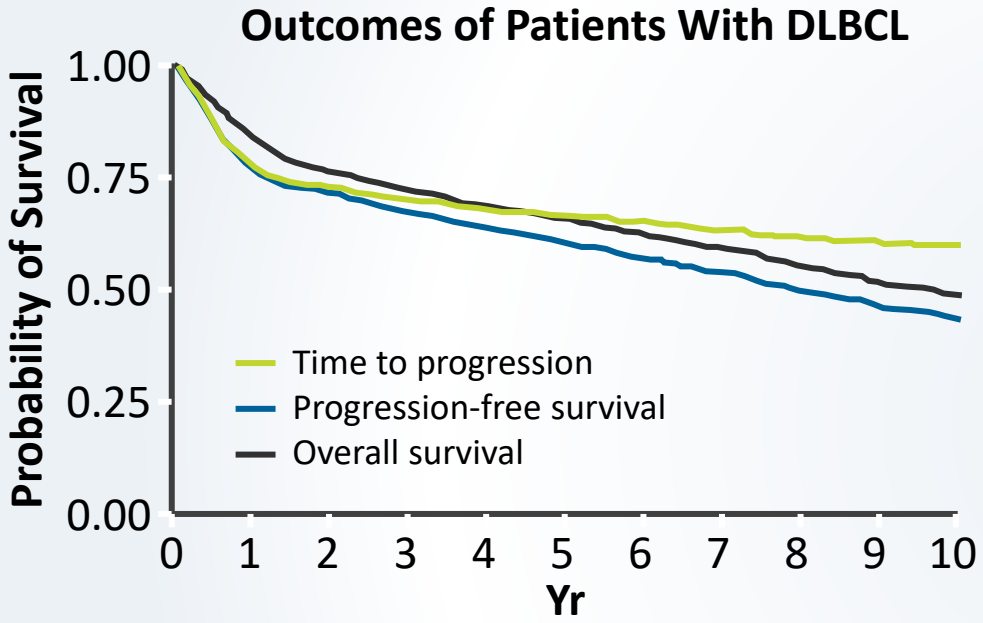






Wilson. *Hematology*. 2013. Meyer. *J Clin Oncol*. 2011;29:200.

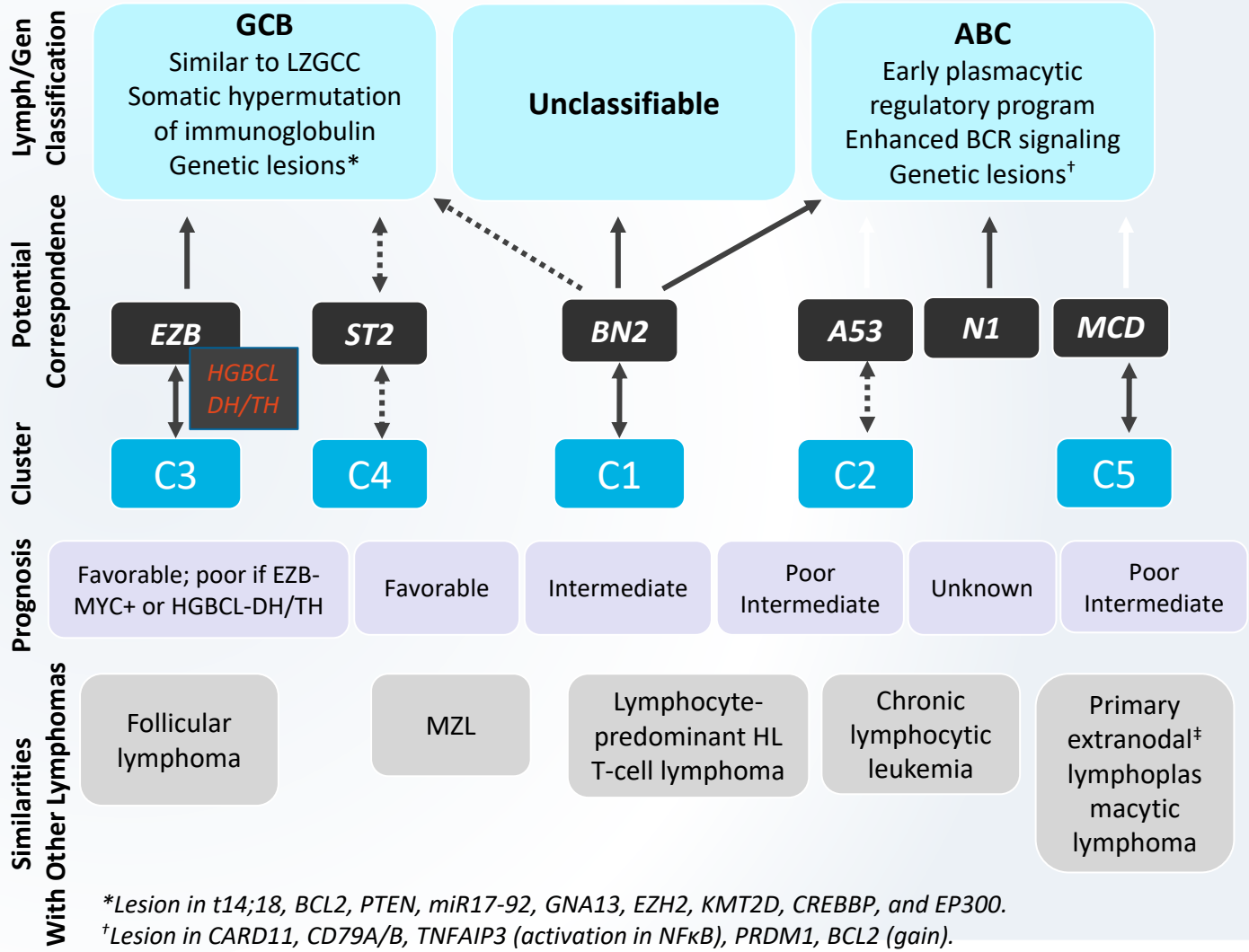
Molecular Diagnosis of Large B-Cell Lymphoma



Risk factors: family history; genetic susceptibility (TNF/LTA; 6p25.3; 6p21.33; 2p23.3; 8q24-21); EBV, HCV, HIV, and HHV8 virus; solid organ transplantation; autoimmune disorders (SLE, Sjogren syndrome, celiac disease)

Increased risk: allergies (hay fever), blood transfusion, alcohol consumption, vegetable consumption, and sun exposure

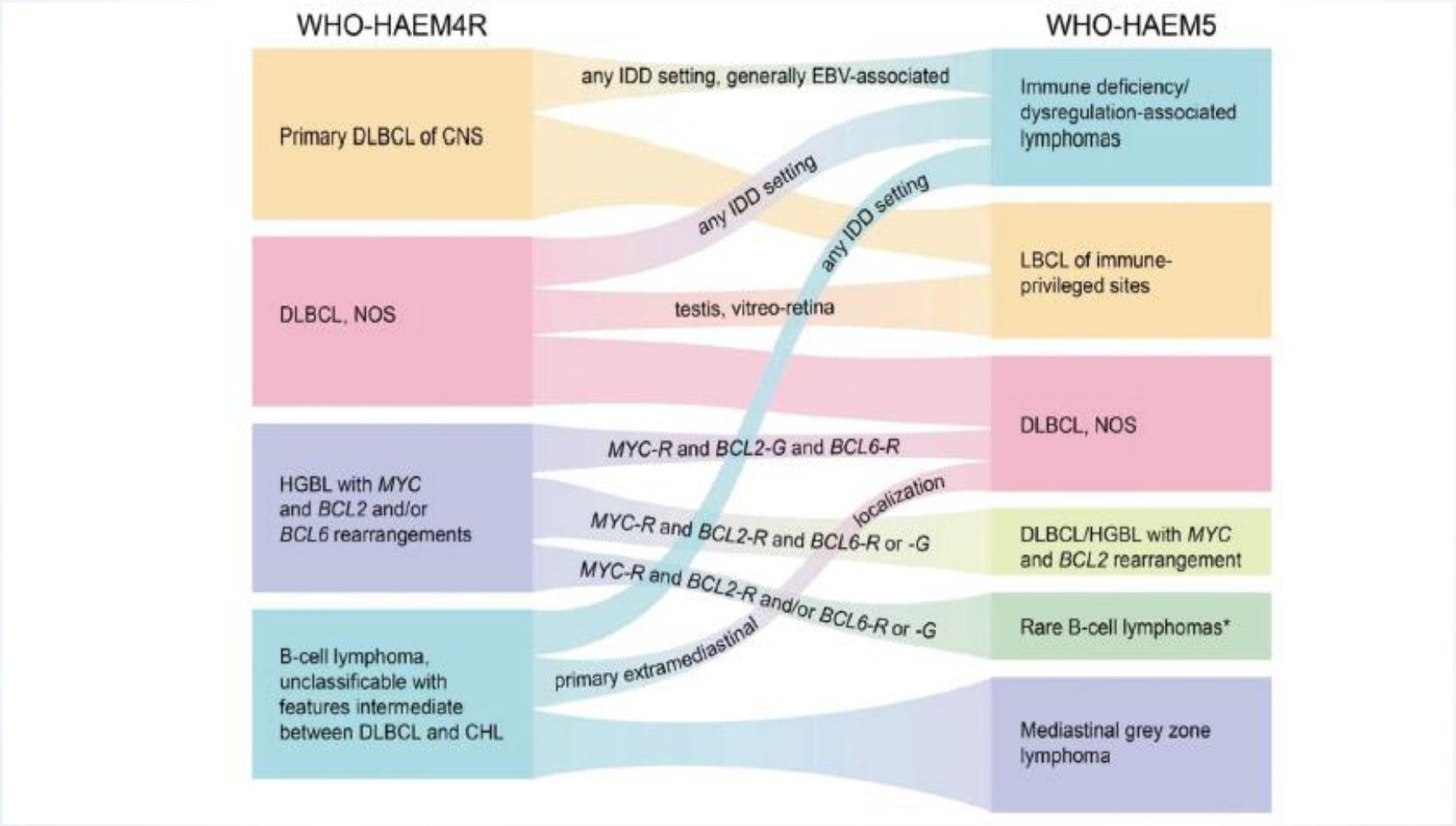
No significant effect: type 2 diabetes



**Lesion in t14;18, BCL2, PTEN, miR17-92, GNA13, EZH2, KMT2D, CREBBP, and EP300.*
†Lesion in CARD11, CD79A/B, TNFAIP3 (activation in NFκB), PRDM1, BCL2 (gain).
‡CNS, testis, or skin.

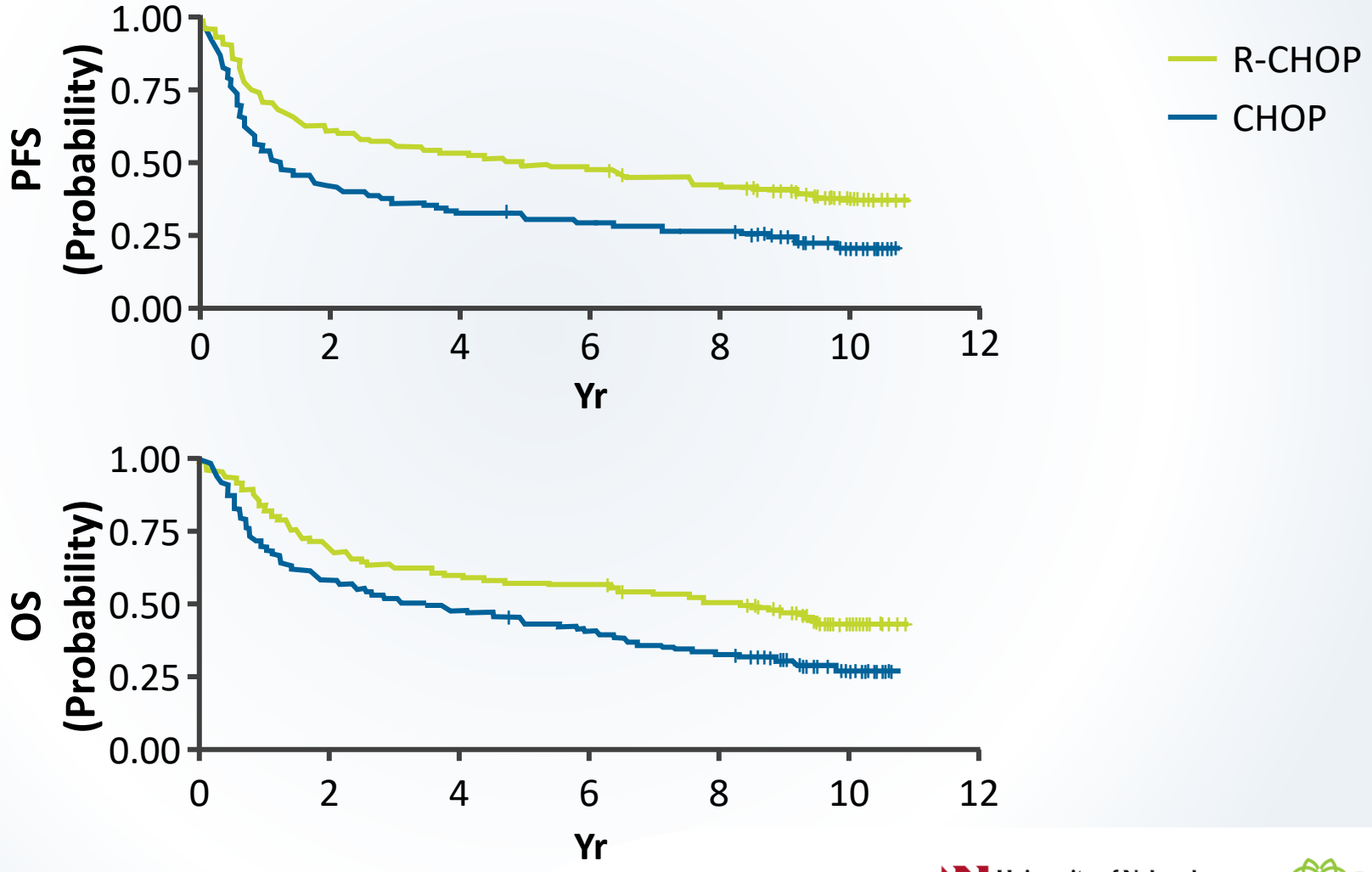
Sehn. *N Engl J Med*. 2021;484:842.

Aggressive NHL in WHO 4th and 5th Version



Alaggio, et al: *Leukemia*. 2022.

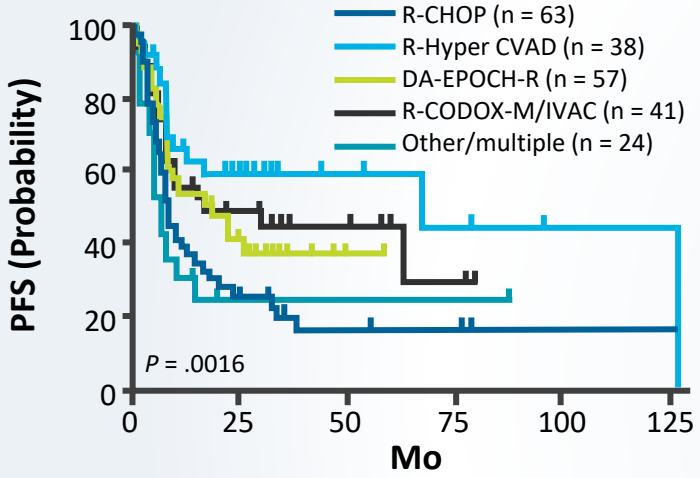
Addition of Rituximab to CHOP in Previously Untreated DLBCL Improves PFS and OS

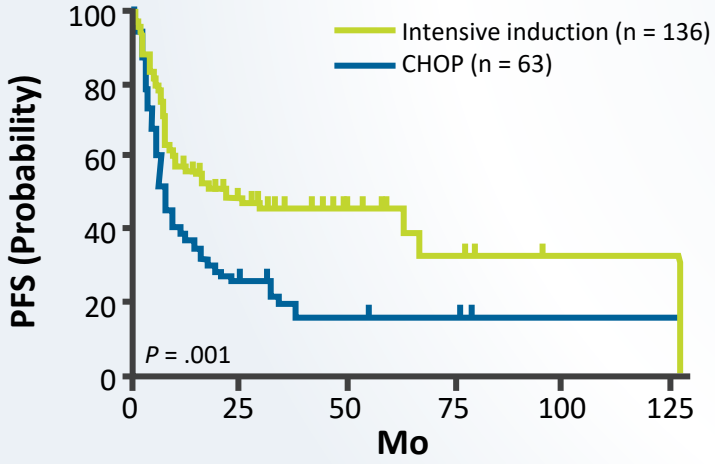


Coiffier. *Blood*. 2010;116:2040.

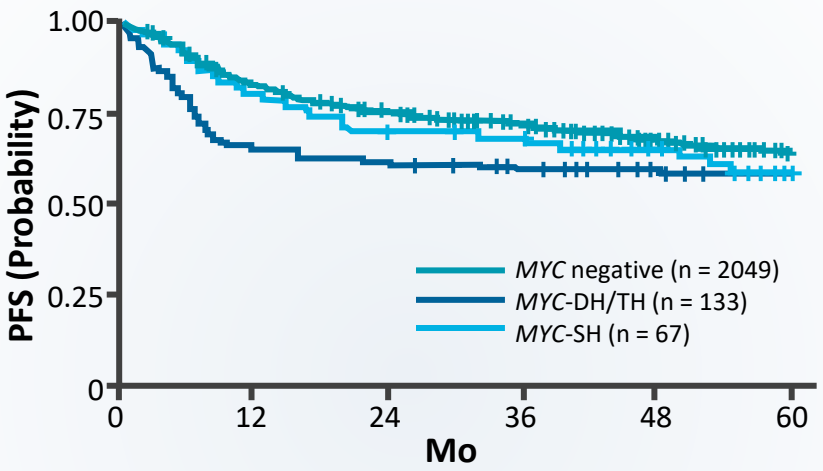
Studies of Rituximab Plus Chemotherapy in Double-Hit Lymphoma: Survival

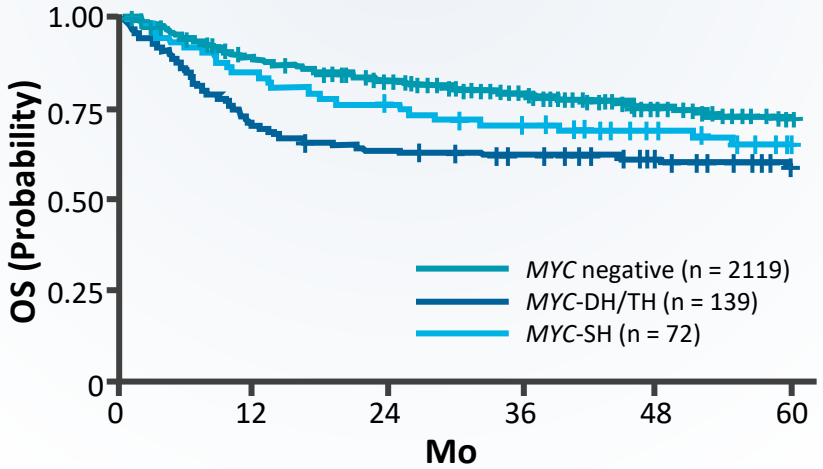
Retrospective Analysis[1]



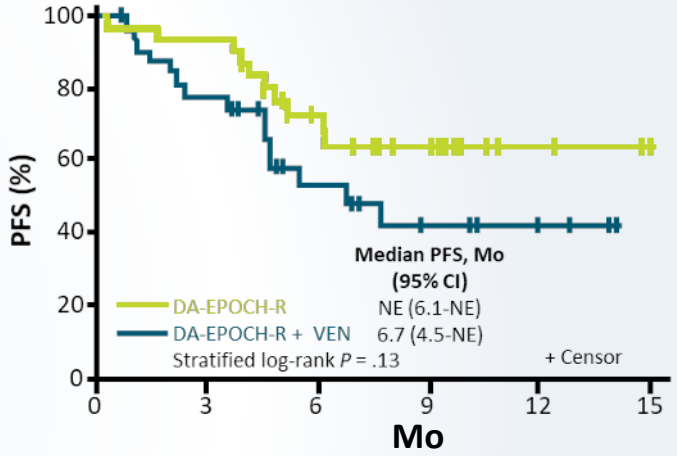


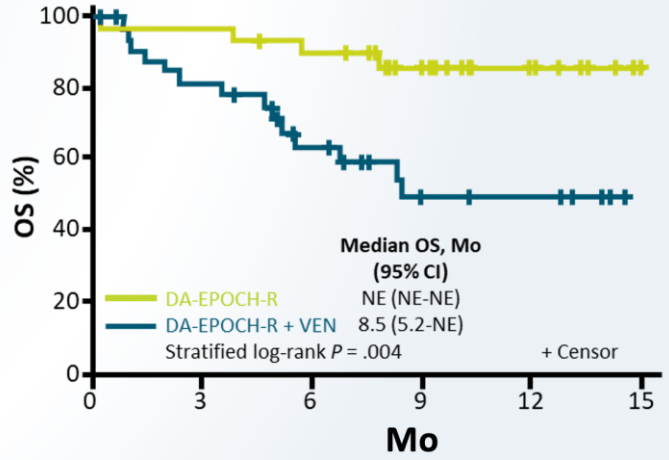
LLBC Study of R-CHOP[2]





A051701 Study of DA-EPOCH-R ± Venetoclax[3]





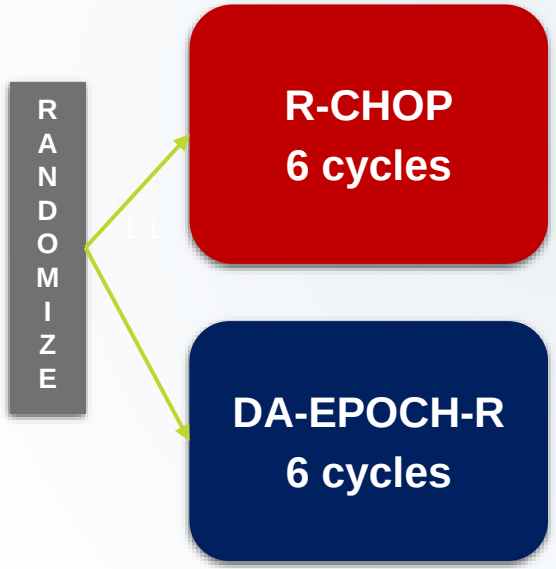
1. Petrich. Blood. 2014;124:2354. 2. Rosenwald. JCO. 2019;37:3359.
3. Abramson. ASH 2021. Abstract 523.

Phase 3 Study of R-CHOP vs DA-EPOCH-R in Patients with Untreated DLBCL (CALGB/Alliance 50303)

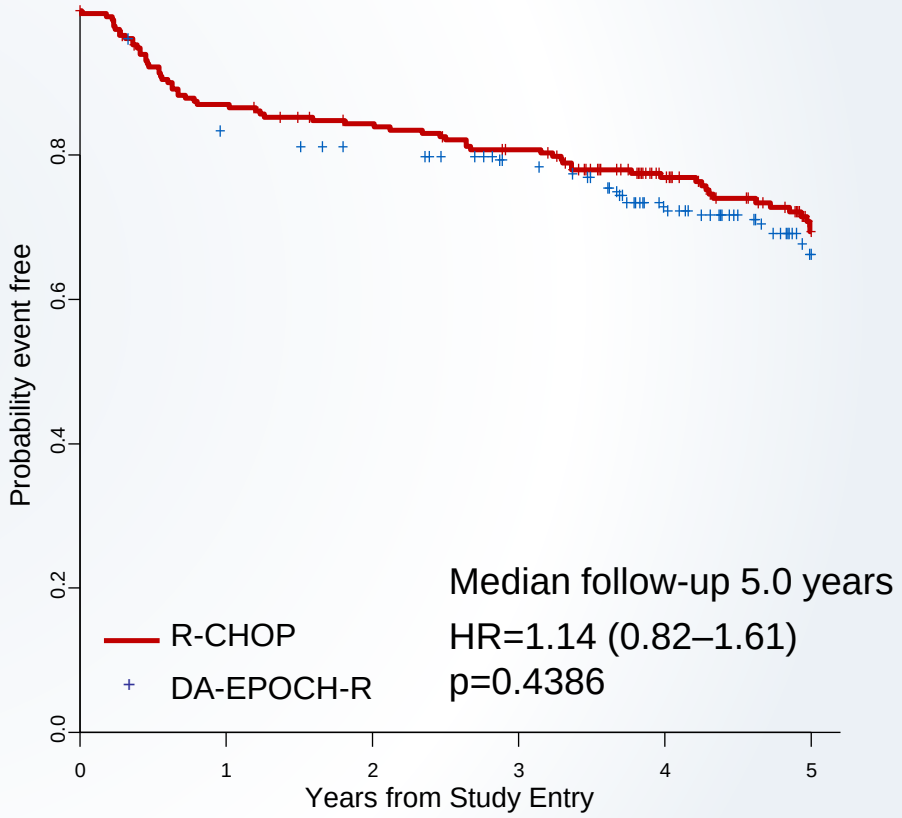
Study schema

Key eligibility criteria (N=524)

- Age ≥18 years
- Stage ≥ II newly diagnosed DLBCL (Stage I PMBCL)
- ECOG PS 0–2
- Fresh/frozen tumor biopsy (4 cores)

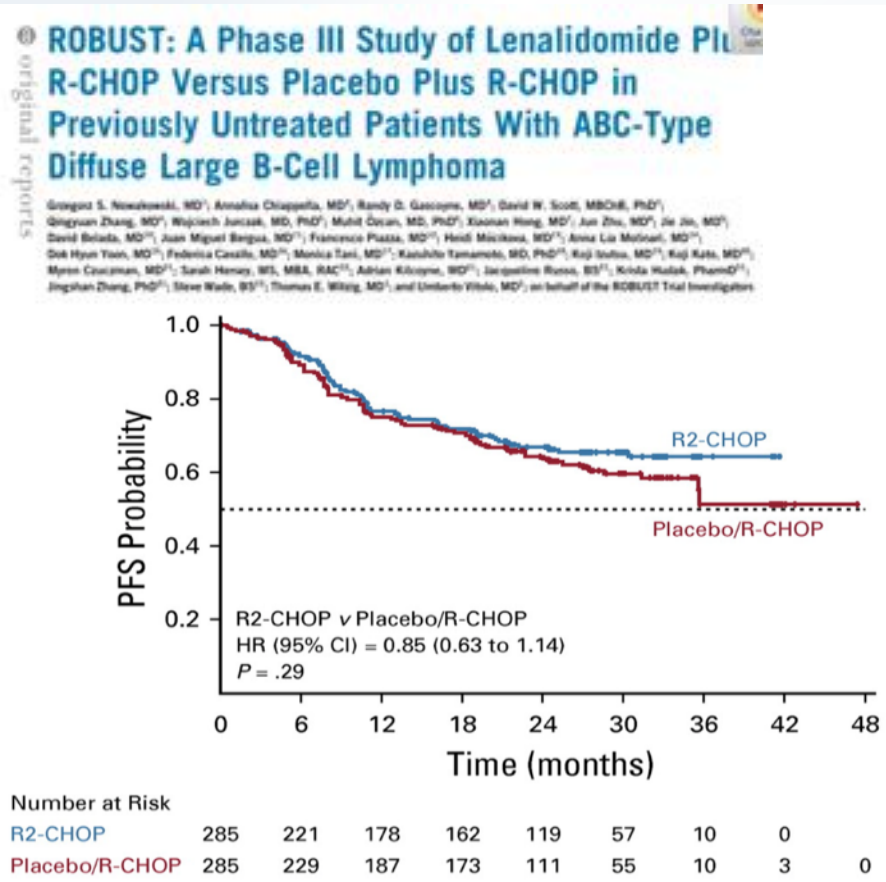


Event-free survival

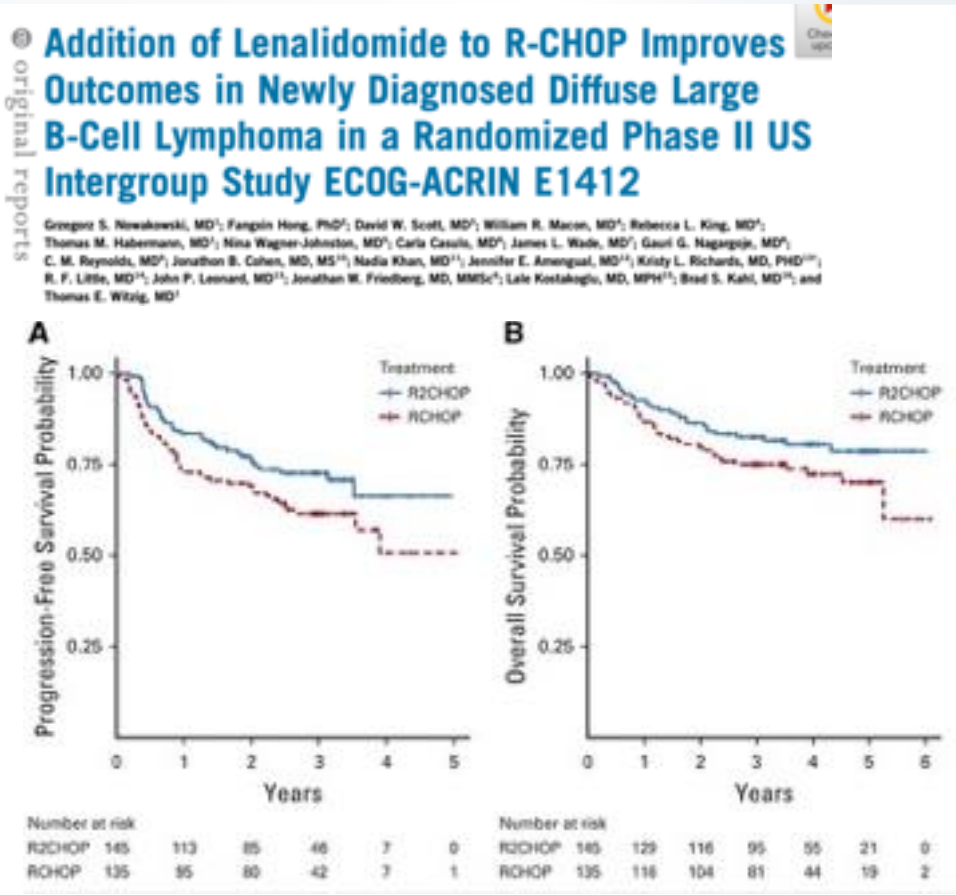


Bartlett NL, et al. *J Clin Oncol*. 2019;37:1790-1799.

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



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

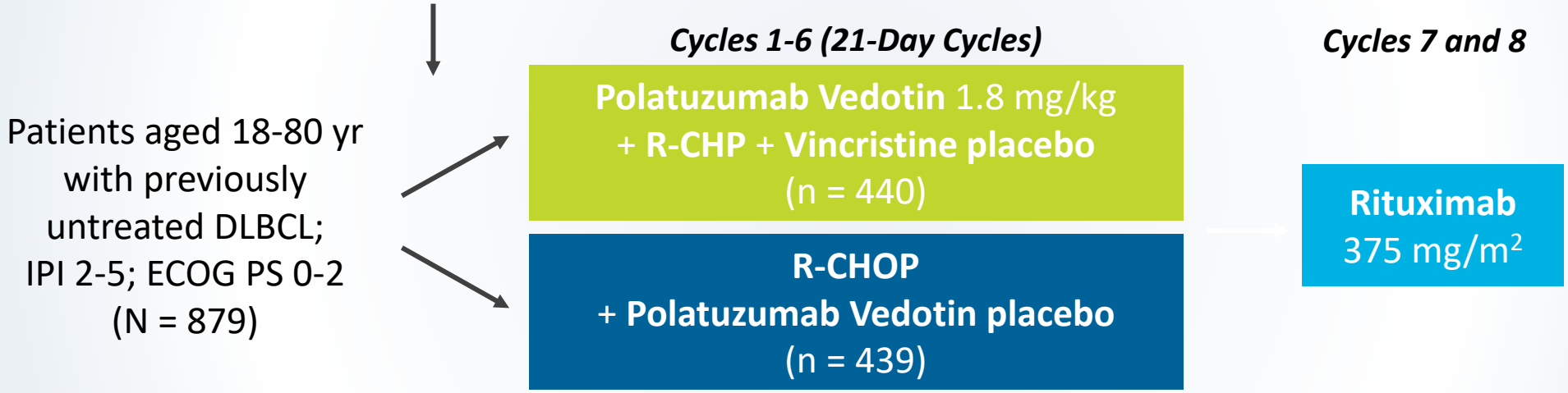


Nowakowski GS et al. *J Clin Oncol*. 2021 Feb 8:JCO2001375

POLARIX: Polatuzumab + R-CHP vs R-CHOP in Previously Untreated DLBCL

Multicenter, double-blind, placebo-controlled phase III trial

Stratification by IPI score (2 vs 3-5), bulky disease (<7.5 vs ≥7.5 cm), and geographic region (Western Europe, US, Canada, and Australia vs Asia vs rest of world)



R-CHOP: IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² administered on Day 1 + oral prednisone 100 mg QD Days 1-5.

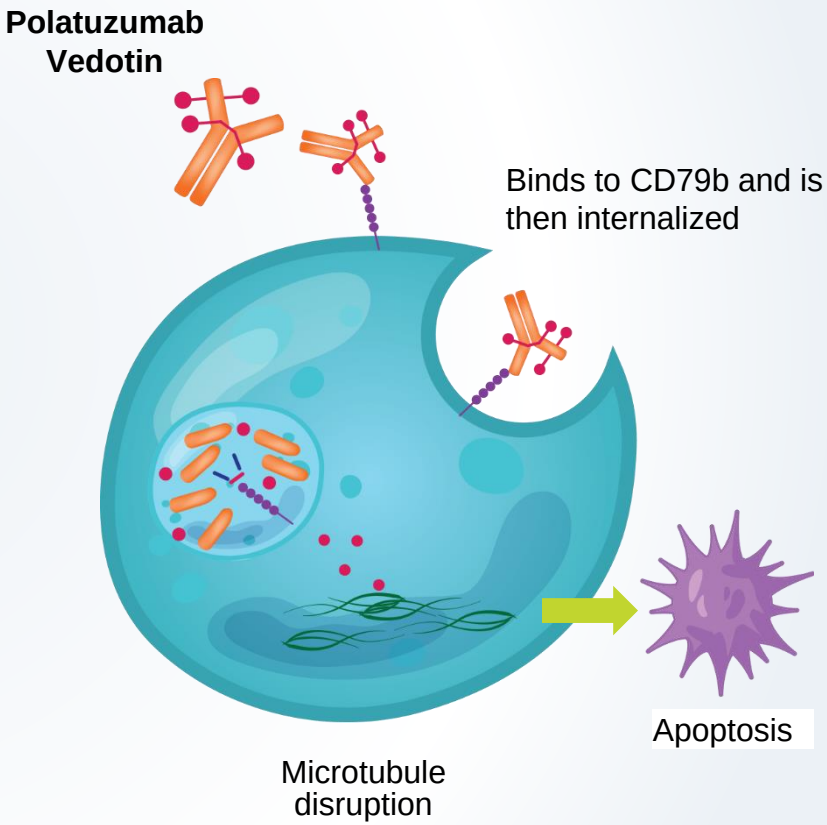
Primary endpoint: investigator-assessed PFS

Secondary endpoints: EFS, CRR at end of treatment, DFS, OS, safety

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021.

Polatuzumab Vedotin in DLBCL: Background

- R-CHOP well established as standard frontline therapy for DLBCL[1]
- Polatuzumab vedotin, ADC targeting CD79b[2]
  - CD79b expressed on mature B-cell lymphomas including DLBCL
- Polatuzumab vedotin + R-CHP or G-CHP demonstrated activity and manageable safety in untreated DLBCL in phase II trial[3]
- Current phase III POLARIX trial compared safety and efficacy of polatuzumab vedotin + R-CHP vs R-CHOP in previously untreated DLBCL[4,5]

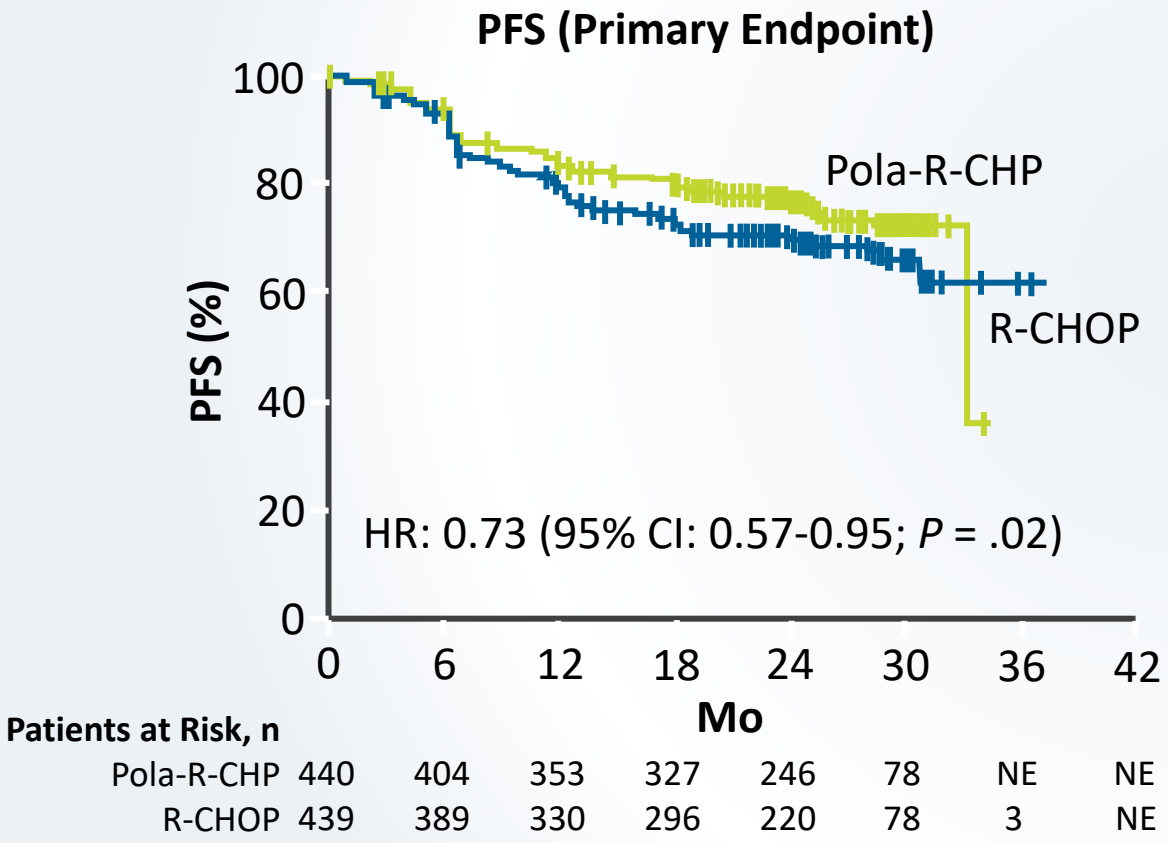


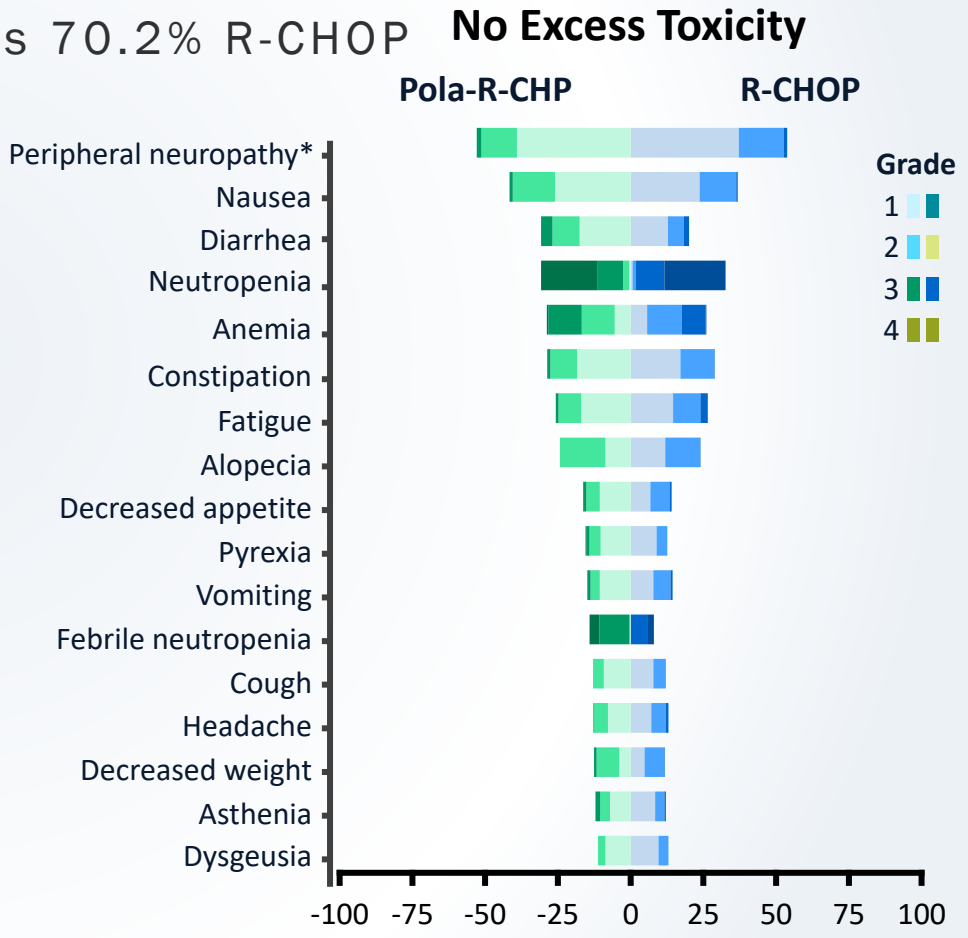
1. Vitolo. JCO. 2017;35:3529. 2. Dornan. Blood. 2009;114:2721.
3. Tilly. Lancet Oncol. 2019;20:998. 4. Tilly. ASH 2021. Abstr LBA1. 5. Tilly. NEJM. 2021;[Epub].

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP PFS and Safety

Median follow-up: 28.2 mo

24-mo PFS: 76.7% polatuzumab vedotin + R-CHP vs 70.2% R-CHOP



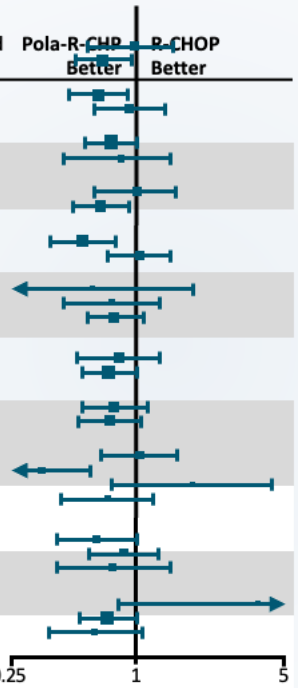


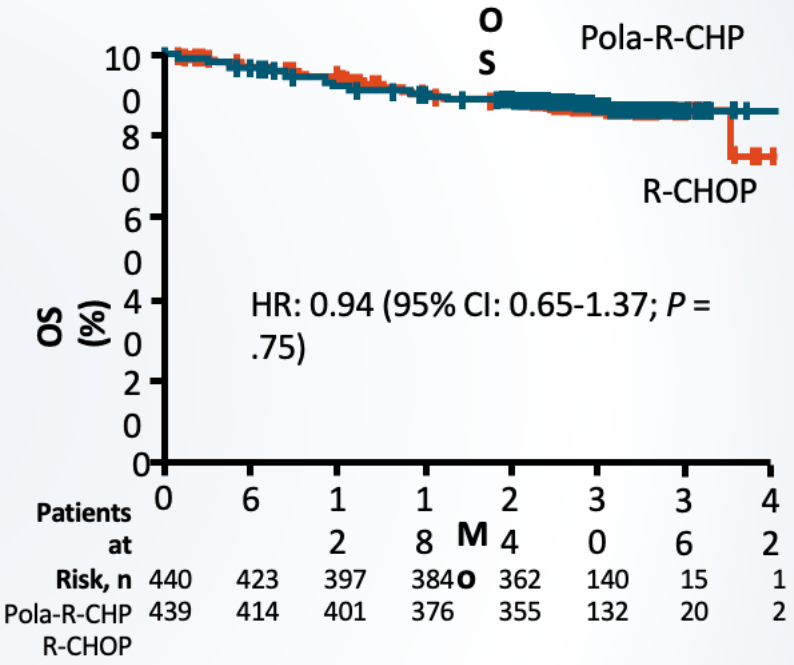
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021.

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP PFS and Subset Analysis and OS

PFS

Baseline Risk Factors	Total N	Pola-R-CHP (N = 440) n	Pola-R-CHP (N = 440) 2-Yr Rate	R-CHOP (N = 439) n	R-CHOP (N = 439) 2-Yr Rate	HR	95% Wald CI
Age Group							
<60	271	140	74.1	131	71.9	0.9	(0.6-1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5-0.9)
Sex							
Male	473	239	75.9	234	65.9	0.7	(0.5-0.9)
Female	406	201	77.7	205	75.2	0.9	(0.6-1.4)
ECOG PS							
0-1	737	374	78.4	363	71.2	0.8	(0.6-1.0)
2	141	66	67.2	75	65.0	0.8	(0.5-1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6-1.6)
IPI 3-5	545	273	75.2	272	65.1	0.7	(0.5-0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4-0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7-1.5)
Ann Arbor stage							
I-II	99	47	89.1	52	85.5	0.6	(0.2-1.8)
III	232	124	80.7	108	73.6	0.8	(0.5-1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6-1.1)
Baseline LDH							
≤ ULN	300	146	78.9	154	75.6	0.8	(0.5-1.3)
> ULN	575	291	75.4	284	67.2	0.7	(0.5-1.0)
Extranodal sites, n							
0-1	453	227	80.2	226	74.5	0.8	(0.5-1.1)
≥2	426	213	73.0	213	65.8	0.7	(0.5-1.0)
Cell of origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7-1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2-0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8-4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4-1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4-1.0)
Non-DEL	438	223	77.7	215	75.7	0.9	(0.6-1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4-1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8-17.6)
No	620	305	76.8	315	70.3	0.7	(0.5-1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4-1.1)





National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2022
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]
An FDA-approved biosimilar is an appropriate substitute for rituximab.[b]

FIRST-LINE THERAPY

Preferred regimens
- RCHOP (rituximab,[c] cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)

Other recommended regimens
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab

FIRST-LINE THERAPY FOR PATIENTS WITH POOR LEFT VENTRICULAR FUNCTION[d,e,f]

Other recommended regimens (in alphabetical order)
- DA-EPOCH[g] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine) (category 2B)
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

FIRST-LINE THERAPY FOR VERY FRAIL PATIENTS AND PATIENTS >80 YEARS OF AGE WITH COMORBIDITIES[e,f]

Other recommended regimens (in alphabetical order)
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine) (category 2B)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- R-mini-CHOP
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone)

FIRST-LINE CONSOLIDATION (OPTIONAL)

- Lenalidomide maintenance (category 2B) for patients 60–80 y of age

CONCURRENT PRESENTATION WITH CNS DISEASE[h]

- Parenchymal: systemic high-dose methotrexate (≥3 g/m² or more given with RCHOP cycle that has been supported by growth factors). Different schedules have been used for the integration of high-dose methotrexate with RCHOP (early- or mid-cycle or day 15 of a 21-day cycle)
- Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya reservoir placement. Systemic high-dose methotrexate (3–3.5 g/m²) can be given in combination with RCHOP or as consolidation after RCHOP + IT methotrexate/cytarabine

See Second-line Therapy on BCEL-C 2 of 6.
See Footnotes on BCEL-C 4 of 6.

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Patient 2

- 78-year-old female presents for follow up 8 months after completing RCHOP for GCB DLBCL, IPI3
- She tolerated therapy poorly with development of peripheral neuropathy and dose reductions due to cytopenia, infections, she has poor appetite and lost 20 lbs
- She had diabetes and Cr =2.2 and pedal edema
- PET scan at the end of therapy - CR
- Now with cervical adenopathy, PET shows PET avid adenopathy below and above the diaphragm
- Bx: DLBCL, CD20+, GCB subtype, FISH BCL2+, MYC-
- Patient PS - 3

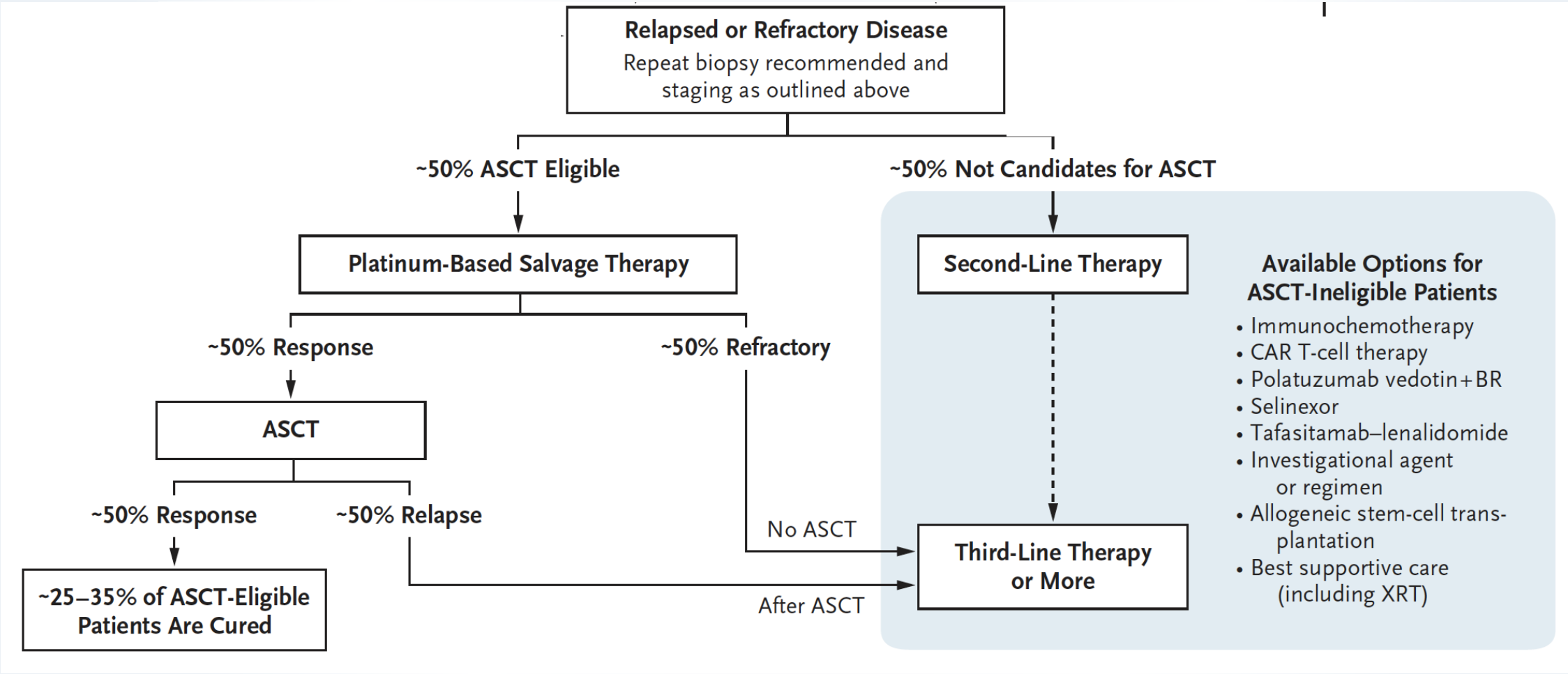
Patient 2

78-year-old female , PS 3, poor appetite with weight loss, residual vincristine induced peripheral neuropathy, pedal edema, with relapse of DLBCL 8 months after RCHOP

How would you treat this patient?

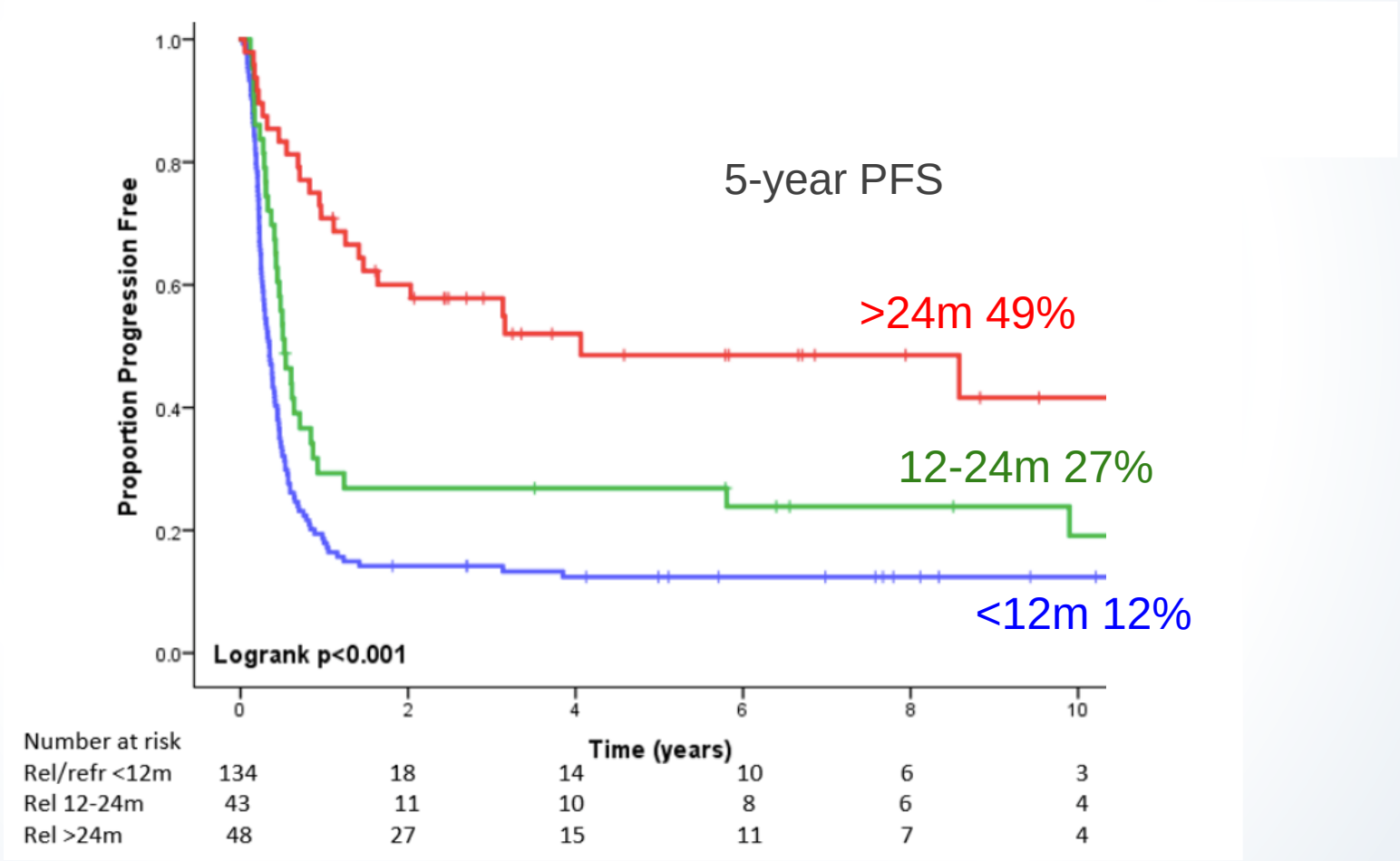
1. RICE followed by ASCT
2. Pola-BR
3. Loncastuximab
4. Tafa-Len
5. Selinexor

Longstanding Management of R/R DLBCL



Adapted from Sehn and Salles, NEJM 2021

PFS in Transplant-Eligible DLBCL Patients According to Timing of Relapse



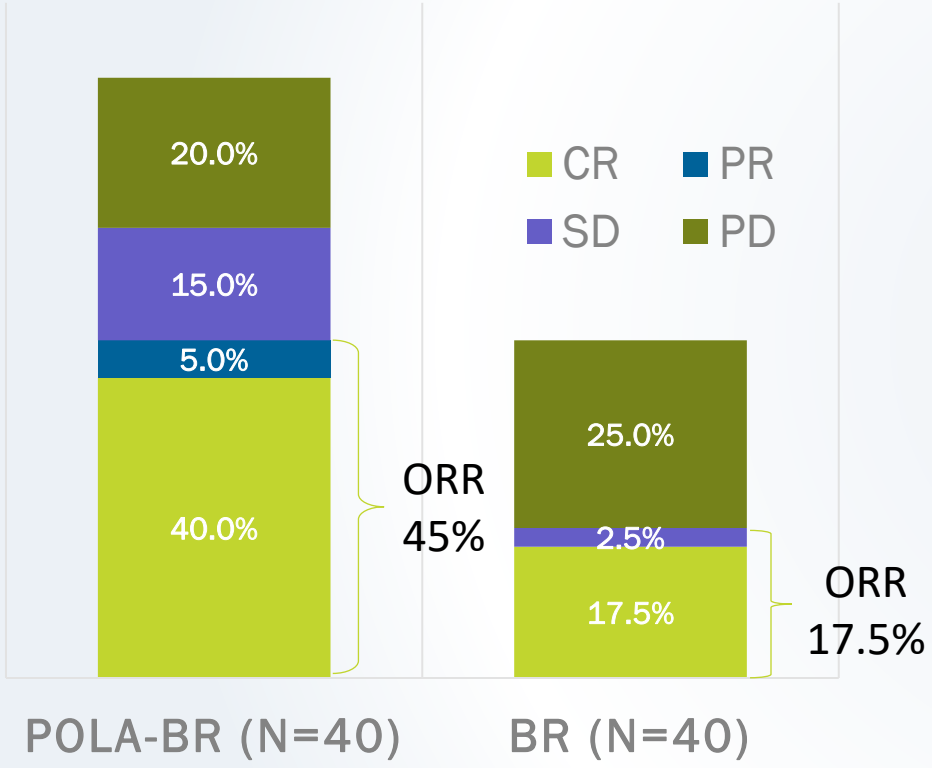
Ngu et al, ASH 2021

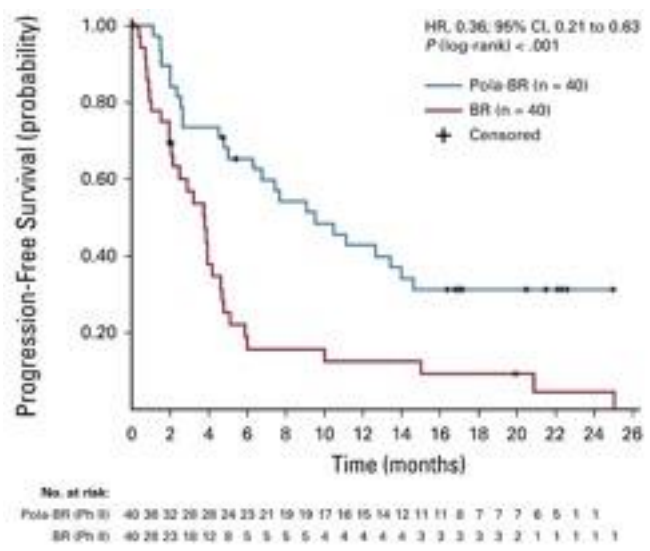
Phase 2 Study of Polatuzumab Vedotin + BR: Efficacy

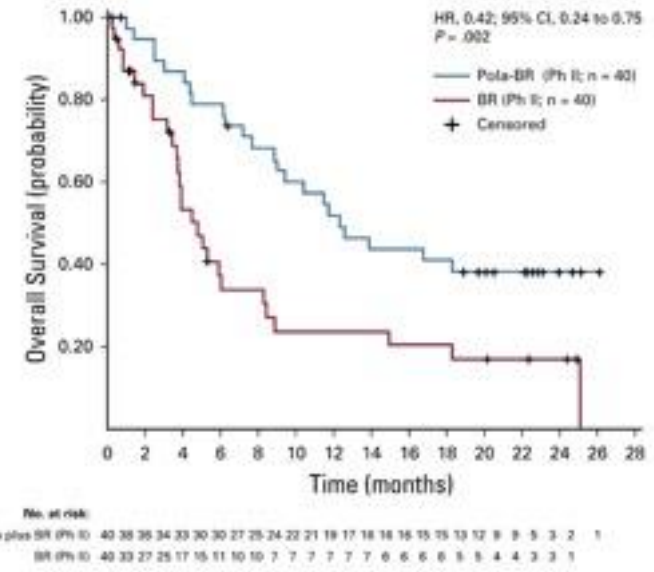
mPFS
9.5 mo vs 3.7 mo

mOS
12.4 mo vs 4.7 mo

ORR END OF TREATMENT
PRIMARY ENDPOINT







mDOR by IRC (Pola + BR vs BR):
12.6 mo vs 7.7 mo

Sehn L, et al. *J Clin Oncol*. 2020;38(2):155-165.

Phase 2 Study of Polatuzumab Vedotin + BR: AEs

	Pola-BR (n = 39)*		BR (n = 39)*	
Adverse Event	**All Grades, No. (%)**	**Grades 3-4, No. (%)**	**All Grades, No. (%)**	**Grades 3-4, No. (%)**
Blood and lymphatic system disorders				
Anemia	21 (53.8)	11 (28.2)	10 (25.6)	7 (17.9)
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)
Lymphopenia	5 (12.8)	5 (12.8)	0	0
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)
GI disorders				
Diarrhea	15 (38.5)	1 (2.6)	11 (28.2)	1 (2.6)
Nausea	12 (30.8)	0	16 (41.0)	0
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)
General disorders and administration site conditions				
Fatigue	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0
Metabolism and nutrition disorders				
Decreased appetite	10 (25.6)	1 (2.6)	8 (20.5)	0
Peripheral neuropathy				
Peripheral neuropathy†	17 (43.6)	0	3 (7.7)	0

Presented by G. S. Nowakowski MD

Sehn L, et al. *J Clin Oncol*. 2020;38(2):155-165.

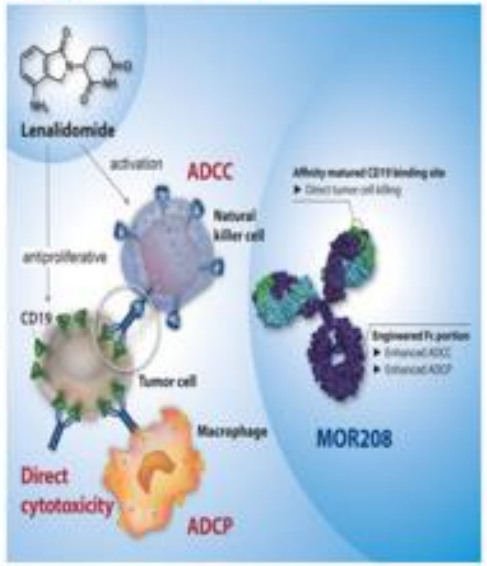
Combination Tafasitamab and Lenalidomide

MOR208
Fc-enhanced, anti-CD19 mAb

+

Lenalidomide

- ADCC ↑
- ADCP ↑
- Direct Cell Death
- Encouraging single agent activity in NHL patients with long DoR in R/R DLBCL



- T and NK Cell Activation/Expansion
- Direct Cell Death
- Demonstrated activity as an anti-lymphoma agent, alone or in combination
- Approved for treatment of MCL and FL/MZL

Potentiation of activity by combining Tafasitamab & LEN in vivo and in vitro

Horton et al., 2008; Awan et al., 2010; Richter et al., 2013; MorphoSys data on file; Wu et al., 2008; Lapalombella et al., 2008; Zhang et al., 2013, Wiernik et al., 2008; Witzig et al., 2011; Czuczman et al., 2017; Jurczak et al, 2018

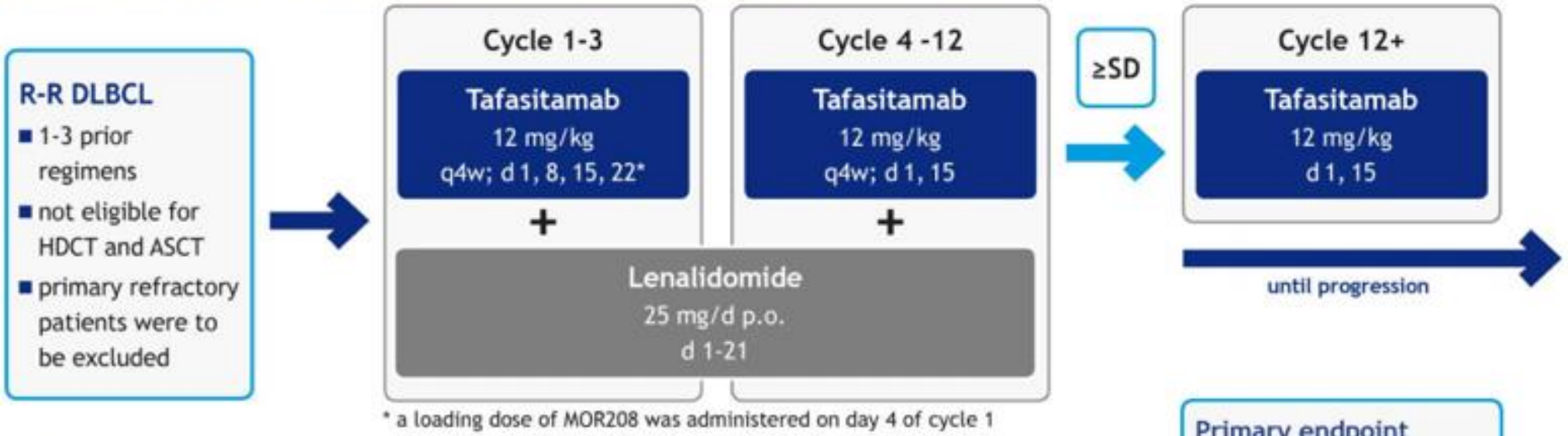
FDA grants accelerated approval to tafasitamab-cxix for diffuse large B-cell lymphoma

On July 31, 2020, the Food and Drug Administration granted accelerated approval to tafasitamab-cxix (MONJUVI, MorphoSys US Inc.), a CD19-directed cytolytic antibody, indicated in combination with lenalidomide for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant.

1. ICML 2019 #124. Salles G, et al. L-MIND. June 22, 2019.

Phase 2 L-MIND Study of Tafasitamab + Lenalidomide: Design

phase 2, single-arm, open-label, multicenter study (NCT02399085)



* a loading dose of MOR208 was administered on day 4 of cycle 1

- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

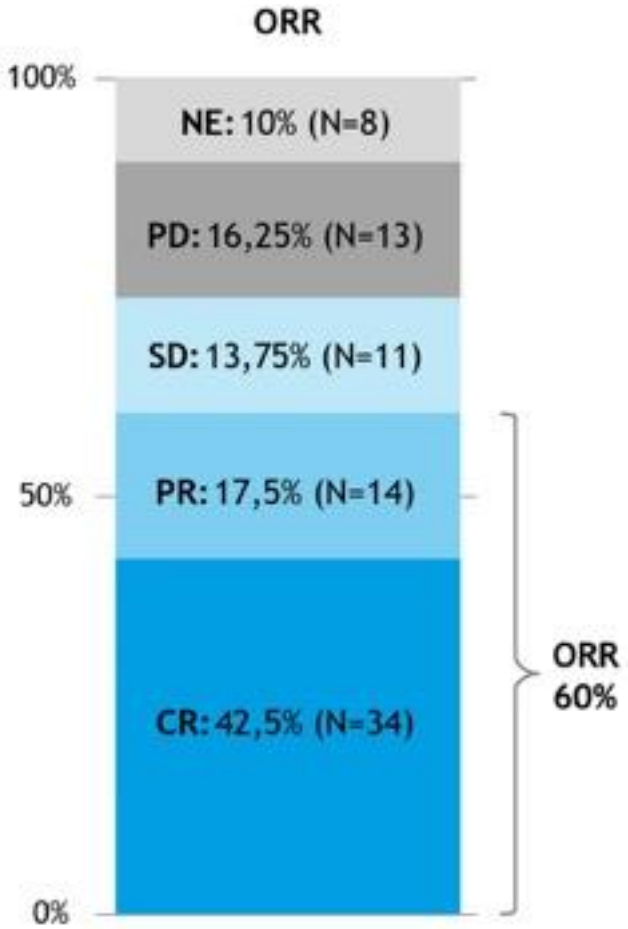
Primary endpoint
- ORR (Central read)

Secondary endpoints
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

-Primary refractory DLBCL was defined as no response to or progression/relapse during or within 6 months of frontline therapy.
-Response assessment (Cheson 2007 Criteria) was after cycles 2, 4, 6, 9 and 12, thereafter every 3 cycles.
-ASCT, autologous stem cell transplant; HDCT, high-dose chemotherapy; SD, stable disease, p.o., per os.

1. ICML 2019 #124. Salles G, et al. L-MIND. June 22, 2019.
2.Salles G, et al. *Lancet Oncol*. 2020;21(7):978-988.

Primary Endpoint: Overall Response Rate (ORR) by IRC



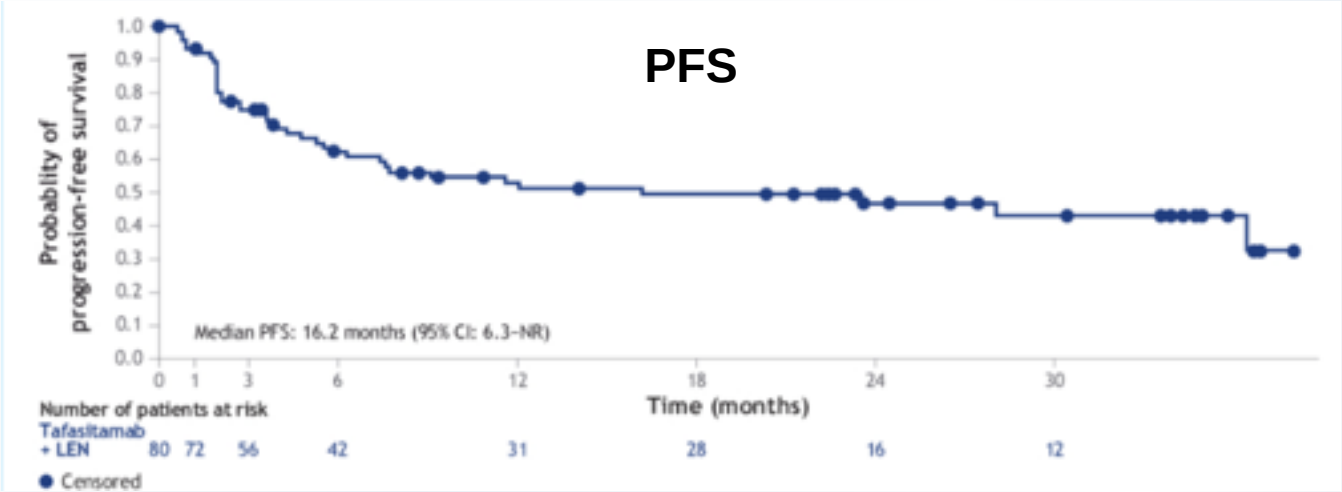
Subgroup	Level	Number of patients	ORR (%) and 95% CI
IPI	Risk low and low-intermediate	40	70
	Risk intermediate-high and high	40	50
Cell of origin (IHC)	Non-GCB	20	75
	GCB	36	50
Rituximab refractory	Yes	33	58
	No	46	61
Refractory to last line	Yes	35	60
	No	45	60
Primary refractory	Yes	15	60
	No	65	60
Number of prior lines	1	40	70
	≥ 2	40	50
Ann-Arbor stage	I-II	20	60
	III-IV	60	60
LDH elevated	Yes	44	57
	No	36	64
Age	≥ 70 years	46	59
	< 70 years	34	62

0 10 20 30 40 50 60 70 80 90 100

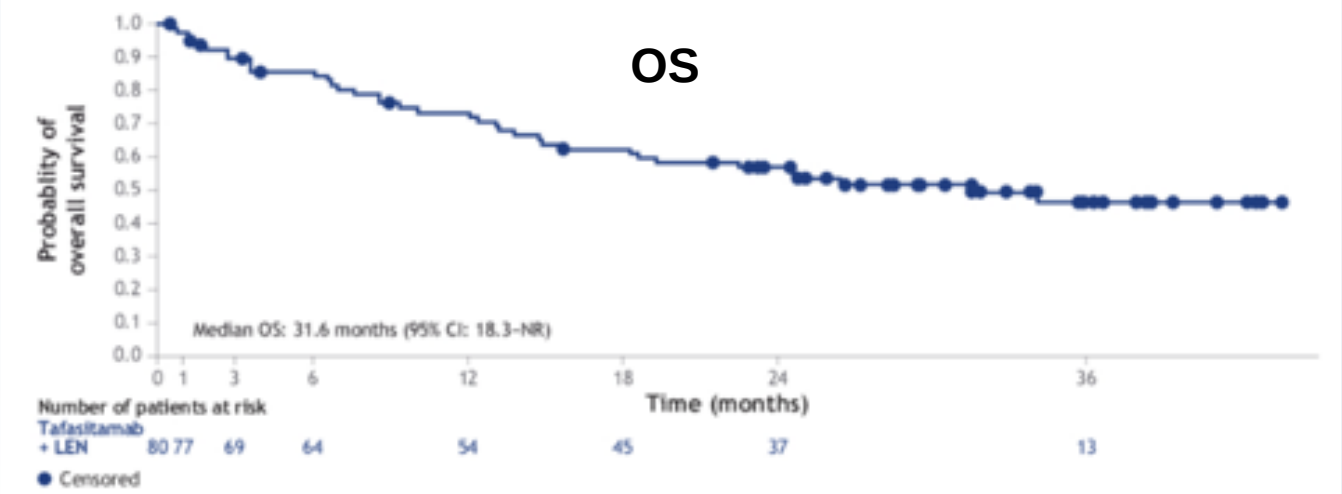
Salles G, et al. Lancet Oncol. 2020;10.1016/S1470-2045(20)30275-8

Phase 2 L-MIND: PFS and OS at ≥ 2 Years of Follow Up

Median PFS: 16.2 mo[a]



Median OS: 31.6 mo[b]



Presented by G. S. Nowakowski MD

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[a]Median follow up, 22.6 months. [b]Median follow up 31.8 months.
Salles G, et al. EHA 2020. EP1201.

University of Nebraska Medical Center

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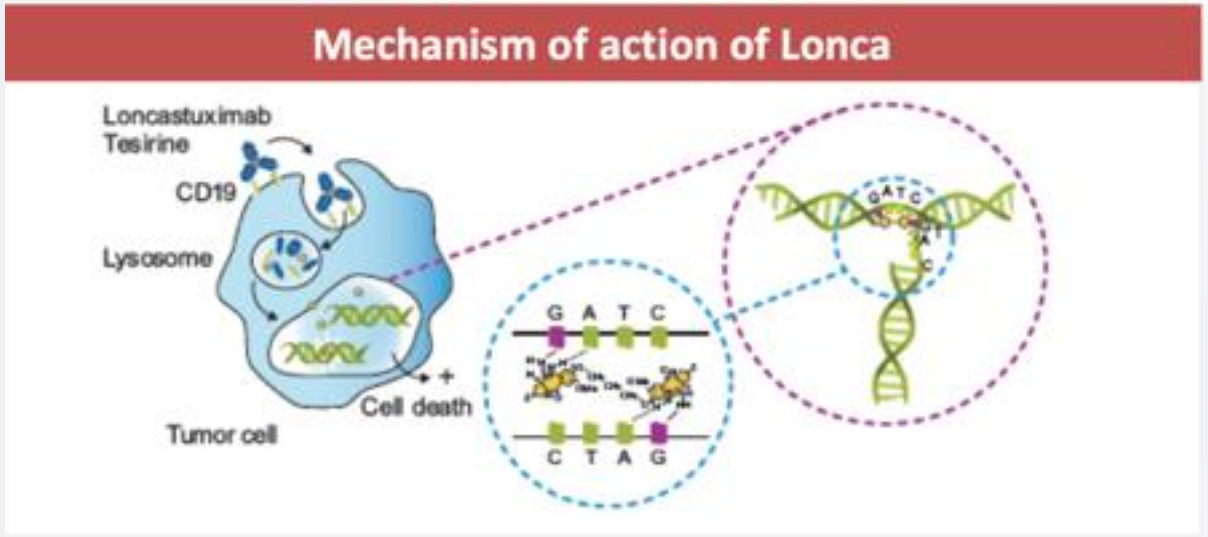
Loncastuximab Tesirine for R/R



FDA grants accelerated approval to loncastuximab tesirine-lpyl for large B-cell lymphoma

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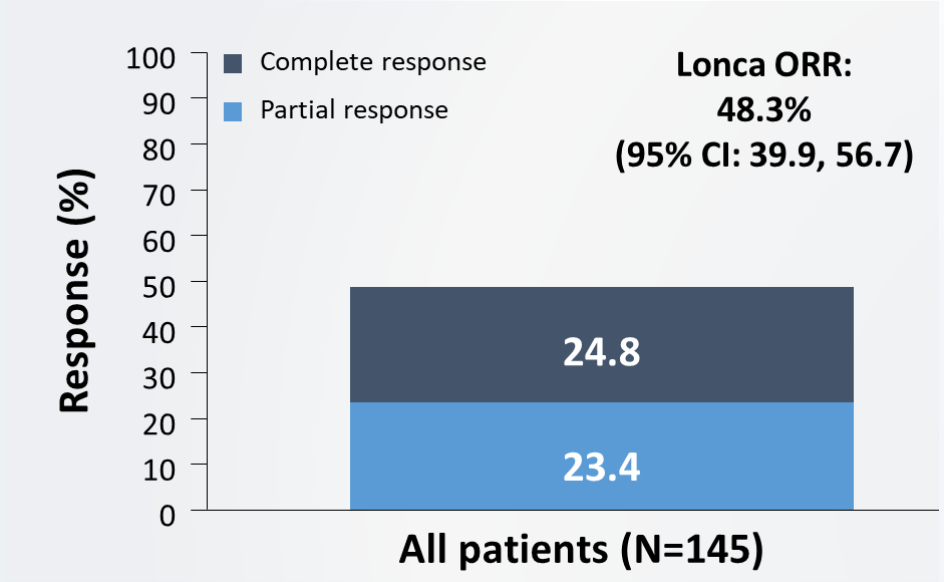
On April 23, 2021, the Food and Drug Administration granted accelerated approval to loncastuximab tesirine-lpyl (Zynlonta, ADC Therapeutics SA), a CD19-directed antibody and alkylating agent conjugate, for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

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

fda.gov, adctherapeutics.com/

12/28/2022

LOTIS-2 Trial: Efficacy Results



mDoR for the 70 responders:
12.58 months
(95% CI: 6.87, -)

Median PFS:
5.09 mo
(95% CI, 2.89-8.31)

mDoR for patients with a CR:
13.37 months
(95% CI: 12.58, -)

Median OS:
9.53 mo
(95% CI, 6.93-11.24)

- ORRs seen in high-risk subgroups (eg, double/triple hit, transformed disease)
- Most responders had response after 2 cycles; median time to first response was 41.0 days (range: 35–247)
- Mean lonca cycles: 4.5 (Std: ± 3.89) (Min, max: 1, 18)*
- Subsequent treatment
  - 15 pts received CD19-directed CAR-T therapy with an INV-assessed ORR of 46.7% (6 CR; 1 PR)
  - 9 patients proceeded to SCT as consolidation after response to lonca

Presented by G. S. Nowakowski MD

ORR was assessed by independent reviewer. Data cut-off: 06 Aug 2020.
*4 patients had treatment ongoing at data cut-off.
Caimi PF, et al. ASH 2020l. Abstract 1183.

LOTIS-2 Trial: Safety Results

TEAEs in ≥20% of the all-treated population			
	Patients n (%)		
Preferred term	<65 years (N=65)	≥65 (N=80)	Total (N=145)
Patients with any TEAE	65 (100)	78 (97.5)	143 (98.6)
GGT increased	33 (50.8)	27 (33.8)	60 (41.4)
Neutropenia	34 (52.3)	24 (30.0)	58 (40.0)
Thrombocytopenia	28 (43.1)	20 (25.0)	48 (33.1)
Fatigue	21 (32.3)	19 (23.8)	40 (27.6)
Anemia	23 (35.4)	15 (18.8)	38 (26.2)
Nausea	17 (26.2)	17 (21.3)	34 (23.4)
Cough	19 (29.2)	13 (16.3)	32 (22.1)
Alkaline phosphatase increased	18 (27.7)	11 (13.8)	29 (20.0)
Peripheral edema	11 (16.9)	18 (22.5)	29 (20.0)

Most common (≥10%) grade ≥3 TEAEs were:

- Neutropenia (38 patients; 26.2%)
- Thrombocytopenia (26 patients; 17.9%)
- GGT increased (25 patients; 17.2%)
- Anemia (15 patients; 10.3%)

Treatment-related TEAEs leading to treatment discontinuation occurred in 26 (17.9%) patients, most commonly (≥2%):

- GGT increased (16 patients; 11.0%)
- Peripheral edema (4 patients; 2.8%)
- Localized edema (3 patients; 2.1%)

No increase in toxicity was seen in patients aged ≥65 years compared with younger patients

TEAEs were reported for the all-treated population. Data cut-off: 06 Aug, 2020.
GGT, gamma-glutamyltransferase; **TEAE**, treatment-emergent adverse event.

Patient 3

- 50-year-old male with DLBCL, non-GCB subtype.
- History of RCHOP X 6; therapy with rapidly progressive adenopathy within 6 months
- PET scan – bulky abdominal disease, PET avid adenopathy above and below diaphragm; bx: DLBCL, CD20+, CD19+, non-GCB subtype, FISH BCL2-, MYC-, BCL2 pos and MYC pos by IHC
- Patient has good PS- 1
- Hb 7, PLT 12, ANC 0.4; organ function preserved

Patient 3

50-year-old male with rapidly progressive disease 6 months after R-CHOP

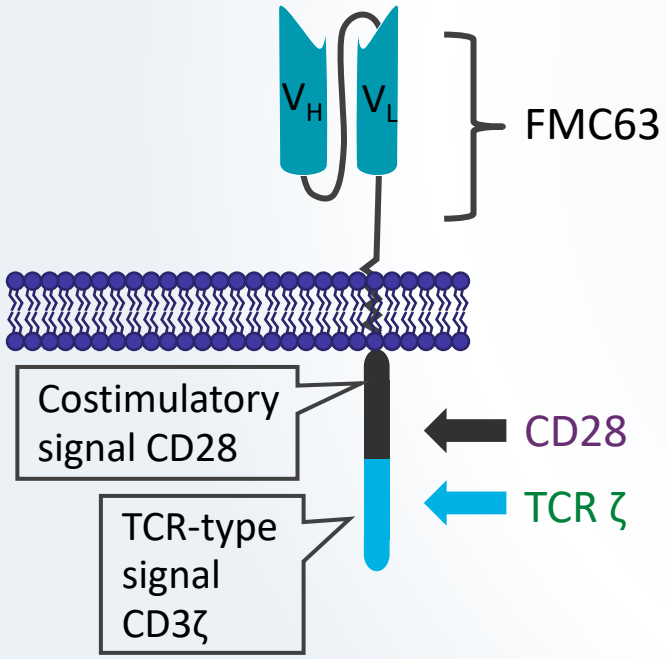
How would you treat this patient?

1. Lenalidomide
2. Loncastuximab
3. Selinexor
4. Pola BR
5. CAR T-cell therapy

CD19-Directed CAR T-Cell Products

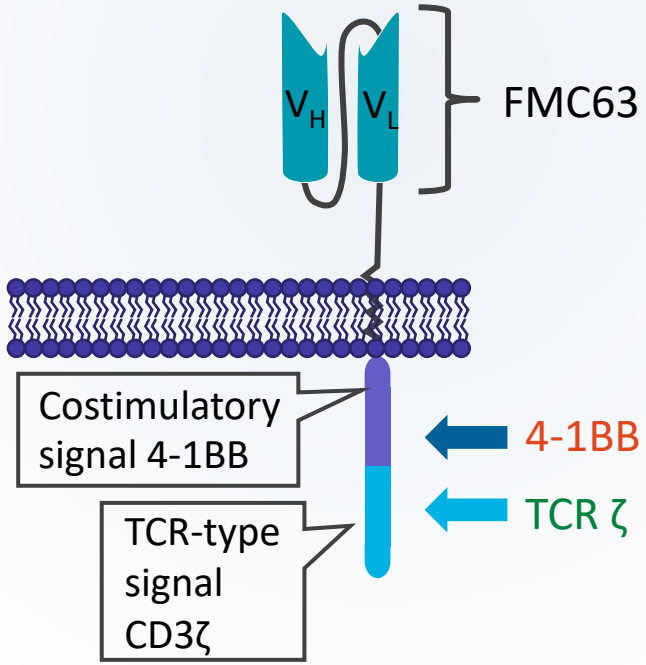
Axicabtagene Ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



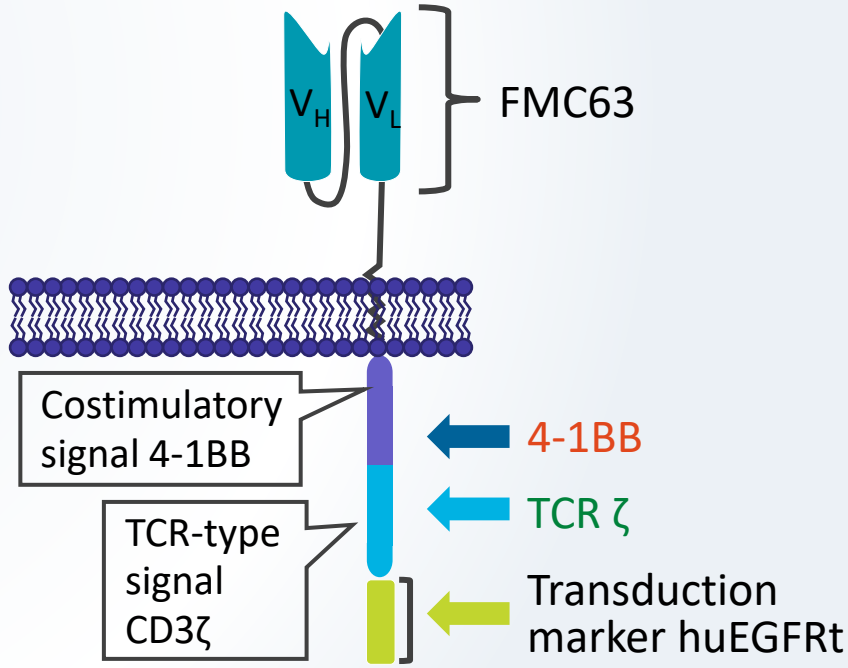
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene Maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



van der Stegen. *Nat Rev Drug Discov*. 2015;14:499.

3 Approved CD19-Targeted T-Cell Therapies for DLBCL and Other Large B-Cell Lymphomas in Third-line or Later Setting

	Axicabtagene Ciloleucel (ZUMA-1)[1,2]	Tisagenlecleucel (JULIET)[3,4]	Lisocabtagene Maraleucel (TRANSCEND)[5,6]
Construct	Anti-CD19/CD28/CD3z	Anti-CD19/4-1BB/CD3z	Anti-CD19/4-1BB/CD3z
T-cell manufacturing	Bulk	Bulk	Defined doses: CD4+, CD8+
ORR/CRR, %	82/54	52/40	73/53
2-yr PFS, %	41	30	41
CRS (any/severe), %	93/13	58/22	42/2
NT (any/severe), %	64/28	21/12	30/10
FDA/EMA-approved indications	DLBCL, high-grade BCL, transformed FL, PMBCL	DLBCL, high-grade BCL, B-ALL (age 3-25 yr), transformed FL	DLBCL (incl transformed iNHL), high-grade BCL, PMBCL, grade 3B FL

1. Neelapu. NEJM. 2017;377:2531. 2. Axicabtagene ciloleucel PI. 3. Schuster. NEJM. 2019;380:45.
4. Tisagenlecleucel PI. 5. Abramson. Lancet. 2020;396:839. 6. Lisocabtagene maraleucel PI.

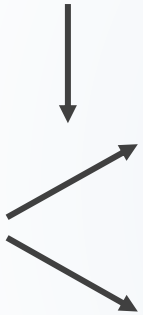
* JULIET used different CRS grading criteria than ZUMA-1 and TRANSFORM

ZUMA-7: Axicabtagene Ciloleucel vs SoC in R/R Large B-Cell Lymphoma

Global, multicenter, randomized phase III trial

Stratified by 1L treatment response, 2L age-adjusted IPI

Patients ≥18 yr with LBCL; ECOG PS 0-1; R/R disease with ≤12 mo of adequate 1L CIT (including anti-CD20 mAb and an anthracycline); intent to proceed to HDT-ASCT (N = 359)



Axi-cel 2 x 10^6 CAR T-cells/kg after conditioning chemotherapy (n = 180)

Conditioning regimen: cyclophosphamide 500 mg/m^2/day + fludarabine 30 mg/m^2/day on Days 5, 4, and 3 prior to CAR T-cell infusion. Optional bridging therapy limited to corticosteroids (no CIT).

SoC*
(2-3 cycles of investigator-selected, protocol defined, platinum-based CIT)
(n = 179)

CR/PR → **HDT-ASCT** (n = 64)

No CR/PR → **Off-Protocol Tx**†

*SoC included R-GDP, R-DHAP, R-ICE, or R-ESHAP. †56% received subsequent cellular immunotherapy.

- Primary endpoints: EFS (BICR)
- Key secondary endpoints: ORR and OS (tested hierarchically)
- Other secondary endpoints: PFS, safety, PROs
- Median follow-up: 24.9 mo

Locke. NEJM. 2022;386:640; Locke. ASH 2021. Abstr 2.

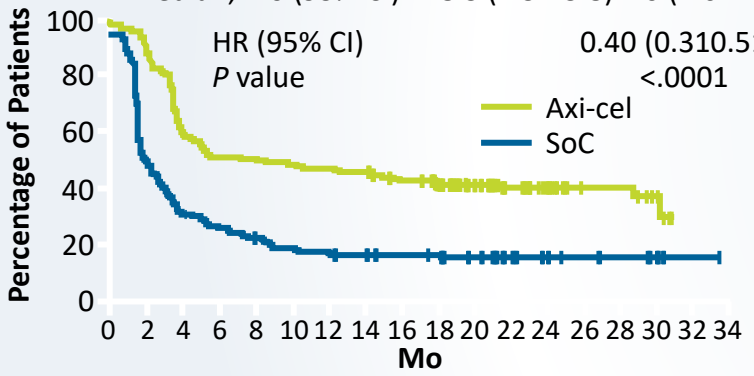
ZUMA-7: Axi-cel vs. SoC as Second-Line Therapy in Primary Refractory or Early Relapsed B-Cell Lymphomas

N = 359; Pts with refractory dx = 75%; Pts with DHL = 16%

Median Follow-up: 24.9 mo

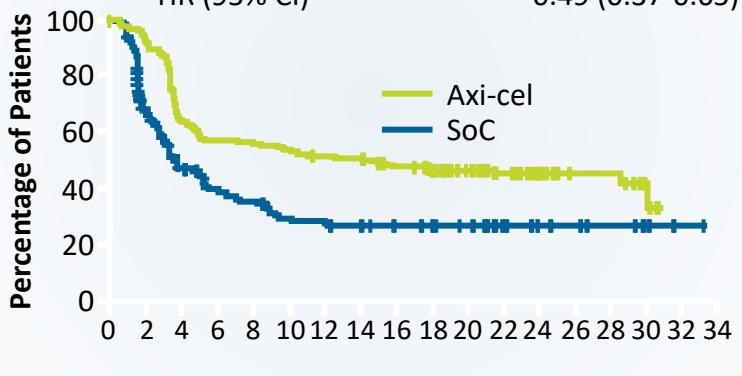
EFS

	Axi-cel (n = 180)	SoC (n = 179)
Median, mo (95% CI)	8.3 (4.5-15.8)	2.0 (1.6-2.8)
HR (95% CI)	0.40 (0.310.51)	
P value	<.0001	



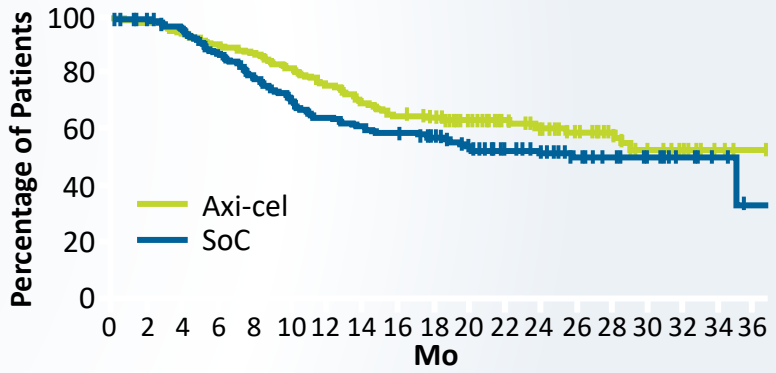
PFS

	Axi-cel (n = 180)	SoC (n = 179)
Median, mo (95% CI)	14.7 (5.4-NE)	3.7 (2.9-5.3)
HR (95% CI)	0.49 (0.37-0.65)	



OS

	Axi-cel (n = 180)	SoC (n = 179)
Median, mo (95% CI)	NR (28.3-NE)	35.1 (18.5-NE)
HR (95% CI)	0.73 (0.53-1.01)	



Response	Axi-cel (n = 180)	SoC (n = 179)	P value
ORR	83%	50%	<.001
▪ CR	65%	32%	

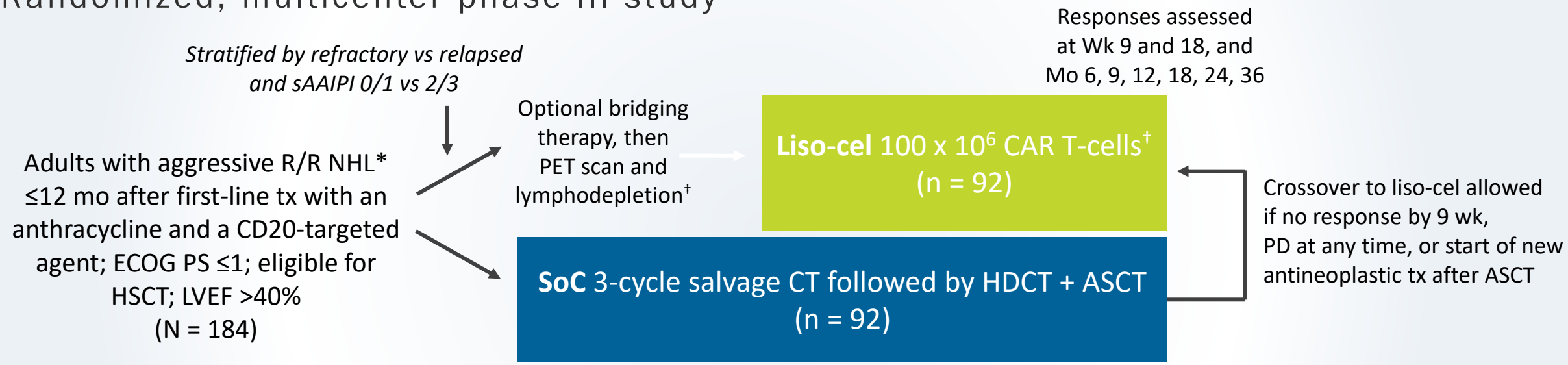
Grade ≥3 AE	Axi-cel (n = 170)	SoC (n = 168)
CRS	6%	--
NE	21%	1%

Axi-cel was associated with improved QoL by PRO

Locke. NEJM. 2022;386:640.

TRANSFORM: Lisocabtagene Maraleucel vs Salvage Chemo + ASCT in Relapsed/Refractory Aggressive NHL

Randomized, multicenter phase III study



*DLBCL NOS, HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL.
†Fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2 x 3 days.

- Primary endpoint: EFS per IRC
- Key secondary endpoints: CR, PFS, OS
- Exploratory endpoints: cellular kinetics, B-cell aplasia
- Primary refractory: 75% in both arms
- Double- or triple-hit lymphoma: 24%

Kamdar. ASH 2021. Abstr 91. NCT03575351.

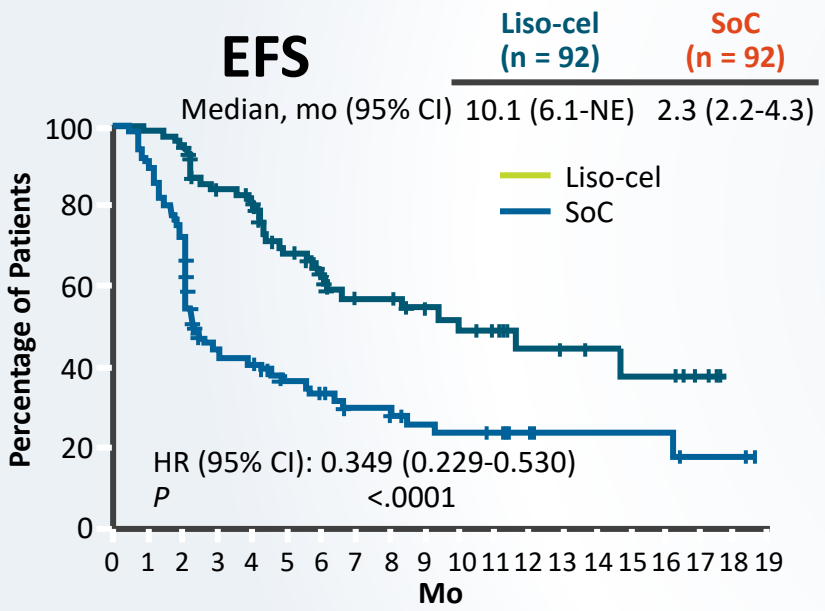
TRANSFORM: Liso-cel vs. SoC as Second-Line Therapy in Primary Refractory or Early Relapsed B-Cell Lymphomas

N = 184; Pts with refractory dx = 75%; Pts with DHL = 24%

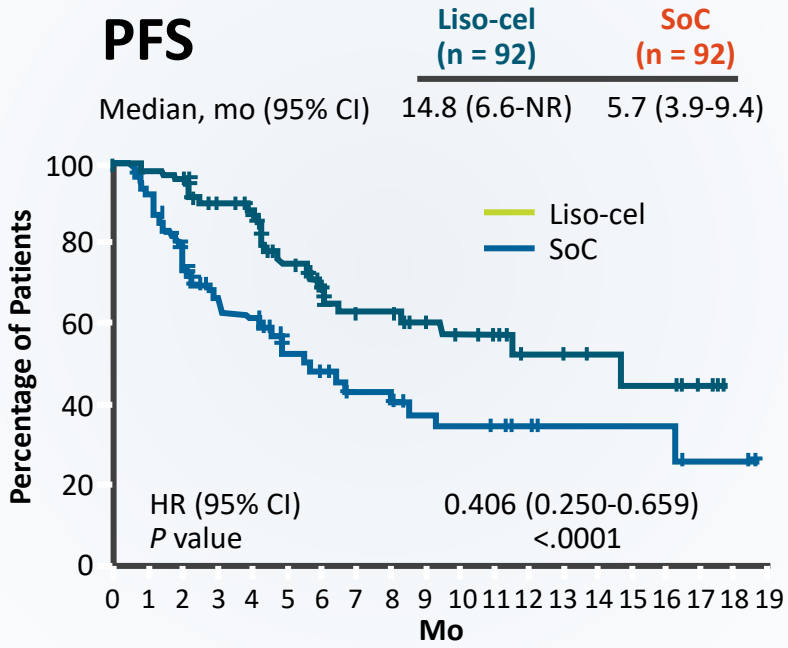
Median Follow-up: 6.2 mo

54% of pts on SoC arm crossed over to liso-cel arm

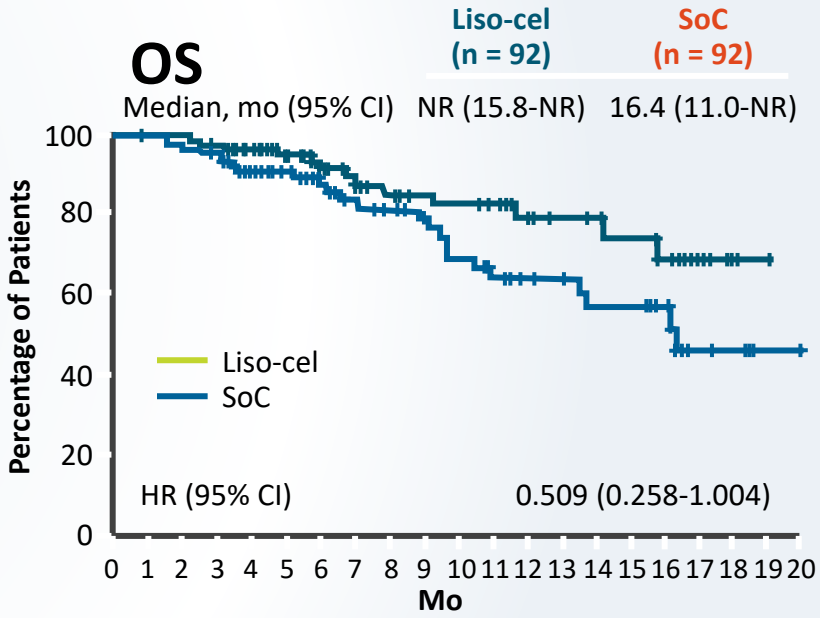
EFS



PFS



OS



Response	Liso-cel (n = 92)	SoC (n = 92)	P value
ORR	86%	48%	<.0001
▪ CR	66%	39%	

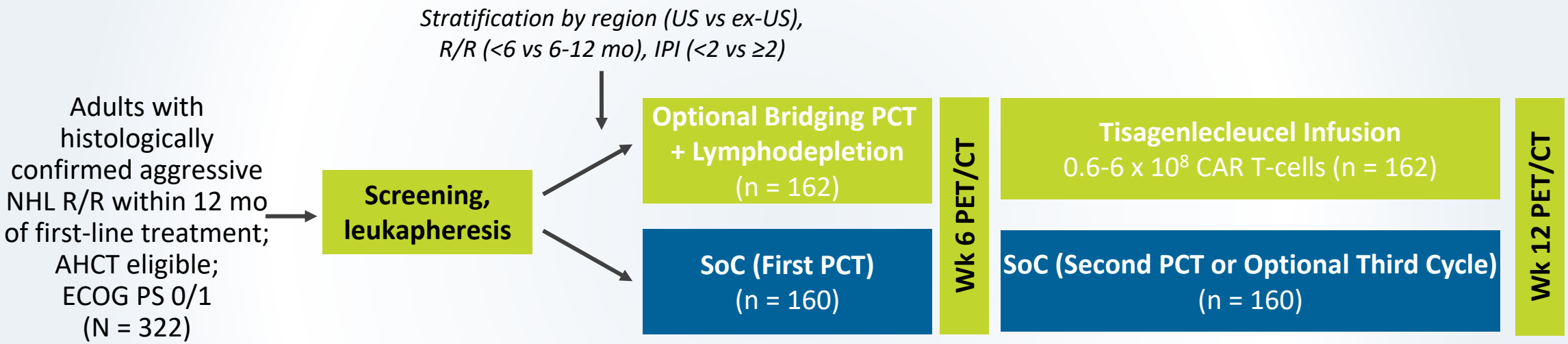
Grade ≥3 AE	Liso-cel (n = 92)	SoC (n = 92)
CRS	1%	--
NE	4%	--

Liso-cel was associated with improved QoL by PRO

Kamdar. ASH 2021. Abstr 91.

BELINDA: Study Design

Multicenter, randomized, open-label phase III trial



SoC arm received first PCT + AHCT for responders or second PCT for nonresponders based on Wk 6 assessment. Crossover to tisagenlecleucel permitted for SoC at Wk 12 for nonresponders. Patients assessed at Wk 6 and 12, then every 3 mo to Mo 12, every 6 mo to Mo 24, and yearly to Mo 60.

Primary endpoint: EFS

EFS event defined as SD/PD per BIRC at/after Wk 12 ± 1 wk or death

Secondary endpoints: ORR, safety, cellular kinetics

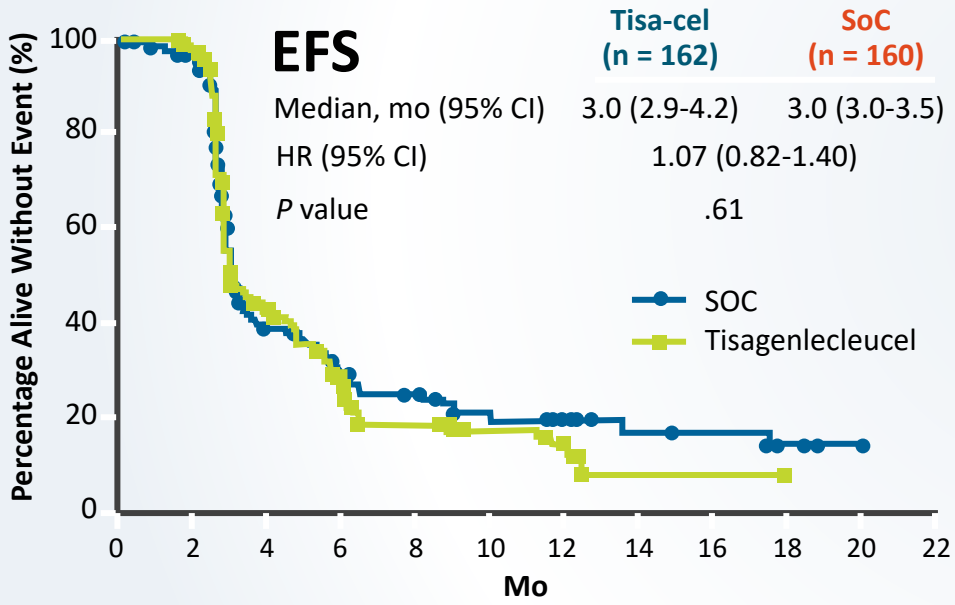
Bishop. NEJM. 2022. 386:629; Bishop. ASH 2021. Abstr LBA-6.

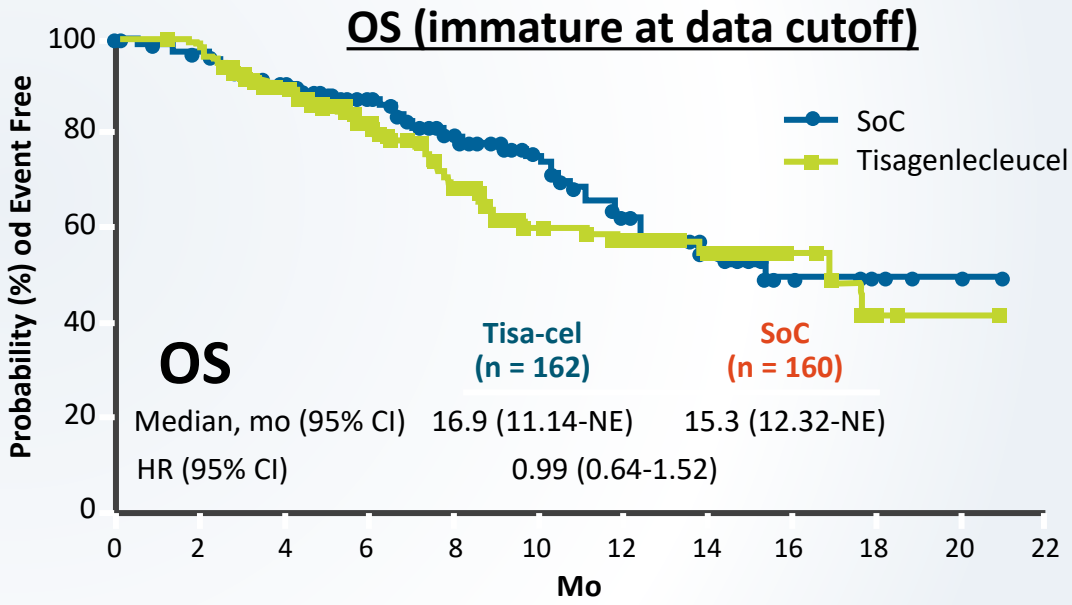
BELINDA: Tisa-cel vs. SoC as Second-Line Therapy in Relapsed Large B-Cell Lymphomas

N = 322; Pts with refractory dx = 75%; Pts with DHL = 15%

Median Follow-up: 10 mo

51% of pts on SoC arm crossed over to tisa-cel arm





Response at Wk 12	Tisa-cel (n = 162)	SoC (n = 160)
ORR	46.3%	42.5%
▪ CR	28.4%	27.5%

Grade ≥3 AE	Tisa-cel (n = 155)	SoC (n = 160)
CRS	5.2%	--
NE	1.9%	--

Bishop. NEJM. 2022.386:629.

Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care (+/- toci)*	Supportive care (+/- steroid)*	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring

- Steroid dosing for neurotoxicity may vary among products
- Patients receiving steroids should receive appropriate fungal prophylaxis

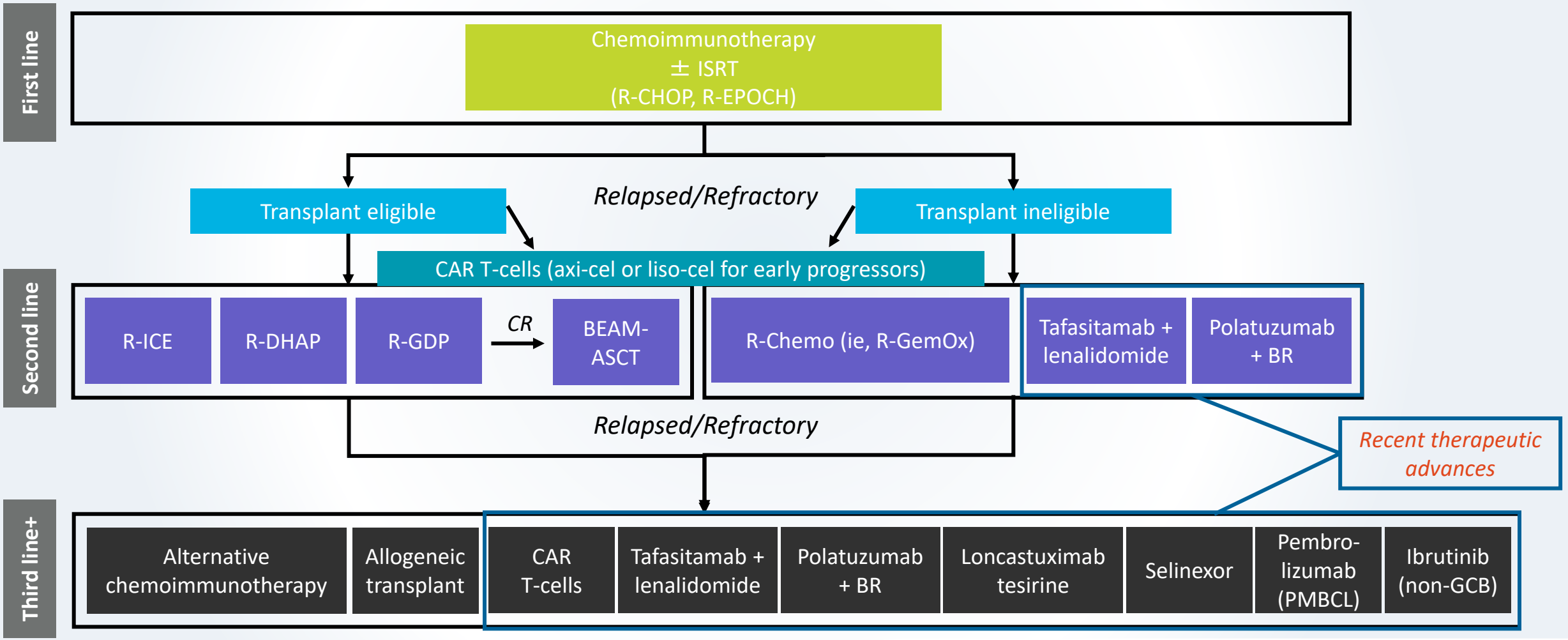
*High-burden, high-risk products, older, comorbidities, etc.

MD Anderson. CAR cell therapy toxicity assessment and management. 2017.
Neelapu. Nat Rev Clin Oncol. 2018;15:47.

Conclusions: The Rapidly Evolving Landscape of R/R DLBCL Therapy

- Targeted therapies have emerged as the dominant treatment options
- Choice of therapy is informed by type and response to prior therapies; timing of relapse; patient age, fitness, and comorbidities; disease kinetics; and product availability
- CAR T-cells have emerged as the treatment of choice in DLBCL in the third line and later for eligible patients and now in the second line for patients with primary refractory and early relapse
- Second-line therapies for patients who are ineligible or decline CAR T-cell therapy include tafasitamab/lenalidomide, polatuzumab/BR, or chemoimmunotherapy (ie, R-GemOx)
- Available third-line and later-line options for patients who are ineligible or decline CAR T-cell therapy or those who have progressed on CAR T-cell therapy include tafasitamab/lenalidomide, polatuzumab/BR, loncastuximab tesirine, and selinexor
- Ibrutinib or pembrolizumab can be considered in selected patients
- Bispecific monoclonal antibodies are emerging as an off-the-shelf immunotherapy option

The Current DLBCL Treatment Landscape



Thank You!

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Next presentation: Wednesday, January 11, 2023
Updates from ASH
Sonali Smith, MD, FASCO