DLBCL: Current Therapeutic Approaches

Julio C Chavez, MD
Associate Professor
Department of Malignant Hematology
Moffitt Cancer Center
Tampa, US
julio.c.chavez@moffitt.org

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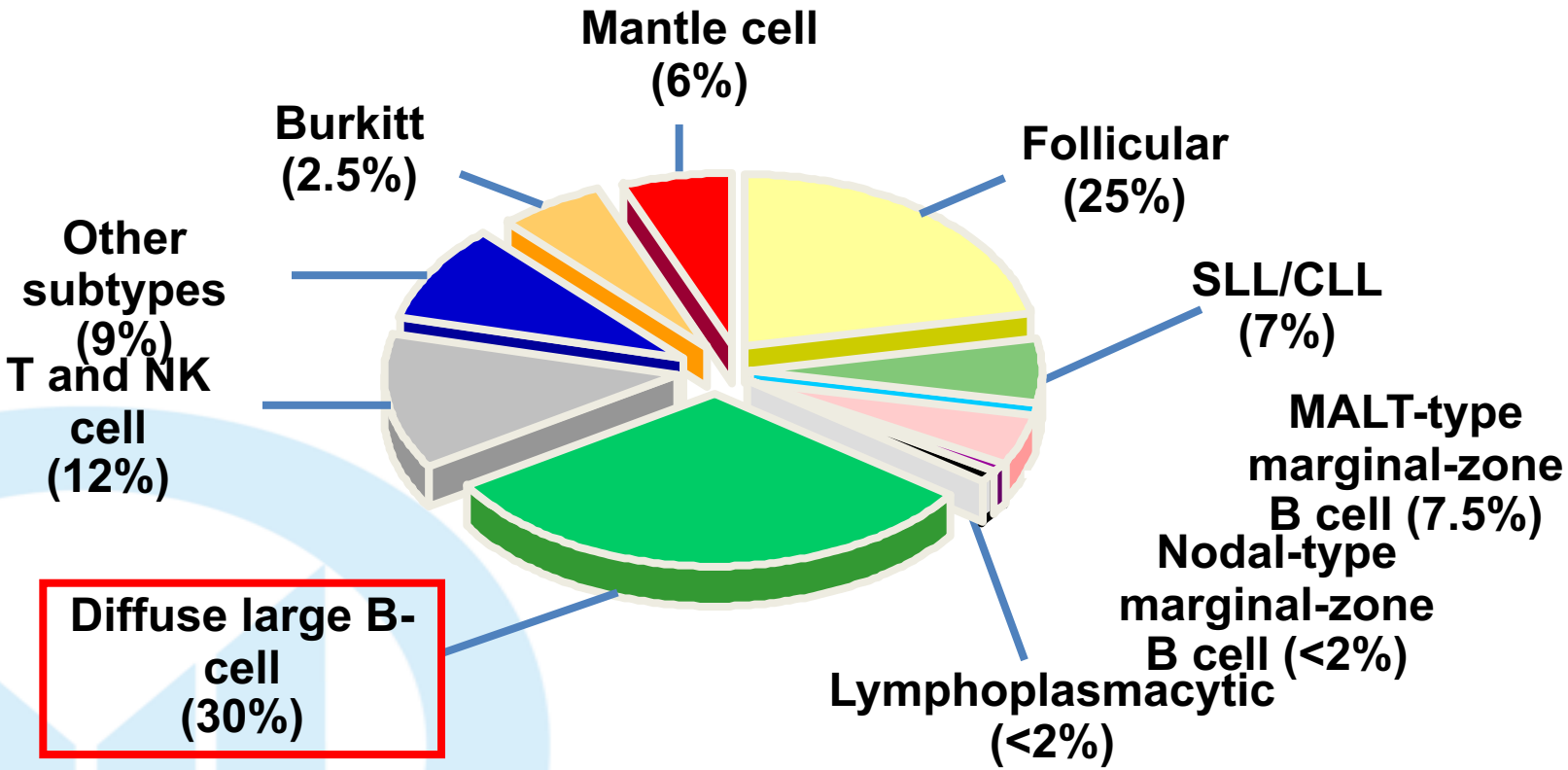
Outline

1. Introduction
2. Treating limited stage DLBCL
3. Treating advanced stage DLBCL
4. Evolving treatment for R/R DLBCL
5. Treating elderly pts with DLBCL

Most Common Subtypes of NHL



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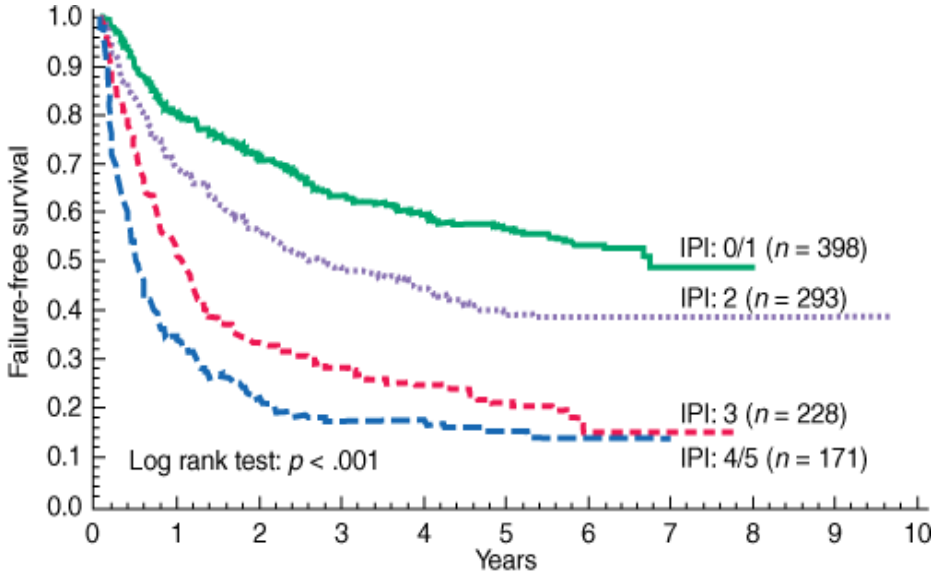
Lichtman MA. Williams Hematology. 7th ed. New York, NY: McGraw Hill. 2006;1408.

Clinical Features

- Lymph nodes enlargement:
  - Neck: Pain or obstructing mass
  - Mediastinal: dyspnea, chest pain, superior vena cava syndrome
  - Retroperitoneal: abdominal mass, abdominal pain, bowel obstruction, hydronephrosis
  - Extranodal disease in 20-40% of cases
  - 60-70% present with advanced disease (III/IV)
- B symptoms: drenching night sweats, persistent fevers, weight loss > 10% in the last 6 months

DLBCL: Risk stratification and International Prognostic Index (IPI score)

- Prognostic factors
  - Age ≥ 60
  - Performance status (ECOG)≥ 2
  - LDH above ULN
  - Stage III/IV
  - Extranodal disease>1
- Risk category
  - Low (0 or 1)
  - Low-intermediate (2)
  - High-intermediate(3)
  - High (4 or 5)



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

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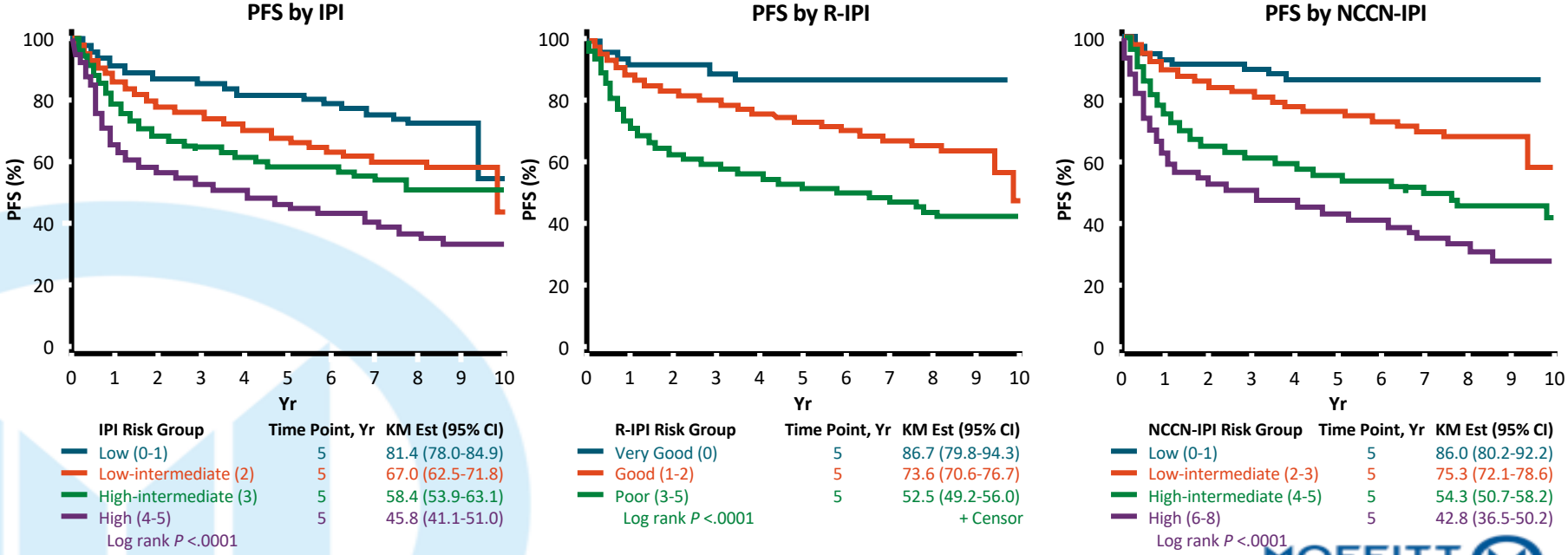
DLBCL prognosis: Comparison of Clinical Prognostic Indexes

- N = 2124 patients with DLBCL who received R-CHOP from 1998-2009 across 7 multicenter randomized clinical trials
- Compared with the IPI, the NCCN-IPI better discriminated low-risk and high-risk subgroups



Ruppert. Blood. 2020;135:2041.

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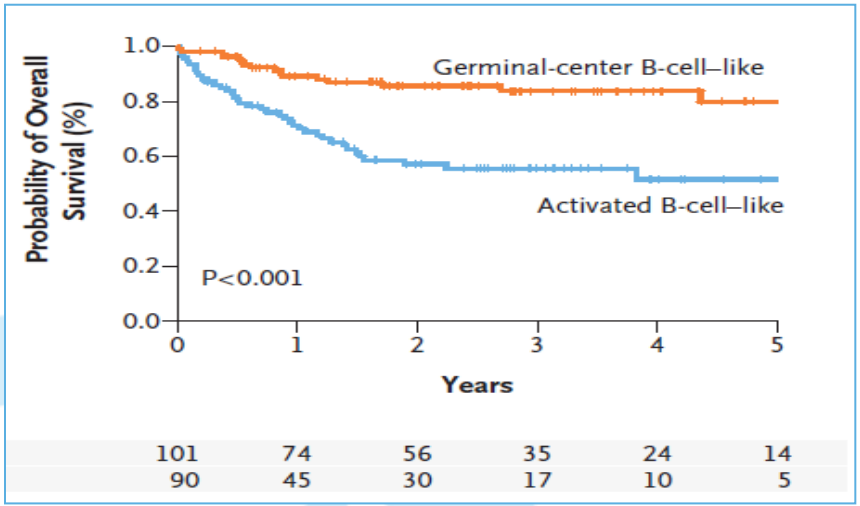
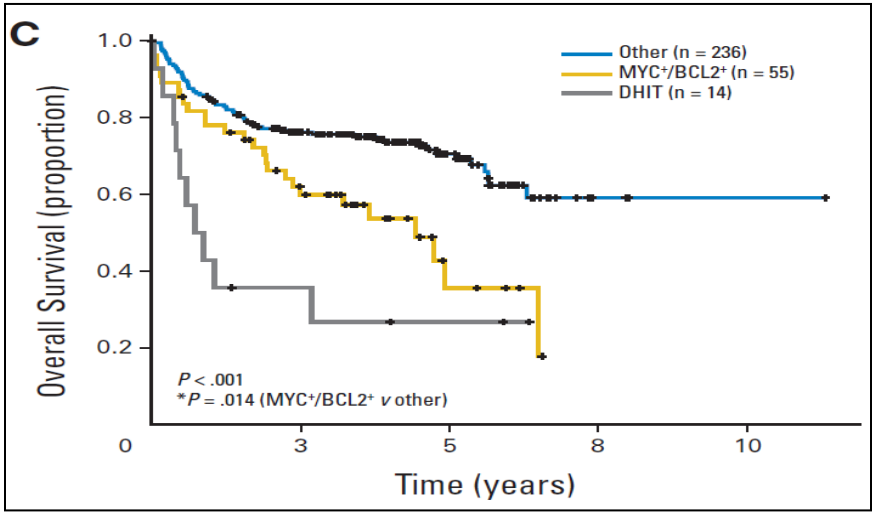
DLBCL is a molecularly heterogeneous disease; certain patient subsets do worse

Patients with ABC DLBCL are less likely to be cured by R-CHOP



N Engl J Med. 2008 Nov 27;359(22):2313-23

"Double-Hit" (Myc + Bcl-2) carries worst prognosis



J Clin Oncol 2012 30:3452-3459.

Additional Unmet Need

- Primary refractory or first relapse within 12 months
- High IPI score at relapse
- Transformed lymphoma
- Relapse post ASCT or not ASCT eligible

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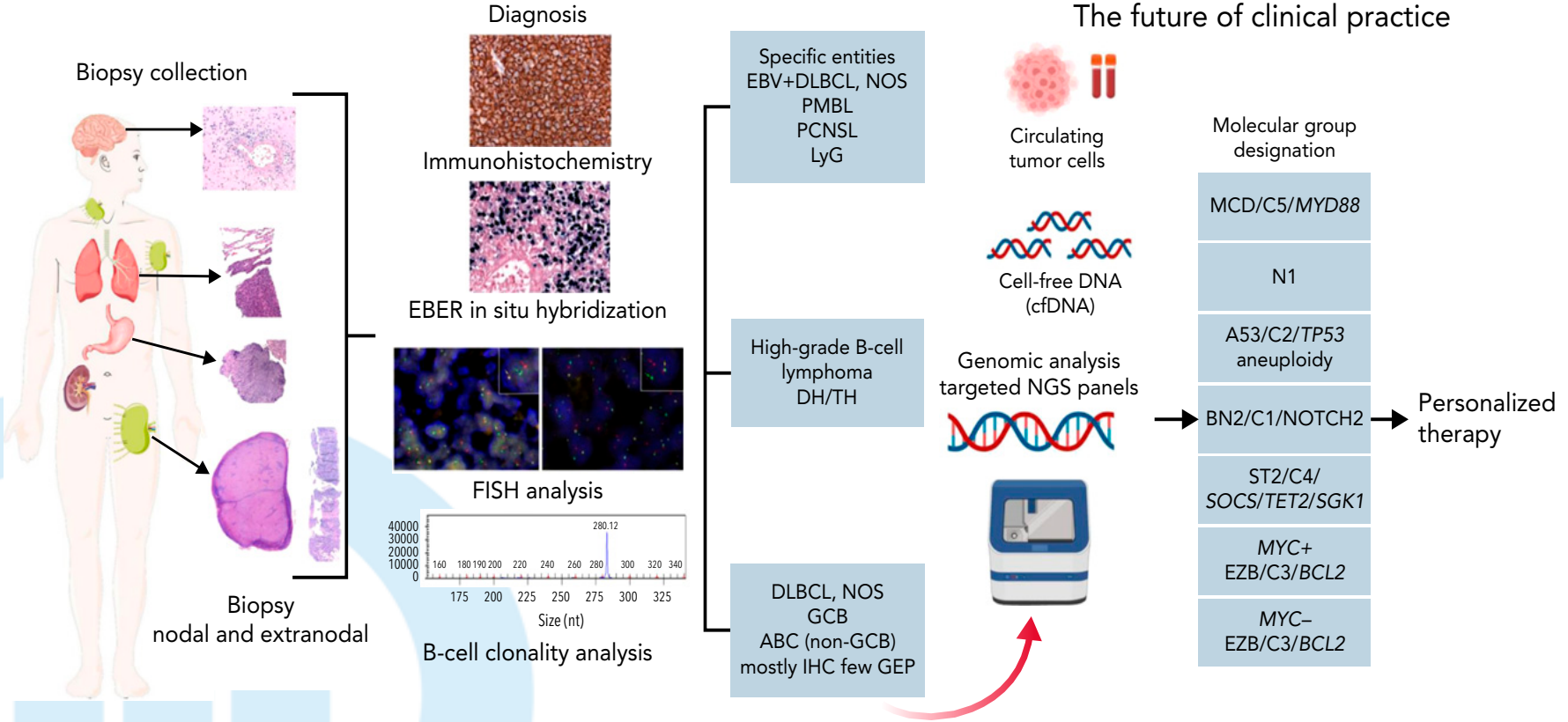
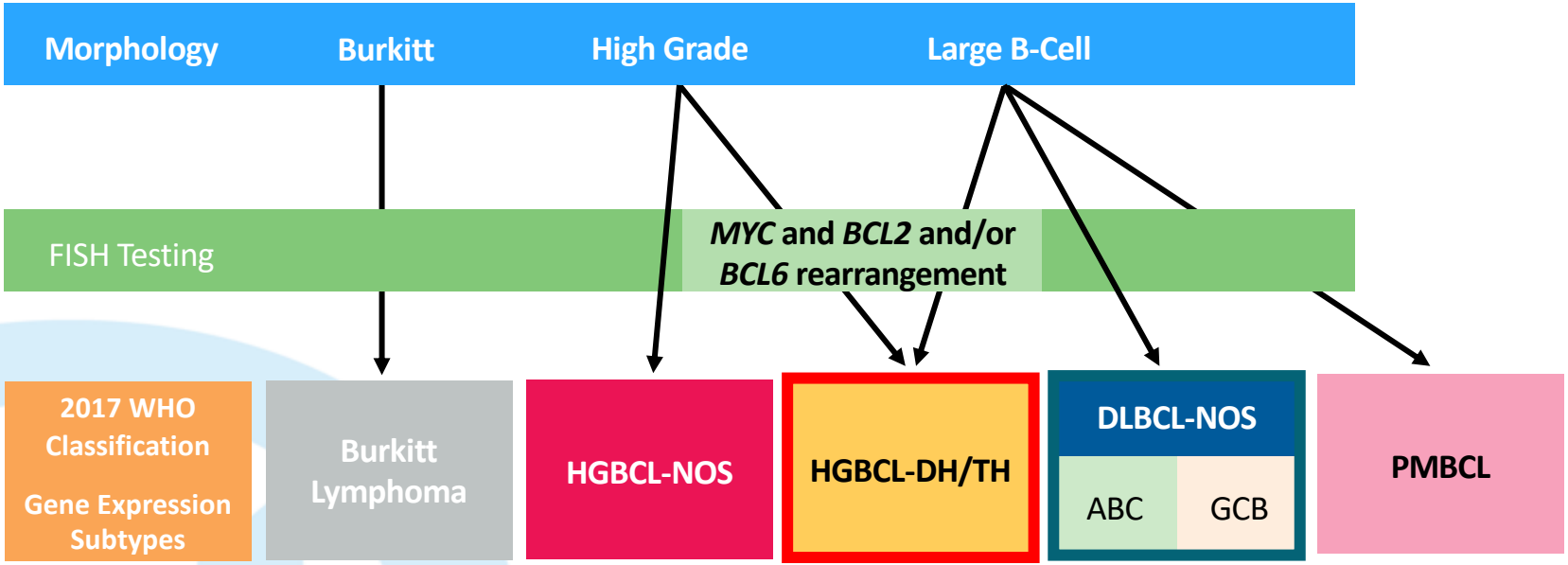
Current and Future Pathology Work Up For DLBCL



WHO Classification: Aggressive B-Cell Lymphoma



HGBCL DH/TH: high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements

Swerdlow. WHO Classification of Tumours, Revised 4th Edition. 2017;2. Alaggio. Leukemia. 2022;36:1720.

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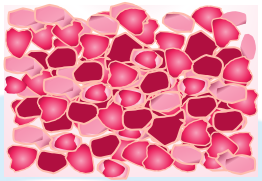
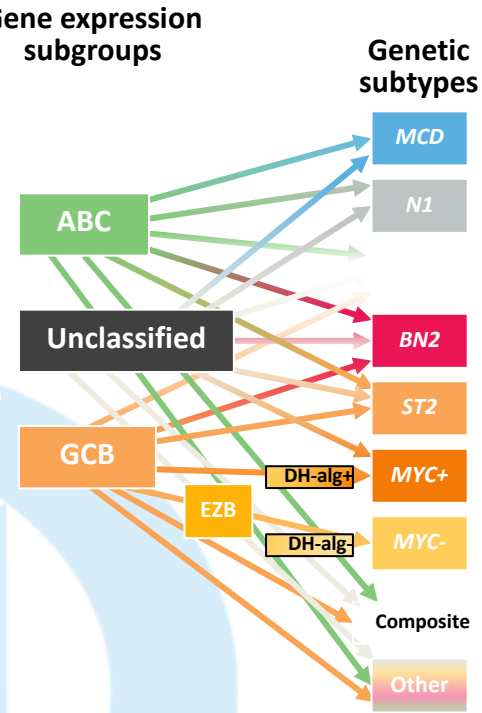
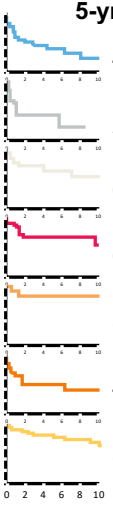
Novel DLBCL Genomic Subtypes

Diffuse large B-cell lymphoma





Hallmark genetic features		Overall survival R-CHOP chemotx	Candidate drug target					
Mutational Group		5-yr OS	BTK	PI3K	BCL2	JAK	IRF4	EZH2
MYD88^{L265P} mutation CD79B mutation		40%	✓	✓	✓	✓	✓	
NOTCH1 mutation		27%	✓					
TP53 inactivation aneuploidy		63%	✓					
BCL6 translocation *NOTCH2* mutation		67%	✓	✓	✓			
SGK1 mutation *TET2* mutation		84%		✓		✓		
EZH2 mutation *BCL2* translocation	*MYC* translocation *DDX3X* mutation	48%		✓	✓			✓
	TNFAIP3 inactivation *CARD11* mutation	82%						



de Level. Blood. 2022;[Epub].

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DLBCL: Limited Stage

- 3-4 cycles or full 6 cycles of R-CHOP?
- Consolidative radiation?
- Bulky limited stage

Studies in limited stage DLBCL: In general good prognosis

Trial	Design	Patients	PFS	OS
SWOG S0014 Persky, JCO 2014	Ph II: R-CHOP + IFRT	Stage modified IPI > 1 (N= 60)	4-y: 88%	4-y: 92%
SWOG S0313 Persky, Blood 2015	Ph II: CHOPx3 + IFRT +RIT	Stage modified IPI > 1	5-y: 82%	5-y: 87%
MINT trial Pfreundschuh, Lancet 2011	Ph III: R-CHOPx6 vs CHOPx6 (IFRT x stage I bulky)	< 60y, aaIPI=0, <7.5 cm (N= 101)	6-y: 90%	6-y: 95%
FLYER trial Poeschel,	**Ph III: R-CHOPx6 vs R-CHOP+2R**	< 60y, aaIPI=0, <7.5 cm (N= 588)	3-y: 94 v 96%	3-y: 98 v 99%
LYSA/GOELAMS Lamy, Blood 2018	Ph III: R-CHOPx4-6 vs R-CHOPx4-6+IFRT (PET guided- pos if DC4)	Stage I/II, < 7cm (n= 319)	5-y EFS 89 v 92%	5-y 92 v 96%
SWOG S1001 Persky, JCO 2020	**Ph III: R-CHOPx4 vs R-CHOPx3+IFRT+RIT** (PET guided-pos if DC4,5)	Stage I/II, < 10 cm	5-y: 87%	5-y: 90%
BCCA Sehn, ASH 2019	Retrospective: R-CHOPx4 if PET-	Stage I/II (n= 319)	5-y: 88%	5-y: 90%

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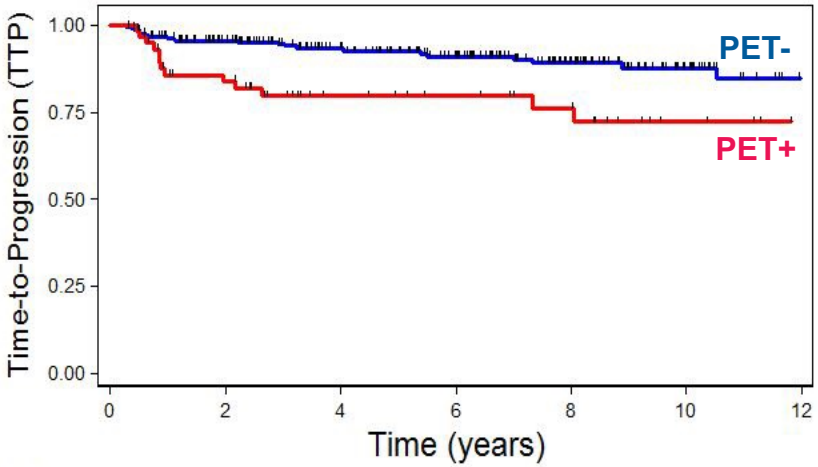
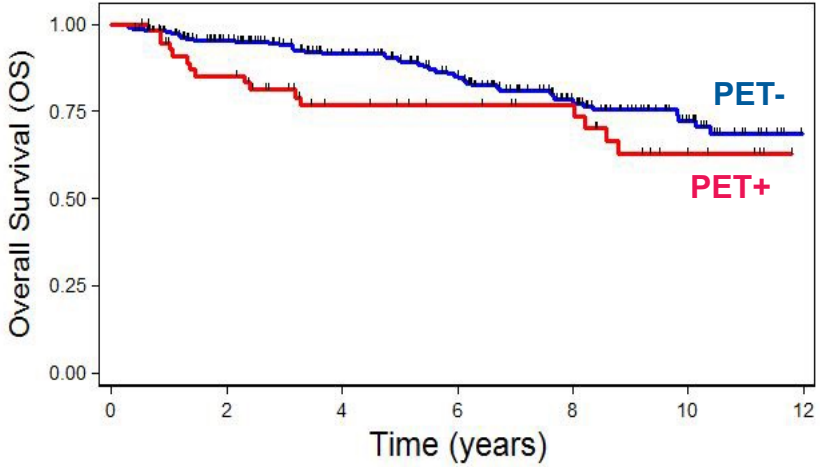
Outcomes in PET+ Stage I/II DLBCL: BCCA Restrospective Experience



Number at risk

PET-NEG	254	205	161	124	82	44	21
PET-POS	59	43	29	25	21	11	6



Number at risk

PET-NEG	254	208	164	127	83	46	21
PET-POS	59	45	31	27	24	13	7

Sehn et al. ASH Meeting 2019

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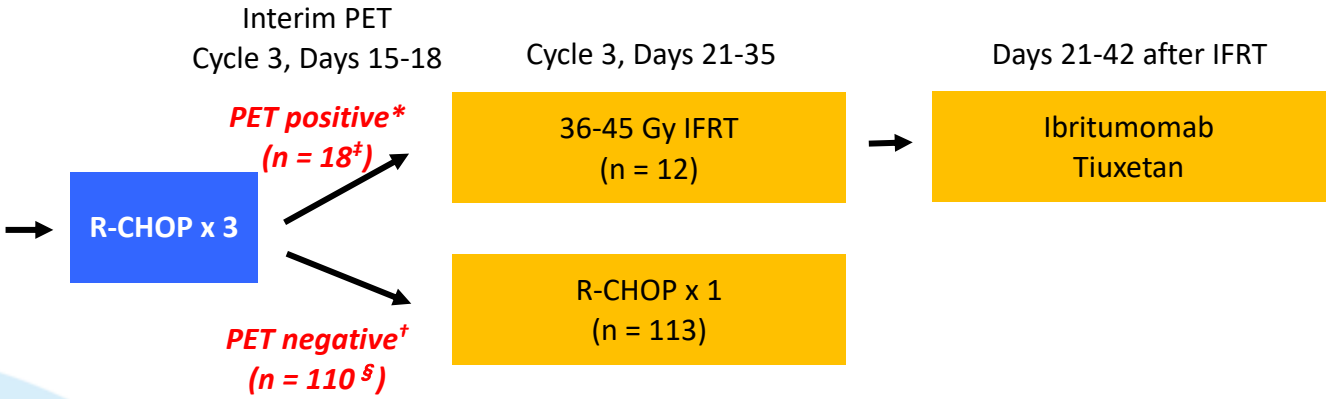
Intergroup NCTN S1001: Study Design- No IFRT in PET- LS DLBCL

Patients with newly diagnosed stage I/II DLBCL (by PET and CT); non-bulky (< 10 cm); measurable disease; no CNS, testicular, primary mediastinal, or concurrent or preceding indolent lymphoma (N = 132)



*PET+: Deauville 4-5. †PET-: Deauville 1-3. ‡n = 2 refused tx; n = 4 with Deaville X transferred to PET- arm. § n = 2 did not receive tx. Patients with stage I/II DLBCL by CT but stage III/IV by PET received R-CHOP x 6 cycles.

- Primary endpoint: 5-yr PFS rate
  - Historical estimate of 85% vs alternative hypothesis of 93%
- Secondary endpoints: PFS within PET-positive and PET-negative subgroups, toxicity of PET-directed therapy, response, OS

Persky. ASH 2019. Abstr 349.

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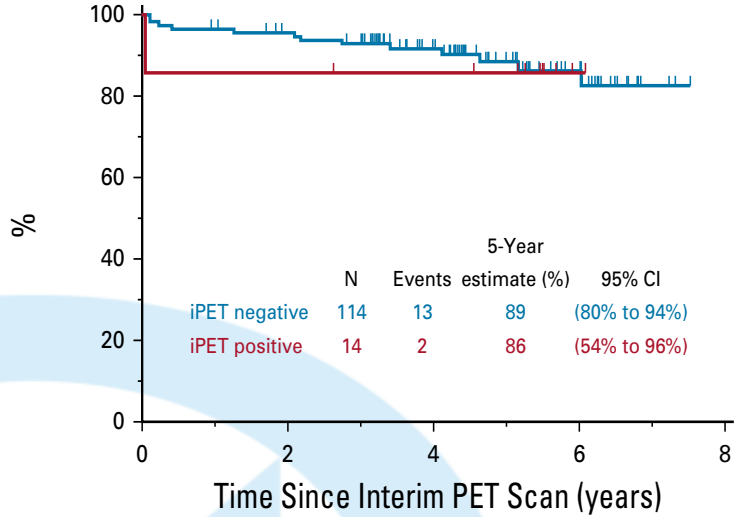
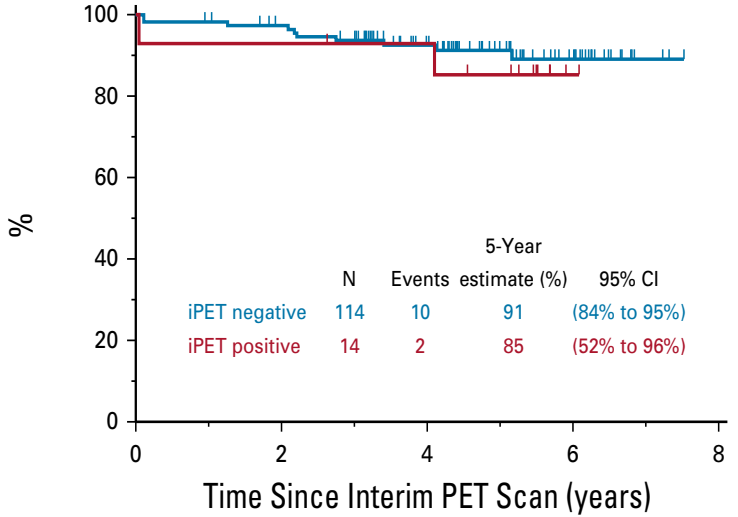
PET+ disease can be salvaged by radiation: SWOG S1001: iPET+ received IFRT



No. at risk:

iPET negative	113	109	104	100	70	46	25	3	0
iPET positive	13	12	12	11	11	10	1	0	0



No. at risk:

iPET negative	113	111	106	101	71	47	25	3	0
iPET positive	14	13	13	12	12	10	1	0	0

Persky et al. *J Clin Oncol* 2020

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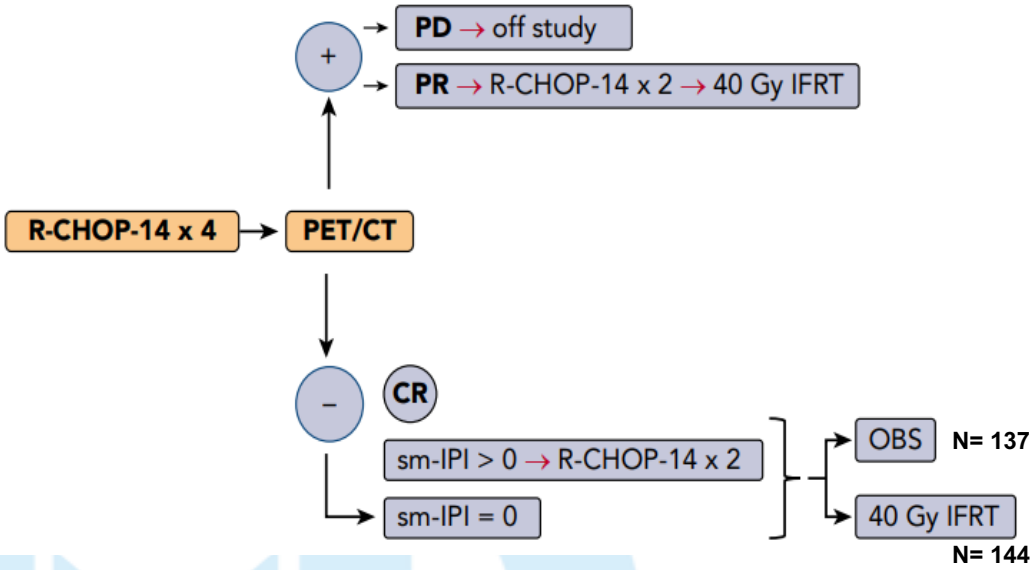
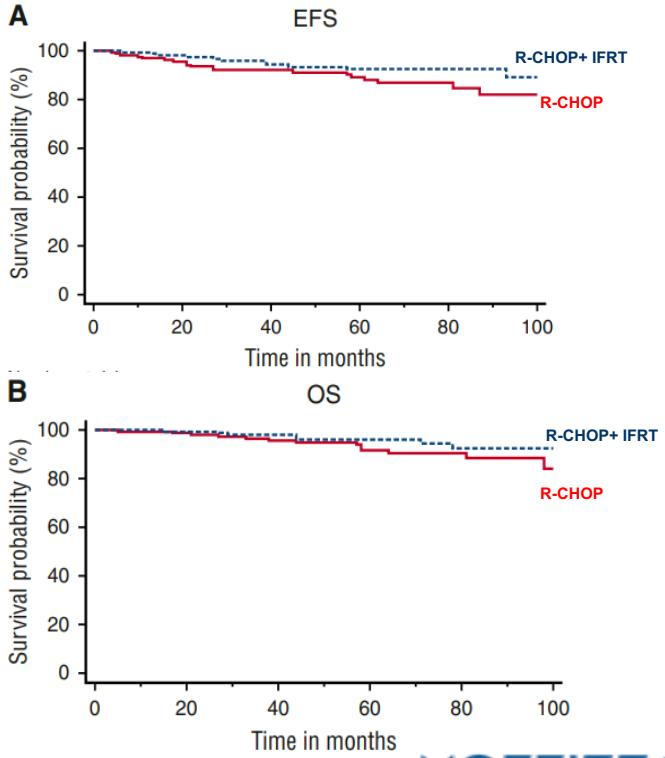
LYSA/GOELAMS: Limited stage DLBCL- PET scan may not be beneficial if PET-





Lamy, T et al. *Blood* 2018

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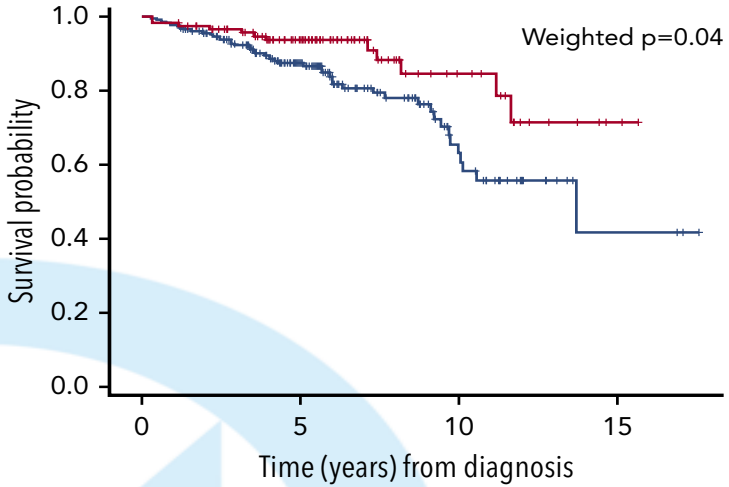
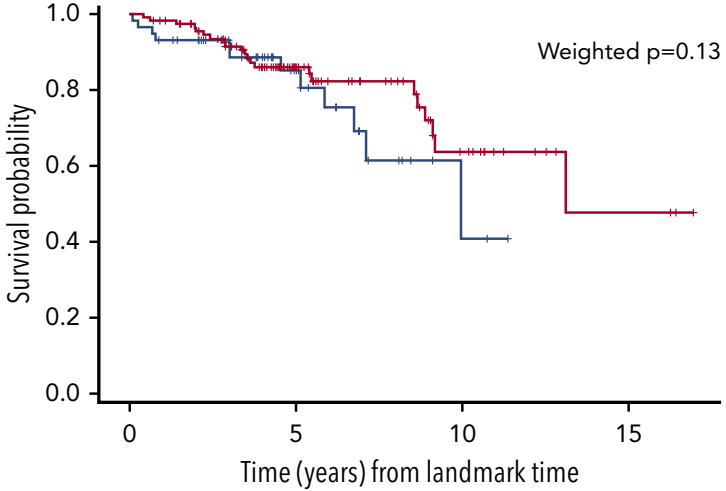
Stage I Extranodal DLBCL: Outcomes with RT and PET- MSKCC

PFS Extranodal vs Nodal



Extranodal	224	124	26	3
Nodal	117	75	17	2

PFS PET- RT vs Observation



No RT	58	21	3	0
RT	113	52	15	3

Bobillo et al. *Blood* 2020

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How I treat limited stage DLBCL?

- Non-Bulky stage I/II DLBCL
- R-CHOPx3 → PET
  - If PET- → R-CHOPx1
  - If PET+ → IFRT
  - If DC5 consider biopsy
- Bulky stage I/II DLBCL: UNFOLDER (RT is beneficial but no data on PET assessment)
- Extranodal stage I/II: IFRT may not be beneficial if PET negative (Bobillo et al, Blood 2020)

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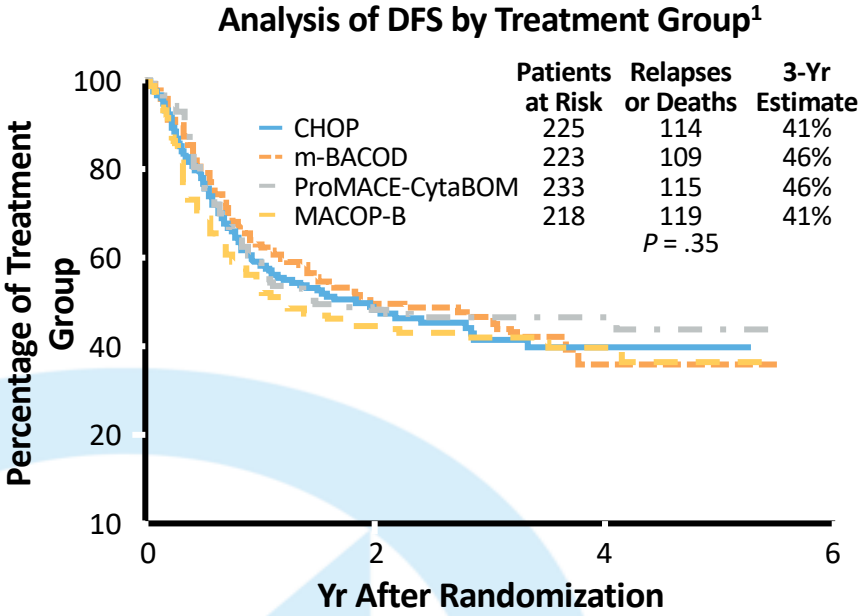
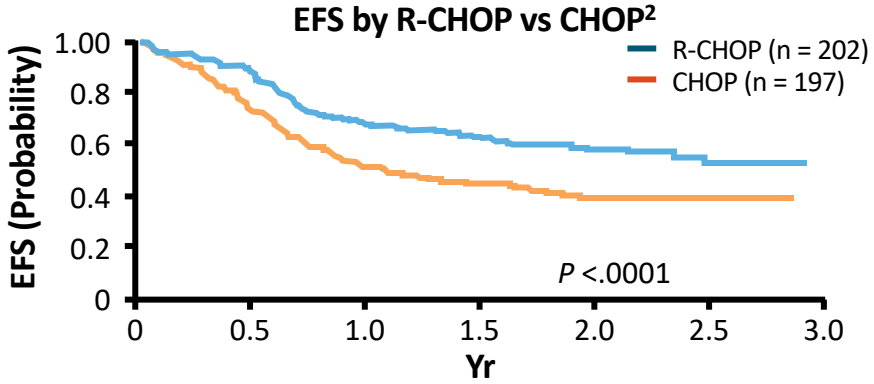
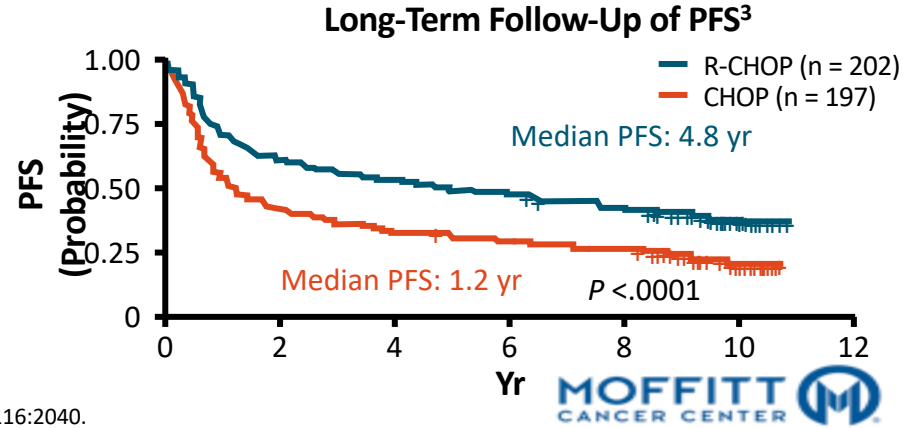
Advanced stage DLBCL

R-CHOP: Established as Standard of Care







1. Fisher. NEJM. 1993;328:1002. 2. Coiffier. NEJM. 2002;346:235. 3. Coiffier. Blood. 2010;116:2040.

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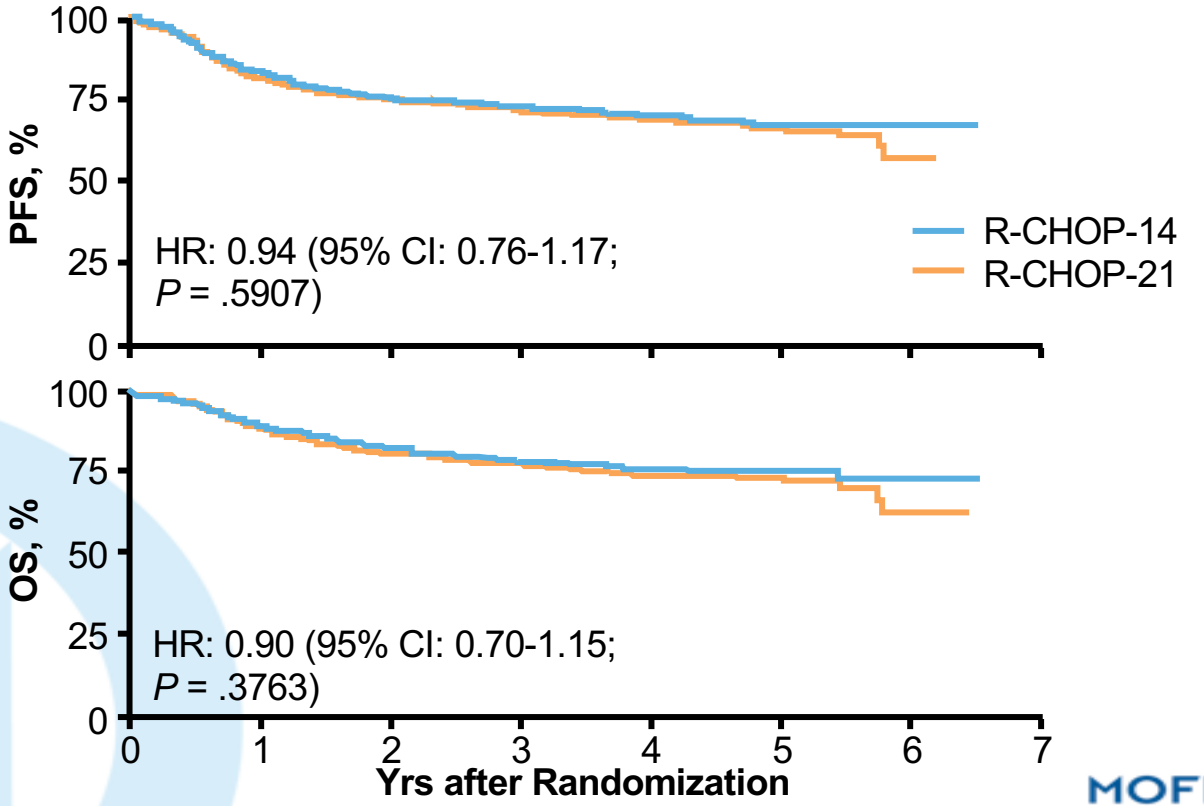
R-CHOP-14 vs R-CHOP-21 in Newly Diagnosed DLBCL (Phase III): PFS, OS



Cunningham D, et al: Lancet 381: 1817-26, 2013.

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Outcomes adding novel agents and DA-EPOCH

Clinical trial	ORR (CR) %	PFS	OS
PYRAMID (bortezomib- non GCB)[1] VR-CHOP (n=92) R-CHOP (n=91)	 96 (56) 98 (49)	 2-yr: 82% 2-yr: 78% p=0.611	 2-yr: 93% 2-yr: 88%; p= 0.763
CALGB/Alliance 50303[2] R-CHOP (n= 233) DA-EPOCH-R (n= 232)	 89.3 (62.3) 88.8 (61.1)	 3-yr: 81% 3-yr: 79%; p= 0.438	 3-yr: 85% 3-yr: 85%; p= 0.420
GOYA (obinutuzumab)[3] R-CHOP (n=712) G-CHOP (n=706)	 77.9 (59.5) 77.4 (56.7)	 3-yr: 66.5% 3-yr: 69.9%; p= 0.92	 3-yr: 81.4% 3-yr: 81.2%; p= 1.0
PHOENIX (Ibrutinib)[4] IR-CHOP (n=419) R-CHOP (n=419)	 89.3 (67.3) 93.1 (68.0)	 HR: 0949 (0.704– 1.279) (p= 0.731)	 HR: 0.991 (0.712-1.183) (p= 0.959)
ROBUST (lenalidomide)[5] R2-CHOP (n=285) R-CHOP (n= 285)	 91 (65) 91 (64)	 HR: 0.85 (0.63-1.14) (*p* = 0.29)	 2-yr: 79% 2-yr: 80%; p= NS
REMARC (lenalidomide maintenance)[6] R-CHOP → Len (n= 323) R-CHOP → Px (n= 327)		 2-yr: 80% 2-yr: 75%, p= 0.0135)	 2-yr: 89% 2-yr: 87%, p= NS

[1]Leonard JP et al JCO 2017, [2]Bartlett NL et al JCO 2019, [3]Vitolo U et al JCO 2017, [4]Younes A et al JCO 2019, [5]Nowakowski et al JCO 2021, [6]Thieblemont C, et al. JCO 2017

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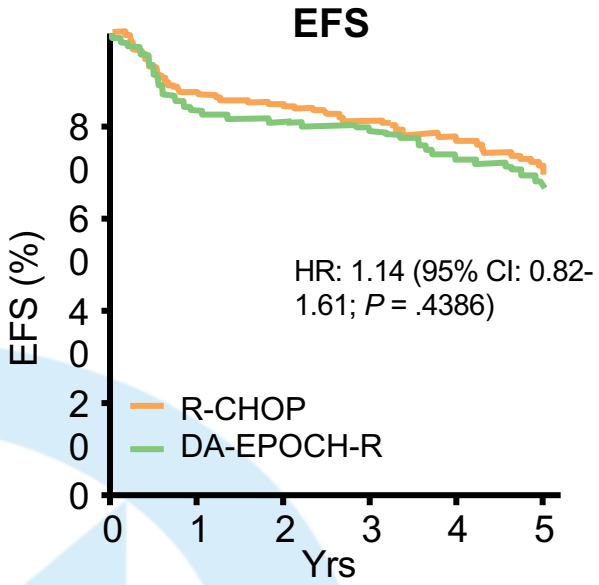
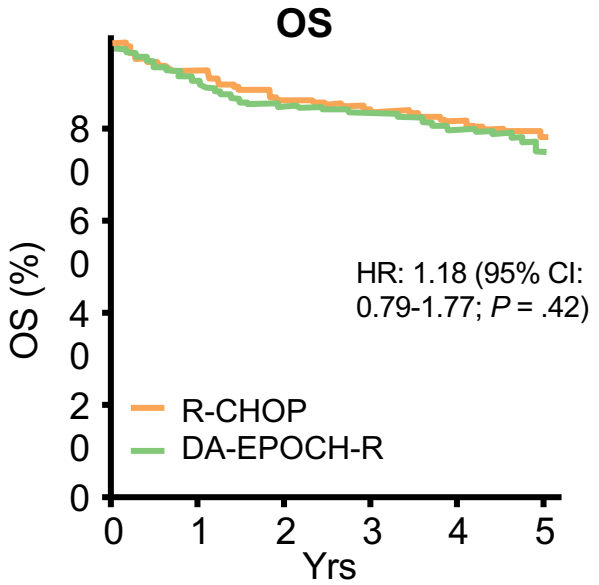
CALGB/Alliance 50303: R-CHOP vs DA-EPOCH-R: Event-Free Survival and OS

*Median follow-up 5 yrs





Arm	N	Events	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

Arm	N	Events	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	233	44	0.85 (0.80-0.89)	0.80 (0.74-0.85)
DA-EPOCH-R	232	50	0.85 (0.79-0.89)	0.76 (0.70-0.71)

Wilson WH, et al. ASH 2016. Abstract 469.

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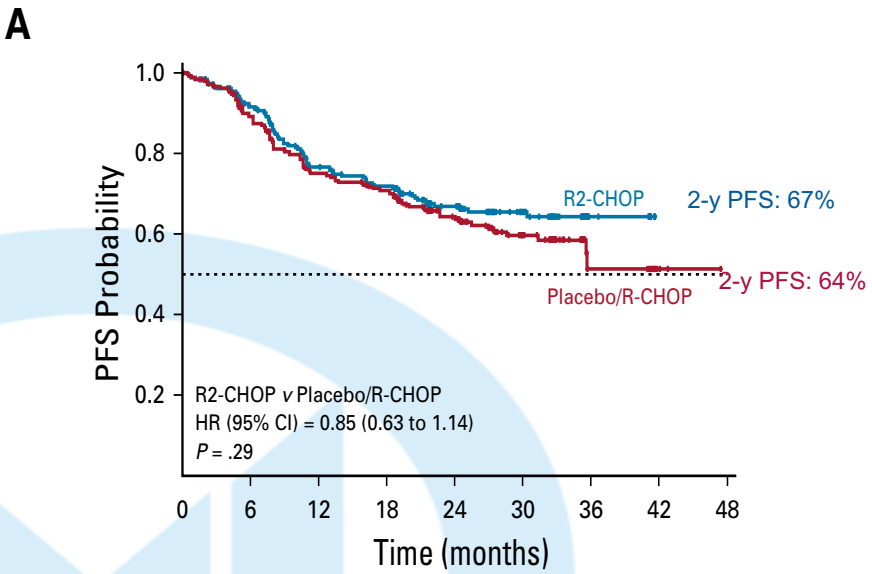
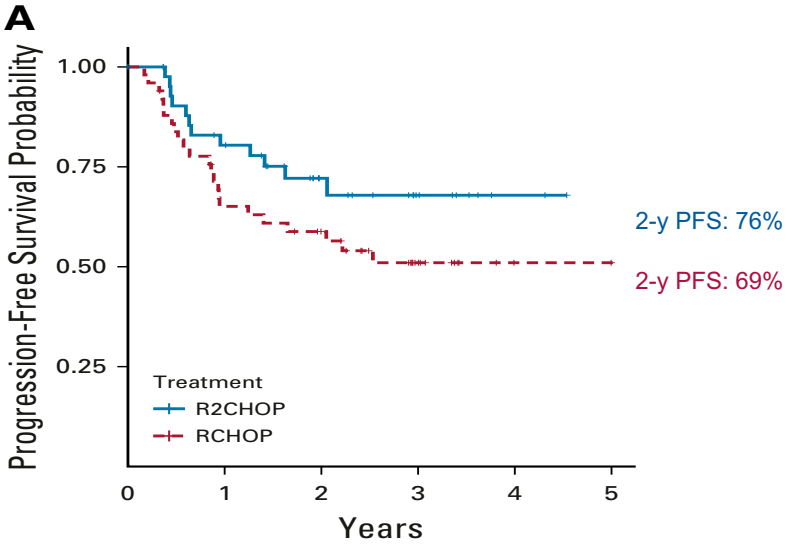
Does lenalidomide + R-CHOP improve outcomes in DLBCL?

ROBUST: R2-CHOP vs R-CHOP



ECOG E1412: R2-CHOP vs R-CHOP



Nowakowski et al JCO 2021/doi10.1200/jco.20.01366, Nowakowski et al JCO 2021/doi10.12100/jco.20.01375

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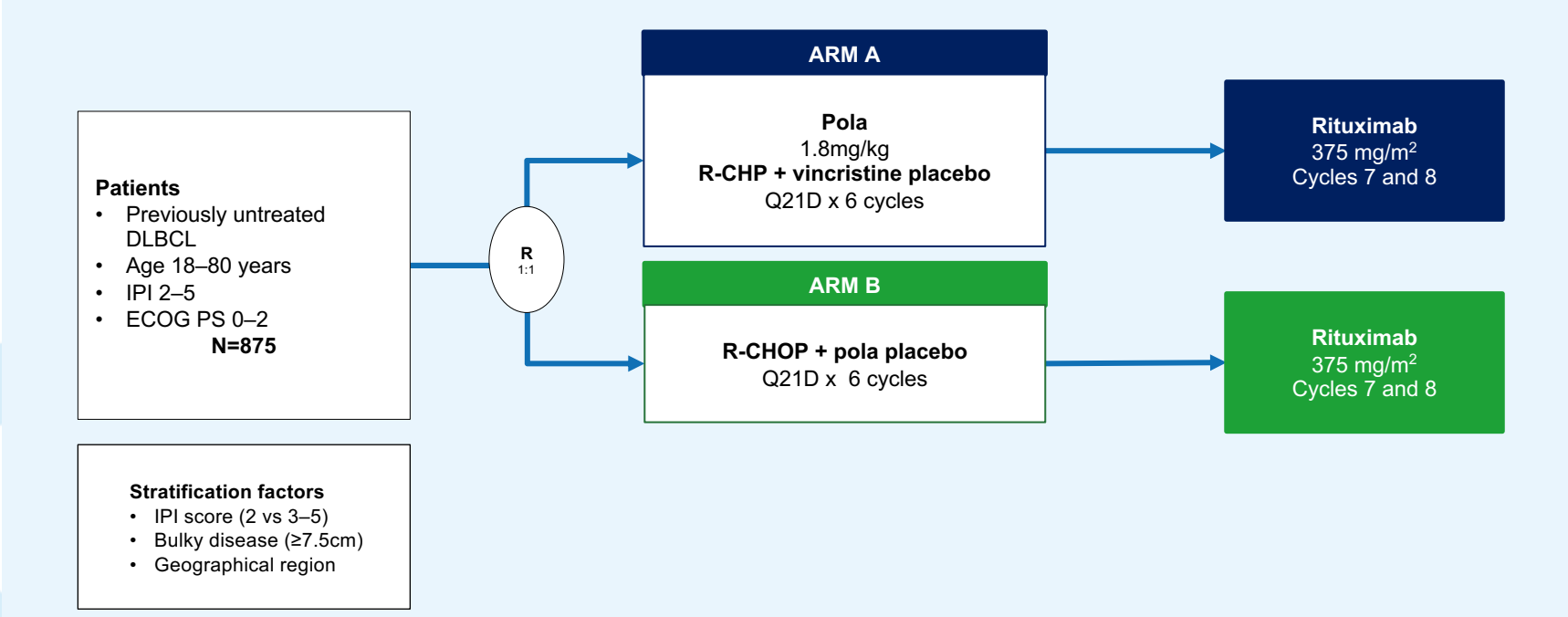
Does lenalidomide + R-CHOP improve outcomes in DLBCL?

ROBUST: R2-CHOP vs R-CHOP	ECOG E1412: R2-CHOP vs R-CHOP
✓ Phase III (Only ABC by GEP (NanosTring)	✓ Phase II (all DLBCL but stratified by COO [also using GEP-NanosTring])
✓ N= 570 (R-CHOP: 285, R2-CHOP= 285). Primary endpoint: PFS	✓ N= 280 (R-CHOP: 145, R2-CHOP: 135). Primary endpoint: PFS
✓ Median age 65 (21 – 83)	✓ Median age 66 (24 – 92)
✓ IPI 3 – 5: 58%, Stage III/IV: 87%	✓ IPI 3-5: 66%, Stage III/IV: 97%
✓ Median time from Dx to treatment: 31 days	✓ Median time from Dx to treatment: 21 days
✓ Lenalidomide dose: 15 mg d1-d14 every three weeks	✓ Lenalidomide dose: 25 mg d1-d10 every three weeks

Nowakowski et al JCO 2021/doi10.1200/jco.20.01366, Nowakowski et al JCO 2021/doi10.12100/jco.20.01375

POLARIX: Study design

A double-blinded, phase 3, placebo-controlled trial



LYSA, the lymphoma study association; IPI, international prognostic index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; Q21D, every 21 days; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

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POLARIX: Baseline Characteristics

Characteristic	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
Median age, yr (range)	65 (19-80)	66.0 (19-80)
Male, n (%)	239 (54)	234 (53)
ECOG PS 0/1, n (%)	374 (85)	363 (83)
Bulky disease (≥7.5 cm), n (%)	193 (44)	192 (44)
Elevated LDH, n (%)	291 (66)	284 (65)
Median time from diagnosis to treatment initiation, days	26	27
Ann Arbor stage III/IV, n (%)	393 (89)	387 (88)
Extranodal sites (≥2), n (%)	213 (48)	213 (49)

Characteristic, n (%)	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
IPI score		
▪ 2	167 (38)	167 (38)
▪ 3-5	273 (62)	272 (62)
Cell of origin		
▪ ABC	102 (31)	119 (35)
▪ GCB	184 (56)	168 (50)
▪ Unclassified	44 (13)	51 (15)
MYC/BCL2 expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement	26 (8)	19 (6)

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub]

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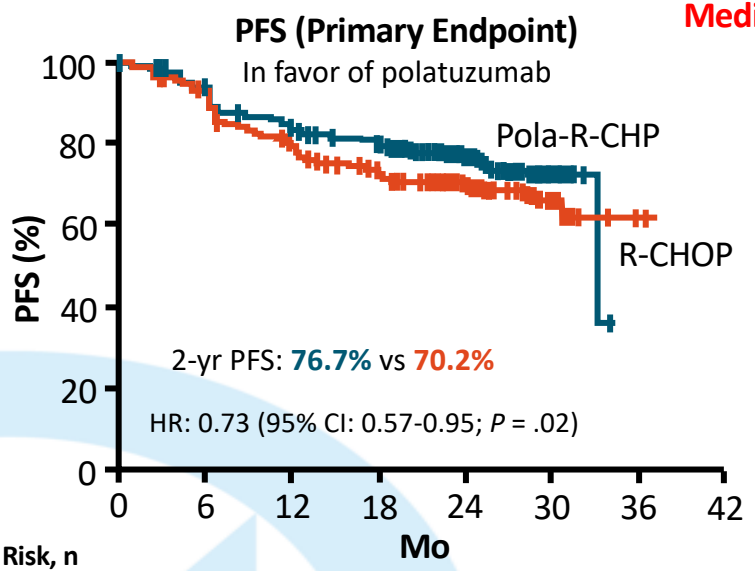
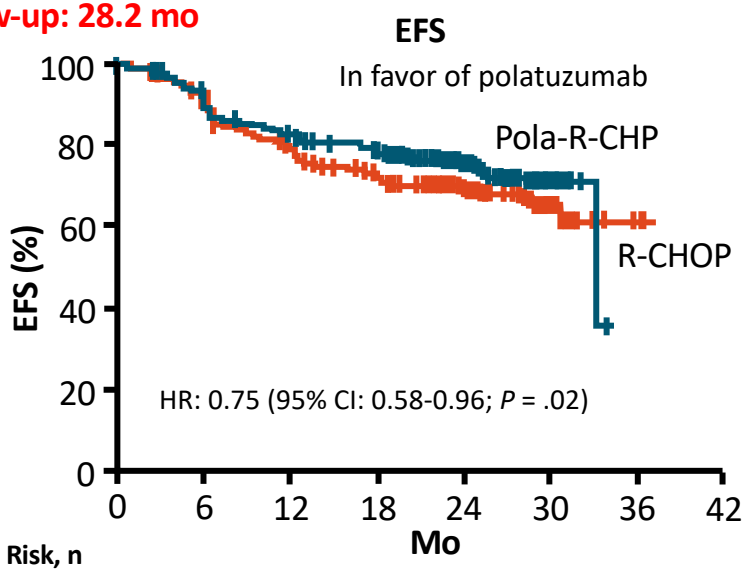
POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP PFS, EFS, and Response



Median follow-up: 28.2 mo



Patients at Risk, n

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

Patients at Risk, n

Pola-R-CHP	440	402	348	323	243	78	NE	NE
R-CHOP	439	386	327	294	218	78	3	NE

- Best overall response rate: **95.9 %** vs **94.1%**
  - Complete response rate: **86.6%** vs **82.7%**

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

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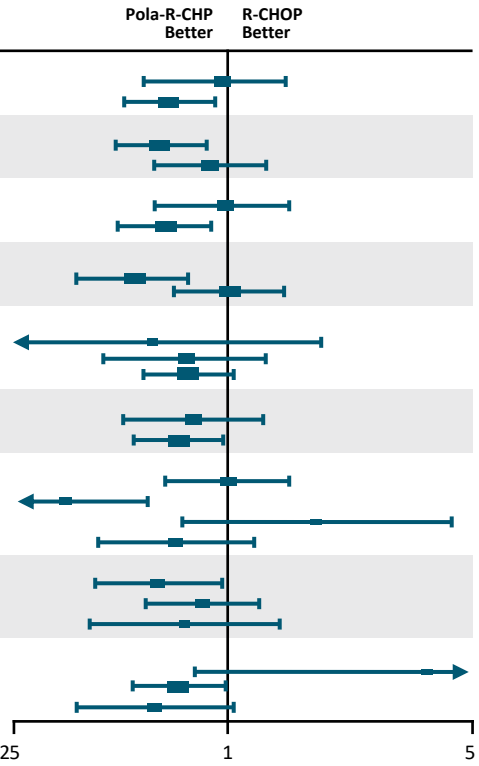
POLARIX: Subgroup Analysis of PFS

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, yr							
≤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)
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)
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)



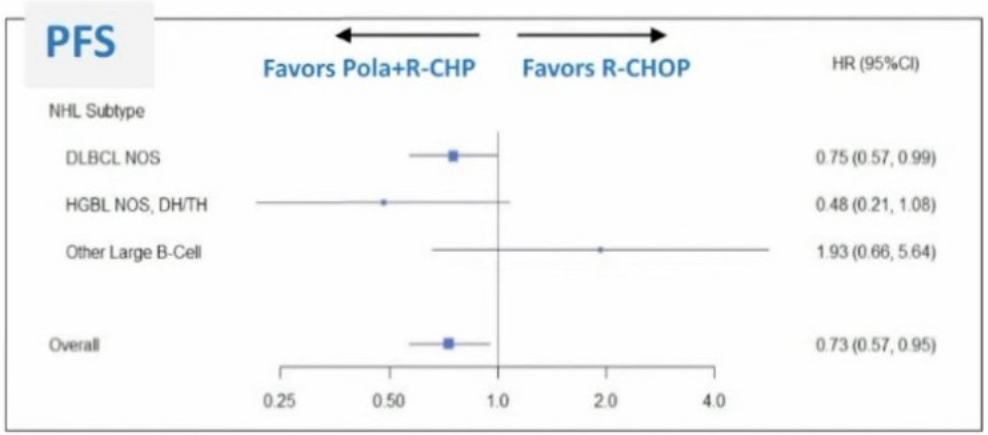
Benefits in

- Younger ≤60 yr?
- Females?
- IPI = 2?
- Bulky disease (≥7.5 cm)?
- GCB subtype?
- DH/TH DLBCL?

Adapted from Tilly. NEJM. 2022;386:351.

Imminent approval of polatuzumab as frontline for DLBCL: Questions remain

- ODAC FDA concerns:
  - Modest PFS benefit
  - Lack of OS benefit
  - Heterogenous population
  - No pathology central review
  - DTI 26- 28 days



Panel agrees that R-CHOP is still acceptable control arm for future trials

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Ongoing Clinical trials in Untreated DLBCL

- Acalabrutinib + R-CHOP vs R-CHOP
- FrontMIND: Tafasitamab + R^2-CHOP vs R-CHOP
- M20-61: Epcoritamab + R-CHOP vs R-CHOP

Is adding X to R-CHOP the answer in the era of highly effective novel therapies?

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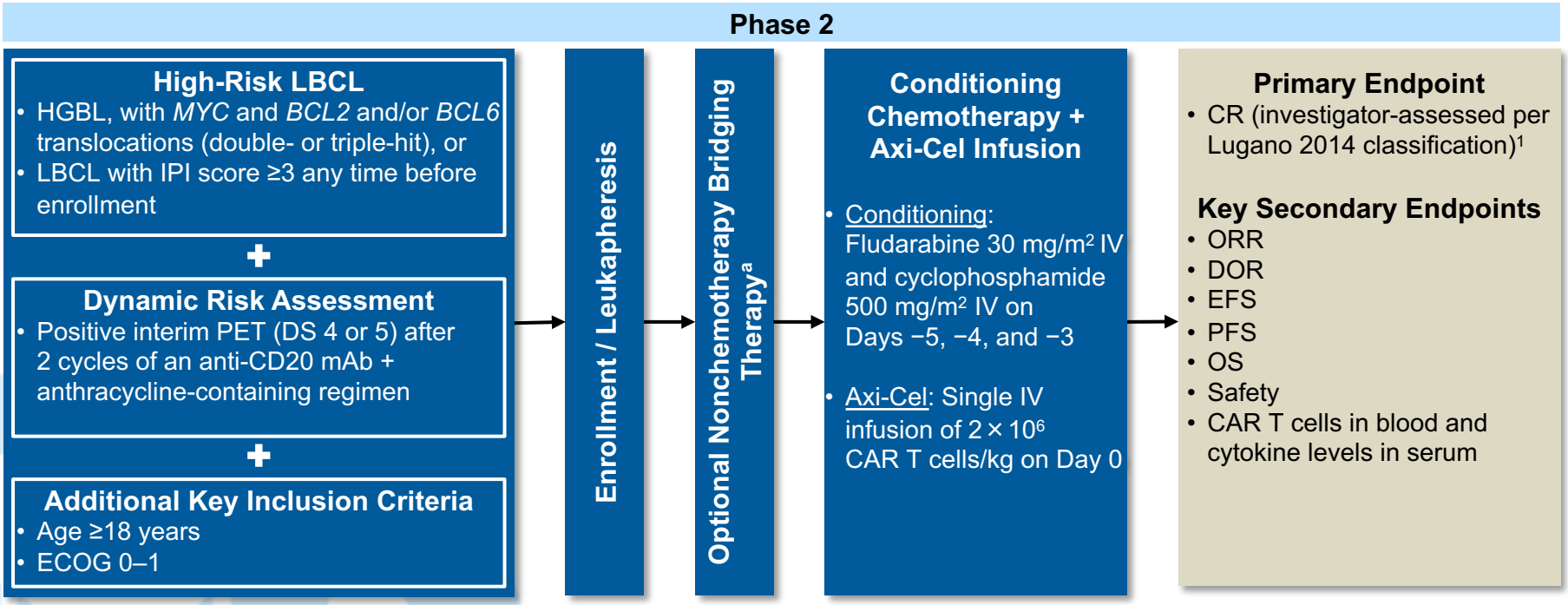
ZUMA-12 Study Design



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ZUMA-12: Baseline Patient Characteristics

Characteristic	All Treated (N=40)
Median age (range), years	61 (23–86)
≥65 years, n (%)	15 (38)
Male, n (%)	27 (68)
Disease stage III/IV, n (%)	38 (95)
ECOG 1, n (%)	25 (63)
1 Prior line of systemic therapy, n (%)	40 (100)
Double- or triple-hit as determined by FISH per investigator, n (%)[a]	**17 (43)**
Double- or triple-hit as determined by FISH per central laboratory, n (%)[a]	10 (25)
IPI score ≥3[b]	31 (78)
Deauville 5-point scale, n (%)	
4	19 (48)
5	21 (53)

Neelapu S et al. Nat Medicine 2022

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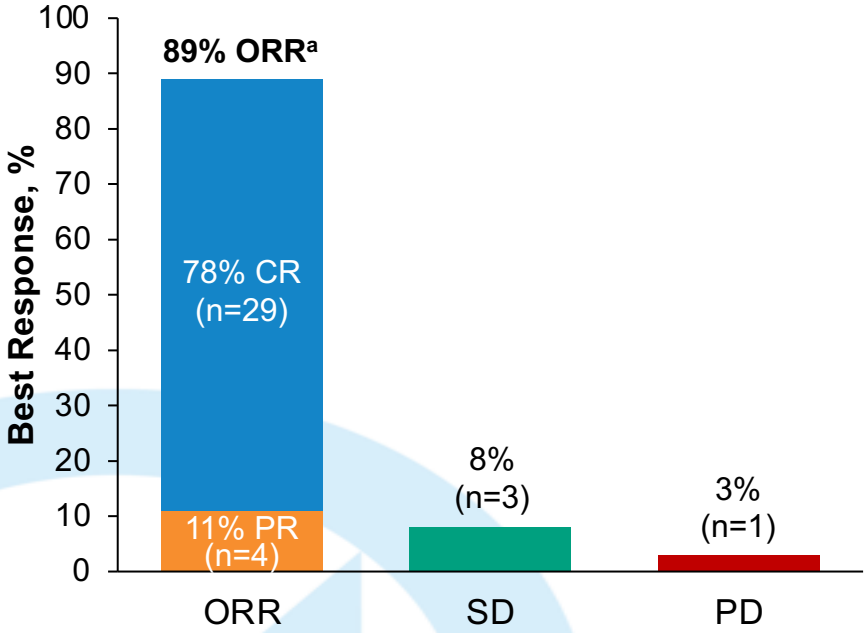
ZUMA-12: Efficacy



	Efficacy Evaluable N=37[b]
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

- Among all treated patients (N=40), ORR Was 90% (95% CI, 76-97); CR Rate Was 80% (95% CI, 64-91)

Neelapu S et al. Nat Medicine 2022

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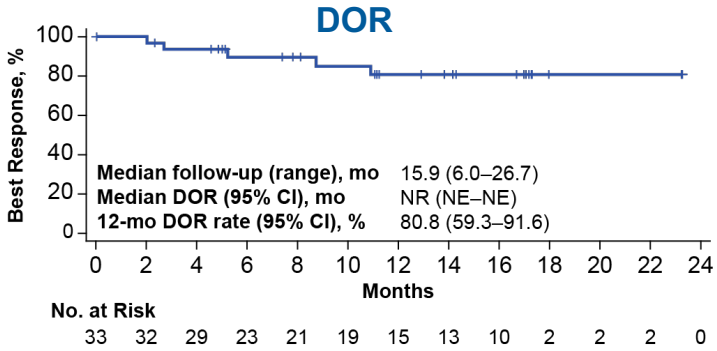
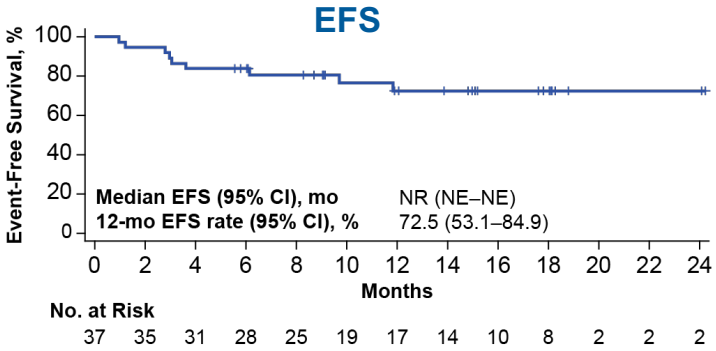
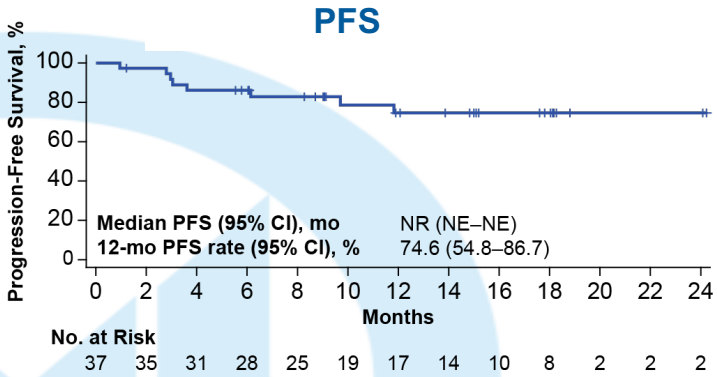
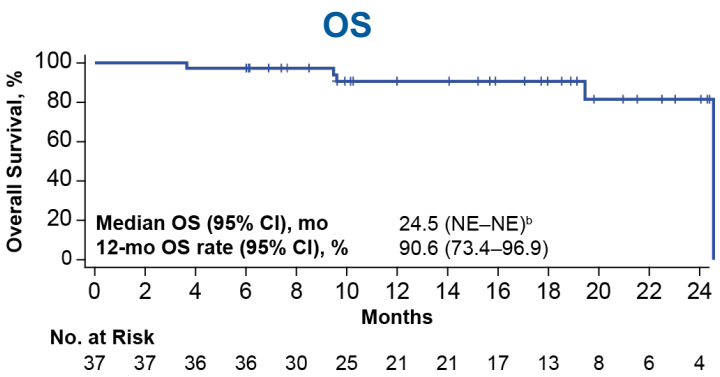
Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival[a]









Neelapu S et al. Nat Medicine 2022

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High Risk Features and Dx to Treatment Interval (DTI) of Frontline DLBCL studies

Factor	DTI	Int- High Risk - 3-5 IPI	High Risk - IPI 4-5	MYC-R	DHL
CALGB (R-EPOCH vs R-CHOP)	NR	29.6%	13.6%	5.2%	< 1%
PHOENIX Ibrutinib R-CHOP	27 days	43.2%	16.5%	NR	NR
GOYA (G-CHOP)	NR	46.9%	15.4%	NR	1.1%
POLARIX Pola R-CHOP	26 days	62%	NR	NR	7.9% (tested)
ROBUST (R2-CHOP)	31 days	58%	NR	NR	
ZUMA-12	?	78%	NR	48%	43%

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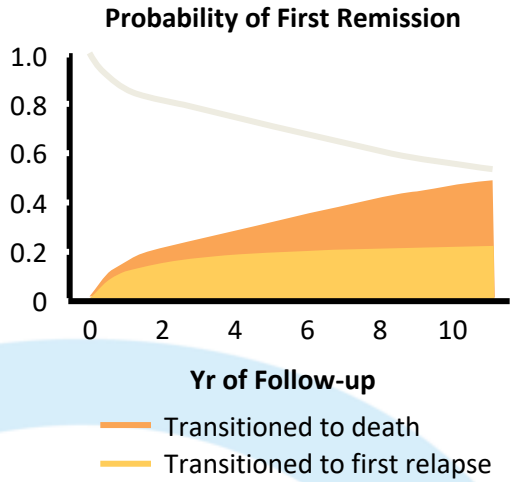
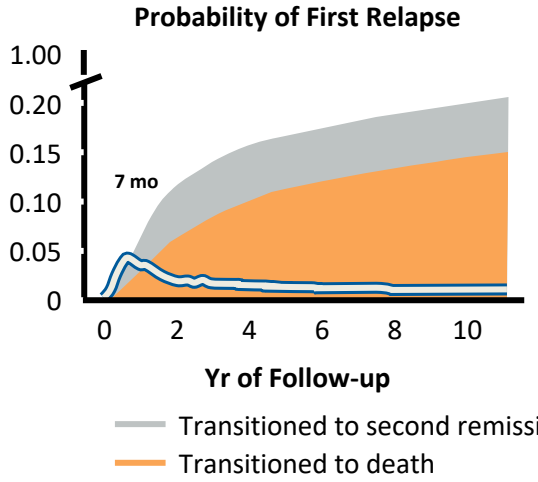
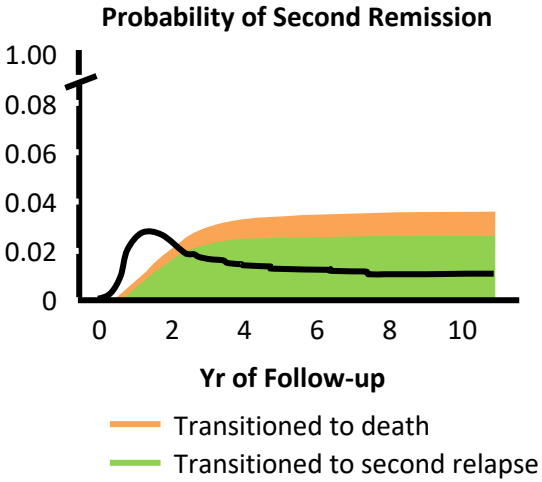
Relapse/Refractory DLBCL

Outcomes of patients with DLBCL







Swedish registry study (median f/u: 5 yr)

- N = 2941 with response to 1L tx
- R-CHOP: 91%
- Completed ≥6 cycles: 90%

Relapsed on 1L tx: 18% (n = 538)

- Within first 2 yr: 72%
- After Yr 5: 1%
- 44% responded to salvage tx

Ekberg. Br J Cancer. 2022;127:1642.

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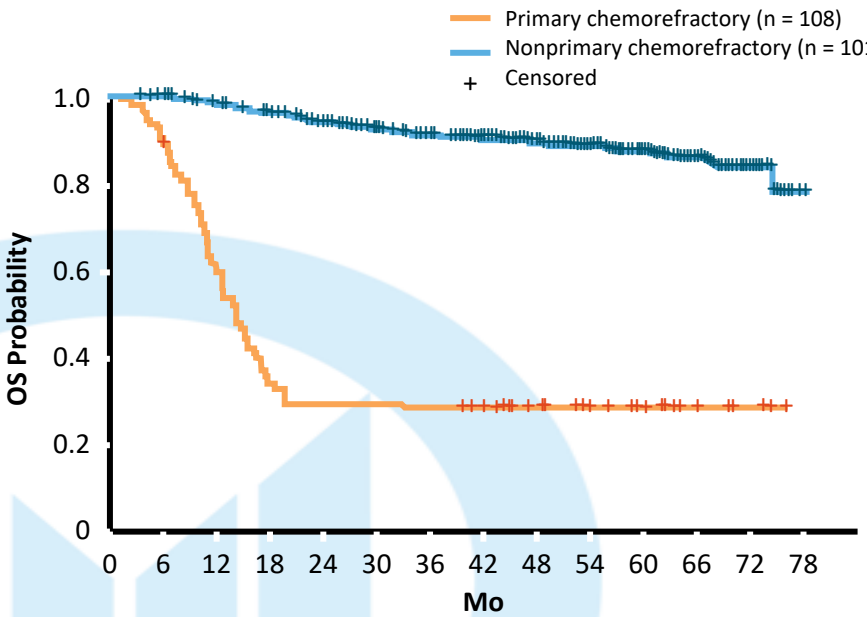
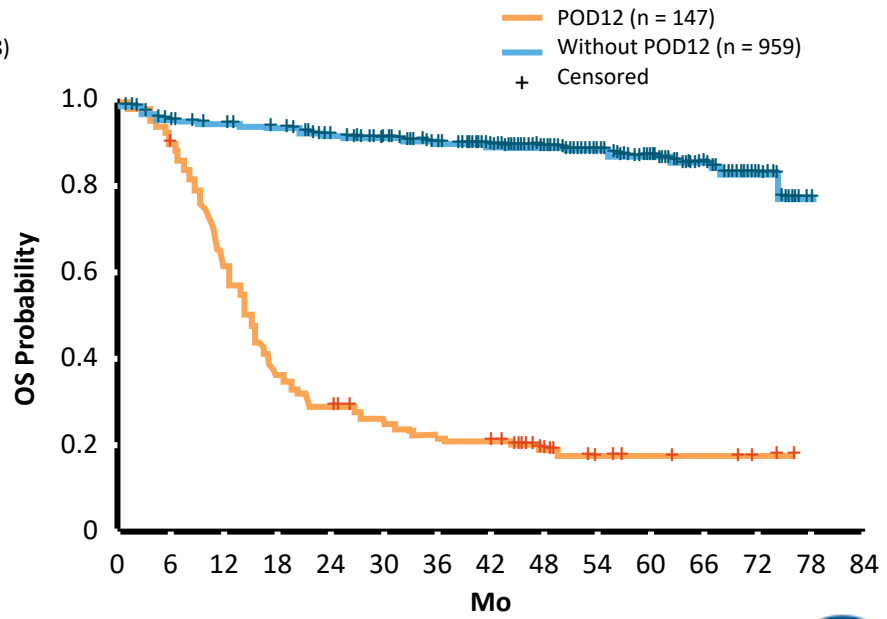
Early Relapse and Refractoriness Associated With Poor Survival in DLBCL

- Data from the phase III GOYA among patients with DLBCL who received 1L rituximab or obinutuzumab + CHOP

GOYA: OS Refractory vs Not



GOYA: OS POD12 vs Not



Canales-Ruiz. Clin Lymph Myeloma Leukemia. 2022;8:e804.

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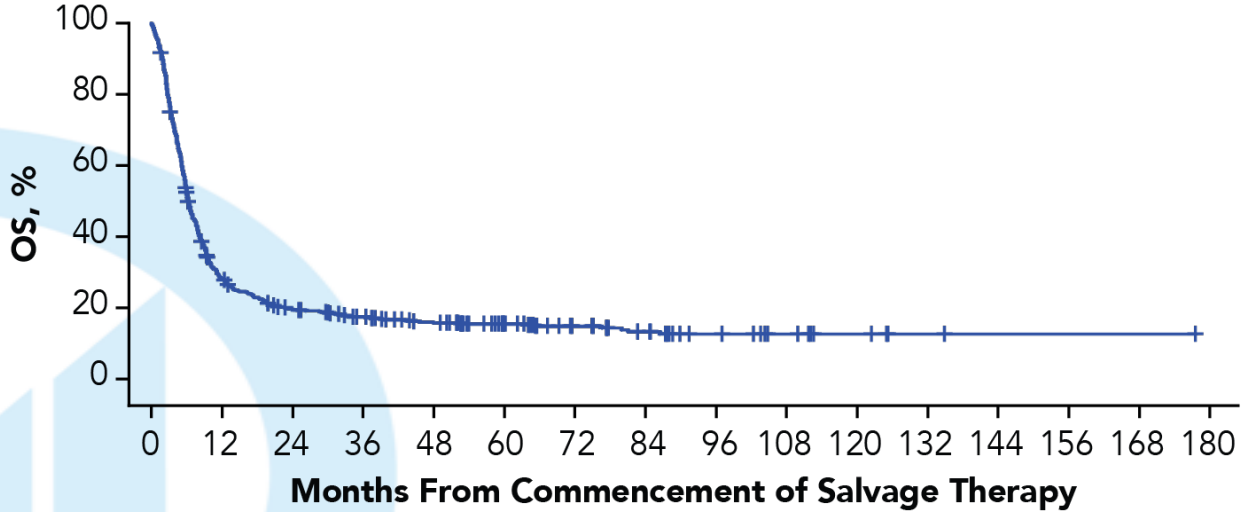
Refractory Diffuse Large B cell Lymphoma carries a poor prognosis

- SCHOLAR-1 patient level meta-analysis of refractory Aggressive NHL
  - ORR of 26% (CR of 7%, PR of 19%)
  - Median OS of 6.6 months



Crump M, et Al. Blood 2017

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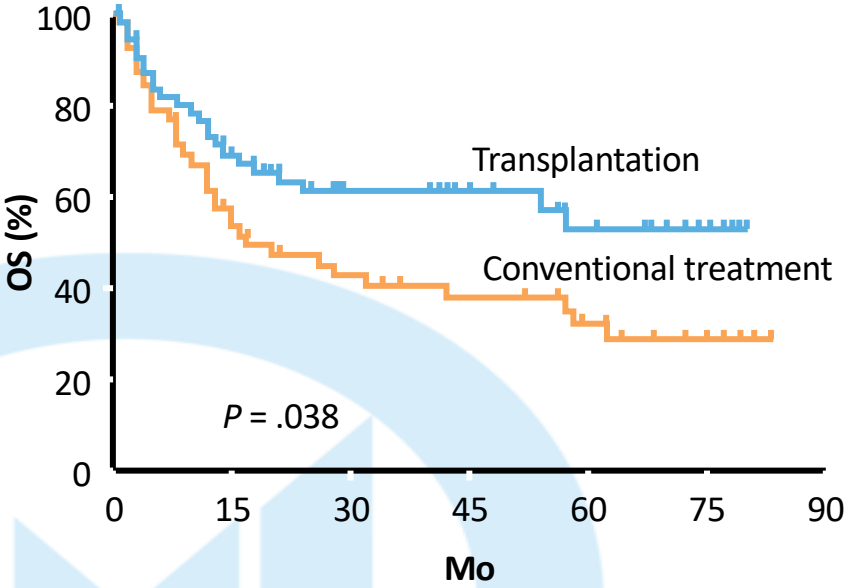
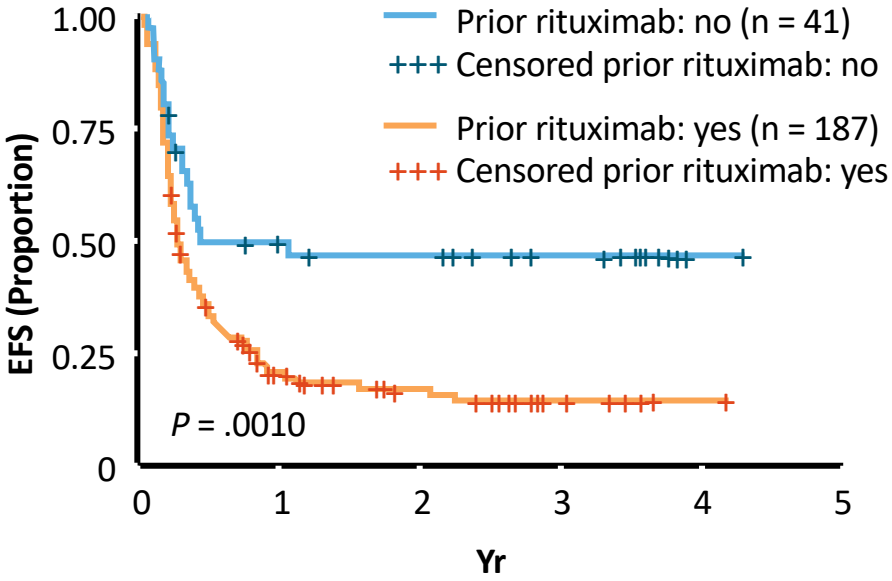
High-Dose Chemotherapy + ASCT in Relapsed NHL

Pre-Rituximab Era[1]



CORAL Trial[2]



1. Philip. NEJM. 1995;333:1540. 2. Gisselbrecht. JCO. 2010;28:4184.

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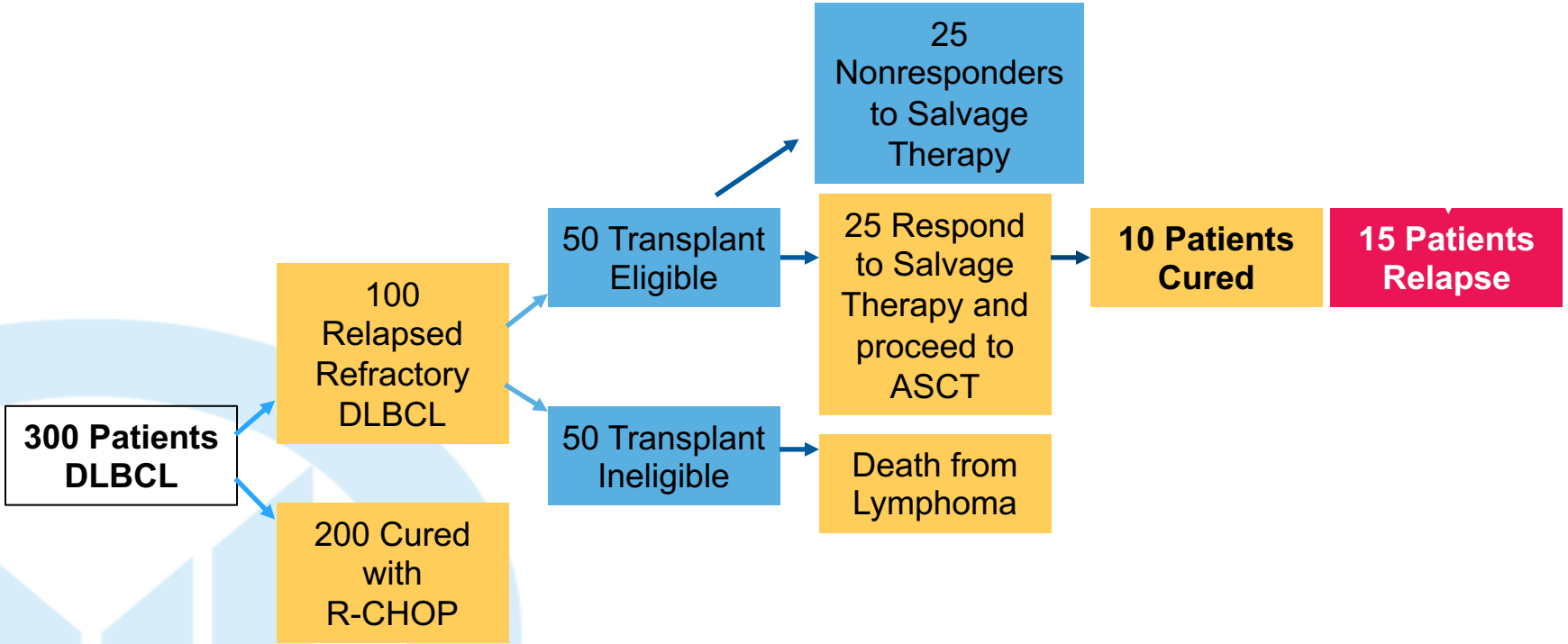
Outcomes of patients with Advanced DLBCL- Historical Outcomes



ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma.
Flow chart adapted from Friedberg. *Hematology Am Soc Hematol Educ Program* 2011;2011:498-505.

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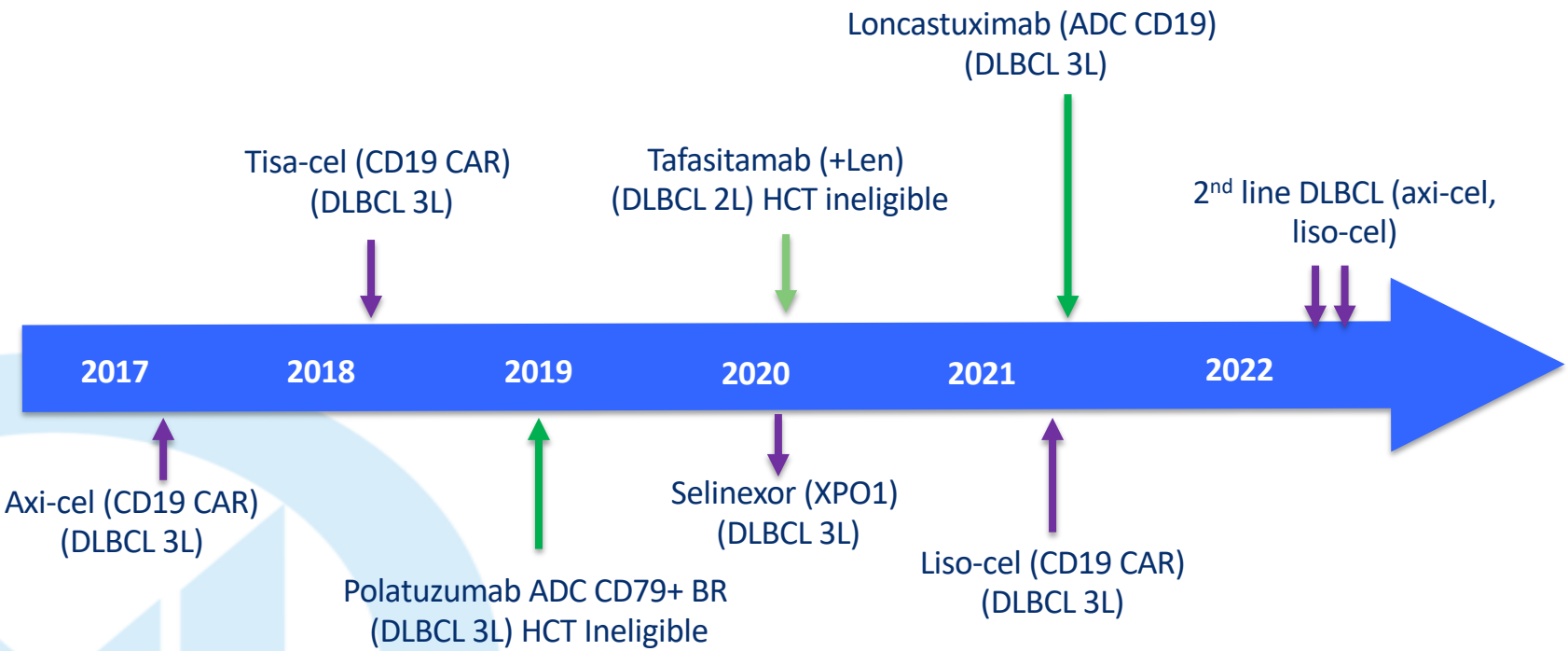
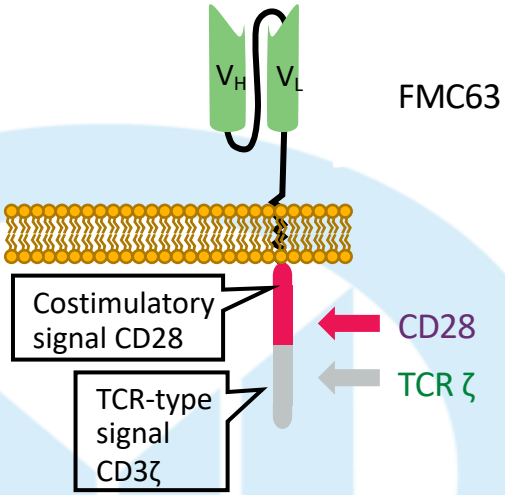
US FDA approvals of R/R DLBCL



CD19-Directed CAR T-Cell Products

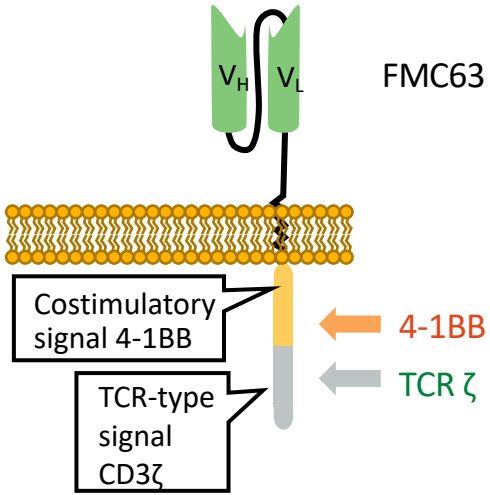
Axicabtagene Ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



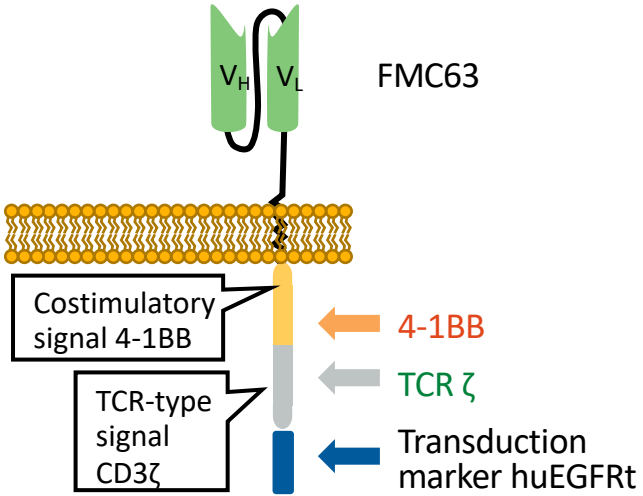
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene Maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



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

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Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL

ZUMA-1
Axicabtagene Ciloleucel

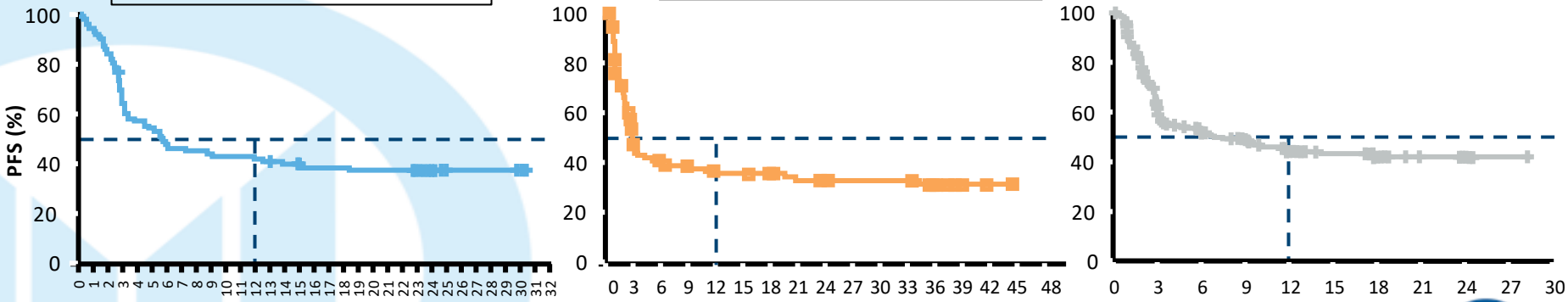
Median F/U 27.8 months
Median age: 58 (23 – 76)
Enrolled (treated): 111 (101)
Best ORR: 83%
Best CR: 54%
Ongoing CR: 39%

JULIET
Tisagenlecleucel

Median F/U 14 months
Median age: 56 (22 – 76)
Enrolled (treated): 165 (111)
Best ORR: 52%
Best CR: 40 %
Ongoing CR: 37%

TRANSCEND NHL 001
Lisocabtagene Maraleucel

Median F/U 12.3 months
Median age: 63 (18 – 86)
Enrolled (treated): 244 (269)
Best ORR: 73%
Best CR: 53 %
Ongoing CR: 45%



Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

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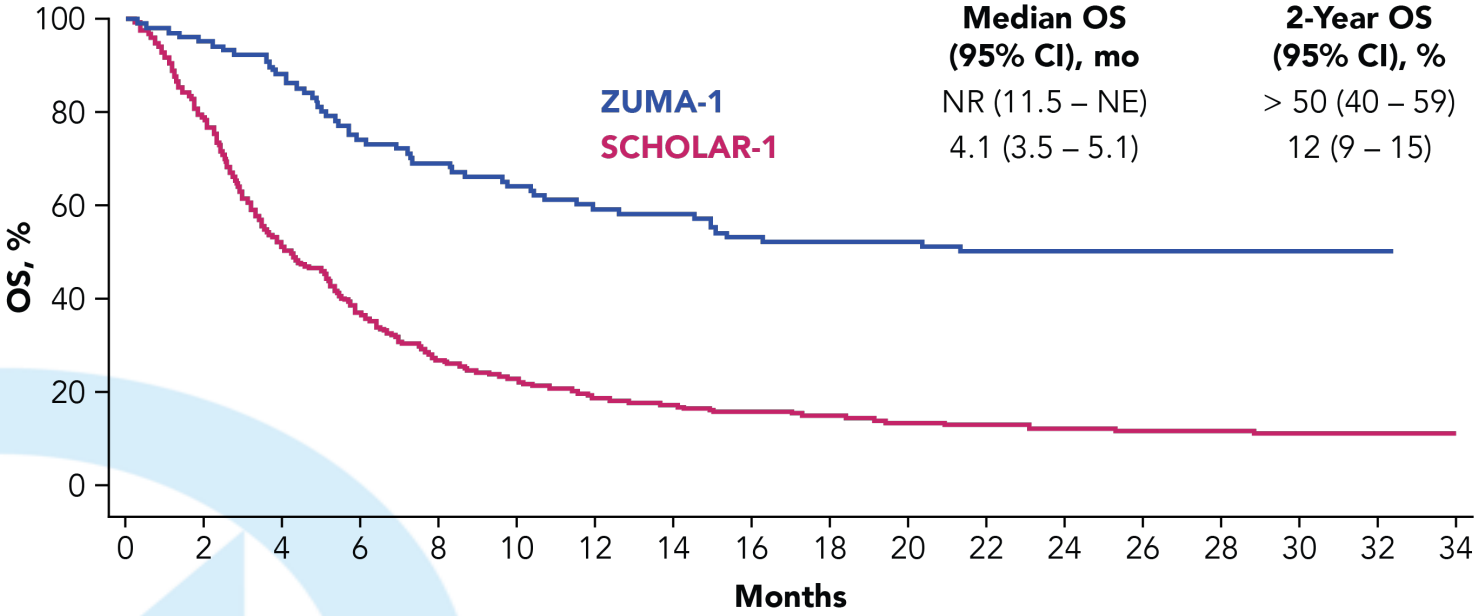
Simulation-Based Standardized OS Curves for ZUMA-1 and SCHOLAR-1



A stratified Cox proportional hazards model indicated a 73% reduction in the risk of death in ZUMA-1 relative to SCHOLAR-1 (hazard ratio, 0.27, 95%CI 0.2-0.38; $P < .0001$)

Neelapu, Locke, et al, ASH 2019

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Will CD19 CAR T-cell Therapy Replace Auto-transplant?

ZUMA-7
Axicabtagene ciloleucel

Locke et al ASH Meeting 2021
Abstract 2

Met endpoint

BELINDA
Tisagenlecleucel

High-risk DLBCL/B-cell lymphomas:
- Refractory to first-line tx
- Relapsed after first-line tx

CAR T-cell therapy

TRANSFORM
Lisocabtagene maraleucel

Mandar et al ASH Meeting 2021
Abstract 91

Met endpoint

Salvage therapy/ auto-transplant

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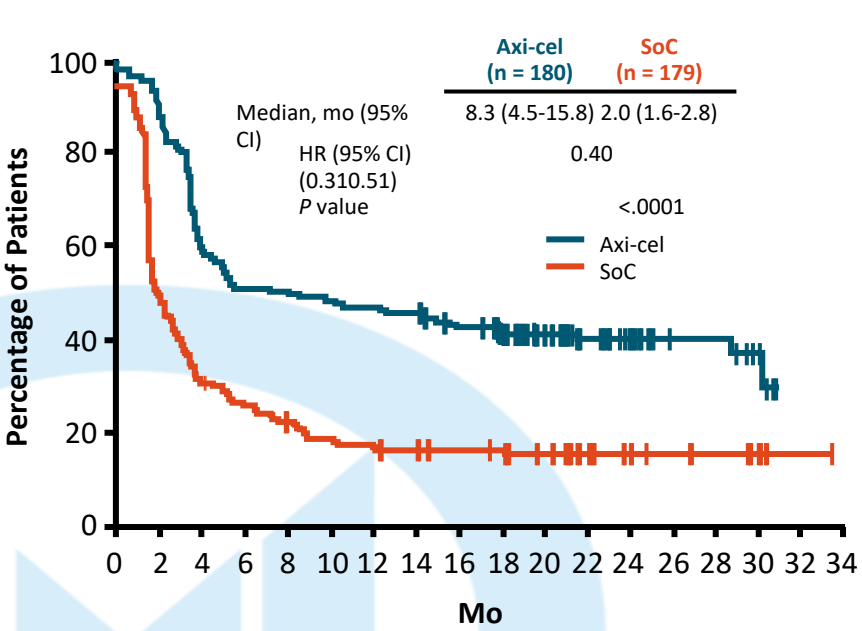
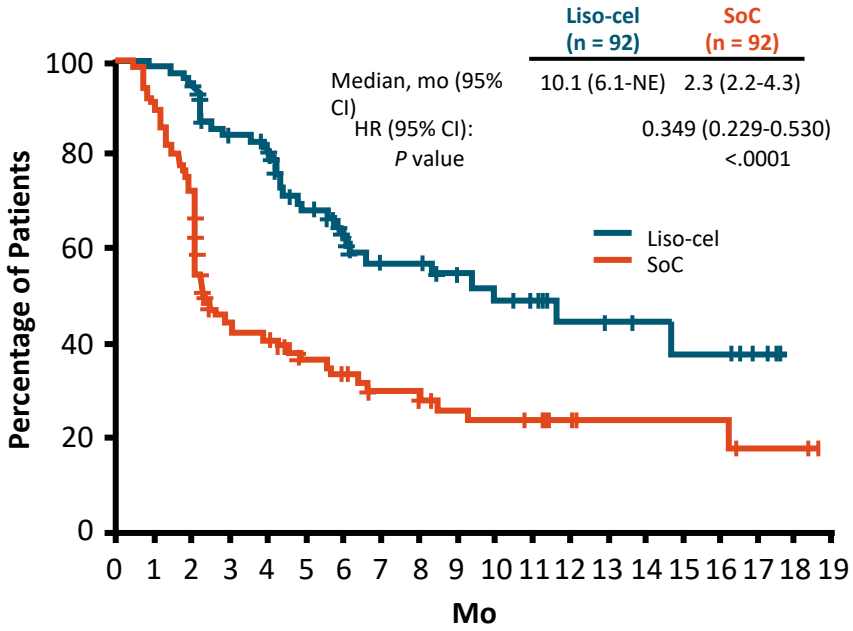
CAR T-Cell Therapy: A New SoC in Early Relapsed DLBCL

ZUMA-7: Median EFS[1]



TRANSFORM: Median EFS[2]



1. Locke. NEJM. 2022;386:640. 2. Kamdar.. Lancet. 2022;399:10343.

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Phase 3 DLBCL trials (CART vs SOC)

CART arm	ZUMA-7	TRANSFORM	BELINDA
Construct	CD19-CD28-CD3z	CD19-41BB-CD3z	CD19-41BB-CD3z
Vector	Retrovirus	Lentivirus	Lentivirus
Dose	2 x 10^6/kg	0.6 – 6.0 x 10^8	1.0 x10^8
Bridging chemoTX	Not allowed (only steroids)	63% (SOC CIT)	83% (SOC CIT)
Conditioning regimen	Flu 30 mg/m^2 x3d Cy 500 mg/m^2 x3d	Flu 25/m^{2}x 3d Cy 250 mg/m^2 x3d	Flu 30 mg/m^2 x3d Cy 300 mg/m^2 x3d
ORR/CR	**83%/65%**	**86%/66%**	**46/28%**
EFS median	8.3 months	10.1 months	3.1 months
G3+ CRS	6%	1%	5%
G3+ ICANS	21%	4%	3%
SOC arm	2L CIT (ICE, GDP, DHAP)	2L CIT (ICE, GDP, DHAP)	2L CIT (ICE, GDP, DHAP)
ASCT	36%	46%	33%
ORR/CR	50%/32%	48%/39%	43%/28%
EFS median	2 months	2.3 months	3.1 months
Crossover CART	56%	55%	51%

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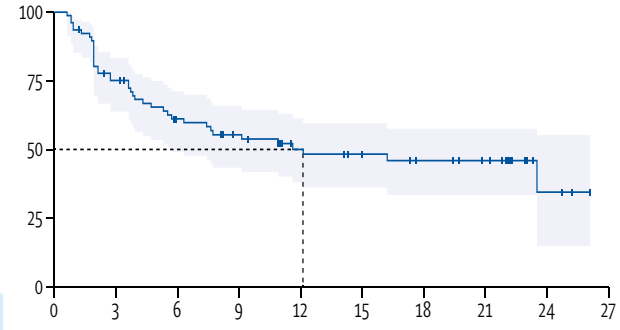
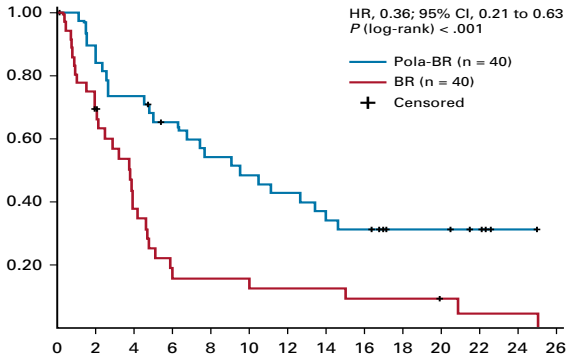
Current non-CART approved therapies for R/R DLBCL

Lenalidomide + Tafasitamab



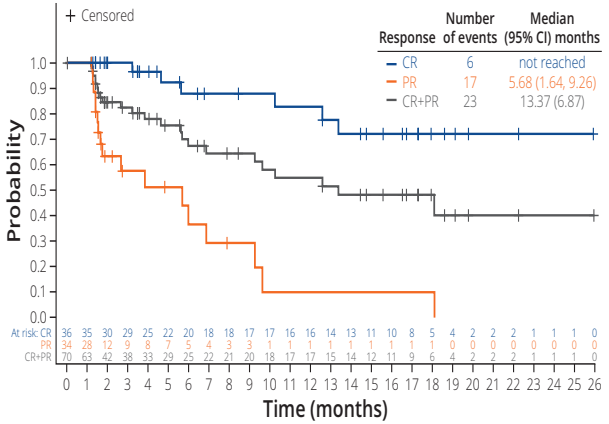
Median follow up: 17.3 months
ORR/CR: 59%/41%
Median PFS: 12.1 months
Median lines: 1
Post CAR-T: No

Polatuzumab + BR



Median follow up: 22.3 months
ORR/CR: 45%/40%
Median PFS: 9.5 months
Median lines: 2
Post CAR-T: No

Loncastuximab



Median follow up: 13.4 months
ORR/CR: 48%/24%
Median PFS: 4.9 months
Median lines: 3
Post CAR-T: yes

Gilles et al *Lancet* 2020, Sehn et al *J Clin Oncol* 2019, Caimi et al *Lancet Oncol* 2021

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Summary of novel approaches for DLBCL

	Selinexor	Polatuzumab + BR	Tafasitamab + Lenalidomide	Loncastuximab
	(N=134)	(N=40)	(N=81)	(n=145)
Median Age, years (range)	67 (35, 91)	67 (33, 86)	**72 (62, 76)**	66 (56, 71)
Study Phase	II	II	II	II
Prior regimens, median (range)	**2 (1 - 5)**	**2 (1 - 7)**	**2 (1-4)**	**3 (2 – 4)**
1, n (%)	0	11 (28)	40 (50)	0
2, n (%)	84 (63)	11 (28)	35 (43)	63 (43)
≥3, n (%)	46 (34)	18 (45)	6 (7)	82 (56)
Type of DLBCL				
De novo DLBCL, n (%)	101 (75)	38 (95)	74 (91)	127 (88)
Transformed DLBCL, n (%)	31 (23)	0	7 (9)	NR
Double hit lymphoma (%)	2 (2)	2 (5)	NR	20 (14)
Prior CART therapy	0	0	0	13 (9)
Responses				
Best ORR (%)	29	45	60*	48.3
Complete Response (%)	13	40	43	24.3
Partial Response (%)	16	5	18	24
Duration of Response (median, months)	9.3	12.6	21.7	10.3
DOR >6 months (%)	38	64	93	
Median PFS, months	2.6	12.4	Not reached	4.9

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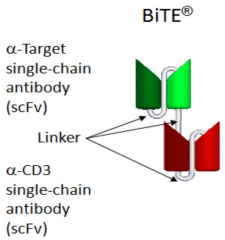
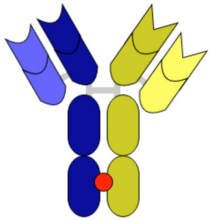
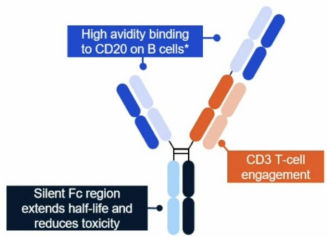
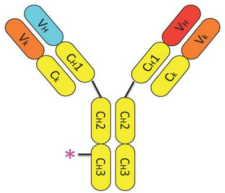
Bispecific Antibodies in Non-Hodgkin Lymphomas

The Original: Proof of Concept	The Emerging: Viable Future Therapies?			
Blinatumomab[1]	**Epcoritamab[2]**	**Mosunetuzumab[3]**	**Glofitamab[4]**	**Odronextamab[5]**
				
CD3 (scFV) x CD19 (scFV)	DuoBody- CD3 x CD20 BsAb	CD3 x CD20 Knobs-in-hole Fc BsAb	CD3 (Fab) x CD20 (Fab x2) Fc BsAb	CD3 x CD20 Common LC Fc BsAb

- Numerous bispecific antibody structures exist
- Properties of the BsAbs vary by construct
- Distinguishing features of BsAbs include:
  - **Off-the-shelf** – rapid access, relative ease of delivery[6,7]
  - **Adaptable** – lack of persistence and ability to modulate dosing may improve tolerability[6]

1. Queudeville M, et al. *Onco Targets Ther*. 2017;10:3567-3578. 2. Clausen MR, et al. *J Clin Oncol*. 2021;39(suppl 15):7518. 3. Budde LE, et al. *Blood*. 2018;132(suppl 1):399. 4. Hutchings M, et al. *Blood*. 2020;136(suppl 1):45-46. 5. Bannerji R, et al. Blood. 2020;136(Suppl_1):42-43. Presented at: ASH 2020. Abstract 400. 6. Husain B, et al. *BioDrugs*. 2018;32(5):441-464. 7. Schuster S. SurvivorNet. Bispecific antibodies: an off-the-shelf approach to treating lymphoma. Accessed June 23, 2022. https://www.survivornet.com/articles/bispecific-antibodies-an-off-the-shelf-approach-to-treating-lymphoma/

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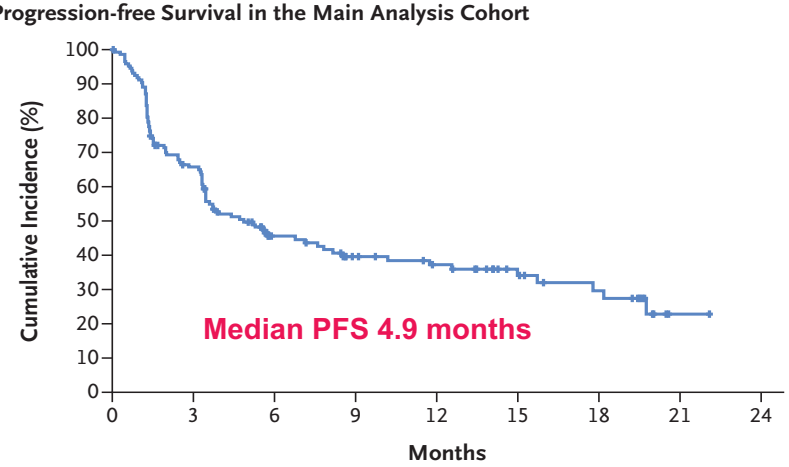
Glofitamab for RR Large B-cell Lymphoma (3L): Phase 2 Pivotal Results

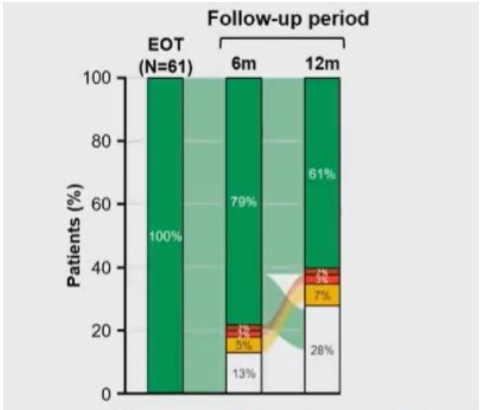
Baseline Characteristics

N= 155 pts
Time limited therapy (12 cycles IV with pretreatment obinutuzumab)
Median lines: 3 (2-7)
Primary refractory: 58%
Prior CAR-T: 38%
Prior auto HCT: 18%

Results

Median f/u: 12.6 months
ORR= 52%
CR= 39%
PFS in CR pts at EOT: Not reached
Median PFS= 4.9 months
CRS all (G≥3)= 63% (4%) Mainly during C1





Dickinson M et Al. *N Eng J Med* 2022.

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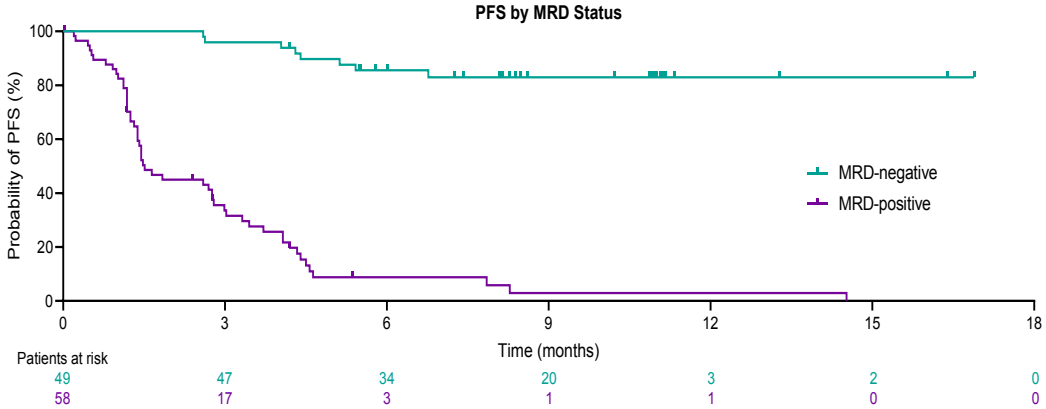
Key trial: Epcoritamab for R/R DLBCL: Phase 2 pivotal study EPCORE

Baseline Characteristics

N= 157 pts
Unlimited treatment (SC)
Median lines: 3 (2-11)
Primary refractory: 61%
Prior CAR-T: 39%
Prior auto HCT: 20%

Results

Median f/u: 10.7 months
ORR= 63%
CR= 39%
PFS in CR pts at EOT: Not reached
Median PFS= 4.4 months. Not reached in MRD-
CRS all (G≥3)= 49.7% (2.5%) Mainly during C1



MRD Results per ctDNA Assay	All LBCL n=107
MRD-negative rate, n (%)	49 (45.8) [95% CI: 36.1–55.7]

Thieblemont at Al. EHA Congress 2022

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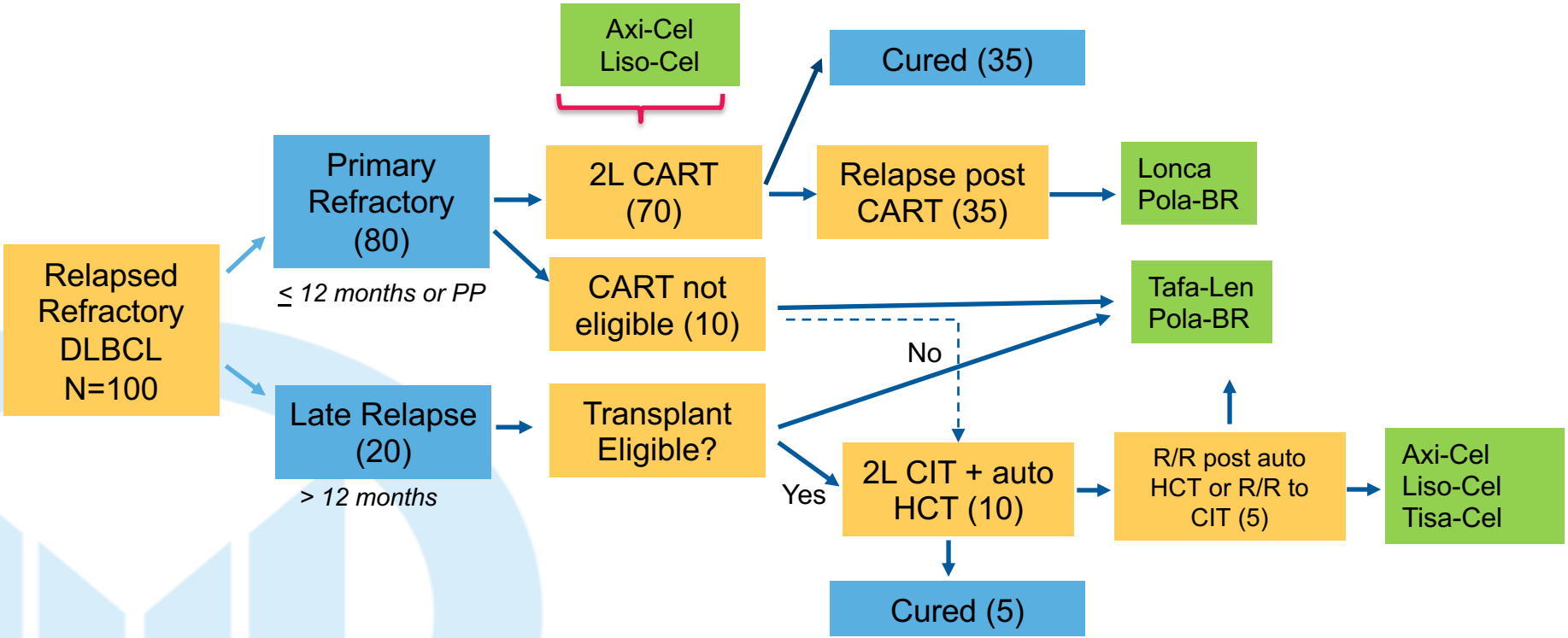
DLBCL: Changing the treatment paradigm

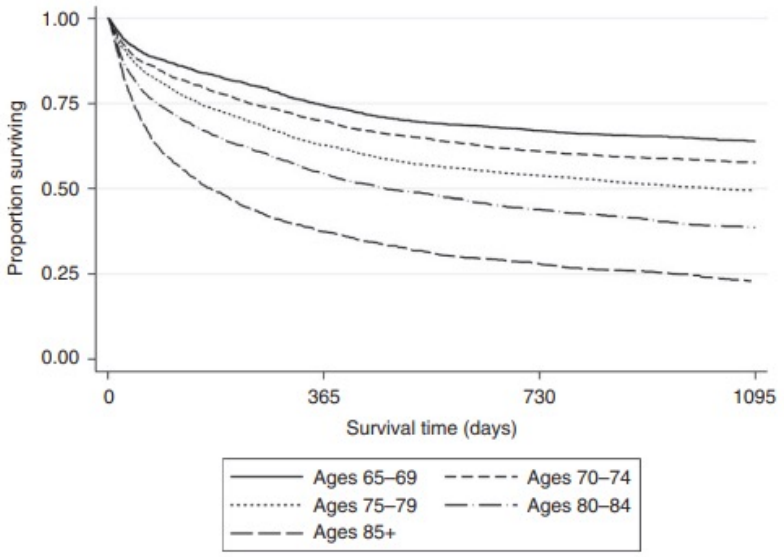


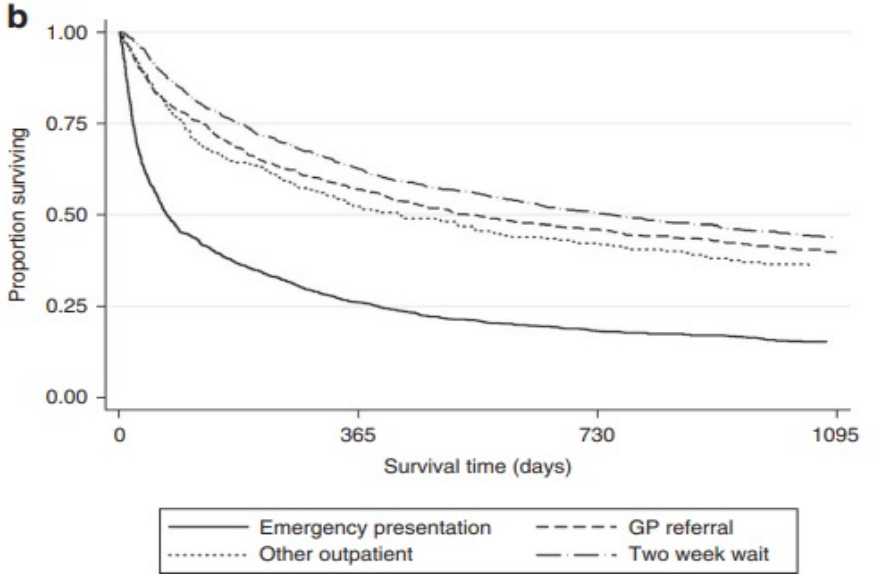
CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma, HCT: hematopoietic cell transplantation, CIT: chemoimmunotherapy),

Unfit or very elderly patients

- No precise definition of frailty:
  - Age older than 75?,80?, 85?
  - Based on geriatric assessments: dependence in ADL, decreased physical activity, exhaustion
- Focus on symptoms control or quality of life: Palliative care team involved
- Few studies available
- Single agent chemotherapy: chlorambucil, etoposide, bendamustine?

Outcomes: Impact of age and site of presentation





Hounsome L et Al. *Br Jr Cancer* 2021

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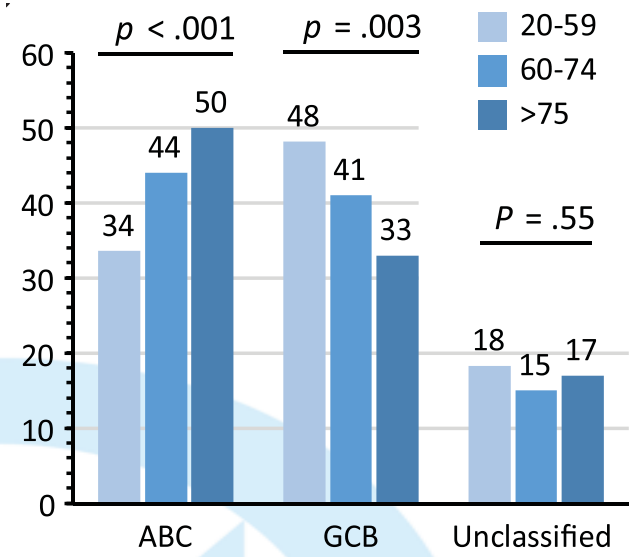
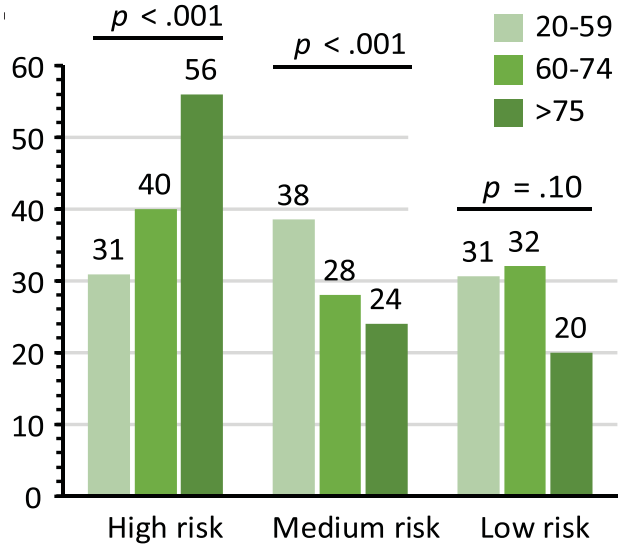
DLBCL in the Elderly: Epidemiology and age comparison





Mengyang et Al. Oncologist 2020. SEER Databse

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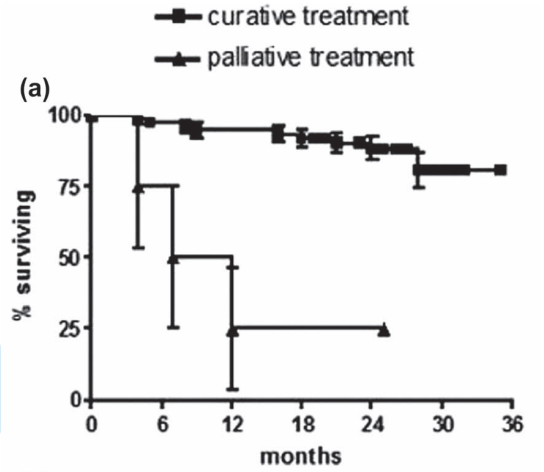
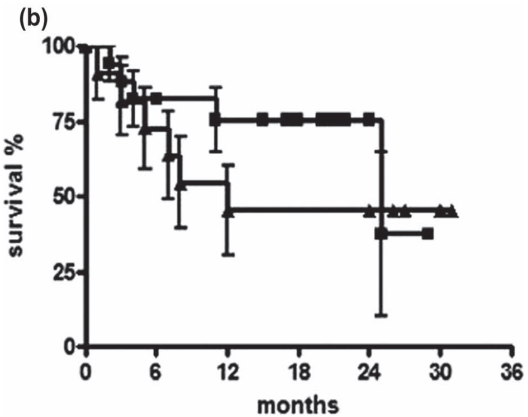
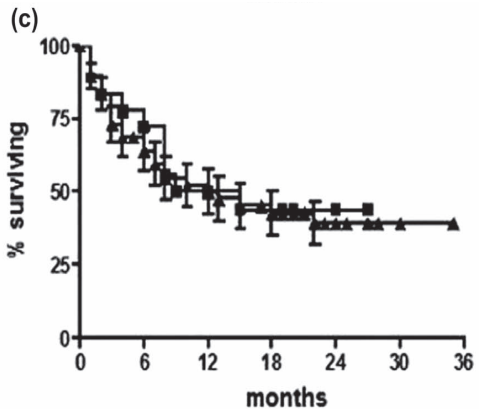
Survival of DLBCL patients per GCA categories



Fit



Unfit



Frail

- Within the single CGA categories, the 2-year OS of patients treated with curative or palliative intent was 88% vs. 25% (p= 0.0001) in fit, 75% vs. 45% (p= 0.32) in unfit and 44% vs. 39% (p = 0.75) in frail patients, respectively
- Multivariate analysis showed only **IPI [HR: 4.60 (1.35–15.64); p= 0.008**] and **CGA [HR: 3.69 (1.09–12.51); p= 0.03]** had strong association with OS

Tucci et al, Leu*kemia & Lymphoma* 2015

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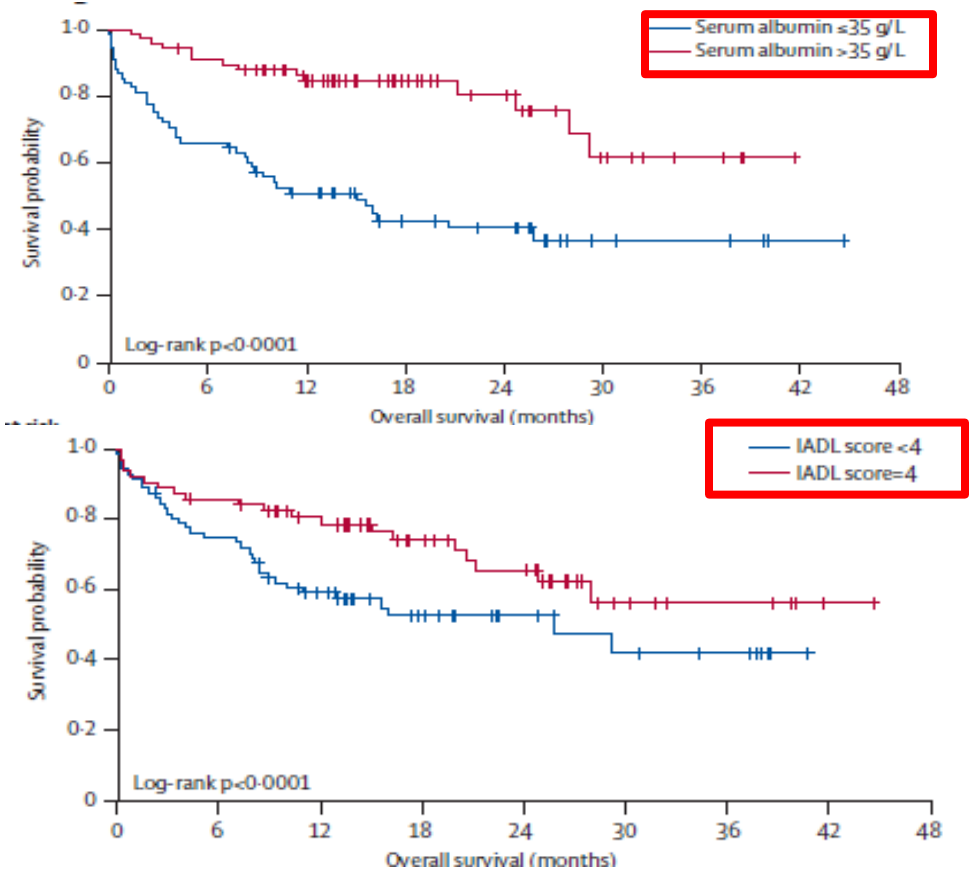
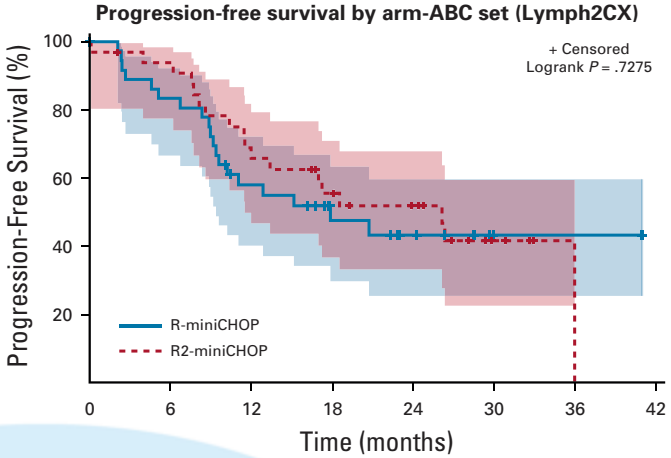
R-miniCHOP in patients older than 80 with DLBCL: Phase II trial (GELA)

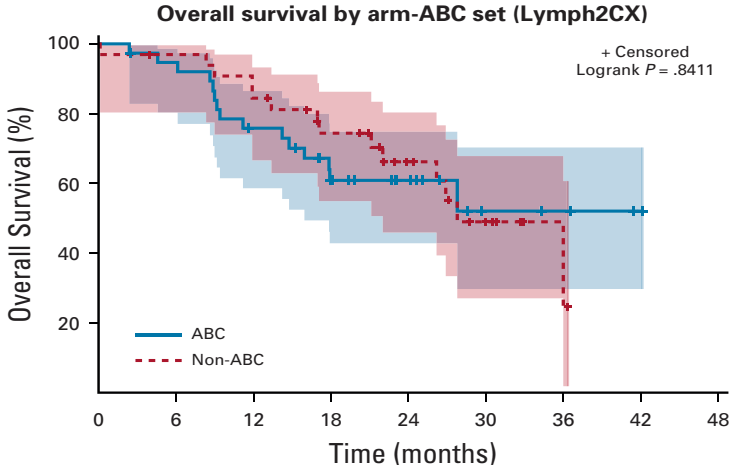
- N=149 (age: 80-95). Multicenter study
- MiniCHOP
  - Rituximab 375mg/m2 d1
  - Doxorubicin 25mg/m2 d1
  - CTX 400mg/m2 d1
  - VCR 1mg d1
  - Prednisone 40mg/m2 d1-5
- Median f/u: 20 months
- Stage III/IV: 75%
- Outcomes:
  - *CR: 63%*
  - *2y OS: 59%*
  - ***2y PFS: 47%***



Peyrade et al. Lancet Oncol 2011;12:460

SENIOR trial: SQ rituximab-mini CHOP +/- lenalidomide in DLBCL > than 80: Outcomes and Prognostic Factors





Variable	HR (95% CI)	*P*
IPI (0-2 *v* 3-5)	0.94 (0.43 to 2.04)	.871
Non-ABC *v* ABC (Lymph2CX)	1.14 (0.68 to 1.92)	.614
IADL scale	0.72 (0.44 to 1.18)	.193
MNA (normal *v* malnourished)	1.16 (0.67 to 2.03)	.596
Ann Arbor stage (II-III *v* IV)	2.01 (0.94 to 4.32)	.073
Lymphocyte count (< 1 *v* ≥1 G/L)	0.80 (0.50 to 1.30)	.373
Albumin (≤35 *v* > 35 g/L)	2.08 (1.25 to 3.57)	**.005**

Oberic L et al *J Clin Oncol* 2021

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Elderly DLBCL: practical points

- Early diagnosis (improves survival)
- GCA better than “physician eye”- Logistics on getting the score
- Fit or unfit: R-CHOP or mini R-CHOP (*Battailard et al Blood Advances 2021*)
  - Dose intensity important up to the age 80
  - > 80 dose intensity less relevant so mini R-CHOP is fine
- For frail pts: NO standard of care. Consider clinical trials

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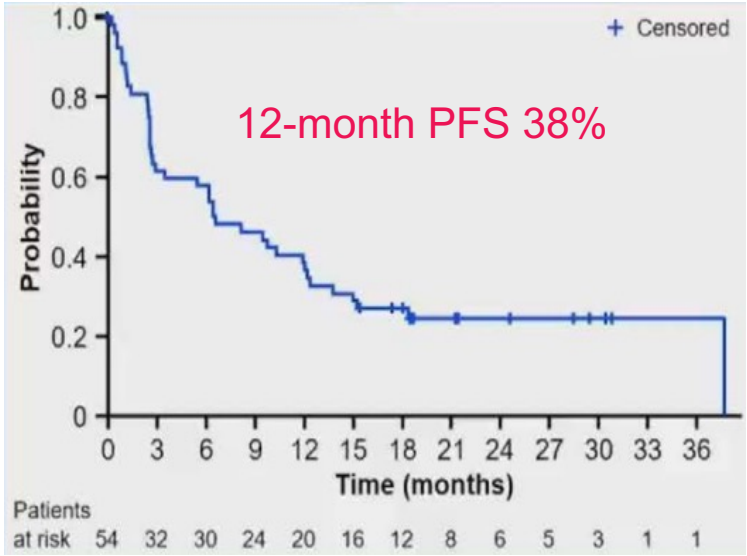
Mosunetuzumab for Untreated Elderly DLBCL ineligible for anthracycline based CIT

Mosun: CD20/CD3 Bispecific antibody
Untreated DLBCL (n=54
Eligible if:

- Age > 80
- Age 60-79 if : impairment > 1 ADL, instrumental ADL, inability to tolerate full dose CHOP

Best response, n (%) [95% CI]	N=54
ORR	30 (**56**) [41–69]
CR	23 (**43**) [29–57]
Response at EOT, n (%) [95% CI]	**N=54**
ORR	24 (**44**) [31–59]
CR	19 (**35**) [23–49]



CRS grade1-2: 26%, No G≥3 GRS, tocilizumab use 0%

Olszewski et Al. ASH 2022

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Conclusions- Unmet needs

- Post CAR-T relapses
- Logistics of CAR-T
- Bi-Specific antibodies in the community practice?
- Cost

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