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Aggressive Lymphoma Workshop

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Frontline Treatments in DLBCL: Focus on High Risk-Patients

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Disclosures

Disclosures of Julio Chavez

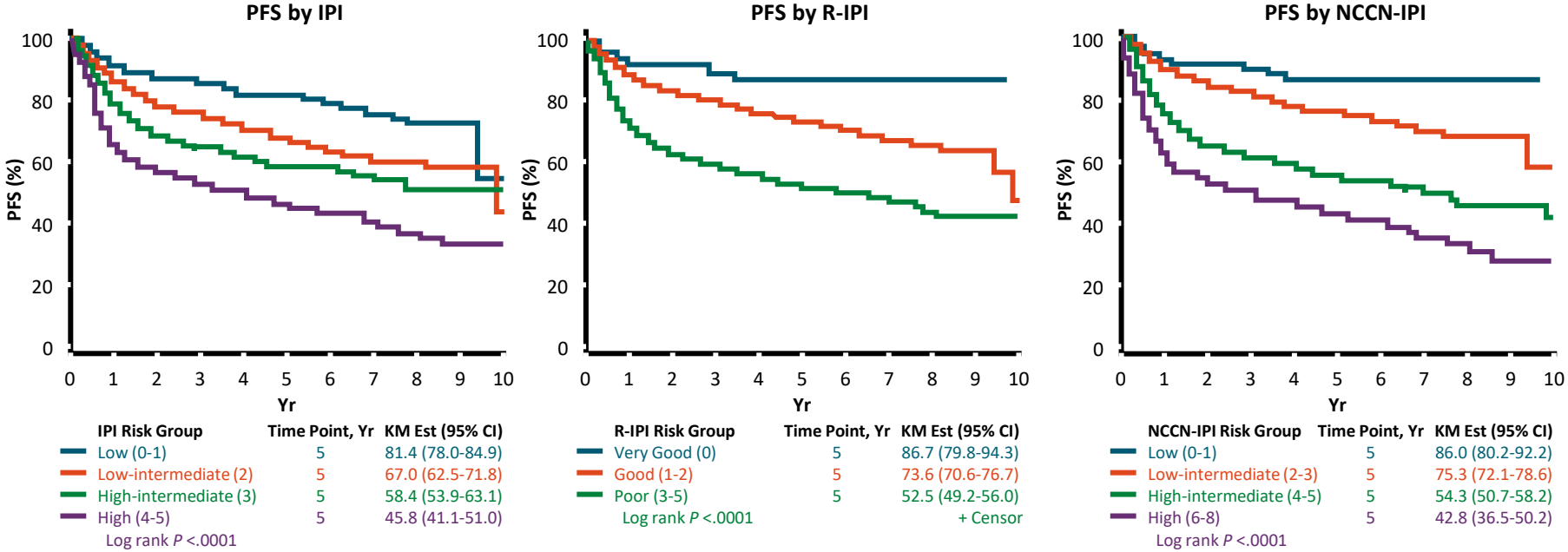
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						X	
Kite/Gilead						X	
BMS						X	
Astrazeneca	X					X	
Janssen	X						
Merck	X						
Cellectar						X	
AdiCet						X	
BeiGene					X	X	
Adaptive	X						
Abbvie						X	

What is High Risk DLBCL?

Sub-group	Freq	R-CHOP		
		CR	PFS	OS
ABC- DLBCL	40-50%	60%	2-yr 28%	2-yr 46%
Double Hit Lymphoma	3-12%	40%	7.7 mo	< 1 yr
Dual expressor Lymphoma (MYC and BCL2)	21%	50-60%	5-yr 27%	5-yr 30%
Elderly DLBCL (> 60 y)	50%	70-80%	5-yr 50%	5-yr 58%
High IPI score (4 – 5)	45%	60-70%	4-yr 53%	4-yr 54%

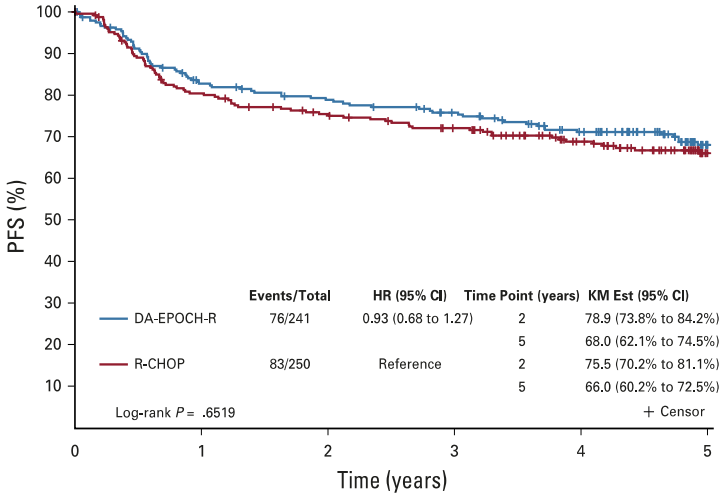
Best stratification? Comparison of Clinical Prognostic Indexes

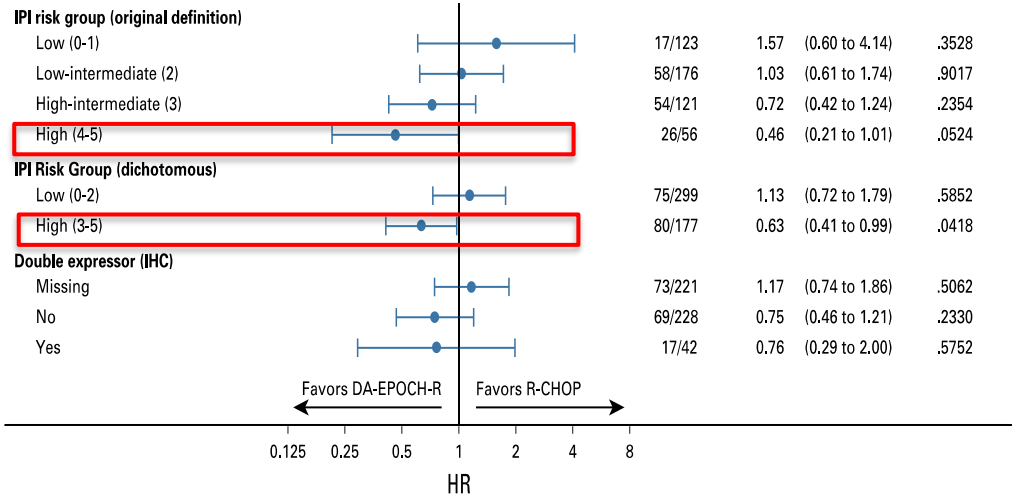
- N = 2124 patients with DLBCL who received R-CHOP from 1998-2009 across 7 multicenter randomized clinical trials
- Compared with the IPI, the NCCN-IPI better discriminated low-risk and high-risk subgroups



Ruppert. Blood. 2020;135:2041.

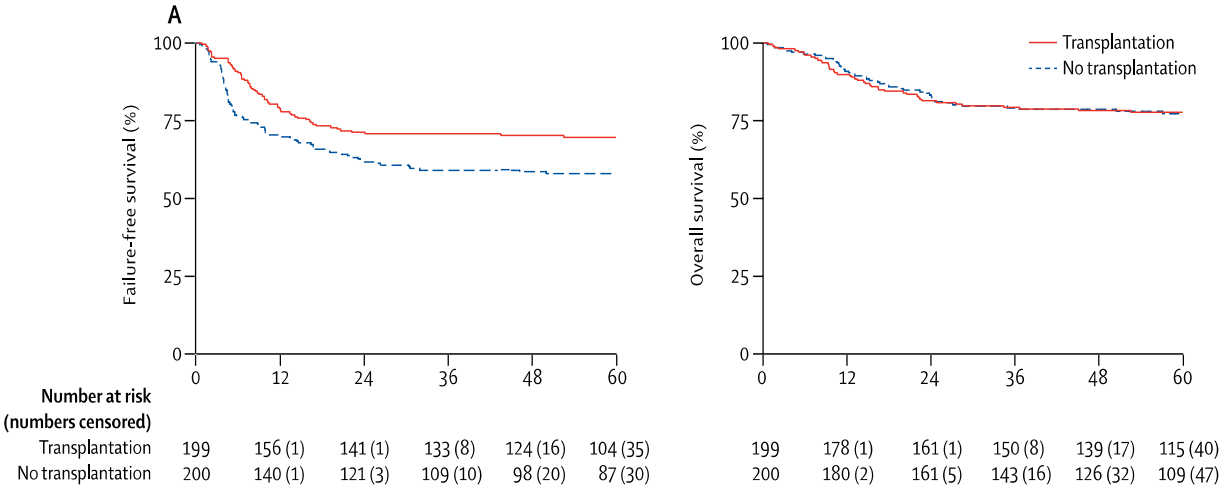
Does Intensification Improve outcomes in IPI 3-5? CALGB 50303: DA-EPOCH-R vs R-CHOP





Bartlett et al. J Clin Oncol 2019

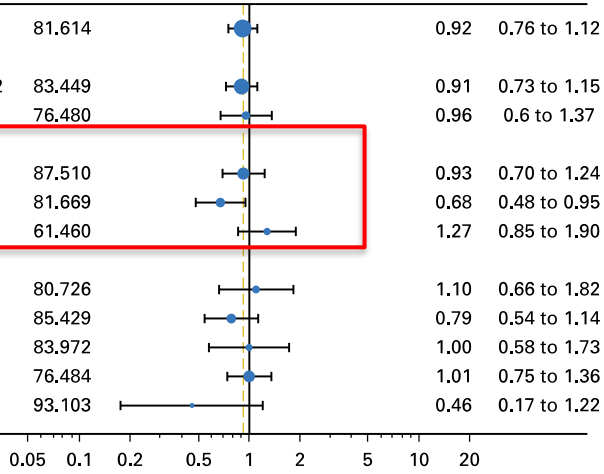
Dose Dense R-CHOP followed by auto HCT: Results of the DLCL04 trial in high risk DLBCL (aa-IPI 2-3)



Chiapella A. et al. *Lancet Oncology* 2017

GOYA: Obinutuzumab + R-CHOP

Stratification Factors	Total No.	R-CHOP (n = 712) No.	R-CHOP Events	R-CHOP 1-Year KM Rate	G-CHOP (n = 706) No.	G-CHOP Events	G-CHOP 1-Year KM Rate	HR	95% Wald CI
All patients	1,418	712	215	79.778	706	201	81.614	0.92	0.76 to 1.12
No. of planned CHOP cycles									
6	1,049	526	152	80.789	523	142	83.449	0.91	0.73 to 1.15
8	369	186	63	76.949	183	59	76.480	0.96	0.6 to 1.37
IPI									
Low-intermediate	785	409	99	84.168	376	86	87.510	0.93	0.70 to 1.24
High-intermediate	413	192	71	75.013	221	62	81.669	0.68	0.48 to 0.95
High	220	111	45	71.577	109	53	61.460	1.27	0.85 to 1.90
Geographic region									
Eastern Europe	196	99	28	77.354	97	32	80.726	1.10	0.66 to 1.82
Western Europe	426	215	61	79.653	211	51	85.429	0.79	0.54 to 1.14
North America	216	107	27	87.556	109	25	83.972	1.00	0.58 to 1.73
Asia	518	258	87	77.830	260	87	76.484	1.01	0.75 to 1.36
Other	62	33	12	77.047	29	6	93.103	0.46	0.17 to 1.22

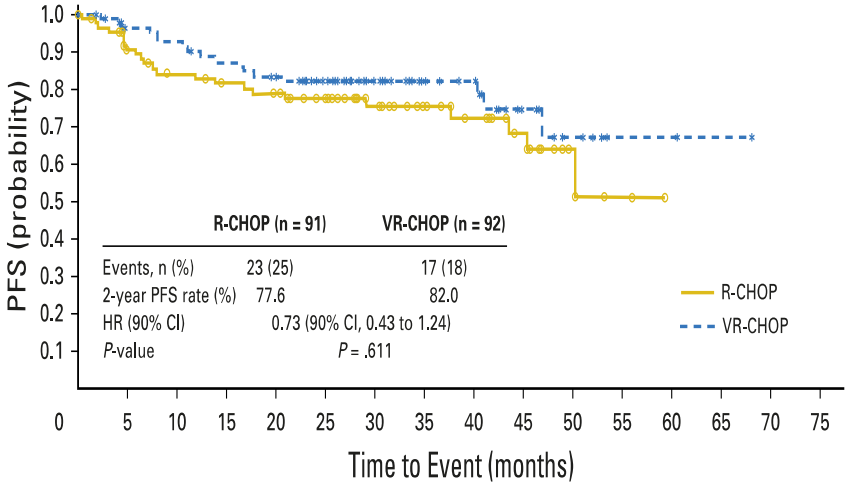


Vitolo U. et al. *J Clin Oncol* 2017

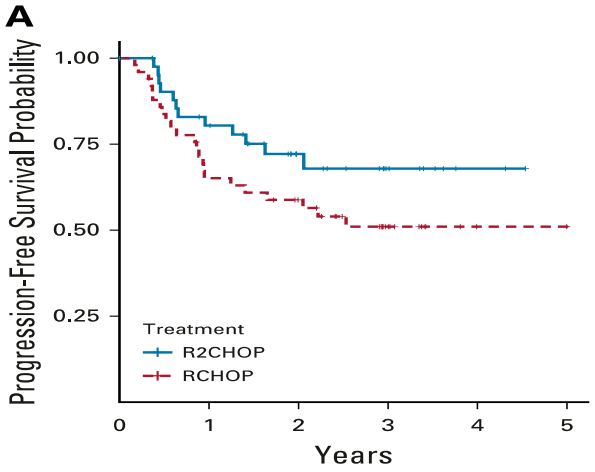
COO: Targeting Activated B-cell DLBCL

- Lenalidomide
- Ibrutinib
- Bortezomib

COO: Targeting Activated B-cell DLBCL: Phase II studies



Bortezomib + R-CHOP

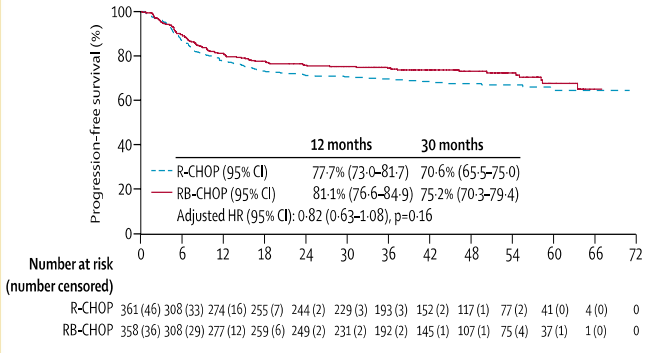


ECOG E1412: Lenalidomide + R-CHOP

Leonard et al. J Clin Oncol 2017, Nowakowski et al 2021

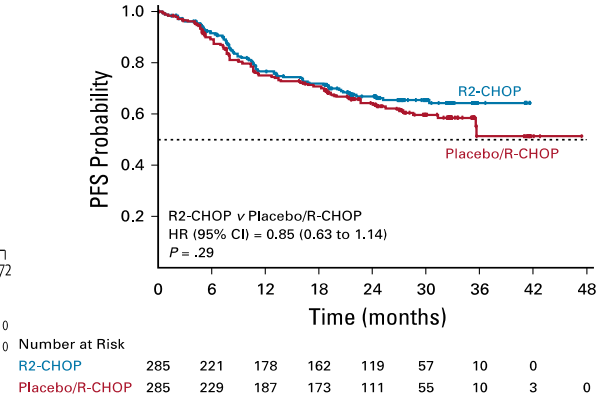
COO: Targeting Activated B-cell DLBCL: Results of Phase III studies

Bortezomib



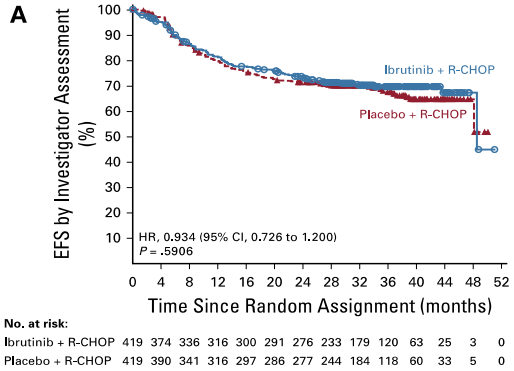
REMoLD-B

Lenalidomide



ROBUST

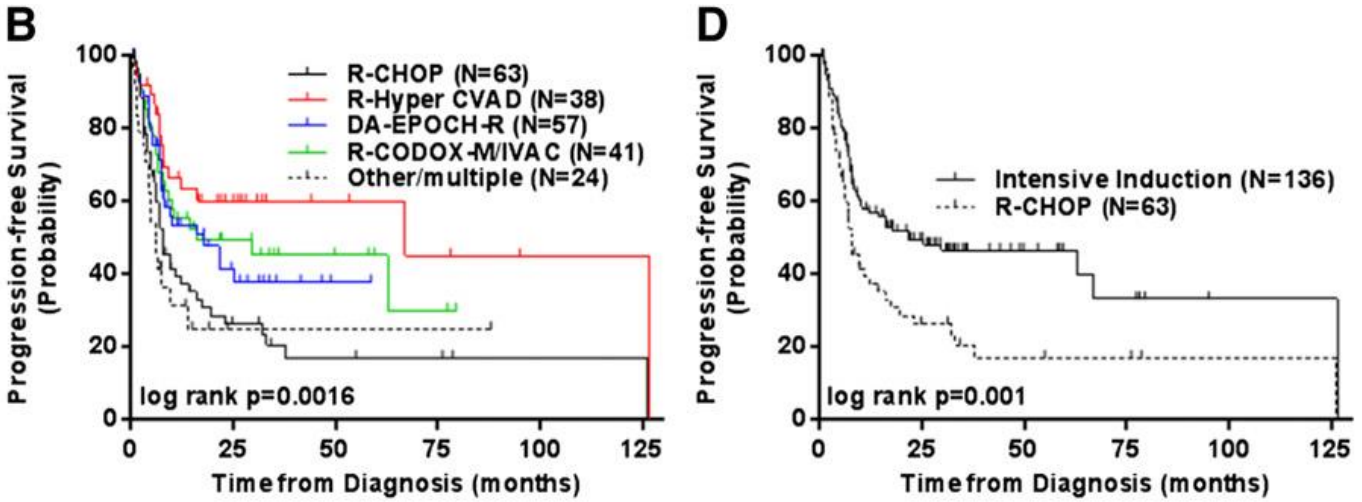
Ibrutinib



PHOENIX

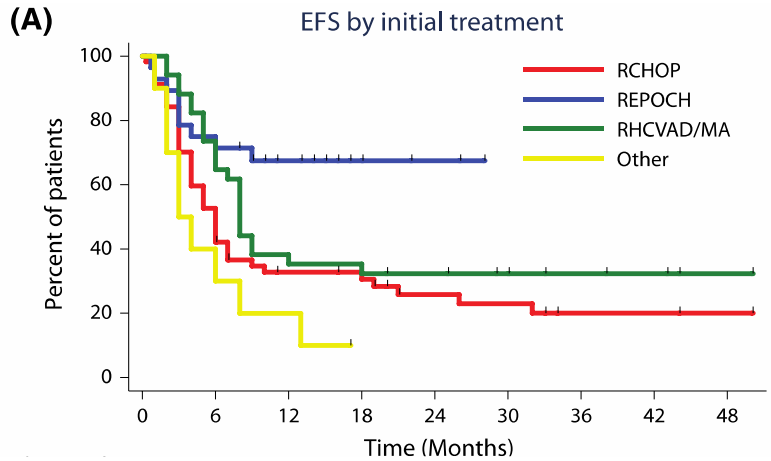
Leonard et al. J Clin Oncol 2017, Nowakowski et al 2021

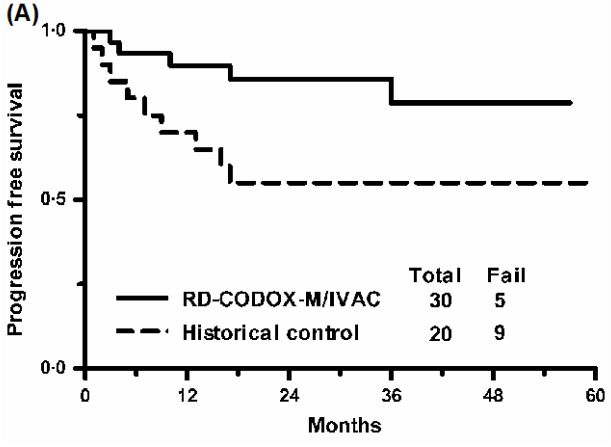
Double Hit Lymphoma: Is intensification better?



Petrich et al. *Blood 2014*

Double Hit Lymphoma: Is intensification better?

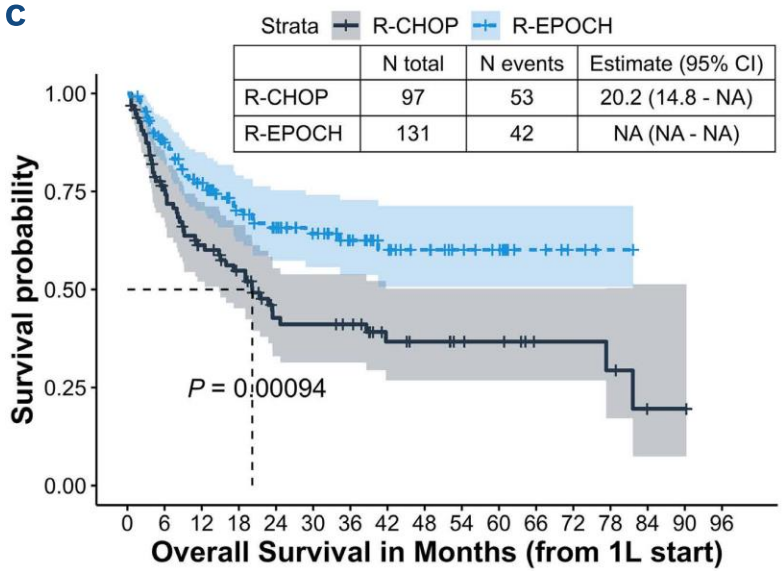


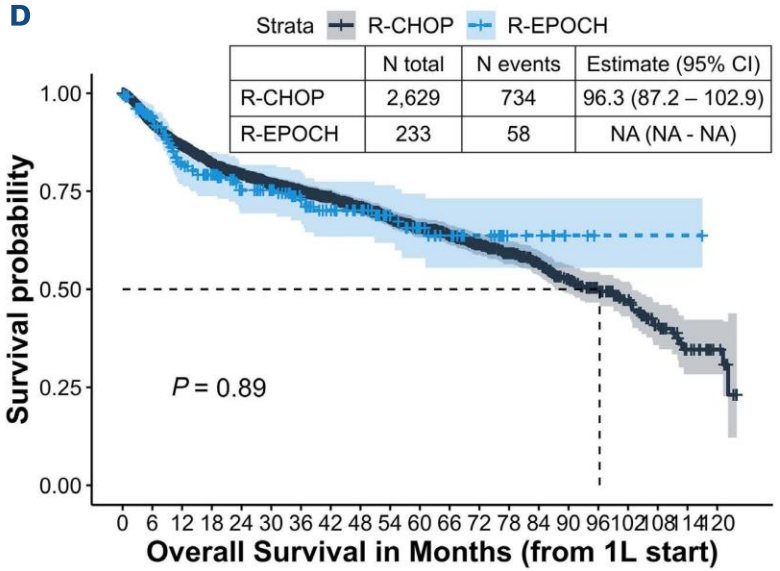


Oki et al *Br J Haematol* 2014, Corazzelli et al. *Br J Haematol* 2011

Overall survival between R-CHOP or R-EPOCH for double hit or triple hit Lymphomas

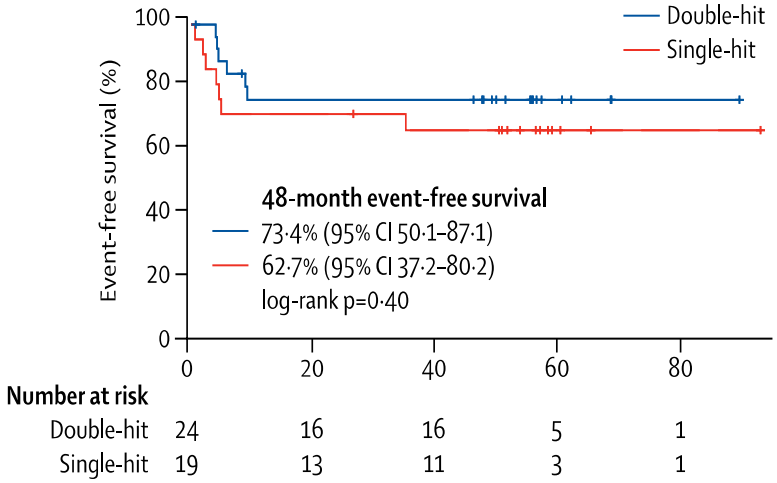
- Retrospective study using Flatiron electronic health record (EHR). About 280 sites



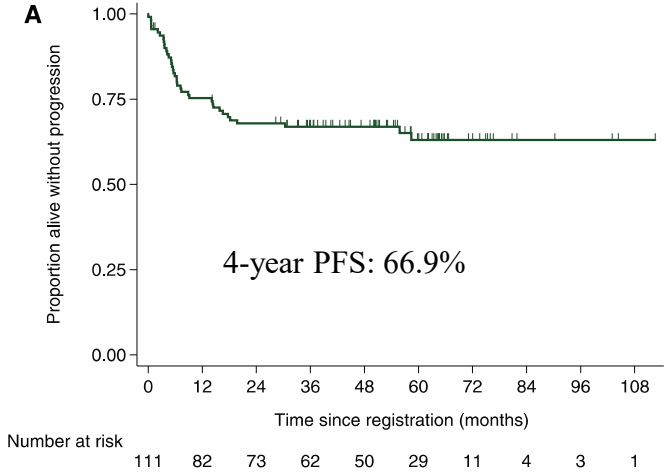


Magnuson et Al. EHA 2021, Goyal et al, Haematologica 2023

Double Hit Lymphoma: Prospective studies



NCI trial DA-EPOCH-R
N= 53 pts, DHL= 24 pts
Treatment related deaths 6%

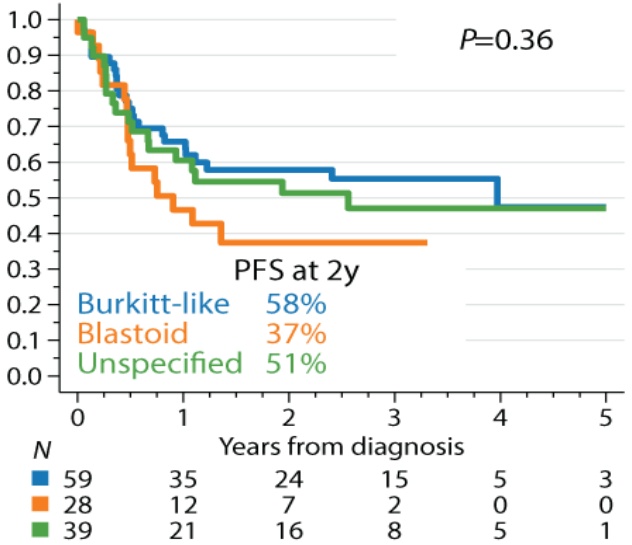


UK NCRI trial: CODOX-R/IVAC
N= 111 pts, DHL= 7 pts, IPI 3-5= 100%
Treatment related deaths 4.3%

Dunleavy et al. *Lancet Haematol 2018;* McMillan et al. *Ann Oncol* 2020

High Grade B-Cell Lymphoma NOS

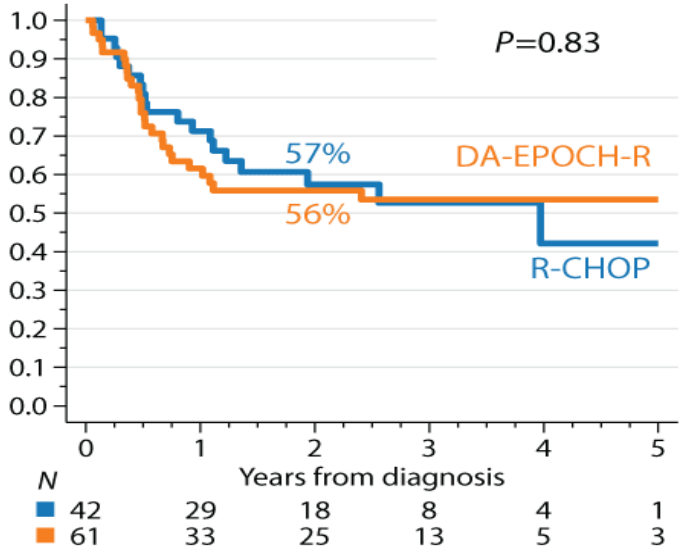
- WHO 4th 2016: HGBCL → Burkitt's like and blastoid type. Recognized by ICC but no by WHO 5th
- Separate entity from double/triple hit lymphomas (HGBCL with *MYC*, *BCL2* and/or *BCL6* rearrangements)
- Important to separate from DLBCL, DLBCL NOS *MYC-R*
- IHC: CD10+ (65%), BCL6+ (91%), BCL2+ (65%)
- Heterogenous mutations: MYC-R (8 – 13%), MYC amplifications (32%), no MYC alterations (60%)



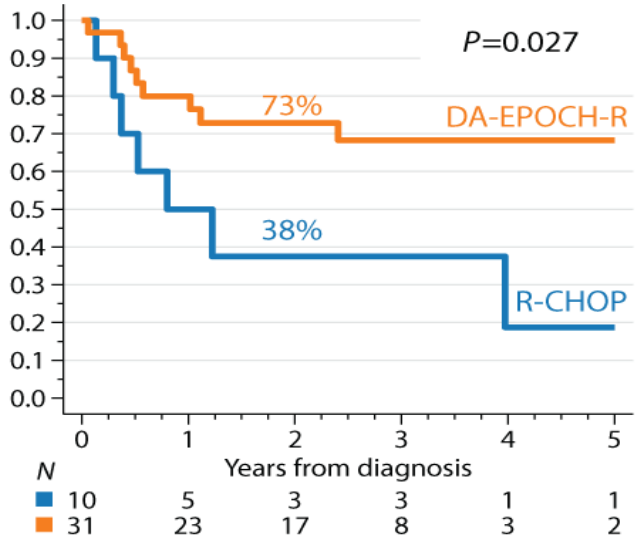
Oki et al. *Pathology* 2020, Li S et al. *Mod Pathol* 2015, Zayac et al ASH 2021Abstract #455

Frontline therapies for HGBCL NOS

All HGBCL Subtypes (blastoid)

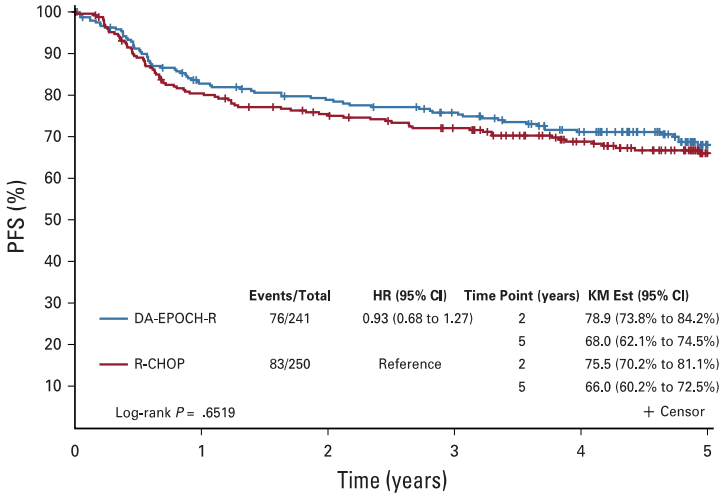


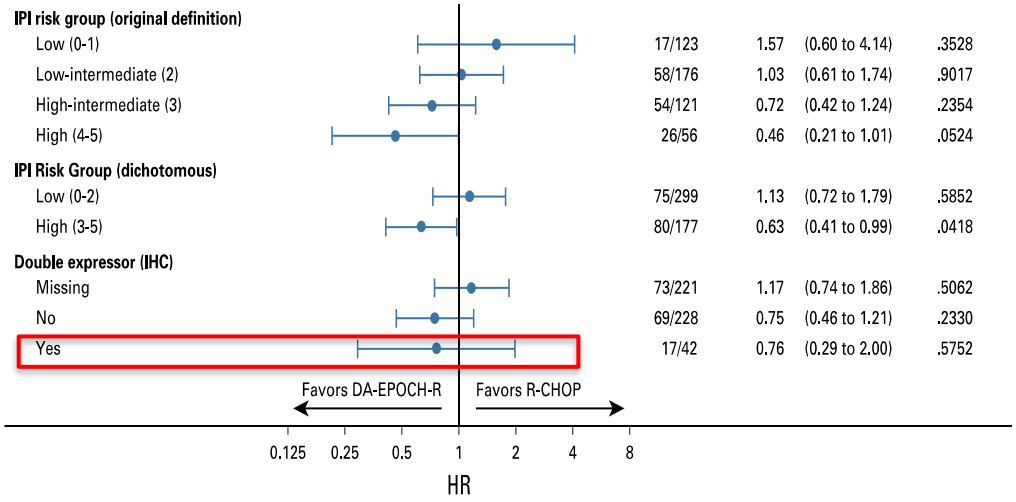
Burkitt-like HGBCL



Zayac A et al. *ASH Meeting Abstracts 2021:523*

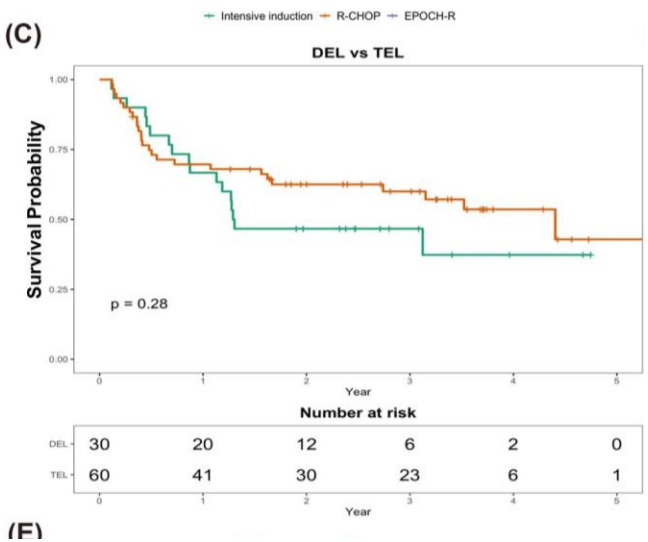
Double Expressor Lymphoma (DEL): Is DA-EPOCH superior?
CALGB 50303: DA-EPOCH vs R-CHOP



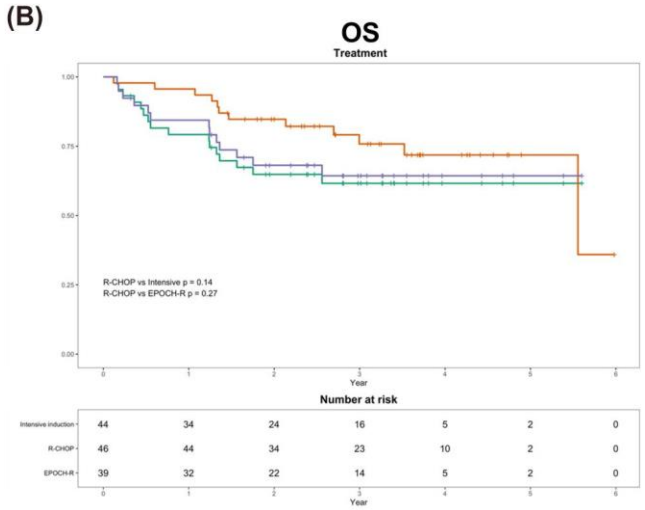


Bartlett et al. J Clin Oncol 2019

Double Expressor Lymphoma (DEL): Is DA-EPOCH superior?



PFS IPI ≥3

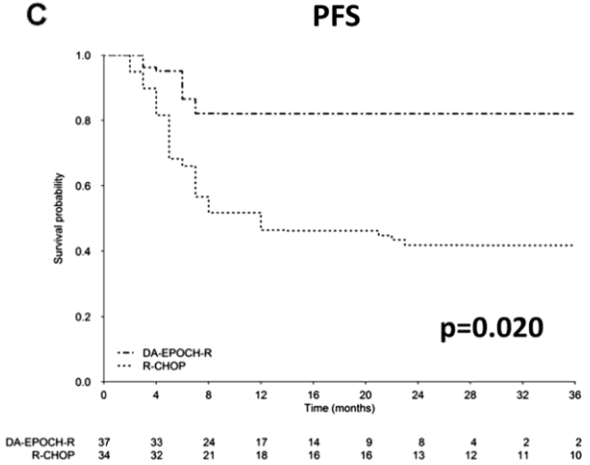


Multicenter Retrospective study (N= 90)
R-CHOP= 46, DA-EPOCH-R= 44

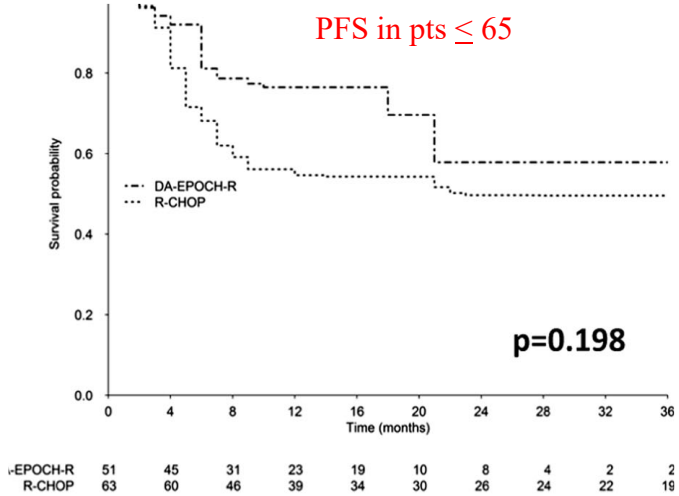
D'Angelo et al. *J Hematol Oncol* 2021

Double Expressor Lymphoma (DEL): Is DA-EPOCH superior?

PFS



PFS in pts ≤ 65

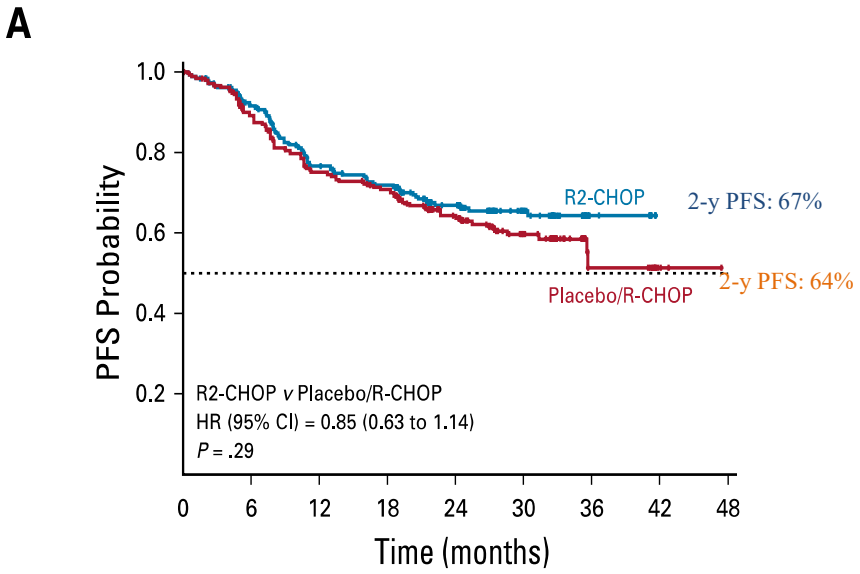


Multicenter Retrospective study (N=114)
R-CHOP= 61, DA-EPOCH-R= 53. Younger than 65= 62%

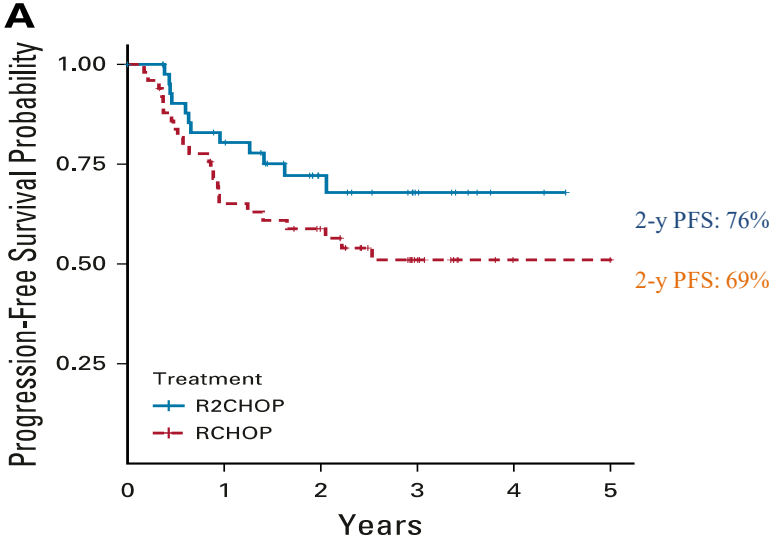
Dodero et al. *Leukemia* 2019 (IRCSS, Milan, Italy)

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

Differences in trial design and administration might have affected outcomes

ROBUST: R2-CHOP vs R-CHOP

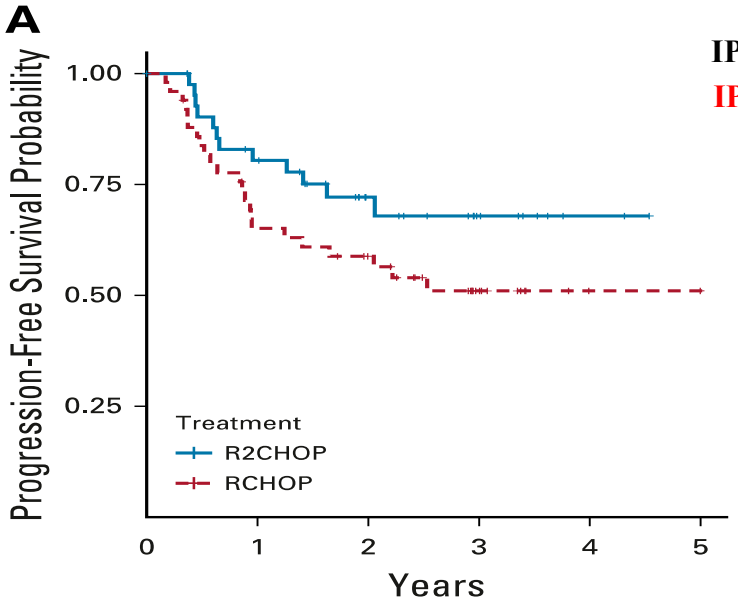
- ✓ Phase III (Only ABC by GEP (NanosTring)
- ✓ N= 570 (R-CHOP: 285, R2-CHOP= 285). Primary endpoint: PFS
- ✓ Median age 65 (21 – 83)
- ✓ IPI 3 – 5: 58%, Stage III/IV: 87%
- ✓ Median time from Dx to treatment: 31 days
- ✓ Lenalidomide dose: 15 mg d1-d14 every three weeks

ECOG E1412: R2-CHOP vs R-CHOP

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

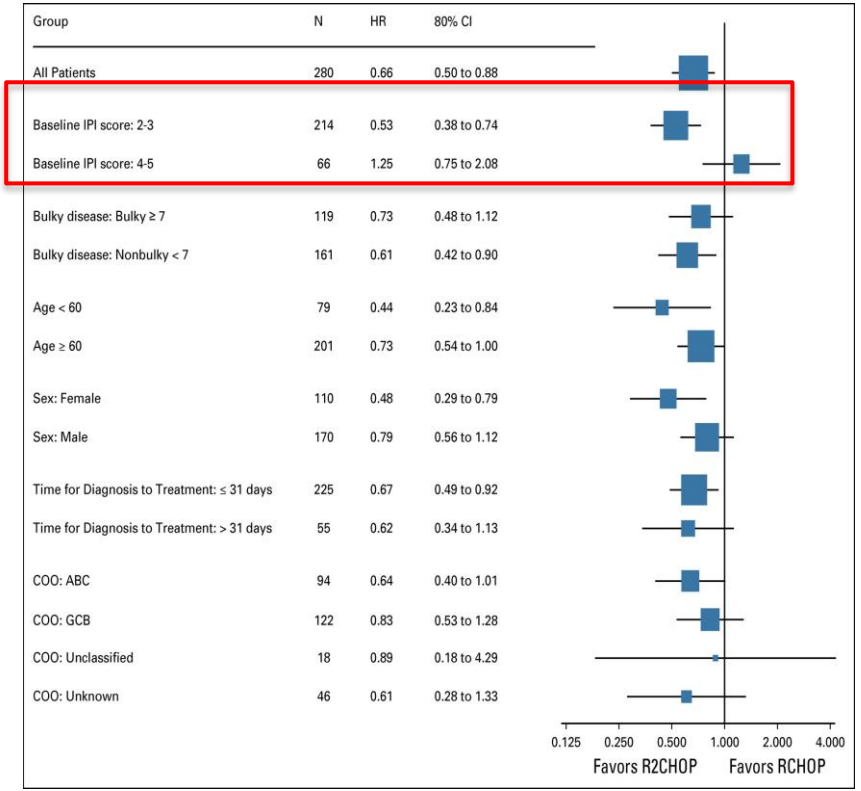
Nowakowski et al JCO 2021/doi10.1200/jco.20.01366, Nowakowski et al JCO 2021/doi10.12100/jco.20.01375

ECOG 1412: Ph II R2-CHOP vs R-CHOP: Do high risk DLBCL pts benefit?



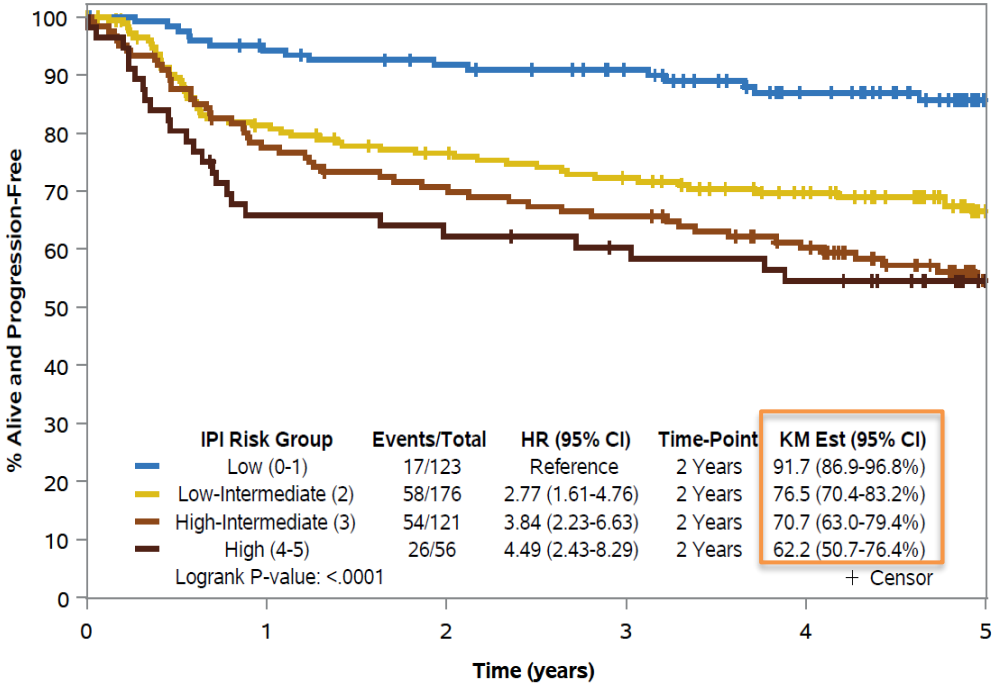
IPI 2-3

IPI 4-5



Nowakowski et al *J Clin Oncol* 2021

IPI 3 – 5 or IPI 4 – 5 for future trials? CALGB/Alliance 50303

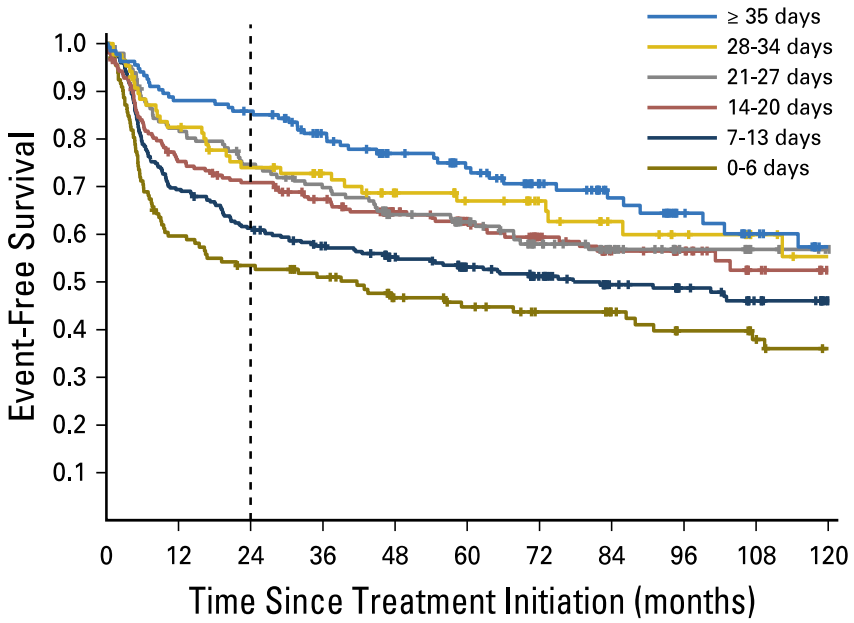


IPI 3: 2-y PFS 70.7%
IPI 4/5: 2-y PFS 62.2%

Barttelt N et Al. *J Clin Oncol* 2019, Suppl

Diagnosis to treatment interval (DTI) as determinant of high risk DLBCL

- DTI < 14 days were more likely:
  - High LDH
  - Poor PS
  - Stage III/IV
  - Bulky disease (> 10 cm)
- These pts are less likely to be enrolled in clinical trials

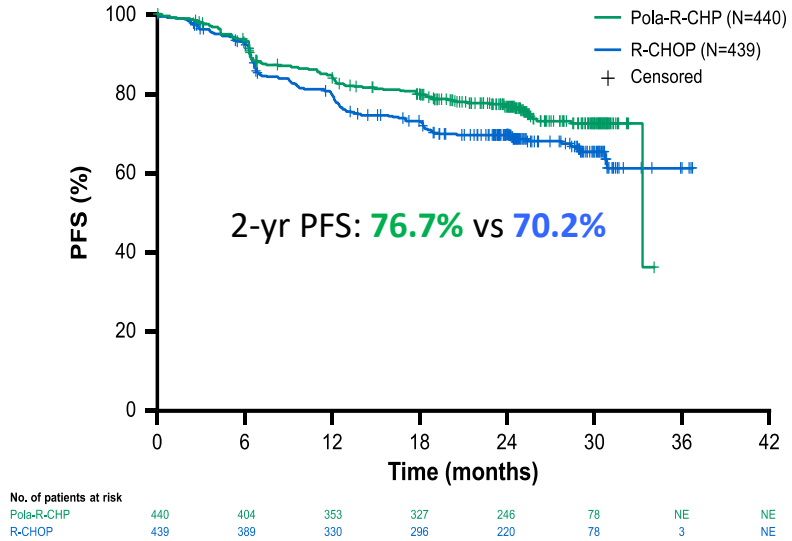


Maurer MJ et al. *J Clin Oncol* 2018

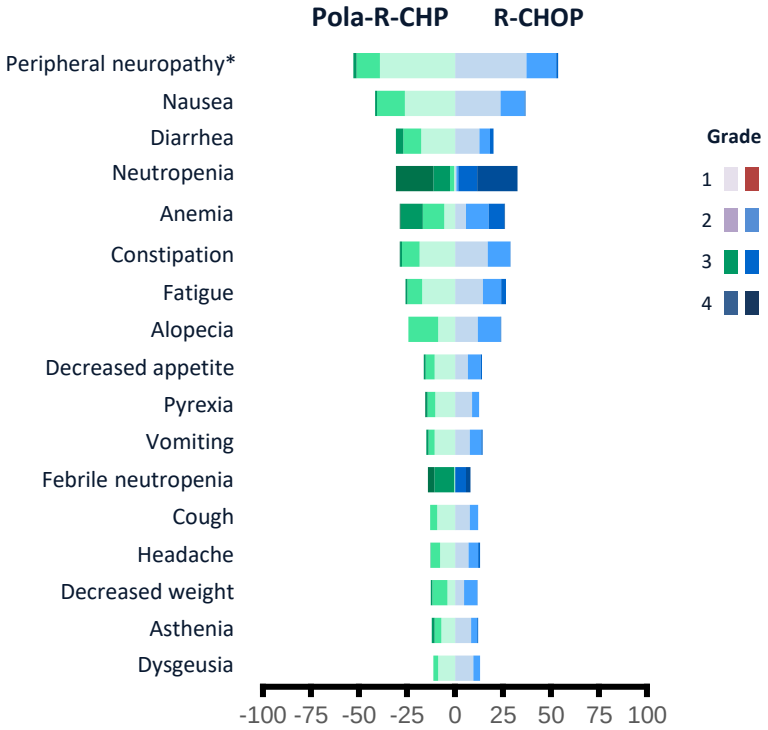
High Risk Features of Frontline DLBCL studies

Factor	DTI	Int- High Risk - 3-5 IPI	High Risk - IPI 4-5	DEL	MYC-R	DHL
CALGB (R-EPOCH vs R-CHOP)	NR	29.6%	13.6%	15.6%	5.2%	< 1%
PHOENIX Ibrutinib R-CHOP	27 days	43.2%	16.5%	31.9%	NR	NR
GOYA (G-CHOP)	NR	46.9%	15.4%	NR	NR	1.1%
POLARIX Pola R-CHOP	26 days	62%	NR	38.4%	NR	7.9% (tested)
ROBUST (R2-CHOP)	31 days	58%	NR	NR	NR	NR
ZUMA-12	?	78%	NR	33%	48%	43%

POLARIX: Can Polatuzumab-R-CHP Treat Effectively High Risk DLBCL?



ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.



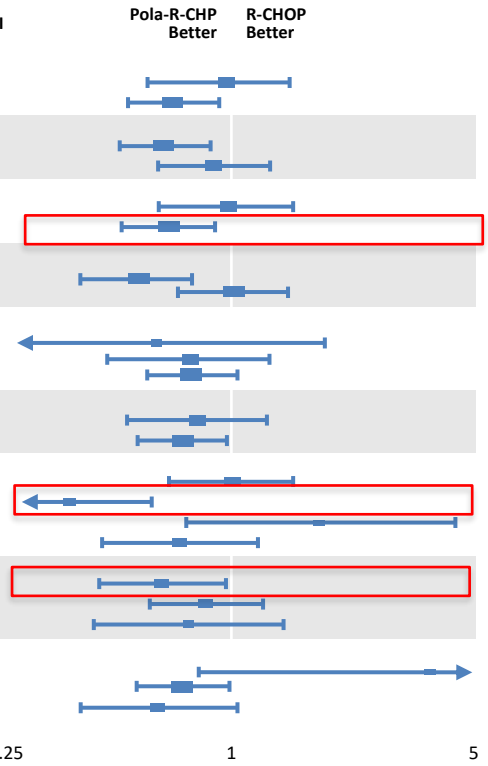
Tilly et al. NEJM 2021

POLARIX: Baseline characteristics

ITT population		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age	Median (range), years	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54)	234 (53)
ECOG PS, n (%)	0–1	374 (85)	363 (83)
	2	66 (15)	75 (17)
Bulky disease (≥7.5cm), n (%)	Present	193 (44)	192 (44)
Elevated LDH, n (%)	Yes	291 (66)	284 (65)
Time from diagnosis to treatment initiation	Median, days	26	27
Ann Arbor Stage, n (%)	III–IV	393 (89)	387 (88)
Extranodal sites, n (%)	≥2	213 (48)	213 (49)
IPI score, n (%)	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, n (%)*	Double expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	26 (8)	19 (6)

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 3-5

Non bulky?

ABC subtype

DEL

Tilly. NEJM. 2022;386:351.

ZUMA-12 Study Design

Phase 2

High-Risk LBCL
- HGBL, with *MYC* and *BCL2* and/or *BCL6* translocations (double- or triple-hit), or
- LBCL with IPI score ≥3 any time before enrollment

+

Dynamic Risk Assessment
- Positive interim PET (DS 4 or 5) after 2 cycles of an anti-CD20 mAb + anthracycline-containing regimen

+

Additional Key Inclusion Criteria
- Age ≥18 years
- ECOG 0–1

→ **Enrollment / Leukapheresis** → **Optional Nonchemotherapy Bridging Therapy[a]** →

Conditioning Chemotherapy + Axi-Cel Infusion

- Conditioning: Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, and −3
- Axi-Cel: Single IV infusion of 2 × 10^6 CAR T cells/kg on Day 0

→

Primary Endpoint
- CR (investigator-assessed per Lugano 2014 classification)[1]

Key Secondary Endpoints
- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

Neelapu et al. ASH 2021 Abstract # 405, Neelapu et Al, Nat Medicine 2022

ZUMA-12: Baseline 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)

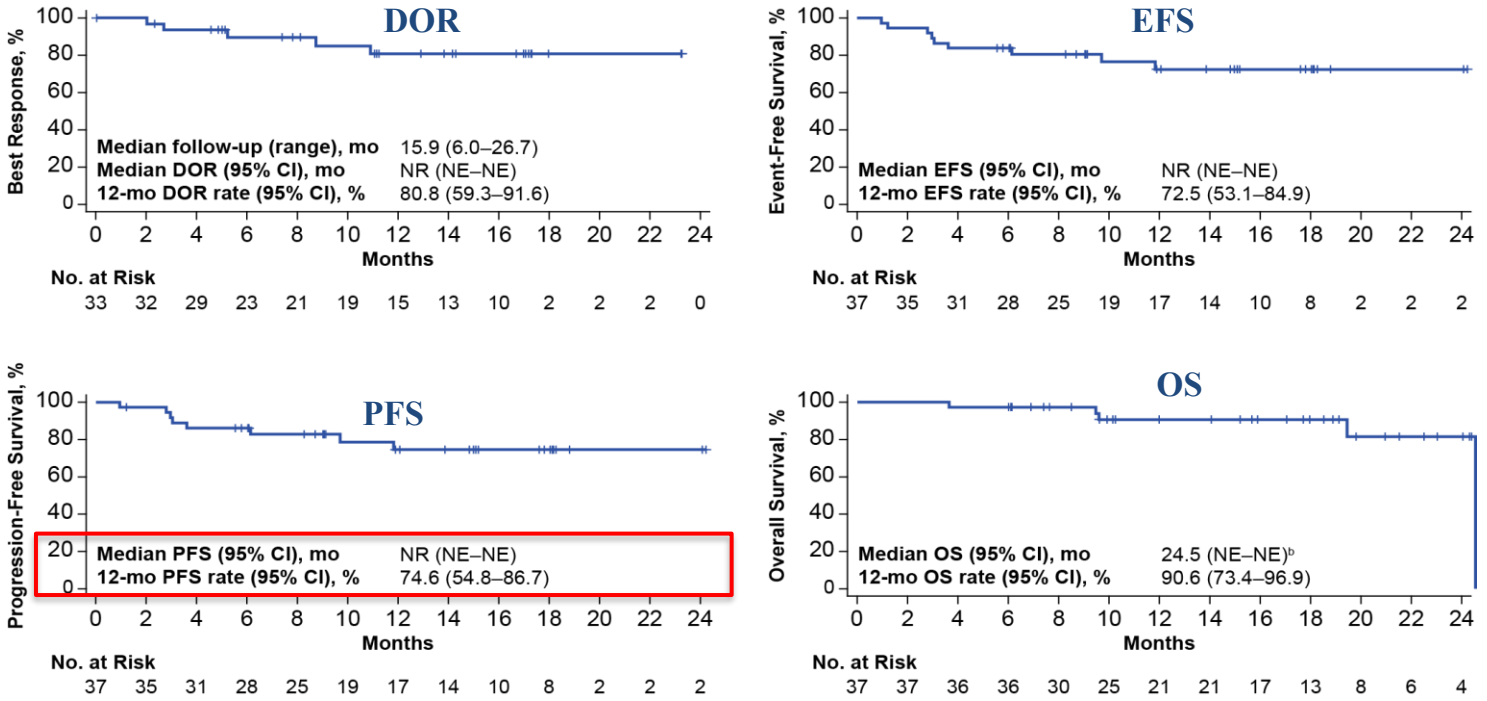
Neelapu et Al. Nature Medicine 2022

Comparison of CRS and Neurotoxicity between ZUMA-1, ZUMA-7 and ZUMA-12

Toxicities	ZUMA-1 (N= 111)	ZUMA-7 (N= 170)	ZUMA-12[a] (N=40)
CRS			
Any grade	93%	92%	100%
Grade ≥ 3	13%	6%	8%
Onset (median):	2d (1 – 12)	3d (1-10)	4d (1-10)
Duration (median)	8d	7d (2– 43)	6d (1-13)
Neurotoxicity			
Any grade	64%	60%	73%
Grade ≥ 3	28%	21%	23%
Onset (median)	5d (1-17)	7d	9d (2 – 44)
Duration (median)	17d	9d	6d (1 – 54)
Toxicity management			
Tocilizumab	43%	65%	53%
Steroids	27%	32%	34%
Vasopressors	17%	6%	3%

[a]ZUMA-12: No treatment related deaths

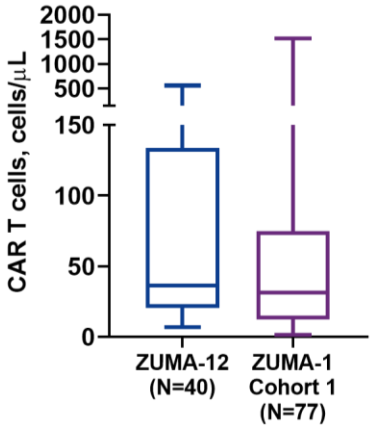
Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival[a]



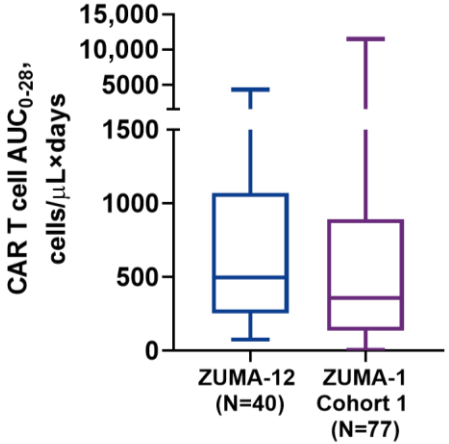
Neelapu et Al. Nature Medicine 2022

CAR T-Cell Expansion in ZUMA-12 versus ZUMA-1

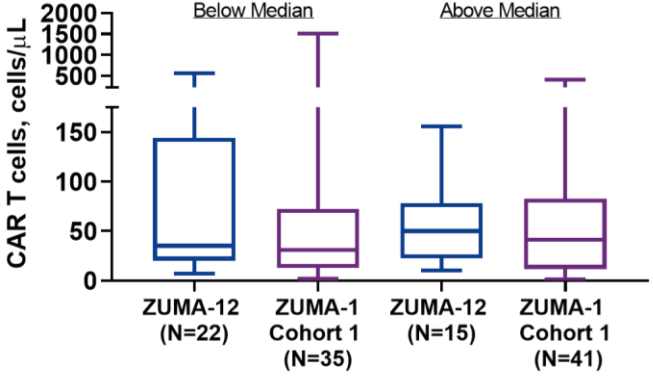
Peak



AUC_{0-28}



Peak by Tumor Burden Median[a]

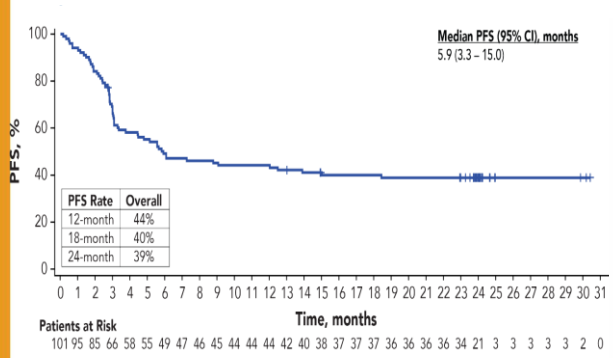


	Min–Median	Median–Max
SPD, mm^2	171–3683.5	>3683.5–26,124

- Median tumor burden appeared lower in ZUMA-12 than in ZUMA-1 Cohort 1 (2778 mm^2 vs 3897 mm^2, respectively)
- Median time to peak levels of CAR T cells in blood was 8 days for ZUMA-12
- PK profiles were similar in patients with double- or triple-hit lymphoma and LBCL with IPI score ≥3

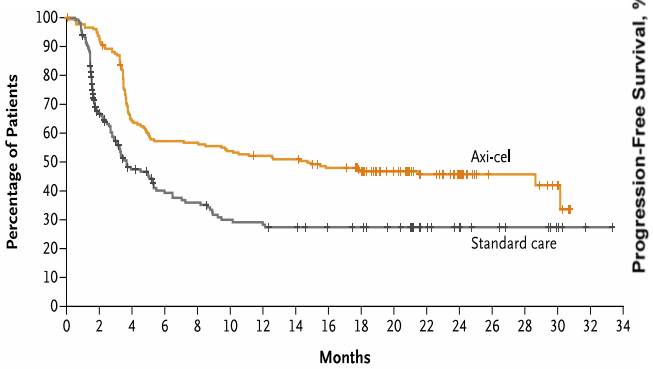
Can earlier use of CART improve outcomes?

ZUMA-1



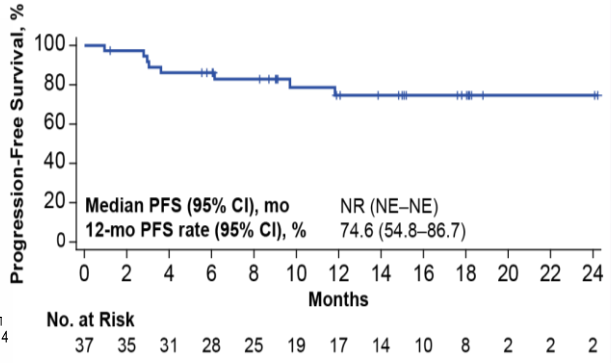
Median PFS 5.9 months

ZUMA-7



Median PFS (axi-cel arm): 14.6 months

ZUMA-12



Median PFS: Not reached

Locke et al. *Lancet Oncol* 2018, Locke et al. *N Eng J Med* 2021, Neelapu ASH Meeting Abstracts 2021

Will bispecifics make a difference in high risk DLBCL?

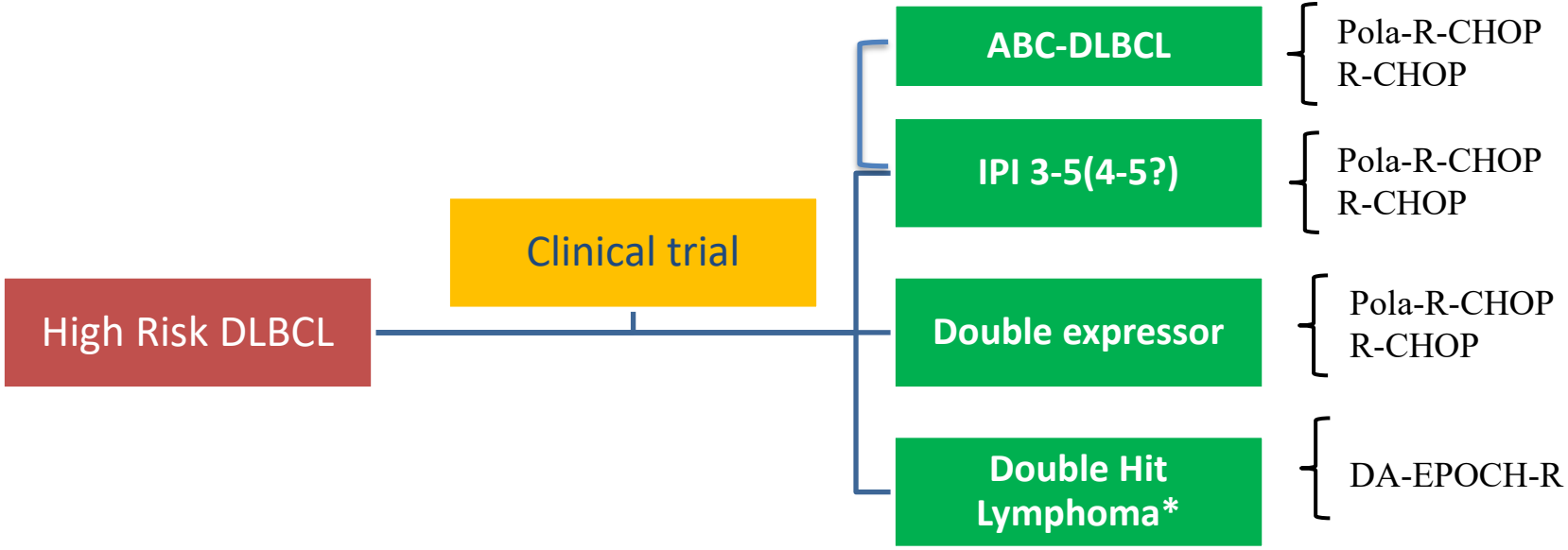
Toxicities	Epcoritamab+ R-CHOP (n= 33)	Glofitamab + R-CHOP (n= 55)
Median age	66	68
IPI 3-5	85%	62.5%
IPI 4-5	30%	26.8%
DHL	24%	NR
DEL	NR	NR
ORR/CMR rates	100/77%	96.2/75.5%

Falchi et al. *ASCO 2022*, Topp et al. *ASH 2022*

Pitfalls for Phase III Frontline Trials in High Risk DLBCL

- Patient population: Defining high risk/Heterogeneity
  - IPI score 4-5 (or NCCN IPI?)
  - Double hit lymphoma + something else (stage III/IV and/or IPI 3 or more)
  - Double expressor? HGBCL NOS?
- Comparator arm:
  - DA-EPOCH, R-CHOP (Pola-R-CHP?)
- Will one cycle of chemotherapy be allowed prior to enrollment?
- Integration of novel molecular methods-logistics
- Cost

High Risk DLBCL- My Current Approach



* For limited stage DHL R-CHOP may be enough

Moffitt ICE-T Clinical Program

Fred Locke (Chair)
Michael Jain (ICE-T Medical Director)
Julio Chavez (Director Clinical Research)
Bijal Shah
Taiga Nishihori
Farhad Khimani
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Javier Pinilla-Ibarz
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Sameh Gaballa

APPs and nurses
Christina Bachmeier + pharmacists

US CAR T Cell Consortium

17 Centers

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