What we recommend for aggressive B and T cell lymphomas in 2022

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Disclosures

Consulting advice:

Abbvie, Astellas, Astrazeneca, Bayer, Beigene, BMS, Calithera, Constellation, Eisai, Lilly, Epizyme, Genmab, Grail, Incyte, Janssen, Karyopharm, Merck, Mustang Bio, Pfizer, Roche/Genentech, Second Genome, Sutro, Caribou Biosciences

FDA approved and non-FDA approved drugs/indications will be discussed

Learning Objectives

- Understand basics of the diagnosis and evaluation of various types of lymphoma
- Learn about the range of treatment options patients with lymphoma
- Become familiar with new therapies in development and clinical trials for lymphoma treatment

Diffuse large B cell lymphoma

- Median age 60, usually with advanced stage disease
  - LAN, extranodal disease, symptoms
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
- Most patients treated same (R-CHOP)
- Unmet need – more cures, reduce toxicity
- Who should we treat differently?
- If refractory to second-line therapy, prognosis is poor

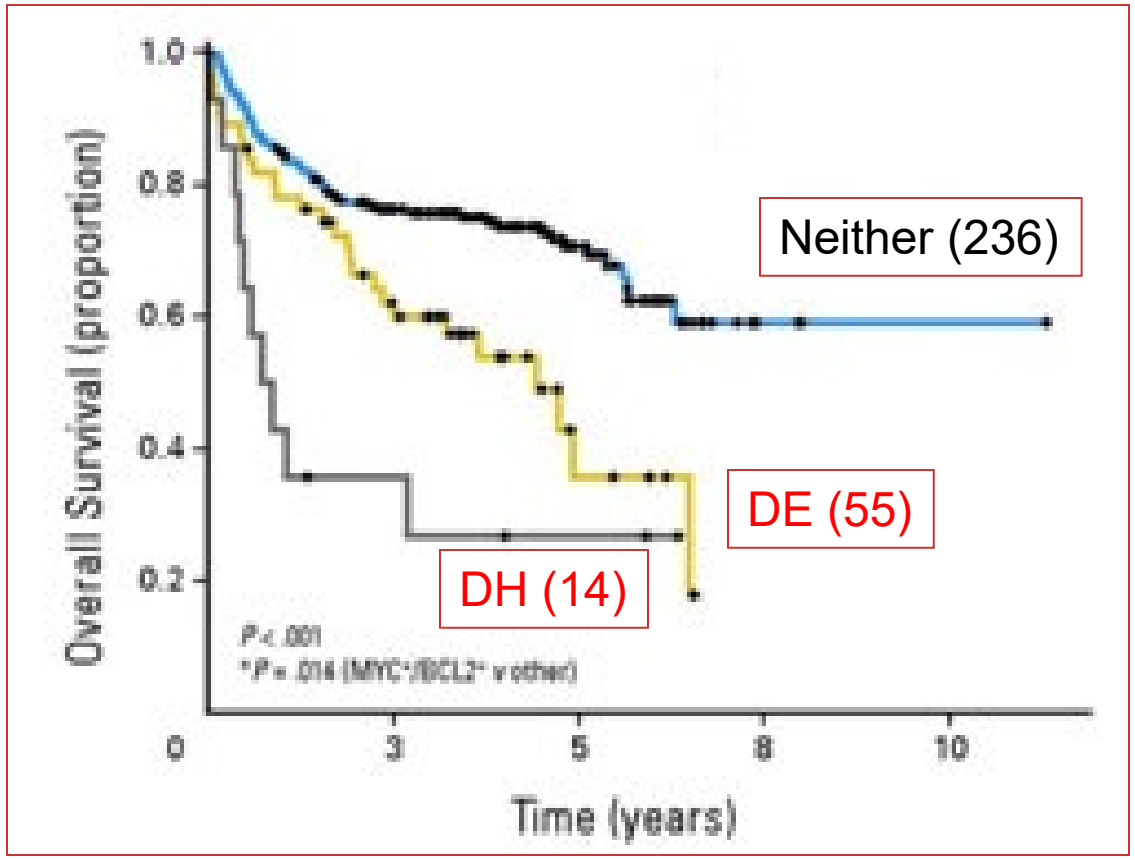
When have I treated patients with DLBCL today with something other than R-CHOP x 6?

- **Double hit subtype**
  - **Data not robust in double protein subtype**
- **Primary mediastinal**
- **HIV associated**
- **Testicular**
- **Limited stage**
- **CNS**
- **Elderly**

Double hit vs Double protein DLBCL
10-25% of DLBCL

- **Double-hit lymphoma: High-grade B-cell lymphoma with translocations of MYC as well as BCL2, BCL6, or both ("triple-hit")**
  - **Histologically classified as DLBCL or B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt Lymphoma**
  - **Cell of origin: Virtually always germinal center subtype**
  - **Outcome poor with standard therapies**
- **Double-expressing lymphomas: DLBCL with dual immunohistochemical expression of MYC (≥40%) and BCL2 (≥70%) in the absence of translocations**
  - **Cell of origin: Usually activated B cell subtype**
  - **Outcome inferior to other DLBCLs, but not as poor as DHL**

Double hit vs Double expression in DLBCL

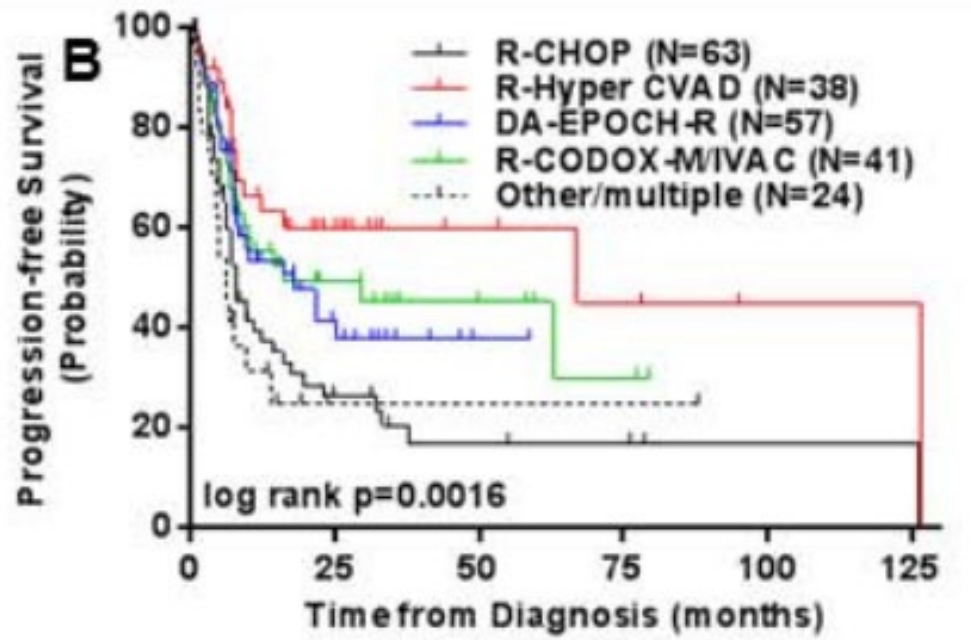


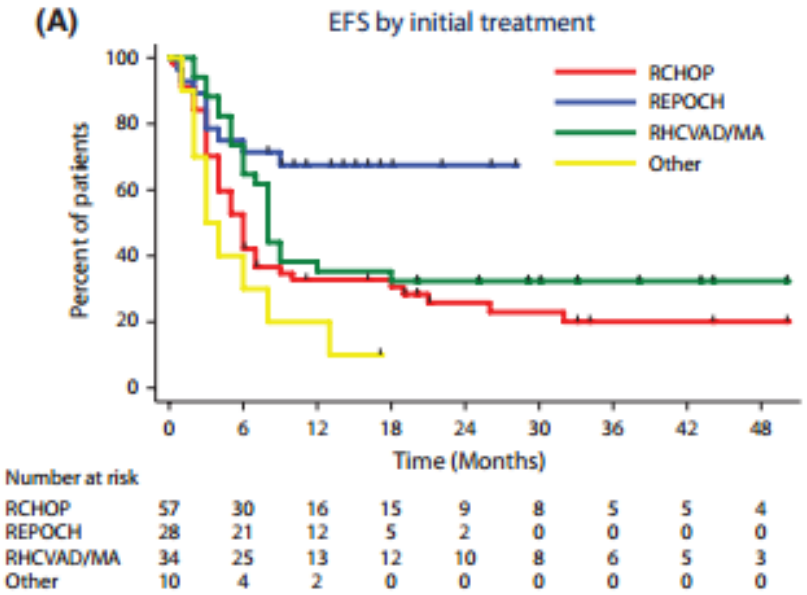
Double expression 4x more common than Double hit

Double expression intermediate in outcome between DH and neither

Johnson et al JCO 2012; 30: 3452

DA-EPOCH-R in double hit lymphoma





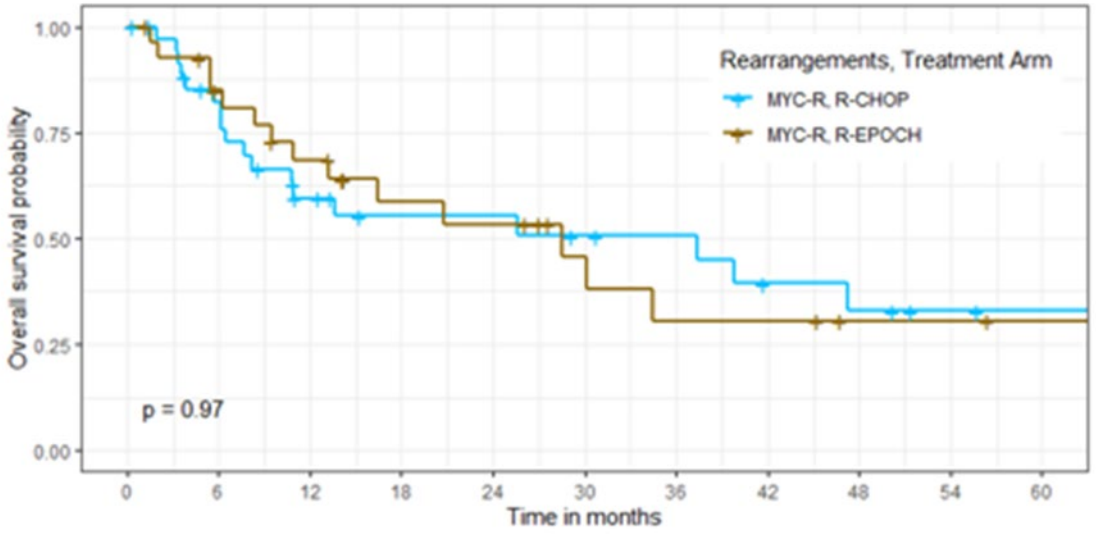
Petrich et al Blood 2014
Oki et al BJH 2014

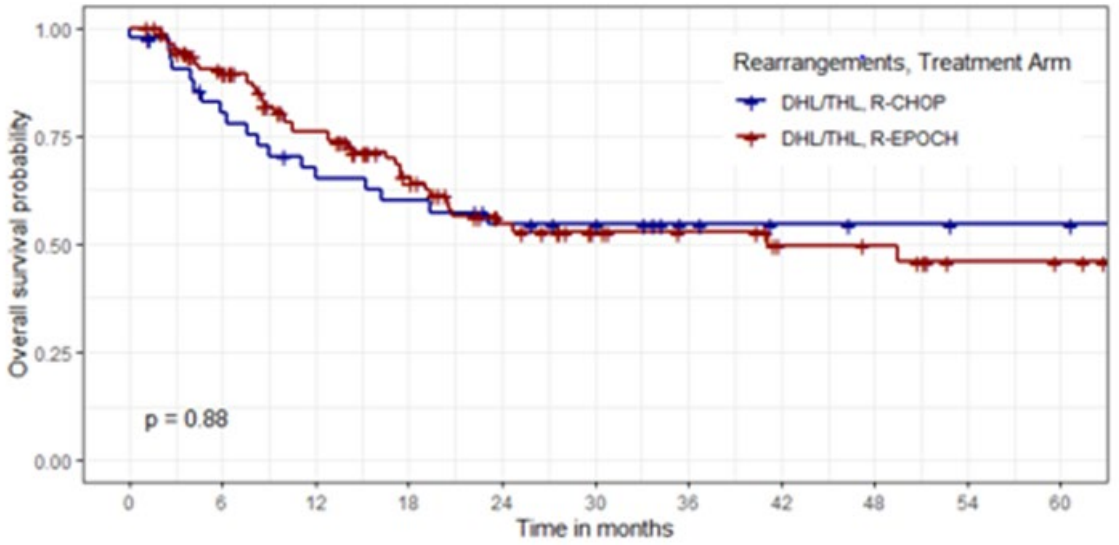
Electronic health record analysis of R-CHOP vs R-EPOCH in double hit lymphoma

- **6809 DLBCL patients (2011-2020), 154 with DHL/THL**
- **43 received R-CHOP (median age 73)**
- **111 received R-EPOCH (median age 67)**
- **Multivariable analysis ECOG 2+ and elevated LDH correlated with worse overall survival**

Magnusson et al, Abstract #S224, EHA 2021

Electronic health record analysis of R-CHOP vs R-EPOCH in double hit lymphoma





Magnusson et al, Abstract #S224, EHA 2021

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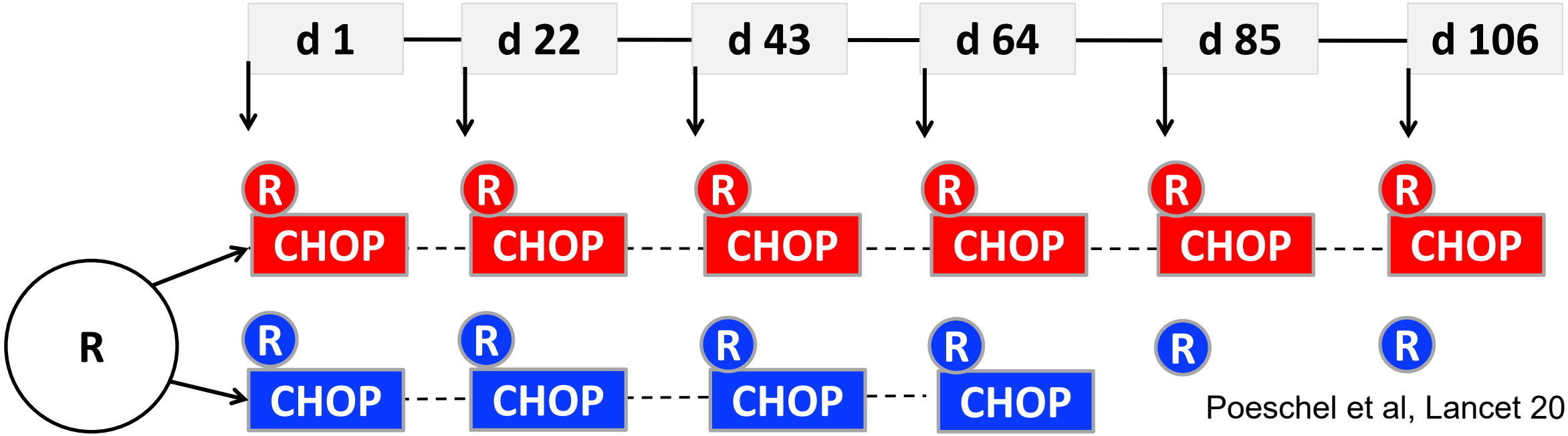
FLYER: Study Design

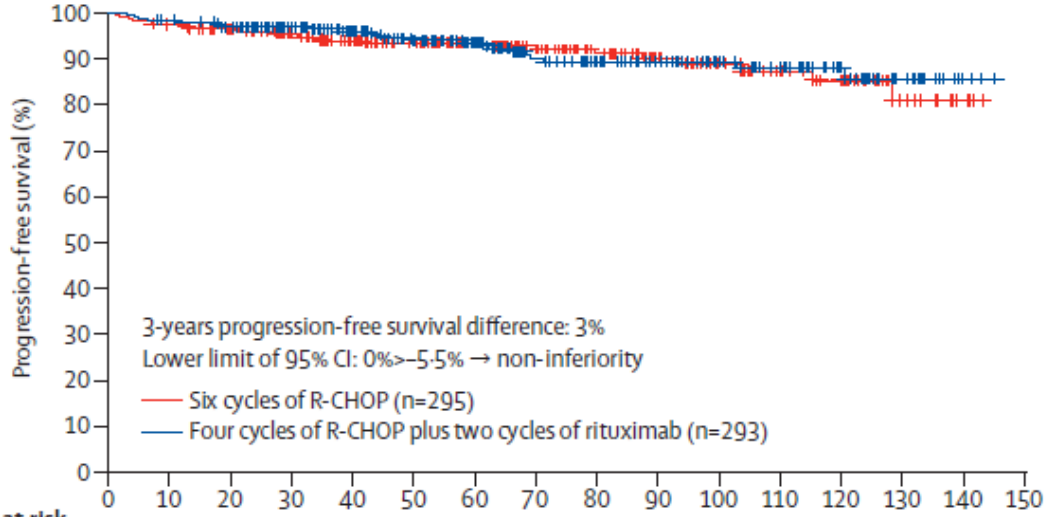
- **Front-line treatment of aggressive B-cell lymphoma**
- **18-60 years, stage I/II, aaIPI = 0, no bulk (max. diameter < 7.5 cm)**



Poeschel et al, Lancet 2019

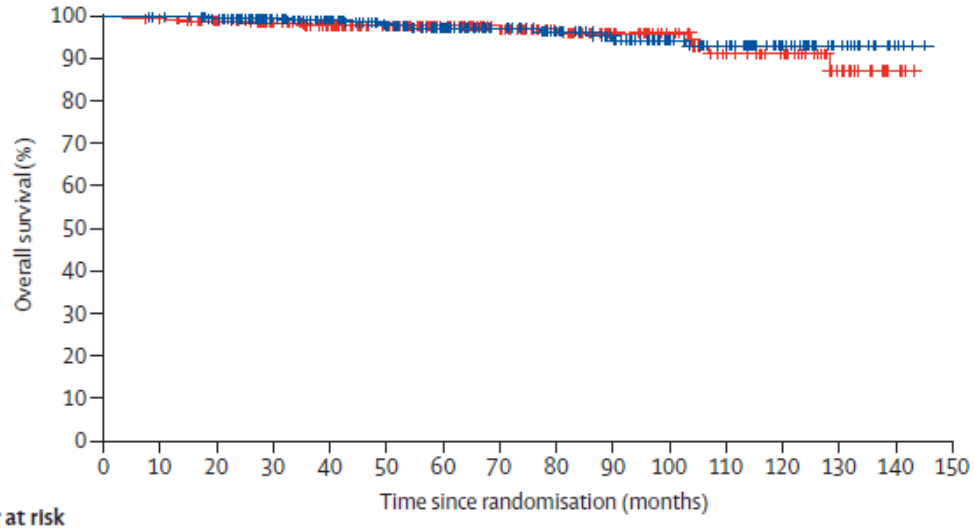
FLYER results
N=588 patients (ITT)

PFS



Number at risk (number censored)															
Six cycles	284	274	245	222	197	165	125	99	77	59	47	37	15	4	0
	(3)	(8)	(26)	(19)	(24)	(32)	(39)	(24)	(21)	(17)	(11)	(9)	(21)	(11)	(4)
Four cycles	286	274	244	215	186	163	124	105	89	71	59	36	18	3	0
	(2)	(8)	(30)	(27)	(25)	(22)	(34)	(18)	(16)	(18)	(11)	(23)	(17)	(15)	(3)

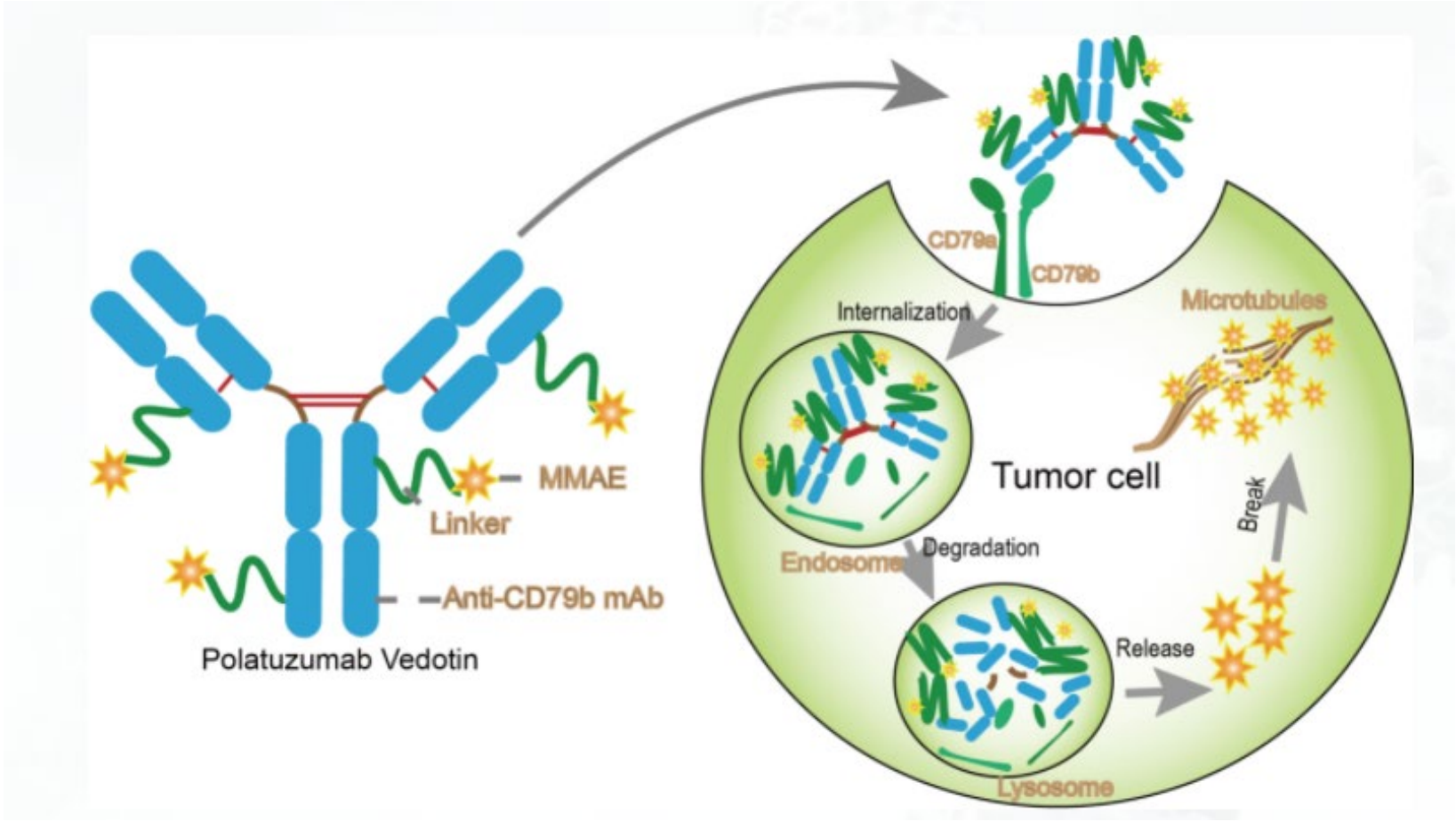
OS



Number at risk (number censored)															
Six cycles	290	280	253	231	206	174	134	107	82	65	50	40	17	4	0
	(3)	(8)	(26)	(20)	(25)	(32)	(40)	(26)	(24)	(17)	(12)	(10)	(22)	(13)	(4)
Four cycles	290	280	250	222	193	170	136	112	92	73	61	37	20	4	0
	(2)	(9)	(30)	(27)	(26)	(22)	(34)	(23)	(18)	(19)	(11)	(24)	(17)	(16)	(4)

Poeschel et al, Lancet 2019

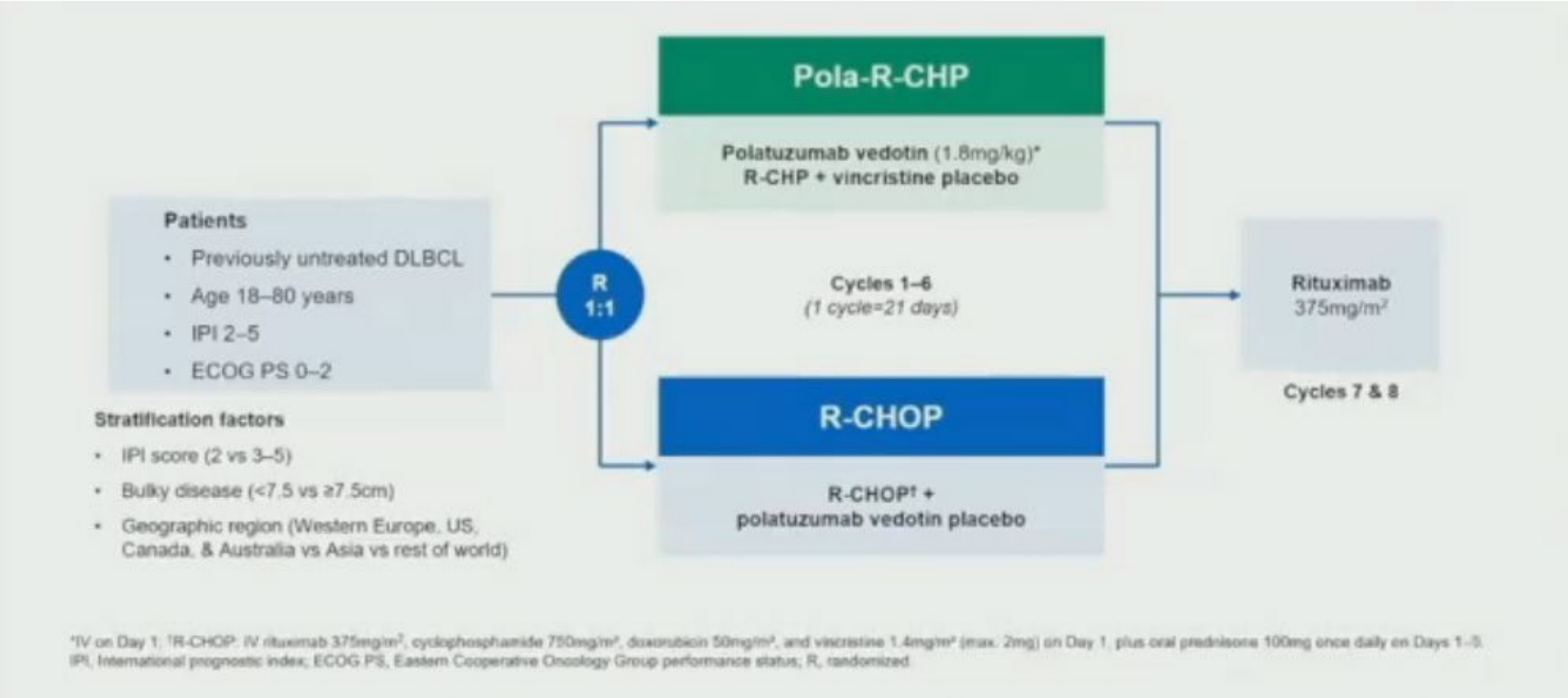
Polatuzumab vedotin (anti-CD79b antibody drug conjugate)



https://www.creativebiolabs.net/polatuzumab-vedotin-overview.htm

R-CHOP vs Polatuzumab-R-CHP in DLBCL (IPI 2-5)

Tilly et al, NEJM 2021



R-CHOP vs Polatuzumab-R-CHP in DLBCL

Tilly et al, NEJM 2021

Characteristic	Pola-R-CHP (N = 440)	R-CHOP (N = 439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)

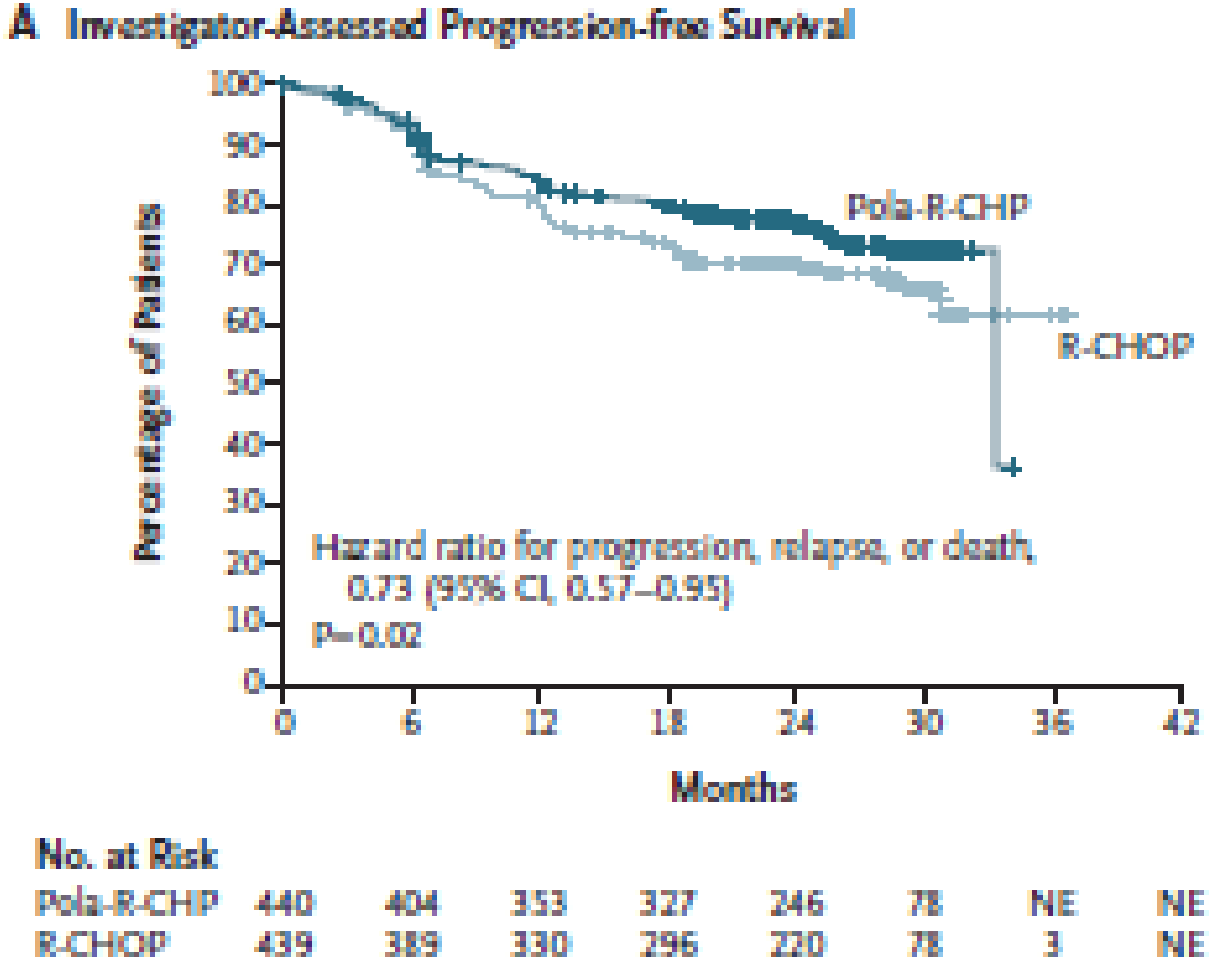
R-CHOP vs Polatuzumab-R-CHP in DLBCL - Toxicity

Tilly et al, NEJM 2021

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

R-CHOP vs Polatuzumab-R-CHP in DLBCL - PFS

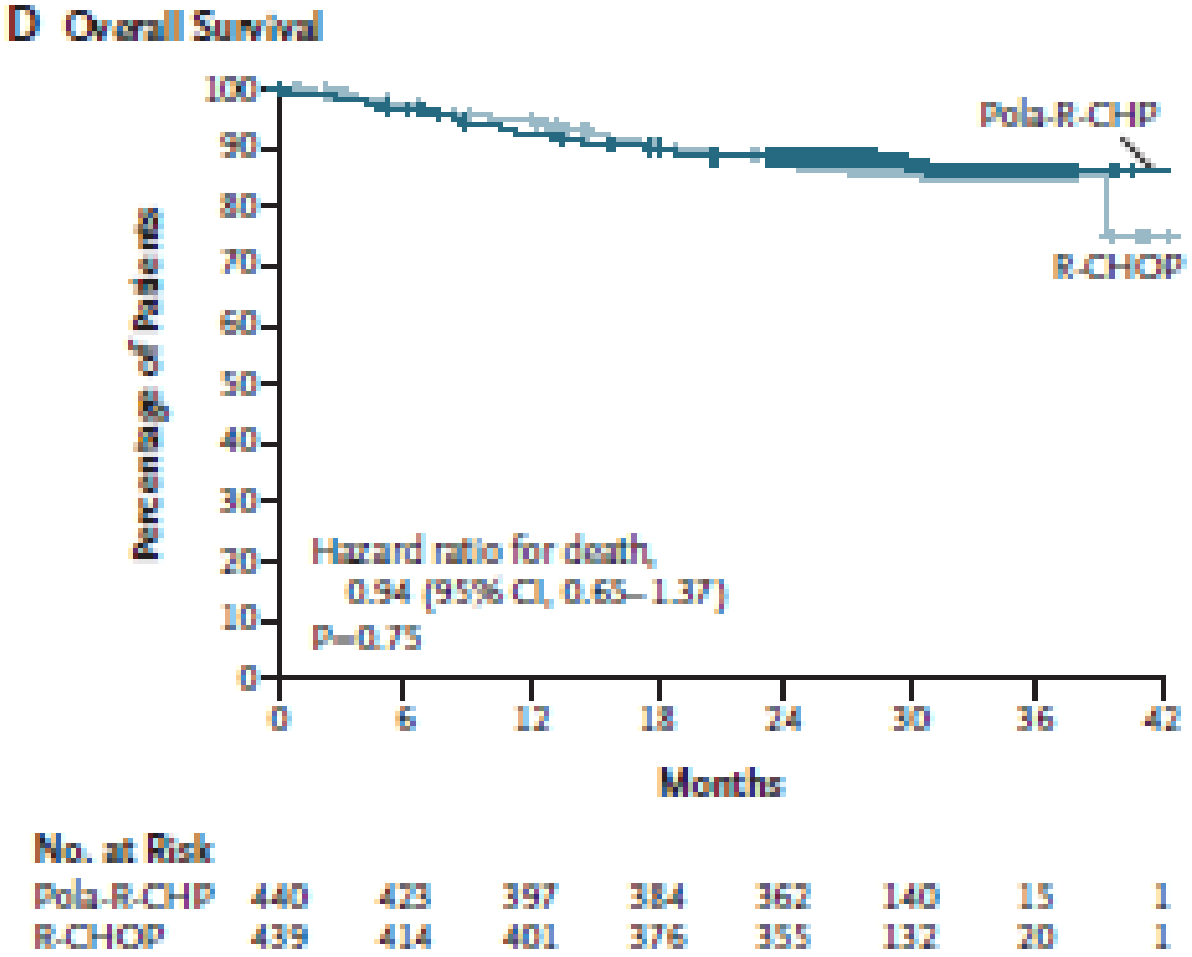
Tilly et al, NEJM 2021



24 mo PFS:
76.7% Pola-R-CHP
70.2% R-CHOP

R-CHOP vs Polatuzumab-R-CHP in DLBCL - OS

Tilly et al, NEJM 2021



Implications of POLARIX study

Positive trial (6.5% benefit in PFS), no OS benefit in IPI 2-5 DLBCL patients

Generally comparable toxicity

Older, male patients, higher risk and ABC subtype benefitted most

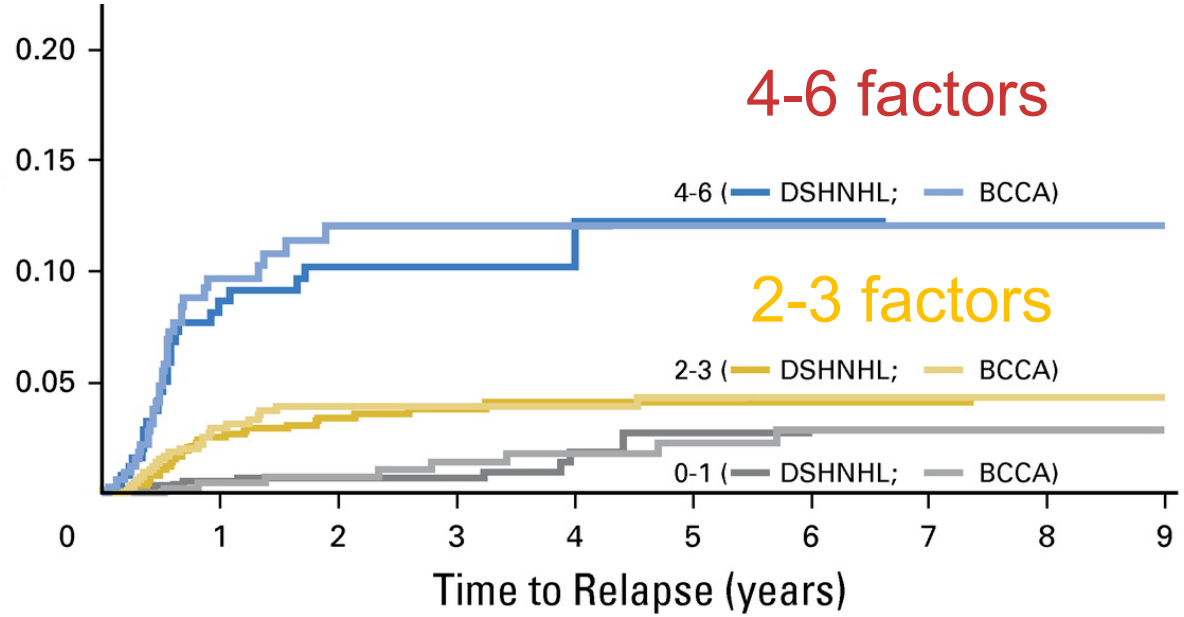
Saves 6.5% (1 of 15 patients) from relapse and more therapy

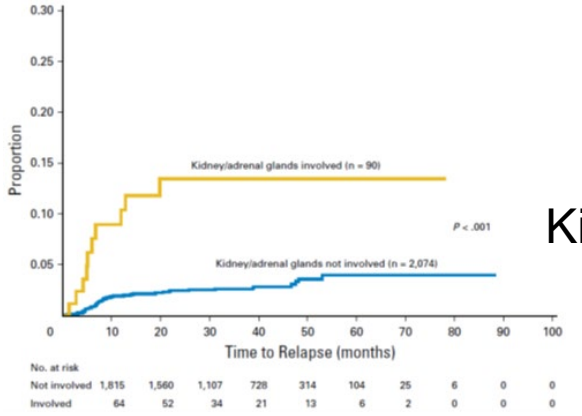
6 doses x $15,669/dose/80kg pt x 15 patients

= $1.4 million/relapse saved

Predicting risk of CNS progression: CNS IPI

Factor	Hazard Ratio
Kidney and/or adrenal glands involved	2.8
Age > 60 years	2.5
LDH > normal	2.4
ECOG PS > 1	2.2
Stage III/IV disease	2.0
Extranodal involvement > 1	1.0





Kidney/adrenal involvement vs not

Schmitz et al., *J Clin Oncol* 34:3150-6 2016

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Timing of CNS prophylaxis

International, retrospective analysis of 1384 patients with DLBCL at high risk of CNS relapse

n=749 systemic MTX intercalated with R-CHOP/like, n=635 after R-CHOP/like

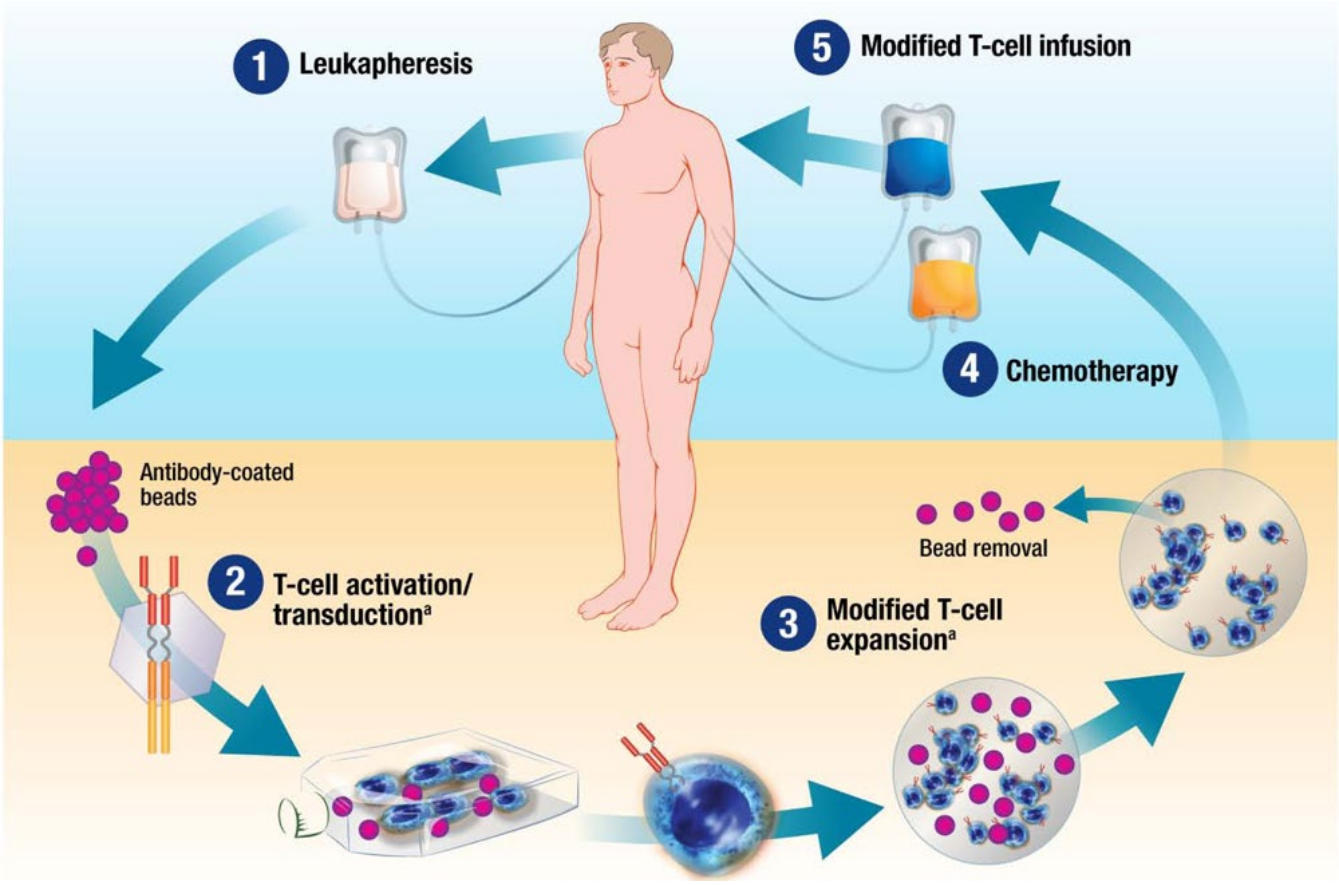
3 year rate of CNS relapses 5.7%, no difference in timing

In high CNS IPI (n=600), rate 9.1%, no difference in timing

In intercalated group, 19.6% of subjects had delays in R-CHOP/like

Wilson M et al, Blood 2022

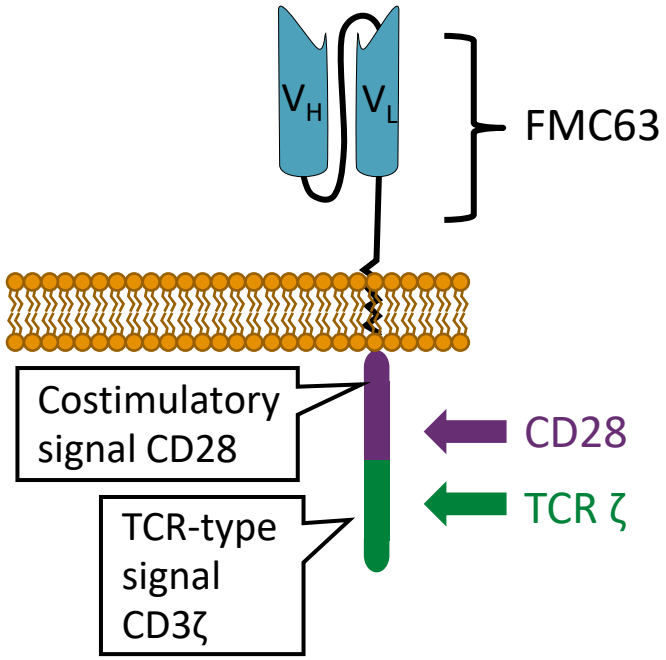
CAR-T cell therapy
Approved for multiply relapsed/refractory aggressive lymphoma



CD19-directed CAR T-cell products in DLBCL

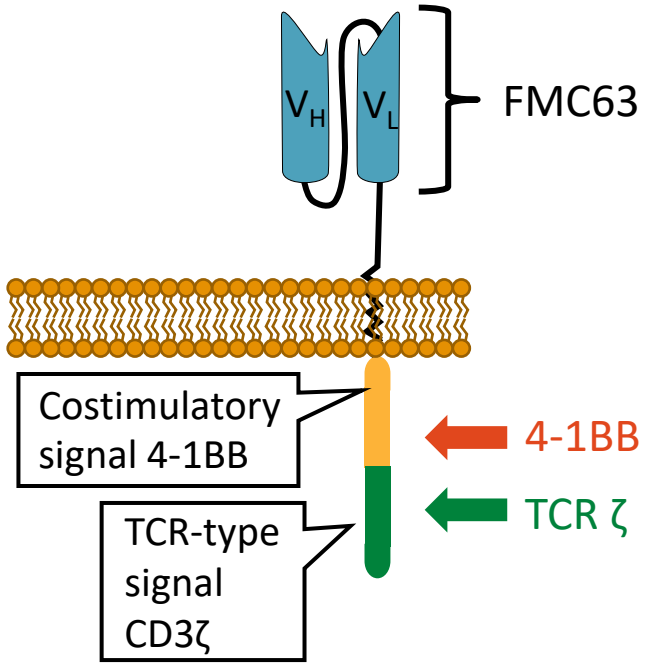
Axicabtagene ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



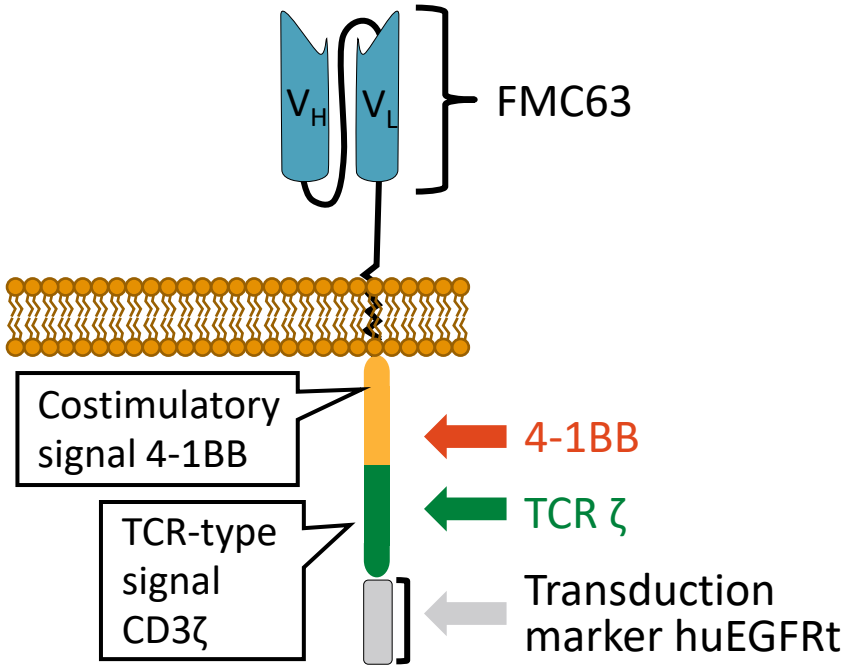
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



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

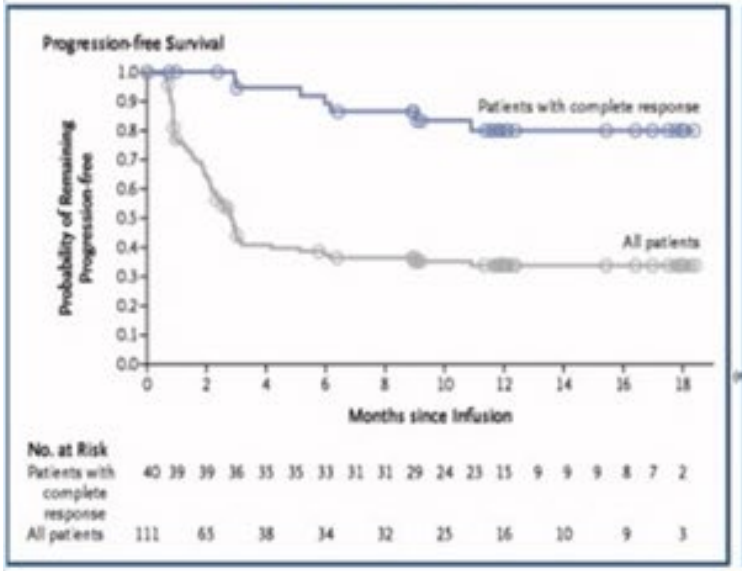
3 approved CAR-T for recurrent DLBCL patients

	ZUMA-1[1,2]	JULIET[3,4]	TRANSCEND CORE[5]
Product	**Axi-cel**	**Tisa-cel**	**Liso-cel**
# pheresed	111	165	344
# treated	101	111	269 (294*)
ORR (%)	82	54	73
CR (%)	54	40	53
6m ORR (%)	41	37	NR
mOS	25.8m	11.1m	21.1m

1. Jacobson, et al. *Blood*. 2020;136 (Supplement 1): 40–42. 2. Locke FL, et al. *Lancet Oncol*. 2019;20(1):31-42. 3.Schuster S, et al. *N Engl J Med*. 2019;380(1):45-56.
4. Maziarz RT, et al. *Blood Adv*. 2020;4(4):629-637. 5. Abramson JS, et al. *Lancet*. 2020;396(10254):839-852.

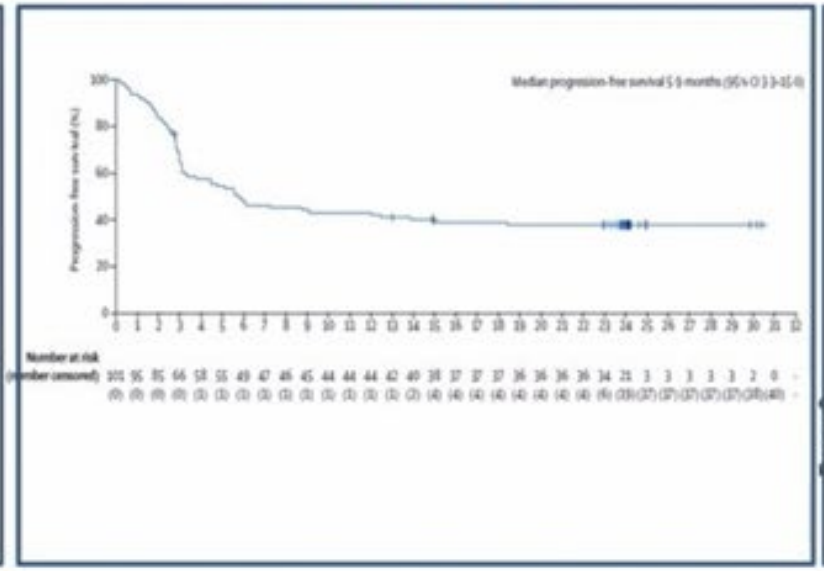
CAR-T agents for recurrent DLBCL with meaningful PFS

JULIET



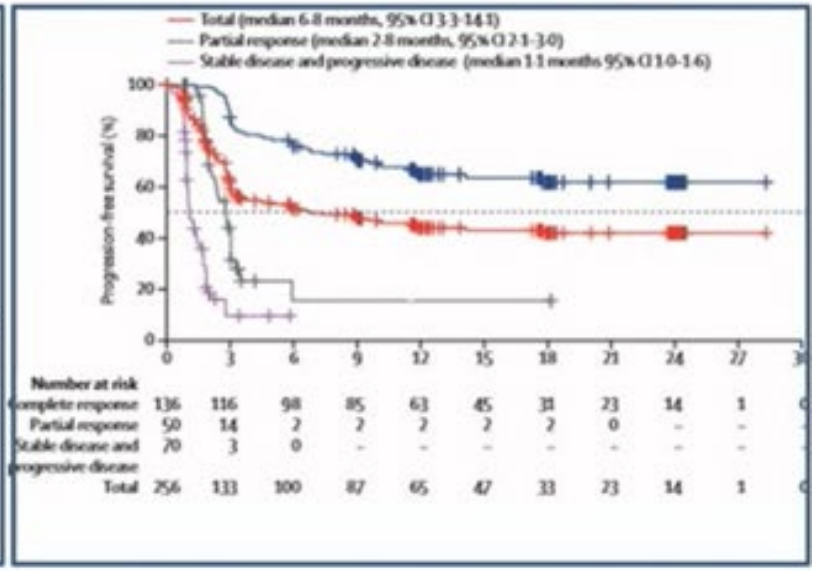
Schuster SJ, et al. *N Engl J Med.* 2019

ZUMA-1



Locke FL, et al. Lancet Oncol. 2018

TRANSCEND-001



Abramson JS, et al. *Lancet.* 2020

Thieblemont et al, EHA 2021

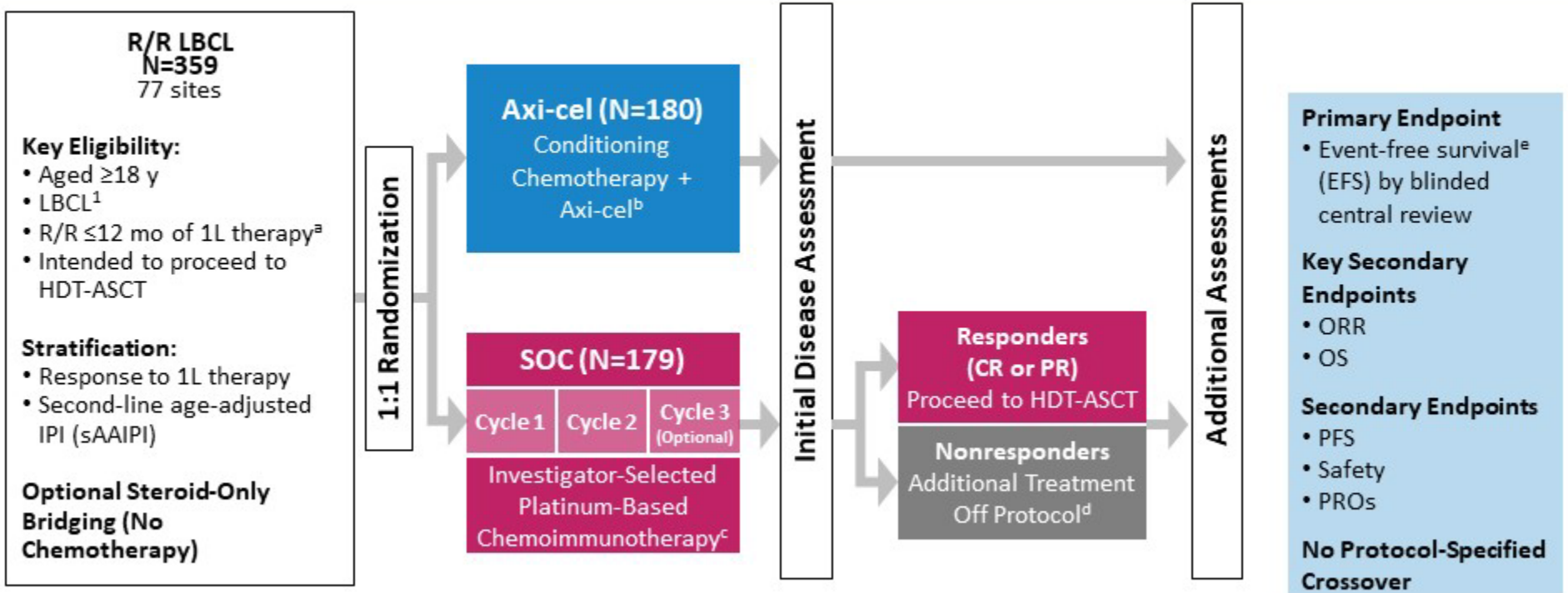
Initial clinical trial data with CAR-T cells

- Studies are generally non-comparative, single arm
- Time in preparing the T cells creates some biases
- Significant responses have been seen (some extending several years) in ALL, CLL and NHL of various types with refractory disease
- Toxicity (cytokine release) involving transient mental status changes/encephalopathy and ICU stays can occur
- ORR about 60-70%, CR about 30% (tend to be more durable)
- About 1/3 non-respond, 1/3 short response, 1/3 longer response
- Cytopenias, immunoglobulin depletion occur

Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL

Locke et al, NEJM 2021

ZUMA-7 Study Schema and Endpoints: Axi-cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL



[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood.* 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

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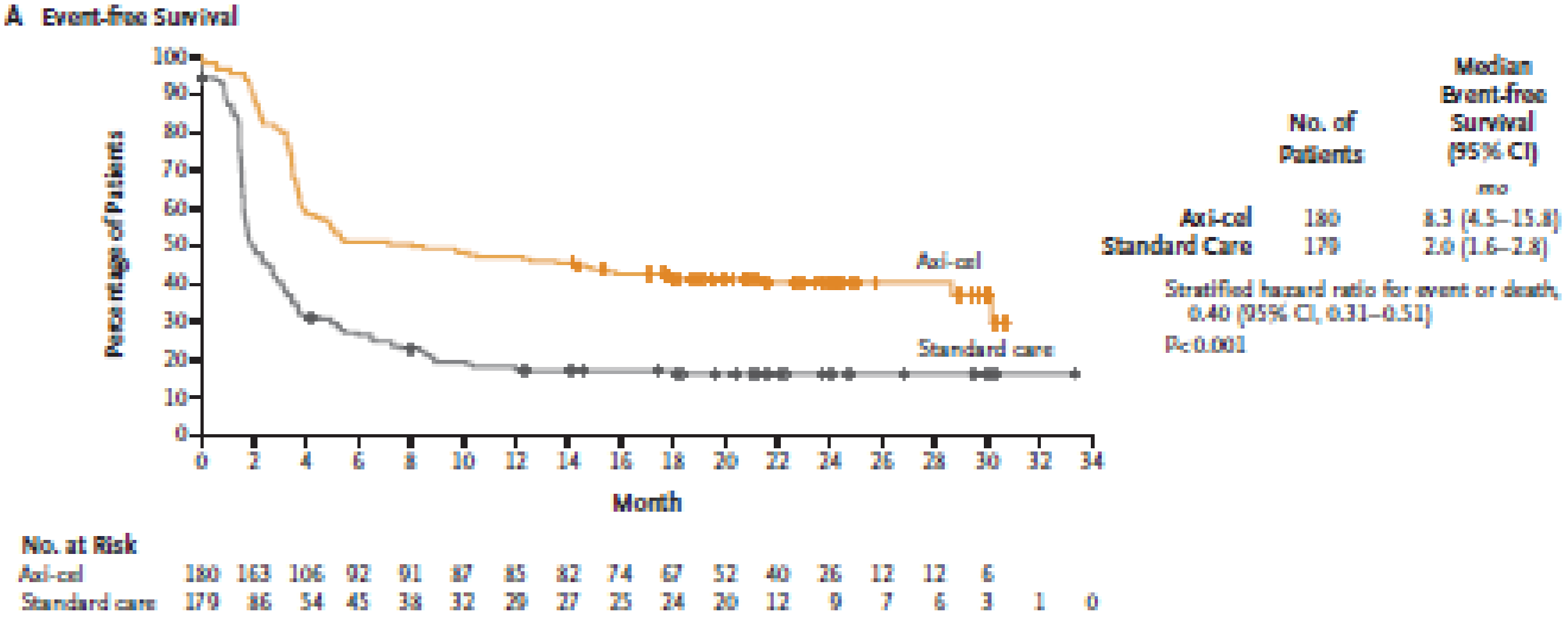
Locke et al, NEJM 2021



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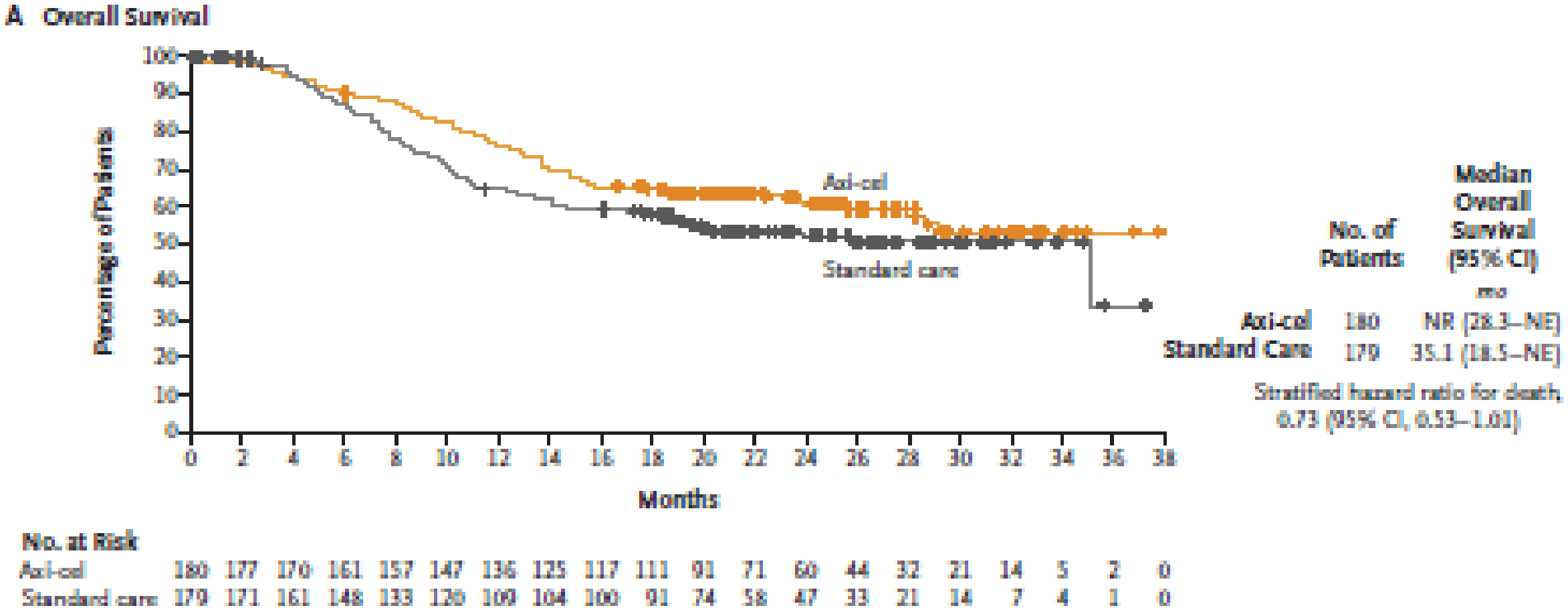
Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL

Locke et al, NEJM 2021



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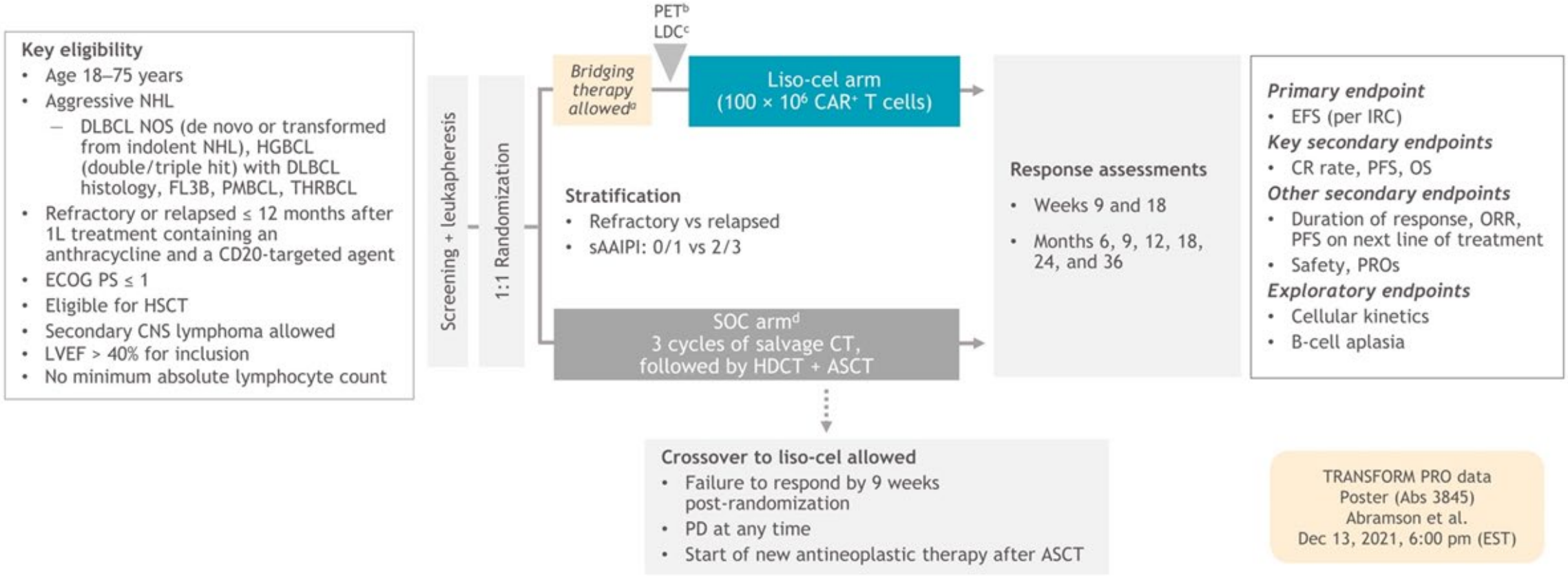
Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

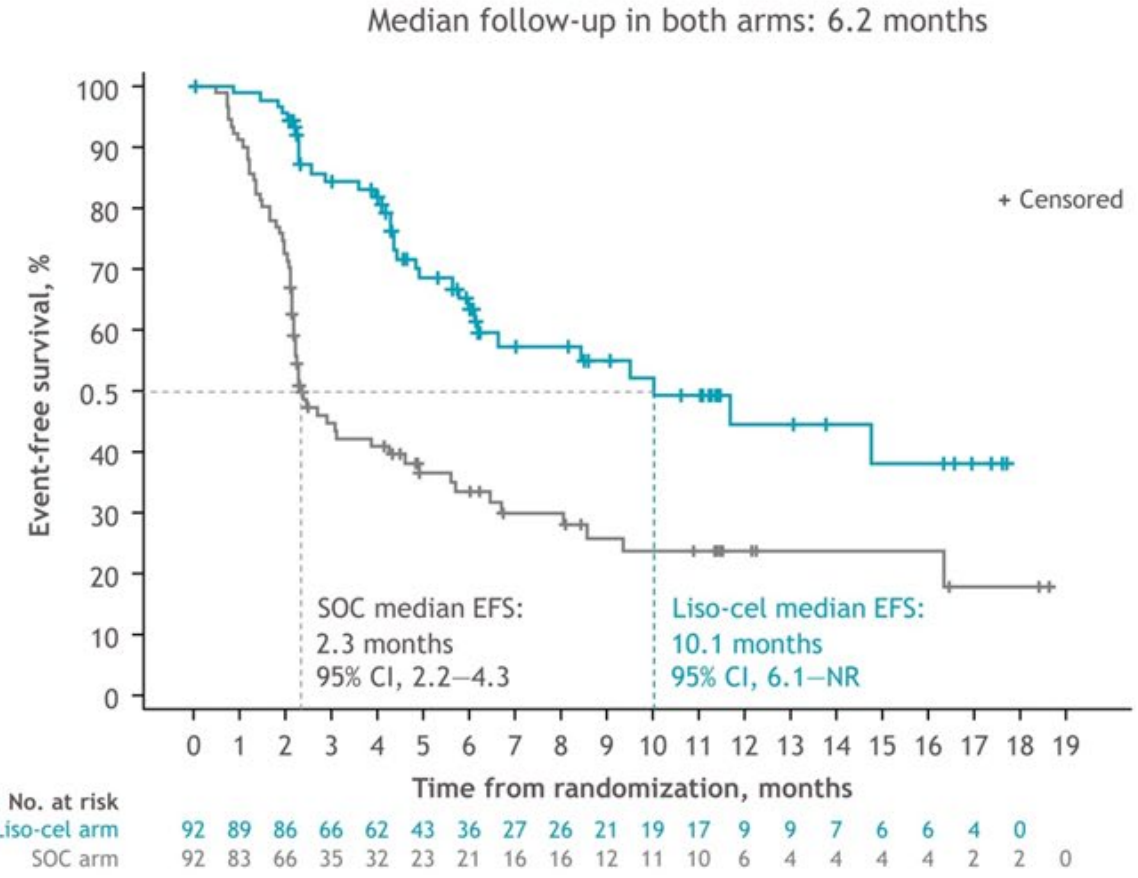
Kamdar et al, ASH 2021



- EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

Kamdar et al, ASH 2021



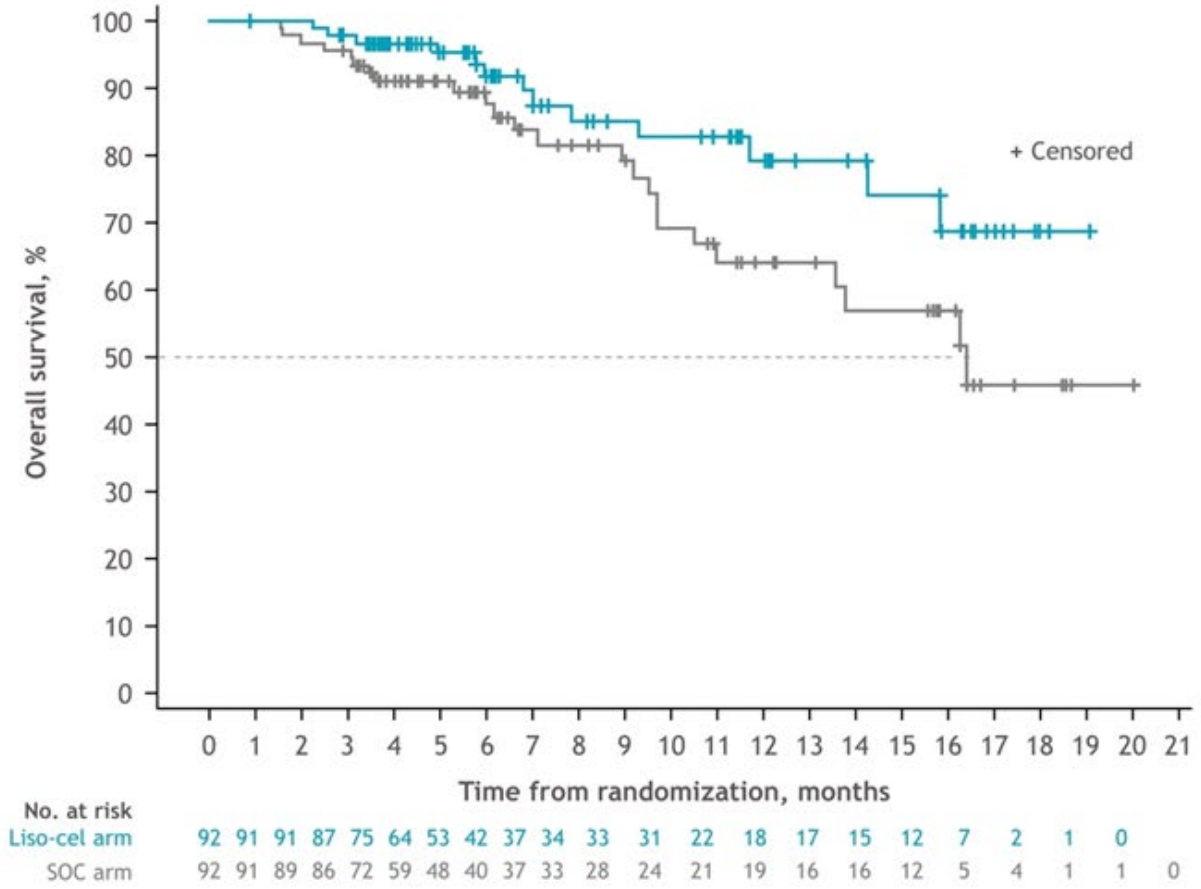
	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	P < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0–74.7	23.0–43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4–59.6	13.4–34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

Kamdar et al, ASH 2021



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	13	24
Stratified HR (95% CI)	0.509 (0.258–1.004) *P* = 0.0257	
Median OS (95% CI), months	NR (15.8–NR)	16.4 (11.0–NR)
6-month OS rate, % (SE)	91.8 (3.29)	89.4 (3.36)
Two-sided 95% CI	85.4–98.2	82.9–96.0
12-month OS rate, % (SE)	79.1 (6.13)	64.2 (6.99)
Two-sided 95% CI	67.1–91.1	50.5–77.9

Patients in the SOC arm that crossed over to receive liso-cel continue to be followed for OS in the SOC arm

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

OS is defined as the time from randomization to death from any cause.

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Summary of second line CAR-T studies

Randomized trials of CAR T-cells vs. SOC in 2nd line transplant-eligible DLBCL with primary refractory disease or relapse within 1 year of 1st line therapy

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell	Axicabtagene Ciloleucel	Lisocabtagene Maraleucel	Tisagenlecleucel
n	359	184	322
% infused in CAR arm	94%	98%	96%
Median EFS	8.3 mo vs. 2 mo	10.1 mo vs. 2.3 mo	3 mo vs. 3 mo
Hazard ratio	0.398 (*P*<*0*.0001)	0.349; (*P* < 0.0001)	1.07 (*P*=0.69)
Median follow-up	25 months	6 months	10 months
CR rate	65% vs 32%	66% vs 39%	28% vs 28%
Grade ≥3 CRS/NT	6% / 21%	1% / 4%	5% / 3%
	Locke, et al. Abstract 2	Kamdar, et al. Abstract 91	Bishop, et al. Abstract LBA-6

Toby Eyre

Implications of second line CAR-T studies

In patients with chemoresistant disease (short first remission), more chemo (and AutoSCT) is not effective

Why different outcome in BELINDA study with Tisagenlecleucel?

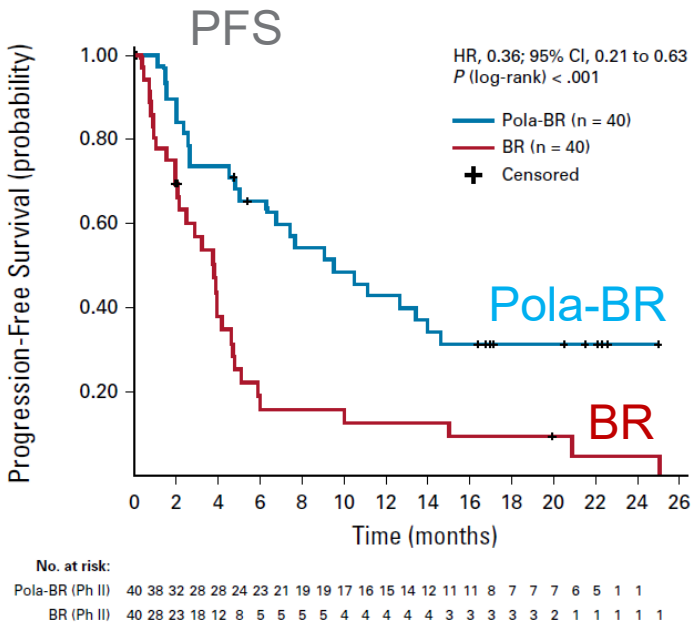
- chemotherapy bridging (sicker patients), additional chemo cycles for standard group, longer time (52d) to get CAR-T (and 25.9% pre-infusion PD), different agent, less lymphodepletion, event definitions

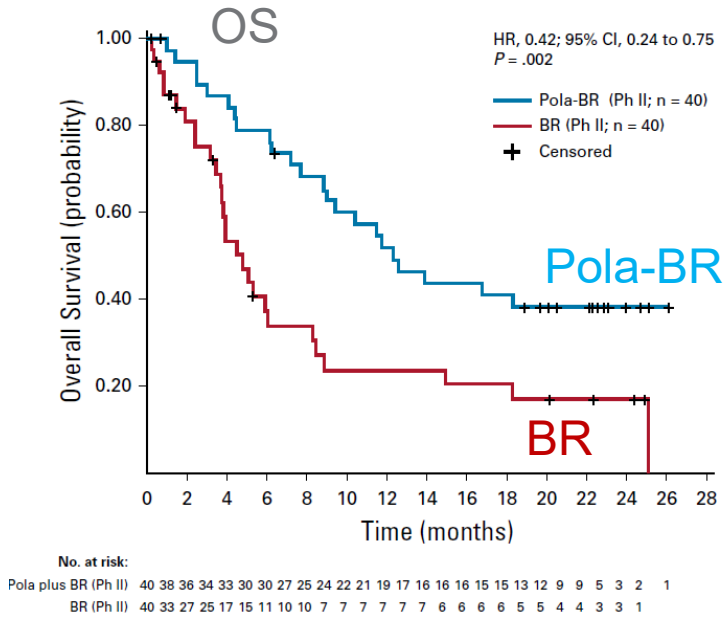
CAR-T will be SOC for those with PD < 1 year

- for practical reasons seems likely there will still be 2nd line chemo for many patients

AutoSCT remains SOC for those with later relapses

BR ± Polatuzumab Vedotin-piiq in Relapsed DLBCL: Randomized Phase 2 CR 40% vs 17.5%

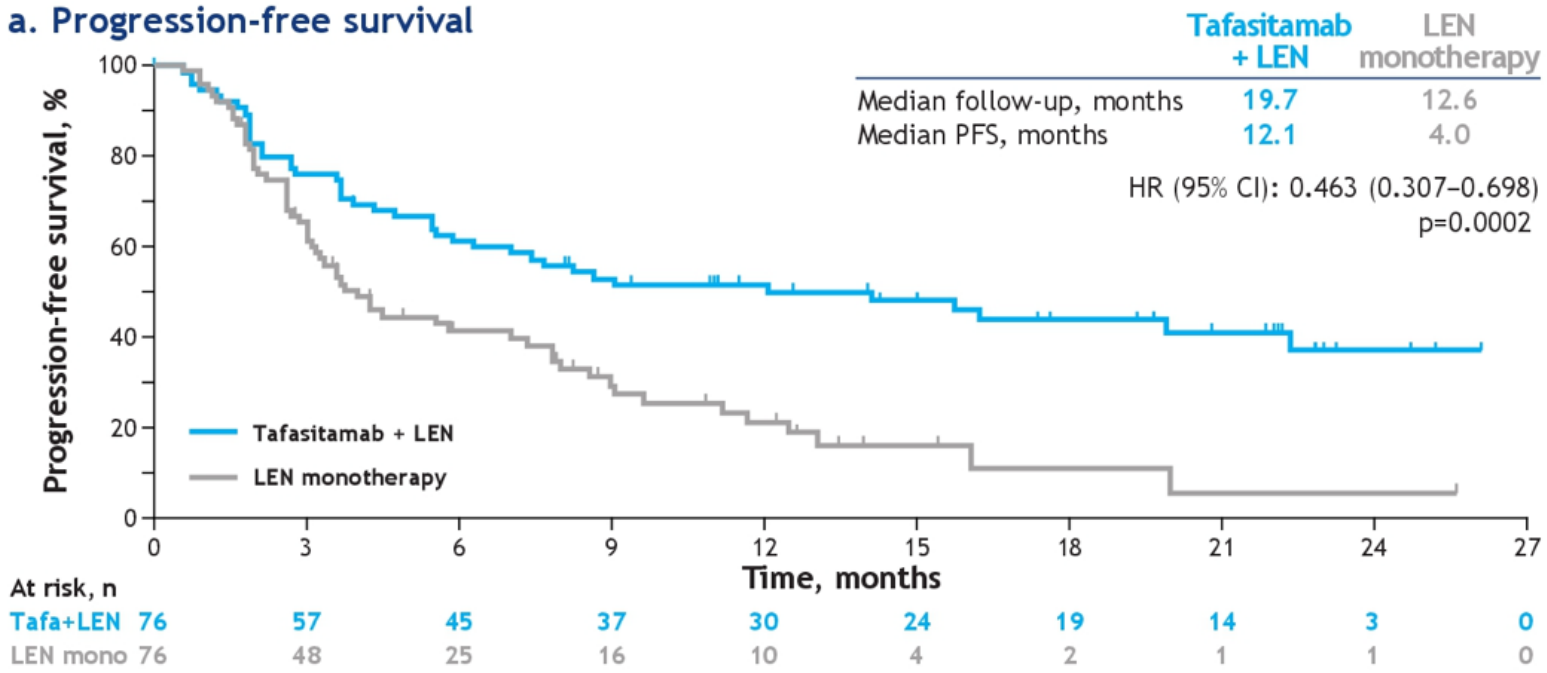




FDA approval 2019: +BR for relapsed/refractory DLBCL, >2 prior therapies

Sehn L et al JCO 2019

Tafasitamab/Lenalidomide (RE-MIND) compared to matched Len alone in recurrent DLBCL pts
ORR 67.1 vs 34.2%



Nowakowski GS, et al. ASCO 2020 (abstr 8020).

Selinexor

- Selective inhibitor of nuclear export (SINE), blocks XPO1
- Phase 2 SADAL study (preprint *Lancet* 2020)
- DLBCL (including tFL), 2-5 prior therapies (N=127)
- Selinexor oral 60 mg days 1 and 3 weekly
- ORR 28%, CR 12%
- Responses in both GCB and non-GCB (Hans)
- Common grade 3-4 AE cytopenias, fatigue, hyponatremia, nausea
- Median response duration 9.3 months

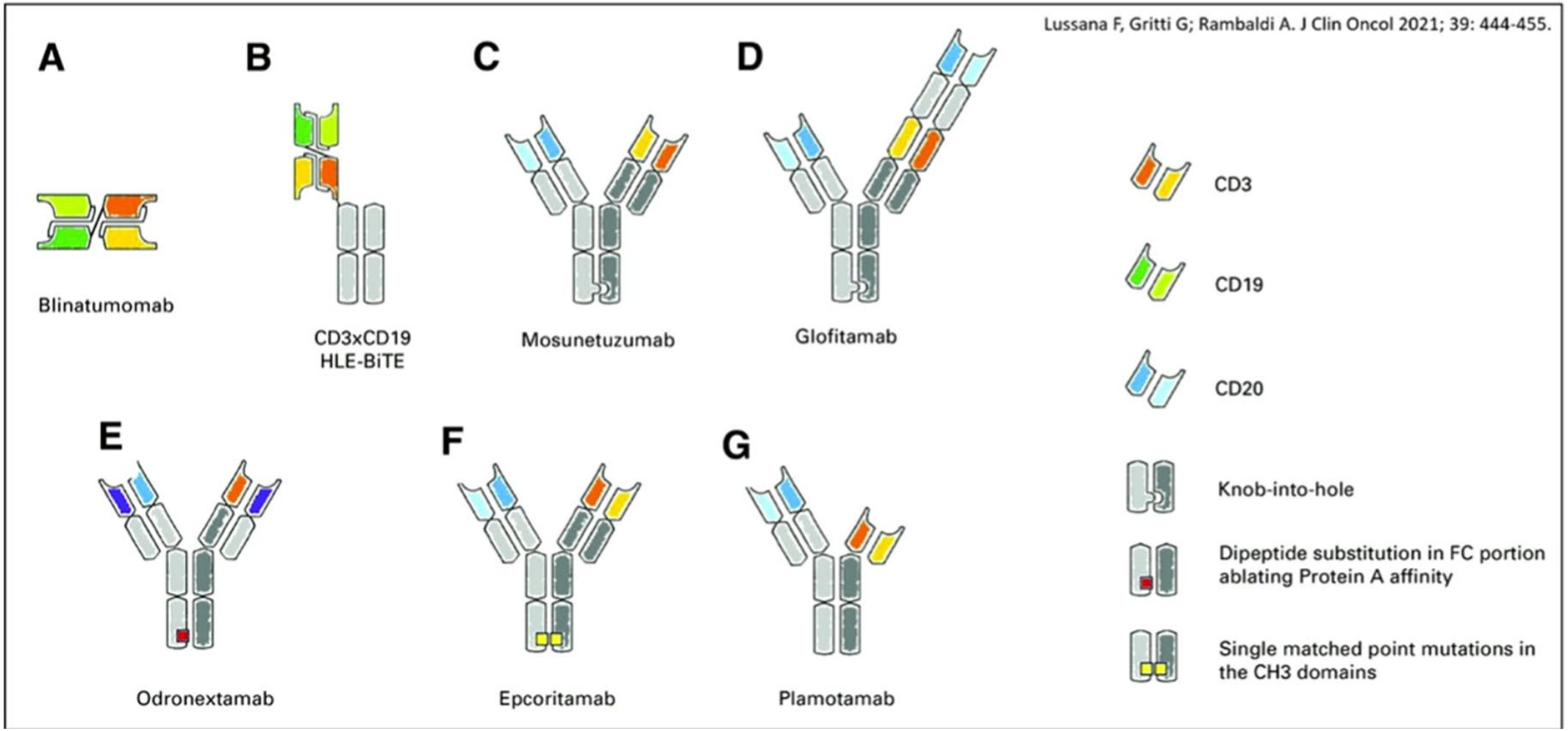
Kalakonda et al, Lancet Haematol 2020

Loncastuximab Tesirine-lypl in DLBCL

- Humanized anti-CD19 antibody conjugated to a PBD dimer toxin
- Administered IV every 3 weeks up to 1 year, then q 12 weeks
- N=145 subjects
- ORR 48.3%, CR rate 24.8%, median PFS about 6 months
- Most common toxicities liver enzymes, cytopenias, fatigue
  - Edema also noted in 20% of patients

Caimi et al, ASH 2020

Structure of selected BITE and bispecific antibodies



Glofitamab in R/R DLBCL pts with 2+ prior therapies

Study overview

Pivotal Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies (NP30179)

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline

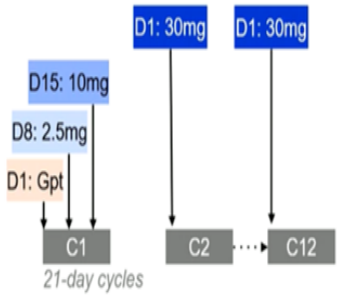
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



Endpoints

- **Primary: CR (best response) rate by IRC***
- **Key secondary:** ORR rate,† DoR, DoCR,† PFS, and OS

Baseline characteristics

n (%)*		N=154†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)

n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

Heavily pre-treated, highly refractory population

Dickinson et al, EHA 2022 # S220

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Glofitamab in R/R DLBCL pts with 2+ prior therapies

Response rates – primary endpoint met

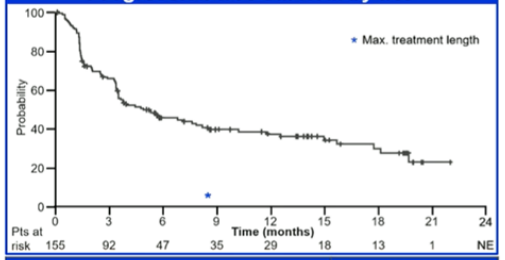
Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)
  - At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†: 35.2% CR rate by IRC significantly greater (p<0.0001) than 20% historical control CR rate‡

High CR/ORR rate at RP2D

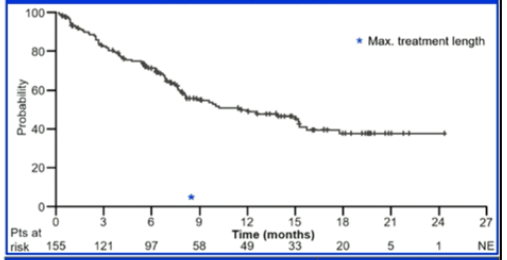
Time-to-event endpoints

Progression-free survival by IRC



	N=155
Median PFS follow-up, mo (range)	12.6 (0–22)
Median PFS, months (95% CI)‡	4.9 (3.4, 8.1)
6-month event-free rate, % (95% CI)	45.5 (37.2, 53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5, 45.8)

Overall survival†



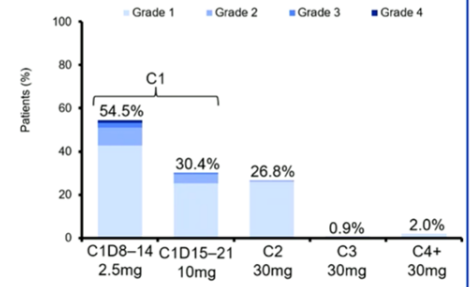
	N=155
Median OS, months (95% CI)‡	11.5 (7.9, 15.7)
12-month OS rate, % (95% CI)	49.8 (41.1, 58.5)

Clinically significant freedom from progression at 12 months and long-term overall survival

Cytokine release syndrome

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

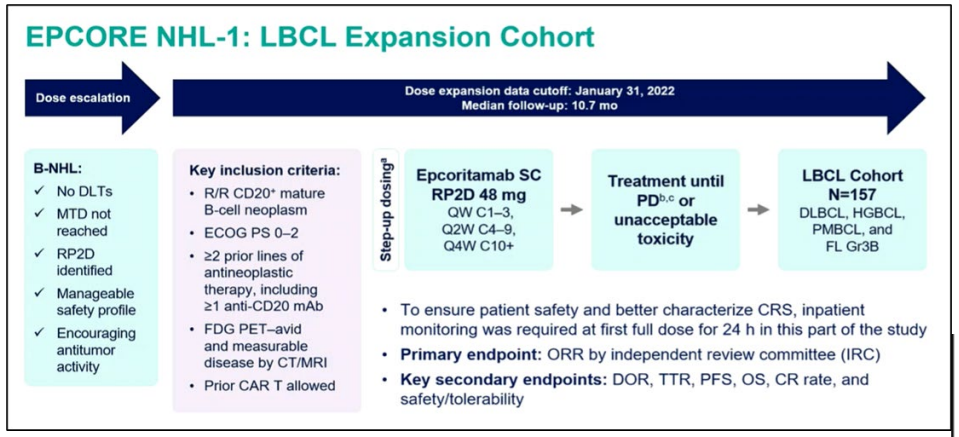
CRS by cycle and grade†



CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

Dickinson et al, EHA 2022 # S220

Epcoritamab in R/R DLBCL pts with 2+ prior therapies



Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
<65 y, n (%)	80 (51)
65 to <75 y, n (%)	48 (31)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Characteristics[a]	**LBCL, N=157**
Disease type, n (%)	
DLBCL	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
Unknown	2/139 (1)
HGBCL	9 (6)
PMBCL	4 (3)
FL Gr3B	5 (3)

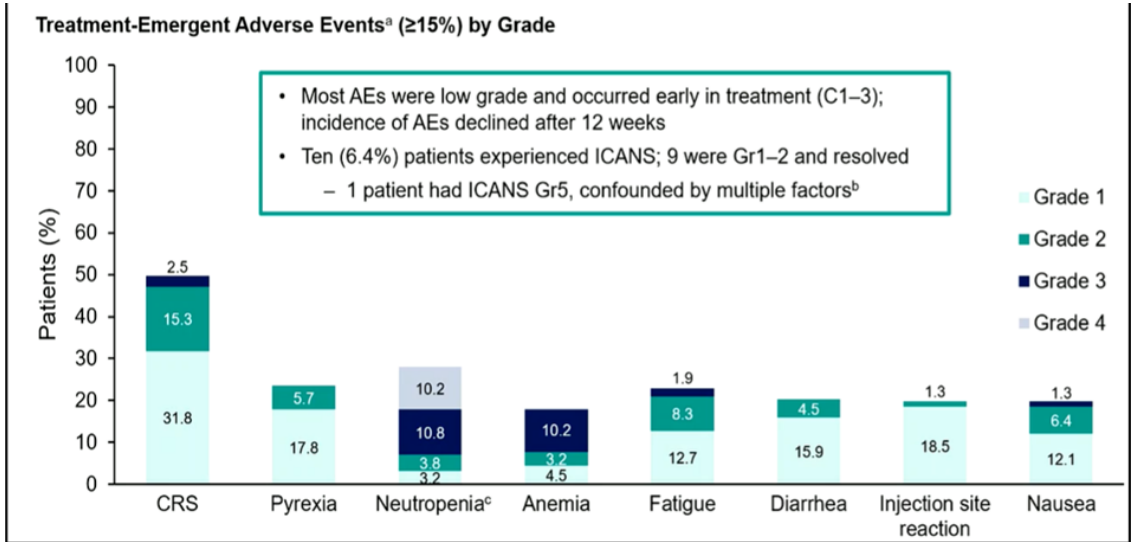
Prior Treatments	LBCL, N=157
Median time from initial diagnosis to first dose, y	1.6
Median time from end of last therapy to first dose, mo	2.4
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory[b] disease, n (%)	96 (61)
Refractory[b] to last systemic therapy, n (%)	130 (83)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Progressed within 6 mo of CAR T therapy	46/61 (75)

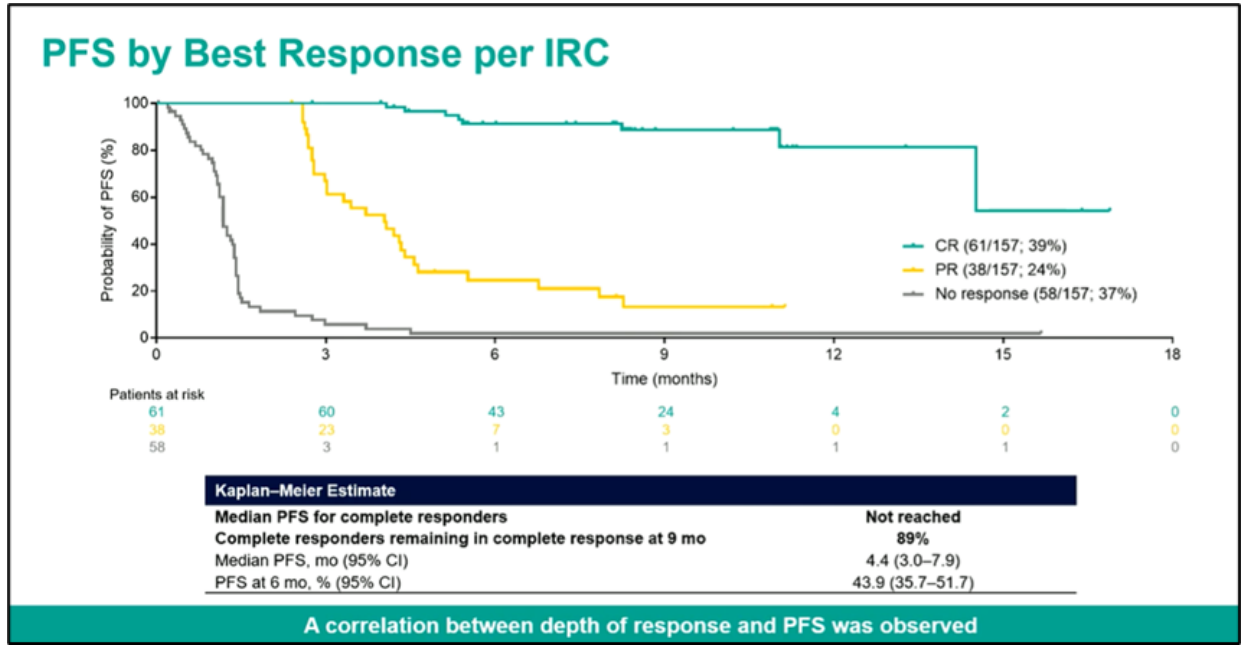
Thieblemont et al, EHA 2022 #LBA 2364

Epcoritamab in R/R DLBCL pts with 2+ prior therapies

Best Overall Response by IRC, n (%)[a]	LBCL N=157
Overall response	**99 (63)** [95% CI: 55–71]
Complete response	**61 (39)** [95% CI: 31–47]
Partial response	38 (24)
Stable disease	5 (3)
Progressive disease	37 (24)

[a]Based on Lugano criteria.





Thieblemont et al, EHA 2022 #LBA 2364

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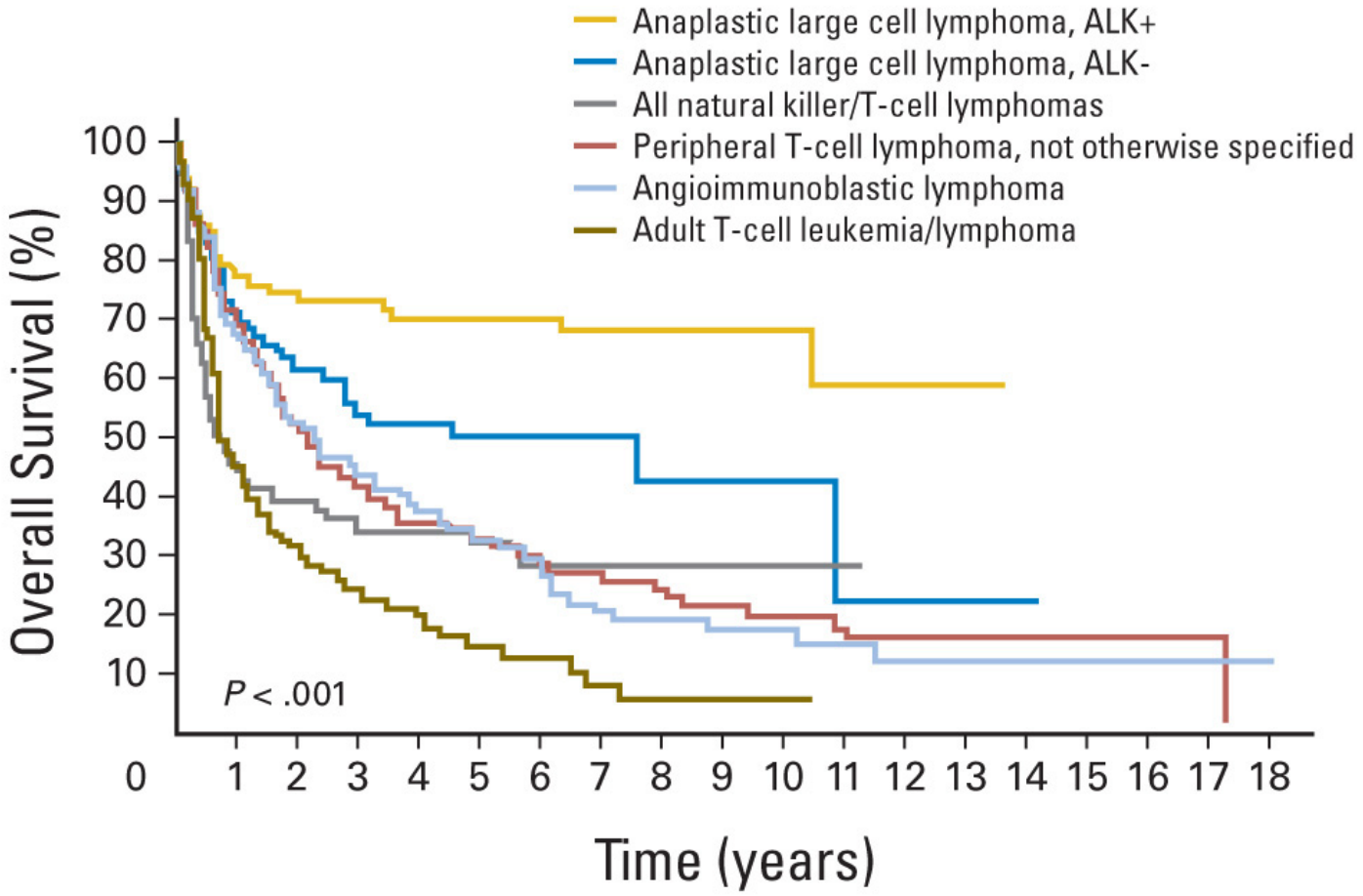
Overall survival in PTCL

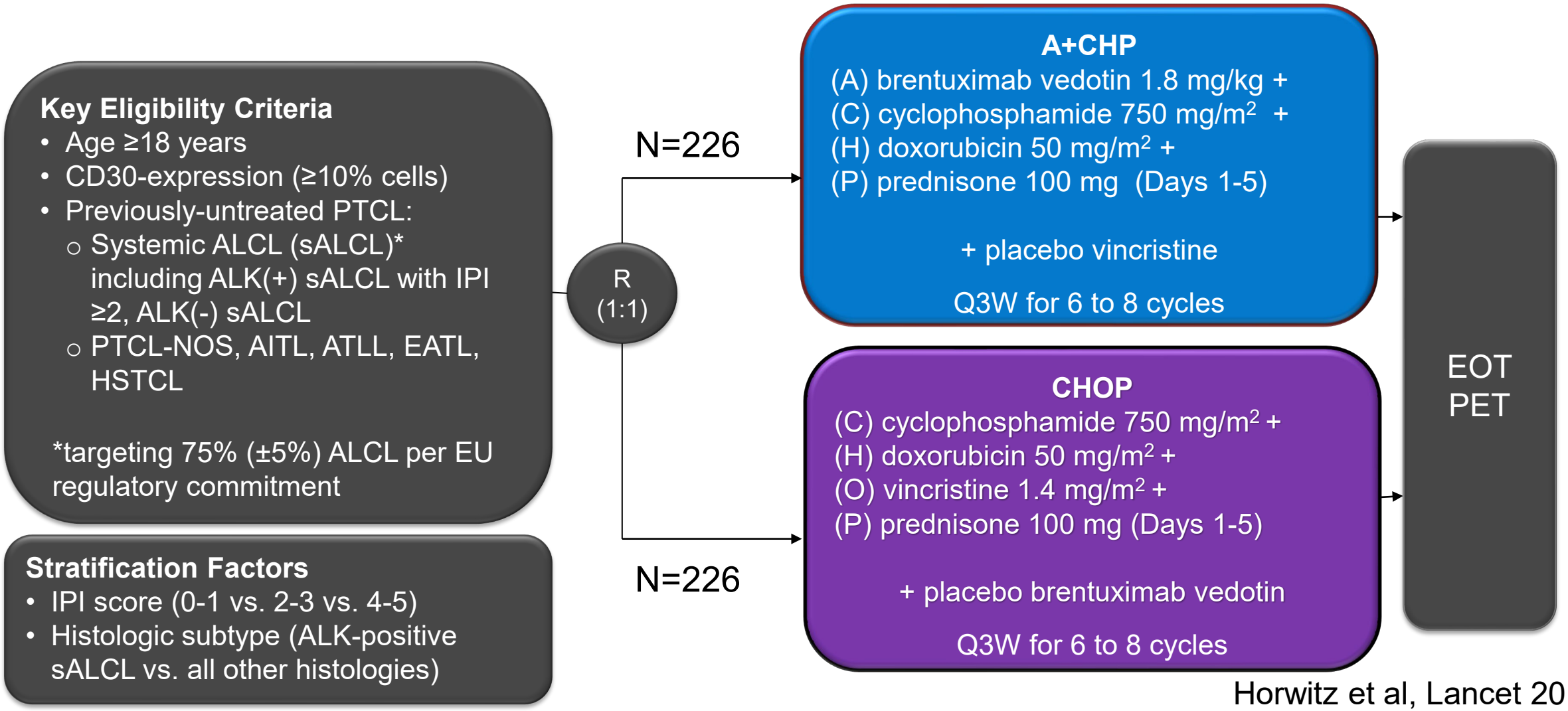


Vose et al: *J Clin Oncol*. 2008;26:4124.

Approach to PTCL

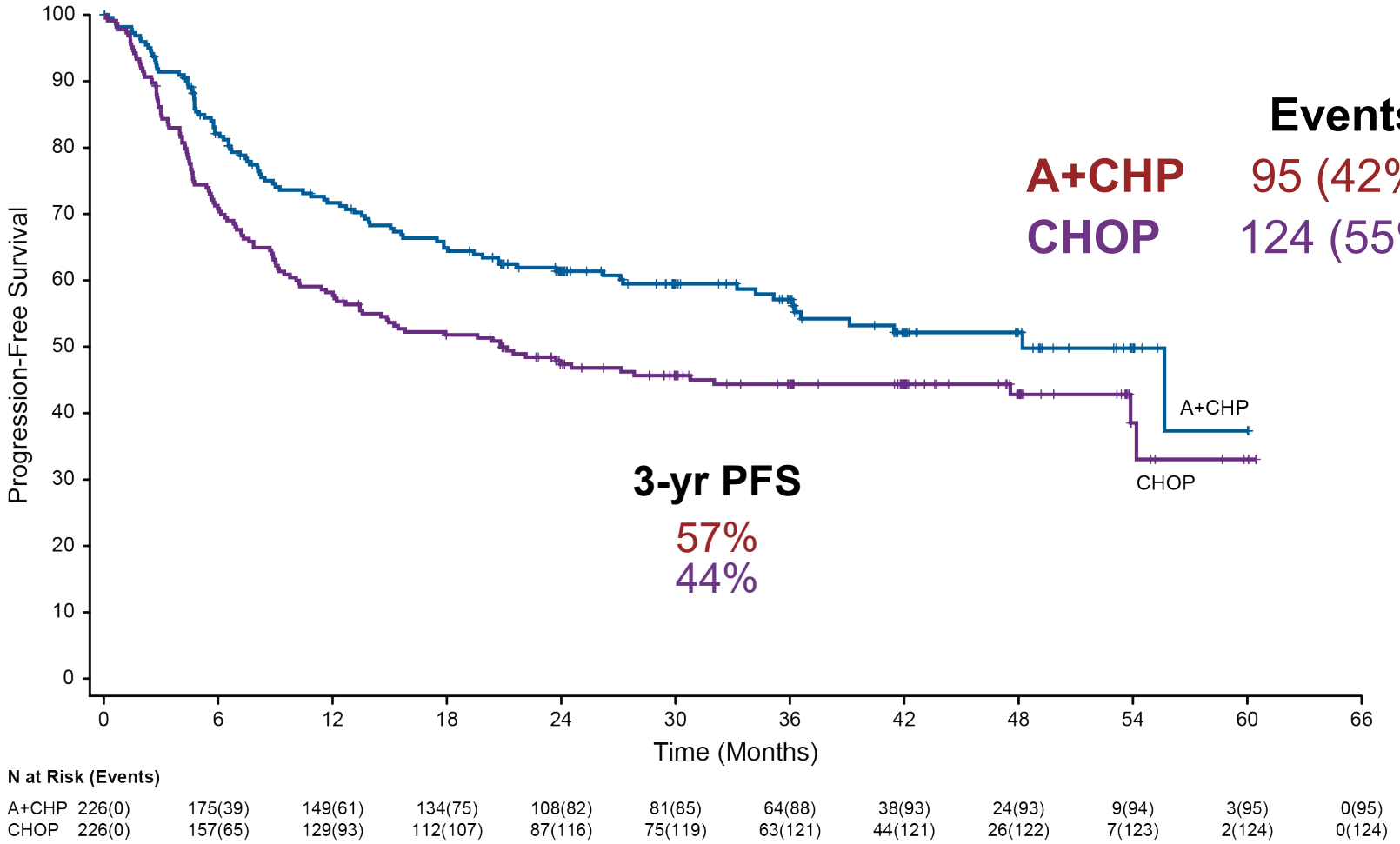
- CHOP vs CHOEP (? Addition of etoposide of value in age <60)
- Unclear value of auto vs allo SCT in first remission vs observation
- Add/use brentuximab vedotin (Anti-CD30 ADC) if CD30+ (>10%)
  - Anaplastic large cell lymphoma (ALCL) is the key CD30+ subtype
- In relapse multiple options (HDAC inhibitors, hypomethylating agents)
  - HDAC inhibitors - romidepsin, vorinostat, belinostat
  - Antimetabolite – pralatrexate
  - Angioimmunoblastic (AITL) – azacitidine with activity

ECHELON-2 Study Design: CD30+ PTCL



Horwitz et al, Lancet 2019

ECHELON-2: Progression-free survival



	Events	HR (95% CI)	*P*
A+CHP	95 (42%)	0.71 (0.54, 0.93)	0.011
CHOP	124 (55%)		

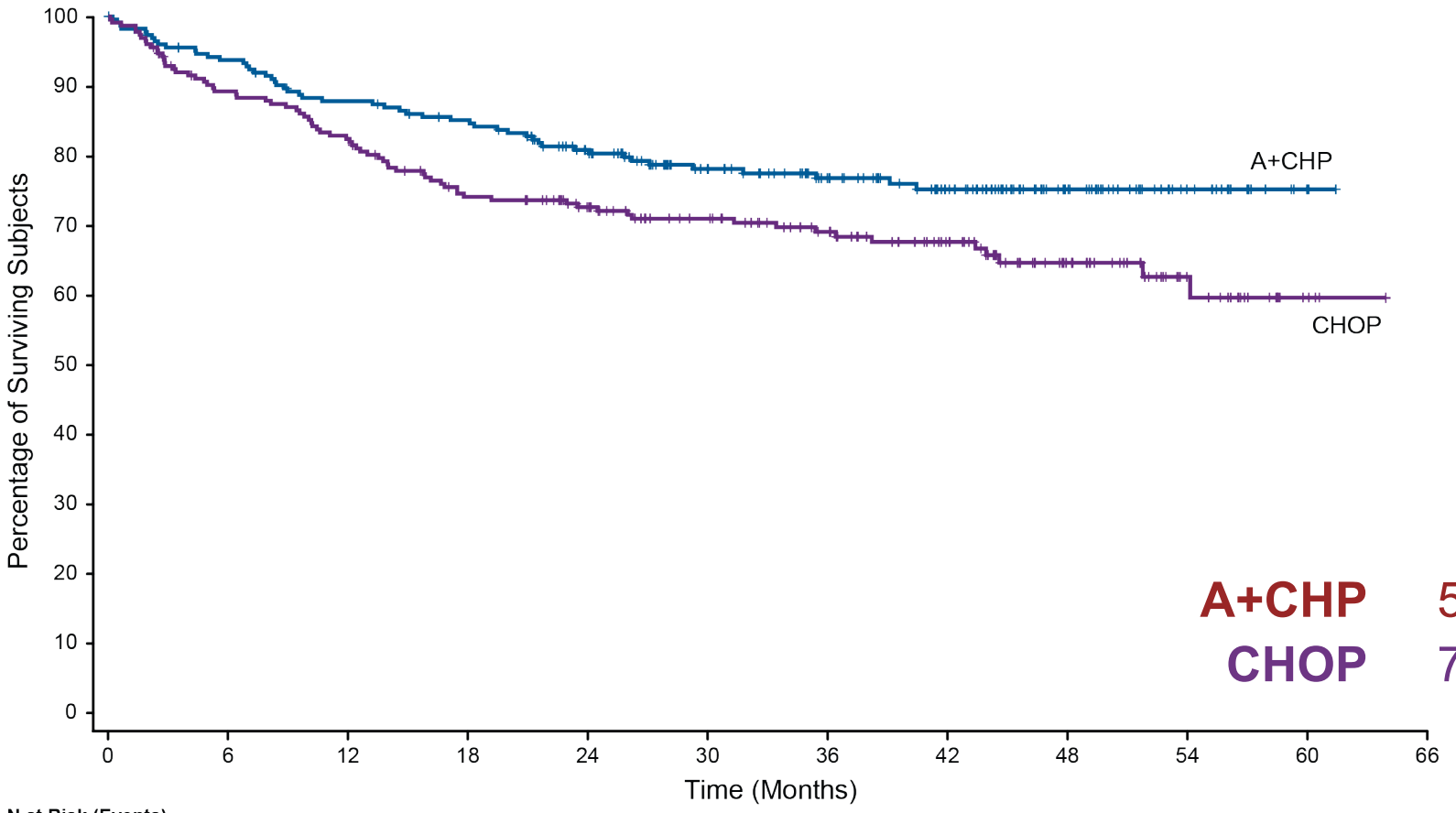
Median PFS (95% CI)

48.2 mo (35.2, NE)
20.8 mo (12.7, 47.6)

Increased diarrhea, neuropathy

Horwitz et al, Lancet 2019

ECHELON-2 Overall Survival



N at Risk (Events)

A+CHP	226(0)	208(14)	193(27)	184(33)	159(42)	128(47)	108(49)	83(51)	45(51)	20(51)	4(51)	0(51)
CHOP	226(0)	196(24)	181(39)	158(57)	140(60)	121(63)	103(66)	79(68)	46(71)	22(72)	4(73)	0(73)

75th Percentile

Not reached
17.5 mo

	Deaths	HR (95% CI)	*P*
A+CHP	51 (23%)	0.66 (0.46, 0.95)	0.0244
CHOP	73 (32%)		

Horwitz et al, Lancet 2019

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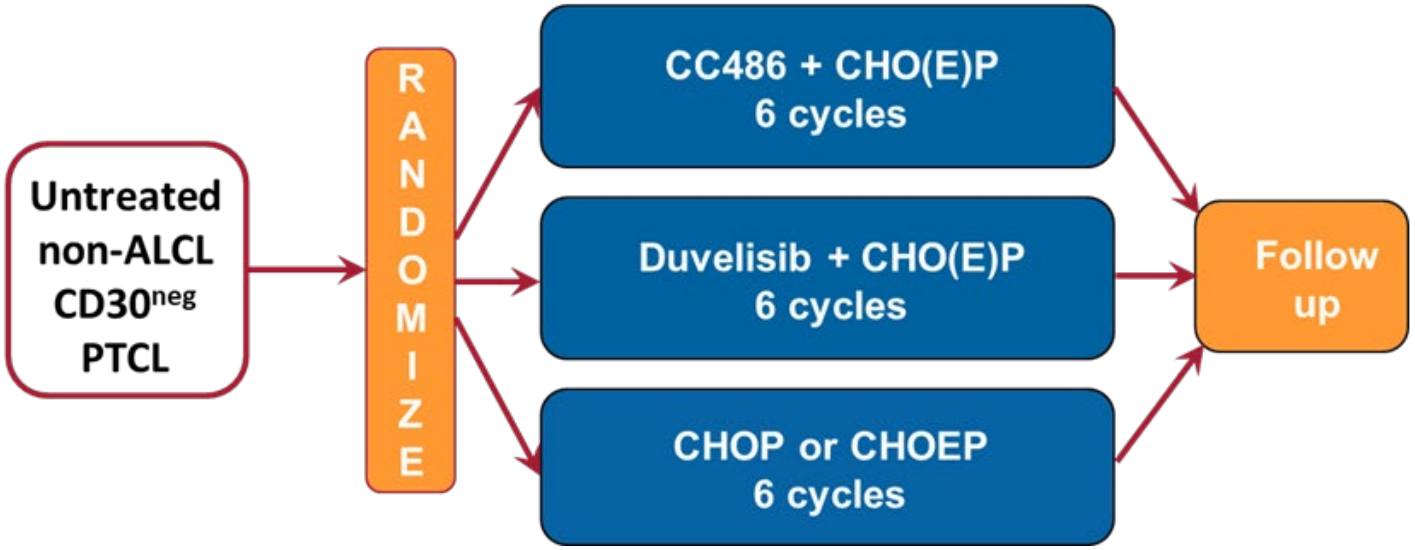
New Alliance/NCTN upfront T cell lymphoma study

- This active combination will be evaluated in the upcoming ALLIANCE Intergroup randomized study A051902, comparing oral azacitidine-CHO(E)P with duvelisib-CHO(E)P against CHO(E)P in patients with CD30-negative PTCL.

A051902 Schema



Key take home points for aggressive lymphoma

- DLBCL
  - ? Role of intensive therapy for double hit
  - PET adapted therapy for limited stage
  - CAR-T clearly have a role (evolving)
  - Multiple novel agents including bispecifics
- T cell
  - CD30-directed therapy of value upfront and relapse
  - Novel combinations under study