Aggressive B and T cell lymphomas: Emerging therapies

John P. Leonard M.D.

Richard T. Silver Distinguished Professor of Hematology and Medical Oncology

Senior Associate Dean for Innovation and Initiatives

Executive Vice Chairman, Joan and Sanford I. Weill Department of Medicine

Disclosures

Consulting advice:

Gilead, Celgene/BMS, Sutro, Genentech/Roche, Bayer, ADC Therapeutics, MEI Pharma, AstraZeneca, Karyopharm, Miltenyi, Regeneron, Epizyme, Abbvie, Incyte, Janssen, GenMab, Eisai

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

Learning Objectives

Understand standard management of patients with aggressive lymphoma

Assess new data on emerging therapies in aggressive lymphoma

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 do I treat 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

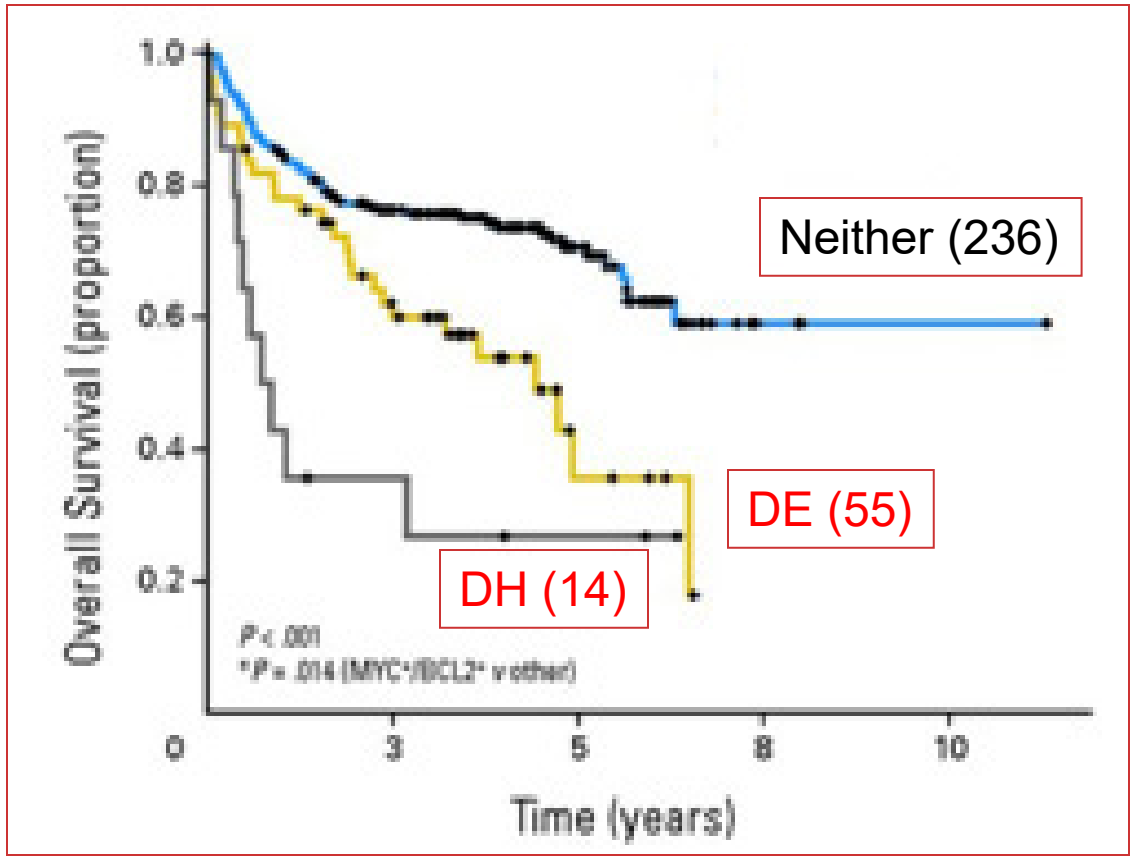
CNS

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

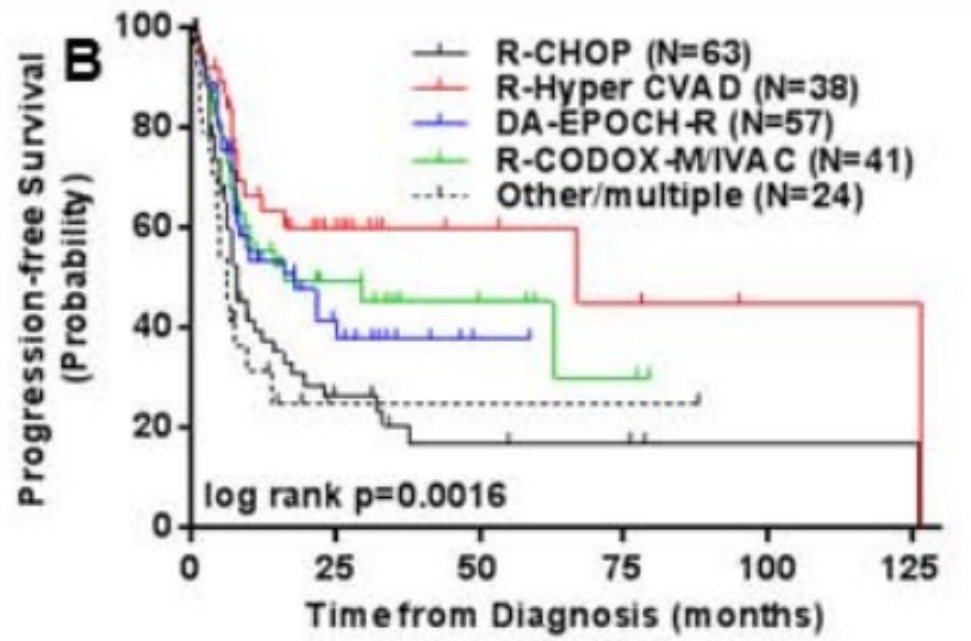


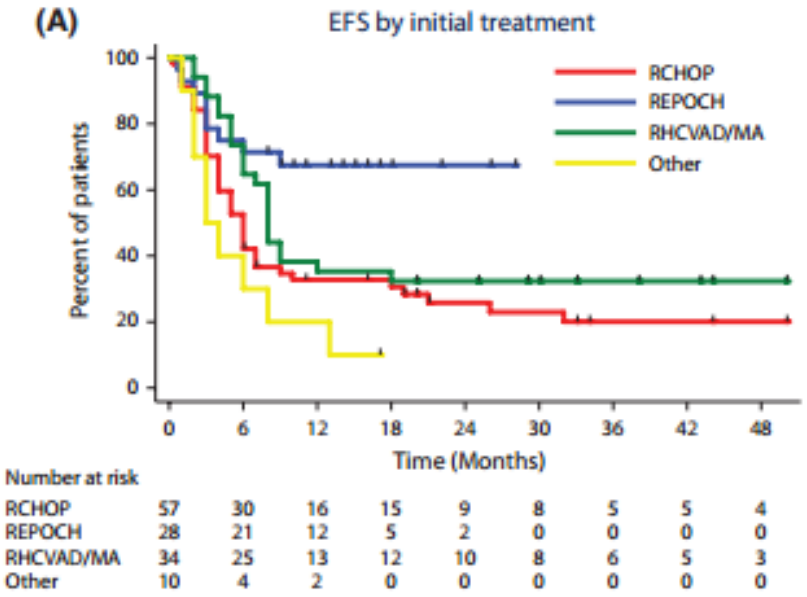
Double expression 4x more common than Double hit

Double expression intermediate in outcome between DH and neither

Johnson et al JCO 2012; 30: 3452

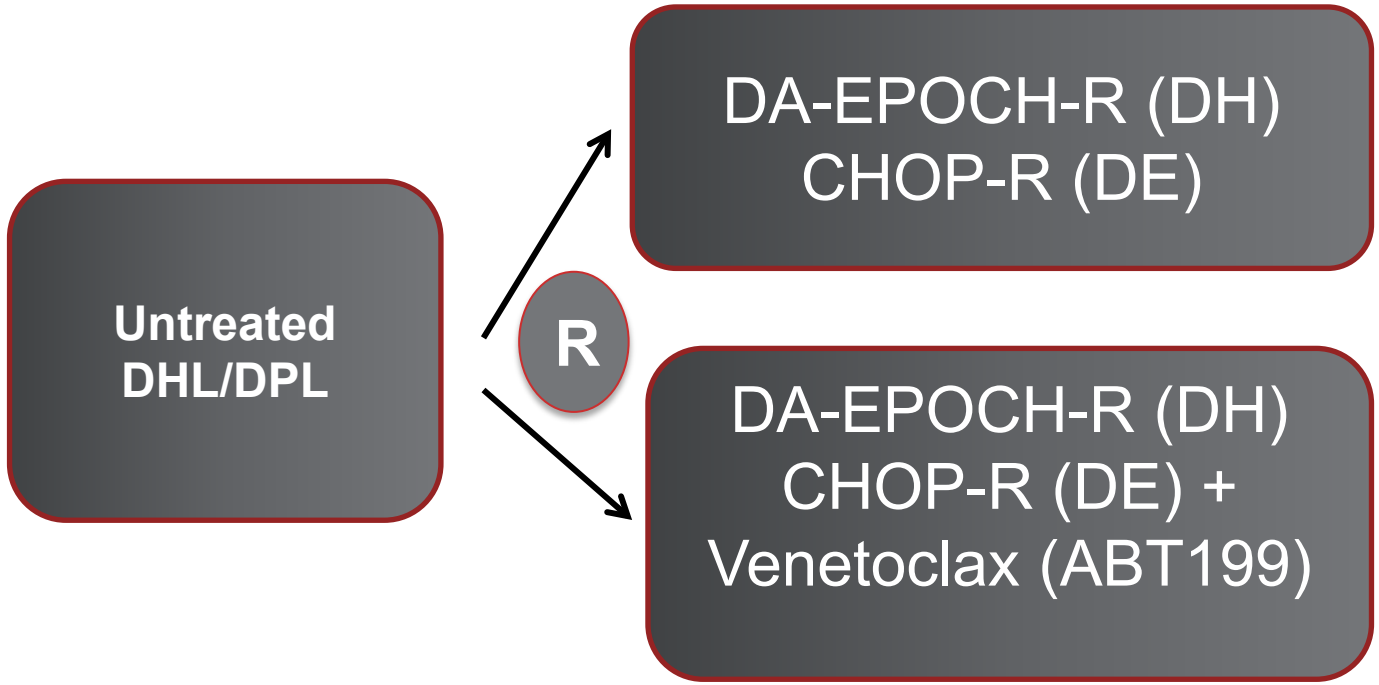
DA-EPOCH-R in double hit lymphoma





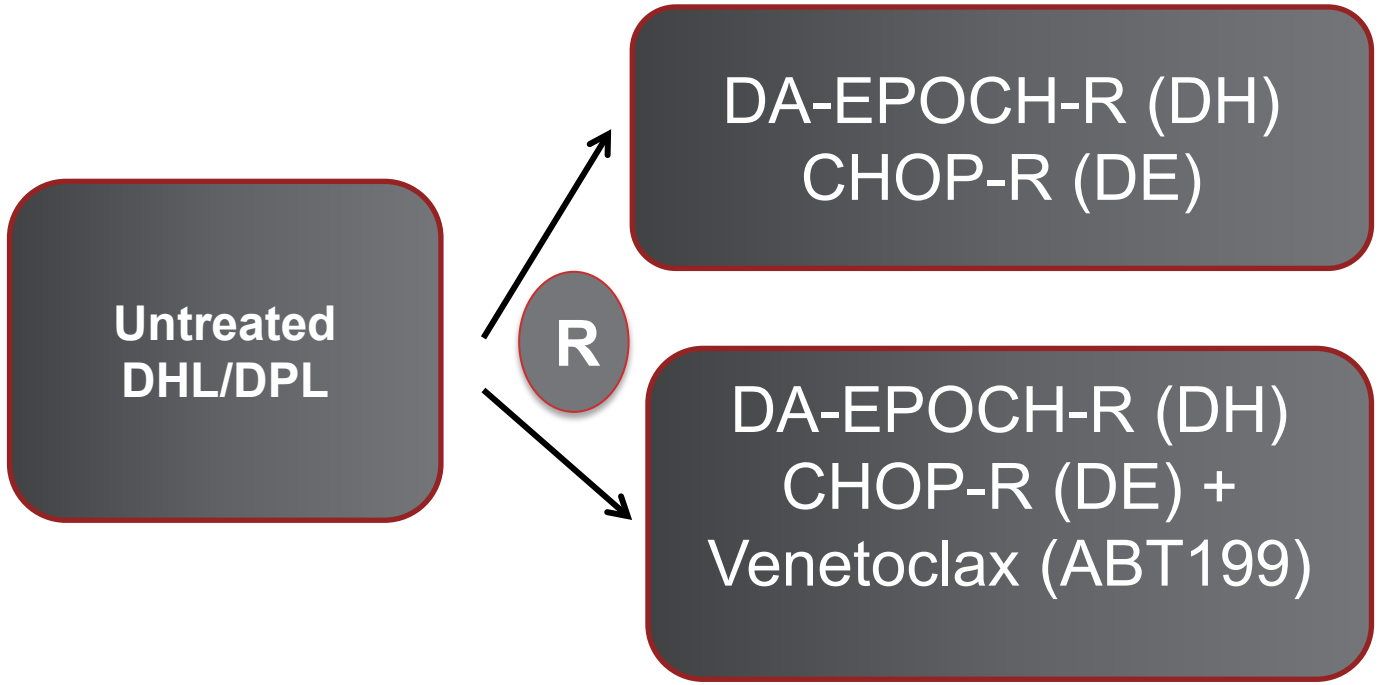
Petrich et al Blood 2014
Oki et al BJH 2014

A51701 Intergroup trial of BCL-2 inhibitor Venetoclax with chemoimmunotherapy in DH/DE DLBCL



Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)

A51701 Intergroup trial of BCL-2 inhibitor Venetoclax with chemoimmunotherapy in DH/DE DLBCL



DH cohort closed due to toxicity issues with Ven/R-EPOCH

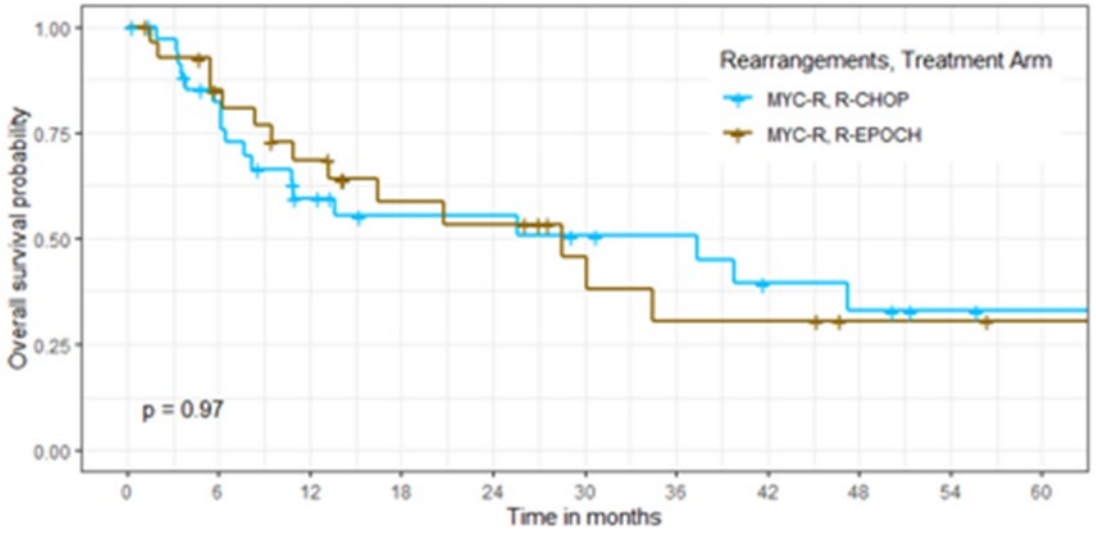
Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)

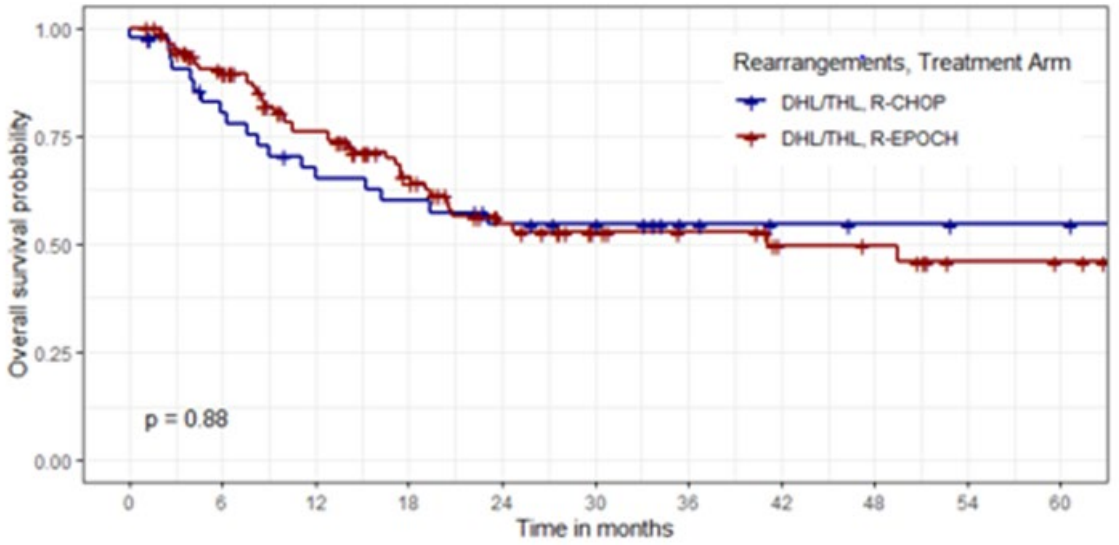
Electronic health record analysis of R-CHOP vs R-EPOCH in double hit lymphoma

- 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, EHA 2021

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



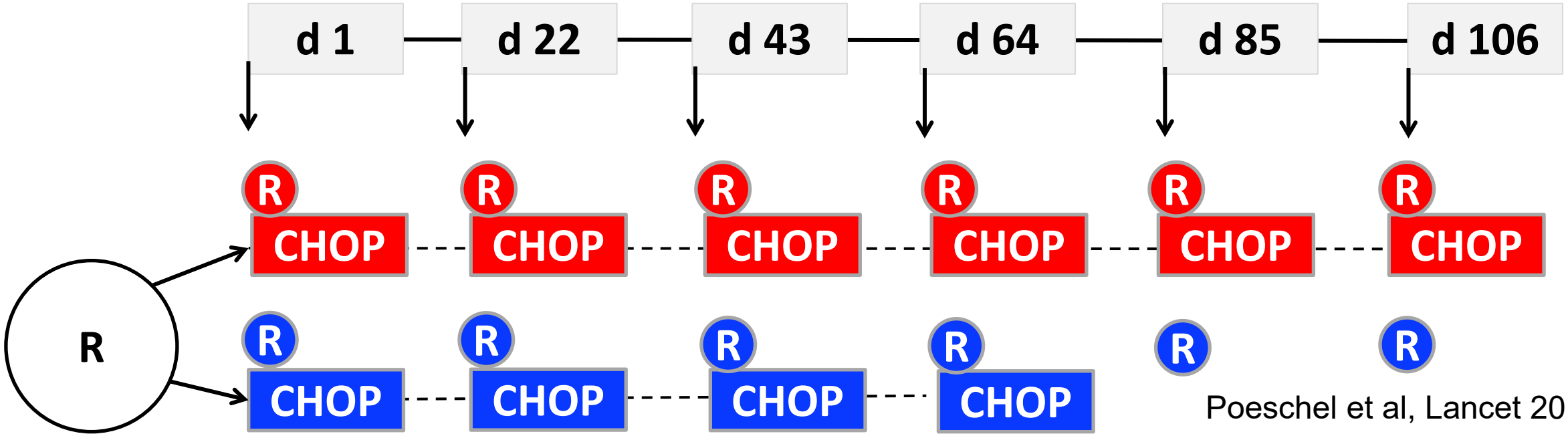


Magnusson et al, EHA 2021

Weill Cornell Medicine NewYork-Presbyterian

FLYER: Study Design

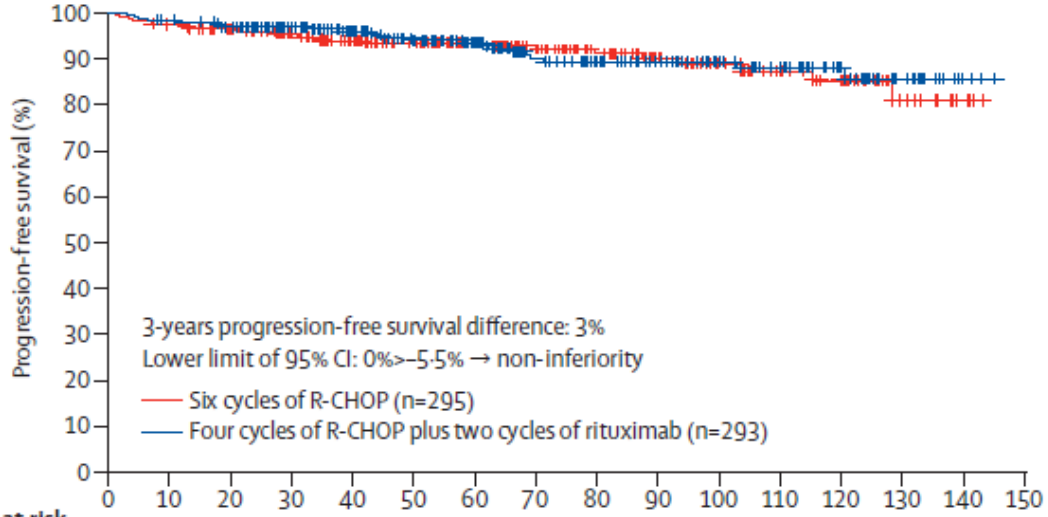
- **Front-line treatment of aggressive B-cell lymphoma**
- **18-60 years, stage I/II, aaIPI = 0, no bulk (max. diameter < 7.5 cm)**



Poeschel et al, Lancet 2019

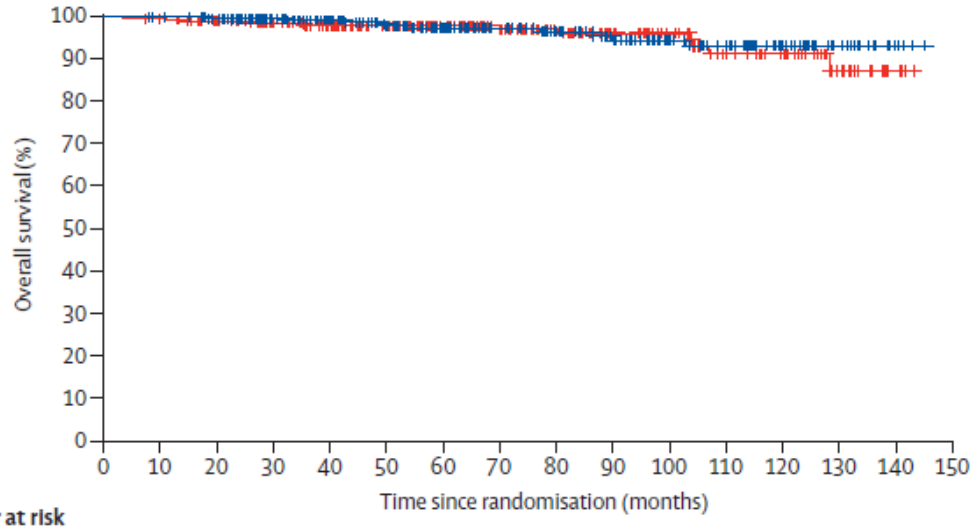
FLYER results
N=588 patients (ITT)

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)

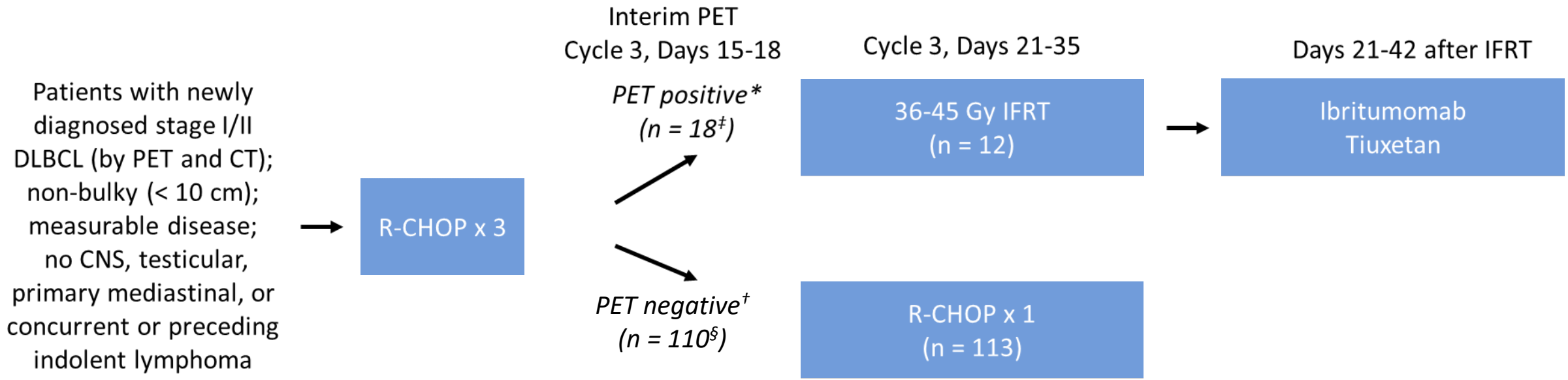
OS



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

Intergroup NCTN S1001: Study design

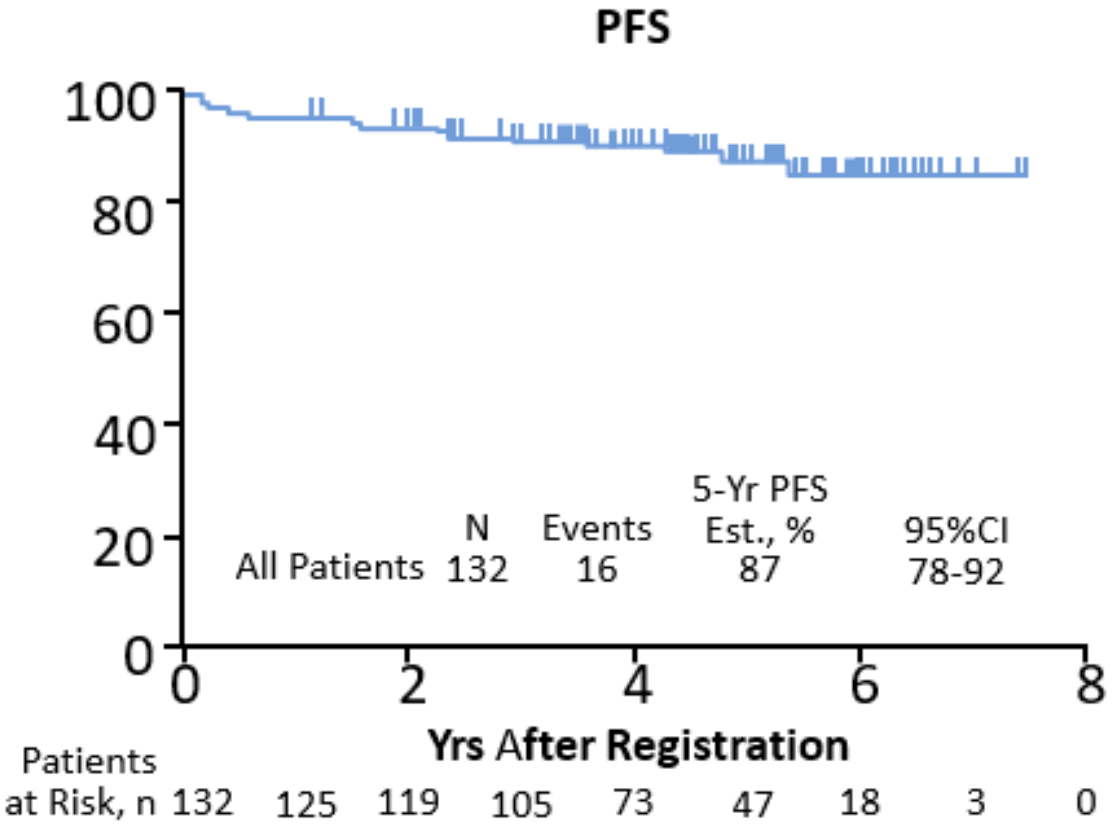


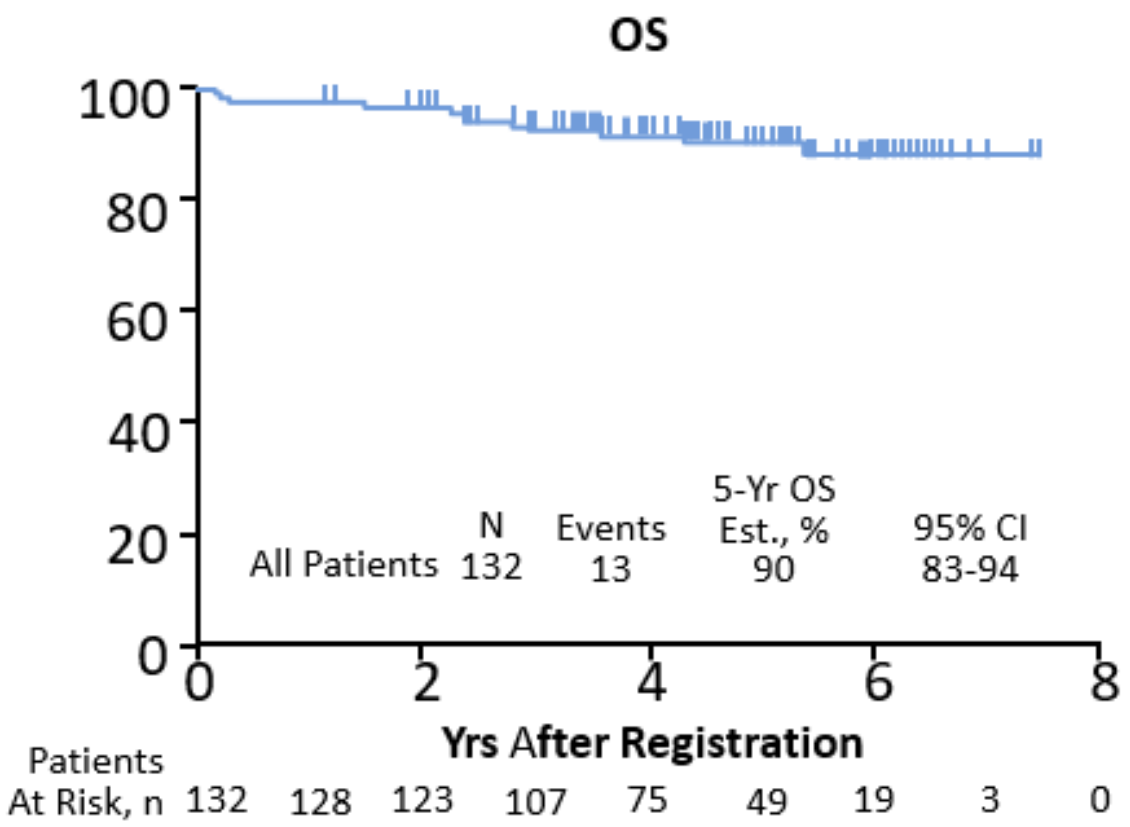
*PET+: Deauville 4-5. †PET-: Deauville 1-3. ‡n = 2 refused tx; n = 4 with Deauville X transferred to PET- arm. §n = 2 did not receive tx. Patients with stage I/II DLBCL by CT but stage III/IV by PET received R-CHOP x 6 cycles.

- 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 et al, ASH 2019

Intergroup NCTN S1001: Survival





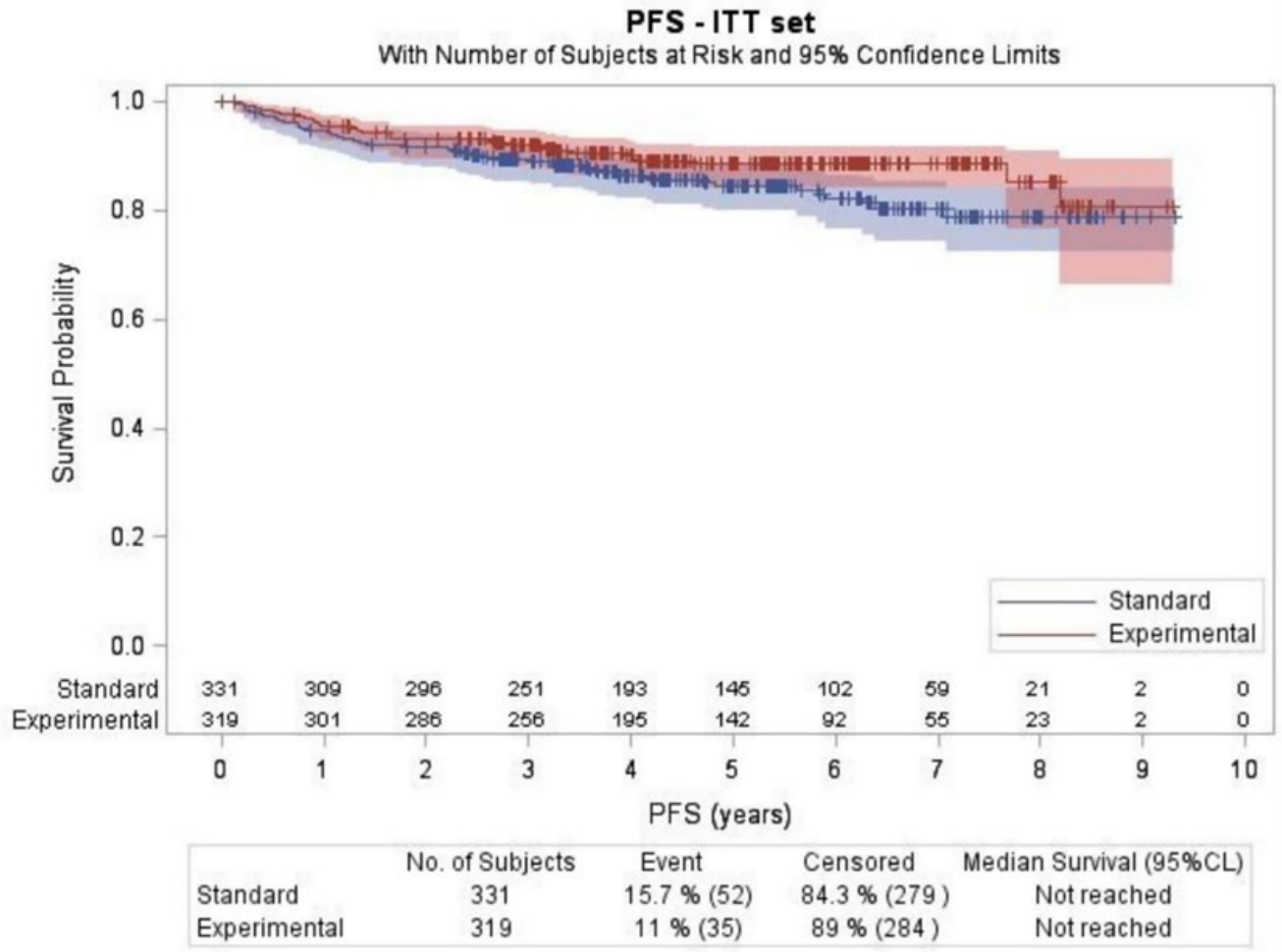
Persky et al, ASH 2019

Early PET response adapted therapy in localized diffuse large B cell lymphoma (LYSA LNH 09-1B)

- 650 patients, age 18-80, aaIPI=0, median f/u 5.1 years
- Standard arm R-CHOP x 6
- Experimental arm PET2 neg 4 cycles vs PET2 pos 6 cycles
  - Deauville 1, 2, 3 = negative
- 44% age 60+, 4% bulky > 10 cm, 53% extranodal disease

Bologna et al, ICML 2021

Early PET response adapted therapy in localized diffuse large B cell lymphoma (LYSA LNH 09-1B)



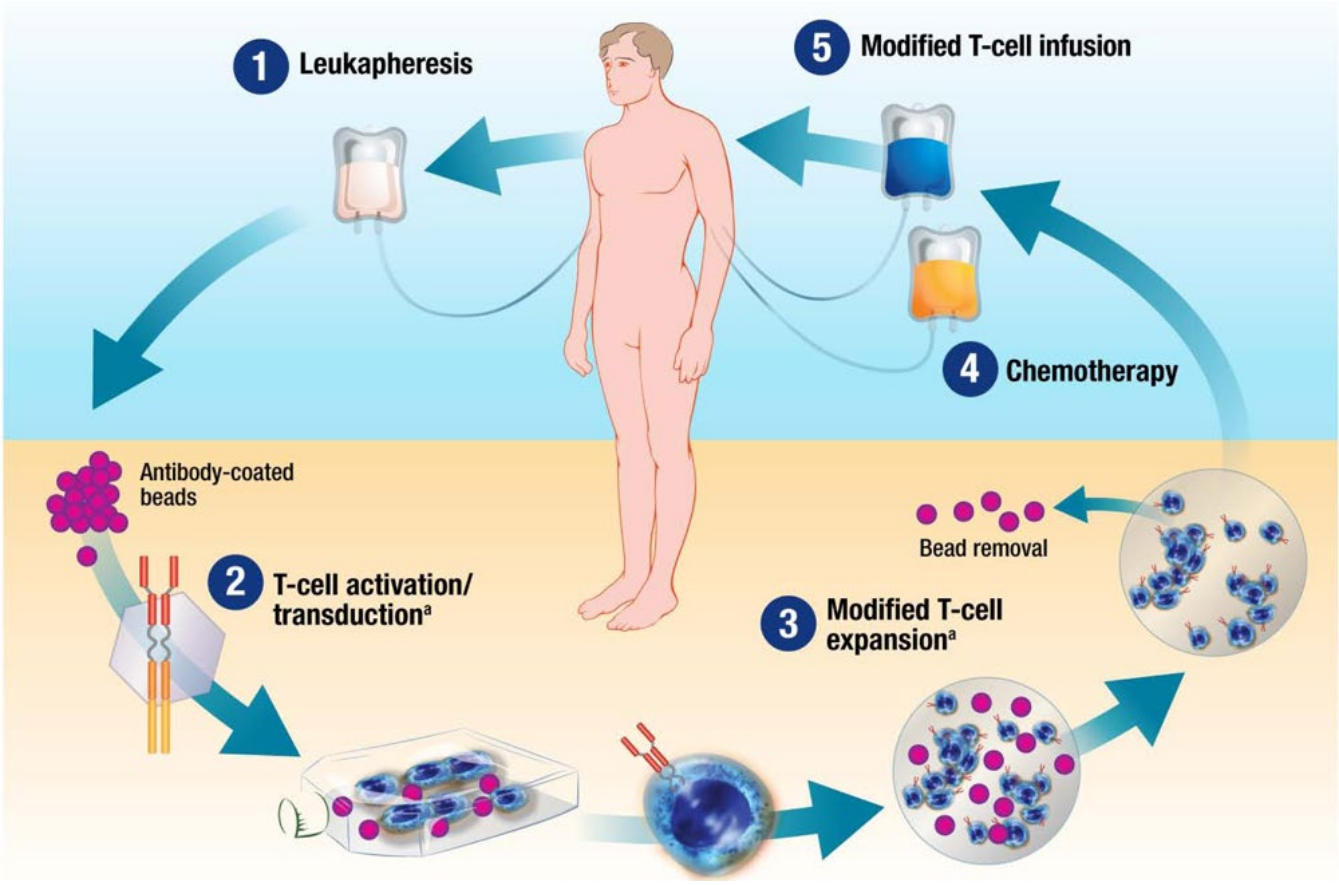
3 year EFS
89.2% (control)
92.0% (experimental)

69 pts relapsed
median 25.9 months
(4.8-75.7 months)

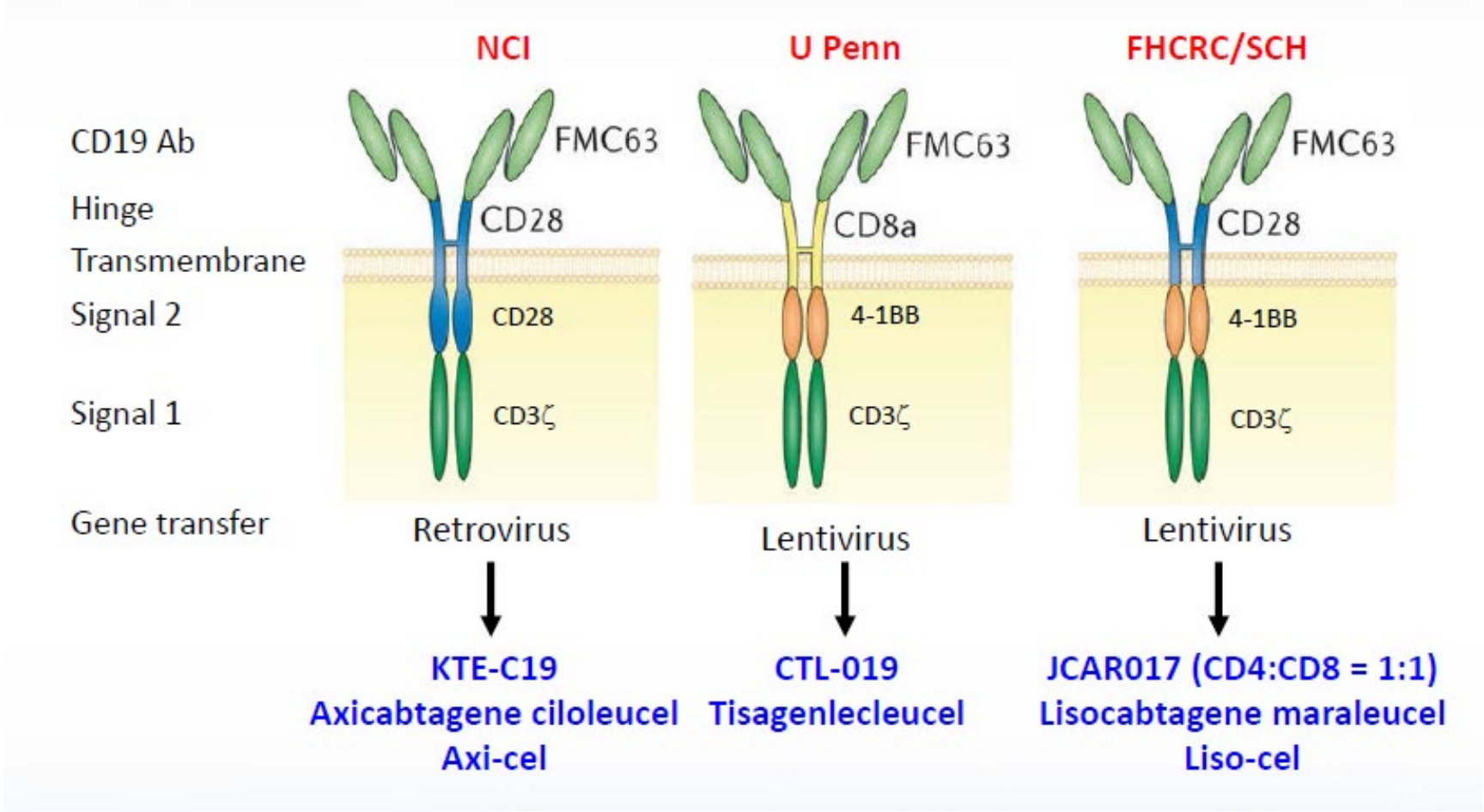
Late relapses may occur

Bologna et al, ICML 2021

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



CAR-T cell constructs



Adapted from van der Steegen et al, Nat Rev Drug Discov 2015

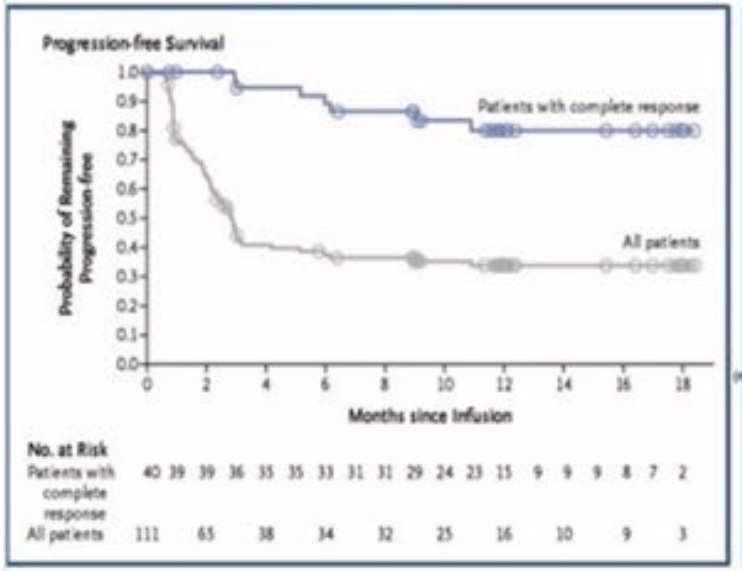
3 FDA approved CAR-T for recurrent DLBCL patients

Study	Number & lympho-depletion	Construct	ORR / CR	1-yr PFS	Grade 3-4 CRS/CRES
Zuma-1 Axi-Cel	111 (101) / Flu/CY / bridge not allow	Retrovirus / CD3ζ / CD28	82% / 54%	44%	13% / 28%
JULIET Tisa-Cel	165 (111) / various LD regimens / 92% bridged	Lentiviral / CD3ζ / 4-1BB	52% / 40%	~35%	22% / 12%
JCAR- 017 Liso-Cel	344 (269) / Flu/CY / 59% bridged	Lentiviral / CD3ζ / 4-1BB	73% / 53%	44%	2% / 10%

Neelapu S. NEJM. 2017;377:2531-44. Schuster S. NEJM. 2019;380:45-56. Abramson J. Lancet. 2020;396:839-852.

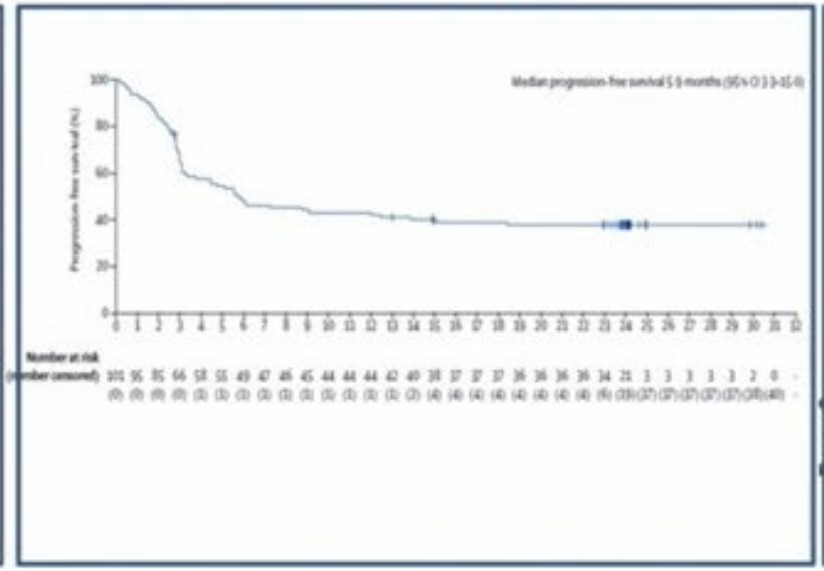
CAR-T agents for recurrent DLBCL with meaningful PFS

JULIET



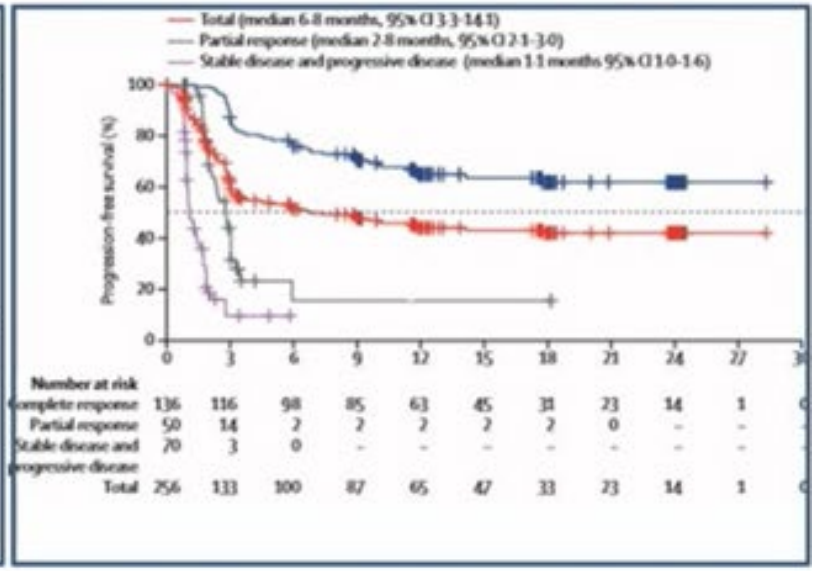
Schuster SJ, et al. *N Engl J Med.* 2019

ZUMA-1



Locke FL, et al. Lancet Oncol. 2018

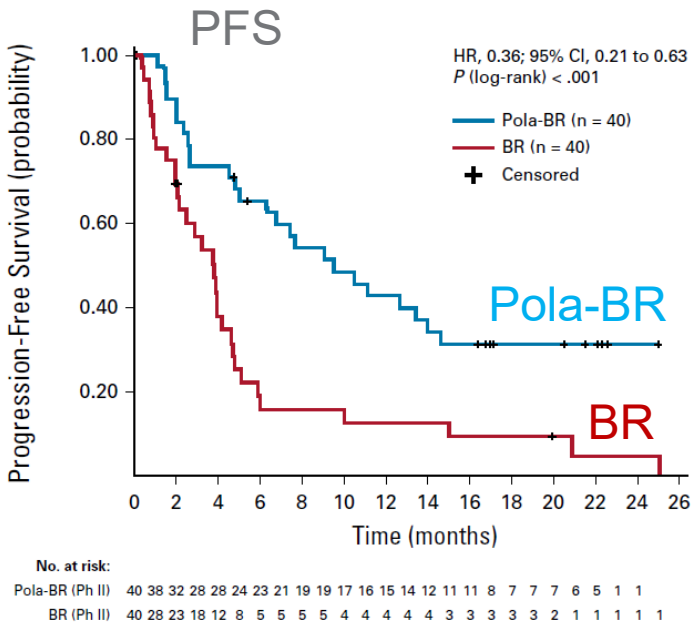
TRANSCEND-001

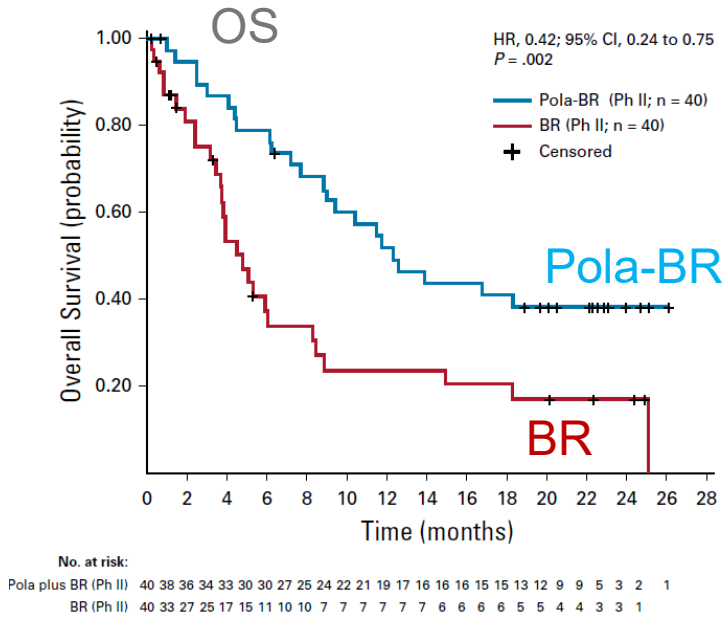


Abramson JS, et al. *Lancet.* 2020

Thieblemont et al, EHA 2021

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

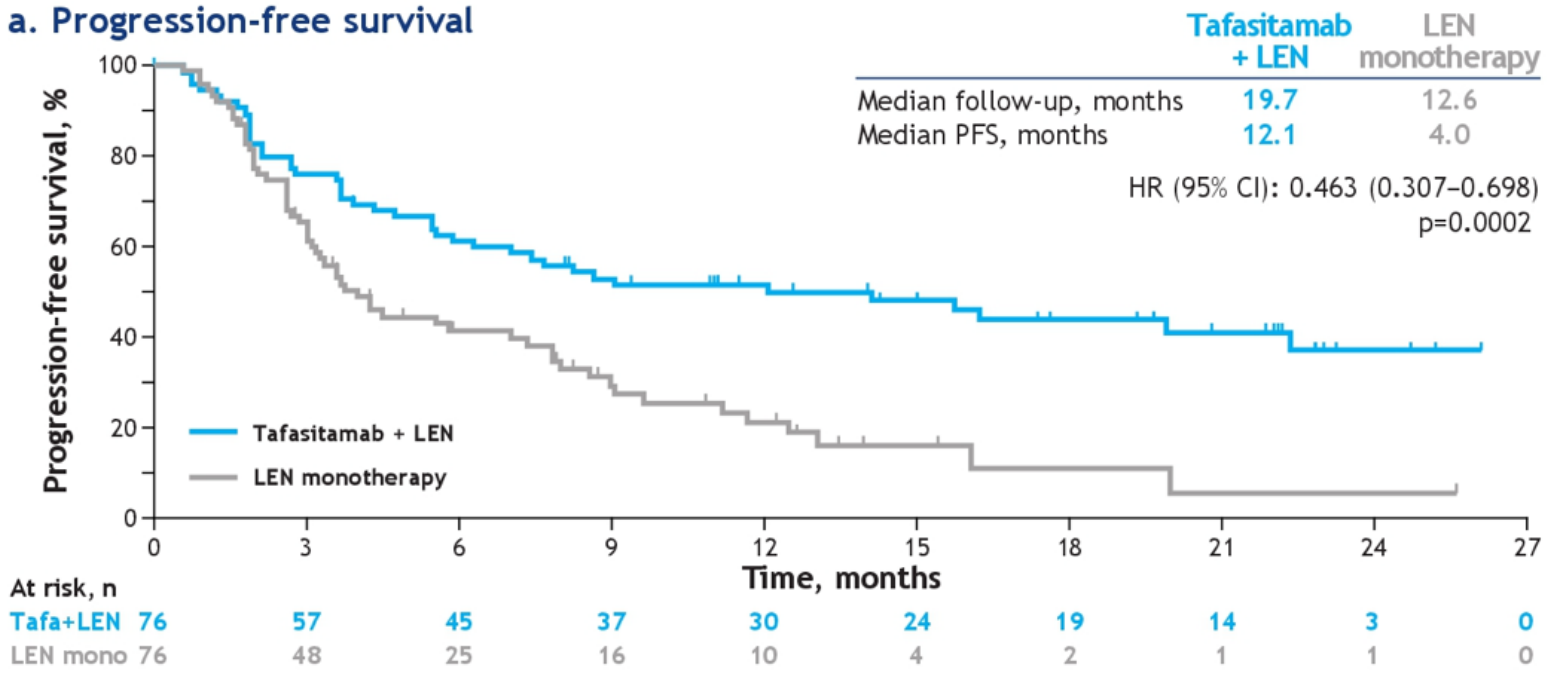




FDA approval 2019: +BR for relapsed/refractory DLBCL, >2 prior therapies

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

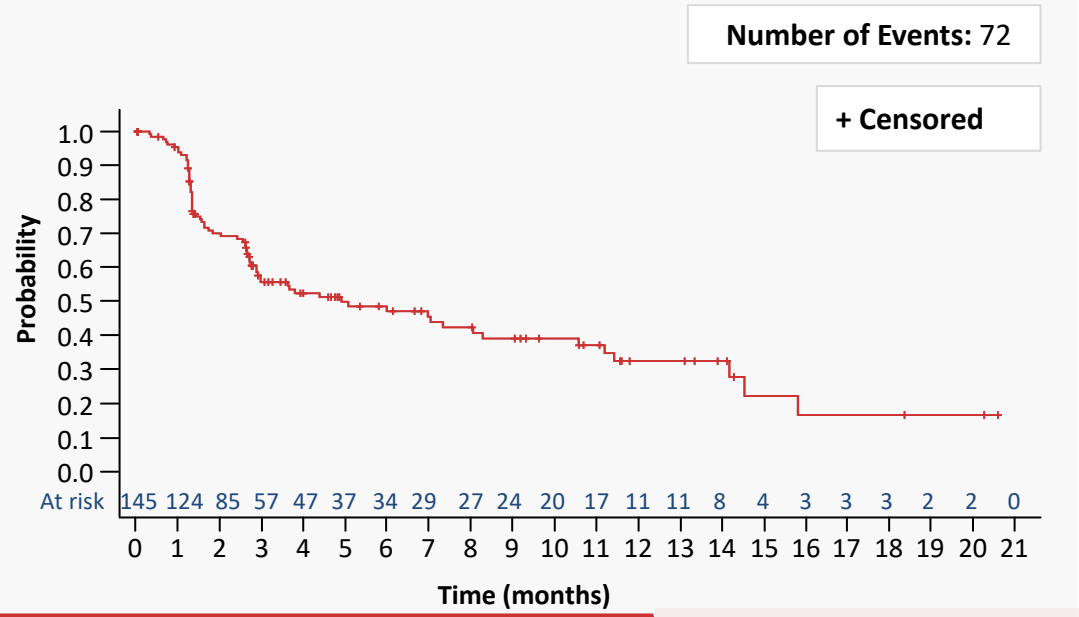
Loncastuximab Tesirine-lypl in DLBCL

- 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%
- Most common toxicities liver enzymes, cytopenias, fatigue
  - Edema also noted in 20% of patients

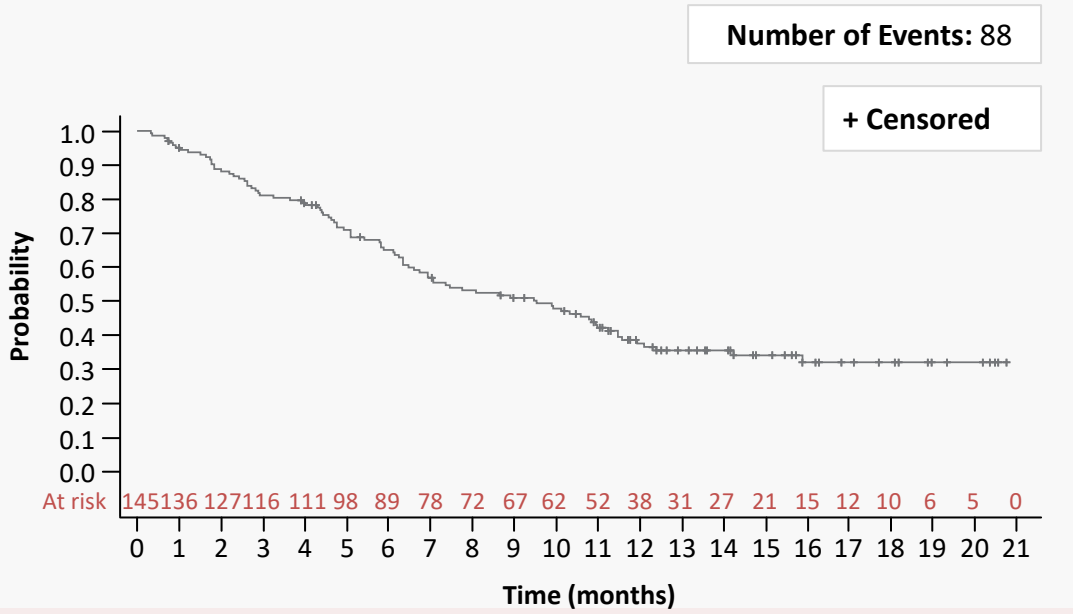
Caimi et al, ASH 2020

Loncastuximab tesirine-lypl in DLBCL

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



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

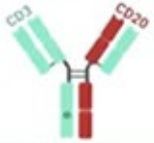


Subsequent Treatment

- **15 patients** received CD19-directed CAR-T therapy with an investigator-assessed ORR of 46.7% (6 CR; 1 PR)
- **9 patients** proceeded to SCT as consolidation after Lonca response

Caimi et al, ASH 2020

Structure of selected BITE and bispecific antibodies

Bispecific Antibody	Targets	Design	Ig Fragment Formats	Ref.
blinatumomab	CD19 x CD3		• two murine scFv joined by a glycine-serine linker • monovalent CD19 and monovalent CD3 binding • cloned from anti-CD19 (clone HD37) and anti-CD3 (clone L2K-07) murine mAbs	1, 2, 3
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	4
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	5
odronextamab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb	6
epcoritamab	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	7

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor

[1]Dufner V, *et al.* Blood Adv (2019) 3:2491; [2]Goebeler ME, *et al.* J Clin Oncol (2016) 34:1104; [3]Viardot *et al.* Blood (2016) 127(11):1410; [4]Schuster SJ, *et al.* ASH 2019, Plenary Abstract 6; [5]Hutchings M, *et al.* ASH 2020, Abstract 403; [6]Bannerji R, *et al.* ASH 2020, Abstract 400; [7]Hutchings M, *et al.* ASH 2020, Abstract 406

Schuster et al, ICML 2021

Data with BITE and bispecific antibodies in patients with recurrent DLBCL

target	Drug	Study	Study phase	No*	Efficacy	References
CD20/CD3	**Blinatumomab**	NCT01741792	2	25	**ORR 43%** **CR 19%**	Viardot et al. Blood 2016
CD20/CD3	**RG6026**	NCT03075696	1b	28	**ORR 48%** **CR 43%**	Morschhauser F ASH2019 # 1584
CD20/CD3	**Mosunetuzumab**	NCT02500407	1/1b	55	**ORR 33%** **CR 21%**	Buddle LI ASH 2018 #399
CD20/CD3	**REGN1979 odronextamab**	NCT02290951	1	53	**ORR 33%** **CR 18%**	Bannerji R ASH 2019 #762
CD20/CD3	**REGN1979 odronextamab**	NCT02290951	expansion	136	**ORR no prior CART 55%** **CR 55%** **ORR prior CART 33%** **CR 21%**	Bannerji R ASH 2020
CD19/CD3	**Epcoritamab subcutaneous**	NCT03625037	1/2	45	**ORR 66.7%** **CR 13%**	Hutchings M ASH 2020
CD20/CD3	**Glofitamab (RG6026)** **D-7obinutuzumab**	NCT03075696	Expansion	12	**ORR 61% in all aNHL** **CR 54% in all aNHL**	Hutchings M ASH 2020

* DLBCL only

Thieblemont et al, EHA 2021

T cell lymphoma

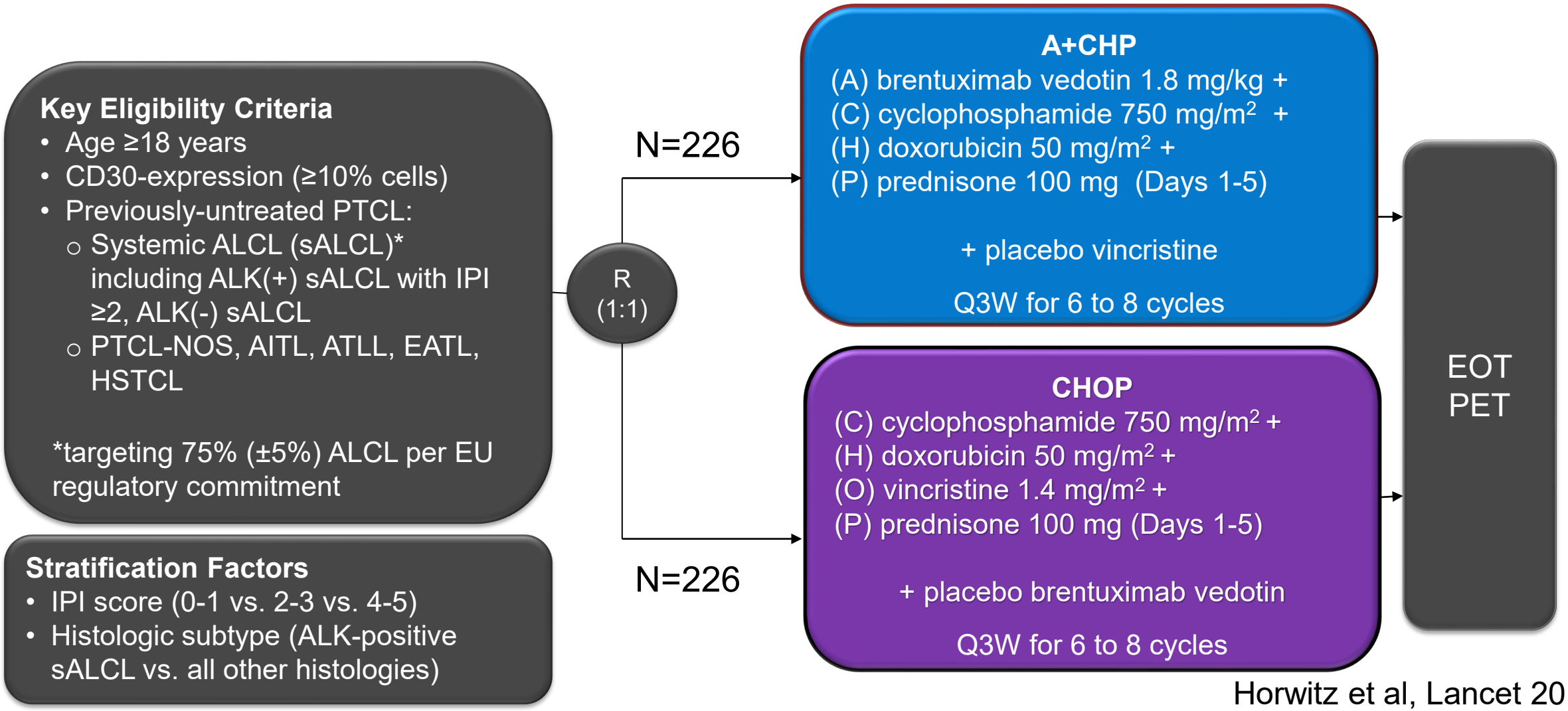
CHOP or CHOEP standard of care

Brentuximab vedotin if CD30+

Consideration of SCT in first remission

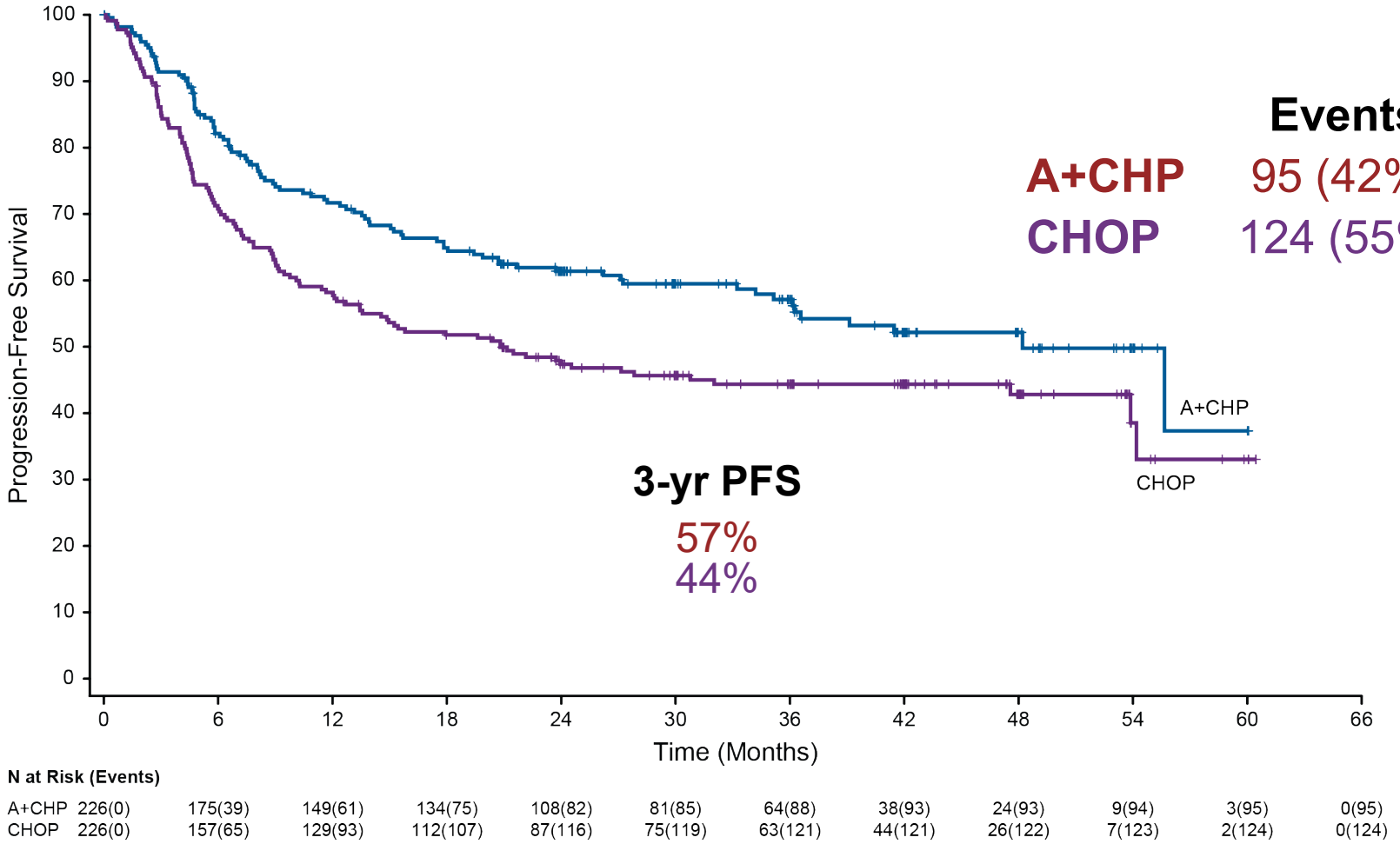
Various approaches and novel agents in relapsed setting

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%)		

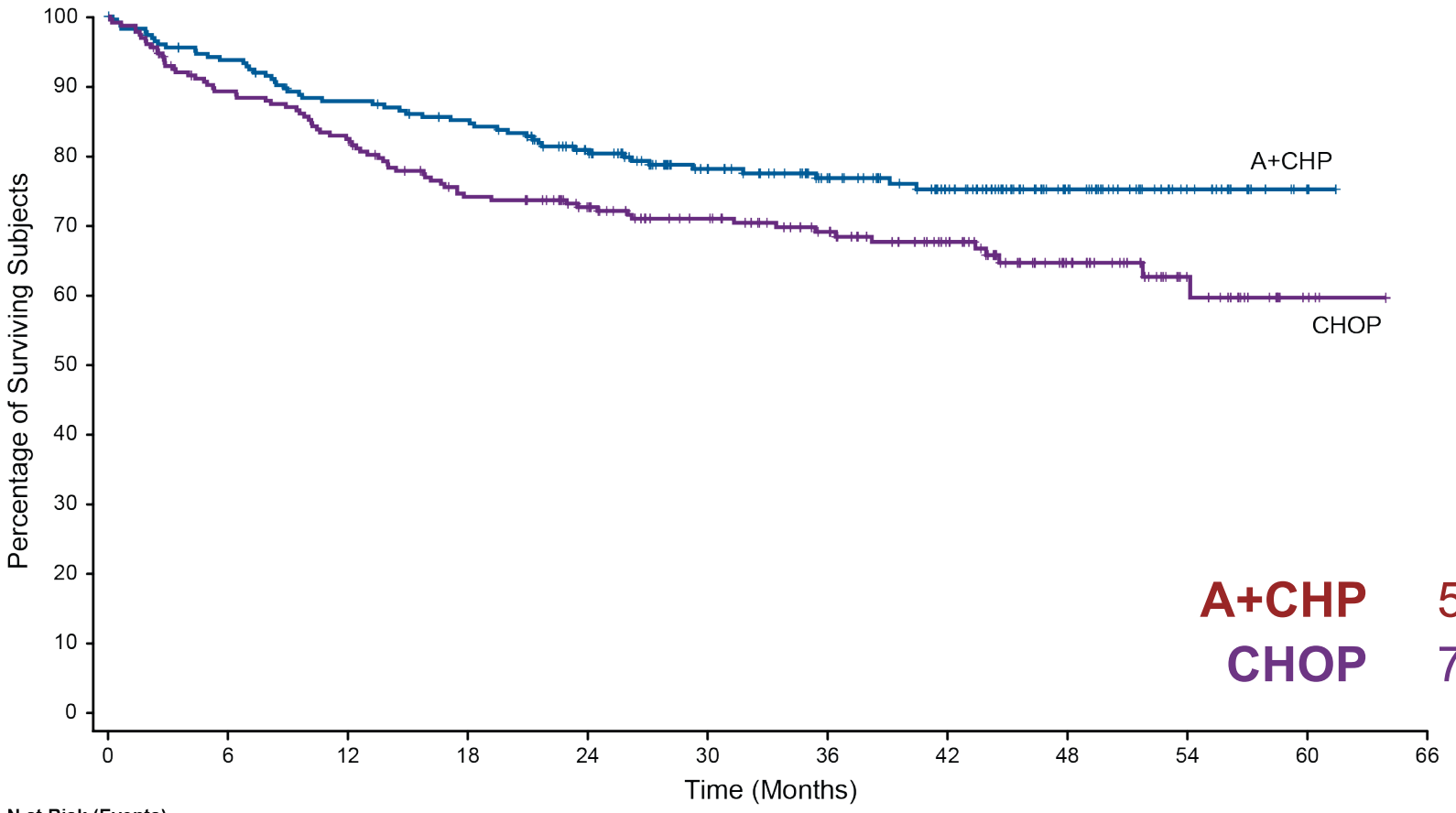
Median PFS (95% CI)

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

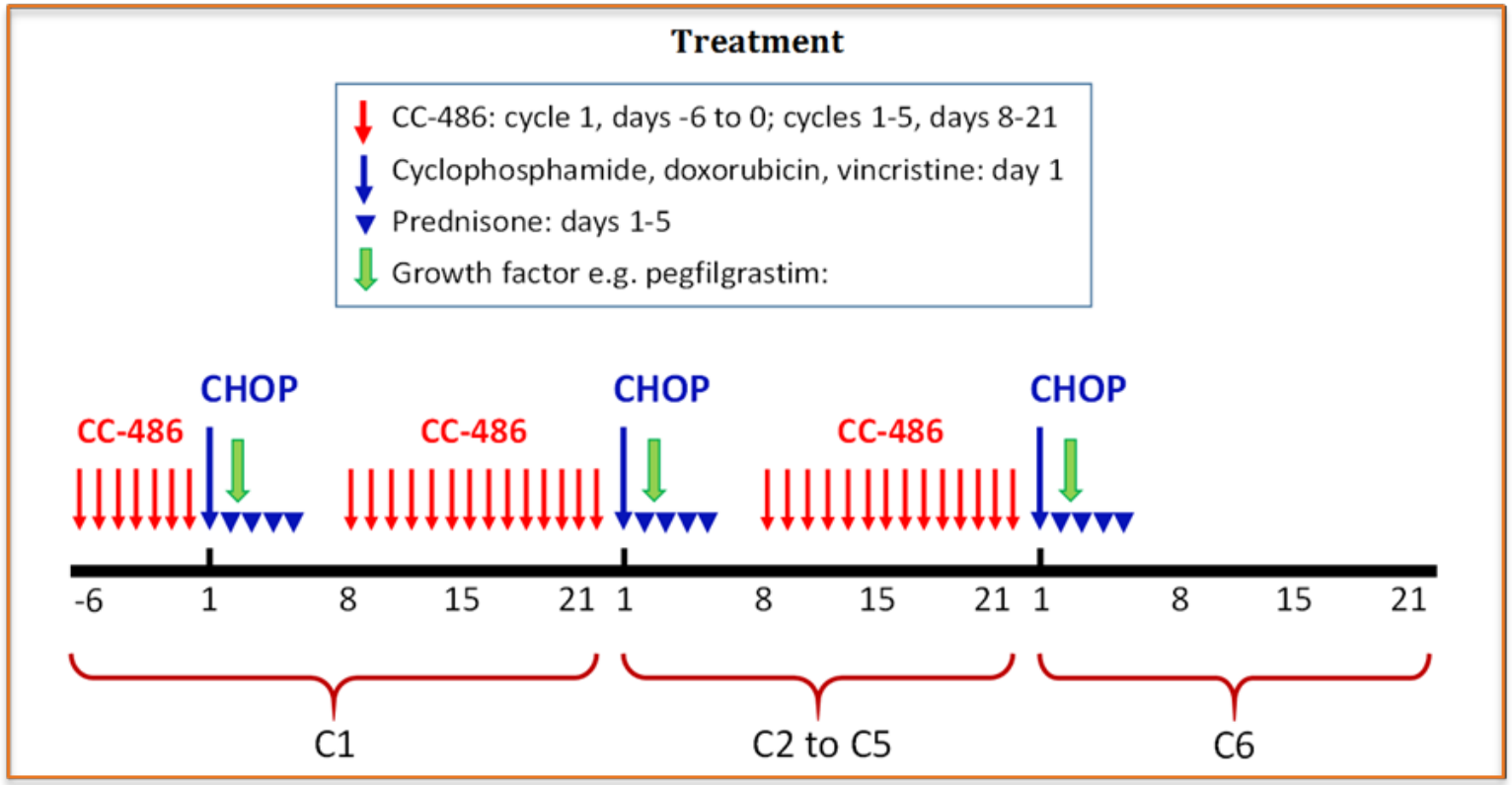
	Deaths	HR (95% CI)	*P*
A+CHP	51 (23%)	0.66 (0.46, 0.95)	0.0244
CHOP	73 (32%)		

Horwitz et al, Lancet 2019

Weill Cornell Medicine

NewYork-Presbyterian

Oral Azacytidine + CHOP in upfront T cell lymphoma



- CC486 at 300 mg daily from day -6 to day 0 for cycle 1 priming, and on days 8-21 following cycles 1-5.
- Patients in CR/PR following 6 cycles of treatment have the option to proceed to consolidative HSCT.

Ruan et al, ASH 2020

Oral Azacytidine + CHOP in upfront T cell lymphoma

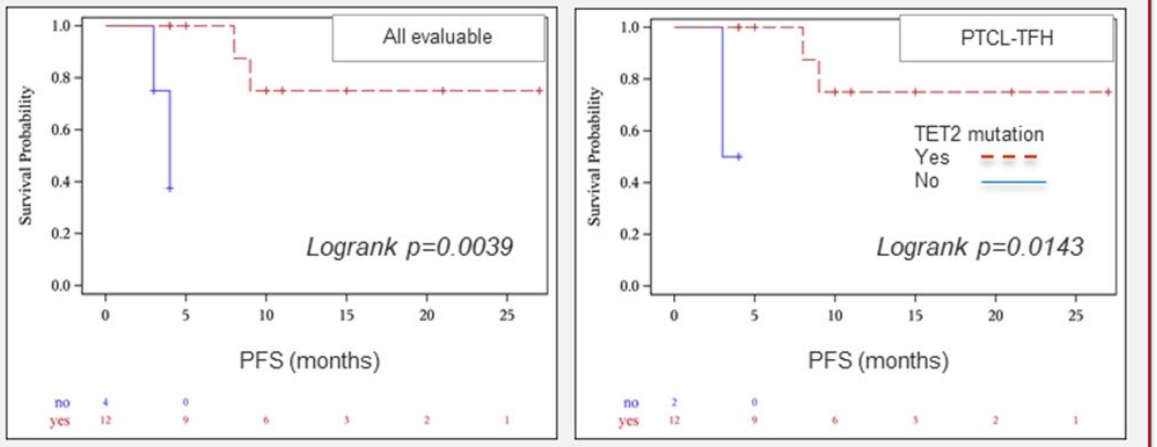
Response	Interim*			EOT*		
	No. Pt	Evaluable (n=20)	PTCL-TFH (n=17)	No. Pt	Evaluable (n=20)	PTCL-TFH (n=17)
ORR	17	85%	94%	15	75%	88%
CR	11	55%	59%	15	**75%**	**88%**
PR	6	30%	35%	0	0	0
SD	2	10%	0	1	5%	0
PD	1	5%	6%	2	10%	6%
Discontinuation	0	0	0	2	10%	6%
Median follow-up		15 months (range 9-23)				

"*": Interim – following 3 cycles of treatment; EOT following 6 cycles of treatment.
"#": Discontinuation due to 1) disease progression; 2) strongyloides infection.

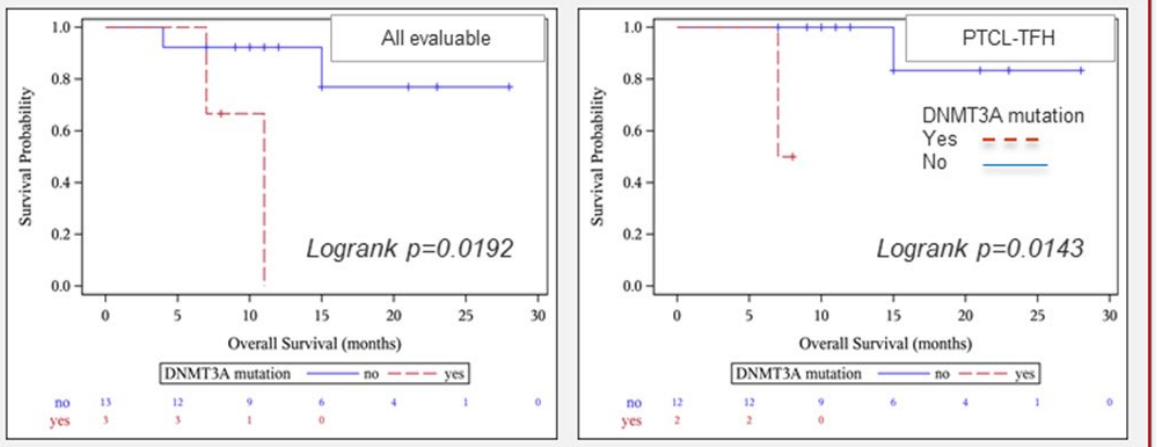
Ruan et al, ASH 2020

Oral Azacytidine + CHOP in upfront T cell lymphoma
Impact of mutational status on PFS

TET2 mutations correlate with favorable PFS



DNMT3A mutations correlate with adverse OS

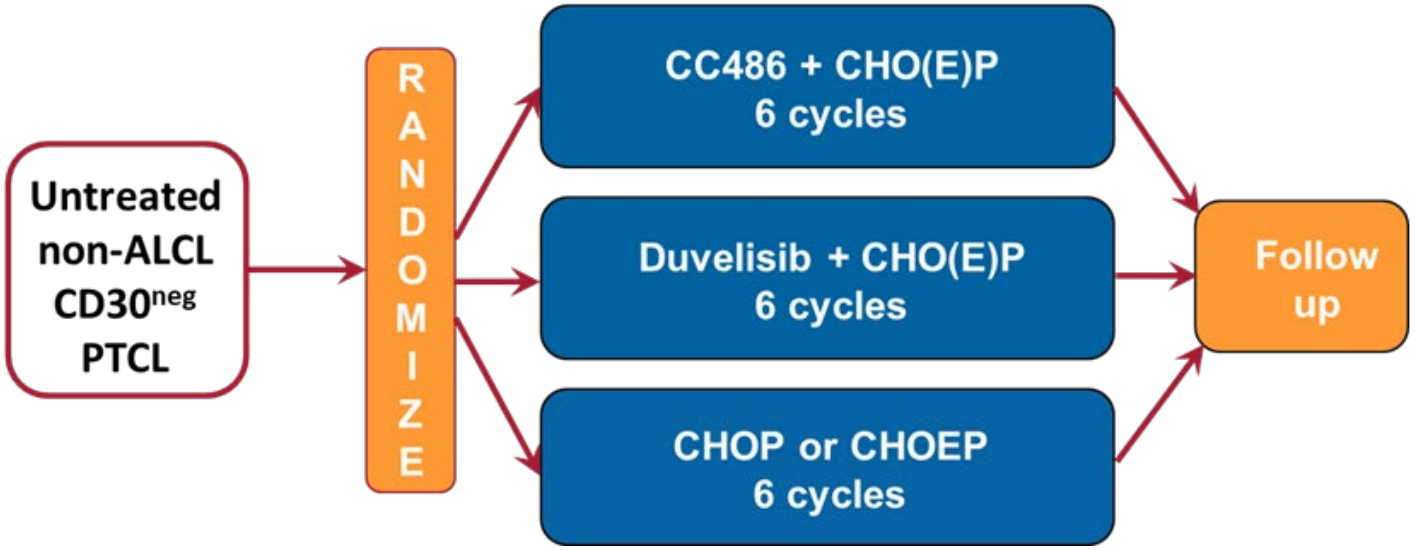


Ruan et al, ASH 2020

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

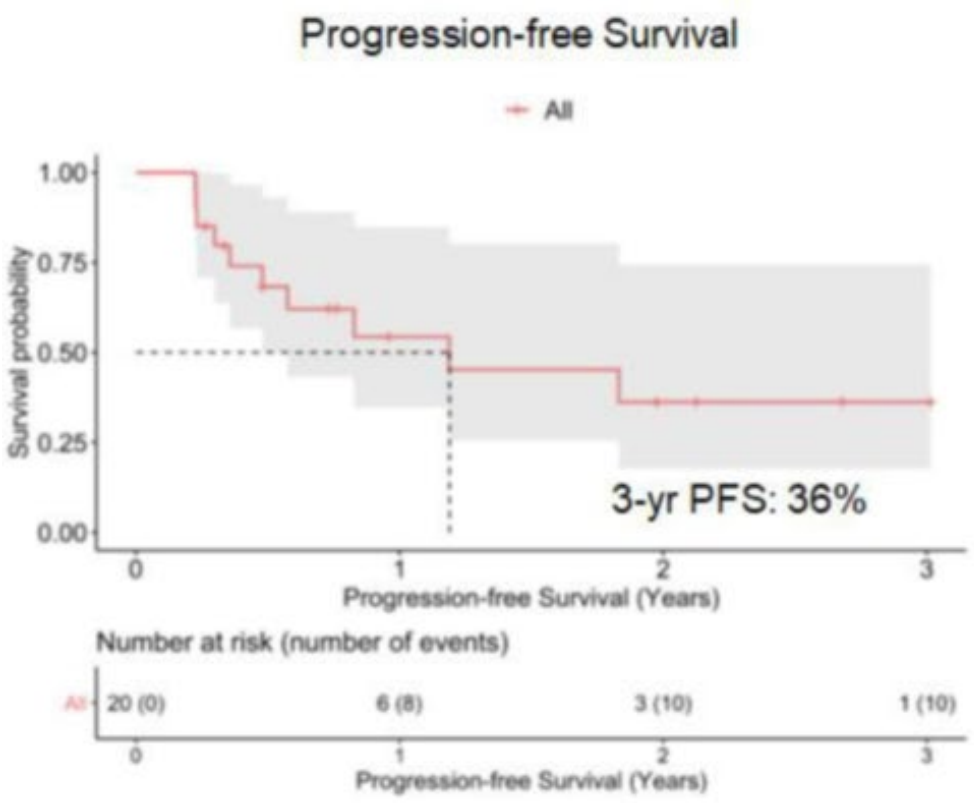


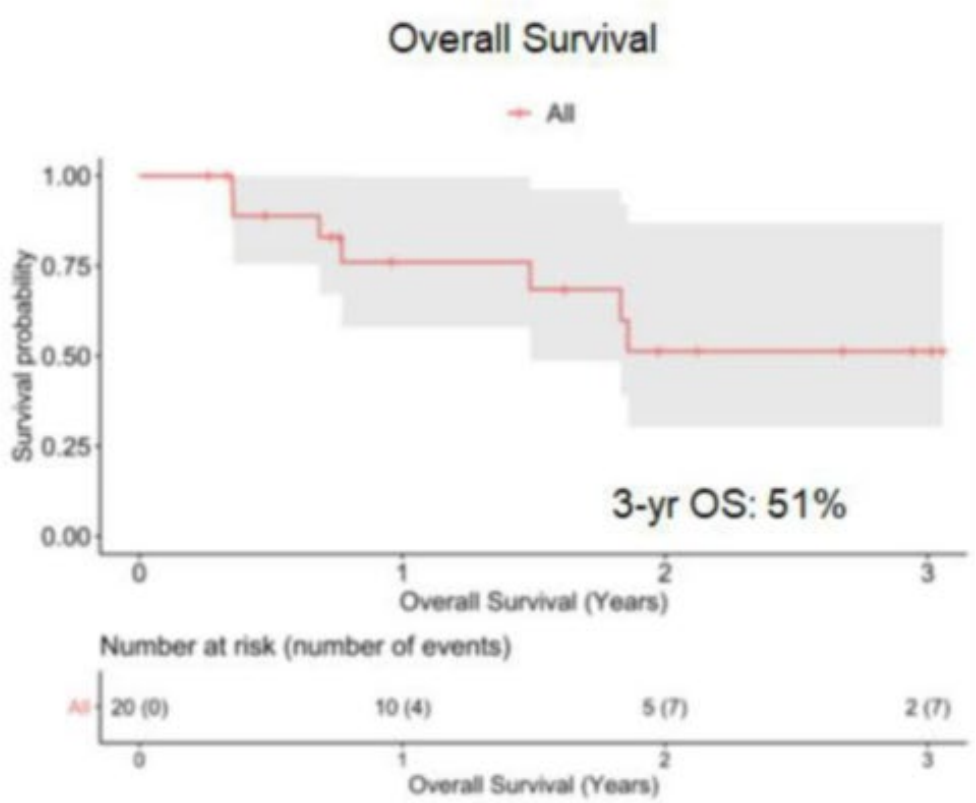
Romidepsin + lenalidomide for previously untreated PTCL

- PTCL patients over 60 and/or with comorbidities
- Romidepsin 10 mg/m2 IV d1, 8, 15
- Lenalidomide 25 mg d 1-21 every 28 days up to 1 year
- 29 subjects, 55% AITL, 38% PTCL, median age 75
- 66% advanced stage, 79% elevated LDH
- Toxicities heme, hyponatremia, HTN, fatigue
- ORR 75%, CR 30% (higher in AITL) , median DOR 4.2 mo

Ruan et al, ICML 2021

Romidepsin + lenalidomide for previously untreated PTCL





Ruan et al, ICML 2021

Duvelisib + romidepsin for recurrent PTCL

- 66 pts, D 75 mg BID, R 10 mg/m2 d1, 8, 15 every 28
- Toxicities heme, liver enzymes, diarrhea, infection
- PTCL ORR 58%, CR 42%
- 43% of responders proceed to AlloSCT

Horwitz et al, ICML 2021

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 (and may be evolving)
  - Multiple novel agents including bispecifics
- T cell
  - CD30-directed therapy of value upfront and relapse
  - Novel combinations under study