Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients

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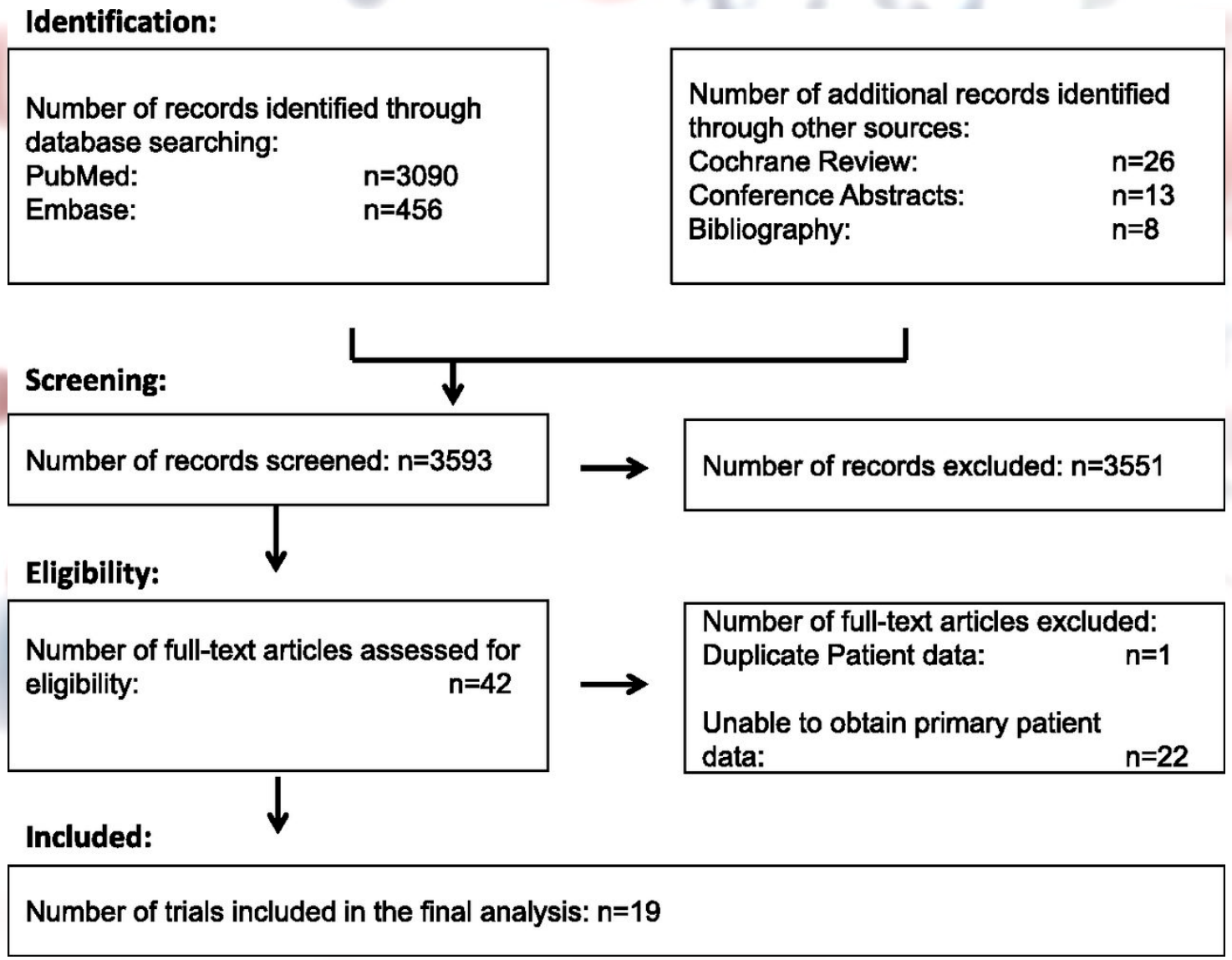
Overview

- Limited comparative data exist for the treatment of HIV-associated non-Hodgkin lymphoma.
- Literature search using PubMed and Embase databases.
- 42 eligible trials – data available from only 19 of those trials.
- Average of 61 patients were enrolled per trial.
- Analyzed pooled individual patient data for 1546 patients.
- Findings provide supporting evidence for current patterns of care.

Diagram documenting the flow of information through the different phases of the systematic review as per the PRISMA statement



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Demographics & Characteristics of the 1546 patients

Table 2. Demographics and characteristics for all 1546 patients included in the pooled analysis

Baseline characteristics	All patients	Rituximab		P
		No (N = 1004)	Yes (N = 542)	
Age in years, median (range)	40 (18-76)	38 (18-73)	42 (20-76)	<.001
Gender, n (%)				
Male	1228 (84)	804 (87)	424 (78)	.011
Histology, n (%)				
BL/BLL	399 (26)	251 (25)	148 (27)	
DLBCL	1059 (69)	680 (68)	379 (70)	
Other	88 (6)	73 (7)	15 (3)	
Age-adjusted IPI, n (%)				
0	151 (12)	104 (12)	47 (11)	.85
1	384 (29)	249 (29)	135 (31)	
2	519 (40)	344 (40)	175 (40)	
3	250 (19)	165 (19)	85 (19)	
Treatment, n (%)				
Intensive regimen	155 (10)	77 (7)	78 (14)	<.001
CHOP	632 (41)	391 (39)	241 (44)	
Low-dose CHOP	165 (11)	165 (16)	0	
EPOCH	166 (11)	17 (2)	149 (27)	
VS	41 (3)	41 (4)	0	
ACVBP/LNHIV91	158 (10)	158 (16)	0	
CDE	191 (12)	117 (12)	74 (14)	
Remick regimen	38 (2)	38 (4)	0	
GCSF, n (%)	1467 (99)	986 (98)	481 (100)	<.001
Concurrent cART, n (%)	779 (52)	423 (43)	356 (69)	<.001
CD4 count, cells/μL (median; IQR)	248 (101-652)	334 (120-1200)	179 (74-330)	<.001
Viral load, copies/μL (median; IQR)	23 801 (600-160 000)	42 000 (930-190 461)	17 420 (442-145 000)	.084
History of prior AIDS	480 (38)	302 (37)	178 (39)	.429
CD4 <50 cells/μL, n (%)	207 (14)	120 (13)	87 (17)	.025
Enrollment date (year)				
89-95	388 (25)	388 (39)	0	<.001
96-97	298 (19)	298 (30)	0	
98-00	396 (26)	256 (26)	140 (26)	
01-04	282 (18)	49 (5)	233 (43)	
05-10	182 (12)	13 (1)	169 (31)	
Median follow-up, years (IQR)	1.2 (0.4-4.4)	0.9 (0.4-4.0)	2.3 (0.6-4.6)	<.001
CR, n (%)	791 (57)	427 (49)	364 (71)	<.001
Progression, n (%)	625 (40)	460 (46)	165 (30)	<.001
Survival,* n (%)	650 (43)	303 (32)	347 (64)	<.001

*Patients alive at the end of follow-up.

Rituximab and outcomes

Table 3. Associations of treatment factors and outcomes for CR rate and progression-free and OS

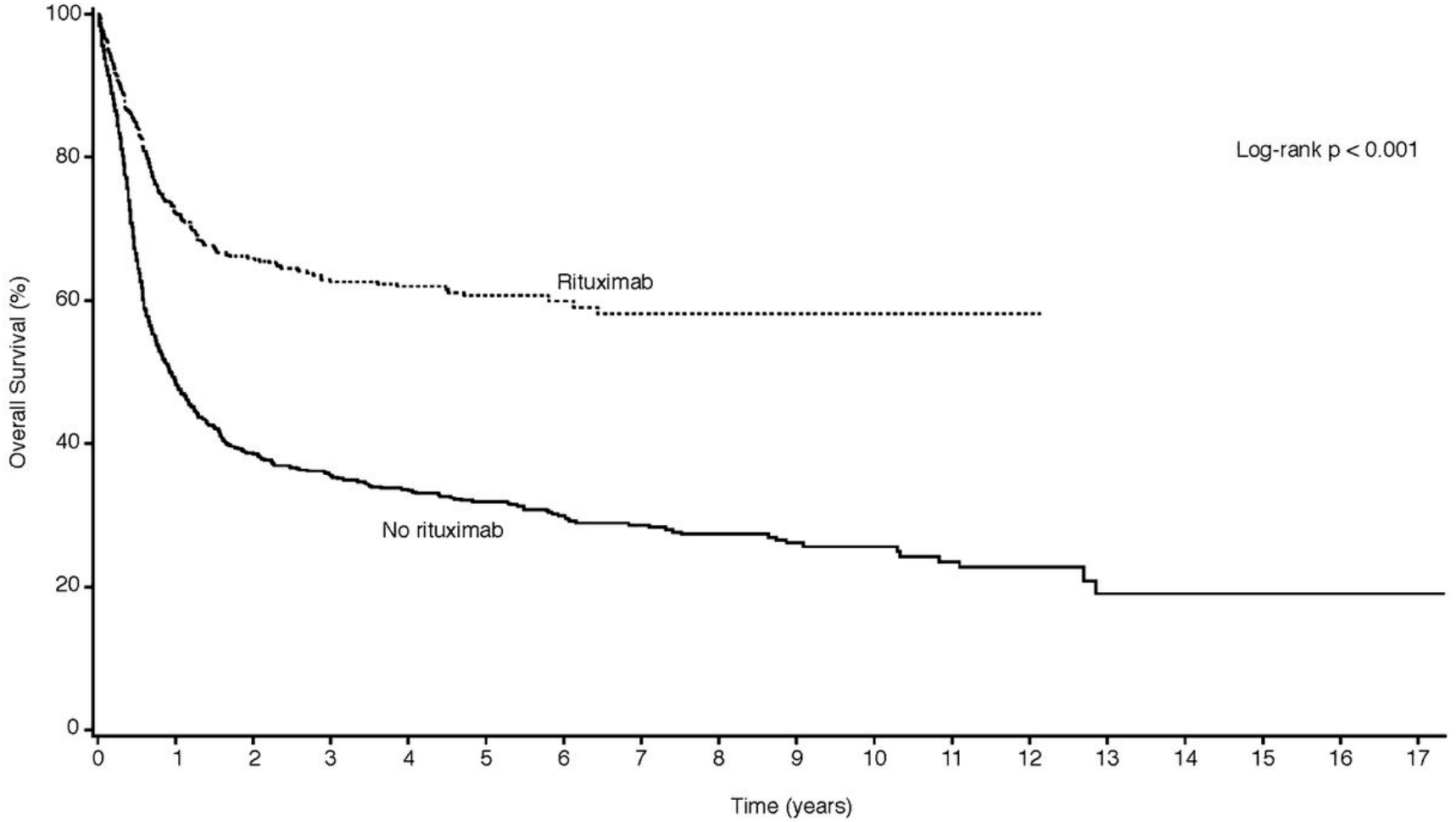
	Outcomes					
	Univariate analysis			Multivariate analysis*		
	OR (95% CI; *P*)	HR (95% CI; *P*)		OR (95% CI; *P*)	HR (95% CI; *P*)	
Treatment factors	**CR**	**PFS**	**OS**	**CR**	**PFS**	**OS**
Rituximab						
Yes = 542; no = 1004	2.49 (1.98-3.15; <.001)	0.53 (0.44-0.63; <.001)	0.43 (0.37-0.51; <.01)	2.89 (1.84-5.08; <.001)	0.50 (0.34-0.72; <.001)	0.51 (0.38-0.71; <.0001)
Chemoregimen						
CHOP (n = 632)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Infusional regimens						
EPOCH; n = 166	1.73 (1.17-2.57; .006)	0.57 (0.41-0.79; <.001)	0.59 (0.44-0.76; <.001)	0.97 (0.42-2.24; .95)	1.11 (0.56-2.05; .75)	0.67 (0.33-1.22; .22)
CDE; n = 191	0.54 (0.39-0.75; <.001)	1.10 (0.85-1.40; .46)	0.95 (0.76-1.18; .64)	0.87 (0.54-1.40; .55)	0.93 (0.67-1.27; .64)	0.73 (0.55-0.96; .03)
Dose-intense regimens						
Intensive (n = 155)	1.57 (0.97-2.55; .07)	0.89 (0.66-1.18; .42)	0.76 (0.58-0.99; .043)	1.65 (0.57-4.77; .36)	0.32 (0.16-0.54; <.0001)	0.54 (0.36-0.82; .004)
ACVBP; 158	1.34 (0.91-1.97; .13)	1.07 (0.81-1.39; .64)	1.01 (0.80-1.26; .94)	1.70 (1.04-2.79; .036)	0.72 (0.52-0.99; .049)	0.86 (0.67-1.16; .38)
Less dose-intense regimens						
Low-dose/modified CHOP; n = 165	0.34 (0.23-0.49; .001)	2.60 (2.04-3.28; <.001)	2.59 (2.08-3.20; <.001)	0.33 (0.19-0.58; <.001)	2.11 (1.53-2.89; <.0001)	1.91 (1.44-2.52; <.0001)
VS; n = 41	0.02 (0.003-0.14; <.001)	7.27 (4.84-10.56; <.001)	5.13 (3.58-7.14; <.001)	0.04 (0.01-0.33; .002)	3.34 (2.06-5.23; <.0001)	2.41 (1.58-3.60; <.0001)
Remick; n = 38	0.32 (0.16-0.64; .001)	NA	2.48 (1.72-3.47; <.001)	0.77 (0.21-2.90; .70)	NA	0.86 (0.46-1.51; .62)
Concurrent cART						
Yes = 779; no = 724	1.39 (1.12-1.73; .003)	0.78 (0.59-0.92; .006)	0.45 (0.29-0.76; .001)	1.89 (1.21-2.93; .005)	0.89 (0.66-1.21; .46)	0.78 (0.60-1.02; .07)

NA, not available.

*All estimates in the multivariate analysis were adjusted for rituximab use, treatment, concurrent use of cART, age, gender, histological subtype, age-adjusted international prognostic index, CD4 count at baseline, prior history of AIDS, and enrollment period.

- Univariate and multivariate analyses performed to show correlated treatment factors with clinical outcomes.
- Univariate analysis – use of Rituximab was strongly associated with improved outcomes.
- Only significantly associated with improved outcomes for patients with $CD4^+$ counts ≥ 50 cells/μl
  - Not if the $CD4^+$ count was < 50 cells/μl

Kaplan-Meier plots comparing the OS for patients treated with rituximab-containing regimens vs non–rituximab-containing regimens



Numbers at risk

No rituximab	954	446	340	296	235	177	119	97	75	55	40	30	17	9	6	4	2	1
Rituximab	542	353	292	222	171	101	73	52	35	23	10	4	2	1				

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Concurrent use of antiretroviral therapy

- Use of cART with chemotherapy was associated with significantly higher CR rates and OS on univariate analysis.

- Compared the effect of rituximab in concurrent cART users and in patients not using cART concurrently with chemotherapy.
  - Neither clinically meaningful nor statistically significant differences between the groups were identified.

- G-CSF use was nearly ubiquitous – no meaningful comparison could be performed.

Chemotherapy Regimen and Outcomes

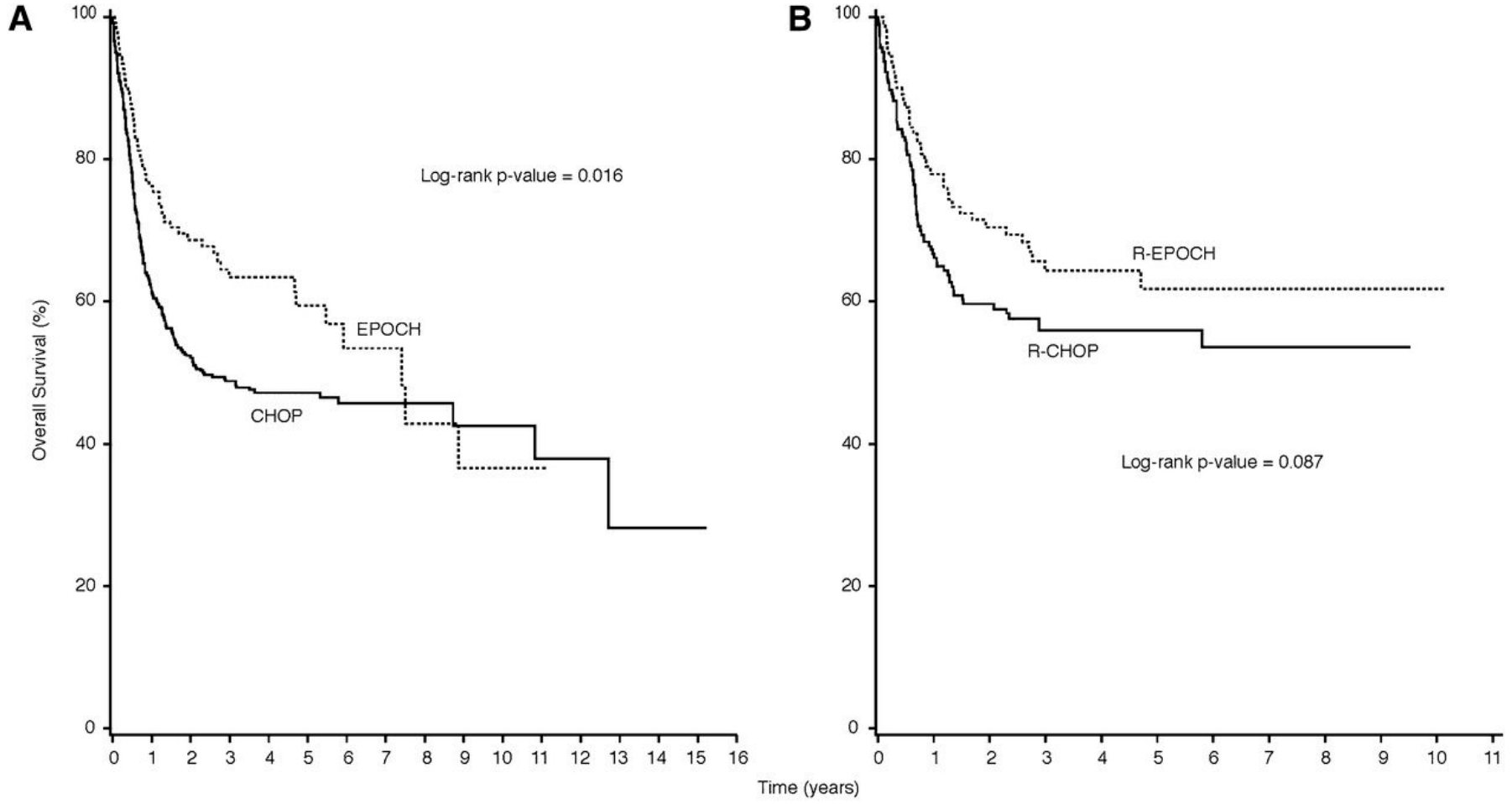
Table 4. Associations of rituximab use, type of initial chemotherapeutic regimen, and baseline CD4 count with cause of death (polytomous model)

Factors	Death from all causes	Cause of death (OR; 95% CI; *P*)			
		TRM (n = 180)	PD (n = 457)	HIV (n = 57)	Other (n = 91)
Non-rituximab use (n = 898)	595	Reference	Reference	Reference	Reference
Rituximab use (n = 537)	190	0.68 (0.44-1.06; .09)	0.30 (0.21-0.41; <.001)	0.58 (0.30-1.12; .11)	0.38 (0.20-0.69; .002)
Chemotherapy regimen					
CHOP (n = 614)	321	Reference	Reference	Reference	Reference
Infusional regimens (EPOCH, n = 145; CDE, n = 184)	41	0.28 (0.14-0.57; <.001)	1.54 (1.12-2.11; .008)	0.64 (0.28-1.49; .30)	1.53 (0.83-2.83; .18)
Dose-intense regimens (n = 312)*	162	1.24 (0.82-1.88; .30)	0.90 (0.66-1.22; .49)	1.85 (0.87-3.93; .11)	0.76 (0.35-1.62; .47)
Less dose-intense regimens (n = 180)†	153	1.26 (0.77-2.06; .37)	1.75 (1.29-2.37; <.001)	0.14 (0.02-1.07; .06)	0.56 (0.22-1.41; .22)
Baseline CD4 count (cells/μL)‡					
<50 (n = 175)	124	0.96 (0.80-1.16; .68)	1.04 (0.91-1.19; .53)	0.74 (0.57-0.97; .03)	0.96 (0.76-1.22; .75)
50-199 (n = 373)	217	0.97 (0.93-1.00; .08)	0.99 (0.96-1.02; .42)	1.00 (0.93-1.08; .93)	0.96 (0.91-1.01; .13)
≥200 (n = 829)	413	1.00 (1.00-1.00; .97)	1.00 (1.00-1.00; .68)	0.96 (0.92-0.99; .02)	1.00 (0.99-1.00; .14)

The model was adjusted for age, gender, history of AIDS, time of enrollment, type of lymphoma, and aaIPI.
*Dose-intense regimens are intensive regimens and ACVBP.
†Less dose-intense regimens are VS, low-dose or modified CHOP, and the Remick regimen.
‡Change in OR as per 10-unit increase of CD4 count.

- Compared effect of the initial choice of chemotherapy regimen while adjusting rituximab use.
- Treatment with less dose-intense regimens was associated with significantly inferior clinical outcomes in both univariate and multivariate analysis – except Remick regimen.
- Oral Remick regimen resulted in lower CR rates and a worse OS on univariate analysis but not on the multivariate analysis.
- Infusional EPOCH had a higher CR rate and improved PFS and OS in the univariate model.

Kaplan-Meier plots comparing OS for patients with DLBCL treated with EPOCH vs CHOP and R-EPOCH vs R-CHOP



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Summary

- Addition of rituximab to any chemotherapy regien was associated with a nearly threefold increase in the CR rate and 50% reduction in risk of progressive lymphoma or death.
- Use of rituximab in this analysis was not associated with increased risk of death due to treatment toxicities or HIV-related complications.
- Dose-intense chemotherapy regimens resulted in better clinical outcomes compared with treatment with CHOP in patients with more aggressive BL or BLL.
- Dose-intensive regimens did not result in an OS advantage compared with the less toxic infusional regimens EPOCH and CDE.
- Patients using cART concurrently with induction chemotherapy experienced higher CR rates and a trend toward improved OS compared with patients who did not take cART during the initial therapy phase.