NCCN 10th Annual Congress:
Hematologic Malignancies™

Management of HIV-associated Non-Hodgkin's Lymphomas

Lawrence D. Kaplan, MD

UCSF Helen Diller Family Comprehensive Cancer Center

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HIV-Associated Lymphoma: Background

- Most HIV-associated lymphomas are diffuse large B-cell (65%) or Burkitt (25%) ie aggressive CD20+ B-cell lymphomas
- Other Lymphoproliferative diseases:
  - Plasmablastic lymphomas (EBV)
  - Primary effusion lymphomas (HHV-8, EBV)
  - Hodgkin Lymphoma (EBV)
  - Multicentric Castleman Disease (HHV-8)
- Seen across a broad range of CD4 counts
- Incidence of NHL in a large database of patients on effective ART(CNICS) was 171 cases/100,000 PY (Achenbach et al. Clin Infect Dis, 2014)
- In non-HIV infected population is 10-20 cases/100,000 PY

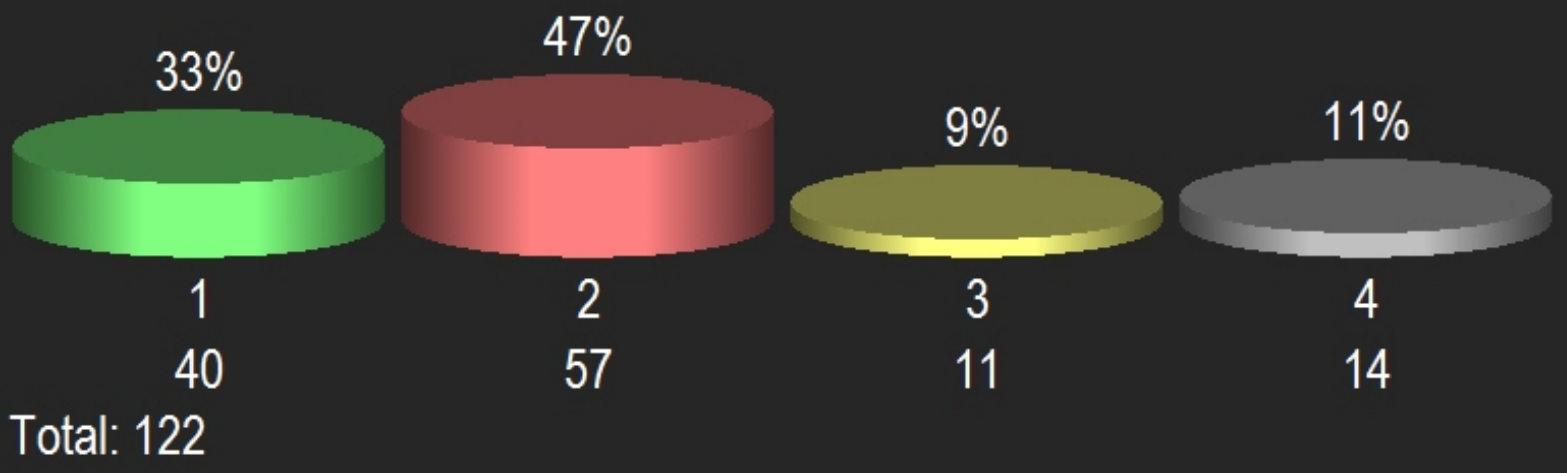
Case

- 41yo HIV-seropositive male presents with a 3 week history of enlarging L neck mass. Drenching night sweats began 5 days prior to clinic visit.
- On exam there is a 7cm L neck mass
- Core needle biopsy demonstrates a CD20+, CD 10-, large B-cell lymphoma which is bcl-6+, MUM-1+. FISH: bcl2-, myc-.
- PET-CT shows disease in neck, mediastinum, retroperitoneum and BM.
- HIV-1 RNA undetectable. CD4: 185
- Patient is receiving ART with zidovudine/lamivudine and lopinavir/ritonavir.

ARS Question

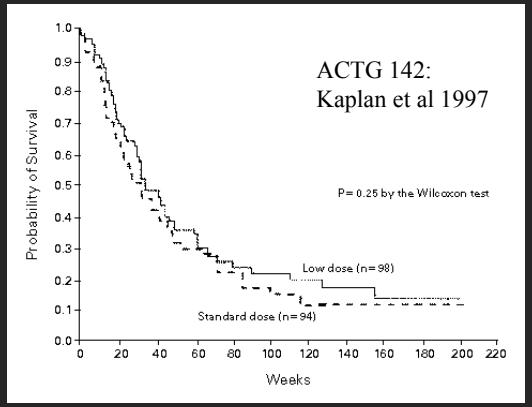
You should now…

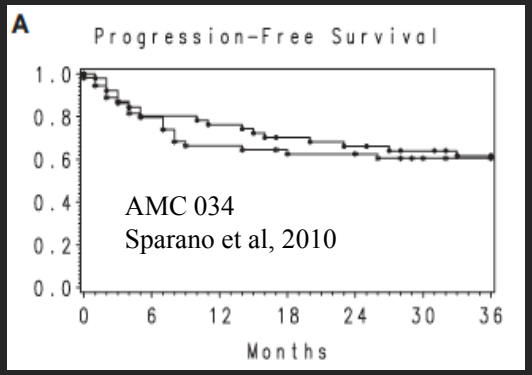
1. Continue current ART regimen, begin R-CHOP chemotherapy
2. Change ART regimen to raltegravir, emtricitabine/tenofovir start, DA-EPOCH-R
3. Hold ART, start R-CHOP
4. Change ART regimen to raltegravir, emtricitabine/tenofovir, start CHOP without rituximab



Improvement in Treatment Outcome for HIV-Associated NHL

- Pre-cART (Combination Antiretroviral Therapy):
  - Standard Chemotherapy for DLBCL CR 50%, 2 yr OS <20%
- cART era:
  - CHOP/R-CHOP CR: 50-77% [1,2]
  - Infusional Chemotherapy (DA-EPOCH-R): CR: 73%. 2yr PFS 66%, OS 70%[3]
  - High-dose chemotherapy with PBSC support
  - Outcome strongly dependent On CD4





1. Kaplan L et al Blood 2005; 106: 1538
2. Boue F et al JCO 2006; 24: 4123
3. Sparano J et al Blood 2010; 115: 3008

Chemotherapy for HIV-Associated NHL in the cART Era

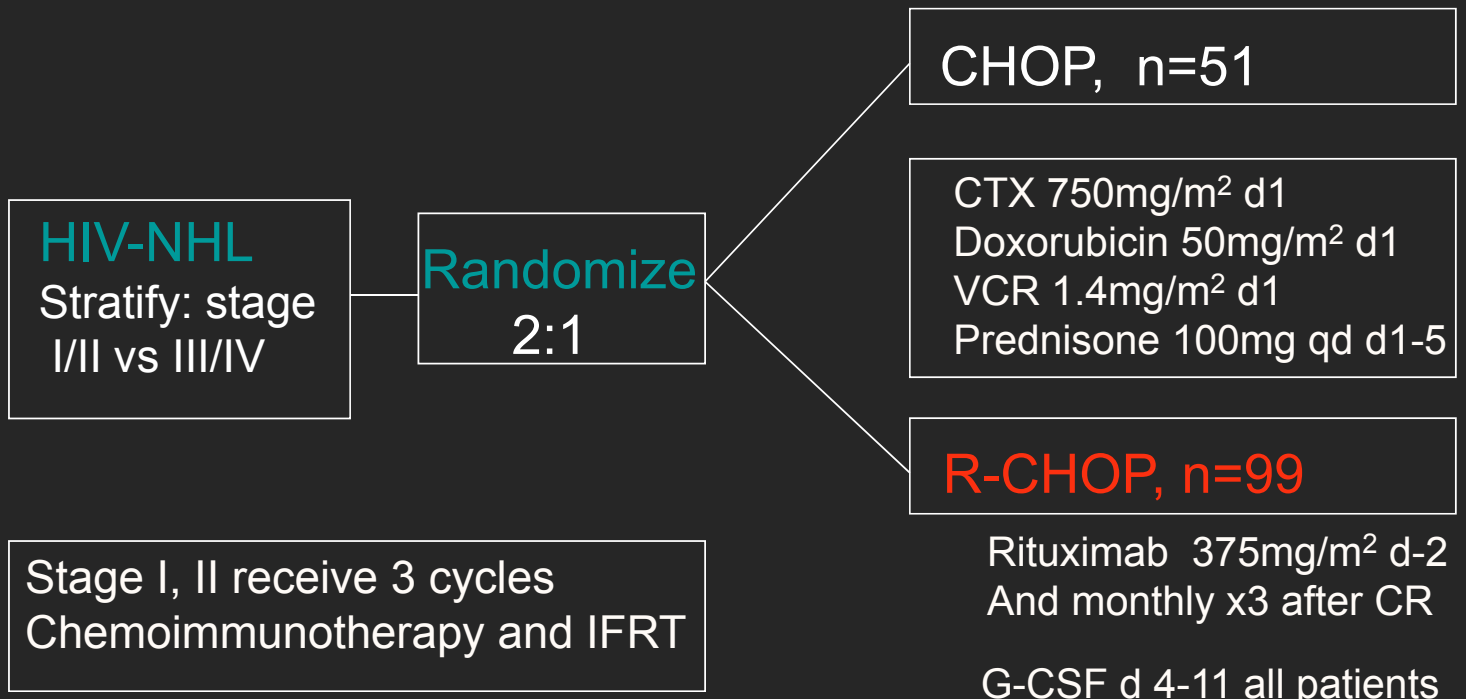
Chemo	N	CR%	Med Survival	OS
CHOP	50	47	27 mo	NS
R-CHOP	99	58	35 mo	NS
CHOP/ACVBP	35	54	22 mo	54% @ 1yr
R-CDE	74	70	>23 mo	64% @ 2yr
CHOP (liposomal)	24	75	>16 mo	58% @ 1yr
CDE (ECOG)	55	44	14 mo	44% @ 2yr
CDE	46	50	26 mo	61% @ 2yr
EPOCH (NCI)	39	74		60% @ 4yr
CHOP	24	55	NR	55% @ 2yr

Brower et al, 2003 (modified)

HIV-Associated NHL Treatment Approaches

- Use of monoclonal antibodies (rituximab)
- Infusional chemotherapy (DA-EPOCH, CDE)
- High-dose chemotherapy with AHCT
- Use of antiretroviral therapy

Role of Rituximab: AMC 010



Stage I, II receive 3 cycles Chemoimmunotherapy and IFRT

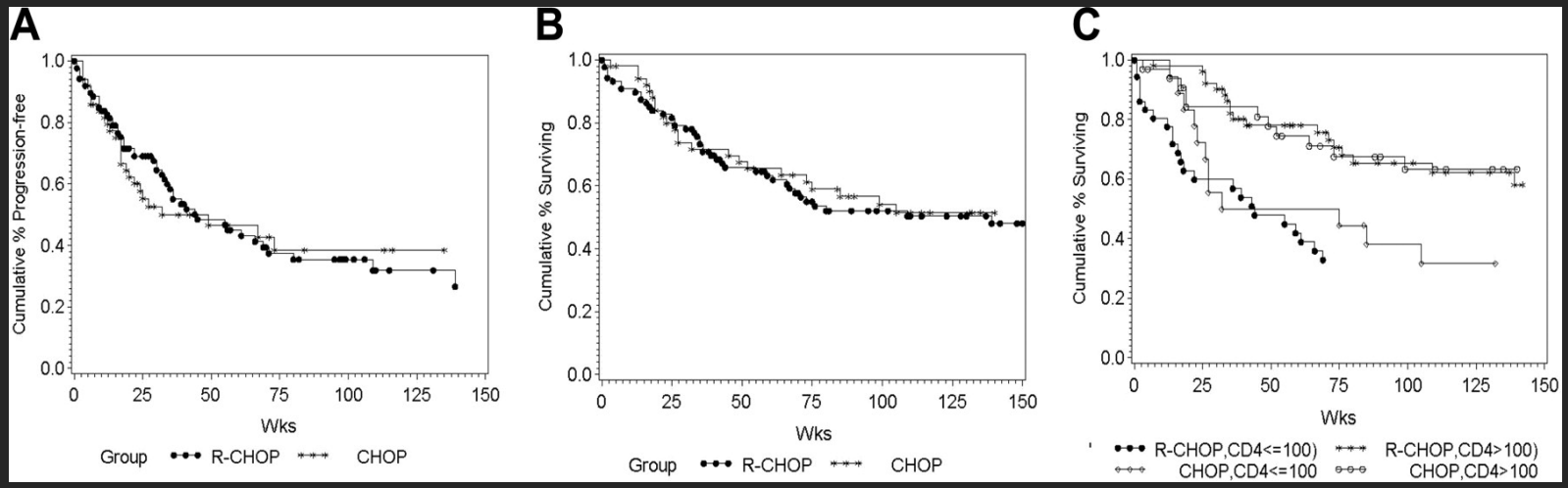
Kaplan, L. D. et al. Blood 2005;106:1538-1543

AMC 010: Response Summary

Parameter	R-CHOP		CHOP	
	n	%	n	%
CR	49	49	21	42
CRu	8	8	3	6
Total CR	57	57	24	48
OI	8 in 6 patients		0	0
Infectious death	15	15	1	2*
NHL Death	14	14	15	29

*p=.027

AMC 010: Progression-Free (A) and Overall Survival (B,C) CHOP vs R-CHOP



Median Followup, 137 weeks

CD4 and IPI prognostic in Multivariate analysis

Group	PFS	OS	TTP
RCHOP	45	139	125
CHOP	38	110	85

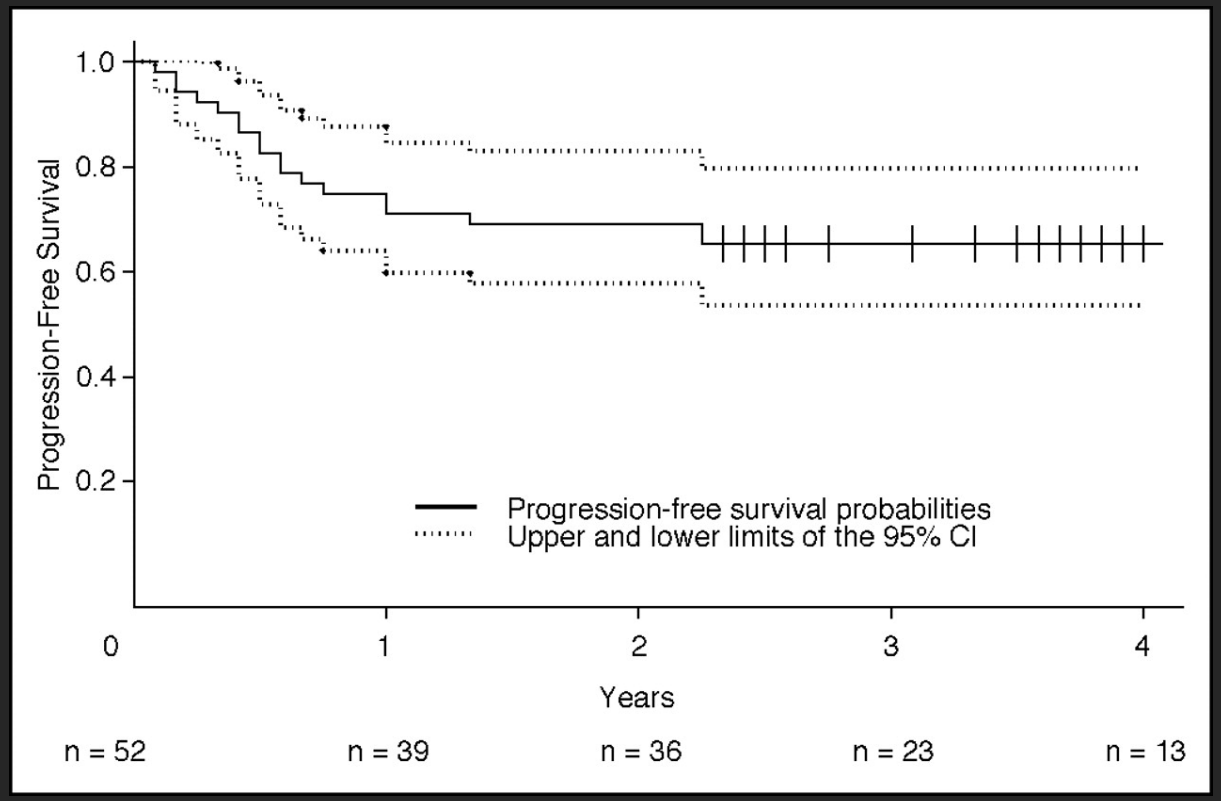
Kaplan, L. D. et al. Blood 2005;106:1538-1543

AMC 010: Infectious Deaths

Category	N (%)
All Infectious deaths	16
Culture-positive sepsis	8
Sepsis syndromes	6
Other	2
CD4+ cells <50/mm^3	60%
Death in cycle 1 or 2	53%
ANC $\leq$ 1000	60%
R-CHOP group:	
If CD4 <50 (n=22)	8 (36%)
If CD4 $\geq$ 50 (n-77)	5 (6%)*

* p=.001

Phase II Trial of CHOP Plus Rituximab in Patients With HIV-Associated Non-Hodgkin's Lymphoma



One possible infectious death

CD4<100 excluded

Boue et al *J Clin Oncol 24:4123-4128.*

Dose-Adjusted EPOCH-R (AMC)

Drug	Dose	Duration	Dose Adjustment
Rituximab	375 mg/m^2	4-6 hours Day 1	
Etoposide	50 mg/m^2/day	Days 1-4	None
Vincristine	0.4 mg/m^2/day	Days 1-4	None
Doxorubicin	10 mg/m^2/day	Days 1-4	None
Prednisone	60 mg/m^2/day	Days 1-5	
Cyclophosphamide CD4 count < 100 CD4 count ≥ 100	Cycle 1: 187 mg/m^2 375 mg/m^2 Cycle 2-6: Escalate dose	Day 5	187mg/m^2 increments up to 750mg/m^2

Sparano, et al Blood.2010;115:3008-16.

Response to EPOCH Without Antivirals

	N	%CR	Relapse	%PFS	%OS
CD4<100	9	56%	1	75%	16%
CD4≥100	20	87%	1	90%	87%
Total (39)	29	74%	2	73%	60%

Median Follow-up: 53 mos

Median CD4+: 198 cells/mm^3

Stage III/IV: 64%

Little et al, Blood 2003;101(12):4653-9.

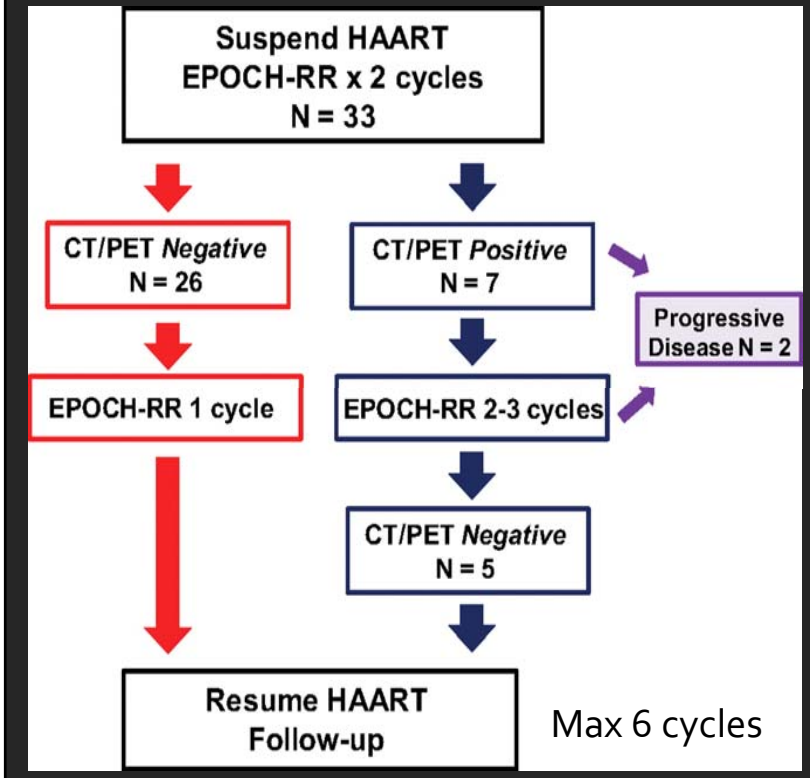
AMC 034: Randomized phase II trial of EPOCH with concurrent vs delayed rituximab

Group	Concurrent	Sequential
Eligible Patients	48	53
CD4 (median/mm^2)	181	194
AA-IPI 2-3 (%)	69	64
CR/CRu	35 (73%)*	29(55%)
Not assessable	4 (8%)	4 (7%)
Infectious Death	2	3

*null hypothesis (CR/CRu 50% vs alternative 75%) rejected

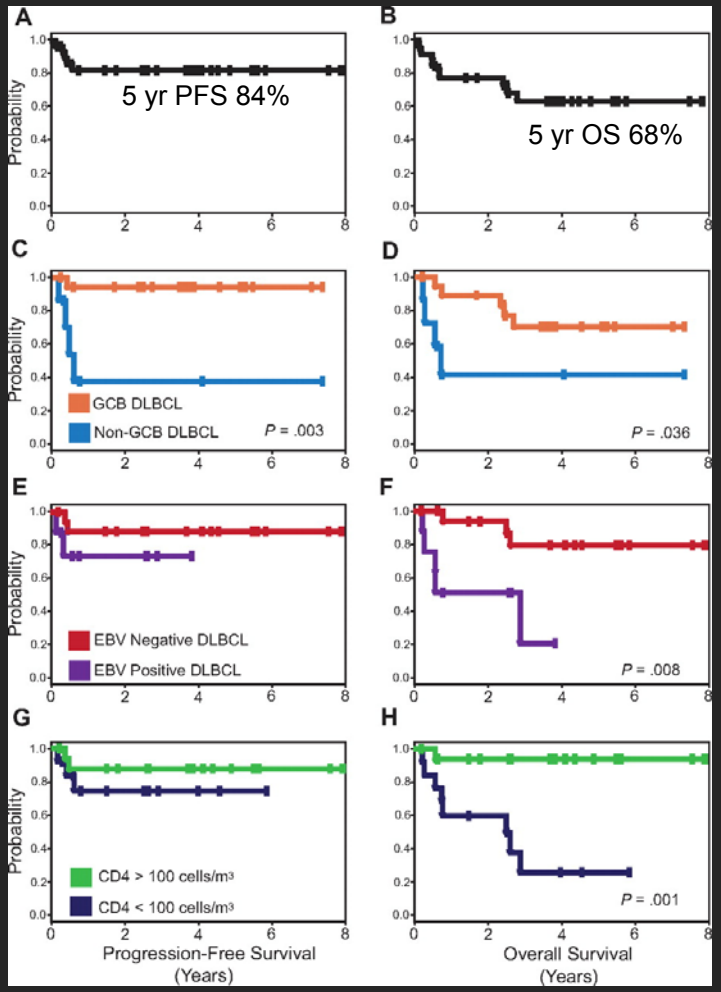
Sparano, et al Blood.2010;115:3008-16.

PFS and OS Short Course-EPOCH-RR



N=33
High/High-Int aaIPI: 76%
3 cycles: 79% of patients
No TRM

Dunleavy et al. Blood 2010;115:3017-3024

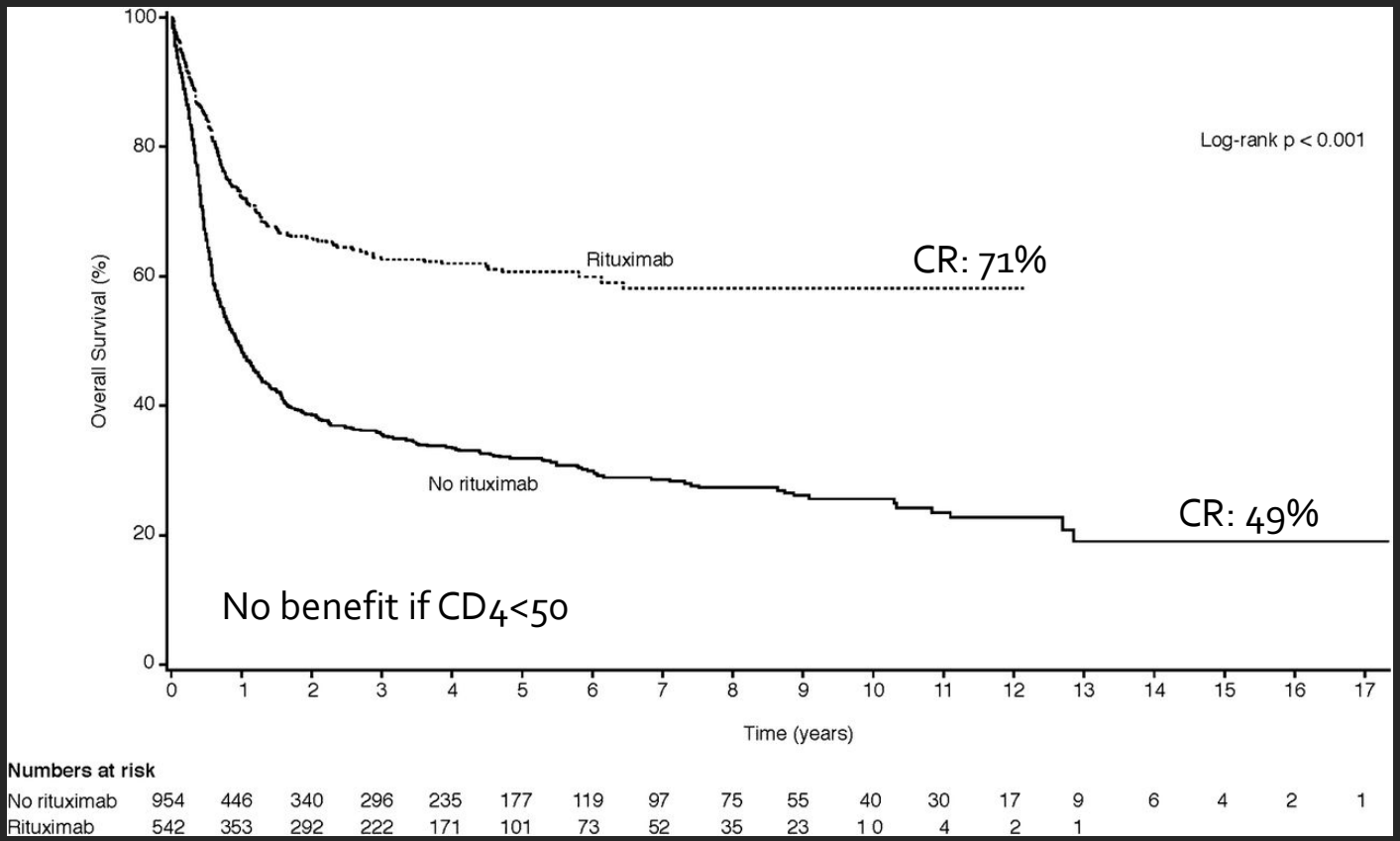


Treatment factors affecting outcomes in HIV-associated Non-Hodgkin's Lymphoma

- Pooled individual patient data for 1546 patients
- 19 prospective clinical trials
- Included DLBCL and BL / BLL(about 25%)
- Influence of treatment-specific factors on outcomes
  - Type of chemotherapy
  - Rituximab
  - Concurrent cART

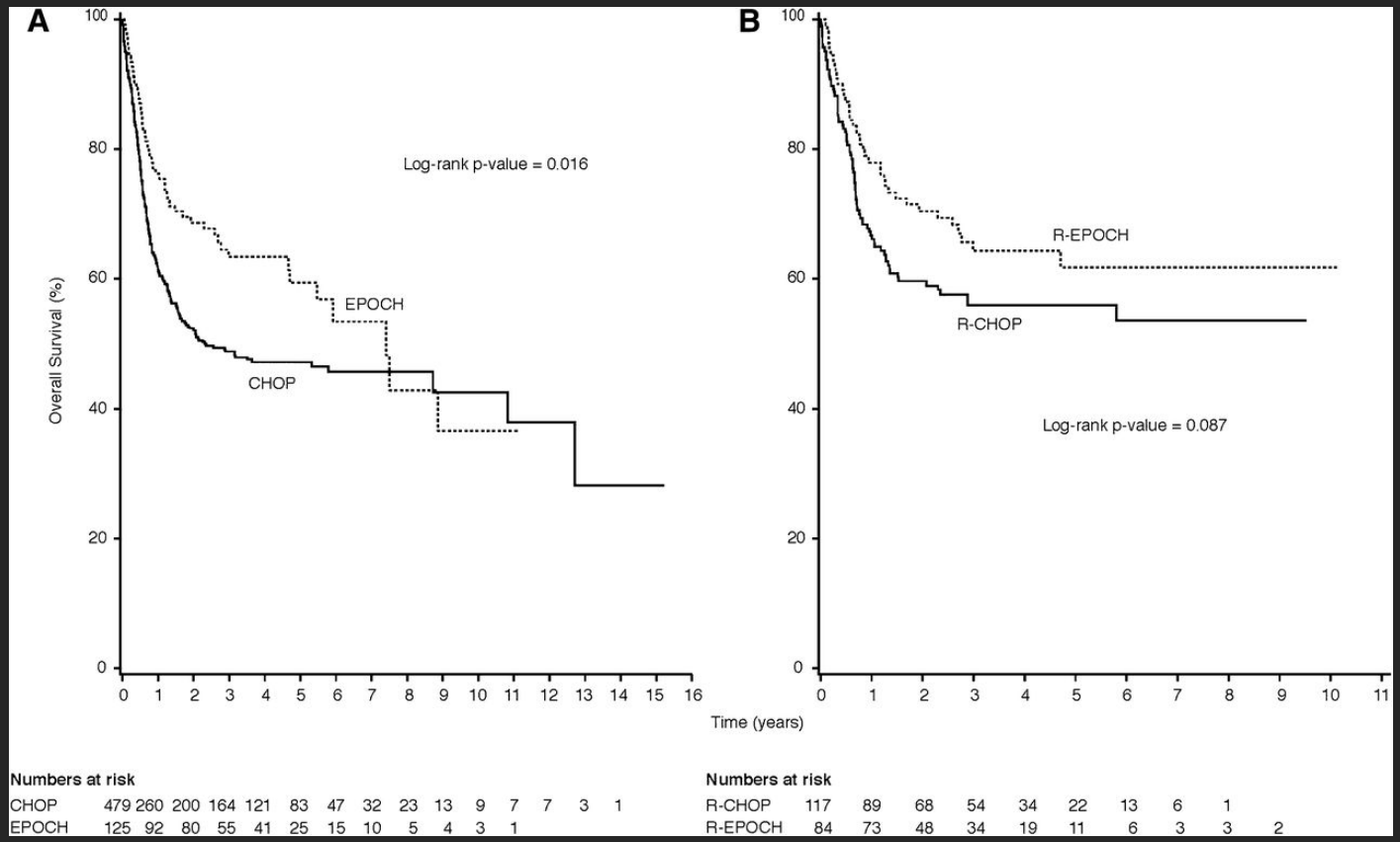
Barta S et al. Blood. 2013;122:3251

OS for patients treated with rituximab-containing regimens vs non–rituximab-containing regimens



Barta et al. Blood 2013;122:3251-3262

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



Barta et al. Blood 2013;122:3251-3262

If R-EPOCH combined with R-CDE p=.043

Pooled Multivariate Analysis

- DLBCL : Overall Survival with EPOCH better than with CHOP
  R-EPOCH / R-CDE better OS than R-CHOP
- Rituximab use associated with improved OS
- In BL more intensive regimens (c/w infusional) better PFS.
- Concurrent cART associated with higher CR rate (p=.005) and trend towards improved OS (p=.07)
- CD4 count <50/mm^2 associated with higher risk of TRM (37% vs 6%)

Barta S et al. Blood. 2013;122:3251

Phase II Burkitt Lymphoma Trials

	Mead[1]	LaCasce[2]	Thomas[3]	Wang[4]	Sparano	Dunleavy*	Noy[5]
N	42	14	28	14	16/11	19	34
Regimen	CODOX-M/IVAC	CODOX-M/IVAC	R-hyper CVAD	CODOX-M/IVAC	R-EPOCH	R-EPOCH	RCODOX-M/IVAC
Hi Risk	42	11	NA	11	NA/NA	NA	32
CR (%)	NA	86	86	63	63/82	100	NA
EFS%(y)	54 (2)	64 (2)	80 (3)+	60 (2)	NA/NA	100	69 (1)
OS%(y)	62 (2)	71 (2)	89 (3)	NA	NA/NA		69 (2)

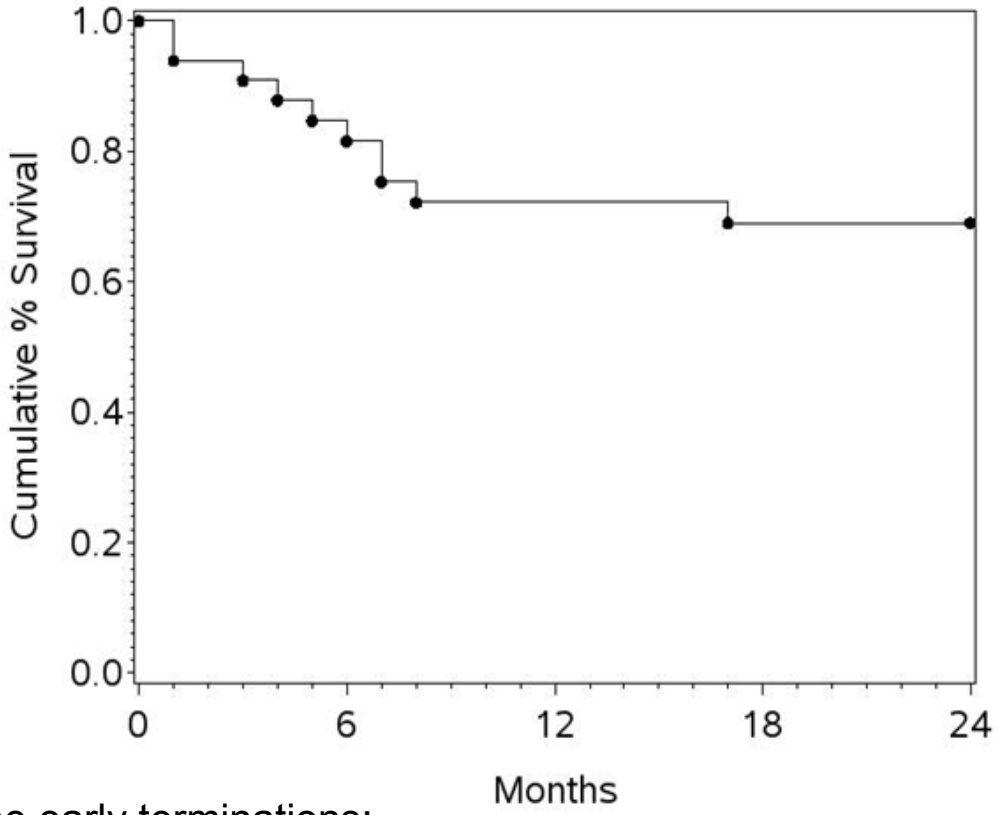
+In multivariate analysis including historical controls not receiving rituximab age and rituximab significant

*HIV+ and -

1. Mead GM, et al. Blood 2008
2. LaCasce A Leuk Lymphoma. 2004;45:761
3. Thomas DA, et al Cancer 2006; 106: 1569
4. Wang ES,et al Cancer 2003; 98: 1196
5. Noy A et al. Blood 2015; 126: 160–166

AMC 048: Overall survival

(Noy, et al. Blood 2015)



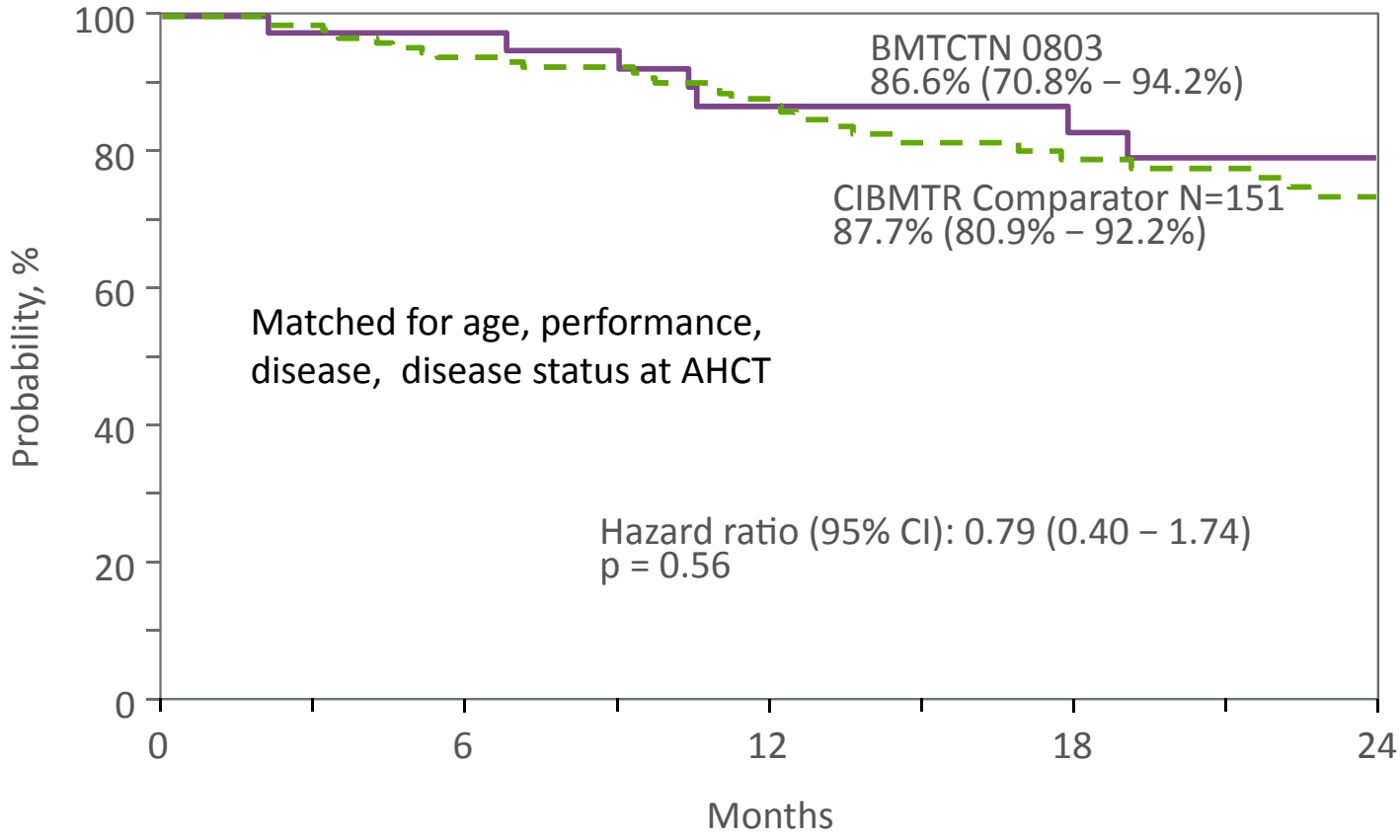
Despite the early terminations:
1 year PFS was 74.1% (55.5%, 86.4%)
1 year OS was 83.1% (95% CI 63.9%, 92.6%).
Little drop off after the first year with only one POD between year 1 and 2.

Autologous HCT in Patients with HIV-Associated Lymphomas

Reference	Failed to Mobilize (n)	Patients Transplanted (n)	TRM	Median Follow-up (months)	Overall Survival (%)
Krishnan[1]	0	20	5%	31.8	85
Spitzer[2]	2	20	5%	5.8	Median EFS: 23 weeks
Re[3]	6	27	0%	44	74.6
Serrano[4]	0	11	0%	32	73
EBMT[5]	NA	68	7.50%	32	61
BMT-CTN-0803[6]	NA	40	5.1%	12	86.6

1. Krishnan A et al. Blood. 2005;105(2):874-8
2. Spitzer TR et al. Biol Blood Marrow Transplant. 2008;14(1):59-66.
3. Re A et al. Blood. 2009;114(7):1306-13.
4. Serrano D et al. Exp Hematol. 2005;33(4):487-94.
5. Balsalobre P et al. J Clin Oncol. 2009;27(13):2192-8.
6. Alvarnas J et al. 2014 ASH Annual Meeting. Abstract 674.

BMT-CTN 0803 / AMC 071– Overall Survival



Alvarnas J et al. 2014 ASH Annual Meeting. Abstract 674.

Autologous HCT Studies: Infectious Complications

Infection	AMC N	Re N	Serrano N	Krish N	Gabarre N
Bacteremia*	4	2	6	4	
C. Difficile	3	1	2		
HSV	1				
CMV	4			3	2
Enterococcus (UTI)	1				
Aspergillus pneumonia			1	1	
Legionella			1		
PCP				2	
VZV				2	

*s viridans, s epidermitis (3), e coli, s. hominis, fusobacterium, proteus

Should Antiretroviral Therapy be administered with Chemotherapy?

- Benefit: Better control of HIV replication. More rapid recovery post-chemo.
- Risk: Chemotherapy-induced toxicities may be greater (neuropathy, mucositis, myelosuppression)
- Interactions with ancillary agents: eg anitbiotics, antifungals
- Experience with conventional dose chemotherapy is favorable even with protease inhibitor (PI)-based ART

Protease inhibitors may potentiate chemotherapy-induced neutropenia

- Protease inhibitors inhibit CYP3A4 and are substrates and inhibitors of Pgp.
- Modest delay in clearance of cyclophosphamide without increased toxicity in AMC trial with R-CHOP[1].
- With vinblastine in ABVD: cytopenias and neuropathy

- Patients in a prospective cohort study treated with infusional CDE and protease inhibitor sparing ART compared with PI-based ART had[2]:
  - higher median d10 ANC
  - Fewer admissions for febrile-neutropenia
  - No response or survival differences.
- No excessive toxicity with R-EPOCH in AMC 034

1. Ratner et al. J Clin Oncol. 2001:19;2171
2. Bower et al . Blood. 2004 ; 104(9):2943-6.

Antiretroviral Therapy Recommendations

- Avoid using zidovudine with chemotherapy
- Be aware that ritonavir has numerous drug interactions (as do other PIs)
- Integrase inhibitor (raltegravir) – based regimens safest (especially with HD chemotherapy/ASCT)
- Communication between Oncologist and HIV-treating physician critical!
- If necessary, cART can be interrupted or held until completion of chemotherapy
- Use of antineoplastic agents in cancer patients with HIV/AIDS. Rudek M, et al The Lancet Oncology. 2011;12:905-912.

Conclusions and Recommendations

- Most patients with HIV-associated NHL can be treated as you would HIV-uninfected patients
- Infusional regimens may be more active. R-EPOCH standard for most
- Rituximab should be included with front-line chemotherapy in most cases
- High-dose chemotherapy with ASCT can be safely and successfully used for relapsed HIV-associated lymphomas
- cART can be continued in most patients but can be interrupted if necessary. Integrase inhibitor – based regimens best
- Standard antibiotic prophylaxis as used in HIV- patients. Include PJP prophylaxis, MAC prophylaxis if CD4<100
- Regular CMV screening suggested after autologous transplant

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