

14TH ANNUAL CONFERENCE
OF THE BRITISH HIV ASSOCIATION (BHIVA)



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Cancer chemotherapy in HIV-infected patients

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After the introduction of HAART the overall prognosis of patients with HIV infection has significantly improved.

Significant improvement has been reached in HIV related lymphomas but it is still an area of intensive research in order to improve the outcome of these patients.

Chemotherapy in HIV lymphomas

- **Pre-HAART era**
- **HAART era**
 - **Role of infusional chemotherapy and role of Rituximab**
 - **Treatment of Burkitt subtype**
 - **Salvage treatment**

Chemotherapy in HIV lymphomas

- Pre-HAART era

TABLE 1. LOW-DOSE AND STANDARD-DOSE m-BACOD CHEMOTHERAPY REGIMENS.*

AGENT	STANDARD-DOSE THERAPY	LOW-DOSE THERAPY
Methotrexate (IV)	200 mg/m ² , day 15	200 mg/m ² , day 15
Bleomycin (IV)	4 U/m ² , day 1	4 U/m ² , day 1
Doxorubicin (IV)	45 mg/m ² , day 1	25 mg/m ² , day 1
Cyclophosphamide (IV)	600 mg/m ² , day 1	300 mg/m ² , day 1
Vincristine (IV)	1.4 mg/m ² , day 1	1.4 mg/m ² , day 1
Dexamethasone (oral)	6 mg/m ² , days 1–5	3 mg/m ² , days 1–5
GM-CSF (SC)	5 μg/kg, days 4–13	5 μg/kg, days 4–13, as needed
Meningeal lymphoma prophylaxis†	Cytarabine (50 mg, IT), days 1, 8, 15, and 22	
Pneumocystis prophylaxis	Trimethoprim–sulfamethoxazole, dapsone, or inhaled pentamidine	

*IV denotes intravenous, GM-CSF granulocyte–macrophage colony-stimulating factor, SC subcutaneous, and IT intrathecal. Doses are given per square meter of body-surface area or per kilogram of body weight.

†Prophylaxis was administered in cycle 1 only.

Kaplan et al. NEJM 1997

TABLE 3. RATES OF RESPONSE TO LOW-DOSE AND STANDARD-DOSE m-BACOD THERAPY.*

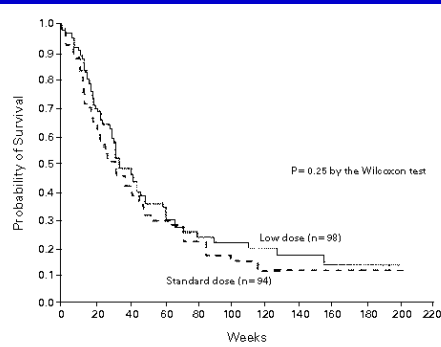
OUTCOME	LOW-DOSE THERAPY (N=94)	STANDARD-DOSE THERAPY (N=81)
	no. (%)	
Complete response	39 (41)	42 (52)
Partial response	26 (28)	21 (26)
Stable disease	11 (12)	8 (10)
Progression of disease	18 (19)	10 (12)
	no./total no. (%)	
Recurrence after complete response	9/39 (23)	17/42 (40)†

*Only patients who could be assessed for the response to chemotherapy are included.

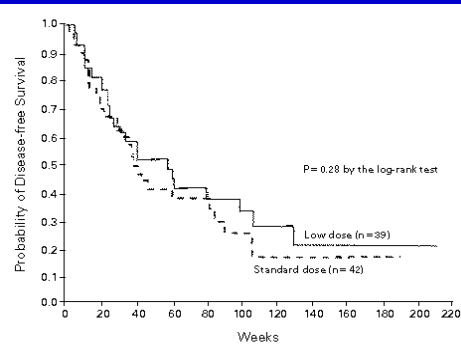
†P= 0.08 for the comparison with the low-dose group.

Kaplan et al. NEJM 1997

Overall Survival



Disease Free Survival



Kaplan et al. NEJM 1997

Low-dose m-BACOD therapy is associated with significantly fewer days of hospitalization than standard-dose therapy.

For these reasons, we recommend that low-dose chemotherapy should be considered for most patients with HIV infection and non-Hodgkin's lymphoma.

**AIDS-related non-Hodgkin's lymphoma:
Final analysis of 485 patients treated with risk-
adapted intensive chemotherapy.**

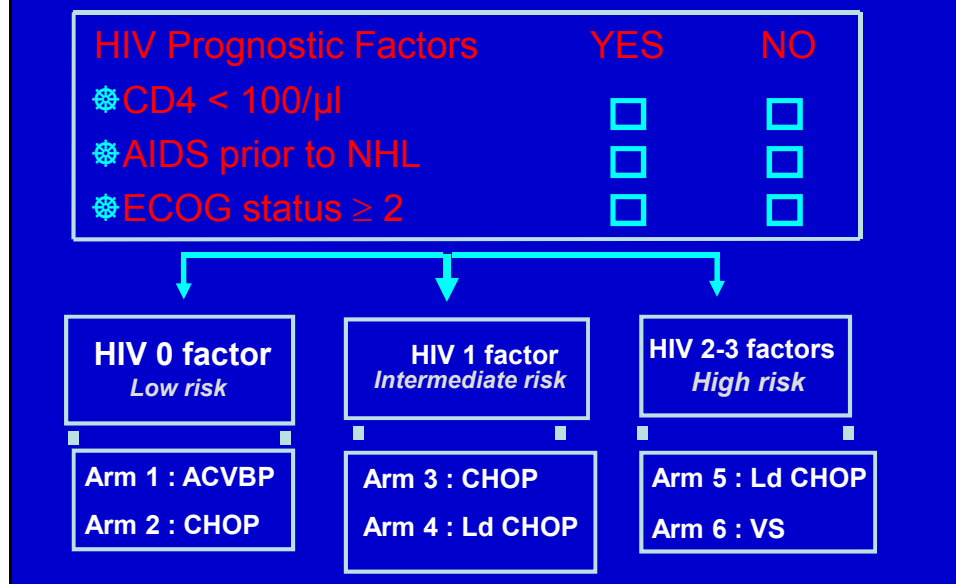
Nicolas Mounier, Michele Spina, Jean Gabarre, Martine Raphael,
Giuliano Rizzardini, JeanBaptiste Golfier, Emanuela Vaccher,
Antonino Carbone, Bertrand Coiffier, Guido Chichino,
Andre Bosly, Umberto Tirelli, Christian Gisselbrecht

for the French-Italian cooperative group



Blood 107 (10): 3832-3840, 2006

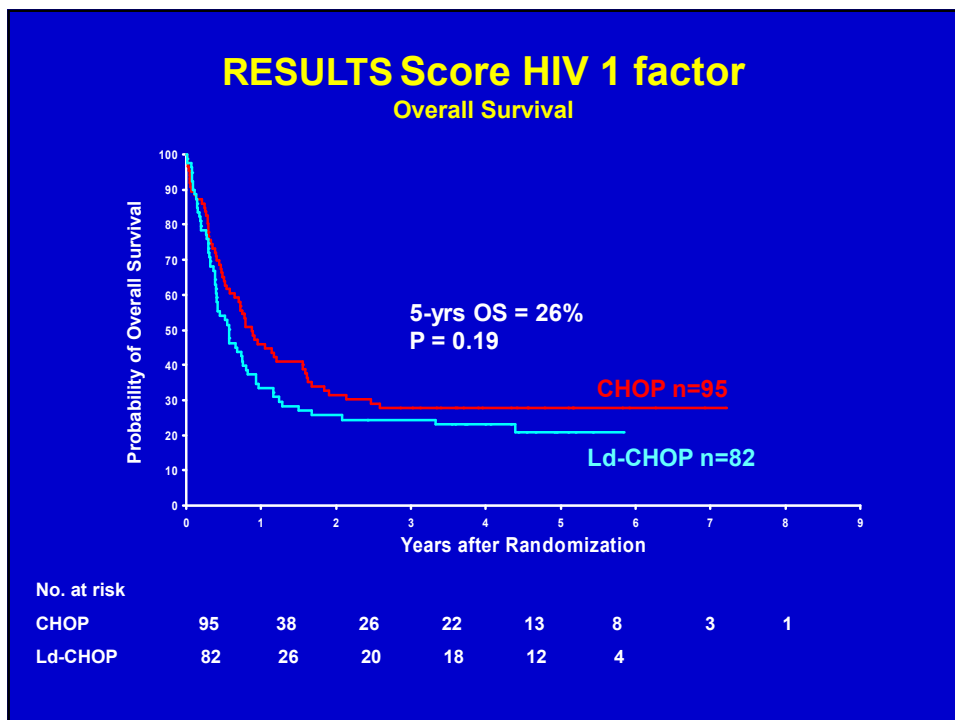
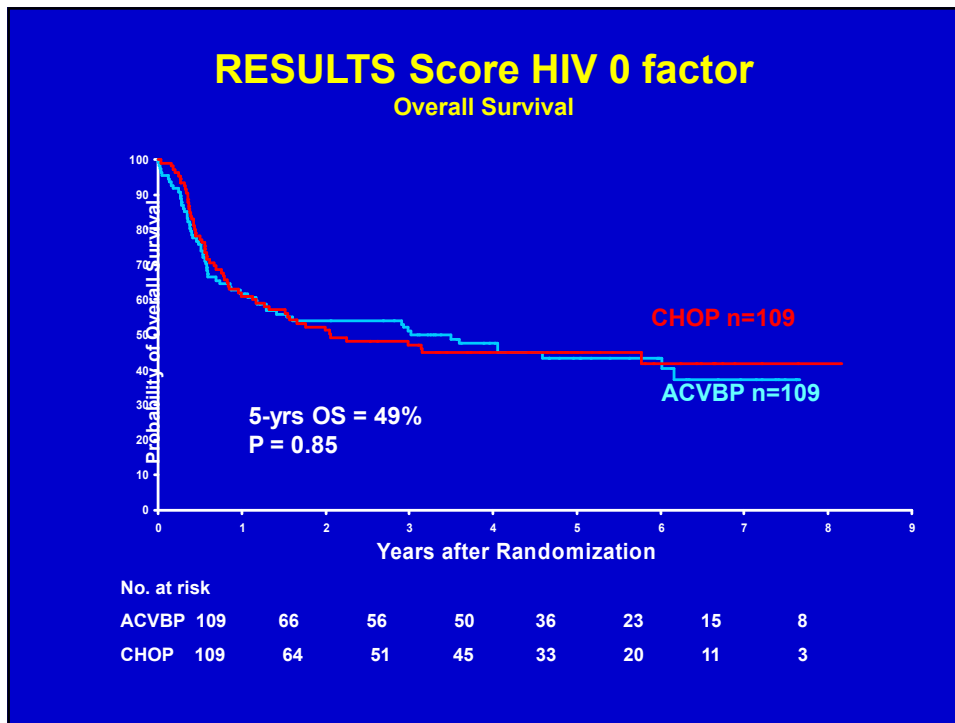
STRATIFICATION - RANDOMIZATION

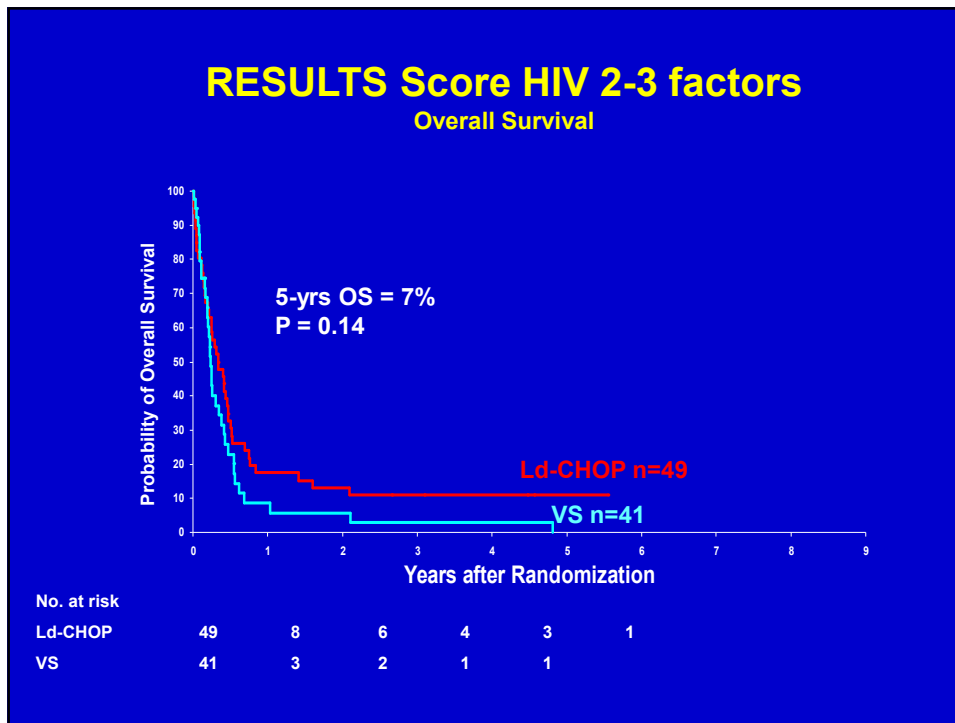


NHL-HIV 93- EUROPEAN STUDY

	HIV 0 N=218 (%)		HIV 1 N=177 (%)		HIV 2-3 N=90 (%)	
	ACVBP N=109	CHOP N=109	CHOP N=95	Ld-CHOP N=82	Ld-CHOP N=49	VS N=41
Response to chemo						
CR/CRu	66 (61)	56 (51)	47 (49)#	26 (32)#	10 (20)	2 (5)
PR	17 (16)	16 (15)	9 (9)	13 (16)	6 (12)	6 (15)
EFS 5 yr %	44%	40%	26%	20%	8%	0
DFS 5 yr %	51%	49%	41%	33%	27%	0

p value < 0.05





Prognostic factors analysis in 335 ARL pts treated by CHOP (n=204) or Ld-CHOP (n=131)

Prognostic Factors	CHOP /Ld-CHOP N=335	PreHAART N=199	PostHAART N=136
3-yrs OS, [CI95%], P value			
aaIPI score 0-1	37 [30-45]	27 [18-35]	54 [42-66]
2-3	16 [8-23] 0.0001*	12 [3-20] 0.0001	22 [8-35] 0.0001*
HIV score 0	46 [37-56]	39 [27-51]	56 [41-71]
1	26 [19-33]	19 [11-17]	50 [35-58]
2-3	10 [2-20] 0.0001*	2 [0-7] 0.0001*	34 [23-45] 0.13
NHL sub-type			
Diffuse large B cell	38 [32-44]	29 [22-34]	49 [41-57]
Immunoblastic	22 [14-30]	17 [7-27]	33 [23-43]
Burkitt	28 [21-36] 0.009*	24 [14-44] 0.21	32 [22-42] 0.10
HAART			
Pre HAART	22 [16-28]	NA	NA
Post HAART	42 [34-51] 0.0002*	NA	NA

•indicate a p-value <0.05 in multivariate analysis. aaIPI: age adjusted International Prognostic Index,
•NA : Not Applicable

CONCLUSION

- ◆ In ARL patients :
 - without severe immunodeficiency (HIV score=0), ACVBP gives 51% 5-yr OS and 61% CR rate. It was not significantly different from CHOP.
 - with HIV score=1, CHOP gives a significantly better CR rate (49%) when compared to Ld-CHOP (32%).
- ◆ OS was affected by IPI score and HAART but not by the dose intensity of a CHOP-based chemo.

Theses factors must be taken into account in the design of Rituximab trials.

Chemotherapy in HIV lymphomas

- **HAART era**
 - Role of infusional chemotherapy and role of Rituximab

**RITUXIMAB plus INFUSIONAL CYCLOPHOSPHAMIDE,
DOXORUBICIN AND ETOPOSIDE (R-CDE) IN HIV-
ASSOCIATED NON-HODGKIN'S LYMPHOMA: POOLED
RESULTS FROM THREE PHASE II TRIALS**

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Simonelli¹, M.Michieli¹, G.Rossi⁵, E.Nigra⁶,
M.Berretta¹, C. Cattaneo⁵, A.C. Rieger⁷, E.Vaccher¹
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M. Spina et al. BLOOD 2005

R-CDE IN NHL-HIV

RITUXIMAB	375 mg/m²	day 1
CYCLOPHOSPHAMIDE	187.5 mg/m²/d	96 h c.i.
DOXORUBICIN	12.5 mg/m²/d	96 h c.i.
ETOPOSIDE	60 mg/m²/d	96 h c.i.
Methotrexate	12 mg i.t.	day 1

CYCLES WERE REPEATED EVERY 28 DAYS FOR 6 CYCLES

R-CDE IN NHL-HIV

RESPONSE	#	(%)
Complete remission	52/74	(70)
Partial remission	4/74	(5)
Progression	18/74	(25)

R-CDE IN NHL-HIV

G3 - G4 NCICTC TOXICITY	#	(%)
Neutropenia	58/74	(78)
Anaemia	24/74	(32)
Thrombocytopenia	18/74	(24)
Mucositis	8/74	(11)
Hepatic toxicity	2/74	(3)
Diarrhea	2/74	(3)
Vomiting	2/74	(3)
Seizure	1/74	(1)
Infections (no AIDS)	19/74	(26)
AIDS defining events	10/74	(14)
Toxic death	2/74	(3)

R-CDE IN NHL-HIV

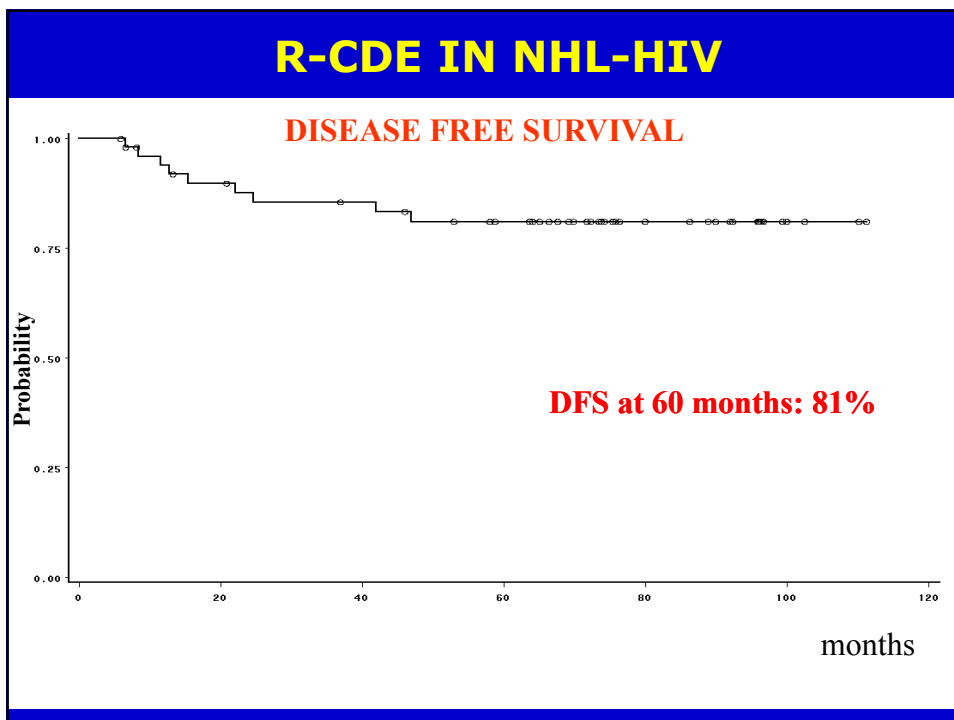
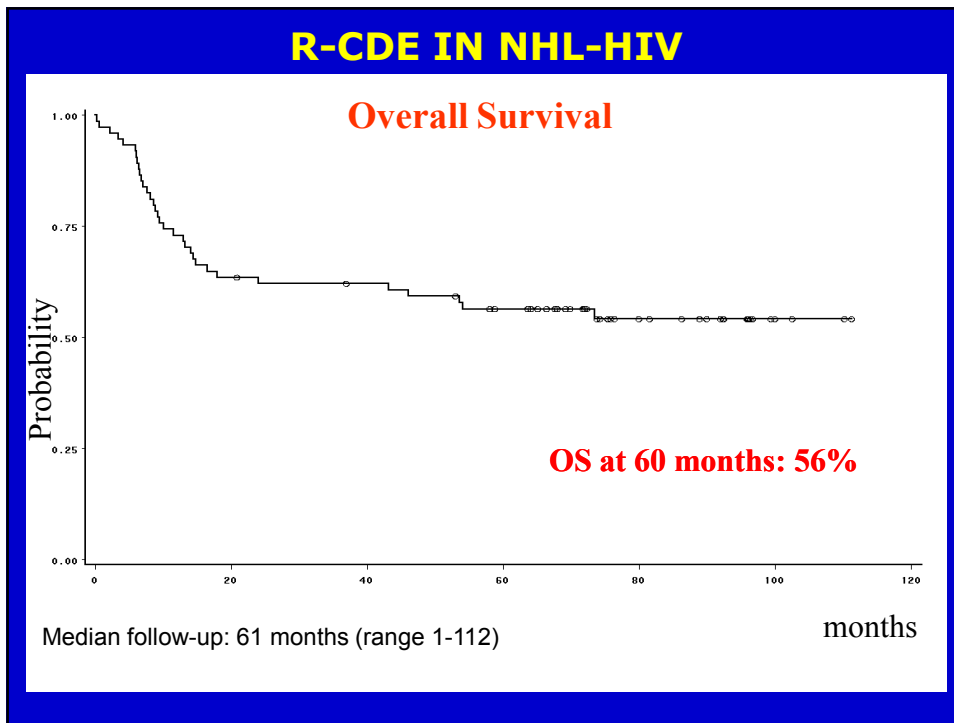
AIDS defining events	10/74 (14)
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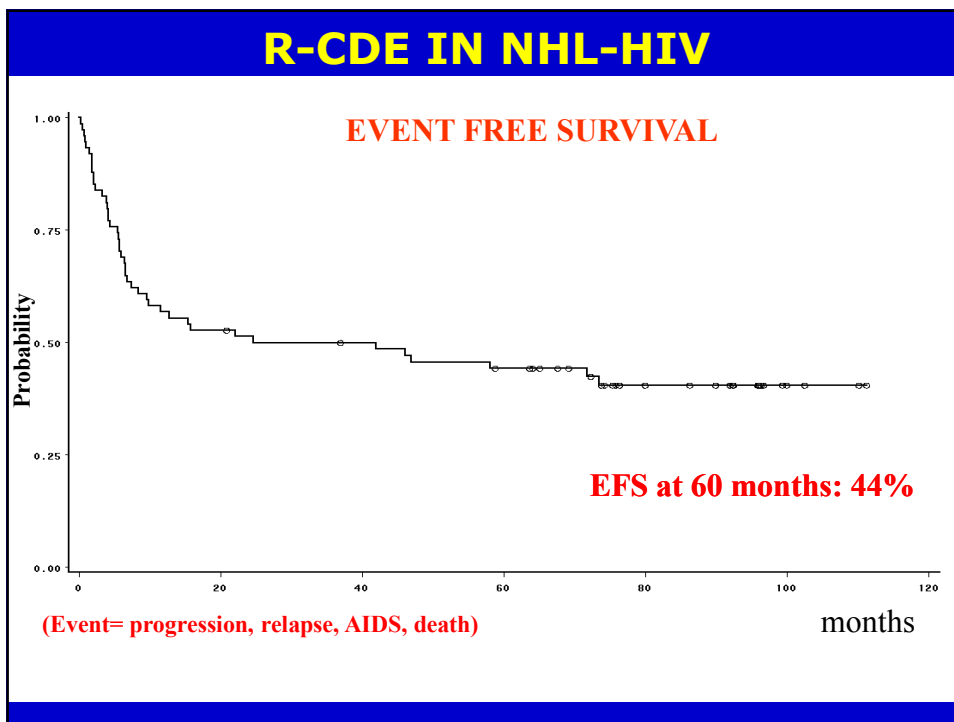
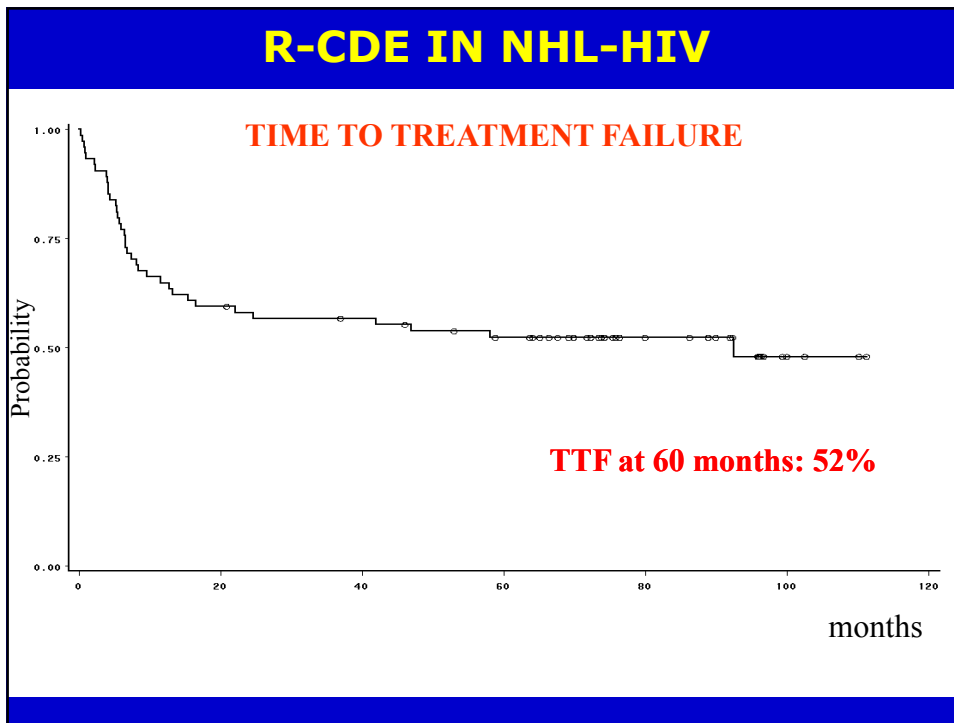
- Cryptosporidium	3
- CMV infection	3
- TB	2
- PCP	1
- Salmonellosis	1

R-CDE IN NHL-HIV

	#	(%)
PATIENTS with NO-AIDS defining events	17/74	(23)

# OF EVENTS	19
- Bacterial Pneumonia	7
- Febrile Neutropenia	4
- Sepsis (Staph.aureus, Enter. cloacae)	3
- Varicella	3
- Disseminated Granulomatoses	1
- Aspergillus pulmonary infection	1



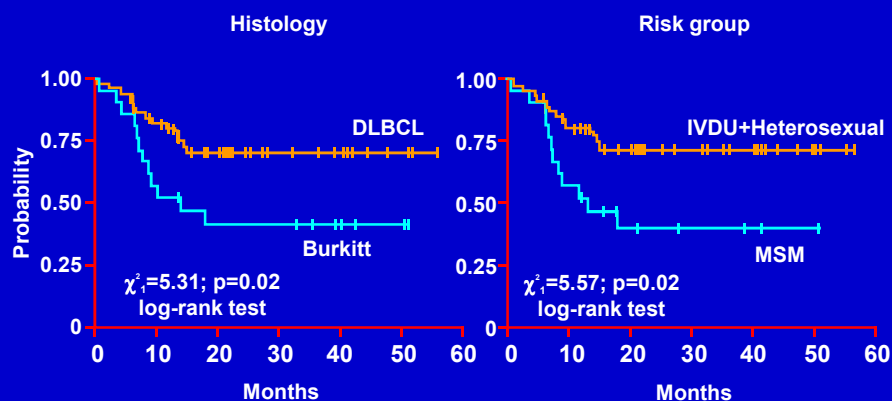


Prognostic factors for survival in univariate and multivariate analyses

Factor	n (%)	Univariate		Multivariate	
		HR (95%CI)	p value	HR (95%CI)	p value
Histology					
DLBCL	53 (72)	1		1	
Burkitt	21 (28)	2.48 (1.15–5.37)	0.02	2.17 (0.99–4.76)	0.05
Risk group					
IVDU +					
Heterosexual	52 (70)	1		1	
MSM	22 (30)	2.54 (1.17–5.51)	0.02	2.34 (1.07–5.11)	0.03
HIV viral load (post CT)					
Undetectable	36 (44)	1		1	
Detectable	26 (33)	2.48 (1.15–5.37)	0.02	2.05 (0.93–4.52)	0.08

M. Spina et al. BLOOD 2005

Rituximab + CDE IN HIV-related NHL survival by histology and risk group



M. Spina et al. BLOOD 2005

INFUSIONAL CHEMOTHERAPY

Study	R-CDE (n=74)	CDE (n=55)	EPOCH (n=39)
Stage III-IV (%)	70	76	67
IPI ≥ 2	57	58	59
CR (%)	70	45	74
2 yrs OS(%)	64	45	60
2 yrs FFS (%)	59	36	73
2 yrs DFS (%)	89	NA	92

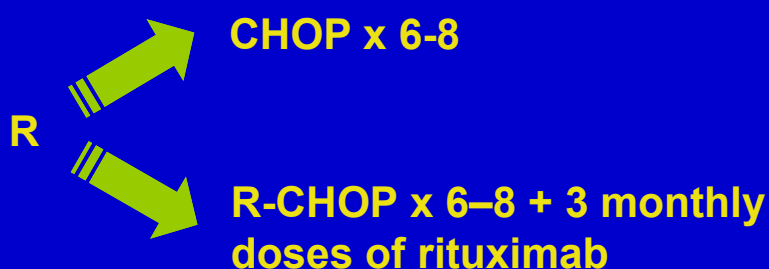
Rituximab + CDE in HIV-related NHL: conclusions – 1-

- Rituximab plus infusional CDE in patients with HIV-associated NHL is safe, feasible and highly active with a significant improvement of CR rate, OS, DFS and EFS
- Burkitt-NHL seems to have a worse outcome in comparison to patients with DLBCL. Therefore a more intensive strategy should be employed
- Given the potential for rituximab to increase the risk for life-threatening infections in this population, however, such evaluations must proceed cautiously.

R-CDE IN NHL-HIV Conclusions – 2 -

Finally, our data confirm that a high proportion of patients with HIV related NHL can be cured with aggressive chemotherapy regimens without a significant negative impact on the HIV infection.

CHOP versus R-CHOP in HIV-related NHL: protocol



Kaplan LD, et al. BLOOD 2005

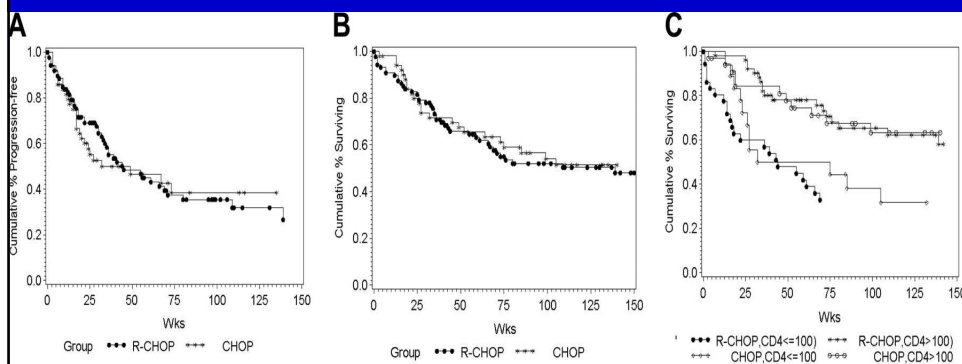
CHOP versus R-CHOP in HIV-related NHL: results

Parameters	R-CHOP (n=99) (%)	CHOP (n=51) (%)	p
CR	58	47	0.15
PR	8	8	0.99
Progression	8	22	0.01
Grade 4 Neutropenia	62	48	0.11
Febrile Neutropenia	31	24	0.35
Death due to infection	14	2	0.035

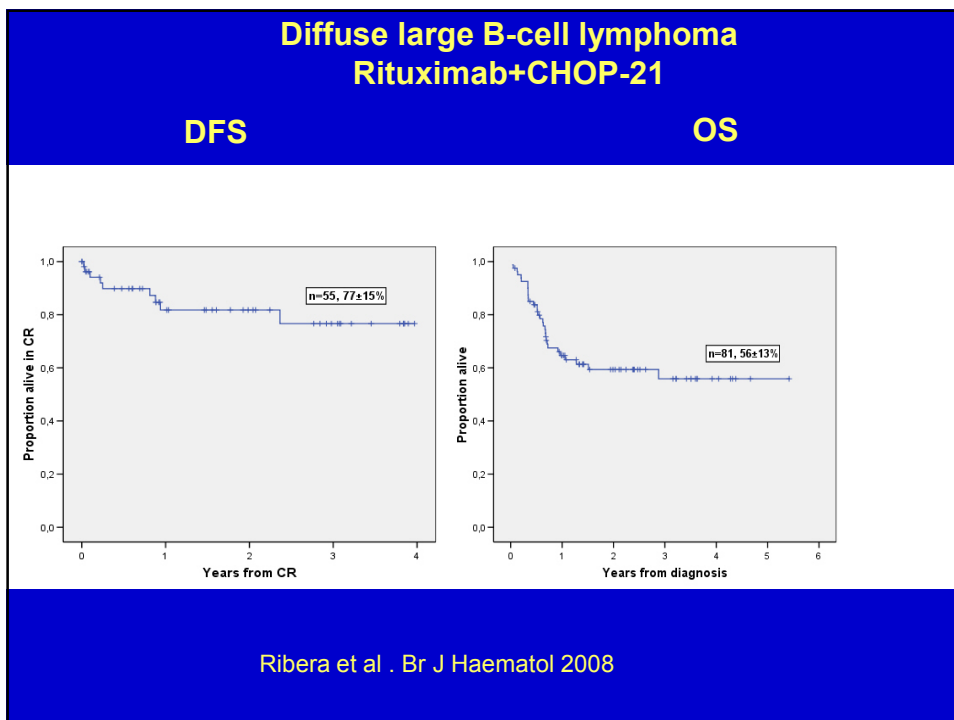
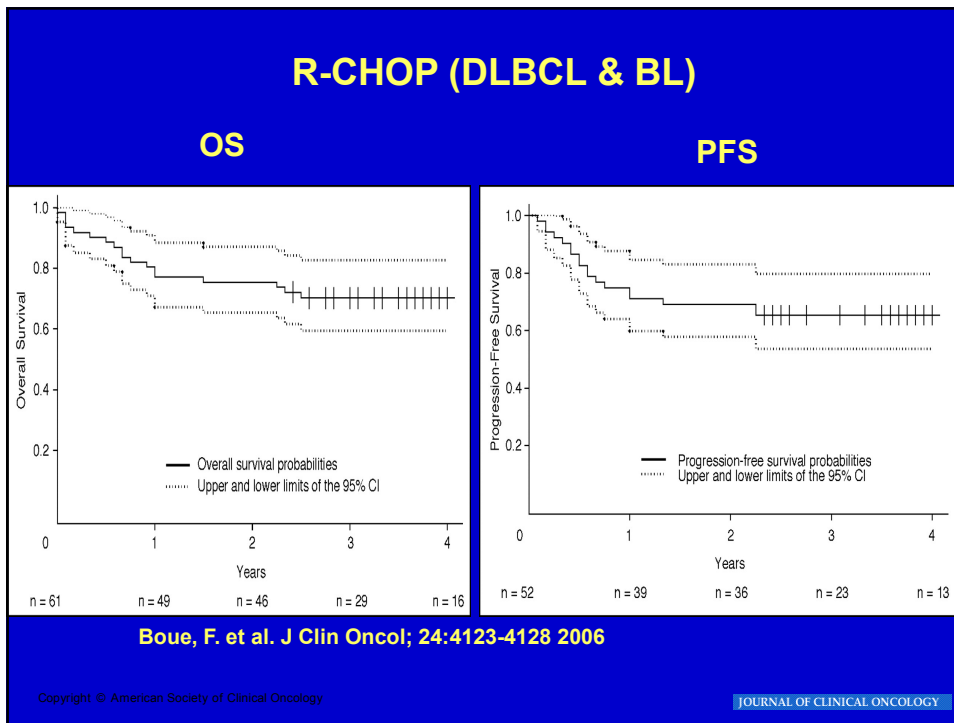
Median follow-up: 19.5 months

Kaplan LD, et al. BLOOD 2005

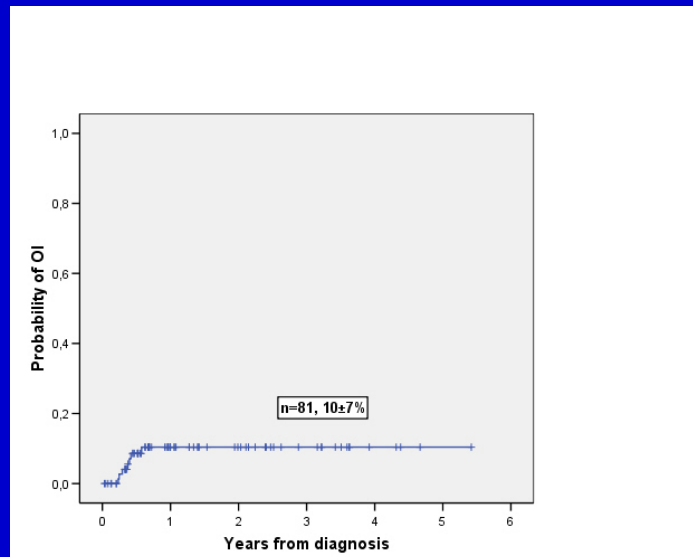
CHOP versus R-CHOP in HIV-related NHL: results



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



R-CHOP-21. Opportunistic infections



Ribera JM et al. Br J Haematol 2008

Immunochemotherapy Be careful with infections!

- **R-CHOP vs. CHOP**
 - Trend to better antitumoral effect with R-CHOP (CR 58% vs. 47%, p: 0,1).
 - Higher infectious mortality in R-CHOP arm (15/16 R-CHOP vs. 1/16 CHOP), especially in patients with CD4<50/ μ L.
- **R-CDE**
 - Better CR rate (70% vs. 45%) and OS (64% vs. 38%) compared with historical control (CDE)
 - Higher frequency of infections (31% vs. 20%) but with low mortality (2% vs. 0%) compared with historical control

Chemotherapy in HIV lymphomas

- HAART era
 - Treatment of Burkitt subtype

**Patients With HIV With Burkitt's Lymphoma
Have a Worse Outcome Than Those With
Diffuse Large-Cell Lymphoma Also in the
Highly Active Antiretroviral Therapy Era**

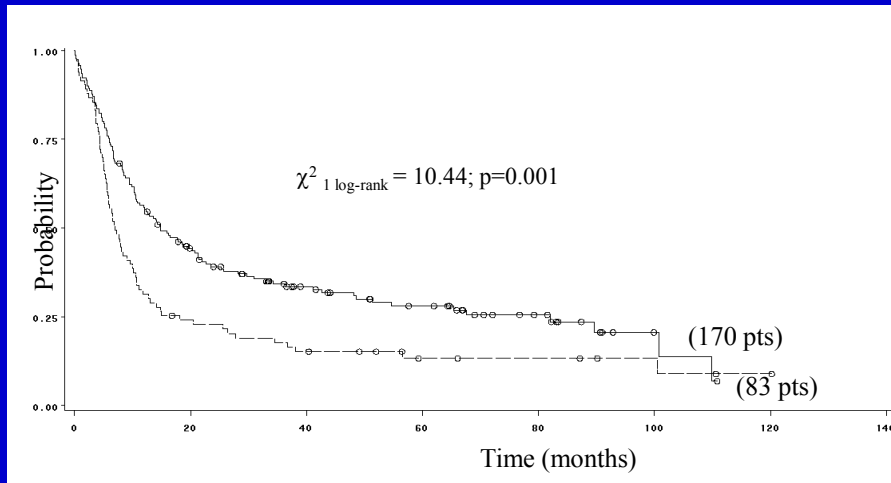
**Michele Spina¹, Cecilia Simonelli¹, Renato Talamini²,
Umberto Tirelli¹**

¹Medical Oncology A, National Cancer Institute, Aviano, Italy

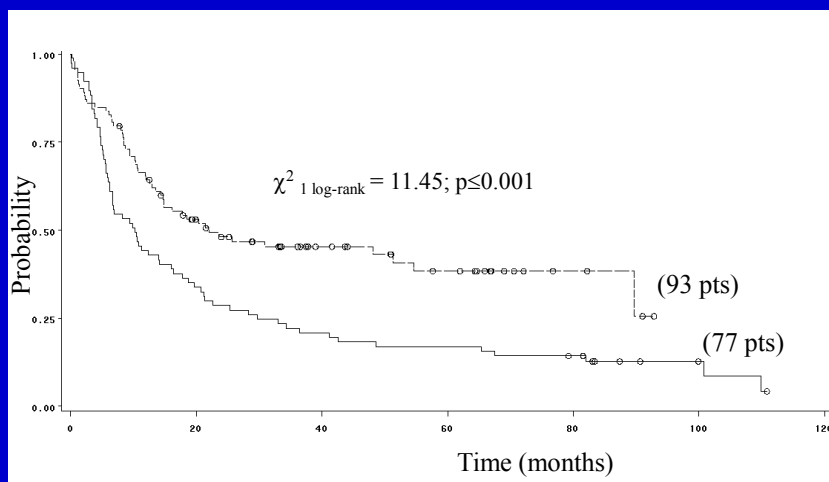
²Epidemiology Unit, National Cancer Institute, Aviano, Italy

J Clin Oncol. 2005;23(31):8132-3

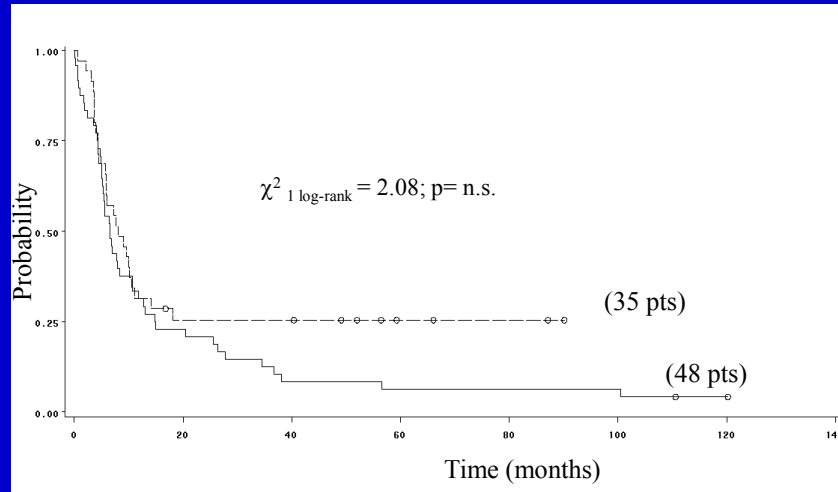
Survival of all patients by Histology (DLCL vs. Burkitt)



Survival of patients with DLCL by HAART era (pre97 vs. post97)



Survival of patients with Burkitt by HAART era (___pre97 vs. __post97)



Intensive chemotherapy regimen (LMB86) for St Jude stage IV AIDS-related Burkitt lymphoma/leukemia: a prospective study

Table 1. LMB86 chemotherapy regimen

Drug, dosage/d	Day
Cytoreductive phase, COP	
Vincristine, 2 mg	d ₁
Cyclophosphamide, 300 mg/m ²	d ₁
Prednisone, 60 mg/m ²	d ₁ to d ₇
Induction	
COPADM 1	
Vincristine, 2 mg	d ₁
Methotrexate, 8 g/m ²	d ₁
Cyclophosphamide, 500 mg/m ²	d ₂ to d ₄
Adriamycin, 60 mg/m ²	d ₂
Prednisone, 60 mg/m ²	d ₁ to d ₇
COPADM 2	
Idem with vincristine, 2 mg	d ₁ , d ₅
Cyclophosphamide, 1000 mg/m ²	d ₂ to d ₄
Prednisone, 60 mg/m ²	d ₁ to d ₇
Consolidation, CYVE, ×2	
Etoposide, 200 mg/m ²	d ₂ to d ₅
ARA-C, 3 g/m ²	d ₂ to d ₅
ARA-C, 50 mg/m ²	d ₁ to d ₄ *

Galicier L, Blood 2007

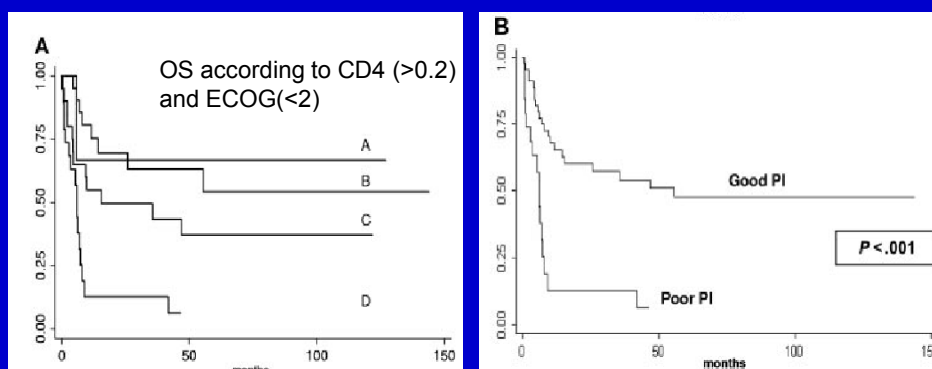
Table 3. Baseline tumor characteristics	
Characteristic	No. (%)
Total	63 (100)
Stage IV St Jude/Murphy	63 (100)
Bulky tumor	19 (30)
Peripheral blasts	17 (27)
BM blasts	50 (79)
BM blasts more than 25%	48 (76)
CNS*	48 (76)
CSF leukemia	12 (19)
Cranial nerve palsy	36 (57)
Epidural mass	10 (16)
BM and CNS disease	37 (59)
Liver	28 (44)
GI tract	19 (30)
Kidney	10 (16)
Patients with other sites	28 (44)
IPI	
2	6 (9)
3	13 (21)
4	42 (67)
5	2 (3)

N=63
 Male 56
 From 1992 to 2006
 Median T4 =0.239

CR rate 70%

**80% febrile neutropenia,
 7 toxic death**

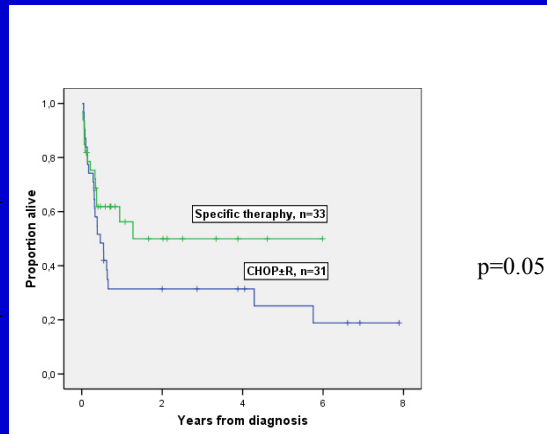
Overall Survival



HIV-related Burkitt's lymphoma CHOP vs. specific therapy

	CR	Failure	Total
CHOP±R	10	21	31
Specific±R	22	11	33

P=0,006



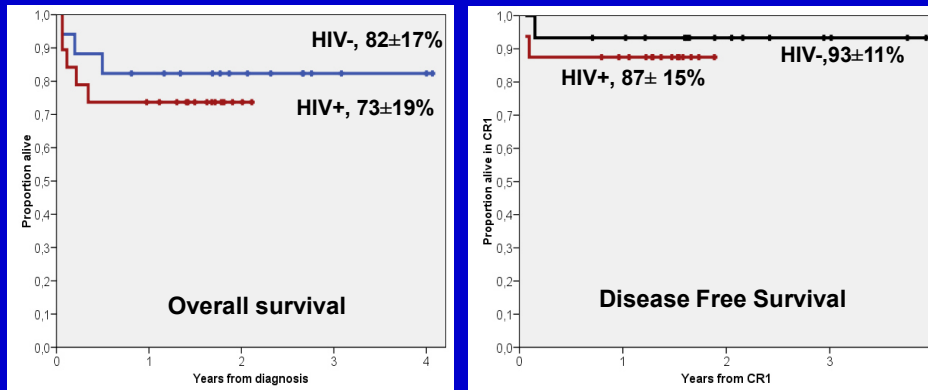
B Xicoy et al 2008 (submitted)

Specific chemotherapy + rituximab (BURKIMAB)

	HIV negative N=17	HIV positive N=19
CR	88%	84%
DFS (2-yr) (CI95%)	93% (82-99)	87% (72-99)
OS (2-yr) (CI95%)	82% (65-99)	73% (54-92)

A Oriol et al, 2008 (submitted)

BURKIMAB



A Oriol et al 2008 (submitted)

Hematological toxicity grade 4

	HIV neg N=62 Median (range)	HIV pos N=38 Median (range)
Days of neutropenia ($<0.5 \times 10^9/L$)	14 (7-23)	15 (7-20)
Days of thrombocytopenia ($<20 \times 10^9/L$)	14 (7-25)	14 (7-31)

Non-hematological toxicity grade > 2

	All cycles N=100	HIV- N=62	HIV+ N=38
Hepatic (%)	8 (8)	3 (5)	5 (13)
Renal failure (%)	2 (2)	1 (2)	1 (3)
Digestive/mucositis (%)	17 (17)	6 (10)	11 (29) *
Infections (%)	17 (17)	4 (6)	13 (34) #

* P=0.055

p=0.025

INTENSIVE CHEMOTHERAPY IN HIV-BURKITT

Recently, the results of a retrospective study suggested that intensive chemotherapy with CODOX-M/IVAC is feasible and well tolerated in HIV positive adults with BL.

In the HAART era, intensive chemotherapy may be appropriate in all adult patients with BL, and especially those with poor prognostic factors, regardless of HIV status.

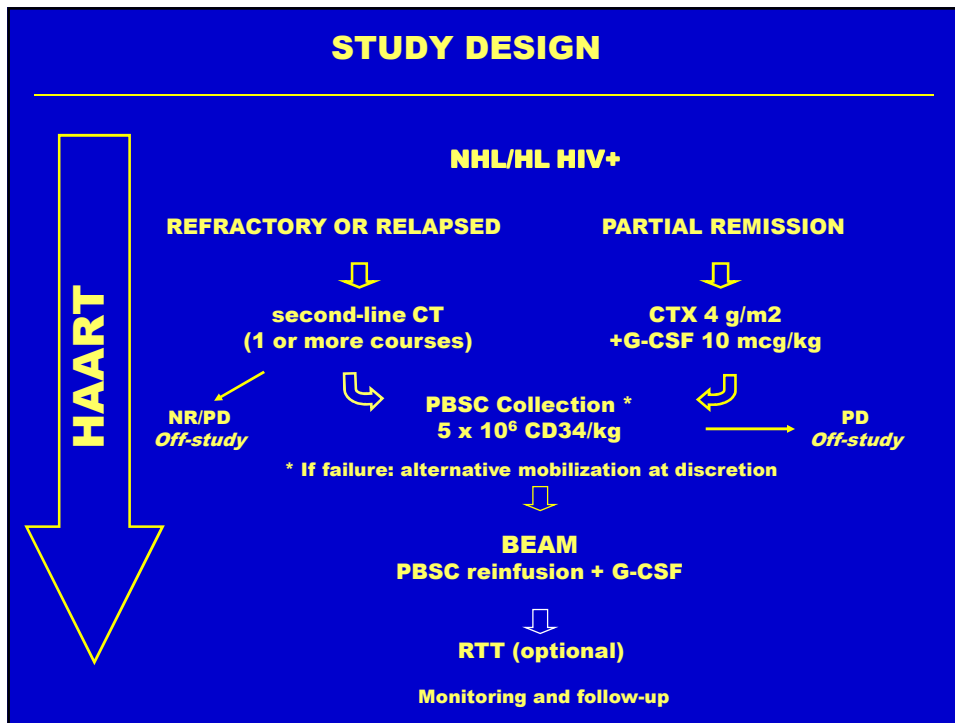
Chemotherapy in HIV lymphomas

- HAART era

– Salvage treatment

CONVENTIONAL SALVAGE TREATMENT IN REFRACTORY/RELAPSED HIV-LYMPHOMA

	VMP (Tirelli, 1996)	Mitoguazone (Levine, 1997)	DHAP/ESHAP (Bi, 2001)	CDE (Spina, 2001)
Patients	13 resistant 8 relapsed	18 resistant 17 relapsed	24 resistant 2 relapsed	34 resistant 6 relapsed
Complete remission	5/19 (26%)	3/26 (12%)	4/26 (15%)	4/40 (10%)
Objective response	7/19 (37%)	6/26 (23%)	8/26 (31%)	11/40 (28%)
Toxicity	TRM 5%	TRM 0%	WHO 4 neutropenia 100%	TRM 12%
Survival overall	2 months	2,6 months	2-7 months	4 months
responders	13 months	14 months		10 months



50 ELIGIBLE PTS

↓

2 early toxic death
10 refractory/progression
6 unsuccessful mobilization
1 refused mobilization

DEBULKING TREATMENT (2-4 cycles)

NHL: platin-based CT (+/-Rit.) (24)
MINE (2)
other (3)

HL: MINE (16)
other (2)

↓

31 CD34+COLLECTIONS

31/37 evaluable pts (84%)

MOBILIZING TREATMENT: 2° line CT (19)

HD-CTX (12)

CD34+ CELLS (X 10e6/Kg) 5.9 (2.5-20.0)

N° OF APHERESIS 2 (1-3)

31 CD34+ COLLECTIONS

4 early disease
progression


ENGRAFTEMENT

Neutrophils > 500/cmm	+10 (8-14)
Platelets > 20.000/cmm	+12 (8-120)

27 TRANSPLANTS**27/50 eligible pts (54%)****TOXICITY and INFECTIONS after PBSCT (N=27)****TREATMENT-RELATED TOXICITY (WHO 3-4)**

GRADE 3 : MUCOSITIS (9), HEPATIC (2), DMSO REACTION (1)

GRADE 4 : MUCOSITIS (1)

INFECTIONS PRIOR TO ENGRAFTMENT

SEPSIS (2) (*E. coli*, *S. epidermidis*)

REACTIVATION OF PERIANAL ABSCESS (2)

PHLEGMON OF THE NECK (1)

C. difficile COLITIS (1)

P. aeruginosa PNEUMONIA (1)

HERPES ZOSTER (1)

FUO (9)

POST-ENGRAFTMENT OPPORTUNISTIC INFECTIONS

HERPES ZOSTER (7)

ASYMPTOMATIC CMV VIREMIA (4)

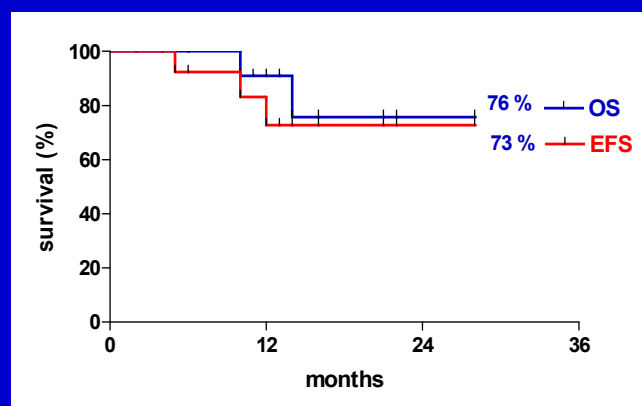
CMV RETINITIS (1)

ESOPHAGUS CANDIDOSIS (2)

HAART and HIV-VIREMIA

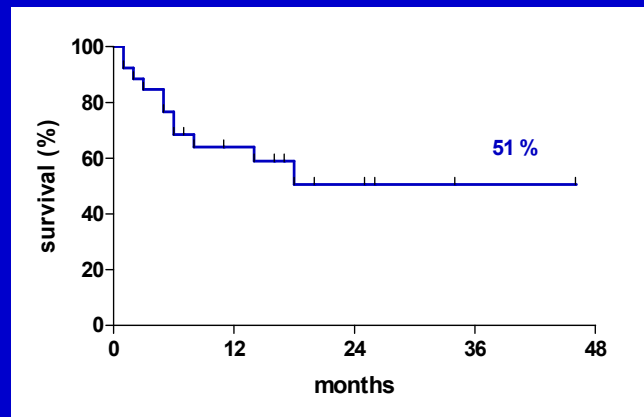
- ❖ HAART was temporarily suspended at PBSCT in 7 pts (6 had transient viremia)
- ❖ 7 pts required changes in HAART regimen during follow-up (due to viral failure in 4 and intolerance in 3)
- ❖ Most pts had undetectable HIV-viral load at 6 ms (89%), 12 ms (69%) and 24 ms (80%) after transplant

Overall survival and event free survival from PBSC transplantation (N = 27)



Median follow-up 44 months (4-70)

**Overall survival of the entire series (N=50)
("intention to treat")**



Median follow-up 45 months (9-86)

CONCLUSIONS

- **The GICAT study confirms, in a large prospective series, the feasibility and safety of HDT with PBSCT in HIV-Ly**
- **It demonstrates the high efficacy of this procedure in refractory and relapsed HIV-Ly, with high OS (75%) and PFS rate (76%) after long-term follow-up (44 ms), and a very low relapse rate for pts achieving CR (13% at > 3y)**
- **In an intention to treat analysis more than 50% of eligible pts could receive transplant with encouraging results (4ys-OS 50%)**

COMMENTS and PERSPECTIVES

- **HDT and PBSCT should be offered to all HIV + pts with refractory and relapsed lymphoma**
- **Due to the high efficacy of the procedure, any effort should be done to bring pts to transplant, *optimizing HIV infection control (more efficient antiretroviral therapy) and debulking treatment (specific treatment for HL and NHL)***
- **CR after transplant should be the goal *(additional treatment for pts with residual disease; more effective conditioning)***
- **Given the low toxicity of this treatment strategy and the negative prognostic impact of advanced lymphoma and HIV disease, it may be worth exploring PBSCT earlier in the history of this pts, at least for those with “high risk” disease**

TAKE HOME MESSAGE

SAME TREATMENT
for patients with HIV- NHL
and
HIV negative patients



14TH ANNUAL CONFERENCE
OF THE
BRITISH HIV ASSOCIATION (BHIVA)

23-25 April 2008, Belfast Waterfront Hall, Northern Ireland, UK