

AIDS-Related Cancers: What's New with the Old

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HIV Management
Hepatitis Management

THE NEW YORK COURSE

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**Infectious organisms can
cause cancer**

14th Report on Carcinogens

Department of Health & Human Services, USA

Released November 3, 2016

Newly reviewed substances		
Substance	Listing Status	Description
Human immunodeficiency virus type 1 (HIV-1)	Known to be a human carcinogen	Virus
Human T-cell lymphotropic virus type (HTLV-1)	Known to be a human carcinogen	Virus
Epstein-Barr virus (EBV)	Known to be a human carcinogen	Virus
Kaposi's sarcoma-associated human herpesvirus / HHV8	Known to be a human carcinogen	Virus
Merkel cell polyomavirus (MCV)	Known to be a human carcinogen	Virus
Trichloroethylene (TCE)	Known to be a human carcinogen	Industrial solvent
Cobalt and cobalt compounds that release cobalt ions in vivo	Reasonably anticipated to be a human carcinogen	A metal and its compounds

**International Agency for Research in Cancer (IARC)
defines 10 organisms as well established carcinogenic agents
in humans, and one (HIV-1) as a co-factor**

Organism	Attributable cancer(s)	
<i>Opisthorchis</i> and <i>Clonorchis</i>	Bile duct cancer	
<i>Schistosoma haematobium</i>	Bladder cancer	
<i>H. pylori</i>	Non-cardiac gastric cancer Gastric cardiac cancer	Gastric lymphoma
HTLV-1	Adult T-cell leukemia / lymphoma	
* HBV	Liver cancer	
* HCV	Liver cancer, lymphoma	
* HPV	Cervical cancer Penile cancer Vulvar cancer	Vaginal cancer Anal cancer Oropharyngeal cancer
* EBV	Hodgkin's NHL, Burkitt Nasopharyngeal cancer	NK / T lymphoma Squamous cell cancer of conjunctiva
* HHV8	Kaposi's sarcoma Castleman's related lymphoma	

* HIV-1 is a co-factor to ↑ risk.

Epidemiology: Infection-Attributable Cancers

- In 2012, 14 million new cancer cases, globally
 - 15.4% attributable to organisms
 - < 5% in USA, Canada, Australia, New Zealand, some Western & Northern European countries
 - Overall, 25% of cancers in resource-poor regions
 - Over 50% in sub-Saharan Malawi and Mozambique
- 92% of these cancers due to *H. pylori*, HPV, HBV, HCV
- These figures likely under-represent true incidence
- Must concentrate on prevention:
 - Vaccines (HPV, HBV)
 - Screen and treat strategies (HPV)
 - Anti-infectives (*H. pylori*, HCV, HIV)

EPIDEMIOLOGY

MALIGNANCIES INCREASED AMONG HIV-INFECTED PERSONS

AIDS-Defining

Kaposi's Sarcoma

High-Grade B-Cell Lymphoma

Cervical Cancer

Non- AIDS-Defining

HPV-Related

Anal cancer

Oropharyngeal cancer

HHV-8 Related

Castleman's

EBV-Related

Hodgkin's lymphoma

HCV / HBV-Related

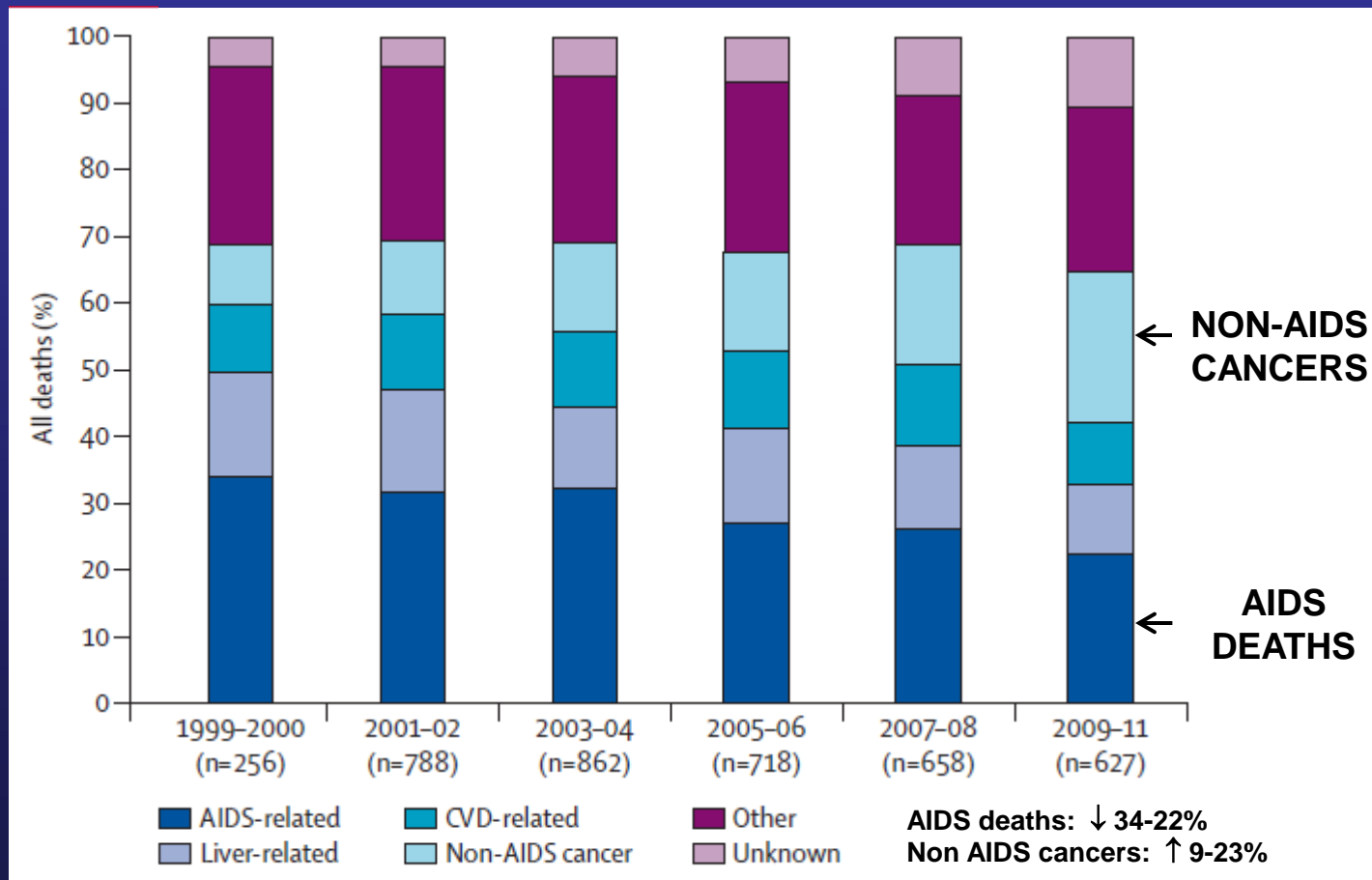
Liver cancer

Lung Cancer

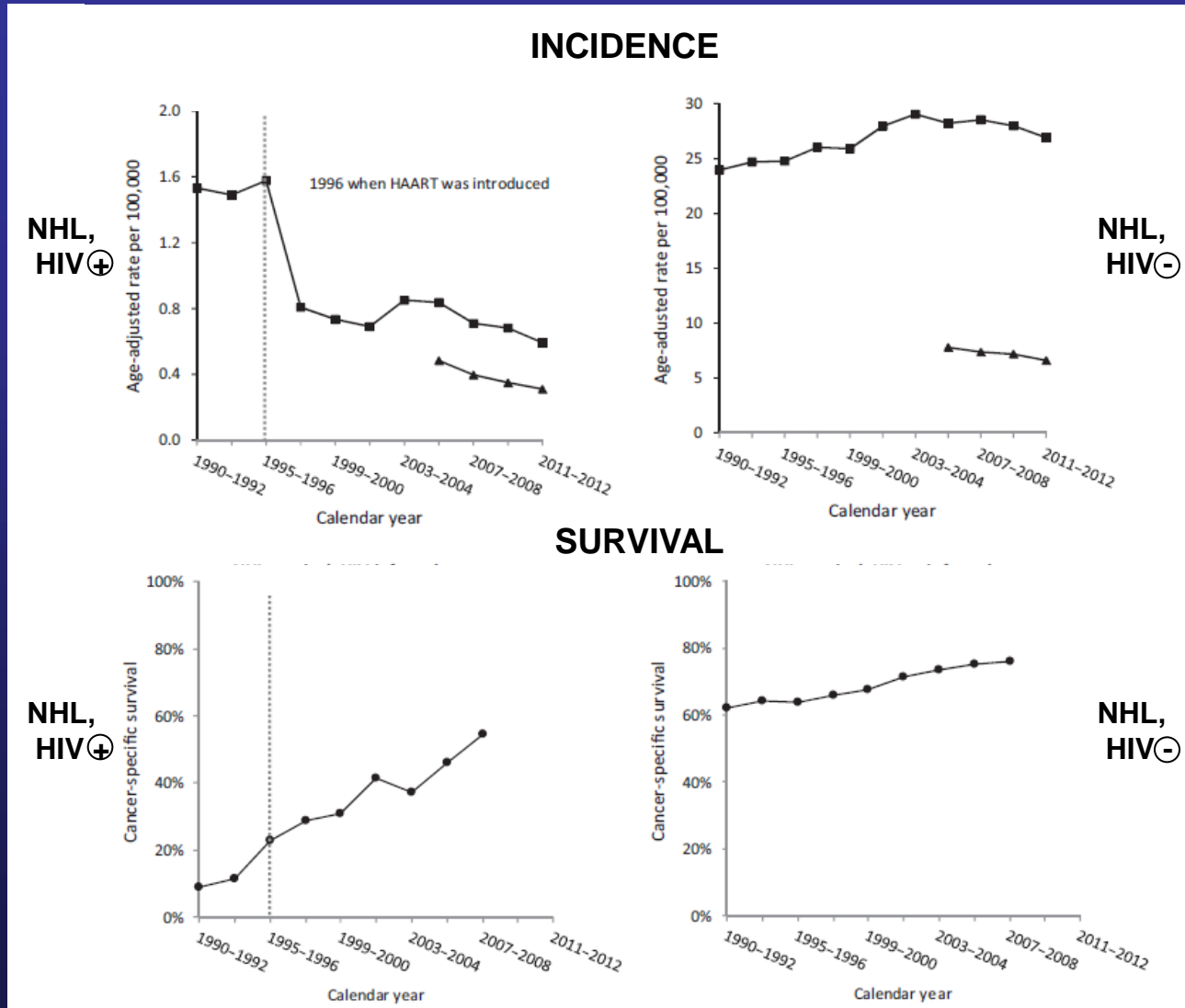
Common causes of death in HIV-infected persons

D:A:D Study: 1999 – 2011

(N = 3,909)



Trends in incidence, survival and incidence-based mortality (IBM) among HIV-positive and HIV-negative lymphoma patients USA: 1990 – 2012, SEER Data



Changes in clinical context of KS and NHL among HIV-infected patients in the USA

- KS or NHL diagnosed from 1996 – 2011
- Derived from 8 clinical cohorts

FACTOR	NHL	KS
On ART > 6 mos	3.4 fold ↑	710 fold ↑
CD4 > 500	3.1 fold ↑	430 fold ↑
HIV RNA < 500 copies/ml	2.9 fold ↑	430 fold ↑



↑ Risk of ADC's continues

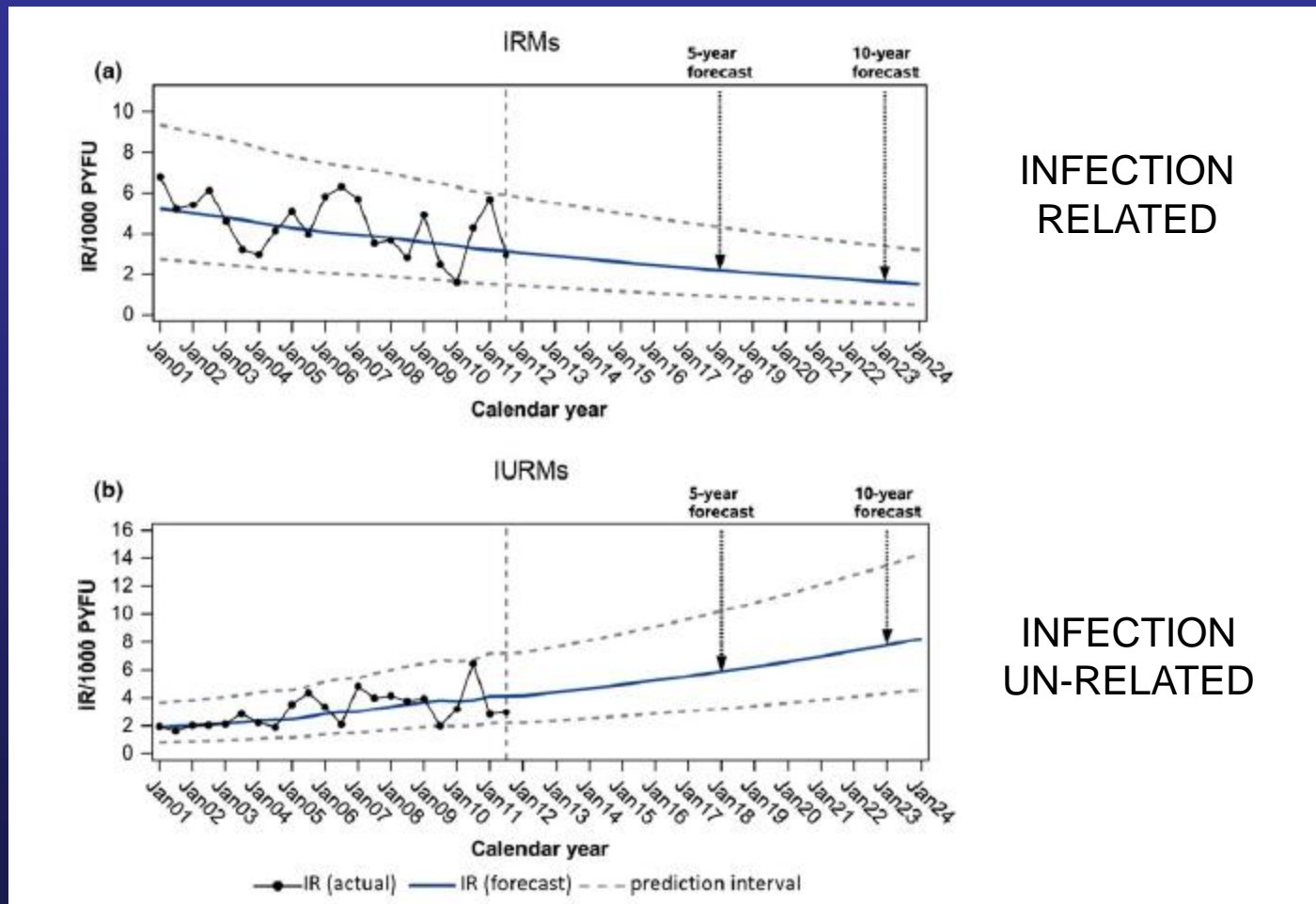
Infection-related vs. infection-unrelated cancers among HIV-infected persons

Effect of aging over time

* Incidence of both infection-related AND -unrelated cancers increased with age.

	Factors associated with infection-related cancers	Factors associated with non-infection-associated cancers
Pts < 50	Low CD4s	Low CD4s
Pts \geq 50	Low CD4s	Smoking

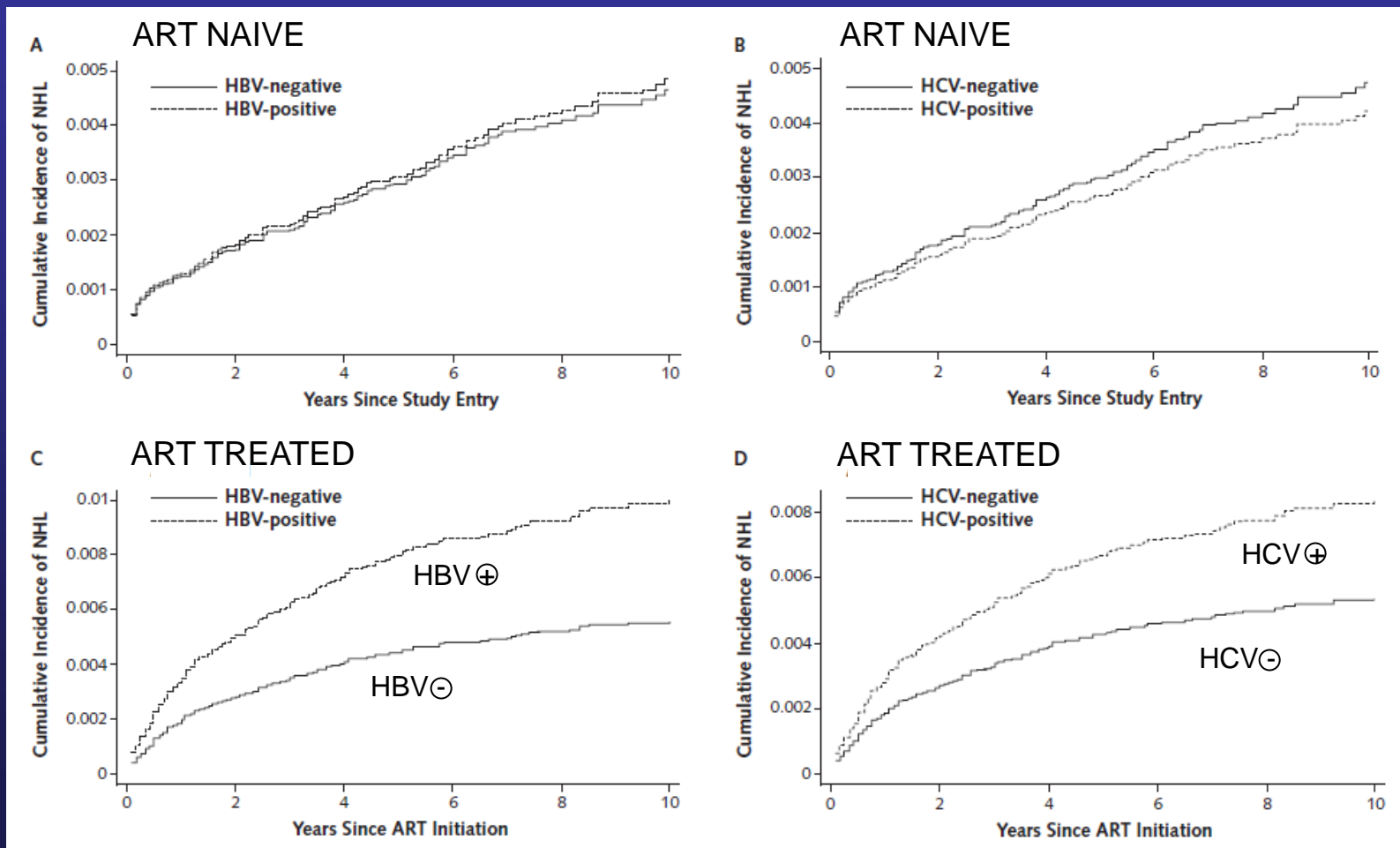
Forecast crude incidence rates of infection-related and infection-unrelated cancers (per 1000 PY's) in 15,648 patients recruited before 2001 (EuroSIDA)



Cumulative incidence of AIDS lymphoma among ART-naive (F/U = 13 mos) vs. ART-treated patients (F/U = 50 mos)

HBV+ = 1,339 pts

HCV+ = 7,507 pts



Ref: Wang Q, et al (COHERE/Europe). *Ann Intern Med* 2016; Oct 18.
doi:10.7326/M16-0240.

Predictors of AIDS Lymphoma

Low CD4 cells (< 200)

Uncontrolled HIV replication

– Serum free Ig light chains

– Serum cytokines / chemokines

sCD27

sCD23

CXCL13

IL-6

↑ miR 21 in PB B cells (vs HIV+ controls or HIV- NHL)

AIDS-Related Lymphoma

Treatment

Treatment factors affecting outcomes in AIDS-related lymphoma

Pooled data from 1,546 patients from 19 prospective clinical trials



Statistically significant results

	CR	PFS	Overall survival
Concomitant ART	↑		Trend ↑
Rituximab use	↑	↑	↑
Infusional EPOCH			↑ in DLBCL
Dose-intensive vs CHOP Rx	↑		↑

Dose-Adjusted EPOCH in AIDS Lymphoma

Continuous Infusion over 96 Hours

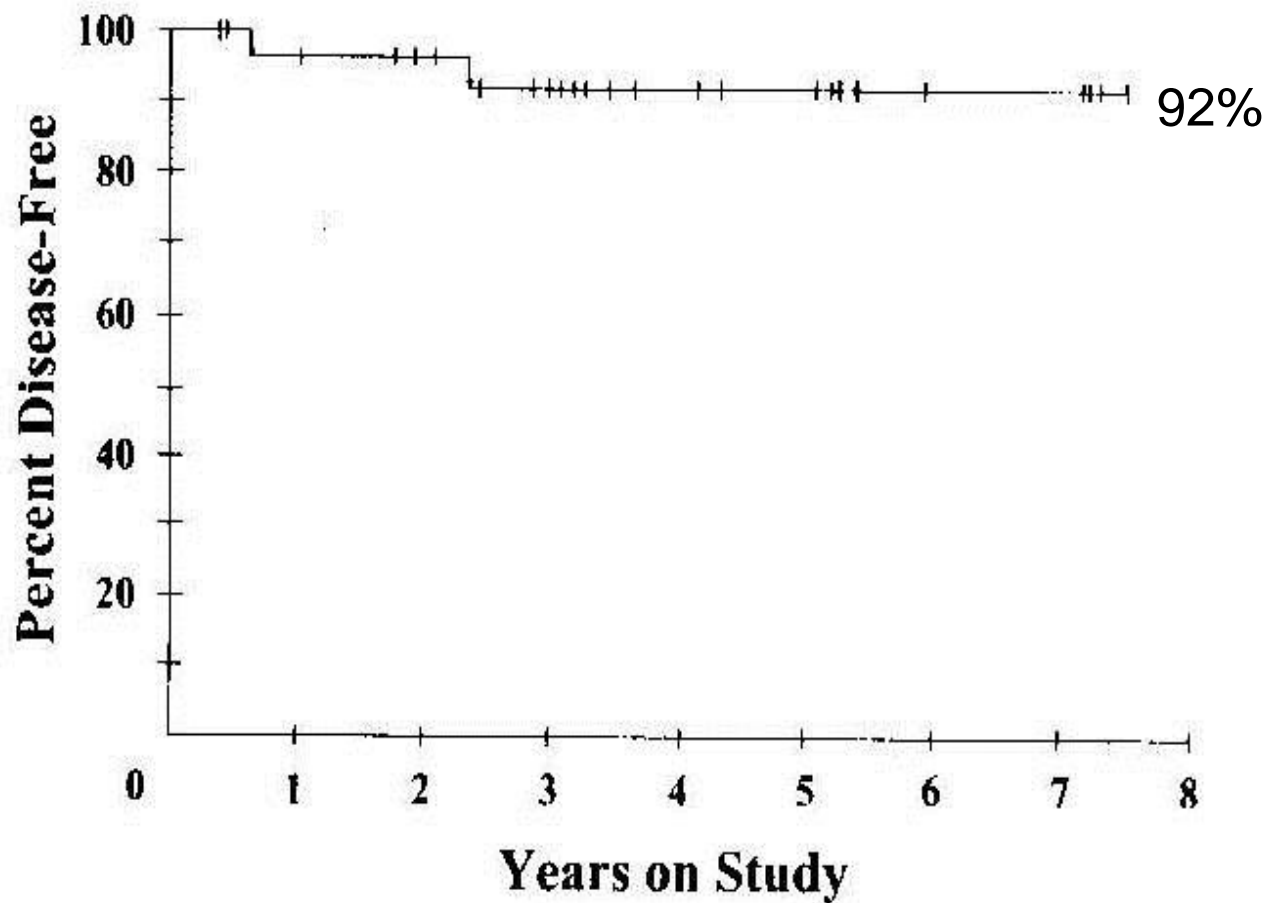
NO ANTI-HIV Rx Until End of 6th Cycle of Chemo

Drug	Dose	Day
Etoposide	50 mg/m ² /d	1-4
Vincristine	0.4 mg/m ² /d	1-4
Doxorubicin	10 mg/m ² /d	1-4
Prednisone	60 mg/m ² /d po	1-5
Cyclophosphamide		
< 100 CD4	187 mg/m ²	5
> 100 CD4	375 mg/m ²	6
G-CSF		6 to ANC > 5000

Dose-Adjusted EPOCH in AIDS NHL Results

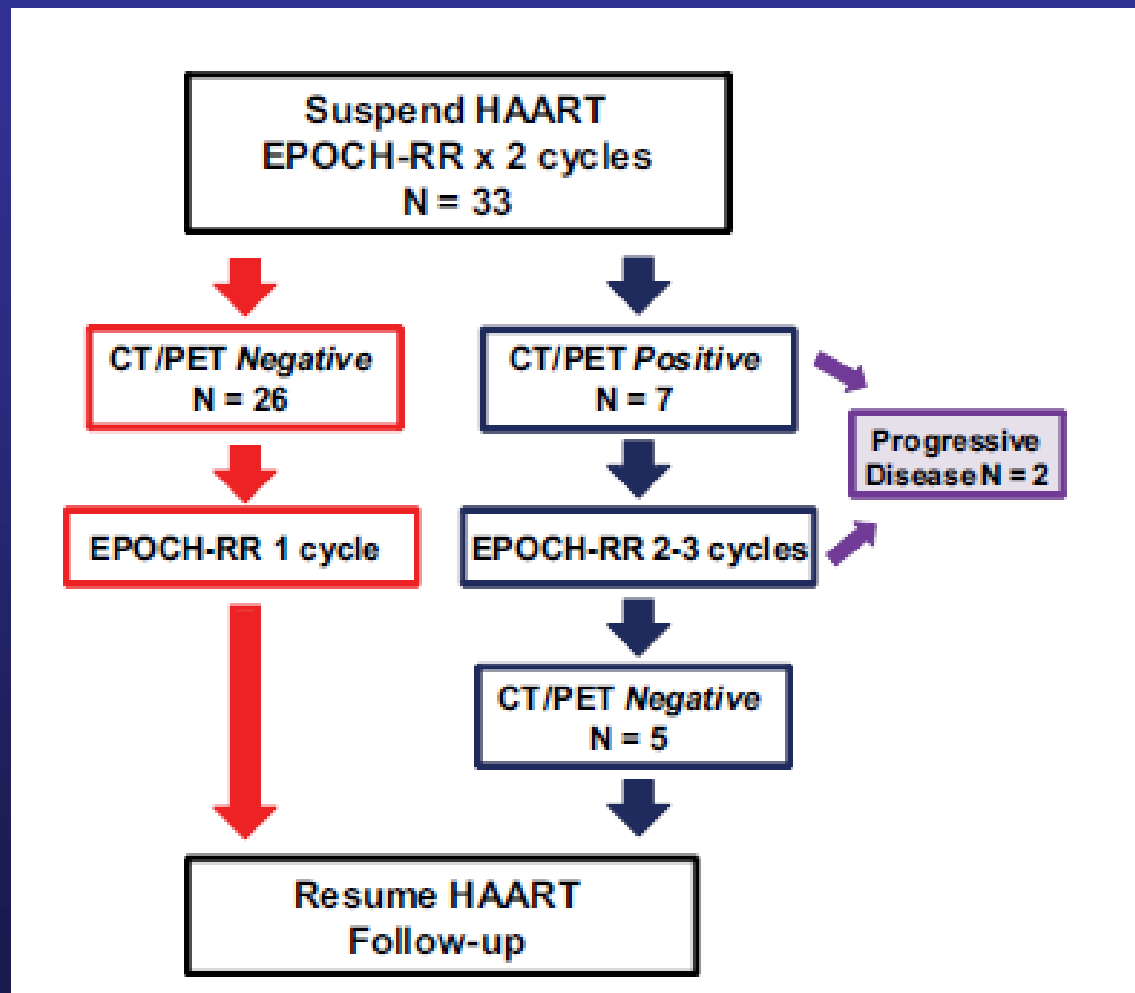
	Total	CD4 < 100	CD4 > 100
Number	39	16	23
Median Age	40 yr		
Stage III/IV	67%		
IPI – 2/3 (age adjusted)	59%		
Complete Remission	74%	56%	87%

Disease-Free Survival at 53 Months in 29 Patients in CR after da-EPOCH



Ref: Little RF, Pittaluga S, Grant N: *Blood* 2003; 101:4653.

SHORT COURSE (SC) EPOCH-RR in AIDS DLBCL



Results: Short-course R-EPOCH-R in AIDS DLBCL

Median F/U = 5 years

PATIENTS

N = 33; median age = 42; 76% = High-Int or Hi IPI

TREATMENT

Rituximab 375/m² day 1 and 5

IT MTX 12 mg day 1+5 of cycle #3; repeat q 3 weeks x 6 total doses (cycles 3 – 5), regardless of systemic Rx

PJP and MAC prophylaxis

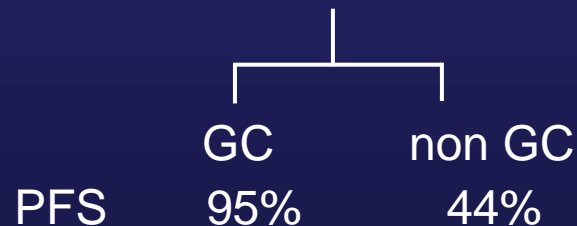
OUTCOME

79% needed only 3 cycles

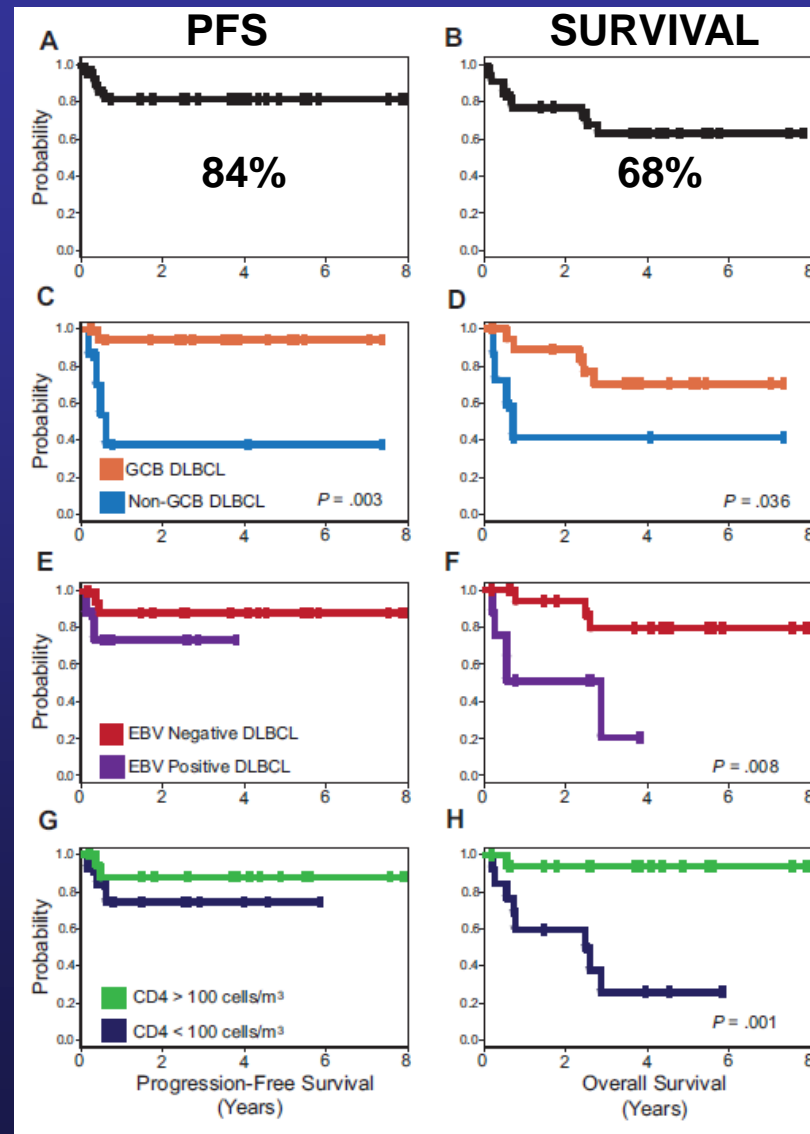
PFS = 84%

OS = 68%

Only predictor of outcome = GC vs non-GC

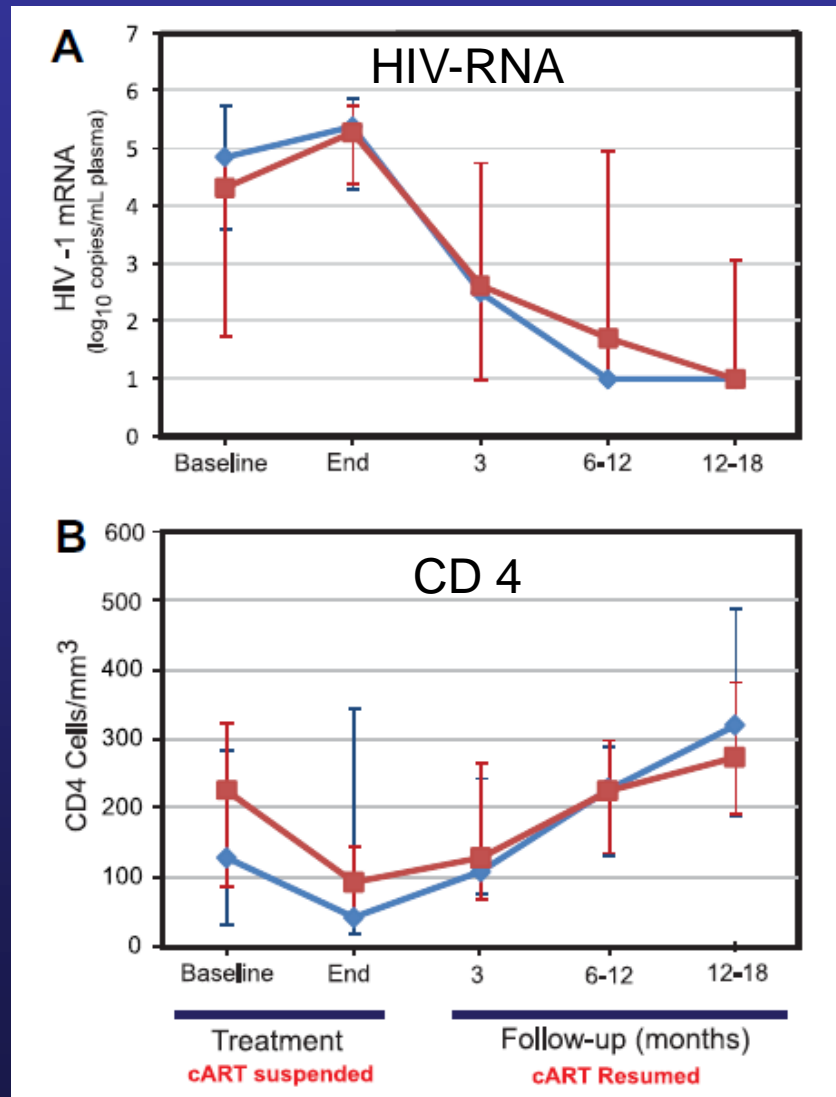


Outcome – AIDS DLBCL s/p SC EPOCH-RR (N = 33; Median F/U = 5 yrs)



Ref: Dunleavy K, et al. Blood 2010; 115:3017-24.

HIV Parameters: SC EPOCH-RR in HIV DLBCL



Ref: Dunleavy K, et al. Blood 2010; 115:3017-24.

Burkitt Lymphoma

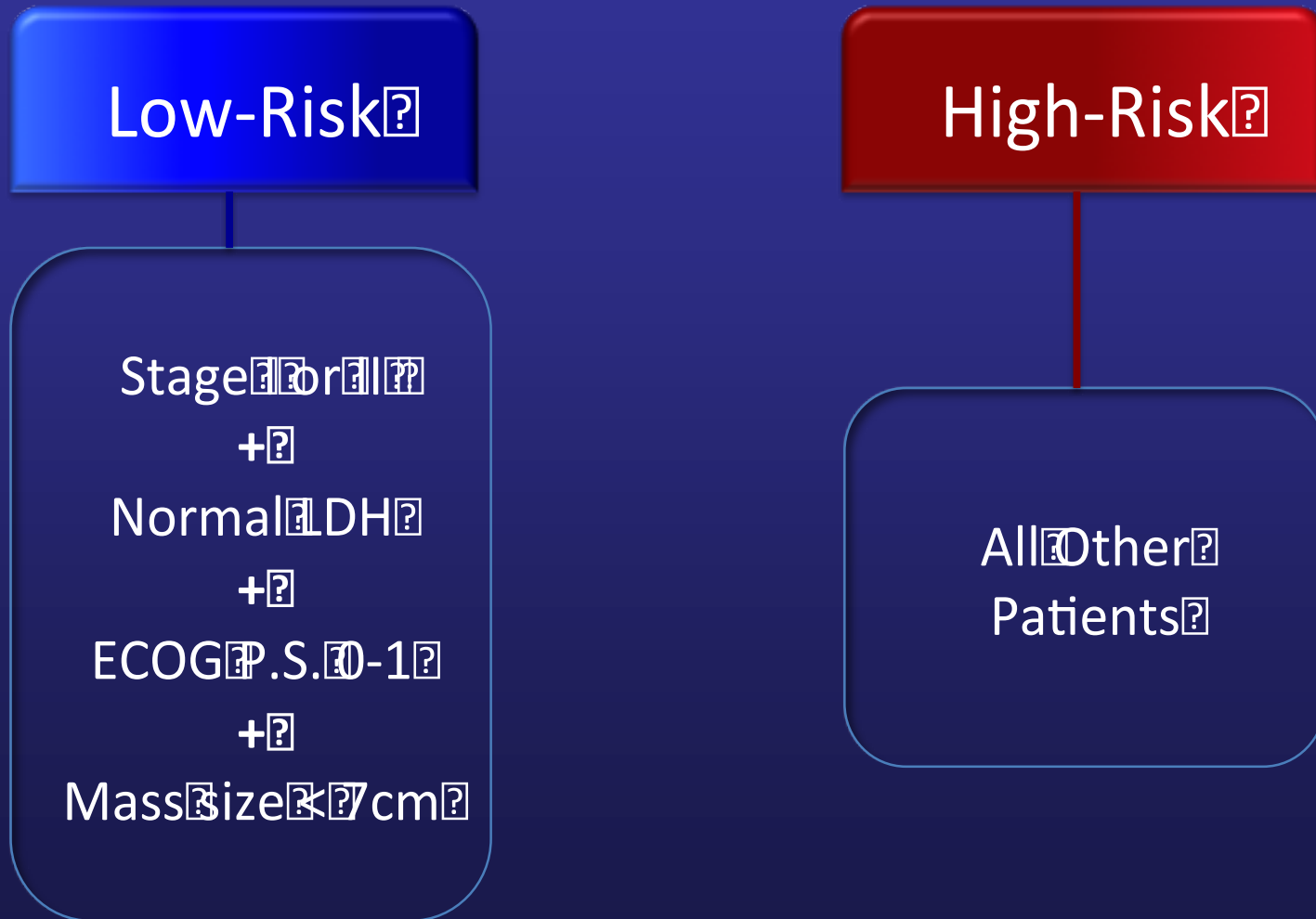
Treatment Strategies

- Multiple agents, high doses, in alternating cycles
- Ex: CODOX-M; CODOX-M IVAC
- Good efficacy but high toxicity

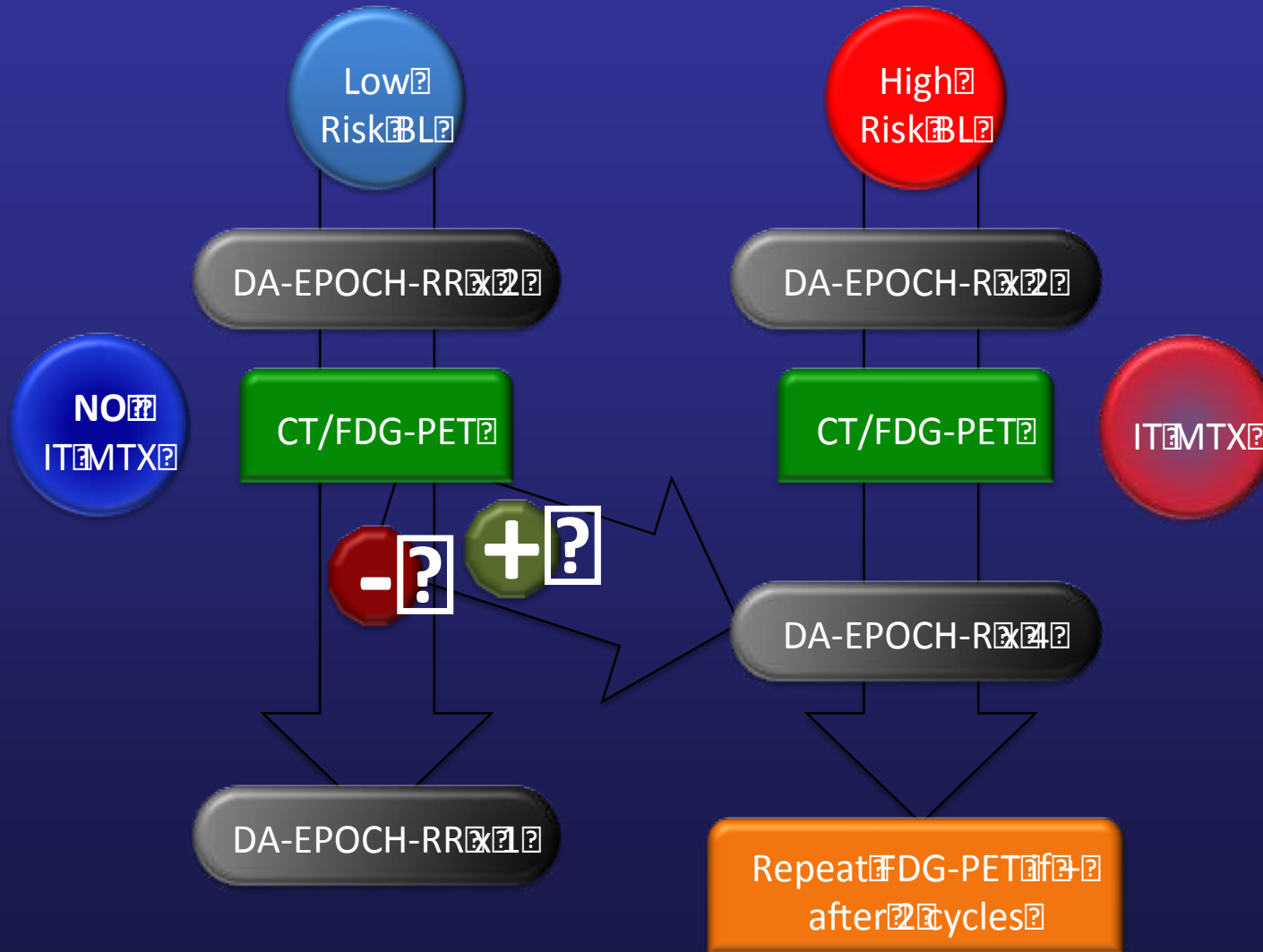
NCI 9177 - Eligibility

- Untreated patients
- Age \geq 18 years
- Histologically confirmed Burkitt Lymphoma
- HIV-negative and -positive
- Low-risk and high-risk groups

Risk-Adapted DA-EPOCH-R in BL



Risk-Adapted DA-EPOCH-R in BL



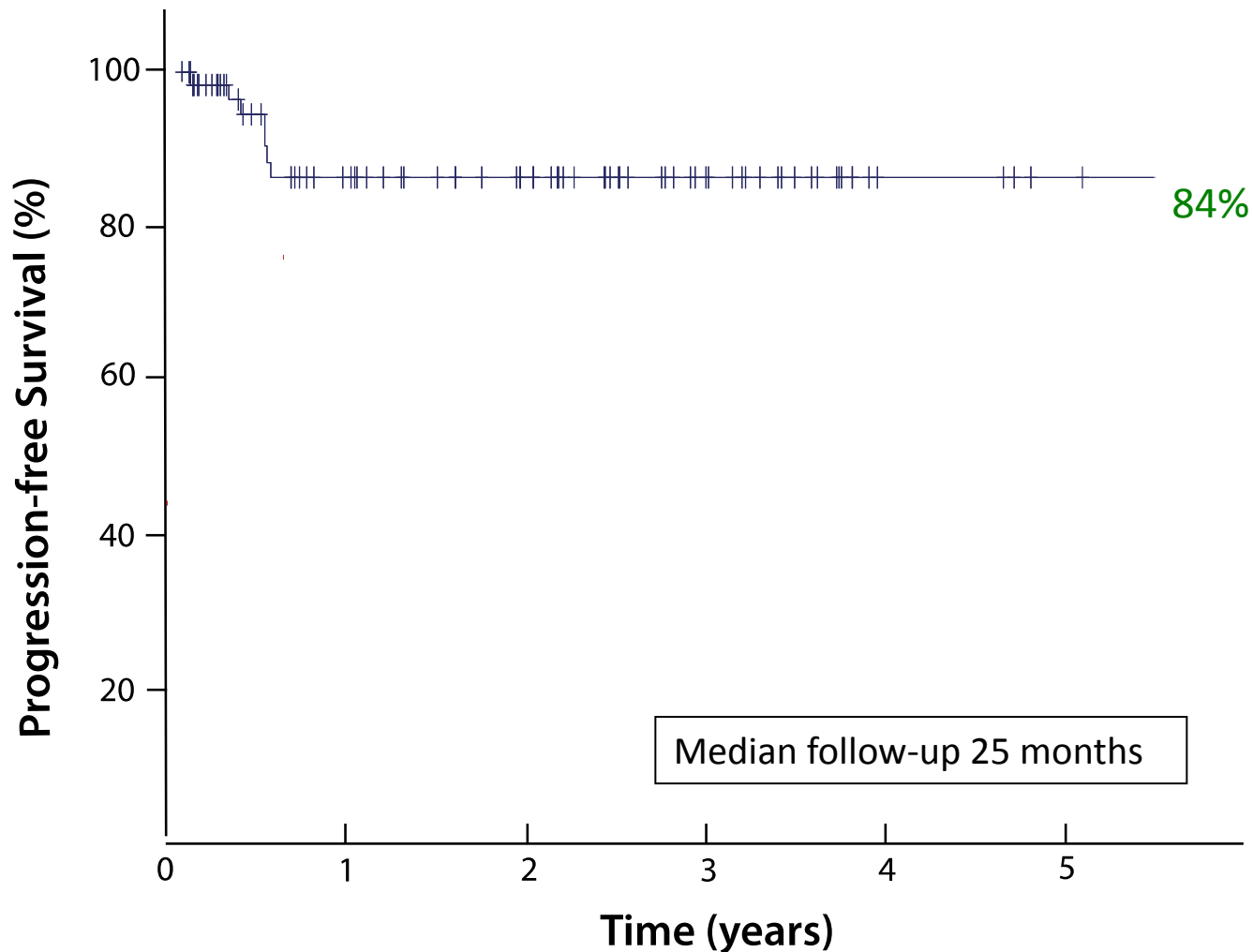
Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.

Characteristics*	All	LR	HR
N	88	11	77
Median Age (range)	46y (18-78)	38y (19-62)	47y (18-78)
≥ 40 Y	57%	45%	58%
≥ 60 Y	25%	9%	27%
Male Sex	82%	64%	84%
Stage III or IV	64%	0	73%
High LDH	56%	0	64%
ECOG ≥ 2	18%	0	21%
Extranodal disease	50%	23%	58%
CNS disease	13%	0	15%
HIV-positive	24%	0	27%

*From 24 sites

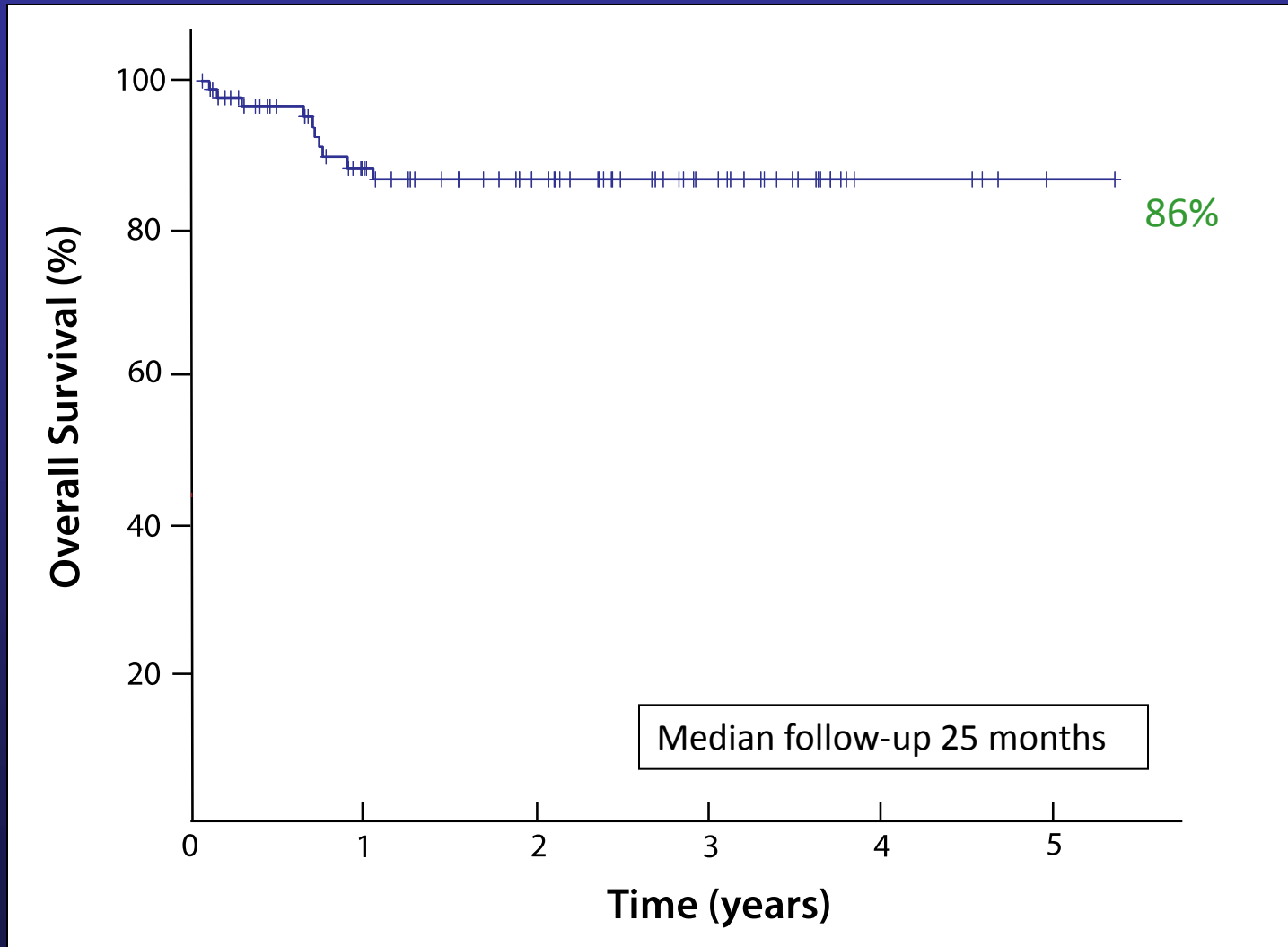
Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.

Progression-Free Survival



Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.

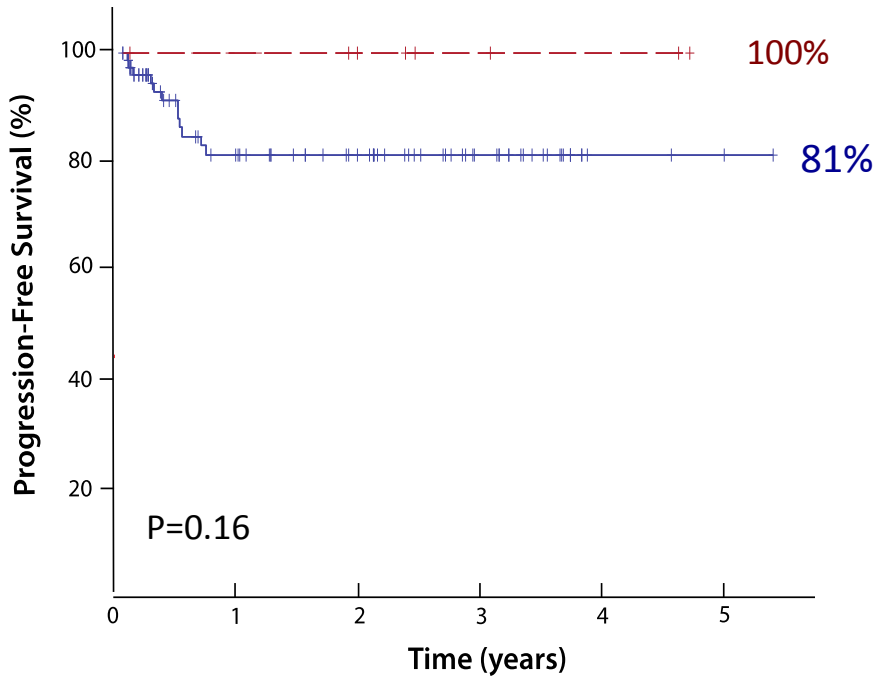
Overall Survival



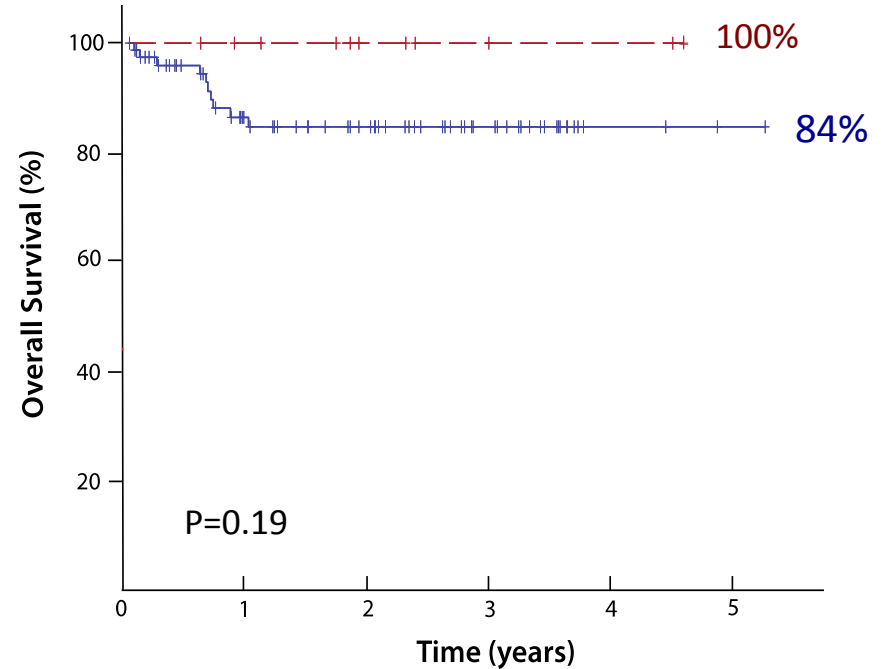
Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.

Outcome by Risk Group - Low vs High

DFS



OVERALL SURVIVAL

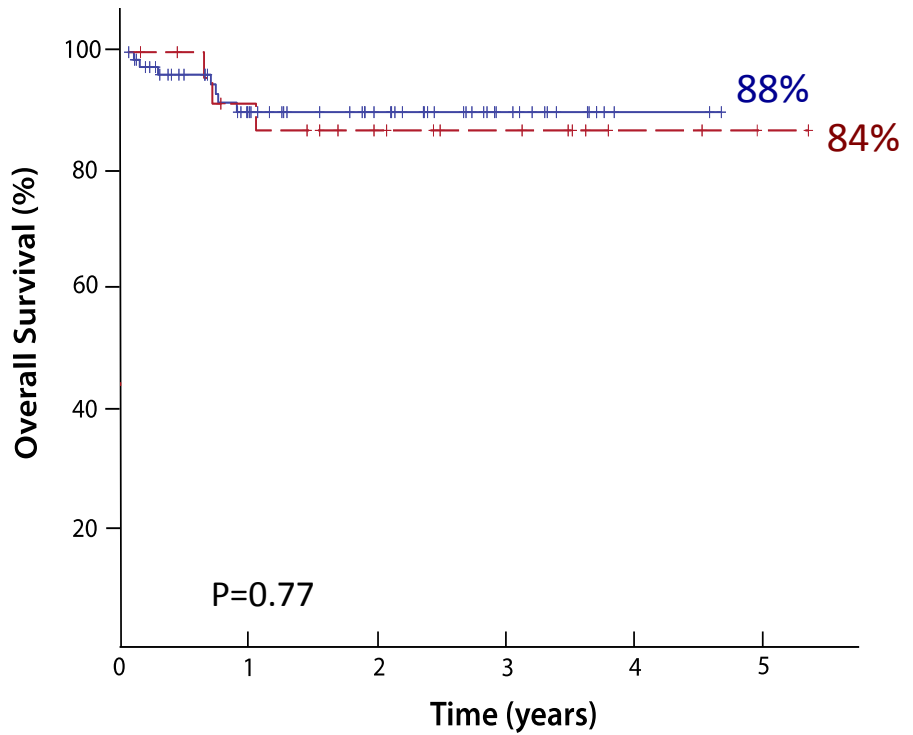
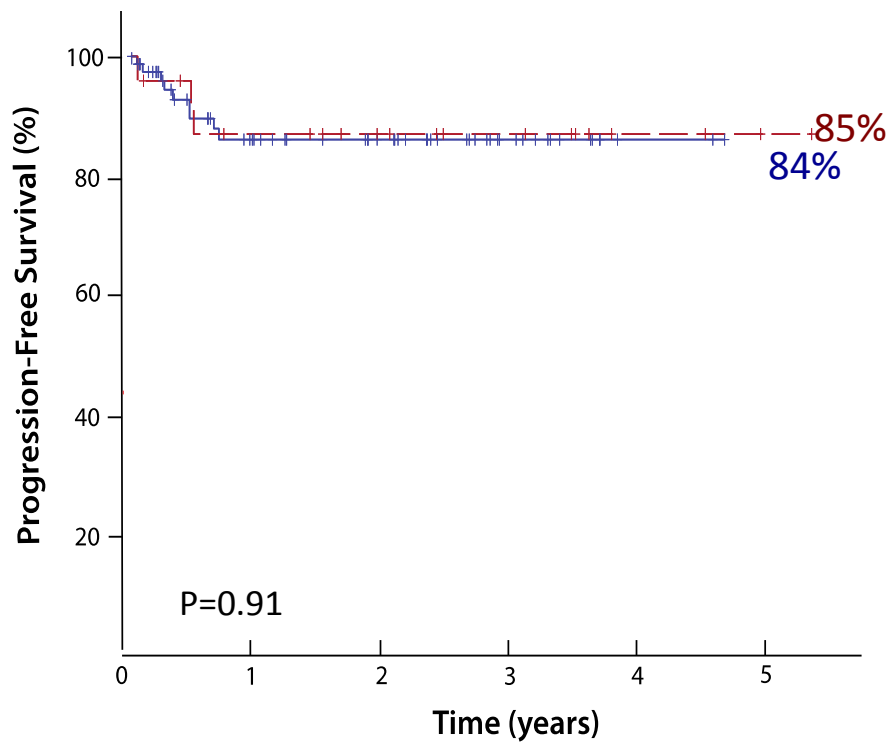


Low-Risk

High-Risk

Median follow-up 25 months

Outcome by HIV Status



HIV +
HIV -

Median follow-up 25 months

Toxicity

- 3 on-treatment infectious deaths in HR arm (Treatment-related mortality = 3.4%)
 - 72 y male: cycle 1
 - 59 y male: cycle 1
 - 52 y female: cycle 4
- Administered as outpatient where feasible

AIDS-Related NHL

Options at Relapse

Autologous hematopoietic cell transplant (SCT) in patients with relapsed or persistent AIDS lymphoma

Prospective study of BMT-Clinical Trials Network (BMT-CTN) and AIDS Malignancy Consortium (AMC)

ISSUES ADDRESSED

Salvage chemo followed by SCT results in long-term disease-free survival (or “cure”) in approximately 60 - 70% of HIV UNinfected patients



WHAT IS OUTCOME IN HIV-INFECTED?

- Survival
- Time to progression
- Progression-free survival
- Mortality from SCT
- Time to heme recovery

SPECIAL CONSIDERATIONS

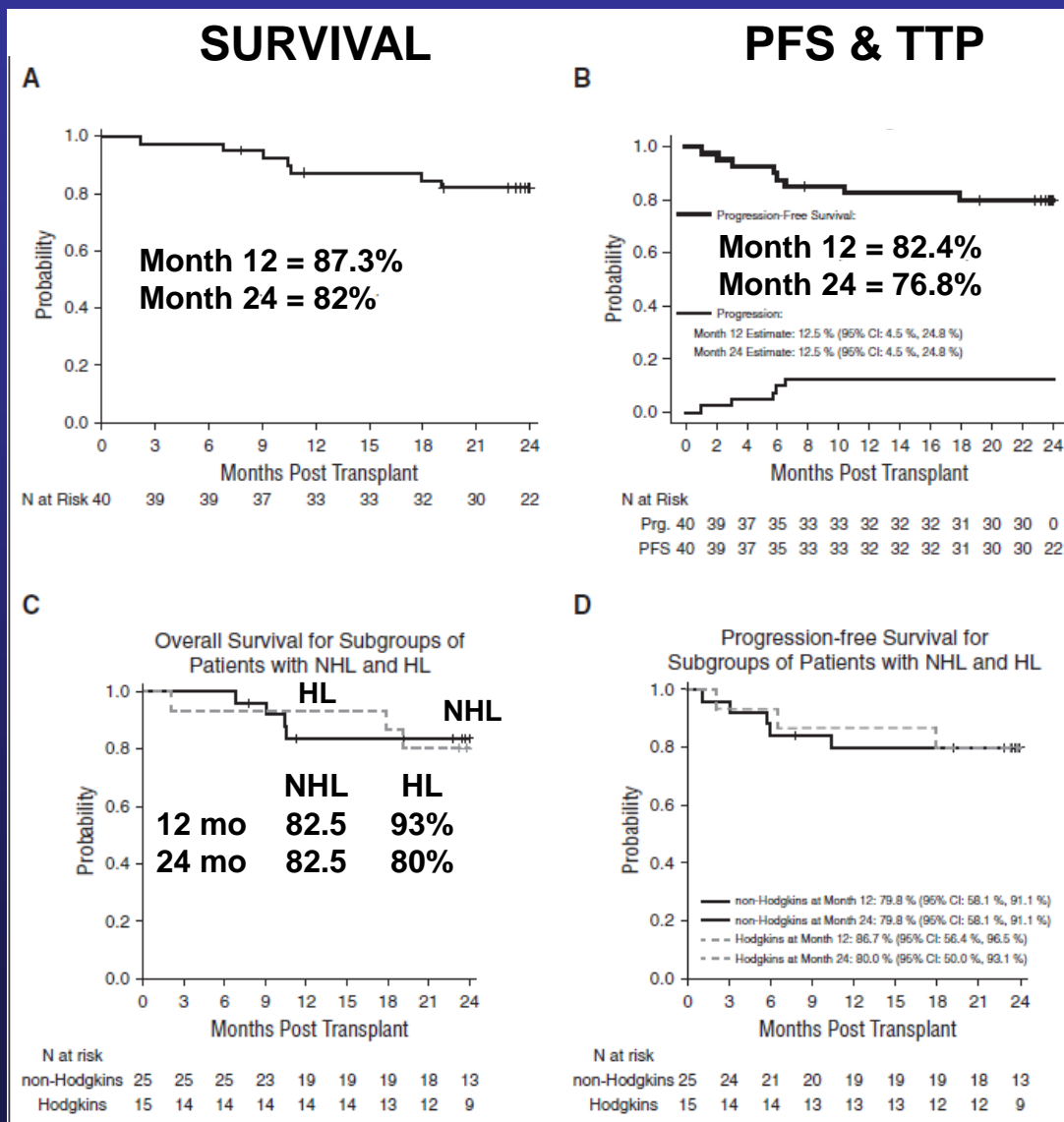
- Conditioning regimen (BEAM)
- How to choose ART
- When to stop/start ART
- Are CD34 cells normally mobilized?
- Immunologic recovery
- HIV virologic changes
- Unique toxicities or adverse events

Autologous stem cell transplant in 40 HIV-infected patients BMT-CTN 0803 + AMC 071 Trial

Method of ART use during transplant

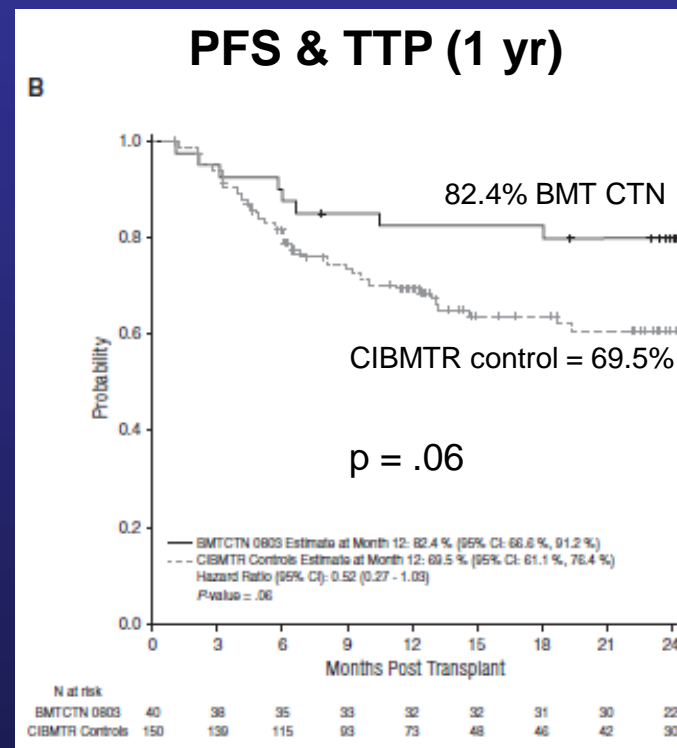
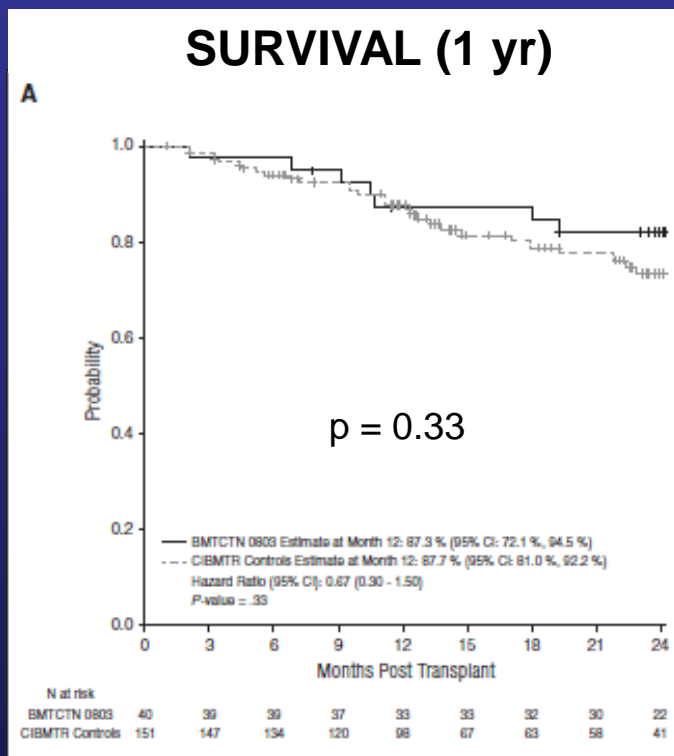
- Review ART regimen before treatment for possible interactions
 - Ritonavir-boosted PIs: Problematic as strong CYP 3A4 inducers. Stop prior to conditioning regimen.
 - Do not use AZT: myelosuppressive
 - Stop efavirenz > 2 weeks from treatment: Long T-1/2 - washout
 - Integrase inhibitors effective, better tolerated than PIs or non-NUC RTIs (Torres HA, et al. Clin Microb Infect 2014; 20:672-79)
- ART uniformly stopped at start of conditioning and resumed ≥ 7 days post BEAM, or after recovery from Rx-related GI toxicity
 - Median duration ART interruption = 15.5 days (11 – 40)

Overall and progression-free survival in 40 patients s/p AuSCT for ARL or HIV- Hodgkins (BMT / CTN 083 + AMC 071 Trial)



Ref: Alvarnas JC, et al. Blood 2016; 128:1050-8.

Survival and progression-free survival in 40 HIV-infected patients on BMT / CTN 0803 + AMC 071 vs 151 matched HIV-negative controls from CIBMTR Registry



Autologous progenitor cell transplant in 40 HIV-infected patients with relapsed or persistent lymphoma

BMT-CTN 0803 +AMC 071 Trial

Toxicities and Mortality

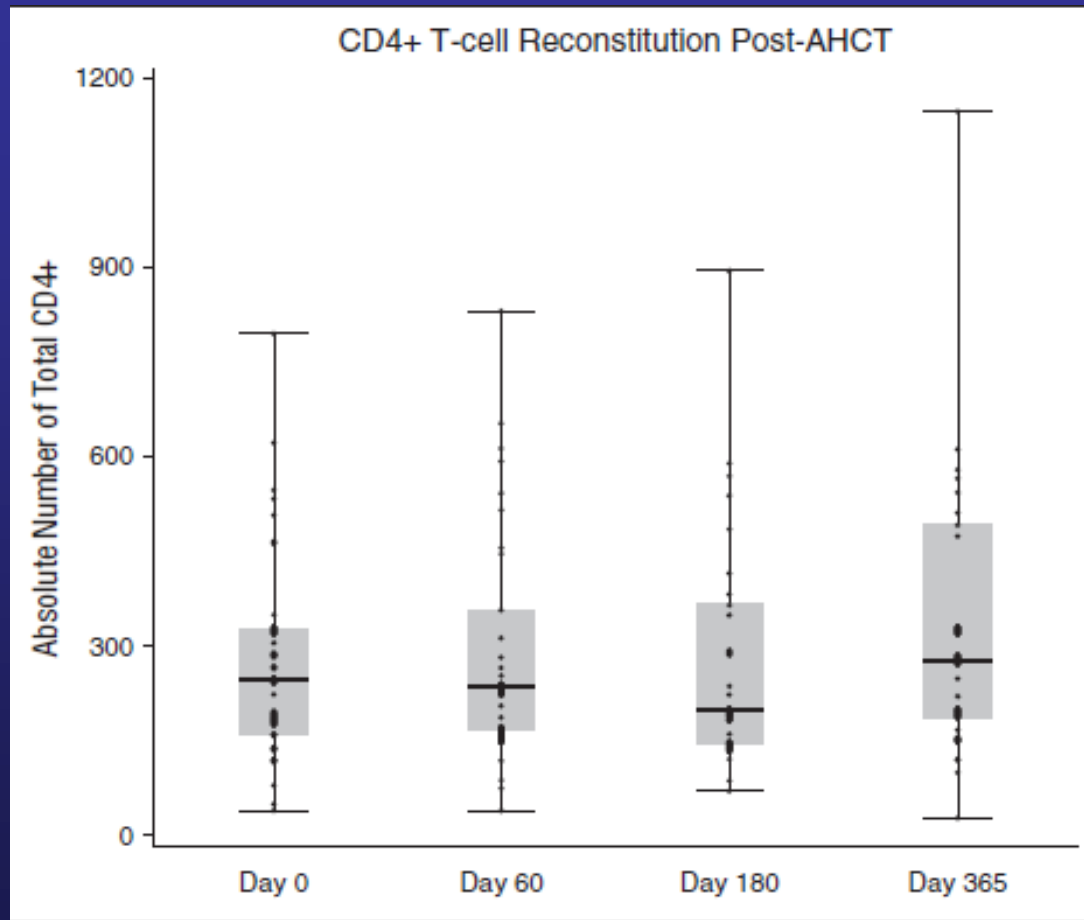
Infections —————→ • 22 pts (55%) had 57 infections in yr post-Tx
• 11 pts (27%) had severe infections
• One death due to infection (fungal)
• No case of *Pneumocystis jiroveci*

Organ Toxicities —————→ • Cardiac arrest in one (death)
• Grade 4 events in 3 pts; Grade 3 in 10

Mortality —————→ 5.2% TRM at one year
 – Cardiac arrest in one
 – Fungal infection in one

—————→ **3 deaths secondary to NHL (yr 1); one in year 2**

CD4 cell reconstitution after AuSCT BMT-CTN 0803 + AMC 071 Trial



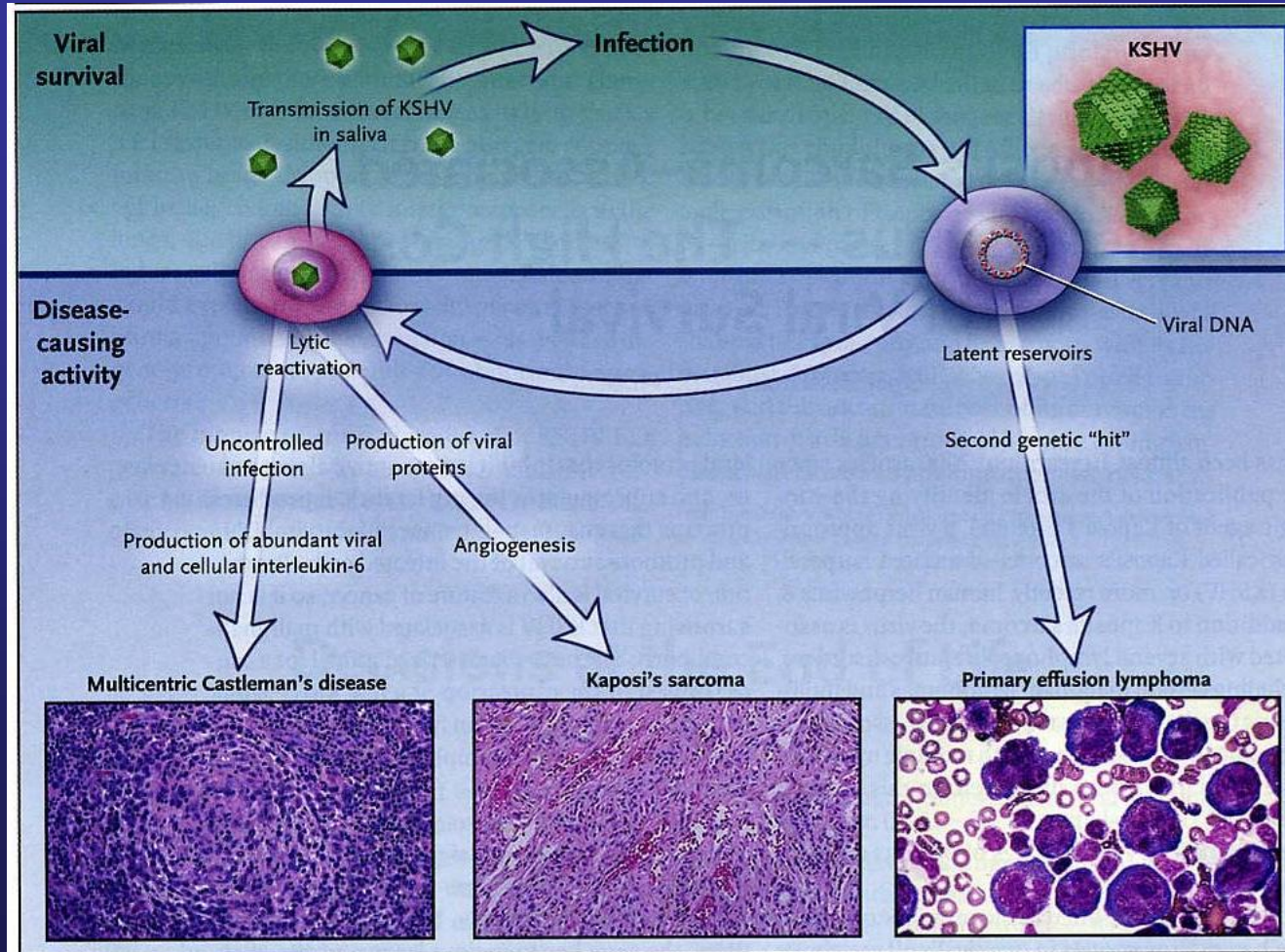
Ref: Alvarnas JC, et al. Blood 2016; 128:1050-8.

HIV viral load over time, s/p AuSCT in BMT-CTN 0803 + AMC 071 Trial

Time	Nondetectable (%)		Detectable	Median VL in Detectables
Baseline	32	(80%)	8	80
Day 100	19	(70%)	8	298
Day 180	20	(69%)	9	84
Day 365	19	(83%)	4	97
Day 730	21	(80%)	5	130

**WHAT'S NEW IN
KAPOSI'S SARCOMA?**

HHV8 (KSHV)-Related Diseases



Ref: Cesarman E: NEJM 2003; 349:1107-9.

Epidemiology of Kaposi's Sarcoma

USUAL SETTINGS

ENDEMIC KS

- Africa
- All population groups affected, including children

“CLASSIC” KS

- Mediterranean Europe
- Elderly men
- Rather indolent, often confined to feet and legs

TRANSPLANT-RELATED KS

- Iatrogenic immunosuppression
- Incidence = 400-500 times expected
- Treatment = stop immunosuppression

AIDS-RELATED KS

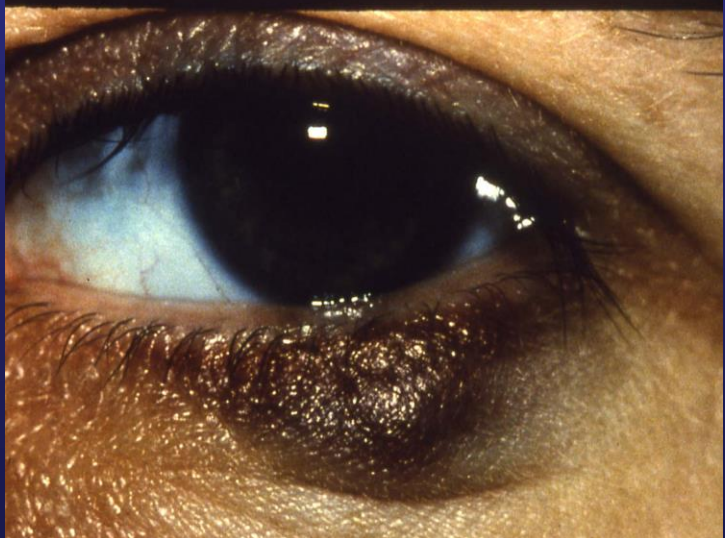
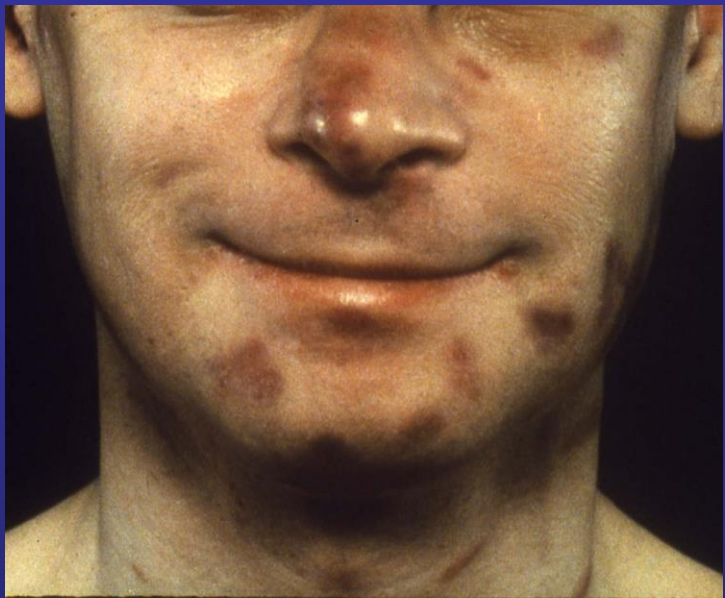
- Primarily affects gays/bisexual men



HHV8 / KSHV ISOLATED IN ALL TYPES







TREATMENT OPTIONS: AIDS-RELATED KAPOSI'S SARCOMA

Effect of HAART Alone on KS

N = 19

ACTG Criteria of Response

	Month 6	Month 12	Month 18	Month 24
Complete Response	11%	32%	42%	58%
Overall Response (CR & PR)	64%	69%	79%	74%

Ref: Dupont C, et al: AIDS 14:987-993, 2000.

Local Therapy of KS

- Surgical excision
- Laser therapy
- Topical 9-cis retinoic acid
- Radiotherapy – electron beam, limited

Commonly used therapies for advanced AIDS Kaposi's Sarcoma

Therapy	Overall Response	CR	Ref
Antiretrovirals ART	64% at month 6 74% at month 24	11% 58%	AIDS 2000; 14:987
Pegylated liposomal doxorubicin 20 mg/m ² q 2 wks IV	46%	1%	JCO 1998; 16:2445
Paclitaxel 135 mg/m ² IV q 3 wks	65%	0	Lancet 1995; 346:26
100 mg/m ² IV q 2 wks	56%	4%	Cancer 2002; 95:142

Unmet Need for Novel Agent(s) in KS

- No treatment is yet curative
- No current oral Rx, other than ART
- Chronic use of chemotherapy (doxorubicin, paclitaxel) poorly tolerated
- Cumulative anthracycline (doxorubicin) causes cardiotoxicity

Pomalidomide: Immune Response Modifier

Orally available small-molecule derivative of thalidomide

PROPERTIES



- Immune modulatory
- Anti-angiogenic
- Anti-proliferative

MECHANISM of ACTION



Targets cerebron (an E3 ubiquitin ligase)



Degradation of ikaros (IKZF1) & aiolos (IKZF2)



DOWNSTREAM EFFECTS:

- Modulation of TNF α
IL-6
VEGF
- ↑ CD4 and CD8 stimulation

Pomalidomide in 22 pts with Kaposi's Sarcoma

Patient Characteristics

	HIV-Infected	HIV-Negative
Number	15	7
Median age	49	61
Median HIV VL	< 50 in all	
Median CD4	378 (135 – 732)	
Advanced T1 Stage	67%	100%
KS-related edema	100%	100%
> 50 KS lesions	53%	71%
Prior KS Rx	87%	86%
Prior chemo	53%	29%
Prior thalidomide or lenalidomide	7%	14%

Oral Pomalidomide in Kaposi's Sarcoma

5 mg qd x 21 every 28 days + ASA 81 mg daily

RESPONSE

	N	Overall Response	Complete Response
All patients	22	73%	18%
HIV-positive	15	60%	20%
HIV-negative	7	100%	14%

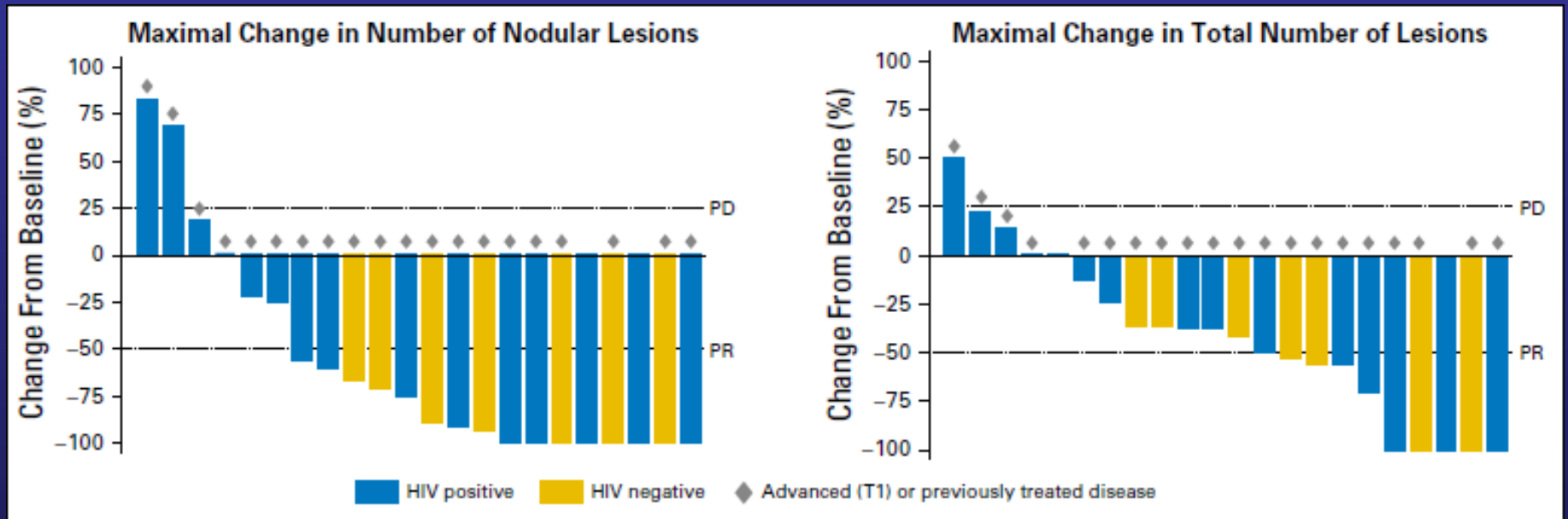


MEDIAN TIME TO RESPONSE

HIV-pos = 8 weeks (4 – 32)

HIV-neg = 4 weeks (4 – 36)

Responses to Pomalidomide in 15 HIV+ and 7 HIV- KS patients



Pomalidomide for symptomatic KS in 51 HIV-positive & 7 HIV-negative patients

- Dose = 5 mg orally / day + ASA, 81 mg daily
No dose-limiting toxicity
- Toxicity = Grade 3 – 4 neutropenia 10 pts (45%) and 13% of cycles
– only grade 4 = 2 pts with benign ethnic neutropenia
One grade 3 infection (pneumonia)
- QOL No decrease; improvements at 3 mos & study end
- CD4 / CD8 cells = – CD4 cells at week 4 (+ 108) and 8 (+ 40)
– CD8 cells at week 4 (+ 101) and 8 (+ 142)
- Virology = No change in HIV-1 VL
KSHV / HHV8 = ↑ at week 4 & in 10 pts. Back to baseline, week 8

HIV Management
Hepatitis Management

THE NEW YORK COURSE

