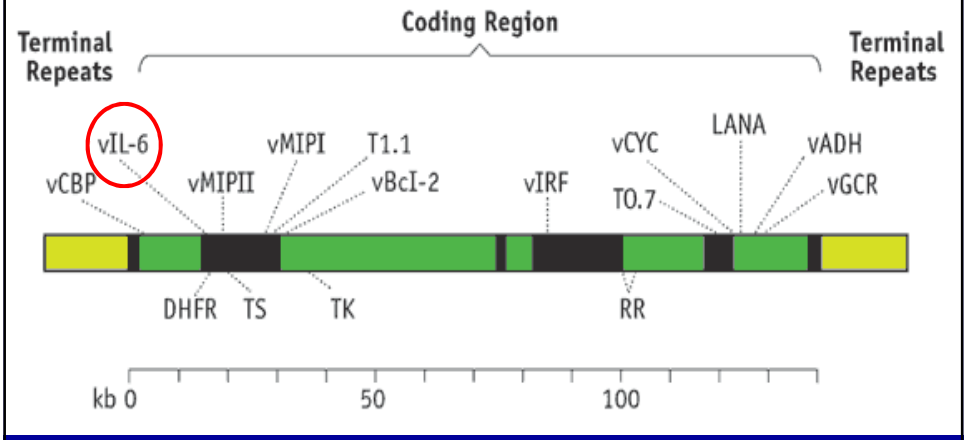
Castleman's disease

	Hyaline vascular	Plasmablastic
Localised		
Multicentric		HIV-MCD

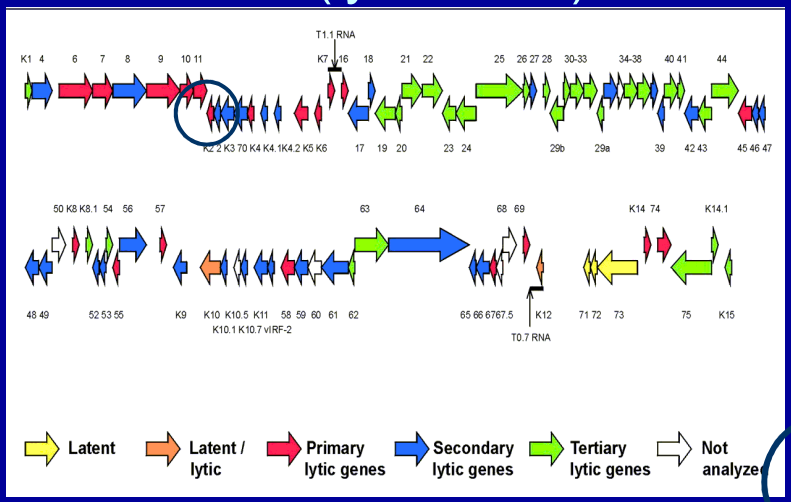
HHV8 in HIV-MCD

Study	HIV status	CD variant	Proportion HHV-8 infected
Soulier *et al* (1995a)	Negative	M-hyaline vascular variant (HVV)	2/3 (66%)
		M-plasma cell variant (PCV)	3/9 (33%)
		M-mixed	2/5 (40%)
		TOTAL	7/17 (41%)
	Positive	M-HVV	1/1 (100%)
		M-PCV	6/6 (100%)
		M-mixed	7/7 (100%)
		Total	14/14 (100%)
Kikuta *et al* (1997)	Negative	M-PCV	2/2 (100%)
		U-HVV	1/1 (100%)
Suda *et al* (2001)	Negative	M-unspecified	0/79 (0%)
	Positive		3/3 (100%)
Yamasaki *et al* (2003)	Negative	M-PCV	13/16 (81%)

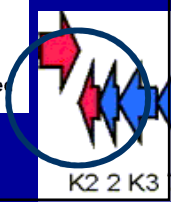
HHV8 genome



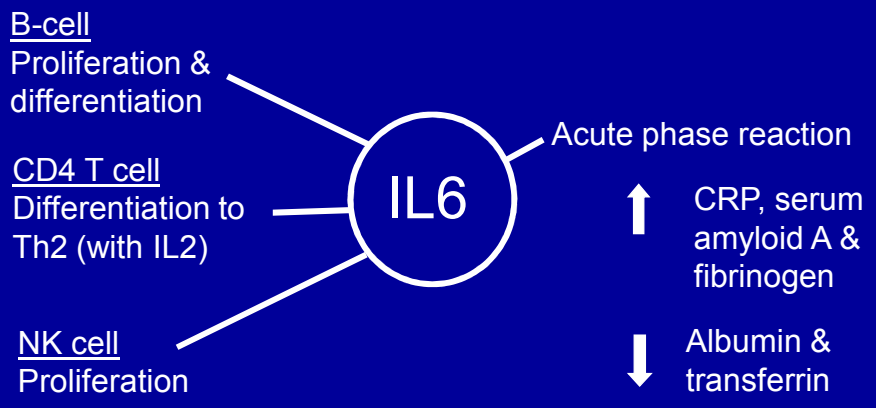
HHV8 genome expression (lytic/latent)



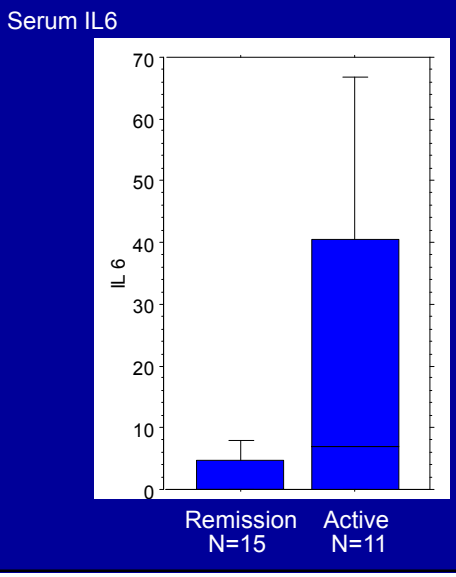
ORF K2 (vIL6) a primary lytic gene



Functions of IL6



Serum IL6 in MCD



MW p=0.06

Castleman's clinical presentation

Fever, night sweats, weight loss

Localised or diffuse lymphadenopathy

Hepatosplenomegally

Anaemia, hypoalbuminaemia, polyclonal hypergammaglobulinaemia

MCD incidence in CWH cohort

10,997 patients

52,035 patient years follow-up

MCD incidence 16.3 /10,000 PY

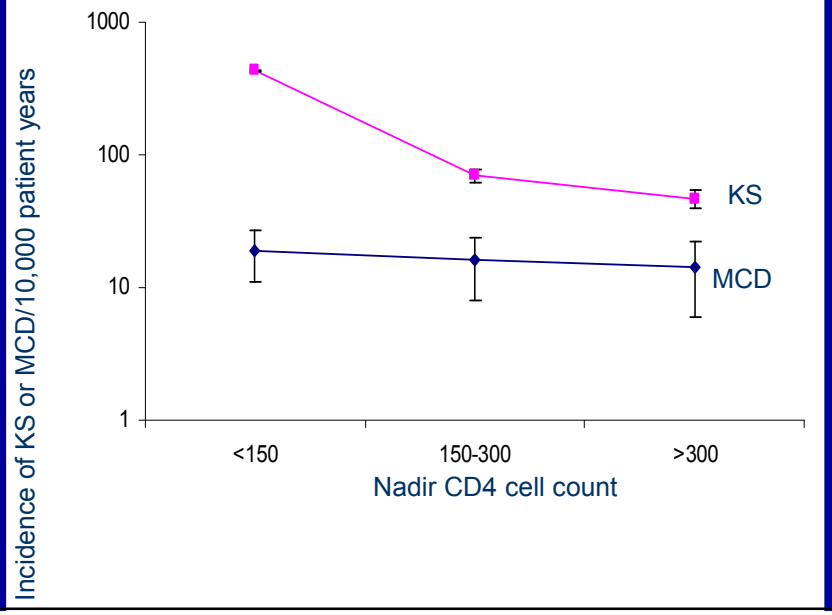
Annals of Oncology 20: 775–779, 2009

MCD incidence

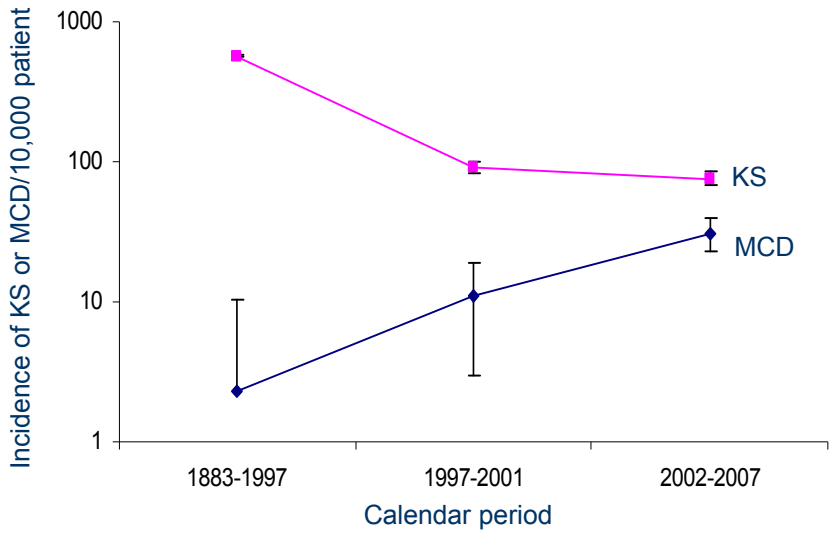
Unlike KS, incidence not related to:

- gender
- duration HIV
- nadir CD4 count
- prior AIDS diagnosis
- use of HAART

Risk of MCD & KS by CD4 count



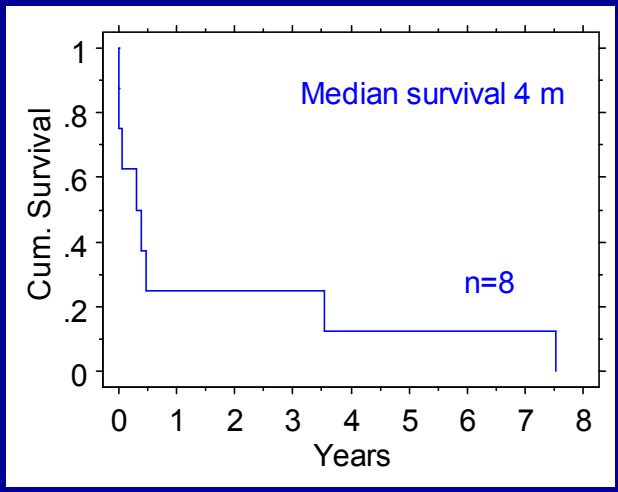
Changing incidence of MCD & KS



HIV MCD treatment options

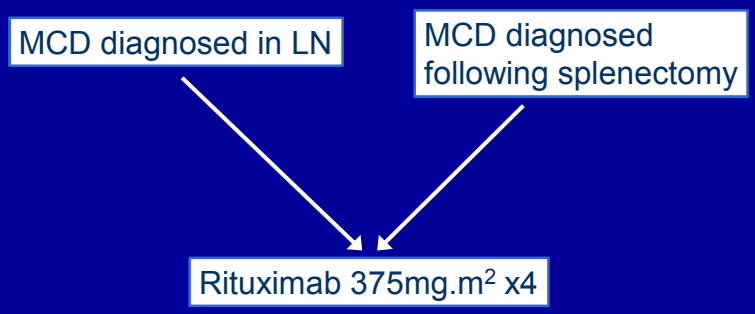
- Splenectomy
- HAART
- Vinblastine
- Etoposide
- Interferon α
- Ganciclovir
- Anti IL6 receptor blocking antibody

Survival pre 2002



Largest published series
n=20
Median survival 14m
AIDS 1996, 10: 61

Algorithm of care for MCD (2002-2006)



Rituximab cohort

First-line therapy (21)

Ann Intern Med. 2007, 147:836-9.

How to measure response?

1 not evaluable died after 2 weeks
(on ITU at diagnosis)

Symptoms ? - PUO resolved in 20/20
Radiology ?
Biochemistry ?

Radiological response by RECIST

Evaluated 1m after completing Rituximab

1 Not evaluable

Partial response	14/20 (70%)
Stable disease	6/20 (30%)

Biochemical response

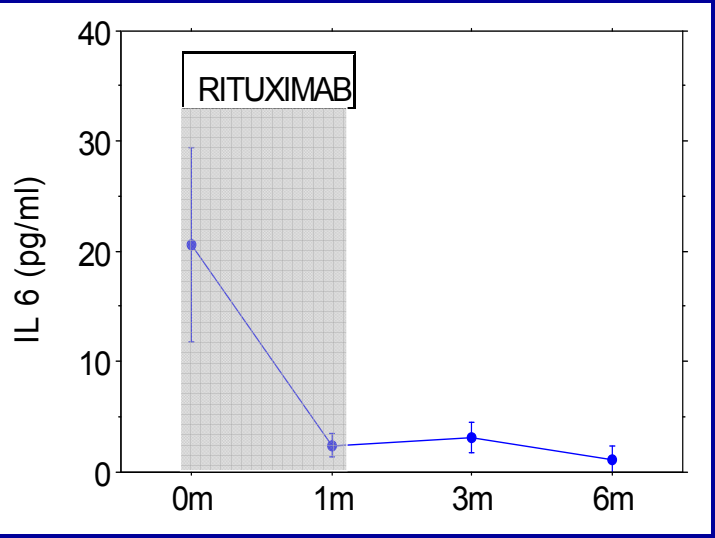
	Start	1m post*	Response*
Hb <10 g/dl	14/21	0/20	100%
Plt <100 x10^9/l	3/21	0/20	100%
CRP >10mg/l	14/17	2/16	12/14 (86%)
ESR >20 mm/hr	18/19	11/17	7/18 (39%)
Albumin <30 g/l	14/21	1/20	13/14 (93%)

*1 patient died within 2 weeks of starting Rituximab so not evaluable

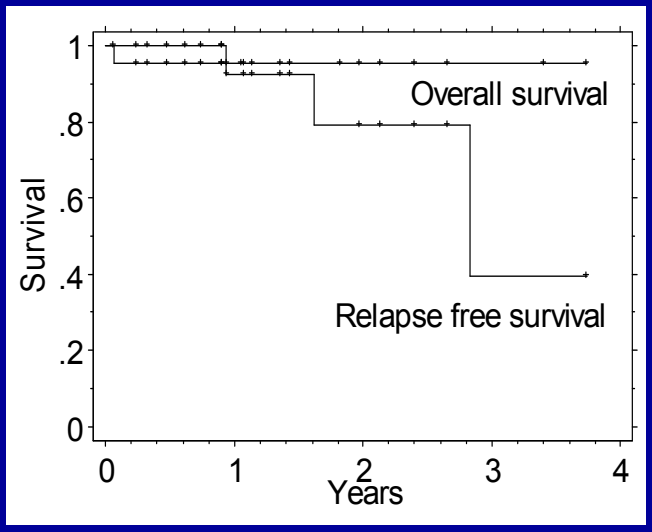
Cytokine responses

Cytokine (Normal Range)	Elevated at Diagnosis (n = 11)	Elevated at End of Rituximab Therapy (n = 9)	Elevated at 3 mo after End of Rituximab Therapy (n = 9)
IL-1β (0–6 pg/mL)	45	66	44
IL-2 (0–3 pg/mL)	64	55	44
IL-4 (0–10 pg/mL)	54	55	44
IL-5 (0–5 pg/mL)	73	66	55
IL-6 (0–5 pg/mL)	54	11	22
IL-8 (0–8 pg/mL)	82	100	100
IL-10 (0–9 pg/mL)	100	55	77
IL-12 (50–92 pg/mL)	73	66	55
IL-13 (0–10 pg/mL)	36	44	44
IL-15 (0–5 pg/mL)	45	55	44
IL-17 (0–14 pg/mL)	18	33	44
GM-CSF (0–19 pg/mL)	45	55	44
TNF (0–12 pg/mL)	0	0	11
IFN-α (0–31 pg/mL)	27	44	44
IFN-γ (0–4 pg/mL)	73	88	55

Plasma IL6

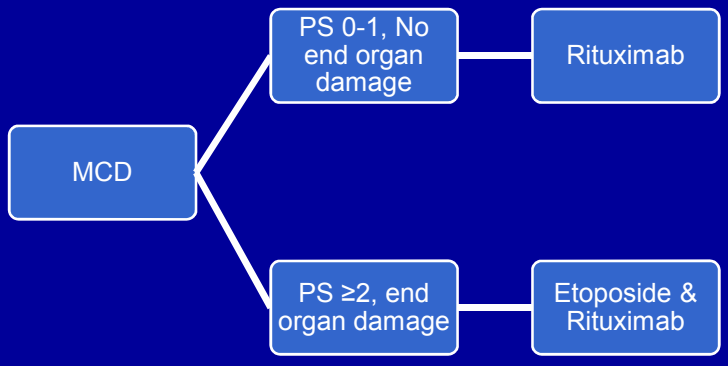


Survival

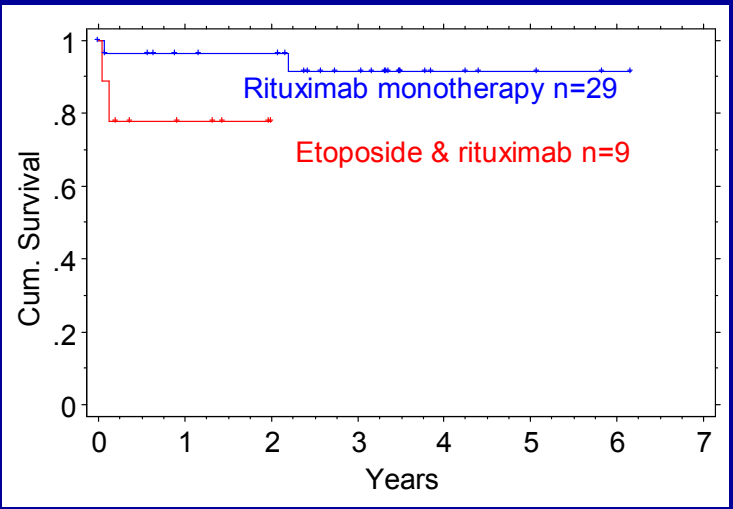


2 year survival 95% (95%CI: 86-100%)

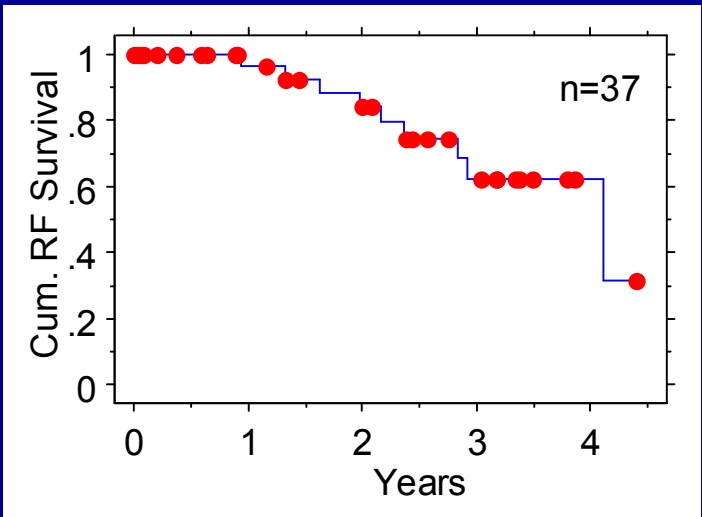
New risk-stratified algorithm 2006-9



Risk stratified approach



Relapse-free survival following remission



Plasma HHV8 viral load as a tumour marker

Uses of tumour markers:

- Diagnosis
- Evaluating response to therapy
- Monitoring remission & diagnosing relapse

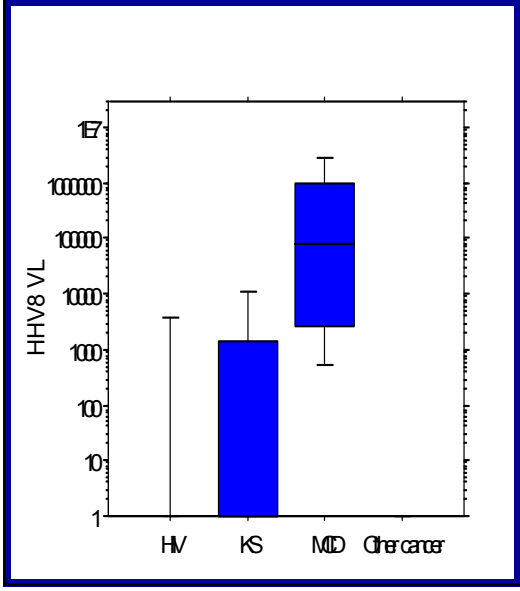
Diagnostic value of plasma HHV8

283 patients

	HHV8 Detectable
MCD	34/39 (87%)
KS	36/94 (38%)
HIV & other cancer	2/78 (2%)
HIV	9/72 (12%)
Total non MCD	45/244 (18%)

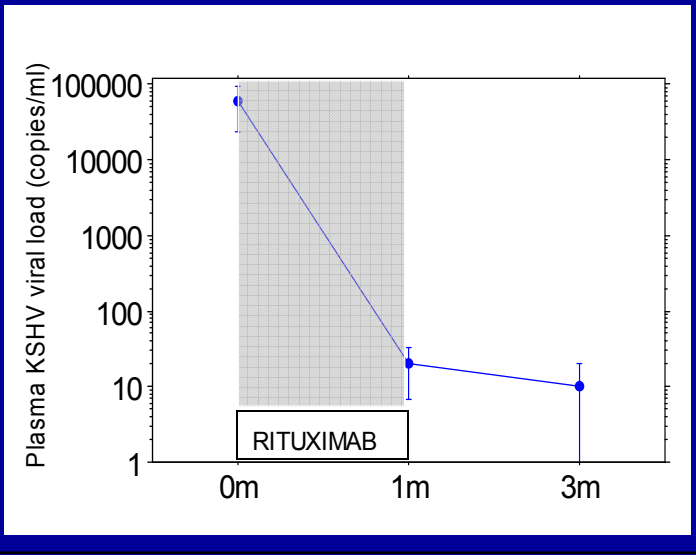
P<0.0001

HHV8 viraemia by disease



	Median HHV8 VL	Median in detected
MCD	76,000	96,500
KS	0	3,950

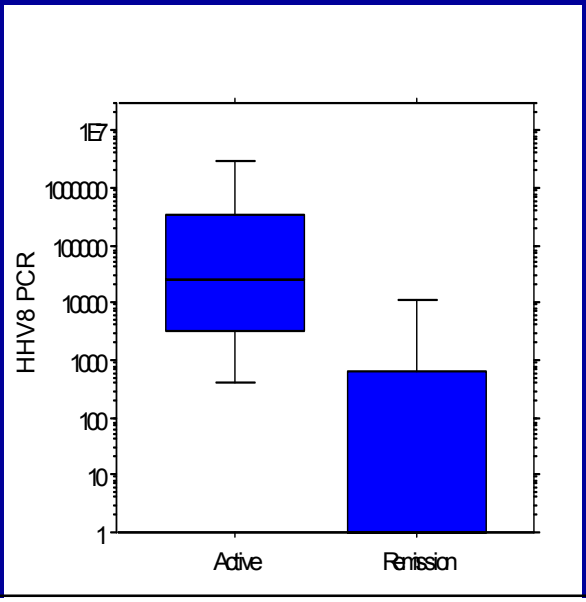
Evaluating response with plasma HHV8



Plasma HHV8 in monitoring MCD

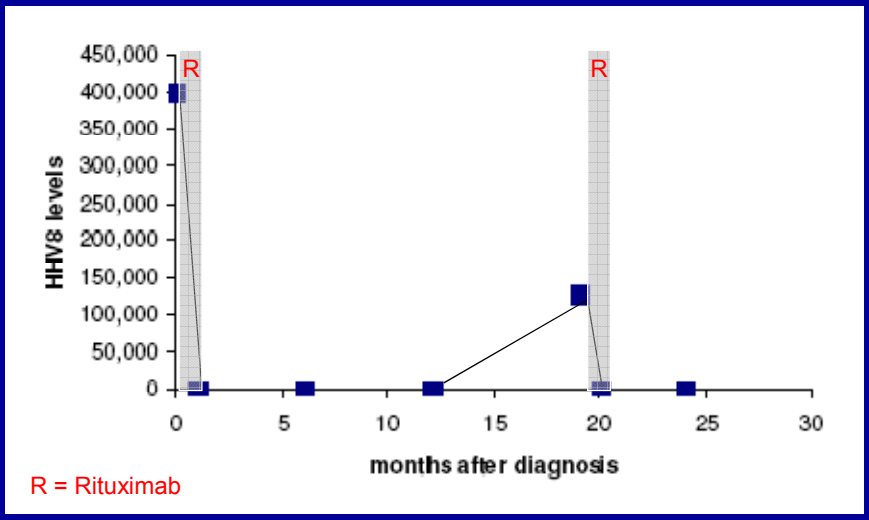
	HHV8 detectable	%	p
"Attack"	120/128	94%	P<0.0001
Remission	58/188	31%	

HHV8 & MCD disease state



128 active &
188 remission
samples
p<0.0001

Patient monitoring

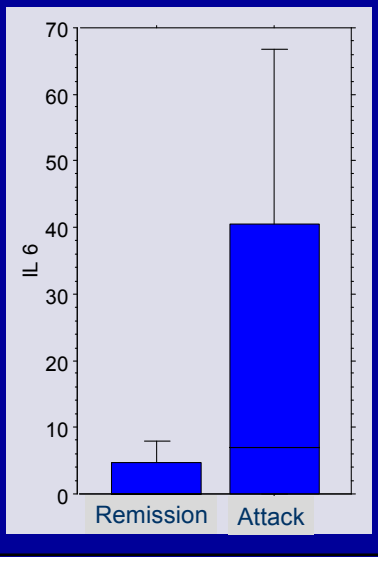


R = Rituximab

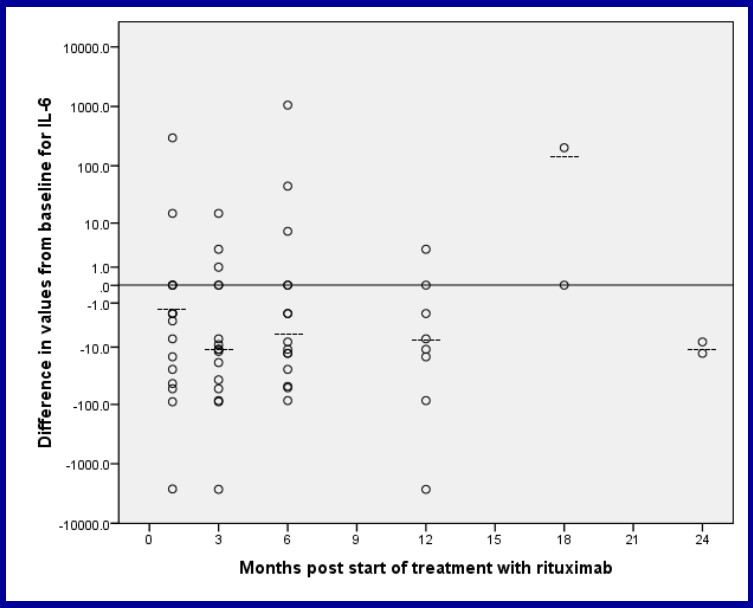
Blood. 2007, 110(12): 4132-3.

Serum IL6 during an attack

Serum IL6



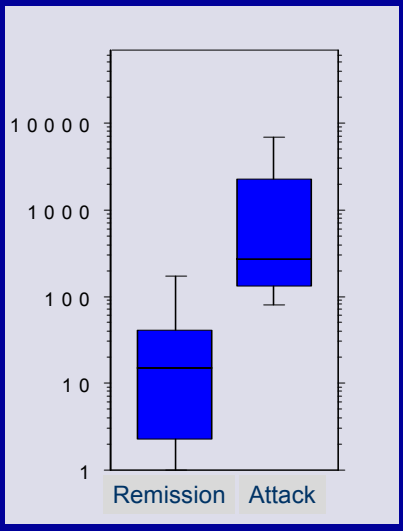
MW p=0.06



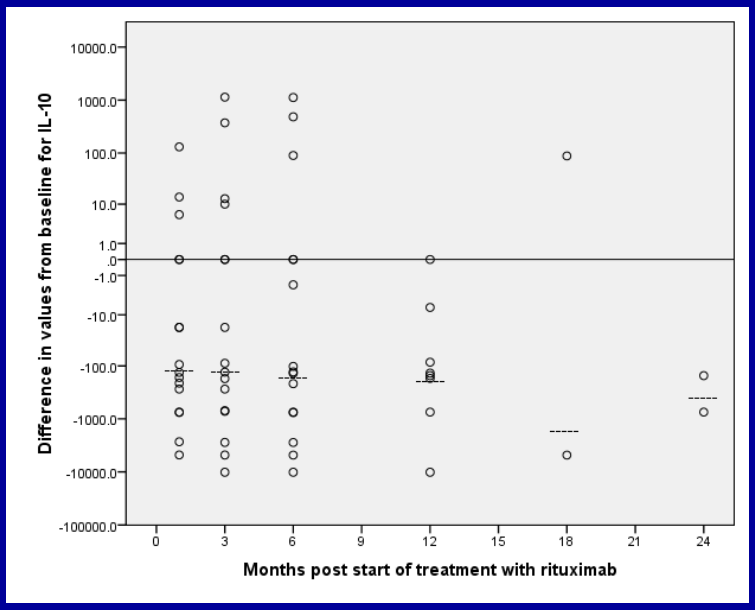
Blood 2009;113: 4521-4.

Serum IL10 during an attack

Log serum IL10



MW p=0.007



Blood 2009;113: 4521-4.

Remaining questions

Role of Maintenance therapy?
Rituximab
Valganciclovir

What constitutes a relapse?
HHV8, CRP, symptoms, biopsy

Conclusions

1. MCD occurs at any CD4/VL
2. HAART does not prevent MCD
3. Usually relapse
4. Plasma HHV8 “tumour marker” in diagnosis and monitoring