

NCCN 10<sup>th</sup> Annual Congress:

**Hematologic Malignancies™**

# Diagnosis and Management of Castleman Disease

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**NCCN.org**

# Castleman Disease (Angiofollicular lymph node hyperplasia)

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

#### CASE 40011

##### PRESENTATION OF CASE

A forty-year-old executive was referred to the hospital because a mediastinal mass had been discovered on a survey chest photofluorogram two weeks previously.

Thirteen years before admission the patient had recurrent pain in the right lower quadrant, occasionally associated with low-grade fever. After several months of recurrent episodes lasting only a few days, he was admitted to the hospital during an exacerbation, and an appendectomy was performed. The pathological diagnosis was "healing appendicitis." Exploration of the abdomen at the operation revealed no Meckel's diverticulum and no mesenteric lymphadenopathy. A barium-enema examination before operation was negative; calcification of several mesenteric lymph nodes was seen. Abdominal

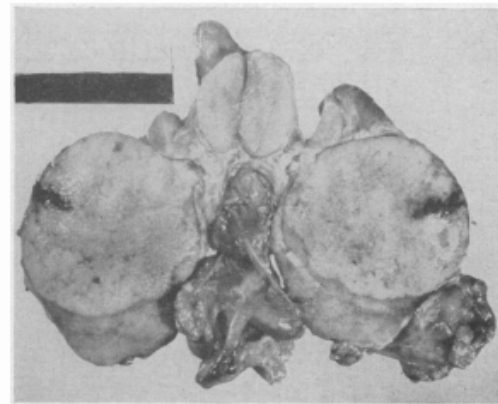


FIGURE 2. Photograph of the Mass of Mediastinal Lymph Nodes, Showing Two Large Lymph Nodes Bisected.

##### CLINICAL DIAGNOSIS

Mediastinal tuberculosis.

##### DR. LEWIS W. KANE'S DIAGNOSIS

Dermoid cyst or teratoma of mediastinum.

##### ANATOMICAL DIAGNOSIS

*Hyperplasia of mediastinal lymph nodes.*

**DR. CHAPMAN:** This is a new disease syndrome that you are presenting to us!



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Castleman, et al. NEJM 1954

## LOCALIZED MEDIASTINAL LYMPH-NODE HYPERPLASIA RESEMBLING THYMOMA

BENJAMIN CASTLEMAN, M.D., LALLA IVERSON, M.D., AND V. PARDO MENENDEZ, M.D.

Castleman, et al. Cancer 1956

Clinically most of these patients had no symptoms, the mediastinal shadow being discovered on a routine chest roentgenogram (Figs. 1,A; 2,A; 3; 4; 5,A). A few of the patients consulted their physician because of frequent colds and cough. There was no history of weakness or symptoms suggesting myasthenia gravis. There was no sex predominance and their ages ranged from 19 to 54 years. The benign character of the lesion is attested to by the fact that some had been present without change in size (radiologically) for as long as eight years and that there have been no recurrences locally nor any evidence of other lesions elsewhere after removal of the mass.

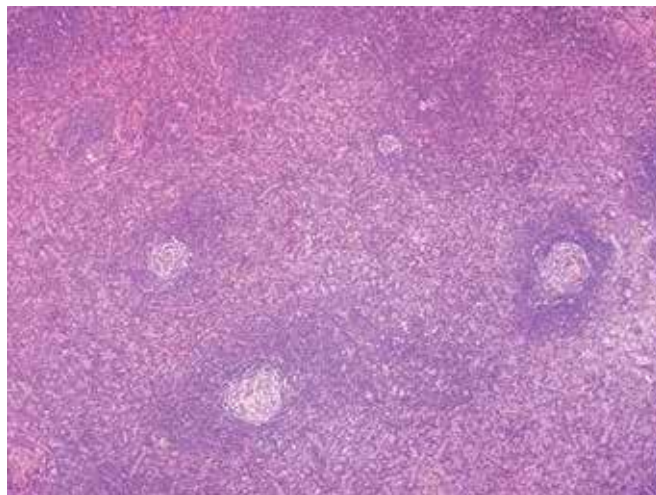
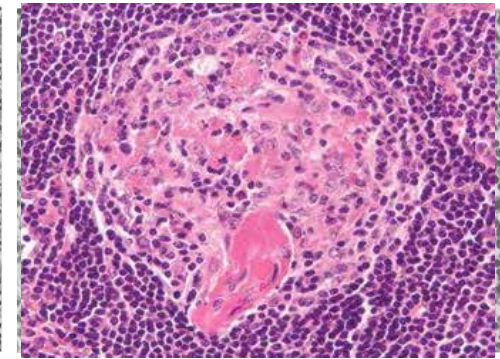
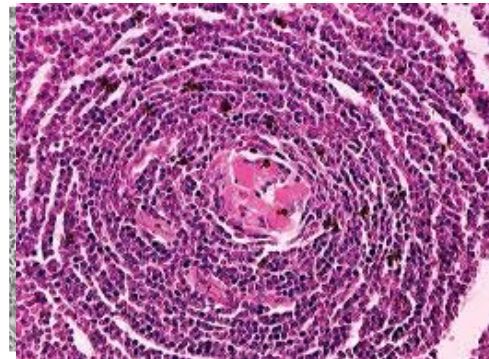


FIG. 7. These germinal centers have more reticulum cells and fewer lymphoblasts and begin to show the illusion of a whorled arrangement. The peripheral cuff of lymphocytes is still present. ( $\times 127$ )

A series of thirteen cases of mediastinal masses resembling thymoma grossly and microscopically are shown to be a peculiar form of lymph-node hyperplasia characterized by germinal-center formation and marked capillary proliferation.

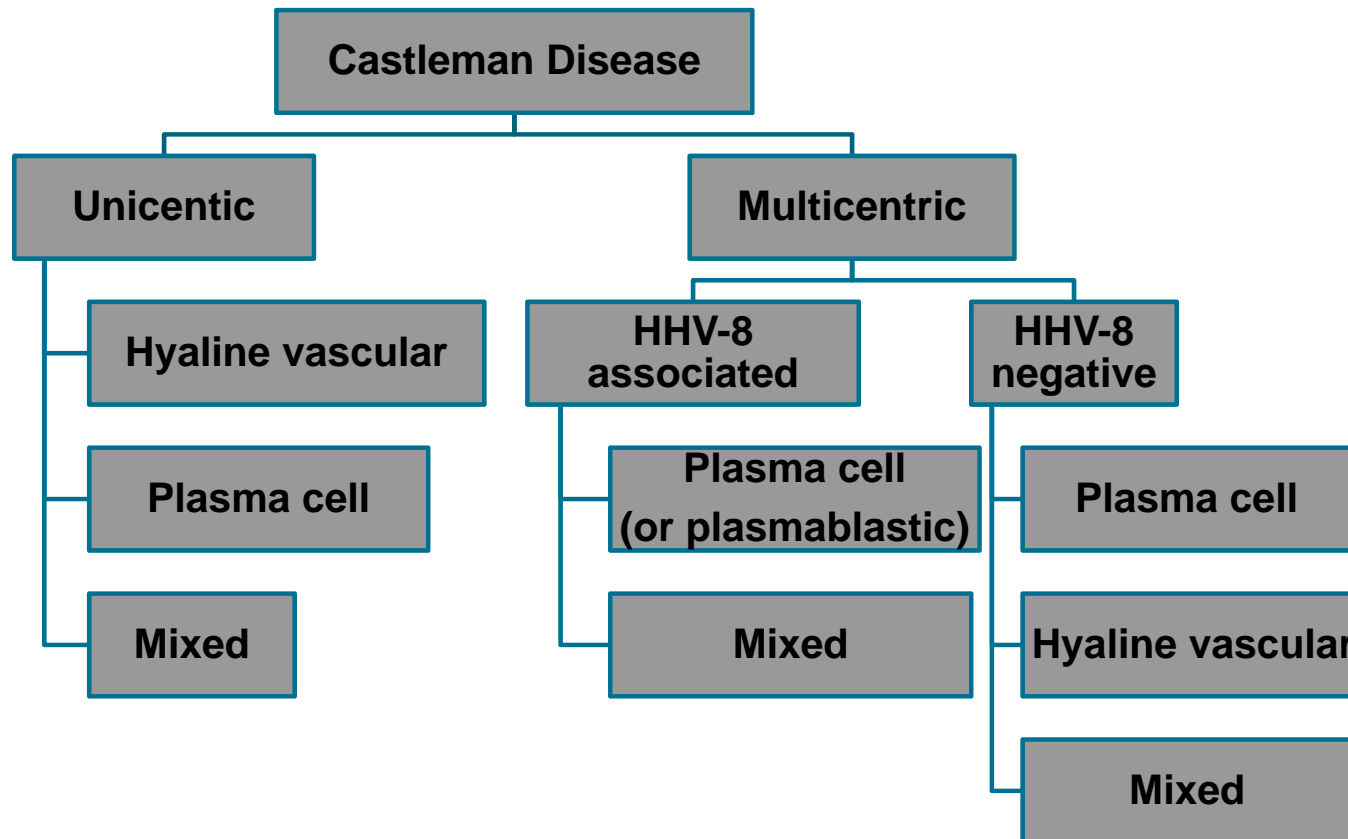
Evidence is presented that the condition is neither neoplastic nor thymic in origin.



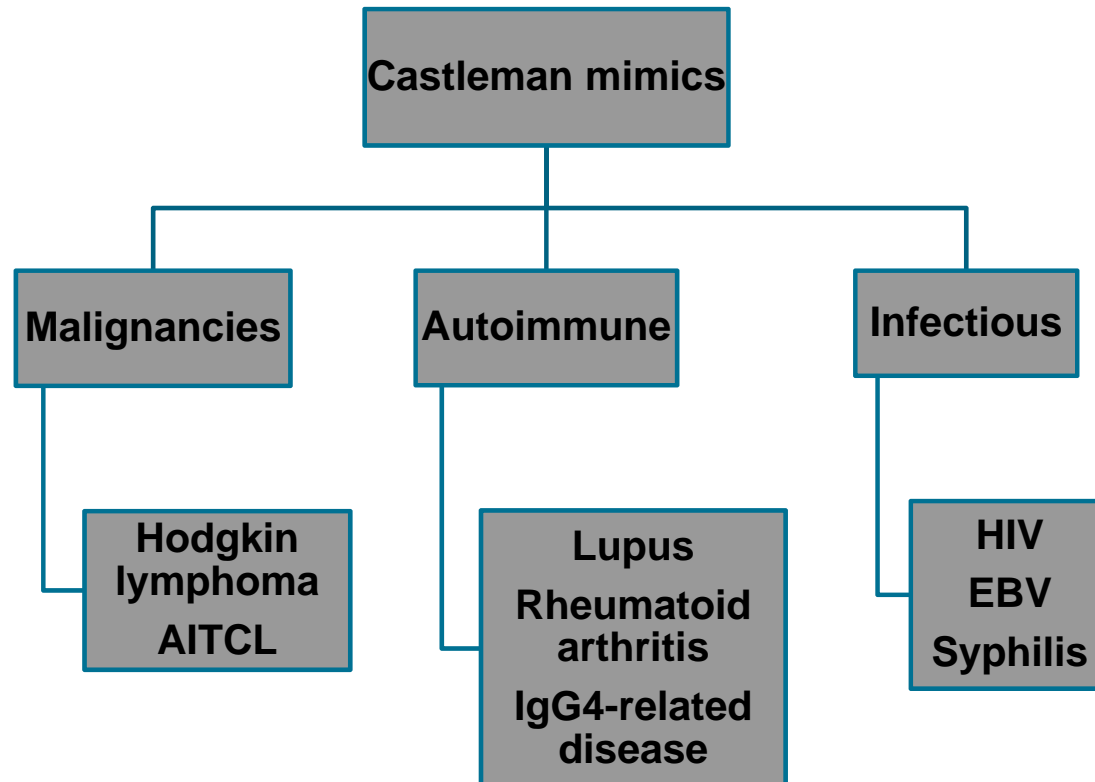
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# Castleman Disease Classification



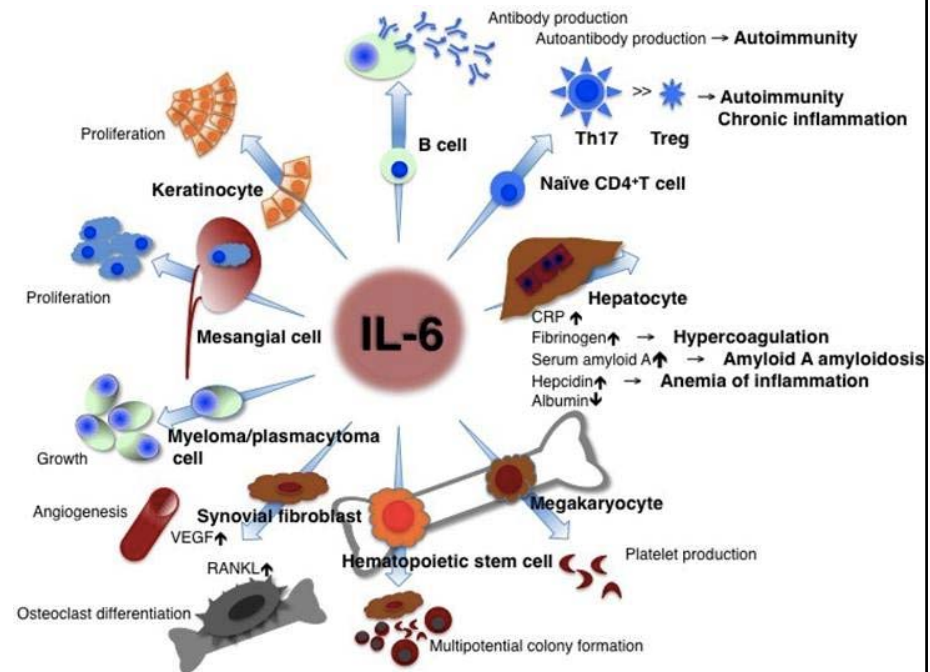
# Castleman Disease Classification





# IL-6 in Castleman Disease

- Central role in UCD and MCD
- Stimulates B-cell proliferation
- Stimulates B-cell and T-cell differentiation
- Induces expression of acute phase reactants, hepcidin
- Induces expression of VEGF
- Activates JAK/STAT, PI3K, and MAPK pathways
- Associated clinically with classic inflammatory syndrome

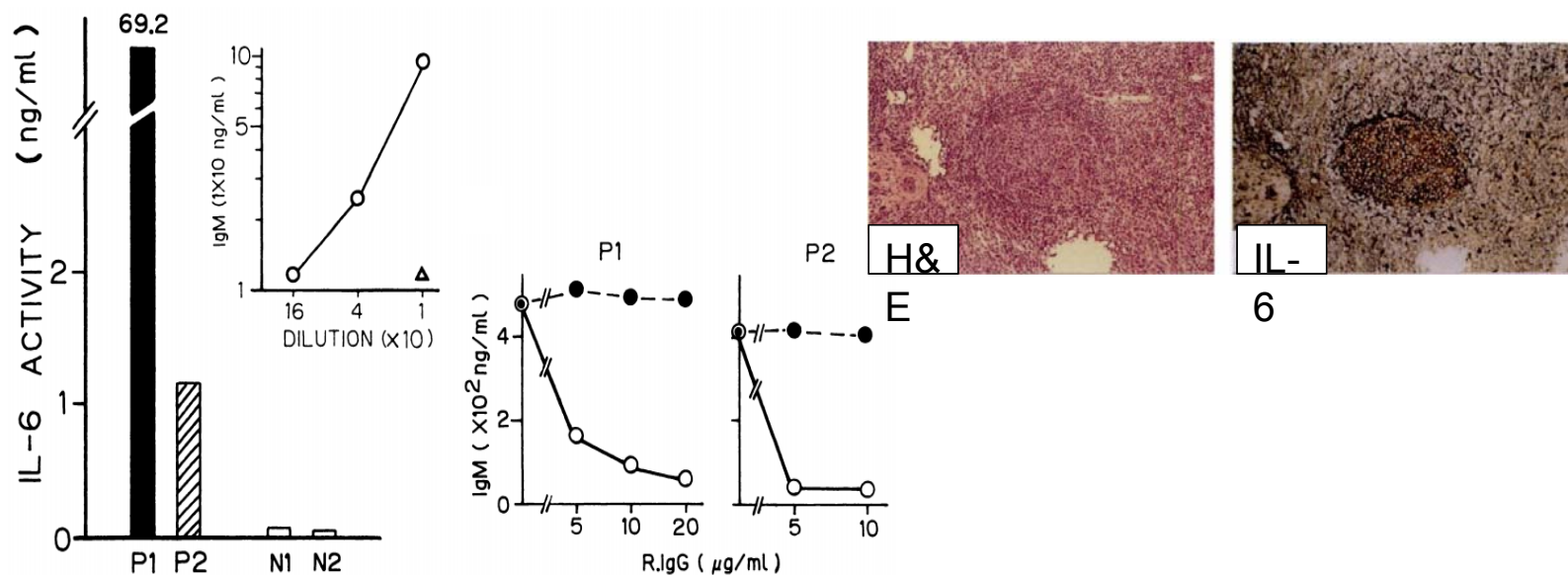


Tanaka et al. Int J Biol Sci 2012

## Pathogenic Significance of Interleukin-6 (IL-6/BSF-2) in Castleman's Disease

By Kazuyuki Yoshizaki, Tadashi Matsuda, Norihiro Nishimoto, Taro Kuritani, Lee Taeho, Katsuyuki Aozasa, Tatsutoshi Nakahata, Hiroshi Kawai, Hiromi Tagoh, Toshihisa Komori, Susumu Kishimoto, Toshio Hirano, and Tadamitsu Kishimoto

Patient (Age, Sex)	Before and After Surgery	Affected Lymph Nodes	Clinical Symptoms	Hb (g/dL)	ESR (mm/h)	TP (g/dL)	$\gamma$ -gl (%)	Immunoglobulins				CRP (mg/dL)	Fibrinogen (mg/dL)
								IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	IgE (u/mL)		
P1 (14, F)	Before	Solitary	(+)	9.1	157	8.9	42.0	4,350	468	332	12	20.7	575
	After (2 wk)	No	(-)	11.6	22	7.7	25.4	2,471	190	253	9	0.05	ND
	After (4 mo)	No	(-)	12.9	6	7.1	19.4	1,813	165	246	ND	0.04	236
P2 (52, F)	Before	Multiple	(+)	10.1	138	9.0	39.9	4,650	1,040	180	19,900	5.8	484
	After (1 mo)	Multiple	(+)	9.0	144	9.6	45.0	5,320	941	179	ND	5.7	644
	After (4 mo)	Multiple	(+)	8.2	144	8.9	37.9	4,280	832	163	13,200	12.4	610



Yoshizaki, et al. Blood 1989

# ARS Question

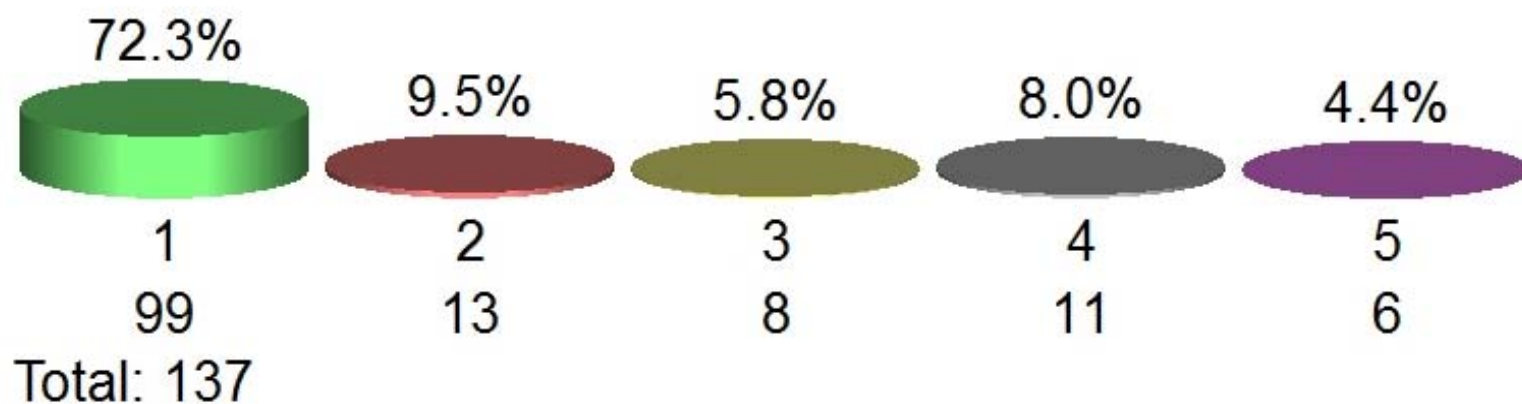




A 40yo woman presents with painless cervical adenopathy. Biopsy shows Castleman disease, hyaline vascular subtype, HHV8-negative. She tests seronegative for HIV. PET-CT scan shows isolated 3cm left cervical adenopathy.

**You recommend:**

1. Surgical excision
2. Radiation
3. Rituximab
4. R-CHOP x 3 followed by radiation
5. Siltuximab

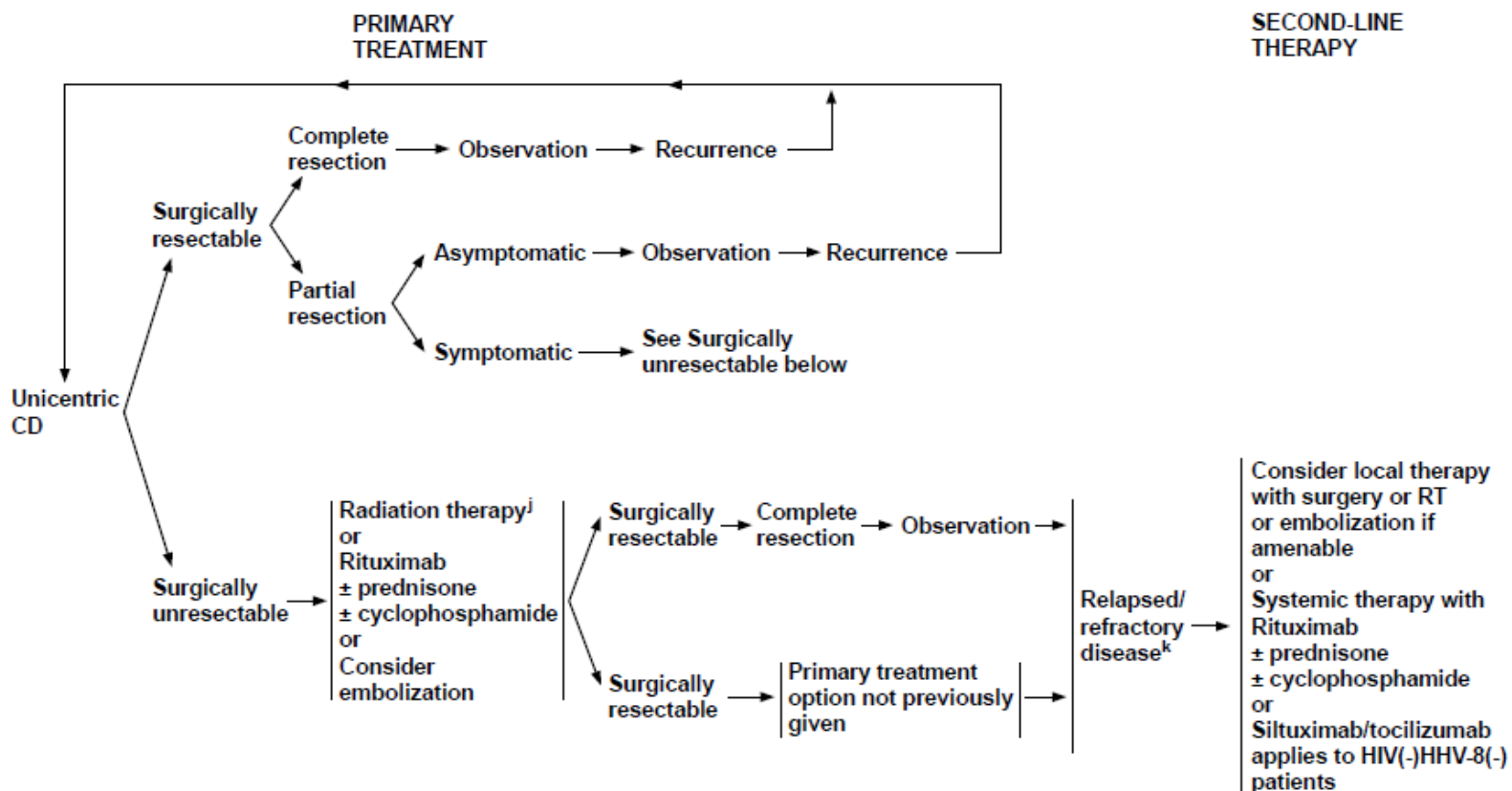


## Features of Unicentric Castleman Disease (UCD)

- Most commonly hyaline vascular variant
- Not generally associated with HIV or HHV8
- Indolent natural history
- Most commonly presents in 30s-40s
- Slight female predominance
- Common sites of presentation include the chest (30%), neck (23%), abdomen (20%), and retroperitoneum

# Unicentric Castleman Disease (UCD)

- Often asymptomatic and diagnosed by routine imaging
- Thoracic disease may present with cough, hemoptysis, dyspnea, or chest discomfort.
- Abdominal, retroperitoneal, and pelvic disease may present with abdominal or back discomfort
- Peripheral disease presents as painless adenopathy
- Systemic B symptoms and Inflammatory laboratory abnormalities are uncommon, and associated with plasma cell or mixed variant



<sup>j</sup>Patients with non-bulky disease may be observed after RT.

<sup>k</sup>Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

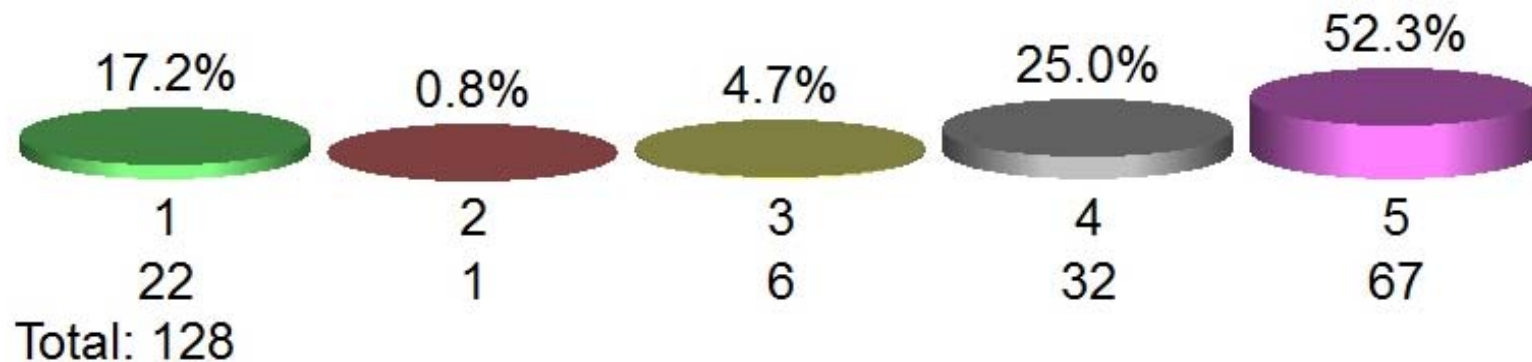
# ARS Question



A 52yo HIV+ man on efavirenz/emtricitabine/tenofovir presents with fevers, malaise, adenopathy, and 2+ peripheral edema. Labs notable for Hgb 10 g/dL, ESR 140 secs, and hypergammaglobulinemia. CD4 count 175/ $\mu$ L. Biopsy shows Castleman disease, plasma cell variant, HHV8-positive. PET-CT scan shows diffuse adenopathy up to 2.5cm, splenomegaly, and small bilateral pleural effusions.

**You recommend:**

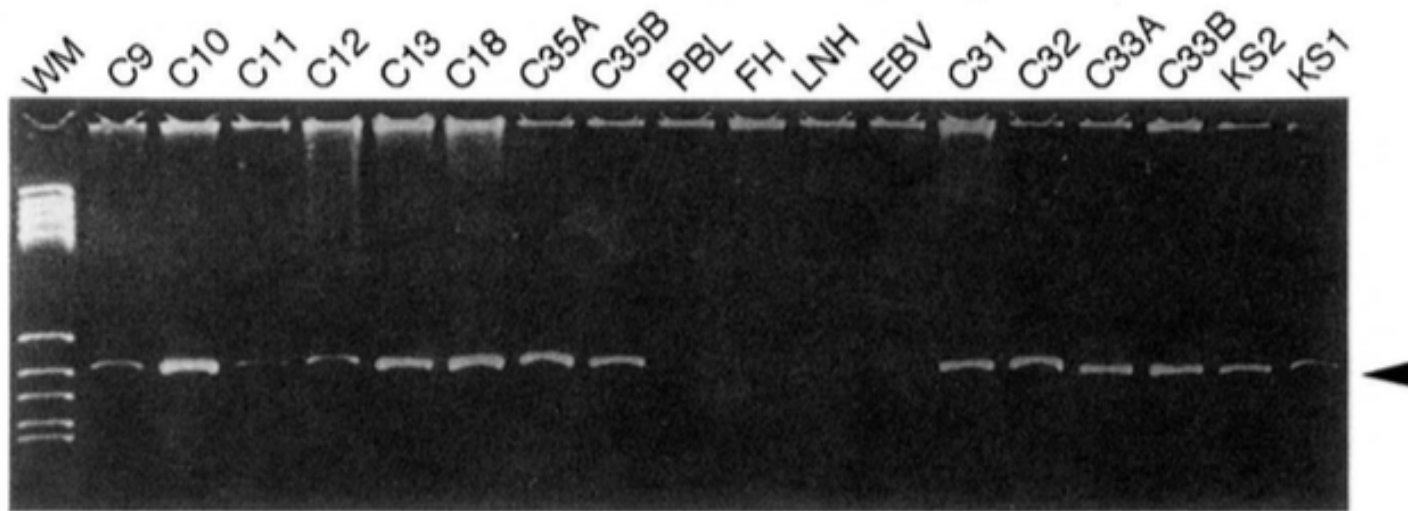
1. Siltuximab
2. Vinblastine
3. Etoposide
4. R-CHOP
5. Rituximab





# HHV8 in Multicentric Castleman Disease

Tissue	HIV <sup>-</sup>	HIV <sup>+</sup>
KS	67/73	88/91*
MCD	7/17‡	14/14§
Reactive lymph nodes	1/51	3/17



Soulier, et al. Blood. 1995;86(4):1276-1280

# Multicentric Castleman Disease (MCD)

- Most commonly seen in HIV, but may be idiopathic
- No correlation with CD4 count or cART
- Most commonly plasma cell or plasmablastic, but may be hyaline vascular in HIV-/HHV8- cases
- Male predominance
- Variable natural history: May be relapsing remitting, indolent disease, or rapidly progressive
- HIV patients with low CD4 may also have opportunistic infections
- HIV+/HHV8+ cases often co-exist with Kaposi sarcoma (up to 70%), and are associated with DLBCL transformation

Bower, et al. Blood. 2010;116(22):4415-4421



# Presentation of MCD

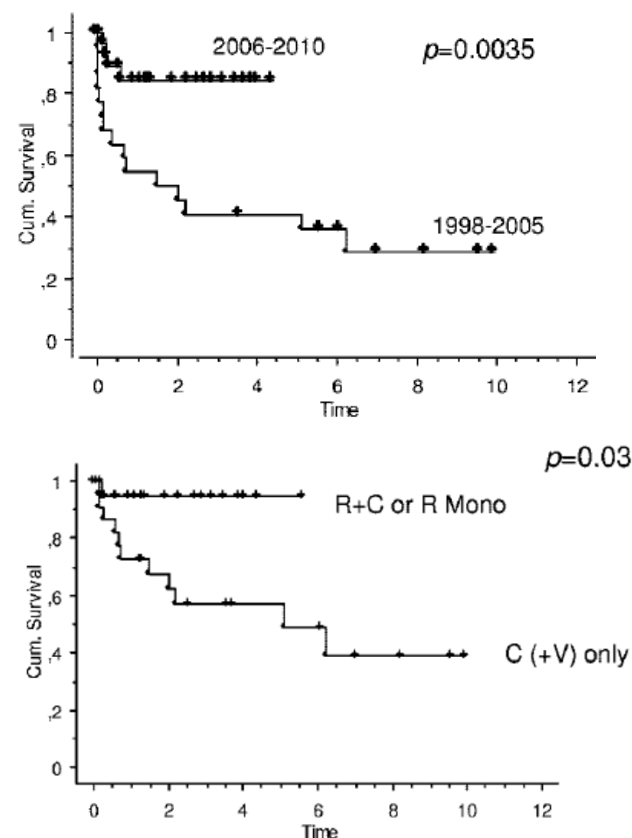
- Clinical features
  - Fevers, drenching night sweats, weight loss, and fatigue.
  - Diffuse non-bulky lymphadenopathy
  - Hepatosplenomegaly
  - Peripheral edema, pleural and pericardial effusions, and abdominal ascites
- Laboratory features
  - Anemia
  - Elevated ESR, CRP, ferritin, sIL-6, sIL-10
  - Hypergammaglobulinemia
  - Hypoalbuminemia

Bower, et al. Blood. 2010;116(22):4415-4421



# Prognosis and Management of MCD

- Median survival has improved with combination antiretroviral therapy (cART) and modern therapy
- No comparative or controlled trials
- cART should be started on all HIV+ patients, but will not induce Castleman remissions
- Treatment indicated for active disease



Hoffmann, et al. Blood. 2011;118(13):3499-3503



## NCCN Guidelines Version 2.2015 Castleman's Disease

### CRITERIA FOR ACTIVE DISEASE<sup>a</sup>

- Fever
- Increased serum C-reactive protein level >20 mg/L in the absence of any other etiology
- At least three of the following other MCD-related symptoms
  - › Peripheral lymphadenopathy
  - › Enlarged spleen
  - › Edema
  - › Pleural effusion
  - › Ascitis
  - › Cough
  - › Nasal obstruction
  - › Xerostomia
  - › Rash
  - › Central neurologic symptoms
  - › Jaundice
  - › Autoimmune hemolytic anemia

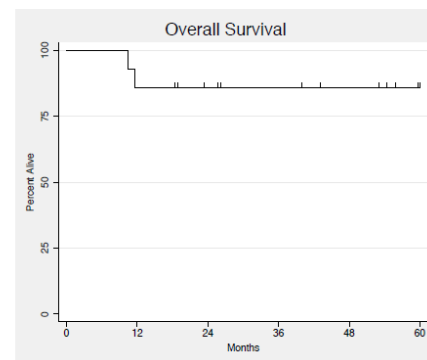
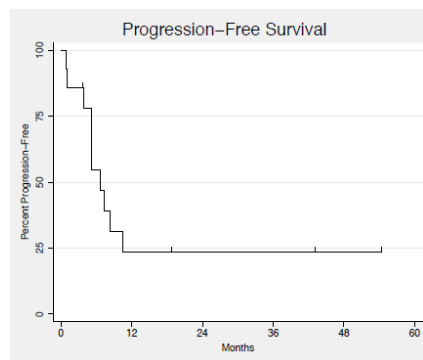
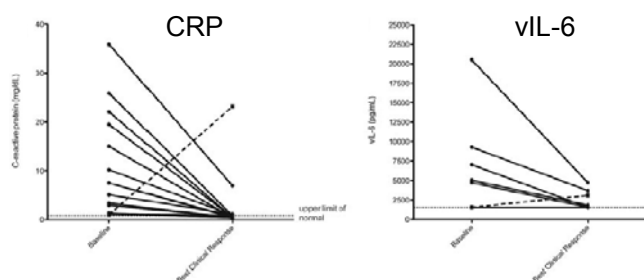
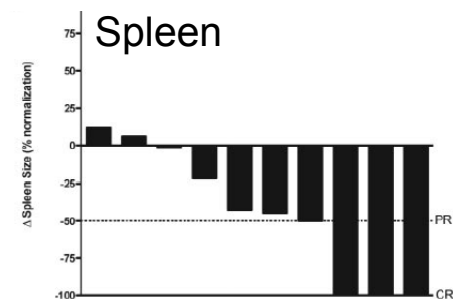
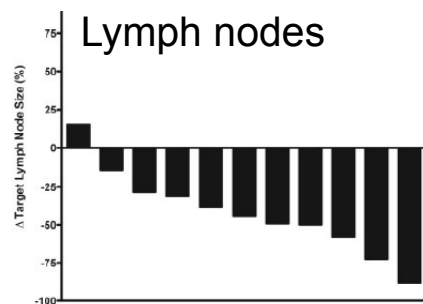
<sup>a</sup>Gérard L, Bérezné A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007;25:3350-3356.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

# Zidovudine plus valganciclovir in HIV+ MCD

- 14 HIV+ HHV8+ MCD
- Zidovudine 600mg po q6h, valganciclovir 900mg po q12h
- Major clinical response 86%
- Major biochemical response 50%



Uldrick, et al. Blood. 2011;117(26):6977-6986



# Chemotherapy Options for MCD

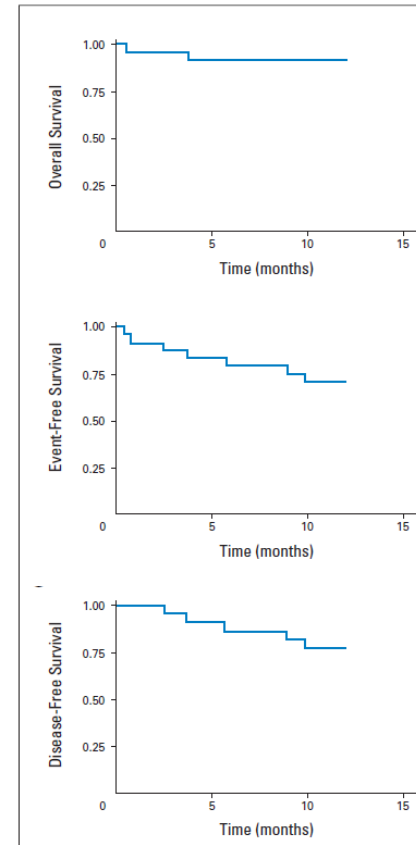
- Single agents
  - Steroids: Initial high response rate about 80%, and can rapidly improve symptoms, but response is short lived
  - Etoposide: 50 - 100 mg PO daily days 1 through 7 of a 14-day cycle until maximal response, or 100-200 mg/m<sup>2</sup> IV weekly for 4 weeks, and may be followed by maintenance.
  - Vinblastine: 4 to 6 mg/m<sup>2</sup> IV every 2 weeks until maximal response, and may be followed by maintenance.
  - Liposomal doxorubicin: 20mg/m<sup>2</sup> IV every 3 weeks
- Combination chemotherapy
  - Rituximab-etoposide
  - Rituximab-liposomal doxorubicin
  - CVP/CHOP +/- rituximab



# Rituximab in HIV-associated MCD

## *CastlemaB Trial*

- 24 subjects with chemotherapy-dependent disease (vinblastine, etoposide, liposomal doxorubicin)
- 4 weekly doses at 375 mg/m<sup>2</sup>
- Median CD4 270/μL
- **22 of 24 achieved chemo independence**



Gerard, et al. JCO 2007;25:3350-3356

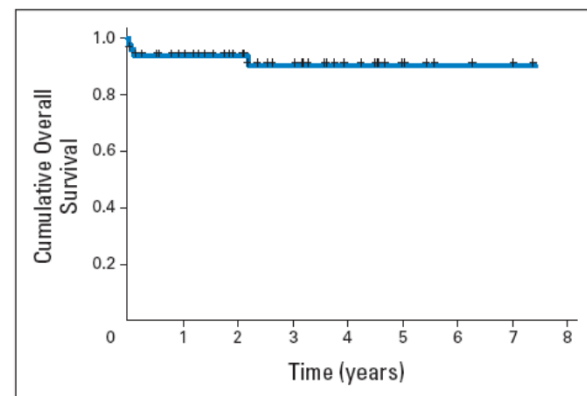
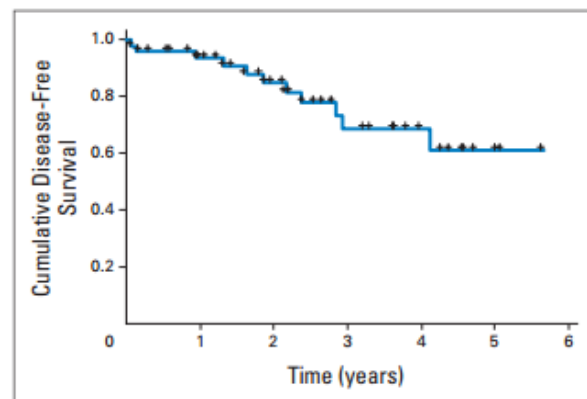
## Retrospective rituximab experience in prospective cohort of newly diagnosed HIV+ MCD (n=61)

### Baseline Characteristics

Median age	42
Male	87%
Median time from HIV	2.4 y
Median CD4	233/ $\mu$ L
Rituximab-based tx	49, 14 with etoposide

5-year OS 77% in entire cohort

Rituximab-treated patients



Bower, et al. JCO. 2011;29:2481-2486

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# Retrospective single-center experience with rituximab

- 113 patients with HIV-associated MCD
- 48 received rituximab
- Half had prior Kaposi sarcoma (KS)
- KS exacerbation in 10 patients (9 with rituximab)
- 5-year probability of NHL: 31% without rituximab vs. 3% with rituximab

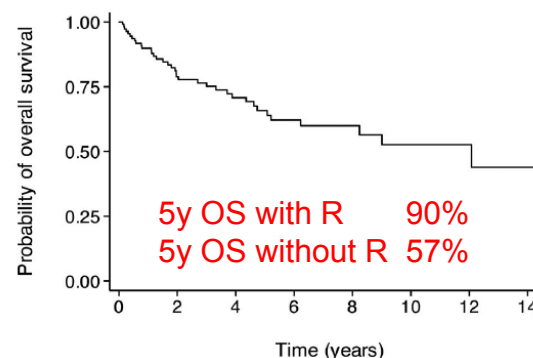


Table 2. Cause of death in 36 patients with HIV-associated MCD

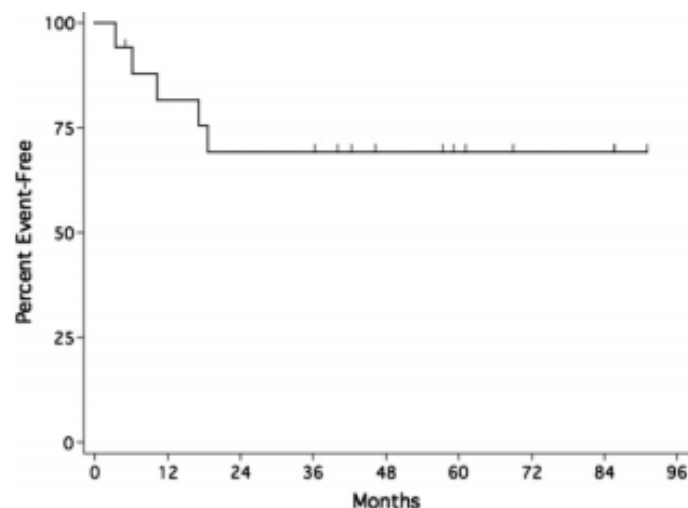
	R- group	R+ group
Cause of death, n		
MCD	4	3
NHL	10	1
AIDS	6 (KS = 1)	0
Non-AIDS-defining infection	0	2
Acute leukemia	0	1
Hodgkin lymphoma	1	0
NHL treatment	2	0
Cancer	1	1
Other	1	0
Unknown	3	0
Total	28	8

Gerard, et al. Blood. 2012;119(10):2228-33.



# Rituximab-liposomal doxorubicin

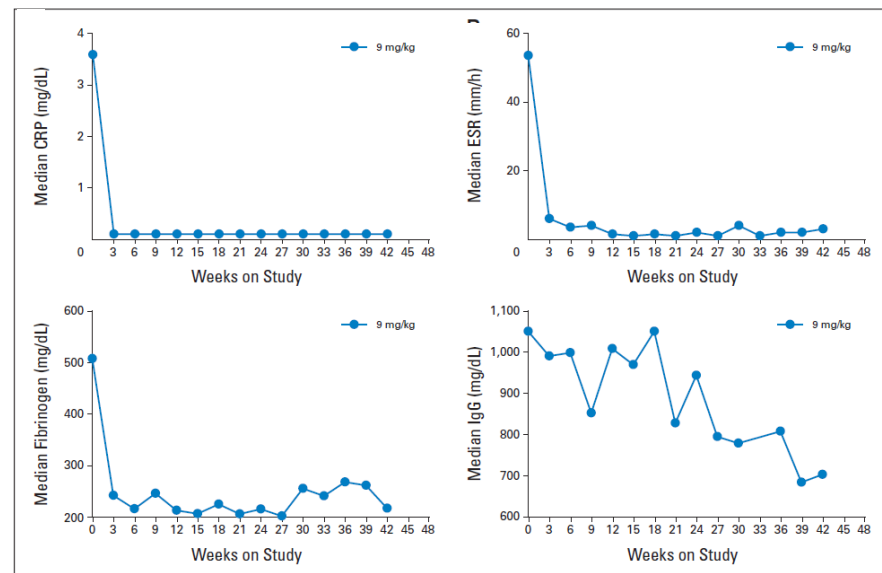
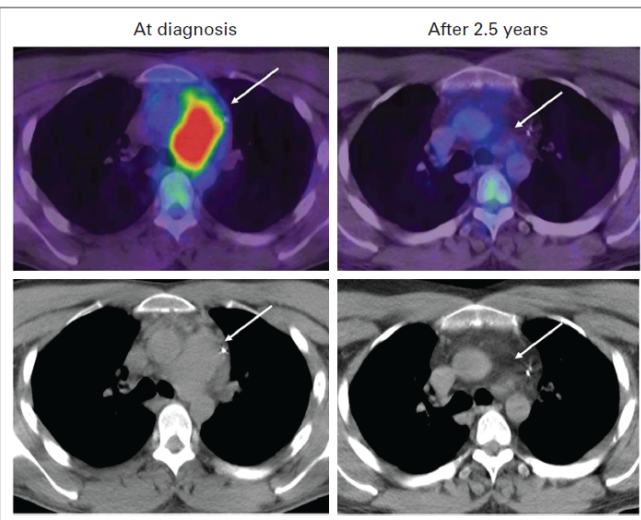
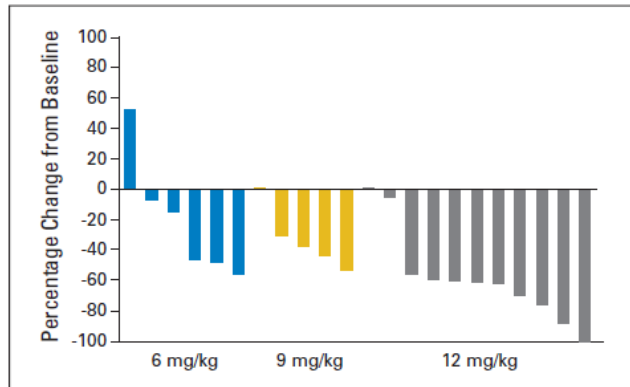
- Rituximab 385 mg/m<sup>2</sup> - liposomal doxorubicin 20 mg/m<sup>2</sup> q 3 weeks
- N=17
- Median 4 cycles (3-9)
- All on cART
- 12 with concurrent KS
- 11 received consolidation IFN-alpha, 6 high dose AZT and valgancyclovir
- CRR 88%



5/6 cutaneous KS patients had improved KS

Uldrick, et al. Blood. 2014;124:3544 - 3552

# Phase I trial of Siltuximab: Anti-IL-6 mAb in HIV-negative CD





## Phase III study of siltuximab vs. placebo in patients with HIV-negative and human HHV-8-negative symptomatic MCD

- Randomized, double-blind, placebo-controlled study at 38 hospitals in 19 countries.
- 2:1 random assignment to siltuximab 11 mg/kg IV q 3 week or placebo, continued until treatment failure
- Primary endpoint was durable tumor and symptomatic response for at least 18 weeks

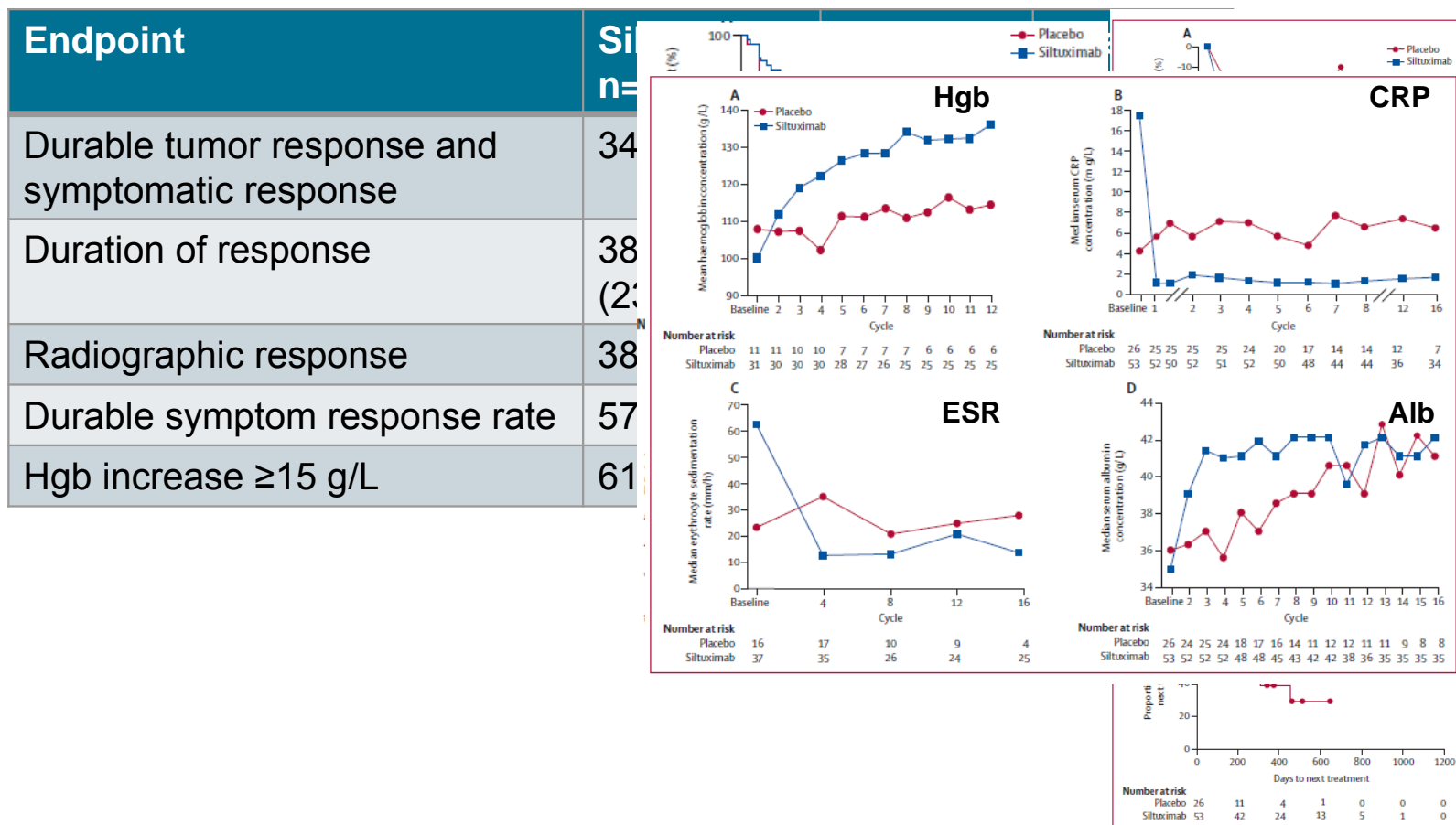
	Siltuximab group (n=53)	Placebo group (n=26)
Age (years)	47 (20-74)	48 (27-78)
Sex (male)	30 (57%)	22 (85%)
Disease histology*		
Hyaline vascular	18 (34%)	8 (31%)
Plasmacytic	13 (25%)	5 (19%)
Mixed	22 (42%)	13 (50%)
Patients who received previous systemic treatment	29 (55%)	17 (65%)
Corticosteroids	28 (97%)	15 (88%)
Chemotherapy	17 (59%)	12 (71%)
Rituximab	5 (17%)	3 (18%)
Immunosuppressants†	1 (3%)	3 (18%)
Interferon	1 (3%)	1 (6%)
Patients concomitantly taking corticosteroid	13 (25%)	9 (35%)
Haemoglobin concentration (g/L)	118 (65-170)	134 (85-181)
Interleukin 6 concentration (pg/mL)	7.13 (0.38-50.6)	4.94 (1.03-19.8)
C-reactive protein concentration (mg/L)	17.6 (0.10-181.0)	4.2 (0.4-107.0)
Erythrocyte sedimentation rate (mm/h)	62.0 (4-120)	23.5 (1-112)
Fibrinogen concentration (μmol/L)	15.14 (6.9-29.4)	12.08 (7.3-29.4)
Albumin concentration (g/L)	35 (15-49)	36 (28-46)

Data are median (range) or n (%). ECOG-PS=Eastern Cooperative Oncology Group performance status. EMEA=Europe, Middle East, and Africa. \* By central pathological review. †Azathioprine, ciclosporin, or thalidomide.

**Table 1: Baseline characteristics**

Van Rhee et al. Lancet Oncol 2014;15(9):966-74

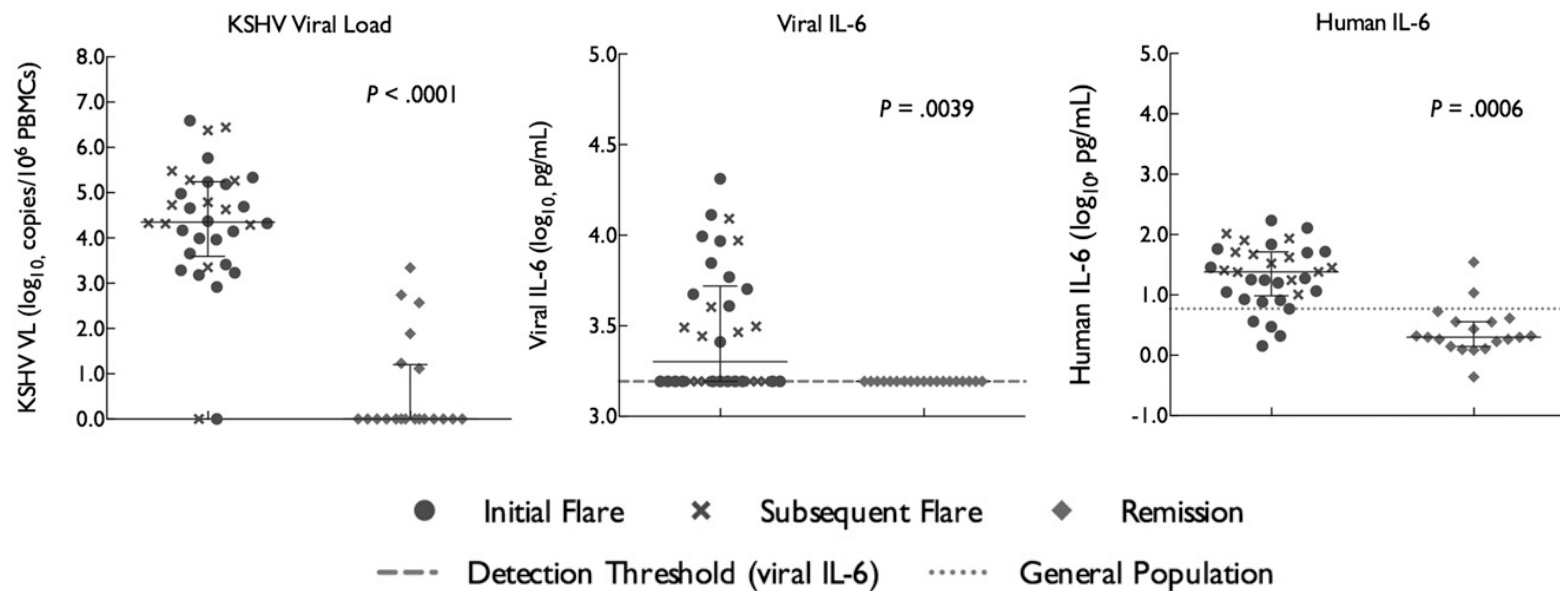
# Phase III study results



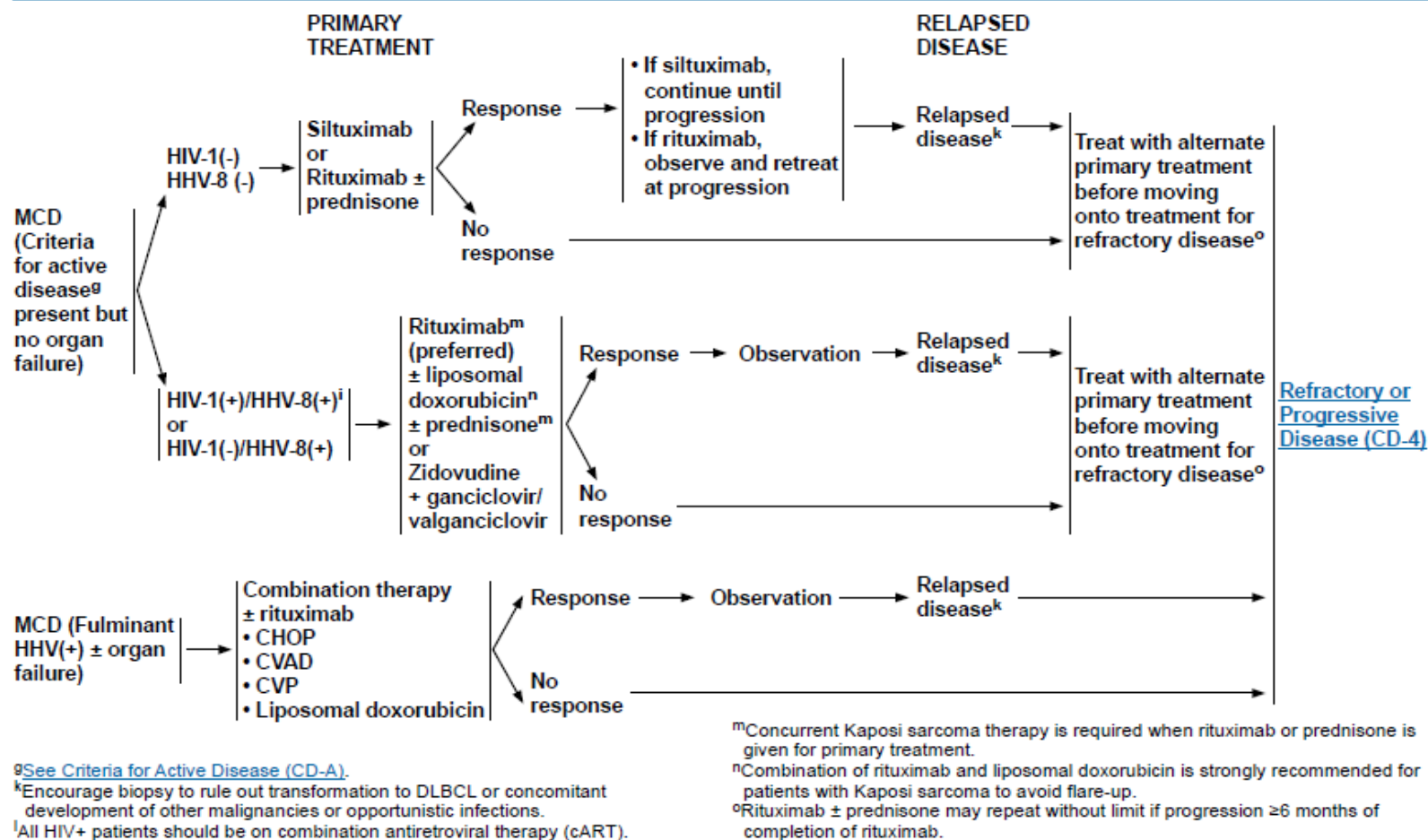
Van Rhee et al. Lancet Oncol 2014;15(9):966-74

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# Anti-IL-6 in HIV+ HHV8+ disease?



Polizzotto et al. Blood 2013;122(26):4189-4198



Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

# Associated conditions

- POEMS syndrome (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormality)
- Follicular dendritic cell sarcomas
- Paraneoplastic pemphigus
- HHV8- associated malignancies
  - Kaposi Sarcoma
  - DLBCL arising out of HHV8+ MCD
  - Primary Effusion lymphoma

# Conclusions (1)

- Castleman disease is a heterogeneous non-malignant lymphoproliferative disease
- Major distinctions:
  - Unicentric versus multicentric presentation
  - Hyaline vascular, plasma cell, or mixed pathology
  - HIV/HHV8-associated versus not
- UCD presents as localized adenopathy, usually hyaline vascular pathology, treated with local control
- MCD is most commonly HHV8+ with plasma cell or plasmablastic pathology in HIV+ patients
- Plasma cell and mixed variants associated with IL-6 mediated-inflammatory syndrome of fevers, malaise, edema, hypergammaglobulinemia, anemia, and increased inflammatory markers





## Conclusions (2)

- MCD is a relapsing remitting disease and treatment is indicated when active disease is present
- Initial treatment is rituximab +/- chemotherapy, which has a high rate of disease control and symptom improvement
- Steroids may be used alone or as an adjunct for rapid but short lived disease control
- Antiviral therapy may be effective in HIV+ HHV8+ patients
- Siltuximab, an anti-IL-6 mAb, is highly effective in inducing durable and symptomatic disease control in HHV8/HIV negative patients with MCD

# NCCN Member Institutions

