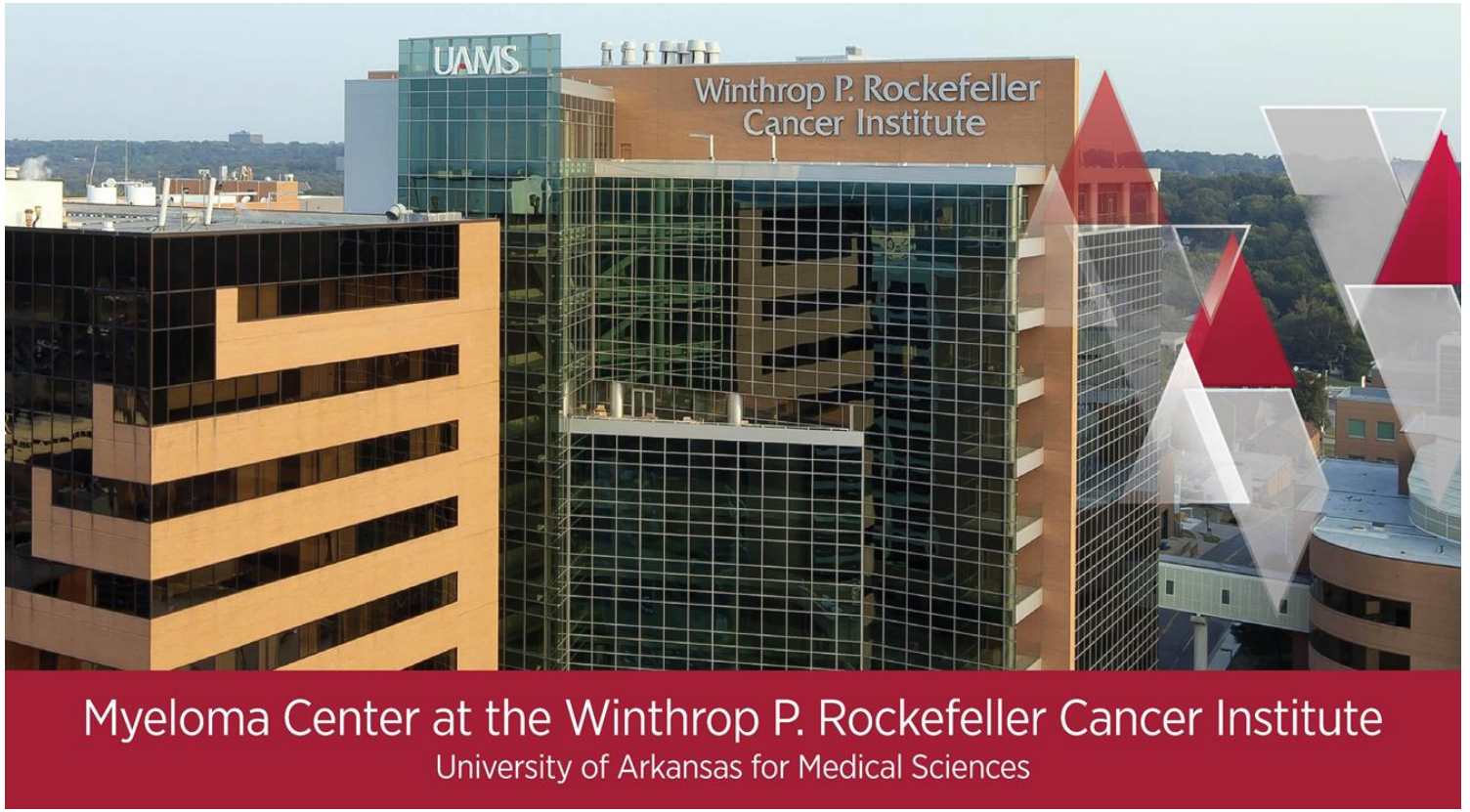
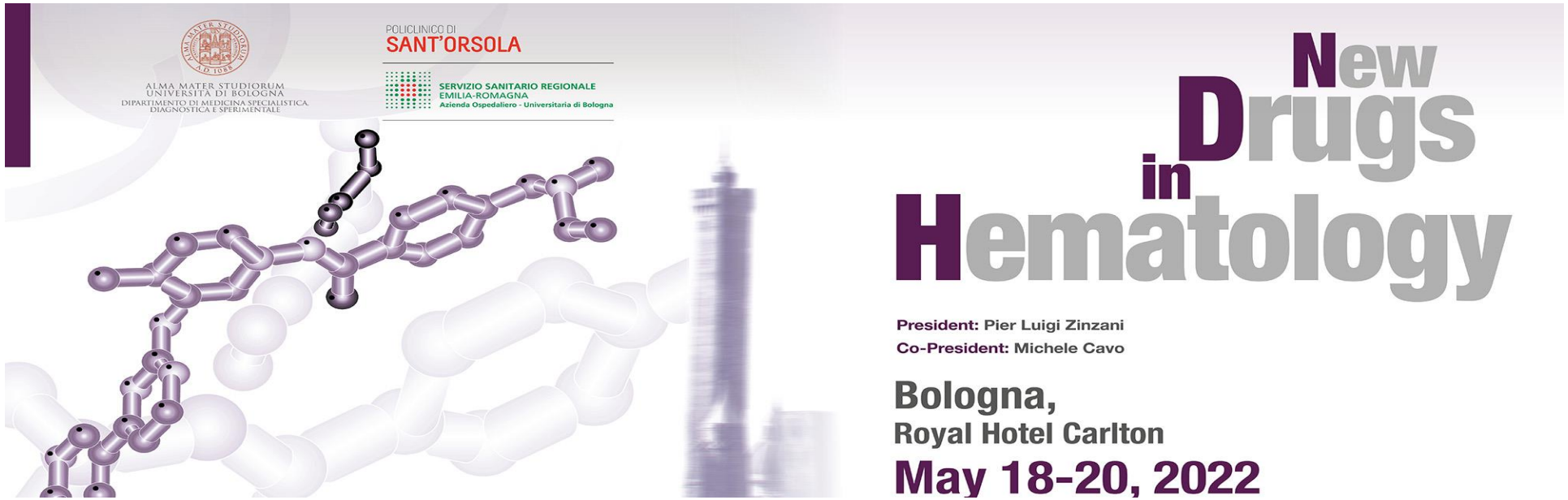
Siltuximab



Frits van Rhee, MD, PhD, MRCP(UK), FRCPath

Clinical Director, Professor of Medicine

UAMS | Myeloma Center

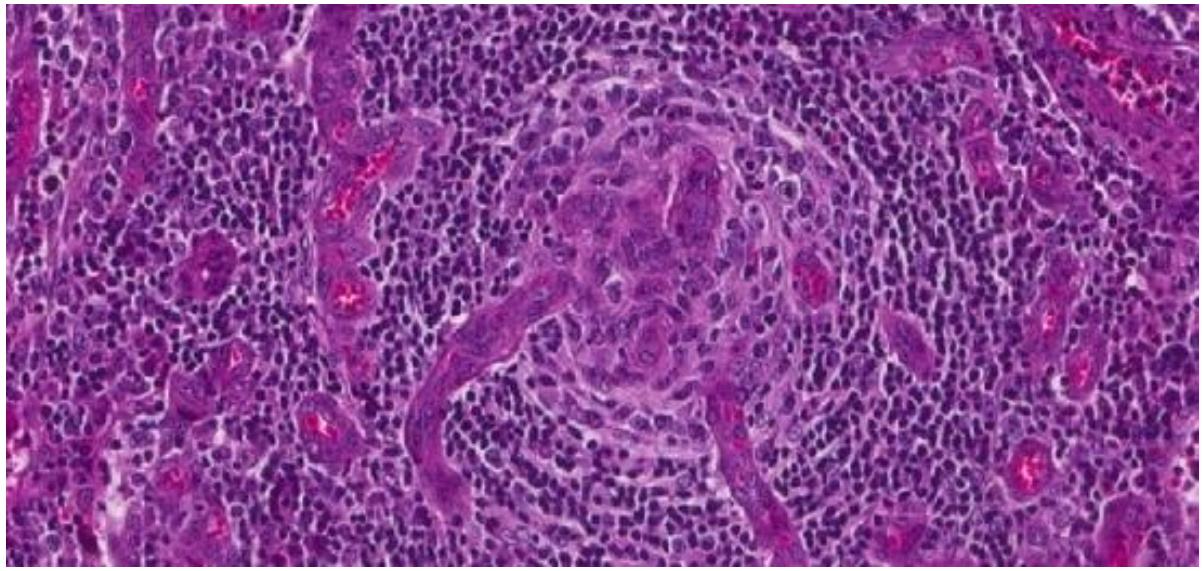


- Frits van Rhee has received consultant fees from EUSA Pharma, GlaxoSmithKline, Takeda, Sanofi, Janssen and the Castleman Disease Collaborative Network and research funding from Janssen Pharmaceuticals and Bristol–Myers Squibb (BMS)

Siltuximab: EMA-& FDA-approved for idiopathic Multicentric Castleman Disease

- Phase I study[1]
- Randomized, double-blind, placebo-controlled study[2]
- Preliminary long-term safety study[3,4]
- Updated long-term safety and efficacy study[4]
- Patients in Italy were granted early access through a Named Patient Program (NPP)
- Used off label for cytokine release syndrome and COVID-19 pneumonia

CDCN, Castleman Disease Collaborative Network; EMA, European Medicines Agency; FDA, US Food and Drug Administration; iMCD, idiopathic multicentric Castleman disease. 1. Kurzrock R et al. *Clin Cancer Res* 2013;19:3659–3670; 2. van Rhee F et al. *Lancet Oncol* 2014;15:966–974; 3. van Rhee F et al. *Oncotarget* 2015;6:30408–30419; 4. van Rhee et al. Lancet Haematology. 2020; 7(3): PE209-E217; 6 van Rhee F et al. *Blood* 2018;132:2115–2124.



CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

Discovery of Castleman Disease (1954)[1]

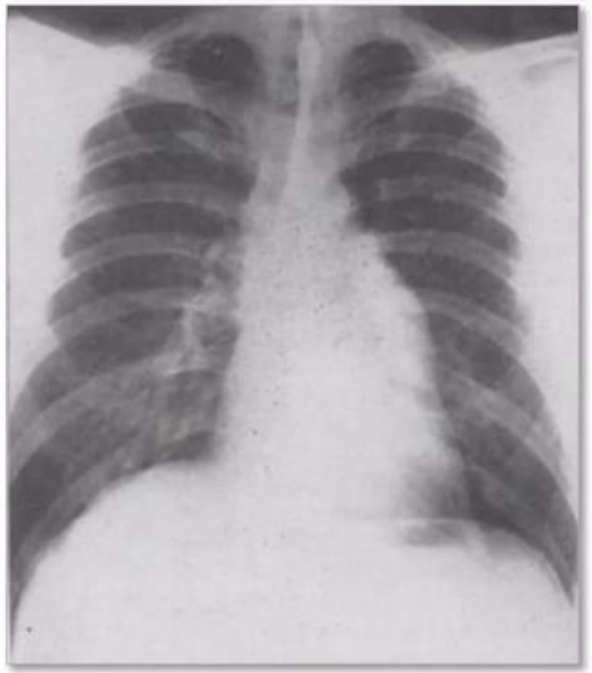
CASE RECORDS OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

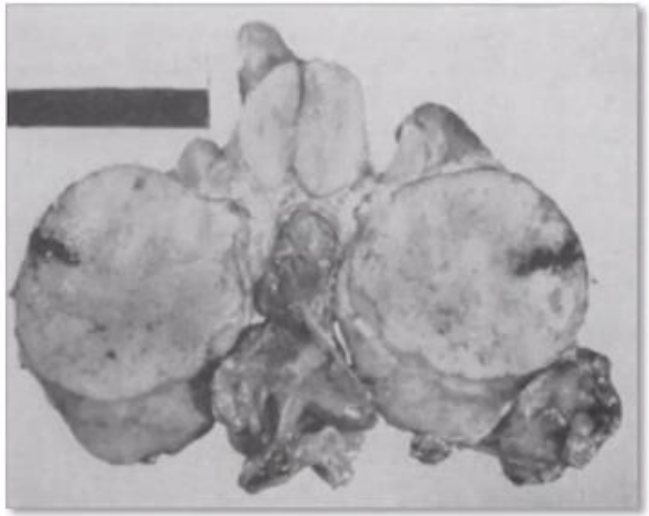
FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*



They were composed of lymphoid tissue, hyperplastic to be sure, with many germinal centers surrounded by mature lymphocytes. Many of these germinal centers contained hyalinized foci, which were not the Hassall corpuscles found in thymic tissue. There were many plasma cells scattered through the lymphoid tissue, another bit of evidence that these were inflammatory or reactive lymph nodes, similar to hyperplastic nodes seen in other parts of the body. It is certainly unusual that these nodes remained so large for so long a time.



I had occasion recently to review the material on thymomas and other mediastinal tumors at the Armed Forces Institute of Pathology and found 4 similar cases. They are not thymomas and have nothing to do with the thymus; they are almost always to the right or left of the midline, often close to a bronchus or lung.

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

Benjamin Castleman

Reference: 1. Case 40011. *N Eng J Med.* 1954; 250: 26-30.

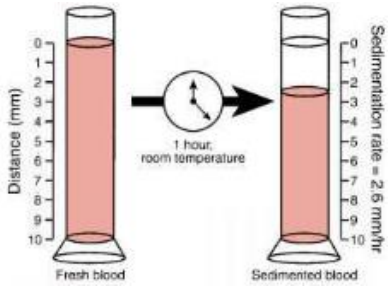
Classification of Castleman Disease

Unicentric Castleman Disease *(UCD)*	▪ Single region of enlarged lymph nodes, few symptoms ▪ ~3,000-5,000 cases diagnosed annually in the US; >95% 5-year OS ▪ Idiopathic; surgical excision is curative
HHV8-positive Multicentric Castleman Disease *(HHV8+MCD)*	▪ Multicentric LAD, systemic inflammation, cytopenias, MSOF ▪ ~1,000 cases diagnosed annually in the US; 90% 5-year OS ▪ HHV-8 drives cytokine release; rituximab is highly effective
POEMS-associated MCD *(POEMS-MCD)*	▪ Multicentric LAD, systemic inflammation, MSOF, neuropathy ▪ Monoclonal plasma cell population drives cytokine release ▪ Treatment: radiation (localized), IMIDs, Auto-SCT
HHV8-negative, idiopathic Multicentric Castleman Disease *(iMCD)*	▪ Multicentric LAD, systemic inflammation, cytopenias, MSOF ▪ ~1,000 cases diagnosed annually in the US; 65% 5-year OS ▪ Etio-Pathogenesis: Cause, cell types, pathways unknown ▪ Treatment: anti-IL-6 mAb is effective in 34-45% of cases

Munshi N, *et al. Leuk Lymphoma.* 2015; 56(5): 1252-1260; Bower M, *et al. J Clin Oncol.* 2011; 29(18): 2483-2486. Fajgenbaum DC, *et al. Blood.* 2017; 129(12): 1646-1655; Dispenzieri A, *et al.* 2012. *Am J Hematol.* 2012; 87(11): 997-1002. van Rhee F, *et al. Blood*. 2018; 132(20): 2115-2124.

CENTRAL ROLE OF IL-6 AND OTHER CYTOKINES

Increased ESR



Fibrinogen elevation

Cytokines: IL-6, VEGF

LIVER

Increased CRP

Inflammatory syndrome

Fluid accumulation

Less albumin production

Decreased iron use

Anemia

CRP; C-reactive protein; ESR; erythrocyte sedimentation rate; IL-6, interleukin-6; VEGF, vascular endothelial growth factor.

Patient Presentation

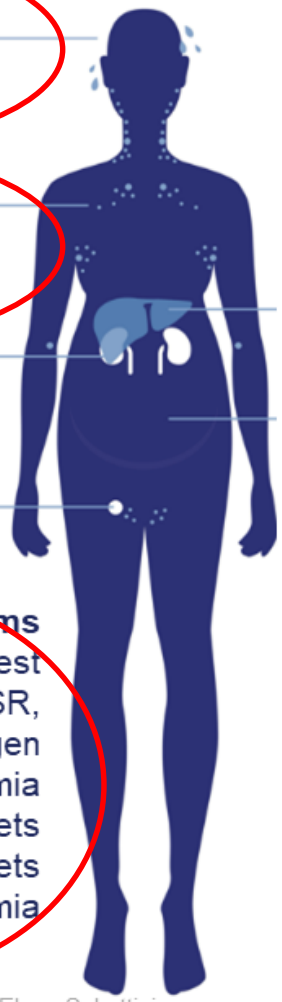
Flu-like symptoms
Fevers, night sweats, fatigue and weight loss

Lymph node
Enlargement of lymph nodes in multiple regions (MCD)

Kidney dysfunction

Lymph node
Enlargement of lymph nodes in only one region (UCD)

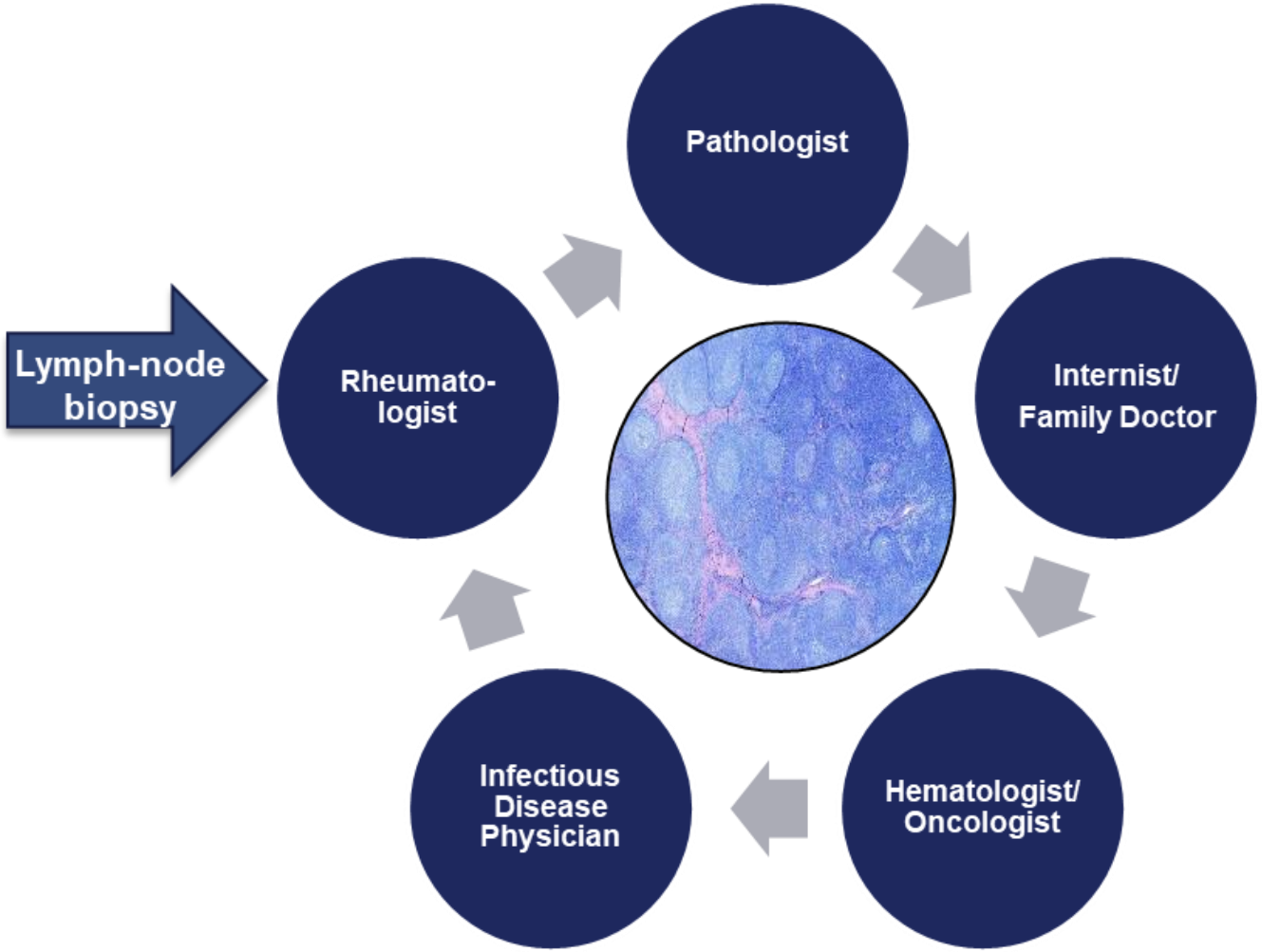
Other symptoms
Elevated CRP (best marker of disease), ESR, and fibrinogen
Anemia
Very low platelets or high platelets
Hypergammaglobulinemia



Liver dysfunction

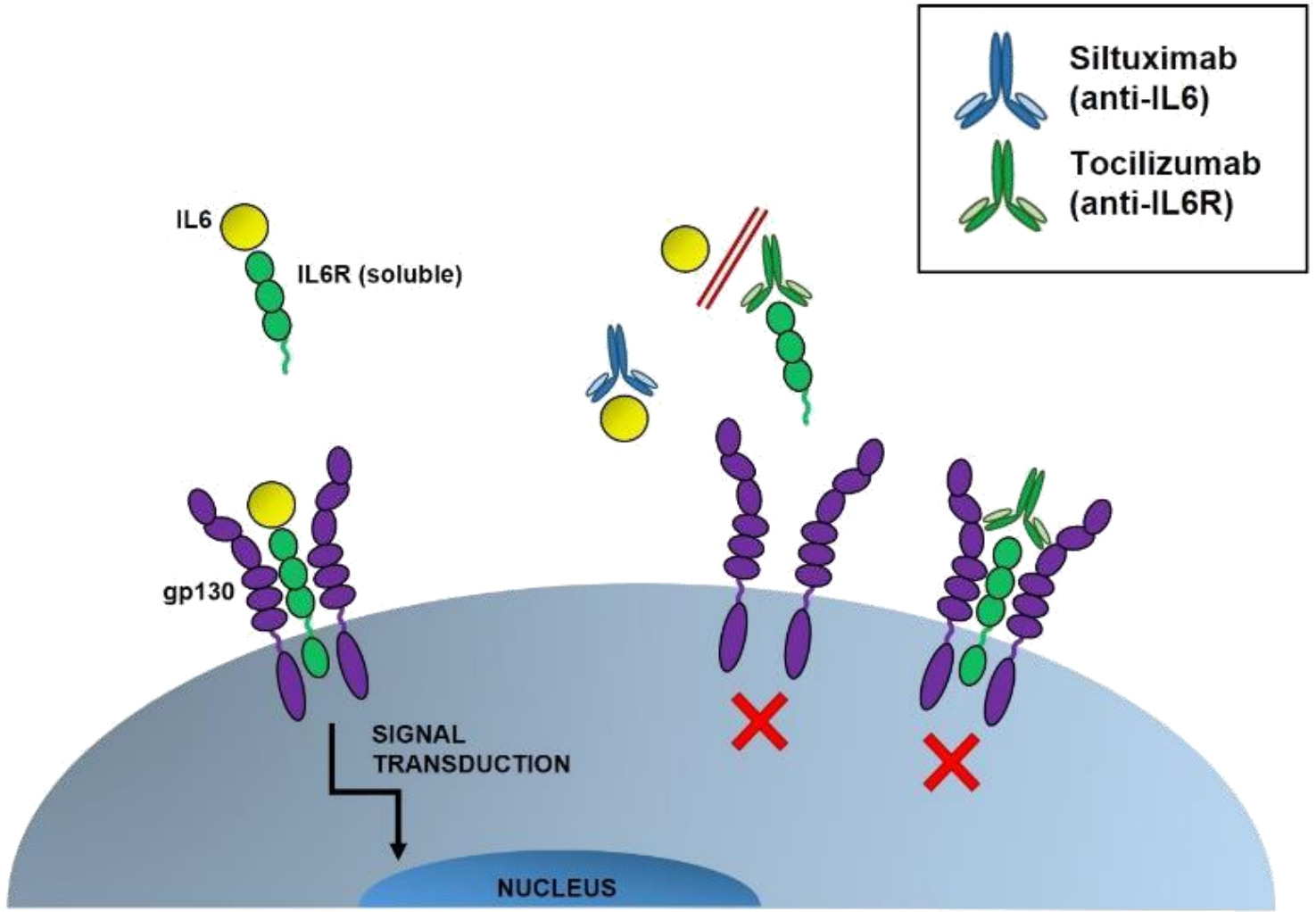
Fluid accumulation
Low albumin levels cause edema, pleural effusion and ascites

Lymph-node biopsy



Pathology image courtesy of Dr. Elena Sabattini.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCD, multicentric Castleman disease; UCD, unicentric Castleman disease.
Wu D et al. *Oncol Clin North Am* 2018;32:37–52. Fajgenbaum DC et al. Blood 2017;129:1646–1657.

IL-6 Targeted Therapy: How It Works

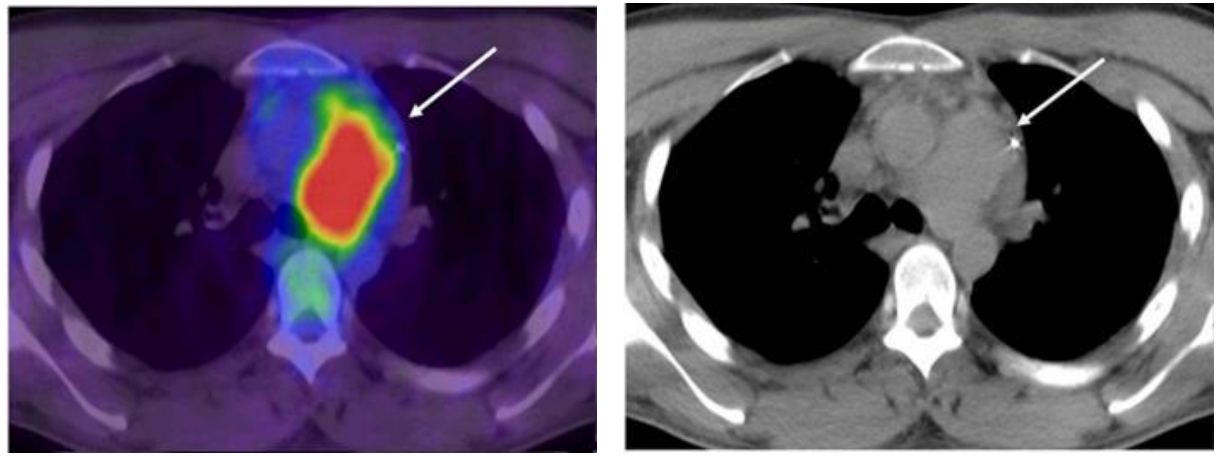


.

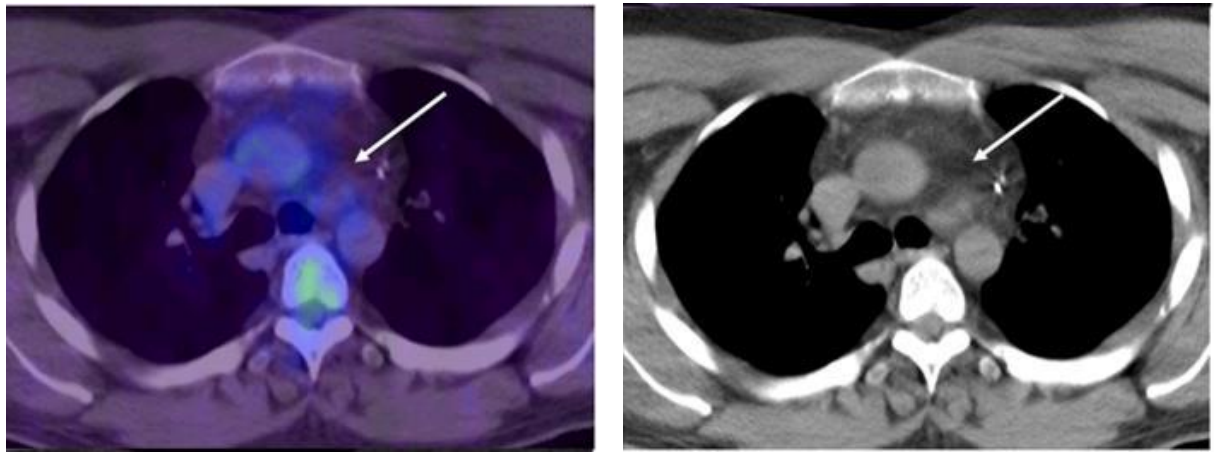
Adapted from van Rhee F et al. *Hematol Oncol N Am* 2018;32:89–106.

Phase I Siltuximab Study

At diagnosis

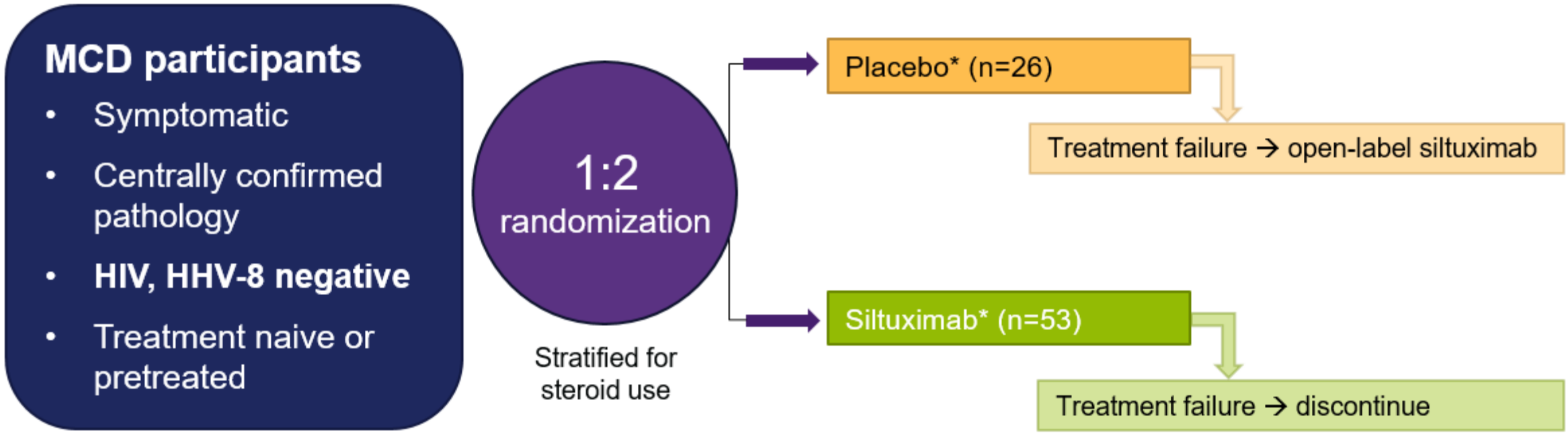


After 2.5 years of siltuximab therapy



Phase II Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Siltuximab in Multicentric Castleman Disease

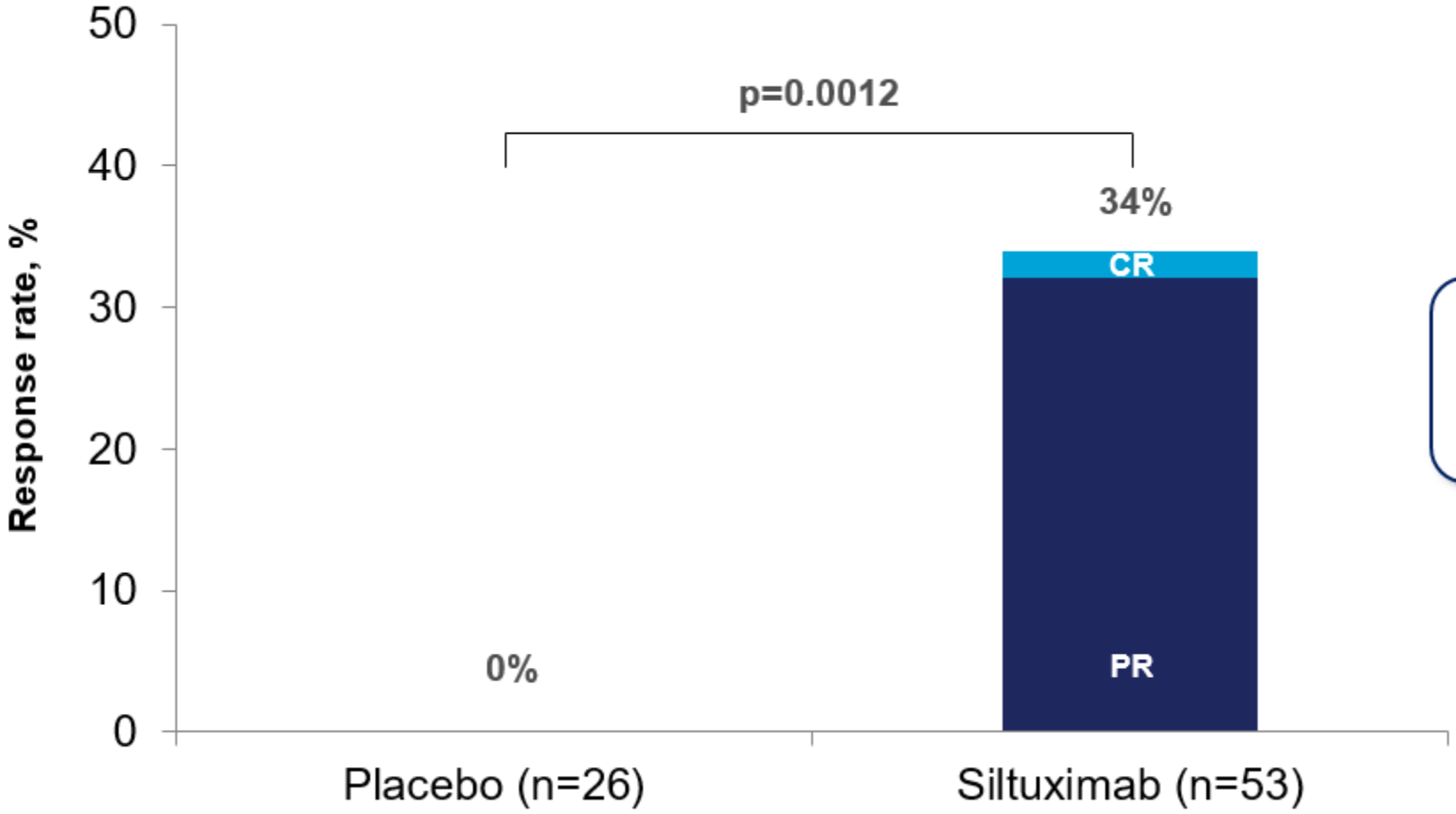
- First and only multinational, randomized, double-blind, placebo-controlled trial in MCD



- Primary study analysis planned at 48 weeks after last patient enrolled

*All patients received best supportive care, allowing up to 1 mg/kg of prednisone.
HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; MCD, multicentric Castleman disease.
van Rhee F et al. *Lancet Oncol* 2014;15:966–974.

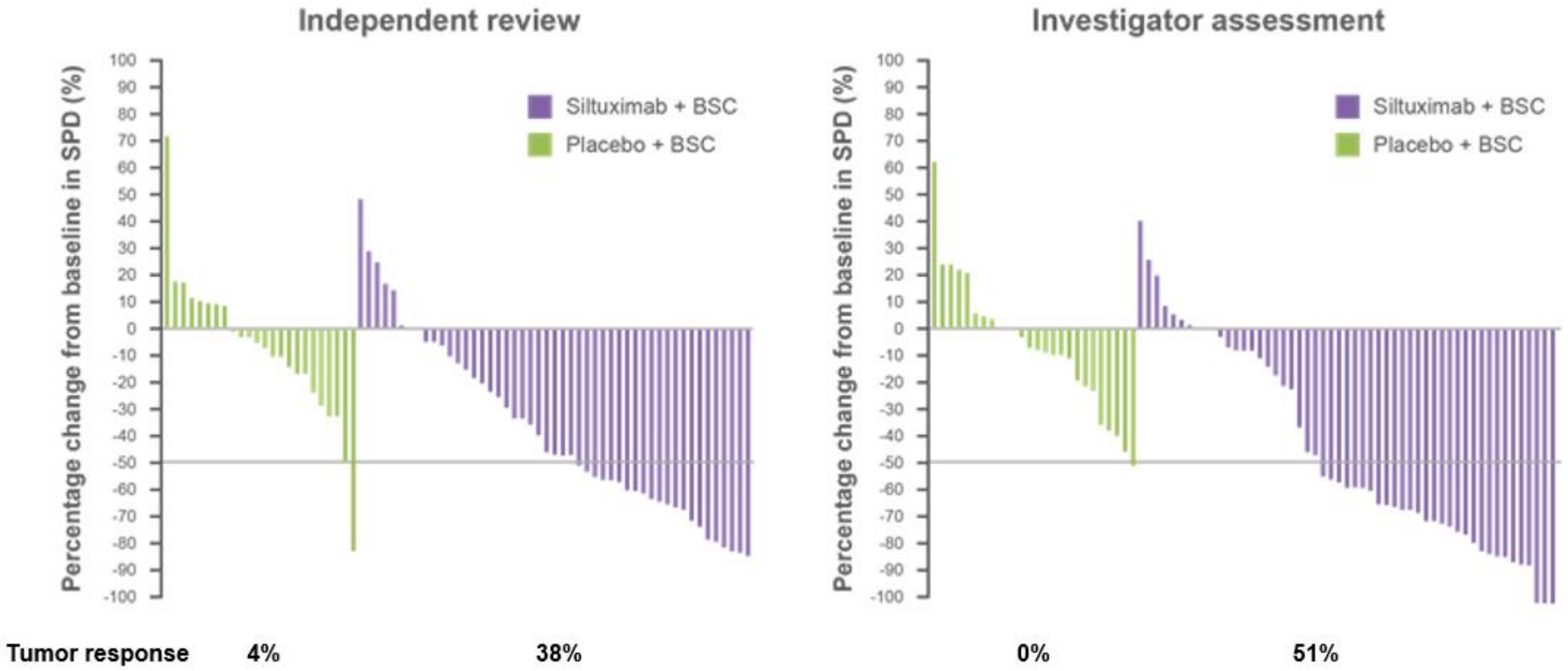
Primary Endpoint Analysis: Durable Tumor and Symptom Response



58% of patients (31/53) remained on siltuximab at primary endpoint analysis

CR, complete response; PR, partial response.
Data from van Rhee F et al. *Lancet Oncol* 2014;15:966–974

Tumor Response

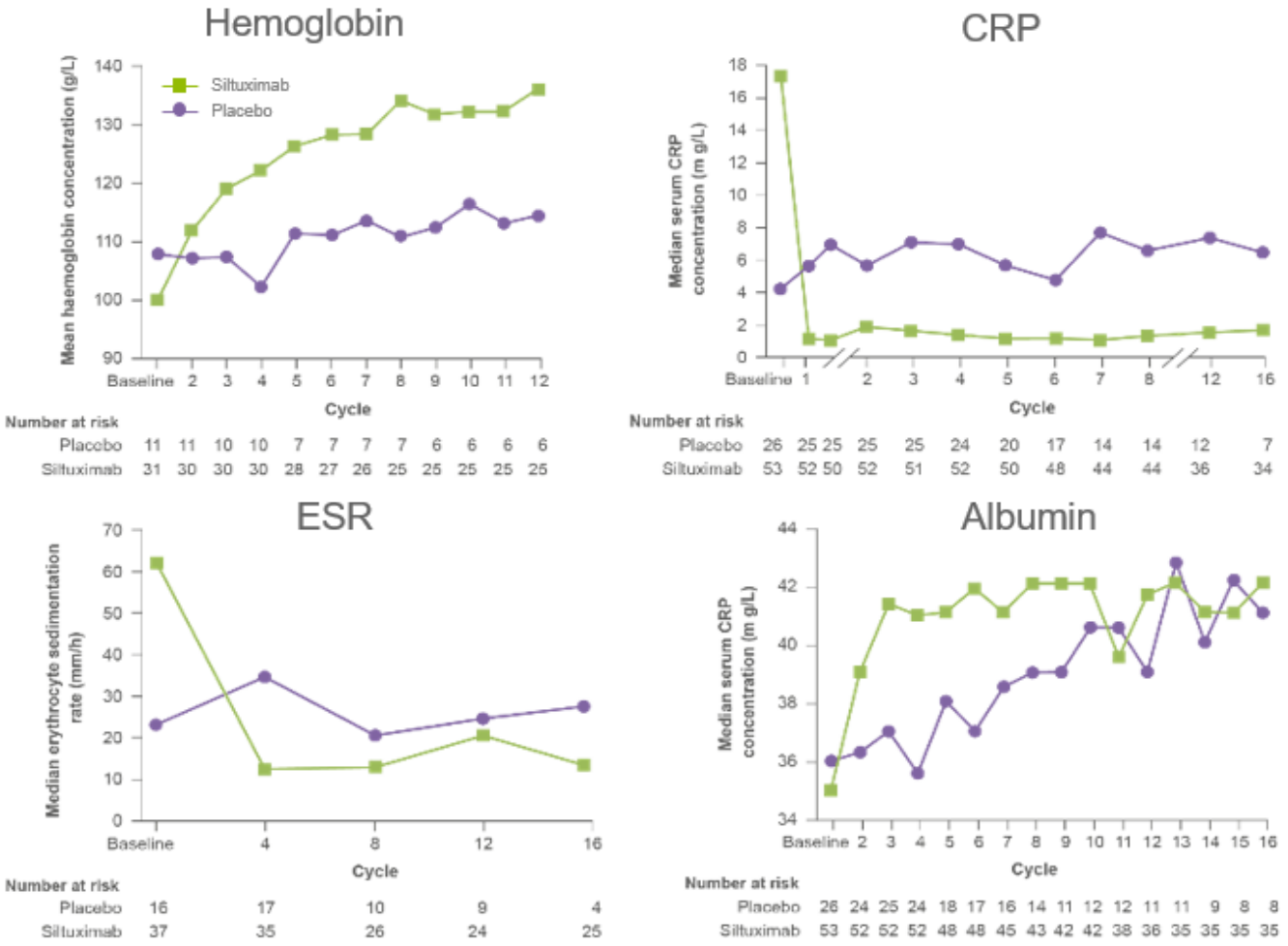


Tumor response	4%	38%	0%	51%

BSC, best supportive care; SPD, sum of product of diameters of index lesions.
Adapted from van Rhee F et al. *Lancet Oncol* 2014;15:966–974.

Changes in Disease-Related Laboratory Measures[1,2]

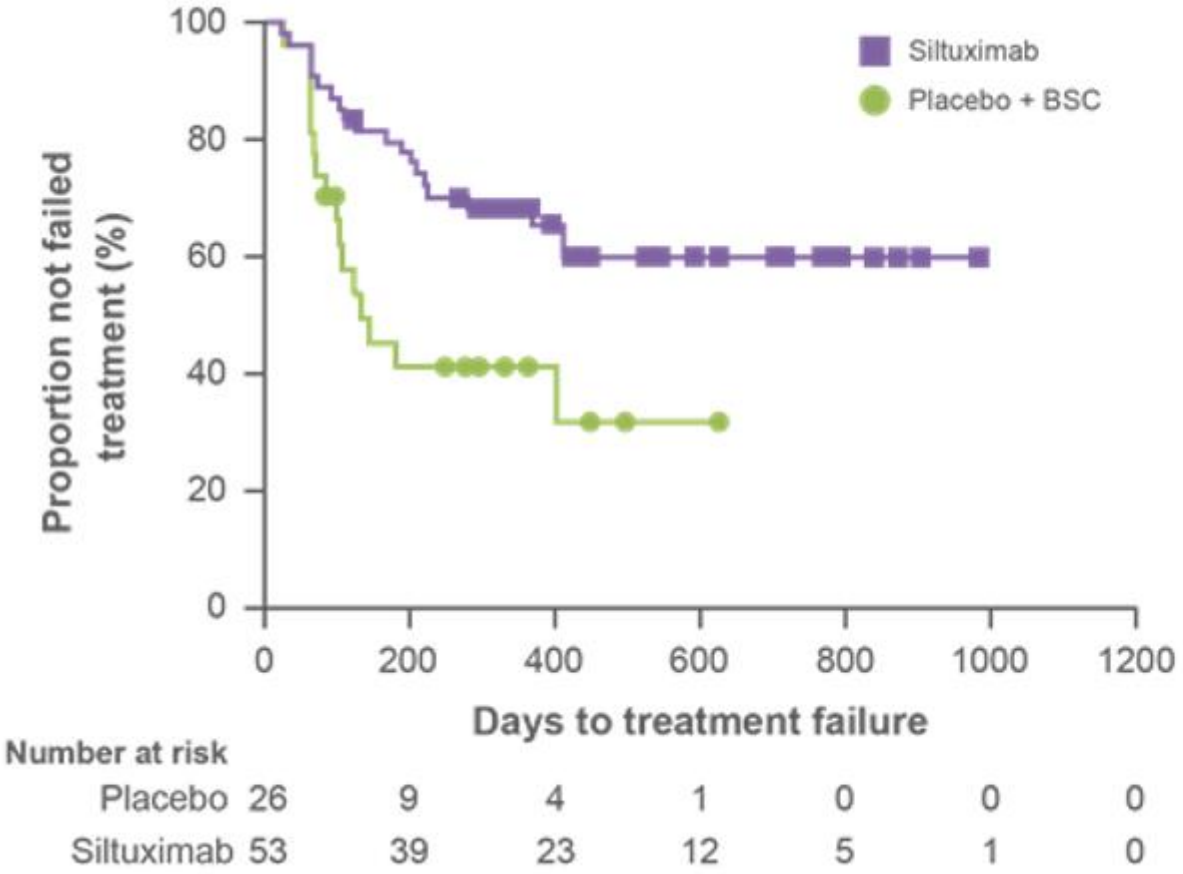
- Improvement in MCD-related laboratory abnormalities observed in siltuximab recipients:
  - Decreased CRP, ESR, and fibrinogen levels
  - Increased hemoglobin and albumin



CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCD, multicentric Castleman disease.

1. van Rhee F et al. *Lancet Oncol* 2014;15:966–974; 2. Wong RS et al. *Blood* 2013;122:505.

Time to Treatment Failure



Median TTF

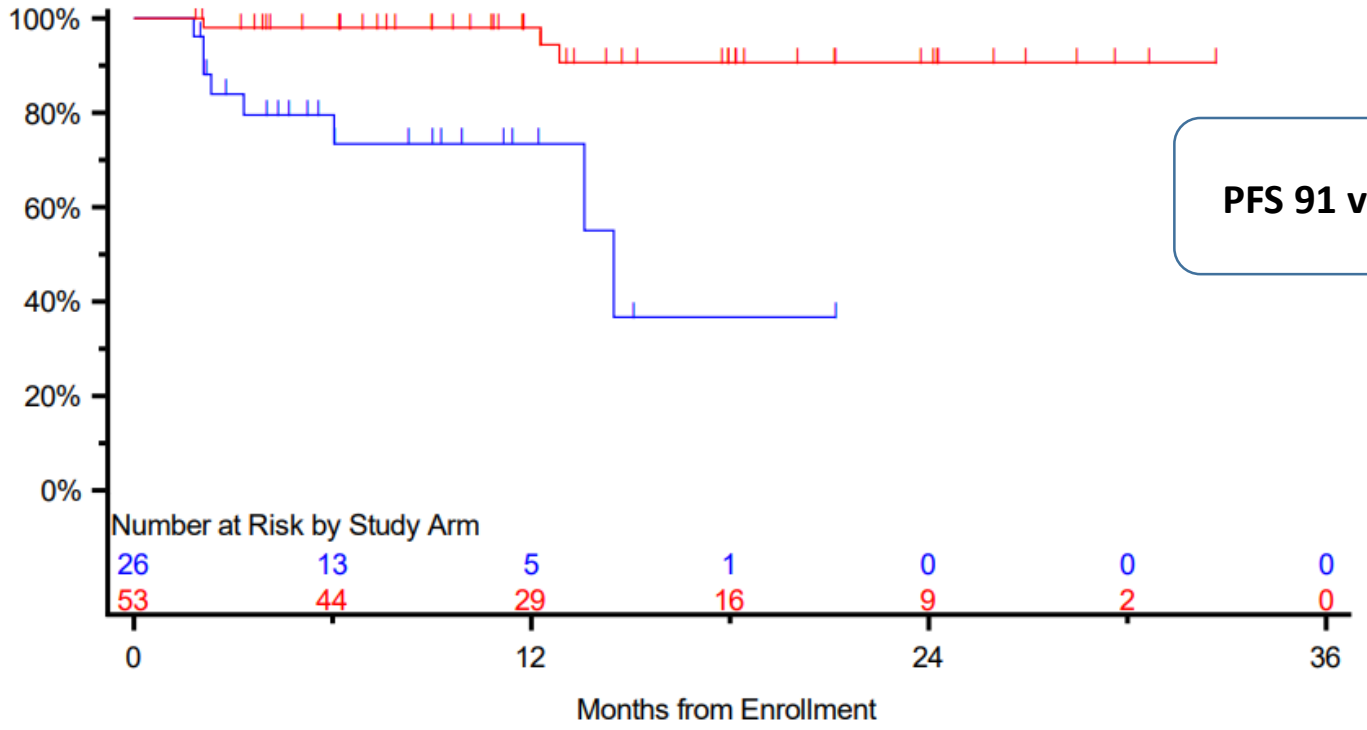
- Placebo: 134 days
- Siltuximab: not reached

HR=0.418

p=0.0084

BSC, best supportive care; HR, hazard ratio; TTF, time to treatment failure.
Adapted from van Rhee F et al. *Lancet Oncol* 2014;15:966–974.

Siltuximab is associated with superior Progression Free Survival



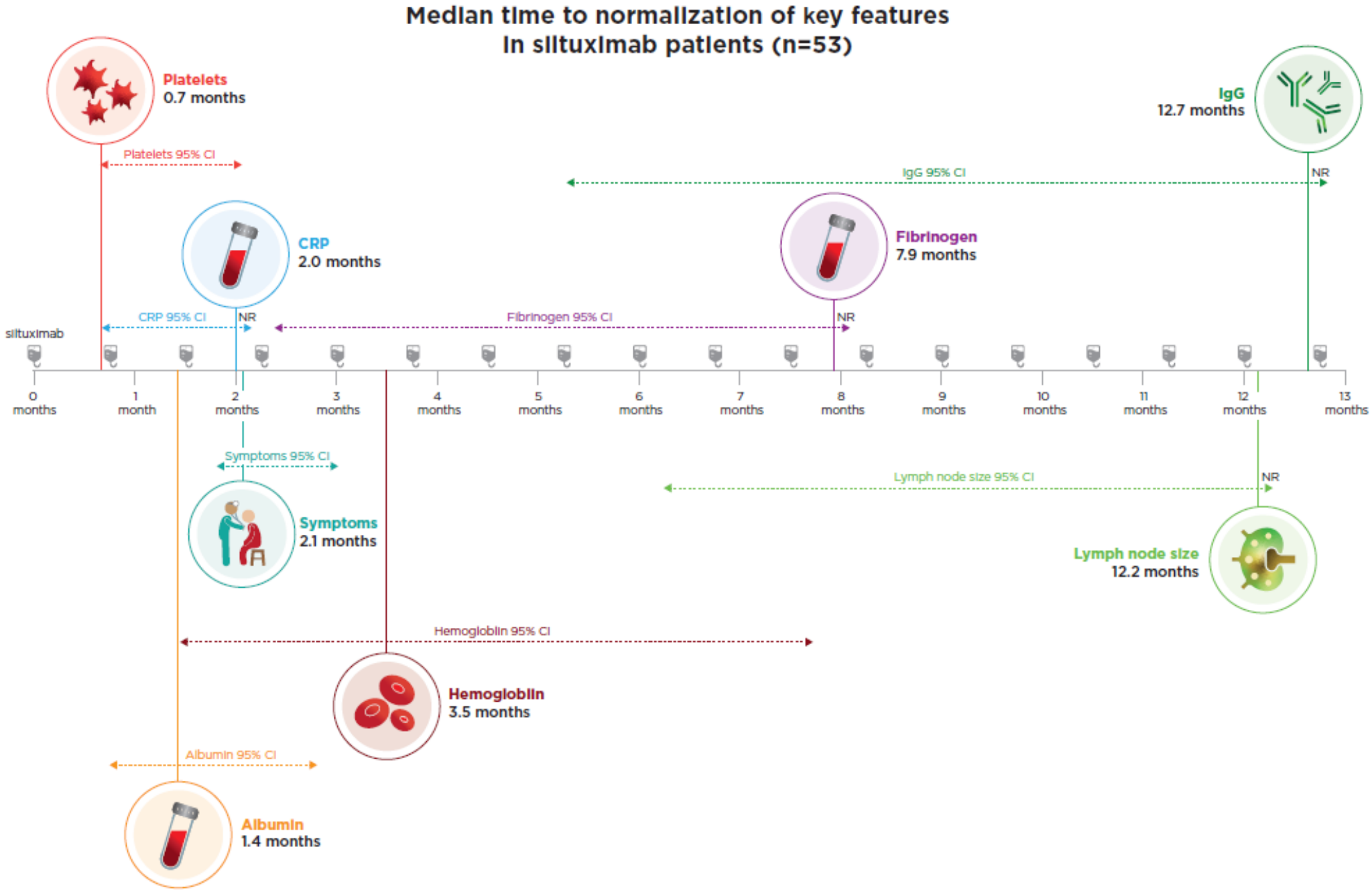
PFS 91 vs 37%, p=0.0001

	Events / N	Median in Months	24-Month Estimate
Placebo + BSC	8 / 26	14.5 (13.6, .)	37% (0, 74)
Siltuximab + BSC	3 / 53	NR	91% (80, 100)

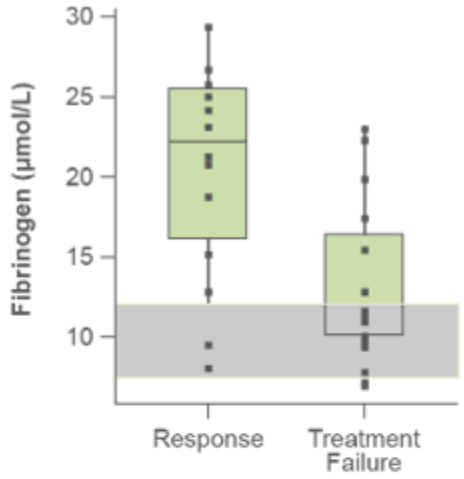
Log-rank *P* value = .0001

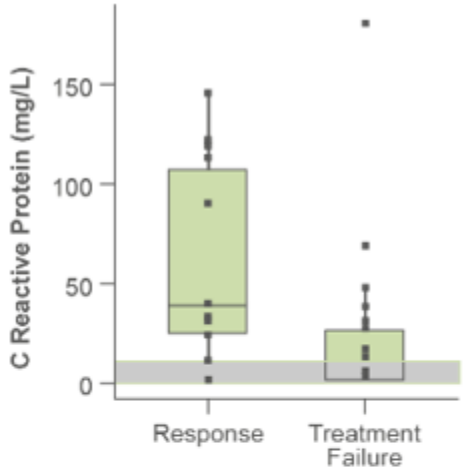
References: 1. van Rhee F, et al. EHA Abstract accepted.

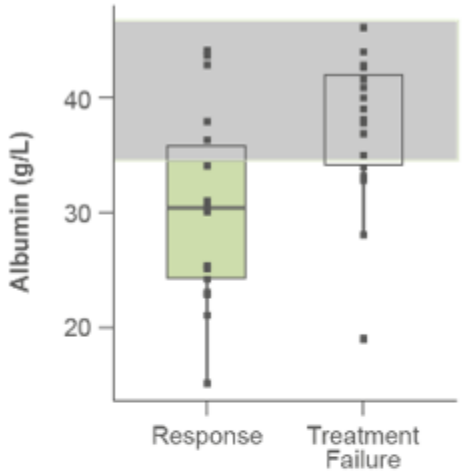
.

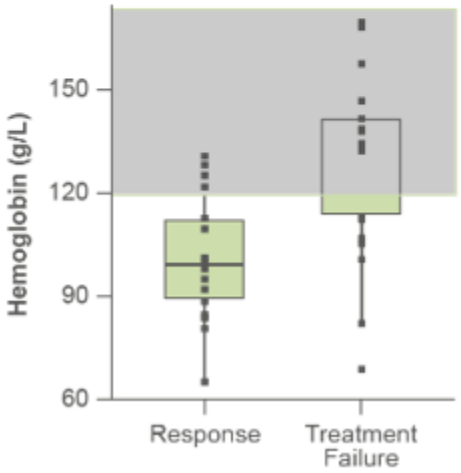

Median time to normalization of key features
in siltuximab patients (n=53)
Platelets
0.7 months
Platelets 95% CI
IgG
12.7 months
IgG 95% CI
NR
CRP
2.0 months
Fibrinogen
7.9 months
CRP 95% CI
NR
Fibrinogen 95% CI
NR
siltuximab
0 months
1 month
2 months
3 months
4 months
5 months
6 months
7 months
8 months
9 months
10 months
11 months
12 months
13 months
Symptoms 95% CI
Lymph node size 95% CI
NR
Symptoms
2.1 months
Lymph node size
12.2 months
Hemoglobin 95% CI
Hemoglobin
3.5 months
Albumin 95% CI
Albumin
1.4 months

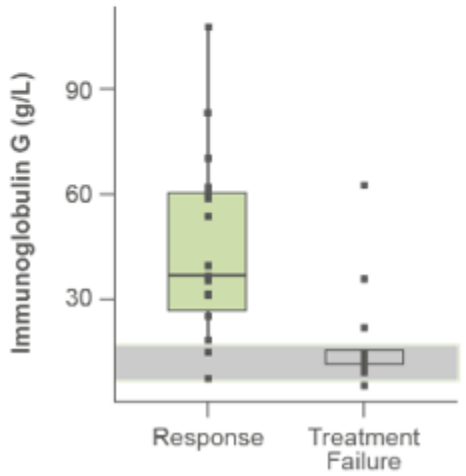
Siltuximab Responders Have A Clear Inflammatory Response, as Shown by Laboratory Markers

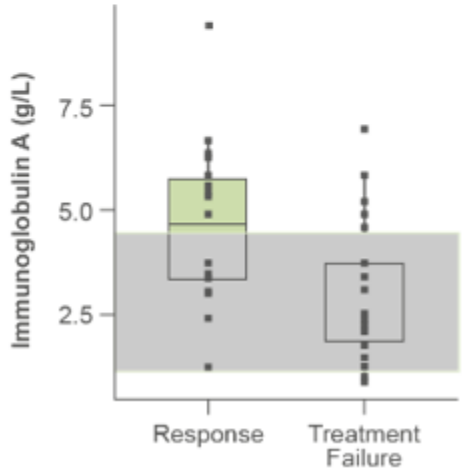






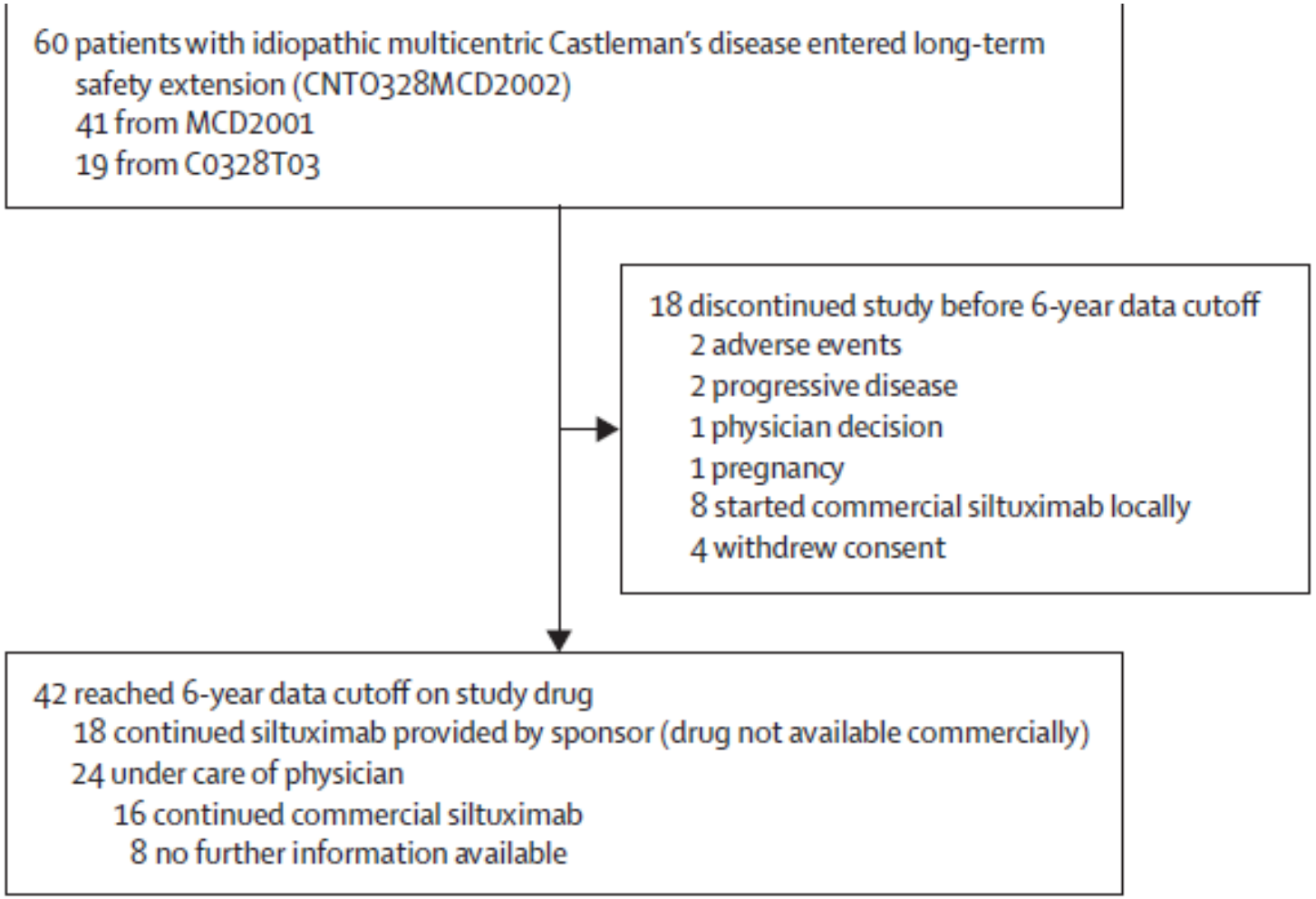






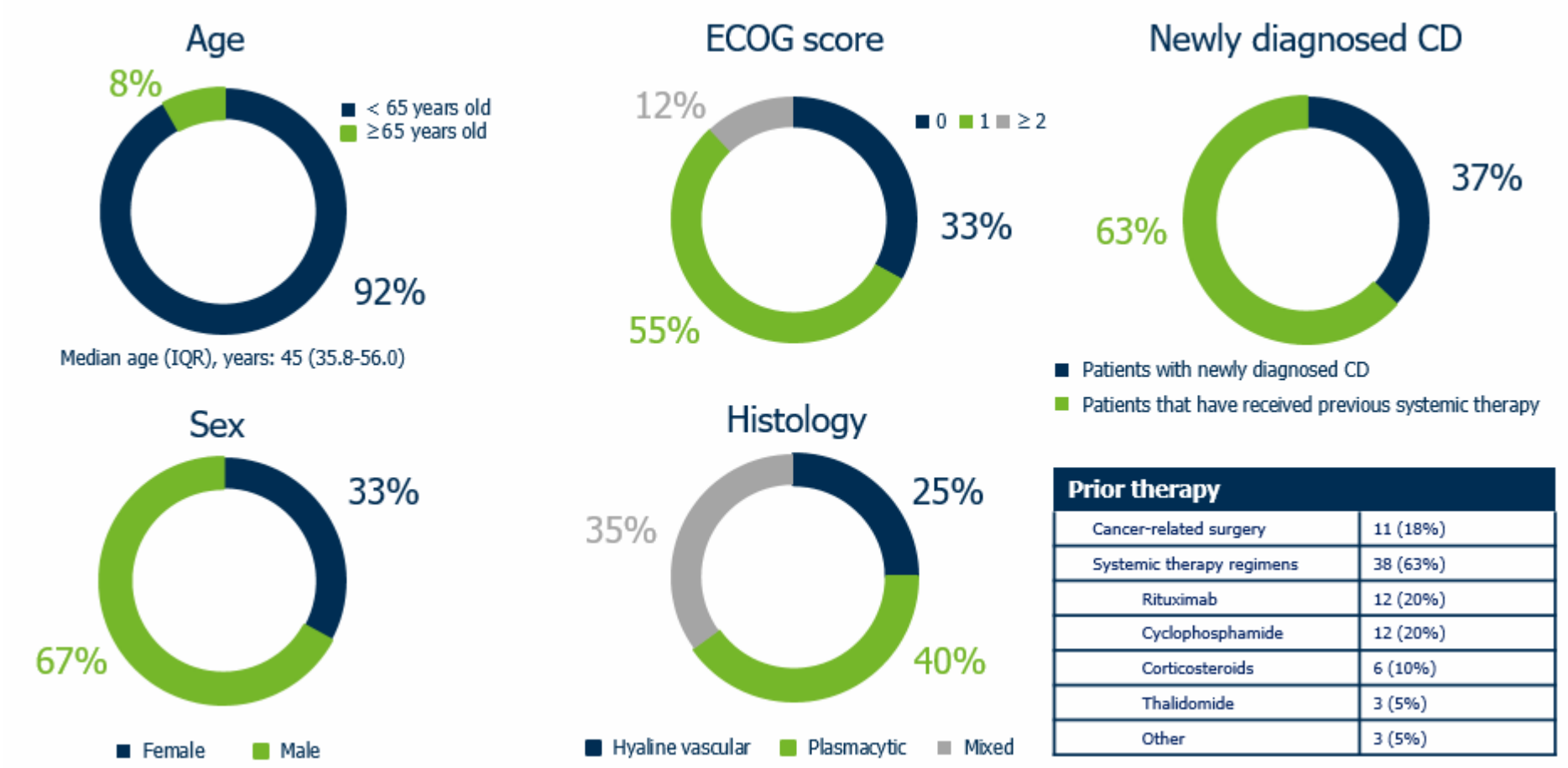
Morra DE et al. *Br J Haematol* 2019;184:232–241.

Long Term Follow-up of Phase I and Phase II Studies



References: 1. van Rhee et al. Lancet Haematology. 2020; 7(3): PE209-E217.

Demographics of long-term safety population



Prior therapy	
Cancer-related surgery	11 (18%)
Systemic therapy regimens	38 (63%)
Rituximab	12 (20%)
Cyclophosphamide	12 (20%)
Corticosteroids	6 (10%)
Thalidomide	3 (5%)
Other	3 (5%)

Median follow-up 6 years (IQR: 3.2–11.2)
Number of siltuximab infusions 86 (IQR: 61-112)
35 patients q3weekly dosing, 25patients q6weekly dosing

Long Term Follow-up Shows Durable Disease Control

Disease control was defined as a stable or better response and no worsening:[1]

- Haemoglobin concentration
- Fatigue
- Anorexia
- Fever
- Weight
- Size of largest lymph node

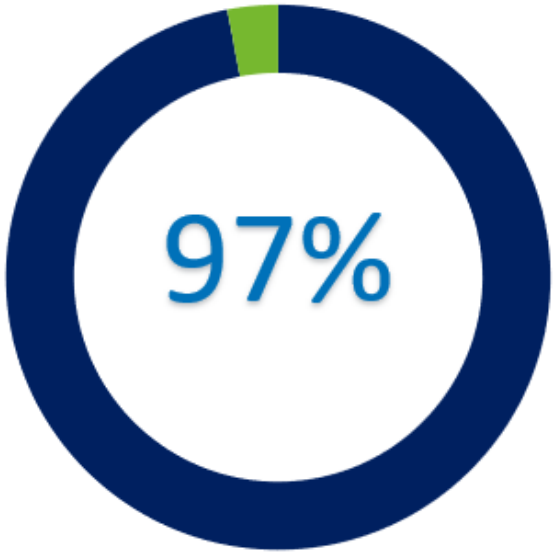
Sustained disease control, n (%)	Siltuximab (n=60)
Patients with disease control at their last on-study assessment*	58 (97)
Patients with disease control after 6 years†	42 (70)
Patients who discontinued before 6 years	18 (40)
To pursue local siltuximab	8 (13)
Due to the withdrawal of consent	4 (7)
Due to adverse events	2 (3)
Due to progressive disease	2 (3)
Due to pregnancy	1 (2)
Due to the physician's decision‡	1 (2)

*58 (97%) of 60 patients reported disease control at their last assessment; however, some of these patients discontinued before the 6-year data cutoff point.
†All patients who completed the trial up to the 6-year data cutoff had disease control; patients who discontinued before were counted as treatment failures.
‡Based on the requirement for growth factors to overcome persistent neutropenia.
van Rhee *et al. Lancet Haematology.* 2020; 7(3): PE209-E217.

Long term Follow-up Durable Disease Control

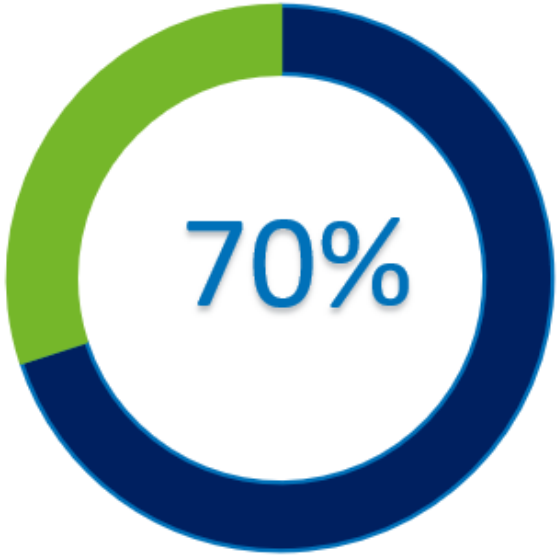
N=60/60

Of patients treated with siltuximab were alive at six years of follow up[1]



N=58/60

Of patients treated with siltuximab had disease control at their last on-study assessment[1]



N=42/60

Of patients treated with siltuximab completed the study after six years with disease control[1]

Median follow-up 6 years (range: 3.2–11.2)

Long Term Follow-up Shows Favorable Tolerability

System organ class/preferred term	Siltuximab (n=60)		
	Grade 1–2	Grade 3	Grade 4
Metabolism and nutrition disorders	19 (31.7)	5 (8.3)	0 (0)
Hypertriglyceridemia	11 (18.3)	2 (3.3)	0 (0)
Hypercholesterolemia	9 (15.0)	0 (0)	0 (0)
Hyponatremia	0 (0)	1 (1.7)	0 (0)
Hypophosphatemia	0 (0)	1 (1.7)	0 (0)
Hypocalcemia	0 (0)	1 (1.7)	0 (0)
Infections and infestations	20 (33.3)	3[a] (5.0)	0 (0)
Upper respiratory tract infections	9 (15.0)	0 (0)	0 (0)
Herpes zoster	3 (5.0)	1 (1.7)	0 (0)
Flu	0 (0)	1 (1.7)	0 (0)
Rectal abscess	0 (0)	1 (1.7)	0 (0)
Tracheobronchitis	0 (0)	1 (1.7)	0 (0)

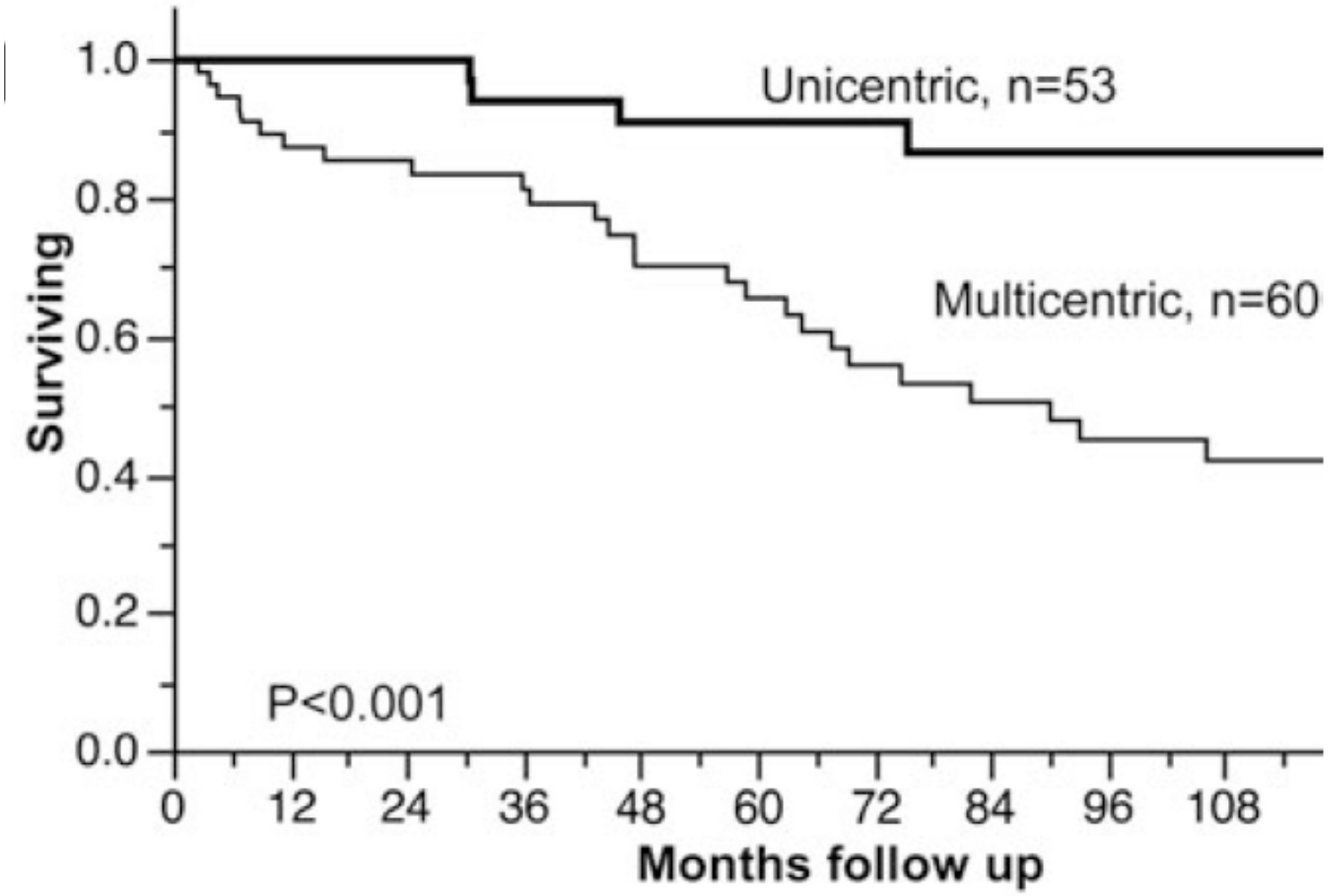
System organ class/preferred term	Siltuximab (n=60)		
	Grade 1–2	Grade 3	Grade 4
Gastrointestinal disorders	20 (33.3)	1 (1.7)	0 (0)
Diarrhea	6 (10.0)	1 (1.7)	0 (0)
Skin and subcutaneous tissue disorders	19 (31.7)	0 (0)	0 (0)
Maculopapular rash	9 (15.0)	0 (0)	0 (0)
Pruritus	8 (13.3)	0 (0)	0 (0)
Blood and lymphatic system disorders	13 (21.7)	5 (8.3)	1 (1.7)
Neutropenia	5 (8.3)	3 (5.0)	1 (1.7)
Lymphopenia	1 (1.7)	1 (1.7)	0 (0)
Polycythemia	0 (0)	1 (1.7)	0 (0)
General and administration site disorders	9 (15.0)	0 (0)	0 (0)
Fatigue	7 (11.7)	0 (0)	0 (0)

[a] Grade 3 cases of flu and tracheobronchitis occurred in the same patient.

van Rhee *et al. Lancet Haematology.* 2020; 7(3 PE209-E217.

Where does Siltuximab fit in the overall therapy for iMCD?

Historical Overall Survival of CD



Dispenzieri, et al. Am. J. Hematology. 2012;87:997-1002

Why is the Historical Outcome of iMCD Poor?

- Until recently, no diagnostic criteria or treatment guidelines[1]
- Orphan disease with an incidence of 1000-1500 patients in the USA[2,3]
- Complex, with different subtypes and varied clinical presentation[1]
- Few published systematic studies[1]
- No uniform response criteria[1]
- Lack of real-world data[1]

iMCD, idiopathic multicentric Castleman disease.

1. van Rhee F et al. *Blood* 2018;132:2115–2124; 2. van Rhee F et al. *Clin Adv Hematol Oncol* 2010;8:486–498. 3. Fajgenbaum DC et al. Blood 2017;129:1646–1657.

How to Use Available Agents?

- Corticosteroids
- Antibodies
  - Rituximab
  - Anti-IL-6 antibody therapy: tocilizumab, siltuximab
- Chemotherapy:
  - As for lymphoma: R-CHOP
  - As for myeloma: VDT (P)ACE
- Immunomodulatory agents:
  - α-interferon, ATRA, bortezomib, thalidomide, lenalidomide, cyclosporine, sirolimus, anakinra
- Stem-cell transplantation

What to use and when?

.

van Rhee F et al. *Blood* 2018;132:2115–2124.


Angela Dispenzieri
Rochester, MN
Elaine Jaffe
Bethesda, MD
Alexander Fossa
Oslo, Norway
David Fajgenbaum
Philadelphia, PA
Pier Luigi Zinzani
Bologna, Italy
Lu Zhang
Beijing, China
Kazuyuki Yoshizaki
Osaka, Japan
Thomas Uldrick
Seattle, Washington
Frits van Rhee
Little Rock, Arkansas
David Simpson
Auckland, New Zealand
OVER 800
CD RESEARCHERS
AND PHYSICIANS
IN OVER 64
COUNTRIES ALL
OVER THE WORLD
CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

CDCN Consensus Treatment Guidelines for iMCD

blood®
Special Report

International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease

Frits van Rhee,[1] Peter Voorhees,[2] Angela Dispenzieri,[3] Alexander Fossa,[4] Gordan Srkalovic,[5] Makoto Ide,[6] Nikhil Munshi,[7] Stephen Schey,[8] Matthew Streetly,[8] Sheila K. Pierson,[9] Helen L. Partridge,[9] Sudipto Mukherjee,[10] Dustin Shilling,[9] Katie Stone,[1] Amy Greenway,[1] Jason Ruth,[11] Mary Jo Lechowicz,[12] Shanmuganathan Chandrakasan,[13] Raj Jayanthan,[14] Elaine S. Jaffe,[15] Heather Leitch,[16] Naveen Pemmaraju,[17] Amy Chadburn,[18] Megan S. Lim,[19] Kojo S. Elenitoba-Johnson,[19] Vera Krymskaya,[20] Aaron Goodman,[21] Christian Hoffmann,[22,23] Pier Luigi Zinzani,[24] Simone Ferrero,[25] Louis Terriou,[26] Yasuharu Sato,[27] David Simpson,[28] Raymond Wong,[29] Jean-Francois Rossi,[30] Sunita Nasta,[31] Kazuyuki Yoshizaki,[32] Razelle Kurzrock,[33] Thomas S. Uldrick,[34] Corey Casper,[35] Eric Oksenhendler,[36] and David C. Fajgenbaum[9]

van Rhee F *et al. Blood* 2018; 13: 2115-2124.

blood® Special Report

International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease

Frits van Rhee,[1] Peter Voorhees,[2] Angela Dispenzieri,[3] Alexander Fossså,[4] Gordan Srkalovic,[5] Makoto Ide,[6] Nikhil Munshi,[7] Stephen Schey,[8] Matthew Streetly,[8] Sheila K. Pierson,[9] Helen L. Partridge,[9] Sudipto Mukherjee,[10] Dustin Shilling,[9] Katie Stone,[1] Amy Greenway,[1] Jason Ruth,[11] Mary Jo Lechowicz,[12] Shanmuganathan Chandrakasan,[13] Raj Jayanthan,[14] Elaine S. Jaffe,[15] Heather Leitch,[16] Naveen Pemmaraju,[17] Amy Chadburn,[18] Megan S. Lim,[19] Kojo S. Elenitoba-Johnson,[19] Vera Krymskaya,[20] Aaron Goodman,[21] Christian Hoffmann,[22] Pier Luigi Zinzani,[23] Simone Ferrero,[24] Louis Terriou,[25] Yasuharu Sato,[26] David Simpson,[27] Raymond Wong,[28] Jean-Francois Rossi,[29] Sunita Nasta,[30] Kazuyuki Yoshizaki,[31] Razelle Kurzrock,[32] Thomas S. Uldrick,[33] Corey Casper,[34] Eric Oksenhendler,[35] and David C. Fajgenbaum[9]

- Review of clinical trials and published literature
- Data from 344 cases reviewed by expert panel
- Recommend stratifying treatment by severity

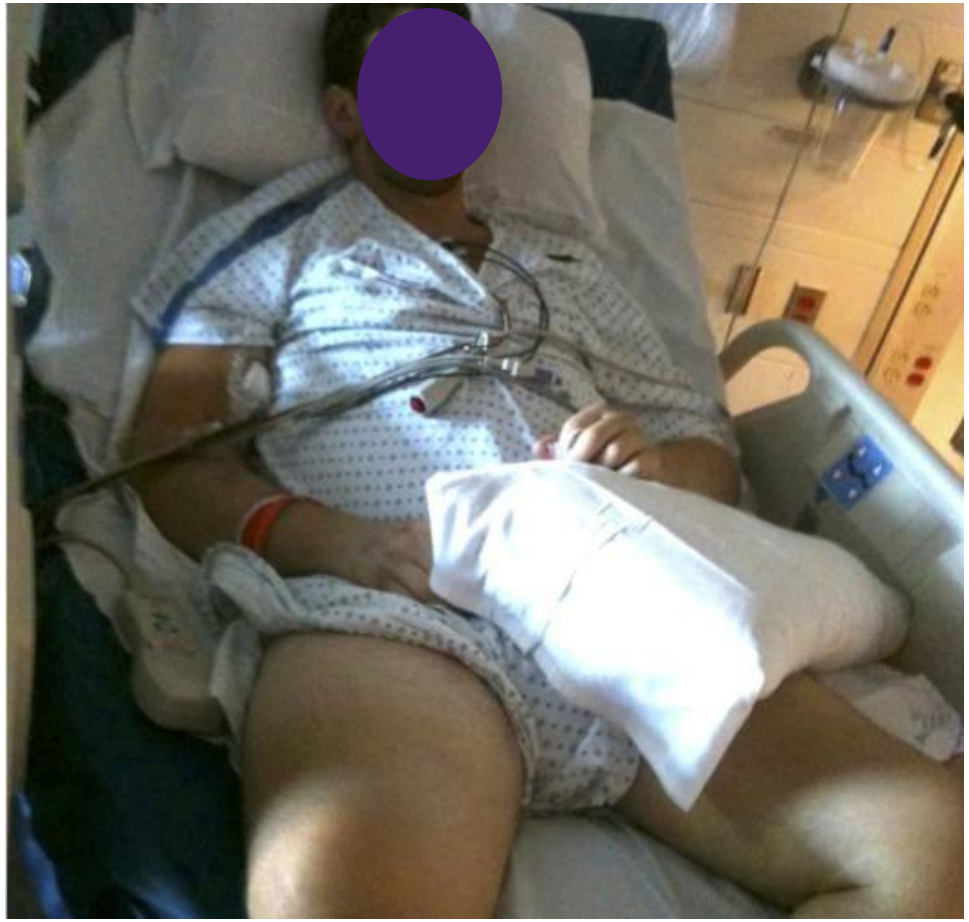
Severe iMCD

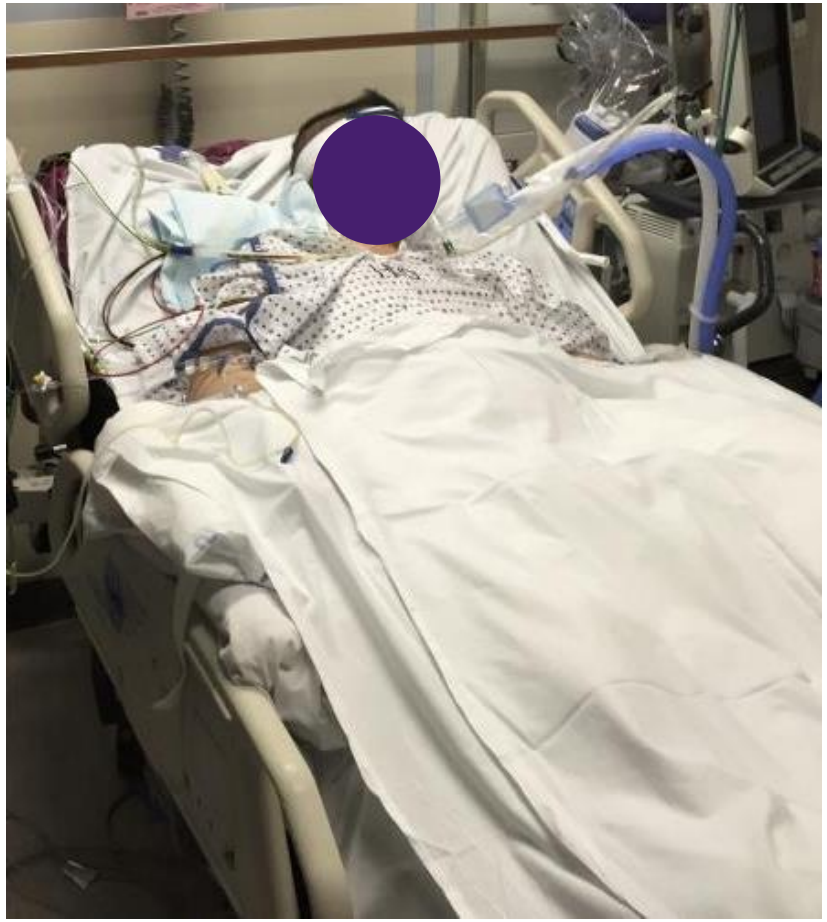
- ECOG ≥ 2
- Stage IV renal dysfunction (eGFR < 30; Creatinine >3.0)
- Anasarca and/or ascites and/or pleural/pericardial effusion (effects of hypercytokinemia/low albumin)
- Hemoglobin ≤ 8.0g/dL
- Pulmonary involvement /interstitial pneumonitis w/dyspnea

CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

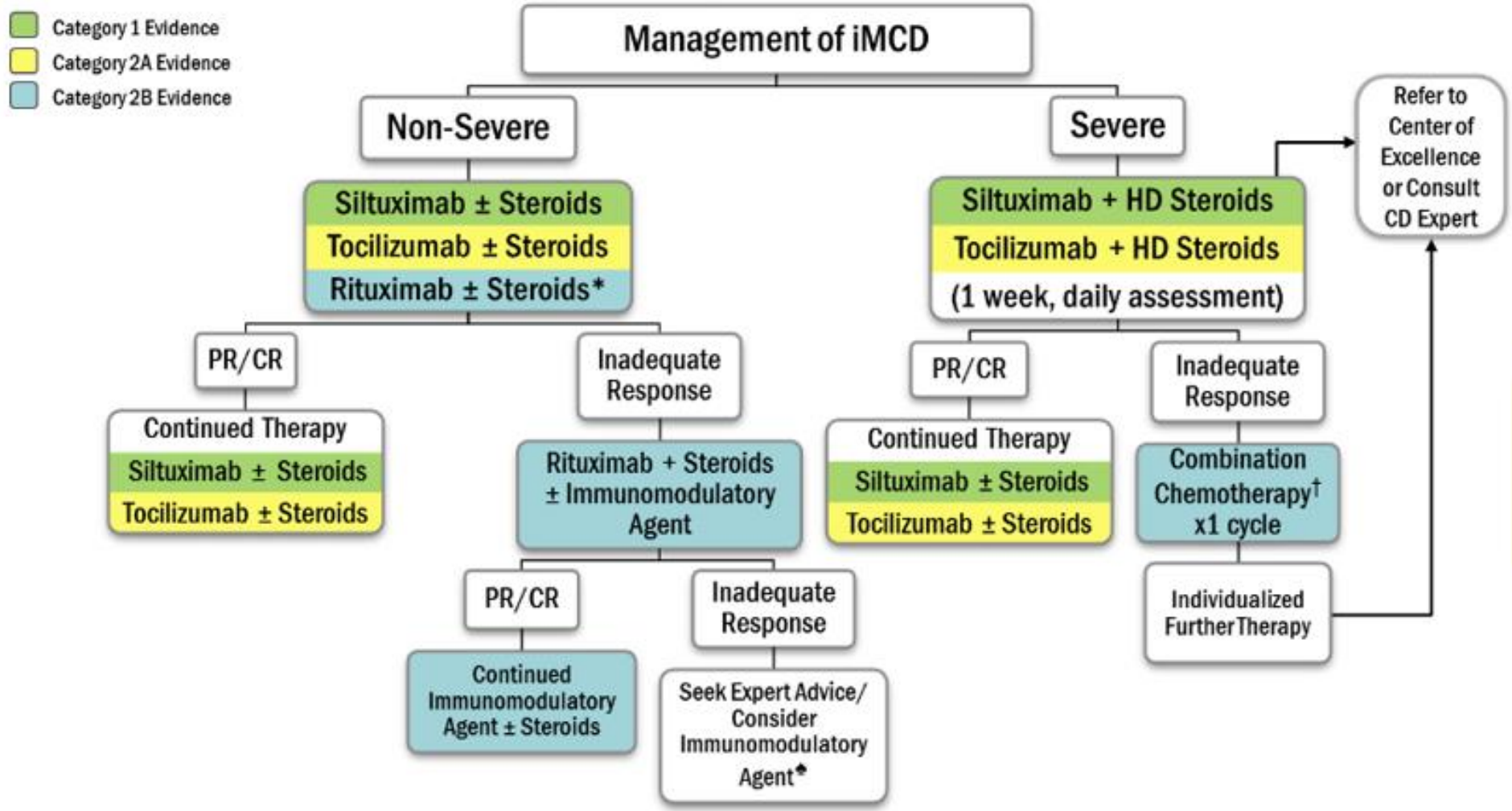
van Rhee F *et al. Blood* 2018; 13: 2115-2124.

Who has severe iMCD?





iMCD, idiopathic multicentric Castleman disease.



If mAbs are not available, consider thalidomide, cyclophosphamide and prednisone∞

Zhang et al. *Blood* 2019;133:1720–1728. Adapted from van Rhee F et al. *Blood* 2018;132:2115–2124

Conclusions

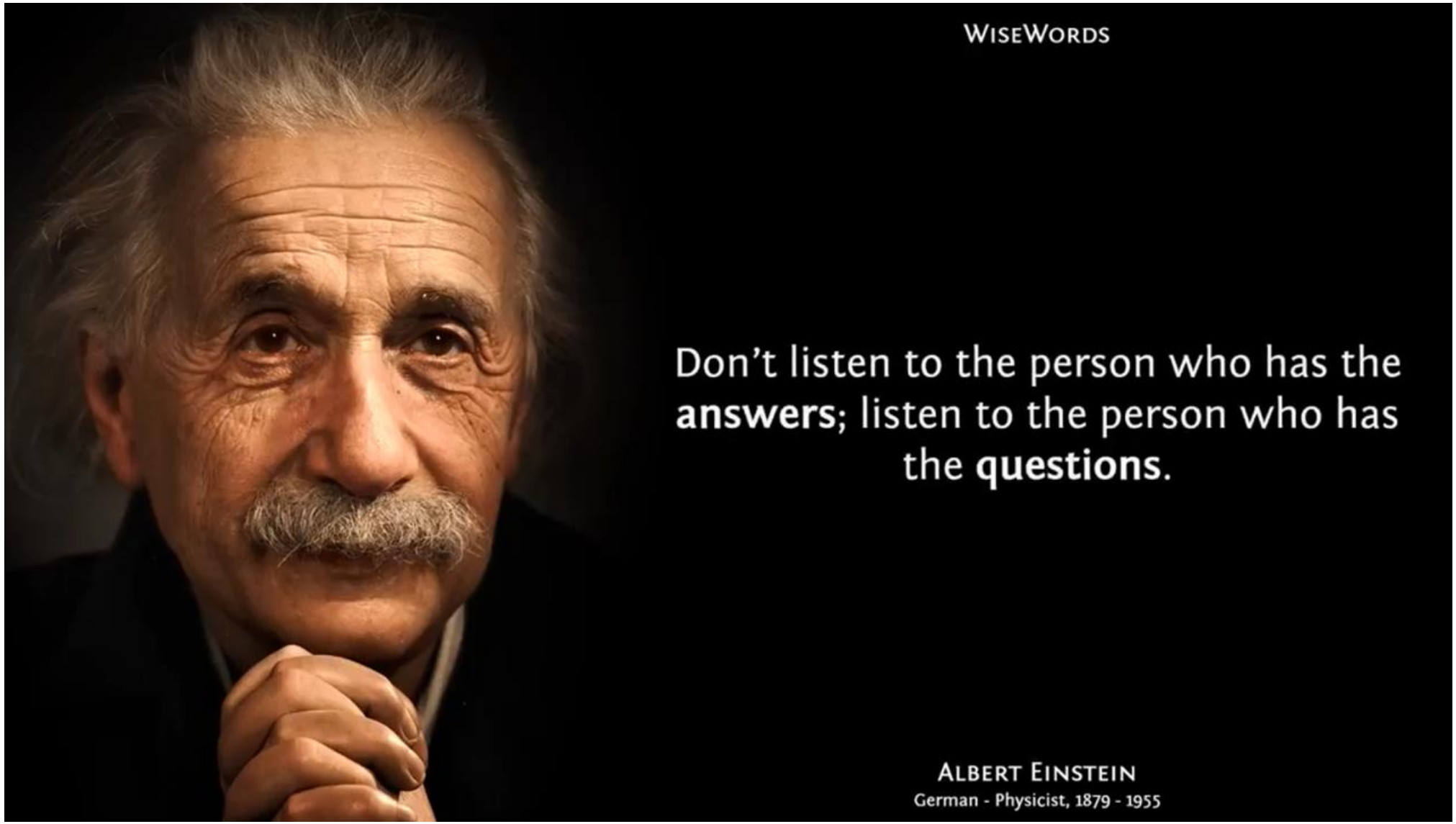
- **Siltuximab, supported by best evidence, is the preferred first-line therapy (Category 1 evidence)[1]**
- **Long term administration is safe and effective; no cumulative toxicity**
- **Symptomatic and laboratory responses occur rapidly with siltuximab; Involution of lymph nodes is slow**

CRP, C-reactive protein; IL-6, interleukin 6.

1. van Rhee F et al. *Blood* 2018;132:2115–2124; 2. van Rhee F et al. *Lancet Oncol* 2014;15:966–974.

Clinical Practice Points

- **Infusion well-tolerated**
- **No opportunistic infections when used as sole agent**
- **Yearly lipid profile**
- **Mild thrombocytopenia may occur (platelets:100,000-150,000)**
- **Occasional patient with mild fleeting rash**
- **Has the potential for masking acute phase reaction**
- **Do not measure IL6 levels post siltuximab**


WiseWords
Don’t listen to the person who has the **answers**; listen to the person who has the **questions**.
Albert Einstein
German - Physicist, 1879 - 1955