
Lymphoma · Leukemia
& Myeloma Congress
October 13–16, 2026
New York City
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Hiding in Plain Sight: Sharpening Recognition, Diagnosis and Treatment of Idiopathic Multicentric Castleman Disease and Cold Agglutinin Disease in Community Practice

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This session is supported by an independent educational grant from Recordati.

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Disclosures

- **Richard R. Furman, MD:** Advisory Board—Abbvie, AstraZeneca, BeOne, Foundation Medicine; consultant—Abbvie, AstraZeneca, BeOne; data safety monitoring committee—BeOne; speaker—BeOne, Secura Bio, Inc.
- **Frits van Rhee, MD, PhD, MRCP(UK), FRCPath:** Advisory Board/consultant: Bristol Myers Squibb, Castleman Disease Collaborative Network, EUSA Pharma/Recordati, Sanofi, Kite, GlaxoSmithKline, Janssen Pharmaceuticals, Myeloma360

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Learning Objectives

- Differentiate iMCD from malignant, infectious, and autoimmune mimics by applying established consensus diagnostic criteria and relevant biomarker evaluation
- Formulate evidence-based, severity-stratified frontline treatment plans for iMCD utilizing targeted anti-IL-6 therapy
- Evaluate the mechanisms of action, onset of action, and durability of response of classical complement inhibition versus B-cell-directed therapy in symptomatic CAD
- Individualize therapeutic selection for CAD based on patient-specific factors including severity of anemia, cold-induced symptoms, cardiovascular risk, and clonal burden

iMCD = idiopathic multicentric Castleman disease; CAD = cold agglutinin disease.

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Sharpening Recognition, Diagnosis, and Treatment for Cold Agglutinin Disease

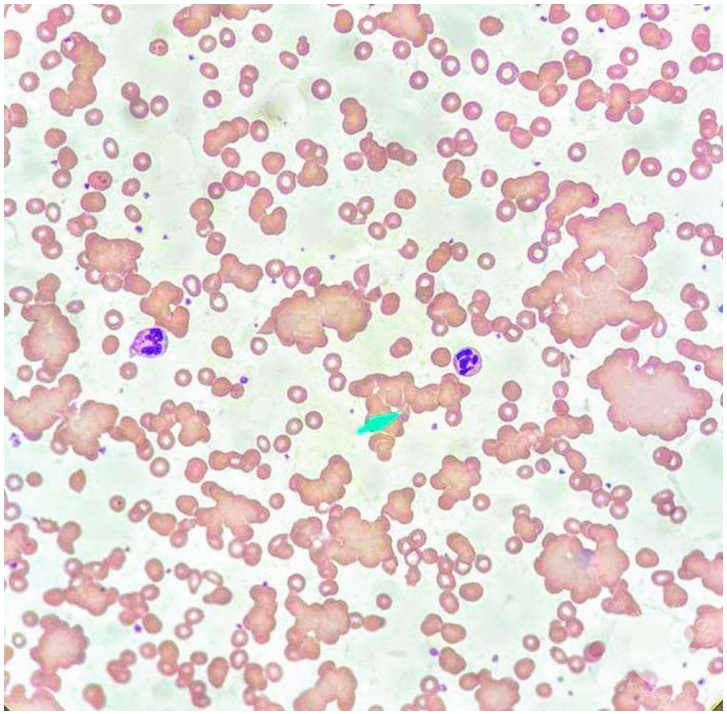
Richard R. Furman, MD

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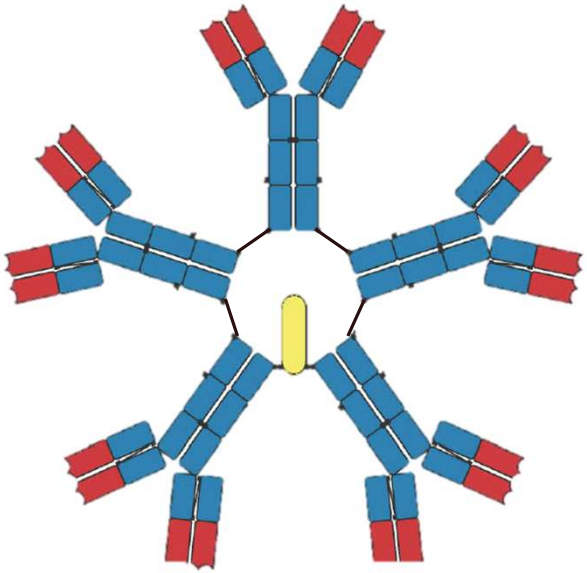
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Cold Agglutinin Disease

Peripheral Blood Smear



IgM



Kaur J [imagebank.hematology.org]. Last updated August 17, 2020. https://imagebank.hematology.org/imageset/60245/a-unique-case-of-transient-cold-agglutinins-and-acute-anemia-in-a-patient-with-covid19.

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Cold Agglutinin Disease: Epidemiology

- Incidence: 15% of AIHA; 1 per million overall
- Median age = 70; M:F = 0.56
- Clinical presentation associated with seasonal variation
- Ethnic and geographic bias (related?)

	Population, 10^6	Prevalence, cases/10^6	Incidence, cases/10^6	Ave temp, °C
Norway	**5.32**	**20.5**	**1.9**	**6.0**
Lombardy, Italy	**7.0**	**5.0**	**0.48**	**13.1**

AIHA = autoimmune hemolytic anemia.
Berentsen S, Vos JMI. *Br J Haematol*. 2026;209(2):444-447.

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Cold Agglutinin Disease: Clinical Presentation

- Agglutination on CBC
  - Hg accurate, but results cancelled due to abnormal indices
  - Spun Hct reported
- Clinical symptoms only present for thermal amplitude >30°C
- Presentation
  - Median Hg=9.2 g/dL
  - Degree of anemia
    - Severe (Hg<8.0 g/dL): 27%
    - Moderate (Hg 8.0—10.0 g/dL): 37%
    - Mild (Hg 10.0 g/dL—LLN): 24%
    - Compensated hemolysis: 12%
  - Acrocyanosis/Raynaud-like symptoms: 52%
- If thermal amplitude <30°C: no symptoms
- Reticulocyte count = best indicator of in vivo activity of CA (hemolysis)

CBC = complete blood count; LLN = lower limit of normal.

Berentsen S, Vos JMI. *Br J Haematol*. 2026;209(2):444-447.

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Kurklinsky AK, et al. *Vasc Med.* 2011;16(4):288-301.

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CAD: Complications

Associated with slight increased risk of venous thrombosis

- Etiology
  - Hemolysis vs agglutination?
  - IgM complement activation leading to vessel injury
  - Increased inflammation
- 12.9% of patients had thromboembolic events
  - 6% venous thrombotic events (PE—57%)
  - 10% arterial thromboembolic events (CVA—50%, MI—42%, peripheral—8%)
- 10-year retrospective matched analysis
  - CAD: 29.6% vs non-CAD: 17.6%; HR=2.34

Ig = immunoglobulin; PE = pulmonary embolism; CVA = cerebrovascular accident; MI = myocardial infarction.
Berentsen S, et al. *Blood*. 2020;136(4):480-488. Broome CM, et al. *Res Pract Thromb Haemost*. 2020;4(4):628-635.

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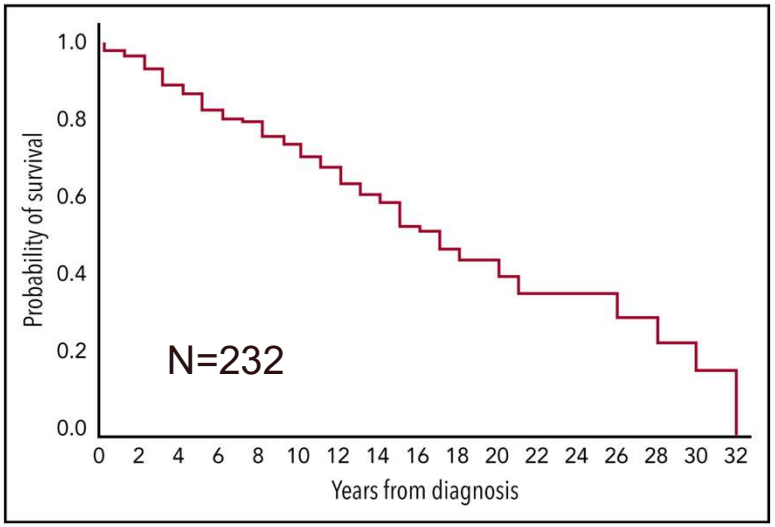
CAD: Complications (Cont.)

- DLBCL: 3.4%
- No iron overload
- Hemolytic crises
  - Complement acute phase reactant
  - Febrile episodes

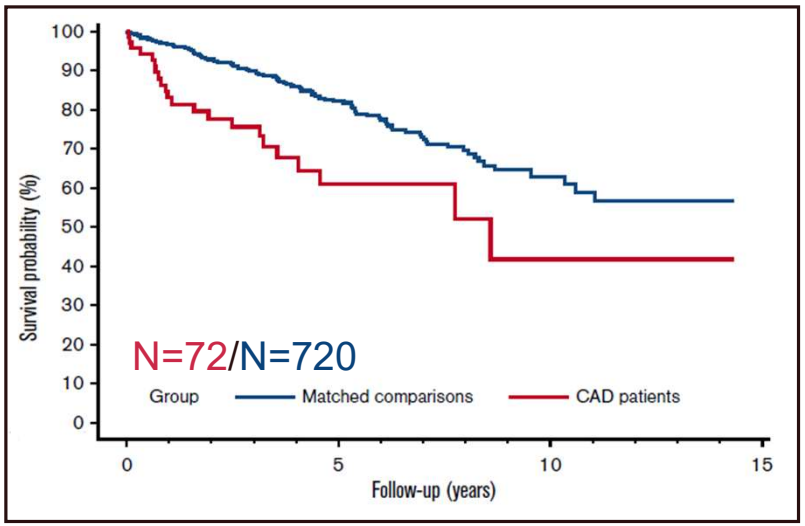
DLBCL = diffuse large B-cell lymphoma.
Berentsen S, et al. *Blood.* 2020;136(4):480-488.

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CAD: Survival from Diagnosis



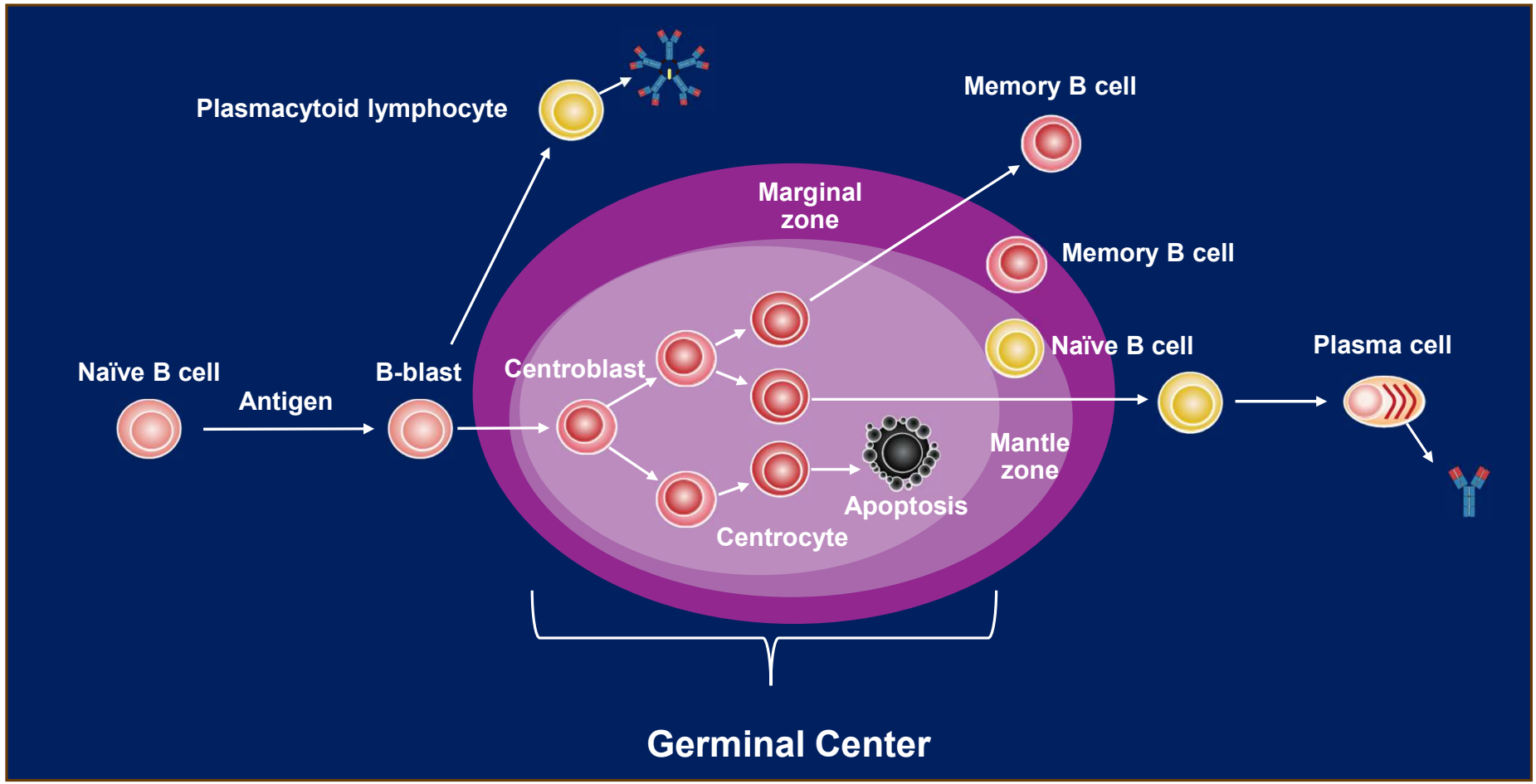
- Median OS = 16 years
- Expected OS = 18.4 years (registry)
- 5-year OS = 83%
- Cause of death: CAD/LPD: 11% (8)
- No higher death rate in first 5 years



- Median OS = 8.5 years
- HR for death = 1.84 (1.10-3.06)
- Highest mortality in first 5 years
  - Year 1: 17% vs 3%
  - Year 5: 39% vs 18%

OS = overall survival; LPD = lymphoproliferative disease.

Berentsen S, et al. *Blood*. 2020;136(4):480-488. Bylsma LC, et al. *Blood Adv*. 2019;3(20):2980-2985.



Küppers R. *Nat Rev Cancer*. 2005;5(4):251-262.

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What Makes a Cold Agglutinin?

- IgM kappa light chain
- IGH: V4-34 (mutated) against I/i antigens
- Poorly specific
- Polyreactive
- Complement activating (compensation of IgM's poor specificity)

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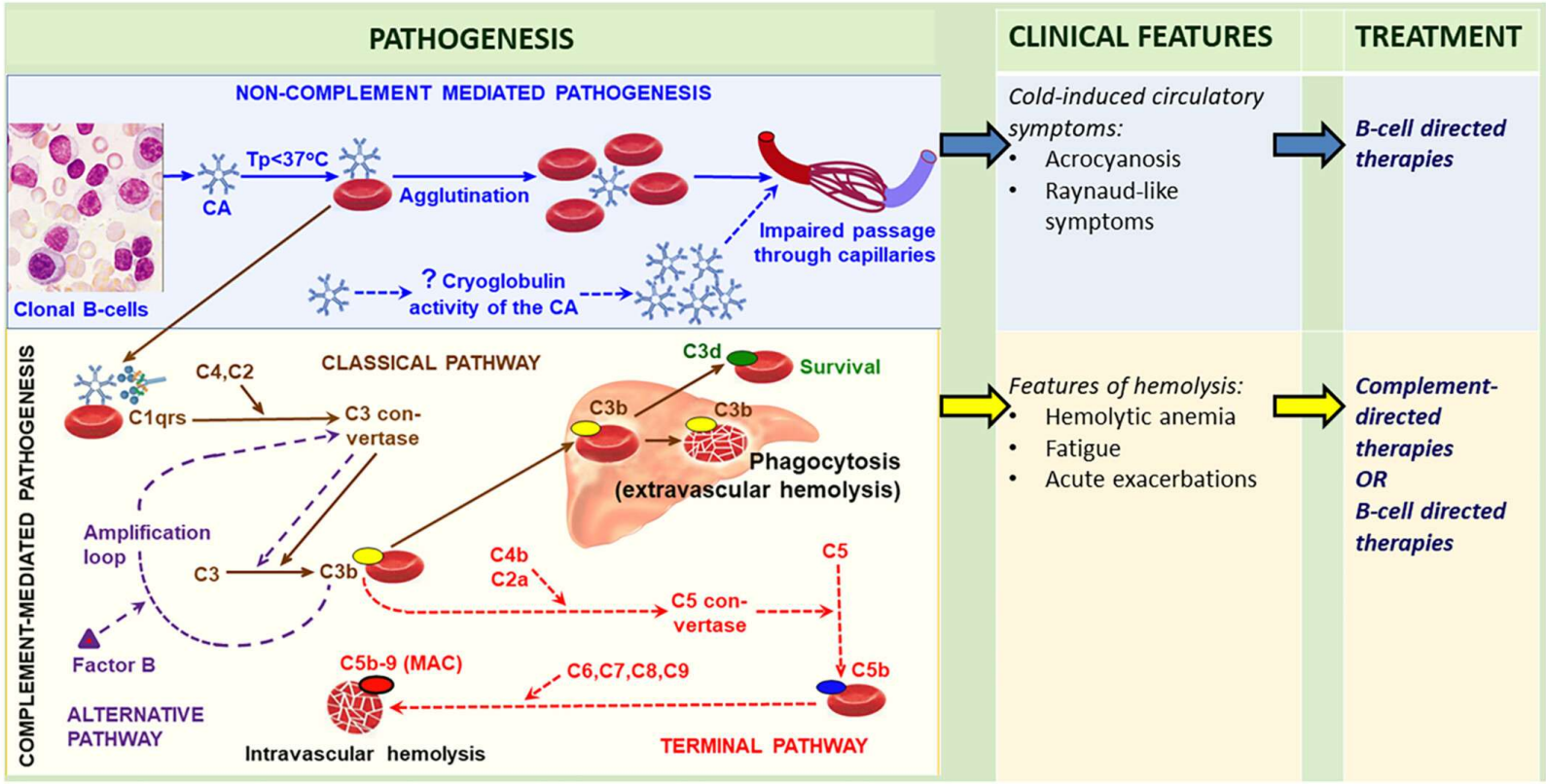
CAD vs CAS

- CAD: hemolytic anemia due to a complement-fixing, agglutinating IgM
- CAS: secondary to underlying infection, autoimmune disease, or over B-cell malignancy
- MYD88 typically negative in CAD
- Cold agglutinin almost always monoclonal
- So, is there a difference?

CAS = cold agglutinin syndrome

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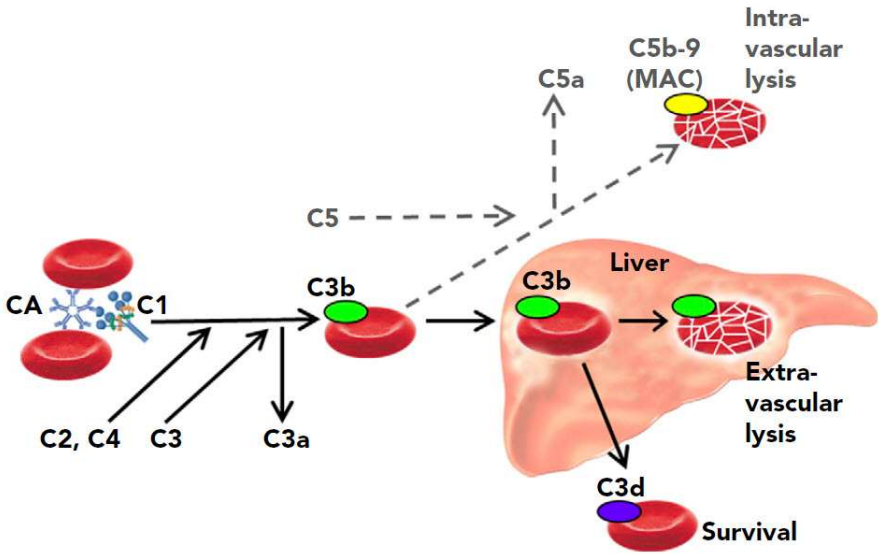
Pathogenesis: Complement vs Non-Complement



Berentsen S, Vos JMI. *Br J Haematol*. 2026;209(2):444-447.

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Pathogenesis: Complement vs Non-Complement



- Hemolysis primarily extravascular
- Complement deposition results in spherocytes
- Depleted haptoglobin secondary to intravascular hemolysis of spherocytes
- CA titer determined at 4°C
- Physiological active CA needs to be >30°C

Berentsen S, Vos JMI. *Br J Haematol*. 2026;209(2):444-447.

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CAD: Laboratory Findings

Parameter	Median	Range	Ref Range	Comments
C3, g/L	0.81	0.22-1.35	0.67-1.29	<LLN in 24%
C4, g/L	0.07	0-4.0	0.13-0.32	<LLN in 72%
CRP, mg/L	2.0	0.1-191	<5.0	>ULN in 24%
Folate, nmol/L	15.0	2.0-54	>5.0	>5 in 97%
Ferritin, ug/L	381	17-14750	20-200	>200 in 70.5%; >1000 in 21%
Transferrin sat, %	40	5.0-71	15-50	>50% in 35%

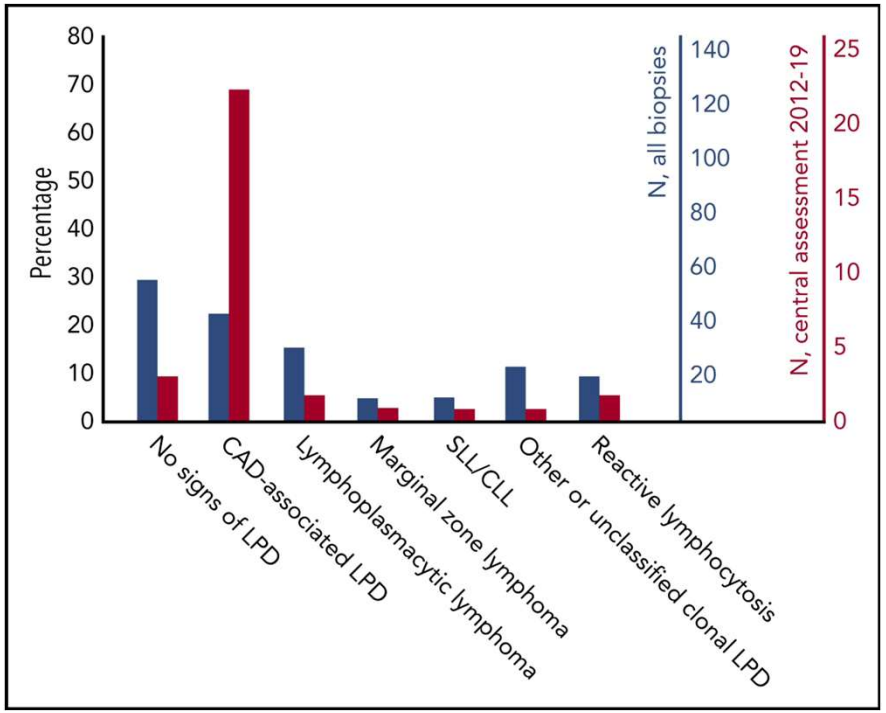
C2 levels most sensitive, but given lability, unreliable

CRP = C-reactive protein; ULN = upper limit of normal.
Berentsen S, et al. *Blood.* 2020;136(4):480-488.

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Bone Marrow Biopsy Findings: CAD/CAS

Central review greatly increased identification of LPD



Blue bars: all biopsies
Red bars: central review

SLL = small lymphocytic lymphoma; CLL = chronic lymphocytic leukemia.
Berentsen S, et al. *Blood.* 2020;136(4):480-488.

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Treatment

B-Cell-Directed Therapy

- Remitting
- Slow onset
- More toxic

Complement-Directed Therapy

- Non-remitting; need to be continued
- Rapid onset
- Non-toxic except for infectious risk
- No impact on circulatory symptoms (may even worsen)

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Treatment

B-Cell-Directed Therapy

- Rituximab
  - ORR: 45-54%
- Bendamustine + rituximab
  - ORR: 71%; 91% PFS at 32 months
- Fludarabine + rituximab
  - ORR: 76%, DOR > 66 months
- Bortezomib (ORR: 31.6%)
- BTK inhibitors (ORR: 13/15)

Complement-Directed Therapy

- Eculizumab (ORR: 7/13)
- Sutimlimab
- Pegcetacoplan (ORR: 77%)
- Iptacopan

ORR = objective response rate; PFS = progression-free survival; DOR = duration of response.

Berentsen S, et al. *Blood*. 2004;103(8):2925-2928. Schöllkopf C, et al. *Leuk Lymphoma*. 2006;47(2):253-260. Rossi G, et al. *Blood*. 2018;132(5):547-550. Berentsen S, et al. *Blood*. 2010;116(17):3180-3184. Berentsen S, et al. *Blood*. 2017;130(4):537-541. Jalink M, et al. *Blood*. 2021;138(20):2002-2005. Röth A, et al. *Blood Adv*. 2018;2(19):2543-2549. Roman E, et al. *Blood*. 2025;145(4):397-408.

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Sutimlimab (BIVV009, TNT009)

- Humanized IgG4 mAb again C1s, depletes serine protease activity
- Only inhibits the classical pathway, not lectin or alternative pathways
- C4 levels used in studies to assess efficacy
- Weight-based dosing
  - <75 kg: 6,500 mg/kg q2 weeks (after weekly x 2)
  - ≥75 kg: 7,500 mg/kg q2 weeks (after weekly x 2)
- Pivotal studies
  - CARDINAL
  - CADENZA

mAb = monoclonal antibodies.

Röth A, et al. *N Engl J Med*. 2021;384(14):1323-1334.

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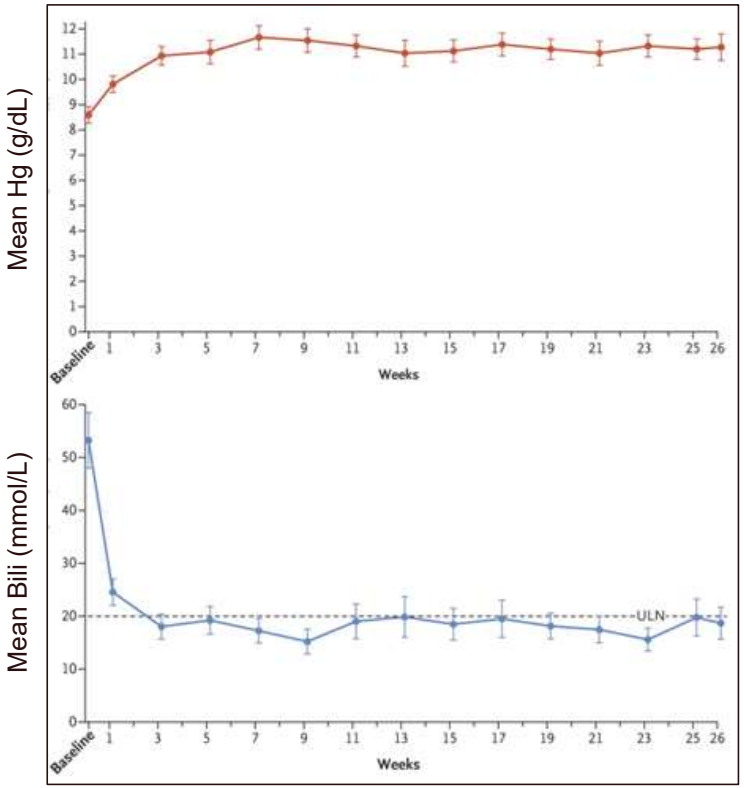
Sutimlimab: CARDINAL Study

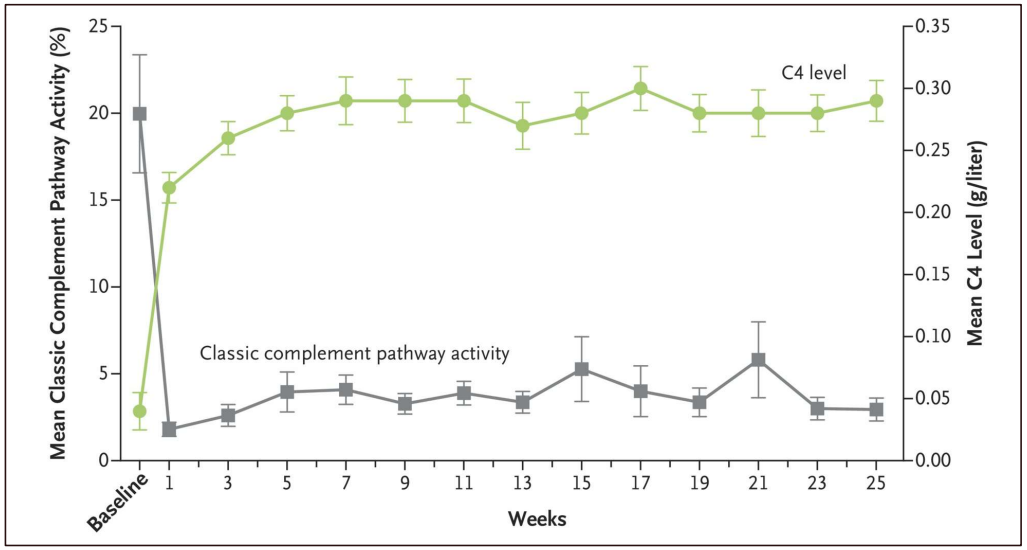
- 26-week multicenter, open-label, phase 2 study (N=24, 16 sites)
- Key eligibility
  - CAD not secondary to infection, rheumatologic disease, or hematologic malignancy
  - RBC transfusion within 6 months of enrollment
  - CAD titer of 1:64 or greater measured at 4°C
  - No overt malignant disease
  - Hg ≤10 g/dL and bilirubin >ULN
  - CAD symptom: symptomatic anemia, acrocyanosis, Raynaud's, hemoglobinuria, circulatory symptoms, major vascular event
- Primary endpoint
  - Hg >12 g/dl at assessment (mean value weeks 23, 25, and 26)
  - Hg increase of >2 g/dL from baseline

RBC = red blood cell.
Röth A, et al. *N Engl J Med*. 2021;384(14):1323-1334.

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CARDINAL Study: Results





Röth A, et al. *N Engl J Med*. 2021;384(14):1323-1334.

CARDINAL Study: Safety

Patients who experienced ≥1 TEAE assessed by the investigator as related to sutimlimab	9 (37.5)
Total number of TEAEs assessed by the investigator as related to sutimlimab, n	13[a]
Infusion-related reaction[b]	2 (8.3)
Abdominal distension	1 (4.2)
Application site hemorrhage	1 (4.2)
Blood pressure increased	1 (4.2)
Cyanosis[c]	1 (4.2)
Cystitis bacterial	1 (4.2)
Edema peripheral	1 (4.2)
Erythema	1 (4.2)
Hypertension	1 (4.2)
Rhinorrhea	1 (4.2)
Tendonitis	1 (4.2)

<u>Infections:</u>
(N=23 in 13 pts)
GI: 2
Nasopharyngitis: 2
URI: 2

No thromboembolic events on study (33% of pts with events at baseline)

TEAE = treatment-emergent adverse event; GI = gastrointestinal; URI = upper respiratory infection.
Röth A, et al. *N Engl J Med*. 2021;384(14):1323-1334.

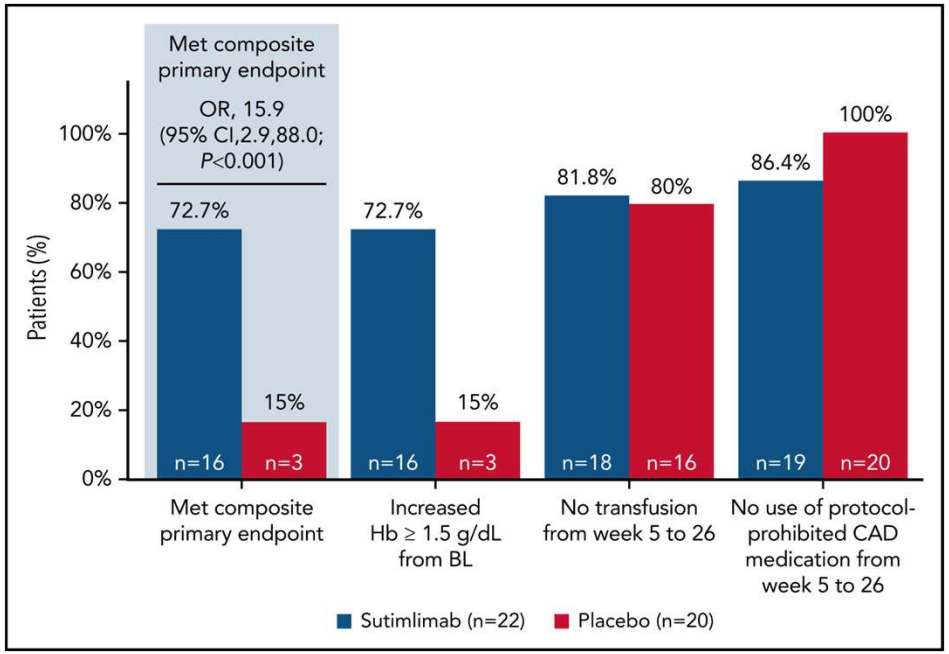
Sutimlimab: CADENZA Study

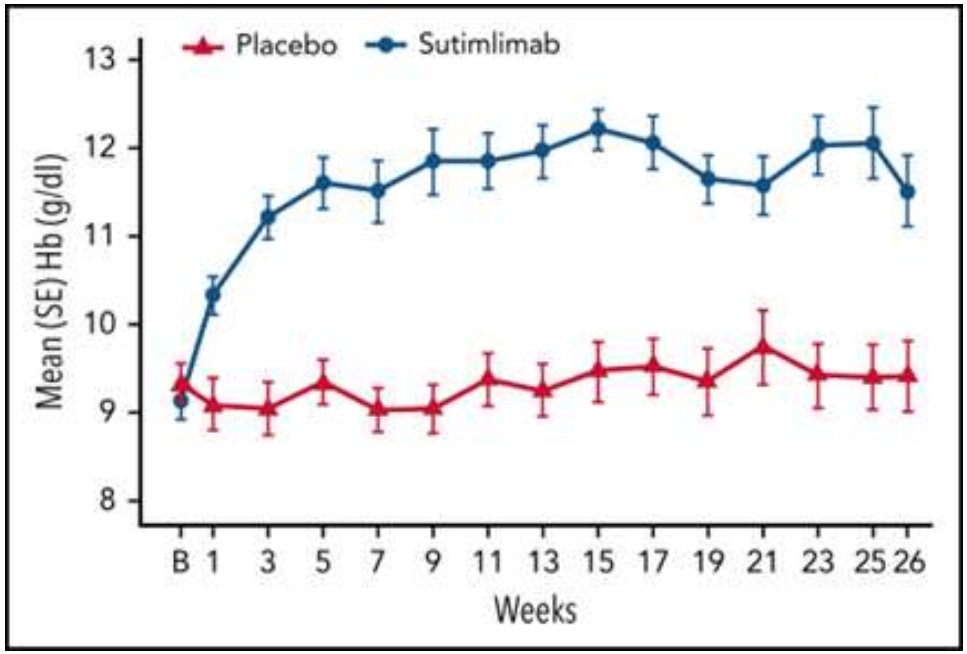
- 26-week multicenter, randomized, placebo-controlled, phase 3 study (N=42)
- Key eligibility
  - CAD not secondary to infection, rheumatologic disease, or hematologic malignancy
  - RBC transfusion within 6 months of enrollment (>1 within 12 months)
  - CAD titer of 1:64 or greater measured at 4°C
  - Hg ≤10 g/dL and bilirubin > ULN
  - CAD symptom: symptomatic anemia, acrocyanosis, Raynaud's, hemoglobinuria, circulatory symptoms, major vascular event
- Primary endpoint
  - Hg increase of >1.5 g/dL at assessment (mean value weeks 23, 25, and 26)
  - Absence of blood transfusions week 5-26

Röth A, et al. *Blood*. 2022;140(9):980-991.

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CADENZA Study: Results



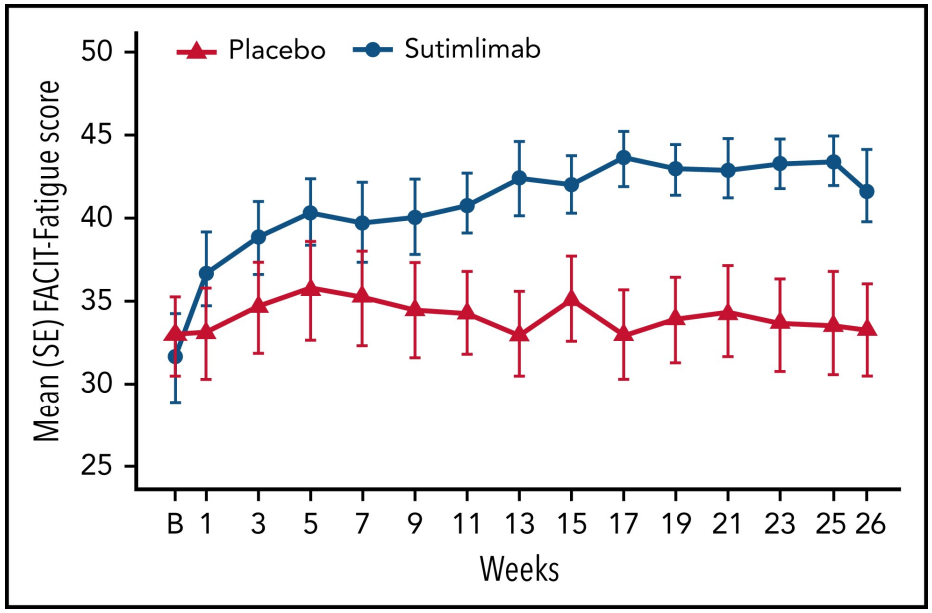


Röth A, et al. *Blood*. 2022;140(9):980-991.

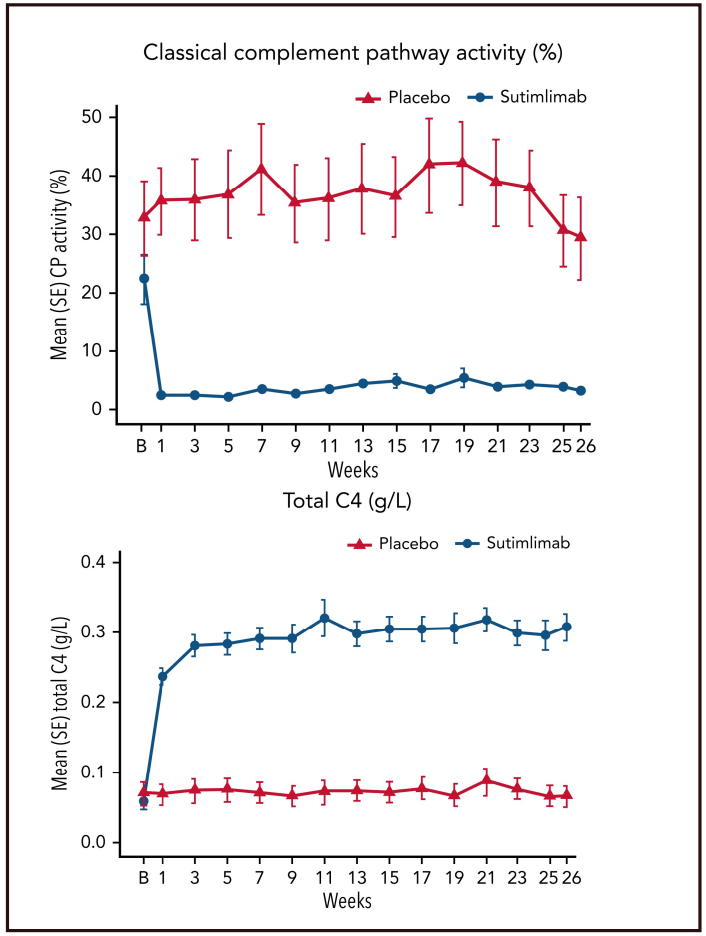
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CADENZA Study: Results

Fatigue



Complement Activity



FACIT = Functional Assessment of Chronic Illness Therapy.
Röth A, et al. *Blood*. 2022;140(9):980-991.

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CADENZA Study: Safety

TEAEs with Difference ≥3 pts

TEAE	Sutimlimab (N=22)	Placebo (N=20)
Headache	5 (23%)	2 (10%)
HTN	5 (23%)	0
Raynaud's	4 (18%)	0
Rhinitis	4 (18%)	0
Acrocyanosis	3 (14%)	0

- No deaths
- 3 sutimlimab patients discontinued Tx

HTN = hypertension; Tx = treatment.
Röth A, et al. *Blood*. 2022;140(9):980-991.

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CAD: Summary

- Need to verify in vivo activity of agglutinin
- Unclear if increased risk of premature death
  - Impacts “watch and wait” approach
  - More clarity on VTE
- Treat hemolysis separate from agglutination symptoms
- Remitting therapies preferable
- Complement-directed therapies quickly efficacious
  - May see worsening acrocyanosis

VTE = venous thromboembolism.

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My Algorithm

- If symptomatic anemia: sutimlimab
- Rituximab
- BTK inhibitor
- Bortezomib
- Daratumumab (CyBorD)
- Bispecifics

CyBorD = cyclophosphamide, bortezomib, dexamethasone

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How to Diagnose and Treat Idiopathic Multicentric Castleman Disease (iMCD)

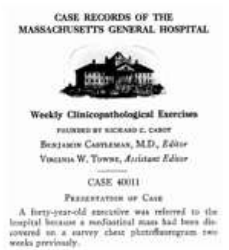
Dr. Frits van Rhee, MD, PhD, MRCP(UK), FRCPath

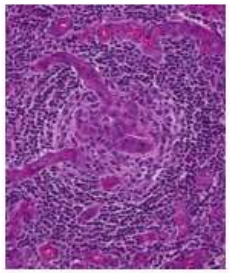
Professor of Medicine
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Myeloma Center, Winthrop P. Rockefeller Cancer Institute
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What Is Castleman Disease?







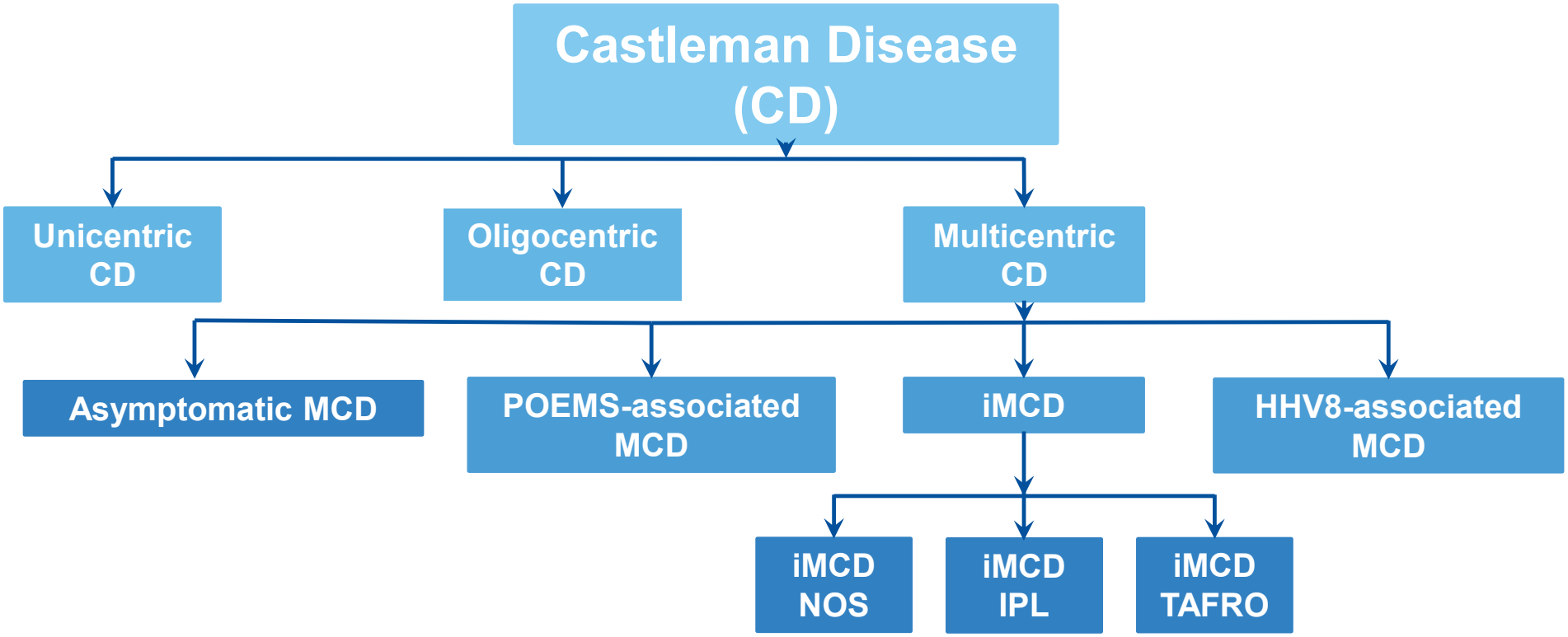
Unicentric Castleman Disease *(UCD)*	▪ Single region of enlarged lymph nodes, few symptoms ▪ ~3,000-5,000 cases diagnosed annually in the US; >95% 5-year OS ▪ Idiopathic; surgical excision is curative
HHV8-positive Multicentric Castleman Disease *(HHV8+MCD)*	▪ Multicentric LAD, systemic inflammation, 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

HHV = human herpesvirus; MSOF = multi-system organ failure; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; IMID = immunomodulatory drug; auto-SCT = autologous stem cell transplantation.

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. *Am J Hematol*. 2012;87(11): 997-1002. Van Rhee F, et al. *Blood*. 2018;132(20):2115-2124.

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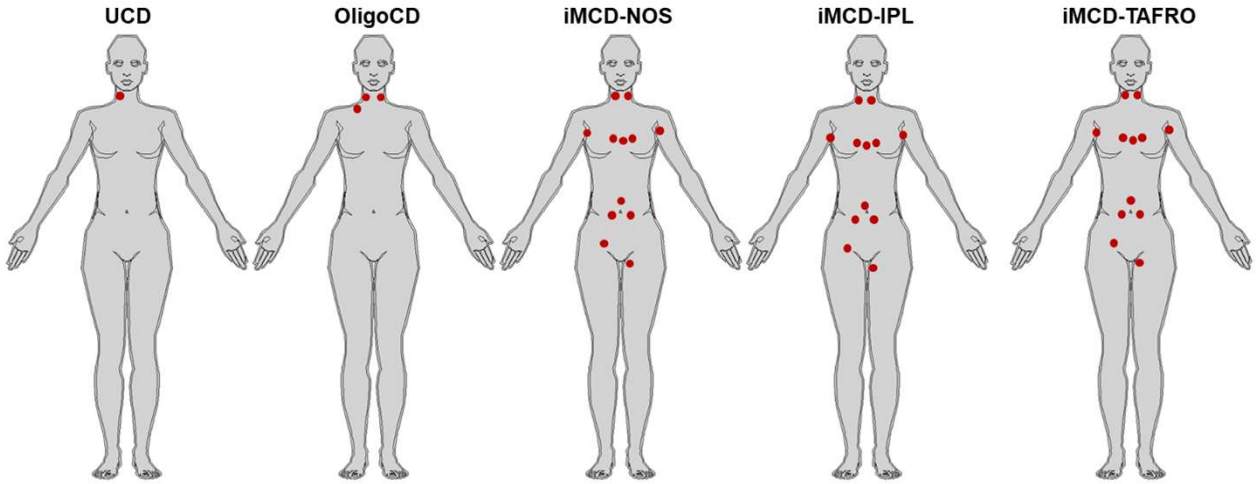
Classification of Castleman Disease



NOS = not otherwise specified; IPL = idiopathic plasmacytic lymphadenopathy; TAFRO = thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, organomegaly.

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Castleman Disease Is a Spectrum

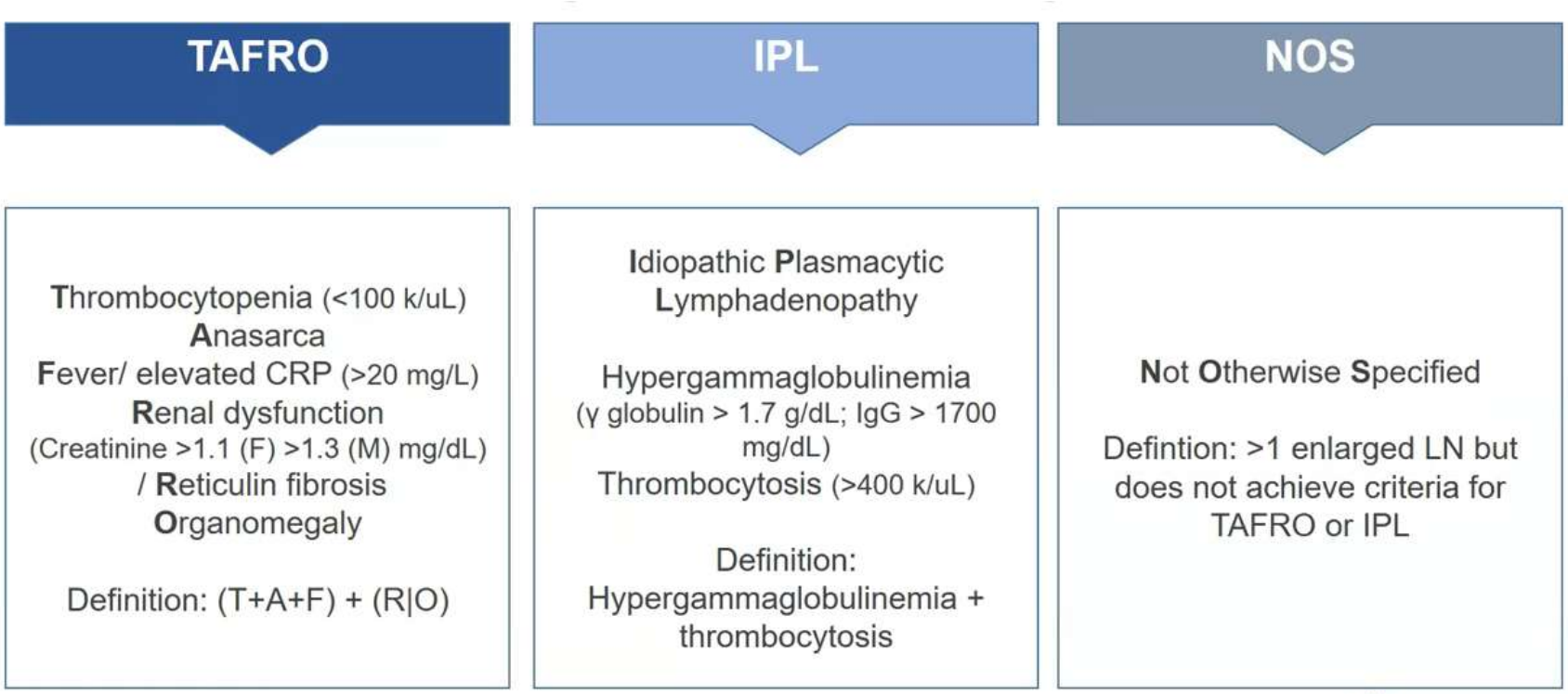


	UCD	OligoCD	iMCD-NOS	iMCD-IPL	iMCD-TAFRO
Lymphadenopathy	Unicentric	Oligocentric	Multicentric	Multicentric	Multicentric
Histopathology	Usually HV	Usually HV	Usually HV to Mixed	Usually mixed to PC	Usually hyperV to mixed
Laboratory abnormalities	Few	Few	Inflammatory markers	↑IgG ↑ Platelets Inflammatory markers	↓Platelets ↓ Renal function Inflammatory markers
Clinical symptoms	Mild	Mild	Moderate	Moderate	Severe
Inflammatory syndrome	Usually absent	Usually absent	Occasionally	Occasionally	Almost always

HV = hyaline vascular; PC = plasmacytic.
Slide adapted from Pierson S, et al. *Blood Adv.* 2025;9(8):1952-1965

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The Clinical Subtypes of iMCD

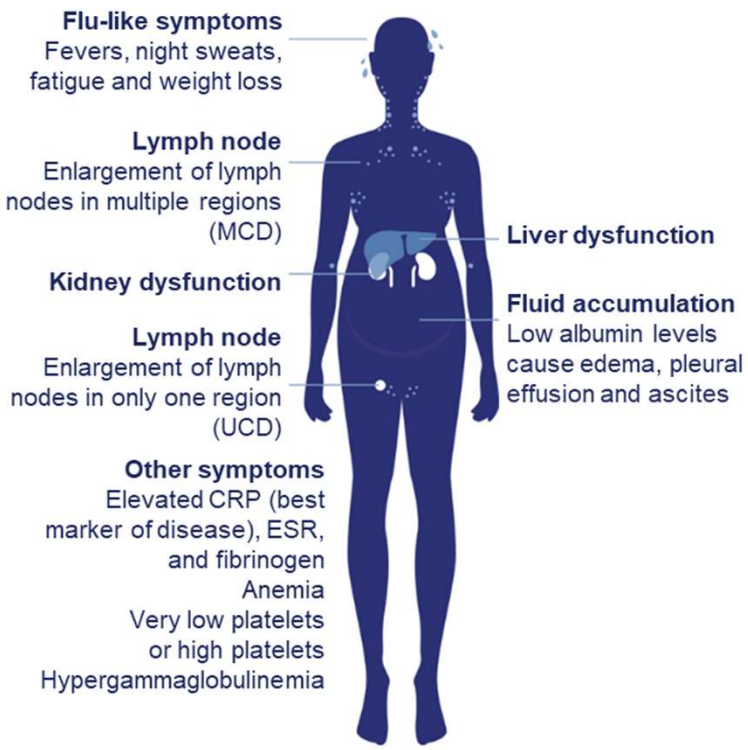


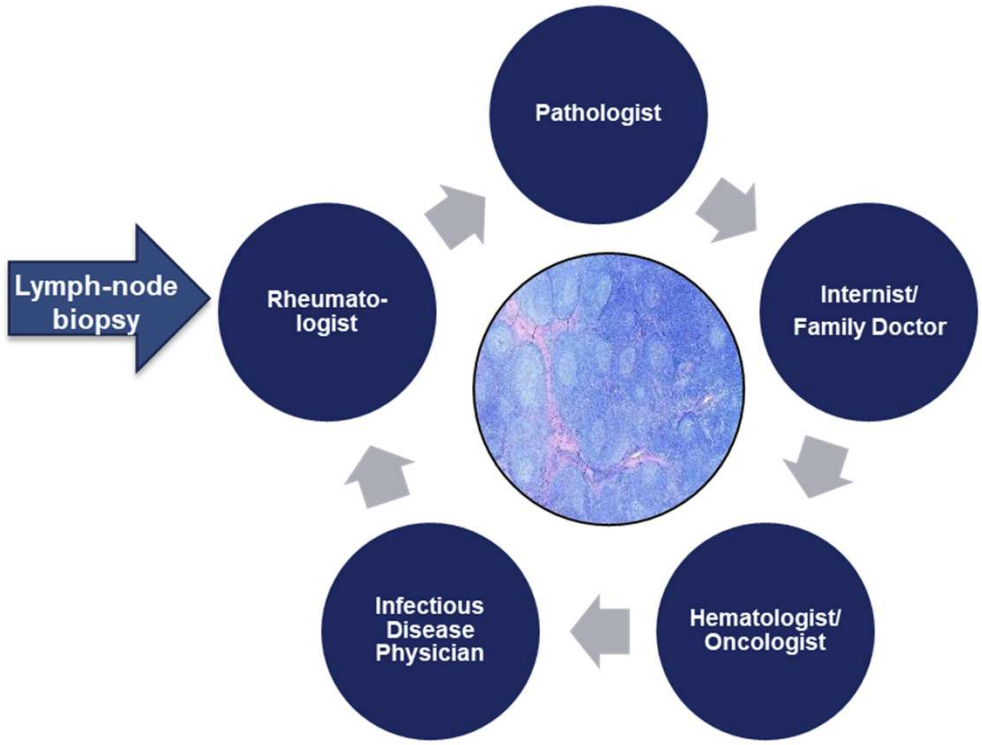
Masaki et al., Int J Hematol., 2016; Iwaki et al., Am J Hematol, 2016; Fajgenbaum et al, Blood, 2017

Mori et al, J Jpn Soc Res; Louis et al, Front Med, 2017; Kurosawa et al., Jpn J Clin Oncol, 2009; Fajgenbaum et al, Blood, 2017;

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The Patient Journey

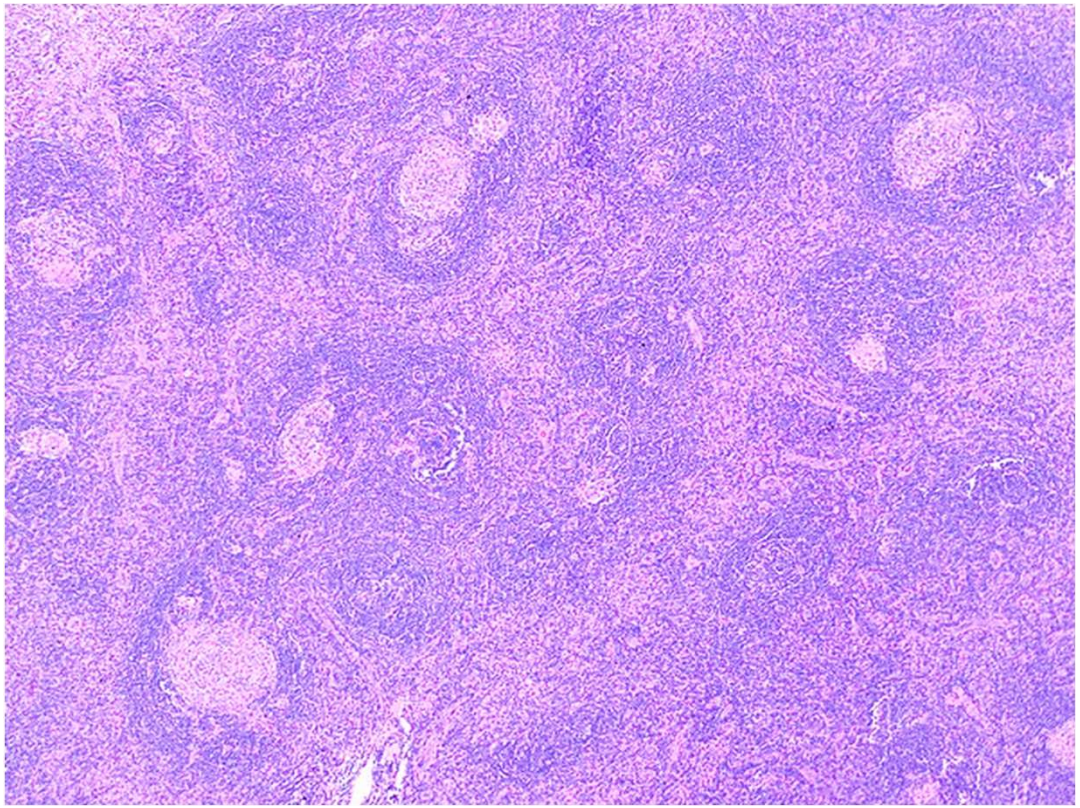




UCD = unicentric Castleman disease; ESR = erythrocyte sedimentation rate.
Adapted from Wu D, et al. *Oncol Clin North Am*. 2018;32(1):37-52. Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. Pathology image used with permission from Sabatinni E, University of Bologna.

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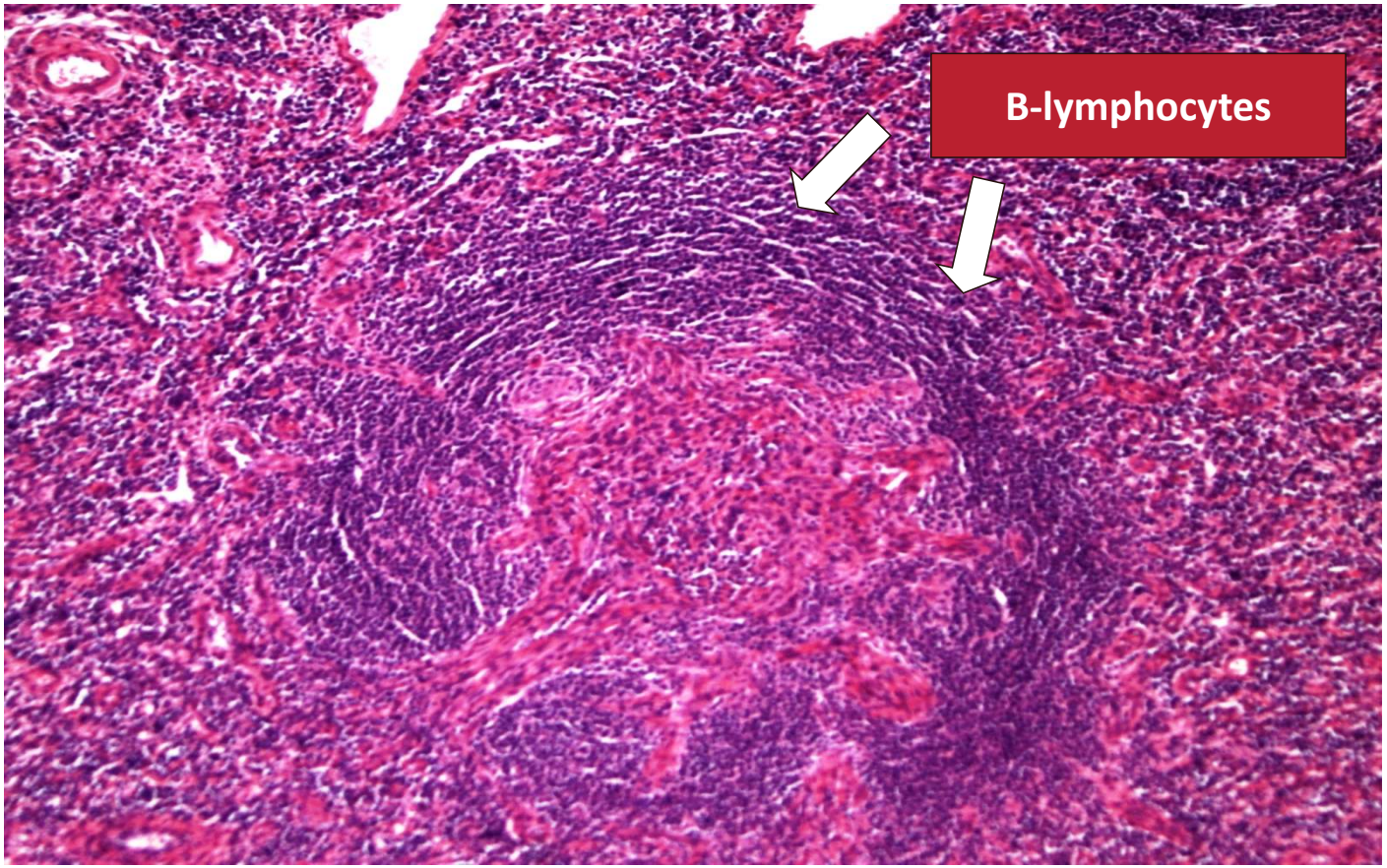
Pathology Hyaline Vascular Variant



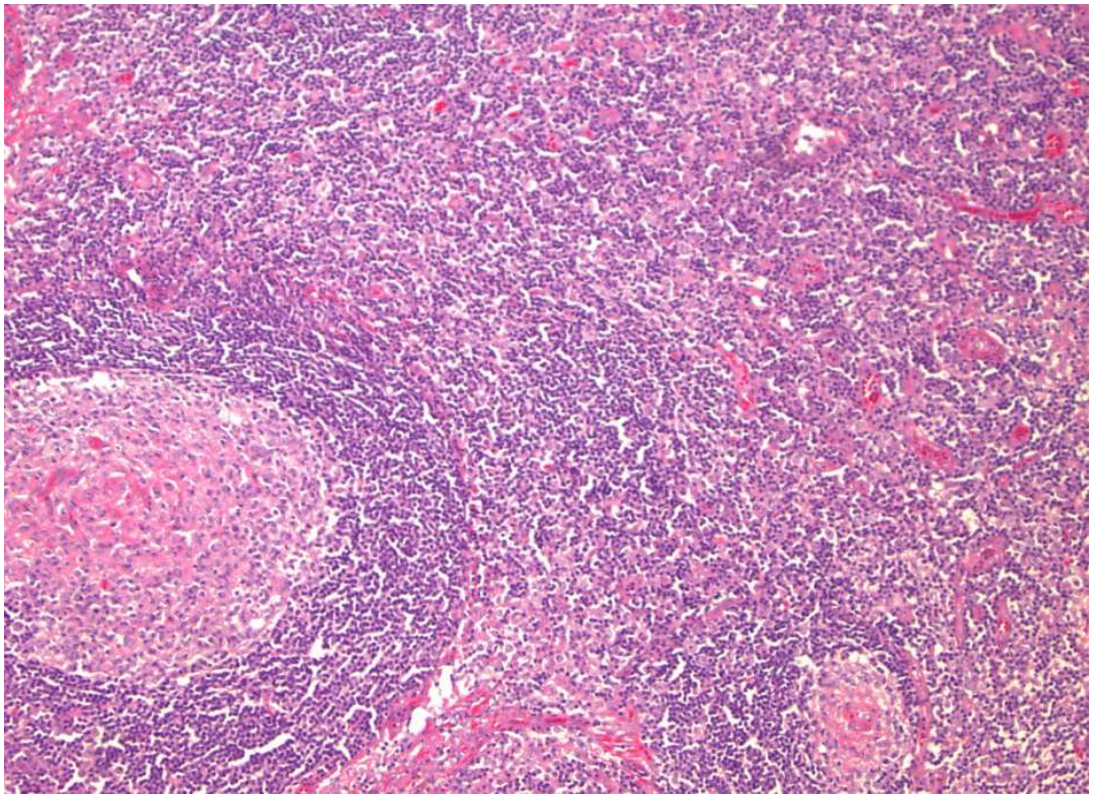
- Atrophic germinal centers
- Concentric ring of small lymphocytes (“onion skinning”)
- Penetrating hyalinized vessels
- “Twinning” follicles
- Dysplastic follicular dendritic cells

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Lollipop Follicle



Plasmacytic Variant

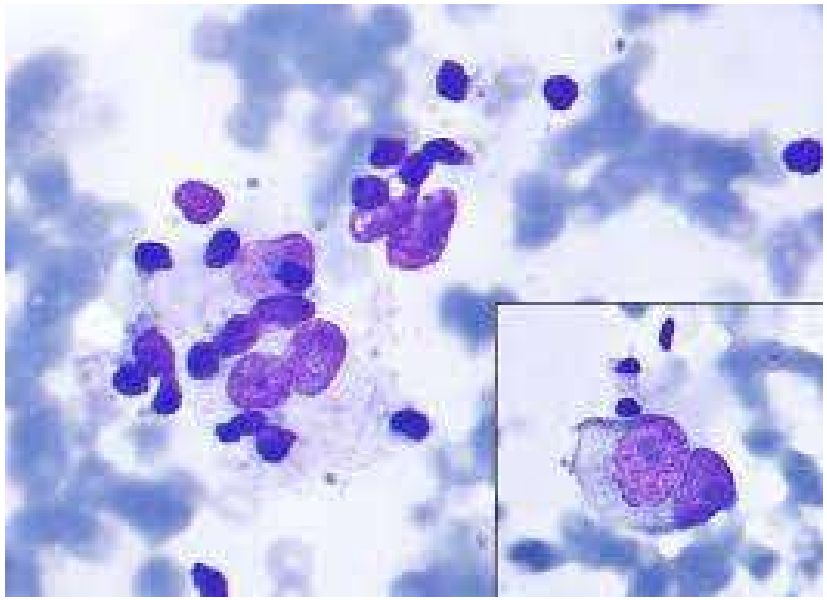


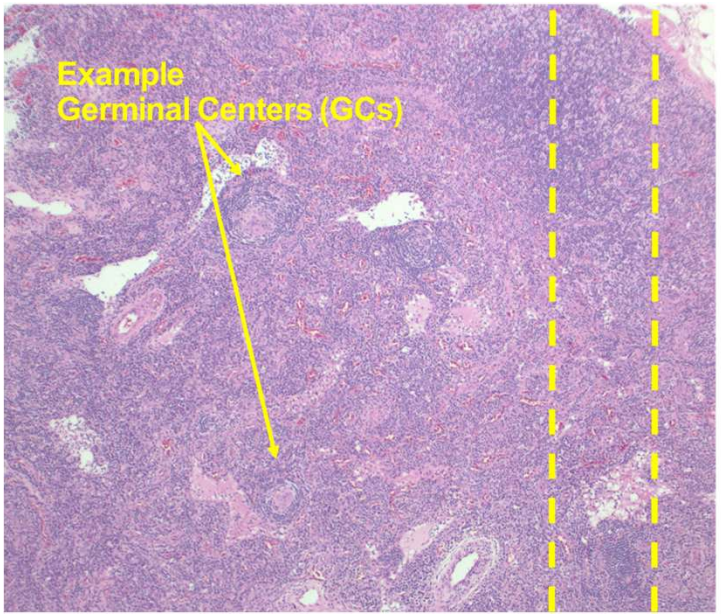
- Hyperplastic germinal center
- Sheets of plasma cells in interfollicular areas
- Vascular proliferations
- Preserved lymph-node architecture
- Normal FDCs

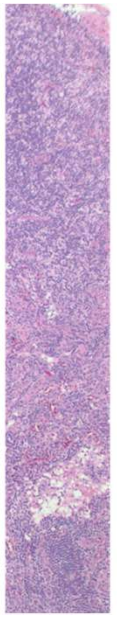
FDC = follicular dendritic cell.

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Please Do Excisional Lymph Node Biopsy







Sufficient lymph node material is required to confirm a diagnosis of iMCD

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Clinical Case

- 20-year-old female college student presenting with fever and fatigue, treated with oral antibiotics to no avail, with persistence of symptoms
- 1 month later, the patient was admitted to a community hospital with high fevers, lymphadenopathy in the neck and axilla, and gross anasarca
- Developed in-hospital renal and respiratory failure; was transferred to ICU requiring dialysis and ventilation
- Diagnosis was not clear in very sick young patient. CD was not considered in differential diagnosis. Not discussed in tumor board

Laboratory assessment	Value
Hemoglobin	8 g/dL
Platelets	30,000/mm^3
Albumin	2.0 g/dL
ESR	>120 mm/hour
CRP	150 mg/L
Creatinine	2 mg/dL

Work-up	Value
ANA, including lupus testing	Negative
Very comprehensive ID work-up	Negative
Evaluation for MAS and HLH	Negative
Cervical lymph-node biopsy	Nonspecific
Bone marrow	Reactive plasmacytosis
Lymphoma or myeloma	No evidence

ANA, antinuclear antibody; CD, Castleman disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome.
Speakers' own experience.

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Clinical Case Cont.

- No specific interaction between pathologist and physician; no further work-up
- Empiric treatment with methylprednisolone 2 mg/kg and 6 plasma exchanges
- She was discharged home 1 month later, with no definite diagnosis and slow tapering of steroids
- Improved sufficiently to resume college 3 months later

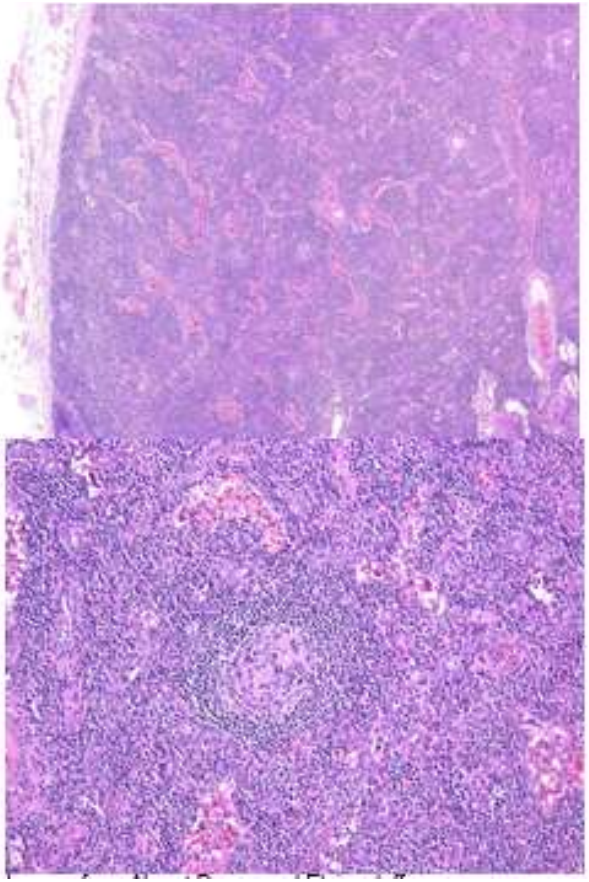
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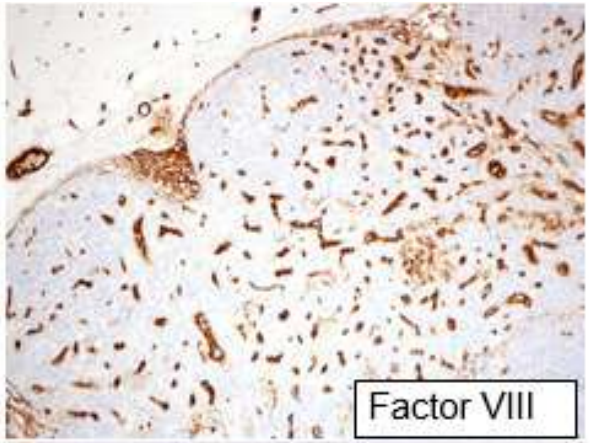
Clinical Case Cont.—Second Major Flare

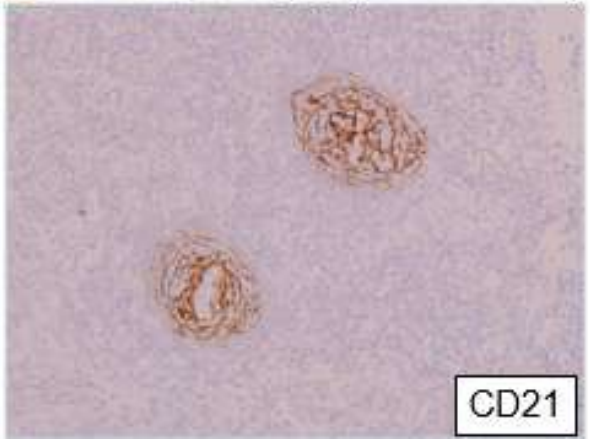
- Readmitted 6 months later with a further crisis, with similar clinical picture:
  - High fevers, shortness of breath, severe edema and fluid overload, generalized lymphadenopathy, hepatosplenomegaly
- Required dialysis for renal failure and intubation for ARDS in ICU again
  - Developed peritonitis, septic shock, and bowel ischemia
  - Laparotomy twice, with surgical removal of a large amount of infarcted small bowel, with ileostomy and splenectomy (spleen nonspecific findings)
  - Left hemiparesis, with CT showing infarct in right corpus callosum, right thalamus, and bilateral gyri
  - Again diagnosis not clear; cytokine panel showed IL-6 >1000 pg/mL

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Lymph Node Biopsy







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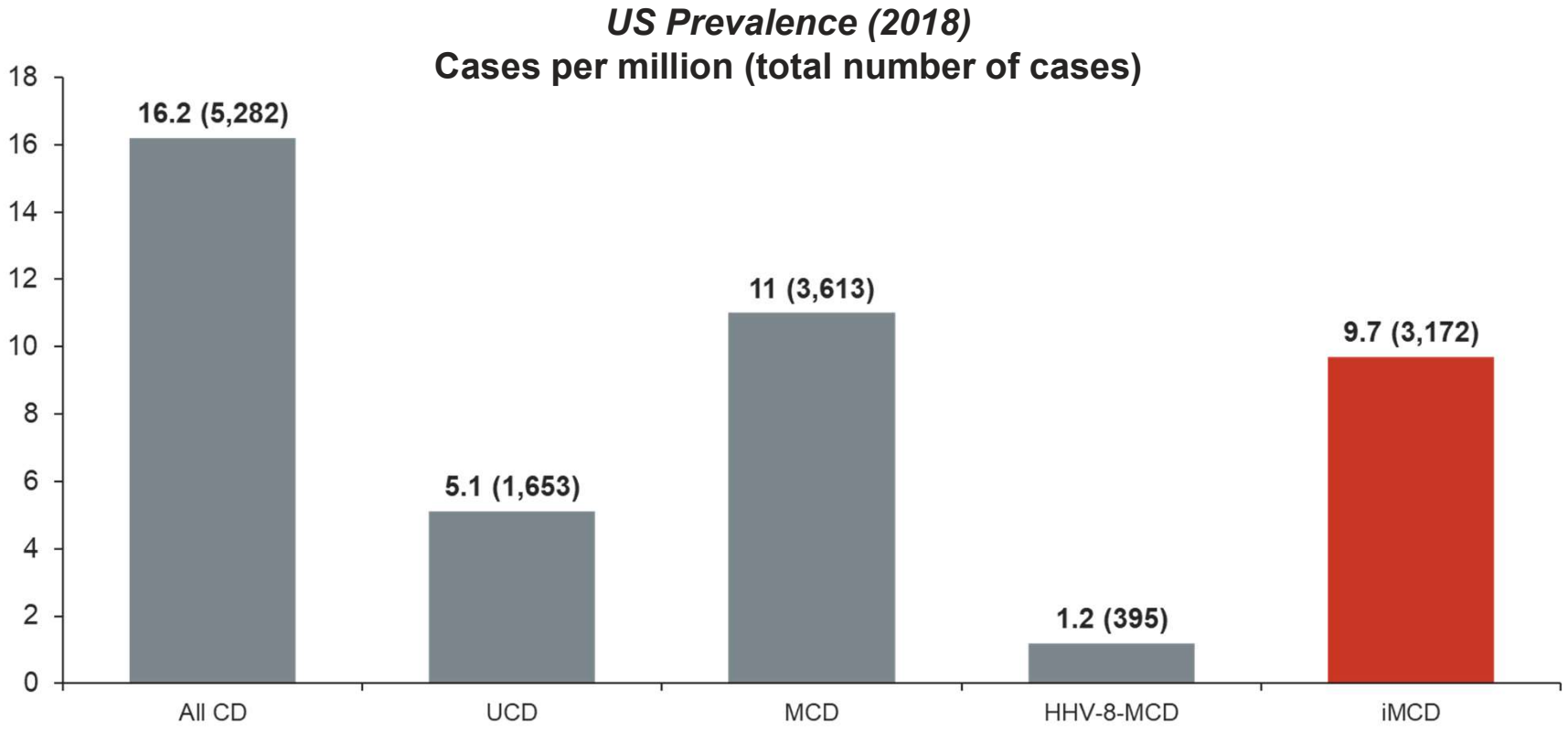
Final Disposition

- CDCN diagnostic guidelines were reviewed in tumor board
- Patient met criteria for iMCD
- Therapy was instituted with siltuximab and high-dose steroids
- Full recovery, but significant neurological residue and short-bowel syndrome
- Now, 5 years later, completed college, is married, and is in full-time employment
- Patient receiving extended therapy on 3-weekly siltuximab

CDCN = Castleman Disease Collaborative Network.

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Castleman Disease Is Rare, Which Can Delay Diagnosis



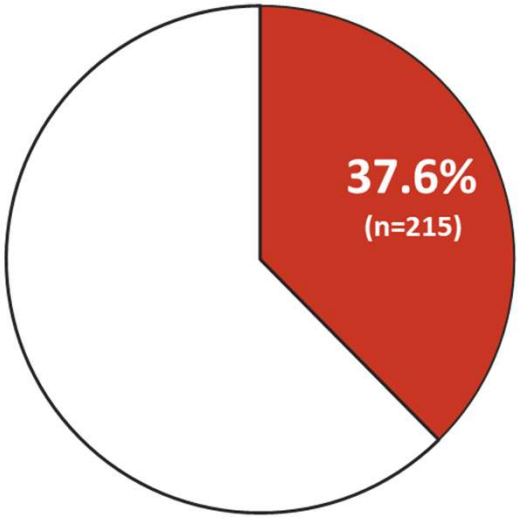
Adapted from Mukherjee S, et al. *Blood Adv*. 2022;6(2):359-367.

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Long Diagnostic Delay

- National, multicenter, retrospective study implementing CDCN criteria, of 1634 CD patients (UCD, n=903; MCD, n=731) from 2000 to 2021 at 40 Chinese institutions
- Of 731 MCD patients, 572 had information on time from symptom onset to diagnosis
- Maximum time interval from symptom onset to diagnosis was 353 months

Percentage diagnosed ≥12 months after initial onset of symptoms (n=572)



Zhang L, et al. *Lancet Reg Health West Pac*. 2023;34:100720.

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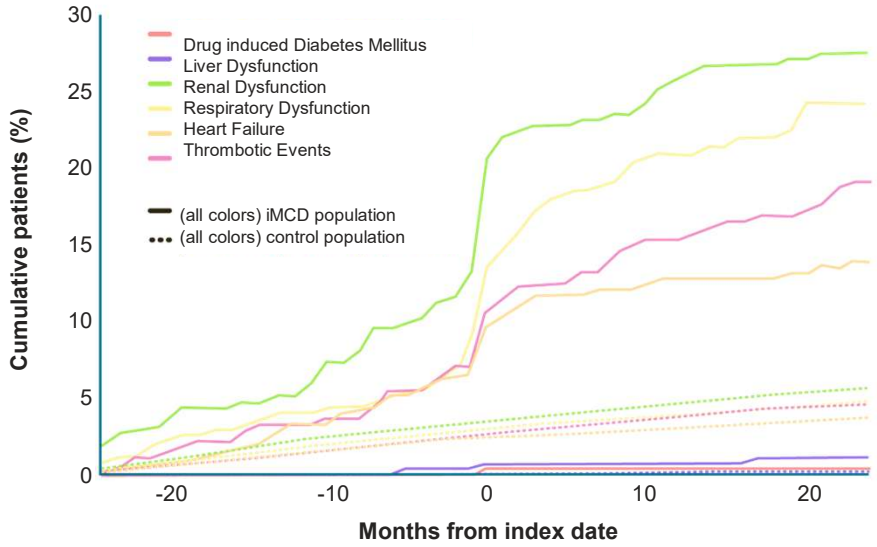
iMCD Is Not Indolent: Consequences of Diagnostic Delay

30.7 million US patients' claims data
Jan 2017-Dec 2020

iMCD (n=271) matched to control population by age, sex, geographic location, insurance status, and follow-up at a frequency of 1:50

Better understand the prevalence and types of morbidity with iMCD

Cumulative proportion of organ dysfunction and thrombotic events were higher in patients with iMCD vs. controls



Adapted from Mukherjee S, et al. *Leukemia*. 2022;36(10):2539-2543.

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iMCD: A Clinical Pathological Diagnosis

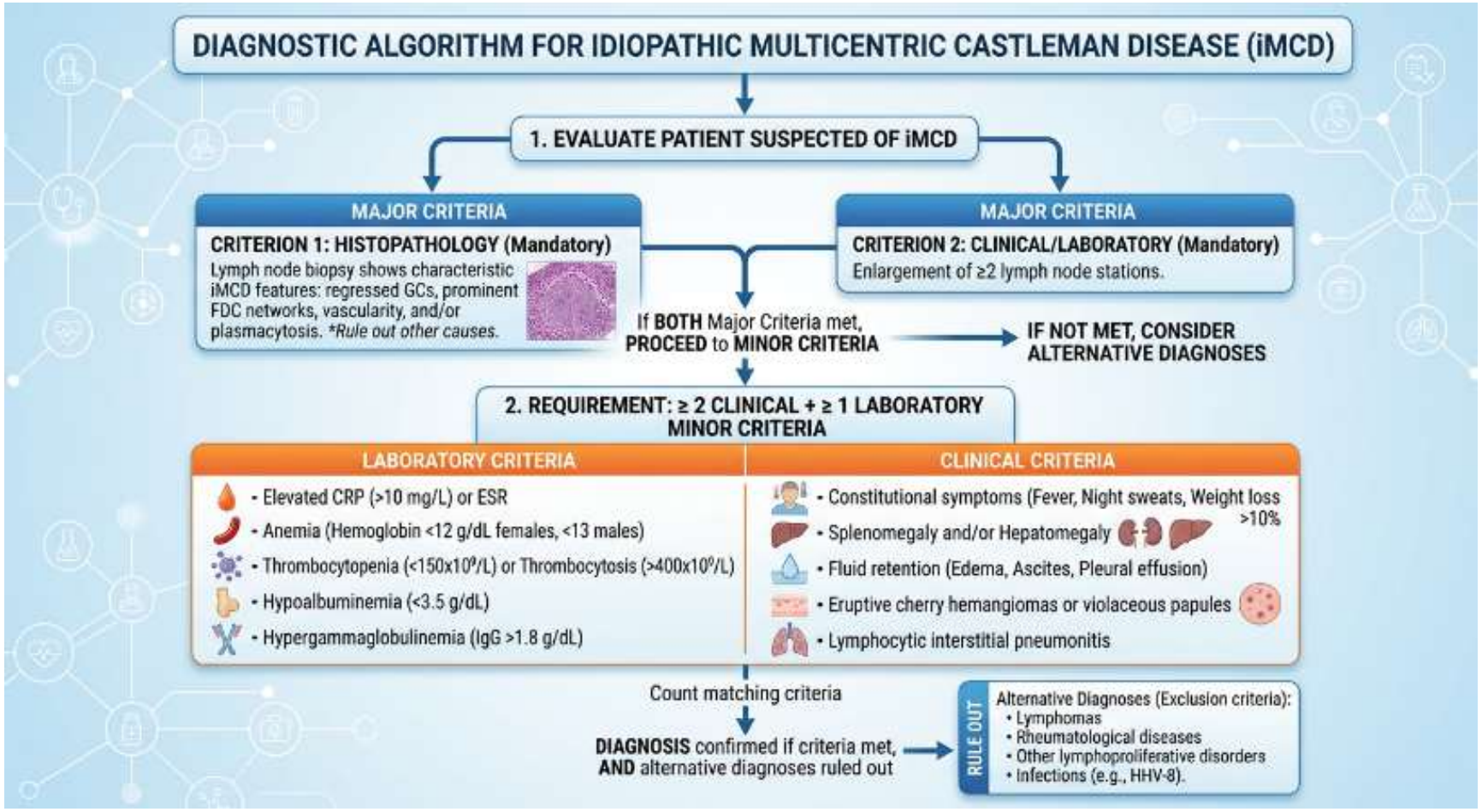
Pathologist



Physician



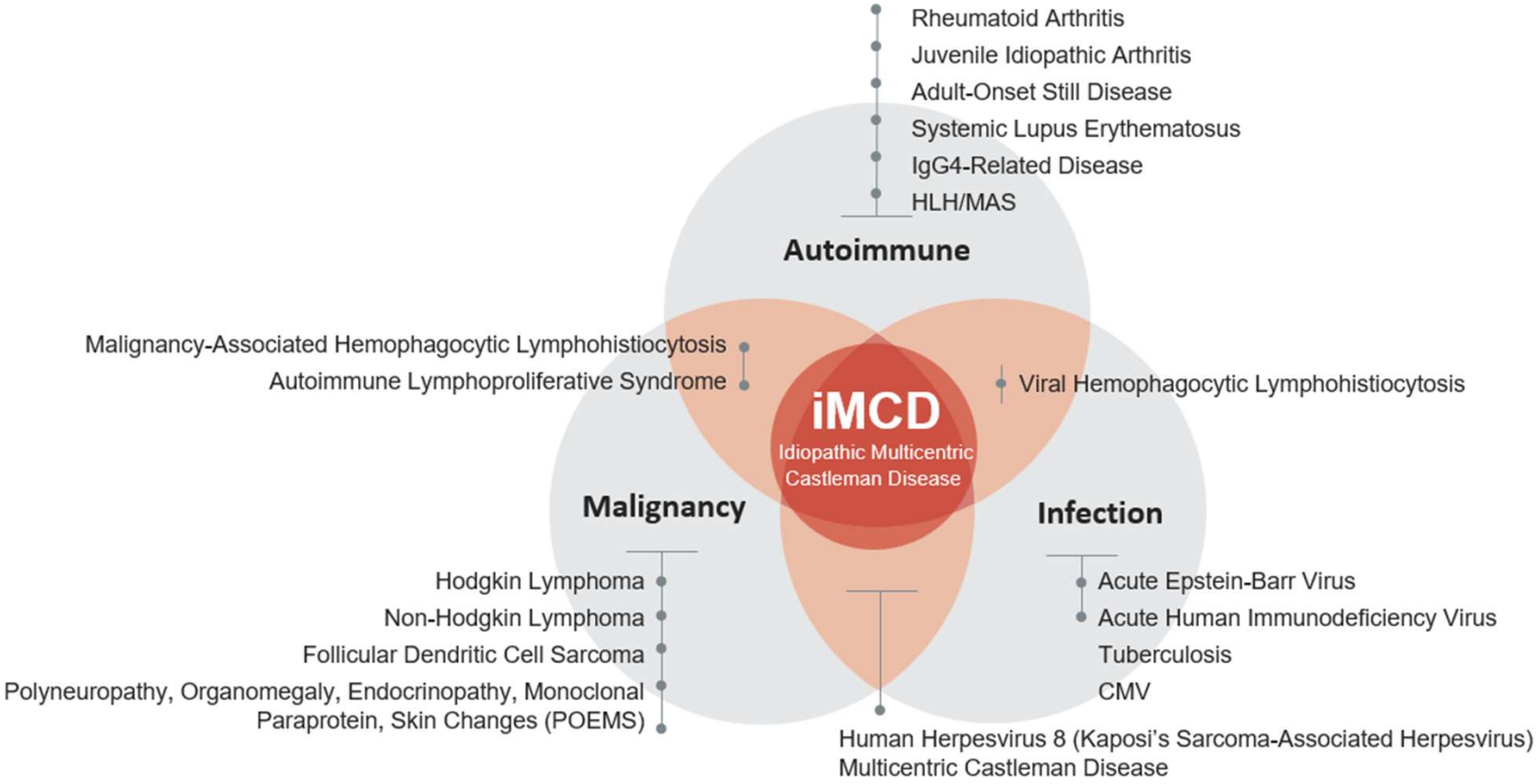
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Slide based on Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657.

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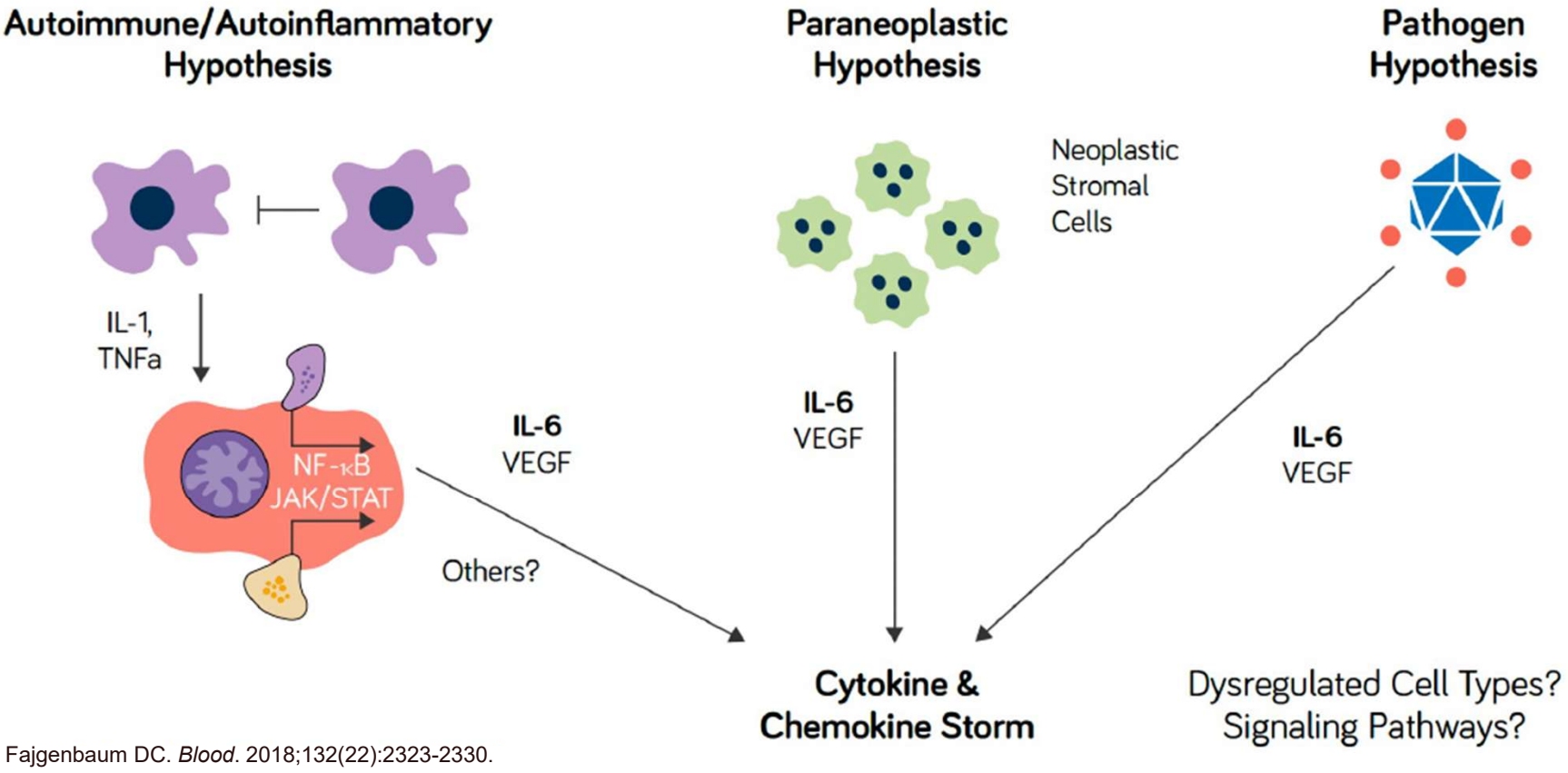
Mimics of iMCD Requiring Exclusion



CMV = cytomegalovirus.

Fajgenbaum DC, et al. *Blood*. 2017;129(12):1646-1657. Yu L, et al. *Blood*. 2017;129(12):1658-1668.

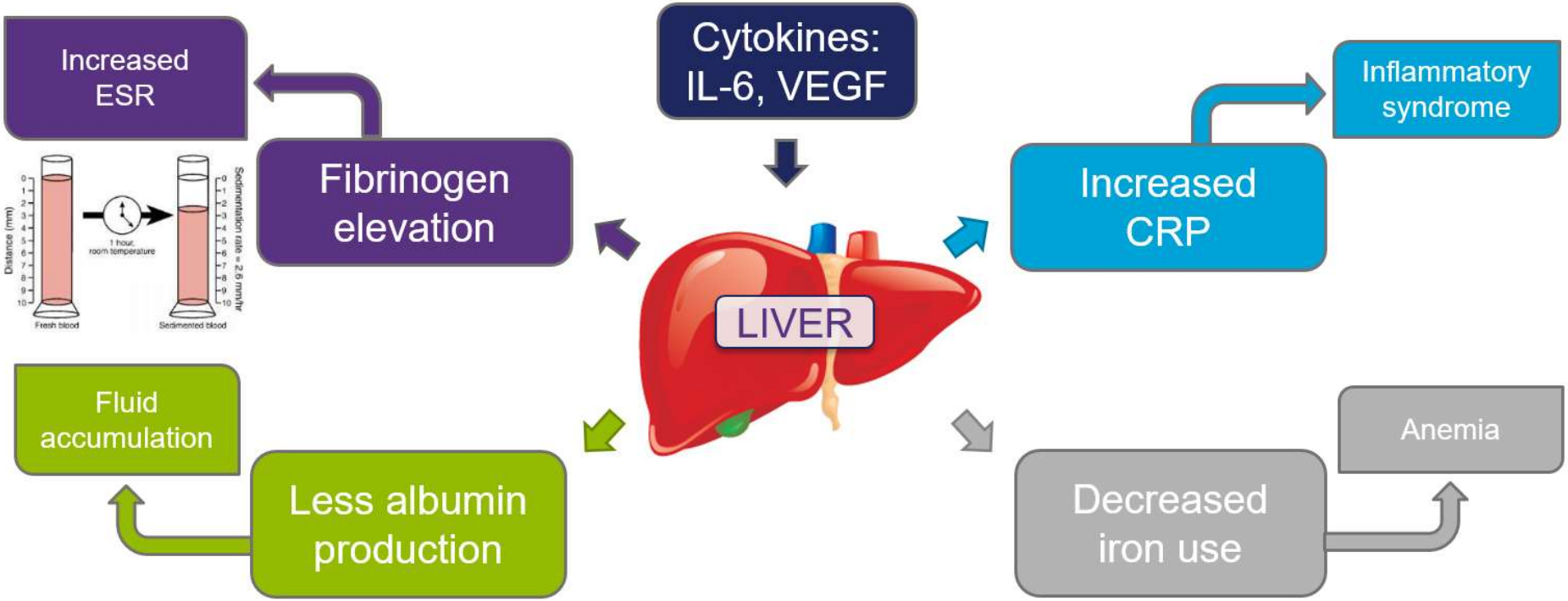
Pathogenesis of iMCD



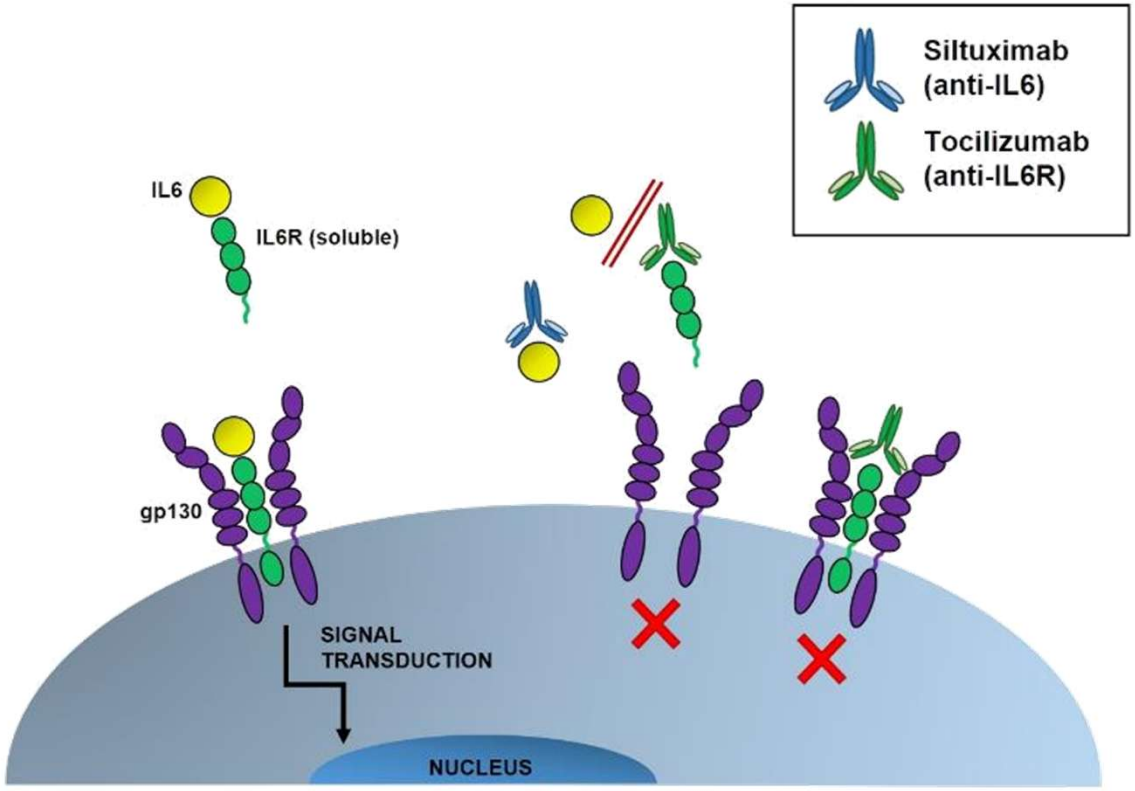
Fajgenbaum DC. *Blood*. 2018;132(22):2323-2330.

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Central Role of IL6 and Other Cytokines



Targeting IL6 with mAb

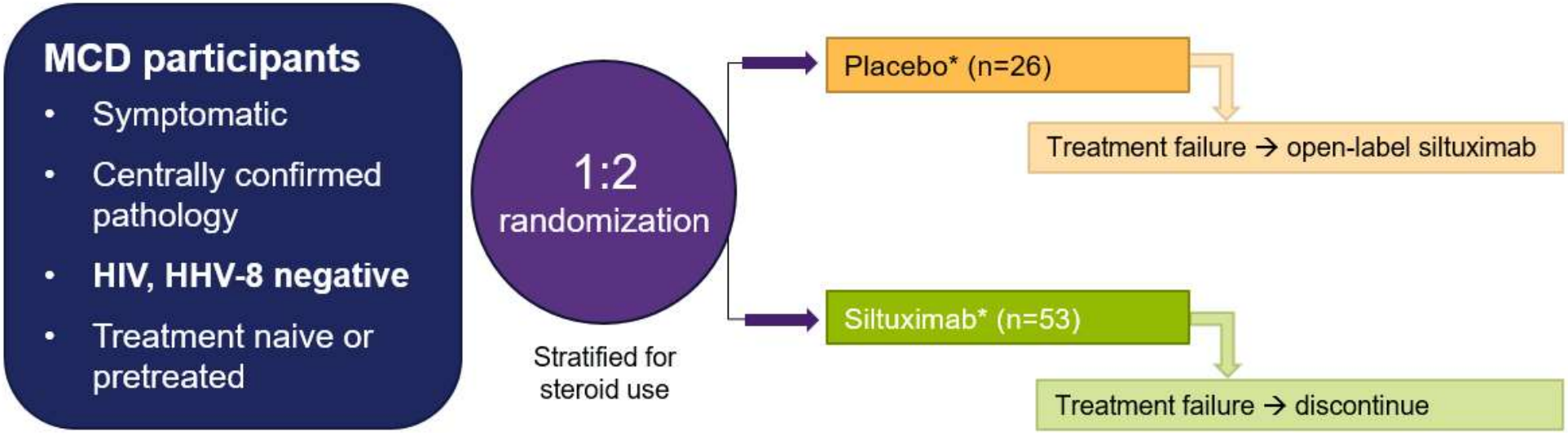


Adapted from Van Rhee F, et al. *Hematol Oncol Clin North Am*. 2018;32(1):89-106.

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Phase II Trial of Siltuximab in iMCD

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

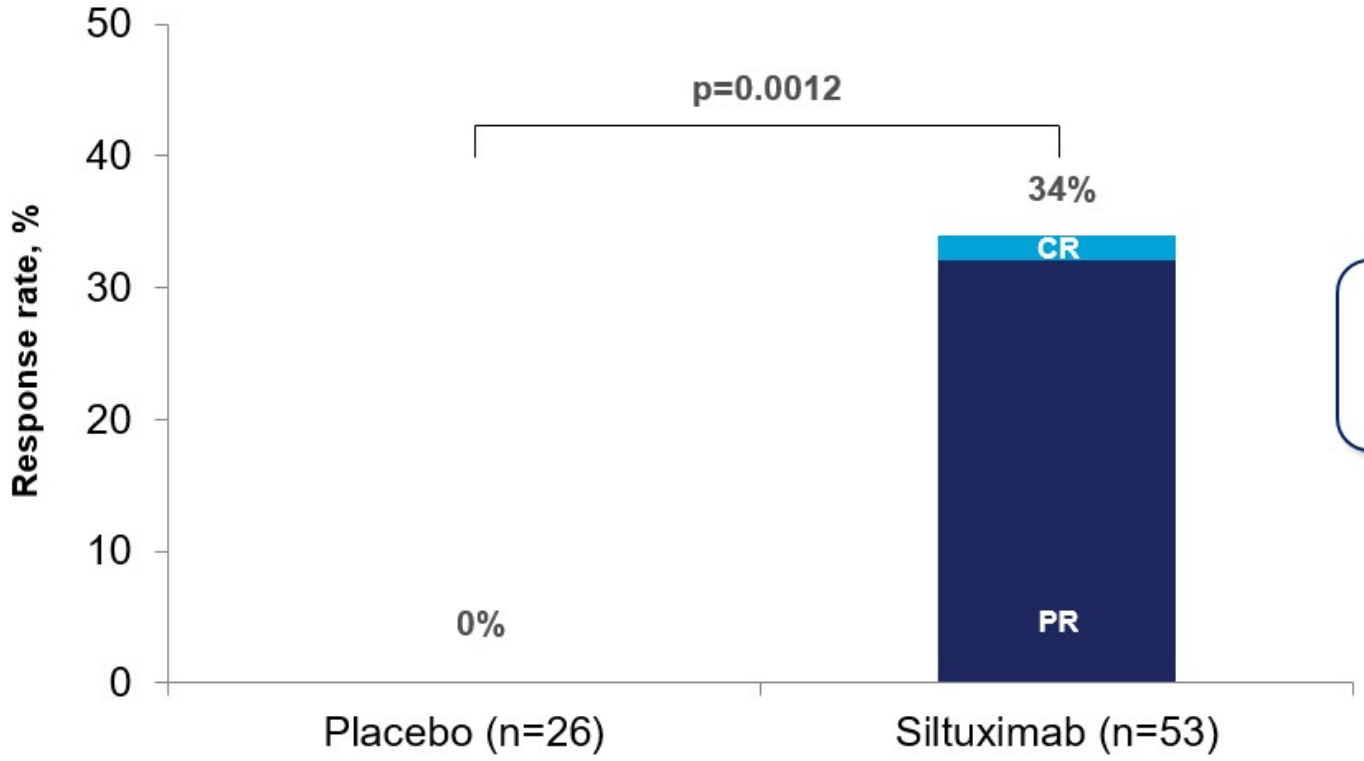


- Primary study analysis planned at 48 weeks after last patient enrolled

Van Rhee F, et al. *Lancet Oncol*. 2014;15(9):966-974.

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Durable Tumor and Symptom Response



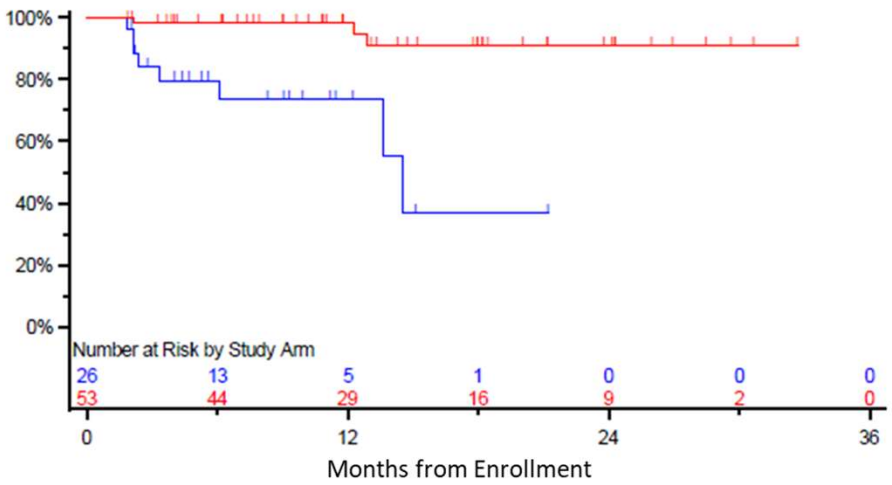
58% of patients (31/53) remained on siltuximab at primary endpoint analysis

Van Rhee F, et al. *Lancet Oncol*. 2014;15(9):966-974.

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Siltuximab Improved Progression-Free Survival

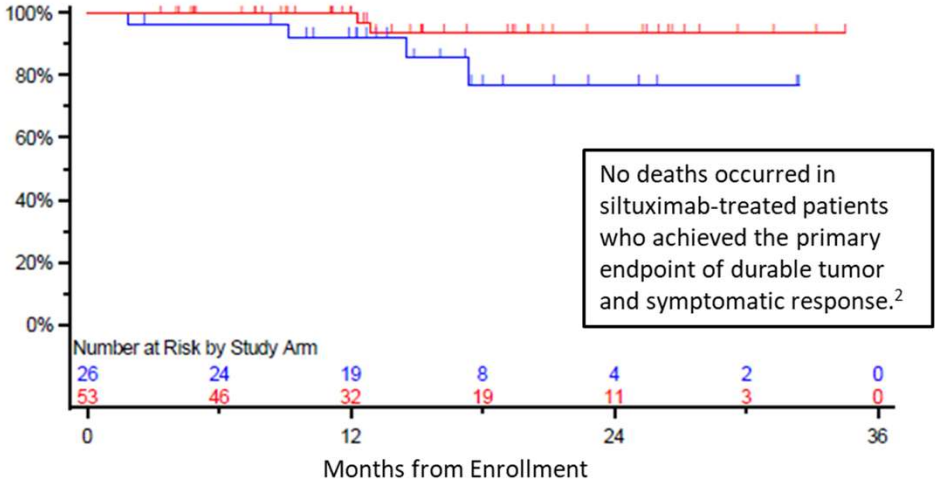
Progression-Free Survival by Study Arm[1]



	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 = 0.001

Overall Survival by Study Arm[2]



No deaths occurred in siltuximab-treated patients who achieved the primary endpoint of durable tumor and symptomatic response.[2]

	Deaths / N	Median in Months	24-Month Estimate
Placebo + BSC	4 / 26	NR	77% (55,98)
Siltuximab + BSC	2 / 53	NR	93% (85,100)

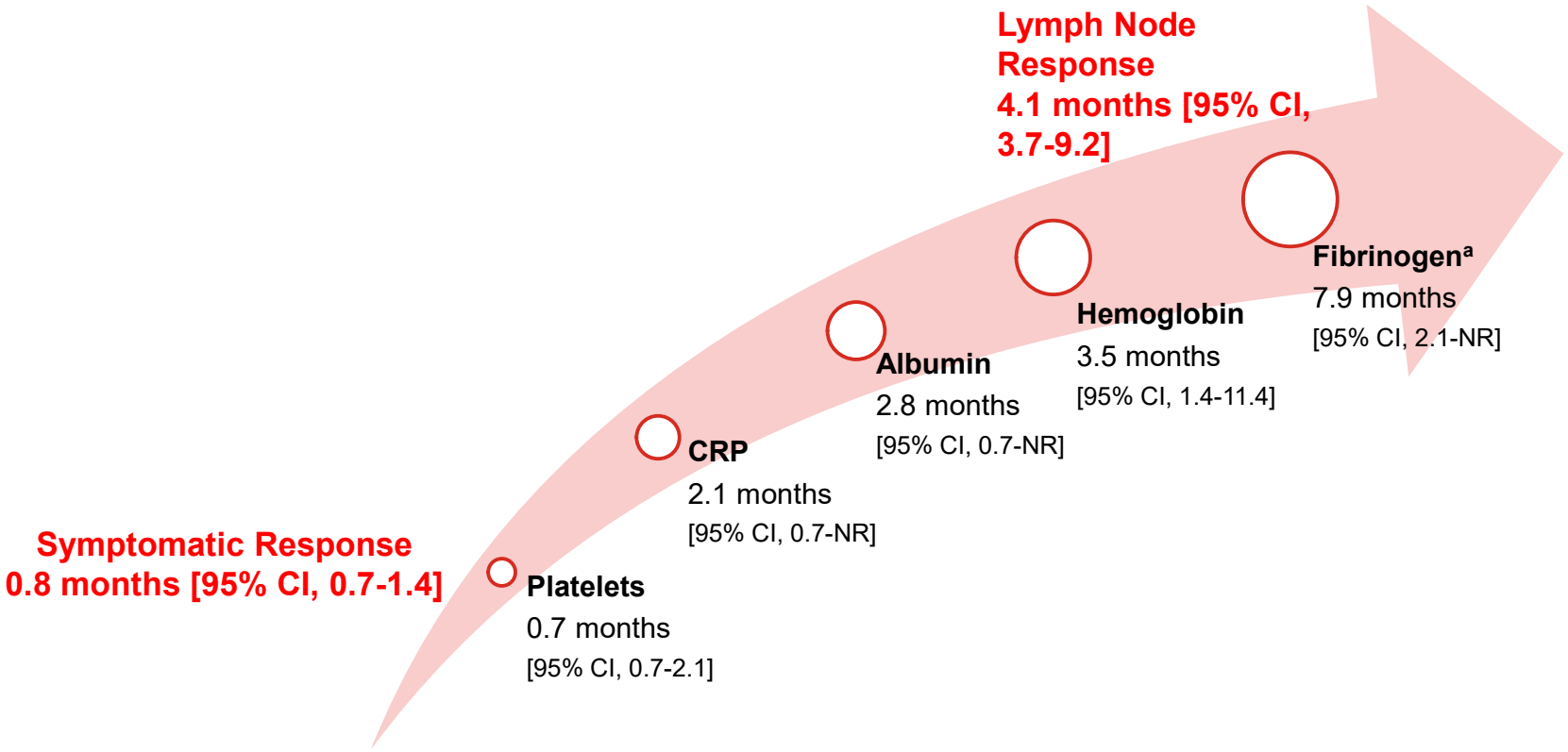
Log-rank *P* value = 0.11

BSC = best supportive care.

Van Rhee F, et al. *Blood Adv*. 2022;6(16):4773-4781.

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Time to Normalization in Responders



Van Rhee F, et al. *Blood Adv*. 2022;6(16):4773-4781.

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Long-Term Siltuximab Extension Study



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)

Van Rhee F, et al. *Lancet Haematol*. 2020;7(3):e209-e217

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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] 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

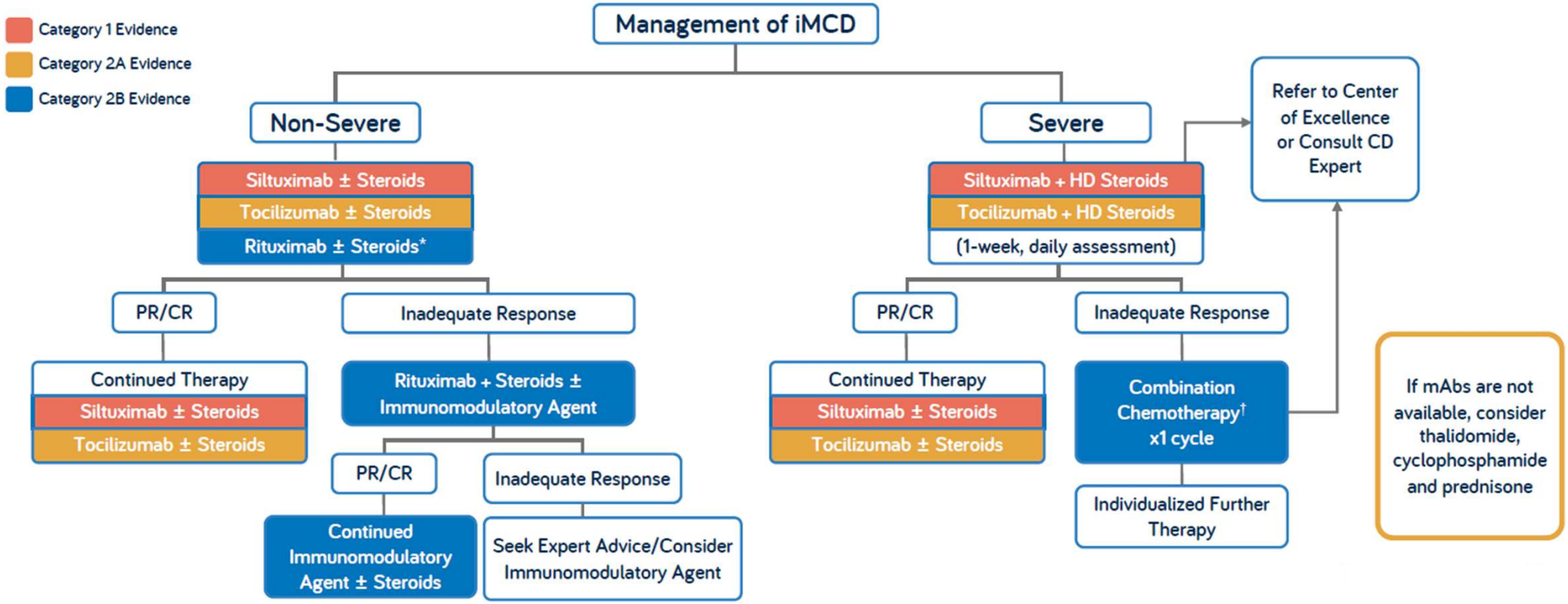
Severe iMCD

- 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

ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate.
Van Rhee F, et al. *Blood*. 2018;132(20):2115-2124.

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Treatment Algorithm for iMCD



PR = partial response; CR = complete response; HD = high-dose.

Zhang L, et al. *Blood*. 2019;133(16):1720-1728. Adapted from van Van Rhee F, et al. *Blood*. 2018;132(20):2115-2124.

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CDCN ACCCELERATE Natural History Registry

Treatment consistent with idiopathic multicentric Castleman disease guidelines is associated with improved outcomes

Sheila K. Pierson,[1] Megan S. Lim,[2] Gordan Srkalovic,[3] Joshua D. Brandstadter,[4] Mateo Sarmiento Bustamante,[1] Saishravan Shyamsundar,[1] Natalie Mango,[1] Criswell Lavery,[1] Bridget Austin,[1] Daisy Alapat,[5] Mary Jo Lechowicz,[6] Adam Bagg,[7] Hongzhe Li,[8] Corey Casper,[9-11] Frits van Rhee,[12] and David C. Fajgenbaum[1]

[1]Department of Medicine, Center for Cytokine Storm Treatment & Laboratory, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York City, NY; [3]Sparrow Herbert-Herman Cancer Center, Michigan State University College of Human Medicine, Lansing, MI; [4]Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [5]Department of Pathology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; [6]Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA; [7]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; [8]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [9]Access to Advanced Health Institute, Seattle, WA; [10]Department of Medicine, University of Washington, Seattle, WA; [11]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA; and [12]Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR

Key Points

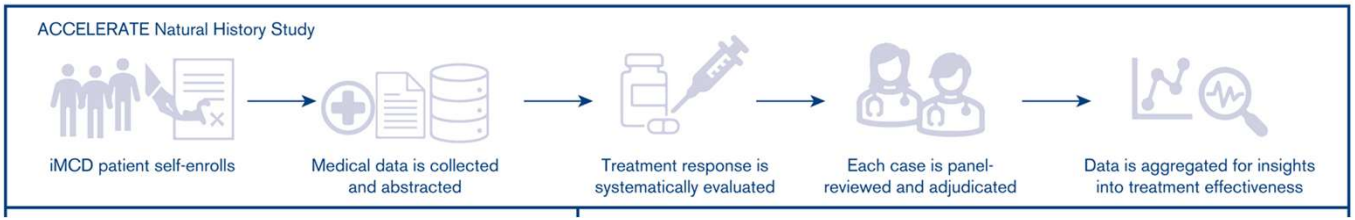
- Fifty-two percent of patients with iMCD treated with siltuximab with/without corticosteroids achieved response.
- Corticosteroids alone are not effective in iMCD symptom management.

Idiopathic multicentric Castleman disease (iMCD) is a rare hematologic disorder with an unknown etiology. Clinical presentation is heterogeneous, ranging from mild constitutional symptoms with lymphadenopathy to life-threatening multiorgan dysfunction. International, consensus treatment guidelines developed in 2018 relied upon a limited number of clinical trials and small case series; however, to our knowledge, real-world performance of these recommendations has not been subsequently studied. Siltuximab, a monoclonal antibody against interleukin 6 (IL6), is approved for the treatment of iMCD and recommended first-line, and tocilizumab, a monoclonal antibody directed against the IL6 receptor, is recommended when siltuximab is unavailable. Chemotherapy, rituximab, and immunomodulators are recommended as second- and third-line treatments based on limited evidence. Corticosteroid monotherapy is used by clinicians, although not recommended. Here, we draw upon the ACCELERATE Natural History Registry to inventory regimens and evaluate regimen response for 102 expert–confirmed iMCD cases. Siltuximab with/without (w/wo) corticosteroids was associated with a 52% response, whereas corticosteroid monotherapy was associated with a 3% response. Anti-IL6–directed therapy with siltuximab or tocilizumab demonstrated better response and more durability than was observed with rituximab w/wo corticosteroids. Cytotoxic chemotherapy was associated with a 52% response and was predominantly administered in patients characterized by thrombocytopenia, anasarca, fever, renal failure/reticulin fibrosis, and organomegaly. Our results provide evidence in support of current recommendations to administer anti-IL6 as first-line treatment, to administer cytotoxic chemotherapy in patients with severe refractory disease, and to limit corticosteroid monotherapy. Evidence remains limited for effective agents for patients who are refractory to anti-IL6–directed therapy. This trial was registered at www.clinicaltrials.gov as #NCT02817997.

Submitted 15 May 2023; accepted 22 August 2023; prepublished online on *Blood Advances* First Edition 1 September 2023; final version published online 1 November 2023. https://doi.org/10.1182/bloodadvances.2023010745.
Data are available upon reasonable request from accelerate@pennmedicine.upenn.edu.
The full-text version of this article contains a data supplement.

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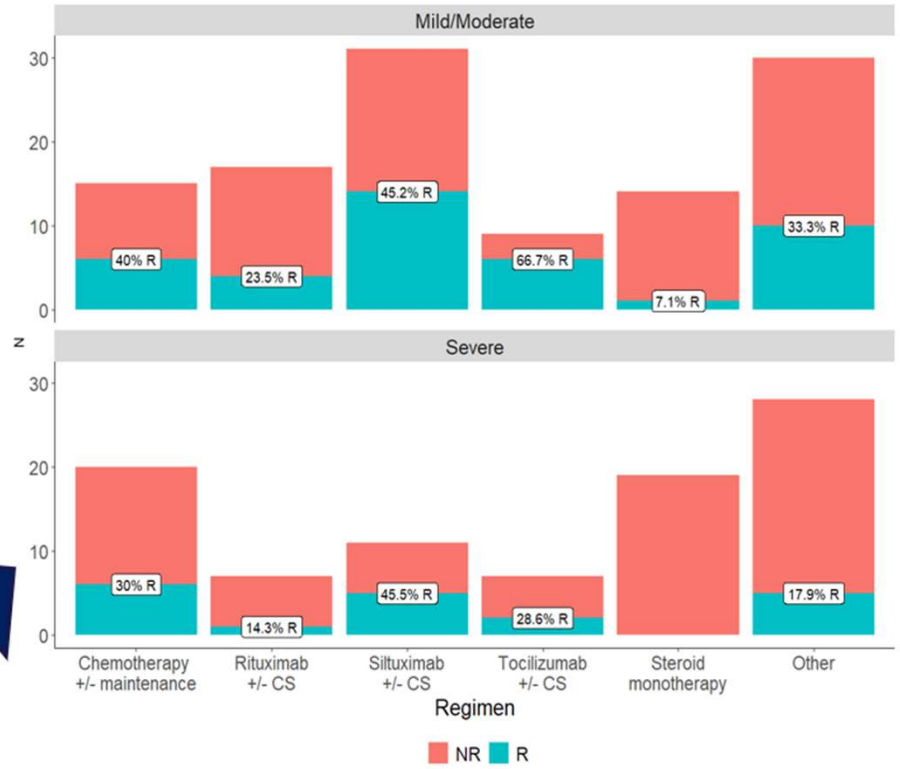
Pierson SK, et al. *Blood Adv*. 2023;7(21):6652-6664.

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Best Response with Siltuximab

Treatment	Responded / Evaluable (%)
Siltuximab +/- CS	22/40 (55%)
Tocilizumab +/- CS	8/17 (47%)
Rituximab +/- CS	6/24 (25%)
Chemotherapy +/- maintenance	11/21 (52%)
Steroid monotherapy	1/33 (3%)

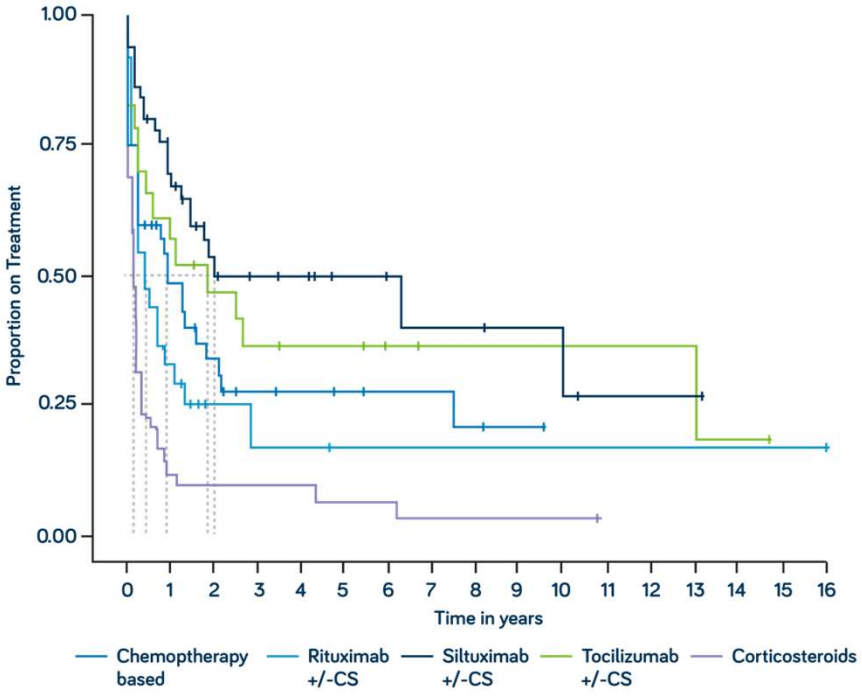
TAFRO

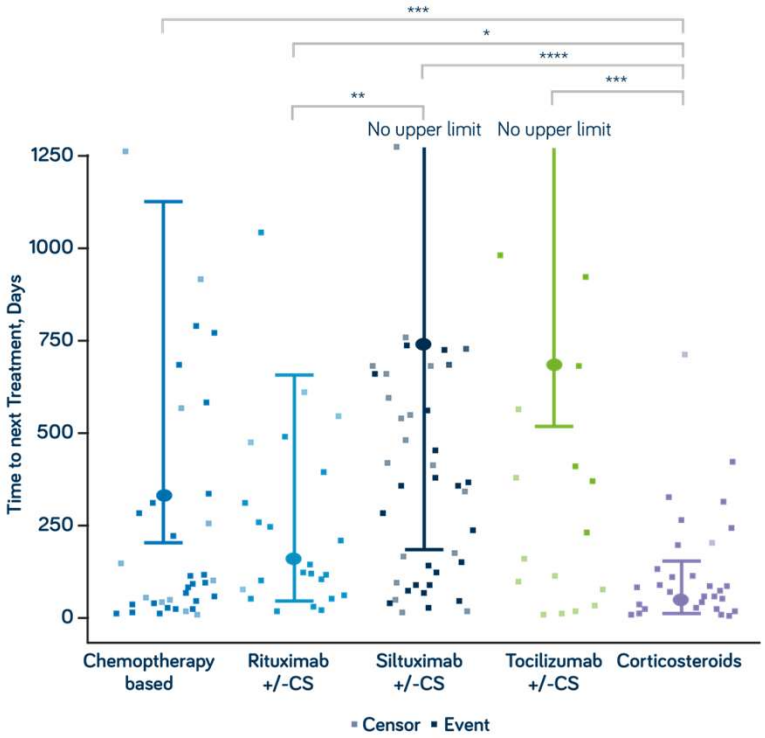


CS = corticosteroids.
Pierson SK, et al. *Blood Adv*. 2023;7(21):6652-6664.

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Time to Next Treatment

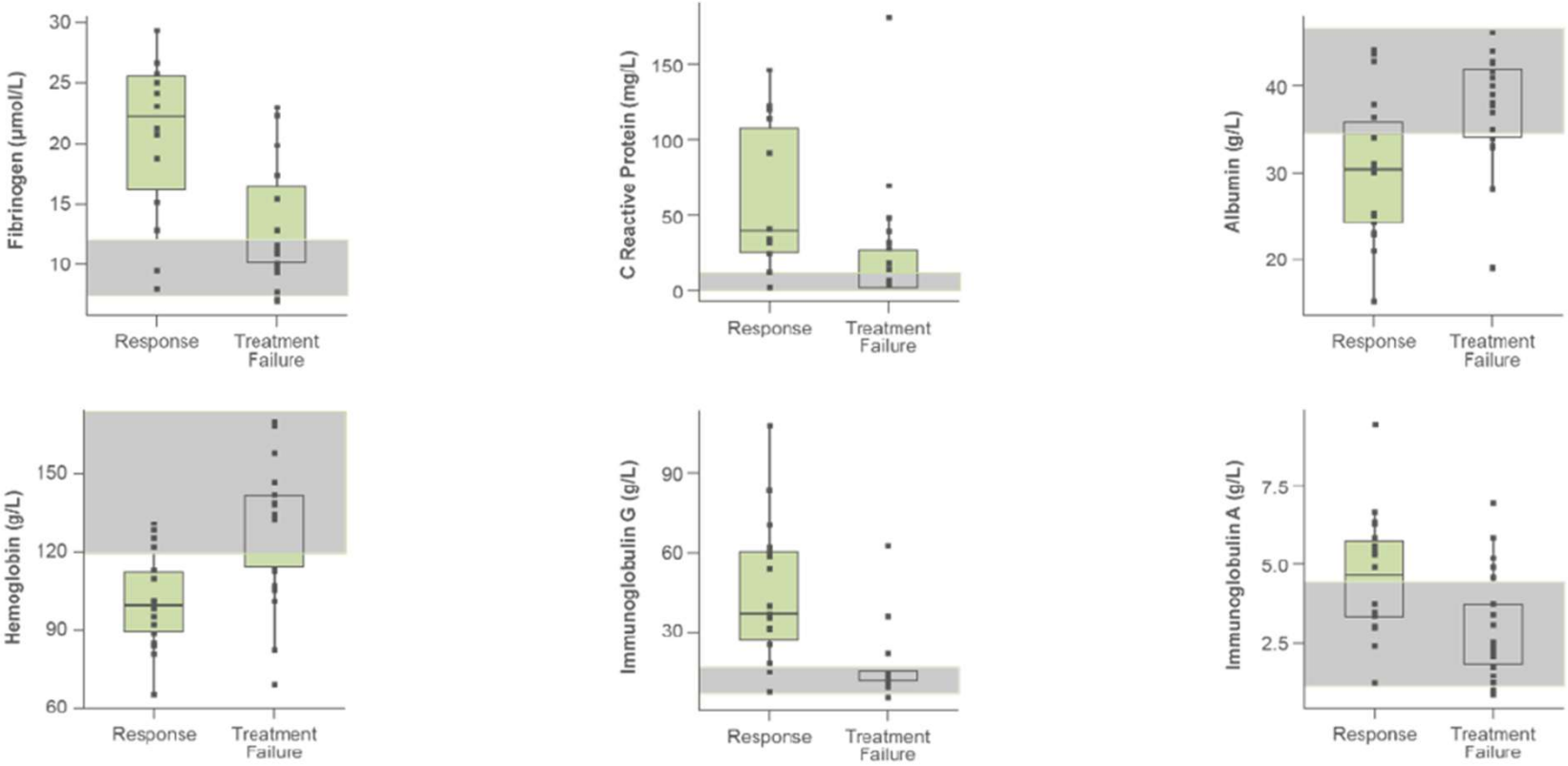




Pierson SK, et al. *Blood Adv*. 2023;7(21):6652-6664.

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Siltuximab Responders Have Inflammatory Response



Morra DE, et al. *Br J Haematol*. 2019;184(2):232-241.

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Siltuximab: What to Know for Clinical Practice

- Infusion well-tolerated
- No opportunistic infections when used as sole agent
- Yearly lipid profile
- Mild thrombocytopenia may occur (platelets: 1000,000-150,000)
- Occasional patient with mild fleeting rash
- Has the potential for masking acute phase reaction
- Do not measure IL6 levels post-siltuximab

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Why Does Anti-IL6 mAb Therapy Fail in iMCD?

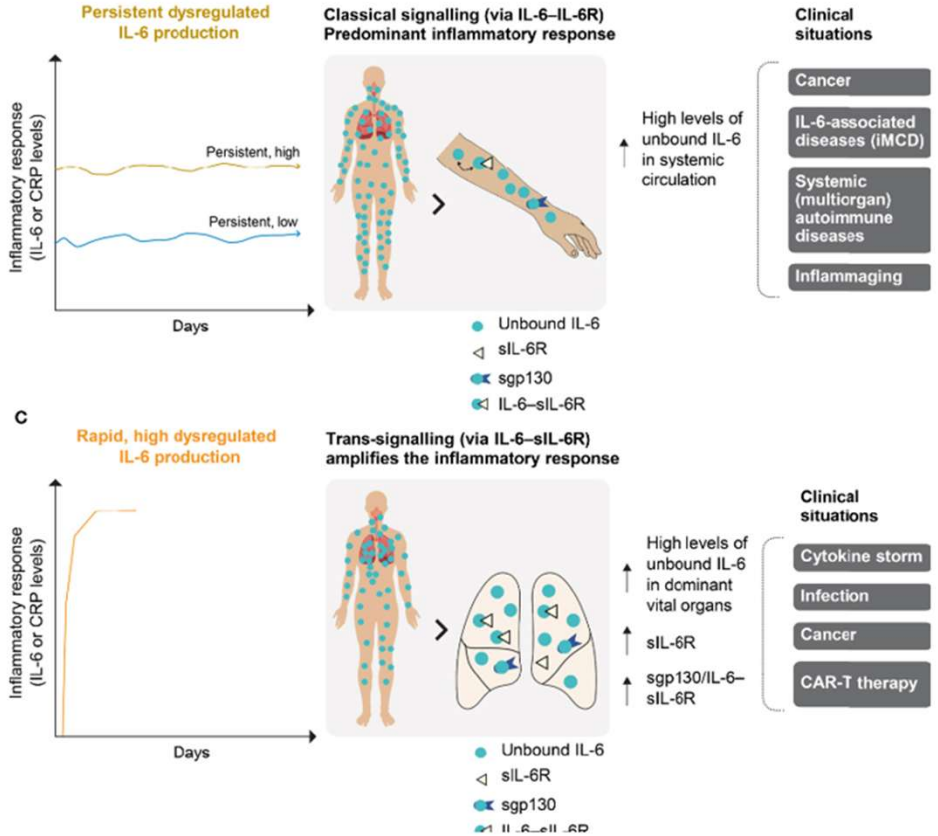
Insufficient neutralization of IL-6 signaling pathway



- Serum IL6 may not be representative of organ/extracellular fluid IL6
- Increased turnover of IL6 mAb in sick (TAFRO) patients (low albumin increases clearance)
- Time to steady state is long with 3-weekly dosing
- Some patients may benefit from rapid loading, especially those with TAFRO in analogy to cytokine release syndrome

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Signaling Pathways in iMCD-IPL vs iMCD-TAFRO



IPL

predominantly classical, chronic IL6 signaling

TAFRO-iMCD and ?severe iMCD-NOS

predominantly trans IL6 signaling

and/or

Multiple other pathways

- **m-TOR/AKT/PI3 kinase**
- **Down stream JAK-STAT**
- **CXCL13/CXCR5 axis**
- **MAPK**
- **Type 1 interferon response**
- **NF-κB**
- **TNF-α**

Rossi JF, et al. *Front Immunol*. 2022;13:919489.

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JAK-STAT: A Novel Target in Siltuximab Non-Responders

Siltuximab Non-Responders

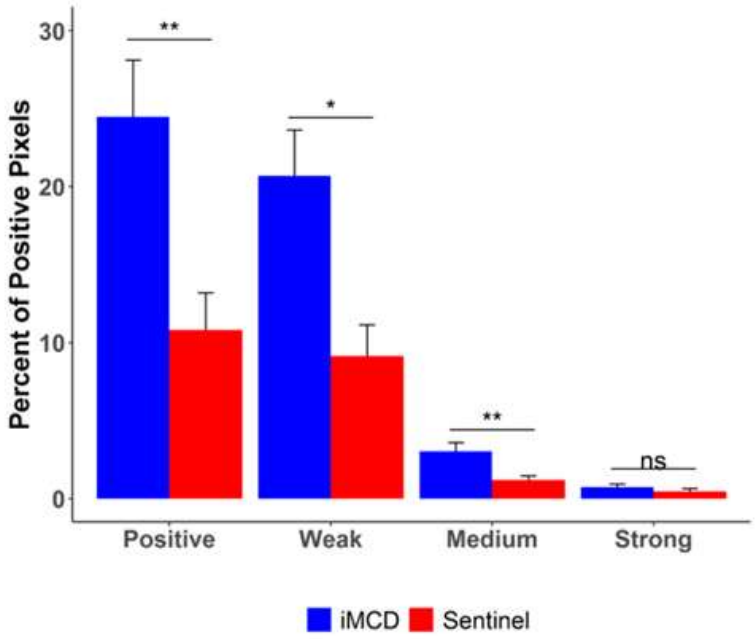
Table 1. Hallmark pathways significantly enriched in the discovery dataset among Cluster-1 anti-IL6 responders and in all siltuximab non-responders

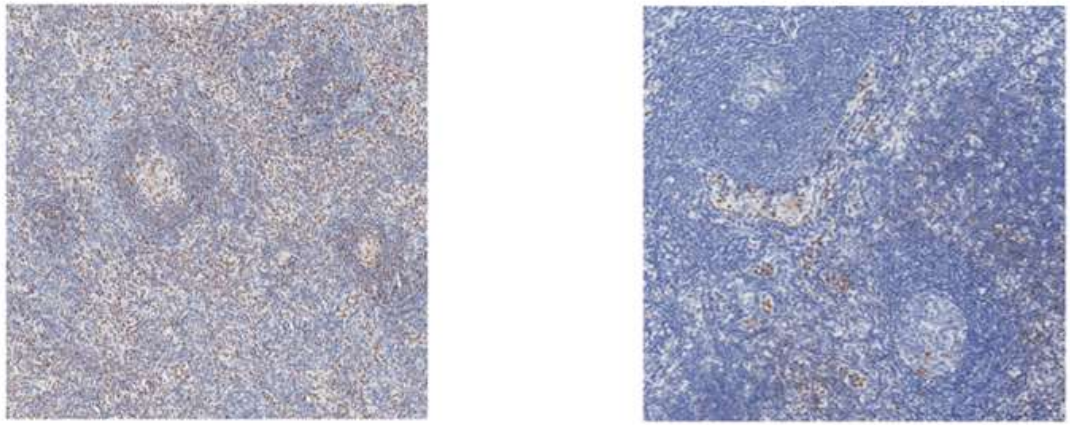
Enriched pathways in Cluster-1 siltuximab responders vs HDs		
Pathway	Nominal P value	FDR q-value
TNFa signaling via NFkB	0.004	0.090
Estrogen Response Early	0.013	0.137
IFN gamma response	0.033	0.149
Allograft Rejection Signature	0.033	0.167
IL-6-JAK STAT3 Signaling	0.020	0.184
Enriched pathways in siltuximab non-responders vs HDs		
Pathway	Nominal P value	FDR q-value
KRAS Signaling Up	0.029	0.118
IL-6-JAK STAT3 Signaling	0.031	0.144
TNFa signaling via NFkB	0.006	0.173
Allograft Rejection Signature	0.043	0.177
IL2 STAT5 Signaling	0.018	0.179

Pierson SK, et al. *Blood Adv*. 2021;5(17):3445-3456.

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Activation of JAK-STAT Pathway in Non-Responder Lymph Nodes





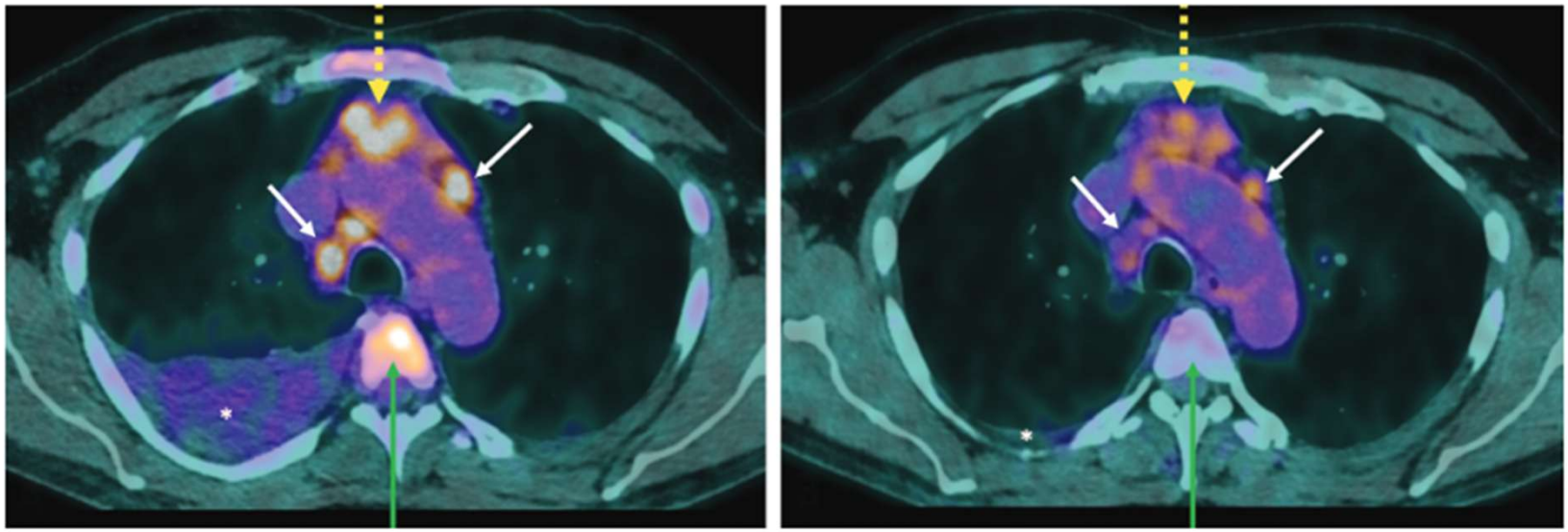
pSTAT3 expression in iMCD and normal lymph node

Pierson SK, et al. *Blood Adv*. 2021;5(17):3445-3456.

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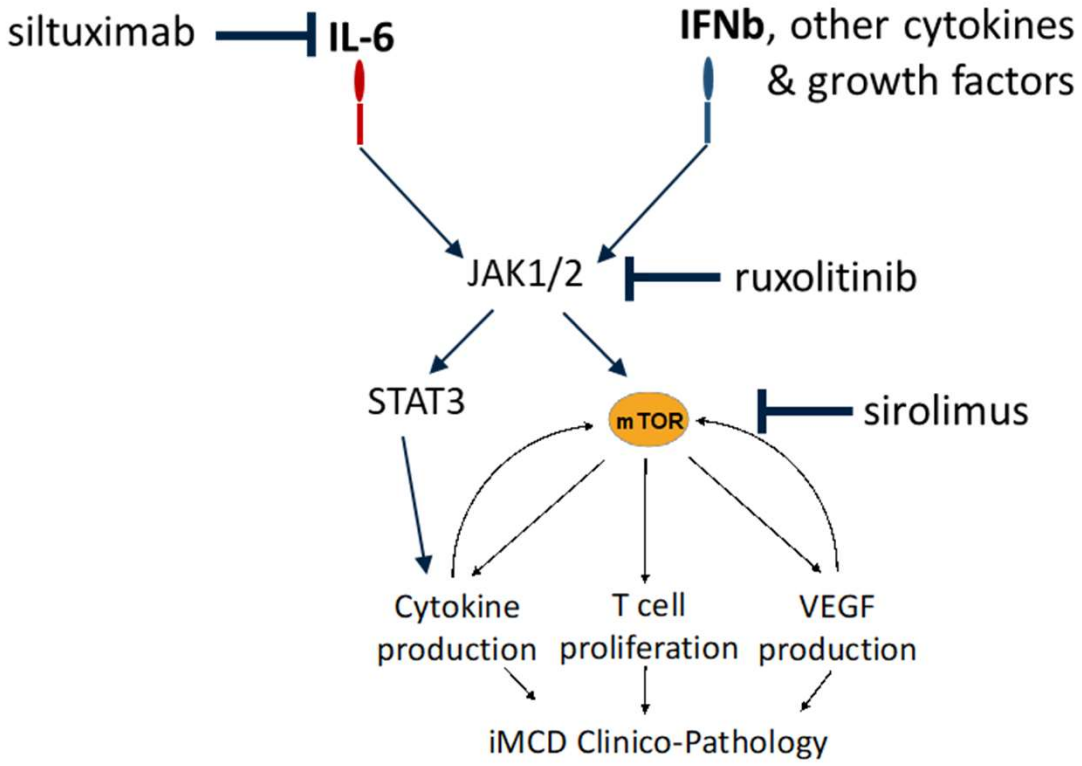
iMCD-TAFRO Treated with Ruxolitinib

Figure. ^{18}FDG PET-CT imaging at admission (^{18}FDG PET-CT imaging at admission (*left*) and at week 48 after 8 months of ruxolitinib (≥20 mg/d) (*right*).



FDG = fluorodeoxyglucose; PET-CT = positron emission tomography computed tomography.
Killian M, et al. *Ann Intern Med*. 2021;174(5):719-721.

Translating Pathophysiology into Therapy

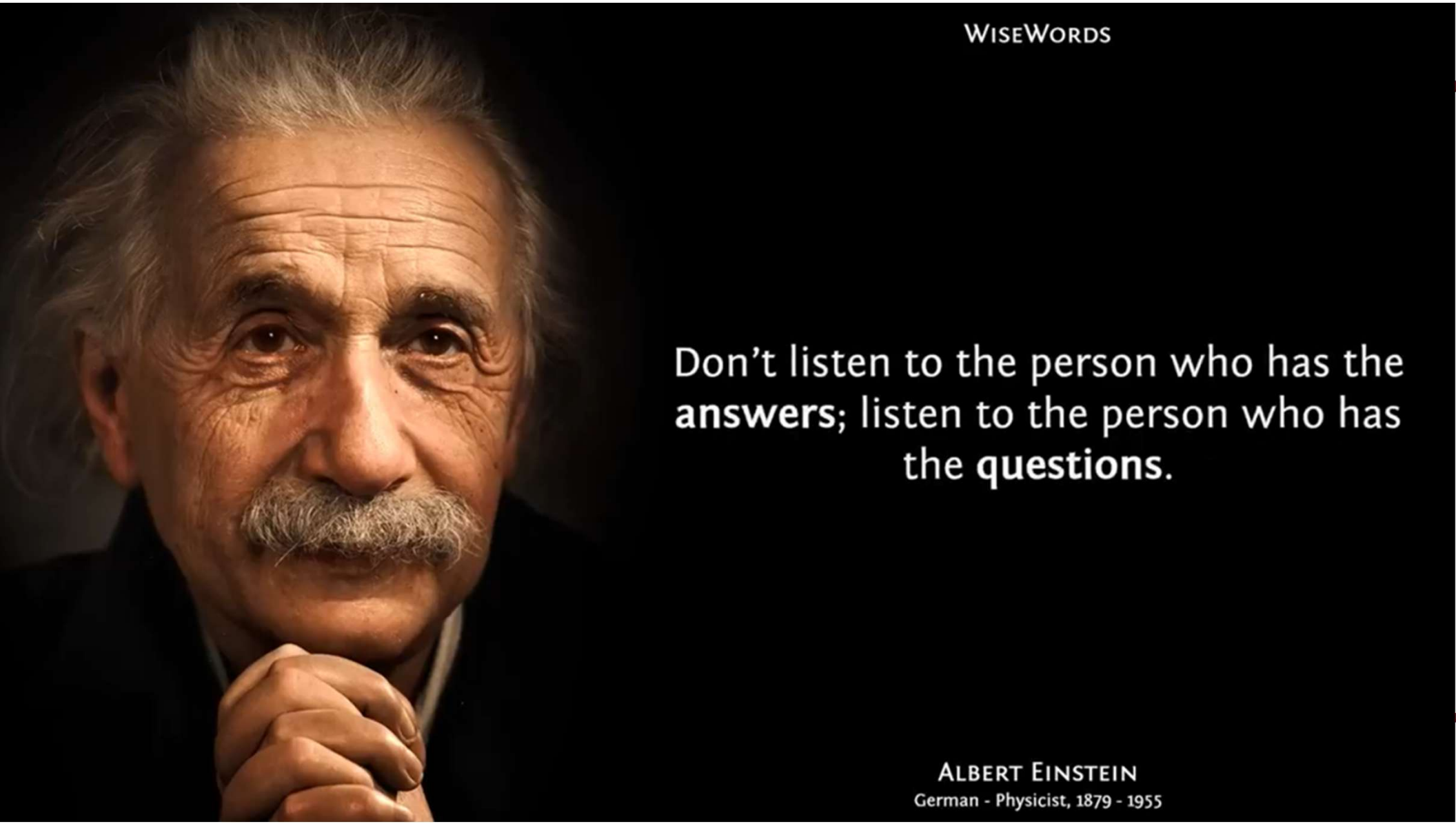


Adapted from Arenas DJ, et al. *Blood*. 2020;135(19):1673-1684.

Castleman Disease Expert Panel



CDCN [www.cdcn.org]. https://cdcn.org/expert-panel. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Castleman Disease V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org.


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

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Q&A Session