UNIVERSITA' DI TORINO

Dipartimento di Biotecnologie
Molecolari e Scienze per la Salute

EMATOLOGIA UNIVERSITARIA
LABORATORIO DI BIOLOGIA
MOLECOLARE

La malattia di Castleman

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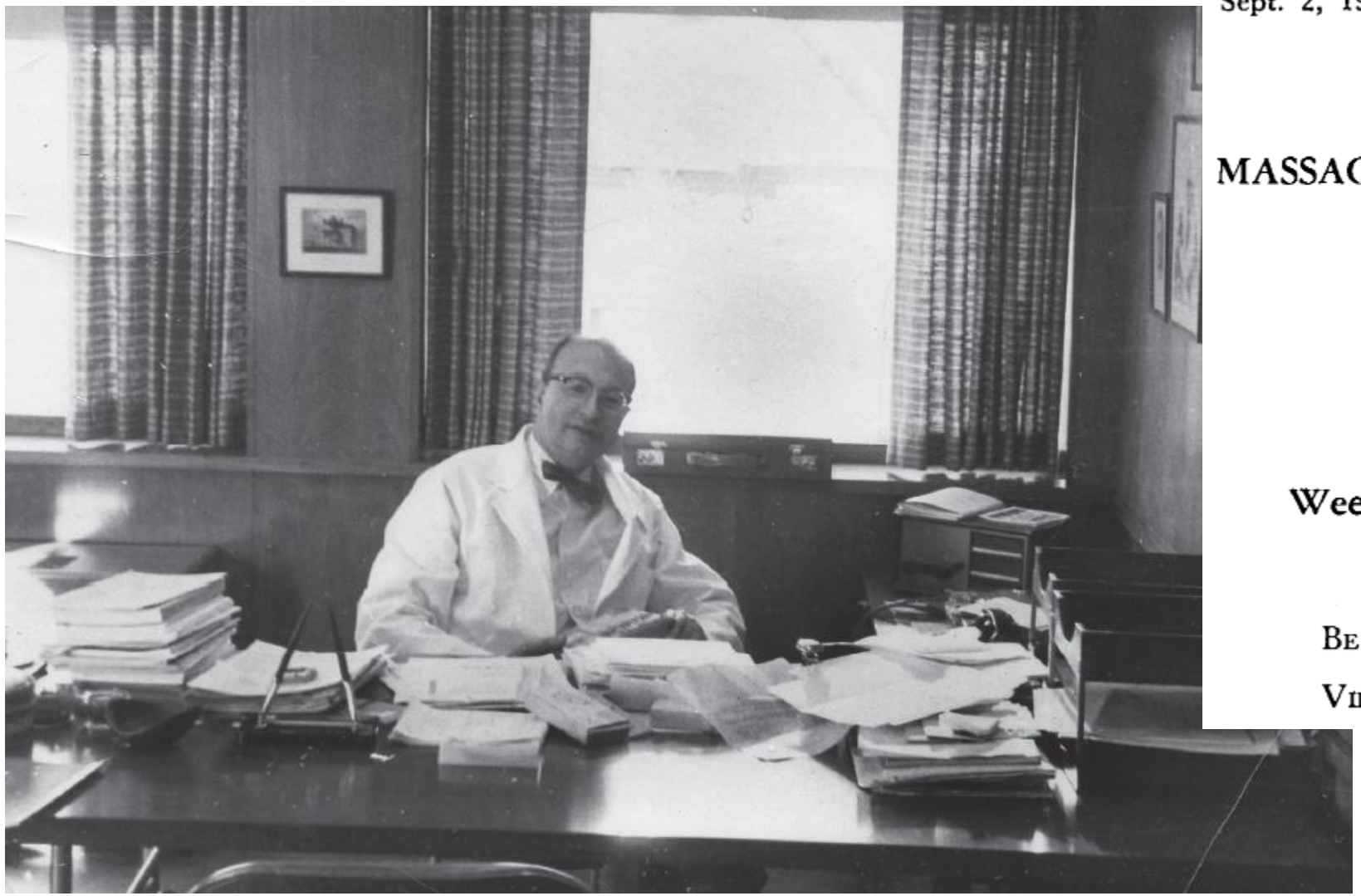
Chair of the FIL Biological & Bioinformatics Studies Committee

HemaSphere AE for lymphoma

Disclosures of Simone Ferrero

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other (travel expenses)
Janssen	x		x		x	x	
EUSA Pharma			x		x	x	
Morphosys	x						
Incyte	x					x	
Gilead	x				x		
Abbvie			x			x	
Roche					x	x	
Eli Lilly					x		x
Astra Zeneca						x	
Gentili					x		
Italfarmaco						x	
Sandoz			x		x		
Beigene					x		
Recordati			x		x	x	
Novartis					x		x
Takeda							x
CSL Behring						x	
SOBI						x	



THE NEW ENGLAND JOURNAL OF MEDICINE

Sept. 2, 1954

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*

Benjamin Castleman
(1906-1982)

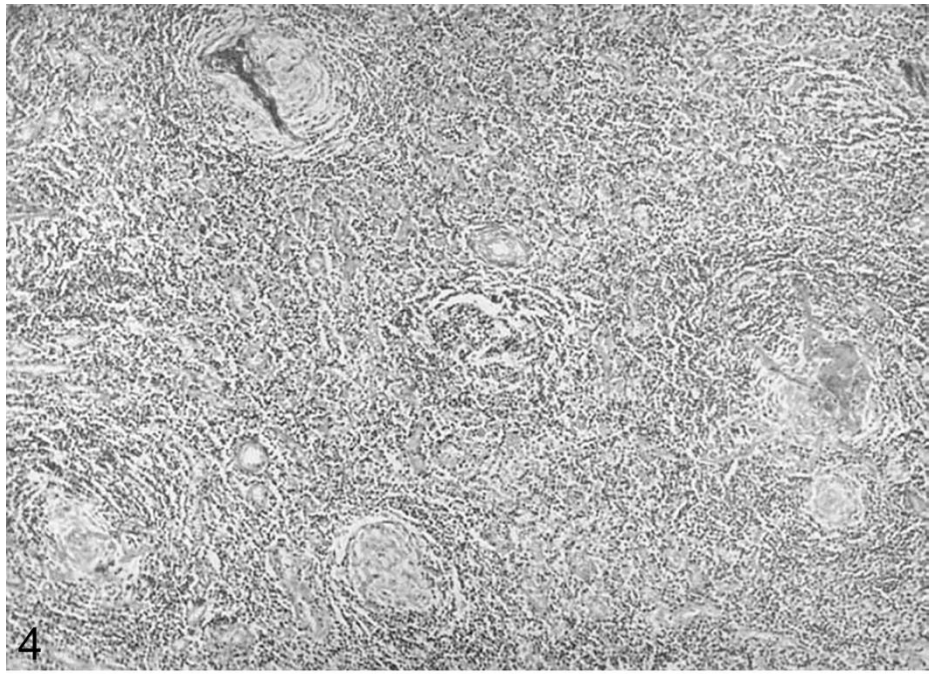


Figure 4. Node with increased density of follicles having germinal centers of variable morphologies (cellular to hyalinized) (hematoxylin-eosin, magnification not stated); from Castleman et al,[2]Cancer, vol 9, 1956, with permission from John Wiley & Sons Inc and American Cancer Society.

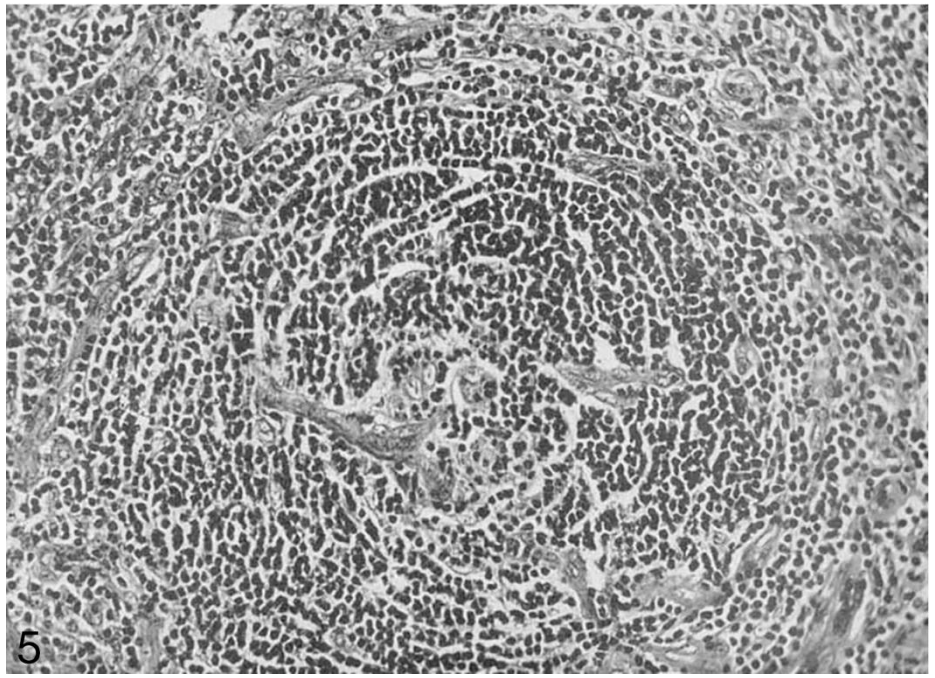
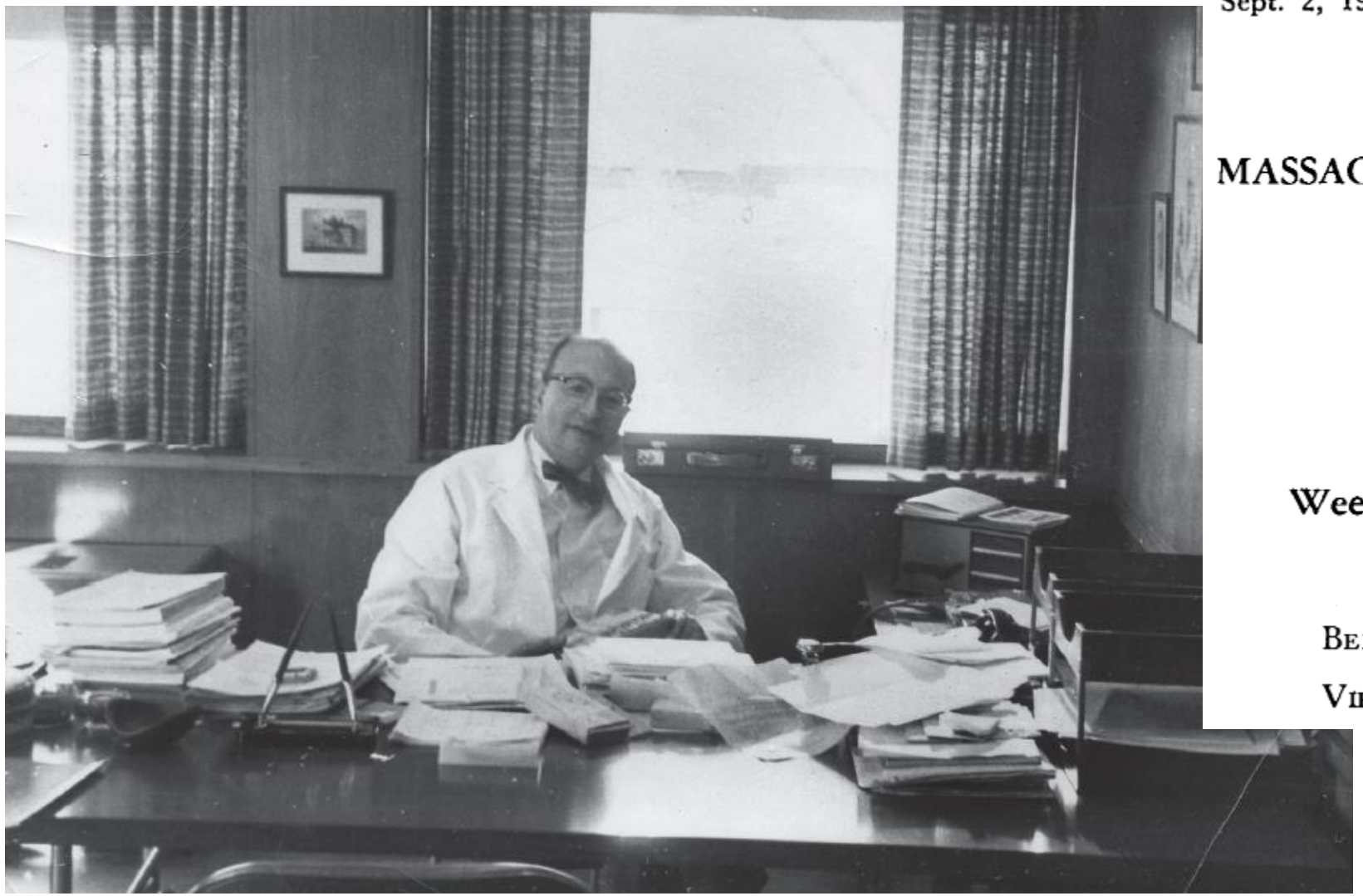


Figure 5. Node with increased vascularity with thick-walled blood vessels with hyalinized walls entering the follicles (hematoxylin-eosin, ×350) from Castleman et al,[2]Cancer, vol 9, 1956, with permission from John Wiley & Sons Inc and the American Cancer Society.

Arch Pathol Lab Med. 2022;146(11):1412-1415. doi:10.5858/arpa.2021-0205-HP



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«Malattia infiammatoria generalizzata associata a linfoadenopatie croniche reattive e a sintomatologia sistemica con rischio di evoluzione a insufficienza multiorgano» [SF*]

*speaker's expert opinion

Malattia di Castleman

-Classificazione

nature reviews disease primers

Castleman disease

Antonino Carbone[1,2]✉, Margaret Borok[3], Blossom Damania[4], Annunziata Gloghini[5], Mark N. Polizzotto[6], Raj K. Jayanthan[7], David C. Fajgenbaum[8] and Mark Bower[9]

UNICENTRICA

- Singola regione linfonodale convolta
- Tipicamente minimi o assenti sintomi sistemici
- Alto tasso di guarigione dopo exeresi linfonodale

MULTICENTRICA

KSHV- MCD
- HHV8-Associata
- Pazienti HIV-positivi
- Pazienti HIV-negativi con altra causa di immunodeficienza

(es. trapianti d'organo)

IDIOPATICA

iMCD- NOS
- HHV-8 e HIV negativi
- Interessa dal 30% al 60% dei casi con MCD
- Aumentata incidenza di neoplasie

iMCD- TAFRO
- **T**rombocitopenia
- **A**scite
- **F**ebbre
- Fibrosi **R**eticulinica
- **O**rganomegalia

iMCD- POEMS
- **P**olineuropatia
- **O**rganomegalia
- **E**ndocrinopatia
- Disordine plasmacellulare **M**onoclonale
- **S** Alterazioni cute

Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6–directed therapy

blood advances

Sudipto Mukherjee,[1] Rabecka Martin,[2] Brenda Sande,[2] Jeremy S. Paige,[3] and David C. Fajgenbaum[4]

[1]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [2]EUSA Pharma, Burlington, MA; [3]Eversana, LLC, Milwaukee, WI; and [4]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

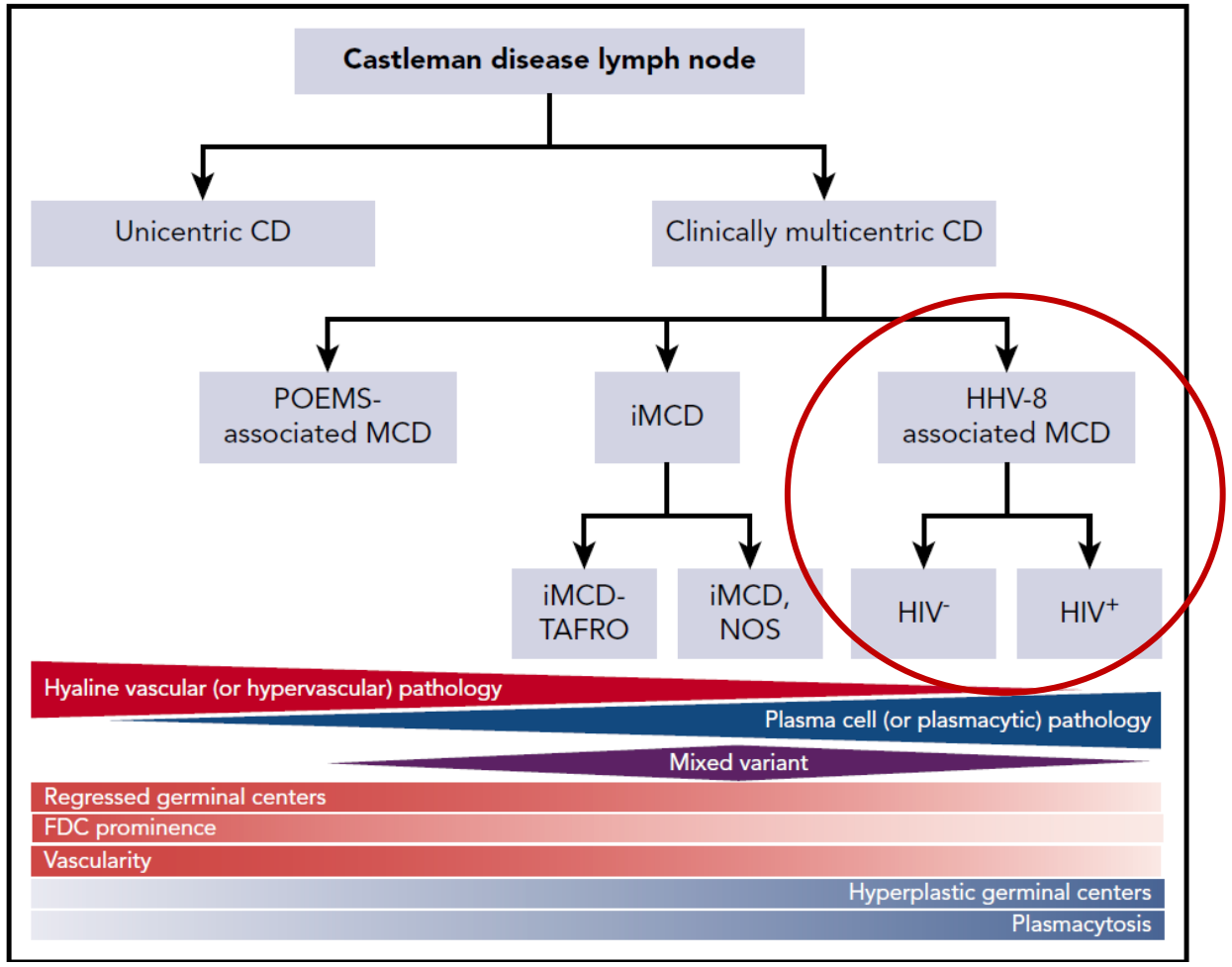
Table 3. Annual incidence and prevalence from 2017 to 2018

	All CD		UCD		MCD		HHV-8-MCD		iMCD	
	Cases per million	Total US cases	Cases per million	Total US cases	Cases per million	Total US cases	Cases per million	Total US cases	Cases per million	Total US cases
Incidence										
2017	5.5 (2.8-11.5)	1804 (928-3768)	1.9 (0.7-5.5)	612 (239-1804)	4 (1.71-9.9)	1303 (560-3250)	0.4 (0.1-1.6)	141 (44-514)	3.4 (1.4-9.2)	1111 (440-2996)
2018	5.8 (3.0-12.9)	1904 (994-4216)	2.5 (0.9-7.9)	800 (307-2572)	3.7 (1.57-10.7)	1213 (513-3503)	0.6 (0.1-3.1)	193 (39-1027)	3.1 (1.2-10.0)	1022 (405-3274)
Prevalence										
2017	10.2 (6.2-17.3)	3326 (2034-5671)	2.7 (1.2-6.6)	894 (409-2174)	7.7 (4.3-14.3)	2504 (1407-4675)	0.7 (0.2-3.1)	235 (65-1024)	6.9 (3.7-13.3)	2246 (1223-4348)
2018	16.2 (10.5-25.6)	5282 (3450-8385)	5.1 (2.6-11.2)	1653 (855-3662)	11 (6.6-19.5)	3613.4 (2154-6381)	1.2 (0.4-4.3)	395 (131-1407)	9.7 (5.6-17.8)	3172 (1820-5835)

Definition of rare disease (WHO): prevalence <= 5 cases in 10000 citizens

1/2000 = RARE

HHV-8 associated MCD

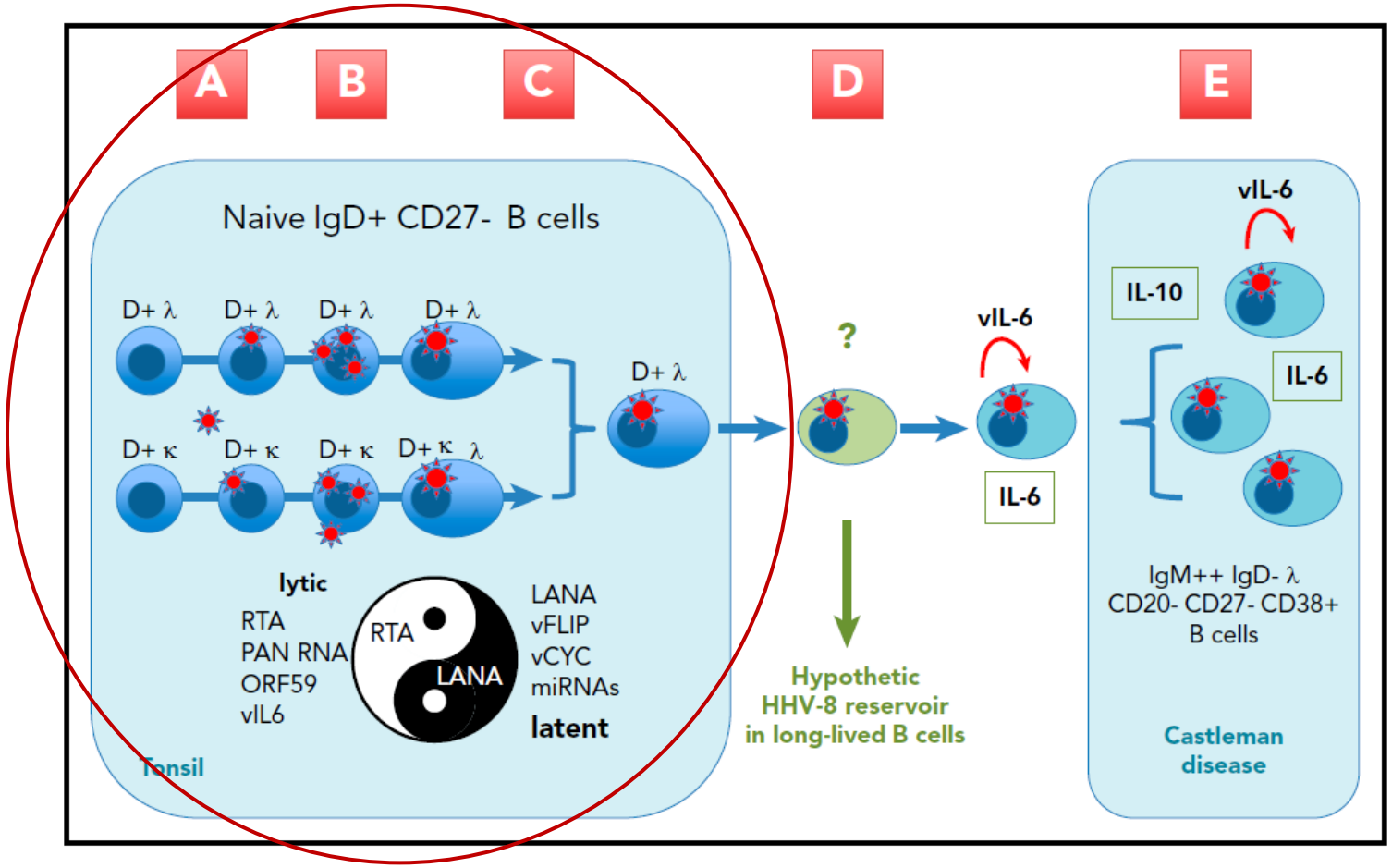


In immunocompromised individuals, **HHV8** can replicate in lymph node plasmablasts and transcribe the **vIL-6** that drives symptoms, signs, and lymph node pathology along with a cascade of **other cytokines** including hIL-6

Incidence of HHV8-MCD seems to have **increased from the pre-ART to the current ART era**
Median age at presentation is in the 40s in HIV+ and in the 60s in HIV- patients.

Dispenzieri A, Fajgenbaum D, Blood 2020

From Infection to MCD



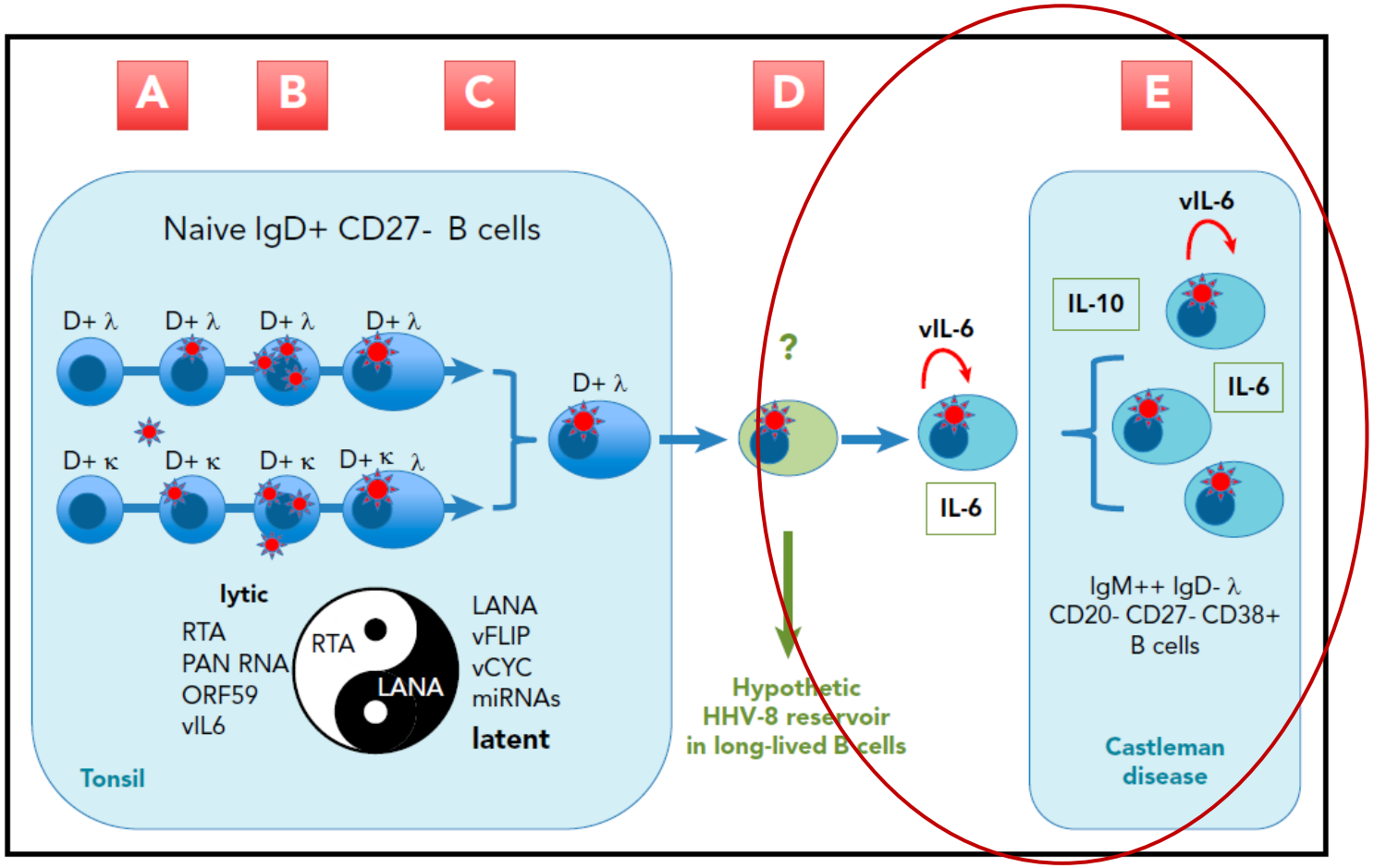
A. Infection

B. HHV8 remains as an episome during **latency**, when only few HHV8-associated genes are expressed, as LANA

C. Phenotype shift occurs through reinduction of **Rag-mediated V(D)J recombination** toward B cells expressing both k and λ light chains and, ultimately, only naive IgM λ B cells. **Blasting, dividing, and proliferation** of the infected cells.

Oksenhendler E. et al, Blood 2019

From Infection to MCD



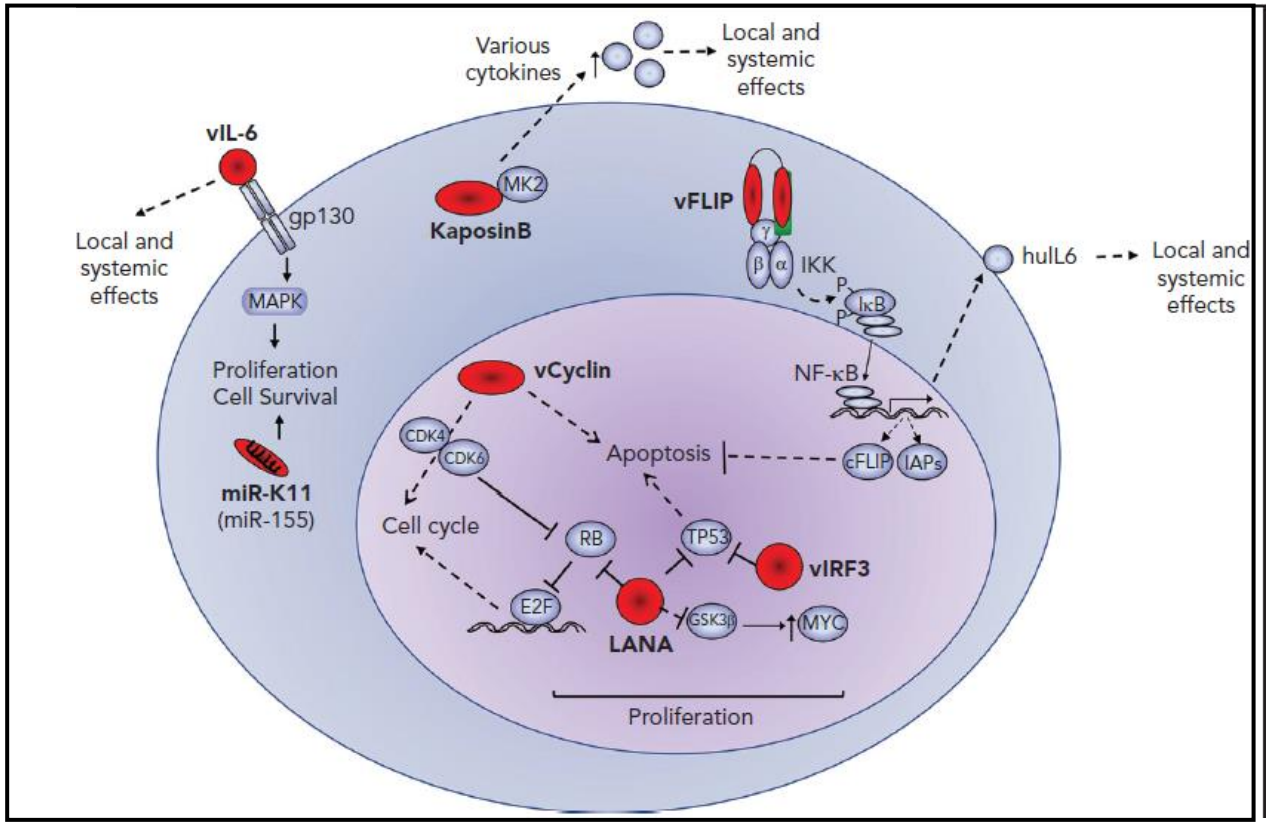
D. At that point HHV-8 have to exhibit a specific strategy to escape immune surveillance and constitute an **KSHV/HHV-8 reservoir.** The exact phenotype of the reservoir cell remains unknown

E. During the lytic phase, nearly every viral gene is expressed, resulting **in infectious virions** and usually subsequent cell death**.** **vIL-6** is probably crucial for HHV-8–infected cells to generate the MCD lesions observed in lymphoid organs.

Oksenhendler E. et al, Blood 2019

From Infection to MCD

LANA: plays an important role in viral replication, it also seems to contribute to lymphoid proliferation binding and inactivating TP53 and RB1.
vIL6: impairs B-cell apoptosis and induces VEGF
Kaposin B: increases cytokine production
vCyc: binds and activates CDK6
vIRF3: plays a role in B-cell differentiation and contributes to KSHV-MCD plasmablasts.
vFLIP: upregulates **NF-kB**, which then induces expression of **downstream antiapoptotic proteins and cytokines**, including hulL-6.
miRs: by inhibiting apoptosis and promoting viral latency.

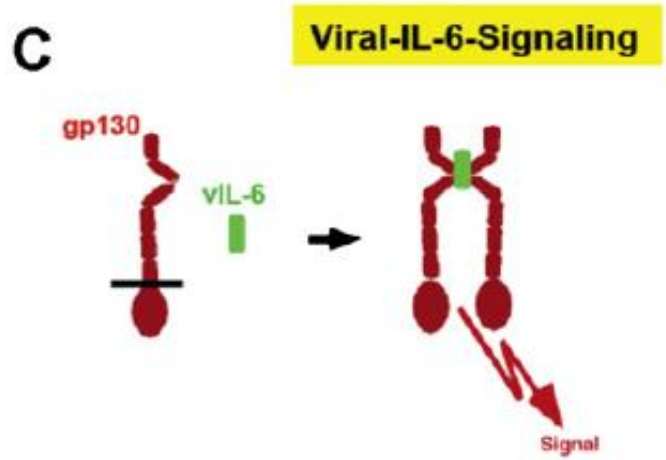


HHV8 induces:
- **Proliferation**
- **Apoptosis inhibition**
- **Pro-inflammatory Cytokines production**

Cesarman E. et al, Blood 2022

vIL6 in HHV8-MCD

- **vIL-6** activates hIL-6R (gp130) **also in the absence of the co-receptor gp80 (IL-6R)**, requested by h-IL6
- other viral mediators (**LANA-1 e vFLIP**) induce hIL-6 expression by **NF-kB** activation
- v-IL6 induces **VEGF**, that induces hIL-6 production from endothelial cells
- v-IL6 can induce **endogenous hIL6** secretion, which may contribute to the clinical features of MCD



Alomari N et al, Viruses 2020

Clinical Features

Symptoms:

- Fever – 100%
- Lymphadenopathy – 96 %
- Splenomegaly – 86%
- Hepatomegaly – 63%
- Pulmonary signs or symptoms – 35%
- Edema – 29%
- Ascites – 6 %

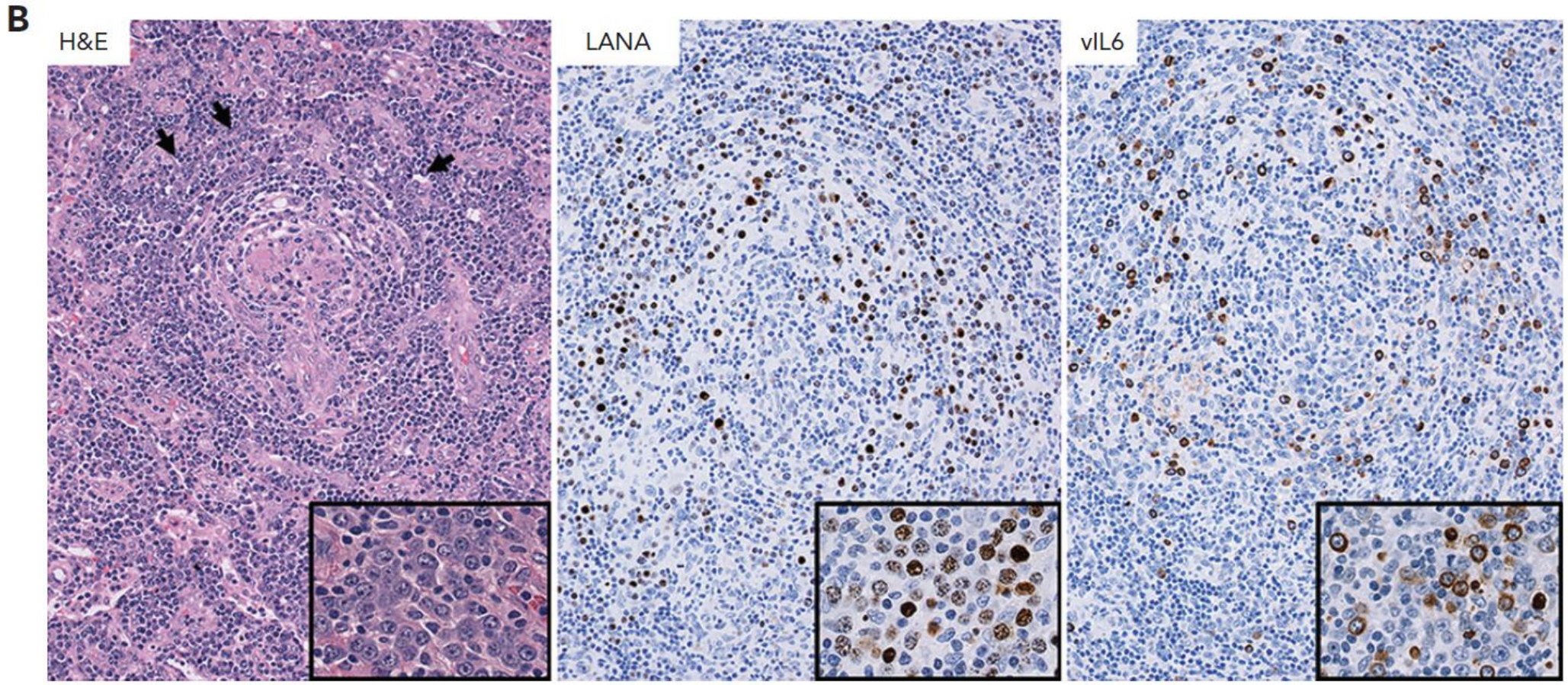
Laboratory abnormalities

- Anemia
- Thrombocytopenia or Thrombocytosis
- Elevated erythrocyte sedimentation rate and C-reactive protein
- Hypoalbuminemia
- Polyclonal hypergammaglobulinemia
- Kidney dysfunction

Most of the symptoms appear to be cytokine-related, involving IL-6, HHV-8 IL-6 (vIL-6), and IL-10.

Cesarman E. et al, Blood 2022
Mylona EE et al, AIDS Rev 2008

Pathologic diagnosis



There are many **plasmablasts in the interfollicular area** and prominent **vascular proliferation**. In addition, a number of HHV8+ plasmablasts are present in mantle cell zones

These cells are usually positive for HHV8 latent nuclear antigen (**LANA-1**) and for **vIL6**.

Phenotypically, these plasmablasts resemble mature B cells, but they originate from **pre–germinal center B cells**. HHV-8 drives them to differentiate into plasmablasts without going through the GC

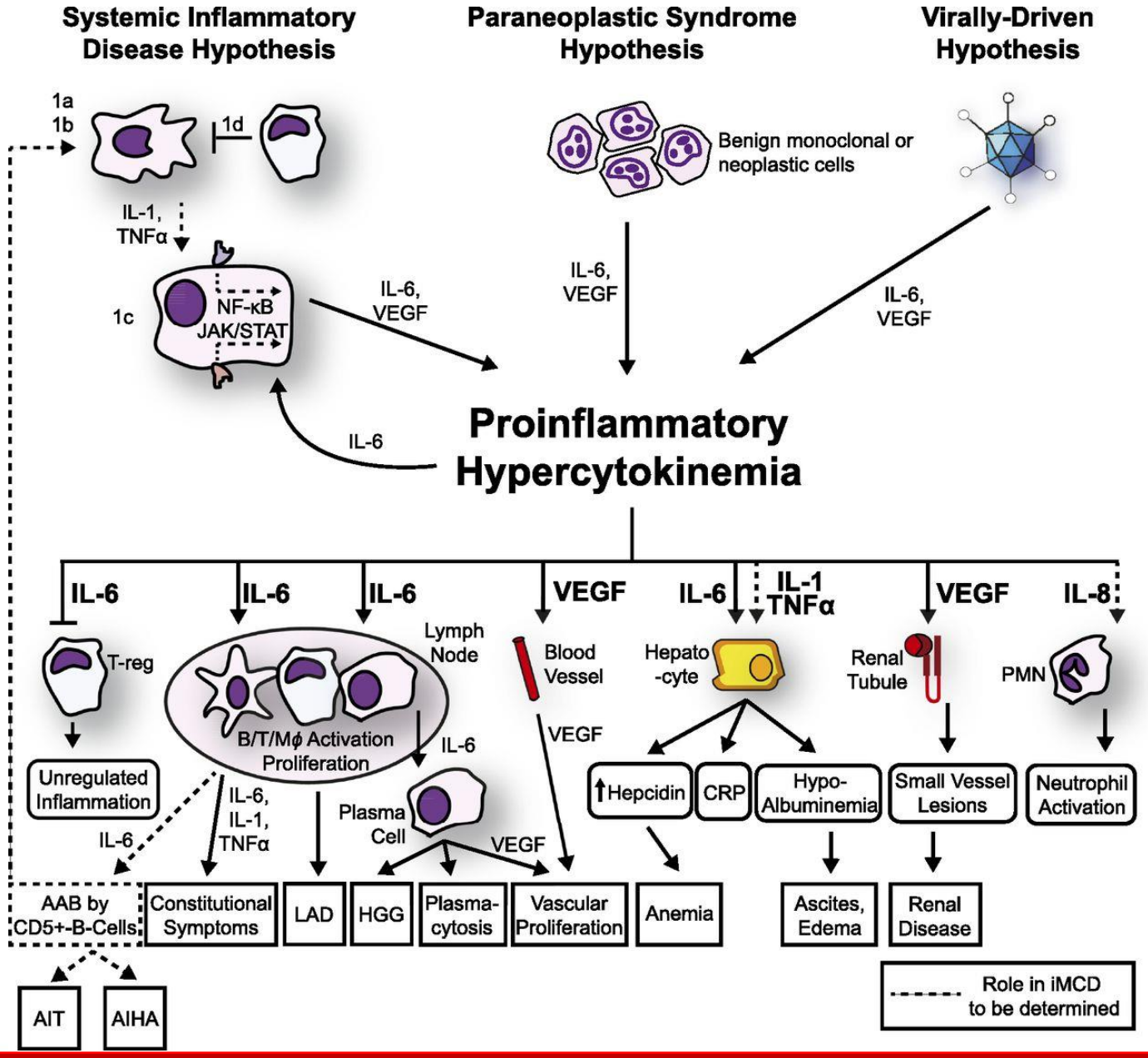
Cesarman E. et al, Blood 2022

Malattia di Castleman multicentrica idiopatica

-Patogenesi

- Processo auto-immune mediato da auto-anticorpi o da un processo auto-infiammatorio (mutazione germinale in un gene infiammatorio?)
- Presenza di una piccola popolazione di cellule stromali monoclonali (tumore?)
- Ruolo di altri virus oltre ad HHV-8 (EBV, HBV, CMV, sconosciuto?)

Rilascio di IL-6 e altre citochine pro-infiammatorie



blood
2014 123: 2924-2933
doi:10.1182/blood-2013-12-545087 originally published online March 12, 2014

Malattia di Castleman multicentrica idiopatica - criteri diagnostici

International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease

David C. Fajgenbaum,[1] Thomas S. Uldrick,[2] Adam Bagg,[3] Dale Frank,[3] David Wu,[4] Gordan Srkalovic,[5] David Simpson,[6] Amy Y. Liu,[1] David Menke,[7] Shanmuganathan Chandrakasan,[8] Mary Jo Lechowicz,[8] Raymond S. M. Wong,[9] Sheila Pierson,[1] Michele Paessler,[10] Jean-François Rossi,[11] Makoto Ide,[12] Jason Ruth,[13] Michael Croglio,[14] Alexander Suarez,[1] Vera Krymskaya,[15] Amy Chadburn,[16] Gisele Colleoni,[17] Sunita Nasta,[18] Raj Jayanthan,[19] Christopher S. Nabel,[20] Corey Casper,[21] Angela Dispenzieri,[22] Alexander Fossâ,[23] Dermot Kelleher,[24] Razelle Kurzrock,[25] Peter Voorhees,[26] Ahmet Dogan,[27] Kazuyuki Yoshizaki,[28] Frits van Rhee,[29] Eric Oksenhendler,[30] Elaine S. Jaffe,[2] Kojo S. J. Elenitoba-Johnson,[3] and Megan S. Lim[3]

blood

Inclusion diagnostic criteria for iMCD
I. Major Criteria (need both):
1. Histopathologic lymph node features consistent with the iMCD spectrum
2. Enlarged lymph nodes (≥ 1 cm in short-axis diameter) in ≥ 2 lymph node stations
II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)
Laboratory*
1. Elevated CRP (>10 mg/L) or ESR (>15 mm/h)
2. Anemia (hemoglobin < 12.5 g/dL for males, hemoglobin < 11.5 g/dL for females)
3. Thrombocytopenia (platelet count < 150 k/mL) or thrombocytosis (platelet count > 400 k/mL)
4. Hypoalbuminemia (albumin < 3.5 g/dL)
5. Renal dysfunction (eGFR < 60 mL/min/1.73m2) or proteinuria (> 150 mg/24 h or > 10 mg/100 ml)
6. Polyclonal hypergammaglobulinemia (total g globulin or immunoglobulin G > 1700 mg/dL)
Clinical
1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue
2. Large spleen and/or liver
3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion
4. Eruptive cherry hemangiomatosis or violaceous papules
5. Lymphocytic interstitial pneumonitis
Select additional features supportive of, but not required for diagnosis
Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M
Diagnosis of other disorders that have been associated with iMCD
Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)

Diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease (iMCD).
Adapted from Fajgenbaum, D. C. et al, Blood, 2017

Malattia di Castleman multicentrica idiopatica

- Criteri diagnostici

1. Devono essere soddisfatti entrambi i criteri maggiori e almeno 2 su 11 criteri minori (tra cui almeno 1 anomalia di laboratorio)

2. Tutte le malattie elencate nei criteri di esclusione devono essere escluse

blood

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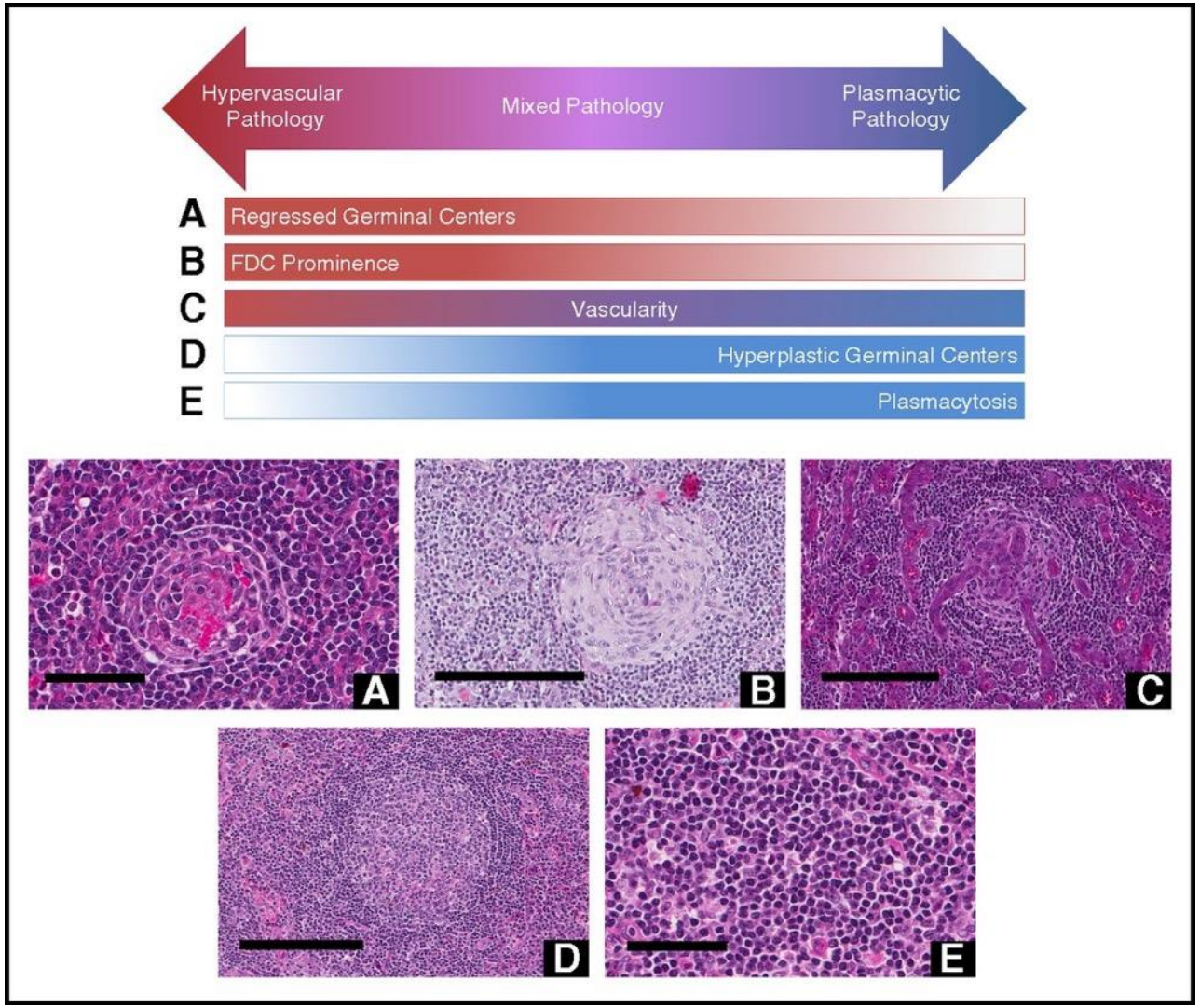
Autoimmune/autoinflammatory diseases
Malignant/lymphoproliferative disorders

Malattia di Castleman multicentrica idiopatica

-Criteri istologici



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Current Therapeutics
Year XXV, N. x, Xxxx 2022

Collection of clinical cases of multicentric Castleman disease

Criteri clinici

(Fajgenbaum et al., 2017)

Regular Article — blood

CLINICAL TRIALS AND OBSERVATIONS

International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease

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- **Sintomi B**: Febbre, sudorazioni notturne, affaticamento e perdita di peso significativa sono indicativi di infiammazione sistemica, (artralgie)

- **Splenomegalia e/o epatomegalia**: L'ingrossamento della milza e/o del fegato è frequente nei pazienti con iMCD

- **Accumulo di liquidi**: Edema, anasarca, ascite o versamento pleurico riflettono disfunzione linfatica

  (Casi gravi con grave infiammazione generalizzata e insufficienza d'organo –> MOF)

- **Emangiomatosi eruttiva o papule violacee**: Manifestazioni cutanee che includono piccoli angiomi eruttivi ("emangioma a ciliegia")

- **Polmonite interstiziale linfocitica (LIP)**: Infiltrati linfocitari polmonari si osservano nelle forme avanzate

Malattia di Castleman multicentrica idiopatica

- Criteri diagnostici

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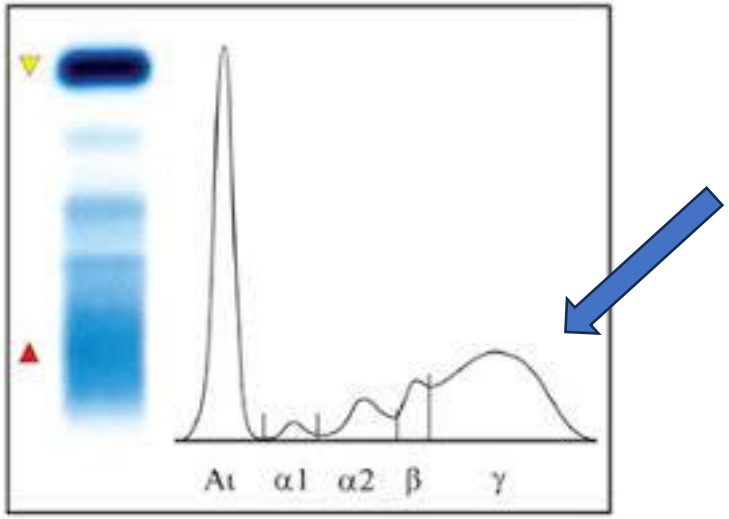
Autoimmune/autoinflammatory diseases
Malignant/lymphoproliferative disorders



Criteri di laboratorio

(Fajgenbaum et al., 2017)

Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease

David C. Fajgenbaum,[1] Thomas S. Uldrick,[2] Adam Bagg,[3] Dale Frank,[3] David Wu,[4] Gordan Srkalovic,[5] David Simpson,[6] Amy Y. Liu,[1] David Menke,[7] Shanmuganathan Chandrakasan,[8] Mary Jo Lechowicz,[8] Raymond S. M. Wong,[9] Sheila Pierson,[1] Michele Paessler,[10] Jean-François Rossi,[11] Makoto Ide,[12] Jason Ruth,[13] Michael Croglio,[14] Alexander Suarez,[1] Vera Krymskaya,[15] Amy Chadburn,[16] Gisele Colleoni,[17] Sunita Nasta,[18] Raj Jayanthan,[19] Christopher S. Nabel,[20] Corey Casper,[21] Angela Dispenzieri,[22] Alexander Fossá,[23] Dermot Kelleher,[24] Razelle Kurzrock,[25] Peter Voorhees,[26] Ahmet Dogan,[27] Kazuyuki Yoshizaki,[28] Frits van Rhee,[29] Eric Oksenhendler,[30] Elaine S. Jaffe,[2] Kojo S. J. Elenitoba-Johnson,[3] and Megan S. Lim[3]

1. **Elevata PCR (>10 mg/L) o VES (>15 mm/h)**: suggerisce uno stato di iperinfiammazione tipico della iMCD
2. **Anemia**: Definita da livelli di emoglobina inferiori a 12,5 g/dL negli uomini e 11,5 g/dL nelle donne, è comune nei pazienti con iMCD a causa della persistente infiammazione
3. **Trombocitopenia o trombocitosi**: Variazioni della conta piastrinica, con trombocitopenia (<150 k/mL) o trombocitosi (>400 k/mL) - Autoanticorpi (anti-eritrociti, anti-piastrine)
4. **Ipoalbuminemia**: Valori di albumina <3,5 g/dL suggeriscono infiammazione sistemica che compromette la sintesi epatica
5. **Disfunzione renale**: La ridotta eGFR (<60 mL/min/1,73 m^2) o proteinuria (>150 mg/24h)
6. **Ipergammaglobulinemia policlonale**: Un aumento delle IgG >1700 mg/dL, riflette una risposta immunitaria anomala tipica dell'iMCD

Malattia di Castleman multicentrica idiopatica
-Presentazione clinica: TAFRO syndrome

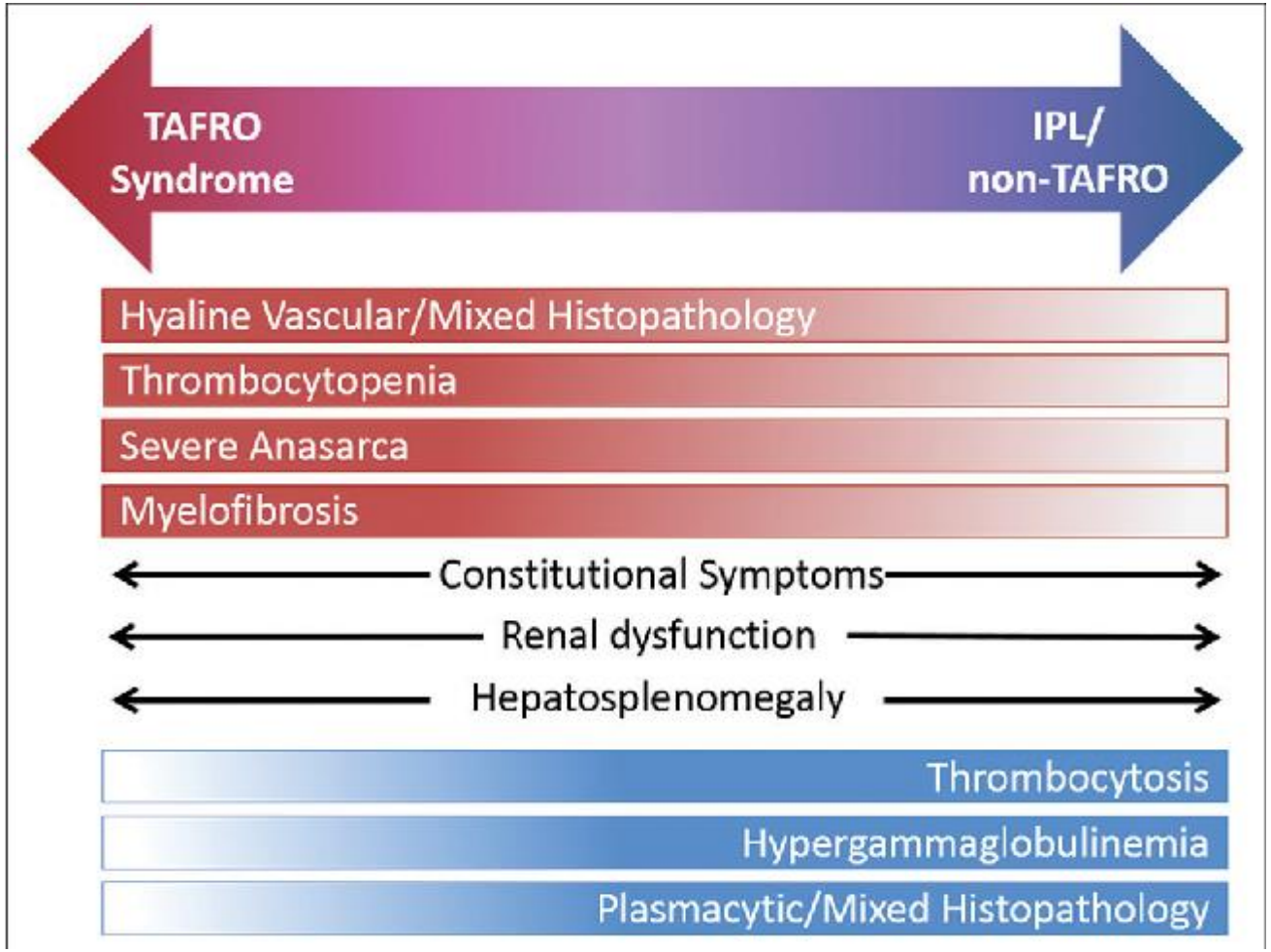


Table I Proposed diagnostic criteria for TAFRO-iMCD

1. Histopathological criteria
   - Compatible with the pathological findings of lymph nodes as TAFRO-iMCD
   - Negative LANA-1 for HHV8
2. Major criteria: 3 of 5 TAFRO symptoms
   - I. Thrombocytopenia
   - II. Anasarca
   - III. Fever
   - IV. Reticulin fibrosis
   - V. Organomegaly

   Absence of hypergammaglobulinemia

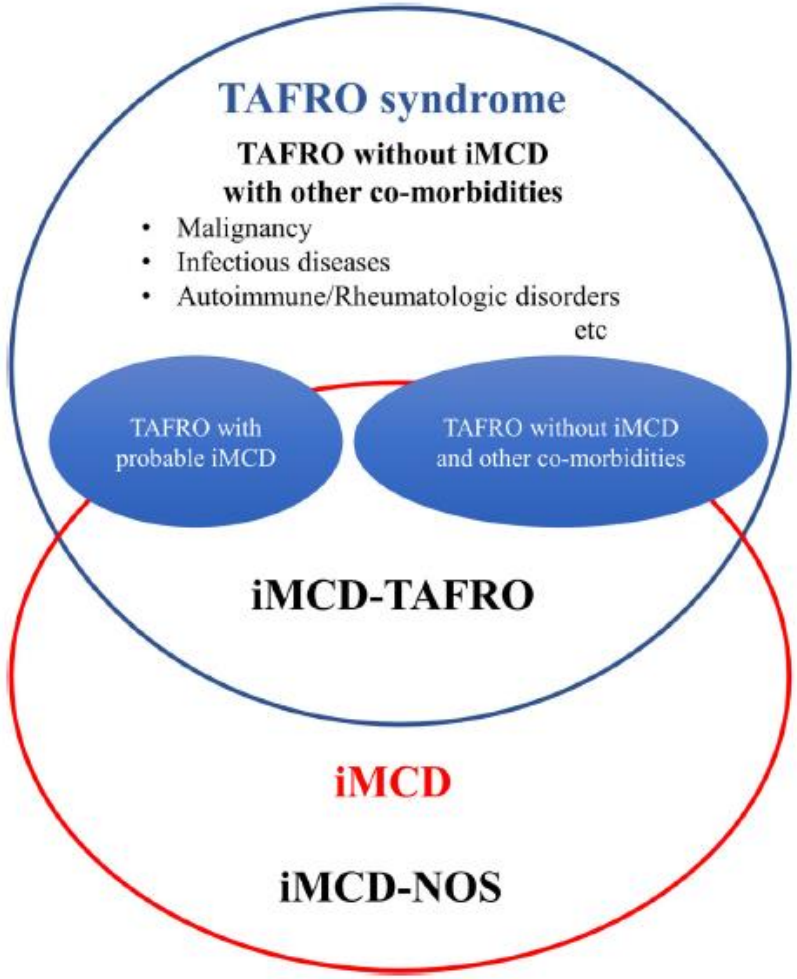
   Small volume lymphadenopathy
3. One or more of the minor criteria

   Hyperplasia/normoplasia of megakaryocytes in bone marrow

   High serum level of ALP without markedly elevated serum transaminase

Image from Srkalović, Gordan et al. "TAFRO syndrome: New subtype of idiopathic multicentric Castleman disease." Bosnian journal of basic medical sciences 17 2 (2017): 81-84 .

Malattia di Castleman multicentrica idiopatica
-Presentazione clinica: TAFRO syndrome



Received: 1 July 2021 | Revised: 3 July 2021 | Accepted: 10 July 2021
DOI: 10.1002/ajh.26292

RESEARCH ARTICLE

AJH WILEY

Validated international definition of the thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly clinical subtype (TAFRO) of idiopathic multicentric Castleman disease

Yoshito Nishimura[1,2] | David C. Fajgenbaum[3] | Sheila K. Pierson[3] | Noriko Iwaki[4] | Asami Nishikori[5] | Mitsuhiro Kawano[6] | Naoya Nakamura[7] | Koji Izutsu[8] | Kengo Takeuchi[9,10,11] | Midori Filiz Nishimura[12] | Yoshinobu Maeda[13] | Fumio Otsuka[1] | Kazuyuki Yoshizaki[14] | Eric Oksenhendler[15,16] | Frits van Rhee[17] | Yasuharu Sato[5]

Malattia di Castleman multicentrica idiopatica

- Criteri diagnostici

1. Devono essere soddisfatti entrambi i criteri maggiori e almeno 2 su 11 criteri minori (tra cui almeno 1 anomalia di laboratorio)

2. Tutte le malattie elencate nei criteri di esclusione devono essere escluse

Inclusion diagnostic criteria for iMCD
I. Major Criteria (need both):
1. Histopathologic lymph node features consistent with the iMCD spectrum
2. Enlarged lymph nodes (≥ 1 cm in short-axis diameter) in ≥ 2 lymph node stations
II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)
Laboratory*
1. Elevated CRP (>10 mg/L) or ESR (>15 mm/h)
2. Anemia (hemoglobin < 12.5 g/dL for males, hemoglobin < 11.5 g/dL for females)
3. Thrombocytopenia (platelet count < 150 k/mL) or thrombocytosis (platelet count > 400 k/mL)
4. Hypoalbuminemia (albumin < 3.5 g/dL)
5. Renal dysfunction (eGFR < 60 mL/min/1.73m2) or proteinuria (> 150 mg/24 h or > 10 mg/100 ml)
6. Polyclonal hypergammaglobulinemia (total g globulin or immunoglobulin G > 1700 mg/dL)
Clinical
1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue
2. Large spleen and/or liver
3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion
4. Eruptive cherry hemangiomatosis or violaceous papules
5. Lymphocytic interstitial pneumonitis
Select additional features supportive of, but not required for diagnosis
Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M
Diagnosis of other disorders that have been associated with iMCD
Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
Exclusion diagnostic criteria for iMCD
Infection-related disorders
Autoimmune/autoinflammatory diseases
Malignant/lymphoproliferative disorders

Diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease (iMCD).
Adapted from Fajgenbaum, D. C. et al, Blood, 2017

Adapted from
Dispenzieri A. et al, Blood 2021

Exclusion criteria

Infection-related disorders

1. HHV8
2. EBV LPD
3. Inflammation and adenopathy by other infection

HIV

Autoimmune/inflammatory disease

1. SLE
2. Rheumatoid arthritis
3. Adult-onset Still disease
4. Juvenile idiopathic arthritis
5. Autoimmune LPS

vasculitis?

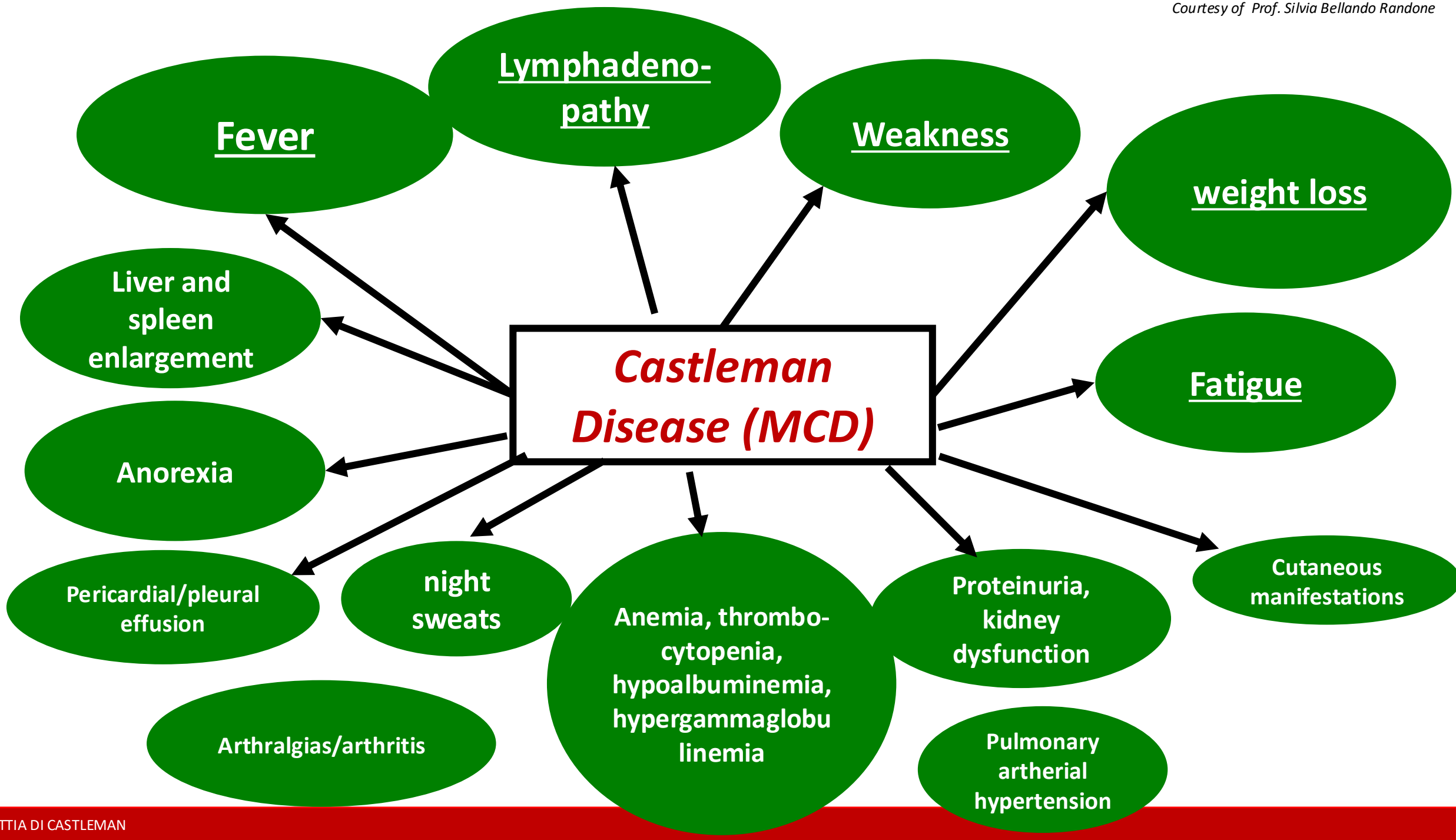
Malignant LPD

1. Lymphoma
2. Multiple myeloma
3. Primary lymph node plasmacytoma
4. FDC sarcoma
5. POEMS syndrome

Solid tumors!

A definitive diagnosis of MCD should be established after excluding the above diseases

Courtesy of Prof. Silvia Bellando Randone



Malattia di Castleman multicentrica idiopatica

- Grado di severità

- Per essere definite una MCI “severa”, devono essere presenti almeno 2 dei 5 criteri stabiliti

Severe iMCD

- ECOG ≥ 2 (PS)
- 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

blood® 2018 132: 2115-2124
doi:10.1182/blood-2018-07-862334 originally published online September 4, 2018

Malattia di Castleman multicentrica idiopatica
- Work-up raccomandato e trattamento

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

Frits van Rhee,[1] Peter Voorhees,[2] Angela Dispenzieri,[3] Alexander Fossâ,[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]

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2018 132: 2115-2124
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Malattia di Castleman multicentrica idiopatica
- Criteri di risposta al trattamento

Overall Response	Biochemical	Lymph Node	Symptoms
CR	Normal CRP, Hemoglobin, Albumin, GFR	CR	Normalization to baseline
PR	>50% improvement in all of CRP, Hemoglobin, Albumin, GFR	PR	Improvement in all 4 symptom categories, but not to baseline
SD	<50% improvement (or < 25% worsening) in all of CRP, Hemoglobin, Albumin, GFR	No PR or CR	Improvement in at least 1 (but not all) symptoms
PD	>25% worsening in any of CRP, Hemoglobin, Albumin, GFR	>25% increase	Any symptoms worse on ≥2 assessments

Symptom	Improvement Criteria
Fatigue	Decrease of ≥1 CTC grade point relative to baseline
Anorexia	Decrease of ≥1 CTC grade point relative to baseline
Fever	Decrease of ≥1°C relative to baseline
Weight	Increase of ≥5% relative to baseline

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

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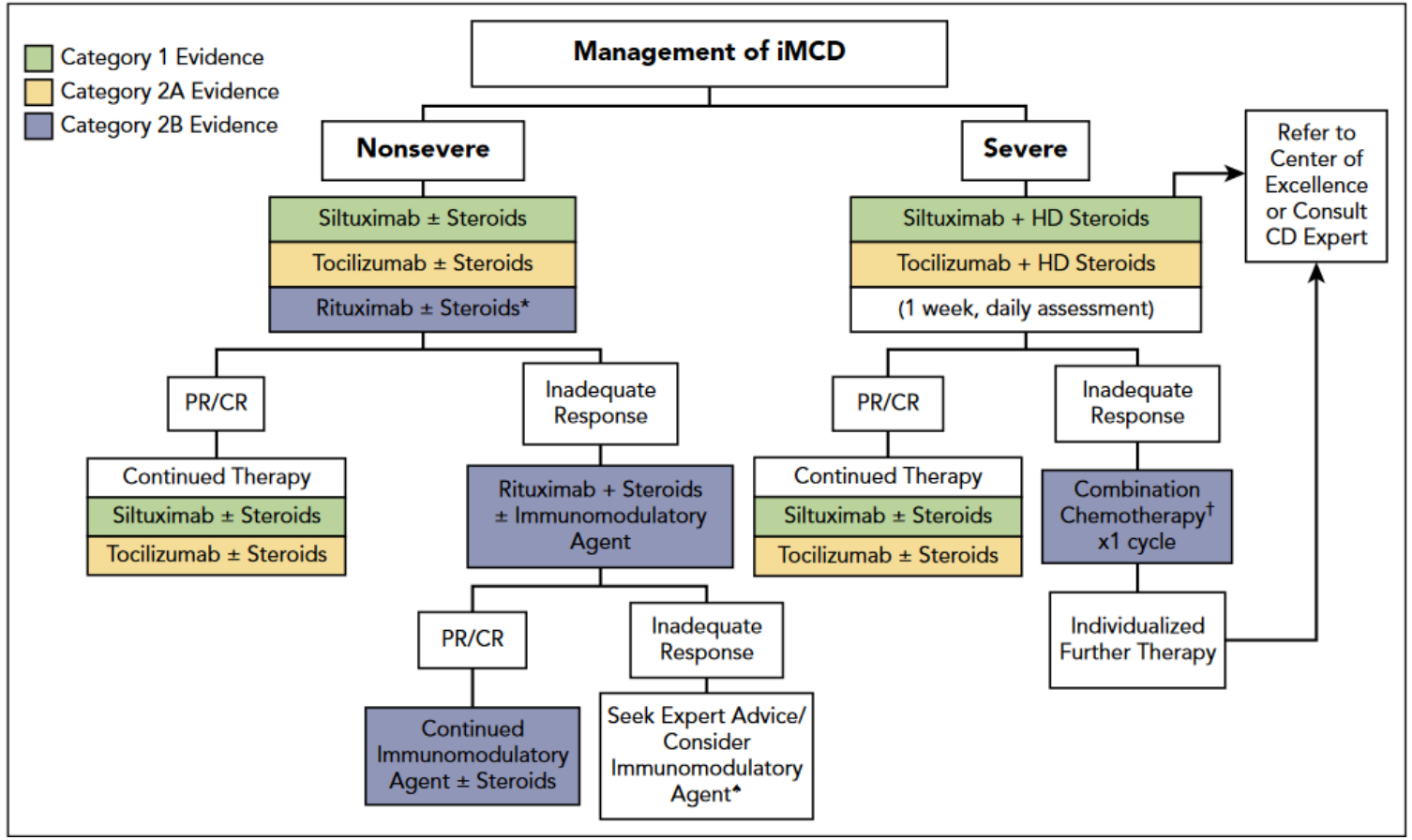


iMCD treatment

IL-6 blockade

- Inhibiting IL-6 → **Siltuximab**

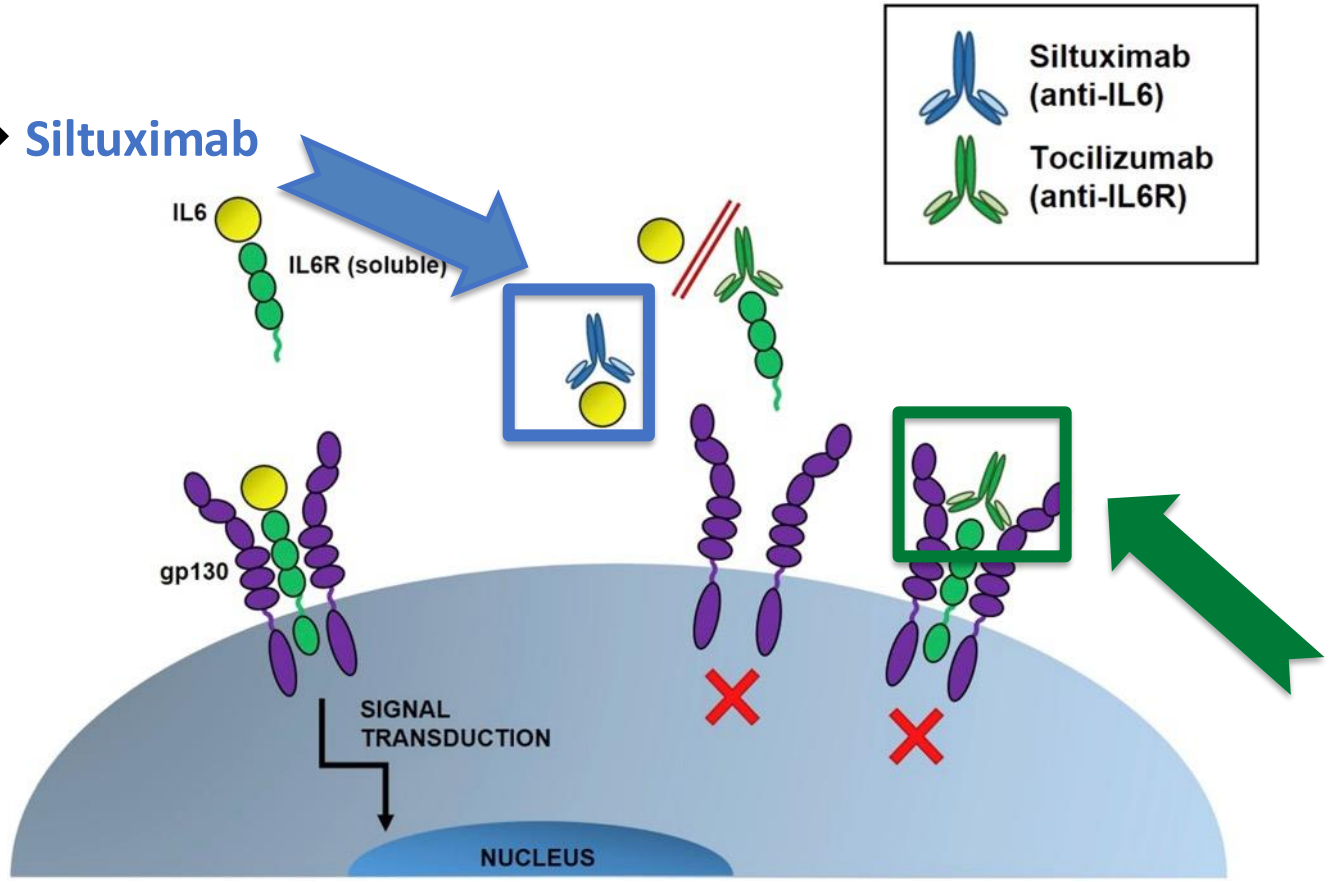


Figure from Treatment of Idiopathic Castleman Disease,
Frits van Rhee, Hematology/Oncology Clinics, 2018

- Inhibiting IL-6 binding on IL-6 receptor

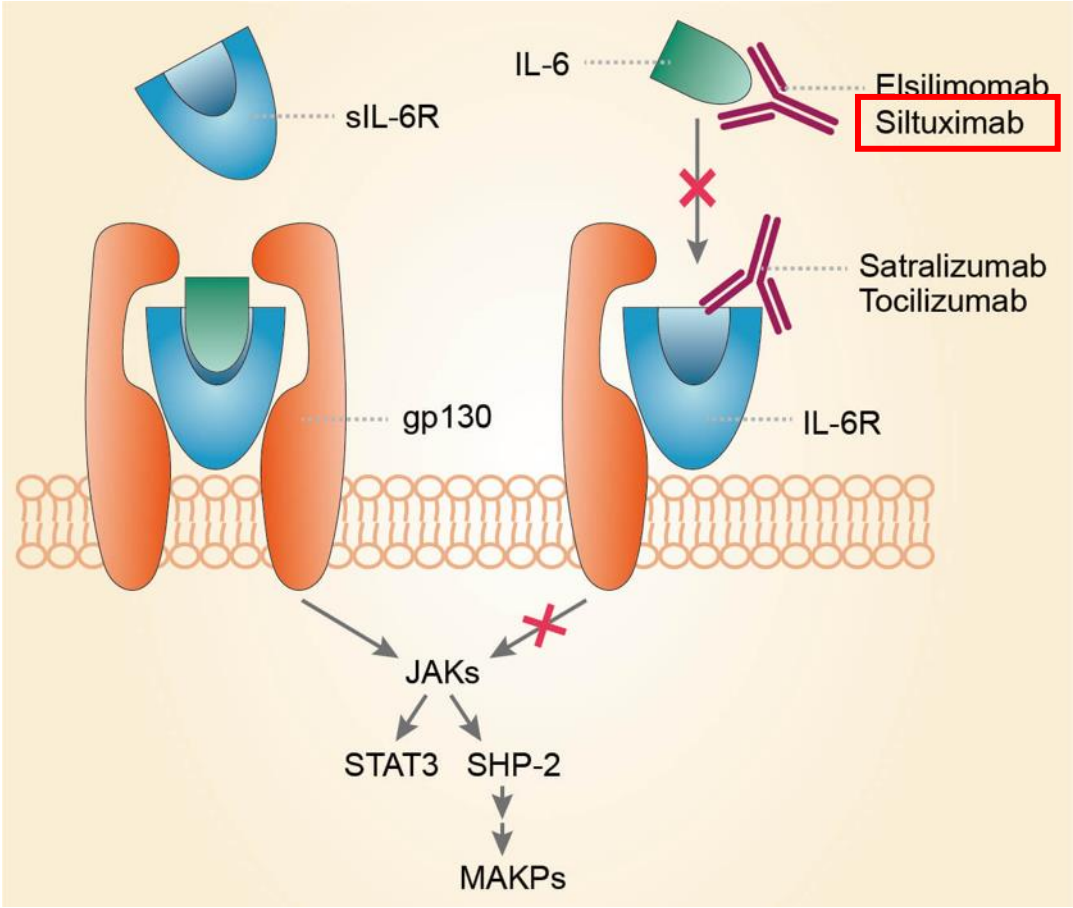
→ **Tocilizumab**

M. di Castleman multicentrica idiopatica non severa: Siltuximab

Siltuximab (11 mg/kg ogni 3 settimane) per tutti i pazienti con diagnosi di iMCD (unico farmaco autorizzato e rimborsato in Italia)

Lo studio di fase 2 costituisce l'unico RCT effettuato su pazienti con MCI:

- **79 pazienti** assegnati al braccio Siltuximab vs Placebo
- Una risposta durevole su adenopatie e sintomi ottenuta nel **34%** (n= 18) dei pazienti appartenenti al braccio Siltuximab **vs 0%** del braccio placebo
- Dei 18 pazienti responders, 1 CR e **17 PR**

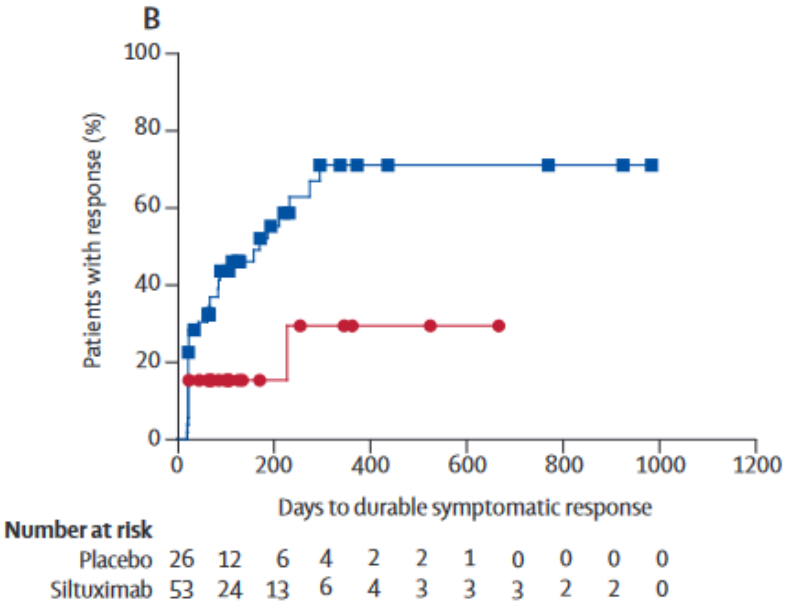


van Rhee F. *Lancet Oncol*, 2014; 15: 966-974

Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial

THE LANCET Oncology
Lancet Oncol 2014; 15: 966–74

Frits van Rhee, Raymond S Wong, Nikhil Munshi, Jean-Francois Rossi, Xiao-Yan Ke, Alexander Fosså, David Simpson, Marcelo Capra, Ting Liu, Ruey Kuen Hsieh, Yeow Tee Goh, Jun Zhu, Seok-Goo Cho, Hanyun Ren, James Cavet, Rajesh Bandekar, Margaret Rothman, Thomas A Puchalski, Manjula Reddy, Helgi van de Velde, Jessica Vermeulen, Corey Casper



Kaplan-Meier plot of time to durable symptomatic response

Median time to durable symptomatic response was 170 days with siltuximab and not reached with placebo (p=0.0288)

Kaplan-Meier plot of time to next treatment in the intention-to-treat population during the masked treatment period

Median time to treatment failure with siltuximab was not estimable and with placebo was 134 days (p=0.0084)

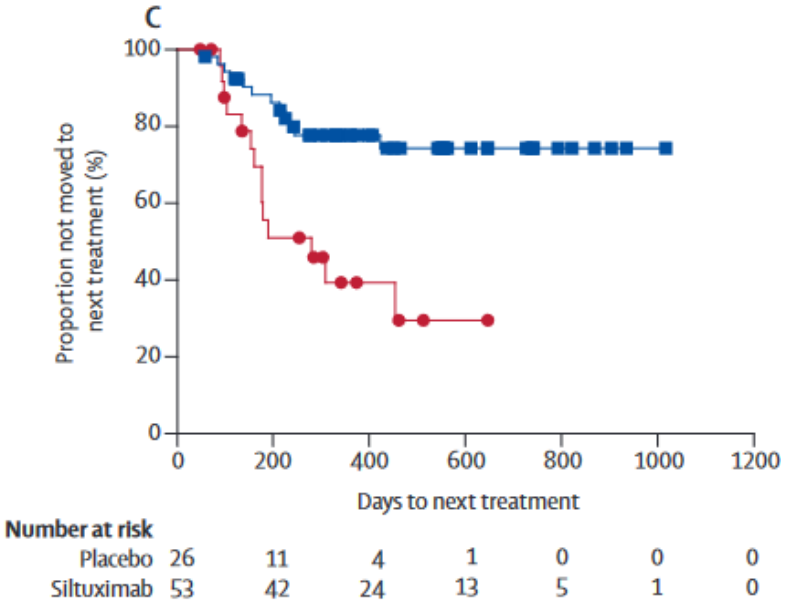
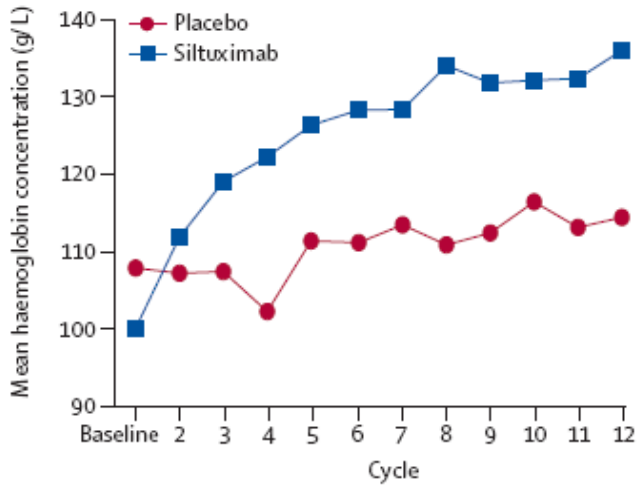
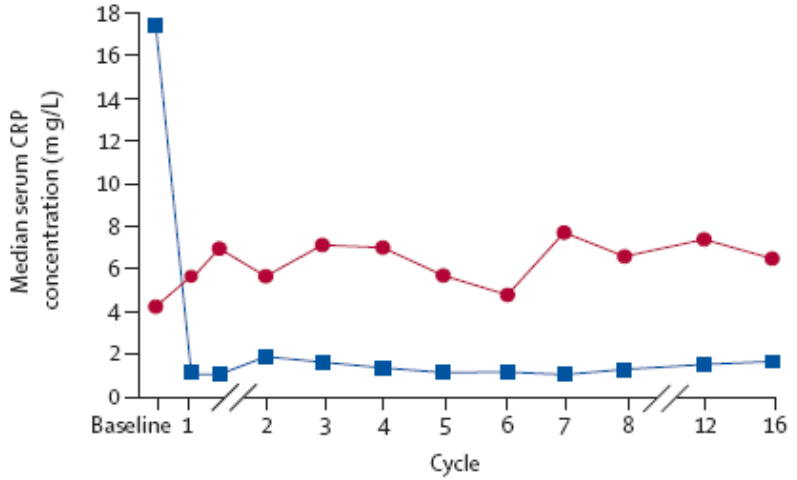


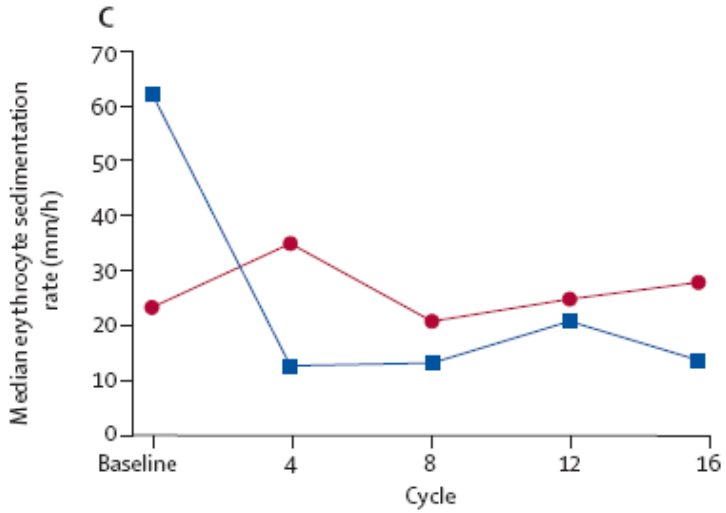
Table of adverse events

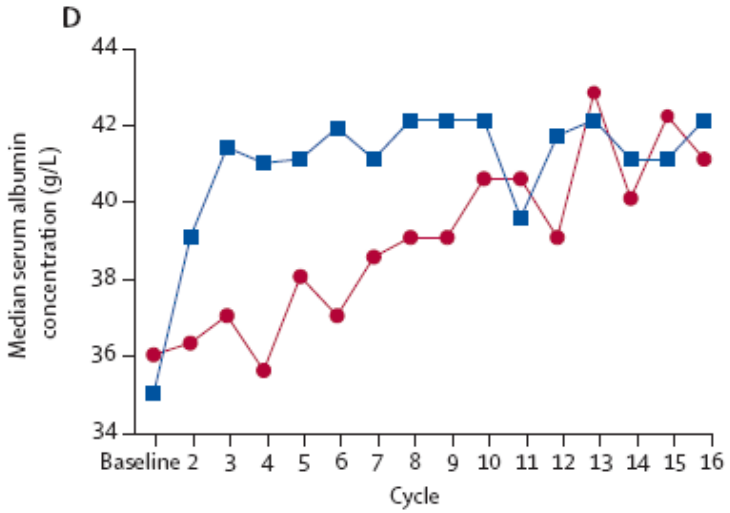
	Siltuximab group (n=53)		Placebo group (n=26)	
	All grades	Grade ≥3	All grades	Grade ≥3
Patients with ≥1 adverse event	53 (100%)	25 (47%)	25 (96%)	14 (54%)
Pruritus	22 (42%)	0 (0%)	3 (12%)	0 (0%)
Upper respiratory tract infection	19 (36%)	0 (0%)	4 (15%)	1 (4%)
Fatigue	18 (34%)	5 (9%)	10 (38%)	1 (4%)
Maculopapular rash	18 (34%)	0 (0%)	3 (12%)	0 (0%)
Peripheral oedema	17 (32%)	1 (2%)	6 (23%)	0 (0%)
Malaise	15 (28%)	0 (0%)	5 (19%)	0 (0%)
Dyspnoea	13 (25%)	1 (2%)	9 (35%)	1 (4%)
Peripheral sensory neuropathy	13 (25%)	0 (0%)	5 (19%)	1 (4%)
Diarrhoea	12 (23%)	0 (0%)	5 (19%)	1 (4%)
Localised oedema	11 (21%)	2 (4%)	1 (4%)	0 (0%)
Weight gain	11 (21%)	2 (4%)	0 (0%)	0 (0%)
Hyperhidrosis	10 (19%)	2 (4%)	4 (15%)	0 (0%)
Decreased appetite	9 (17%)	1 (2%)	4 (15%)	0 (0%)
Night sweats	9 (17%)	4 (8%)	3 (12%)	1 (4%)
Cough	8 (15%)	0 (0%)	6 (23%)	0 (0%)
Abdominal pain	8 (15%)	0 (0%)	1 (4%)	1 (4%)
Thrombocytopenia	8 (15%)	2 (4%)	1 (4%)	1 (4%)
Nasopharyngitis	8 (15%)	0 (0%)	1 (4%)	0 (0%)
Hyperuricaemia	7 (13%)	2 (4%)	0 (0%)	0 (0%)
Neutropenia	7 (13%)	2 (4%)	2 (8%)	1 (4%)
Nausea	5 (9%)	1 (2%)	5 (19%)	0 (0%)
Anaemia	5 (9%)	1 (2%)	4 (15%)	3 (12%)
Weight loss	4 (8%)	0 (0%)	4 (15%)	0 (0%)
Tumour pain	4 (8%)	0 (0%)	4 (15%)	0 (0%)
Hypertension	4 (8%)	2 (4%)	1 (4%)	0 (0%)
Hyperkalemia	2 (4%)	2 (4%)	0 (0%)	0 (0%)

Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial









van Rhee F. *Lancet Oncol*, 2014; 15: 966-974

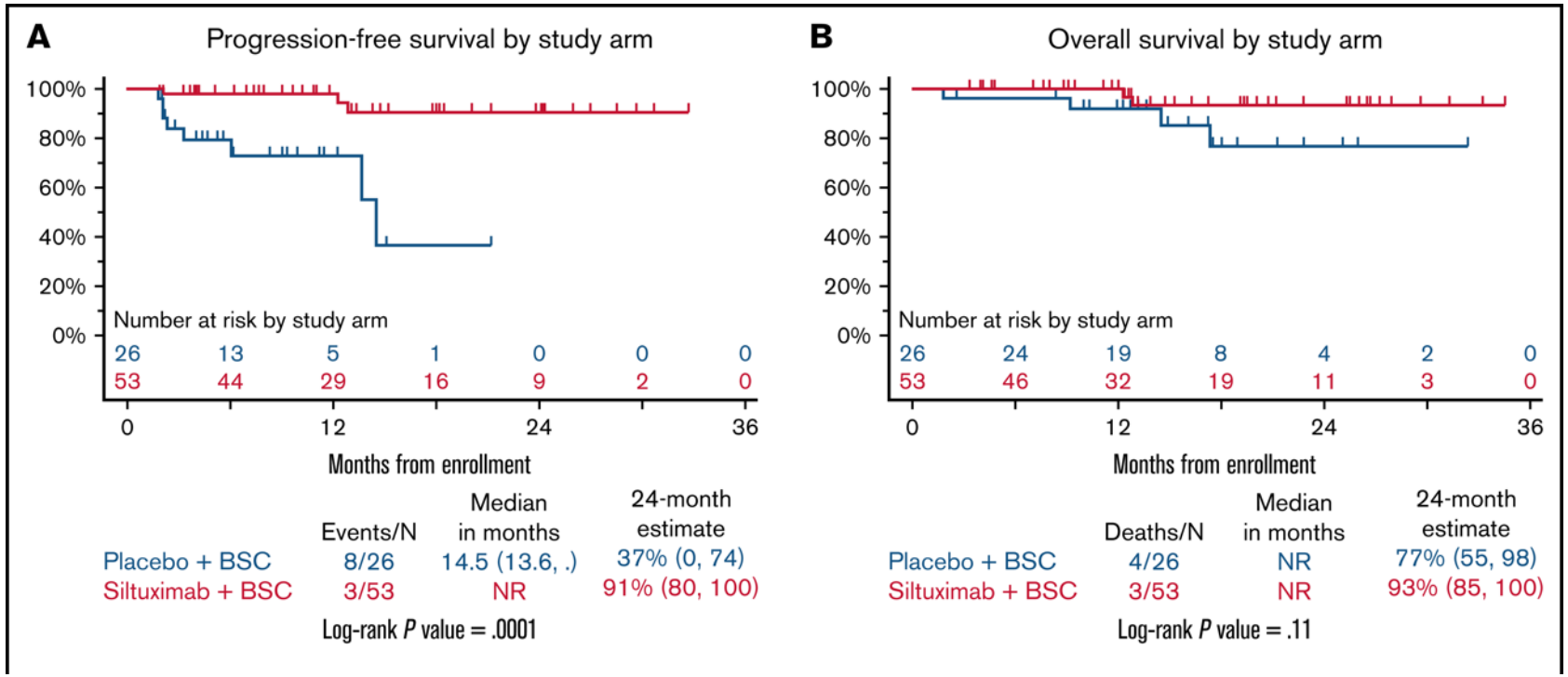
IMMUNOBIOLOGY AND IMMUNOTHERAPY | AUGUST 17, 2022

blood advances

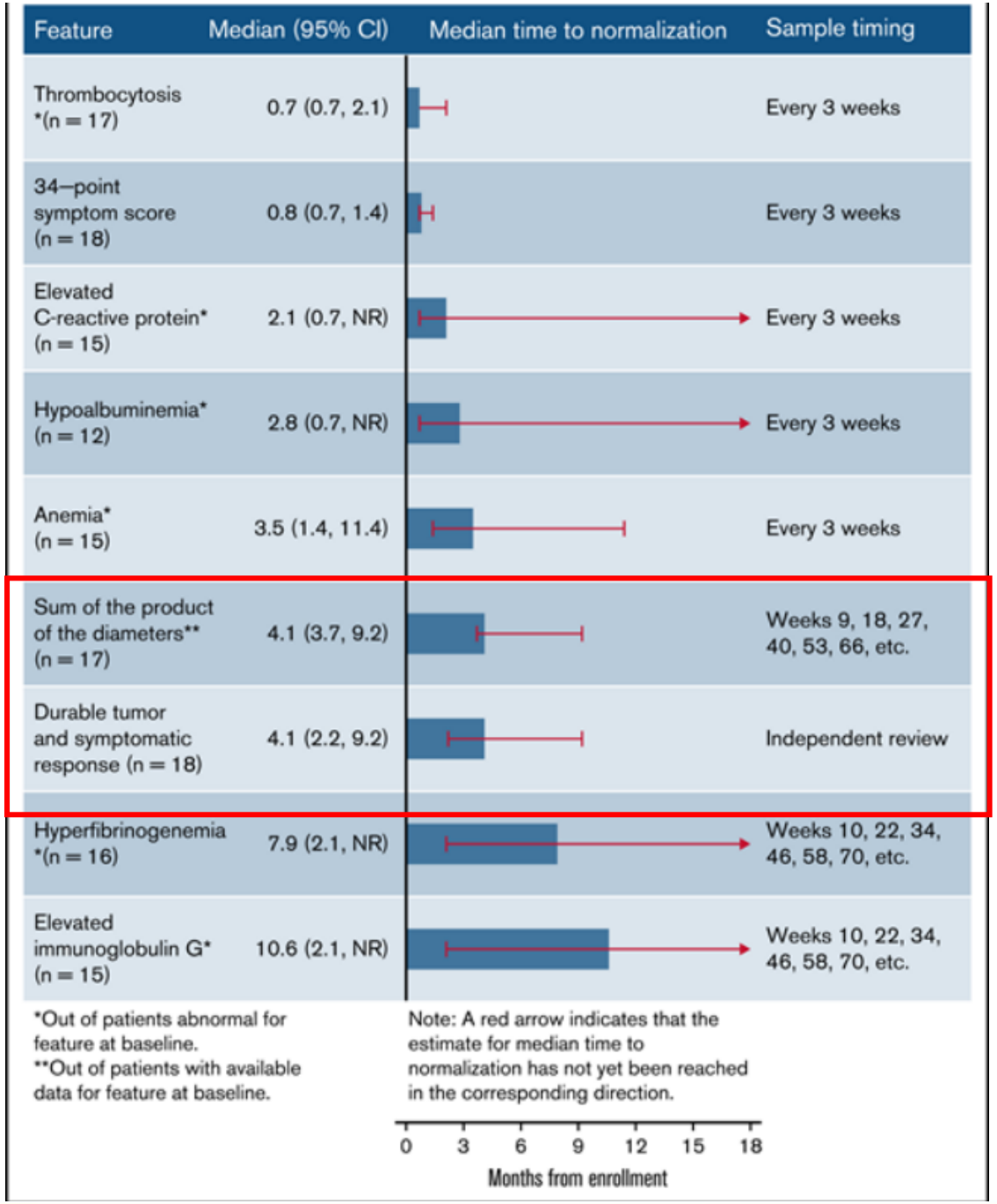
Siltuximab is associated with improved progression-free survival in idiopathic multicentric Castleman disease

Frits van Rhee,[1] Adam Rosenthal,[2] Karan Kanhai,[3] Rabecka Martin,[3] Katherine Nishimura,[2] Antje Hoering,[2] and David C. Fajgenbaum[4]

[1]Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR; [2]Cancer Research and Biostatistics, West Lake Union Center, Seattle, WA; [3]Medical Affairs, EUSA Pharma, Hemel Hempstead, United Kingdom; and [4]Center for Cytokine Storm Treatment & Laboratory, Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA



Median PFS was 14.5 months for patients receiving placebo but was not reached for patients receiving siltuximab



blood advances

IMMUNOBIOLOGY AND IMMUNOTHERAPY | AUGUST 17, 2022

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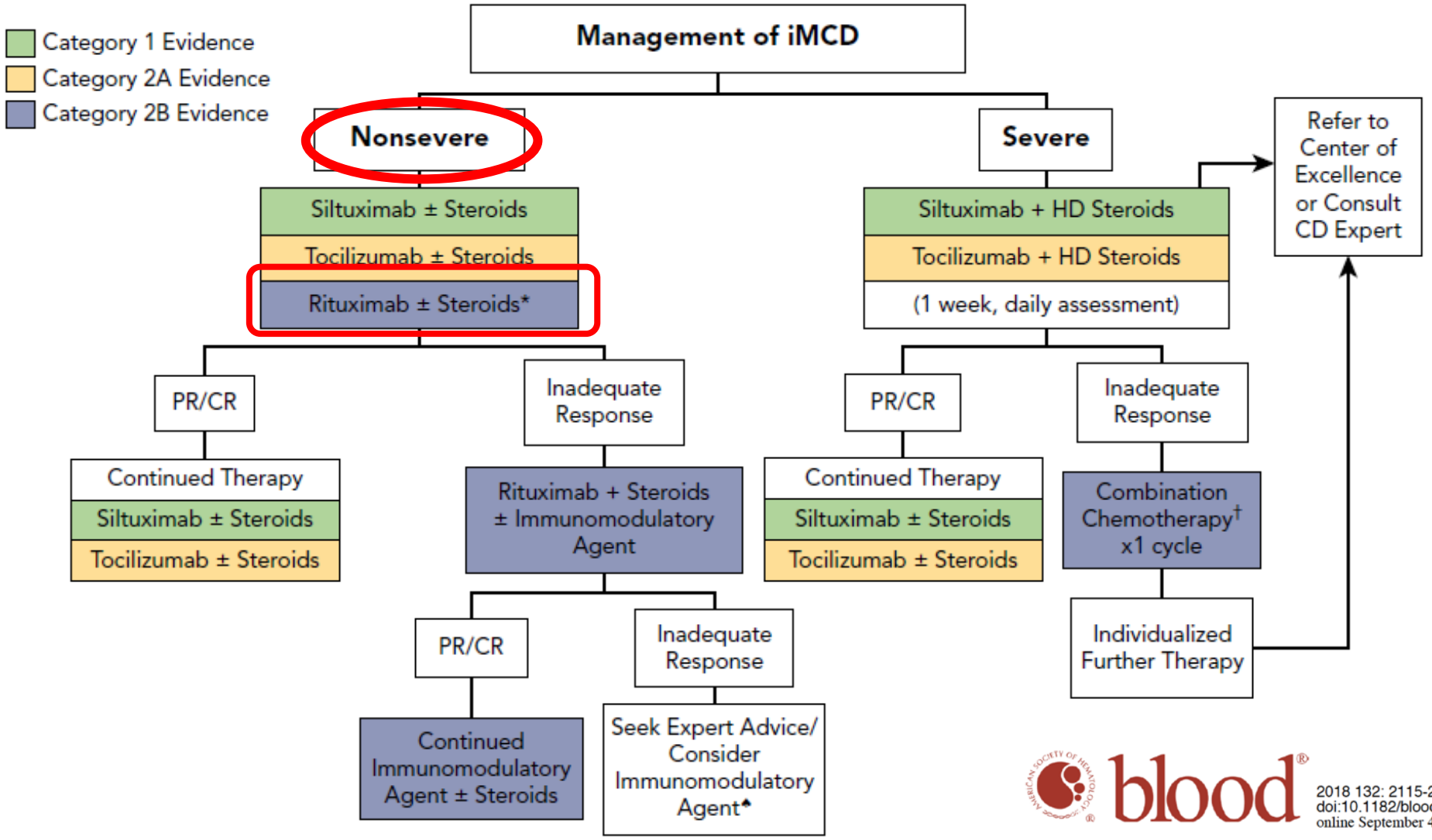
[1]Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR; [2]Cancer Research and Biostatistics, West Lake Union Center, Seattle, WA; [3]Medical Affairs, EUSA Pharma, Hemel Hempstead, United Kingdom; and [4]Center for Cytokine Storm Treatment & Laboratory, Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Sequence of normalization of laboratory, clinical, and lymph node responses in siltuximab responders.

M. di Castleman multicentrica idiopatica non severa: Rituximab



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iMCD treatment

Anti CD20 drugs

Rituximab

- Rituximab (375 mg/m2 x 4-8 doses) might be an alternative to anti IL-6 mAb therapy for patients with nonsevere iMCD who do not have marked cytokine-driven symptomatology (Frits van Rhee, Blood, 2018).

- Rituximab recommendation based on limited data set, because rituximab has not been subjected to systematic study in iMCD and data are confined to case reports or small series

- Most papers report the use of rituximab along with conventional chemotherapies.

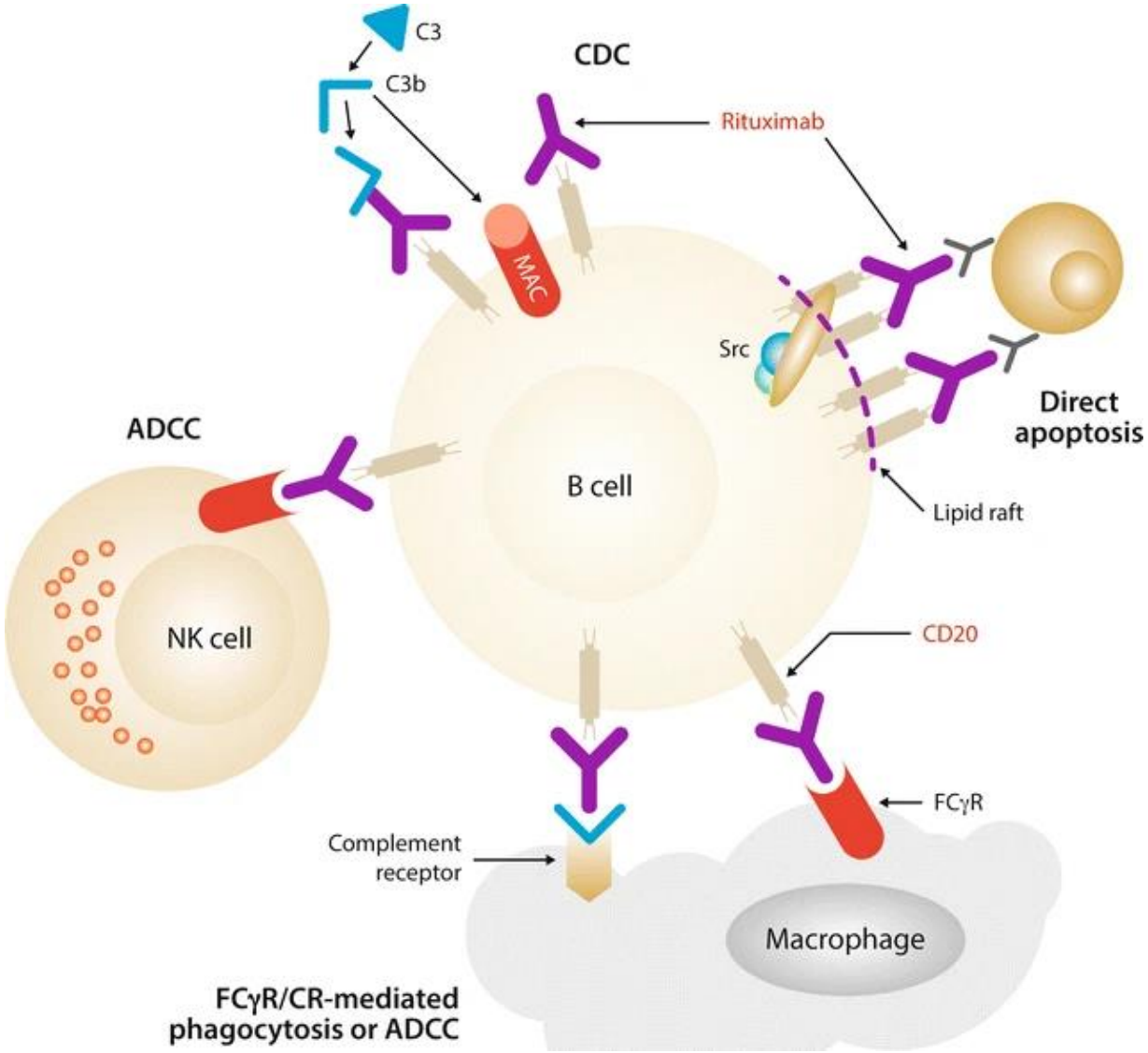


Figure retrieved from Salles G, Adv Ther. 2017

iMCD treatment

Anti CD20 drugs

Rituximab

- Off-label in Italia

- Evidenze su piccole casistiche:
  Tasso di CR e PR del 20% e del 48%, rispettivamente

  Minor EFS rispetto ai pazienti trattati con Siltuximab, circa il 50% di non responders

- Il Rituximab potrebbe essere usato per pazienti nei quali è ragionevole un trattamento limitato nel tempo (attenzione al rischio infettivo -> COVID???)

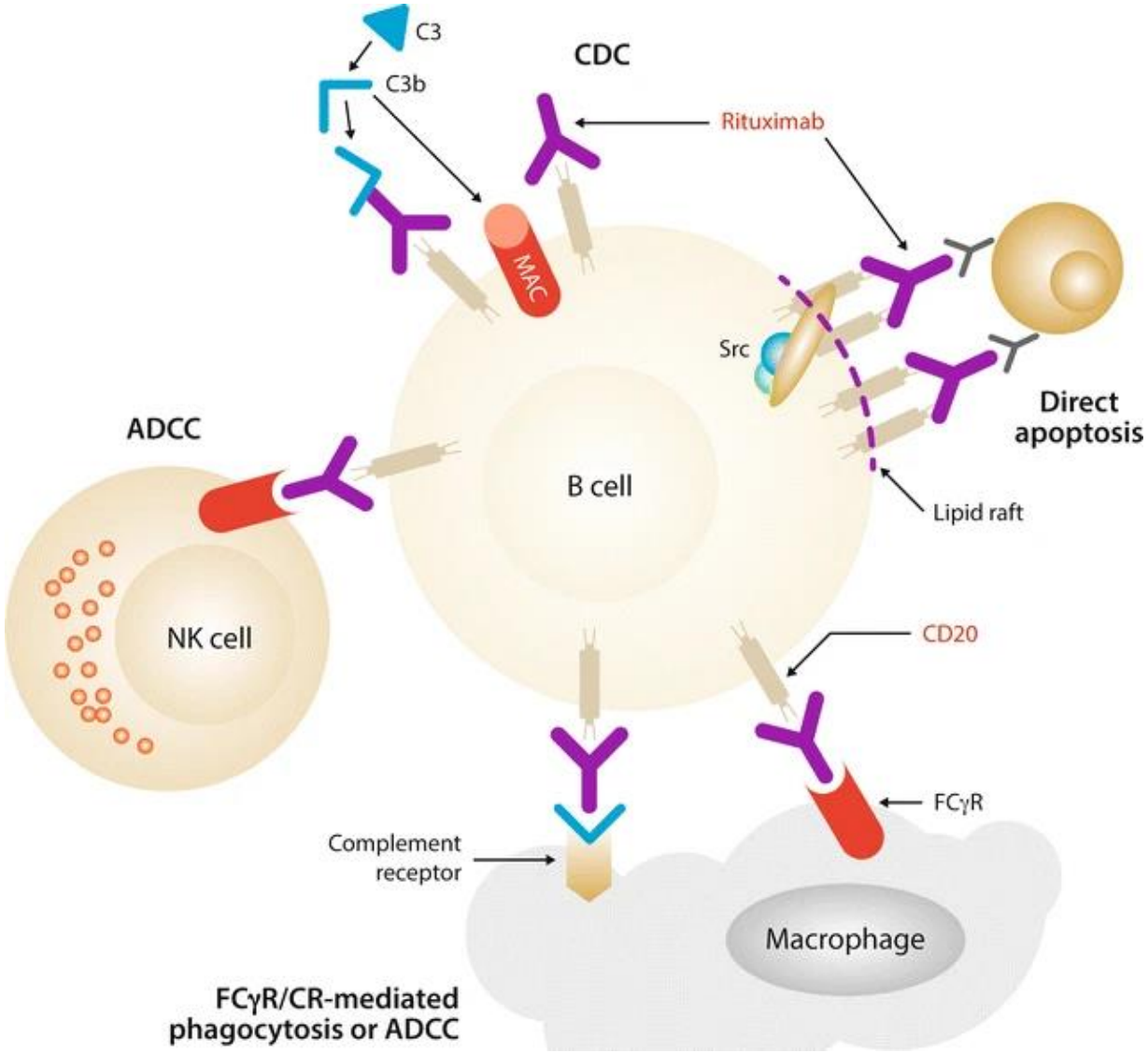
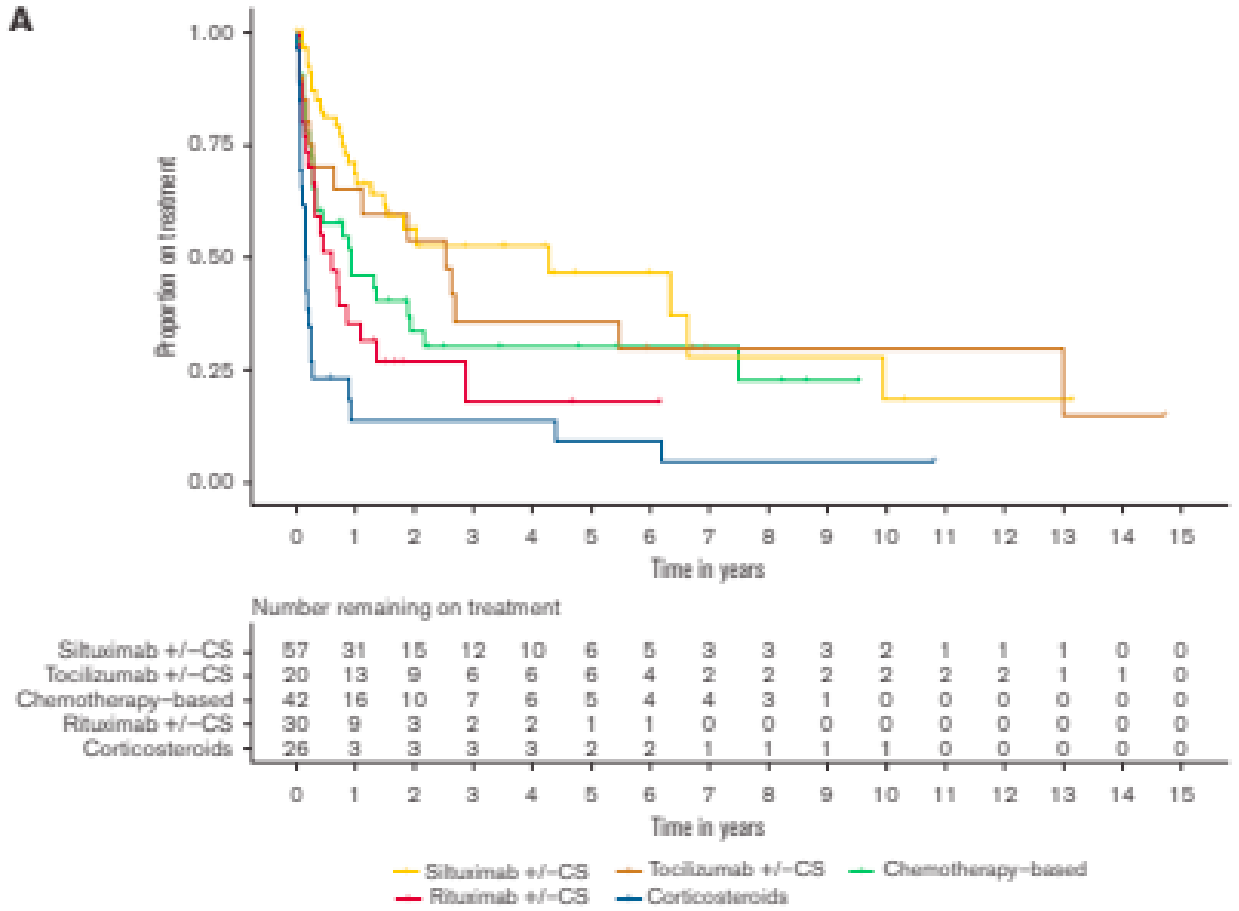


Figure retrieved from Salles G, Adv Ther. 2017


Mild/Moderate
50% R
31.6% R
56.7% R
60.0% R
5.3% R
40.7% R
Severe
46.7% R
14.3% R
41.7% R
25% R
0% R
25.0% R
Chemotherapy-based
Rituximab +/− CS
Siltuximab +/− CS
Tocilizumab +/− CS
Corticosteroids
Other
Non-Responder
Responder


A
Proportion on treatment
1.00
0.75
0.50
0.25
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time in years
Number remaining on treatment
Siltuximab +/−CS 57 31 15 12 10 6 5 3 3 3 2 1 1 1 0 0
Tocilizumab +/−CS 20 13 9 6 6 6 4 2 2 2 2 2 2 1 1 0
Chemotherapy−based 42 16 10 7 6 5 4 4 3 1 0 0 0 0 0 0
Rituximab +/−CS 30 9 3 2 2 1 1 0 0 0 0 0 0 0 0 0
Corticosteroids 26 3 3 3 3 2 2 1 1 1 1 0 0 0 0 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time in years
Siltuximab +/−CS
Tocilizumab +/−CS
Chemotherapy−based
Rituximab +/−CS
Corticosteroids

Unmeet clinical need #3: Choice and management of therapy in patients resistant to siltuximab

- **At least 30% of patients do not experience a durable symptomatic response**
- The Panel advised **reconsidering the diagnosis of iMCD** for patients who have not achieved a satisfactory response with siltuximab, ruling out a diagnosis of lymphoma or inflammatory disease

- However, in the meantime, **most severe patients should be started on alternative therapeutic options immediately** to avoid deterioration and risk of death.
  - **Nonsevere iMCD** → Immunomodulatory/immunosuppressive drugs, such as thalidomide, lenalidomide, sirolimus, CSA, rituximab, or anti-IL-1 receptor anakinra
  - **Severe iMCD** → Second-line salvage chemotherapy combination with rituximab (eg, R-CHOP/R-CVP/R- bortezomib, dexamethasone, and thalidomide [VTD]-PACE)

Unmet Clinical Needs in the Management of Idiopathic Multicentric Castleman Disease: A Consensus-based Position Paper From an ad hoc Expert Panel

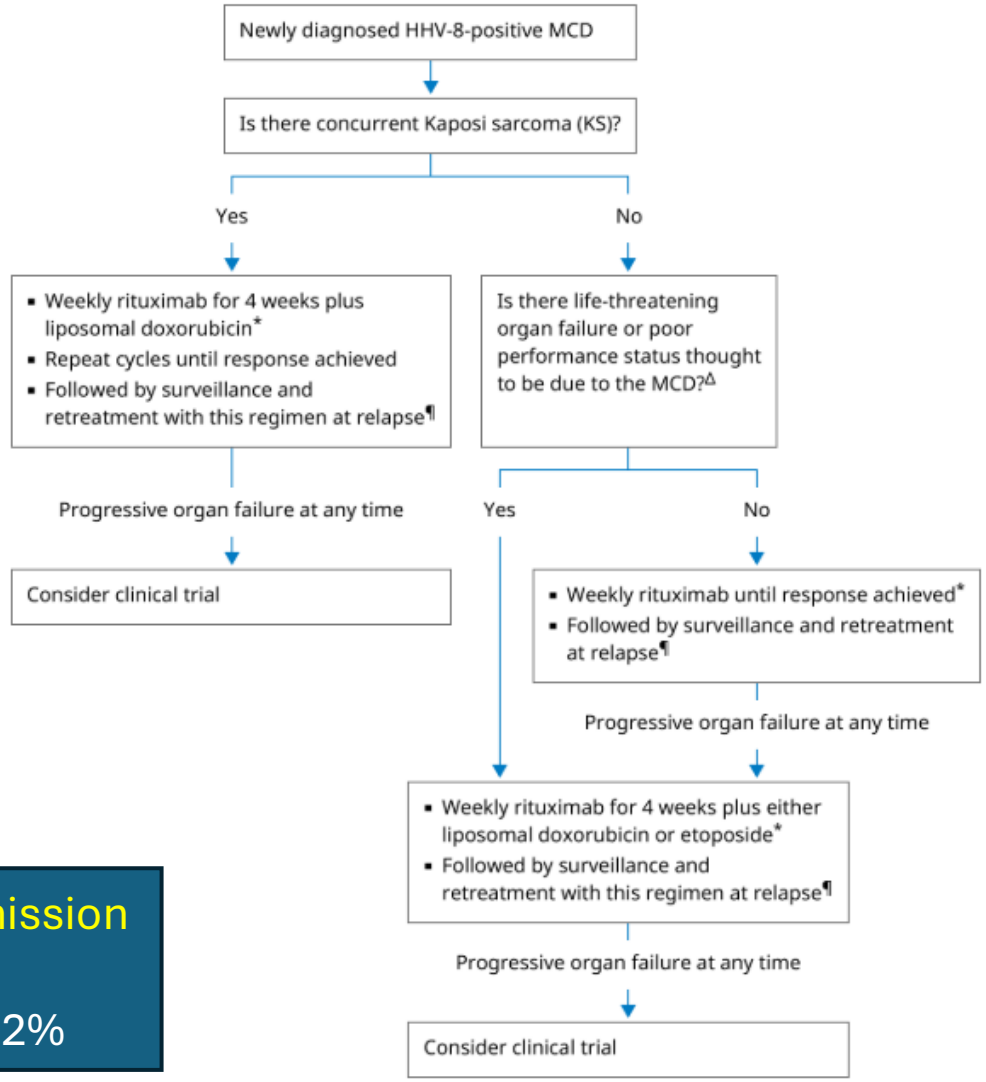
(2023) 7:6

HemaSphere

Pier Luigi Zinzani[1,2], Marco Paulli[3], Luca Arcaini[4,5], Emanuel Della Torre[6,7], Simone Ferrero[8,9], Amalia Figuera[10], Ferdinando Frigeri[11], Maurizio Martelli[12], Elena Sabattini[13], Riccardo Scarpa[14,15], Giovanni Barosi[16]

HHV8-MCD treatment: CDCN recommendations

In HIV+ patients, start or continue ART



CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

95% of patients achieved clinical remission
5-year OS was 92%
5-year relapse-free survival was 82%

blood Review Series

RARE SYSTEMIC HEMATOLOGIC DISORDERS

Overview of Castleman disease

Angela Dispenzieri[1] and David C. Fajgenbaum[2]

Dispenzieri A, Fajgenbaum D, Blood 2020

CDCN recommendations: rituximab-based treatment

1. Concurrent Kaposi sarcoma

- Weekly rituximab for 4 weeks plus liposomal doxorubicin*
- Repeat cycles until response achieved
- Followed by surveillance and retreatment with this regimen at relapse¶

Progressive organ failure at any time

Consider clinical trial

Weekly intravenous rituximab (375 mg/m$^{2)}$ for four weeks plus liposomal doxorubicin (20 mg/m^2) every three weeks until adequate control of KS

RARE SYSTEMIC HEMATOLOGIC DISORDERS

Overview of Castleman disease

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CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

Dispenzieri A, Fajgenbaum D, Blood 2020

CDCN recommendations: rituximab-based treatment

2. Without concurrent Kaposi sarcoma

Without life-threatening organ failure or poor perfomance status

- Weekly rituximab until response achieved*
- Followed by surveillance and retreatment at relapse¶

* Intravenous rituximab (375 mg/m2 weekly for four weeks

If progressive organ failure

With life-threatening organ failure or poor perfomance status

- Weekly rituximab for 4 weeks plus either liposomal doxorubicin or etoposide*
- Followed by surveillance and retreatment with this regimen at relapse¶

* Intravenous rituximab (375 mg/m2 weekly for four weeks) plus either liposomal doxorubicin (20 mg/m2 once every three weeks) or etoposide (100 mg/m2 weekly for four weeks)

Progressive organ failure at any time

Consider clinical trial

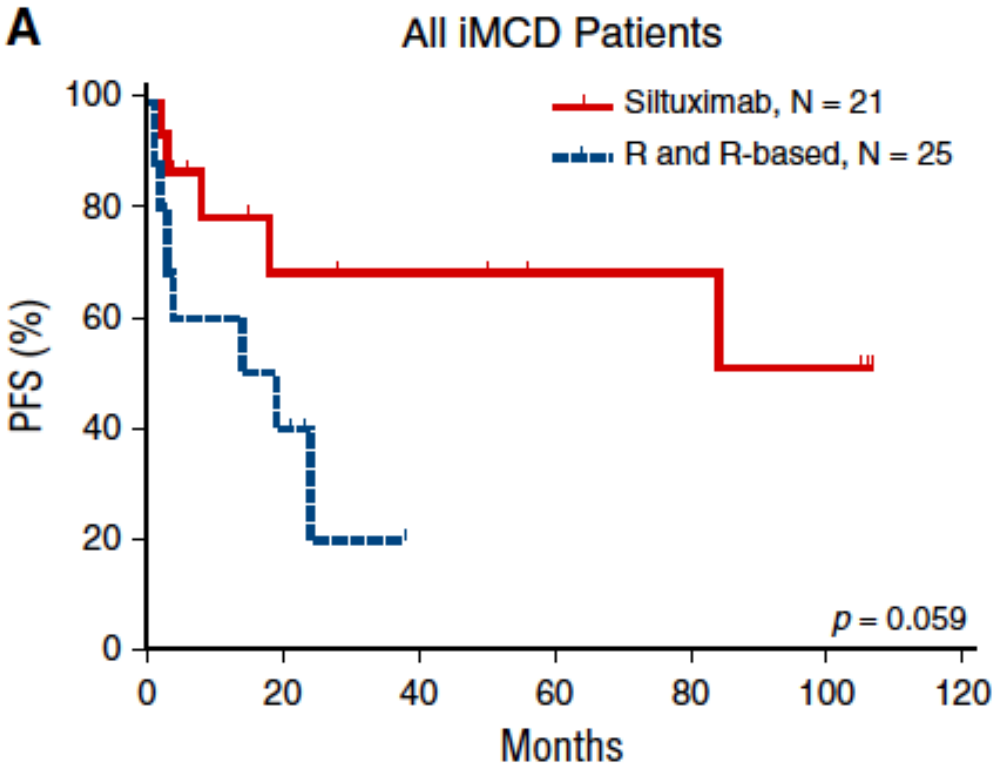
CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

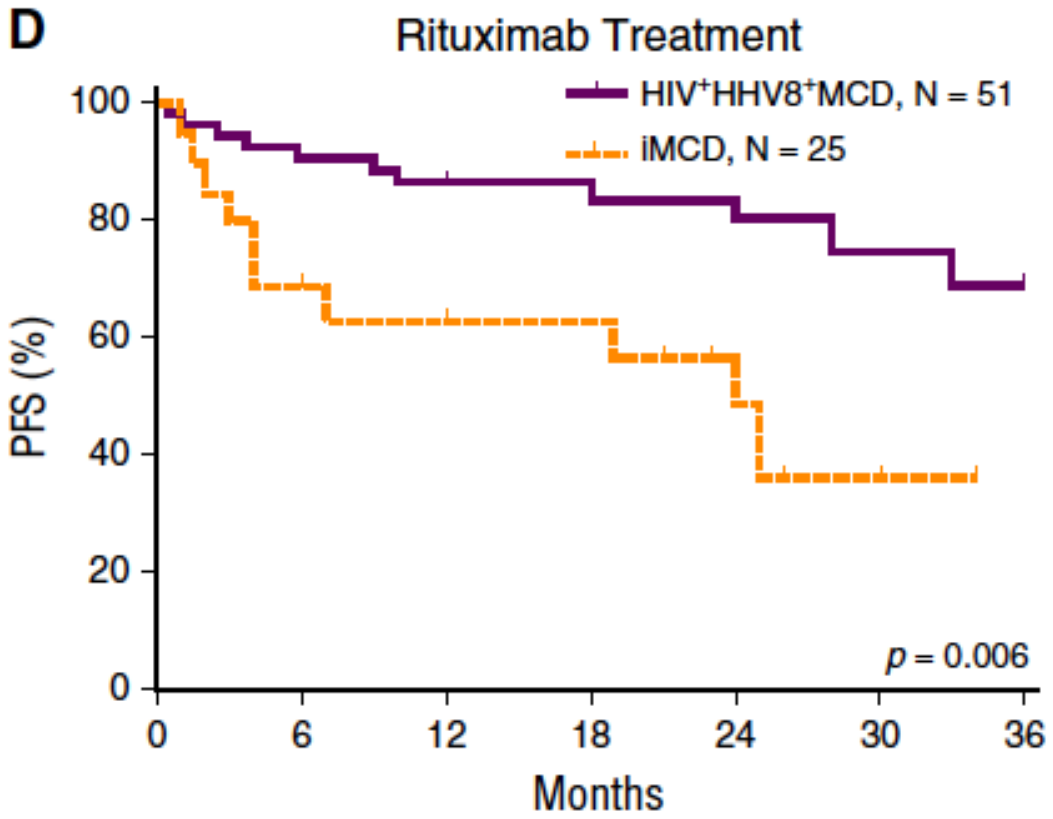
Dispenzieri A, Fajgenbaum D, Blood 2020

blood®
2017 129: 1658-1668
doi:10.1182/blood-2016-11-748855 originally published online January 18, 2017

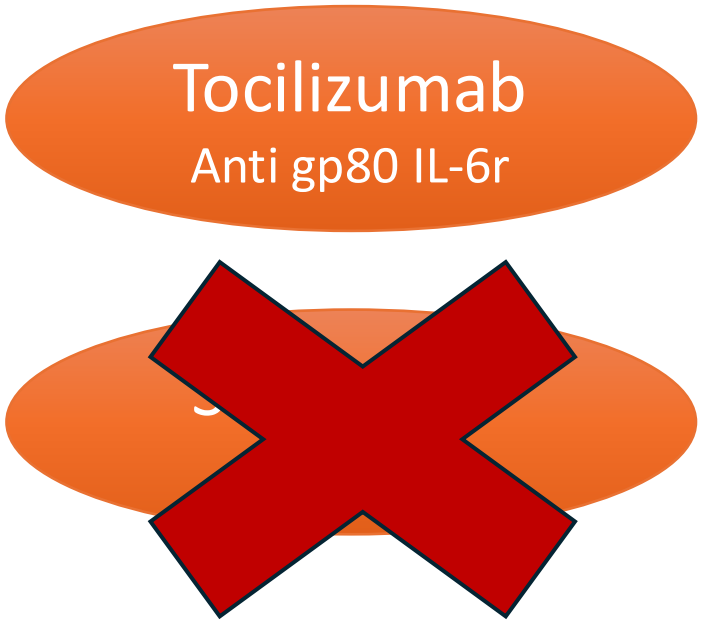
Clinical and pathological characteristics of HIV- and HHV-8–negative Castleman disease

Li Yu, Meifeng Tu, Jorge Cortes, Zijun Y. Xu-Monette, Roberto N. Miranda, Jun Zhang, Robert Z. Orlowski, Sattva Neelapu, Prajwal C. Boddu, Mary A. Akosile, Thomas S. Uldrick, Robert Yarchoan, L. Jeffrey Medeiros, Yong Li, David C. Fajgenbaum and Ken H. Young





What about new strategies?



It does not bind to vIL6

→ **Crosstalk** between vIL6 and huIL6

→ vIL6 and huIL6 **similar functions** or **interactions**

→ Improvement of inflammatory symptoms and biochemical abnormalities ?

Alomari N et al, Viruses 2020

Tocilizumab in patients with symptomatic Kaposi sarcoma herpesvirus–associated multicentric Castleman disease

Ramya Ramaswami,[1] Kathryn Lurain,[1] Cody J. Peer,[2] Anna Serquiña,[1] Victoria Wang,[1] Anaida Widell,[1] Priscila Goncalves,[1] Seth M. Steinberg,[3] Vickie Marshall,[4] Jomy George,[5] William D. Figg,[2] Denise Whitby,[4] Joseph Ziegelbauer,[1] Thomas S. Uldrick,[1] and Robert Yarchoan[1]

Baseline characteristics

ID	Sex/Race	Age at study entry, y	Concurrent KS/(Stage)	Time from HIV Dx, mo	Time from MCD Dx, mo	Prior therapy for KSHV-MCD or KS
1	M/Black	50	N	189	107	Rituximab monotherapy
						Rituximab/LD
2	M/Asian	47	N	51	4	Paclitaxel
3	M/Black	28	N	25	2	None
4	F/Black	30	N	2	1	Prednisone
5	M/White	63	Y/(T1I0S1)	108	52	Rituximab, vinorelbine, rituximab/LD, carfilzomib, sirolimus, LD
6	M/White	42	Y/(T1I1S1)	5	1	None
7	M/White	64	N	206	18	Rituximab
8	M/Black	54	N	279	12	None
		49†	—	79†	8†	—

Study treatment and response

No. of Tx cycles	Best response on TCZ alone	Addition of AZT/VGC*	Best response on TCZ +AZT/VGC	Response at EOT	Subsequent therapy	Time to next therapy, mo
6	PR	Y from C4	PR	PR	Rituximab	4
5	PR	Y from C4	PR	PD	Rituximab/LD	2
6	PD	Y from C2	CR	CR	Rituximab/LD	8
6	CR	N	—	CR	None	—
6	PR	N	—	PR	Pom/LD	4
2	PR	N	—	PD	Pom/LD	1
6	SD	N	—	PD	Rituximab	3
2	SD	N	—	PD	Rituximab	1
6†	—	—	—	—	—	3†

Oral AZT (zidovudine) and VGC (valganciclovir) was added if patients had an inadequate response or relapse on tocilizumab monotherapy

Ramaswami R et al, Blood 2020

Tocilizumab is **safe** and **has activity (4 PR, 1 CR)** in KSHV-MCD and HIV.
PFS was short (median 3.2 mo), and tocilizumab did not alter KSHV-VL, IL-10, or IL-1β levels.

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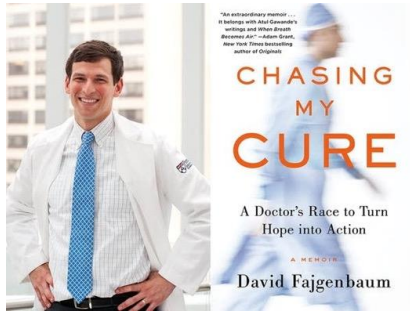
CASTLEMAN DISEASE COLLABORATIVE NETWORK

David Fajgenbaum
Fritz van Rhee



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