# LA MALATTIA DI CASTLEMAN

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Medicina I
SS Ematologia

# MALATTIA DI CASTLEMAN:

- CLASSIFICAZIONE CLINICA, EPIDEMIOLOGIA
- FISIOPATOGENESI
- CRITERI DIAGNOSTICI
- TERAPIA

# MALATTIA DI CASTLEMAN:

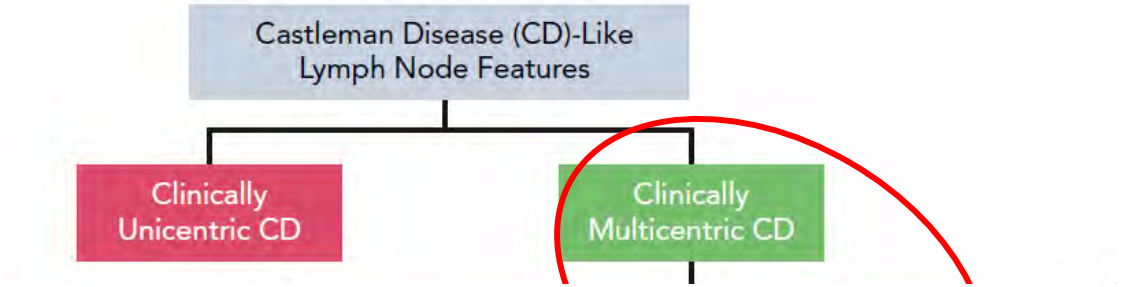
## Classificazione clinica, epidemiologia

# THE CASTLEMAN DISEASE SPECTRUM
# THE IMCD

Castleman disease describes a group of heterogeneous clinicopathological disorders now included in the **tumor-like lesions with B-cell predominance** of the World Health Organization classification (5th edition) that share common morphological features on lymph node biopsy

According to the clinical presentation and disease course, CD is divided into:

- **Unicentric CD** (UCD), a localized and reversible disease involving a single lymph node, and
- **Multicentric CD** (MCD), a systemic, progressive and often fatal disease with lymphadenopathy in multiple nodes



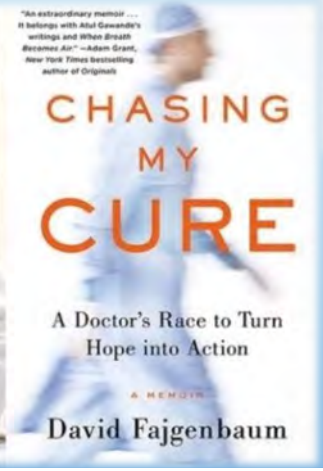

CD, Castleman disease; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; iMCD, idiopathic multicentric Castleman disease; MCD, multicentric Castleman disease; NOS, not otherwise specified; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; TAFRO, thrombocytopenia, anasarca,fever,reticulin fibrosis, organomegaly; UCD, unicentric Castleman disease

- CARBONE A. NAT REV DIS PRIM 2021
  FAJGENBAUM DC. *BLOOD* 2018

# DAL 1956 ……..AL 2024

**Se Benjamin Castleman ( 1908-1982)**
**ha dato il proprio nome alla Malattia di Castleman**

**OGGI POSSIAMO FORSE DEFINIRE IL «PADRINO» DELLA MALATTIA DI CASTLEMAN, IL PROF DAVID FAJGENBAUM CHE NEGLI ULTIMI 10 ANNI ANNI SI È DEDICATO ALL'IMPONENTE LAVORO DI DARNE FINALMENTE UN INQUADRAMENTO DIAGNOSTICO, UNA CLASSIFICAZIONE E DELLE LINEE GUIDA DI TERAPIA**

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Blood. 2017 Mar 23; 129(12): 1646–1657. PMCID: PMC5364342
Prepublished online 2017 Jan 13. doi: [10.1182/blood-2016-10-746933] PMID: 28087540

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]

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,[9] 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]

# EPIDEMIOLOGY OF CASTLEMAN DISEASE

The estimated incidence of **CD** is 6500 to 7700 cases/year in the United States

The estimated incidence of **UCD** is ~ 5000-6000 cases/year in the United States, and ~ 1650 cases of **MCD**[1]

iMCD accounts for 33% to 58% of published MCD cases[1]

iMCD can occur in individuals of any age with a range of 2–80 years; however, it tends to affect patients in their fourth to sixth decade of life[1,3,4]

More commonly females (F 56.7% vs M 43.6%)[2]

Historically, **35% die within 5 years of diagnosis,** 60% die within 10 years[1]

Patients have a **3-fold increase in the prevalence of malignancies**[1]

IMCD, IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE.

1. FAJGENBAUM DC *ET AL. BLOOD* 2017; 2.MUKHERJEE S *ET AL. BLOOD ADV* 2022; 3. FAJGENBAUM DC *ET AL. BLOOD* 2018; 4. DISPENZIERI A *ET AL. BLOOD* 2020

# iMCD incidence and prevalence in Italy*

## USA[1]

**Estimated incidence:**
(iMCD/Mil. of population)
**3.40**

**Estimated prevalence:**
(iMCD/Mil. of population)
**6.90**

## ITALY*

**Expected annual incidence:**

**204 *cases***

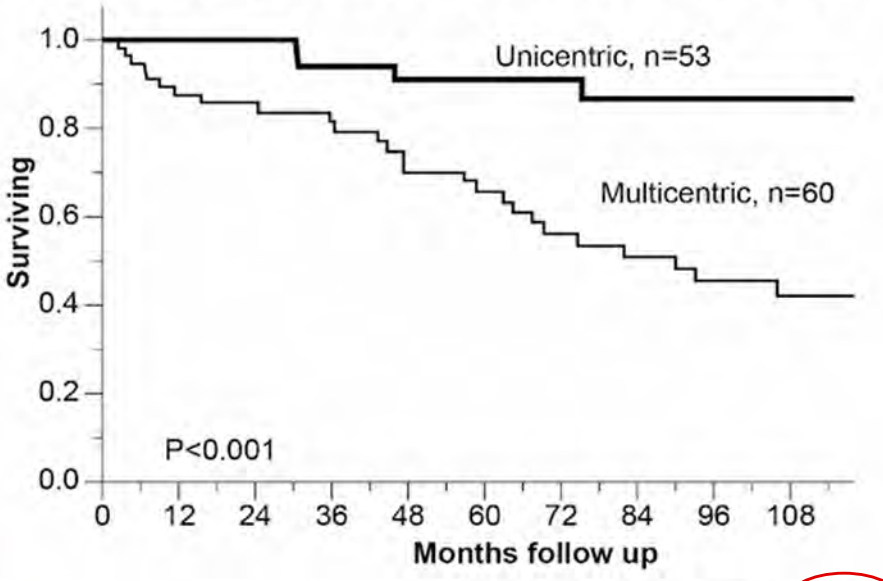
**Expected prevalence:**

**414 *cases***

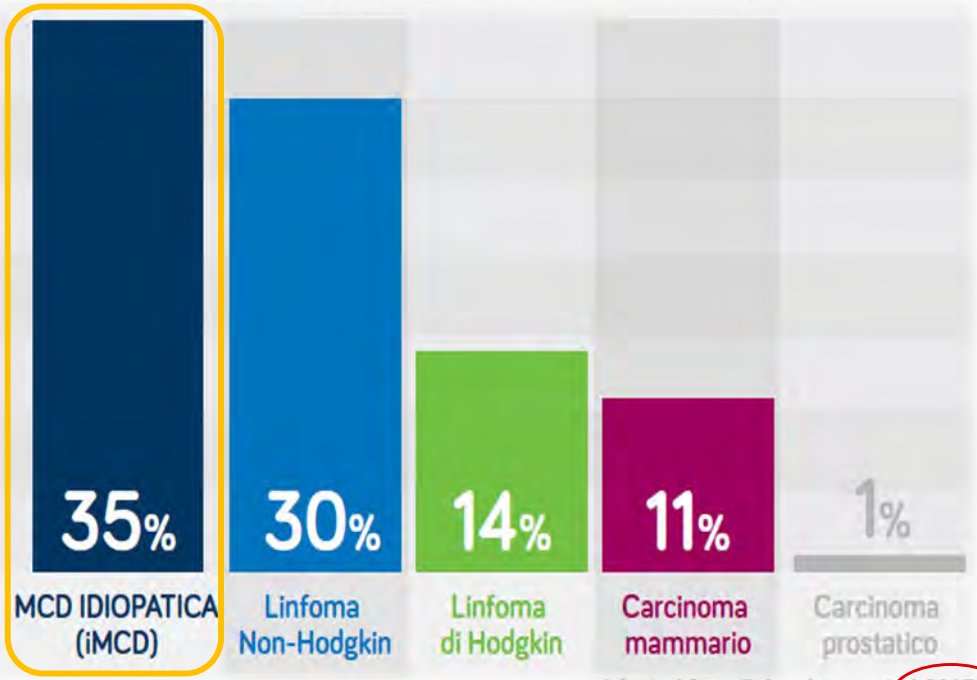
- *1.Mukherjee S, et al.: «Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6 directed therapy» BLOOD ADV. 2022 JAN 25;6(2):359-367*ESTIMATION FROM MUKHERJEE S, BLOOD ADV. 2022*

# Characteristics of iMCD

**Similar 5-year OS (65%) to all cancers (68%)[1,2]**




Adapted from Dispenzieri *et al.* 2012.




Adapted from Fajgenbaum *et al.* 2017.

ALPS, autoimmune lymphoproliferative syndrome; EBV, Epstein–Barr virus; FDC, follicular dendritic cell; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; HLH-MAS, hemophagocytic lymphohistiocytosis–macrophage activation syndrome; iMCD, idiopathic multicentric Castleman's disease; MCD, multicentric Castleman's disease; OS, overall survival; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; V-HLH, viral hemophagocytic lymphohistiocytosis.

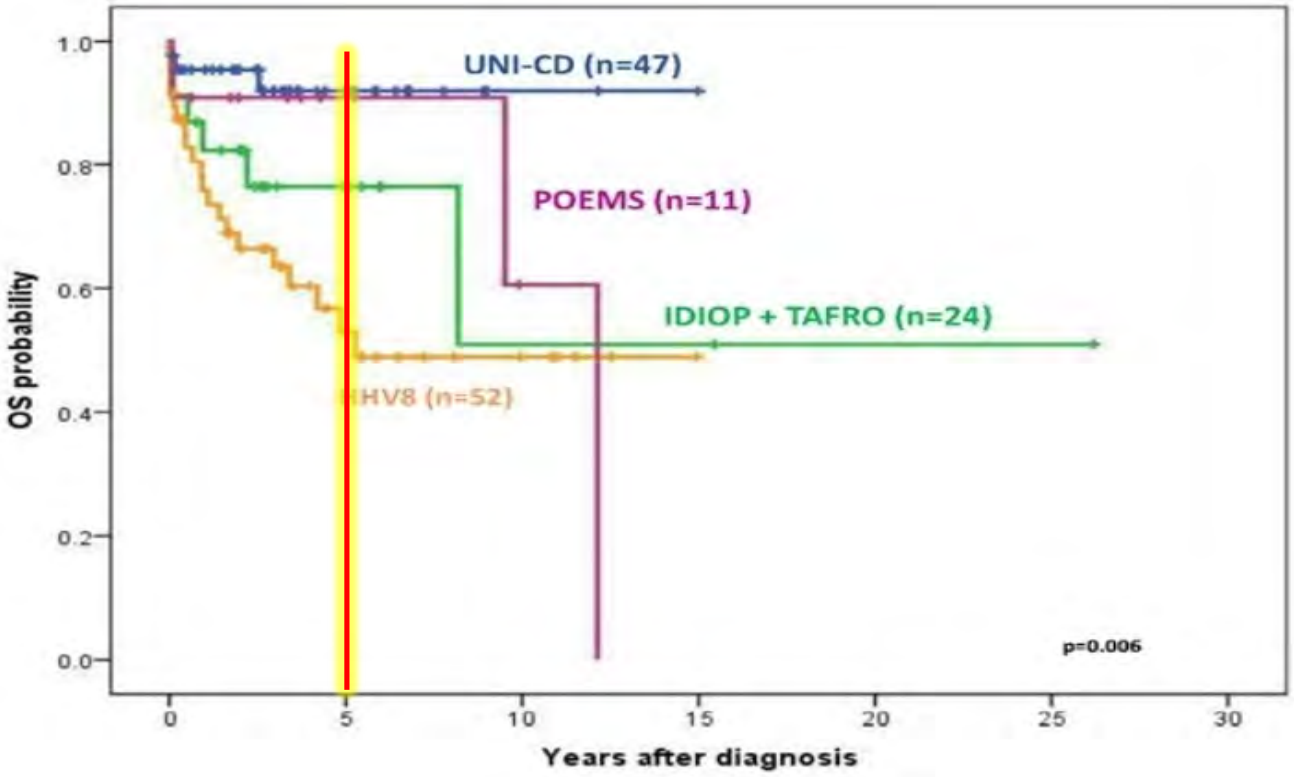
1. 5-year Survival Rates, CSR 1975-2017. Available at: https://seer.cancer.gov/csr/1975_2017/results_merged/topic_survival.pdf. Accessed June 2020. 2. Dispenzieri A *et al. Am J Hematol* 2012; 87: 997–1002. 3. Fajgenbaum DC *et al. Blood* 2017; 129 (12): 1646–1657.

# OVERALL SURVIVAL NEWS FROM EHA 2022

**Clinical features and outcome of patients with Castleman Disease: a Spanish multicentric study of 134 patients from GELTAMO**

JT. Navarro[1,2,3], C. Celades[3,3], O. García[1,2,3,4], E. González-Barca[3,4,7], F. Climent[4,8], A. Feu[4,8], A. Jiménez[9], A. Gutiérrez de la Peña[9], M. Bastos-Oreiro[10,11], T. Aldaniz-Echevarría[10], A. Gutiérrez[12,13], L. Bento[12,13], P. Abrisqueta[14], CM. Alonso[15], C. Tejada-Chávez[15], EM. Ocio[16], N. Fernández Escalada[16], MB. Navarro Matilla[17], JM. Mateos-Pérez[17], A. López-García[18], C Castillo-Girón[19], S. Felipe-Pinzón[20], E. Pérez-Ceballos[21], JA. Hernández-Rivas[22], R. del Campo García[13,23], E. Pardal de la Mano[24], R. García-Sanz[25], J. Rovira[26], JM. Sancho[1,2,3], G. Tapia[1,27].

## PROBABILITY of OS at 5 years




UCD: 95%

IMCD + TAFRO: 77%

HHV8-MCD: 53%

POEMS: 91%

*EHA 2022* Poster Navarro J T et al.

LETTER

EPIDEMIOLOGY

Organ dysfunction, thrombotic events and malignancies in patients with idiopathic multicentric castleman disease: a population-level US health claims analysis

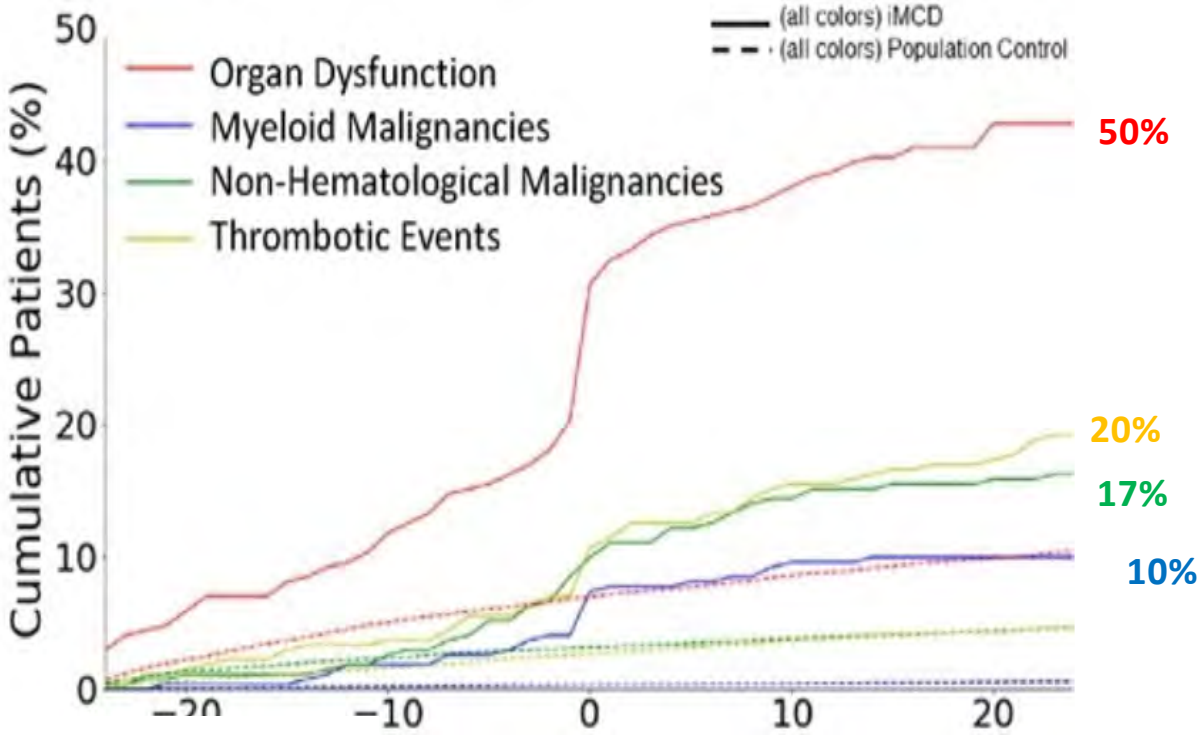
Sudipto Mukherjee[1], Karan Kanhai[2], David Kauffman[3], Rabecka Martin[4], Jeremy S. Paige[3], Anirvan Ghosh[3], Hannah Kannan[3], Francis Shupo[2] and David C. Fajgenbaum[5]



*Leukemia* (2022) 36:2539–2543; https://doi.org/10.1038/s41375-022-01690-2

# INCREASE IN THE PREVALENCE OF EVENTS

NON-HEMATOLOGICAL MALIGNANCIES IN IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE PATIENTS: A MATCHED COHORT ANALYSIS USING A HEALTH CLAIMS-BASED DATASET




50%

20%

17%

10%

**Events are significantly higher in i-MCD population vs the non – iMCD control**

**Proportion of cases with Myeloid and solid malignancies, organ dysfuction and trombotic events**

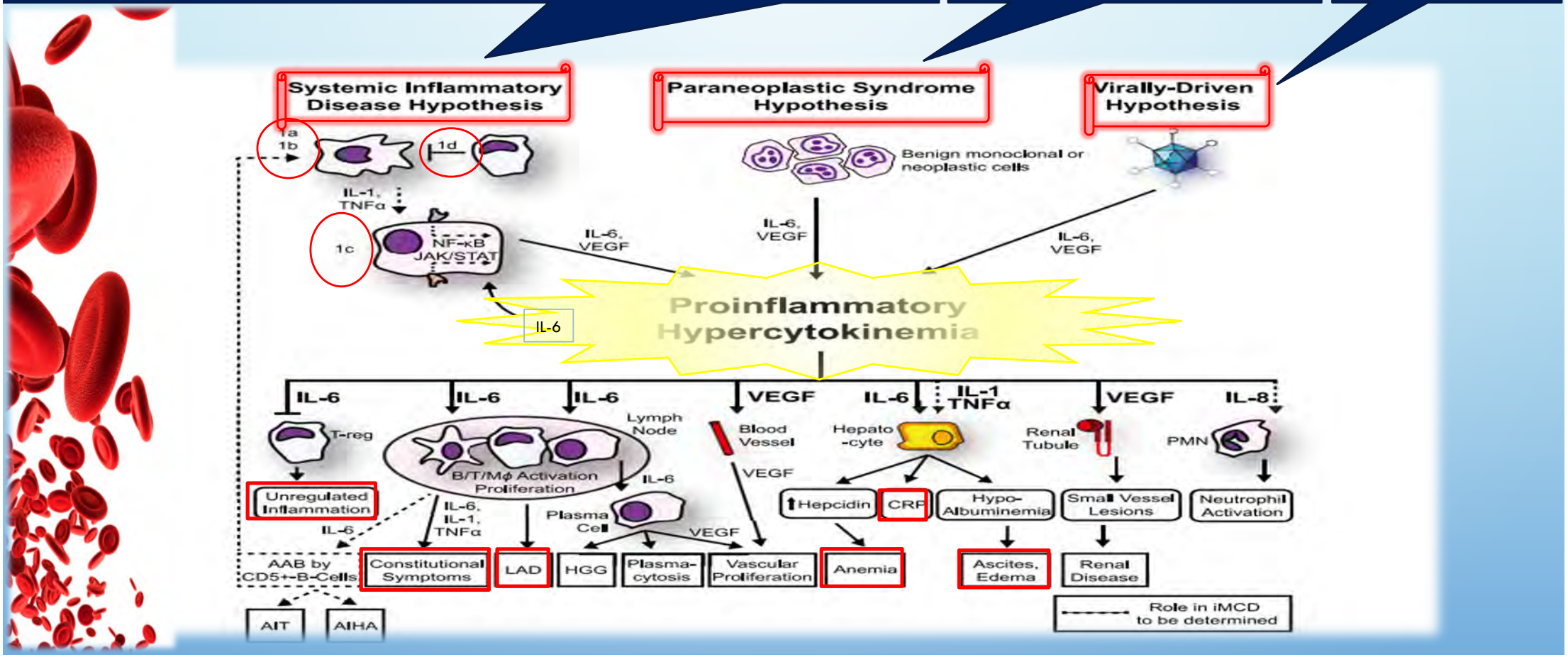
*EHA 2022 Poster Mukherjee s, Kanhai K et al.*

# MALATTIA DI CASTLEMAN MULTICENTRICA IDIOPATICA: FISIOPATOGENESI

**1)l'ipotesi della malattia infiammatoria sistemica** comprende (1a)autoanticorpi scatenanti il rilascio di citochhine pro-infiammatorie da parte delle antigen presenting cell con ipersecrezione di citochine, tra cui l'IL6; (1b/c) un errore in un segnale kinasico o inibitorio in una antigen presenting cell o in un'altra cellula ipersecernente citochine con conseguente ipersecrezione di IL6 o, (1d) un difetto di regolazione delle cellule infiammatorie ativate. L'infiammazione sistemica è perpetuata dal feed-back positivo dell'IL6 o forse da ulteriori stimolazioni autoanticorpali

**2)l'ipotesi della sindrome (para)neoplastica** coinvolgeuna mutazione somatica in cellule benigne o maligne all'interno o all'esterno del linfonodo che causa un costitutivo rilascio di citochine pro-infiammatorie.

**3) l'ipotesi virale** implica un non HHV8 virus ( es: EBV, HHV6) che porti al rilascio di citochine pro-infiammatorie.



# PATHOGENESIS: THE ROLE OF IL-6 IN IMCD

In some patients with iMCD, increased IL-6 is a critical driver of disease and is ofte accompanied by increased VEGF levels:[1]


| | | |
|---|---|---|
| Increased B cell growth[2] | Overgrowth of B cells and plasma cells | Increased size of lymph nodes; lymphoma, myeloma |
| Increased VEGF[2] | Formation of blood vessels | Increased blood supply to tumor |
| Increased $T_h2$ cells[2] | Autoimmune reactions | Autoantibodies targeted to organs |
| Inflammatory response[2] | Elevated ESR, CRP, and IgG; anemia; and DVT | Systemic symptoms |

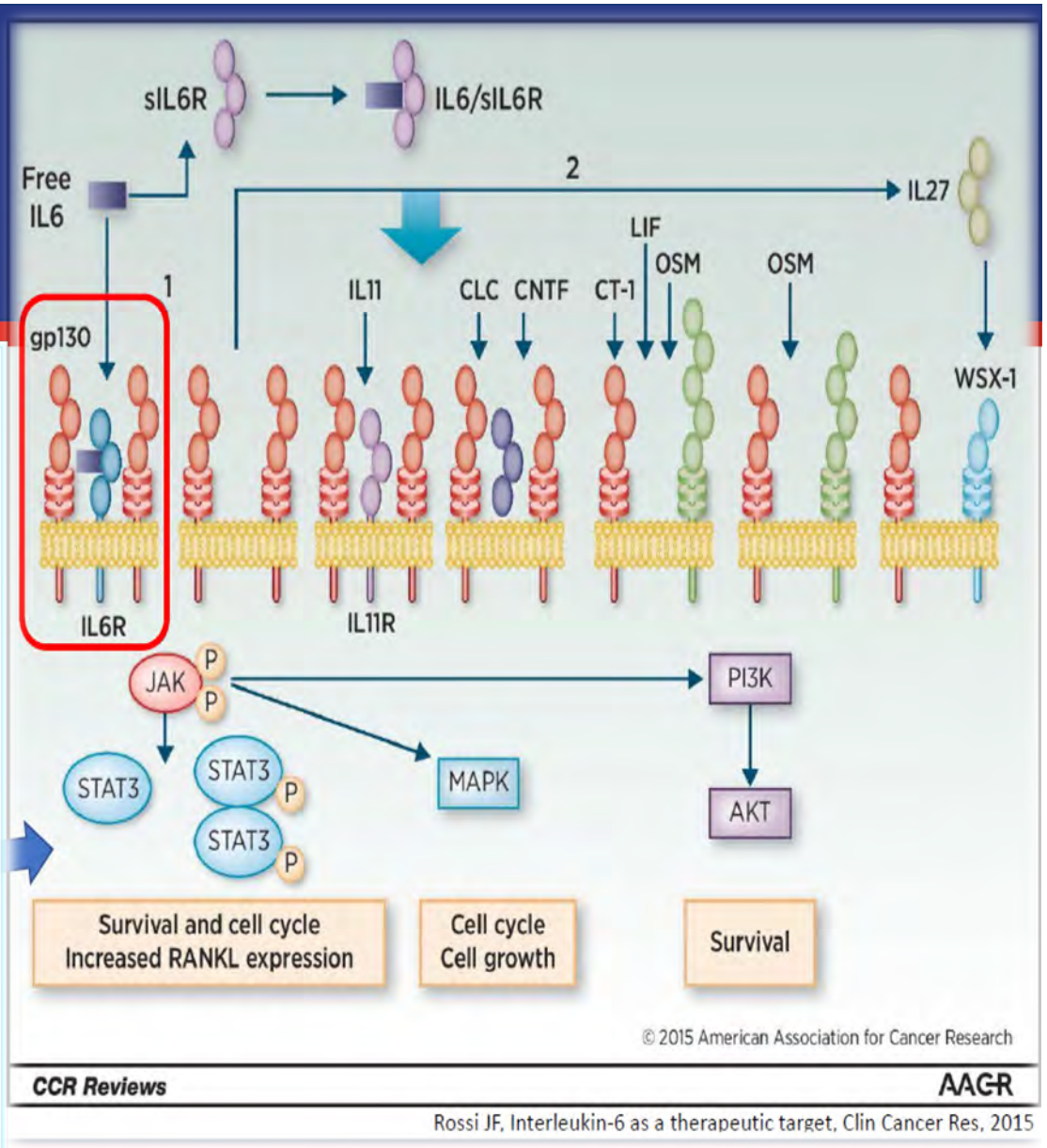
Adapted from van Rhee *et al.* 2010.

ı thrombosis; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; IL-6, interleukin 6; iMCD, idiopathic multicentric Castleman disease; $T_h2$, T helper type 2; VEGF, vascular endothelial growth factor.

16): 1353–1364. 2. van Rhee F *et al. Clin Adv Hematol Oncol* 2010; 8 (7): 486–498.

# MECCANISMO D'AZIONE DELL'IL6

- L'IL6 È UNA **CITOCHINA MULTIFUNZIONALE** CHE HA MOLTEPLICI ATTIVITÀ BIOLOGICHE E VARIE CELLULE TARGET
- REGOLA LA **RISPOSTA IMMUNE**, LA **REAZIONE DI FASE ACUTA**, L'**EMATOPOIESI** E IL **METABOLISMO OSSEO** (ROSSI JF, INTERLEUKIN)
- IL SEGNALE DELL'IL-6 È MEDIATA DAL **RECETTORE PER L'IL6 (IL-6R)** (ROSSI JF, INTERLEUKIN)
- L'IL6 SI LEGA AL RECETTORE DI MEMBRANA O ALLA SUA FORMA SOLUBILE (SIL-6R)
- **IL COMPLESSO IL6/ IL-6R O IL-6/SIL6-R SI LEGA AL TRASDUTTORE DI IL6 GP130 (CD130)**
- **QUESTO LEGAME PORTA ALL'ATTIVAZIONE DI GP130E ALL'ATTIVAZIONE DELLE KINASI RECETTORE ASSOCIATE ( JAK1, JAK2 E TYK2**




Rossi JF, Interleukin-6 as a therapeutic target, Clin Cancer Res, 2015

# MALATTIA DI CASTLEMAN MULTICENTRICA IDIOPATICA:

# CRITERI DIAGNOSTICI

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Blood. 2017 Mar 23; 129(12): 1646–1657.
Prepublished online 2017 Jan 13. doi: [10.1182/blood-2016-10-746933]
PMCID: PMC5364342
PMID: 28087540

# 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 Fosså,[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]

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## Key Points

**An international panel of 34 experts established the first ever diagnostic criteria for iMCD based on review of 244 clinical cases and 88 tissue samples.**

# CONSENSUS DIAGNOSTIC CRITERIA

*Fajgenbaum Blood 2017*

A patient must fulfil the **major**, **minor**, and **exclusion** criteria:

## Major criteria

**Both features must be present:**

- ✓ **Histopathological lymph node features** consistent with the iMCD spectrum
- ✓ **Enlarged lymph nodes** (≥1 cm in short-axis diameter) in ≥2 lymph node stations

## Minor Criteria:

**≥2 of the following 11 features (including ≥1 laboratory condition) must be present:**

- LABORATORY (6 FEATURES)
- CLINICAL (5 FEATURES)

## Exclusion criteria

**Each of the following diseases/disorders must be ruled out:**

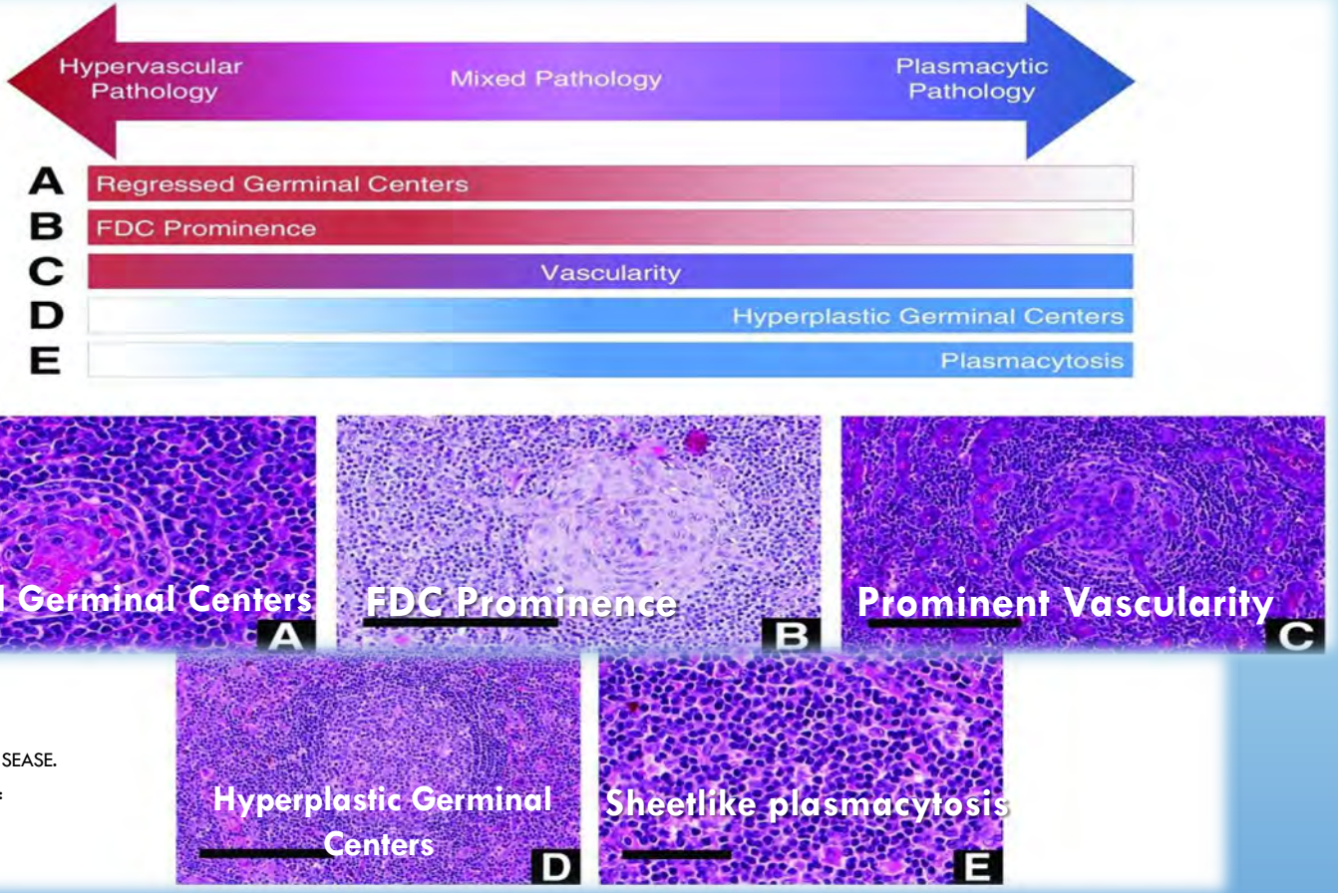
- **Infection-related disorders**
- **Malignant/lymphoproliferative disorders**
- **Autoimmune/autoinflammatory diseases**

# INTERNATIONAL DIAGNOSTIC GUIDELINES:

## MAJOR CRITERIA:

**both features must be present**

- ✓ **Histopathological lymph node features** consistent with the iMCD spectrum
- ✓ **Enlarged lymph nodes** (≥1 cm in short-axis diameter) **in ≥2 lymph node stations**




- IMCD, IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE.
- FAJGENBAUM DC *ET AL. BLOOD* 2017; 129 (12): 1646–1657.

# INTERNATIONAL DIAGNOSTIC GUIDELINES:
## MINOR CRITERIA

**≥2 of the following 11 features (including ≥1 laboratory condition) mu present:**

### LABORATORY

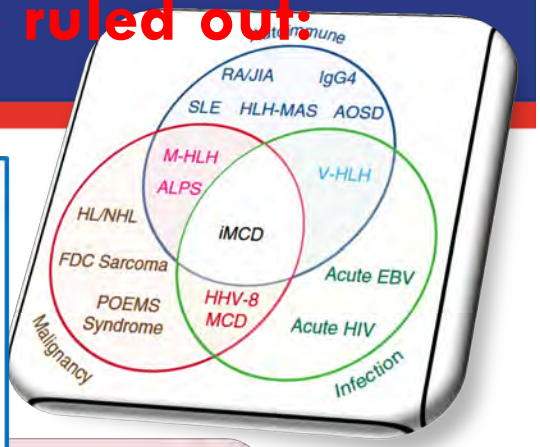
- ☐ Elevated CRP or ESR
- ☐ Anemia
- ☐ Thrombocytopenia or thrombocytosis
- ☐ Hypoalbuminemia
- ☐ Renal dysfunction or proteinuria
- ☐ Polyclonal hypergammaglobulinemia

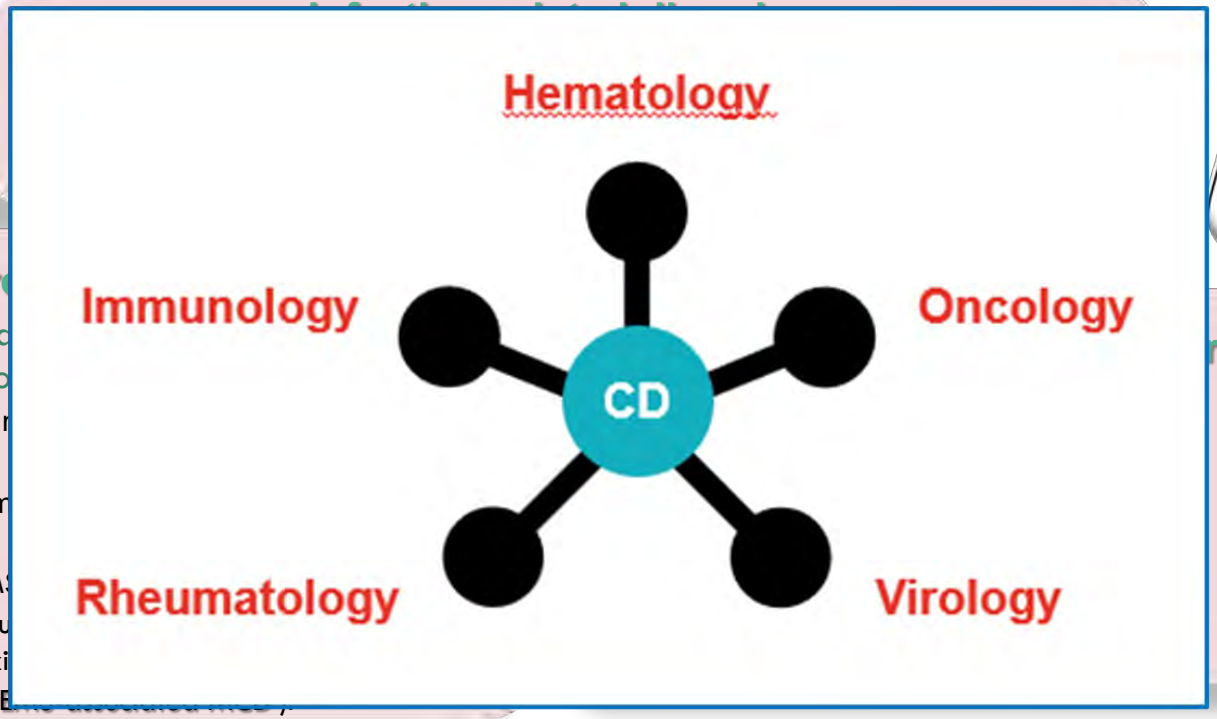
### CLINICAL

- ☐ **Constitutional symptoms** such as night sweats, fever, weight loss or fatigue
- ☐ **Hepatomegaly** and/or **splenomegaly**
- ☐ **Fluid accumulation**: oedema, anasarca, ascites or pleural effusion
- ☐ Eruptive cherry hemangiomatosis or violaceous papules
- ☐ Lymphocytic interstitial pneumonitis

# INTERNATIONAL DIAGNOSTIC GUIDELINES:
# EXCLUSION CRITERIA

**each of the following diseases/disorders must be ruled out:**




**Malignant/lymphopr**

These disorders must be dic
time as iMCD to be exclusio

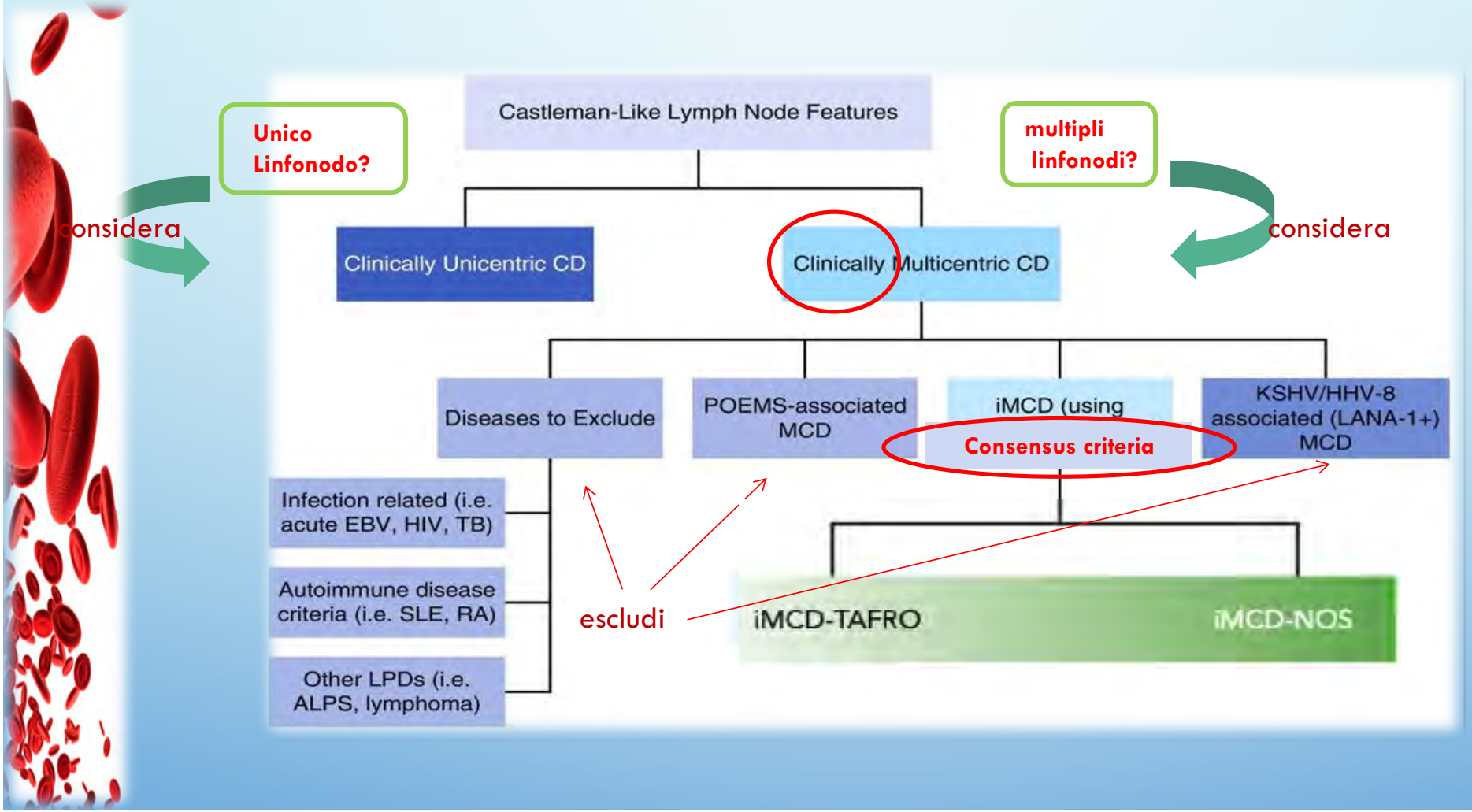
- Lymphoma (Hodgkin and
- Multiple myeloma
- Primary lymph node plasm
- FDC sarcoma
- POEMS syndrome (POEM
  'associated' with CD; becau
  believed to drive the cytoki
  to be iMCD but rather 'POE

**ry diseases**

autoimmune

MUNE LYMPHOPROLIFERATIVE SYNDROME; AOSD, ADULT-ONSET STILL'S DISEASE; CD, CASTLEMAN DISEASE; EBV, EPSTEIN–BARR VIRUS; FDC, FOLLICULAR DENDRITIC CELL;
N HERPESVIRUS 8; IMCD, IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE; MCD, MULTICENTRIC CASTLEMAN DISEASE; POEMS, POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY,
L GAMMO PATHY, SKIN CHANGES; SLE, SYSTEMIC LUPUS ERYTHEMATOSUS.
DC *ET AL*. *BLOOD* 2017; 129 (12): 1646–1657.

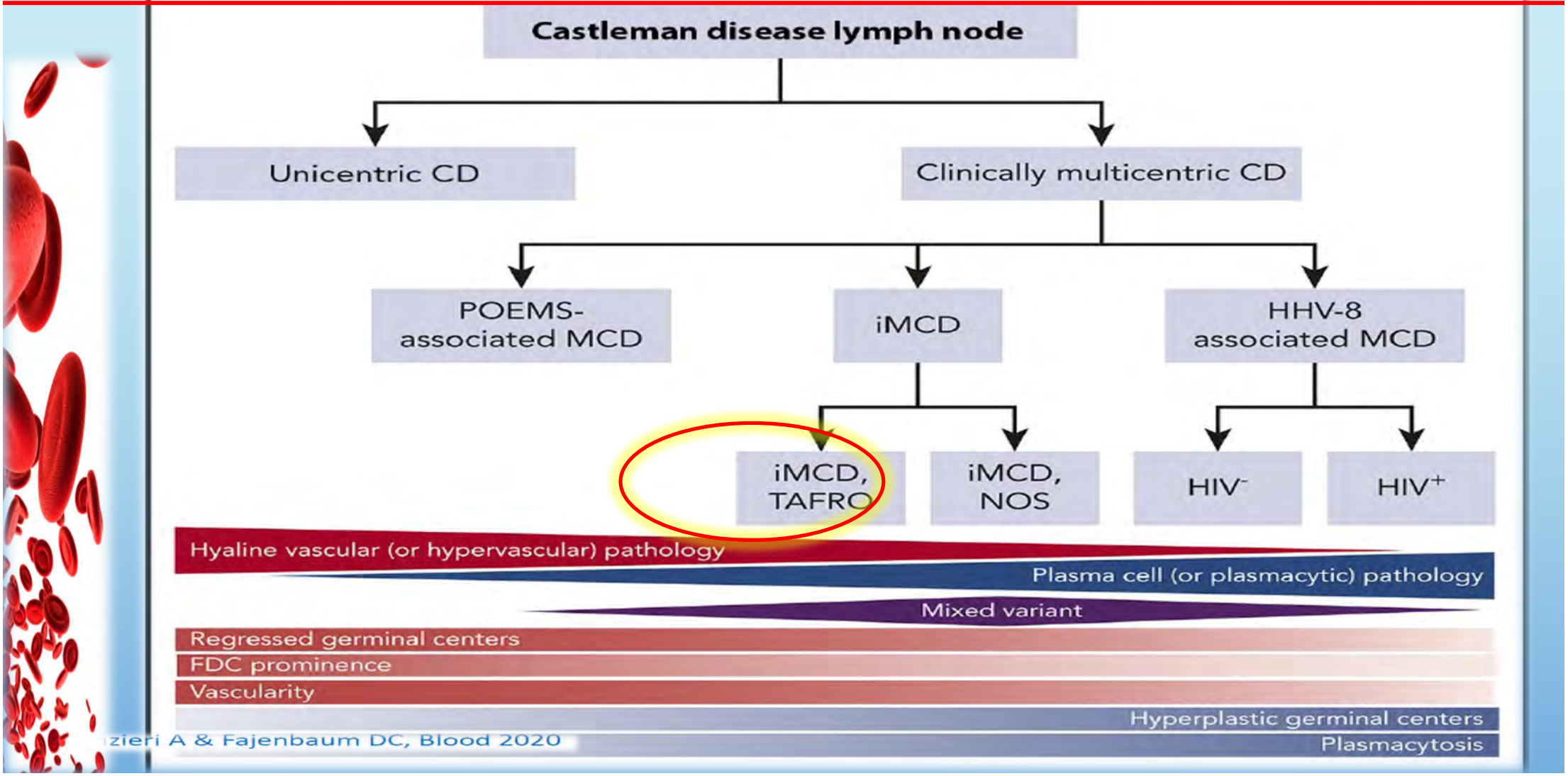
# ALGORITMO DELL'APPROCCIO PER L'INQUADRAMENTO DEL LINFONODO CON CARATTERISTICHE DI CD



# MALATTIA DI CASTLEMAN MULTICENTRICA IDIOPATICA TAFRO

# EMERGENZA EMATOLOGICA

# The Castleman Disease spectrum




zieri A & Fajenbaum DC, Blood 2020

# TAFRO syndrome

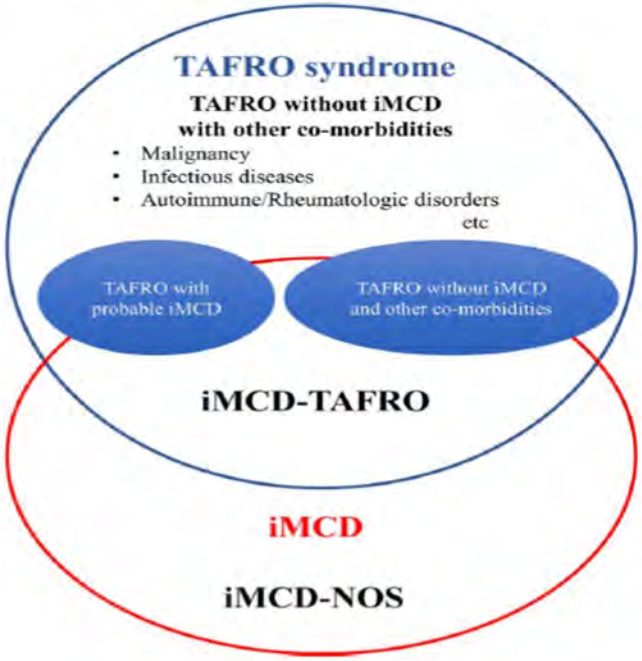
This heterogeneous clinical entity can occur in the context of:

- Infectious diseases
- Malignancies
- Rheumatologic disorders
- Idiopathic multicentric Castleman disease (iMCD)

*Iwaki et al. AJH 2016*
*Fajgenbaum et al. AJH 2018*

# TAFRO syndrome

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




**TAFRO syndrome is not idiopathic multicentric Castleman disease-TAFRO**

*Nishimura et al. AJH 2021*

# iMCD-TAFRO

A distinct group of patients present with an aggressive subtype of iMCD; these patients have specific symptoms:[1]

**T**hrombocytopenia
**A**nasarca
**F**ever
**R**eticulin fibrosis or
**R**enal
Insufficiency
**O**rganomegaly

1. Dispenzieri A *et al. Blood* 2020; 135 (16): 1353–1364

## EAHP22-BMWS-1206: TAFRO Syndrome in a Patient with Multicentric Castleman Disease (Idiopathic, HHV8-Negative)

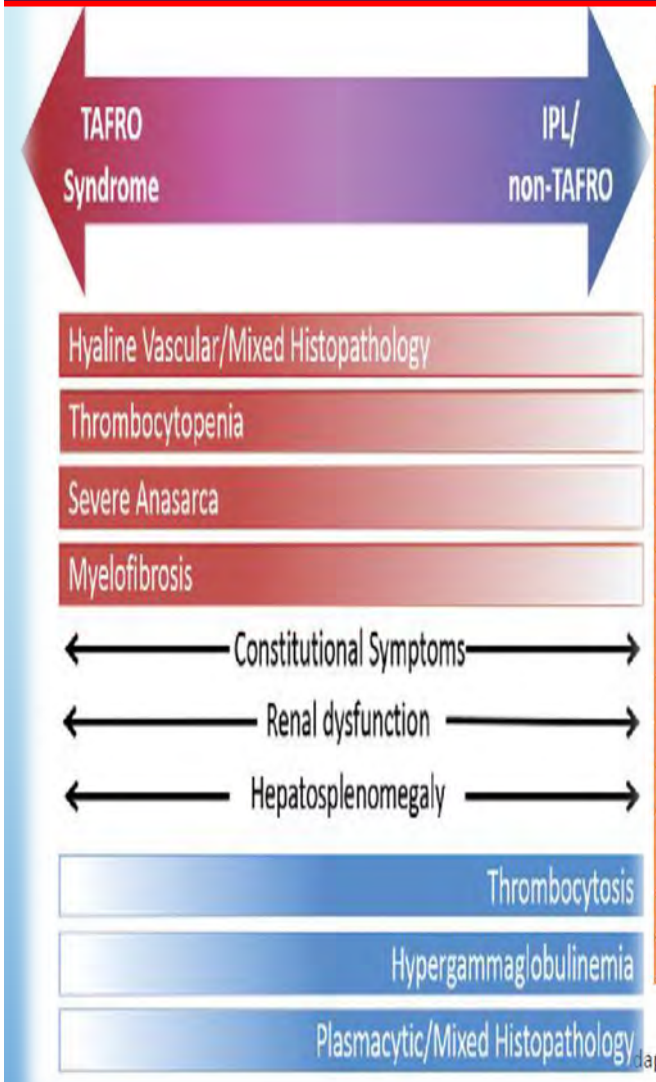
Clarissa E. Jordan, M.D.; Mazen Osman, M.B., B.Ch.; Prasuna Muppa, M.B.B.S.; Matthew Howard, M.D.; Rebecca L. King, M.D.
Mayo Clinic, Rochester, Minnesota, USA

## VALIDATED INTERNATIONAL DEFINITION OF iMCD-TAFRO

(Nishimura et al)

- Clinical criteria (all 4 required)
  - Thrombocytopenia
  - Anasarca
  - Fever or hyperinflammatory status
  - Organomegaly
- Pathological criteria (required): lymph node consistent with idiopathic multicentric Castleman disease
- Exclusion of a variety of infectious diseases, autoimmune/rheumatologic diseases, and malignancy (required)
- Additional clinical and pathological criteria (at least one required)
  - Renal insufficiency or renal failure
  - TAFRO-consistent bone marrow, including reticulin fibrosis or megakaryocytic hyperplasia
- Additional clinical and pathological criteria (not required but contributory)
  - Absence of polyclonal hypergammaglobulinemia
  - High alkaline phosphatase with mild to no increase in bilirubin and transaminases

# Diagnostic Criteria of iMCD-TAFRO




Definite iMCD-TAFRO Criteria

| | |
|---|---|
| **1. Clinical Criteria (all four required)** | |
| Thrombocytopenia (T): Pre-treatment nadir platelet level ≤ 100 103/μl | |
| Anasarca (A): Pleural effusion, ascites, or subcutaneous edema with CT scan | |
| Fever or hyperinflammatory status (F): Fever ≥ 37.5°C of unknown etiology or CRP ≥ 2.0 mg/dl | |
| Organomegaly (O): Small volume lymphadenopathy in two or more regions, hepatomegaly, or splenomegaly on CT scan | |
| **2. Pathological Criteria (required)** | |
| Lymph node consistent with iMCD: must be consistent with histopathologic features of the International iMCD Diagnostic Criteria | |
| **3. Additional Clinical and Pathological Criteria (at least one)** | |
| Renal insufficiency (R) | |
| TAFRO-consistent bone marrow: Reticulin fibrosis (R) or megakaryocytic hyperplasia, without evidence of an alternative diagnosis | |
| **4. Exclusion Criteria (required)** | |
| **5. Supportive Clinical Criteria (not required but strongly supportive)** | |
| Renal insufficiency (R) | |
| TAFRO-consistent bone marrow: Reticulin fibrosis (R) or megakaryocytic hyperplasia, without evidence of an alternative diagnosis | |
| Absence of polyclonal hypergammaglobulinemia | |
| Elevated alkaline phosphatase with mild to no elevation in bilirubin and transaminases | |

**Exclusion Criteria**

Infectious diseases - including:
1. HHV-8
2. EBV-associated lymphoproliferative disorders
3. Acute HIV infection
4. Tuberculosis
5. Covid-19 cytokine storm syndrome

Autoimmune/rheumatologic diseases:
1. Systemic lupus erythematosus
2. Sjögren syndrome
3. Rheumatoid arthritis
4. Adult-onset Still disease
5. Juvenile idiopathic arthritis
6. IgG ≥ 3400 mg/dl (suggestive of autoimmune diseases or plasma cell dyscrasias)
7. Primary hemophagocytic lymphohistiocytosis

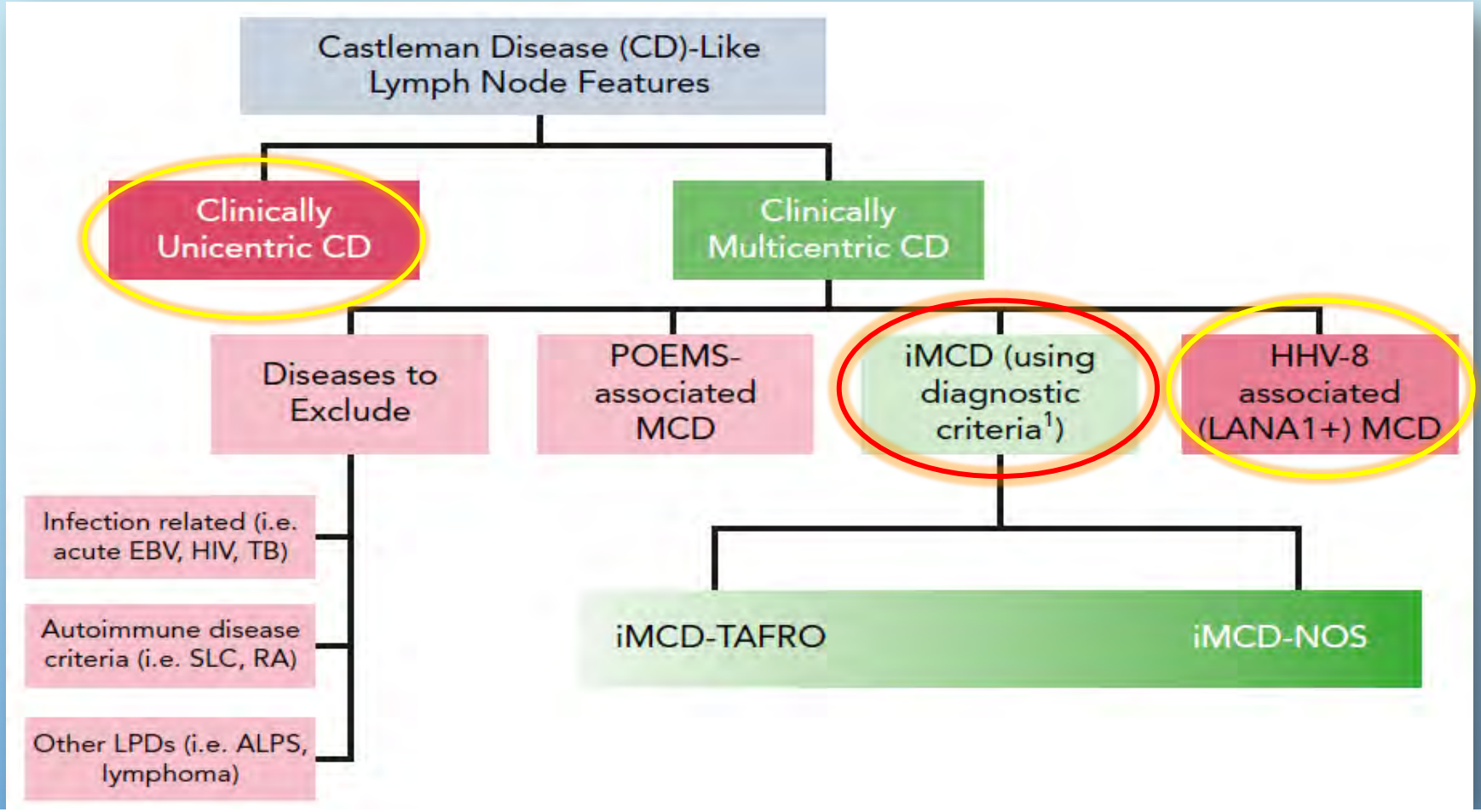
Malignancy - including:
1. Malignant lymphoma
2. Multiple myeloma
3. Metastatic cancer
4. POEMS syndrome

dapted from Nishimura Y. , *American Journal of Hematology*; 2021:1-12

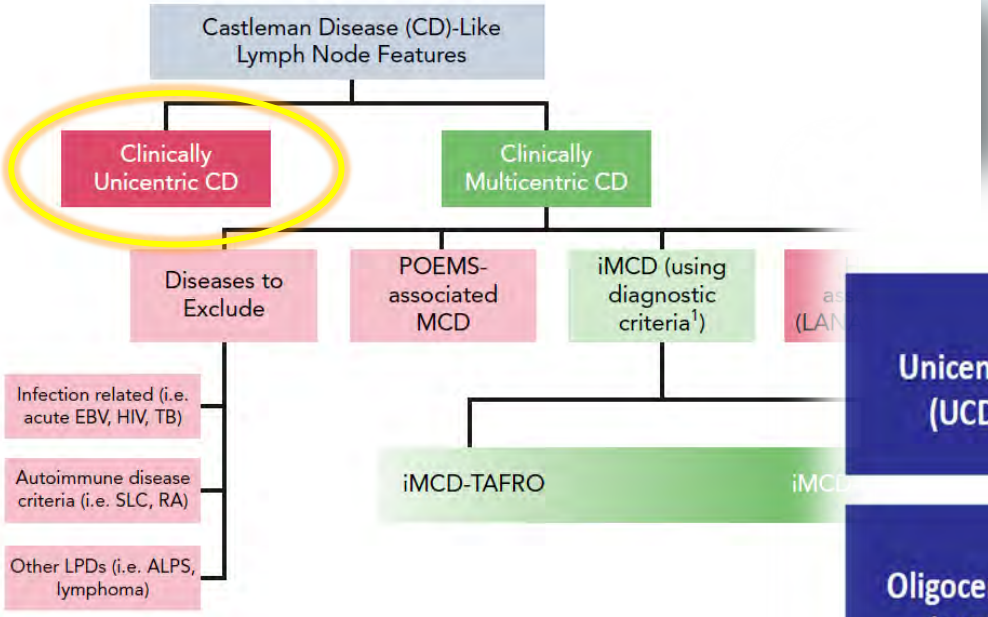
# MALATTIA DI CASTLEMAN

# TERAPIA

# DIVERSA A SECONDA DEL TIPO DI CD

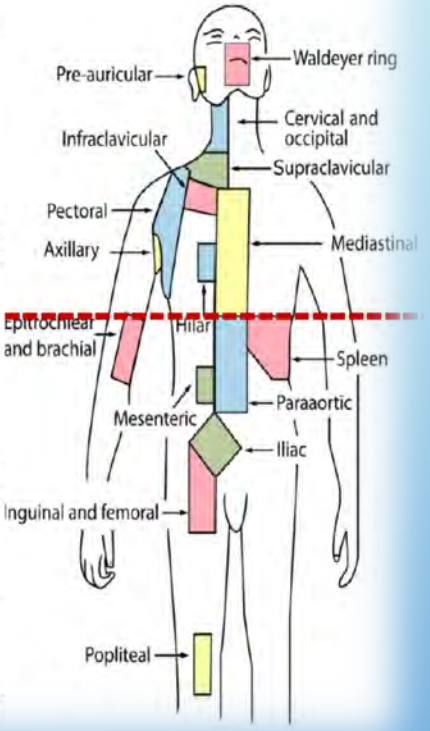


# TERAPIA DELLA MALATTIA DI CASTLEMAN UNICENTRICA
## UNICO LINFONODO O UN'UNICA STAZIONE LINFONODALE COINVOLTA

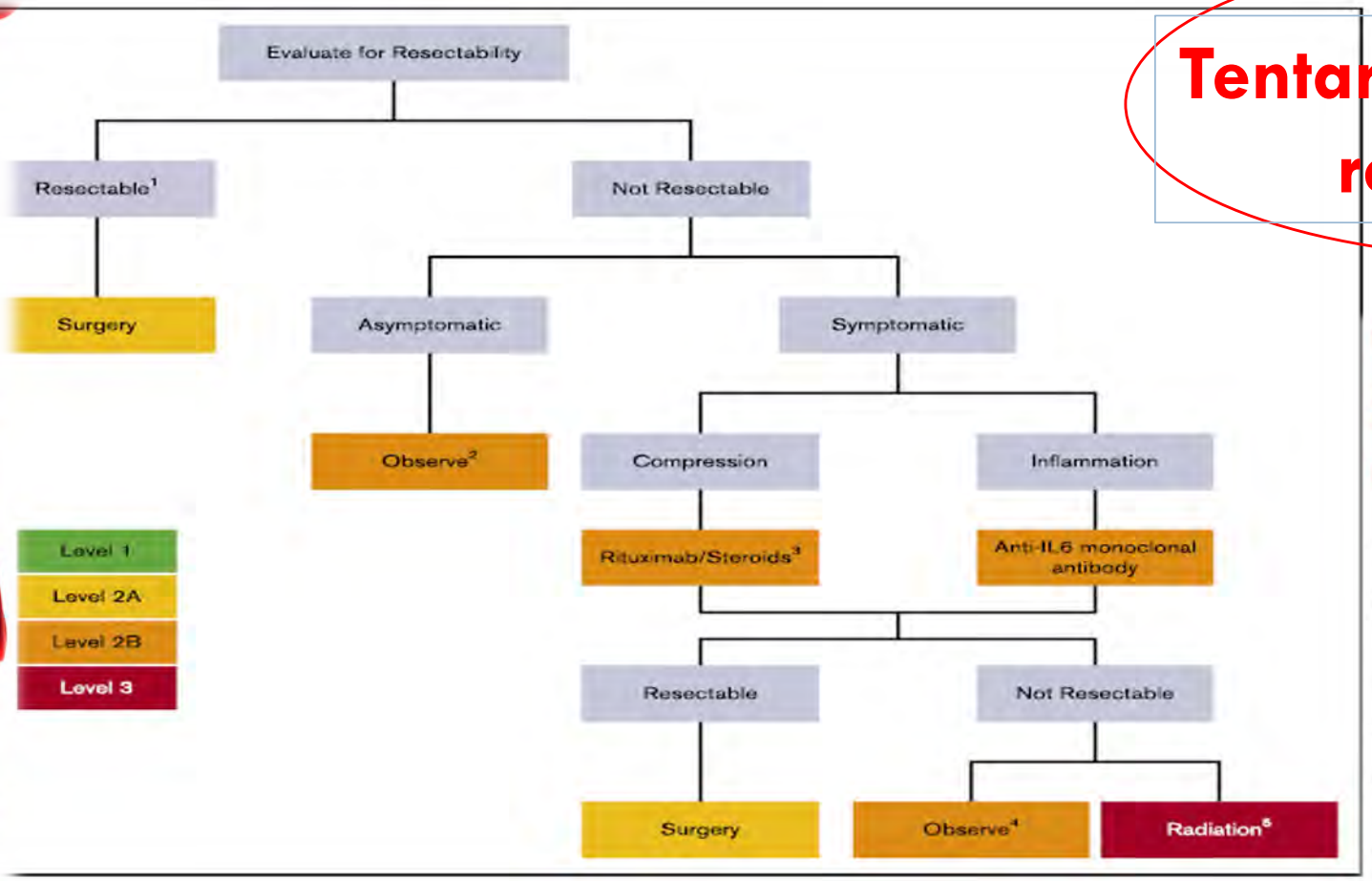



## Regional CD subtypes

| | |
|---|---|
| **Unicentric (UCD)** | 1 station of enlarged LNs |
| **Oligocentric (OCD)** | ≥2 stations of enlarged LNs, either above or below the diaphragm |
| **Multicentric (iMCD)** | ≥2 stations of enlarged LNs, both above and below the diaphragm |



# TERAPIA DELLA MALATTIA DI CASTLEMAN UNICENTRICA
# RESEZIONE CHIRURGICA




**Tentare di ottenere la resecabilità**

**RESECTABLE**

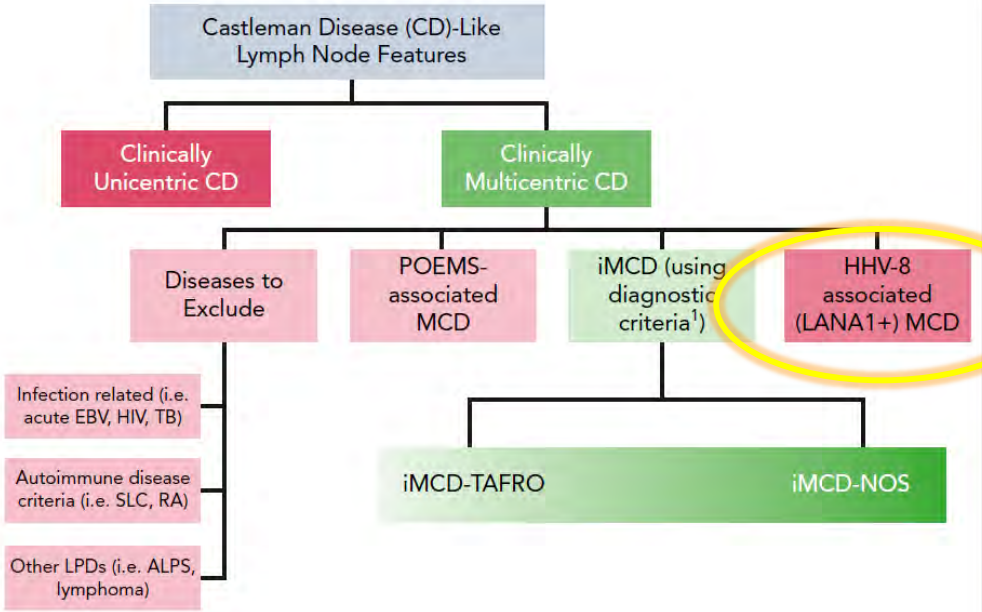
**SURGERY (2A evidence)**

**EMBOLIC DEVASCULARIZATION (2B)**

- Larger than MCD, intraoperative bleeding (vascularization)
- Also regression of systemic symptoms, AA amyloid, renal dysfunction and lab abnormalities
- Spontaneous involution of small sattelite LN

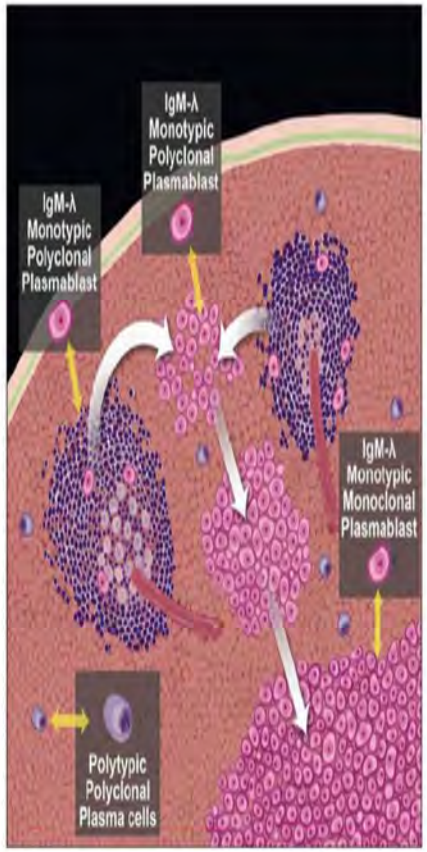
OS > 90% at 5 yrs (*Dispenzieri et al AJH 2012*)

# TERAPIA DELLA MALATTIA DI CASTLEMAN MULTICENTRICA HHV8 CORRELATA



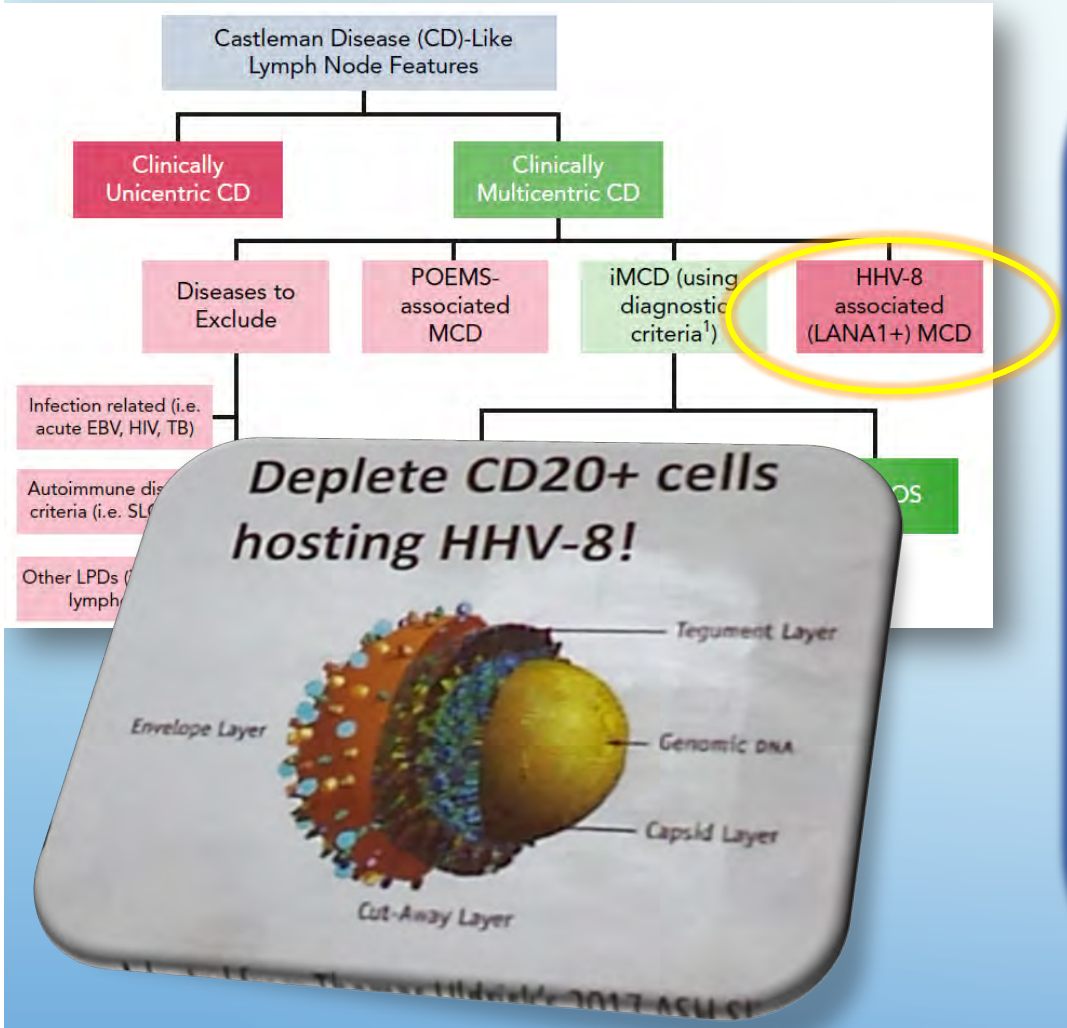

L'HHV8 si osserva nel 60-100% dei pazienti associata all'HIV, ma anche nel 20-40% dei pazienti HIV-negativi.

L'HHV8 si localizza negli immunoblasti e nei linfociti B CD20+. L'HHV8 induce la produzione di un omologo virale dell'interleuchina-6 (vIL6), che facilita la comparsa dei linfociti B con componente monoclonale o policlonale.




Il **meccanismo fisiopatologico è chiaro.**
L'**immunocompromissione** secondaria all'infezione da HIV o ad altre cause permette una **incontrollata infezione e replicazione dell'HHV-8 all'interno dei plasmoblasti e delle cellule B** del linfonodo che porta all'increzione dell'IL-6 virale e di altre citochine pro-infiammatorie.

# TERAPIA DELLA MALATTIA DI CASTLEMAN MULTICENTRICA HHV8 CORRELATA




**Da modulare in base alla severità dei sintomi e alle comorbidità**

- ***MCD HHV-8+ ASINTOMATICA***
  **monitoraggio ogni 3 mesi con visita, esami di laboratorio e pcr quantitativa per HHV-8**

- ***MCD HHV-8+ MODERATAMENTE SINTOMATICA***
  **Anti CD 20 settimanale**

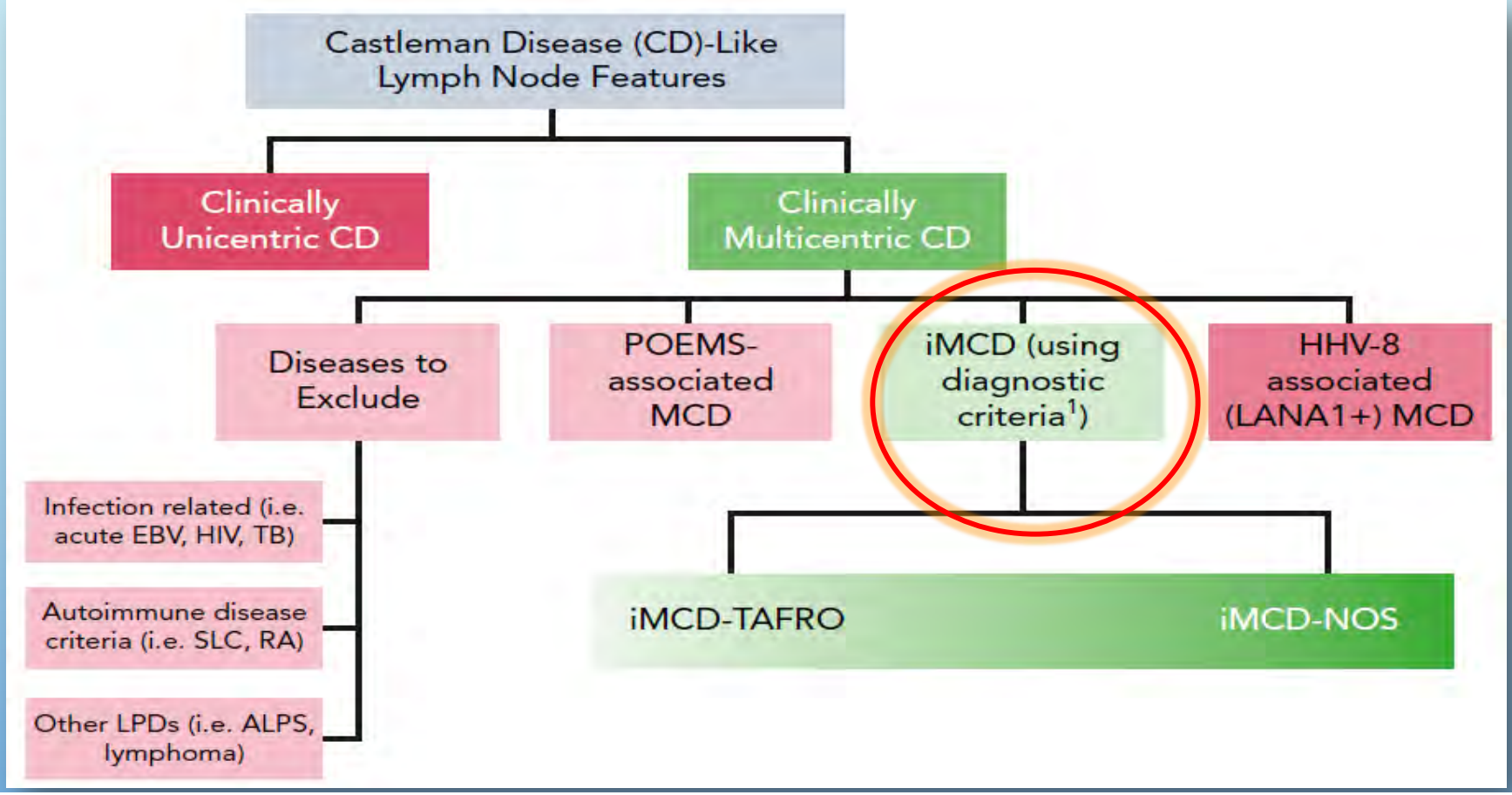
- ***MCD HHV8+ SEVERAMENTE SINTOMATICA***
  **Anti CD20 + Etoposide/adriblastina liposomiale**

- ***MCD HHV-8+ +HIV***
  **Anti CD20 + HAART**

- ***MCD HHV8+ S. di Kaposi***
  **Anti CD20 + Adriblastina liposomiale**

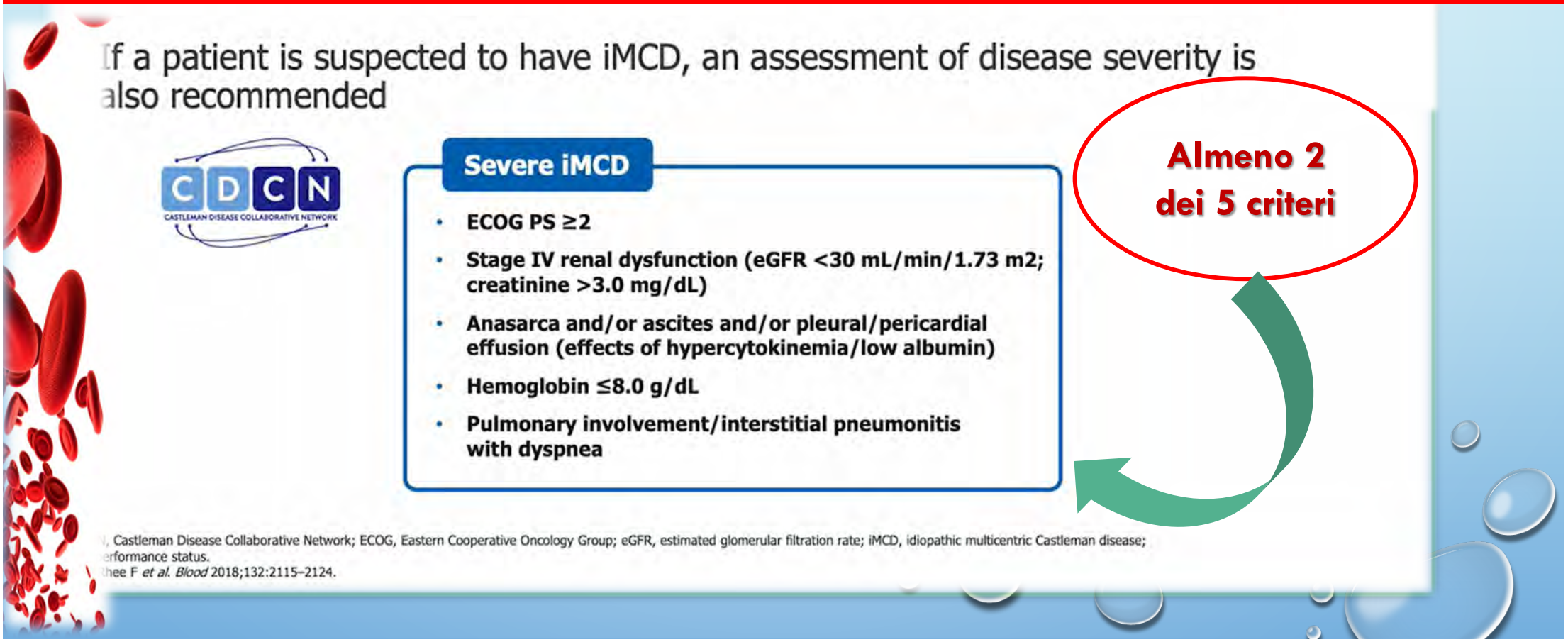
- ***MCD HHV8+ + PEL***
  **Terapia della PEL**

# MALATTIA DI CASTLEMAN MULTICENTRICA IDIOPATICA: TERAPIA



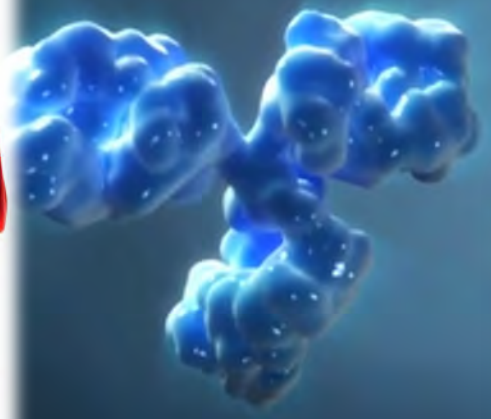
# SEVERITY: Criteria for defining severe iMCD

- Patients with **non-severe iMCD** typically have a good performance, without evidence of abnormal organ function
- Patients with **severe iMCD** usually have evidence of organ failure and are likely to require critical care; they often present as the TAFRO subtype

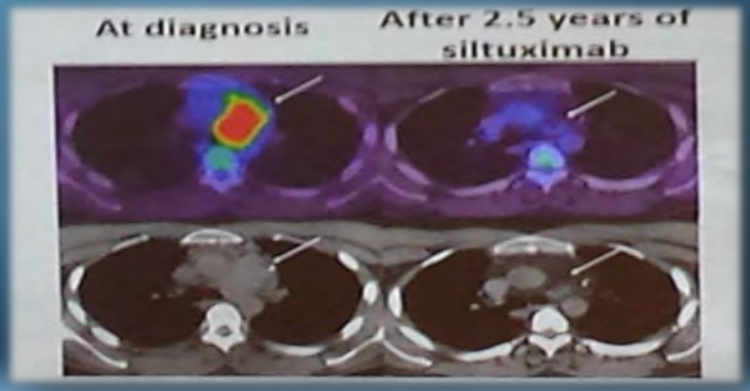


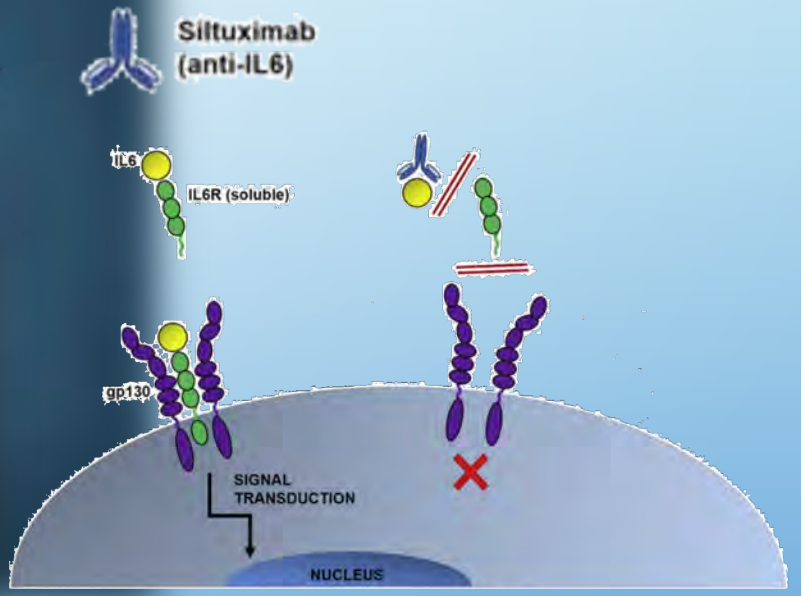
# Come bloccare l'IL-6?

**Siltuximab è un anticorpo monoclonale che si lega all'IL-6 impedendone il legame al recettore per l'IL6, sia alla forma solubile che a quella di mebrana. Si lega solo all'IL-6 umano e non a quello virale, per cui non è indicato nelle forme di MCD HHV-8 +.**



11 mg/kg of Siltuximab given over 1 hour as intravenous infusion administered every 3 weeks



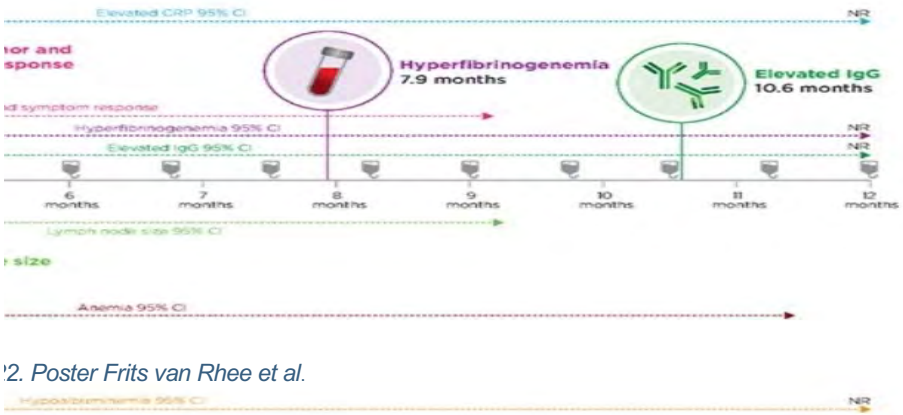



# SILTUXIMAB PER IL TRATTAMENTO DELLA IMCD

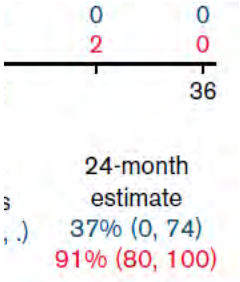
## Key Points

- Siltuximab leads to rapid normalization of symptomatology and most abnormal laboratory parameters and prolongs PFS in patients with iMCD.
- The findings in this study reinforce the use of siltuximab as the first iMCD treatment choice, as recommended by international guidelines.

**PPROVATO DA FDA E**
**TAMENTO DELL'IMCD**

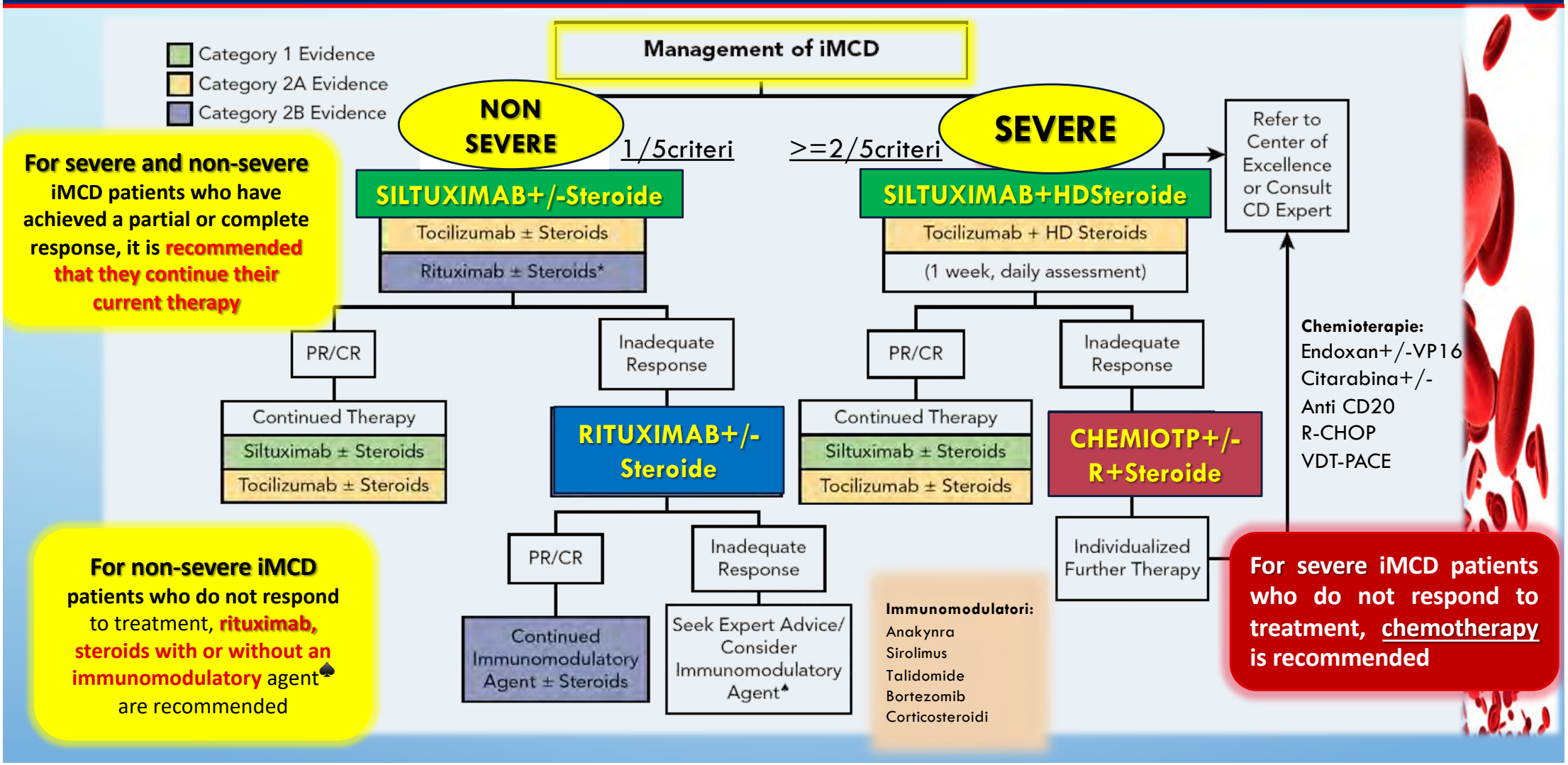




*2. Poster Frits van Rhee et al.*




Fritz van Rhee et al, Blood Advances. August 2022

# CDCN international treatment algorithm for iMCD[1]



# RISPOSTA ALLA TERAPIA

## CDCN response criteria: How should response to treatment be evaluated?

- The CDCN response criteria is based on the evaluation of biochemical, lymph node, and symptom response

| Overall response | Biochemical (CRP, Hb, albumin, GFR) | Lymph node | Symptoms (fatigue, anorexia, fever, weight) |
|---|---|---|---|
| **CR** | All measures normal | CR | Normalization to baseline |
| **PR** | >50% improvement in all measures | PR | Improvement in all 4 categories, but not to baseline |
| **SD** | <50% improvement (or <25% worsening) in all measures | No PR or CR | Improvement in 1–3 categories |
| **PD** | >25% worsening in any measure | >25% increase | Any symptoms worse on ≥2 assessments |

| Symptom | Improvement criteria |
|---|---|
| Fatigue | Decrease of ≥1 CTCAE grade point relative to baseline |
| Anorexia | Decrease of ≥1 CTCAE grade point relative to baseline |
| Fever | Decrease of ≥1°C relative to baseline |
| Weight | Increase of ≥5% relative to baseline |

**Adapted from van Rhee *et al.* 2018.**

CDCN, Castleman Disease Collaborative Network; CR, complete response; CRP, C-reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; GFR, glomerular filtration rate; Hb, hemoglobin; PD, progressive disease; PR, partial response; SD, stable disease.

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

# Management of siltuximab therapy

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Guideline Article – Consensus based

Open Access

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

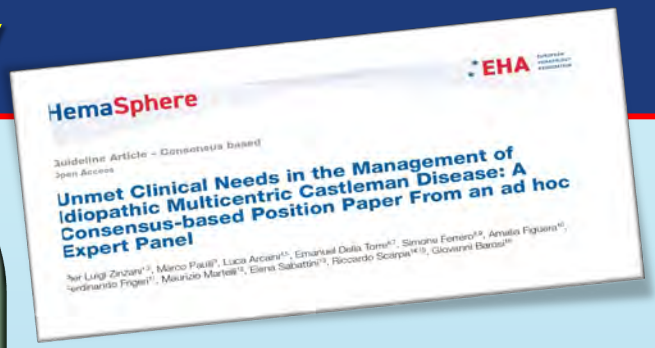
Pier Luigi Zinzani[1,2], Marco Paulli[3], Luca Arcaini[4,5], Emanuel Della Torre[6,7], Simone Ferrero[8,9], Amalia Figuera[10], Ferdinando Frigeri[11], Maurizio Martelli[12], Elena Sabattini[13], Riccardo Scarpa[14,15], Giovanni Barosi[16]

**Correspondence:** Pier Luigi Zinzani (pierluigi.zinzani@unibo.it).

# Management of Siltuximab therapy

## TREATMENT GUIDELINES:

1) **Corticosteroid monotherapy is not recommended** in iMCD because of a response failure rate of over 50% and nonnegligible side effects.
2) **Anti-IL-6 siltuximab therapy** (11 mg/kg every 3 weeks) is recommended as **first-line therapy, with corticosteroids** as initial adjuvant therapy if necessary and with a **dosing regimen tailored to the severity of symptoms.**
3) Due to the side effects of corticosteroids**, anti-IL-6 siltuximab therapy should be initiated early to discontinue steroids as soon as possible.**
4) **Severe iMCD cases should be started immediately on siltuximab combined with high-dose corticosteroid (500 mg/daily)** therapy to prevent deterioration and death.
5) An aggressive treatment with **weekly doses of siltuximab may be used for the 1st month of therapy;** if a response is obtained, then siltuximab should be administered every 3 weeks indefinitely with gradual tapering of steroids.


HemaSphere

EHA

Guideline Article – Consensus based

Open Access

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

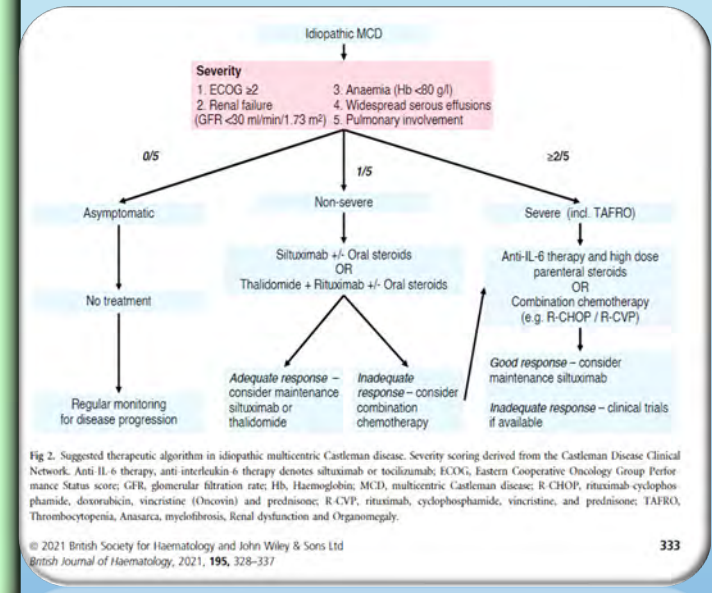



Fig 2. Suggested therapeutic algorithm in idiopathic multicentric Castleman disease. Severity scoring derived from the Castleman Disease Clinical Network. Anti IL-6 therapy, anti-interleukin 6 therapy denotes siltuximab or tocilizumab; ECOG, Eastern Cooperative Oncology Group Performance Status score; GFR, glomerular filtration rate; Hb, Haemoglobin; MCD, multicentric Castleman disease; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine (Oncovin) and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; TAFRO, Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction and Organomegaly.

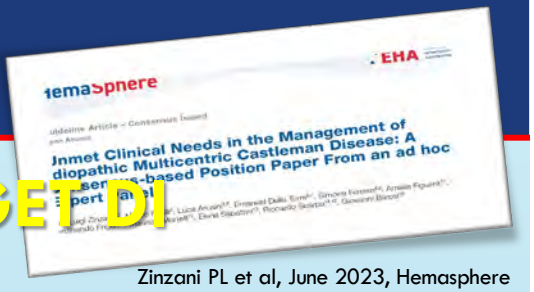


British Journal of Haematology, 2021, **195**, 328–337



**CLINICAL STUDIES ANALYSIS:** Phase I single arm CT; Phase II randomised CT; International Treatment Guideline; Post hoc analysis Blood 2022; phase II extension; Morra et al.

# Management Of Siltuximab Therapy




Zinzani PL et al, June 2023, Hemasphere

## PATHWAYS CITOCHINICI POTENZIALMENTE TARGET DI TERAPIE MIRATE

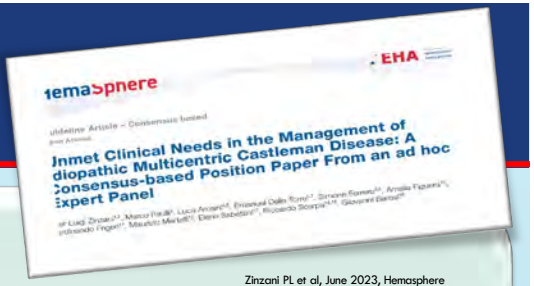
**The Panel agreed on**

- **It's possible to reduce the dose** in responding patients? that is, de-escalating treatment intensity by **switching siltuximab administration at 11 mg/kg every 6 weeks?** retrospective registry-based clinical data on no severe iMCD
- The signature by **proteomics** represents a potential new clinical predictive tool for siltuximab therapy response
- **Recommending tocilizumab as a reasonable alternative** therapy to siltuximab if the latter is not readily available: 8 mg/kg IV every 2 weeks

| ecommended<br>herapeutic Options | Unmet Clinical Needs<br>Still to be Addressed |
|---|---|
| **herapy** | |
| iltuximab 11 mg/kg every 3 weeks (as irst-line therapy) | De-escalating treatment intensity to 11 mg/kg every 6 weeks in responding patients |
| ccelerated weekly dosing of siltuximab in ost severe cases for 1 month | None |
| djunctive corticosteroids (in highly symp-omatic iMCD) tailored to disease severity | Considering gradual corticosteroid dose tapering |
| ocilizumab (if siltuximab is not available) | Performing studies to establish the optimal regimen for iMCD |

M = bone marrow; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography/computed omography; HHV-8 = human herpesvirus-8; iMCD = idiopathic multicentric Castleman disease; LANA-1 = latency-associated nuclear antigen-1; SUVmax = maximum standardized uptake value; TAFRO = hrombocytopenia, Anasarca, Fever, Reticulin myelofibrosis, Organomegaly; UCN = unmet clinical need.

# CHOICE AND MANAGEMENT OF THERAPY IN PATIENTS **RESISTANT/INTOLERANT TO SILTUXIMAB**




Zinzani PL et al, June 2023, Hemasphere

**PUBLISHED EVIDENCE:**

- About **50%–66%** of patients with iMCD **do not obtain or lose their response** during first-line siltuximab therapy.
- The consensus guidelines suggest
  - for NON SEVERE anti-IL-6 mAb refractory iMCD: **rituximab and corticosteroids with or without immunomodulatory /immunosuppressive** agents: cyclosporine A, sirolimus, thalidomide, lenalidomide, bortezomib, **anakinra**, derivatives of retinoic acid, and IFN-α(in this … CD pathology and phisiopathogenesis)
  - **for SEVERE iMC**

## CONCLUSION

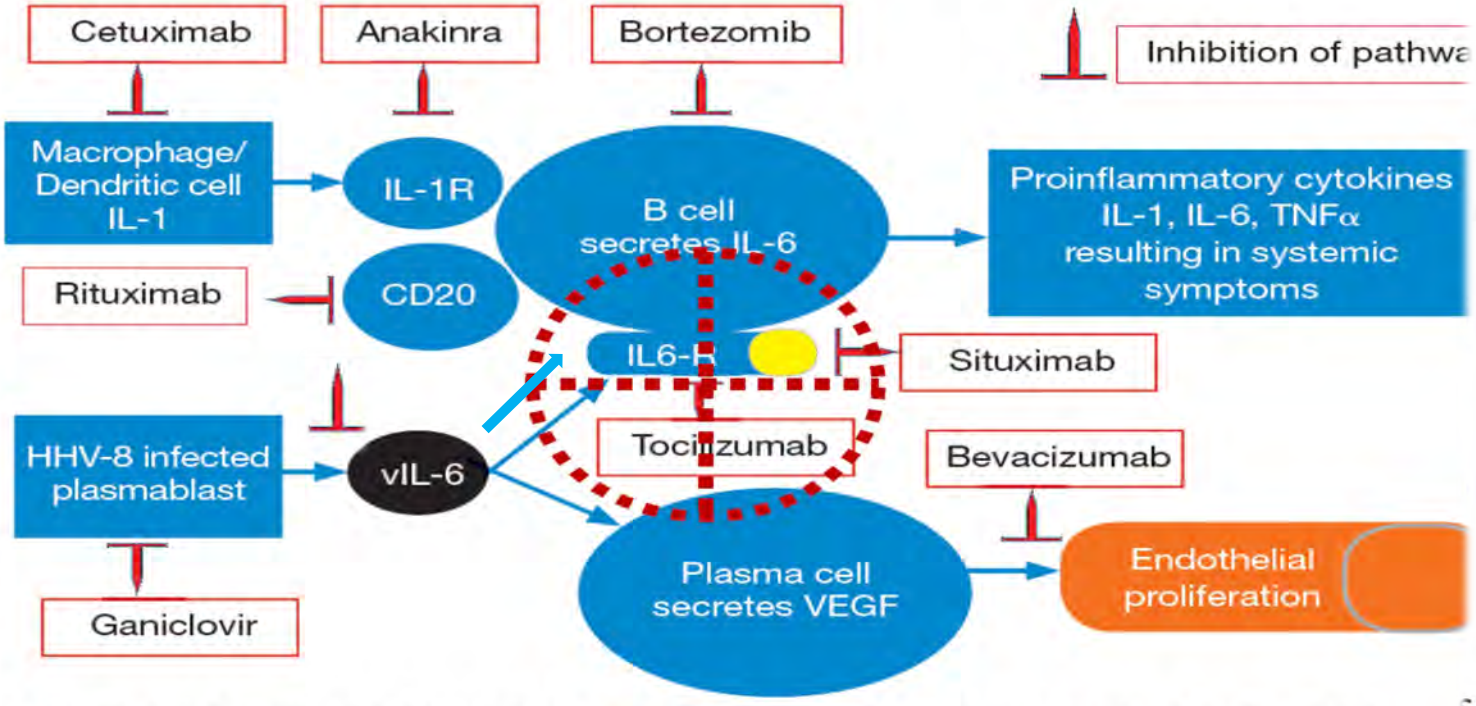
**The management of severe iMCD that fails anti-IL-6 mAbs and cytotoxic chemotherapy** is not well defined and should be considered for each patient, taking into account previous responses, comorbidities, performance status, and cytokine profile

**mTOR inhibitor**: **Sirolimus** indu… o activated **iMCD** patients and induced rem… **L-6–JAK–STAT3** iMCD with multiple relapses af… chemotherapy. **Increased PI3K/A… may activate the **has been observed in the lymph nodes of anti-IL-6 mAb refractory iMCD cases**: **A clinical trial** on using sirolimus to treat iMCD **is still ongoing**. mTOR is **a promising target** pathway **also for** the therapy of IL-6 inhibitor-refractory **iMCD-NOS**

JAK–STAT3 pathway and that **JAK1/2 inhibitors** may represent a valuable therapeutic strategy for siltuximab no responders. **IFN-I** signalling seems involved in the JAK-mediated activation of mTOR in iMCD-TAFRO and **may represent another pharmacological target.**

# PATHWAYS CITOCHINICI POTENZIALMENTE TARGET DI TERAPIE MIRATE

**Figure 1.** Pathophysiology of Castleman Disease




Pathways showing potential therapeutic targets and inhibition of pathway with drugs.

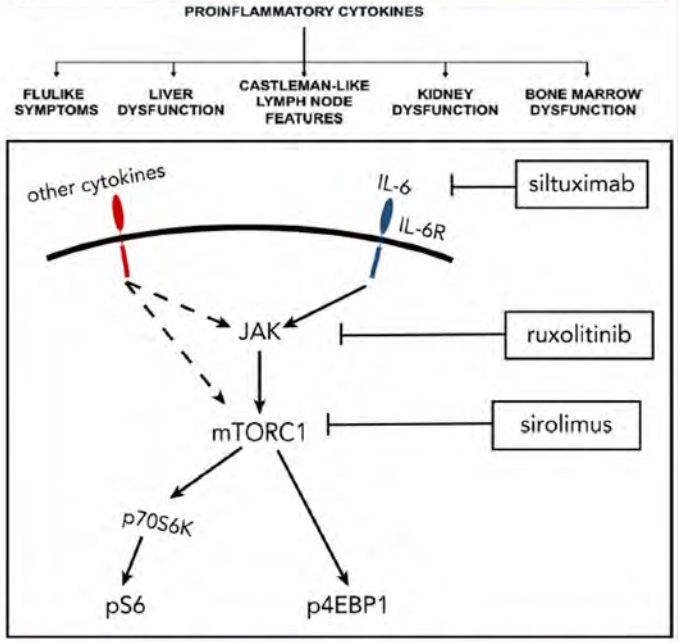
Castleman Disease | AVAHO

Abbreviations: HHV-8, human herpesvirus-8; IL-1, interleukin-1; IL-1R, interleukin-1 receptor; IL-6, interleuk
TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; vIL-6, viral analog of interleukin-6.

**The Role of Interleukin-6 in Castleman Disease**

Hematol Oncol Clin N Am 32 (2018) 23–36

Kazuyuki Yoshizaki, MD, PhD[a,*], Shinichi Murayama, PhD[a], Hiroki Ito[a], Tomohiro Koga, MD, PhD[b,c]




Increased mTOR activation in idiopathic multicentric Castleman disease

Daniel J. Arenas,[1] Katherine Flores,[1] Dale Kobrin,[1] Ruth-Anne Langan Pai,[1] Maya B. Srkalovic,[1] Mark-Avery Tamaklloe,[1] Rozena Rasheed,[1] Jasira Ziglar,[1] Johnson Khor,[1] Sophia A. T. Parente,[1] Sheila K. Pierson,[1] Daniel Martinez,[2] Gerald B. Wertheim,[2] Taku Kambayashi,[1] Joseph Baur,[1] David T. Teachey,[3] and David C. Fajgenbaum[1]

# TAKE HOME MESSAGES

- La malattia di Castleman (CD) comprende un gruppo eterogeneo di disturbi ematologici che condividono particolari caratteristiche istopatologiche dei linfonodi

- La iMCD, è una malattia rara, potenzialmente fatale, che comporta sintomi infiammatori sistemici, linfoproliferazione policlonale, citopenia, disfunzione multiorgano indotti da una «tempesta» di citochine che spesso include l'interleuchina-6.

- La iMCD può verificarsi in individui di qualsiasi età e la diagnosi precisa è impegnativa, perché vi è una significativa sovrapposizione con disturbi e processi neoplastici, autoimmuni ed infettivi.


GRAZIE
DELL'ATTENZIONE