



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Castleman Disease

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***Andrew D. Zelenetz, MD, PhD/Chair † P**
Memorial Sloan Kettering Cancer Center

***Leo I. Gordon, MD/Vice Chair ‡ §**
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

***Jeremy S. Abramson, MD, MMSc † ‡**
Mass General Cancer Center

Ranjana H. Advani, MD †
Stanford Cancer Institute

Babis Andreadis, MD, MSCE † ‡
UCSF Helen Diller Family
Comprehensive Cancer Center

Nancy L. Bartlett, MD †
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

L. Elizabeth Budde, MD, PhD † §
City of Hope National Medical Center

Paolo F. Caimi, MD ‡ † §
Case Comprehensive Cancer Center/University
Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

Julie E. Chang, MD ‡
University of Wisconsin
Carbone Cancer Center

Beth Christian, MD †
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Sven DeVos, MD, PhD ‡ † P
UCLA Jonsson Comprehensive Cancer Center

Bhagirathbhai Dholaria, MD ‡ † §
Vanderbilt-Ingram Cancer Center

Luis E. Fayad, MD ‡ † P
The University of Texas
MD Anderson Cancer Center

Thomas M. Habermann, MD ‡ §
Mayo Clinic Comprehensive Cancer Center

Muhammad Saad Hamid, MD ‡
St. Jude Children's Research Hospital/The
University of Tennessee Health Science Center

Francisco Hernandez-Ilizaliturri, MD †
Roswell Park Comprehensive Cancer Center

Boyu Hu, MD † ‡ P
Huntsman Cancer Institute
at the University of Utah

Yasmin Karimi, MD ‡
University of Michigan
Rogel Cancer Center

Christopher R. Kelsey, MD §
Duke Cancer Institute

Rebecca King, MD ≠
Mayo Clinic Comprehensive Cancer Center

Justin Kline, MD †
The UChicago Medicine
Comprehensive Cancer Center

Susan Krivacic, MPAff ¥
Consultant

Ann S. LaCasce, MD, MMSc †
Dana-Farber/Brigham and Women's
Cancer Center

Megan Lim, MD, PhD ≠
Memorial Sloan Kettering Cancer Center

Marcus Messmer, MD † ‡
Fox Chase Cancer Center

Mayur Narkhede, MD † ‡
O'Neal Comprehensive Cancer Center at UAB

Rachel Rabinovitch, MD §
University of Colorado Cancer Center

Praveen Ramakrishnan, MD, MS ‡
UT Southwestern Simmons
Comprehensive Cancer Center

Erin Reid, MD ‡
UC San Diego Moores Cancer Center

Kenneth B. Roberts, MD §
Yale Cancer Center/Smilow Cancer Hospital

Hayder Saeed, MD † ‡ P
Moffitt Cancer Center

Naoyuki G. Saito, MD, PhD §
Indiana University Melvin and Bren Simon
Comprehensive Cancer Center

Stephen D. Smith, MD ‡
Fred Hutchinson Cancer Center

Jakub Svoboda, MD ‡
Abramson Cancer Center
at the University of Pennsylvania

Lode J. Swinnen, MBChB, MD † ‡ §
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Joseph Tuscano, MD ‡
UC Davis Comprehensive Cancer Center

Julie M. Vose, MD, MBA ‡ §
Fred & Pamela Buffett Cancer Center

NCCN

Mary Dwyer, MS

Hema Sundar, PhD

ξ Bone marrow transplantation	≠ Pathology
‡ Hematology/Hematology oncology	¥ Patient advocacy
P Internal medicine	§ Radiotherapy/Radiation oncology
† Medical oncology	* Discussion Writing Committee Member

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[NCCN B-Cell Lymphoma Panel Members Summary of the Guidelines Updates](#)

- [Diagnosis \(CD-1\)](#)
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- [Unicentric Castleman Disease \(UCD\) \(CD-3\)](#)
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- [Refractory or Progressive Disease \(CD-6\)](#)
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- [Subtypes of Idiopathic MCD \(CD-A\)](#)
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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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Updates in Version 1.2024 of the NCCN Guidelines for Castleman Disease from Version 6.2023 include:

[CD-1](#)

- Footnote d revised: There are 3 variants: ~~hyaline vascular (virtually always unicentric, HHV8), plasma cell, and HHV8+ multicentric~~ *hypervascular (hyaline vascular), plasmacytic, and mixed variants. Hypervascular variant is virtually always unicentric and human herpesvirus 8 (HHV8) (-). Plasmacytic and mixed variants are multicentric and HHV8+.*

[CD-3](#)

- UCD, for surgically unresectable, "observation in asymptomatic patients" added.
- Footnote k added: See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the NCCN Guidelines for B-Cell Lymphomas. (Also for CD-4 through CD-6)
- Footnote m updated: The optimal dose of RT in unresectable UCD is not established. Doses as high as 40 Gy in 1.5–2 Gy fractions have been used Chronowski GM et al. Cancer 2001;92:670-676. Lower doses may be considered depending upon clinical circumstances (eg, proximity to critical structures, treatment intent). Advanced radiation techniques (eg, IMRT, IGRT, protons) are recommended to limit dose to surrounding normal tissues (Matthiesen C et al. Radiol Oncol 2012;46:265-270). RT Dose Constraint Guidelines for Lymphoma - Recommendations for normal tissue dose constraints can be found in the Principles of Radiation Therapy section of the NCCN Guidelines for Hodgkin Lymphoma.

[CD-4](#)

- Footnote r revised by adding: For principles of concurrent HIV management and supportive care, see the NCCN Guidelines for Cancer in People with HIV.
- Footnote t, 2nd sentence revised: Consider baseline imaging and direct visualization to screen for pulmonary ± gastrointestinal (GI) KS ~~as well as in~~ *patients receiving* concurrent KS-directed therapy.

[MS-1](#)

- Discussion has been updated to reflect changes in the algorithm.

**DIAGNOSIS**

- **Excisional or incisional biopsy. A fine-needle aspiration (FNA) biopsy alone is not generally suitable for the initial diagnosis of lymphoma. A core needle biopsy is not optimal but can be used under certain circumstances. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy (multiple biopsies preferred) and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry [IHC], flow cytometry, molecular analysis to detect immunoglobulin [Ig] gene rearrangements, karyotype or fluorescence in situ hybridization [FISH] for major translocations^a) may be sufficient for diagnosis.**
- **Histologic grading cannot be performed on an FNA.**
- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**

ADDITIONAL DIAGNOSTIC TESTING^{a,b,c,d}**ESSENTIAL:**

- **Adequate immunophenotyping to establish diagnosis**
 - **IHC panel: kappa/lambda, CD20, CD3, CD5, CD138, HHV8**
 - **EBER-ISH**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect Ig and TCR gene rearrangements**
- **IHC: Ki-67 index; Ig heavy chains,^e CD10, BCL2, BCL6, cyclin D1, CD21, or CD23, CD38, IRF4/MUM1, PAX5**
- **Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen: kappa/lambda, CD19, CD20, CD5, CD23, CD10**

Workup
([CD-2](#))

^a If a high suspicion of a clonal process remains and other techniques have not resulted in a clear identification of a clonal process, then next-generation sequencing (NGS) can be used.

^b See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A) in the [NCCN Guidelines for B-Cell Lymphomas](#).

^c For HIV-related lymphomas associated with Castleman disease (CD), see [NCCN Guidelines for B-Cell Lymphomas](#) - HIVLYM. For DLBCL-associated with CD in patients without HIV infection, see [NCCN Guidelines for B-Cell Lymphomas](#) - DLBCL.

^d There are 3 variants: hypervascular (hyaline vascular), plasmacytic, and mixed variants. Hypervascular variant is virtually always unicentric and human herpesvirus 8 (HHV8) (-). Plasmacytic and mixed variants are multicentric and HHV8+.

^e In plasma cell variant HHV8+, plasmablasts are IgM lambda while normal plasma cells are IgG or IgA polytypic.

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WORKUP^f

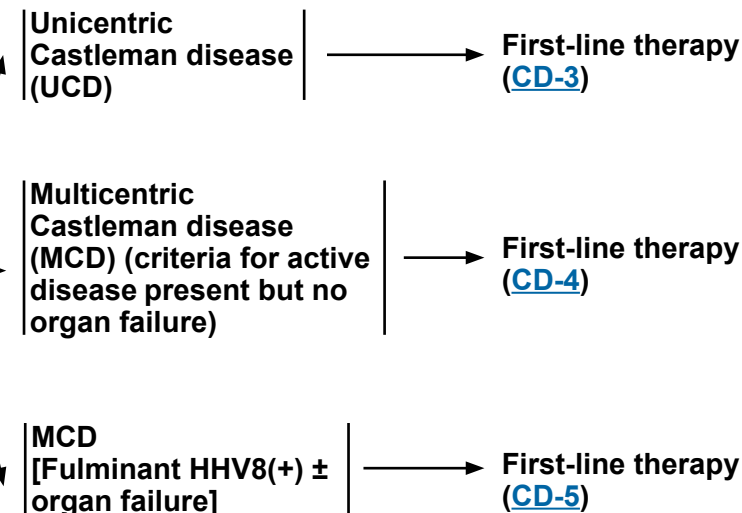
ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- Assess for criteria for active disease^g
- CBC with differential
- Comprehensive metabolic panel
- LDH, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)
- Beta-2-microglobulin, SPEP and urine electrophoresis with immunofixation, serum light chains, quantitative Ig
- HIV, HHV8, hepatitis B testing,^h EBV PCR
- PET/CT scan (preferred) or C/A/P CT with contrast of diagnostic quality
- Pregnancy testing in patients of childbearing age (if chemotherapy or radiation therapy [RT] planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES

- If HHV8 or HIV positive, screening for concurrent Kaposi sarcoma (KS) is strongly recommended
- Bone marrow biopsy + aspirate
- Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
- Neck CT with contrast
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- IgG4, sIL6, sIL10, VEGF, uric acid, ferritinⁱ
- Hepatitis C testing
- Discuss fertility preservation^j

CASTLEMAN DISEASE SUBTYPE



^f See [Subtypes of Idiopathic MCD \(CD-A\)](#). Rule out other diseases that can mimic idiopathic MCD (see Exclusion Criteria on [CD-B 1 of 2](#)). If concurrent polyneuropathy and monoclonal plasma cell disorder, a workup for POEMS syndrome is recommended.

^g [Criteria for Active Disease \(CD-A\)](#).

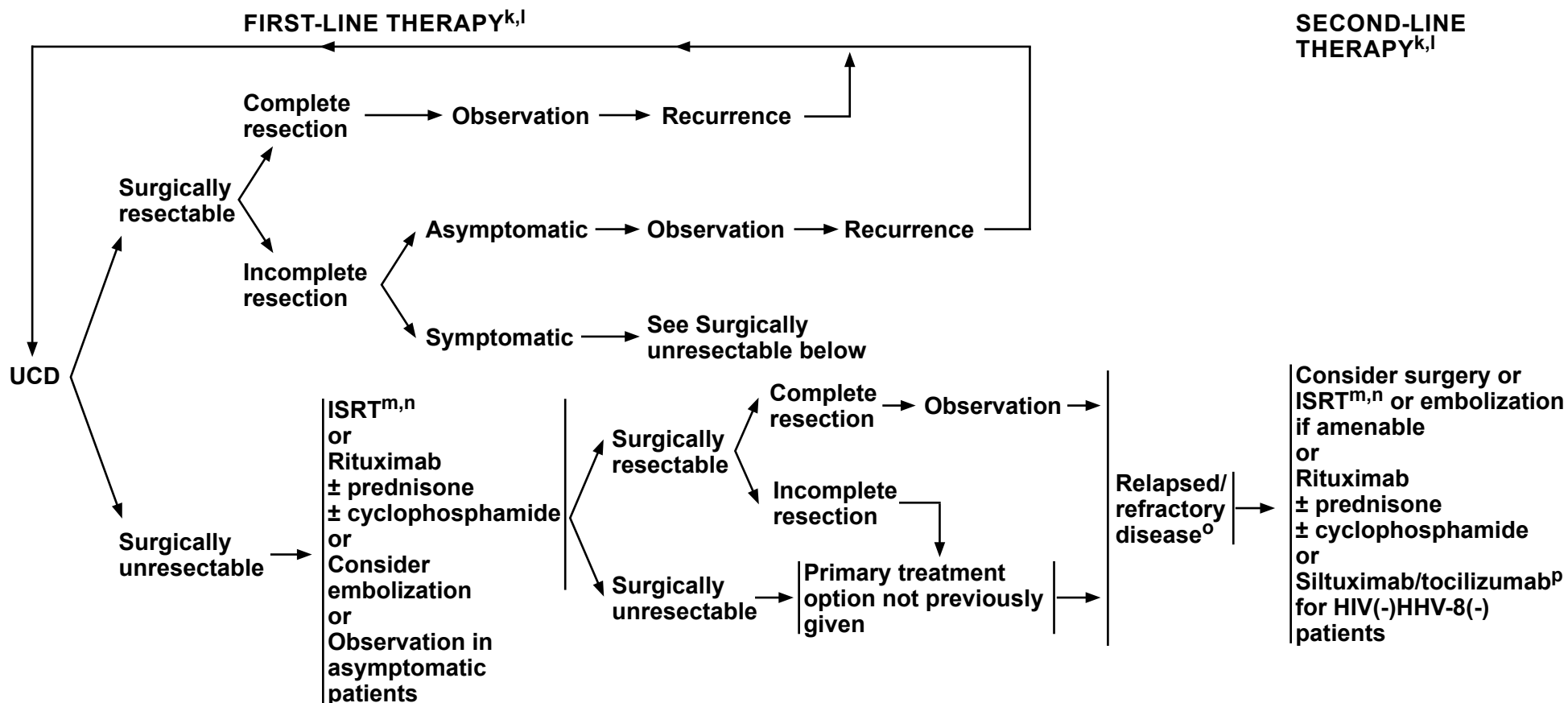
^h Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. See Monoclonal Antibody Therapy and Viral Reactivation (NHODG-B) in the [NCCN Guidelines B-Cell Lymphomas](#). Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consider consult with gastroenterologist.

ⁱ Measurement of acute phase reactants may be helpful in monitoring therapy.

^j Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

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^k See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the [NCCN Guidelines for B-Cell Lymphomas](#).

^l Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. An FDA-approved biosimilar is an appropriate substitute for rituximab.

^m The optimal dose of RT in unresectable UCD is not established. Doses as high as 40 Gy in 1.5–2 Gy fractions have been used Chronowski GM et al. Cancer 2001;92:670-676. Lower doses may be considered depending upon clinical circumstances (eg, proximity to critical structures, treatment intent). Advanced radiation techniques (eg, IMRT, IGRT, protons) are recommended to limit dose to surrounding normal tissues (Matthiesen C et al. Radiol Oncol 2012;46:265-270). RT Dose Constraint Guidelines for Lymphoma - Recommendations for normal tissue dose constraints can be found in the Principles of Radiation Therapy section of the [NCCN Guidelines for Hodgkin Lymphoma](#).

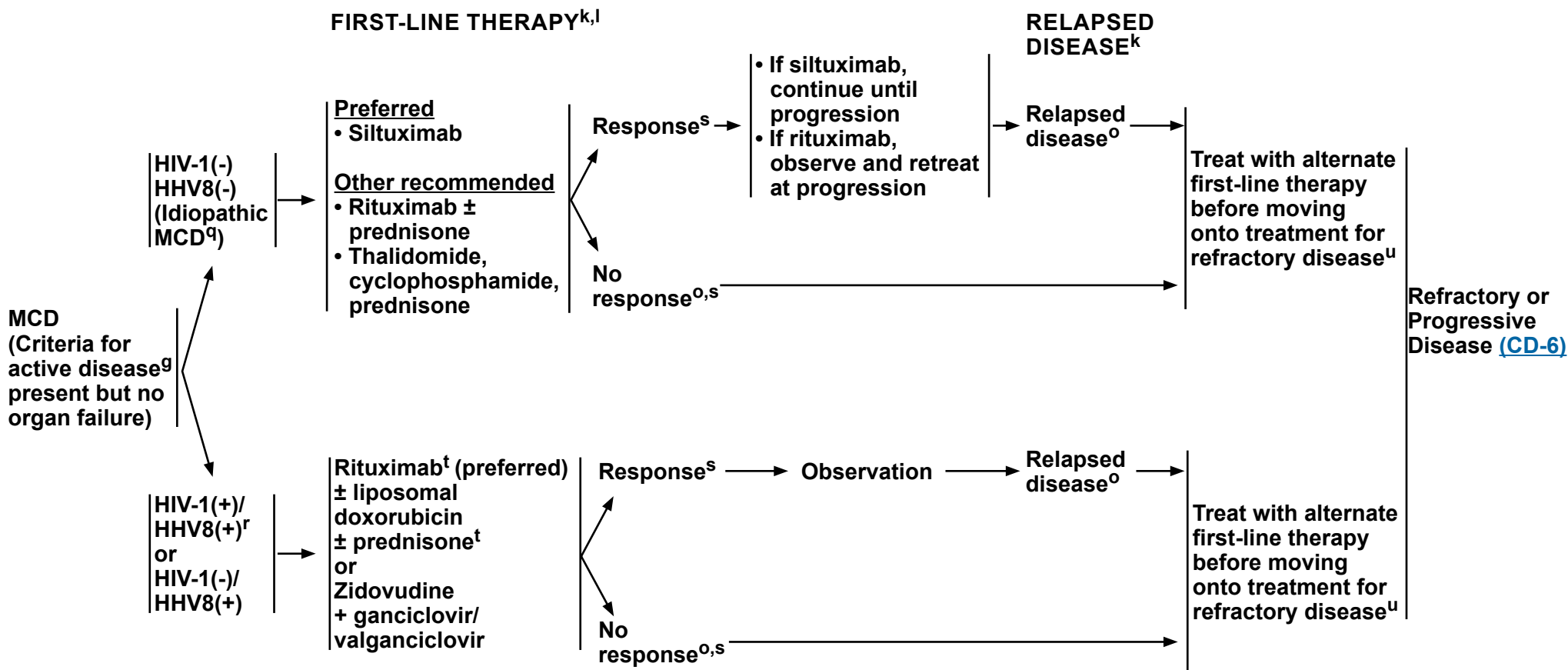
ⁿ Patients with non-bulky disease may be observed after ISRT.

^o Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

^p An FDA-approved biosimilar is an appropriate substitute for tocilizumab.

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^g [Criteria for Active Disease \(CD-A\)](#).

^k See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the [NCCN Guidelines for B-Cell Lymphomas](#).

^l Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. An FDA-approved biosimilar is an appropriate substitute for rituximab.

^o Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

^q [Diagnostic Criteria for Idiopathic MCD \(CD-B\)](#).

^r All patients with HIV should be on combination antiretroviral therapy (cART). For principles of concurrent HIV management and supportive care, see the [NCCN Guidelines for Cancer in People with HIV](#).

^s Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).

^t Occult KS is prevalent in HIV/HHV8+ MCD and may flare after rituximab or prednisone. Consider baseline imaging and direct visualization to screen for pulmonary ± gastrointestinal (GI) KS in patients receiving concurrent KS-directed therapy (ie, addition of liposomal doxorubicin). See [NCCN Guidelines for Kaposi Sarcoma](#).

^u Rituximab ± prednisone may be repeated without limit if progression ≥6 months after completion of rituximab.

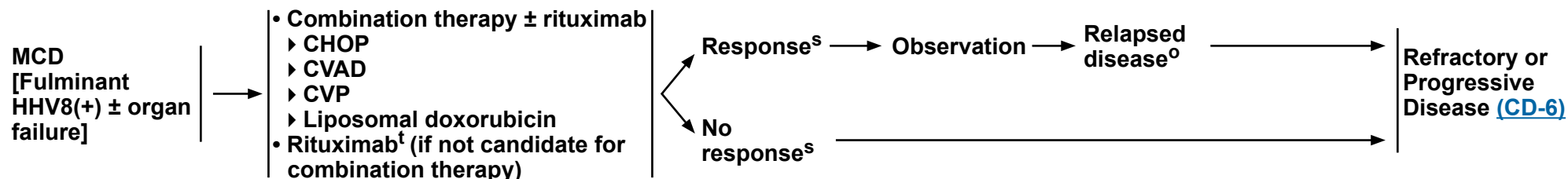
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FIRST-LINE THERAPY^{k,l}

RELAPSED DISEASE^k



^k See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the [NCCN Guidelines for B-Cell Lymphomas](#).

^l Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. An FDA-approved biosimilar is an appropriate substitute for rituximab.

^o Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

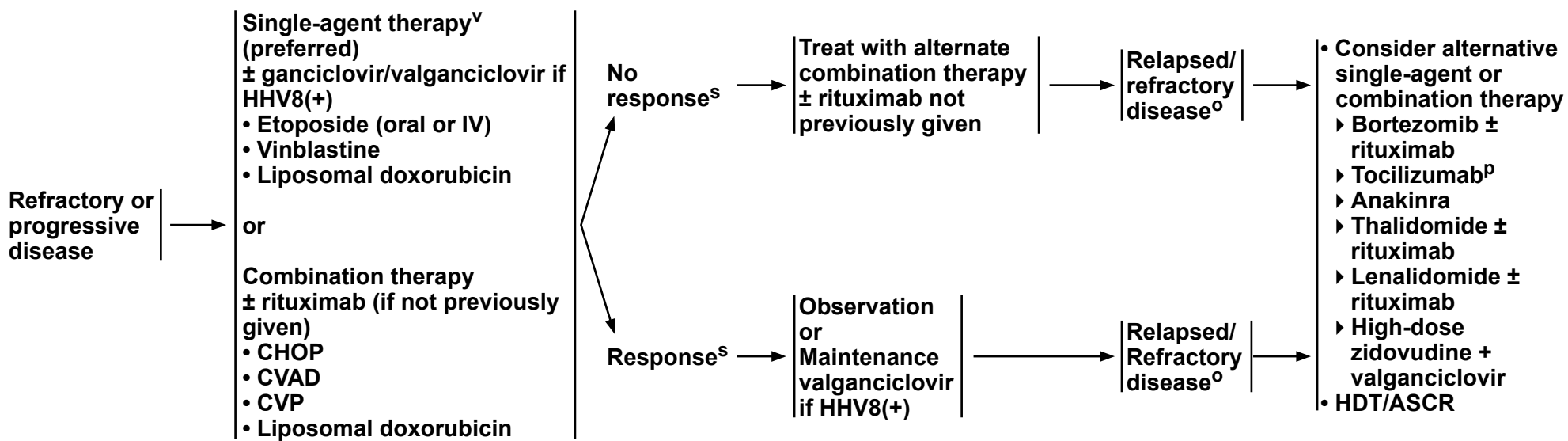
^s Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).

^t Occult KS is prevalent in HIV/HHV8+ MCD and may flare after rituximab or prednisone. Consider baseline imaging and direct visualization to screen for pulmonary ± GI KS as well as concurrent KS-directed therapy (ie, addition of liposomal doxorubicin). See [NCCN Guidelines for Kaposi Sarcoma](#).

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REFRACTORY OR PROGRESSIVE DISEASE^{k,l}



^k See Supportive Care for B-Cell Lymphomas for the management of complications associated with anti-CD20 monoclonal antibody (mAb) therapy in the [NCCN Guidelines for B-Cell Lymphomas](#).

^l Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. An FDA-approved biosimilar is an appropriate substitute for rituximab.

^o Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

^p An FDA-approved biosimilar is an appropriate substitute for tocilizumab.

^s Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).

^v Single-agent therapy is preferred for asymptomatic patients with no organ failure; combination therapy is preferred for patients with fulminant disease and organ failure.

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CRITERIA FOR ACTIVE DISEASE^a

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

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

SUBTYPES OF IDIOPATHIC MCD^a

- **Idiopathic MCD (iMCD-TAFRO)**
 - ▶ **Marked inflammatory syndrome**
 - ▶ **Thrombocytopenia, anasarca, fever/elevated C-reactive protein (CRP), renal dysfunction/reticulिन myelofibrosis, organomegaly**
 - ▶ **Megakaryocytic hyperplasia, hypervascular or mixed histopathology**
 - ▶ **Normal immunoglobulin levels**
- **Idiopathic MCD - not otherwise specified (iMCD-NOS)**
 - ▶ **Less intense inflammatory syndrome**
 - ▶ **Normal/elevated platelet counts**
 - ▶ **Plasmacytic or mixed histopathology**
 - ▶ **Polyclonal hypergammaglobulinemia**

^a Iwaki N, Fajgenbaum DC, Nabel CS, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol* 2016;91:220-226.

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Consensus Diagnostic Criteria for Idiopathic MCD ^a		
<p>I. Major Criteria (need both):</p>	<p>1. Histopathologic lymph node features consistent with the iMCD spectrum. Features along the iMCD spectrum include (need grade 2–3 for either regressive GCs or plasmacytosis at minimum):</p> <ul style="list-style-type: none"> - Regressed/atrophic/atretic germinal centers, often with expanded mantle zones composed of concentric rings of lymphocytes in an “onion skinning” appearance - FDC prominence - Vascularity, often with prominent endothelium in the interfollicular space and vessels penetrating into the GCs with a “lollipop” appearance - Sheetlike, polytypic plasmacytosis in the interfollicular space - Hyperplastic GCs <p>2. Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations</p>	
<p>II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)</p>	<p>Laboratory*</p> <ol style="list-style-type: none"> 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 μ/mL) or thrombocytosis (platelet count >400 μ/mL) 4. Hypoalbuminemia (albumin <3.5 g/dL) 5. Renal dysfunction (eGFR <60 mL/min/1.73m²) or proteinuria (total protein 150 mg/24 h or 10 mg/100 mL) 6. Polyclonal hypergammaglobulinemia (total γ globulin or immunoglobulin G >1700 mg/dL) 	<p>Clinical</p> <ol style="list-style-type: none"> 1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (≥2 CTCAE lymphoma score for B-symptoms) 2. Large spleen and/or liver 3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion 4. Eruptive cherry hemangiomas or violaceous papules 5. Lymphocytic interstitial pneumonitis
<p>III. Exclusion Criteria (must rule out each of these diseases that can mimic iMCD)</p>	<p><u>Infection-related disorders</u></p> <ol style="list-style-type: none"> 1. HHV-8 (infection can be documented by blood PCR; diagnosis of HHV-8–associated MCD requires positive LANA-1 staining by IHC, which excludes iMCD) 2. Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (detectable EBV viral load not necessarily exclusionary) 3. Inflammation and adenopathy caused by other uncontrolled infections (eg, acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis) <p><u>Autoimmune/autoinflammatory diseases</u> (requires full clinical criteria; detection of autoimmune antibodies alone is not exclusionary)</p> <ol style="list-style-type: none"> 1. Systemic lupus erythematosus 2. Rheumatoid arthritis 3. Adult-onset Still disease 4. Juvenile idiopathic arthritis 5. Autoimmune lymphoproliferative syndrome <p><u>Malignant/lymphoproliferative disorders</u> (these disorders must be diagnosed before or at the same time as iMCD to be exclusionary):</p> <ol style="list-style-type: none"> 1. Lymphoma (Hodgkin and non-Hodgkin) 2. Multiple myeloma 3. Primary lymph node plasmacytoma 4. FDC sarcoma 5. POEMS syndrome‡ 	

^a Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood* 2017;129:1646-1657.

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[Continued](#)



Consensus Diagnostic Criteria for Idiopathic MCD (continued)^a

- Select additional features supportive of, but not required for diagnosis
 - ▶ Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M
 - ▶ Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)
 - ▶ Diagnosis of disorders that have been associated with iMCD: paraneoplastic pemphigus, bronchiolitis obliterans organizing pneumonia, autoimmune cytopenias, polyneuropathy (without diagnosing POEMS[‡]), glomerular nephropathy, inflammatory myofibroblastic tumor

^a Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood* 2017;129:1646-1657.

Footnotes for [CD-B 1 of 2](#)

* Laboratory cutoff thresholds are provided as guidance. Since some laboratories have slightly different ranges, the upper and lower ranges from a particular laboratory should be used to determine if a patient meets a particular laboratory Minor Criterion.

† Evaluation of CRP is mandatory and tracking CRP levels is highly recommended, but ESR will be accepted if CRP is not available.

‡ POEMS is considered to be a disease “associated” with CD. Because the monoclonal plasma cells are believed to drive the cytokine storm, we do not consider it iMCD, but rather “POEMS-associated MCD.”

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Classification

Table 1

The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)
Mature B-cell lymphomas
<i>HHV-8–associated lymphoproliferative disorders</i>
Multicentric Castleman disease
Primary effusion lymphoma
HHV8-positive diffuse large B-cell lymphoma, NOS
HHV8-positive germinotropic lymphoproliferative disorder

Table 2

WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (2022; 5th edition)
Tumour-like lesions with B-cell predominance
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma
IgG4-related disease
Unicentric Castleman disease
Idiopathic multicentric Castleman disease
KSHV/HHV8-associated multicentric Castleman disease

The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. *Blood* 2022;140:1229-1253. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia* 2022;36:1720-1748.



ABBREVIATIONS

5-PS	five-point scale	HDT	high-dose therapy	mAb	monoclonal antibody
		HHV8	human herpesvirus 8	MCD	multicentric Castleman disease
ASCR	autologous stem cell rescue	HIV	human immunodeficiency virus	MUGA	multigated acquisition
C/A/P	chest/abdomen/pelvis	Ig	immunoglobulin	NGS	next-generation sequencing
cART	combination antiretroviral therapy	IGRT	image-guided radiation therapy	NOS	not otherwise specified
CBC	complete blood count	IHC	immunohistochemistry		
CD	Castleman disease	iMCD	idiopathic multicentric Castleman disease	PCR	polymerase chain reaction
CMV	cytomegalovirus	IMRT	intensity-modulated radiation therapy	POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin change
CTCAE	Common Terminology Criteria for Adverse Events	ISRT	involved-site radiation therapy		
		IVF	in vitro fertilization	SPEP	serum protein electrophoresis
DLBCL	diffuse large B-cell lymphoma	KS	Kaposi sarcoma	UCD	unicentric Castleman disease
		KSHV	Kaposi sarcoma-associated herpesvirus		
EBER-ISH	Epstein-Barr virus-encoded RNA in situ hybridization			VEGF	vascular endothelial growth factor
EBV	Epstein-Barr virus	LDH	lactate dehydrogenase		
eGFR	estimated glomerular filtration rate				
ESR	erythrocyte sedimentation rate				
FDC	follicular dendritic cell				
FISH	fluorescence in situ hybridization				
FNA	fine-needle aspiration				
GC	germinal center				
GI	gastrointestinal				



NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



Discussion

This discussion corresponds to the NCCN Guidelines for Castleman Disease. Last updated: January 18, 2024.

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Overview

Castleman disease (CD) is a relatively uncommon heterogenous group of lymphoproliferative disorders with an annual incidence of approximately 4,300–5,200 in the United States.¹ These disorders share common histopathologic features and certain subtypes are associated with an increased risk of developing diffuse large B-cell lymphoma (DLBCL), Kaposi sarcoma (KS), and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) syndrome.²⁻⁴

Unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) are the two main clinical subtypes. In the 2022 newly revised WHO classification of hematolymphoid tumors (WHOHAEM5), UCD and MCD are classified as tumour-like lesions with B-cell predominance.⁵ In the 2022 International Consensus Classification, UCD is not included and MCD is classified as HHV-8–associated lymphoproliferative disorders.⁶

MCD is further divided into human herpesvirus 8 (HHV8)-positive (also known as KS herpesvirus [KSHV]-positive), HHV8-negative (also known as idiopathic MCD [iMCD]), and POEMS-MCD.⁵ KSHV/HHV8-positive MCD is most commonly diagnosed in people with HIV or otherwise immunocompromised individuals.⁷

iMCD is subclassified into two clinicopathologic subgroups: iMCD-TAFRO (defined by thrombocytopenia [T], anasarca [A], fever [F], reticulin fibrosis of the bone marrow [R], and organomegaly [O] but generally has normal γ -globulin levels) and iMCD-not otherwise specified (NOS), which is typically characterized by hypergammaglobulinemia and thrombocytosis.^{8,9}

The National Comprehensive Cancer Network (NCCN[®]) Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) provide recommendations for diagnostic workup and treatment for UCD and MCD.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Literature Search Criteria

Prior to the initial development of the NCCN Guidelines for Castleman disease, an electronic search of the PubMed database was performed to obtain key literature in Castleman disease. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.¹⁰



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The search results were narrowed by selecting relevant studies in humans published in English. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Clinical Presentation

The clinical presentation of CD is often relatively nonspecific with enlarged lymph nodes, lymphadenopathy, and systemic symptoms.

UCD is characterized by involvement of a single lymph node or lymph node station and usually the absence of systemic symptoms. This subtype generally has an indolent disease course with an excellent prognosis. UCD is most commonly (but not always) the histopathologic hypervascular (hyaline vascular) variant and is nearly always HIV negative and HHV8 negative.⁷ While often asymptomatic, some patients may experience compression symptoms due to compression of vital organs or other structures.¹¹⁻¹⁴ In a series of 404 patients with UCD, the most common sites of involvement were the mediastinum (29%), neck (23%), abdomen (21%), and retroperitoneum (17%).¹¹ In another analysis of 74 patients (43 patients with UCD and 31 patients with iMCD), systemic inflammatory symptoms, elevated inflammatory factors, and abnormal bone marrow features were more common in patients with iMCD than UCD.¹²

MCD is a remitting-relapsing disease with a variable natural history ranging from indolent disease with a very slow progression to acute and fulminant disease.^{3,15} HHV8-positive MCD follows a more aggressive course. Immunocompromising conditions is a primary risk factor for HHV8-positive MCD, with HIV being the most common.¹⁶ HHV8-positive MCD is more commonly associated with systemic symptoms such as fluid

accumulation, cytopenias, liver and kidney dysfunction, and constitutional symptoms driven by cytokines such as interleukin 6 (IL-6).^{12,15,17}

iMCD affects multiple lymph node stations and exhibits lymphadenopathy in more than 1 lymph node or lymph node region. Clinical presentation can range from mild constitutional symptoms to life-threatening organ failure. iMCD-TAFRO generally has a more aggressive disease course and poorer outcomes than iMCD-NOS.^{8,9}

Diagnosis

Due to the nonspecific and heterogenous nature of the disease, CD can often mimic other benign and malignant conditions.²⁻⁴ Therefore, a high index of suspicion and histopathologic analysis is required for diagnosis of CD.

Histopathologically, CD has been divided into hypervascular (also called hyaline vascular), plasmacytic, and mixed histologic subtypes.¹⁸ The hypervascular variant is most commonly associated with UCD, whereas the plasmacytic and mixed variants are more common in HHV8-associated MCD. Idiopathic MCD-NOS may exhibit any of the three histologic patterns, whereas MCD-TAFRO is most commonly either hypervascular or mixed.

A combination of clinical, imaging, and pathologic features should be used to establish the diagnosis of UCD, HHV8-positive MCD, and iMCD.^{19,20} In an asymptomatic patient, histopathology consistent with CD along with the involvement of a single lymph node or region of lymph nodes can establish a diagnosis of UCD.²⁰

In 2017, international diagnostic consensus criteria for the diagnosis of iMCD was published.¹⁹ These diagnostic criteria include two major criteria (histopathologic lymph node features consistent with the iMCD spectrum and enlarged lymph node in at least 2 lymph node stations) and eleven minor criteria (anemia, thrombocytopenia, hypoalbuminemia, polyclonal



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hypergammaglobulinemia, renal dysfunction [elevated glomerular filtration rate (GFR) or proteinuria], elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP], constitutional symptoms, enlarged spleen and/or liver, fluid accumulation, eruptive cherry hemangiomas or violaceous papules, and lymphocytic interstitial pneumonitis). See *Consensus Diagnostic Criteria for Idiopathic MCD (CD-B)* in the algorithm.

The diagnosis of iMCD requires the presence of both major criteria, at least 2 of 11 minor criteria with at least 1 laboratory abnormality, and exclusion of infectious, malignant, and autoimmune disorders that can mimic iMCD.¹⁹

Adequate immunophenotyping of a surgically excised lymph node is required to confirm the diagnosis and exclude malignancy and other diseases.¹⁹ The recommended immunohistochemistry (IHC) panel essential for diagnosis includes: CD20, CD3, CD5, CD138, HHV8, kappa, and lambda. Additional IHC markers may be useful under certain circumstances: Ki-67 index, Ig heavy chains, CD10, BCL2, BCL6, cyclin D1, CD21, CD23, CD38, IRF4/MUM1, and PAX5. Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen of kappa/lambda, CD19, CD20, CD5, CD23, and CD10 may also be useful in certain circumstances. EBER-ISH immunophenotyping is also an essential diagnostic test. Other diagnostic testing that may be useful under certain circumstances includes molecular analysis to detect immunoglobulin and *TCR* gene rearrangements.

Workup

Initial workup should include a physical examination (with attention given to node-bearing areas, liver, and spleen) and evaluation of performance status. Laboratory assessments should include standard blood work including complete blood count (CBC) with differential, and a comprehensive metabolic panel. Serum lactate dehydrogenase (LDH), CRP, and ESR should be measured. Serum protein electrophoresis

should be evaluated if there is concern for POEMS syndrome. Pregnancy testing should be done in patients of childbearing potential if chemotherapy or radiation therapy (RT) is planned. PET/CT scan (preferred) or a chest/abdomen/pelvis CT with contrast of diagnostic quality are recommended as part of an initial diagnostic workup to confirm extent of disease and total nodal involvement.^{21,22}

Testing to detect the presence of HIV, HHV8, and Epstein-Barr virus (EBV) polymerase chain reaction (PCR) should also be done as part of routine workup. HHV8-positive MCD is distinguished by positive testing for HHV8 in lymph node tissue as well as PCR positivity for HHV8 in plasma in addition to multiple affected lymph nodes and histopathology consistent with CD.¹⁵ Screening for concurrent KS is recommended in the setting of HHV8 or HIV positivity since HHV8-positive MCD may occur with concomitant KS in up to 72% of patients.²³ Hepatitis B testing is an essential component of workup if rituximab-containing regimens are being considered due to the risk of viral reactivation anti-CD20 monoclonal antibody (mAb)-based regimens.

Bone marrow biopsy and aspirate as well as reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome) may be useful under certain circumstances.²⁴ An echocardiogram or multigated acquisition (MUGA) scan can be considered if anthracycline or anthracenediones are being considered for treatment. Other components of workup that may be useful in certain circumstances include neck CT with contrast, hepatitis C testing, IgG4, sIL6, sIL10, vascular endothelial growth factor (VEGF), uric acid, and ferritin.

Treatment Recommendations

Unicentric Castleman Disease

Surgical resection is the optimal treatment, wherever possible, as it has been associated with very low rates of recurrence and high relapse-free survival (RFS) in multiple case series and retrospective studies.^{2,11,14,20,25-27}



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One case series of 53 patients reported a 5-year overall survival (OS) rate of 91%,² and another retrospective analysis of 278 patients showed an OS rate of over 90% with up to 10-year follow up.¹¹ Therefore, all patients with a diagnosis of UCD should be evaluated for resectability of disease.²⁰

Observation until recurrence is recommended following complete resection. Patients who are asymptomatic following an incomplete resection may be observed until recurrence. Patients who remain symptomatic following incomplete resection should be managed as described below for unresectable disease.

Asymptomatic patients with unresectable UCD should be observed. Available evidence (mostly from case reports) supports the use of RT or rituximab with or without steroids in patients with symptomatic unresectable UCD.^{20,28,29} Patients with unresectable disease could be treated with involved-site RT (ISRT) or systemic therapy (rituximab ± prednisone ± cyclophosphamide), with the intent of eventual surgical resection.^{20,28,29} Patients with non-bulky disease may be observed after ISRT.

RT should be reserved for severe symptomatic and unresectable disease due to potential long-term complications following RT.²⁰ The optimal dose of RT in unresectable UCD is not established. Doses as high as 40 Gy in 1.5-2 Gy fractions have been used.²⁸ Lower doses may be considered depending upon clinical circumstances and advanced radiation techniques are recommended to limit the RT dose to surrounding normal tissues.³⁰ Embolization may also be considered in certain situations to render surgical resection more feasible and reduce the risk of severe perioperative bleeding.²⁰

Treatment options for relapsed/refractory disease are the same as described above for unresectable disease (ISRT or systemic therapy with rituximab ± prednisone ± cyclophosphamide [with the intent of eventual surgical resection] or embolization, if amenable).²⁰

Patients with inflammatory symptoms (eg, night sweats, fevers, weight loss) or laboratory disturbances (increased ESR or CRP) may have excessive cytokine production and may benefit from anti-IL-6 mAbs such as siltuximab and tocilizumab, although evidence in this setting is sparse.²⁰ Siltuximab/tocilizumab is included as an option for relapsed/refractory disease that is HIV-negative and HHV8-negative. Biopsy is encouraged in patients with relapsed/refractory disease to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

Overall UCD has an indolent disease course with an excellent prognosis. Careful consideration should be given to the risks and benefits of any therapy for patients with UCD, and observation can be considered in asymptomatic patients.²⁰

Multicentric Castleman Disease

Treatment recommendations for MCD are based on the presence of criteria for active disease, presence of fulminant disease, or organ failure and HHV8 status. Patients may experience symptoms related to an excess of IL-6 production; establishing the severity of symptoms is a vital component of management, as severity can vary widely between patients. Corticosteroid monotherapy has a high treatment failure rate but may be combined with other therapies for symptom control. Due to the rarity of the condition, available evidence for most of the treatment options is based on case reports making comparison between treatment options difficult.^{21,31,32}

Combination chemotherapy with rituximab is an appropriate treatment option for patients with fulminant HHV8-positive disease with or without organ failure, and may be associated with durable remissions.^{21,28,31-33}

Combination chemotherapy regimen options include R-CHOP, R-CVAD, and R-CVP. Liposomal doxorubicin with or without rituximab is an option, as well as rituximab monotherapy if not a candidate for combination chemotherapy.³⁴⁻³⁶



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In patients with criteria for active MCD (fever, increased serum CRP level >20 mg/L in the absence of any other etiology, and at least three other MCD-related symptoms) with no organ failure, first-line therapy options are based on HHV8 status (iMCD [HIV and HHV8 negative] vs. HHV8-positive MCD) as described below.

Patients with POEMS-associated MCD should have treatment directed at POEMS syndrome with regimens recommended for the treatment of multiple myeloma.

Idiopathic MCD

In a double-blind international trial for patients with iMCD, siltuximab (anti-IL-6 mAb) resulted in durable tumor and symptomatic responses in 18 of 53 patients (34%) compared to 26 patients in the placebo group ($P = .0012$).³⁷ Long-term follow-up data (median follow-up of 6 years) also established the safety of siltuximab.³⁸ Siltuximab was also associated with significantly improved progression-free survival (PFS) compared to placebo (median PFS was not reached for siltuximab compared to 15 months for placebo; $P = .0001$).³⁹ Adverse events of grade ≥ 3 were reported in 60% of patients with hypertension (13%), fatigue (8%), nausea (7%), neutropenia (7%), and vomiting (5%) being the most common adverse events.

Siltuximab is FDA approved for the treatment of patients with iMCD that is HIV and HHV8 negative and is the preferred first-line treatment option for this patient population.³⁸⁻⁴⁰ It is worth noting that responses in the pivotal trial were predominant in patients with the plasmacytic or mixed histologic variants and were not seen in hyaline vascular disease where it may have less clinical activity.³⁷ In patients with disease responding to siltuximab, treatment should be continued until disease progression, as disease may relapse on discontinuation of therapy.²¹ Importantly, the clinical trial compared siltuximab with placebo, rather than an active treatment comparator, so it is unknown whether siltuximab is superior to chemoimmunotherapy. Accordingly, chemoimmunotherapy can be

considered as an appropriate treatment option in selected patients, particularly in patients with fulminant disease. Chemoimmunotherapy is a time-limited option, unlike siltuximab that is given intravenously every 3 weeks continuously in the absence of progression or intolerance. Patients who receive chemoimmunotherapy as initial treatment may receive siltuximab if needed subsequently for relapsed/refractory disease.

Rituximab (with or without prednisone) and thalidomide, cyclophosphamide and prednisone (TCP) are included as options for other recommended regimens. In a retrospective study of 27 patients with iMCD, rituximab- and cyclophosphamide-containing regimens resulted in an overall response rate of 56% (33% complete response [CR]).⁴¹ In a single-arm, phase 2 study of 25 patients with newly diagnosed iMCD treated with the TCP regimen, primary endpoint (durable tumor and symptomatic response for at least 24 weeks) was achieved in 48% of patients; 12% of patients had stable disease and the estimated 1-year PFS and OS rates were 60% and 88%, respectively.⁴²

Patients with disease responding to rituximab-based regimens should be observed until disease progression requiring retreatment. iMCD-TAFRO generally presents as more severe disease, but the evaluation and determination of treatment should be similar to iMCD-NOS.

HHV8-Positive MCD

Rituximab as a single agent or in combination with liposomal doxorubicin or prednisone is the preferred first-line treatment option.³⁴⁻³⁶ Combination antiretroviral therapy (cART) should be given to all patients with HIV-positive disease.

The strongest evidence for rituximab monotherapy comes from two phase II studies.^{34,35} In one prospective study of rituximab in HIV-associated MCD, 24 patients with relapsed/refractory, chemotherapy-dependent disease were given 4 weekly doses of rituximab at 375 mg/m². Twenty-two of the 24 patients were able to become independent of chemotherapy, and



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more than three quarters remained free from symptoms and progression 2 years after treatment.³⁴ In another phase II study of 21 patients with plasmablastic MCD, 20 patients achieved remission of symptoms, and 14 (67%) achieved a radiologic response. The median follow-up was 12 months. The OS and disease-free survival (DFS) rates at 2 years were 95% and 79%, respectively. The main adverse effect was reactivation of KS.³⁵ In another retrospective analysis of 113 patients (48 had previously received rituximab and 60 were previously diagnosed with KS), treatment with rituximab was associated with a higher 5-year OS rate compared to treatment with chemotherapy alone (90% vs. 47%).⁴³

Occult KS is prevalent in HIV/HHV8 (+) MCD and may flare after treatment with rituximab or prednisone.⁴³ The use of rituximab in combination with liposomal doxorubicin may reduce the incidence of KS exacerbation and may be particularly useful for patients with HHV8-positive MCD with concurrent KS.^{36,44} Rituximab has also been shown to decrease the risk of lymphoma in patients with HIV-associated disease.⁴³

Zidovudine with either ganciclovir or valganciclovir is also included as a first-line therapy option for HHV8-positive MCD. Zidovudine with valganciclovir has also been shown to be active in HHV8-positive MCD.^{44,45} In a study that included 20 patients with HHV8-MCD alone and 34 patients with HHV8-MCD and KS, the 5-year PFS rate was 26% for treatment with the combination of zidovudine and valganciclovir.⁴⁴ The median PFS was 6 months. In a pilot study of 14 patients with HHV8-positive MCD, high-dose zidovudine in combination with valganciclovir resulted in major clinical and biochemical responses being attained in 86% and 50% of patients, respectively.⁴⁵

Refractory or Progressive Disease

Biopsy is encouraged in patients with relapsed/refractory disease to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

Single-agent therapy is preferred (oral or intravenous etoposide, vinblastine, and liposomal doxorubicin +/- ganciclovir/valganciclovir) for asymptomatic patients with HHV8 (+) disease and no organ failure.^{21,31,32} Combination therapy (CHOP, CVAD, CVP) or liposomal doxorubicin +/- rituximab is preferred (if not used in a previous line of therapy) for patients with fulminant disease and organ failure.^{21,31,32}

Observation or maintenance with valganciclovir may be considered for HHV8 (+) disease responding to treatment. Alternative single-agent or combination therapy should be considered for disease progression following sequential combination therapies. Options include bortezomib +/- rituximab, thalidomide +/- rituximab, lenalidomide +/- rituximab, high-dose zidovudine + valganciclovir, tocilizumab (anti-IL6 mAb), and anakinra (IL-1 receptor antagonist), based on case reports and case series.^{21,44-55}

Tocilizumab is an effective treatment option for patients with MCD that is refractory to rituximab and chemoimmunotherapy.⁵²⁻⁵⁵ An FDA-approved biosimilar is an appropriate substitute for tocilizumab.

High-dose therapy followed by autologous stem cell rescue (HDT/ASCR) may also result in favorable outcomes, particularly for patients with MCD associated with POEMS.^{54,56}



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