Submitted by:
Name: David C. Fajgenbaum, MD, MBA, MSc
Company/Organization: Castleman Disease Collaborative Network (CDCN)
Address: P.O. Box 3614, Paso Robles, CA 93447
Phone: 919-810-0453
Email: davidfa@pennmedicine.upenn.edu
Date of request: September 8, 2020
NCCN Guidelines Panel: B-cell Lymphoma Panel

On behalf of the Castleman Disease Collaborative Network's (CDCN) Scientific Advisory Board, I respectfully request that the NCCN B-cell Lymphoma Panel review the enclosed data and consider revising its guidelines for the treatment of idiopathic multicentric Castleman disease (iMCD).

Specific Changes: Insufficient evidence exists to use histopathologic subtype to guide treatment of iMCD. Therefore, we strongly suggest that histopathological subtype should not be used to guide treatment decisions of iMCD and that siltuximab should be recommended first line for all iMCD patients regardless of histopathological subtype assigned (changed from the current NCCN recommendation against its use for patients categorized as having hyaline vascular histopathology; see page CD-3, preferred iMCD treatment, footnote p).

FDA Clearance: Siltuximab is FDA approved for the treatment of iMCD patients categorized as having any of the three histopathological subtypes, so this change would be consistent with the FDA's approval in 2014.

Rationale: In support of the proposed change, the 2018 international, evidence-based consensus iMCD treatment guidelines published in *Blood* recommend siltuximab (or tocilizumab, if siltuximab is not available) first-line for all iMCD patients, regardless of histopathological subtype. Further, recently accepted published data were synthesized into a manuscript, "Insufficient evidence exists to use histopathologic subtype to guide treatment of idiopathic multicentric Castleman disease" published in the *American Journal of Hematology*.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors of these publications.

1. Fajgenbaum, D.C, Wu D., et al. Insufficient evidence exists to use histopathologic subtype to guide treatment of idiopathic multicentric Castleman disease [Epub ahead of print September 7, 2020]. American Journal of Hematology. doi.org/10.1002/ajh.25992

2. van Rhee, F., Voorhees, P., Dispenzieri, A., et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018; 132: 2115–2124.

3. Fajgenbaum, D.C., Uldrick, T.S., Bagg, A., et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman

disease. Blood 2017; 129:1646–1657.

4. Liu, A.Y., Nabel, C.S., Finkelman, B.S., et al. Idiopathic multicentric Castleman's disease: a systematic literature review. Lancet Hematology 2016; 3: e163–75.

5. Igawa, T. & Sato, Y. TAFRO syndrome. Hematol Oncol Clinics NA 2018; 32: 107–118.

6. Fujimoto, S., Sakai, T., Kawabata, H., et al. Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease? Amer J Hematol 2019; 94:975–983.

7. Kurzrock, R., Voorhees, P.M., Casper, C., et al. A phase I, open-label study of siltuximab, an anti-IL-6 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma, multiple myeloma, or Castleman disease. Clinical Cancer Research 2013; 19: 3659–3670.

8. van Rhee, F., Casper, C., Voorhees, P.M., et al. A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. Oncotarget 2015;6(30):30408-30419.

9. van Rhee, F., Casper, C., Voorhees, P.M., et al. Long-term safety of siltuximab in patients with idiopathic multicentric Castleman disease: a prespecified, open-label, extension analysis of two trials. Lancet Hematology 2020; 7: e209–217.

10. van Rhee, F., Wong, R.S., Munshi, N., et al. Siltuximab for multicentric Castleman's disease: a randomized, double-blind, placebo-controlled trial. Lancet Oncology 2014; 15, 966–974.

11. Morra, D.E., Pierson, S.K., Shilling, D., et al. Predictors of response to anti-IL6 monoclonal antibody therapy (siltuximab) in idiopathic multicentric Castleman disease: secondary analyses of phase II clinical trial data. Brit J Haematol 2019; 184(2):232-241

Thank you for considering this revision to the NCCN guidelines for the treatment of iMCD. Please do not hesitate to reach out with any questions.

Sincerely,

David C. Fajgenbaum
Department of Medicine, Perelman School of Medicine, University of Pennsylvania
Co-Chair, Scientific Advisory Board, Castleman Disease Collaborative Network
davidfa@pennmedicine.upenn.edu

September 8, 2020

Attention:
Andrew D. Zelenetz, MD, PhD
Chair, NCCN B-cell Lymphoma Panel
Leo I. Gordon, MD
Vice Chair, NCCN B-cell Lymphoma Panel,

Dear Drs. Zelenetz and Gordon,
We are writing on behalf of the Castleman Disease Collaborative Network's (CDCN) Scientific Advisory Board to respectfully request that the NCCN B-cell Lymphoma Panel consider revising its guidelines for the treatment of idiopathic multicentric Castleman disease (iMCD). The NCCN guidelines were recently revised to recommend the anti-interleukin-6 (IL-6) monoclonal antibody, siltuximab, first-line for iMCD patients categorized as having plasmacytic (PC) or mixed histopathology and recommend against using siltuximab to treat iMCD patients categorized as having hyaline vascular (HV) histopathology (see page CD-3, preferred iMCD treatment, footnote p). Based on recently accepted and in press data, published in the *American Journal of Hematology*,[1] published guidelines in *Blood* in 2018,[2] and consistent with the FDA's approval of siltuximab in 2014 for all iMCD patients, we strongly believe that siltuximab should be recommended first line for all iMCD patients and that histopathological subtype should not be used to guide treatment decisions. We provide a background on iMCD and highlight the data supporting this request below.

Background on iMCD
Idiopathic multicentric Castleman disease is a rare immunologic disorder characterized by systemic inflammation, cytopenias, multicentric lymphadenopathy, and organ dysfunction due to proinflammatory hypercytokinemia often including IL-6. Enlarged lymph nodes in iMCD demonstrate a spectrum of characteristic but variable histopathologic features, including atrophic germinal centers, expanded mantle zones, hypervascularization, and interfollicular plasmacytosis. Historically, iMCD patients have been divided into histopathological subtypes based on which of the above features are more prominent than others. These subgroups include hyaline vascular (HV) on one end and plasmacytic (PC) on the other with a "mixed" subgroup in between. In 2017, we established international, consensus diagnostic criteria for iMCD that recommended using hypervascular (HyperV) instead of HV when referring to these HV-like features in the setting of iMCD.[3] Currently, both HV and HyperV are being used to describe patients with similar histopathologic features. Due to the subjective nature of the histologic features and the varying degrees of tissue involvement, it is currently challenging to reproducibly classify these subtypes resulting in discrepancies even among expert pathologists, and the clinical implications of this classification are unclear. Therefore, we recommended using histopathology for diagnosing iMCD, but we de-emphasized the importance of determining where on the spectrum cases may lie from HyperV to PC. Instead, the field has begun to subclassify iMCD based on clinically-meaningful clinicopathologic subgroups: iMCD-TAFRO (defined by thrombocytopenia [T], anasarca [A], fever [F], reticulin fibrosis [R], and organomegaly [O]) and

iMCD-NOS (not otherwise specified, typically have thrombocytosis and hypergammaglobulinemia). iMCD-TAFRO cases are more acutely ill, often demonstrate HV (or HyperV) or mixed histopathology and have an inferior 2-year overall survival.[4-6]

We suspect that the NCCN guidelines were revised to recommend against siltuximab in iMCD patients with HV histopathology because no patients with HV histopathology achieved the primary endpoint in the Phase II study of siltuximab. We have investigated whether histopathologic subtype should guide siltuximab treatment decisions based on review of Phase I, Phase II, and long-term extension studies as well as real-world evidence. We present our findings below as well as in a recently accepted and in press manuscript.[1]

Clinical Trial Data to Support this Request:

Siltuximab Phase I study. The Phase I trial included 34 iMCD patients, 16 of which were classified as having HV histopathological subtype.[7] 31% (5/16) of iMCD patients with HV histopathology achieved radiologic response criteria and 88% (14/16) achieving clinical benefit response (CBR), a score summarizing symptomatic and biochemical response criteria. This response was similar to patients with plasmacytic (PC) histopathology where 35% (6/17) of patients met radiologic response criteria and 88% (15/17) achieved a CBR. Further, 10/16 patients with HV histopathology in the Phase I study went on to the long-term safety study, and 90% (9/10) of these patients achieved CBR at their last assessment.[8,9] In total, these individuals remained on study drug for a median of 121.5 administrations and a median duration of 8.3 years. The table below (in submission) demonstrates the similar overall radiologic response and CBR for iMCD patients with HV and PC histopathology.

	Hyaline vascular (N=16)	**Plasmacytic (N=17)**	**Mixed (N=2)**
Best overall radiologic response (N, %)*			
Not Evaluable	0	1 (6%)	0
Progressive Disease (PD)	0	1 (6%)	0
Stable Disease (SD)	10 (63%)	7 (41%)	1 (50%)
Unconfirmed Partial Response	1 (7%)	2 (12%)	0
Partial Response (PR)	5 (31%)	5 (29%)	1 (50%)
Complete Response (CR)	0	1 (6%)	0
Clinical benefit response (CBR) (N, %)†			
No improvement or worsening of any components	2 (13%)	2 (12%)	0
Improvement in ≥1 component	14 (88%)	15 (88%)	2 (100%)
Improvement in ≥2 components	13 (81%)	13 (76%)	2 (100%)
Improvement in ≥3 components	11 (69%)	9 (53%)	1 (50%)

*Best overall radiologic response was evaluated using Cheson criteria (Cheson *et al,* 1999), modified to include the assessment of measurable cutaneous lesions.

†Clinical benefit response (CBR) is defined as improvement in any number of the following components: hemoglobin, fatigue, anorexia, fever, weight and size of largest lymph node (CT or physical examination) and/or cutaneous disease, with no worsening of other components.

Siltuximab Phase II study. Siltuximab became the first FDA approved treatment for iMCD in 2014 based on a 34% durable radiologic and symptomatic response in siltuximab-treated patients

compared to 0% in controls. None of the patients who achieved a durable radiologic and symptomatic response to siltuximab were classified as having HV histopathology by central review; all such responders had PC or mixed histopathology.[9] This likely led to the current NCCN guidance to not recommend siltuximab for patients with HV histopathology. However, further review of the supplementary data suggests siltuximab activity in a relevant number of these patients. In fact, 6/18 (33%) of patients with HV histopathology treated with siltuximab achieved a durable symptomatic response (complete durable symptomatic response: 3/18, 17%) compared to 1/8 (13%) of placebo-treated patients with HV histopathology achieving a durable symptomatic response (complete durable symptomatic response: 0/8, 0%). Furthermore, 3/18 (17%) patients with HV histopathology met criteria for durable combined radiologic (by modified Cheson criteria according to investigator assessment) and symptomatic response by investigator assessment (versus 0/8 placebo-treated patients). Median time to treatment failure for patients with HV histopathology was nearly three-times longer for siltuximab-treated patients (206 days) than placebo (70 days). 6/18 (33%) siltuximab-treated individuals with HV histopathology from the Phase II trial continued into the long-term safety study;[8,9] one failed screening, but the remaining five showed durable stable disease control at their last on-study assessment (median number of siltuximab administrations: 58; median duration of treatment: 4.8 years).

There are also several factors that may have contributed to the lack of response by central review in the Phase II trial. The inclusion and exclusion criteria may have contributed to differences between the phenotypes of patients with various histopathology patterns. Specifically, the strict inclusion/exclusion criteria for the study would have resulted in exclusion of patients with the more aggressive iMCD-TAFRO clinical subtype, who often have HV histopathology. In fact, the enrolled HV cases tended to have a milder clinical phenotype compared to PC and mixed histopathologies. Patients with greater clinical disease burden and abnormal laboratory tests tend to have an increased likelihood of response to siltuximab.[11] Patients with a lower disease burden may simply have fewer symptoms against which to demonstrate observable treatment effects.

Overall, there was clinically relevant efficacy for siltuximab among individuals with HV histopathology in the Phase I, Phase II, and long-term extension studies.[7-10] In addition, soon to be published data of real-world setting results has indicated that iMCD-TAFRO patients and iMCD-NOS patients with HV histopathology often respond well to IL-6 blockade. Failure to apply effective anti-IL-6 therapy in a timely manner may present a serious risk to the sickest iMCD-TAFRO patients who often demonstrate HyperV or HV histopathology and are most in need of urgent effective therapy. This point is particularly important given that no therapies other than anti-IL-6 are currently licensed for iMCD anywhere in the world.

There are also significant variation between pathologists in assigning histopathological subtypes, which may be partly a function of exposure to these cases and experience with the recently published diagnostic criteria,[3] making it difficult to evaluate treatment outcomes as a function of a single reviewer's histopathology classification. In fact, a retrospective review of histopathological subtype assignment by the local site pathologists, central review, and a CDCN panel revealed vastly different subtypes assigned for the same exact slides from the siltuximab Phase II study (in submission). Only 23% (18/79) of patients had the same iMCD histopathological subtype selected by all three groups of evaluators. See Figure 1 Appendix (accepted and in press). These data

suggest that relying on histopathologic subtype alone is insufficient to make crucial treatment decisions.

In summary, the data support a role for siltuximab across all histopathologic subtypes and recent data suggest histopathologic subtype is defined subjectively and inconsistently. While we acknowledge that certain disease features, such as mild or limited disease activity should elevate the index of suspicion that treatment failure is possible, and that second-line therapy may be needed more rapidly, we ask that the B-cell lymphoma panel please consider the data and information summarized in this letter to recommend siltuximab as the preferred therapy for iMCD, regardless of histopathology, as per consensus guidelines.[2]

Thank you for considering this request. Below is contact information for the 24 signatories on this letter if you require additional information.

Sincerely,

David C. Fajgenbaum, MD, MBA, MSc
Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
Co-Chair, Scientific Advisory Board, Castleman Disease Collaborative Network
davidfa@pennmedicine.upenn.edu

Frits van Rhee MD PhD MRCP(UK) FRCPath
Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
Co-Chair, Scientific Advisory Board, Castleman Disease Collaborative Network
vanrheefrits@uams.edu

Megan Lim, MD, PhD
Department of Pathology/Lab Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network
megan.lim@pennmedicine.upenn.edu

David Wu, MD
Department of Laboratory Medicine, University of Washington, Seattle, WA, USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Alexander Fossa, MD, PhD
Department of Oncology, Oslo University Hospital – Norwegian Radium Hospital, Oslo, Norway
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Raymond Wong, MD
Sir Y.K. Pao Centre for Cancer & Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Amy Chadburn, MD
Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY. USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Sunita Nasta, MD
Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Thomas Uldrick, MD, MS
Global Oncology, University of Washington School of Medicine, Seattle, WA, USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Gordan Srkalovic, MD PhD
Sparrow Cancer Center, Edward W. Sparrow Hospital Association, Lansing, MI, USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Steve Schey, MD
Department of Haematological Medicine, Kings' College, London University, London, UK
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Mary Jo Lechowicz, MD
Department of Hematology & Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Angela Dispenzieri, MD
Division of Hematology, Mayo Clinic, Rochester, MN, USA
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Eric Oksenhendler, MD
Department of Clinical Immunology at Hopital Saint-Louis, Paris, FR
Member, Scientific Advisory Board, Castleman Disease Collaborative Network

Sudipto Mukherjee, MD, MPH
Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Naveen Pemmaraju, MD
Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Heather Leitch, MD, PhD
Division of Hematology, University of British Columbia, Vancouver, BC, CA
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Raj Jayanthan, MD
Department of Pediatrics, Montefiore Medical Center, Bronx, NY, USA
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Simone Ferrero, MD
Division of Hematology, University of Torino, Torino, IT
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Yasuharu Sato, MD
Department of Pathology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, JP
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Pier Luigi Zinzani, MD, PhD
Institute of Haematology, University of Bologna, Bologna, IT
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Adam Bagg, MD, PhD
Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
Diagnostic Criteria International Working Group, Castleman Disease Collaborative Network

Aaron Goodman, MD
UC San Diego Moores Cancer Center, Division of Blood and Marrow Transplantation, San Diego, CA, USA
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

Christian Hoffmann, MD, PhD
ICH Center GmbH & Co KG, Hamburg, Germany
Treatment Guidelines International Working Group, Castleman Disease Collaborative Network

on behalf of the Castleman Disease Collaborative Network Scientific Advisory Board (resolution unanimously passed on 4/3/2020) as well as the members of the iMCD diagnostic criteria international working group and iMCD treatment guidelines international working group

References:

1. Fajgenbaum, D.C., Wu, D., et al. Insufficient evidence exists to use histopathologic subtype to guide treatment of idiopathic multicentric Castleman disease [Epub ahead of print September 7, 2020]. American Journal of Hematology. doi.org/10.1002/ajh.25992
2. van Rhee, F., Voorhees, P., Dispenzieri, A., et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018; 132: 2115–2124.
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