



EUSA Pharma (US) LLC
15 Wayside Road, Ste 2
Burlington, MA 01803
Tel: 609-528-5620
Fax: 609-528-5601

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Rabecka Martin PhD
Head of US Medical
EUSA Pharma, Inc.
Address: 155 Federal Street, Suite 700, Boston, MA 02110
Phone: 617-755-8960
E-mail: rabecka.martin@eusapharma.com
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Kristina M. Gregory, RN, MSN, OCN
Vice President, Clinical Information Operations
National Comprehensive Cancer Center
3025 Chemical Road, Suite 100
Plymouth Meeting, PA 19462

On behalf of EUSA Pharma, Inc., I respectfully request that the NCCN B-Cell Lymphomas Panel consider the enclosed data as support for the inclusion of siltuximab as the first-line treatment for Idiopathic Multicentric Castleman disease (iMCD).

Specific changes recommended within the NCCN Guidelines

Currently, the guidelines recommend rituximab and siltuximab as first-line options. Published clinical data and expert consensus guidance based on extensive evidence supports siltuximab as a preferred intervention over rituximab for the treatment of herpesvirus-8 (HHV-8)/idiopathic Multicentric Castleman disease (iMCD); please consider siltuximab as a preferred intervention for iMCD.

Statement of whether the submitted use is or is not FDA approved for that indication

Siltuximab is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative, otherwise known as iMCD. Siltuximab is the only FDA approved treatment for iMCD. Rituximab has never been prospectively studied as a therapeutic intervention for iMCD and thus never considered for FDA approval.

Rationale for recommended change.

1. The US FDA approved siltuximab based on data from an open-label Phase I and randomized controlled Phase II clinical trials demonstrating efficacy and safety; an extension study has demonstrated durable responses and tolerable safety profiles. Retrospective analyses of the Phase II study data revealed that patients meeting at least 2-4 minor criteria outlined in the newly defined diagnostic criteria for iMCD have a significantly higher response rate than the full cohort from the trial.^{1,2} Rituximab has never been prospectively studied as a therapeutic intervention for iMCD.
2. An international expert panel organized by the Castleman Disease Collaborative Network (CDCN) recently established the first treatment guidelines to be published in a peer-reviewed journal based on data from a systematic literature review of case reports, series, and clinical trials.³ The panel recommended siltuximab first line based on Category 1 evidence for all iMCD patients (both non-severe and severe), whereas rituximab was recommended as an alternative first line option only in a rare sub-set of non-severe cases based on Category 2B evidence and as second-line therapy for all other cases.
3. A real-world data source also support siltuximab as a preferred intervention for iMCD. Yu et al (Blood, 2017) found that iMCD patients treated with siltuximab (N=21) had a greater proportion of complete responses and longer progression free survival ($p = 0.059$) than rituximab and rituximab-containing regimens (N=25).⁴
4. Several lines of evidence related to disease biology and pathogenesis also support siltuximab as a preferred intervention to rituximab for iMCD.^{6,7,8,9} Siltuximab targets interleukin-6, the well-established driver of pathogenesis in a large portion of iMCD patients. Rituximab targets CD20+ B cells, which are known to be pathological drivers in Human Herpesvirus-8 (HHV-8)-associated MCD, but not currently implicated in the pathogenesis of iMCD.
5. Importantly, siltuximab is accessible to iMCD patients in ways rituximab is not. EUSA offers a free siltuximab prescription program which is available to individuals who meet certain income requirements, uninsured, rendered uninsured, being treated by a U.S. licensed doctor, and live in the U.S. or a U.S. Territory.⁵

Thank you for your kind consideration. Please see my contact information should you need to contact me for additional information.

Yours sincerely,

Rabecka Martin, PhD
Head of Medical
EUSA Pharma, Inc.

Citations of literature and published manuscripts recommending this change:

- ¹ Yujun Dong, et al. Effectiveness of rituximab-containing treatment regimens in idiopathic multicentric Castleman disease. *Annals of Hematology*. 7 May 2018.
- ² Makoto Ide, et al. Successful treatment of multicentric Castleman's disease with bilateral orbital tumour using rituximab. *British Journal of Haematology*. 28 May 2003. 121: 815-819.
- ³ Frits van Rhee, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. *Blood*. 15 November 2018, Volume 132, Number 20.
- ⁴ Li Yu, et al. Clinical and pathologic characteristics of HIV- and HHV-8-negative Castleman Disease. *Blood*. 23 March 2017, Volume 129, Number 12.
- ⁵ Janssen CarePath helps simplify access to SYLVANT® (siltuximab) patient assistance. (2019, July 9). Referenced from <https://www.sylvant.com/hcp/patient-support>.
- ⁶ Van Rhee, Frits; Munshi, Nikhil. Treatment of Kaposi Sarcoma Herpesvirus-Associated Multicentric Castleman Disease. *Hematology Oncology Clinics of North America. Castleman Disease; Clinics Reviews*. 2018, pages 80-84.
- ⁷ Mark Bower, et al. Brief Communication: Rituximab in HIV-Associated Multicentric Castleman Disease. *Annals of Internal Medicine*. 18 December 2007, Volume 147, Number 12.
- ⁸ Mario Corbellino, et al. Long-term remission of Kaposi sarcoma-associated herpesvirus-related multicentric Castleman disease with anti-CD20 monoclonal antibody therapy. *Blood*. 1 December 2001, Volume 98, Number 12.
- ⁹ Anne-Genevieve Marcelin, et al. Rituximab therapy for HIV-associated Castleman disease. *Blood*. 15 October 2003, Volume 102, Number 8.