pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Siltuximab (Sylvant) for Multicentric Castleman's Disease

June 22, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of siltuximab (Sylvant) for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpes virus-8 (HHV-8)-negative.

Siltuximab is a chimeric (human–mouse) immunoglobulin G1*k* monoclonal antibody against human interleukin 6 and has a Health Canada indication for the treatment of patients with MCD who are HIV-negative and HHV-8-negative.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized, double blind, placebo controlled trial which randomized patients 2:1 to siltuximab plus best supportive care (BSC) (n=53) or placebo plus BSC (n=26).[1] Siltuximab, or matched placebo, was administered at 11 mg/kg every 3 weeks (one cycle).

Baseline characteristics in the study were not well balanced. Overall, most patients had received previous systemic treatment and all patients had symptomatic disease, with 62 (78%) having more than three symptoms. Notable differences in patient characteristics between the siltuximab and placebo arms included higher proportion of male patients in the placebo arm (57% vs. 85%), higher number of ECOG PS 1 patients in placebo arm (45% vs. 62%), higher number of ECOG PS 3 patients in siltuximab arm (13% vs. 0%). Differences were also noted for interleukin 6 concentration, c-reactive protein concentration (CPR) and erythromycin sedimentation rate (ESR). Variation may however appear greater due to lower numbers of patients in the study.

Patients assigned to siltuximab discontinued study treatment at treatment failure. At first treatment failure, patients assigned to placebo could crossover to receive open-label siltuximab plus BSC. Thirteen (50%) patients assigned to placebo received open-label siltuximab after treatment failure. All patients were included in the final analysis and patients that discontinued were followed up until the primary analysis.

Efficacy

The primary outcome in the Van Rhee et al study[1] was durable tumour and symptomatic response which was statistically improved in the siltuximab arm compared to placebo (34% vs. 0%, respectively p=0.0012). This is a newly developed outcome measure in MCD and rigorous validation of this endpoint has not been completed.

Secondary endpoints included 1 year overall survival (OS) and quality of life. One year survival rate was 100% vs. 92% in the siltuximab arm versus placebo arm, respectively. Patients in the placebo arm crossed over to the siltuximab arm upon progression of disease.

Quality of life was evaluated using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) scale and the Short Form (SF)-36. Multicentric Castleman's Disease Symptom Scale (MCD–SS), a newly developed patient reported outcome scale, was also used. This patient reported outcome measure had not been validated. Statistically significant improvements were seen in the SF-36 domains of role physical, role emotional, vitality, bodily pain, and mental health for patients treated with siltuximab. Early and durable improvements in symptoms

compared with subjects in the placebo arm were also observed for both the FACIT-Fatigue scale and the MCD-SS. Improvements in the FACIT-Fatigue scale were clinically meaningful.

Harms

Fatigue (5 vs. 1 patients) and night sweats (4 vs. 1 patients) were the most frequently occurring grade ≥3 event with higher proportion occurring in the siltuximab treatment arm. Anemia (grade ≥ 3) occurred more frequently in the placebo arm (1 vs. 3 patient). Overall adverse events were evenly balanced, when treatment time and population size are considered. Among those in siltuximab arm, 6% withdrew due to serious adverse events related to treatment, and no treatment related deaths were reported.

1.2.2 Additional Evidence

pCODR received input on siltuximab (Sylvant) for MCD from one patient advocacy group, Canadian Organization for Rare Disorders (CORD). Provincial Advisory Group input was obtained from seven of the nine provinces participating in pCODR.

- One poster presentation was available on the development and testing of the Multicentric Castleman's Disease Symptom Scale (MCD–SS), a new measure for quality of life in patients with MCD.
- A summary of a meta-analysis providing information on a method to estimate minimal clinically important difference (MID/CID) For FACIT-F and SF-36 Quality of life Scales.

No supplemental issues were identified during the development of the review process.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder. Due to the rarity of this disorder, the burden of disease in Canada is not clear. However, based on US estimates, the 10 year prevalence of MCD is 2.4 cases per million[2], which could be extrapolated to less than 90 cases in Canada. Patients are often symptomatic with fevers, drenching sweats, weight loss and fatigue. The more aggressive subtypes of this disorder have a 3 year survival of only 45%[1].

Evidence for treating MCD is limited due to the heterogeneity of this disorder, as well as the low incidence. Consequently, trials have been limited to case reports or small case series. Additionally, there are no consistent outcome measures uniformly applied to this population, confounding interpretation of data. There is currently no clear standard of care for HIV negative, HHV-8 negative MCD.

Effectiveness

The results of the primary endpoint, durable tumour and symptomatic response, favoured siltuximab. While this unique endpoint combines an objective radiologic response and symptomatic improvement to create a clinically relevant measurement, rigorous validation of this endpoint has not been completed. Overall, the results support that siltuximab may be an effective and clinically relevant therapy for MCD. The optimal duration of therapy has not been defined, and patients with ongoing response remained on therapy indefinitely.

Due to immature data, and small sample size, no conclusions can be drawn with respect to the impact of siltuximab on overall survival.

Compared to placebo, siltuximab-treated patients demonstrated an improvement in several quality of life domains across multiple patient-reported outcome surveys.[3] Among these, the MCD-SS is a new scale created for the purposes of this trial and has not been validated. Although there is improvement in five out of eight SF-36 domains, SF-36 scores were just shy of clinical important differences.

Quality of life benefits of siltuximab are seen early in the MCD-SS and the FACIT-Fatigue scales and there is a sustained improvement compared to the placebo arm over time. The magnitude of improvement in the FACIT-Fatigue scores correlate with a clinically meaningful benefit in QOL based on other literature using this scale.[9] Despite these limitations, based the data currently available, the results consistently favour an improvement of QOL in the siltuximab arm.

Safety

The side effects of siltuximab are generally mild, and relatively straightforward to manage.

1.3 Conclusions

The pCODR Clinical Guidance Panel concluded that there may be a net overall clinical benefit to the use of siltuximab for HIV and HHV-8 negative Multicentric Castleman's disease. The CPG conclusions are based on one randomized controlled trial of siltuximab versus usual care that demonstrated a statistically significant benefit in the combined endpoint of radiologic response and improved symptom control (especially fatigue) as compared to usual care. A novel symptom scale (MCD-SS), the FACIT-fatigue scale and SF-36 were used to assess symptom control and quality of life. Statistically significant improvements were noted with siltuximab on all three scales; clinically important improvements were demonstrated in FACIT-fatigue scores. SF-36 scores were just shy of clinical important, and minimal clinical difference has not been established for the MCD-SS. Siltuximab also appears to result in a decreased radiologic burden of disease, however the clinical importance of radiologic response in this disease has not been clearly established. A survival benefit has not been demonstrated. Although there was an increased rate of adverse events in the treatment arm, the rate of grade 3 toxicity is low, and the side-effect profile of this drug is manageable.

In making this conclusion, the Clinical Guidance Panel also considered that:

- This is the first phase III study to be conducted in Multicentric Castleman's disease, allowing the establishment of a new standard of care.
- Based on the inclusion criteria of this study, newly diagnosed as well as relapsed cases would be eligible for therapy with siltuximab.
- Siltuximab would be restricted to patients who are HIV and HHV8 negative. Results cannot be generalized to the HIV positive populations. Testing patients for HHV-8 would be required prior to initiation of therapy.
- Infusion time and monitoring for infusion-related reactions are similar to other biologic therapies.
- The combined endpoint of radiologic response plus symptomatic benefit increases the clinical relevance of this outcome measure, but rigorous validation of this endpoint has not been complete.
- According to patients it is both the adenopathy and symptoms that are debilitating. Relief in both areas is a priority amongst patient advocacy groups.
- Randomization is unequally balanced for ECOG, baseline haemoglobin levels, gender, IL-6 levels, CRP, and ESR. Due to small sample size it is impossible to determine whether these imbalances have influenced outcome measures.

- Quality of life data may be confounded by small sample size. There is a clear trend favouring the siltuximab group across many domains suggesting overall benefit. However, clinical meaningfulness is uncertain due to small absolute differences in QOL data. The improvement in QOL is a priority for patients.
- Determining overall survival is not possible with the small sample size, and short duration of follow-up. With crossover allowed in the study design, it is unlikely that meaningful data for this endpoint will be available.
- There is insufficient evidence to use response to therapy as a surrogate measurement for overall survival.
- Optimal duration of therapy is unknown. Based on this trial, treatment would carry on indefinitely as long as benefit is maintained. Fixed number of cycles or intermittent therapy has not been studied.
- Adverse events appear to be manageable. The significance of severe adverse events such as infections and anaphylaxis is to be determined once more patients have been treated with siltuximab.
- Although need for travel to get therapy may be a barrier to implementation, patients surveyed had a willingness to do this if necessary.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding siltuximab (Sylvant) for multicentric Castleman's disease (MCD). The Clinical Guidance Report is one source of information that is considered in the pERC Deliberative Framework. The pERC Deliberative Framework is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding siltuximab conducted by the Hematology Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; and input from the Provincial Advisory Group.

The systematic review is fully reported in Section 6. Background Clinical Information provided by the CGP, a summary of submitted patient advocacy group input on siltuximab and a summary of submitted Provincial Advisory Group input on siltuximab are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Castleman disease (CD) is a nonclonal lymphoproliferative disorder that can affect single lymph node stations or, alternatively, can be generalized.[4] Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder characterized by overproduction of IL-6 within the lymph nodes, resulting in an angiofollicular hyperplasia and adenopathy. The epidemiology of MCD is not well known due to the rarity of the disease. Ten year prevalence estimates in the U.S. population are approximately 2.4 per million, translating to about 90 patients in Canada. [2]

There are no established treatment protocols for MCD but options for treatment include any appropriate systemic therapy including best supportive care such as CVP, CHOP, or tocilizumab. Interleukin 6 (IL6) plays a pivotal role in the pathophysiology of CD. Human herpesvirus 8 (HHV8), which encodes a viral homolog of IL6, is the driving force in HIV-positive patients. The role of HHV8 in HIV-negative CD is controversial. Historically, the prognosis of patients with generalized or MCD has been thought to be poor. However, CD responds extremely well to monoclonal antibodies directed at the IL6 receptor or IL6 itself, and in general, the long-term outcome of HIV-negative CD is excellent. Important strides forward have also been made in the management of HIV-positive CD.[4] Siltuximab is a chimeric (human–mouse) immunoglobulin G1*k* monoclonal antibody against human interleukin 6.

2.1.2 Objectives and Scope of pCODR Review

The objective for this review is to evaluate the effectiveness and safety of siltuximab (Sylvant) for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpes virus-8 (HHV-8)-negative.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Trial and Patient Characteristics

One randomized, double blind, placebo controlled trial met the eligibility criteria for this review.[1] Two complementary publications were also used to report quality of life outcomes from this study. The Van Rhee study examined best supportive care (BSC) and placebo versus Siltuximab and BSC, in patients with MCD who were HIV and HHV-8 negative. Patients were centrally randomized (2:1) using block randomisation procedure stratified by baseline concomitant corticosteroid use. Details on eligibility criteria for inclusion into the study can be found in Table 2 - Summary of Trial characteristics in Section 6.3.2.1. Of note, patients were eligible if they had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–2.
Siltuximab was administered as 11 mg/kg by 1 hour IV infusion, every 3 weeks which represented one cycle and patients continued on treatment until treatment failure.

The primary endpoint for the study was a composite endpoint of durable tumour and symptomatic response. Secondary endpoints included response, safety and quality of life.

Seventy nine patients were enrolled, and baseline characteristics were un-balanced with notable differences between genders where 57% of patients were male in the treatment arm versus 85% in the placebo arm. ECOG status levels were slightly different across arms where there was higher number of patients with ECOG PS of 1 in the placebo arm, 62% versus 45%. There were also a higher number of patients with ECOG PS of 3 in the siltuximab arm (13% versus 0%). Differences were also noted for interleukin 6 concentration, c-reactive protein concentration and erythrocyte sedimentation rate.

Efficacy

The composite endpoint of durable tumour and symptomatic response was found to be statistically improved in the siltuximab treatment arm versus placebo. This was seen in 34% vs. 0% of patients in the siltuximab vs. placebo arms, respectively (p=0.0012). Tumour response, both investigator assessed as well as independent review, and hemoglobin response were found to have the same pattern of result with statistically improved responses found in the siltuximab arm. One year survival rate was 100% vs. 92% in the siltuximab arm versus placebo arm, respectively. Corticosteroid use was discontinued in 31% vs. 11% of patients in the siltuximab versus placebo arm, respectively (p=0.3602).

Harms

The most commonly occurring (≥10% difference between arms) all grades adverse events in the siltuximab treatment group were pruritus, upper respiratory infection, fatigue, maculopapular rash and localised oedema. Fatigue (5 vs. 1 patients) and night sweats (4 vs. 1 patients)were the most frequently occurring grade ≥3 event with higher proportion occurring in the siltuximab treatment arm. Anemia (≥grade 3) occurred more frequently in the placebo arm (1 vs. 3 patient). Overall adverse events were evenly balanced, when treatment time and population size are considered. Among those in siltuximab arm, 6% withdrew due to serious adverse events related to treatment, and no treatment related deaths were reported.

Quality of Life

Quality of life was evaluated using the Multicentric Castleman's Disease Symptom Scale (MCD–SS), the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) scale, and the Short Form (SF)-36 at predetermined time points throughout the treatment period. MCD-SS is a new patient reported outcome scale, that has only just been developed and initial testing has been carried out. SF-36 and FACIT-Fatigue scales are commonly used and have been tested extensively. The patients treated with siltuximab showed early and durable improvements in symptoms compared with the patients in the placebo arm on both the MCD–SS (p=0.02) and

FACIT–Fatigue scale (p=0.0364) when analyzed using a mixed-effects repeated measures model. There was also positive change in SF-36 physical and mental component scores by an amount that was close to one standard deviation from baseline which may indicate minimal clinical importance. Statistically significant improvements were also seen in the SF-36 domains of role physical, role emotional, vitality, bodily pain, and mental health for patients treated with siltuximab. Analyses were conducted on the intention to treat population. Fatigue was a frequently occurring adverse event in both arms with a larger proportion of patients experiencing improvements in fatigue from the siltuximab arm (35% vs. 11%, p=0.0475). For patients experiencing fatigue, a larger proportion had more severe fatigue in the siltuximab arm (9% vs. 4%). Based upon methods that use standard deviation to extrapolate an important difference, there is a clinically important change in the FACIT-Fatigue scale as an increase of greater than three points from baseline to end was observed, in the siltuximab arm while a clinically meaningful decrease in Fatigue was seen in the placebo arm.

Limitations and Bias

There were many limitations in the Van Rhee et al 2014 study including: patient characteristics that were not well balanced, the use of a primary endpoint that has not been validated, and a study population size that is very small; all leading to considerable uncertainty regarding the study results.

2.1.4 Comparison with Other Literature

Development and testing of the Multicentric Castleman's Disease Symptom Scale (MCD-SS)
One poster presentation was included in submission documents provided by the manufacturer.[5] This poster summarized the development and testing of the Multicentric Castleman's Disease Symptom Scale (MCD–SS) which is a new measure for quality of life in patients with MCD. The MCD-SS are categorized into domains where reduction in scores over time indicates improvement. The domains are: Fatigue (tiredness, fatigue, lack of energy, feeling weak), Rash/Itching (sores/rash on skin, itch), and Sweats (night sweats, daytime sweats). Remaining symptoms were not categorised.

Results from the poster indicated that test re-test correlation exceeded the accepted thresholds of 0.70 for the domains of fatigue and sweats. The results also correlated with ECOG PS scale patterns in which patients with the lowest MCD-SS scores correlated with lower ECOG PS and increased with higher ECOG PS. Convergent validity with SF-36 and correlation with FACIT-F also demonstrated positive results for MCD-SS validity. It was also reported that patients saw early improvements in fatigue when treated with Siltuximab, p=0.02, with the improvements lasting throughout the study period. While a correlation was seen with validated scales there was no description of how testing was conducted, sample sizes were small and the results were presented without any presentation of methods. Comparative testing was not declared as an objective within this presentation.

Minimal clinically important difference (MID/CID) For FACIT-F and SF-36 Quality of life Scales
Following a request by the pCODR Review team, materials were submitted for review by the manufacturer to help understand clinically importance/significance differences in the FACIT-Fatigue and SF-36 quality of life measures in Cancer. Among the provided information, a meta-analysis in various cancer sites that analysed the association between distribution characteristics, standard deviation (SD), and clinically important change was provided.[6] Potential limitations were identified in this analysis. While the meta-analysis included the SF-36 and FACIT scales, it did not include the associated fatigue subscales. This analysis was also from the patient perspective meaning results are not informed by clinical information which limits

the ability to make a decision about "clinically important changes" Additionally, weakness in the analysis arise from the heterogeneity of cancer sites and the potential for unique symptoms being associated with the different diseases, heterogeneity of treatments used and subjectivity of quality of life reporting.

Based on the findings of this analysis, 0.5 SD is consistent with a minimal clinically important difference. As noted above there are limitations regarding the use of this method, and these have been described. Using this concept that 0.5 SD, or 1 standard error of measurement in baseline score change in quality of life scale creates a minimal important difference, a numeric value of change can be determined for different scales.[7] Results from this analysis showed that a 0.5 SD change translated into a change of 3 or more whole units when applied to the FACIT-fatigue scale. Based upon information submitted there was no similar analysis conducted on changes in SF-36 scores.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, MCD impacts not only the patient but the entire family. Respondents spoke about the devastating and debilitating impact on their lives. Specifically, respondents indicated that when the disease was most active, patients were unable to work, go to school, or to participate in any regular activities. As a result of debilitating symptoms (e.g., fatigue, lack of appetite, GI issues, and pain), CORD indicated that patients are often reliant on caregivers for care as well as emotional support. Because the disease is so rare, there are limited treatments for patients with MCD. While respondents understand that siltuximab is not a cure and not every patient in the clinical trials had experienced success with the treatment, respondents expect that the treatment will result in time free of tumour growth, regaining in energy levels, and return to "near normal" life for up to four years. All respondents recognize the burden of getting injections on a regular basis but they feel this would be an acceptable trade-off if the therapy manages to keep their tumour growth in check and relieves the other symptoms and allows them to get back their lives. Of the nine respondents who have experienced with siltuximab, about half of the respondents reported they experienced benefits after the first injection. At the same time, almost all respondents reported at least some adverse effects, including fatigue, GI issues (e.g., diarrhea, stomach ache, nausea), and respiratory infections (e.g., congestion, cough, shortness of breath); however, these respondents were able to manage the effects with other supportive therapy. The greatest challenge reported by those on this therapy is the need to go to a health care facility for injection every 3 weeks. Respondents whose symptoms have subsided report the temptation to "skip" treatments or to prolong the interval between treatments. Most respondents report a "reoccurrence" of symptoms (e.g., fatigue, malaise, fever) when they delayed use, prompting them to "improve adherence."

PAG Input

Input on the siltuximab review was obtained from seven of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, an enabler to implementation is that siltuximab is a new targeted treatment option for a subgroup of patients with MCD.

In addition to the high cost of siltuximab, barriers to implementation include additional resources associated required to regularly monitor for serious adverse events, pharmacy preparation time and administration time. PAG also noted implementation of siltuximab would depend on how each province organizes care for patients with MCD and what program they each would deliver treatments for MCD under, which is variable.

2.2 Interpretation and Guidance

Burden of Illness and Need

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder characterized by overproduction of IL-6 within the lymph nodes, resulting in an angiofollicular hyperplasia and adenopathy. Patients are often symptomatic with fevers, drenching sweats, weight loss and fatigue. Pleural effusions, edema, and ascites can also occur. The more aggressive subtypes of this disorder have a 3 year survival of only 45%[8]. Due to the rarity of this disorder, the burden of disease in Canada is not clear. However, based on US estimates, the 10 year prevalence of MCD is 2.4 cases per million[2], which could be extrapolated to less than 90 cases in Canada.

Evidence for treating MCD is limited due to the heterogeneity of this disorder, as well as the low incidence. Consequently, trials have been limited to case reports or small case series. Further complicating matters, there are no consistent outcome measures uniformly applied to this population, confounding interpretation of data. High dose steroid therapy and multi-agent chemotherapy have been tried, but there is no clear standard of care for HIV negative, HHV-8 negative MCD.

The only phase III study in HIV negative, HHV8 negative MCD compared siltuximab, an IL-6 inhibitor, to supportive care[1]. Although there are limitations to this study, a phase III trial in such a rare disorder is worth acknowledging as a new benchmark for future research. Also, using a novel endpoint combining radiographic response, and sustained clinical benefit takes into account the waxing and waning of symptoms that can occur in the natural history of this disorder. While rigorous validation has not been completed, this may be used as a standardized endpoint for future studies.

Effectiveness

Primary Endpoint—Durable tumour and symptomatic response:

The primary endpoint for this study combined both radiologic findings and symptomatic improvement sustained for greater than 18 weeks. The results favoured siltuximab with a 34% response compared to 0% in the control group (p=0.0004). While this unique endpoint combines an objective radiologic response, and symptomatic improvement to create a clinically relevant measurement, rigorous validation of this endpoint has not been completed. The requirement of a sustained response takes into account the fluctuating symptoms that can occur in this disease to minimize the confounding effects of this normal disease variation. The results support that siltuximab may be an effective and clinically relevant therapy for MCD.

The median time to tumour response was 155 days, and the time to durable symptomatic response was 170 days suggesting a prolonged course of therapy for approximately 6 months may be necessary in order to achieve this primary endpoint. The optimal duration of therapy has not been defined, and patients with ongoing response remained on therapy until treatment failure. No long-term data were available around the median time to treatment failure for responding patients.

Other outcome measures include tumour response which favours siltuximab, but its clinical relevance is unclear since it does not factor in symptomatic improvement for patients. Similarly, hemoglobin response favours siltuximab, but this is confounded by discrepancies in randomization and small number of subjects making it difficult to firmly establish a clinically relevant result.

Overall Survival (OS):

Overall survival was a secondary endpoint of this study. However, due to immature data, and small sample size, no conclusions can be drawn with respect to the impact of siltuximab on this outcome measure. Also, crossover was allowed after progression in the supportive care arm, and this will likely confound future analysis of survival results. There is insufficient evidence to use the response rate demonstrated in this trial as a surrogate marker for survival.

Quality of life analysis:

Compared to placebo, siltuximab-treated patients demonstrated an improvement in several quality of life domains across multiple patient-reported outcome surveys[3]. The MCD-SS showed overall trend in improvement over time as well, based on a predetermined threshold of change (p=0.0515). It should be noted that the MCD-SS is a new scale created for the purposes of this trial and has not been validated. The SF-36 showed significant changes in five out of eight domains--physical, pain, vitality, and mental health scores. Although there is improvement in these quality of life scores, it is unclear whether the degree of change is important. At baseline, the majority of respondents reported their symptoms as mild. Consequently, determining whether the changes in these QOL domains led to a clinically meaningful improvement is unknown. Incorporating the feedback from patient advocacy groups clearly show that some patients have a marked improvement in quality of life, but this is anecdotal, and difficult to know what percentage of patients truly benefit.

Fatigue is a common and debilitating symptom limiting quality of life as noted in the clinical trial, and also reported by patient advocacy groups. The MCD-SS and the FACIT-Fatigue were used to look specifically at fatigue. Both scores showed statistically significant improvement in fatigue scores comparing pre-treatment values with cycle 18 day 1 assessments. The benefits of siltuximab are seen early and there is a sustained improvement compared to the placebo arm over time. The magnitude of improvement in the FACIT-Fatigue scores correlate with a clinically meaningful benefit in QOL based on other literature using this scale.[9] Whether the improvement in fatigue is clinically meaningful using the MCD-SS scale is uncertain as this tool has not been adequately validated. Finally, the determination of statistical significance at cycle 18 day 1 is confounded by a low number of respondents and a sudden worsening of fatigue in the placebo group after cycle 14. Whether this abrupt change affects statistical significance is unclear.

Despite these limitations, based on the data currently available, the results consistently favour an improvement of QOL in the siltuximab arm.

Safety

Toxicity:

Siltuximab had a higher rate of pruritis and upper respiratory tract infections compared to placebo. Other adverse events such as edema, rash, weight gain, and sweats were more common in the treatment arm, but the reactions were usually mild. Anaphylaxis was reported in one patient receiving siltuximab. Due to small sample size the significance and relevancy of this is uncertain. Further safety data is required in order to clarify. Otherwise, the side effects of siltuximab are generally mild, and relatively straightforward to manage.

2.3 Conclusions

The pCODR Clinical Guidance Panel concluded that there may be a net overall clinical benefit to the use of siltuximab for HIV and HHV-8 negative Multicentric Castleman's disease. The CPG conclusions are based on one randomized controlled trial of siltuximab versus usual care that demonstrated a statistically significant benefit in the combined endpoint of radiologic response and improved symptom control (especially fatigue) as compared to usual care. A novel symptom scale (MCD-SS), the FACIT-fatigue scale and SF-36 were used to assess symptom control and quality of life. Statistically significant improvements were noted with siltuximab on all three scales; clinically important improvements were demonstrated in FACIT-fatigue scores. SF-36 scores were just shy of clinical important, and minimal clinical difference has not been established for the MCD-SS. Siltuximab also appears to result in a decreased radiologic burden of disease, however the clinical importance of radiologic response in this disease has not been clearly established. A survival benefit has not been demonstrated. Although there was an increased rate of adverse events in the treatment arm, the rate of grade 3 toxicity is low, and the side-effect profile of this drug is manageable.

In making this conclusion, the Clinical Guidance Panel also considered that:

- This is the first phase III study to be conducted in Multicentric Castleman's disease, allowing the establishment of a new standard of care.
- Based on the inclusion criteria of this study, newly diagnosed as well as relapsed cases would be eligible for therapy with siltuximab.
- Siltuximab would be restricted to patients who are HIV and HHV8 negative. Results cannot be generalized to the HIV positive populations. Testing patients for HHV-8 would be required prior to initiation of therapy.
- Infusion time and monitoring for infusion-related reactions are similar to other biologic therapies.
- The combined endpoint of radiologic response plus symptomatic benefit increases the clinical relevance of this outcome measure, but rigorous validation of this endpoint has not been complete.
- According to patients it is both the adenopathy and symptoms that are debilitating. Relief in both areas is a priority amongst patient advocacy groups.
- Randomization is unequally balanced for ECOG, baseline haemoglobin levels, gender, IL-6 levels, CRP, and ESR. Due to small sample size it is impossible to determine whether these imbalances have influenced outcome measures.
- Quality of life data may be confounded by small sample size. There is a clear trend favouring the siltuximab group across many domains suggesting overall benefit. However, clinical meaningfulness is uncertain due to small absolute differences in QOL data. The improvement in QOL is a priority for patients.

- Determining overall survival is not possible with the small sample size, and short duration of follow-up. With crossover allowed in the study design, it is unlikely that meaningful data for this endpoint will be available.
- There is insufficient evidence to use response to therapy as a surrogate measurement for overall survival.
- Optimal duration of therapy is unknown. Based on this trial, treatment would carry on indefinitely as long as benefit is maintained. Fixed number of cycles or intermittent therapy has not been studied.
- Adverse events appear to be manageable. The significance of severe adverse events such as infections and anaphylaxis is to be determined once more patients have been treated with siltuximab.
- Although need for travel to get therapy may be a barrier to implementation, patients surveyed had a willingness to do this if necessary.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Leukemia Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Castleman Disease (CD) is a rare heterogenous lymphoproliferative disorder characterized by an angiofollicular hyperplasia typically presenting with adenopathy. Although little is known about the pathogenesis of this disease, it is characterized by the overproduction of Interleukin-6 (IL-6) within the lymph node follicles. A subset of cases are also associated with the HIV virus, and Human Herpesvirus-8 (HHV-8). It can present as unicentric Castleman's disease (UCD) with adenopathy confined to one region, or multicentric disease (MCD) with diffuse adenopathy. Due to its rarity, there is limited data with respect to the epidemiology of this disease. The estimated US 10 yr prevalence of MCD is 2.4 cases/million.[2]

Castleman disease can be classified into different subgroups based on histology and clinical findings. There are two main histology subtypes; hyaline vascular, plasma cell variant. The hyaline-vascular variant has increased lymphoid follicles with hyalinization within the germinal centre, and increased vascularisation between the follicles.[10] The plasma cell variant has less hyalinization, and the germinal centre is surrounded by concentric layers of plasma cells that extend into the interfollicular space. Prognosis varies depending on histologic subtype and centricity .[8] For example, unicentric hyaline vascular CD rarely have systemic symptoms and patients with this classification have a 3 yr survival of 92%. Conversely, patients with multicentric disease and plasma cell variant histology have a 3 yr survival of 45%, and frequently have systemic symptoms. For patients with HIV-associated CD, there is a strong correlation with HHV-8 infection. It is hypothesized that HHV-8 stimulates over production of IL-6 from the surrounding follicle cells .[4] The mechanism for excess IL-6 production in patients with HIV-negative, and HHV-8 negative is unknown. However, this cytokine plays a central role in the pathophysiology of the disease. When IL-6 binds to its receptor, it actives the JAK/STAT signalling pathway promoting B-cell proliferation, it induces a pro-inflammatory syndrome leading to constitutional symptoms, and it also induces VEGF which increases angiogenesis and vascularisation within the lymph node.

The clinical manifestations of CD can vary greatly based on the extent of disease. Often unicentric CD is asymptomatic. Conversely, patients with MCD are more likely to have diverse adenopathy, and hepatosplenomegaly.[4] Constitutional symptoms of fever, drenching sweats and weight loss are common, as is a rash. Edema, pleural effusions and ascites can also occur due to increased vascular permeability from increased VEGF. Fifteen percent of patients with MCD have features of POEMS syndrome including a polyneuropathy, organomegaly, endocrine abnormalities, a monoclonal gammopathy, and sclerotic bone disease.[10] Hematologic malignancies such as lymphoma, myeloma, or amyloidosis are more common in patients with CD. There is also a higher incidence of other auto-immune disorders such as haemolytic anemia, immune thrombocytopenia, pure red cell aplasia, and lupus. Rapidly progressive respiratory failure from bronchiolitis obliterans can occur due to T-cell infiltration in the lungs.

Management of patient can vary depending on the extent of disease and symptoms. Asymptomatic patients can be observed, reserving therapy for symptomatic disease. Alternatively, for patients with unicentric disease, surgical resection may be curative, and this should be considered if feasible. For unresectable UCD, radiation can also be considered.[4] Symptomatic multicentric CD may require chemotherapy, which will be discussed below.

3.2 Accepted Clinical Practice

Due to the rarity of this disorder and, until recently, the lack of phase III studies, there is no clear standard of care for management of MCD. Treatment strategies also differ depending on HIV status of the patient. For the purposes of this review, HIV-negative MCD will be discussed. The majority of studies are small case series, or case reports, and interpretation of the data is difficult due to inconsistency in the definition of response to therapy.

Numerous systemic therapies have been reported for management of MCD. For initial control of symptoms, high dose steroid therapy has been used, and complete responses achieved.[11] However, long-term therapy with prednisone is often required, as tapering of the steroids results in progression. Rituximab has also been used, however data are limited in HIV-negative MCD, with only 7 patients reported in the literature.[4] Four out of the seven patients had complete responses to rituximab but three of these responses were in patients with hyaline vascular histology. Rituximab showed no benefit on patients with plasma-cell variant CD. Multi-agent lymphoma-based chemotherapy regimens have been tried in a small number of patients.[12] Relapses are common, and median survival in this group is 19 months. Other chemotherapies such as interferon, bortezomib, and thalidomide have been reported as case reports, but efficacy of these therapies requires more rigorous study.[4]

Interleukin-6 plays a key role in the pathophysiology of HIV-negative MCD, and can be a potential target for therapy. A phase II study with the humanized anti-IL-6 receptor monoclonal antibody, tocilizumab, was conducted.[13] Twenty-eight patients were treated every 2 weeks for 16 weeks, with a marked improvement in lymphadenopathy, as well as inflammatory and nutritional markers such as CRP, cholesterol, and albumin. Hemoglobin also improved, and constitutional symptoms and fatigue resolved. Also, eleven of the 15 patients on long-term steroid therapy had their steroid dose reduced from an average of 15 mg daily, to less than 10 mg daily. Side effects included the common cold, malaise, pruritus urinary tract infections, diarrhea and mouth ulcers. Upon completion of the therapy, disease progression was common, suggesting long-term therapy may be required.

More recently, a phase III study using the human-murine anti-IL-6 monoclonal antibody, siltuximab, was published.[1] This is the first phase III study to be conducted in HIV-negative MCD. Patients were randomized two to one, to receive siltuximab or placebo, and all patients received supportive care. The response rate for siltuximab was 34% (p=0.0012) for a durable and symptomatic improvement. No patients had a response in the placebo arm. Also, time to treatment failure was not reached in the siltuximab arm, versus 134 days for placebo. Quality of life improved with this therapy and the treatment was relatively well tolerated. This study provides the first randomized study for MCD. However, it is unclear how siltuximab compares to other therapies such as multi-agent chemotherapy, or rituximab. This study will be the focus of this submission.

3.3 Evidence-Based Considerations for a Funding Population

Based on the phase III study comparing siltuximab with best supportive care, patients to be considered for this therapy would be HIV-negative, and HHV-8 negative by PCR. The treatment would be limited to patients with newly diagnosed or previously treated MCD, and also have symptomatic disease.

3.4 Other Patient Populations in Whom the Drug May Be Used

Based on the published literature, siltuximab therapy would be limited to the patient population defined in the study.[13] Use in patients with HIV-positive Castleman disease or in unicentric disease has not been studied, and results should not be extrapolated to these patient groups.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Canadian Organization for Rare Disorders (CORD), provided input on siltuximab (Sylvant) for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpes virus-8 (HHV-8) – negative, and their input is summarized below.

CORD reported that patient information was collected through using several approaches, including one-on-one patient interviews, email exchanges and responses to emailed questions, interviews with expert patients (patients who are also healthcare professionals and/or head of patient organizations), as well as reading patient stories and testimonials on social media sites.

Although CORD was unable to find patient groups for MCD in Canada and that they could not identify specialty clinics, CORD found that there are several international groups for patients and research in this area. To collect information for this submission, CORD reached out to three key groups: Castleman Disease (CD) Community (on Rare Connect), International Castleman's Disease Organization, including Castleman's Disease Blogcast, and Castleman Disease Collaborative Network (CDCN Facebook). CORD posted a request on the CDCN Facebook site and started a discussion on the CD Community site, asking any patient who had experience with siltuximab to contact CORD. In addition, CORD also read through all of the patient stories and conversations in these three sites to identify patients or family members who reported MCD and had received treatment. CORD posted "reply" to each of those patients who had been on treatment asking them to reply with their experience regarding benefits and adverse effects, and to request if they were willing to be interviewed about their treatment experience.

Because of the small patient numbers and the short timeframe to submit the patient evidence information, CORD elected not to set up a survey but emailed questions to those who responded to CORD's enquiry. In total, CORD contacted 20 MCD patients, of which nine (9) who were on treatment with siltuximab and two (2) respondents who were on a different treatment regimen, tocilizumab. None of the Canadian respondents were receiving siltuximab; however, one respondent was receiving tocilizumab. Respondents ranged in age from 21 to 63 years and had been diagnosed for less than one to 19 years. CORD interviewed seven (7) respondents by phone. Three of those respondents interviewed were Canadians.

From a patient perspective, MCD impacts not only the patient but the entire family. Respondents spoke about the devastating and debilitating impact on their lives. Specifically, respondents indicated that when the disease was most active, patients were unable to work, go to school, or to participate in any regular activities. As a result of debilitating symptoms (e.g., fatigue, lack of appetite, GI issues, and pain), CORD indicated that patients are often reliant on caregivers for care as well as emotional support. Because the disease is so rare, there are limited treatments for patients with MCD. While respondents understand that siltuximab is not a cure and not every patient in the clinical trials had experienced success with the treatment, respondents expect that the treatment will result in time free of tumour growth, regaining in energy levels, and return to "near normal" life for up to four years. All respondents recognize the burden of getting injections on a regular basis but they feel this would be an acceptable trade-off if the therapy manages to keep their tumour growth in check and relieves the other symptoms and allows them to get back their lives. Of the nine respondents who have experienced with siltuximab, about half of the respondents reported they experienced benefits after the first injection. At the same time, almost all respondents reported at least some adverse effects, including fatigue, GI issues (e.g., diarrhea, stomach ache, nausea), and respiratory infections (e.g., congestion, cough, shortness of breath); however, these respondents were able to manage the effects with other supportive therapy. The greatest challenge reported by those on this therapy is the need to go to a health care facility for injection every 3 weeks. Respondents whose symptoms have subsided report the temptation to "skip" treatments or to prolong the interval between treatments. Most respondents

report a "reoccurrence" of symptoms (e.g., fatigue, malaise, fever) when they delayed use, prompting them to "improve adherence."

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Multicentric Castleman's Disease

According to CORD, the respondents (includes patients and families) who were contacted reported being HIV-negative, although there are some who were HHV-8 positive. Respondents had various subtypes of MCD, including hydraline vascular, plasma cell, or both.

CORD indicated that respondents reported a variety of symptoms, including fevers, fatigue, and night sweats were common to all. Most respondents also reported pain (joints, legs, shoulders, hands) as well as weakness and numbness, especially in the hands and feet. All respondents reported instances of swollen lymph nodes in the chest, underarms, neck or groin area. Many respondents also had bouts of swollen glands or enlarged organs, pressing on their abdomen or chest area. About half of the respondents reported outbreaks of rashes, sometimes isolated and sometimes widespread, that were often painful and itchy. A couple of respondents reported swelling or "lumps" in the legs and several mentioned they had experienced massive discolouration (purple mass) in the legs.

Most respondents said they had experienced weight loss, sometimes severe, due in part to a loss of appetite and "*feeling full*" even when they had eaten just a little. Some respondents were concerned about shortness of breath as a result of tumours in the lungs, which increased feelings of tiredness and also kept them from being able to sleep at night. A couple of respondents reported having had a stroke, and one respondent reported having had multiple strokes. The respondent with the multiple strokes believed this was related to very low red blood cell and platelet counts, as the respondent also had bone marrow fibrosis.

A few respondents reported that they (or their family member) had experienced symptoms for a period of time and then the disease had seemingly gone into remission, sometimes as long as 10 years or more, to suddenly become symptomatic again.

According to CORD, MCD impacts the entire family. Respondents spoke about the devastating and debilitating impact on their lives. Respondents indicated that when the disease was most active, patients were unable to work, go to school, or to participate in any regular activities. Because the disease is so rare and the progression varied and was almost unique to each patient, their doctors could not predict when it would get worse or how it would progress or life expectancy. Many respondents, including patients, parents, and other caregivers reported living in continuous anxiety and worried about what was coming next, and felt unable to make plans for the future.

4.1.2 Patients' Experiences with Current Therapy for Multicentric Castleman's Disease

CORD described that because symptoms, progression, therapy and responses varied considerably for patients with MCD, some respondents reported receiving treatment before their MCD was diagnosed, and as such, these patients were treated to deal with the symptoms or perhaps based

on an erroneous diagnosis. Some respondents stated their initial diagnosis was leukemia, lymphoma, or auto-inflammatory disease. In some cases, respondents reported that therapy was initiated without identifying the subtype of MCD, so the choice of therapy was not very effective. According to CORD, some respondents were initially diagnosed as having unicentric Castleman's Disease, so they were surprised (and devastated) when it came back elsewhere. Based on CORD's findings, all respondents had undergone computed tomography (CT) scans, magnetic resonance imaging (MRI), and biopsies (lymph nodes and bone), and some had received positron emission tomography (PET) scans. About half of the respondents had undergone some surgery with varying degrees of success. Respondents reported having lymph nodes removed from their skin, armpits, neck, and inside their chest or abdomen area. In most cases, it was noted that the lymph nodes reappeared. Four (4) respondents reported they had had their spleen removed (though this may have been true for others also). According to CORD, most of these respondents appeared to have been diagnosed earlier, in the late 90's or early 2000's. One respondent reported surgery to place a rod in his leg to support it against fracture.

CORD reported that about half of the respondents received radiation therapy, either following surgery or as an alternative to surgery. Respondents felt this was primarily to manage the enlarged lymph nodes and not as a "cure", since the symptoms often returned. Slightly less than half of respondents had received some form of chemotherapy, again with varying responses. Almost all respondents reported having a recurrence or relapse.

In addition, while no numbers were reported, almost all respondents stated that they have also been treated with corticosteroids (prednisone), either initially or when they received chemotherapy. Respondents felt it had some limited, short-term benefit, though most respondents were unsure and reluctant to stay on steroids for long term. About one-fifth of respondents said they had received another immunosuppressant (cyclosporine).

CORD reported that four (4) respondents were prescribed rituximab (Rituxan), alone or with chemotherapy. One (1) respondent stated symptoms had subsided, but other respondents said after a period of time (up to two years), the drug seemed to have stopped working noting that tumours were growing again. All respondents reported severe side effects with the drug, making it an undesirable option. According to CORD, none of the respondents had been informed that the drug was mostly effective in those who were HHV-8 positive.

There were two (2) respondents who reported receiving tocilizumab (Actemra), one residing in the USA and one in Canada. They have been on therapy for three to 11 years and indicated they have not experienced recurrence of enlarged lymph nodes, and their other symptoms, including fatigue, fevers, joint pain and rash have subsided.

CORD also noted that there were nine (9) respondents who had received siltuximab (Sylvant), ranging in duration from six months to over 4 years. Two (2) respondents had discontinued treatment because they had not experienced a response (i.e., tumour shrinkage or reduced symptoms). The three (3) respondents on treatment under one year felt they were benefitting. For example, they noted more energy, no tumours, better breathing and sleep, and fewer infections; while the other respondents felt they had significant improvement in symptoms and tumour shrinkage.

4.1.3 Impact of Multicentric Castleman's Disease and Current Therapy on Caregivers

CORD observed that families affected by Castleman's Disease compared the devastating impact to cancer, both in terms of the burden of the disease and the challenges of treatments such as chemotherapy, radiation, and surgery. Because of debilitating symptoms (e.g., fatigue, lack of

appetite, GI issues, and pain), CORD indicated that patients are often reliant on caregivers for care as well as emotional support. For caregivers, it was reported there is an overwhelming feeling of helplessness, since there are almost no effective treatments. It was considered that current treatments provide, at best, only temporary remission of symptoms. Because the trajectory of the disease is unknown, it is difficult for families to make plans or provide assurance. Moreover, short-term survival with MCD is low, and this takes a huge emotional toll on the whole family, regardless of the age of the patient.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Siltuximab

According to CORD, when asked to speak about their expectations for siltuximab, respondents were "guardedly optimistic", in part, because the drug was not known to be a cure, and not every patient in the clinical trials had experienced success. Moreover, there were no clear indicators as to who would respond. Respondents were however optimistic because it was the "*only thing out there*" and some respondents had achieved long-term remission of tumours and symptoms.

Respondents noted that they knew some who have been on therapy have not experienced recurrence of tumours, were feeling well, and have been able to resume their daily lives. Because this is a new therapy, there are not many respondents who have been on the drug for long, but respondents report examples of others who have been free of tumour growth, regained energy levels, and returned to "near normal" life for up to four years. Accordingly, this provides a chance to return to work, to take care of their families, to pursue education without constant disruption, and to resume living.

Respondents stated they are aware of some people experiencing "difficult side effects" but most of these seemed to be the same as the symptoms of the disease so not likely to be any worse as no treatment. The respondents are also aware that some side effects, such as low WBC counts, may be life-threatening and may require them to cease treatment, or get other supportive therapy. While this possibility is anxiety-provoking, respondents have all been on various treatments with limited long-term benefit so reduction of tumours and symptoms with some hope of continued effectiveness are considered major milestones.

All respondents recognize the burden of getting injections on a regular basis but they feel this is an acceptable trade-off if the therapy manages to keep their tumour growth in check and relieves the other symptoms and allows them to get back their lives. Most said that they would be willing to try the therapy, in hopes that it worked. They are also realistic that many people go off therapy because they do not respond, but stated: "*it is worth trying*."

CORD indicated that respondents, whether or not they had experience with siltuximab and whether they had succeeded with this therapy, were unanimous in calling for access to the therapy for all patients who might be appropriate. In particular, respondents were advocating for access for those who were HIV-negative and HHV-8-negative because the trials were conducted with these patients, and the majority had a positive response. Moreover, when asked about the opportunity for other patients (HIV-positive; HHV-8 positive) to be offered access through an extended open trial or other arrangement, all respondents were unanimous in saying this should be done.

There were no Canadian respondents who have experience with this therapy. CORD noted that respondents who had experience with the drug through the clinical trials or compassion access

had all been on various other therapies, with no, limited, or declining effectiveness. Of the nine respondents who have experienced with the drug, about half of the respondents reported they experienced benefits after the first injection of siltuximab. At the same time, almost all respondents reported at least some adverse effects, including fatigue, GI issues (e.g., diarrhea, stomach ache, nausea), and respiratory infections (e.g., congestion, cough, shortness of breath).

All respondents said they were able to manage the effects with other supportive therapy; for most, the side effects decreased with continued use (i.e., six months or longer). The greatest challenge for those on therapy (for long term) was the need to go in for injection every 3 weeks, or so. Respondents whose symptoms have subsided report the temptation to "skip" treatments or to prolong the interval between treatments. Most respondents report a "reoccurrence" of symptoms (e.g., fatigue, malaise, fever) when they delayed use, prompting them to "improve adherence."

One respondent reported "*I am not sure why it [Sylvant] works for me and not so well for others, but it has been my lifesaver. I don't know if it will continue to be effective forever, but every month has been a miracle for me, my wife, and my children. I just wish it had been available when I was first diagnosed so I could have avoided all those other surgeries and treatments that didn't work. I also wish every CD patient at least had the opportunity to see if it works. If you don't get a chance, you won't know*."

4.3 Additional Information

CORD stated that it is very challenging to collect sufficient information from rare disease patients when the numbers are very, very small and there have been no clinical trials in Canada. It would be so much better to implement some form of "coverage with evidence development" that would allow "appropriate" patients to gain access while more evidence is collected in "real world" settings.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for siltuximab for multicentric Castleman's disease (MCD). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the siltuximab review was obtained from seven of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, an enabler to implementation is that siltuximab is a new targeted treatment option for a subgroup of patients with MCD.

In addition to the high cost of siltuximab, barriers to implementation include additional resources associated required to regularly monitor for serious adverse events, pharmacy preparation time and administration time. PAG also noted implementation of siltuximab would depend on how each province organizes care for patients with MCD and what program they each would deliver treatments for MCD under, which is variable.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

There is no standard of care for patients with MCD. In the very small number of patients in Canada, treatment with cytotoxic chemotherapy, rituximab and more recently, tocilizumab have been used.

5.2 Factors Related to Patient Population

MCD is a very uncommon disease and the subgroup of these patients who are HIV negative and human herpes virus-8 negative is even smaller. Siltuximab would be a new treatment option that would fill the therapeutic gap for this specific subgroup of patients with MCD. This would be an enabler.

PAG noted that there may be funding requests for siltuximab in patients who are HIV positive and/or human herpes virus positive, although there were no clinical studies in this subgroup.

5.3 Factors Related to Accessibility

In some jurisdictions, patients with MCD are treated with intravenous chemotherapy at the cancer clinics; however, in other jurisdictions, these patients would be treated through the hospital or other outpatient infusion clinics.

As an intravenously administered drug, siltuximab would be fully funded, which would be an enabler for patients. However, some patients would need to travel far to specialized centers for administration since siltuximab is a new monoclonal antibody that is associated with infusion related reactions. Thus, siltuximab would be administered in a setting that has equipment for resuscitation and health care staff trained in resuscitation.

5.4 Factors Related to Dosing

PAG noted that there are no dose adjustments necessary with siltuximab, which is an enabler to implementation. It was also noted that siltuximab is administered every three weeks until disease progression. The indefinite treatment duration could be a barrier to implementation because the impact on resources is unknown.

5.5 Factors Related to Implementation Costs

PAG has concerns for incremental costs due to drug wastage, since vial sharing is unlikely given the very small number of patients and the cost of the drug is high. The dose is based on weight and the vial sizes are in 100mg and 400mg. Thus, a dose of 770mg (11mg/kg x 70kg) would result in drug wastage.

As siltuximab is a new monoclonal antibody, healthcare staff would need to become familiar with the preparation and administration of siltuximab. In addition, additional healthcare resources are needed to monitor and treat infusion related reactions, infections, gastrointestinal perforations and other adverse events, as well as monitor for drug-drug interactions.

Based on the prescribing information available in the United States, PAG estimated that the pharmacy preparation time could be more than 90 minutes. This includes the 30 minutes for the vials to come to room temperature prior to reconstitution and another 60 minutes to dissolve the lyophilized powder once reconstituted. PAG also noted that the reconstituted vials have a very short stability and the infusion solution must be administered within four hours of preparation. As such, the wait time for the patients and nursing staff could be frustrating.

PAG indicated that chair time could be lengthy as well, since the infusion time is 60 minutes and the time required to prepare for the infusion and monitor for infusion-related reactions.

In addition, PAG noted that siltuximab requires refrigeration for storage, as with many other monoclonal antibodies, and refrigerator space is an issue in some centers.

5.6 Other Factors

PAG also noted implementation of siltuximab would depend on how each province organizes care for patients with MCD and what program they each would deliver treatments for MCD under, which is variable.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of siltuximab (Sylvant) in for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpes virus-8 (HHV-8)-negative.

- No supplemental questions were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 1 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized control trials	Patients with MCD who are HIV-negative and HHV-8-negative Subgroups: NA	Siltuximab (Sylvant)	Any appropriate systemic therapy including best supportive care such as(CVP or CHOP Chemotherapy, Tocilizumab, steroids or rituximab)	**Efficacy:** OS DFS RFS Durable tumour & symptomatic response CR OR Steroid dose reduction TRD Hemoglobin response Quality of Life (QOL) Time to tumour response** **Harms:** AE's and Grade 3-4 AE's • hematologic AE • non-hematologic AE • neutropenia • infusion reactions • upper respiratory • rash • **fatigue** • **diarrhea** • dyspnoea • hypertension • hyperleukaemia

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				• local/peripheral oedema • weight gain • weight loss • hyperhidrosis • night sweats • **nausea** • anaemia • thrombocytopenia • hyperuricaemia • nasopharyngitis • withdrawal due to adverse events (WDAE)

MCD= Multicentric Castleman's disease; HIV= human immunodeficiency virus; HHV-8= human herpes virus-8; CVP = Cyclophosphamide, Vincristine, Prednisone; CHOP= Cyclophosphamide, hydroxyldaunorubicin, oncovin, prednisone; OS= Overall survival; CR= complete response; OR= overall response; DFS= disease free survival; RFS= relapse-free survival; TRD= treatment related death; QoL= quality of life; AE= adverse events; WDAE= withdrawal due to adverse events.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
*** Time to tumour response is an endpoint that was added to this protocol following the initial search. Based upon review the clinical guidance panel determined this outcome was important.*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-May 6, 2015) with in-process records & daily updates via Ovid; EMBASE (1980-May 6, 2015) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were siltuximab (Sylvant) and MCD.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The initial search was completed on February 23, 2015 and was updated during the review. The search is considered up to date as of May 6th, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Ontario Institute for Cancer Research - Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and ESMO and ASH were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

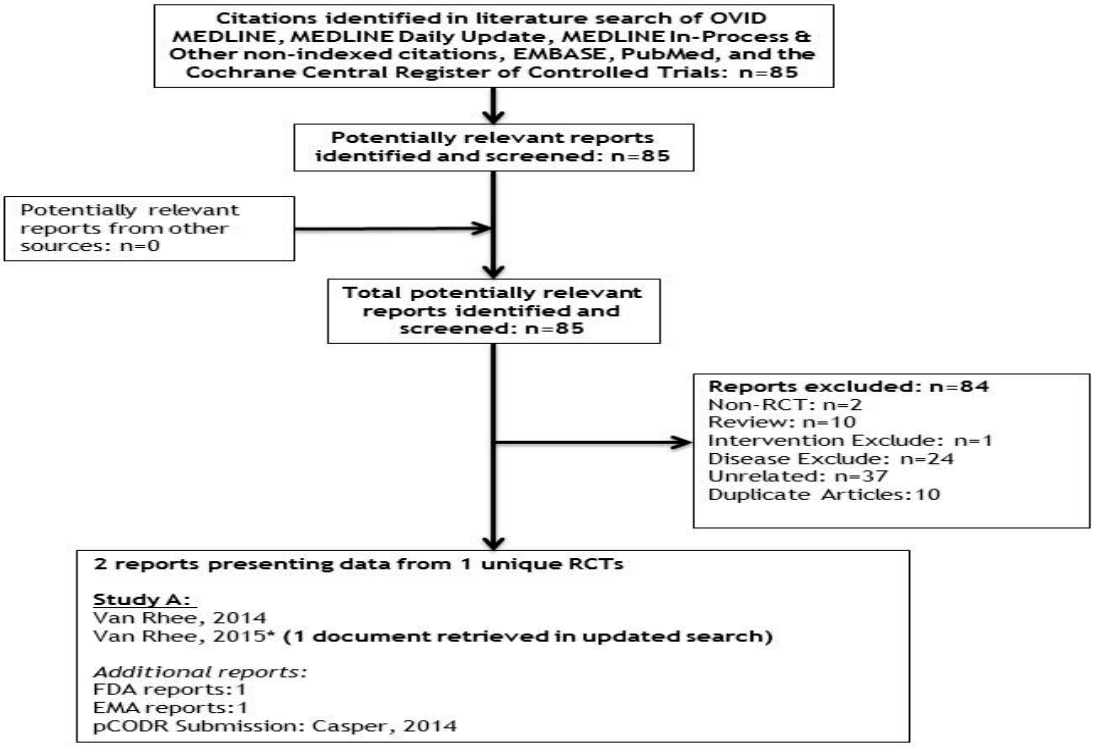
6.3 Results

6.3.1 Literature Search Results

Of the 85 potentially relevant reports identified, 1 study was included in the pCODR systematic review[1] and 84 studies were excluded. Studies were excluded because they were not randomized control trials [14, 15], they were reviews or editorial articles [16-25], did not use an appropriate intervention or comparator[26], did not meet disease specific inclusion criteria [27-50], their content was not related to siltuximab or MCD)[51-83], studies with safety or quality of life as primary outcomes[84-87], or were duplicate documents from the final review process that contained descriptive information about studies.[16-25].

NOTE: One additional publication was found in the updated search conducted on May 6th, 2015. It has been included in the quorum diagram below and is discussed in appropriate context below.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional information related to the Vah Rhee study was also obtained through requests to the Submitter by pCODR[88]

6.3.2 Summary of Included Studies

One randomized trial met the inclusion criteria and was selected for inclusion. Van Rhee et al, 2014[1] is a randomized, double-blind, placebo-controlled study that was conducted in 19 countries globally. Details of the trial are summarized in [Table 2] below.

Further information was also available from EPAR reports as well as FDA reports.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics of the included study of siltuximab for multicentric Castleman's disease

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT01024036 Funded by: Janssen Research and Development LLC Randomized: n= 79 Double Blind placebo-controlled study Randomized in a 2:1 ratio Siltuximab n=53 Placebo n=26 Multi-national: 38 hospitals in 19 countries Patients enrolled from February 2010 to February 2012	**Eligible patients** • 18 yrs or older • Diagnosed MCD (determined on the basis of patient history, physical examination, laboratory abnormalities, pathological diagnosis, radiological imaging, histologically confirmed diagnosis) • Newly diagnosed or previously treated (except for previous IL-6 targeted treatment) • Measurable disease not limited to cutaneous lesions, grade 1 or greater disease symptoms according to the NCICTCAE Version 4.0. • ECOG performance Status score of 0-2. • Specified treatment criteria prior to each dose in trial **Exclusion criteria:** • HIV-seropositive • Evidence of HHV-8 infection • Other clinically significant infections including hepatitis B or C, or history of or concurrent lymphoma	**Intervention:** Siltuximab (11 mg/kg administered by 1 hour IV infusion every 3 weeks (one cycle)) plus BSC **Comparator:** Placebo (administered by 1 hour IV infusion every 3 weeks) plus BSC	**Primary Endpoint:** Durable tumour and symptomatic response **Secondary Endpoints - (efficacy):** • Duration of tumour and symptomatic response • tumour response • time to treatment failure • 15 g/L or greater increase of hemoglobin concentration between baseline and week 13 • steroid dose reduction • treatment failure rate • improvement of MCD -related symptoms • 1 yr OS • Patient-reported outcomes **Harms Outcomes** • AE's • Serious AE's • AE leading to Discontinuation

Abbreviations MCD= Multicentric Castleman's disease; HIV= human immunodeficiency virus; HHV-8= human herpes virus-8; NCICTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; ECOG= Eastern Cooperative Oncology Group ; BSC= Best Supportive Care; AE = Adverse Event; OS = Overall Survival

Van Rhee, 2014 [1]

a) Trials

One randomized, double blind, placebo controlled trial met the inclusion criterion for this review. (Van Rhee et al, 2014).[1] Patients in the study were centrally randomized (2:1) using block randomization procedure stratified by baseline concomitant corticosteroid use. Key inclusion and exclusion criteria for entry into the study are detailed in Table 2 above.

The primary endpoint of the study was durable tumour and symptomatic response defined as a complete response (CR) or partial response (PR) by modified Cheson criteria (adjusted to include assessment of cutaneous lesions caused by MCD) with improvement or stabilization of disease-related symptoms for at least 18 weeks during masked treatment. CR was defined as complete disappearance of all measurable and evaluable disease (e.g. pleural effusion) and resolution of baseline symptoms attributed to MCD. PR was defined as a 50% decrease in sum of the product of the diameters (SPD) of index lesion(s), with at least stable disease (SD) in all other evaluable disease in the absence of treatment failure. Symptomatic response was assessed by investigators and was based on the sum of the disease related overall symptom score. Symptoms raised in the patient input align well with the symptoms in the list of 34 symptoms used to measure symptomatic response. Secondary endpoints were duration of tumour and symptomatic response, tumour response, time to treatment failure, 15 g/L or greater increase of haemoglobin concentration between baseline and week 13, discontinuation of corticosteroids, treatment failure rate (data not shown),improvement of MCD-related symptoms, overall survival at 1 year. Safety outcomes included adverse events, withdrawal due to adverse events, treatment related deaths, steroid dose reduction, hematologic/non-hematologic adverse events, neutropenia, infusion reactions, upper respiratory infections, rash, fatigue, diarrhea, dyspnoea, hypertension, hyperleukaemia, local/peripheral oedema, weight gain, weight loss, hyperhidrosis, night sweats, nausea, anaemia, thrombocytopenia, hyperuricaemia, and nasopharyngitis. Patient-reported outcomes including changes from baseline in Functional Assessment of Chronic Illness Therapy—Fatigue score, Short Form-36 Health Survey subscale scores, and MCD Signs and Symptom Scores were also collected.

The primary endpoint, durable tumour and symptomatic response was analysed with a two-sided significance level of 5%. The study was designed to achieve 80% power, with an assumption of 30% response in the treatment arm and a 5% response in the control arm. To achieve this power, a sample size of 78 subjects was required. Response analysis included independent assessment of responses and analyses were presented for both investigator and independent assessments. Tumour response was assessed centrally by investigators and independent radiological review, masked to treatment failure (Biocor, Princeton, NJ, USA).) Comparative testing was done using an exact Cochran-Mantel-Haenszel test, stratified by concomitant corticosteroid use. Intention to treat analysis population included all patients.

b) Populations

There were 79 patients enrolled following assessment of eligibility (53 assigned to siltuximab, 26 assigned to placebo). Baseline characteristics were not well balanced between groups. Gender in the study arms was unbalanced with 57% male patients in the treatment arm versus 85% in the placebo arm. According to central pathological review, patients had mixed, hyaline vascular, or plasmacytic histological subtypes. The median age was 48 years (range 20–78). All patients had symptomatic disease, with 62 (78%) having more than three symptoms including fatigue (86%), malaise (61%), night sweats (52%), peripheral sensory neuropathy (38%), anorexia (37%), pruritus (37%), dyspnoea (35%), oedema of limbs (30%), hyperhidrosis (30%), or weight loss (30%). A wide range of inflammatory laboratory values was recorded in both groups. ECOG performance status was slightly different between treatment arms. More patients had an ECOG PS of 1 in the placebo arm compared to patients in the siltuximab arm (62% versus 45%). There were also more patients with an ECOG PS of 3 in the siltuximab arm compared to the placebo arm (13% versus 0%). Differences were also noted for interleukin 6 concentration, c-reactive protein concentration and erythromycin sedimentation rate, and disease related overall symptom score. Variation may appear greater due

Table 3. Baseline Patient Characteristics

	Siltuximab & BSC	Placebo & BSC
	N=53	N=26
Characteristic		
Median age (age range)	47 (20-74)	48 (27-78)
Gender (male) (number (%)	30 (57%)	22 (85%)
Ethnic Origin		
White	19 (36%)	12 (46%)
Asian	27 (51%)	11 (42%)
Black	3 (6%)	0 (0%)
Other	4 (8%)	3 (12%)
Region		
North America	10 (19%)	5 (19%)
EMEA	13 (25%)	8 (31%)
Asia Pacific	26 (49%)	11 (42%)
Latin America	4 (8%)	2 (8%)
ECOG		
0	22 (42%)	10 (38%)
1	24 (45%)	16 (62%)
2	7 (13%)	0 (0%)
Disease Histology		
Hyaline Vascular	18 (34%)	8 (31%)
Plasmatic	13 (25%)	5 (19%)
Mixed	22 (42%)	13 (50%)
Haemoglobin concentration (g/L)	118 (65-170)	134 (85-181)
Interleukin 6 concentration (pg/mL)	7.13 (0.38-50.6)	4.94 (1.03-19.8)
C-reactive protein concentration (mg/L)	17.6 (0.10-181.0)	4.2 (0.4-107.0)
Erythrocyte sedimentation rate (mm/h)	62.0 (4-120)	23.5 (1-112)
Fibrinogen concentration (µmol/L)	15.14 (6.9-29.4)	12.08 (7.3-29.4)
Albumin concentration (g/L)	35 (15-49)	36 (28-46)
Disease related overall symptom score	6 (2-31)	10 (1-30)
Previous Systemic Treatment	29 (55%)	17 (65%)
Corticosteroids	28 (97%)	15 (88%)
Chemotherapy	17 (59%)	12 (71%)
Rituximab	5 (17%)	3 (18%)
Immunosuppressant	1 (3%)	3 (18%)
Interferon	1 (3%)	1 (6%)
Concomitant Steroid	13 (25%)	9 (35%)
BSC=Best Supportive Care; EMEA=Europe, Middle east and Africa; ECOG= Eastern Cooperative Oncology Group		

Van Rhee, 2014[1]

c) Interventions

Patients were randomized to receive siltuximab and best supportive care (BSC) or placebo and BSC. Siltuximab, or matched placebo, was administered at 11 mg/kg every 3 weeks (one cycle). BSC in all patients included management of effusions, use of antipyretic, antipruritic, antihistamine, and pain drugs, management of infections, transfusions, and standard management of infusion related reactions as specified in institutional guidelines.

Before each dose, patients had to meet retreatment criteria (absolute neutrophil count ≥1.0 × 10^9/L, platelets ≥50 × 10^9/L, and recovery of other clinically significant toxic effects to grade ≤2

or baseline) or dosing would be delayed by no more than 3 weeks until retreatment criteria were met. Patients assigned to siltuximab discontinued study treatment at treatment failure (defined as sustained increase in grade ≥2 disease-related symptoms persisting ≥3 weeks; new disease-related grade ≥3 symptoms; sustained >1 point increase in ECOG-PS persisting for ≥3 weeks; radiological progression by modified Cheson criteria12 or initiation of another treatment for Multicentric Castleman's disease). At first treatment failure, patients assigned to placebo could crossover to receive open-label siltuximab plus BSC until second treatment failure. Patients who discontinued study treatment were followed up until the primary analysis. Dose reductions were not permitted. The following were also not allowed: use of erythropoietin-stimulating agents (ESA), anti-tumour treatments, biological treatments, and an increase from baseline use for these agents, or a new course of corticosteroids. All patients on corticosteroids received stable or decreasing dose =< 1 mg/kg per day prednisone or equivalent for more than 4 weeks before randomisation.[1]

d) Patient Disposition

One hundred and forty patients were screened for entry requirements to the study. Sixty one patients were excluded, 56 due to ineligibility and 5 that withdrew consent. During masked treatment, patients completed a median of 19 cycles of siltuximab and eight cycles of placebo. At first treatment failure, patients in the placebo arm were able to cross-over to open label siltuximab treatment and best supportive care until secondary failure occurred. Thirteen (50%) patients assigned to placebo received open-label siltuximab after treatment failure. All patients were included in the final analysis and patients that discontinued were followed up until the primary analysis.

Sixteen (30%) of 53 patients taking siltuximab and 14 (54%) of 26 taking placebo discontinued because of treatment failure. Thirteen of 26 (50%) patients assigned to placebo crossed over to receive open-label siltuximab after treatment failure.[1]

Patients discontinued treatment as a result of adverse events in 12 (23%) and 10 (38%) of patients in the treatment versus placebo arms respectively. Discontinuation of treatment due to adverse events was the result of treatment failure other than for one patient per treatment arm. Three (6%) of patients in the siltuximab arm had serious adverse events that were reasonably related to treatment. These events were lower respiratory tract infection, anaphylactic reaction, and sepsis. Two patients taking siltuximab, and four patients on placebo, died due to disease progression. The two patients (4%) in the siltuximab arm that died due to progression died while they were in the follow-up period after treatment had been discontinued.[88] No treatment related deaths were reported. [1]

e) Limitations/Sources of Bias

1. Durable tumour and symptomatic response is used as the primary endpoint in this study. However, as the study authors acknowledge, there are no standardized criteria to assess tumour or symptomatic response in MCD and the study used the Cheson criteria for this purpose. It is uncertain how this lack of standardized criteria could affect the generalizability and certainty of the results of the primary outcome.

2. While the study met its target sample size for the primary outcome, it is small and therefore there may be substantial uncertainty around other outcomes.

3. Difference in study population, baseline characteristics between arms may influence both efficacy and safety outcomes. The direction and magnitude of any potential bias this may introduce is unknown.

4. Differences in quality of life we measured on day of cycles 1 through 18. Study population was 33 by the last cycle (6 Best supportive care (BSC), 27 Siltuximab + BSC). Given the sample size at this point and the fact that statistical analysis was conducted with such a small sample, these results should be used with caution.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 4 - Primary & Secondary Efficacy Outcomes

Outcome	Siltuximab N=53	Placebo N=26	Unadjusted* p-value	Adjusted p-value
Durable tumour and symptomatic response (independent assessment) n(%)	18 (34.0%)	0 (0%)	*p*=0.0004	*p*=0.0012
Tumour Response (independent review) n(%)	20 (38.0%)	1 (4.0%)	*p*=0.001	*p*=0.0022
Tumour Response (investigator review) n(%)	27 (51.0%)	0 (0%)	*p*<0.0001	p<0.0001
Hemoglobin Response n(%)	19 (61%)	0 (0%)	P=0.0003	P=0.0002
Patients who discontinued corticosteroids n(%)**	4 (31%)	1 (11%)		P=0.3602
Survival Rate 1 yr (%) patients	100%	92%		

*Unadjusted p-value is likelihood of difference after patient population adjusted for baseline concomitant corticosteroid use
**Patients taking corticosteroid at baseline: Siltuximab=13, Placebo=9

Van Rhee, 2014[1]

Efficacy Outcomes

Durable tumour and symptomatic response (independent assessment)
Tumour response was assessed centrally by investigators and independent radiological review, masked to treatment failure (Biocor, Princeton, NJ, USA).) - note: includes both complete response and partial response categories. Eighteen patients had durable tumour and symptomatic response and all of these patients were in the Siltuximab arm resulting in a statistically significant difference in the primary outcome. One patient had complete response and 17 patients had partial response. Median response duration for these patients was 383 days. Similar results were seen in both adjusted and unadjusted analyses where adjustments were made by stratification factor. [1]

Tumour Response (complete & partial) -independent assessment
Tumour response was assessed by an independent review committee and was found to be achieved by 20 patients in the siltuximab group and one in the placebo group. Investigator results were also reported and showed 27 patients had a response in the siltuximab group and none in the placebo group. Of the patients achieving response in the independent review, 2 patients achieved complete response in siltuximab group while none achieved complete response in the placebo group. Eighteen patients achieved a partial response in the siltuximab group while one patient achieved partial response from the placebo group. Of patients achieving a response in the investigator review, 3 achieved a complete response and 24 achieved partial response, all from the siltuximab arm. [1]

Hemoglobin Response
Nineteen subjects versus no subjects, in the siltuximab versus placebo groups respectively, had a ≥15 g/L haemoglobin response. The ≥15 g/L haemoglobin response rate was 61.3% in the siltuximab group and 0% in the placebo group. Thirteen subjects in the siltuximab group and no subject in the placebo group had a ≥20 g/L haemoglobin response. The ≥20 g/L hemoglobin response rate was 42% in the siltuximab group and 0% in the placebo group (95% CI of the difference: 7.8-70.7; p=0.0195).[1]

Steroid dose reduction
Four (31%) and 1 (11%) patients discontinued corticosteroid use from the siltuximab and placebo arms respectively. Although the difference was not found to be statistically significant (p=0.3603) the number of patients in this subgroup was very small and comparative testing does not produce a valid result in this case. [1]

Overall survival (OS)
Overall survival as a time-to-event outcome was not reported, and both the FDA (REF) and EPAR (REF) documents indicated that overall survival data were not mature and/or not available. One-year survival was reported as 100% (95% CI 100–100) in the siltuximab group and 92% (95% CI 72–98) in the placebo group but no statistical analysis of these data were reported. [1]

Overall response, disease free survival (DFS), and relapse-free survival
These outcomes were not reported.

Time To Tumour Response

The median time to tumour response was 155 days, and the time to durable symptomatic response was 170 days suggesting a prolonged course of therapy for approximately 6 months may be necessary in order to achieve this primary endpoint. The optimal duration of therapy has not been defined, and patients with ongoing response remained on therapy indefinitely. [1]

Table 5. Harms Outcomes

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

Van Rhee, 2014[1]

Grade 3-4 adverse events (AE's)

Forty-seven percent and 54% of patients experienced an adverse event that was ≥ grade 3, in the siltuximab and placebo arms respectively. Fatigue was the most common AE occurring in 9% and 4% of patients in these arms respectively. Thirty percent of patients experienced weight loss as a baseline characteristic. [1] Weight gain is reported above as an adverse event. It should be noted that this event may be associated with improved nutrition and health and not an adverse event. Although many patients experienced weight loss following diagnosis, and

throughout treatment, 21 patients in the Siltuximab arm experienced weight gain versus none in the placebo arm.[1]

Withdrawal due to adverse events
Three (6%) of 53 patients had serious adverse events reasonably related to siltuximab (lower respiratory tract infection, anaphylactic reaction, sepsis). Two (4%) of 53 patients taking siltuximab died because of disease progression, and four (15%) of 26 patients taking placebo who did not crossover died (three as a result of disease progression and one because of bronchopneumonia and congestive cardiac failure).[1]

Treatment related deaths
No treatment related deaths were reported. [1]

Infusion reactions
Four (8%) of 53 patients reported siltuximab infusion reactions of low grade, except for one grade 3 anaphylactic reaction. [1]

Non-Hematologic Adverse Events
Non-hematologic adverse events in the siltuximab and placebo arms are reported in detail in Table 5. While statistical testing was not conducted, the categories of non-hematologic events with the greatest absolute difference in rates (siltuximab arm minus placebo arm) between the arms were maculopapular rash (22% abs. diff.), weight gain (21% abs. diff.), localised oedema (17% abs. diff.) and nasopharyngitis (11% abs. diff.), Non-hematologic adverse events were in general more common on the siltuximab arm compared to the placebo arm. Grade 3 or greater non-hematologic events were infrequent (less than 5%) in both arms, with the exception fatigue (9% in the siltuximab arm), night sweats (8% in the siltuximab arm) and anemia (12% in the placebo arm).[1]

Quality of life
The primary study report ref Van Rhee did not report on QoL. The data in the following paragraph is from a publication from outside the search dates noted above in section 6.3.1. An additional publication reporting QOL results from the Van Rhee/Siltuximab randomized trial was identified.

Quality of life was evaluated using the Multicentric Castleman's Disease Symptom Scale (MCD–SS), the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) scale, and the Short Form (SF)-36 at predetermined time points throughout the treatment period. Analyses were conducted on intention to treat population and there was no indication that patients that did cross-over to the treatment arm were included. The MCD–SS and FACIT–Fatigue instruments were assessed at Days 1, 8, and 15 of treatment Cycle 1, and on Day 1 of each subsequent cycle. SF-36 was assessed on Cycle 1 Day 1, Cycle 3 Day 1, and Day 1 of every three subsequent cycles. [3] Pre-specified analyses of repeated measures were conducted comparing the areas under the curve (AUC), adjusted for baseline, for each PRO measure over the first 18 cycles of treatment.

Results were compared at baseline and over time between the treatment arms and PRO instruments. Siltuximab-treated subjects showed early and durable improvements in symptoms compared with subjects in the placebo arm on both the MCD–SS (p=0.02) and FACIT–Fatigue scale (p=0.0364) when analyzed using a mixed-effects repeated measures model (Figure 2a and b Van Rhee 2015).[3] Fatigue was widely experienced on both arms, but a larger proportion (35% vs. 11%, p=0.0475) of patients on the siltuximab arm experienced an improved score (>=44) on the FACIT-Fatigue scale for 120 days or more. Overall improvements were seen through time in patients with fatigue and there was a higher proportion of patients with more severe (≥grade 3) fatigue in the siltuximab arm versus placebo (9% vs. 4%).[3] Using the concept that 0.5 SD (1

standard error of measurement) in baseline score change in quality of life scale creates a minimal important difference[7], this translates into a change of 3 or more whole units when applied to the FACIT-fatigue scale. Given this result, there was a clinically meaningful change in quality of life in the Siltuximab treatment arm. The Van Rhee study reported increase of 6.6 (32 – 38.6) between cycles 1 and 18 in the FACIT-fatigue scale for the siltuximab arm. Additionally a clinically significant decrease of 4.2 (31.1-26.9) was reported for patients in the placebo arm.

Statistically significant improvements were also seen in role physical, role emotional, vitality, bodily pain, and mental health SF-36 domains in siltuximab treated patients. In the SF-36 QOL analysis[3], mental component summary (MCS) and physical component summary (PCS) scores were reported. Forty eight percent and 31% of patients experienced a ≥5 point improvement in PCS score in the siltuximab versus placebo arms respectively. It was also reported that a ≥5 point improvement was seen in the SF-36 MCS score among 34 (68 %) vs. 9 (35%) of patients in the siltuximab group vs. placebo group, respectively. Based on the concept that 0.5 SD (1 standard error of measurement) in baseline score change in quality of life scale creates a minimal important difference[6], this result of ≥5 is slightly below what is required for clinically important improvement given a PCS mean (SD) of 41.6 (11.1) and MCS mean of 43.3 (12.3). From this perspective it is not clear as to what proportion of patients achieving a clinically important change in the SF-36 score as this would require reporting of patients with changes greater than 5.5 points for PCS and 6.1 points for MCS. It does provide an estimate of the effect.

A poster presentation that was submitted as one of the submission documents evaluated the development (validity and reliability) of the MCD-SS. This document does not meet the inclusion criteria for the review, and the data it provides appears to be superseded by that found in Van Rhee 2015 described above. Information described in this poster presentation is described above in section 2.1.4.

6.4 Ongoing Trials

No additional trials out of fifteen were identified through a search on U.S. National Institutes of Health ClinicalTrials.gov or on Ontario Institute for Cancer Research Ontario Cancer Trials (OCRN).

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on siltuximab (Sylvant) for Multicentric Castleman's disease. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Leukemia Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. multicentric castleman's.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. (siltuximab or sylvant).ti,ab,rn,nm,sh,hw,ot. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. *siltuximab/
4. or/2-3
5. 1 and 4
6. exp animals/
7. exp animal experimentation/
8. exp models animal/
9. exp animal experiment/
10. nonhuman/
11. exp vertebrate/
12. or/6-11
13. exp humans/
14. exp human experiment/
15. or/13-14
16. 12 not 15
17. 5 not 16
18. (randomized controlled trial or controlled clinical trial).pt.
19. randomized controlled trial/
20. randomized controlled trials as topic/
21. controlled clinical trial/
22. controlled clinical trials as topic/
23. randomization/
24. random allocation/
25. double-blind method/
26. double-blind procedure/
27. double-blind studies/
28. single-blind method/
29. single-blind procedure/
30. single-blind studies/
31. placebos/
32. placebo/
33. control groups/
34. control group/
35. (random: or sham or placebo:).ti,ab,hw.
36. ((singl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
37. ((tripl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
38. (control: adj3 (study or studies or trial:)).ti,ab.
39. (nonrandom: or non random: or non-random: or quasi-random: or quasirandom:).ti,ab,hw.
40. allocated.ti,ab,hw.
41. ((open label or open-label) adj5 (study or studies or trial:)).ti,ab,hw.
42. or/18-41
43. 17 and 42
44. remove duplicates from 43
45. limit 44 to english language

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