

# pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada’s provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

### pERC Final Recommendation

Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

<b>Drug:</b> Siltuximab (Sylvant)	
<b>Submitted Funding Request:</b> 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	
<b>Submitted By:</b> Janssen Inc.	<b>Manufactured By:</b> Janssen Inc.
<b>NOC Date:</b> December 3, 2014	<b>Submission Date:</b> January 30, 2015
<b>Initial Recommendation:</b> June 4, 2015	<b>Final Recommendation:</b> June 22, 2015

### pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding siltuximab (Sylvant) conditional on the cost effectiveness being improved to an acceptable level. Funding should be for previously treated or untreated patients with multicentric Castleman’s disease (MCD) who are human immunodeficiency virus (HIV) negative, human herpes virus-8 (HHV-8) negative and who have an ECOG performance status  $\leq 2$ . Treatment should be continued until treatment failure. The Committee made this recommendation because it was satisfied that there is a net clinical benefit for siltuximab based on clinically meaningful improvements in quality of life, which were important outcomes to patients, and because there are very limited treatment options for this group of patients. Siltuximab also had a manageable toxicity profile and aligns with patient values. However, the Committee noted that siltuximab could not be considered cost-effective at the submitted price and the Economic Guidance Panel’s range of estimated incremental cost-effectiveness ratios.

**POTENTIAL NEXT STEPS  
FOR STAKEHOLDERS**

**Pricing Arrangements to Improve Cost-effectiveness**

Given that pERC was satisfied that there is a net clinical benefit of siltuximab in patients with MCD who are HIV negative and HHV-8 - negative, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of siltuximab to an acceptable level.

**Managing Monthly Drug Costs to Improve Cost-Effectiveness**

In addition to the above, and given the high incremental cost of siltuximab, jurisdictions may want to consider implementing measures to manage the monthly cost of siltuximab, which could improve cost-effectiveness to an acceptable level. These measures could include ongoing monitoring for response since treatment duration may be indefinite if patients continue to respond.

**Implementation of Siltuximab and Testing for HIV and HHV-8 status**

Because use of siltuximab requires patients to have the HHV-8 and HIV negative subtype of MCD, diagnostic testing for patients HHV-8 and HIV status will need to be implemented concurrent with funding for siltuximab.

## SUMMARY OF pERC DELIBERATIONS

pERC noted that multicentric Castleman’s disease (MCD) is a rare and heterogeneous lymphoproliferative disorder. The prevalence is estimated to be less than 90 cases in Canada, with the HIV and HHV-8 negative subtype of MCD making up an even smaller proportion of this number. Patients with MCD are often symptomatic with fevers, fatigue, night sweats and weight loss. In particular, patients experience debilitating fatigue as a result of their disease. Survival for patients with MCD is about 45% at 3-years. While a variety of treatment options have been tried in patients, such as steroid therapy for symptom control and multi-agent chemotherapies, relapses are common and the evidence for efficacy of currently used therapies is limited to case reports. pERC, therefore, agreed that in this rare and highly symptomatic disease with no established standard of care, there is a need for effective treatments that provide both disease and symptom control.

[pERC’s Deliberative Framework](#) for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

One randomized, double-blind, placebo-controlled trial was included in the pCODR systematic review, MCD 2001 (Van Rhee 2014). This study assessed the safety and efficacy of siltuximab plus best supportive care (BSC) (n=53) compared to placebo plus BSC (n=26). pERC deliberated upon the results of this study and concluded that there is a net clinical benefit from treatment with siltuximab. pERC’s reached this conclusion of net clinical benefit based on the statistically significant and clinically meaningful improvements in fatigue favouring siltuximab. This was measured through the FACIT-Fatigue scale, one of three quality of life (QoL) measures employed in the study. pERC acknowledged that fatigue is a debilitating symptom of MCD and agreed that improvements in this symptom represented a clinically meaningful outcome for patients. Additionally, statistically significant improvements in quality of life were also observed in the SF-36 and a newly developed QoL measure, the multicentric Castleman’s disease symptom scale (MCD-SS). pERC further agreed that these improvements in quality of life provide supportive evidence that siltuximab had biological activity in patients with MCD. Therefore, pERC concluded that siltuximab was effective based on improvements in fatigue and quality of life.

In deliberating on the results of the MCD 2001 study, pERC also discussed the statistically significant improvement in the primary outcome, a composite of durable tumour and symptomatic response. While agreeing that this outcome provided evidence for biological activity, pERC was unable to determine the clinical meaningfulness of this outcome, that has not been validated. pERC also discussed overall survival, a secondary outcome in the study, noting that the trial was not designed to detect a survival difference and there were no OS differences between treatment arms at one year. The survival analyses were likely confounded by the cross-over of patients from the placebo group to the siltuximab arm upon treatment failure. In discussing these factors, pERC acknowledged the potential difficulty in conducting a randomized controlled trial and validating outcome measures in a disease with a very low prevalence. pERC did acknowledge the significant effort demonstrated to collect relevant data within the trial, particularly the development of a primary outcome measure designed to capture sustained response in a disease where the disease symptoms may wax and wane as part of the natural disease process. pERC also commended the investigators in their efforts to collect QoL data using both validated scales and the development of a quality of life measure specific to the disease.

pERC discussed the safety profile of siltuximab. It was noted that the proportion of patients experiencing adverse events was similar between the two arms. pERC also noted that the adverse events described by patients who had direct experience with siltuximab, as reported in patient advocacy group input, aligned with those reported in the MCD study. In addition, these patients considered the side effects of siltuximab to be manageable with supportive therapy. Overall, pERC agreed that the toxicity profile of siltuximab was manageable.

pERC reviewed input from one patient advocacy group and was impressed by both the methodology used to collect information on patient experiences with this rare condition and the number of patients identified who had experience with siltuximab, despite the low prevalence of the disease. pERC found the descriptions of patients’ experiences with siltuximab and quality of the input to be very useful in determining whether siltuximab aligned with patient values. Patients providing input indicated that there

are few treatments available for them and that there is a need for effective therapies. pERC also noted that patients having experience with siltuximab had improvements in quality of life symptoms such as fatigue, and that these improvements enabled them to return to normal activities. This input was concordant with the results of the MCD 2001 study which demonstrated statistically significant and clinically meaningful improvements in fatigue for patients treated with siltuximab. These quality of life benefits stemming from reduced fatigue related to treatment were highly valued by patients. These patients also noted that the side effects experienced with siltuximab were tolerable, when considering the benefits of symptom control and improved quality of life. Therefore, pERC concluded that siltuximab aligned with patient values.

pERC deliberated on the cost-effectiveness of siltuximab and agreed that siltuximab is not cost-effective at the submitted price, based on the Economic Guidance Panel's reanalysis estimates. In discussing the cost-effectiveness estimates, pERC noted that despite the important improvements in symptom control and quality of life that were observed in the MCD 2001 study and described in patient advocacy group input, the incremental cost-effectiveness ratio was quite sensitive to the estimates of long term survival benefit. In light of the short trial follow up of one year and the lack of demonstration of a survival benefit within this timeframe, pERC agreed there was considerable uncertainty in the estimates of long term survival benefit with siltuximab. pERC agreed with the restriction of quality of life benefit to the trial period and the reduction of the economic model's time horizon to 20 years (from 30 years). Both were considered by the CGP to be more clinically plausible scenarios compared to the submitter's assumptions. Further to this, pERC acknowledged that there may be differences in opinion as to the approach used to minimize uncertainties in the long term survival benefit with siltuximab. The Committee however agreed that real world or long term survival data would be needed to reduce this uncertainty and accepted the EGP's approach. Additionally, pERC discussed that there was uncertainty in the estimates of incremental cost due to the indefinite duration of treatment for patients who continue to respond to siltuximab. Therefore, pERC agreed that there was considerable uncertainty in the cost-effectiveness estimates provided for siltuximab which contributed to the EGP's wide range of incremental cost-effectiveness estimates.

pERC also considered factors affecting the feasibility of implementing a positive funding recommendation for siltuximab. The Committee noted that MCD is a very uncommon condition; therefore, the burden of illness is likely small from a population perspective. pERC also noted that to enhance feasibility and manage the costs associated with siltuximab use in actual practice, provinces may need to consider factors such as reduction in the cost of the drug to minimize budget impact, drug wastage (since dosing is weight based and there are few patients) and the unknown duration of therapy.

## EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from two patient advocacy groups (Canadian Organization for Rare Disorders [CORD])
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (Janssen Inc.)

The pERC initial recommendation was to fund siltuximab (Sylvant) conditional on the cost effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the manufacturer agreed in part and pCODR's Provincial Advisory Group agreed with the initial recommendation. The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

## OVERALL CLINICAL BENEFIT

### pCODR review scope

The purpose of the review was 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.

### Studies included: One randomized controlled trial, early treatment switching allowed

The pCODR systematic review included one randomized, double-blind, placebo-controlled trial which assessed the safety and efficacy of siltuximab plus best supportive care (BSC) (n=53) compared to placebo plus BSC (n=26) (Van Rhee 2015). Siltuximab, or matched placebo, was administered at a dose of 11 mg/kg by 1 hour intravenous infusion, every 3 weeks until treatment failure. At first treatment failure, patients assigned to placebo could be switched over to receive open-label siltuximab plus BSC. Thirteen (50%) patients assigned to placebo received open-label siltuximab after treatment failure.

Patients were treated until treatment failure which was defined as a sustained increase in grade  $\geq 2$  disease-related symptoms persisting  $\geq 3$  weeks; new disease-related grade  $\geq 3$  symptoms; sustained  $>1$  point increase in ECOG-PS persisting for  $\geq 3$  weeks; radiological progression by modified Cheson criteria or initiation of another treatment for Multicentric Castleman's disease. pERC therefore acknowledged a substantial uncertainty regarding duration of treatment as patients are treated until treatment failure. All patients were included in the final analysis and patients that discontinued were followed up until the primary analysis.

### Patient populations: Most with symptomatic disease, imbalance between treatment arms

The Van Rhee et al study enrolled 79 eligible patients that were HIV negative and HHV-8 negative MCD and randomized them 2:1 to the siltuximab or placebo arm, respectively. Baseline characteristics were unbalanced between the two arms with notable differences in gender and ECOG performance status (PS). Among these 57% of patients were male in the siltuximab versus 85% in the placebo arm. As well, ECOG PS levels differed slightly between the two groups with a higher proportion of patients with ECOG PS 1 in the placebo arm compared to the siltuximab arm (62% versus 45%, respectively) while a higher number of patients with ECOG PS 2 were in the siltuximab arm versus the placebo arm (13% vs. 0%, respectively). Differences were also noted between treatment arms for interleukin-6 concentration, c-reactive protein concentration and erythrocyte sedimentation rate. pERC noted the differences in baseline characteristics of patients and was unable to determine the potential impact of these factors on the results. All patients had symptomatic disease, with 62 patients (78%) having more than three symptoms including fatigue,

malaise, night sweats and peripheral neuropathy. In addition, most patients reported having received previous systemic treatments.

### **Key efficacy results: Significant improvement in composite endpoint of tumour and symptom response**

The primary outcome of the Van Rhee study was a composite endpoint of durable tumour and symptomatic response. The results for this endpoint showed a statistically significant improvement in the siltuximab arm compared to the placebo (34% vs. 0%, respectively  $p=0.0012$ ). pERC discussed the significance of this newly developed outcome measure and agreed that there is clear biological activity of siltuximab in patients. pERC was, however, unable to determine how clinically meaningful the results were as this endpoint has not been validated. Further to this, pERC discussed the feasibility of conducting multiple trials in this rare disease setting to allow for validation of outcome measures specific to this disease, and concluded that this would be difficult to complete. pERC agreed that the measures undertaken by the investigators in designing a randomized controlled trial and developing a primary outcome specific to the disease was commendable in the setting of a very rare disease.

Overall survival was also measured as a secondary endpoint with survival rates remaining similar between arms at one year (100% vs. 92% in the siltuximab and placebo arms, respectively). pERC noted that the study was not designed to detect differences in overall survival. Early treatment switching of half of the patients in the placebo arm to siltuximab arm is also expected to confound the results. pERC therefore agreed that there is considerable uncertainty as to whether siltuximab offers a survival benefit compared to placebo.

### **Quality of life: Statistically significant and clinically meaningful improvement in fatigue**

pERC discussed the measurement and reporting of quality of life in the MCD 2001 (Van Rhee) study. Quality of life was evaluated at pre-determined time points throughout the treatment period using three different scales. These included the functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue) scale and the short form (SF)-36. Both of these scales were also used to determine convergent validity with a newly developed quality of life measure in patients with MCD, the Multicentric Castleman's Disease Symptom Scale (MCD-SS),

pERC noted that a larger proportion of patients in the siltuximab arm (35% vs. 11%,  $p=0.0475$ ) experienced an improved score ( $\geq 44$ ) on the FACIT-Fatigue scale for 120 days or more. Overall improvements were seen over time in patients with fatigue. Patients in the siltuximab arm showed early and durable improvements in symptoms as measured by the FACIT-Fatigue scale compared with patients on the placebo arm ( $p=0.0364$ ) when analyzed using a mixed-effects repeated measures model. The MCD 2001 study reported an increase in score of 6.6 (32 – 38.6) between cycles 1 and 18 in the FACIT-fatigue scale for the siltuximab arm. Given that a change in the score of 3 or more is considered clinically meaningful, pERC agreed that siltuximab demonstrated a meaningful improvement in quality of life. Additionally, a clinically significant decrease in the score of 4.2 (31.1-26.9) was reported for patients in the placebo arm.

pERC also discussed statistically significant improvements in the MCD-SS and in the SF-36 scales for siltuximab treated patients. Clinically meaningful differences were, however, not observed in these two scales, as the changes observed in the SF-36 composite scales were slightly below what is generally considered a clinically important improvement. pERC discussed this and agreed that these results further supported the Committee's conclusion that siltuximab has biological activity and results in a clinically meaningful improvement in the FACIT-Fatigue scale.

### **Safety: manageable toxicity profile**

pERC discussed the toxicity profile of siltuximab and noted that the proportion of patients experiencing adverse events was approximately the same between the two arms. Deaths occurred in both arms with 2 (4%) vs. 4 (15%) occurring in the siltuximab vs. placebo arms, respectively. Deaths in the siltuximab arm occurred due to disease progression; those in the placebo arm were due to disease progression ( $n=3$ ) or bronchopneumonia and congestive cardiac failure ( $n=1$ ). No treatment-related deaths were reported. A higher incidence of pruritus and upper respiratory tract infections was observed in the siltuximab arm compared to the placebo arm. Serious adverse events that are reasonably related to siltuximab occurred in 3/53 (6%) of patients and included lower respiratory tract infection, anaphylactic reaction and sepsis. Grade  $\geq 3$  non-hematologic events were infrequent (less than 5%) in both arms, with the exception of

fatigue (9% vs. 4%), night sweats (8% vs. 4%) and anemia (2 vs. 12%) in the siltuximab vs. placebo arms, respectively. Moreover, other adverse events such as edema, rash, weight gain and sweats were more common in the treatment group. pERC also noted that the adverse events described by patients who had direct experience with siltuximab, as reported in patient advocacy group input, aligned with those reported in the MCD 2001 study. In addition, these patients considered the side effects of siltuximab to be manageable with supportive therapy. Overall, pERC agreed that the toxicity profile of siltuximab is manageable.

### **Need: Symptomatic and rare disease with no treatment options**

pERC noted that MCD is a heterogeneous lymphoproliferative disorder with very low prevalence. It is estimated that there is a prevalence of less than 90 cases of MCD in Canada with estimates for the HIV and HHV-8 negative subtype expected to be even fewer. These patients are often symptomatic with fevers, fatigue, night sweats and weight loss. Survival of patients with MCD is 45% at 3-years. pERC agreed that there is currently no clear standard of care for HIV negative, HHV-8 negative MCD. pERC noted limitations in the available evidence for treatment options due to the heterogeneity of this disorder, as well as its low prevalence. Consequently, trials have been limited to case reports or small case series until the recent publication of MCD 2001. 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. However, long-term therapy with prednisone is often required, as tapering of the steroids results in disease progression. Rituximab has also been used; however, data are limited in HIV negative MCD, with only 7 patients reported in the literature. Multi-agent lymphoma-based chemotherapy regimens have been tried in a small number of patients. Relapses are common and median survival for 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 evaluation. Additionally, no consistent outcome measures have been uniformly applied to this population, confounding the interpretation of data. Therefore, pERC agreed that there is a need for more effective treatment options in this patient population.

## **PATIENT-BASED VALUES**

### **Values of patients with multicentric Castleman's disease: Quality of life impact**

pERC considered patient advocacy group input highlighting that patients with MCD experience a number of devastating impacts on their lives. Specifically, patients are unable to work, go to school, or to participate in any regular activities when the disease is most active. As a result of debilitating symptoms (e.g., fatigue, lack of appetite, GI issues, and pain), patients are often reliant on caregivers for care as well as emotional support. Patients with MCD are also often misdiagnosed and may initially receive the wrong therapies as a result. Patients and caregivers reported living in continuous anxiety and worrying about future circumstances, and felt unable to make plans for the future.

pERC also considered the impact of MCD on caregivers, noting that caregivers experience an overwhelming feeling of helplessness as there are almost no effective treatment options and current treatments provide, at best, only temporary remission of symptoms. Due to the unknown trajectory of the disease, it is difficult for families to make plans or provide assurance to their loved ones. 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.

### **Patient values on treatment: Effective treatment, symptom control, willing to tolerate side effects**

pERC was impressed by both the methodology used to collect information on patient experiences and the number of patients identified who had experience with siltuximab, particularly in a disease with a very low prevalence. pERC found descriptions of patients' experiences with siltuximab and the quality of the input to be very useful in determining if siltuximab aligned with patient values. pERC discussed patient advocacy group input indicating that there are limited treatments for patients with MCD. pERC noted that patients understand siltuximab is not a cure and that not every patient enrolled in the clinical trial experienced success with the treatment. Patients anticipate that siltuximab will result in time that is free of tumour growth, improved energy levels, and a return to "near normal" life. pERC noted that patients described the burden of receiving injections on a regular basis but acknowledged that this would be an acceptable trade-off if the therapy manages to keep their tumour growth in check and relieves the other symptoms that prevents them from leading normal lives. pERC discussed this input and considered

that the results of the MCD 2001 study demonstrating a clinically meaningful improvement in fatigue and statistically significant improvement in other quality of life measures aligned with patient values.

pERC noted that no Canadian patients had been identified who had experience with siltuximab. Of the nine patients who had direct experience with siltuximab, about half of the respondents reported that they experienced benefits after the first injection. At the same time, almost all of the 9 patients with experience using siltuximab 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 patients reported they could manage the adverse events with other supportive therapy. Overall pERC agreed that siltuximab aligned with patient values.

## ECONOMIC EVALUATION

### **Economic model submitted: Cost-effectiveness and cost-utility analysis**

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and a cost-utility analysis that compared siltuximab plus best supportive care (BSC) to placebo plus BSC for patients with multicentric Castleman's disease (MCD) who are HIV negative and Human Herpes Virus-8 (HHV-8) negative.

### **Basis of the economic model: Clinical and economic inputs**

Costs considered in the analysis included administration costs, treatment costs, routine follow-up costs and the costs associated with adverse events.

The clinical effect considered in the analysis was based on extrapolations of survival after the duration of the MCD2001 study and on estimates of quality of life originating from the MCD2001 study. pERC noted that the submitted study is based on short term (1 year) survival data originating from the MCD2001 and MCD2002 studies which were not adequately powered to observe differences in survival. Long term survival effects used in the economic model also originated from a review of case studies. While pERC acknowledged the rarity of the disease and associated difficulty in understanding the long term effects of treatment, the committee agreed with the Clinical Guidance Panel (CGP) and the EGP that there is considerable uncertainty in the data sources used to estimate long term survival with siltuximab.

### **Drug costs: wastage, unknown treatment duration**

Siltuximab costs \$697.70 and \$2,790.80 per 100mg and 400mg vial respectively. At the recommended dose of 11 mg/kg IV and assuming a mean weight of 70kg, siltuximab costs \$255.82 per day and \$7,163.05 per 28 day cycle. At the recommended dose and taking wastage into consideration, siltuximab costs \$265.79 per day and \$7444.13 per 28-day cycle.

pERC noted that optimal duration of therapy was not defined in the study and patients with ongoing response remained on therapy indefinitely. pERC agreed this created uncertainty in the duration of therapy and is likely to have an impact on the cost-effectiveness of siltuximab. pERC also noted that drug wastage is a concern since the dosing is weight based. Due to the rarity of the disease, vial sharing will not be possible in most instances, as such, drug remaining in partially used vials would be discarded.

### **Cost-effectiveness estimates: uncertainty in OS and QoL benefit beyond trial period**

pERC deliberated on the cost-effectiveness of siltuximab compared with placebo in patients with MCD. pERC reviewed the incremental cost-effectiveness ratio estimates provided by both the manufacturer and the EGP and agreed with the EGP's estimates. pERC noted that the EGP estimates were considerably higher than those provided by the manufacturer noting where the biggest impact involved the assumptions for long term survival. pERC discussed the EGP's concern regarding data extrapolation for overall survival benefit beyond the end of the trial period. They agreed that, given the relatively short one year follow up period for the clinical trial (which demonstrated no difference in survival between the two arms) the EGP's approach to limit the added benefit of siltuximab to QoL improvements seen in the study and the removal of OS survival advantage was appropriate. pERC agreed that in the absence of long term survival data, the cost effectiveness estimates of siltuximab is uncertain and likely near the upper bound of the EGP's estimates. In considering this, pERC agreed that the price of siltuximab is a major driver in the economic model and a substantial reduction in the drug cost would be needed to offset the uncertainty in the incremental cost-effectiveness estimates. pERC also noted the EGP reduced the economic model's time horizon to 20 years and adjusted for assumptions regarding quality of life benefit that is independent of tumour response. This effect was further assumed to extend beyond the trial period. Based on the pivotal study, pERC agreed that quality of life benefit is likely correlated with tumor



response and agreed with the EGP's approach of removing the QoL benefit that extends beyond the trial period. pERC noted that these changes in the estimates of incremental effect had a large impact on the ICER estimates. Therefore, pERC concluded that siltuximab could not be considered cost-effective based on the submitted or the EGP's re-analysis estimates.

## ADOPTION FEASIBILITY

### **Considerations for implementation and budget impact: wastage, high drug cost, duration of treatment**

pERC discussed the feasibility of implementing a funding recommendation for siltuximab and noted that MCD is an uncommon condition; therefore, the burden of illness is likely small from a population perspective. pERC also agreed that siltuximab is a new treatment option that would fill a therapeutic gap for this specific subgroup of patients with MCD. Treatment would however, be limited to the HIV negative and HHV-8 negative subtype of MCD. pERC noted that patients in the study were treated until treatment failure and acknowledged a substantial uncertainty regarding duration of treatment. pERC noted that the above mentioned factors and market assumptions had the greatest impact on the submitter's budget impact analysis. pERC noted additional health care resource costs that will be needed to implement this recommendation, including a long drug preparation time, management of toxicities and chemotherapy chair time. pERC also agreed that jurisdictions will need to determine whether HIV and HHV-8 testing is widely available and consider making these available concurrently with the implementation of siltuximab. Lastly, pERC agreed that the high drug cost and potential for wastage of siltuximab will need to be considered by jurisdictions as vial sharing is not practical in a disease with a very low prevalence.

## DRUG AND CONDITION INFORMATION

### Drug Information

- Chimeric immunoglobulin G1k monoclonal antibody against human interleukin-6
- 100 mg or 400 mg single-use vial reviewed by pCODR
- Recommended dosage of 11 mg/kg, administered as a constant-rate intravenous infusion over 1 hour every 3 weeks

### Cancer Treated

- Multicentric Castleman's Disease (MCD) for patients who are human immunodeficiency virus HIV and HHV-8 negative

### Burden of Illness

- Rare lymphoproliferative disorder
- The prevalence is estimated to be less than 90 cases in Canada with the prevalence of the HIV and HHV-8 negative subtype being a small proportion of this number
- Patients present with adenopathy and are symptomatic with fevers, night sweats, fatigue and weight loss. Survival is generally 45% at 3 years.

### Current Standard Treatment

- High dose steroid therapy, monoclonal antibody therapy and multi-agent chemotherapy have been previously used for treatment based on case reports and small case series
- Best supportive care

### Limitations of Current Therapy

- Due to its rarity, there is currently no clear standard of care for HIV and HHV-8-negative MCD

## ABOUT THIS RECOMMENDATION

### The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)  
 Dr. Maureen Trudeau, Oncologist (Vice-Chair)  
 Dr. Scott Berry, Oncologist  
 Bryson Brown, Patient Member  
 Dr. Matthew Cheung, Oncologist  
 Mario de Lemos, Pharmacist  
 Dr. Sunil Desai, Oncologist  
 Mike Doyle, Economist

Dr. Bill Evans, Oncologist  
 Dr. Allan Grill, Family Physician  
 Dr. Paul Hoskins, Oncologist  
 Danica Wasney, Pharmacist  
 Carole McMahon, Patient Member Alternate  
 Jo Nanson, Patient Member  
 Dr. Tallal Younis, Oncologist  
 Dr. Kelvin Chan, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Drs. Scott Berry and Allan Grill who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

#### **Avoidance of conflicts of interest**

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of Siltuximab (Sylvant) for MCD, through their declarations, no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and no one was excluded from voting.

#### **Information sources used**

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

#### **Consulting publicly disclosed information**

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

#### **Use of this recommendation**

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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