NHS England Evidence Review:

Siltuximab for Idiopathic Multicentric Castleman Disease

NHS England URN: 2124

NHS England Evidence Review

Siltuximab for Idiopathic Multicentric Castleman Disease

Drafted: July 2022

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care for the treatment of patients with a diagnosis of idiopathic multicentric Castleman disease (iMCD).

Idiopathic MCD is a rare disorder of uncontrolled growth of cells in lymph nodes. Idiopathic MCD has no known cause.

Siltuximab is a monoclonal antibody that blocks the action of a chemical called interleukin-6. It is given by intravenous infusion over one hour once every three weeks with therapy continuing until treatment failure. Siltuximab received European Marketing Authorisation for the treatment of iMCD in 2014 and is currently the only licensed therapy for iMCD.

Best supportive care includes the management of effusions, use of antipyretic, antipruritic, antihistamine, and analgesic pain drugs, management of infections, transfusions, and standard management of infusion related reactions. There is no agreed current standard of care for the treatment of iMCD in the UK. Standard care might include corticosteroids, rituximab, chemotherapy, rituximab and chemotherapy or thalidomide. There may be prior or concomitant use of corticosteroids.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from siltuximab more than others, the criteria used by the included studies to define iMCD and the dosage (size/ frequency/ duration) of siltuximab used.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care for the treatment of patients with a diagnosis of idiopathic multicentric Castleman disease (iMCD). The searches for evidence published since January 2012 were conducted on 27th May 2022 and identified 201 potential references. These were screened using their titles and abstracts and 19 full text papers potentially relating to the use of siltuximab for iMCD were obtained and assessed for relevance.

Two studies (published in four papers) were identified for inclusion, one randomised controlled trial (RCT) and one retrospective cohort study. The RCT (multi-centre (38 centres, 19 countries) compared siltuximab plus best supportive care (n=53) to placebo plus best supportive care (n=26) in adults with iMCD with median (range) follow-up of 422 days (5 to 1,051). The main RCT results were published in van Rhee et al (2014) with patient reported measures reported in van Rhee et al (2015). Another paper, (van Rhee et al 2021) focused on subgroup analysis of the RCT results. The retrospective cohort study used data from one US centre and an international database and compared siltuximab (n=21) to rituximab (n=25) and to chemotherapy or corticosteroids[1] (n=19) in patients[2] with iMCD (Yu et al 2017). Median follow-up was not reported.

No studies were identified comparing siltuximab and thalidomide.

In terms of clinical effectiveness:

- **Overall response (critical outcome).**
  - *For siltuximab plus best supportive care (BSC) vs placebo plus BSC:* One RCT provided moderate certainty evidence that a statistically significantly higher proportion of patients had an overall response with siltuximab[3] (51% vs 0%) at a median of approximately 14 months follow-up.
  - *For siltuximab vs rituximab:* One retrospective cohort study provided very low certainty evidence that a higher proportion of patients had an overall response with siltuximab[4] (76% vs 68%). The follow-up timeframe was not clear and the treatments were not statistically compared.
  - *For siltuximab vs chemotherapy or corticosteroids:* One retrospective cohort study provided very low certainty evidence that a statistically significantly higher proportion of patients had an overall response with siltuximab[5] (76% vs 63%). The follow-up timeframe was not clear.

- **Durability of response (critical outcome).**
  - *For siltuximab plus BSC vs placebo plus BSC:* One RCT provided high to moderate certainty evidence that a statistically significantly higher proportion of patients had

[1] Comparator of 'chemotherapy or corticosteroids' as described by the study authors. This included cyclophosphamide, hydroxyldoxorubicin, hydrochloride, vincristine and prednisone. The authors stated that the dose, order and regimen of drugs given was not uniform across patients
[2] This study included 43 iMCD patients. It is unclear if all the patients were adults. More than 50% of patients received ≥2 treatment agents. The number of patients receiving each treatment is taken from the results table which includes outcomes for 65 cases of treatment for the 43 patients
[3] Of the 27 siltuximab responders, three had a complete response and 24 a partial response
[4] Of the 16 siltuximab responders, nine had a complete response and seven a partial response. Of the 17 rituximab responders, five had a complete response and 12 a partial response
[5] Of the 16 siltuximab responders, nine had a complete response and seven a partial response. Of the 12 chemotherapy or corticosteroids responders, two had a complete response and ten a partial response.

durable tumour and symptomatic responses with siltuximab at a median of approximately 14 months follow-up. Differences between groups ranged from 25% to 34% for the different ways this outcome was reported in the RCT[6]. The same RCT also provided high to moderate certainty evidence that time to treatment failure and time to next treatment were statistically significantly longer with siltuximab.
  - *For siltuximab vs rituximab:* One retrospective cohort study provided very low certainty evidence of no statistically significant difference in the proportion of patients with progression free survival[7] between the two treatments. The follow-up timeframe was not clear.
  - *For siltuximab vs chemotherapy or corticosteroids:* One retrospective cohort study provided very low certainty evidence of no statistically significant difference in the proportion of patients with progression free survival[77] between the two treatments. The follow-up timeframe was not clear.

- **Survival (critical outcome).**
  - *For siltuximab plus BSC vs placebo plus BSC:* One RCT provided moderate certainty evidence of higher overall survival at one year with siltuximab (100% vs 92%). The groups were not statistically compared.
  - No evidence relating to survival was identified for siltuximab compared to rituximab, compared to chemotherapy or compared to corticosteroids.

- **Quality of life (important outcome).**
  - *For siltuximab plus BSC vs placebo plus BSC:* One RCT provided moderate to high certainty evidence that a higher proportion of siltuximab patients reported an improvement in quality of life at a median of approximately 12 months. This difference was statistically significant for the mental component of the quality of life measure used (68% vs 35%), but the difference for the physical component (48% vs 31%) was not statistically compared.
  - No evidence relating to quality of life was identified for siltuximab compared to rituximab, compared to chemotherapy or compared to corticosteroids.

- **Symptom alleviation (important outcome).**
  - *For siltuximab plus BSC vs placebo plus BSC:* One RCT provided high certainty evidence of statistically significantly higher improvements with siltuximab on two measures of fatigue at up to approximately 12 months. A statistically significantly higher proportion of siltuximab patients had a fatigue score that improved to above the population mean threshold with durability for more than 120 days (35% vs 11%). The same RCT also reported an improvement of at least one point (considered a meaningful change by the study authors) in MCD-Symptom Scale for 63% of siltuximab patients and 50% of placebo patients during the blinded treatment period (375 and 152 days respectively). The groups were not statistically compared.
  - No evidence relating to symptom alleviation was identified for siltuximab compared to rituximab, compared to chemotherapy or compared to corticosteroids.

- **Tumour response (important outcome).**
  - *For siltuximab plus BSC vs placebo plus BSC:* One RCT provided high certainty evidence that a statistically significantly higher proportion of patients had a tumour response with siltuximab (38% vs 4%) at a median of approximately 14 months follow-up.

[6] Durable tumour and symptomatic response, durable symptomatic response and durable complete symptomatic response
[7] Progression free survival percentage was only reported graphically in the retrospective cohort study

- No evidence relating to tumour response was identified for siltuximab compared to rituximab, compared to chemotherapy or compared to corticosteroids.

- **Haematological markers (important outcome).**
  - *For siltuximab plus BSC vs placebo plus BSC:* One RCT provided moderate certainty evidence that a statistically significantly higher proportion of patients had an increase in haemoglobin concentration between baseline and week 13 with siltuximab (61% vs 0%).
  - No evidence relating to haematological markers was identified for siltuximab compared to rituximab, compared to chemotherapy or compared to corticosteroids.

In terms of safety:

- *For siltuximab plus BSC vs placebo plus BSC:* One RCT provided moderate certainty evidence of similar proportions of serious adverse events[8] (23% vs 19%), Grade ≥3 adverse events (47% vs 54%) and adverse events (all grades) (100% vs 96%) with siltuximab and placebo. The groups were not statistically compared.
- No evidence relating to safety was identified for siltuximab compared to rituximab, compared to chemotherapy or compared to corticosteroids

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One RCT conducted pre-planned subgroup analysis. Time to treatment failure was compared between newly diagnosed and previously treated patients with no statistically significant difference between the subgroups. Other pre-planned subgroup outcomes were reported as siltuximab plus BSC vs placebo plus BSC for the different patient subgroups. The RCT reported a statistically significantly higher overall response rate and haematological response rate for siltuximab vs placebo for both newly diagnosed patients and previously treated patients but no statistically significant difference between siltuximab and placebo for durable complete symptomatic response rate for either newly diagnosed or previously treated patients. For other outcomes the results differed for the two subgroups. For durable tumour and symptomatic response rate and tumour response rate there was no statistically significant difference between siltuximab and placebo for newly diagnosed patients, however there was a statistically significant advantage for siltuximab over placebo for previously treated patients. Whereas for durable symptomatic response rate and time to treatment failure there was a statistically significant advantage for siltuximab over placebo for newly diagnosed patients but not for previously treated patients.

Criteria used to define iMCD:

- In the RCT by van Rhee et al (2014), the diagnosis of iMCD was based on:
  - A detailed patient history, physical examination, assessment of laboratory abnormalities, pathological diagnosis and radiological imaging

[8] Not further defined

- A histologically confirmed diagnosis using pre-specified criteria[9] by a central pathology laboratory from an excisional lymph node biopsy sample

Additional inclusion criteria for the RCT were that patients had measurable disease not limited to cutaneous lesions, grade I or greater disease symptoms according to the National Cancer Institute Common Terminology Criteria for Adverse Events and an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 to 2. Patients were excluded if they were Human immunodeficiency virus (HIV)-seropositive, had evidence of Human herpesvirus-8 (HHV8) infection or had other clinically significant infections including hepatitis B or C or had a history of concurrent lymphoma.

- In the retrospective cohort study by Yu et al (2017), the diagnosis of Castleman disease was based on clinical, laboratory and pathological findings. MCD was defined by the involvement of at least two lymph nodes in at least two separate regions. Patients with concomitant malignancies, HIV infection, HHV8 or POEMS syndrome were excluded.

Dosage of siltuximab used:

- In the RCT by van Rhee et al (2014), the siltuximab dose was 11mg/kg as a single intravenous infusion every three weeks. Patients had to meet retreatment criteria[10] before each dose. Dose reductions were not permitted. Siltuximab patients discontinued study treatment at treatment failure[11]. The median (range) duration of masked treatment for siltuximab was 375 days (1 to 1,031).
- In the retrospective cohort study by Yu et al (2017), the siltuximab dose was 11mg/kg as a single intravenous infusion every three weeks or every six weeks at the investigator's discretion. Median duration of treatment was not reported.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:

The RCT by van Rhee et al was well conducted and no risk of bias issues were identified for many of the outcomes reported. However, statistical comparison between the groups was not reported for survival or safety outcomes and some outcomes were downgraded for imprecision due to no events occurring in the placebo group or wide confidence intervals around a hazard ratio. Limitations in the design, conduct and reporting of the retrospective cohort study by Yu et al (2017) reduced certainty in its results. These limitations included a lack of information about whether the groups were similar at baseline, lack of identification of and adjustment for potential confounding factors, lack of information about the duration of follow-up and whether this was complete and, for some outcomes, lack of statistical analysis comparing the treatment groups.

Conclusion:

This evidence review includes one RCT comparing siltuximab plus best supportive care to placebo plus best supportive care and one retrospective cohort study comparing siltuximab to rituximab and to chemotherapy or corticosteroids. The populations of both studies were

[9] Cronin DM, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol. 2009, 16:236–46

[10] Absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥50 x 10^9/L and recovery of other clinically significant toxic effects to grade ≤2 or baseline. If these were not met dosing would be delayed by no more than 3 weeks until retreatment criteria were met

[11] 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 criteria or initiation of another treatment for MCD

patients with iMCD. No evidence was identified comparing siltuximab and thalidomide. There was no evidence on cost effectiveness.

There were RCT data comparing siltuximab and placebo for all the critical and important clinical effectiveness outcomes of interest. These reported an advantage for siltuximab plus best supportive care. The difference was statistically significant when groups were statistically compared, although statistical analysis was not always performed. There were fewer data available comparing siltuximab to rituximab or to chemotherapy or corticosteroids. Results for overall response rate favoured siltuximab although the difference was only statistically compared for the comparison with chemotherapy or corticosteroids. There was no difference between the treatment groups for progression free survival rate.

For safety outcomes, the numbers of adverse events reported were similar for siltuximab plus best supportive care and placebo plus best supportive care. However, the groups were not statistically compared.

The results of the subgroup analysis did not indicate a clear advantage for a subgroup of patients over the wider population of interest.

The studies identified for this review therefore provide high to moderate evidence of better outcomes with siltuximab plus best supportive care than placebo plus best supportive care in adults with iMCD. The evidence comparing siltuximab to rituximab and chemotherapy or corticosteroids was limited and of very low certainty and should be treated with caution.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In patients with iMCD, what is the clinical effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care?

2. In patients with iMCD, what is the safety of siltuximab and best supportive care compared to best supportive care alone or with standard care?

3. In patients with iMCD, what is the cost effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care?

4. From the evidence selected, are there any subgroups that may benefit from siltuximab and best supportive care more than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define iMCD?

6. From the evidence selected, what dosage (size/ frequency/ duration) of siltuximab was used?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 27 May 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Two studies (published in four papers) were identified for inclusion. One RCT compared siltuximab plus best supportive care to placebo plus best supportive care in adults with iMCD (van Rhee et al 2014, van Rhee et al 2015, van Rhee et al 2021). One retrospective cohort study compared siltuximab to rituximab and to chemotherapy or corticosteroids in patients with iMCD (Yu et al 2017). No studies were identified comparing siltuximab and thalidomide.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

No cost effectiveness studies were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
van Rhee et al RCT (reported in van Rhee et al 2014, van Rhee et al 2015 and van Rhee et al 2021) RCT Multi-centre (38 centres) in 19 countries	79 adults with iMCD (HIV-negative and HHV8-negative) Siltuximab: n=53 • Newly diagnosed: 24 (45.3%) • Previously treated: 29 (54.7%) Placebo: n=26 • Newly diagnosed: 9 (34.6%) • Previously treated: 17 (65.4%) The authors stated that baseline characteristics were well balanced between the groups except for sex, with a higher proportion of males in the placebo group Outcomes reported for newly diagnosed and previously treated subgroups	**Intervention** Siltuximab 11mg/kg as a single intravenous infusion every 3 weeks plus best supportive care **Comparison** Placebo plus best supportive care Best supportive care 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	Outcomes reported at median (range) follow-up of 422 days (5 to 1,051), unless otherwise stated **Critical outcomes** • Overall response • Durability of response • Durable tumour and symptomatic response • Durable symptomatic response • Durable complete symptomatic response • Time to treatment failure • Time to next treatment • Survival at 1 year **Important outcomes** • Quality of life • SF-36[a] • Symptom alleviation • MCD-Symptom Scale[b] • FACIT-Fatigue Scale[c] • Tumour response • Haematological marker • ≥15g/L increase in haemoglobin concentration to week 13 • Safety • Serious adverse events • Adverse events
Yu et al 2017 Retrospective cohort study Single US centre and an	43 patients[d] with iMCD (HIV and HHV8-negative) More than 50% of patients received ≥2 treatment agents. The results table includes outcomes for 65	**Intervention** Siltuximab 11mg/kg as a single intravenous infusion every 3 weeks or every 6 weeks at the investigator's discretion **Comparison**	Median follow-up not reported. Timeframe for outcomes reported not stated **Critical outcomes** • Overall response • Durability of response

Study	Population	Intervention and comparison	Outcomes reported
international database	cases of treatment for the 43 patients Siltuximab: n=21 Rituximab: n=25 Chemotherapy or corticosteroids: n=19 No baseline characteristics reported for the population of interest No subgroups reported	Rituximab 375mg/m^2 as a single intravenous infusion every week for 4 weeks[e] Chemotherapy or corticosteroids (This included cyclophosphamide, hydroxyldoxorubicin, hydrochloride, vincristine and prednisone. The authors stated that the dose, order and regimen of drugs given was not uniform across patients) No details were provided about whether any concurrent treatments were received	• Progression free survival

Abbreviations
g: gram; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue scale; HHV8: Human herpesvirus-8; HIV: Human immunodeficiency virus; iMCD: Idiopathic multicentric Castleman disease; kg: Kilogram; L: Litre; MCD: multicentric Castleman disease; m: Metre; mg: Milligram; RCT: Randomised controlled trial; SF: Short-Form; US: United States

a The SF-36 is a 36-item questionnaire with eight domains (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and general mental health). Physical component and mental health component scores can also be calculated. Scores range from 0 to 100 with higher scores indicating better health
b The MCD-Symptom Scale is a 16-item questionnaire with a fatigue domain (4 items), a rash/ itching domain (2 items), a sweats domain (2 items) and eight items not categorised to a domain (cough, shortness of breath, fever, loss of appetite, numbness or tingling, pain, swollen lymph nodes, swelling or oedema). Respondents are asked to recall symptom severity in the previous 24 hours on a six-point scale of 0=did not experience, 1=very mild, 2= mild, 3=moderate, 4=severe, 5=very severe. The domain scores are reported as the sum of the individual domain items rescaled to a 0 (very mild) to 10 (very severe) range, with higher scores indicating greater symptom severity. The total score is calculated out of ten from the three domains and seven of the eight individual items (excluding fever)
c The FACIT-Fatigue Scale is a 13-item patient-reported measure of fatigue based on experiences in the last week. Scores range from 0 to 52, with lower scores indicating greater fatigue severity and impact of fatigue on daily activities
d Patients treated at the US centre were all adults (>18 years). However, no information was provided on the age range of patients from the database
e Elsewhere in the paper patients were described as receiving rituximab or rituximab-based therapy (not further defined)

5. Results

In patients with iMCD, what is the clinical effectiveness and safety of siltuximab and best supportive care compared to best supportive care alone or with standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall response **Certainty of evidence:** Moderate to very low	Overall response is important for patients because it provides a global indicator of the response to treatment/ treatment effect. In total, one RCT and one retrospective cohort study provided evidence relating to overall response rate in patients with iMCD. Results comparing siltuximab plus best supportive care (BSC) to placebo plus BSC were available from the RCT. Results comparing siltuximab to rituximab and to chemotherapy or corticosteroids[12] were available from the retrospective cohort study. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had an overall response[13] with siltuximab (27/53, 50.9%) vs placebo (0/26, 0%). Difference between groups: 50.9% (95%CI 29.2 to 70.1), p<0.0001. Of the 27 siltuximab responders, three had a complete response and 24 a partial response. Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** **At an unknown timeframe:** *Siltuximab vs rituximab* • One retrospective cohort study (Yu et al 2017) reported an overall response[14] in 16 of 21 (76.2%) patients receiving siltuximab and 17 of 25 (68.0%) patients receiving rituximab. No statistical test comparing the treatments was reported. Of the 16 siltuximab responders, nine had a complete response and seven a partial response. Of the 17 rituximab responders, five had a complete response and 12 a partial response. Median follow-up was not reported. **(VERY LOW)** *Siltuximab vs chemotherapy or corticosteroids* • One retrospective cohort study (Yu et al 2017) reported that a *statistically significantly higher* proportion of patients had an overall response with siltuximab (16/21, 76.2%) vs chemotherapy or corticosteroids (12/29, 63.2%), p=0.034. Of the 16 siltuximab responders, nine had a complete response and seven a partial response. Of the 12 chemotherapy or corticosteroids responders, two had a complete response and ten a partial response. Median follow-up was not reported. **(VERY LOW)** **One RCT provided moderate certainty evidence that a statistically significantly higher proportion of patients had an overall response with siltuximab plus BSC vs placebo plus BSC at a median of approximately 14 months follow-up. One retrospective cohort study provided very low certainty evidence that a higher proportion of patients had an overall response with siltuximab vs rituximab or vs chemotherapy or corticosteroids (timeframe not**

[12] Comparator of 'chemotherapy or corticosteroids' as described by the study authors. This included cyclophosphamide, hydroxyldoxorubicin, hydrochloride, vincristine and prednisone. The authors stated that the dose, order and regimen of drugs given was not uniform across patients
[13] Tumour response by investigator assessment
[14] Complete response was a 100% improvement in CD symptoms and laboratory abnormalities. A partial response was 50-99% of CD symptoms and laboratory abnormalities returned to normal

Outcome	Evidence statement
	stated). This was statistically significant vs chemotherapy or corticosteroids but siltuximab and rituximab were not statistically compared[15].
Durability of response **Certainty of evidence:** High to very low	Durability of response is important for patients because it gives an indicator of how long any response to treatment may last. In total, one RCT and one retrospective cohort study provided evidence relating to durability of response rate in patients with iMCD. Results comparing siltuximab plus BSC to placebo plus BSC were available from the RCT. Results comparing siltuximab to rituximab and to chemotherapy or corticosteroids were available from the retrospective cohort study. Durability of response was assessed by durable tumour and symptomatic response[16], durable symptomatic response[17], durable complete symptomatic response, time to treatment failure, time to next treatment and progression free survival. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had a durable tumour and symptomatic response with siltuximab (18/53, 34.0%) vs placebo (0/26, 0%). Difference between groups: 34.0% (95%CI 11.1 to 54.8), p=0.0012. Of the 18 siltuximab responders, one had a complete response and 17 a partial response. Median (range) duration of durable tumour and symptomatic response for siltuximab: 383 days (232 to 676). Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** • van Rhee et al (2014) also reported that a *statistically significantly higher* proportion of patients had a durable symptomatic response with siltuximab (30/53, 56.6%) vs placebo (5/26, 19.2%). Difference between groups: 37.4% (95%CI 14.9 to 58.2), p=0.0018. Median (range) follow-up: 422 days (5 to 1,051). **(HIGH)** • van Rhee et al (2014) also reported that a *statistically significantly higher* proportion of patients had a durable complete symptomatic response with siltuximab (13/53, 24.5%) vs placebo (0/26, 0%). Difference between groups: 24.5% (95%CI 1.4 to 46.2), p=0.0037. Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** • van Rhee et al (2014) also reported a *statistically significantly longer* time to treatment failure for siltuximab vs placebo (HR 0.418 (95%CI 0.214 to 0.815), p=0.0084). The median time to treatment failure (days) was not reached for siltuximab (95%CI 378 to not estimable). For placebo this was 134 (95%CI 85 to not estimable). **(MODERATE)** • van Rhee et al (2014) also reported a *statistically significantly longer* time to next treatment for siltuximab vs placebo (HR 0.298 (95%CI 0.137 to 0.652), p=0.0013). The median time to next treatment (days) was not reached for siltuximab (95%CI not estimable). For placebo this was 280 (95%CI 161 to not estimable). **(HIGH)** **At an unknown timeframe:** *Siltuximab vs rituximab* • One retrospective cohort study (Yu et al 2017) reported *no statistically significant difference* in the proportion of patients with progression free survival between siltuximab (n=21) and rituximab (n=25) (p=0.059). Progression free survival percentage was only presented graphically. Median follow-up was not reported. **(VERY LOW)**

[15] In the text of the article the authors state that siltuximab was associated with a significantly higher rate of complete response than rituximab. However, the results table states that the comparison made was siltuximab vs chemotherapy or corticosteroids and does not report a statistical comparison between siltuximab and rituximab. The figures and detail from the table are used here

[16] Defined as a complete response or partial response by modified Cheson criteria (adjusted to include assessment of cutaneous lesions caused by MCD) with improvement or stabilisations of disease-related symptoms for ≥18 weeks during masked treatment

[17] >50% decrease in disease-symptom score. Symptomatic response was assessed by investigators based on the sum of the severity of 34 disease-related signs and symptoms

Outcome	Evidence statement
	Siltuximab vs chemotherapy or corticosteroids • One *retrospective* cohort study (Yu et al 2017) reported *no statistically significant difference* in the proportion of patients with progression free survival between siltuximab (n=21) and chemotherapy or corticosteroids (n=25) (p=0.335). Progression free survival percentage was only presented graphically. Median follow-up was not reported. **(VERY LOW)** **One RCT provided high to moderate certainty evidence that a statistically significantly higher proportion of patients had durable tumour and symptomatic responses with siltuximab plus BSC vs placebo plus BSC at a median of approximately 14 months follow-up. The same RCT also provided high to moderate certainty evidence that time to treatment failure and time to next treatment were statistically significantly longer with siltuximab. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in the proportion of patients with progression free survival between siltuximab and rituximab, or between siltuximab and chemotherapy or corticosteroids. The follow-up timeframe was not clear.**
Survival **Certainty of evidence:** Moderate	Survival is important for patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to survival in adults with iMCD. No evidence was identified relating to survival for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At one year:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported overall survival at one year for siltuximab (100% (95%CI 100 to 100)) and placebo (92% (95%CI 72 to 98)). The groups were not statistically compared. **(MODERATE)** **One RCT provided moderate certainty evidence of higher overall survival at one year with siltuximab plus BSC than placebo plus BSC. The groups were not statistically compared.**
Important outcomes	
Quality of life **Certainty of evidence:** High to moderate	Quality of life is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to quality of life in adults with iMCD. Quality of life was assessed using the SF-36[18] which includes a physical component score (PCS) and a mental component score (MCS). No evidence was identified relating to quality of life for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 12 months[19]:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2015) reported an improvement of at least five points on the SF-36 PCS for 24 of 50 (48%) siltuximab patients and eight of 26 (31%) placebo patients during the blinded treatment period. The median (range) masked treatment duration was 375 days (1 to 1,031) for siltuximab

[18] A 36-item questionnaire with eight domains (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and general mental health). Physical component and mental health component scores can also be calculated. Scores range from 0 to 100 with higher scores indicating better health

[19] Based on the median masked treatment duration for siltuximab

Outcome	Evidence statement
	and 152 days (23 to 666) for placebo. The groups were not statistically compared. **(MODERATE)** • van Rhee et al (2015) also found that a *statistically significantly higher* proportion of patients receiving siltuximab reported an improvement of at least five points on the SF-36 MCS during the blinded treatment period. Siltuximab: 34/50, 68% vs placebo: 9/26, 35% (p=0.0074). The median (range) masked treatment duration was 375 days (1 to 1,031) for siltuximab and 152 days (23 to 666) for placebo. **(HIGH)** • Mean (SD) PCS and MCS scores were only reported at baseline. For the PCS these were 42.9 (9.9) for siltuximab and 41.6 (11.1) for placebo. For the MCS these were 39.7 (10.8) for siltuximab and 43.3 (12.3) for placebo. **One RCT provided moderate to high certainty evidence that a higher proportion of siltuximab plus BSC patients reported an improvement in quality of life than placebo plus BSC patients at a median of approximately 12 months. This difference was statistically significant for the mental component of the quality of life measure used but the groups were not statistically compared for the physical component.**
Symptom alleviation **Certainty of evidence:** High to moderate	Symptom alleviation is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to symptom alleviation in adults with iMCD. Symptom alleviation was assessed by the MCD-Symptom Scale (MCD-SS)[20] and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale[21]. No evidence was identified relating to symptom alleviation for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 12 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2015) reported an improvement of at least one point[22] on the MCD-SS total score for 32 of 51 (63%) siltuximab patients and 13 of 26 (50%) placebo patients during the blinded treatment period. The median (range) masked treatment duration was 375 days (1 to 1,031) for siltuximab and 152 days (23 to 666) for placebo. The groups were not statistically compared. **(MODERATE)** • Mean (SD) MCD-SS total score was only reported at baseline. This was 2.9 (2.1) for siltuximab and 2.3 (1.2) for placebo. • van Rhee et al (2015) also reported a *statistically significant improvement* in the MCD-SS fatigue domain score for siltuximab vs placebo (p=0.02). The mean (SD) baseline scores were 4.1 (2.4) for siltuximab (n=52) and 4.5 (3.3) for placebo (n=26). The mean score at approximately one year (cycle 18 day 1) follow-up was 2.6 for siltuximab and 5.7 for placebo (SD not reported). **(HIGH)** • van Rhee et al (2015) also reported a *statistically significant improvement* in the FACIT-Fatigue scale for siltuximab vs placebo (p=0.0364). The mean (SD) baseline scores were 32.4 (11.0) for siltuximab (n=52) and 31.0 (14.6) for placebo (n=26). The mean score at approximately one year (cycle 18

[20] A 16-item questionnaire with a fatigue domain (4 items), a rash/ itching domain (2 items), a sweats domain (2 items) and eight items not categorised to a domain (cough, shortness of breath, fever, loss of appetite, numbness or tingling, pain, swollen lymph nodes, swelling or oedema). Respondents are asked to recall symptom severity in the previous 24 hours on a six-point scale of 0=did not experience, 1=very mild, 2= mild, 3=moderate, 4=severe, 5=very severe. The domain scores are reported as the sum of the individual domain items rescaled to a 0 (very mild) to 10 (very severe) range, with higher scores indicating greater symptom severity. The total score is calculated out of ten from the three domains and seven of the eight individual items (excluding fever)

[21] A 13-item patient-reported measure of fatigue based on experiences in the last week. Scores range from 0 to 52, with lower scores indicating greater fatigue severity and impact of fatigue on daily activities

[22] The authors used a threshold of 1.0 to represent a meaningful change in total MCD-SS score

Outcome	Evidence statement
	day 1) follow-up was 38.6 for siltuximab and 26.9 for placebo (SD not reported). **(HIGH)** ***At ≥120 days*** • van Rhee et al (2015) also reported that a *statistically significantly higher* proportion of patients with a FACIT-Fatigue baseline score of <44[23] achieved an improved score of ≥44 with durability for ≥120 days with siltuximab (35%) vs placebo (11%) (p=0.0475). The number of patients with a fatigue score of <44 at baseline was 43/52 (83%) for siltuximab and 19/26 (73%) for placebo. **(HIGH)** **One RCT provided high certainty evidence of statistically significantly higher improvements with siltuximab plus BSC vs placebo plus BSC on two measures of fatigue at up to approximately 12 months. The proportion of patients achieving a result that the study authors considered meaningful was higher with siltuximab on one measure of fatigue and one broader measure of symptoms. The difference was statistically significantly different for the measure of fatigue but the groups were not statistically compared for the broader measure.**
Tumour response **Certainty of evidence:** High	Tumour response is important to patients because it is a key indicator of the effectiveness of treatment. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to tumour response rate[24] in adults with iMCD. No evidence was identified relating to tumour response for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had a tumour response with siltuximab (20/53, 37.7%) vs placebo (1/26, 3.8%). Difference between groups: 33.9% (95%CI 11.1 to 54.8), p=0.0022. Median (range) follow-up: 422 days (5 to 1,051). **(HIGH)** **One RCT provided high certainty evidence that a statistically significantly higher proportion of patients had a tumour response with siltuximab plus BSC vs placebo plus BSC at a median of approximately 14 months follow-up.**
Haematological markers **Certainty of evidence:** Moderate	Haematological markers are important for patients as they provide a secondary indicator as to the efficacy of treatment. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to haematological markers in adults with iMCD. Haematological markers were assessed as the number of patients with anaemia at baseline who had a ≥15g/L increase in haemoglobin concentration between baseline and week 13. No evidence was identified relating to haematological response for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At week 13:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported that a *statistically significantly higher* proportion of patients had an increase in haemoglobin concentration between baseline and week 13 with siltuximab (19/31, 61.3%) vs placebo (0/11, 0%). Difference between groups: 61.3% (95%CI 28.3 to 85.1), p=0.0002. **(MODERATE)** **One RCT provided moderate certainty evidence that a statistically significantly higher proportion of patients had an increase in haemoglobin**

[23] A score of 44 represented the normal population mean. A threshold of ≥44 was used to indicate a normal level of fatigue

[24] Tumour response by independent radiological review

Outcome	Evidence statement
	concentration between baseline and week 13 with siltuximab plus BSC vs placebo plus BSC.
Safety	
Adverse events **Certainty of evidence:** Moderate	Safety is important to patients as it reflects the risks involved in taking siltuximab and allows a risk to benefit assessment to be undertaken. In total, one RCT comparing siltuximab plus BSC to placebo plus BSC provided evidence relating to safety in adults with iMCD. No evidence was identified relating to safety for siltuximab vs rituximab, vs chemotherapy or vs corticosteroids. **At approximately 14 months:** *Siltuximab plus BSC vs placebo plus BSC* • One RCT (van Rhee et al 2014) reported serious adverse events (not further defined) for 12 of 53 (23%) siltuximab patients and five of 26 (19%) placebo patients. The groups were not statistically compared. Three siltuximab patients had serious adverse events judged to be related to siltuximab (lower respiratory tract infection, anaphylactic reaction and sepsis). The authors also stated that no Grade 4 or higher haematological or chemistry abnormalities occurred with siltuximab. Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** • van Rhee et al (2014) also reported the number of patients with at least one Grade ≥3[25] adverse event. This was 25 of 53 (47%) for siltuximab patients and 14 of 26 (54%) for placebo patients. The groups were not statistically compared. The most common (>5% of patients) Grade ≥3 adverse events with siltuximab were fatigue (9%) and night sweats (8%). The most common (>5% of patients) Grade ≥3 adverse event with placebo was anaemia (12%). Median (range) follow-up: 422 days (5 to 1,051). **(MODERATE)** • van Rhee et al (2014) also reported the number of patients with at least one adverse event (all grades). This was 53 of 53 (100%) for siltuximab patients and 25 of 26 (96%) for placebo patients. The groups were not statistically compared. The most common (≥25% of patients) adverse events with siltuximab were pruritus (42%), upper respiratory tract infection (36%), fatigue (34%), maculopapular rash (34%), peripheral oedema (32%), malaise (28%), dyspnoea (25%) and peripheral sensory neuropathy (25%). The most common (≥25% of patients) adverse events with placebo were fatigue (38%) and dyspnoea (35%). Median (range) follow-up 422 days (5 to 1,051). **(MODERATE)** **One RCT provided moderate certainty evidence of similar proportions of serious adverse events, Grade ≥3 adverse events and adverse events (all grades) with siltuximab plus BSC and placebo plus BSC. The groups were not statistically compared.**
Abbreviations BSC: Best supportive care; CI: Confidence intervals; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue scale; g: grams; HR: Hazard ratio; iMCD: Idiopathic multicentric Castleman disease; L: Litre; MCD-SS: Multicentric Castleman Disease-Symptom Scale; MCS: Mental component score; PCS: Physical component score; RCT: Randomised controlled trial; SD: Standard deviation; SF: Short-Form	

In patients with iMCD, what is the cost effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

[25] Defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) where Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe or medically significant but not immediately life threatening; Grade 4 = life-threatening consequences; Grade 5 = death related to adverse event

From the evidence selected, are there any subgroups that may benefit from siltuximab and best supportive care more than the wider population of interest?

Outcome	Evidence statement
Subgroups	Subgroup results for newly diagnosed and previously treated patients were reported from one RCT for the critical outcomes of overall response and durability of response and for the important outcomes of tumour response and haematological markers. Subgroup analysis was pre-planned in the RCT and results were primarily reported as siltuximab plus BSC vs placebo plus BSC for the different patient subgroups. Only one outcome (time to treatment failure) included a comparison between newly diagnosed and previously treated patients. **Overall response** • One RCT (van Rhee et al 2021) reported a *statistically significantly higher* overall response rate[26] for siltuximab vs placebo for both newly diagnosed patients (11/24, 46% vs 0/9, 0%, p=0.022) and previously treated patients (16/29, 55% vs 0/17, 0%, p=0.0003). The proportion of patients showing a complete or partial response was not reported. Median (range) follow-up: 422 days (5 to 1,051). **Durability of response** • One RCT (van Rhee et al 2021) reported *no statistically significant difference* in **durable tumour and symptomatic response rate**[27] between siltuximab (8/24, 33%) and placebo (0/9, 0%) for newly diagnosed patients (p=0.09). Of the eight siltuximab responders, one had a complete response and seven a partial response. The proportion of non-responders with stable disease was 16/24 (67%) for siltuximab and 7/9 (78%) with placebo and the proportion with progressive disease was 0/24 (0%) with siltuximab and 2/9 (22%) with placebo. Median (range) follow-up: 422 days (5 to 1,051). • van Rhee et al (2021) reported a *statistically significantly higher* **durable tumour and symptomatic response rate** for siltuximab (10/29, 34%) vs placebo (0/17, 0%) for previously treated patients (p=0.013). All ten siltuximab responders had a partial response. The proportion of non-responders with stable disease was 15/29 (52%) for siltuximab and 15/17 (88%) with placebo and the proportion with progressive disease was 4/29 (14%) with siltuximab and 2/17 (12%) with placebo. Median (range) follow-up: 422 days (5 to 1,051). • One RCT (van Rhee et al 2021) reported a *statistically significantly higher* **durable symptomatic response rate** for siltuximab (17/24, 71%) vs placebo (1/9, 11%) for newly diagnosed patients (p=0.0040). For previously treated patients, the difference between siltuximab (13/29, 45%) and placebo (4/17, 24%) was *not statistically significant* (p=0.1478). Median (range) follow-up: 422 days (5 to 1,051). • van Rhee et al (2021) reported *no statistically significant difference* in **durable complete symptomatic response rate** between siltuximab and placebo for either newly diagnosed patients (8/24, 33% vs 0/9, 0%, p=0.0891) or previously treated patients (5/29, 17% vs 0/17, 0%, p=0.1290). Median (range) follow-up: 422 days (5 to 1,051). • van Rhee et al (2021) also reported *no statistically significant difference* in **time to treatment failure** between newly diagnosed and previously treated patients (p=0.11). Time to treatment failure was *statistically significantly longer* for siltuximab vs placebo (HR 0.19 (95%CI 0.06 to 0.61), p=0.005) for newly diagnosed patients but there was *no statistically significant difference* for previously treated patients (HR 0.60 (95%CI 0.26 to 1.38), p=0.23). The median time to treatment failure (days) was not reached for siltuximab for either subgroup and was 106 and 184 for newly diagnosed and previously treated placebo patients respectively.

[26] Tumour response by investigator assessment
[27] Durable tumour and symptomatic response by independent radiological review

	Tumour response • One RCT (van Rhee et al 2021) reported *no statistically significant difference* in tumour response rate[28] between siltuximab (10/24, 42%) and placebo (1/9, 11%) for newly diagnosed patients (p=0.1941). For previously treated patients, there was a *statistically significantly higher* tumour response rate for siltuximab (10/29, 34%) vs placebo (0/17, 0%) (p=0.0208). The proportion of patients showing a complete or partial response was not reported. Median (range) follow-up: 422 days (5 to 1,051). **Haematological markers** • One RCT (van Rhee et al 2021) reported a *statistically significantly higher* haemoglobin response rate[29] for siltuximab vs placebo for both newly diagnosed patients (9/14, 64% vs 0/4, 0%, p=0.0373) and previously treated patients (10/17, 59% vs 0/7, 0%, p=0.0160). Median (range) follow-up: 422 days (5 to 1,051). **One RCT compared time to treatment failure between newly diagnosed and previously treated patients and reported no statistically significant difference between the subgroups. For other outcomes, results for the two subgroups of patients were separately reported. These suggested a mixed pattern of results for the different outcomes reported with no clear advantage for one subgroup over the other.**
Abbreviations BSC: Best supportive care; HR: Hazard ratio; RCT: Randomised controlled trial	

From the evidence selected, what are the criteria used by the research studies to define iMCD?

Outcome	Evidence statement
Criteria to define iMCD	In the RCT by van Rhee et al (2014), the diagnosis of iMCD was based on: • A detailed patient history, physical examination, assessment of laboratory abnormalities, pathological diagnosis and radiological imaging • A histologically confirmed diagnosis using pre-specified criteria[30] by a central pathology laboratory from an excisional lymph node biopsy sample Additional inclusion criteria for the RCT were that patients had measurable disease not limited to cutaneous lesions, grade I or greater disease symptoms according to the NCICTC for Adverse Events and an ECOG-PS score of 0 to 2. Patients were excluded if they were HIV-seropositive, had evidence of HHV8 infection or had other clinically significant infections including hepatitis B or C or had a history of concurrent lymphoma. In the retrospective cohort study by Yu et al (2017), the diagnosis of Castleman disease was based on clinical, laboratory and pathological findings. MCD was defined by the involvement of ≥2 lymph nodes in at least two separate regions. Patients with concomitant malignancies, HIV infection, HHV8 or POEMS syndrome were excluded.
Abbreviations ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HHV8: Human herpesvirus-8; HIV: Human immunodeficiency virus; iMCD: Idiopathic multicentric Castleman disease; NCICTC: National Cancer Institute Common Terminology Criteria; POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin pigmentation; RCT: randomised controlled trial	

[28] Tumour response by independent radiological review
[29] ≥15g/L increase haemoglobin response
[30] Cronin DM, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol. 2009, 16:236–46

From the evidence selected, what dosage (size/ frequency/ duration) of siltuximab was used?

Outcome	Evidence statement
Dosage of siltuximab	In the RCT by van Rhee et al (2014), the siltuximab dose was 11mg/kg as a single intravenous infusion every three weeks. Patients had to meet retreatment criteria[31] before each dose. Dose reductions were not permitted. Siltuximab patients discontinued study treatment at treatment failure[32]. The median (range) duration of masked treatment for siltuximab was 375 days (1 to 1,031). In the retrospective cohort study by Yu et al (2017), the siltuximab dose was 11mg/kg as a single intravenous infusion every three weeks or every six weeks at the investigator's discretion. Median duration of treatment not reported.
Abbreviations kg: Kilograms; mg: Milligrams; RCT: randomised controlled trial	

[31] Absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥50 x 10^9/L and recovery of other clinically significant toxic effects to grade ≤2 or baseline. If these were not met dosing would be delayed by no more than 3 weeks until retreatment criteria were met

[32] 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 criteria or initiation of another treatment for MCD

6. Discussion

This evidence review considered the clinical effectiveness and safety of siltuximab and best supportive care compared to best supportive care alone or with standard care for the treatment of patients with a diagnosis of iMCD. The critical outcomes of interest were overall response, durability of response and survival. Important outcomes were quality of life, symptom alleviation, tumour response, haematological markers and safety. Evidence on cost effectiveness was also sought.

Evidence was available from one RCT and one retrospective cohort study. The RCT compared siltuximab plus best supportive care to placebo plus best supportive care and provided data for all the outcomes of interest. The retrospective cohort study compared siltuximab to rituximab and to chemotherapy or corticosteroids and provided data for the critical outcomes of overall response and durability of response. No studies were identified comparing siltuximab and thalidomide.

The RCT was a multi-centre study (38 centres) conducted in 19 countries, including the UK. The retrospective cohort study was conducted in the US, but also used data from an international database. It is not clear to what extent the results of these studies might be generalisable to the UK population.

All studies included patients with iMCD based on clinical, laboratory and pathological findings. The patients in the RCT were all adults. The retrospective cohort study included adult patients, but it is not clear whether all the patients were adults. Patients with HIV or HHV8 infection were excluded from both studies. The RCT groups were similar at baseline, except for sex, due to a higher proportion of males in the placebo group. Limited information was provided about the iMCD patients included in the retrospective cohort study and patients were taken from two different sources. Due to this, and the absence of baseline characteristics for the patient group of interest to this review, it is not known if the patients receiving the different treatments were similar at baseline.

The dose of siltuximab used was the same in both studies and was usually administered every three weeks. However, administration up to every six weeks was permitted.

The RCT included 53 siltuximab patients and 26 placebo patients. The power calculation suggests the number of patients included in the analysis was sufficient to show a difference between treatment groups with a two-sided significance level of 5% and 80% power. At the time of the primary analysis, 31 (59%) siltuximab patients were still receiving masked treatment. In the placebo group, six (23%) patients were still receiving placebo and ten had crossed over to, and were still receiving, siltuximab. Reason for discontinuation was stated and was mainly due to disease progression in both groups. Patients who discontinued study treatment were followed-up until the primary analysis and intention-to-treat analysis was conducted for primary and secondary efficacy outcomes.

The length of follow-up was unlikely to be adequate for some outcomes. For example, overall survival was reported at one year in the RCT and was 100% for siltuximab patients and 92% for placebo. However, in the text the authors stated that two siltuximab patients and four placebo patients had died during the follow-up period.

In the RCT, patients, the investigators giving treatment and the investigators and independent assessors evaluating outcomes were blinded to treatment allocation until protocol-defined treatment failure. Laboratory assessments that would reveal treatment allocation were assessed centrally and investigators did not have the results during the blinded phase. The outcomes were either objective or used standardised assessment measures. One of the measures used, the MCD-Symptom Scale was newly developed.

For the symptom alleviation outcome the authors provided an indication of the change in score that they considered to be meaningful. It was not clear if these were established minimally clinically important differences. No information about what any minimal clinically important thresholds or differences might be was reported for any of the other outcomes considered.

The RCT was well conducted and no risk of bias issues were identified for many of the outcomes reported. However, statistical comparison between the groups was not reported for survival or safety outcomes and some outcomes were downgraded for imprecision due to no events occurring in the placebo group or due to wide confidence intervals around a hazard ratio. Limitations in the design, conduct and reporting of the retrospective cohort study reduced certainty in its results. The study included a broad population and there was a lack of information about the specific population of interest to this review although results for this population were separately reported. Additional concerns included lack of identification of and adjustment for potential confounding factors, lack of information about the duration of follow-up and lack of statistical analysis comparing the treatment groups for some outcomes.

The RCT reported pre-planned subgroup analysis for newly diagnosed and previously treated patients. However, the two subgroups were only directly compared in terms of time to treatment failure, with no statistically significant difference between the groups reported. For other outcomes, results for the two subgroups of patients were separately reported. These suggested a mixed pattern of results for the different outcomes reported with no clear advantage for one subgroup over the other.

7. Conclusion

This evidence review includes one RCT comparing siltuximab plus best supportive care to placebo plus best supportive care and one retrospective cohort study comparing siltuximab to rituximab and to chemotherapy or corticosteroids. The populations of both studies were patients with iMCD. No evidence was identified comparing siltuximab and thalidomide.

There were RCT data comparing siltuximab and placebo for all the critical and important clinical effectiveness outcomes of interest. These reported an advantage for siltuximab plus best supportive care. The difference was statistically significant when groups were statistically compared, although statistical analysis was not always performed. There were fewer data available comparing siltuximab to rituximab or to chemotherapy or corticosteroids. Results relating to overall response favoured rituximab although the difference was only statistically compared for the comparison with chemotherapy and corticosteroids. There was no difference between the treatment groups for progression free survival.

For safety outcomes, the numbers of adverse events reported were similar for siltuximab plus best supportive care and placebo plus best supportive care. However, the groups were not statistically compared.

Limitations reducing certainty in the comparison of siltuximab plus best supportive care and placebo plus best supportive care for some outcomes included lack of statistical comparison and imprecision because no events occurred in the placebo group or because of wide confidence intervals around a hazard ratio. Limitations reducing certainty in the comparison of siltuximab and rituximab and siltuximab and chemotherapy or corticosteroids included lack of information about the similarity of the groups at baseline, lack of identification of and adjustment for potential confounding factors, lack of information about the duration of follow-up and whether this was complete and, for some outcomes, lack of statistical analysis comparing the treatment groups.

The results of the subgroup analysis did not indicate a clear advantage for any subgroup of patients over the wider population of interest.

The studies identified for this review therefore provide high to moderate evidence of better outcomes with siltuximab plus best supportive care than placebo plus best supportive care in adults with iMCD. The evidence comparing siltuximab to rituximab and chemotherapy or corticosteroids was limited and of very low certainty and should be treated with caution.

Appendix A PICO Document

The review questions for this evidence review are:

1. In patients with iMCD, what is the clinical effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care?

2. In patients with iMCD, what is the safety of siltuximab and best supportive care compared to best supportive care alone or with standard care?

3. In patients with iMCD, what is the cost effectiveness of siltuximab and best supportive care compared to best supportive care alone or with standard care?

4. From the evidence selected, are there any subgroups that may benefit from siltuximab and best supportive care more than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define iMCD?

6. From the evidence selected, what dosage (size/ frequency/ duration) of siltuximab was used?

P-Population and Indication	Patients with a diagnosis of idiopathic multicentric Castleman [or Castleman's] Disease (iMCD). [Other terms for iMCD include Non-HIV MCD, Non-HHV8 MCD] [iMCD has no known cause. International consensus diagnostic criteria are based on the lymph node pathology, the presence of enlarged lymph nodes in at least 2 lymph node sites (multicentricity) and the presence of at least 2 defined clinical and/or laboratory features.] Subgroups of interest: • Newly diagnosed iMCD patients who have not received standard care treatments. • Previously diagnosed iMCD patients who have relapsed after treatment with standard care treatments but who are siltuximab naïve. [Standard care treatments include corticosteroids, rituximab, chemotherapy and thalidomide used alone or in combination]
I-Intervention	Siltuximab and best supportive care [Best supportive care includes management of effusions, use of antipyretic, antipruritic, antihistamine, and analgesic pain drugs, management of infections, transfusions, and standard management of infusion related reactions.] [There may be prior or concomitant use of corticosteroids]
C-Comparator	1. Best supportive care 2. Best supportive care and standard care with a) Corticosteroids b) Rituximab* c) Chemotherapy [including but not limited to R-CHOP, R-CVP]* d) Rituximab and chemotherapy* e) Thalidomide*

	*There may be prior or concomitant use of corticosteroids
O-Outcomes	**<u>Clinical Effectiveness</u>** Minimally Clinical Important Difference (MCIDs) are not known. <u>*Critical to decision-making:*</u> • **Overall response** This outcome is important to patients because it provides a global indicator of the response to treatment/ treatment effect. [Other terms used to describe or indicate 'overall response' include, but not limited to: complete response, partial response, stable disease, progressive disease, disease control/ disease remission.] • **Durability of response** This outcome is important to patients because it gives an indicator of how long any response to treatment may last. [Other terms used to describe or indicate 'durability of response include but are not limited to: duration of tumour response/ duration of symptomatic responses/ time to treatment failure/ progression free survival /time to next therapy.] • **Survival** This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time. [Other terms used to describe or indicate survival include but are not limited to overall survival, survival rate, death.] <u>*Important to decision-making:*</u> • **Quality of life** This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. [Other terms used to describe or indicate quality of life include but are not limited to: patient-reported quality of life outcomes, health related quality of life. Examples of metrics to assess quality of life include but are not limited to: Short Form (SF)-36, EuroQuality of Life Five Dimensions (EQ-5D). Other methods of assessing quality of life include but are not limited to subjective/self-reported/carer reported quality of life experiences.] • **Symptom alleviation** This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.

	[Other terms used to describe or indicate symptom alleviation include but are not limited to symptoms, symptomatic response, alleviating disease symptoms. Examples of metrics to assess patient-reported symptomatic outcomes include but are not limited to: MCD–Symptom Scale (MCD–SS), the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) scale.] • **Tumour response** This outcome is important to patients because it is a key indicator of the effectiveness of treatment. [Other terms used to describe or indicate tumour response include lymph node size e.g. assessed using modified Cheson criteria which requires radiological imaging.] • **Haematological markers** This outcome is important to patients as it provides a secondary indicator as to the efficacy of treatment. [Haematological markers include but are not limited to: - reduction in serum CRP levels - ≥15 g/l increase in haemoglobin concentration - increase in serum albumin (if reduced at diagnosis) - reduction in ESR (if elevated at diagnosis).] **<u>Safety</u>** Safety is important to patients as it reflects the risks involved in taking siltuximab and allows a risk to benefit assessment to be undertaken. [Other terms used to describe or indicate safety include, but are not limited to: - Adverse events - Serious adverse events] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines.
Study design	Case reports, resource utilisation studies.

Appendix B Search strategy

Medline, Embase, the Cochrane Library, PubMed and the TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2012 to 27 May 2022

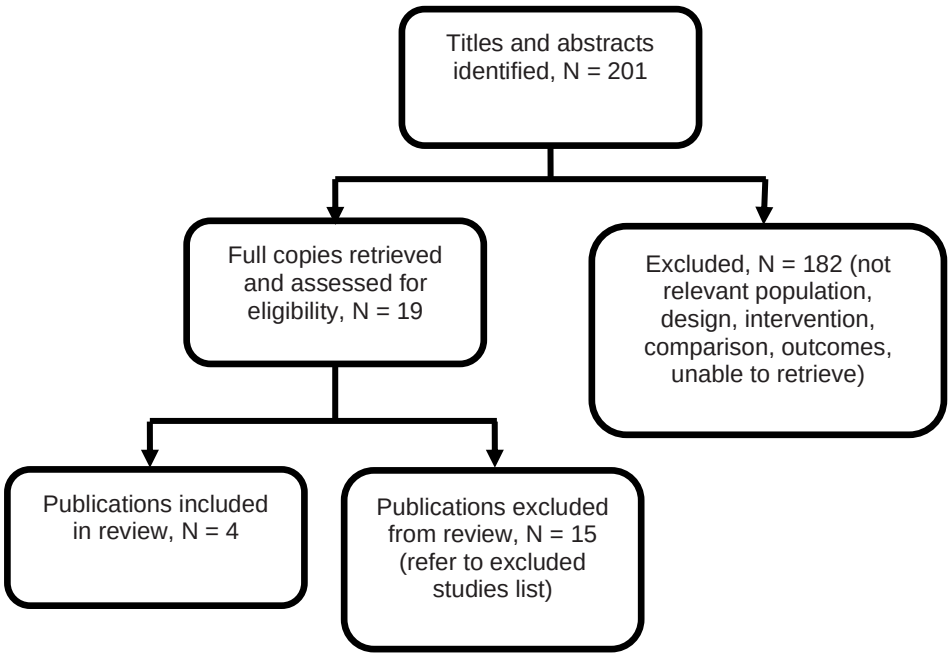
Medline search strategy:

1 Castleman Disease/
2 castleman*.ti,ab,kf.
3 (imcd or non-hiv mcd or nohiv mcd or non-hhv8 mcd or nonhhv8 mcd).ti,ab,kf.
4 angiofollicular lymph node hyperplasia?.ti,ab,kf.
5 1 or 2 or 3 or 4
6 (siltuximab or sylvant).mp.
7 5 and 6

Appendix C Evidence selection

The literature search identified 201 potential references. These were screened using their titles and abstracts and 19 references potentially relating to the use of siltuximab for iMCD were obtained in full text and assessed for relevance. Of these, four references are included in this evidence review. The 15 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J, Casper C. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014, 15(9):966-974.	Included in the review
van Rhee F, Casper C, Voorhees PM, Fayad LE, Gibson D, Kanhai K, Kurzrock R. Long-term safety of siltuximab in patients with idiopathic multicentric Castleman disease: a prespecified, open-label, extension analysis of two trials. Lancet Haematol 2020, 7(3): e209-e217.	Excluded. This is a non-comparative study. Comparative evidence is available for the outcomes specified in the PICO
van Rhee F, Rossi JF, Simpson D, Fosså A, Dispenzieri A, Kuruvilla J, Goh YT, Cho SG, Capra M, Liu T, Casper C, Cavet J, Wong RS. Newly diagnosed and previously treated multicentric Castleman disease respond equally to siltuximab. British Journal of Haematology 2021, 192:e28-e31.	Included in the review

Appendix D Excluded studies table

Study reference	Reason for exclusion
Casper C, Chaturvedi S, Munshi N, Wong R, Qi M, Schaffer M, et al. Analysis of Inflammatory and Anemia-Related Biomarkers in a Randomized, Double-Blind, Placebo-Controlled Study of Siltuximab (Anti-IL6 Monoclonal Antibody) in Patients With Multicentric Castleman Disease. Clin Cancer Res. 2015;21(19):4294-304.	This reports association between baseline IL6 and C-reactive protein level and clinical response from the RCT data. Not a specified subgroup of interest. Does not report any additional outcomes not already captured.
Fajgenbaum DC, Wu D, Goodman A, Wong R, Chadburn A, Nasta S, et al. Insufficient evidence exists to use histopathologic subtype to guide treatment of idiopathic multicentric Castleman disease. Am J Hematol. 2020;95(12):1553-61.	This is a secondary analysis of patients who received siltuximab in several studies focusing on histopathologic subtypes. It is not a study comparing siltuximab to another intervention and comparative evidence is available.
Jiang JP, Shen XF, Du JF, Guan WX. A retrospective study of 34 patients with unicentric and multicentric Castleman's disease: Experience from a single institution. Oncol. 2018;15(2):2407-12.	Non-comparative study. Comparative evidence available for the outcomes of interest.
Kurzrock R, Voorhees PM, Casper C, Furman RR, Fayad L, Lonial S, et al. A phase I, open-label study of siltuximab, an anti-IL-6 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma, multiple myeloma, or Castleman disease. Clin Cancer Res. 2013;19(13):3659-70.	Non-comparative study. Comparative evidence available for the outcomes of interest.
Liu AY, Nabel CS, Finkelman BS, Ruth JR, Kurzrock R, van Rhee F, et al. Idiopathic multicentric Castleman's disease: A systematic literature review. The Lancet Haematology. 2016;3(4):e163-e75.	Systematic review with no meta-analysis of results. Individual studies considered separately for eligibility for inclusion in this review.
Min GJ, Jeon YW, Park SS, Park S, Shin SH, Yahng SA, et al. The clinical, laboratory, and radiologic improvement due to siltuximab treatment in idiopathic multicentric Castleman's disease. Korean J Intern Med. 2021;36(2):424-32.	Non-comparative study. Comparative evidence available for the outcomes of interest.
Morra DE, Pierson SK, Shilling D, Nemat S, Appiani C, Guilfoyle M, et al. Predictors of response to anti-IL6 monoclonal antibody therapy (siltuximab) in idiopathic multicentric Castleman disease: secondary analyses of phase II clinical trial data. British Journal of Haematology. 2019;184(2):232-41.	Secondary analysis of a subset of RCT patients. Not a study comparing siltuximab to another intervention. Comparative evidence is available.
Rokx C, Rijnders BJA, van Laar JAM. Treatment of multicentric Castleman's disease in HIV-1 infected and uninfected patients: A systematic review. Netherlands Journal of Medicine. 2015;73(5):202-10.	Descriptive review of included studies with broad range of populations and interventions considered and no meta-analysis of results. Eligible studies separately considered for inclusion.
Sitenga J, Aird G, Ahmed A, Silberstein PT. Impact of siltuximab on patient-related outcomes in multicentric Castleman's disease. Patient relat. 2018;9:35-41.	Descriptive review of included studies with no meta-analysis of results. Eligible studies separately considered for inclusion.
Sun Y, Wang D, Salvadore G, Hsu B, Curran M, Casper C, et al. The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. Brain Behav Immun. 2017;66:156-64.	Post-hoc analysis of a subset of RCT patients based on depression status at baseline. Comparative quality of life outcomes included from the main RCT results. This analysis does not relate to a specified subgroup of interest.
Tang D, Guo Y, Tang Y, Wang H. Treatment and Outcome of Castleman Disease: A Retrospective Report of 31 Patients. Ther Clin Risk Manag. 2022;18:499-509.	Non-comparative study. Comparative evidence available for the outcomes of interest.
Tonialini L, Bonfichi M, Ferrero S, Malipiero G, Nozza A, Argnani L, et al. Siltuximab in relapsed/refractory multicentric Castleman disease: Experience of the Italian NPP program. Hematol Oncol. 2018;36(4):689-92.	Non-comparative study. Comparative evidence available for the outcomes of interest.

van Rhee F, Casper C, Voorhees PM, Fayad LE, Gibson D, Kanhai K, et al. Long-term safety of siltuximab in patients with idiopathic multicentric Castleman disease: a prespecified, open-label, extension analysis of two trials. Lancet Haematol. 2020;7(3):e209-e17.	Non-comparative study. Comparative evidence available for the outcomes of interest.
van Rhee F, Casper C, Voorhees PM, Fayad LE, van de Velde H, Vermeulen J, et al. A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. Oncotarget. 2015;6(30):30408-19.	Non-comparative study. Comparative evidence available for the outcomes of interest.
Vernon M, Robinson D, Jr., Trundell D, Ishak J, Jen MH, Brazier J. Deriving health utility values from a randomized, double-blind, placebo-controlled trial of siltuximab in subjects with multicentric Castleman's disease. Curr Med Res Opin. 2016;32(7):1193-200.	This uses data from the RCT to calculate QALY gain. Not an outcome of interest. Not a cost-effectiveness study.

Appendix E Evidence Table

For abbreviations see list after table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
van Rhee F, Rossi JF, Simpson D, Fosså A, Dispenzieri A, Kuruvilla J, Goh YT, Cho SG, Capra M, Liu T, Casper C, Cavet J, Wong RS. Newly diagnosed and previously treated multicentric Castleman disease respond equally to siltuximab. British Journal of Haematology 2021, 192:e28-e31. **Study location** Multi-centre (38 centres) in 19 countries (see van Rhee et al 2014 for further details) **Study type** RCT – subgroup analysis **Study aim** Pre-planned subgroup analysis from an RCT, reporting results for newly diagnosed and previously treated patients	Adults with iMCD (HIV-negative and HHV8-negative) This paper reports a pre-planned subgroup analysis from an RCT. See van Rhee et al 2014 for the trial inclusion/ exclusion criteria and baseline characteristics **Total sample size** n=79 Siltuximab: n=53 • Newly diagnosed: 24 (45.3%) • Previously treated: 29 (54.7%) Placebo: n=26 • Newly diagnosed: 9 (34.6%) • Previously treated: 17 (65.4%)	This paper reports patient reported outcomes from an RCT. The intervention group received siltuximab plus best supportive care. The comparator group received placebo plus best supportive care See van Rhee et al 2014 for further details	Median (range) follow-up: 422 days (5 to 1,051) Median (range) masked treatment duration: • Siltuximab: 375 days (1 to 1,031) • Placebo: 152 days (23 to 666) Proportion of patients showing a complete or partial response not reported unless stated **Critical outcomes** **Overall response** Tumour response rate by investigator assessment (n,%): *For newly diagnosed patients* • Siltuximab: 11/24 (46%) • Placebo: 0/9 (0%) p=0.022 *For previously treated patients* • Siltuximab: 16/29 (55%) • Placebo: 0/17 (0%) p=0.0003 **Durability of response** Durable tumour and symptomatic response rate by independent radiological review (n,%) (see van Rhee et al 2014 for outcome definition):	This study was appraised using the JBI checklist for RCTs. See van Rhee et al 2014 for ratings and comments relating to the design and conduct of this RCT **Other comments** This is a pre-planned subgroup analysis of outcomes reported in the 2014 RCT. Safety subgroup results were not extracted as these were reported for specific adverse events (experienced by a minimum percentage of patients) rather than as a figure of the number of patients in each group who experienced an adverse event. As it is possible that some less common adverse events also occurred, it was not possible to use the data presented to calculate what the total number of adverse events for each group was. **Source of funding:** See van Rhee et al (2014)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study dates 2010 to 2013			*For newly diagnosed patients* Siltuximab: • Overall response: 8/24 (33%) • Complete response: 1/8 • Partial response: 7/8 • Stable disease: 16/24 (67%) • Progressive disease: 0/24 (0%) Placebo: • Overall response: 0/9 (0%) • Stable disease: 7/9 (78%) • Progressive disease: 2/9 (22%) No statistically significant difference in the overall response between siltuximab and placebo (p=0.09) *For previously treated patients* Siltuximab: • Overall response: 10/29 (34%) • Complete response: 0/10 • Partial response: 10/10 • Stable disease: 15/29 (52%) • Progressive disease: 4/29 (14%) Placebo: • Overall response: 0/17 (0%) • Stable disease: 15/17 (88%) • Progressive disease: 2/17 (12%) Statistically significantly higher overall response for siltuximab vs placebo (p=0.013)	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Durable symptomatic response rate (n,%) (see van Rhee et al (2014) for definition): *For newly diagnosed patients* • Siltuximab: 17/24 (71%) • Placebo: 1/9 (11%) p=0.0040 *For previously treated patients* • Siltuximab: 13/29 (45%) • Placebo: 4/17 (24%) p=0.1478 Durable complete symptomatic response rate (n,%): *For newly diagnosed patients* • Siltuximab: 8/24 (33%) • Placebo: 0/9 (0%) p=0.0891 *For previously treated patients* • Siltuximab: 5/29 (17%) • Placebo: 0/17 (0%) p=0.1290 Median time to treatment failure (days): *For newly diagnosed patients* • Siltuximab: Not reached • Placebo: 106 HR 0.19 (95%CI 0.06 to 0.61) p=0.005 *For previously treated patients* • Siltuximab: Not reached • Placebo: 184	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			HR 0.60 (95%CI 0.26 to 1.38) p=0.23 There was no statistically significant difference in time to treatment failure between newly diagnosed and previously treated patients (p=0.11) **Important outcomes** **Tumour response** Tumour response rate (n,%) by independent radiological review: *For newly diagnosed patients* • Siltuximab: 10/24 (42%) • Placebo: 1/9 (11%) p=0.1941 *For previously treated patients* • Siltuximab: 10/29 (34%) • Placebo: 0/17 (0%) p=0.0208 **Haematological markers** Patients (n,%) with ≥15g/L increase haemoglobin response: *For newly diagnosed patients* • Siltuximab: 9/14 (64%) • Placebo: 0/4 (0%) p=0.0373 *For previously treated patients* • Siltuximab: 10/17 (59%) • Placebo: 0/7 (0%) p=0.0160	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
van Rhee F, Rothman M, Ho KF, Fleming S, Wong RS, Fosså A, Dispenzieri A, Cavet J, Munshi N, Vermeulen J, Casper C. Patient-reported outcomes for multicentric Castleman's disease in a randomised, placebo-controlled study of siltuximab. Patient 2015, 8:207-216. **Study location** Multi-centre (38 centres) in 19 countries (see van Rhee et al 2014 for further details) **Study type** RCT **Study aim** To assess the effect of siltuximab on patient perception of symptoms, functional status and wellbeing in patients with iMCD **Study dates**	Adults with iMCD (HIV-negative and HHV8-negative) This paper reports patient reported outcomes from an RCT. See van Rhee et al 2014 for the trial inclusion/ exclusion criteria and baseline characteristics **Total sample size** n=79 Siltuximab: n=53 Placebo: n=26	This paper reports patient reported outcomes from an RCT. The intervention group received siltuximab plus best supportive care. The comparator group received placebo plus best supportive care See van Rhee et al 2014 for further details	Median (range) follow-up: 422 days (5 to 1,051) Median (range) masked treatment duration: • Siltuximab: 375 days (1 to 1,031) • Placebo: 152 days (23 to 666) **Important outcomes** **Quality of life** Assessed using the SF-36[33] *Physical component score (PCS):* Number (%) of patients achieving a ≥5-point improvement in PCS during the blinded treatment period: • Siltuximab: 24/50 (48%) • Placebo: 8/26 (31%) No significance test reported Baseline (mean, SD): • Siltuximab (n=50): 42.9 (9.9) • Placebo (n=26): 41.6 (11.1) Follow-up mean (SD) not reported *Mental component score (MCS):* Number (%) of patients achieving a ≥5-point improvement in MCS during the blinded treatment period: • Siltuximab: 34/50 (68%)	This study was appraised using the JBI checklist for RCTs. See van Rhee et al 2014 for ratings and comments relating to the design and conduct of this RCT **Other comments** This paper reported the patient-reported outcomes relating to quality of life and symptom alleviation from the van Rhee et al (2014) RCT. The outcomes were assessed via self-administered questionnaires completed by patients who were blinded to their treatment group. The MCD-Symptom Scale was newly developed. The other scales used were established assessment tools. SF-36 baseline data were available for 76 of the 79 patients. MCD-SS and FACIT-Fatigue baseline data were available for 78 patients. Fewer patients contributed data over the follow-up period due to

[33] A 36-item questionnaire with eight domains (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and general mental health). Physical component and mental health component scores can also be calculated. Scores range from 0 to 100 with higher scores indicating better health

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
2010 to 2013			• Placebo: 9/26 (35%) p=0.0074 Baseline mean (SD): • Siltuximab (n=50): 39.7 (10.8) • Placebo (n=26): 43.3 (12.3) Follow-up mean (SD) not reported The authors also reported a statistically significant improvement from baseline with siltuximab for 5 (of 8) SF-36 domains. No comparison between siltuximab and placebo reported for the SF-36 domains **Symptom alleviation** Assessed using the MCD-Symptom Scale (MCD-SS)[34] *MCD-SS total score:* The authors used a threshold of 1.0 to represent a meaningful change in total MCD-SS score Number (%) of patients achieving an improvement of ≥1.0 in total MCD-SS during the blinded treatment period: • Siltuximab: 32/51 (63%)	disease progression. The duration of masked follow-up varied from less than a month to years in both groups. For outcomes assessed at cycle 18, the number of siltuximab patients had reduced from 52 to 29 and the number of placebo patients had reduced from 26 to 6. The authors reported mean scores for the 5 (of 8) SF-36 domains that showed statistically significant improvements from baseline with siltuximab. These domains were role limitations due to physical health, bodily pain, vitality, general mental health and role limitations due to emotional problems. No scores were provided for the remaining domains and no statistical tests comparing siltuximab and placebo, or comparing baseline to follow-up for placebo, were reported for these domains. These data were therefore not extracted.

[34] A 16-item questionnaire with a fatigue domain (4 items), a rash/ itching domain (2 items), a sweats domain (2 items) and eight items not categorised to a domain (cough, shortness of breath, fever, loss of appetite, numbness or tingling, pain, swollen lymph nodes, swelling or oedema). Respondents are asked to recall symptom severity in the previous 24 hours on a six-point scale of 0=did not experience, 1=very mild, 2= mild, 3=moderate, 4=severe, 5=very severe. The domain scores are reported as the sum of the individual domain items rescaled to a 0 (very mild) to 10 (very severe) range, with higher scores indicating greater symptom severity. The total score is calculated out of ten from the three domains and seven of the eight individual items (excluding fever)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Placebo: 13/26 (50%) No significance test reported Baseline mean (SD) MCS total score: • Siltuximab (n=52): 2.9 (2.1) • Placebo (n=26): 2.3 (1.2) Follow-up mean (SD) not reported *MCD-SS fatigue domain score:* • Baseline (mean, SD) • Siltuximab (n=52): 4.1 (2.4) • Placebo (n=26): 4.5 (3.3) • Follow-up (cycle 18 day 1) (mean) (SD not reported) • Siltuximab (n=29): 2.6 • Placebo (n=6): 5.7 Reported as a significant improvement in fatigue for siltuximab compared to placebo (p=0.02) *Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale*[35] • Baseline (mean, SD) • Siltuximab (n=52): 32.4 (11.0) • Placebo (n=26): 31.0 (14.6) • Follow-up (cycle 18 day 1) (mean) (SD not reported) • Siltuximab (n=29): 38.6 • Placebo (n=6): 26.9	Results reported graphically were not extracted. **Source of funding:** See van Rhee et al (2014)

[35] A 13-item patient-reported measure of fatigue based on experiences in the last week. Scores range from 0 to 52, with lower scores indicating greater fatigue severity and impact of fatigue on daily activities

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Reported as a significant improvement in fatigue for siltuximab compared to placebo (p=0.0364) Number (%) pf patients with a fatigue score of <44[36] at baseline (n=78) • Siltuximab: 43/52 (83%) • Placebo: 19/26 (73%) Proportion of patients with a baseline score of <44 who achieved an improved score of ≥44 with durability for ≥120 days: • Siltuximab: 35% • Placebo: 11% p=0.0475 Number of patients not reported	
van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J, Casper C. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014, 15(9):966-974.	Adults with iMCD (HIV-negative and HHV8-negative) **Inclusion criteria** Patients aged ≥18 years with: • MCD based on a detailed patient history, physical examination, assessment of laboratory abnormalities, pathological diagnosis and radiological imaging	**Intervention** Siltuximab 11mg/kg as a single intravenous infusion every 3 weeks plus best supportive care Siltuximab patients discontinued study treatment at treatment failure (defined below) **Comparison** Placebo plus best supportive care	Median (range) follow-up: 422 days (5 to 1,051) Median (range) masked treatment duration: • Siltuximab: 375 days (1 to 1,031) • Placebo: 152 days (23 to 666) **Critical outcomes** **Overall response** Tumour response rate by investigator assessment (n,%): • Siltuximab: 27/53 (50.9%) • Complete response: 3/27 • Partial response: 24/27 • Placebo: 0/26 (0%)	This study was appraised using the JBI checklist for RCTs: 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes **Other comments**

[36] A score of 44 represented the normal population mean. A threshold of ≥44 was used to indicate a normal level of fatigue

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study location Multi-centre (38 centres) in 19 countries (Australia, Belgium, Brazil, Canada, China, Egypt, France, Germany, Hong Kong, Israel, New Zealand, Norway, Russia, Singapore, South Korea, Spain, Taiwan, UK and USA) **Study type** RCT **Study aim** To assess the efficacy and safety of siltuximab for iMCD **Study dates** 2010 to 2013	• A histologically confirmed diagnosis of MCD using pre-specified criteria[37] by a central pathology laboratory from an excisional lymph node biopsy sample taken before enrolment • Measurable disease not limited to cutaneous lesions, grade I or greater disease symptoms according to the NCICTC for Adverse Events and ECOG-PS score of 0 to 2 Patients could be newly diagnosed or previously treated (with a non-interleukin-6 targeted treatment) **Exclusion criteria** • HIV-seropositive patients • Patients with evidence of HHV8 infection by	At first treatment failure, placebo patients could crossover to open-label siltuximab plus best supportive care until second treatment failure **Concurrent treatments:** Best supportive care 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	Difference between groups: 50.9% (95%CI 29.2 to 70.1), p<0.0001 **Durability of response** *Durable tumour and symptomatic response rate[38] by independent radiological review (n,%):* • Siltuximab: 18/53 (34.0%) • Complete response: 1/18 • Partial response: 17/18 • Placebo: 0/26 (0%) Difference between groups: 34.0% (95%CI 11.1 to 54.8), p=0.0012 Median (range) duration of durable tumour and symptomatic response for siltuximab: 383 days (232 to 676) *Durable symptomatic response rate[39] (n,%):* • Siltuximab: 30/53 (56.6%) • Placebo: 5/26 (19.2%) Difference between groups: 37.4% (95%CI 14.9 to 58.2), p=0.0018 *Durable complete symptomatic response rate (n,%):* • Siltuximab: 13/53 (24.5%)	This was a double-blind, multicentre RCT comparing siltuximab to placebo. The computer-generated block randomisation was stratified by baseline concomitant corticosteroid use. Groups were similar at baseline. Previous systemic treatments included corticosteroids, chemotherapy, rituximab, immunosuppressants and interferon. Patients and investigators giving treatment were blinded to allocation until protocol-defined treatment failure. Laboratory assessments that could reveal treatment allocation were assessed centrally and investigators did not have the results during the blinded phase. Investigators and independent assessors evaluating outcomes were also blinded to allocation.

[37] Cronin DM, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol. 2009, 16:236–46
[38] Defined as a complete response or partial response by modified Cheson criteria (adjusted to include assessment of cutaneous lesions caused by MCD) with improvement or stabilisations of disease-related symptoms for ≥18 weeks during masked treatment
[39] >50% decrease in disease-symptom score. Symptomatic response was assessed by investigators based on the sum of the severity of 34 disease-related signs and symptoms

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	quantitative PCR in plasma by a central laboratory • Patients with other clinically significant infections including hepatitis B or C, or with a history of or concurrent lymphoma • Patients who had previously received interleukin-6 targeted treatment **Total sample size** n=79 Siltuximab: n=53 Placebo: n=26 **Baseline characteristics** *Siltuximab* Age median (range): 47 years (20-74) Male: 57% ECOG-PS score: • 0: 42% • 1: 45% • 2: 13% Disease-related overall symptom score median (range): 6 (2 to 31) Received previous systemic treatment: 55% Concurrent corticosteroids: 25%	Patients receiving corticosteroids were given a stable or decreasing dose of no more than 1mg/kg per day of prednisone or equivalent for more than 4 weeks before randomisation A new course of corticosteroids or increase from baseline was not permitted Use of erythropoietin-stimulating agents, anti-tumour treatments or biological treatments was not permitted **Retreatment criteria**: Before each dose, patients had to meet retreatment criteria: absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥50 x 10^9/L and recovery of other clinically significant toxic effects to grade	• Placebo: 0/26 (0%) Difference between groups: 24.5% (95%CI 1.4 to 46.2), p=0.0037 *Median time to treatment failure (days)* • Siltuximab: Not reached (95%CI 378 to not estimable) • Placebo: 134 (95%CI 85 to not estimable) HR 0.418 (95%CI 0.214 to 0.815), p=0.0084 *Median time to next treatment (days)* • Siltuximab: Not reached (95%CI not estimable) • Placebo: 280 (95%CI 161 to not estimable) HR 0.298 (95%CI 0.137 to 0.652), p=0.0013 **Survival** Overall survival at 1 year: • Siltuximab: 100% (95%CI 100 to 100) • Placebo: 92% (95%CI 72 to 98) No statistical comparison between groups **Important outcomes** **Tumour response** Tumour response rate (n,%) by independent radiological review: • Siltuximab: 20/53 (37.7%) • Complete response: 2/20 • Partial response: 18/20 • Placebo: 1/26 (3.8%) • Partial response: 1/1	22 of the 53 (41.5%) patients randomised to siltuximab discontinued due to disease progression (n=16), withdrew consent (n=4), physician decision (n=1) and adverse event (n=1). 20 of the 26 (76.9%) patients randomised to placebo discontinued due to disease progression (n=14), withdrew consent (n=3), died (n=2) and adverse event (n=1). 13 placebo patients crossed over to siltuximab. Of these, 3 (23.1%) discontinued due to disease progression (n=2) and adverse event (n=1). Patients who discontinued study treatment were followed-up until the primary analysis. The primary efficacy analysis was intention-to-treat. At the time of the primary analysis, 31 (59%) siltuximab patients were still receiving masked treatment. In the placebo group, 6 (23%) patients were still receiving placebo and 10 had crossed over to, and were still receiving, siltuximab. The secondary efficacy analysis was primarily intention-to-treat. The safety population consisted

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Placebo Age median (range): 48 years (27-78) Male: 85% ECOG-PS score: • 0: 38% • 1: 62% • 2: 0% Disease-related overall symptom score median (range): 10 (1 to 30) Received previous systemic treatment: 65% Concurrent corticosteroids: 35% The authors stated that baseline characteristics were well balanced between the groups except for sex, with a higher proportion of males in the placebo group	≤2 or baseline. If these were not met dosing would be delayed by no more than 3 weeks until retreatment criteria were met. Dose reductions were not permitted **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 criteria or initiation of another treatment for MCD	Difference between groups: 33.9% (95%CI 11.1 to 54.8), p=0.0022 **Haematological markers** Patients (n,%) with anaemia at baseline who had ≥15g/L increase in haemoglobin concentration between baseline and week 13: • Siltuximab: 19/31[40] (61.3%) • Placebo: 0/11 (0%) Difference between groups: 61.3% (95%CI 28.3 to 85.1), p=0.0002 **Safety** No statistical comparison between groups reported for safety outcomes No treatment-related deaths were reported *Serious adverse events (not further defined) (n,%):* • Siltuximab: 12/53 (23%) • Placebo: 5/26 (19%) Three (6%) siltuximab patients had serious adverse events judged to be related to siltuximab. These were lower respiratory tract infection, anaphylactic reaction and sepsis The authors stated that no Grade 4 or higher haematological or chemistry abnormalities occurred with siltuximab	of all randomly assigned patients who received at least 1 dose of study drug. The number of patients included in the analysis was sufficient to show a difference between treatment groups with a two-sided significance level of 5% and 80% power. The outcomes were objective or used standardised assessment measures. The length of follow-up was unlikely to be adequate for some outcomes. For example, overall survival was reported at one year and was 100% for siltuximab patients and 92% for placebo. However, in the text the authors stated that 2 siltuximab patients and 4 placebo patients had died during the follow-up period. Statistical comparison between the groups was not reported for survival or safety outcomes. Results only presented graphically were not extracted.

[40] This outcome was assessed in treated patients with baseline haemoglobin concentration below the lower limit of normal and ≥1 post-baseline haemoglobin evaluation

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Patients with ≥1 Grade ≥3[41] adverse event (n,%): • Siltuximab: 25/53 (47%) • Placebo: 14/26 (54%) The most common (>5% of patients) Grade ≥3 adverse events with siltuximab were fatigue (9%) and night sweats (8%). The most common (>5% of patients) Grade ≥3 adverse event with placebo was anaemia (12%) *Patients with ≥1 adverse event (all grades) (n,%):* • Siltuximab: 53/53 (100%) • Placebo: 25/26 (96%) The most common (≥25% of patients) adverse events of any grade with siltuximab were pruritus (42%), upper respiratory tract infection (36%), fatigue (34%), maculopapular rash (34%), peripheral oedema (32%), malaise (28%), dyspnoea (25%) and peripheral sensory neuropathy (25%). The most common (≥25% of patients) adverse events of any grade with placebo were fatigue (38%) and dyspnoea (35%)	The study was conducted in 38 centres in 19 countries (Australia, Belgium, Brazil, Canada, China, Egypt, France, Germany, Hong Kong, Israel, New Zealand, Norway, Russia, Singapore, South Korea, Spain, Taiwan, UK and USA). The authors reported the proportion of patients who can from different geographical regions: • Asia Pacific: 49% siltuximab; 42% placebo • EMEA: 25% siltuximab; 31% placebo • North America: 19% siltuximab; 19% placebo • Latin America: 8% siltuximab; 8% placebo This paper reported some subgroup analysis for the durability of response outcome for newly diagnosed and previously treated patients. However, the same results, with more detail, were also reported in van Rhee et al (2021). The van Rhee et al (2021) paper was therefore used to report subgroup results**.**

[41] Defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) where Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe or medically significant but not immediately life threatening; Grade 4 = life-threatening consequences; Grade 5 = death related to adverse event

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				Source of funding: The study was funded by Janssen Research and Development. Representatives of the study sponsors were involved in the study design, data collection, data analysis, data interpretation and writing of the report.
Yu L, Tu M, Cortes J, Xu-Monette ZY, Miranda RN, Zhang J, Orlowski RZ, Neelapu S, Boddu PC, Akosile MA, Uldrick TS, Yarchoan R, Medeiros LJ, Li Y, Fajgenbaum DC, Young KH. Clinical and pathological characteristics of HIV and HHV8-negative Castleman disease. Blood 2017, 129(12):1658-1668. **Study location** Single US centre and an international database **Study type**	Patients with iMCD[42] (HIV and HHV8-negative) **Inclusion criteria** Patients diagnosed and treated at one US centre between 1994 and 2014 Additional patients were taken from the Castleman Disease Collaborative Network (CDCN) Research Database and the National Institutes of Health • Patients had a diagnosis of Castleman disease based on clinical, laboratory and pathological findings	**Intervention** Siltuximab 11mg/kg as a single intravenous infusion every 3 weeks or every 6 weeks at the investigator's discretion **Comparison** Rituximab 375mg/m^2 as a single intravenous infusion every week for 4 weeks[45] Chemotherapy or corticosteroids (This included cyclophosphamide, hydroxyldoxorubicin, hydrochloride,	Median (range) follow-up not reported for the population of interest **Critical outcomes** **Overall response** Overall response rate (n,%)[46]: • Siltuximab: 16/21 (76.2%) • Complete response: 9/16 • Partial response: 7/16 • Rituximab: 17/25 (68.0%) • Complete response: 5/17 • Partial response: 12/17 • Chemotherapy or corticosteroids: 12/19 (63.2%) • Complete response: 2/12 • Partial response: 10/12	This study was appraised using the JBI checklist for cohort studies: 1. No 2. Yes 3. Yes 4. No 5. No 6. Yes 7. Yes 8. No 9. Unclear 10. Unclear 11. Yes **Other comments** This retrospective study included a broad population of patients with unicentric and multicentric CD and patients who were positive or negative for HIV and

[42] Patients treated at the US centre were all adults (>18 years). However, no information was provided on the age range of patients from the database
[45] Elsewhere in the paper patients were described as receiving rituximab or rituximab-based therapy (not further defined)
[46] Complete response was a 100% improvement in CD symptoms and laboratory abnormalities. A partial response was 50-99% of CD symptoms and laboratory abnormalities returned to normal

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Retrospective cohort study **Study aim** To characterise the diagnostic features, treatments and prognosis for unicentric and MCD **Study dates** 1994 to 2014	• MCD was defined by the involvement of ≥2 lymph nodes in at least 2 separate regions **Exclusion criteria** • Patients with concomitant malignancies, HIV infection, HHV8 or POEMS syndrome • Patients without sufficient clinical data **Total sample size** n=43[43] (65 treatments) More than 50% of patients received ≥2 treatment agents. The results table includes outcomes for 65 cases of treatment for the 43 patients Siltuximab: n=21 Rituximab: n=25	vincristine and prednisone. The authors stated that the dose, order and regimen of drugs given was not uniform across patients) No details were provided about whether any concurrent treatments were received	Siltuximab was associated with a statistically significantly higher response vs chemotherapy or corticosteroids (p=0.034)[47] No statistical test comparing siltuximab and rituximab reported (see footnote) **Durability of response** There was no statistically significant difference in progression free survival rate between siltuximab and rituximab (p=0.059) There was no statistically significant difference in progression free survival rate between siltuximab and chemotherapy or corticosteroids (p=0.335) Progression free survival percentage was only presented graphically	HHV8. Some outcomes were separately reported for patients with iMCD who had received treatment with siltuximab, rituximab or chemotherapy or corticosteroids. Only these results were extracted. The primary source of patient outcomes was a retrospective review of patients treated at one US centre. However, this was supplemented by patient outcomes taken from an international database. The proportion of patient from these two sources that provided data for the population and outcomes of interest to this review was not clear. As patient outcomes came from different sources, it cannot be concluded that patients were recruited from the same population. No baseline characteristics were reported for the patient group of interest to

[43] The figure of 43 patients is taken from the table reporting outcomes for iMCD patients who received monoclonal antibody therapy and/ or chemotherapy. The breakdown of where the 43 patients were taken from is not clear. However, the authors stated that the data from the single US centre included 31 patients with iMCD (8 of which were observed only) and that 22 additional HIV and HHV8-negative patients were provided from a database. This figure of 22 patients is likely to include both unicentric and MCD patients although this is not clear

[47] In the text of the article the authors state that siltuximab was associated with a significantly higher rate of complete response than rituximab. However, the results table states that the comparison made was siltuximab vs chemotherapy or corticosteroids and does not report a comparison between siltuximab and rituximab. The figures and detail from the table are used here

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Chemotherapy or corticosteroids: n=19 **Baseline characteristics** Mean (range) age (US centre population[44]): 46 years (18 to 78) No baseline characteristics were provided for patients from the database No baseline characteristics were provided for the 43 patients with iMCD reported in the outcomes table The population included patients who were receiving first line therapy and subsequent therapy. No separate results were reported for these subgroups			this review. It is not known if the patients receiving different treatments were similar. No potentially confounding factors were identified or adjusted for in the analysis of the outcomes of interest. Cheson criteria were used to assess treatment response by the authors and by independent radiologists who reviewed the results. Results only presented graphically were not extracted. Comparisons between rituximab and chemotherapy or corticosteroids were not extracted. Median follow-up was not reported for the population of interest. It is not clear if follow-up was complete or of sufficient duration. Statistical analysis between treatments was conducted but was not clearly reported in the paper.

[44] This includes patients with unicentric CD and MCD

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				Limited information was available about the patients who provided the outcomes of interest to this review. The generalisability of the results to the NHS in England is unclear. **Source of funding:** The study was supported by grants from the National Institutes of Health National Cancer Institute.

Abbreviations
CD: Castleman disease; CI: Confidence intervals; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EMEA: Europe, Middle East and Africa; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue scale; g: gram; HHV8: Human herpesvirus-8; HIV: Human immunodeficiency virus; HR: Hazard ratio; iMCD: Idiopathic multicentric Castleman disease; kg: Kilogram; L: Litre; m: metre; mg: milligram; MCD-SS: Multicentric Castleman Disease-Symptom Scale; MCS: Mental component score; NCICTC: National Cancer Institute Common Terminology Criteria; PCR: Plasma creatinine; PCS: Physical component score; POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin pigmentation; RCT: Randomised controlled trial; SD: Standard deviation; SF: Short-Form

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisations, parallel groups) accounted for in the conduct and analysis of the trial

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Appendix G GRADE profiles

In patients with iMCD, what is the clinical effectiveness and safety of siltuximab and best supportive care compared with best supportive care alone or with standard care?

For abbreviations and footnotes see end of tables.

Table 2. Siltuximab and best supportive care compared to placebo and best supportive care

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Siltuximab	Placebo	Result		
Overall response (1 RCT)									
Tumour response rate by investigator assessment (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	27/53 (50.9%)	0/26 (0%)	Difference between groups: 50.9% (95%CI 29.2 to 70.1), p<0.0001 3/27 siltuximab responders had a complete response and 24 a partial response	Critical	Moderate
Durability of response (1 RCT)									
Durable tumour and symptomatic response rate by independent radiological review (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	18/53 (34.0%)	0/26 (0%)	Difference between groups: 34.0% (95%CI 11.1 to 54.8), p=0.0012 1/18 siltuximab responders had a complete response and 17 a partial response Median (range) duration of durable tumour and symptomatic response for siltuximab: 383 days (232 to 676)	Critical	Moderate

Durable symptomatic response rate (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	Not calculable	30/53 (56.6%)	5/26 (19.2%)	Difference between groups: 37.4% (95%CI 14.9 to 58.2), p=0.0018	Critical	High
Durable complete symptomatic response rate (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	13/53 (24.5%)	0/26 (0%)	Difference between groups: 24.5% (95%CI 1.4 to 46.2), p=0.0037	Critical	Moderate
Time to treatment failure. Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[2]	53	26	HR 0.418 (95%CI 0.214 to 0.815), p=0.0084 Median time to treatment failure (days): • Siltuximab: Not reached (95%CI 378 to not estimable) • Placebo: 134 (95%CI 85 to not estimable)	Critical	Moderate
Time to next treatment. Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	53	26	HR 0.298 (95%CI 0.137 to 0.652), p=0.0013 Median time to next treatment (days): • Siltuximab: Not reached (95%CI not estimable) • Placebo: 280 (95%CI 161 to not estimable)	Critical	High
Survival (1 RCT)									
Overall survival at 1 year (%)									
1 RCT van Rhee et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	53	26	• Siltuximab: 100% (95%CI 100 to 100) • Placebo: 92% (95%CI 72 to 98) No statistical comparison between groups	Critical	Moderate

Quality of life (1 RCT)									
Number (%) of patients achieving a ≥5-point improvement in SF-36 PCS score during the blinded treatment period. Median (range) 375 days (1 to 1,1031) for siltuximab and 152 days (23 to 666) for placebo									
1 RCT van Rhee et al 2015	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	24/50 (48%)	8/26 (31%)	No statistical comparison between groups	Important	Moderate
Number (%) of patients achieving a ≥5-point improvement in SF-36 MCS score during the blinded treatment period. Median (range) 375 days (1 to 1,1031) for siltuximab and 152 days (23 to 666) for placebo									
1 RCT van Rhee et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	34/50 (68%)	9/26 (35%)	Statistically significantly higher for siltuximab (p=0.0074)	Important	High
Symptom alleviation (1 RCT)									
Number (%) of patients achieving an improvement of ≥1.0 in total MCD-SS score during the blinded treatment period. Median (range) 375 days (1 to 1,1031) for siltuximab and 152 days (23 to 666) for placebo									
1 RCT van Rhee et al 2015	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	32/51 (63%)	13/26 (50%)	No statistical comparison between groups	Important	Moderate
MCD-SS fatigue domain score (mean, SD) at baseline and at cycle 18, day 1 (approximately 1 year) (benefit indicated by lower scores)									
1 RCT van Rhee et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	Baseline: 52 Follow-up: 29	Baseline: 26 Follow-up: 6	Baseline: • Siltuximab: 4.1 (2.4) • Placebo: 4.5 (3.3) Follow-up: (SD not reported) • Siltuximab: 2.6 • Placebo: 5.7 p=0.02	Important	High
FACIT-Fatigue score (mean, SD) at baseline and at cycle 18, day 1 (approximately 1 year) (benefit indicated by higher scores)									
1 RCT van Rhee et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	Baseline: 52 Follow-up: 29	Baseline: 26 Follow-up: 6	Baseline: • Siltuximab: 32.4 (11.0) • Placebo: 31.0 (14.6) Follow-up: (SD not reported) • Siltuximab: 38.6 • Placebo: 26.9	Important	High

							p=0.0364		
Proportion of patients with a FACIT-Fatigue baseline score of <44 who achieved an improved score of ≥44 with durability for ≥120 days									
1 RCT van Rhee et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	43	19	• Siltuximab: 35% • Placebo: 11% p=0.0475 (n not reported)	Important	High
Tumour response (1 RCT)									
Tumour response rate by independent radiological review (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	Not calculable	20/53 (37.7%)	1/26 (3.8%)	Difference between groups: 33.9% (95%CI 11.1 to 54.8), p=0.0022 2/20 siltuximab responders had a complete response and 18 a partial response. The placebo responder had a partial response	Important	High
Haematological markers (1 RCT)									
Patients (number,%) with anaemia at baseline who had ≥15g/L increase in haemoglobin concentration between baseline and week 13									
1 RCT van Rhee et al 2014	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	19/31 (61.3%)	0/11 (0%)	Difference between groups: 61.3% (95%CI 28.3 to 85.1), p=0.0002	Important	Moderate
Safety (1 RCT)									
Serious adverse events (not further defined) (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	12/53 (23%)	5/26 (19%)	3 siltuximab patients had serious adverse events judged to be related to siltuximab No Grade 4 or higher haematological or chemistry abnormalities occurred with siltuximab	Important	Moderate
Patients with ≥1 Grade ≥3 adverse event (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	25/53 (47%)	14/26 (54%)	Most common (>5% of patients) Grade ≥3 adverse events with siltuximab: fatigue (9%) and night sweats (8%).	Important	Moderate

							Most common (>5% of patients) Grade ≥3 adverse event with placebo: anaemia (12%)		
Patients with ≥1 adverse event (all grades) (number, %). Median (range) follow-up 422 days (5 to 1,051)									
1 RCT van Rhee et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	53/53 (100%)	25/26 (96%)	Most common (≥25% of patients) adverse events with siltuximab: pruritus (42%), upper respiratory tract infection (36%), fatigue (34%), maculopapular rash (34%), peripheral oedema (32%), malaise (28%), dyspnoea (25%) and peripheral sensory neuropathy (25%) Most common (≥25% of patients) adverse events with placebo: fatigue (38%) and dyspnoea (35%)	Important	Moderate

Abbreviations
CI: Confidence intervals; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue scale; g: Gram; HR: Hazard ratio; iMCD: Idiopathic multicentric Castleman disease; L: Litre; MCD-SS: Multicentric Castleman Disease-Symptom Scale; MCS: Mental component score; PCS: Physical component score; RCT: Randomised controlled trial; SD: Standard deviation; SF: Short-Form

1. Imprecision: Serious imprecision due to 0 events in the comparator arm
2. Imprecision: Serious imprecision due wide 95% confidence intervals that cross the default minimal clinically important difference lower threshold
3. Risk of bias. Serious limitations due to lack of statistical analysis

Table 3. Siltuximab compared to rituximab

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Siltuximab	Rituximab	Result		
Overall response (1 retrospective cohort study)									
Overall response rate (number, %). Median follow-up not reported									
1 retrospective cohort study Yu et al 2017	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	16/21 (76.2%)	17/25 (68.0%)	No statistical test comparing siltuximab and rituximab 9/16 siltuximab responders had a complete response and 7 a partial response 5/17 rituximab responders had a complete response and 12 a partial response	Critical	Very low
Durability of response (1 retrospective cohort study)									
Progression free survival rate. Median follow-up not reported									
1 retrospective cohort study Yu et al 2017	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	21	25	No statistically significant difference between siltuximab and rituximab (p=0.059) Progression free survival percentage only presented graphically	Critical	Very low

1. Risk of bias. Very serious limitations due to lack of information about whether the groups were similar at baseline, lack of identification of and adjustment for potential confounding factors, lack of information about the duration of follow-up and whether follow-up was complete and lack of statistical analysis
2. Risk of bias. Very serious limitations due to lack of information about whether the groups were similar at baseline, lack of identification of and adjustment for potential confounding factors and lack of information about the duration of follow-up and whether follow-up was complete

Table 4. Siltuximab compared to chemotherapy or corticosteroids

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Siltuximab	Chemotherapy/ corticosteroids	Result		
Overall response (1 retrospective cohort study)									
Overall response rate (number, %). Median follow-up not reported									
1 retrospective cohort study Yu et al 2017	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	16/21 (76.2%)	12/19 (63.2%)	Statistically significantly higher response for siltuximab (p=0.034) 9/16 siltuximab responders had a complete response and 7 a partial response 2/12 chemotherapy or corticosteroids responders had a complete response and 10 a partial response	Critical	Very low
Durability of response (1 retrospective cohort study)									
Progression free survival rate. Median follow-up not reported									
1 retrospective cohort study Yu et al 2017	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	21	19	No statistically significant difference between siltuximab and chemotherapy or corticosteroids (p=0.335) Progression free survival percentage only presented graphically	Critical	Very low

1. Risk of bias. Very serious limitations due to lack of information about whether the groups were similar at baseline, lack of identification of and adjustment for potential confounding factors and lack of information about the duration of follow-up and whether follow-up was complete

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Comparative cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- van Rhee F, Rossi JF, Simpson D, Fosså A, Dispenzieri A, Kuruvilla J, Goh YT, Cho SG, Capra M, Liu T, Casper C, Cavet J, Wong RS. Newly diagnosed and previously treated multicentric Castleman disease respond equally to siltuximab. British Journal of Haematology 2021, 192:e28-e31.
- van Rhee F, Rothman M, Ho KF, Fleming S, Wong RS, Fosså A, Dispenzieri A, Cavet J, Munshi N, Vermeulen J, Casper C. Patient-reported outcomes for multicentric Castleman's disease in a randomised, placebo-controlled study of siltuximab. Patient 2015, 8:207-216.
- van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J, Casper C. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014, 15(9):966-974.
- Yu L, Tu M, Cortes J, Xu-Monette ZY, Miranda RN, Zhang J, Orlowski RZ, Neelapu S, Boddu PC, Akosile MA, Uldrick TS, Yarchoan R, Medeiros LJ, Li Y, Fajgenbaum DC, Young KH. Clinical and pathological characteristics of HIV and HHV8-negative Castleman disease. Blood 2017, 129(12):1658-1668.

NHS England

Wellington House

133-155 Waterloo Rd

London

SE1 8UG