



## Siltuximab: a targeted therapy for idiopathic multicentric Castleman disease

Human herpes virus-8 (HHV-8)-negative or idiopathic multicentric Castleman disease (iMCD) is a rare and deadly disorder that sits at the nexus of hematology/oncology, virology and immunology. Management of iMCD has been challenging due to limited understanding of etiology and pathogenesis and few treatment options. The recent approvals in North America, Europe and Brazil of siltuximab, a monoclonal antibody against IL-6, for iMCD now provide a safe and effective therapy that targets a key aspect of pathogenesis. In the first ever randomized, placebo-controlled trial in iMCD, siltuximab significantly reduced disease burden and symptoms in a large portion (34%) of patients. The optimal dose is 11 mg/kg intravenously every 3 weeks. At this time, duration of treatment is often life-long or until treatment failure. Additional research is needed to identify biomarkers that may assist with predicting treatment effectiveness in iMCD and to investigate the role of siltuximab in HHV-8-positive MCD and pediatric iMCD patients.

**Keywords:** hematology • interleukin-6 • lymphoproliferative disorder • multicentric Castleman disease • siltuximab

### Introduction to idiopathic multicentric Castleman disease

Castleman disease (CD) describes a group of three heterogeneous lymphoproliferative disorders that share common lymph node histopathological features due to excessive proinflammatory cytokines, most notably of IL-6 [1–3]. CD can present as a single enlarged lymph node or region of lymph nodes, which is referred to as unicentric (UCD), or it can present with multiple regions of enlarged lymph nodes, which is referred to as multicentric (MCD). The epidemiology of CD is poorly understood, and results from the two existing epidemiological studies are inconsistent with one another. A study of insurance claims databases estimates the incidence of all cases of CD in the USA to be 5500–7700 new diagnoses per year [4]. Another study, authored by Robinson and colleagues, estimated the prevalence of MCD (not including UCD) to be 2.5 per million (~795 alive in the USA at any one time) [5]. Clinical

experience and expert commentary suggests that the estimated prevalence by Robinson *et al.* is likely to be closer to the real world epidemiology.

UCD patients typically have few symptoms, and surgical excision of the enlarged lymph nodes is generally curative [6,7]. The cause of UCD is unknown. MCD patients demonstrate a wide range of symptoms and disease severity. Some patients experience episodes of multicentric lymphadenopathy with mild constitutional symptoms while others experience progressive, life threatening and sepsis-like multiple organ dysfunction [2]. The 5-year survival rate of MCD in a large series was 65% [8]. Septic shock, multiorgan failure and malignancy are the most common causes of death in a systematic literature review of iMCD. Common clinical features include fatigue, fever, night sweats, generalized lymphadenopathy, weight loss, fluid retention, eruptive cherry hemangiomatosis and hepatosplenomegaly [9,10]. Laboratory

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abnormalities may include anemia, thrombocytopenia, hypoalbuminemia, elevated C-reactive protein (CRP), hypergammaglobulinemia and renal dysfunction [9]. The histopathological features of CD lymph nodes are nonspecific and can include regressed follicles ('hyaline vascular follicles'), hyperplastic follicles, interfollicular vascular proliferation and plasmacytosis. CD histological subtypes include plasmacytic (PC), hyaline vascular (HV), mixed (M) and plasmablastic variants [11].

MCD clinical and histopathological features are caused by excessive proinflammatory cytokine release [2,3,12]. Active infection with human herpes virus-8 (HHV-8) drives the excessive cytokine release, which includes a viral homologue to IL-6, in approximately half of MCD cases (HHV-8-associated MCD) [9]. These patients are often HIV positive or immunocompromised for another reason [13]. In MCD patients not infected with HHV-8, the cause of the excessive proinflammatory cytokine release is unknown, and these HHV-8-negative MCD cases are referred to as idiopathic MCD (iMCD). Proposed etiologies of iMCD include a germline mutation in a gene that regulates the immune system, pathological autoantibodies, a somatic driver mutation in a small population of malignant cells and an as yet to be discovered virus [2]. Though HHV-8-positive MCD and iMCD share common lymph node features and overlapping symptoms, there are important differences in pathogenesis and optimal treatment regimens.

HHV-8 lives in B-cells and lytically replicates in immunocompromised hosts, because it is able to avoid immune system control. Therefore, treatment of HHV-8-associated MCD focuses on B-cell depletion with rituximab and antiherpes viral therapy with ganciclovir or valganciclovir. In patients also infected with HIV, control of the HIV infection with highly active antiretroviral therapy is strongly recommended [14,15]. In a recent study, the overall 5-year survival for HHV-8-associated MCD patients on rituximab was 90% (95% CI: 81–100%) compared with 33% (95% CI: 6–60%) in 12 patients treated before introduction of rituximab (log-rank  $p < 0.001$ ) [16].

Limited understanding of iMCD pathogenesis has slowed the development of targeted therapies. For instance, the pathological, hypercytokine-secreting cell type and activated intracellular signaling pathways in iMCD are unknown and, thus, unable to be targeted [2]. While the cause of the excessive proinflammatory cytokine release in iMCD is unknown, it is clear that IL-6 is a driver cytokine in iMCD [3,17]. IL-6 is a polyfunctional, proinflammatory cytokine produced by various cell types, including monocytes, macrophages, lymphocytes, fibroblasts, endothelial cells and some tumor cells. IL-6 induces B-cell differentiation, plas-

macytosis, hypergammaglobulinemia, VEGF secretion, thrombocytosis, hepatic acute phase reactions and activation of macrophages and T cells [18]. Serum IL-6 levels are often elevated in iMCD and they typically parallel symptoms [17]. It is also important to note that there are iMCD patients with low or normal IL-6 levels [19]. Mice infected with an IL-6 expressing recombinant retrovirus and human-IL-6 transgenic mice develop a syndrome like iMCD, which improves with administration of an anti-IL-6 receptor monoclonal antibody (mAb) [20–22]. Finally, the administration of recombinant IL-6 to humans can lead to an iMCD-like syndrome [23].

The iMCD treatment literature consists mostly of case series. The first case report of anti-IL-6 therapy used to effectively treat a patient with MCD was published in 1994 [24]. In 2005, tocilizumab, an anti-IL-6 receptor mAb, was approved for MCD in Japan following an open-label trial [25]. Tocilizumab was subsequently approved for rheumatoid arthritis in the USA [26], and it is frequently used off-label for iMCD in the USA and other parts of the world. In 2014, siltuximab (Sylvant<sup>TM</sup>, Janssen Pharmaceuticals, NJ, USA), a chimeric human-murine immunoglobulin G1κ mAb that binds to IL-6, became the first and only drug approved for iMCD (e.g., HIV-negative and HHV-8-negative) in Europe [27], the USA [28], Canada [29] and Brazil [30]. Siltuximab is the only iMCD treatment that underwent a randomized placebo-controlled trial. Other therapies used to treat iMCD (off-label) include: corticosteroids and other immunosuppressive agents, B-cell depletion with rituximab, cytotoxic elimination of immune cells and immunomodulatory agents [9]. Corticosteroids can improve symptoms in iMCD, but most patients require very high doses and relapse during tapering [31]. Rituximab, which is often used first- or second-line in iMCD, is variably effective and typically does not provide long-term disease control [32–34]. Cytotoxic chemotherapeutic regimens (e.g., cyclophosphamide, doxorubicin, vincristine and prednisone [CHOP]) induce remission in a proportion of the most severely ill iMCD patients by eliminating a large portion of activated immune cells, but relapses are common and side effects are significant [35,36]. A recent systematic literature review of 129 published cases of iMCD found that 41% of patients failed first-line treatment and 22% of patients died by follow-up, with a median survival among fatal cases of 26 months (range: 1–120 months) [9].

Thus, siltuximab is an attractive treatment option given its strong safety profile, extensive investigation and effectiveness in a significant portion of patients.

### Introduction to siltuximab

Siltuximab is a glycosylated human-murine chimeric immunoglobulin mAb that binds to IL-6 with high

affinity and specificity ( $K_D = 34$  pmol/l) [37,38]. Siltuximab blocks IL-6 from binding to both the membrane-bound and soluble IL-6 receptors. Therefore, siltuximab prevents the proinflammatory and proliferative activity of IL-6 that occurs through activation of JAK1/JAK2-STAT3 and MAPK [39].

Siltuximab was studied in several other disease states including multiple myeloma [40,41], myelodysplastic syndrome [42], non-Hodgkin lymphomas [43] and several solid tumors [44]. It was well tolerated, but did not demonstrate significant benefit, so clinical development has been discontinued for most of these diseases [45]. There is an ongoing study in smoldering multiple myeloma (NCT01484275).

### Pharmacodynamics

Three of the most important ways in which siltuximab exerts its effect in iMCD is through stopping the production of acute phase reactants, such as CRP, reducing hepcidin levels to alleviate anemia, and halting the proliferation of lymphoid cells. As IL-6 is the main inducer of hepatocyte-synthesized CRP [46], CRP is a useful surrogate marker for the effect of siltuximab on IL-6 activity [37,38]. This is particularly important since IL-6 levels are no longer reliable per commercial assay after siltuximab has been initiated [38]. IL-6 is known to induce hepcidin, which is an iron regulatory peptide hormone produced by the liver that contributes to hemoglobin homeostasis and may cause anemia of inflammation [47–49]. Neutralization of IL-6 with siltuximab has been found to decrease hepcidin and improve anemia, which is believed to occur because sequestered iron is released [19]. A systematic literature review found an increased rate of malignancies among patients with iMCD than would be expected in an age-matched cohort [2]. IL-6 driven cellular proliferation may play a role in this increased rate of malignancies [50]. Therefore, siltuximab may play a role in modulating the risk of developing a malignancy.

### Pharmacokinetics & metabolism

The recommended dosage of siltuximab is 11 mg/kg administered intravenously once every 3 weeks [51]. The serum half-life for siltuximab in patients after the first infusion of 11 mg/kg is 21 days (range: 14–30 days), and it is cleared at a mean rate of 4.59 ml/kg/day [43]. Body weight is the only significant covariant [52]. After repeated dosing, there was moderate systemic accumulation, and steady-state serum concentration was reached by the sixth infusion [37,38].

CYP450 enzyme activity can be downregulated by IL-6, so siltuximab may increase metabolism of CYP450 substrates compared with before treatment with siltuximab and dosing of concomitant medi-

cations may need to be adjusted. No initial dosage adjustment is necessary for patients with baseline mild to moderate hepatic impairment or baseline mild to severe renal impairment [52]. The pharmacokinetic profile also does not appear to be altered by age, gender or ethnicity [37,38].

Only one patient out of both trials of iMCD developed detectable, non-neutralizing antibodies to siltuximab by 45 days after last dose [53]. Siltuximab can cross the placenta, so it should not be used during pregnancy or in women who may become pregnant [37,38].

### Clinical efficacy

Because of the established relationship between CD and elevated IL-6, patients with CD were included in an open-label, dose-finding, Phase I study along with non-Hodgkin lymphoma and multiple myeloma patients (see Table 1). Thirty-four patients with iMCD, one patient with HHV-8-associated MCD and two patients with UCD were placed into one of seven dosage cohorts (3–12 mg/kg administered every 1–3 weeks). Response to therapy was determined by radiological shrinkage of lymph nodes and symptomatic improvement [43]. According to central radiological review, one patient had a complete response (CR), 11 had a partial response (PR), three an unconfirmed partial response, 20 had stable disease and three had progressive disease as determined by modified Cheson criteria [54]. Nine of the 12 responders by radiological criteria had received the highest siltuximab dosage, which demonstrated a dose-related response. Treatment with siltuximab also improved clinical symptoms. Eighty-six percent of the 37 patients achieved a clinical benefit response, which was defined as improvement from baseline in one or more of six parameters and no worsening in the other parameters. Regarding the individual parameters with the greatest response, 78% of patients experienced a grade one or greater decrease in fatigue, 65% had at least a 25% decrease in the bidirectional size of the largest lymph node, 60% had at least a 5% increase in weight and 55% had at least a 2°C decrease in fever or improvement in night sweats. Only three patients died over the course of follow-up (median: 2.4 years). The drug was well tolerated. Adverse events greater than grade 2, which were possibly related to siltuximab, were only reported in 11% of CD cases. Only three CD patients discontinued treatment due to adverse events [43]. Nineteen patients from the Phase I study went on to enroll in a Phase II extension study. All patients had sustained disease control and no patients died by time of interim analysis, which occurred at a median time of 5.1 years after treatment was initiated [55].

Taken together, these data supported a safe and efficacious siltuximab dose of 11 mg/kg given over 1 h

intravenously every 3 weeks. A randomized, placebo-controlled, double-blind, multinational, Phase II trial was conducted to study the efficacy and safety of siltuximab in iMCD. This was the first randomized and largest-ever trial of iMCD. In this study, 79 iMCD patients aged 18 years or older, who met stringent inclusion criteria, were randomized (2:1) to receive either intravenous siltuximab and best supportive care (BSC; management of effusions, infections, transfusions, infusion related reactions and other supportive care) or placebo and BSC every 3 weeks until treatment failure (increase from baseline in grade  $\geq 2$  disease-related symptoms or  $\geq 2$  point worsening in ECOG-PS persisting for at least 3 weeks, new grade  $\geq 3$  disease-related symptoms, radiologic progression by modified Cheson criteria or initiation of another iMCD treatment), discontinuation of treatment, withdrawal from the study or until 48 weeks after the last subject started the study drug. Inclusion criteria included disease not only limited to cutaneous lesions, newly diagnosed or pretreated on low-dose corticosteroids ( $\leq 1$  mg/kg prednisone) for at least 4 weeks, disease symptoms greater than or equal to grade one based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and Eastern Co-operative Oncology Group Performance Status (ECOG-PS) scores of 0–2. Exclusion criteria included history of lymphoma and infection with HIV, HHV-8 or other infection. Patients could continue to receive their pretrial corticosteroid treatment at a stable or reduced dose, but could not receive a dosage increase, erythropoietin stimulating agents or any antitumor or other treatments for iMCD. Patients in the placebo group that failed therapy could cross over to receive unblinded siltuximab.

Fifty-three patients were randomized to receive siltuximab plus BSC and 26 were randomized to placebo plus BSC. The patients had a median age of 48 years, and they were enrolled in 19 countries.

The primary end point was defined as durable and symptomatic response after 48 weeks of treatment [53]. A CR for the combined end point was defined as complete disappearance of all measurable and evaluable disease using modified Cheson criteria [54] and resolution of 34 clinician-reported iMCD-related symptoms for a minimum of 18 weeks [53]. A PR was defined as a decrease in at least half of the sum of the product of the diameters of the largest lesion with at least stable disease in all other evaluable criteria for a minimum of 18 weeks. The primary end point was achieved in 34% of patients on siltuximab plus BSC and no patients on placebo plus BSC ( $p = 0.0012$ ). Seventeen of the 18 responders experienced a partial response (PR) as determined by independent reviewers. Twenty-five percent of patients on siltuximab achieved a complete

symptom response versus none on placebo ( $p = 0.0037$ ). Median duration of treatment was 375 days for the siltuximab arm and 152 days for the placebo arm because of treatment failures and discontinuations in patients on placebo. There were patients that did not achieve an official PR or CR, who continued to receive treatment at 48 weeks, as 59% of patients on siltuximab and 23% on placebo were still on treatment.

The percentage of siltuximab responders was higher in patients with greater disease severity. Of the 33 patients with an overall symptoms score of 10 or more, 42.1% responded ( $p = 0.010$ ). All 18 siltuximab responders had PC or mixed pathological subtype. None of the 18 patients with HV subtype responded, but the median time to treatment failure for HV patients was longer in the siltuximab arm (206 days) than the placebo arm (70 days) [53]. A recent subanalysis found no strong relationship between baseline IL-6 and response, and there was no association between baseline CRP and symptom scores or baseline IL-6 and symptom scores [19]. Additionally, there was no difference in the primary end point between previously treated or treatment naive patients [56].

Nineteen out of 21 patients on siltuximab with baseline anemia had an increase of 1.5 g/dl in hemoglobin by week 13 compared with none of the 11 anemic patients in the placebo arm ( $p = 0.0002$ ).

Generally, lymph node shrinkage occurred more slowly than normalization of laboratory values. The median time to resolution of lymphadenopathy was 155 days whereas median CRP levels decreased from 17.60 mg/l at baseline to 1.04 mg/l by Day 8 in siltuximab patients [53]. CRP actually increased during that same period from 4.18 mg/l to 5.63 mg/l in patients on placebo. Seventy-seven percent of patients on siltuximab experienced a reduction in CRP of 80% or more by Day 8 compared with none in the placebo arm [19]. However, CRP decrease was not associated with durable tumor and symptomatic response [53].

### Safety & tolerability

In studies of iMCD, siltuximab was generally well tolerated. The adverse events from the Phase II study that were more than 10% more frequent in the siltuximab group than the placebo group were pruritus (42% for siltuximab vs 12% for placebo), upper respiratory tract infection (36 vs 15%), maculopapular rash (34 vs 12%), localized edema (21 vs 4%), weight gain (19 vs 0%), abdominal pain (15 vs 4%), thrombocytopenia (15 vs 4%), nasopharyngitis (15 vs 4%) and hyperuricemia (13 vs 0%). Fifteen patients had at least one dose delayed due to adverse events. Though weight gain was recorded as an adverse event, iMCD patients can experience cachexia due to their disease and siltuximab.

Table 1. Clinical trials of siltuximab in HHV-8-negative multicentric Castleman disease.							
Study (year), Phase	Size (n)	Type of Castleman disease	Prior treatments	Duration	Dose of siltuximab and control arm	Clinical response	Ref.
Kurzrock <i>et al.</i> (2013), Phase I, open label	37	34 iMCD, 2 UCD, 1 HHV-8-positive MCD	Any prior treatment allowed	43 days plus option to continue treatment at the investigators discretion	3 mg/kg q2w 6 mg/kg q2w 12 mg/kg q3w 6 mg/kg qw 12 mg/kg q2w 12 mg/kg q3w 9 mg/kg or 12 mg/kg q3w No control arm	Radiologic review: – Complete response (CR): 3% – Partial response (PR): 39% – Stable disease: 56% – Progressive disease: 3% – Clinical benefit response: 86%	[43, 73]
Van Rhee <i>et al.</i> (2015), Phase II, open label, extension study	19	iMCD	Any prior treatment allowed	Ongoing (median 5.1 years, up to 7.2 years)	11 mg/kg q3w No control arm	All 19 patients alive and have sustained disease control (stable disease or better) by investigator assessment, including 8 patients who had their dosing interval increased to q6w after established prolonged PR/CR (median q6w treatment duration 11 months)	[55]
Van Rhee <i>et al.</i> (2014), Phase II, randomized, double-blind, placebo-controlled trial	79	iMCD	Any prior treatment allowed except for tocilizumab	48 weeks	11 mg/kg q3w plus BSC Control arm: placebo plus BSC	Durable tumor and symptomatic response: – Siltuximab: 34% (CR: 2%, PR: 32%) – Placebo: 0% (p = 0.0012)	[53]
<p>Best supportive care: management of effusions, infections, transfusions, infusion related reactions and other supportive care.</p> <p>Clinical benefit response: improvement from baseline in one or more of six parameters and no worsening in the other parameters. The individual response parameters included a grade one or greater decrease in fatigue, a 25% or greater decrease in the bidirectional size of the largest lymph node, a 5% or greater increase in weight, a 2°C or greater decrease in fever or improvement in anorexia.</p> <p>BSC: Best supportive care. qw: Every week. q2w: Every 2 weeks. q3w: Every 3 weeks.</p>							



tuximab has been found to increase lean body mass in patients [57]. Infusion reactions, such as chest pain, nausea and vomiting, flushing and palpitations, were observed in 8% of siltuximab patients compared with none in the placebo arm. One patient had an anaphylactic reaction, and one patient developed detectable, non-neutralizing antibodies to siltuximab 45 days after last dose. No adverse events lead to death [53].

Long-term safety data have also been reported on 19 patients (median: 5.1 years, range: 3.4–7.2 years) from an interim analysis of the Phase II extension study, which was derived from the initial Phase I study. No deaths or evidence of new or cumulative toxicity were reported with long-term treatment. The most common adverse reactions were upper respiratory tract infections (63%), diarrhea (32%), pain in extremities (21%), arthralgia (21%) and fatigue (21%) [55].

In general, duration of therapy is *ad infinitum* or until treatment failure, though patients have successfully discontinued treatment after complete remission and a prolonged maintenance period [KURZROCK R, UNPUBLISHED DATA]; longer follow up will be necessary to determine if these patients eventually relapse and if so, whether or not retreatment is successful.

### Regulatory affairs

Siltuximab was approved in April 2014 in the USA [28], June 2014 in Europe [27], December 2014 in Canada [29], and July 2015 in Brazil [30] for the treatment of HHV-8-negative/HIV-negative multicentric Castleman disease. It is the first and only approved treatment for iMCD in these regions. Siltuximab's efficacy and safety has not been established in pediatric patients and is only approved for use in adults in Europe [51,58].

### Future research questions

#### Long-term treatment

Currently, siltuximab is often considered to be a life-long therapy for iMCD patients. The extension study from the Phase I trial demonstrated that efficacy could be maintained in responders when dosage was spread out to every 6 weeks [55]. It is not known if remission can be maintained following siltuximab discontinuation. Studies of anti-IL-6 receptor mAb therapy in Japan have shown that iMCD symptoms recur when treatment is discontinued [59]. Future studies are needed to investigate the effects of tapering or discontinuing treatment with siltuximab.

#### Predictors of response & resistance, & the challenge of mixed responses

Siltuximab was found to be safe in most patients and effective in a large portion (34%) of patients in the Phase II trial [53]. Given the totality of data and cur-

rently available treatment alternatives, we believe that all iMCD patients, who are in a region where siltuximab is approved, should be treated first with siltuximab. There is also a large group of patients who do not respond to siltuximab [53], and it is currently unclear how to best treat these patients. Laboratory changes [53] and patient reported improvements in symptoms [60] occur relatively quickly in responders to siltuximab, so additions or changes in therapy should be considered if no response is observed within a few doses of starting siltuximab. Patients who do not respond sufficiently to siltuximab may need adjuvant therapy or they may need to discontinue siltuximab before starting a new treatment regimen. Unfortunately, no current biomarkers exist to predict which patients may respond to siltuximab and inform decisions about alternative options. There are iMCD patients who do not have elevated levels of IL-6 [53], and these patients' disease may be driven by a related cytokine, such as IL-1 $\beta$ , tumor necrosis factor- $\alpha$  or vascular endothelial growth factor. Of interest in this regard, Gherardi and colleagues [61] showed elevated serum levels of IL-1 $\beta$  and IL-6 in five patients with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes), four of whom had concomitant MCD. Anecdotal reports indicate that some patients resistant to siltuximab may respond to IL-1 $\beta$  inhibitors, such as anakinra (IL-1 $\beta$  receptor antagonist) [62]. Mixed responses to anti-IL6 therapy may also occur and not always indicate resistance. For instance, one 'mixed'/partial response was reported to be due to concomitant sarcoidosis [63]. As noted previously, none of the 18 iMCD patients with HV variant, which demonstrates relatively increased vascularization in the lymph node, responded to siltuximab in the Phase II study [53]. Additional research is needed to identify additional histological and clinical features as well as biomarkers that may assist with personalizing therapies for all patients with iMCD.

#### HHV-8-positive MCD patients

Siltuximab has not been formally studied in patients with HHV-8-associated MCD, because it did not bind to viral IL-6 in a nonclinical study [51,58]. However, viral IL-6 can induce human IL-6 [64], and data generated from a murine model of HHV-8-associated MCD suggest that human IL-6 may play an important role in HHV-8-associated MCD [65]. Further, a prospective analysis of HHV-8-associated MCD cases found that viral IL-6 and human IL-6 can independently or together lead to HHV-8-associated-MCD flares and suggests that viral IL-6 and human IL-6 may jointly contribute to disease severity [66]. A recent case report described a response to siltuximab in a patient with

HHV-8-positive MCD [67]. Furthermore, a study investigating the role of tocilizumab in HHV-8-associated MCD is currently enrolling patients [68]. Further research is warranted.

### Other patient populations

Pregnant women and children with iMCD have not been included in clinical trials of siltuximab, and the effect of siltuximab is not known in these populations. Siltuximab can cross the placenta, so it should not be used during pregnancy or in women who may become pregnant [37,38]. Pediatric cases of iMCD are becoming increasingly better recognized [69,70], but the effectiveness of siltuximab has not been studied in children. Considering the toxicities associated with available cytotoxic chemotherapeutic regimens, siltuximab may be a safe alternative for children with iMCD.

Also, patients with unresectable UCD and cutaneous-only CD were not included in the Phase II clinical

trial, but two case reports have demonstrated complete responses to siltuximab in two patients with cutaneous-only Castleman disease on siltuximab [71,72]. Evaluation of the effectiveness of siltuximab in patients with unresectable UCD is needed.

Currently, the lack of consensus-based diagnostic criteria for iMCD greatly hinders the prompt identification of iMCD patients, who may benefit from siltuximab. Establishing a uniform diagnostic criteria and disease activity scoring system is urgently needed to assist with the diagnosis and management of iMCD patients.

### Conclusion

Idiopathic MCD has been a challenging disease for patients and physicians because our limited understanding of etiology and pathogenesis slowed progress for drug development. Recently, a major breakthrough occurred for the iMCD patient and physician com-

#### Executive summary

##### Mechanisms of action

- Siltuximab (Sylvant®, Janssen Pharmaceuticals, NJ, USA) is a chimeric human-murine monoclonal antibody (mAb) directed against IL-6, a multifunctional, proinflammatory and proliferative cytokine.
- HHV-8-negative (idiopathic) multicentric Castleman disease (iMCD) is characterized by constitutional symptoms, lymph node enlargement and multiple organ system dysfunction due to excessive release of IL-6 and other proinflammatory cytokines.
- Siltuximab binds IL-6 and prevents it from binding to the soluble and the membrane-bound IL-6 receptor, blocking IL-6's activity in iMCD.

##### Pharmacokinetic properties

- Serum half-life is 21 days (range: 14–30 days).
- It is cleared at a mean rate of 4.59 ml/kg/day.
- Steady-state serum concentration is reached by the sixth infusion.

##### Clinical efficacy

- Siltuximab improves symptoms and shrinks lymph nodes significantly in iMCD.
- Siltuximab induced a durable complete or partial symptomatic response and lymph node response in 34% of patients in a randomized, placebo controlled registration trial.
- Improvement in laboratory values and symptoms occurred more quickly than lymph nodes regression.
- Existing data suggest that patients who initially respond will experience prolonged remission.
- The ability to discontinue treatment and maintain remission has not been evaluated, but findings from anti-IL-6 receptor mAb treatment in iMCD suggest that administration must be life long.
- Serum IL-6 levels did not significantly predict response to siltuximab in the Phase II trial.
- No biomarkers have been identified to predict response to therapy.

##### Safety & tolerability

- There was only one case of an anaphylactic reaction to siltuximab in the clinical trials for siltuximab.
- Commonly reported side effects in the Phase II studies included pruritus, upper respiratory tract infection, maculopapular rash and localized edema.
- Most patients have few if any side effects, and patients often feel better on siltuximab, perhaps because the effects of IL-6 are attenuated.

##### Drug interactions

- No known drug interactions.
- CYP450 enzyme activity can be downregulated by IL-6, so siltuximab may increase metabolism of CYP450 substrates compared with before treatment and dosing of concomitant medications may need to be adjusted.

##### Dosage & administration

- Siltuximab is available as an intravenous infusion of 11 mg/kg administered every 3 weeks.
- Siltuximab has not been evaluated as a second line therapy for iMCD or in combination with other treatments.

munity when siltuximab became the first approved therapy for iMCD in the USA [28], Europe [27], Canada [29] and Brazil [30] based on results from the only randomized controlled trials in iMCD. The drug is remarkably well tolerated even for long-term use, particularly relative to conventional chemotherapy and immunosuppressive therapies. A significant portion of patients shows clinical benefit with siltuximab, including about one-third who achieve a partial or complete response. Greater education about iMCD is needed to improve recognition now that there is a safe and effective therapy. Moving forward, future research is needed to assess the optimal duration of treatment in responders, investigate predictive biomarkers and new therapeutic targets for nonresponders and evaluate siltuximab in MCD populations not previously studied. ACCELERATE, a global patient registry and nat-

ural history study of iMCD that will launch in 2016, will help to facilitate the above efforts by generating real-world data and clinical evidence to correlate with translational research.

### Financial & competing interests disclosure

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