A Phase I, Open-Label Study of Siltuximab, an Anti-IL-6 Monoclonal Antibody, in Patients with B-Cell Non-Hodgkin’s Lymphoma, Multiple Myeloma, or Castleman’s Disease

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**Running head:** Phase I, Open-Label Siltuximab in Hematologic Malignancies

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This manuscript presents original, integrated results of a phase I study of siltuximab. Preliminary results on 23 of 37 patients with Castleman’s disease from this study have been previously published as:


Preliminary or partial results from this study have also been presented as the following abstracts:


• van Rhee F, Fayad L, Borghaei H, et al. CNTO 328, an anti-interleukin (IL)-6 monoclonal antibody (mAb) - preliminary results of subjects with Castleman's disease from a phase 1 study in selected hematological malignancies. 48th Annual Meeting of the American Society of Hematology; 2006 December 9-12; Orlando, FL. Abstract 2728.

Statement of Translational Relevance

Interleukin (IL)-6 is involved in the pathogenesis of B-cell lymphoid malignancies and multiple myeloma. Overproduction of IL-6 from affected lymph nodes is responsible for systemic manifestations in Castleman’s disease (CD), an atypical lymphoproliferative disorder. In this phase I, open-label, dose-finding study, we demonstrate that siltuximab, a chimeric anti-IL-6 monoclonal antibody, has clinical activity as a single agent in patients with B-cell non-Hodgkin’s lymphoma or multiple myeloma (MM). A high rate of clinical response was seen in CD patients, including similar rates of radiologic response in all 3 histological types of multicentric CD. There was no apparent dose-related or cumulative toxicity across all 3 disease indications after a maximum duration of treatment of 60.5 months. A dose of 12 mg/kg every 3 weeks was recommended based on the high response rates in CD and the sustained C-reactive protein suppression. Randomized studies of siltuximab are ongoing in multicentric CD and MM.
ABSTRACT

Purpose: To evaluate the safety and pharmacokinetics of siltuximab, an anti-interleukin-6 chimeric mAb in patients with B-cell non-Hodgkin’s lymphoma (NHL), multiple myeloma (MM), or Castleman’s disease (CD).

Experimental Design: In an open-label, dose-finding, seven-cohort, phase I study, patients with NHL, MM, or symptomatic CD received siltuximab 3, 6, 9, or 12 mg/kg qw, q2w, or q3w. Response was assessed in all disease types. Clinical benefit response (CBR: composite of hemoglobin, fatigue, anorexia, fever/night sweats, weight, largest lymph node size) was also evaluated in CD.

Results: Sixty-seven patients received a median of 16 siltuximab doses for a median of 8.5 (maximum 60.5) months; 29 were treated ≥1 year. There was no DLT, antibodies to siltuximab, or apparent dose-toxicity relationship. The most frequently reported possibly drug-related AEs were thrombocytopenia (25%), hypertriglyceridemia (19%), neutropenia (19%), leukopenia (18%), hypercholesterolemia (15%), and anemia (10%). None of these events led to dose delay/discontinuation except for neutropenia and thrombocytopenia (n=1 each). No treatment-related deaths occurred. CRP suppression was most pronounced at 12-mg/kg q3w. Mean terminal-phase half-life ranged 17.73–20.64 days. 32/37 (86%) CD patients improved in ≥1 CBR component; 12/36 evaluable CD patients had radiologic response (CR, n=1; PR, n=11), including 8/19 treated with 12 mg/kg; 2/14 (14%) evaluable NHL patients had PR; 2/13 (15%) MM patients had CR.

Conclusion: No dose-related or cumulative toxicity was apparent across all disease indications. A dose of 12-mg/kg-q3w was recommended based on the high response rates in CD and the sustained CRP suppression. Randomized studies are ongoing in CD and MM.
INTRODUCTION

Interleukin (IL)-6 is involved in the pathogenesis of B-cell lymphoid malignancies and plays an important role in multiple myeloma (MM), inducing proliferation and preventing programmed cell death in neoplastic plasma cells (1-4). High serum IL-6 levels correlate with worse prognosis and survival in lymphoma and MM patients (5-11). Castleman’s disease (CD) is an atypical lymphoproliferative disorder. Overproduction of IL-6 from affected lymph nodes is responsible for systemic manifestations (12). Targeting IL-6 signaling by tocilizumab, a humanized IL-6 receptor antibody, improved or resolved systemic symptoms and associated laboratory abnormalities with reduction in lymphadenopathy in plasma-cell multicentric CD (MCD) patients in a Japanese phase II study (13, 14).

Siltuximab is a chimeric (murine-human) monoclonal antibody (mAb) with high binding affinity for human IL-6 (15-17). This study evaluated the safety and pharmacokinetics of siltuximab in patients with B-cell non-Hodgkin’s lymphoma (NHL), MM, or CD. Based on emerging data (18), dosage regimens with escalating dose intensity were planned to evaluate dose-response relationship, safety, and to select the dose for future studies. Interim results from the study have been reported on 23 CD patients (19). Herein, we report integrated dose-escalation, safety, pharmacokinetics, pharmacodynamics, and efficacy results from a completed phase I study of siltuximab in 67 treated patients with NHL (n=17), MM (n=13), or CD (n=37, including plasma-cell, hyaline vascular, and mixed cellularity histology) and including mature safety data on prolonged treatment for up to 60.5 months.

METHODS

Patients
Eligible patients were ≥18 years old and had histologically documented B-cell NHL (including chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL] with ≥1 measurable lesions or >5000/μL mature-appearing peripheral blood lymphocytes, Waldenström’s macroglobulinemia [WM] with measurable serum M-protein, diffuse large B-cell lymphomas, extranodal marginal zone B-cell mucosa-associated lymphoid tissue [MALT] lymphoma, follicular lymphoma, mantle cell lymphoma); MM; or symptomatic CD ( multicentric/unresectable unicentric). Other key entry criteria and corticosteroid use rules have been previously described (19). This study was conducted according to the Declaration of Helsinki and was approved by the local institutional review board for each study site. All patients provided written informed consent.

**Study Design**

This was an open-label, seven-cohort, phase I study; cohorts 1 to 6 enrolled patients with B-cell NHL, MM, or CD, and cohort 7 only enrolled CD patients. Cohorts 1 to 5 evaluated escalating siltuximab doses administered via a 2-hour intravenous (IV) infusion at 3 mg/kg q2w, 6 mg/kg q2w, 12 mg/kg q3w, 6 mg/kg qw, and 12 mg/kg q2w, respectively, with increasing dose intensity at 1.5, 3, 4, and 6 mg/kg/week. Enrollment in cohorts 1 to 5 proceeded sequentially if ≤1 of 6 patients in a cohort had a dose-limiting toxicity (DLT) upon data monitoring committee (DMC) review. Cohort 6 evaluated a shorter siltuximab administration via a 1-hour IV infusion at 12 mg/kg q3w. If ≤1 of 6 initial patients in Cohort 6 had a DLT, expansion to 12 patients was allowed upon DMC review. Cohort 7 was an extension cohort to further evaluate siltuximab at 9 mg/kg q3w (cohort 7a) or 12 mg/kg q3w (cohort 7b) via a 1-hour IV infusion in CD patients in order to optimize dose and endpoint selection for the MCD registration study.
The treatment period was 43 days for cohorts 1 to 6, and patients received 3, 4, or 7 doses of siltuximab for dosing schedules of q3w, q2w, or qw, respectively. At the investigator’s discretion, responders in cohorts 1 to 6 achieving stable disease (SD) or better could receive extended treatment. After administration via 1-hour IV infusion was deemed safe, patients in cohorts 1 to 5 who had received $\geq$1 extended dose over a 2-hour IV infusion were allowed to receive subsequent doses via a 1-hour IV infusion. Patients in cohort 7 received doses until progressive disease (PD) or unacceptable/unmanageable treatment-related toxicity. At study completion (April 2011), all ongoing patients still benefiting from siltuximab treatment had the option to continue siltuximab treatment in other studies.

Safety

All treatment-emergent adverse events (AEs) were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0. DLT was defined as any treatment-related nonhematologic toxicity grade $\geq$3 or any investigator-attributed allergic/hypersensitivity reaction grade $\geq$2 observed before the second siltuximab infusion in cohorts 1 to 6.

Pharmacokinetics

Pharmacokinetics sampling and analysis methods are described elsewhere (Supplementary Methods).

Immunogenicity

Serum samples were collected pre-dose at day 1; follow-up weeks 12, 18, and 24; and if a reaction during administration resulted in study-agent discontinuation and were evaluated using a validated bridging immunoassay in which siltuximab-derived reagents were used to capture and detect antibodies to siltuximab.
**Efficacy**

Disease assessments were performed on days 36 and 57 and every 9 to 12 weeks thereafter for cohorts 1 to 6 and every 2 cycles from cycle 4 to 18 and then every 4 cycles for cohort 7. For NHL patients, disease response was based on investigator assessment of Cheson criteria (1999) (20) except for CLL/SLL, which were evaluated by Cheson criteria (1996) (21), and WM, which was evaluated by Weber criteria (2003) (22). For MM patients, disease response was based on investigator assessment of Bladé criteria (1998) (23). For CD patients, disease response was evaluated using Cheson criteria (1999) modified to include the assessment of measurable cutaneous lesions as previously described (19) and was independently reviewed by central radiology facility CoreLab (Princeton, NJ).

Clinical benefit response (CBR) was evaluated by an investigator for CD patients on days 36 and 57 and during extended treatment for cohorts 1 to 6 and every cycle for cohort 7. CBR was defined as improvement from baseline in ≥1 and no worsening in the remaining of the following: ≥2 g/dL increase in hemoglobin without transfusions; ≥1 grade decrease in fatigue; ≥1 grade decrease in anorexia; ≥2°C decrease in fever/return to 37°C or improvement in night sweats; ≥5% increase in weight; or ≥25% decrease bidimensionally in the size of the largest lymph node (19). Best CBR during the study is reported.

**Pharmacodynamics**

Levels of C-reactive protein (CRP), a downstream marker for IL-6 activity, significantly correlated with IL-6 levels in NHL patients (24), and anti-IL-6 treatment decreased CRP in B-lymphoproliferative disorders and MM (15). We therefore measured CRP concentrations as a surrogate marker for IL-6 bioactivity.
IL-6 is a potent inducer of hepcidin, a liver-produced iron regulatory hormone implicated in anemia of lymphoma, MM, and CD (25-27). Siltuximab treatment has been associated with hemoglobin increases and hepcidin decreases in renal cancer patients in an earlier clinical study (28). Hepcidin evaluation was performed retrospectively in MM and CD patients to further investigate the association between changes in hepcidin levels and hemoglobin improvement.

Methods for the biomarker analyses are described elsewhere (Supplementary Methods).

**Statistical Analyses**

Descriptive statistics were used to summarize data. No formal hypothesis testing was planned. A minimum of 6 patients was planned per cohort for Cohorts 1 to 5. Six (with potential expansion to 12) patients were planned for Cohort 6. Twelve and up to 20 patients were planned, respectively, for Cohorts 7a and 7b. Other statistical methods have been previously described (19).
RESULTS

From June 2005 to September 2009, 67 patients were enrolled at 9 centers in the US. Forty-seven (70%) patients discontinued study treatment, including 13 (19%) due to disease progression, 7 (10%) due to AEs (including 4 possibly related to study agent), and none due to death (Fig. 1). Other reasons for discontinuation were lack of response ($n=9$ [13%]), completion of the study-treatment period without further siltuximab administration ($n=8$ [12%]), consent withdrawal or personal reasons (each $n=3$ [4%]), drug hold ($n=2$ [3%]), or protocol violation or loss to follow-up (each $n=1$ [1%]). This study reports all available data at study closure in April 2011, when the last enrolled patient had been treated for 7 months and the maximum treatment duration was 60.5 months. At that time, 20 (30%; 1 MM and 19 CD) patients who were still receiving siltuximab continued to receive single-agent siltuximab in other studies.

Of the 67 treated patients, 17 (25%) had NHL, 13 (19%) had MM, and 37 (55%) had CD (Table 1). Approximately half of patients were male in NHL (53%), MM (46%), and CD (51%) disease types; and most were Caucasian (94%, 77%, 73%, respectively). Median age was 69, 57, and 48 years in NHL, MM, and CD, respectively. Fifty-four (81%) patients had prior therapy, 10 (15%) had autologous transplant, 8 (12%) had radiotherapy, and 7 (10%) had cancer-related surgery. The median number of prior systemic therapies was 2 (range 0, 17). Median disease duration in NHL, MM, and CD patients was 3.5 (range 0.4, 16.6) years, 3.0 (range 1.4, 9.5) years, and 0.7 (0.1, 7.8) years, respectively. A majority of patients had a Karnofsky performance status score of 80 (NHL 29%, MM 62%, CD 41%) or $\geq$90 (NHL 59%, MM 31%, CD 41%). Twelve (32%) of 37 CD patients were newly diagnosed at baseline, 35 had multicentric disease, and only 1 was HHV-8-positive.

Safety
Patients received a median of 16 (maximum 110) siltuximab doses (Table 2). Median treatment duration was 8.5 (maximum 60.5) months, including a clinical hold due to drug supply issue that interrupted the treatment of 7 patients for 2.5 to 5.3 months. No DLTs were observed in cohorts 1 to 6 per DMC review after each cohort. After completion of the cohort 6 safety review, the DMC determined that the safety profiles of siltuximab administered as a 1-hour versus 2-hour IV infusion were similar; therefore, the 1-hour infusion was used for all future patients, and enrolled patients were allowed to switch to 1-hour infusion.

No dose-related toxicity was apparent. AEs reported in ≥15% of patients overall regardless of relationship to siltuximab are shown in Fig. 2A; most AEs were low grade except for grade 3–4 neutropenia (21%) and grade 3 hypertension (9%). Hypertension was manageable by antihypertensive medications and did not lead to any study-agent discontinuations. Forty-four (66%) patients had all-grade AEs of infection; the all-grade infection event rate per patient-year in NHL, MM, and CD patients was 5.2, 1.8, and 1.9, respectively, and was 2.1 in all treated patients. Most infections were low grade and not reported in more than 1 patient. The most common infections regardless of relationship to siltuximab were upper respiratory tract infection (URTI; 39%), urinary tract infection (UTI; 16%), sinusitis (12%), cellulitis (9%), nasopharyngitis (7%), and ear infection (6%); among these, 1 case of URTI and 4 cases of cellulitis occurred at grade ≥3.

The most frequently reported all-grade AEs considered possibly related to siltuximab were thrombocytopenia (25%), neutropenia (19%), hypertriglyceridemia (19%), leukopenia (18%), hypercholesterolemia (15%), and anemia (10%; Fig. 2B). However, none of these events led to dose delay or discontinuation except for neutropenia and thrombocytopenia (each n=1). Grade ≥3 AEs possibly related to siltuximab were reported more frequently in patients with MM
(69%) than NHL (35%) or CD (11%). Of these, only neutropenia (n=11) and thrombocytopenia (n=3) were reported in more than 1 patient, with only 1 case each of grade 4 neutropenia, thrombocytopenia, sepsis, and hyperlipidemia.

Eight (12%) patients (2 NHL, 3 MM, 3 CD) permanently discontinued siltuximab due to AEs, including 4 patients with AEs more likely associated with PD (renal impairment, relapsed diffuse large B-cell lymphoma, abdominal pain) and 4 patients with AEs most likely related to siltuximab (neutropenia in 1 NHL patient, thrombocytopenia/peripheral sensory neuropathy in 1 MM patient each, and drug eruption [erythematous rash] in 1 CD patient). Four patients experienced reversible infusion-related reactions (grade 3 hypertension, grade 2 rash, grade 1 pruritus, grade 1 dizziness and flushing) that did not recur or lead to treatment discontinuation. Three deaths occurred within 90 days of the last siltuximab dose, including 2 (3%) because of an AE (PD in a NHL patient considered not related to siltuximab and renal impairment in a MM patient considered unlikely related to siltuximab) and 1 CD patient who died due to other reasons (sepsis after receiving subsequent chemotherapy that was considered not related to siltuximab).

There was no evidence of cumulative toxicity upon prolonged exposure. Twenty-nine patients were treated for 1 year or longer; none of these patients discontinued treatment due to an AE, and there were no treatment-related deaths. There was no increase in the incidence of grade ≥3 AEs or SAEs over time. Grade ≥3 AEs regardless of relationship to siltuximab were reported more frequently in year 0–1 (52%) and year 1–2 (41%) than in year 2–3 (21%) and year >3 (33%). SAEs regardless of relationship to siltuximab did not increase over time (n=4 in year 0–1, n=5 in year 1–2, n=2 in year 2–3, n=4 in year >3).

Pharmacokinetics
For cohorts 1 to 6, a summary of siltuximab pharmacokinetic parameter estimates after the first administration and day 43 administration are presented in Table 3. Serum concentrations of siltuximab declined in a bi-exponential manner, with a mean terminal-phase half-life following the first dose ranging from 17.73 to 20.64 days and the mean clearance ranging from 4.03 to 4.59 mL/day/kg. Following the first dose and repeated doses, approximate dose-proportional increases in maximum observed concentration (Cmax) and area under the serum concentration-time curve (AUC0-t) were observed. The accumulation following repeated doses was consistent with the terminal-phase half-life following the first dose, suggesting no time-dependent changes in pharmacokinetics. No apparent differences in pharmacokinetic profiles were observed when comparing patients with NHL, MM, or CD (Supplementary Fig. S1).

**Immunogenicity**

None of the 31 patients with appropriate samples, defined as having ≥1 sample collected after dosing, were positive for antibodies to siltuximab.

**Efficacy**

Of the 14 evaluable NHL patients, 2 (WM treated with 6 mg/kg q2w, extranodal marginal zone B-cell MALT lymphoma treated with 12 mg/kg q3w) had confirmed PRs lasting 4.1 and 6.2 months, 7 had SD (range 0.9, 5.6 months), and 5 had PD. Of the 13 evaluable MM patients, 2 (treated with 6 mg/kg qw and 12 mg/kg q3w) had confirmed CR with response duration lasting 11.7 and 16.7 months, 8 had SD (range 0.5, 18.0 months), and 3 had PD. Supplementary Fig. S2 shows serum CRP and gamma M-spike levels over time for 1 of the 2 MM patients with CR. Among the 36 evaluable CD patients, according to central radiologic review, 1 had a best response of CR, 11 had a best response of PR, 3 had unconfirmed PR, and 20 had SD (median 6.2 [range 1.3+, 22.0+] months), and 1 had PD. Of note, 5 of 18 patients with hyaline vascular
CD, 1 of 2 patients with mixed cellularity CD, and 6 of 17 patients with plasma-cell CD had radiologic response. Eleven of 12 responders with CD (1 CR, 10 PR) were without PD at study completion and were censored at the last radiologic assessment for time-to-event analysis. Based on Kaplan-Meier estimate, their median duration of response was not reached; using descriptive statistics, their median response duration was CR 6.0+ months, PR 11.1+ (range 5.6+, 34.6+) months. After a median follow-up of 29.4 months, the median time to progression was not reached for responders with CD. The 1 CR and 8 of 11 PRs in CD were achieved at the highest dose of siltuximab (12 mg/kg). In addition, mean hemoglobin level increased 1–2 g/dL over time in all cohorts at almost all timepoints tested. This trend was most apparent in cohort 7, possibly due to longer siltuximab treatment in these CD patients (Fig. 3).

Of the 37 CD patients evaluable for CBR, 32 (87%) improved in ≥1 component, 28 (76%) improved in ≥2 components, 21 (57%) improved in ≥3 components, and 16 (43%) improved in ≥4 components (Table 4). The majority of CD patients improved in fatigue (78%), size of the largest lymph node (65%), weight (60%), and fever/night sweats (51%) with siltuximab.

Median overall survival was 67.8 months for all treated patients, 33.1 months for NHL patients (with a median duration of 2.5 years follow up), and was not reached for patients with MM or CD. Only 6 of the 13 MM patients had died after a median of 3.3 years of follow-up. Only 3 (8%) of the 37 CD patients had died after a median follow-up of 2.4 years.

Pharmacodynamics

Decreases from baseline in CRP concentration were observed as early as day 8 in cohorts 1 to 6 across all disease types, with median levels remaining low at later timepoints. CD patients treated with 12 mg/kg q3w showed greater CRP decrease (Cohort 7b: 77% median reduction)
than those treated with 9 mg/kg q3w (Cohort 7a: 52% median reduction, both at cycle 3 day 1) (Supplementary Table S1).

Twenty-seven (42%) of 64 tested patients showed evaluable baseline IL-6 concentrations above the level of detection. Circulating serum IL-6 levels were not predictive of clinical response in the limited number of patients tested.

Hepcidin decreased post-treatment in most (97%) MM and CD patients, with 75% of these patients showing an increase in hemoglobin of ≥1.5 g/dL.

There were no apparent treatment-related changes in the serum levels of a select panel of cytokines associated with inflammation, markers of angiogenesis (except a decreasing trend of VEGF concentrations in some patients), or bone resorption markers.

Analysis of markers associated with the IL-6 pathway (p-STAT1, p-STAT3, p-STAT5) in T cells, B cells, and monocytes from peripheral blood showed a decreasing trend in the expression levels of these markers, with no apparent association with clinical response. Exploratory immunohistochemical analysis of IL-6 and markers associated with the IL-6 pathway (p-STAT3 and p-MAPK) indicated cytoplasmic, nuclear, and stromal staining of these markers in tissue samples. An association of IL-6 and IL-6 pathway marker expression with clinical response was not evident in the very limited number (n=11) of samples tested and requires further evaluation.
DISCUSSION

In this large phase I study of 67 treated patients with B-cell NHL, MM, or CD, the multiple dosing regimens of the anti-IL-6 mAb siltuximab tested in all 3 disease types were well tolerated with no DLTs observed. The most frequently reported AEs considered by investigators to be possibly related to siltuximab were thrombocytopenia, neutropenia, hypertriglyceridemia, leukopenia, hypercholesterolemia, and anemia. These events were all laboratory-related, transient, and reversible. Interestingly, hemoglobin increase was also observed in some patients, especially in MCD (Fig. 3). Sixty-six percent of patients had at least 1 infection during treatment, although most were low-grade. The infection event rate per patient-year was 5.2, 1.8, and 1.9 for NHL, MM, and CD patients, respectively, which is not unexpected in each disease type, especially through an observation period encompassing multiple years. A contribution of IL-6 inhibition to the occurrence or severity infections cannot be excluded a priori but is impossible to quantify in this dataset since a background incidence is to be expected. In a recently published randomized placebo-controlled study of the anti-IL-6 receptor mAb tocilizumab in systemic juvenile idiopathic arthritis (29), the event rate of infections per patient-year reported in the placebo group (2.9) and in the tocilizumab group (3.4 during double-blind phase, 3.0 during open-label treatment) was similar to the event rate of 2.1 per patient-year in our study. Reversible infusion reactions in this study were reported in only 4 (6%) patients, who were all able to continue siltuximab with or without prophylactic treatment without recurrence. Only 4 (6%) patients discontinued due to a possibly siltuximab-related AE, and no siltuximab-related deaths were reported through >3 years of treatment. The safety profile of siltuximab was similar at all dose levels. Siltuximab could be given for a prolonged duration without evidence of
cumulative toxicity, with a median duration of treatment of 8.5 (maximum 60.5) months and 29 (43%) of 67 patients treated for ≥1 year.

Serum concentrations of siltuximab following the first dose declined in a bi-exponential manner with a mean terminal half-life ranging from approximately 18 to 21 days. Clearance was dose-independent and ranged from 4.0 to 4.6 mL/day/kg. Additionally, apparent dose-proportional increases in the Cmax and AUC0-t were observed following the first dose and repeated doses. This pharmacokinetic behavior is consistent with the expected behavior of an immunoglobulin G1 subtype mAb and its mechanism of action targeting a soluble ligand (30). For the same dose and schedule, the first-dose pharmacokinetic parameters estimates of Cmax and AUC0-t are similar to the values previously reported in renal cell carcinoma patients (18). Additionally, the observed accumulation following repeated doses to steady-state in this study is consistent with the previously reported half-life of approximately 17 days.

Siltuximab-neutralized antibody-IL-6 complexes distort current immunologic-based IL-6 quantification methods, therefore, accurate quantification of IL-6 in post-treatment samples is not currently possible. Additionally, systemic IL-6 levels do not necessarily reflect IL-6 concentrations in the tumor niche or the IL-6 dependence of tumor cells, which are more likely to influence response to treatment (31). Therefore we measured CRP as a pharmacodynamic marker for IL-6 bioactivity. CD patients treated with 12 mg/kg q3w showed greater decreases in CRP than those treated with 9 mg/kg q3w. This is in agreement with the observed dose-response relationship for clinical benefit in CD patients. However, for MM and NHL, the small number of patients in each dose cohort makes it difficult to examine the true relationship between CRP suppression and clinical response.
The cohort of 37 CD patients reported here is to our knowledge the largest dataset of CD patients prospectively studied in a therapeutic trial. The clinical activity of siltuximab was long-lasting in this CD cohort, as demonstrated at the time of study closure by 65% of CD patients having been treated long-term for ≥12 months. One CD patient treated with siltuximab 12 mg/kg q3w and then q6w as maintenance therapy after achieving CR for a total of 57.3 months continues to receive siltuximab along with 18 other CD patients in an extension protocol. Only 3 (8%) of the 37 CD patients had died after a median follow-up of 2.4 years, which is consistent with the retrospective survival data reported by Dizpenzieri et al. (32) and Talat et al. (33). Although only a minority of NHL or MM patients responded, the 2 CRs seen in MM are notable, including 1 MM patient who continued siltuximab treatment after study closure through a single-patient compassionate use program. The 13 MM patients in our study had received a median of 4 prior lines of systemic therapy, and 6 (46%) had died after a median follow-up of 3.3 years, which is consistent with the mortality rate seen in a cohort of MM patients who similarly received 4 prior lines of treatment (34). Median survival was 33.1 months for NHL patients after a median follow-up of 2.5 years. Because a heterogeneous population of 17 NHL patients with 6 different subtypes were included in this study, it is difficult to compare their outcomes with any historical data.

Importantly, in addition to the high response rates in seen in CD patients, the radiologic response rate was similar in all 3 histologic types of CD (6/17 plasma-cell, 5/18 hyaline vascular, and 1/2 mixed cellularity). To date, response has only been reported with tocilizumab in plasma-cell CD patients (14). Because the majority of CD patients with unicentric disease have the hyaline vascular variant (32, 33), it is therefore possible that siltuximab may also have clinical benefit in unicentric CD patients who are unsuitable for surgery.
The clinical activity of siltuximab was most evident at the higher dose levels. The efficacy data suggest a dose response, with 1 CR and 8 of 11 PRs seen in CD patients treated at 12 mg/kg, regardless of dosing schedule. Among the 4 responders in NHL or MM patients, durable response was seen with 12 mg/kg q3w, which supports the above observation in CD responders. Furthermore, 12 mg/kg q3w siltuximab was safe and well tolerated, with no DLTs observed. To date, no therapy has been shown to be effective for MCD in a randomized trial. The response rates observed in this MCD population with severe disease, as evidenced by their low performance scores, is likely to be an important addition to the available therapeutic options for MCD should these preliminary efficacy estimates be borne out in an ongoing randomized controlled trial (35). In addition, preliminary pharmacokinetic/pharmacodynamic modeling results showed that this dose would decrease CRP to below 1 mg/L in MCD patients (36). Pharmacokinetic/pharmacodynamic modeling suggests that lower doses, including 9 mg/kg q3w, only decrease CRP to below 4 mg/L throughout dosing (18). Results of the current study support a dose intensity equivalent to 12 mg/kg q3w for future clinical development. Randomized trials of 12 mg/kg q3w siltuximab in MM and MCD are ongoing.

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Table 1. Baseline demographics and disease characteristics

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<td>61 ± 10.2</td>
<td>47 ± 13.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 ± 14.5</td>
<td>90 ± 22.0</td>
<td>86 ± 31.6</td>
</tr>
<tr>
<td>Karnofsky</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>80</td>
<td>5</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>90</td>
<td>7</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>100</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>3.5 [0.4, 16.6]</td>
<td>3.0 [1.4, 9.5]</td>
<td>0.7 [0.1, 7.8]</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>IV</td>
<td>13</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Category</td>
<td>n1</td>
<td>n2</td>
<td>n3</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>17</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Autologous transplant</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Cancer-related surgery</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>17</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>1 regimen</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>2 regimens</td>
<td>6</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>3 regimens</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>≥4 regimens</td>
<td>6</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

Data presented as n, mean ± standard deviation, or median [range]. Abbreviations: CD, Castleman’s disease; MM, multiple myeloma; NA, not applicable; NHL, non-Hodgkin’s lymphoma.
Table 2. Disease type and exposure

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cohort 7&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cohort 7&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg</td>
<td>6 mg/kg</td>
<td>12 mg/kg</td>
<td>6 mg/kg</td>
<td>12 mg/kg</td>
<td>12 mg/kg</td>
<td>9 mg/kg</td>
<td>12 mg/kg</td>
</tr>
<tr>
<td>q2w</td>
<td>q2w</td>
<td>q3w</td>
<td>qw</td>
<td>q2w</td>
<td>q3w</td>
<td>q3w</td>
<td>q3w</td>
</tr>
<tr>
<td>Patients treated</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphomas</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Extranodal marginal zone B-cell MALT lymphoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Waldenström’s macroglobulinemia</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Castleman’s disease</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Unicentric</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Multicentric</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Duration of siltuximab administration, months</td>
<td>3.4 [1.4, 38.4]</td>
<td>2.8 [0.5, 60.5]</td>
<td>17.0 [0.0, 58.1]</td>
<td>5.4 [1.4, 51.6]</td>
<td>34.1 [1.4, 48.2]</td>
<td>4.9 [0.0, 39.8]</td>
<td>23.1 [0.0, 38.7]</td>
</tr>
<tr>
<td>Total siltuximab dose received, mg</td>
<td>2159.2 [1000, 48631]</td>
<td>3300.0 [1125, 104479]</td>
<td>14753.5 [893, 2113]</td>
<td>8884.8 [4000, 723]</td>
<td>57526.8 [759, 723]</td>
<td>6553.6 [723, 6670]</td>
<td>28902.7 [759, 88109]</td>
</tr>
</tbody>
</table>

Data presented as $n$ or median [range]. Abbreviations: MALT, mucosa-associated lymphoid tissue. * Patients in these cohorts received siltuximab via a 1-hour IV infusion.
Table 3. Siltuximab pharmacokinetic parameter estimates for cohorts 1 to 6

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg q2w</td>
<td>6 mg/kg q2w</td>
<td>12 mg/kg q3w</td>
<td>6 mg/kg qw</td>
<td>12 mg/kg q2w</td>
<td>12 mg/kg q3w^a</td>
</tr>
<tr>
<td>Patients evaluable</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Following day 1 administration

AUC<sub>0-t</sub> (µg.day/mL)<sup>b</sup>

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>400.5 ± 81.14</td>
<td>548.2 ± 162.40</td>
<td>2116.7 ± 787.85</td>
<td>549.6 ± 180.94</td>
<td>2046.5 ± 162.49</td>
<td>1720.4 ± 674.44</td>
</tr>
</tbody>
</table>

Cmax (µg/mL)

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>55.0 ± 8.98</td>
<td>91.0 ± 28.54</td>
<td>307.8 ± 102.55</td>
<td>143.5 ± 28.44</td>
<td>328.2 ± 108.89</td>
<td>191.5 ± 52.29</td>
</tr>
</tbody>
</table>

t1/2 (day)

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>17.73 ± 6.948</td>
<td>NA</td>
<td>NA</td>
<td>20.64 ± 6.976</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>Cohort 2</td>
<td>Cohort 3</td>
<td>Cohort 4</td>
<td>Cohort 5</td>
<td>Cohort 6</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>3 mg/kg q2w</td>
<td>6 mg/kg q2w</td>
<td>12 mg/kg q3w</td>
<td>6 mg/kg qw</td>
<td>12 mg/kg q2w</td>
<td>12 mg/kg q3w</td>
</tr>
</tbody>
</table>

**CL (mL/day/kg)**

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>4.03 ± 2.279</td>
<td>NA</td>
<td>NA</td>
<td>4.59 ± 3.064</td>
<td></td>
</tr>
</tbody>
</table>

Following day 43 administration

**AUC₀-ₜ (µg.day/mL)³**

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>1806.1 ±</td>
<td>4321.0 ±</td>
<td>3044.4 ±</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1128.9 ± 517.84</td>
<td>1747.2 ± 863.79</td>
<td>3250.9 ±</td>
<td>NA</td>
<td>1027.74</td>
<td>1067.95</td>
<td>1180.64</td>
</tr>
</tbody>
</table>

**Cmax (µg/mL)**

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>116.6 ± 34.99</td>
<td>184.3 ± 40.17</td>
<td>282.0 ± 45.77</td>
<td>358.0 ± 94.15</td>
<td>462.2 ± 94.05</td>
<td>297.1 ± 88.30</td>
<td></td>
</tr>
</tbody>
</table>

**RAC (AUC₀-ₜ following day 43 administration/AUC₀-ₜ following day 1 administration)**


<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg q2w</td>
<td>6 mg/kg q2w</td>
<td>12 mg/kg q3w</td>
<td>6 mg/kg qw</td>
<td>12 mg/kg q2w</td>
<td>12 mg/kg q3w</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2.77 ± 0.766</td>
<td>2.41 ± 0.879</td>
<td>1.54 ± NA</td>
<td>2.77 ± 0.636</td>
<td>2.10 ± 0.435</td>
<td>1.72 ± 0.433</td>
</tr>
</tbody>
</table>

Data presented as \( n \) patients evaluable or mean ± standard deviation. \(^a\) Patients in these cohorts received siltuximab via a 1-hour IV infusion. \(^b\) 0-t = the first dose interval following the first administration. \(^c\) 0-t = dose interval following the day 43 administration.

Abbreviations: AUC, area under the serum concentration-time curve; Cmax, maximum observed concentration; CL, clearance; NA, not available; RAC, accumulation ratio; t1/2, half-life.
Table 4. Clinical benefit response in CD patients

<table>
<thead>
<tr>
<th>Patients evaluable for clinical benefit response</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit response (ie, improvement in ≥1 and no worsening in the other components)</td>
<td>37</td>
</tr>
<tr>
<td>Overall improvement in ≥2 and no worsening in the other components</td>
<td>32 (87)</td>
</tr>
<tr>
<td>Overall improvement in ≥3 and no worsening in the other components</td>
<td>28 (76)</td>
</tr>
<tr>
<td>Overall improvement in ≥4 and no worsening in the other components</td>
<td>21 (57)</td>
</tr>
<tr>
<td></td>
<td>16 (43)</td>
</tr>
</tbody>
</table>

Data presented as n or n (%). CD, Castleman’s disease.
FIGURE LEGEND

Fig 1. Patient disposition

Abbreviations: AE, adverse event; PD, progressive disease. See the Results section for details on “Other” reasons for discontinuation.

Fig 2. (A) Adverse events reported in $\geq 15\%$ of treated patients overall and (B) adverse events considered at least possibly related to study drug reported in $\geq 5\%$ of treated patients with NHL, MM, or CD

Abbreviations: CD, Castleman’s disease; MM, multiple myeloma; NHL, non-Hodgkin’s lymphoma.

Fig 3. Mean change ($\pm$ standard deviation) from baseline in hemoglobin concentration over time in treated Castleman’s disease patients in cohort 7.
Patients treated (n = 67)

Cohort 1
3 mg/kg q2w (n = 6)
- Discontinued study agent (n = 6)
- AE (n = 0)
- PD (n = 2)
- Other (n = 4)
- Continued receiving siltuximab (n = 1)

Cohort 2
6 mg/kg q2w (n = 7)
- Discontinued study agent (n = 6)
- AE (n = 1)
- PD (n = 2)
- Other (n = 3)
- Continued receiving siltuximab (n = 1)

Cohort 3
12 mg/kg q3w (n = 10)
- Discontinued study agent (n = 5)
- AE (n = 1)
- PD (n = 2)
- Other (n = 3)
- Continued receiving siltuximab (n = 1)

Cohort 4
6 mg/kg qw (n = 6)
- Discontinued study agent (n = 3)
- AE (n = 1)
- PD (n = 1)
- Other (n = 3)
- Continued receiving siltuximab (n = 1)

Cohort 5
12 mg/kg q2w (n = 6)
- Discontinued study agent (n = 3)
- AE (n = 0)
- PD (n = 1)
- Other (n = 4)
- Continued receiving siltuximab (n = 1)

Cohort 6
12 mg/kg q3w (n = 12)
- Discontinued study agent (n = 10)
- AE (n = 0)
- PD (n = 4)
- Other (n = 6)
- Continued receiving siltuximab (n = 1)

Cohort 7
9 mg/kg or 12 mg/kg q3w (n = 20)
- Discontinued study agent (n = 11)
- AE (n = 3)
- PD (n = 3)
- Other (n = 7)
- Continued receiving siltuximab (n = 1)
Figure 3

Mean change in hemoglobin from baseline (g/dL)

Cycle

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A Phase I, Open-Label Study of Siltuximab, an Anti-IL-6 Monoclonal Antibody, in Patients with B-Cell Non-Hodgkin's Lymphoma, Multiple Myeloma, or Castleman's Disease

Razelle Kurzrock, Peter M. Voorhees, Corey Casper, et al.

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