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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 Lymphoma, Multiple Myeloma, or Castleman Disease

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Abstract

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

Experimental Design: In an open-label, dose-finding, 7 cohort, phase I study, patients with NHL, multiple myeloma, or symptomatic Castleman disease received siltuximab 3, 6, 9, or 12 mg/kg weekly, every 2 weeks, or every 3 weeks. 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 Castleman disease.

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 or longer. There was no dose-limiting toxicity, antibodies to siltuximab, or apparent dose–toxicity relationship. The most frequently reported possible drug-related adverse events 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. C-reactive protein (CRP) suppression was most pronounced at 12 mg/kg every 3 weeks. Mean terminal-phase half-life of siltuximab ranged 17.73 to 20.64 days. Thirty-two of 37 (86%) patients with Castleman disease improved in 1 or more CBR component; 12 of 36 evaluable Castleman disease patients had radiologic response [complete response (CR), $n = 1$; partial response (PR), $n = 11$], including 8 of 19 treated with 12 mg/kg; 2 of 14 (14%) evaluable NHL patients had PR; 2 of 13 (15%) patients with multiple myeloma had CR.

Conclusion: No dose-related or cumulative toxicity was apparent across all disease indications. A dose of 12 mg/kg every 3 weeks was recommended on the basis of the high response rates in Castleman disease and the sustained CRP suppression. Randomized studies are ongoing in Castleman disease and multiple myeloma. *Clin Cancer Res; 19(13); 3659–70. ©2013 AACR.*

Introduction

Interleukin (IL)-6 is involved in the pathogenesis of B-cell lymphoid malignancies and plays an important role in multiple myeloma, 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 patients with lymphoma and multiple myeloma (5–11). Castleman disease is an atypical lymphoproliferative disorder. Overproduction of IL-6 from affected lymph nodes is responsible for systemic manifestations

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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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 disease, an atypical lymphoproliferative disorder. In this phase I, open-label, dose-finding study, we show that siltuximab, a chimeric anti–IL-6 monoclonal antibody, has clinical activity as a single agent in patients with B-cell non-Hodgkin lymphoma or multiple myeloma. A high rate of clinical response was seen in patients with Castleman disease, including similar rates of radiologic response in all 3 histologic types of multicentric Castleman disease (MCD). 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 on the basis of the high response rates in Castleman disease and the sustained C-reactive protein suppression. Randomized studies of siltuximab are ongoing in MCD and multiple myeloma.

(12). Targeting IL-6 signaling with tocilizumab, a humanized IL-6 receptor antibody, improved or resolved systemic symptoms and associated laboratory abnormalities with reduction in lymphadenopathy in plasma cell multicentric Castleman disease (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 lymphoma (NHL), multiple myeloma, or Castleman disease. On the basis of 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 patients with Castleman disease (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 ($n = 17$), multiple myeloma ($n = 13$), or Castleman disease ($n = 37$, including plasma cell, hyaline vascular, and mixed cellularity histology) and including mature safety data on prolonged treatment for up to 60.5 months.

Materials and Methods

Patients

Eligible patients were at least 18 years old and had histologically documented B-cell NHL [including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with $\geq$1 measurable lesions or >5,000/μL mature-appearing peripheral blood lymphocytes, Waldenström macroglobulinemia 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], multiple myeloma, or symptomatic Castleman disease (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, 7 cohort, phase I study; cohorts 1 to 6 enrolled patients with B-cell NHL, multiple myeloma, or Castleman disease, and cohort 7 only enrolled patients with Castleman disease. Cohorts 1 to 5 evaluated escalating siltuximab doses administered via a 2-hour intravenous infusion at 3 mg/kg every 2 weeks, 6 mg/kg every 2 weeks, 12 mg/kg every 3 weeks, 6 mg/kg weekly, and 12 mg/kg every 2 weeks, 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 or fewer 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 intravenous infusion at 12 mg/kg every 3 weeks. If 1 or fewer 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 every 3 weeks (cohort 7a) or 12 mg/kg every 3 weeks (cohort 7b) via a 1-hour intravenous infusion in patients with Castleman disease 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 every 3 weeks, every 2 weeks, or weekly, respectively. At the investigator's discretion, responders in cohorts 1 to 6 achieving stable disease or better could receive extended treatment. After administration via 1-hour intravenous infusion was deemed safe, patients in cohorts 1 to 5 who had received 1 or more extended doses over a 2-hour intravenous infusion were allowed to receive subsequent doses via a 1-hour intravenous infusion. Patients in cohort 7 received doses until progressive disease 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 were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events 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 Materials and Methods).

Immunogenicity

Serum samples were collected predose 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 conducted 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 patients with NHL, disease response was based on investigator assessment of Cheson criteria (1999; ref. 20) except for CLL/SLL, which were evaluated by Cheson criteria (1996; ref. 21), and Waldenström macroglobulinemia, which was evaluated by Weber criteria (22). For patients with multiple myeloma, disease response was based on investigator assessment of Bladé criteria (23). For patients with Castleman disease, 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 a central radiology facility (CoreLab).

Clinical benefit response (CBR) was evaluated by an investigator for patients with Castleman disease 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 or more and no worsening in the remaining of the following: $\geq$2 g/dL increase in hemoglobin without transfusions; $\geq$1 grade decrease in fatigue; $\geq$1 grade decrease in anorexia; $\geq$2°C decrease in fever/return to 37°C or improvement in night sweats; $\geq$5% increase in weight; or $\geq$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 patients with NHL (24), and anti–IL-6 treatment decreased CRP in B-lymphoproliferative disorders and multiple myeloma (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, multiple myeloma, and Castleman disease (25–27). Siltuximab treatment has been associated with hemoglobin increases and hepcidin decreases in patients with renal cancer in an earlier clinical study (28). Hepcidin evaluation was conducted retrospectively in patients with multiple myeloma and Castleman disease to further investigate the association between changes in hepcidin levels and hemoglobin improvement.

Methods for the biomarker analyses are described elsewhere (Supplementary Materials and 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 United States. Forty-seven (70%) patients discontinued study treatment, including 13 (19%) due to disease progression, 7 (10%) due to adverse events (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 multiple myeloma and 19 Castleman disease) 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 multiple myeloma, and 37 (55%) had Castleman disease (Table 1). Approximately half of the patients were male in NHL (53%), multiple myeloma (46%), and Castleman disease (51%) types, and most were Caucasian (94%, 77%, 73%, respectively). Median age was 69, 57, and 48 years in NHL, multiple myeloma, and Castleman disease, 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 patients with NHL, multiple myeloma, and Castleman disease was 3.5 (range 0.4–16.6) years, 3.0 (range 1.4–9.5) years, and 0.7 (range 0.1–7.8) years, respectively. A majority of patients had a Karnofsky performance status score of 80 (NHL 29%, multiple myeloma 62%, Castleman disease 41%) or 90 or more (NHL 59%, multiple myeloma 31%, Castleman disease 41%). Twelve (32%) of 37 patients with Castleman disease 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

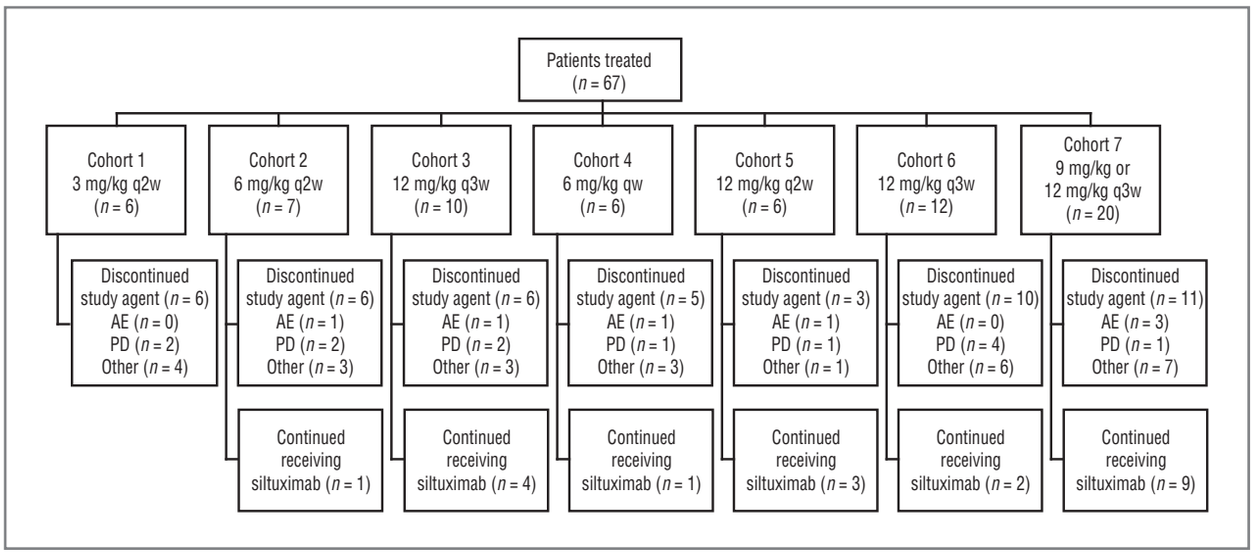

Figure 1. Patient disposition. AE, adverse event; PD, progressive disease; qw, weekly; q2w, every 2 weeks; q3w, every 3 weeks. See the Results section for details on "Other" reasons for discontinuation.

(maximum 60.5) months, including a clinical hold due to a 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 intravenous 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. Adverse events reported in at least 15% of patients overall regardless of relationship to siltuximab are shown in Fig. 2A, most adverse events were low grade except for grade 3 to 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 adverse events of infection; the all-grade infection event rate per patient-year in patients with NHL, multiple myeloma, and Castleman disease 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 (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 $\geq$3.

The most frequently reported all-grade adverse events 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 $\geq$3 adverse events possibly related to siltuximab were reported more frequently in patients with multiple myeloma (69%) than NHL (35%) or Castleman disease (11%). Of these, only neutropenia ($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 multiple myeloma, 3 Castleman disease) permanently discontinued siltuximab due to adverse events, including 4 patients with adverse events more likely associated with progressive disease (renal impairment, relapsed diffuse large B-cell lymphoma, abdominal pain) and 4 patients with adverse events most likely related to siltuximab [neutropenia in 1 patient with NHL, thrombocytopenia/peripheral sensory neuropathy in 1 patient with multiple myeloma each, and drug eruption (erythematous rash) in 1 patient with Castleman disease]. 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 adverse event (progressive disease in a patient with NHL considered not related to siltuximab and renal impairment in a patient with multiple myeloma considered unlikely related to siltuximab) and 1 patient with Castleman disease 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 adverse event, and there were no treatment-related deaths. There was no increase in the incidence of grade $\geq$3 adverse events or serious adverse events (SAE) over

Table 1. Baseline demographics and disease characteristics

	NHL	MM	CD
Patients treated	17	13	37
Male	9	6	19
Race			
Caucasian	16	10	27
Black	1	3	6
Asian	0	0	4
Age, y	65 ± 15.6	61 ± 10.2	47 ± 13.6
Weight (kg)	74 ± 14.5	90 ± 22.0	86 ± 31.6
Karnofsky performance status score			
≤70	2	1	7
80	5	8	15
90	7	2	7
100	3	2	8
Disease duration (y)	3.5 (0.4–16.6)	3.0 (1.4–9.5)	0.7 (0.1–7.8)
Disease stage			
I	1	6	NA
II	1	4	NA
III	2	3	NA
IV	13	0	NA
Prior therapy	17	13	28
Radiotherapy	3	4	1
Autologous transplant	1	8	1
Cancer-related surgery	0	0	7
Systemic therapy	17	12	25
1 regimen	1	2	7
2 regimens	6	1	11
3 regimens	4	2	4
≥4 regimens	6	7	3

NOTE: Data presented as *n*, mean ± SD, or median (range).
Abbreviations: NHL, non-Hodgkin lymphoma; CD, Castleman disease; MM, multiple myeloma; NA, not applicable.

time. Grade ≥3 adverse events regardless of relationship to siltuximab were reported more frequently in year 0 to 1 (52%) and year 1 to 2 (41%) than in year 2 to 3 (21%) and beyond 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, and $n = 4$ in year >3).

Pharmacokinetics

For cohorts 1 to 6, a summary of siltuximab pharmacokinetic parameter estimates after the day 1 administration and day 43 administration are presented in Table 3. Serum concentrations of siltuximab declined in a biexponential 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 (C_{max}) and area under the serum concentration–time curve (AUC_{0-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, multiple myeloma, or Castleman disease (Supplementary Fig. S1).

Immunogenicity

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

Efficacy

Of the 14 evaluable NHL patients, 2 (Waldenström macroglobulinemia treated with 6 mg/kg every 2 weeks, extranodal marginal zone B-cell MALT lymphoma treated with 12 mg/kg every 3 weeks) had confirmed partial responses (PR) lasting 4.1 and 6.2 months, 7 had stable disease (range 0.9–5.6 months), and 5 had progressive disease. Of the 13 evaluable multiple myeloma patients, 2 (treated with 6 mg/kg weekly and 12 mg/kg every 3 weeks) had confirmed complete response (CR) with response duration lasting 11.7 and 16.7 months, 8 had stable disease (range 0.5–18.0 months), and 3 had progressive disease. Supplementary Figure S2 shows serum CRP and γ M-spike levels over time for 1 of the 2 patients with multiple myeloma with CR. Among the 36 evaluable Castleman disease 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 stable disease [median 6.2 (range 1.3+–22.0+) months], and 1 had progressive disease. Of note, 5 of 18 patients with hyaline vascular Castleman disease, 1 of 2 patients with mixed cellularity Castleman disease, and 6 of 17 patients with plasma cell Castleman disease had radiologic response. Eleven of 12 responders with Castleman disease (1 CR, 10 PR) were without progressive disease at study completion and were censored at the last radiologic assessment for time-to-event analysis. On the basis of 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 Castleman disease. The 1 CR and 8 of 11 PRs in Castleman disease were achieved at the highest dose of siltuximab (12 mg/kg). In addition, mean hemoglobin level increased 1 to 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 patients with Castleman disease (Fig. 3).

Of the 37 patients with Castleman disease 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 patients with Castleman disease improved in fatigue (78%), size of the largest lymph node (65%), weight (60%), and fever/night sweats (51%) with siltuximab.

Table 2. Disease type and exposure

	Cohort 1 3 mg/kg q2w	Cohort 2 6 mg/kg q2w	Cohort 3 12 mg/kg q3w	Cohort 4 6 mg/kg qw	Cohort 5 12 mg/kg q2w	Cohort 6[a] 12 mg/kg q3w	Cohort 7a[a] 9 mg/kg q3w	Cohort 7b[a] 12 mg/kg q3w
Patients treated	6	7	10	6	6	12	12	8
Non-Hodgkin lymphoma	2	4	1	1	1	8	0	0
Diffuse large B-cell lymphoma	0	1	0	1	0	2	0	0
Extranodal marginal zone B-cell MALT lymphoma	0	0	0	0	0	1	0	0
Follicular lymphoma	0	1	0	0	0	0	0	0
Mantle cell lymphoma	1	0	1	0	0	1	0	0
Small lymphocytic lymphoma	1	0	0	0	0	2	0	0
Waldenström's macroglobulinemia	0	2	0	0	1	2	0	0
Multiple myeloma	3	1	3	2	2	2	0	0
Castleman disease	1	2	6	3	3	2	12	8
Unicentric	0	0	0	0	0	0	2	0
Multicentric	1	2	6	3	3	2	10	8
Duration of siltuximab administration, months	3.4 (1.4–38.4)	2.8 (0.5–60.5)	17.0 (0.0–58.1)	5.4 (1.4–51.6)	34.1 (1.4–48.2)	4.9 (0.0–39.8)	23.1 (0.0–38.7)	10.9 (5.7–21.3)
No. of siltuximab administrations received	7.5 (4–110)	7 (2–97)	14 (1–84)	20 (7–81)	61 (4–95)	8 (1–58)	32 (1–57)	16.5 (9–31)
Total siltuximab dose received, mg	2159.2 (1000–48631)	3300.0 (1125–104479)	14753.5 (893–125571)	8884.8 (2113–49554)	57526.8 (4000–129991)	6553.6 (723–52759)	28902.7 (759–88109)	18633.9 (6670–43907)

NOTE: Data presented as *n* or median (range).

Abbreviations: qw, weekly; q2w, every 2 weeks; q3w, every 3 weeks.

[a]Patients in these cohorts received siltuximab via a 1-hour intravenous infusion.

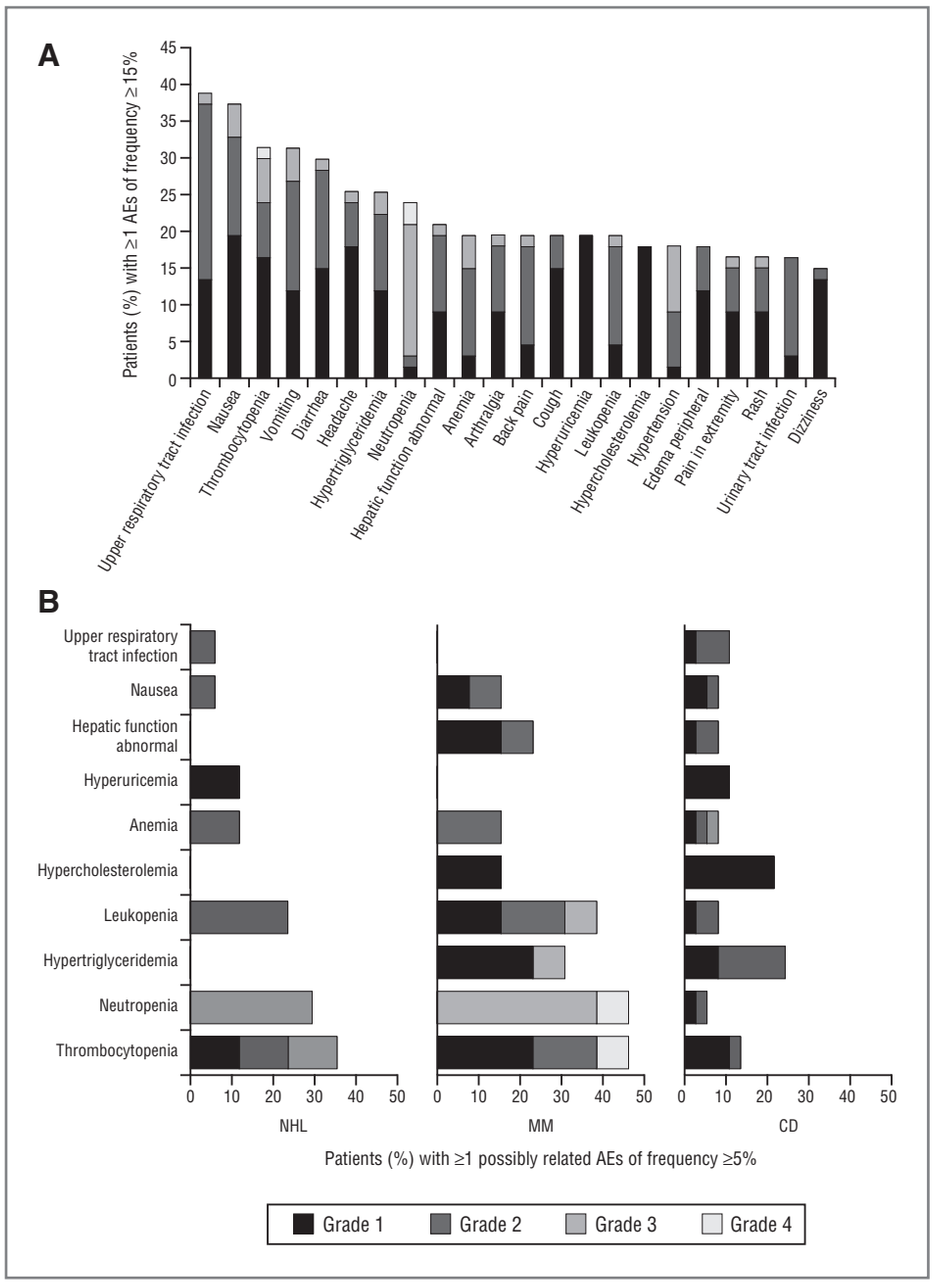

Figure 2. Adverse events reported in 15% or more of treated patients overall (A) and adverse events considered at least possibly related to study drug reported in 5% or more of treated patients with NHL, multiple myeloma, or Castleman disease (B). CD, Castleman disease; MM, multiple myeloma; AE, adverse event.

Median overall survival was 67.8 months for all treated patients, 33.1 months for patients with NHL (with a median duration of 2.5 years follow-up), and was not reached for patients with multiple myeloma or Castleman disease. Only 6 of the 13 patients with multiple myeloma had died after a median of 3.3 years of follow-up. Only 3 (8%) of the 37 patients with Castleman disease 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. Patients with Castleman disease treated with 12 mg/kg every 3 weeks showed greater CRP decrease (cohort 7b: 77% median reduction) than those treated with 9 mg/kg every 3 weeks (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 posttreatment in most (97%) patients with multiple myeloma or Castleman disease, with

Table 3. Siltuximab pharmacokinetic parameter estimates for cohorts 1 to 6

	Cohort 1 3 mg/kg q2w	Cohort 2 6 mg/kg q2w	Cohort 3 12 mg/kg q3w	Cohort 4 6 mg/kg qw	Cohort 5 12 mg/kg q2w	Cohort 6 12 mg/kg q3w[a]
Patients evaluable	6	7	6	6	4	8
Following day 1 administration						
AUC_{0-t} (μg.day/mL)[b]						
	6	6	6	5	4	5
	400.5 ± 81.14	548.2 ± 162.40	2116.7 ± 787.85	549.6 ± 180.94	2046.5 ± 162.49	1720.4 ± 674.44
C_{max} (μg/mL)						
	6	6	6	5	4	7
	55.0 ± 8.98	91.0 ± 28.54	307.8 ± 102.55	143.5 ± 28.44	328.2 ± 108.89	191.5 ± 52.29
$t_{1/2}$ (day)						
	0	0	6	0	0	5
	NA	NA	17.73 ± 6.948	NA	NA	20.64 ± 6.976
CL (mL/day/kg)						
	0	0	6	0	0	5
	NA	NA	4.03 ± 2.279	NA	NA	4.59 ± 3.064
Following day 43 administration						
AUC_{0-t} (μg.day/mL)[c]						
	5	3	1	2	4	6
	1128.9 ± 517.84	1747.2 ± 863.79	3250.9 ± NA	1806.1 ± 1027.74	4321.0 ± 1067.95	3044.4 ± 1180.64
C_{max} (μg/mL)						
	5	4	2	5	4	6
	116.6 ± 34.99	184.3 ± 40.17	282.0 ± 45.77	358.0 ± 94.15	462.2 ± 94.05	297.1 ± 88.30
RAC (AUC_{0-t} following day 43 administration/AUC_{0-t} following day 1 administration)						
	5	3	1	2	4	5
	2.77 ± 0.766	2.41 ± 0.879	1.54 ± NA	2.77 ± 0.636	2.10 ± 0.435	1.72 ± 0.433

NOTE: Data presented as *n* patients evaluable or mean ± standard deviation.

Abbreviations: CL, clearance; NA, not available; RAC, accumulation ratio; $t_{1/2}$, half-life; qw, weekly; q2w, every 2 weeks; q3w, every 3 weeks.

[a]Patients in these cohorts received siltuximab via a 1-hour intravenous infusion.

[b]0–t = the first dose interval following the day 1 administration.

[c]0–t = dose interval following the day 43 administration.

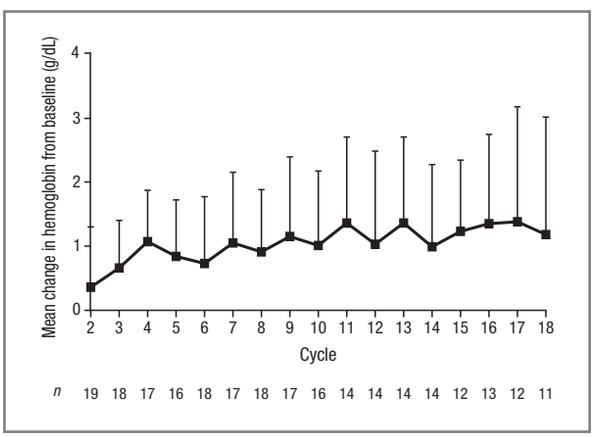

Figure 3. Mean change (+ SD) from baseline in hemoglobin concentration over time in treated patients with Castleman disease in cohort 7.

75% of these patients showing an increase in hemoglobin of 1.5 g/dL or more.

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 phosphorylated mitogen-activated protein kinase) 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

Table 4. CBR in patients with Castleman disease

	CD
Patients evaluable for CBR	37
CBR (i.e., improvement in ≥1 and no worsening in the other components)	32 (87)
Overall improvement in ≥2 and no worsening in the other components	28 (76)
Overall improvement in ≥3 and no worsening in the other components	21 (57)
Overall improvement in ≥4 and no worsening in the other components	16 (43)

NOTE: Data presented as *n* or *n* (%).
Abbreviation: CD, Castleman disease.

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, multiple myeloma, or Castleman disease, 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 adverse events 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 patients with NHL, multiple myeloma, and Castleman disease, 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 of infections cannot be excluded *a priori* but is impossible to quantify in this dataset because 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 adverse event, and no siltuximab-related deaths were reported through more than 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 or longer.

Serum concentrations of siltuximab following the first dose declined in a biexponential 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. In addition, apparent dose-proportional increases in the C_{max} and AUC_{0-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 parameter estimates of C_{max} and AUC_{0-t} are similar to the values previously reported in patients with renal cell carcinoma (18). In addition, 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 posttreatment samples is not currently possible. In addition, 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. Patients with Castleman disease treated with 12 mg/kg every 3 weeks showed greater decreases in CRP than those treated with 9 mg/kg every 3 weeks. This is in agreement with the observed dose–response relationship for clinical benefit in patients with Castleman disease. However, for multiple myeloma 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 patients with Castleman disease reported here is to our knowledge the largest dataset of patients with Castleman disease prospectively studied in a therapeutic trial. The clinical activity of siltuximab was long lasting in this Castleman disease cohort, as shown at the time of study closure by 65% of patients with Castleman disease having been treated long term for 12 months or more. One patient with Castleman disease treated with siltuximab 12 mg/kg every 3 weeks and then every 6 weeks as maintenance therapy after achieving CR for a total of 57.3 months continues to receive siltuximab along with 18 other patients with Castleman disease in an extension protocol. Only 3 (8%) of the 37 patients with Castleman disease had died after a median follow-up of 2.4 years, which is consistent with the retrospective survival data reported by Dizpenzieri and colleagues (32) and Talat and colleagues (33). Although only a minority of patients with NHL or multiple myeloma responded, the 2 CRs seen in multiple

myeloma are notable, including 1 patient with multiple myeloma who continued siltuximab treatment after study closure through a single-patient compassionate use program. The 13 patients with multiple myeloma 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 patients with multiple myeloma who similarly received 4 prior lines of treatment (34). Median survival was 33.1 months for patients with NHL after a median follow-up of 2.5 years. Because a heterogeneous population of 17 patients with NHL 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 seen in patients with Castleman disease, the radiologic response rate was similar in all 3 histologic types of Castleman disease (6/17 plasma cell, 5/18 hyaline vascular, and 1/2 mixed cellularity). To date, response has only been reported with tocilizumab in patients with plasma cell Castleman disease (14). Because the majority of patients with unicentric Castleman disease have the hyaline vascular variant (32, 33), it is therefore possible that siltuximab may also have clinical benefit in unicentric Castleman disease 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 patients with Castleman disease treated at 12 mg/kg, regardless of dosing schedule. Among the 4 responders in patients with NHL or multiple myeloma, durable response was seen with 12 mg/kg every 3 weeks, which supports the above observation in Castleman disease responders. Furthermore, 12 mg/kg every 3 weeks 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, are 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 less than 1 mg/L in patients with MCD (36). Pharmacokinetic/pharmacodynamic modeling suggests that lower doses, including 9 mg/kg every 3 weeks, only decrease CRP to less than 4 mg/L throughout dosing (18). Results of the current study support a dose intensity equivalent to 12 mg/kg every 3 weeks for future clinical development. Randomized trials of 12 mg/kg every 3 weeks siltuximab in multiple myeloma and MCD are ongoing.

Appendix

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

- van Rhee F, Fayad L, Voorhees P, Furman R, Lonial S, Borghaei H, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. J Clin Oncol 2010;28:3701–8.

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

- Kurzrock R, Voorhees PM, Casper C, Furman RR, Fayad L, Lonial S, et al. Long-term safety in a phase 1 study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in patients with B-cell non-Hodgkin's lymphoma, multiple myeloma, or Castleman's disease. 53rd Annual Meeting of the American Society of Hematology; 2011 December 10–13; Atlanta, GA. Abstract 3959.
- van Rhee F, Fayad L, Voorhees P, Furman RR, Borghaei H, Lonial S, et al. CNTO 328, a monoclonal antibody to interleukin-6, is active as a single agent in Castleman's disease: preliminary results of a phase I study. 50th Annual Meeting of the American Society of Hematology; 2008 December 6–9; San Francisco, CA. Abstract 1008.
- Kurzrock R, Fayad L, Voorhees P, Furman RR, Lonial S, Borghaei H, et al. A phase I study of CNTO 328, an anti-interleukin-6 monoclonal antibody in patients with B-cell non-Hodgkin's lymphoma, multiple myeloma, or Castleman's disease. 50th Annual Meeting of the American Society of Hematology; 2008 December 6–9; San Francisco, CA. Abstract 1009.
- van Rhee F, Fayad L, Borghaei H, Voorhees PM, Orlowski RZ, Furman RR, 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.
- Kurzrock R, Voorhees P, Fayad L, Orlowski R, van Rhee F, Furman R, et al. Phase I, multicenter trial of CNTO 328, an anti-interleukin(IL)-6 monoclonal antibody (mAb) in subjects with selected hematologic malignancies. 2006 American Society of Clinical Oncology Annual Meeting; 2006 June 2–6; Atlanta, GA. Abstract 2513.

Disclosure of Potential Conflicts of Interest

R. Kurzrock has a commercial research grant from Janssen Research & Development. P.M. Voorhees has commercial research support from Janssen and is a consultant/advisory board member for MedImmune. C. Casper has a commercial research grant from and is a consultant/advisory board member for Janssen Biotech. S. Lonial is a consultant/advisory board member of Millennium, Celgene, Johnson & Johnson, Novartis, Onyx, and Bristol-Myers Squibb. H. Borghaei has honoraria from speakers' bureau and is a consultant/advisory board member for Genentech. H. van de Velde has ownership interest (including patents) in Johnson & Johnson. T.A. Puchalski has ownership interest (including patents) in Johnson & Johnson. B. Hall has ownership interest (including

patents) in Johnson & Johnson. F. Van Rhee has a commercial research grant from Janssen. No potential conflicts of interest were disclosed by the other authors.

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