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An Open-Label, Single-Arm, Phase 1 Study to Assess Biomarker Effects, Efficacy, and Safety of Ofatumumab in Patients With Refractory Chronic Lymphocytic Leukemia

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Abstract

This open-label, phase 1 study evaluated the effects of ofatumumab on QTc intervals, safety, efficacy, B-cell and neutrophil counts, complement levels, and cytokine and chemokine concentrations. Fourteen fludarabine-refractory chronic lymphocytic leukemia patients received 12 ofatumumab infusions. A higher maximum infusion rate of 400 mL/h was tested at the first two doses and was well-tolerated. The 43% overall response rate was similar to previous data (42%-51%). B-cell depletion was observed along with complement consumption; median C2 and CH50 levels appeared lower during monthly dosing in patients who responded. Responding patients appeared to have higher median levels of certain proinflammatory cytokines and lower median levels of certain immunotolerant cytokines than patients who did not respond. Ofatumumab-induced CDC activity can be detected clinically by measuring complement and may

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be associated with clinical activity. The potential relationship between changes in complement or cytokines and clinical response to ofatumumab warrants further study.

Keywords

chronic lymphocytic leukemia; ofatumumab; CD20; biomarkers; complement; cytokines; chemokines

Introduction

Chronic lymphocytic leukemia (CLL) is a hematologic neoplasm of unknown etiology in which peripheral clonal B cells progressively accumulate. The disease is characterized by monomorphic small, round, malignant B lymphocytes in the peripheral blood, bone marrow, and lymph nodes that co-express T-cell ($CD5^+$) and B-cell ($CD19^+$, $CD23^+$) surface markers with a low expression of CD20. Chronic lymphocytic leukemia is the most common adult leukemia in the United States (US) and Western Europe, accounting for 40% of all leukemia types in individuals over the age of 65 [1] and with almost 70% of patients being elderly (65 years or older) at the time of diagnosis [2]. It is estimated that in 2013, 15,680 new cases of CLL and 4580 deaths from CLL will have occurred in the United States. The prevalence of CLL increases with age, and the median age at the time of diagnosis is 65-70 years [3].

Ofatumumab is a human monoclonal antibody that exhibits high binding affinity to the CD20 antigen on the surface of B lymphocytes. CD20 engagement by ofatumumab results in maximal B-cell killing through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) in cells expressing either high or low levels of CD20 [4]. The importance of CDC in the activity of anti-CD20 monoclonal antibodies was demonstrated in a study of rituximab in patients with refractory CLL, where complement was added via infusion of fresh-frozen plasma [5]. Preclinical studies show enhanced CDC and similar ADCC with ofatumumab compared to rituximab [6]. The effects of ofatumumab on biomarkers such as complement levels, cytokines, and chemokines have not been studied clinically.

Patients with fludarabine-refractory CLL have few treatment options. Overall response rates after treatment with single-agent ofatumumab were 51% in patients with CLL refractory to both fludarabine and alemtuzumab and 44% in patients with bulky CLL (lymph node >5 cm) refractory to fludarabine [7].

This study assessed the effect of ofatumumab on QTc changes, safety, efficacy, tumor B-cell counts, neutrophil counts, complement levels, and cytokine and chemokine concentrations. A higher maximum infusion rate was tested at the first two doses compared to the registration study [7, 9].

Materials and Methods

Study Design

This multicenter, open-label study, single-arm, phase 1 study was designed to collect data on the potential effect of ofatumumab on QTc intervals in patients with fludarabine-refractory CLL. The study also examined a higher maximum infusion rate at the first two infusions, biomarker changes, efficacy, and safety in patients with refractory CLL. Patients who satisfied all eligibility requirements within four weeks prior to study start received 12 total intravenous (IV) doses of ofatumumab over a 25-week treatment period. The study was registered at www.clinicaltrials.gov (NCT01110031).

Patient Selection

Men and women who were 18 years of age or older with a diagnosis of refractory B-cell CLL requiring treatment were eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and serum potassium and magnesium levels within normal limits. Patients were excluded from the study if they had abnormal ECG or cardiac conduction findings, had received alemtuzumab or radioimmunotherapy within six weeks, or had other significant uncontrolled medical conditions.

Treatment

Patients received eight weekly IV infusions, followed by four monthly infusions. The initial infusion was 300 mg, and the remaining infusions were 2000 mg each. The first infusion was initiated at 12 mL/h, and the infusion rate was doubled every 30 minutes up to 200 mL/h, then increased to 300 mL/h and 400 mL/h at 30-minute intervals, if tolerated. Second and subsequent infusions were initiated at 25 mL/h, and the infusion rate was doubled every 30 minutes up to 400 mL/h, if tolerated.

Assessments

B-cell counts were measured at screening and at day 1 of weeks 2, 8, 13, 25, 29, 37, and 49. Biomarkers included complement (C2, C3, and CH50), cytokines (interferon gamma [IFN-γ], granulocyte-macrophage colony–stimulating factor [GM-CSF], tumor necrosis factor alpha [TNFα], interleukin [IL]-1β, IL-2, IL-6, IL-8, IL-10, IL-12), and chemokines (monocyte chemoattractant protein-1 [MCP-1], mitogen-inducible gene [MIG], interferon-inducible protein-10 [IP-10]), which were assessed at baseline and at day 1 of weeks 2, 5, 9, 13, 17, 21, 25, 29, 37, and 49.

Efficacy parameters of overall response were followed for six months after the last dose of ofatumumab. Assessment of clinical efficacy was performed by the investigator based on the criteria defined by the International Workshop for Chronic Lymphocytic Leukemia [8] at screening and at day 1 of weeks 5, 9, 13, 17, 21, 25, 29, 37, and 49.

Safety data included extent of exposure, adverse events (AEs), serious adverse events (SAEs), infusion reactions, clinical chemistry values, hematology, vital signs, ECOG

performance status, and immunogenicity and were collected throughout the study and for an additional six months after treatment was completed (at months 1, 3, and 6).

Analytical Methods

Analyses of B-cell counts were performed by flow cytometry. Analyses of the 12 target proteins in human EDTA plasma samples were performed using multiplexed custom array testing: GM-CSF, IP-10, MIG, MCP-1, IFNγ, TNFα, IL-1, IL-2, IL-6, IL-10, IL-12 and IL-8 (Aushon BioSystems, Inc., Billerica MA, USA). Each sample was analyzed in duplicate and the mean was reported. The complement C3 assay was performed by immunonephelometry. The complement CH50 and C2 function was measured by a hemolytic assay based on lysis of antibody-coated sheep red blood cells due to activation of complement on the cell's surface (Covance Central Laboratory Services, Indianapolis IN, USA).

Statistical Evaluation

All safety and efficacy analyses were performed using the intent-to-treat (ITT) population, defined as all patients who received at least one dose of ofatumumab. Biomarker and QTc analyses were performed on the pharmacodynamic population. Biomarker, safety, and efficacy data were summarized. Cell count and biomarker data were presented as values, change from baseline, and percentage change from baseline. Infusion durations were summarized for each infusion. Overall response rate (ORR) was defined as the percentage of patients achieving a best response of either a complete response or partial response.

Results

Study Population

Of the 14 patients enrolled, five were female and nine were male, with a median age of 62 years. All 14 patients were white and had been previously treated with fludarabine, and nine (64%) patients had been previously treated with biologic therapy regimens (e.g., rituximab or alemtuzumab).

Two (14%) patients were fludarabine- and alemtuzumab-refractory (double refractory), five (36%) patients had bulky fludarabine-refractory disease, and seven (50%) patients were considered as other because they were fludarabine-refractory but without bulky disease or previous treatment with alemtuzumab. The baseline median lymphocyte and absolute neutrophil counts were 26.15×10^9/L and 2.175×10^9/L, respectively.

Safety

Adverse events—All 14 patients experienced an AE, and eight patients experienced an AE with a maximum toxicity grade of ≥3 (Table I). Seven patients experienced grade 3 AEs. Two patients experienced grade 4 AEs (one case of febrile neutropenia and one case of hypotension). Two patients experienced grade 5 pneumonia.

Reduced infusion duration and infusion reactions: Thirteen of 14 patients (93%) completed the eight weekly infusions. Of these, eight patients received all 12 infusions, two patients received 10 infusions, two patients received nine infusions, and one patient received

eight infusions. One patient received two infusions. The median duration of the first infusion (300 mg) was 4.9 hours and of the second infusion (2000 mg) was 4.4 hours; the median durations of subsequent 2000-mg doses (4.1 to 4.25 hours) were consistent with the planned duration of approximately 4.0 hours.

Thirteen (93%) patients experienced an infusion reaction. The most common were chills in six subjects (43%), flushing in five subjects (36%), diarrhea, pyrexia, tachycardia, oral hypoesthesia in three subjects each (21%), and dyspnea, ear pain, feeling hot, headache, hyperhydrosis, hypertension, hypotension, nausea, palpitations, paresthesia, and sneezing in two subjects each (14%). Overall, the percentage of patients experiencing infusion reactions declined over the course of treatment, from 11 (79%) patients at the first infusion and eight (57%) patients at the second infusion to 0-4 (0%-30%) patients at the subsequent infusions (Figure 1). Most infusion-related reactions were grade 1-2 and resolved, allowing for completion of infusion. Only two (14%) patients had grade 3 infusion-related reactions (hypertension and bronchospasm in one patient at the second infusion, and perioral numbness in one patient at the first infusion). One (7%) infusion reaction (perioral numbness) was considered serious. No grade 4 or fatal infusion reactions were observed. The incidence of infusion reactions leading to dose interruption was 43% (6/14). Nevertheless, patients did not withdraw from treatment due to infusion reactions and were able to complete their scheduled doses.

During the first infusion, no patients had an infusion reaction during the first hour, four (36%) patients had an infusion reaction in the second hour, and seven (64%) patients had an infusion reaction start after the second hour. During the second infusion, six patients (75%) had an infusion reaction start during the first hour, and two patients had an infusion reaction start after two hours. For subsequent infusions, more patients had an infusion reaction after 2 hours of infusion than during the first hour of infusion.

Infections

Ten (71%) patients had infections reported as AEs, with respiratory tract infections (71%) being the most commonly reported infections (Table II). The incidence of infections of the lower respiratory tract was identical to those of the upper respiratory tract. Some adverse events reported individually in Table I are combined in Table II.

Infections were reported as SAEs in five (36%) patients (Table III). Pneumonia was the most common lower respiratory tract infection reported as an SAE (3 [21%]). Of the three events of pneumonia, two were fatal infections.

QTcF interval and changes from baseline in QTcF interval

No patient had a worst-case QTcF interval greater than 480 msec during the study, and no patient had a QTcF interval increase of greater than 60 msec compared to baseline values. No QTc-related adverse events were reported. The QTc data from this study will be combined with data from other clinical studies for analysis and will be reported separately.

Efficacy

The investigator-assessed ORR was 43%. Six (43%) patients had a partial response, and seven (50%) patients had stable disease as their best response. One patient was not evaluable because the patient died before the first post-baseline disease assessment was completed. No patient had a complete response or progressive disease. At the end of the study period, nine patients had progressed, while two patients remained in partial response and two maintained stable disease.

Biomarkers

B-cell counts: Tumor B-cell counts ($CD5^+CD19^+$) decreased rapidly after the initiation of ofatumumab treatment, with a median percent decrease from baseline of 41 % one week after the first 300-mg dose (week 2) and 98% at the next assessment (week 8). The counts remained low (median percent decrease from baseline of 99% or more) throughout treatment until the six-month follow-up visit, when the median percent decrease from baseline was 65%. A similar pattern was seen for normal B cells.

Neutrophils: The median absolute neutrophil count for study participants was 2.175×10^9/L at screening and decreased until week 5 of treatment to 0.900×10^9/L. Median neutrophil counts were generally higher during and after treatment in patients who responded than in patients who did not (Figure 2). Median neutrophil counts were below baseline during the weekly infusions in patients who did not respond.

Complement: Baseline C2, C3, and CH50 concentrations did not appear to differ between patients who responded and patients who did not respond. Median C2 and CH50 concentrations decreased initially in both patients who responded and patients who did not respond and seemed to remain below the normal range in patients who responded, whereas median C2 and CH50 concentrations appeared to return to the normal range after starting monthly dosing in patients who did not respond (Figure 3 and Figure 4).

Median C3 concentrations did not appear to differ between patients who responded and patients who did not respond over the course of treatment (data not shown).

Cytokines and chemokines: Median concentrations of inflammatory cytokines TNFα and IL-2 (Figure 5) appeared to be higher in patients who responded than in patients who did not respond throughout the study. Median concentrations of chemokine GM-CSF (Figure 5) were similar between groups; however, high concentrations were observed only in individual patients who responded.

Median concentrations of immunotolerant cytokines IL-6 and IL-8 (Figure 5) appeared to be lower in patients who responded than in patients who did not respond throughout the study, with the largest difference seen at week 9. Median concentrations of MCP-1 (Figure 5) were similar between patients who responded and who did not respond except at weeks 9 and 13, when they were higher in patients who did not respond.

Median concentrations of IFN-γ, IL-10, IL-1β, IL-12, MIG, and IP-10 did not show a clear pattern of higher concentrations in either patients who responded or who did not respond (data not shown).

Discussion

This study assessed the effect of ofatumumab on safety, efficacy, B-cell counts, neutrophil counts, complement levels, and cytokine and chemokine concentrations.

Safety results were similar to previous studies, and the safety profile was as expected, namely infusion reactions, infections, and cytopenias. The most frequently reported AEs (occurring in at least 10% of the patients) were diarrhea, headache, decreased appetite, fatigue, neutropenia, and pyrexia. Infections were expected given the immunocompromise experienced by patients with refractory CLL. Adverse events of infection occurred during both the study treatment and follow-up period, suggesting that the infections are likely related to the underlying immunosuppressive effects of fludarabine-refractory CLL. No unexpected safety signals were observed.

The maximum infusion rate for each infusion in this study was 400 mL/h The registration trial in this patient population with this dosing regimen [7, 9] used a maximum infusion rate of 200 mL/h for the first two infusions. The infusion rates for subsequent infusions were the same in the studies. Increasing the maximum infusion rate for the first and second infusions from 200 mL/hr to 400 mL/hr reduced the median duration of those infusions by approximately 2-2.5 hours. The more rapid infusion rate was well tolerated. The incidence of first- and second-infusion reactions was numerically higher in this study than in the registration study (79% vs 43% and 57% vs 31% for first and second infusions, respectively); however, the types of infusion reactions were similar, mostly grade 1-2 that resolved and allowed for completion of scheduled infusion, and no grade 4 or fatal infusion reactions were observed.

The majority of infusion reactions started at least two hours after the start of the first infusion in this study. In contrast, the majority of infusion reactions in the registration study began within the first two hours after the start of the first infusion [9]. For the second infusion where the dose was 2000 mg instead of 300 mg, most infusion reactions occurred within the first hour, similar to what was observed in the registration trial. The concentration of ofatumumab used for infusion was identical in both studies, as were the infusion rates for the first two hours. The reasons for the differences in the incidence and onset of infusion reactions between the two studies are unknown.

Overall, a similar pattern of infusion reactions was observed in the current study as in the registration study in this patient population: most infusion reactions were grade 1-2, with only two patients having a grade 3 infusion reaction and no patients with grade 4 or 5 infusion reactions, and the incidence of infusion reactions lessened with subsequent infusions. Clinical benefit with ofatumumab in this fludarabine-refractory CLL population was again demonstrated. The 43% overall response rate was similar to the 42%-51% ORR seen in the registration study in this patient population [7, 9].

Rapid, profound, and sustained B-cell depletion was induced by the administration of ofatumumab, as was observed in previous studies. B-cell recovery was seen by the last assessment at six months after the last ofatumumab infusion.

Statistical analysis could not be properly performed on complement, cytokine, or chemokine results due to the small number of subjects and the declining numbers of subjects at later timepoints. Descriptive observations were made for hypothesis generation purposes for future studies.

Complement-dependent cytotoxicity is one of the key mechanisms of action of ofatumumab. In all evaluable patients, complement appeared to be consumed, as measured by falling median C2, C3, and CH50 levels that decreased to below the lower limit of normal during the weekly treatment period. Around the beginning of the monthly infusion period (week 5), patients who responded appeared to demonstrate continued complement consumption, with continued lower-than-normal median C2 and CH50 levels, whereas patients who did not respond appeared to have median C2 and CH50 levels returning into the normal range, suggesting loss of complement consumption. C3 levels were less informative. The time course of complement consumption and recovery was similar to that seen with B cells. The role of complement in anti-CD20 antibody-based CLL therapy warrants further study.

The balance of the immune system as measured by changes in cytokine levels seemed to favor inflammation over tolerance among patients who responded and the opposite among patients who did not respond. Median levels of pro-inflammatory cytokines such as IL-2 and TNFα, and to a lesser extent GM-CSF, seemed to be higher in patients who responded than in patients who did not respond, whereas median levels of immunotolerant cytokines such as IL-6 and IL-8, and to a lesser extent MCP-1, appeared to be lower in patients who responded than in patients who did not respond. Type I monoclonal antibodies, such as ofatumumab, also induce ADCC, and these cytokine changes in patients who responded may be a reflection of such activity. No obvious differences in the baseline values of complement, cytokines, or chemokines were observed between patients who responded and patients who did not respond, so the ability to use levels of these biomarkers at baseline to predict response may be limited.

Conclusions

Ofatumumab administered more quickly than the prescribing information for the first two infusions was associated with a greater incidence of first-infusion reactions, though grade 3 or higher first-infusion reactions were similar to the original infusion schedule and all patients were able to complete their scheduled dose. Efficacy and safety data, including infusion reactions, were similar to previously reported data. Exploratory biomarker data suggest a possible trend toward increased complement consumption and a shift toward a pro-inflammatory cytokine pattern among patients who responded compared with patients who did not respond. Complement-dependent cytotoxicity induced by ofatumumab may be detected clinically through serial measurements of complement levels and may be associated with clinical activity. The complement, cytokines, and chemokines data are exploratory and are based on a limited number of patients; however, changes in cytokines over time were

measurable, and the results warrant future study to understand the action of ofatumumab better.

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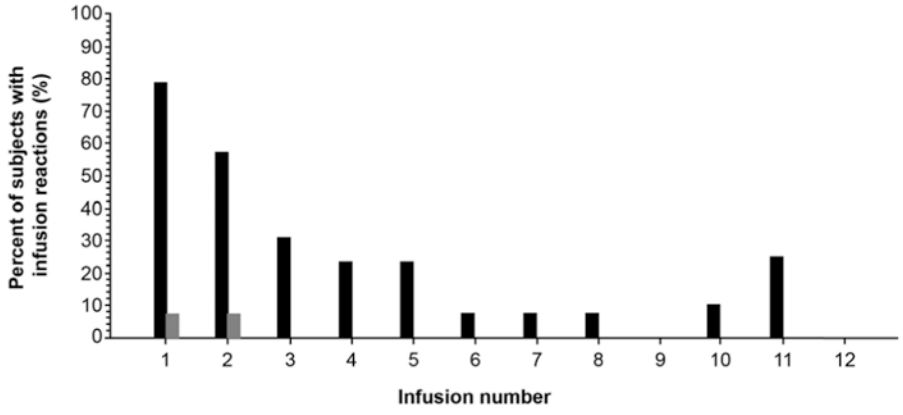

Number of Patients	All					Grade ≥3						
n	14	14	13	13	13	13	13	13	12	10	8	8
Count (All)	11	8	4	3	3	1	1	1	0	1	2	0
Percent (All)	79	57	31	23	23	8	8	8	0	10	25	0
Count (Grade ≥3)	1	1	0	0	0	0	0	0	0	0	0	0
Percent (Grade ≥3)	7	7	0	0	0	0	0	0	0	0	0	0

Figure 1. Percent of Patients Who Experienced Infusion Reactions by Infusion

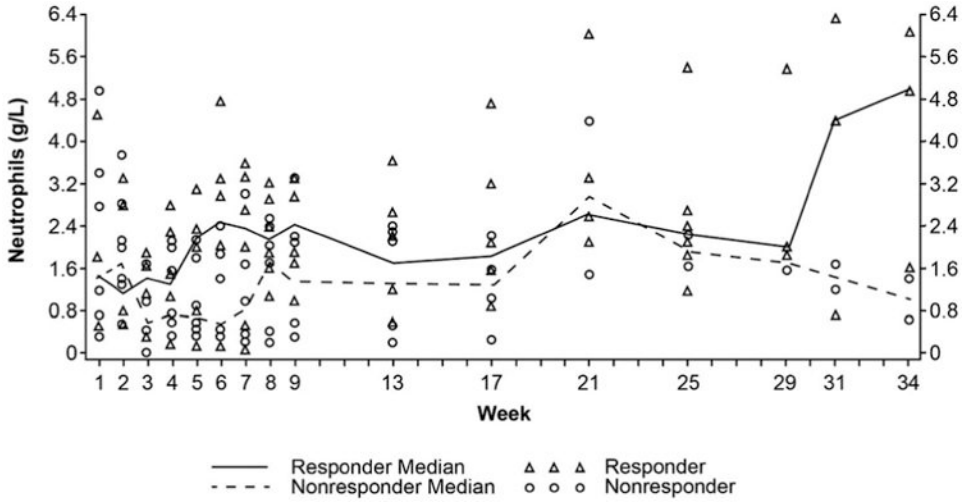

Figure 2. Plot of Neutrophils Over Time for Patients Who Responded and Patients Who Did not Respond (All Patients)

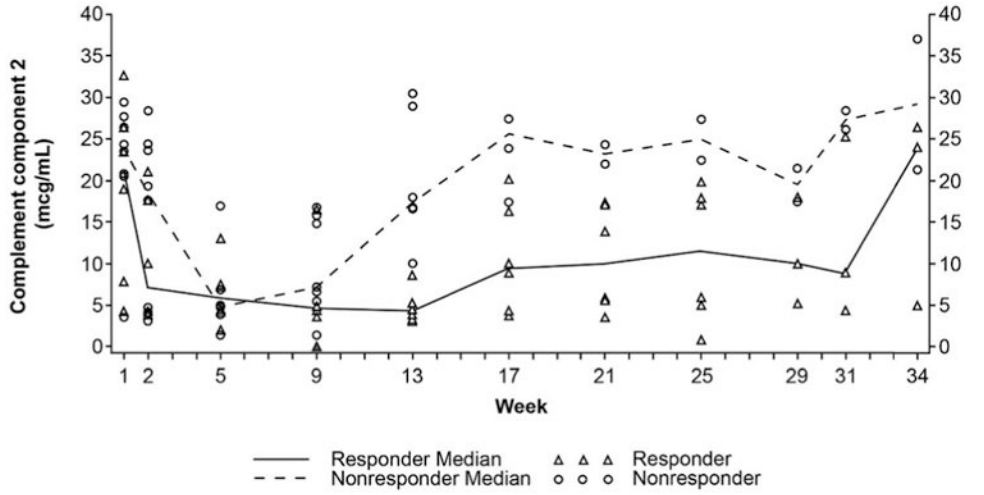

Figure 3. Plot of C2 Over Time for Patients Who Responded and Patients Who Did not Respond (All Patients)

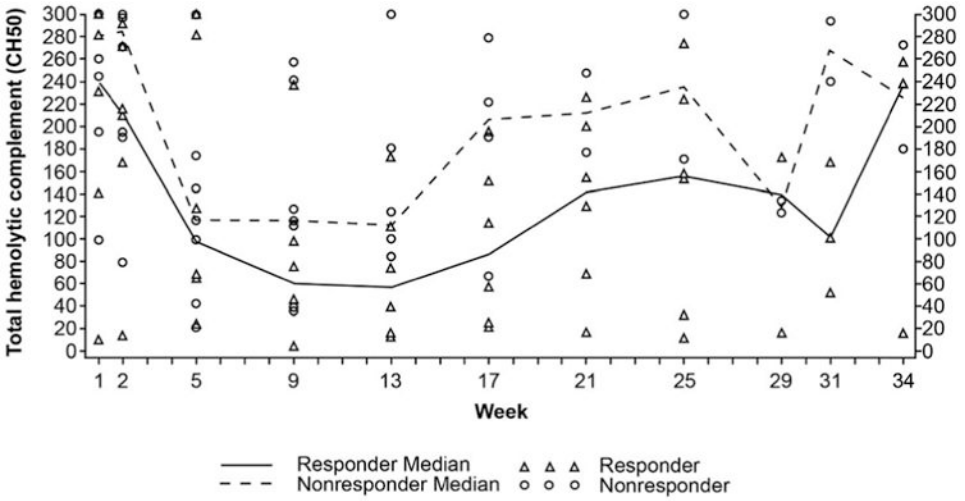

Figure 4. Plot of CH50 Over Time for Patients Who Responded and Patients Who Did not Respond (All Patients)

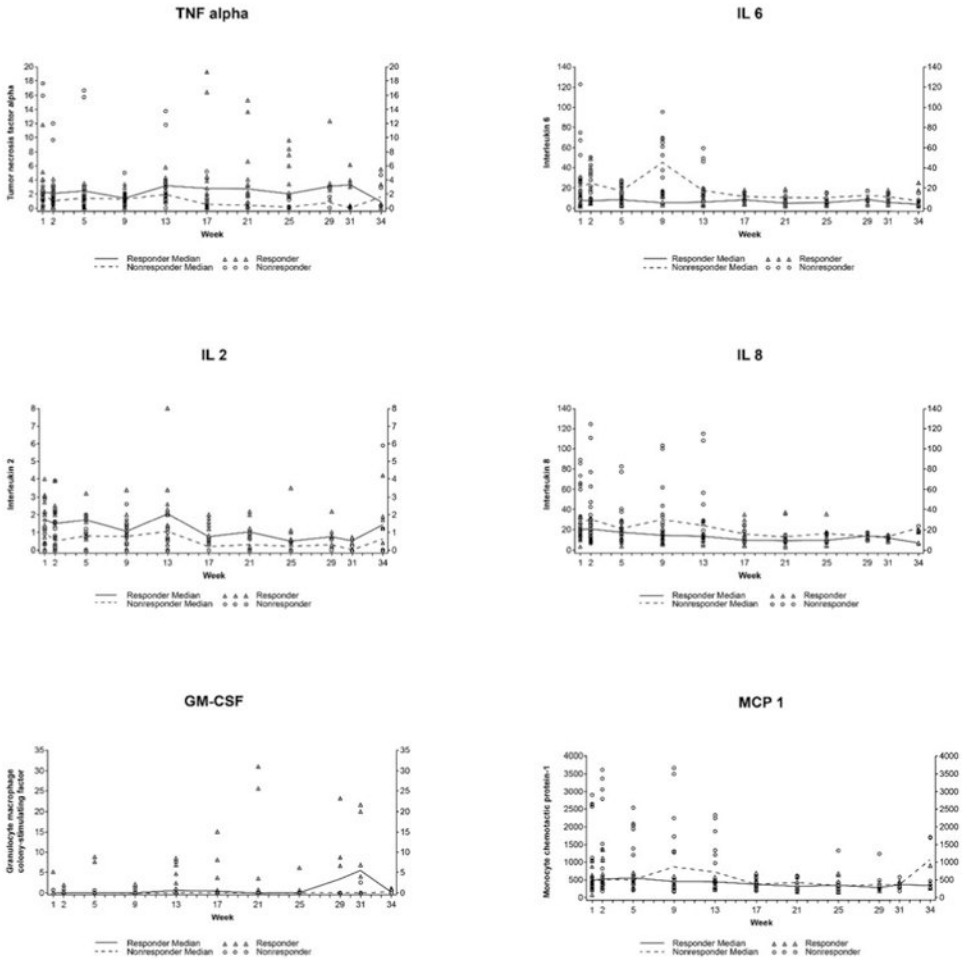

Figure 5. Plot of TNFα, IL-2, GM-CSF, IL-6, IL-8, and MCP-1 Over Time for Patients Who Responded and Patients Who Did not Respond (All Patients)

Table I

Summary of Adverse Events in at Least 20% of Patients and Patients With Grade ≥3 Adverse Events

Summary of Adverse Events in at least 20% of Patients	No. (%) of Patients (N=14)	Patients with Grade ≥3 Adverse Events	No. (%) of Patients (N=14)
Any event	14 (100)	Any event	8 (57)
Diarrhea	6 (43)	Lower respiratory tract infection	2 (14)
Headache	5 (36)	Pneumonia	2 (14)
Decreased appetite	4 (29)	Bronchospasm	1 (7)
Fatigue	4 (29)	Epistaxis	1 (7)
Neutropenia	4 (29)	Febrile neutropenia	1 (7)
Pyrexia	4 (29)	Hypertension	1 (7)
Abdominal pain	3 (21)	Hypoesthesia oral	1 (7)
Chills	3 (21)	Hyponatremia	1 (7)
Constipation	3 (21)	Hypotension	1 (7)
Dizziness	3 (21)	Lung infection pseudomonal	1 (7)
Dry mouth	3 (21)	Neutropenia	1 (7)
Flushing	3 (21)	Pneumonia streptococcal	1 (7)
Insomnia	3 (21)	Post-herpetic neuralgia	1 (7)
Lethargy	3 (21)	Pseudomonal bacteremia	1 (7)
Nausea	3 (21)	Sinusitis fungal	1 (7)
Rash	3 (21)	Skin bacterial infection	1 (7)
Rhinitis	3 (21)	Spinal compression fracture	1 (7)
Lower respiratory tract infection	3 (21)	Squamous cell carcinoma	1 (7)
Upper respiratory tract infection	3 (21)	Streptococcal bacteremia	1 (7)
		Superinfection	1 (7)
		Upper respiratory tract infection	1 (7)

Table II
Summary of Infections Reported as Adverse Events (All Patients)

Adverse Event Preferred Term	No. (%) of Patients (N=14)
All infections	10 (71)
All respiratory tract infections	10 (71)
Combined Lower respiratory tract infections	6 (43)
Pneumonia	3 (21)
Lung infection	1 (7)
Combined Upper respiratory tract infections	6 (43)
Unknown type	9 (64)

Table III
Summary of Serious Infections (All Patients)

Adverse Event Preferred Term	No. (%) of Patients (N=14)
All infections	5 (36)
All respiratory tract infections	5 (36)
Combined Lower respiratory tract infections	5 (36)
Pneumonia	3 (21)
Lung infection	1 (7)
Upper respiratory tract infections	1 (7)
Unknown type	3 (21)