Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study

While fludarabine-based regimens are a standard for treatment of chronic lymphocytic leukemia (CLL), patients who become refractory to fludarabine have had low response rates with salvage therapy and poor survival outcomes.[1-3] We reported that ofatumumab, a human monoclonal antibody that binds to a distinct epitope of the CD20 molecule on B cells,[4] was effective as monotherapy for fludarabine-refractory CLL at the interim analysis.[5] Here we report the final analysis of the study, including a landmark analysis demonstrating the clinical benefits in patients who responded, and the results of both pharmacokinetic and exploratory analyses to identify factors associated with ofatumumab pharmacokinetics and clinical outcomes.

The study design and patient selection criteria were previously reported.[5] Patients were required to be refractory to at least one fludarabine-containing regimen and either refractory to at least one alemtuzumab-containing regimen (FA-ref), or considered unsuitable for alemtuzumab due to bulky (>5 cm) lymphadenopathy (BF-ref) and were assigned to the population subgroups by the Independent Review Committee (IRC).

All patients were to receive eight weekly intravenous infusions of ofatumumab, followed by four monthly infusions (Dose 1: 300 mg; Doses 2–12: 2000 mg). Of the 223 patients, 89% received all 8 weekly infusions, and 51% of patients received all 12 infusions.

The primary endpoint was objective response rate (ORR) assessed by the IRC using the 1996 NCI-WG criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS), pharmacokinetics, and adverse events (AEs).

The efficacy observed in the final analysis confirmed the results of the previous interim analysis.[5] Responses were rapid and consistent across subgroups (Table 1). The response rate and the lower bound of the 95% CI for ORR exceeded the pre-planned null hypothesis response rate of 15% (P<0.001 in both groups). Response rates were not significantly different between patient groups in regard to demographics, prior CLL therapy, disease characteristics, chromosomal abnormalities, CD38 status, and Fc receptor polymorphism, with the exception of patients with 17p deletion who had a lower response rate (30%) than patients without 17p deletion (53%; P=0.0055).

Ofatumumab demonstrated significant benefits in responders. Most responses had occurred by Week 12; on

Table 1. Overview of udated efficacy outcomes and adverse events during treatment and follow-up to 24 months.

	FA-ref (N=95)	BF-ref (N=112)
Efficacy Endpoint		
ORR, %	49	43
95.3% CI	39, 60	33, 53
Duration of response (months), median	5.5*	6.4†
Duration of response after last infusion (months), median	2.3*	2.5†
PFS (months), median	4.6	5.5
OS (months), median	13.9	17.4
Safety Results		
Any AE	90 (95)	107 (96)
AEs Grade 3	67 (71)	60 (54)
Any AE leading to withdrawal from treatment	15 (16)	13 (12)
Non-fatal SAEs	53 (56)	55 (49)
Fatal (Grade 5) SAEs	20 (21)	17 (15)
Infusion-related AEs	79 (83)	87 (78)
Infection AEs	72 (76)	77 (69)

*ORR: overall response rate; OS: overall survival; PFS: progression-free survival. *n=47; †n=48.*

Table 2. Summary of Ofatumumab pharmacokinetic parameter values.

Parameter	N	Infusion 1 (300 mg)	N	Infusion 8 (2000 mg)	N	Infusion 12 (2000 mg)
C_{max} (μg/mL)	215	61.4 (73)	193	1391 (46)	106	827 (41)
C_{trough} (μg/mL)	–	–	192	549 (234)	106	32.1 (5883)
AUC(0-T)* (μg.h/mL)	–	–	163	171286 (48)	84	165617 (123)
AUC(0-∞) (μg.h/mL)	–	–	133	463418 (94)	83	203536 (164)
CL (mL/h)	–	–	163	11.7 (48)	84	12.1 (123)
Vss (L)	–	–	133	4.84 (30)	83	3.73 (30)
t½ (days)	–	–	141	13.6 (56)	81	11.5 (87)

*Data are presented as geometric mean (% coefficient of variation). C_{max}: maximum observed concentration; C_{trough}: observed concentration prior to next infusion; AUC (0-τ): area under the concentration-time curve over the dosing interval τ; AUC(0-∞), area under the concentration-time curve extrapolated to infinity; CL: clearance; Vss: volume of distribution at steady state; t½, half-life. *τ: 168 h at Infusion 8 and 672 h at Infusion 12.*

the basis of a landmark analysis[6,7] starting at Week 12 (Figure 1A,B), median OS was significantly longer among responding patients compared with non-responding patients (FA-ref: 24.9 months *vs.* 9.9 months [*P*=0.0003, log- rank test] and BF-ref : 28.9 months *vs.* 15.5 months [*P*=0.0154]). This significantly longer survival among responders compared to non-responders indicated that achievement of a partial remission is an important goal and confers meaningful clinical benefit in patients with CLL, even heavily pretreated CLL.

Similar to the interim analysis, the final analysis showed that ofatumumab was well tolerated with no unexpected toxicities and no formation of anti-ofatumumab antibodies. Infusion-related reactions were mostly Grade 1-2 and occurred predominantly during the first and second infusion, decreasing from 43% at the first infusion to 6% at the final (twelfth) infusion. Only 30 patients (13%) discontinued ofatumumab early due to AE.

Overall, 24% of patients had at least one Grade 3 or 4 infection. Major infections (leading to hospitalization for >48 hours during or within four weeks of completing treatment) occurred in 64 (29%) patients. Analysis of infections by CLL risk factors suggested that underlying disease was the major risk factor for infections ≥ Grade 3. Twenty infections during treatment (9% of patients) led to death. Other causes of death during treatment or follow-up were neutropenia (n=1), disease progression (n=1), cardiovascular events (n=4), and pulmonary edema/respiratory failure (n=1).

Cytopenias appeared to be mainly related to the underlying disease, given that improvements in median hemoglobin and platelet levels were observed, and median neutrophil counts remained in the normal range during the study.

Ofatumumab pharmacokinetic analysis was performed using a population approach with a two-compartment model, with an additional estimated target-mediated clearance component to describe the effect of B-cell binding on ofatumumab pharmacokinetics using NONMEM VI (ICON, Ellicott City, MD). The development and performance characteristics of the model have been described.[8] Serum ofatumumab concentrations for pharmacokinetic analysis were determined using a validated ELISA with a lower limit of quantification of 0.1 μg/mL, as previously described.[9]

Pharmacokinetic parameter values were comparable among the FA-ref, BF-ref, and Other groups (*data not shown*), and all summaries and analyses combined pharma-

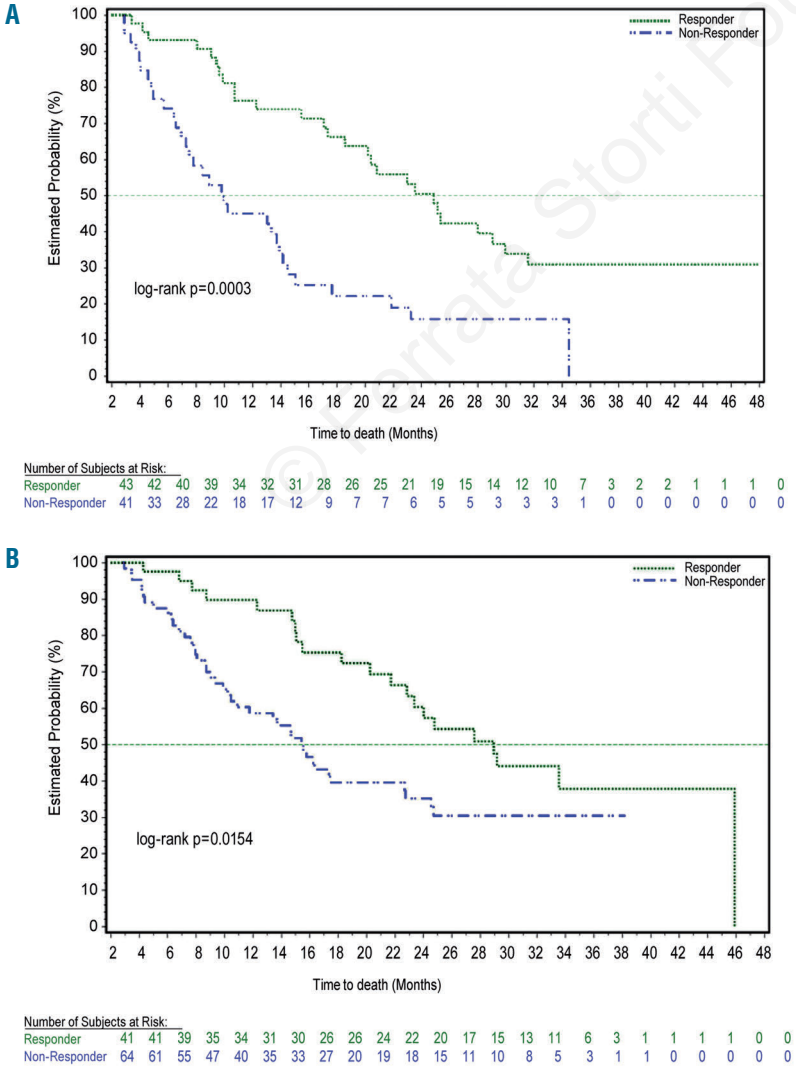

Figure 1. Kaplan-Meyer Curves for overall survival; landmark analysis. (A) By response in week 12 survivors in FA-ref group. (B) By response in week 12 survivors in BF-ref group.

cokinetic data from the three patient groups (Table 2). The geometric mean clearance, volume of distribution at steady state, and half-life values after the eighth or twelfth infusion were approximately 12 mL/h, 4 to 5 L, and 12 to 14 days. These pharmacokinetic parameter values are similar to those reported previously in patients with CLL.[10,11]

Demographic and disease factors at baseline associated with ofatumumab pharmacokinetic parameter values were identified by exploratory univariable and multivariable regression analyses. The factors identified as potentially significant (P<0.10) in univariable analyses were combined in a multivariable analysis, and factors were removed by backward elimination with retention in the final model at P<0.05. Relationships between clinical outcome measures (OR, PFS, and OS) and the same patient and disease factors at baseline, as well as ofatumumab exposure measures (C_{max}, C_{trough}, and AUC at Doses 1, 8, and 12), were evaluated by exploratory logistic regression analyses (OR) or Cox regression analyses (PFS and OS).

In multivariable analyses, higher Cmax values at the first infusion were associated with smaller body surface area, lower percentage of marrow involvement, lower baseline lymphocyte count, lower Rai stage, and lower β2-microglobulin. Ofatumumab exposure measures (C_{max}, C_{trough}, and AUC) at Dose 8 were higher in female patients than in male patients, and were lower in patients with higher baseline β2-microglobulin; C_{max} and AUC values were lower in patients with higher percentages of CLL marrow involvement and higher baseline total IgG concentrations. Higher percentages of marrow involvement, IgG concentrations, β2-microglobulin, and body surface area were associated with higher ofatumumab clearance values at Dose 8, while female subjects had lower clearance values. The results of this analysis demonstrate an association between ofatumumab pharmacokinetic parameter values and baseline factors reflecting disease burden, gender, and body surface area.

These findings are consistent with current understanding of the mechanisms involved in the clearance of ofatumumab. Like other IgG antibodies, ofatumumab is cleared via uptake into cells of the reticuloendothelial system and catabolism by ubiquitous proteolytic enzymes, a mechanism that is not saturated by administration of typical doses of therapeutic monoclonal antibodies. In addition, ofatumumab is cleared by binding to the CD20 epitope on B cells (target-mediated clearance). The observed associations of ofatumumab pharmacokinetics with measures of disease burden at baseline are consistent with a large contribution of target-mediated clearance to ofatumumab total clearance at high B-cell counts and high B-cell input rates. The association of exposure with gender and/or body surface area is consistent with the distribution of monoclonal antibodies largely in the systemic circulation.

Based on univariable analyses, higher C_{max}, C_{trough}, and AUC(0-∞) values at Dose 8 were associated with objective response (OR); ofatumumab C_{max}, C_{trough}, and AUC values at Dose 1, Dose 8, and Dose 12 were significantly associated with PFS, with higher exposure at all three infusions associated with longer PFS; and higher C_{max} and C_{trough} values at Dose 8 were associated with longer OS. In multivariable analyses including ofatumumab pharmacokinetic parameter values as well as demographic and baseline characteristics, ofatumumab pharmacokinetic parameter values were not retained in the final models for OR, PFS, or OS. For OR, clinical disease factors (β_2-microglobulin concentration, number of lymph nodes, and 17p deletion) were the significant factors. Disease and patient factors (β_2-microglobulin concentration, thymidine concentration, age ≥75 years, and lymph node size) were the significant factors associated with PFS in multivariable analysis. For OS, disease and patient factors (β_2-microglobulin concentration, thymidine concentration, lymph node size, ECOG status, and platelet counts) were the significant factors. These results showed that measures of disease burden at baseline and patient factors, rather than ofatumumab exposure, were associated with clinical outcomes.

Based on the relationship between disease burden and ofatumumab clearance, patients with a high disease burden (B-cell mass) may benefit from ofatumumab at high-dose intensity, particularly early in treatment. Patients with highly refractory CLL, as in this study, may benefit from high and frequent individual doses early in therapy to elicit response, and a long duration of dosage to maintain response. Responses persisted for a median of less than three months after the last dose of ofatumumab, and early progression following cessation of treatment provides support for the suggestion that patients with refractory CLL may benefit from a longer dosage duration. This is further supported by two recently presented phase 3 trials.[12,13] While ofatumumab as a standard-length monotherapy was inferior to continuous ibrutinib treatment in a recent comparative study,[14] it remains a therapeutic option for patients who relapse after treatment with kinase inhibitors.

In summary, this final analysis of the pivotal trial in fludarabine-refractory CLL demonstrates that ofatumumab provides meaningful clinical benefit for difficult-to-treat CLL patient groups and warrants further investigation in earlier disease settings, with longer-term administration, and in combination with drugs which have different mechanisms of action, including targeted therapies such as ibrutinib and idelalisib.

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