Abstract # 2750

Pharmacokinetic and Pharmacodynamic Analysis of Ocaratuzumab in 50 Patients with Relapsed Follicular Lymphoma and Low-Affinity FcγRIIIa (CD16a) Polymorphisms

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ABSTRACT

Ocaratuzumab, previously known as AME-133v, is a Fc- and Fab-engineered humanized anti-CD20 monoclonal antibody designed for optimized affinity to the CD20 antigen as well as to the FcγRIIIa (CD16a) receptor on effector cells. It demonstrates 13-20 fold higher affinity for CD20 and 6-fold higher antibody-dependent cellular cytotoxicity compared to rituximab.

In a Phase II study, 50 patients received IV ocaratuzumab at 375 mg/m^2 weekly for 4 doses, the standard dosing schedule of rituximab. The median age (range) was 61 (39-83) years and the median number of prior systemic therapies (range) was 2 (1-9). Two patients were rituximab naïve.

This abstract describes the pharmacokinetics (PK) and pharmacodynamics of ocaratuzumab. The steady state concentration of ocaratuzumab was reached by the 2nd dose and started to decline 1 week after the last dose. The PK of ocaratuzumab is best characterized by a 2-compartment model with a typical clearance estimate of 0.26 L/day. The typical volume estimates for the central and peripheral compartments were 3.15 L and 3.31 L respectively, which corresponds to a terminal half-life of approximately 19 days.

As expected, there was significant inter-patient variability in the clearance of ocaratuzumab. Analysis of the serum concentration of ocaratuzumab revealed no correlation between serum ocaratuzumab concentration and progression free survival (PFS) as some patients with low concentrations had prolonged PFS and some patients with high concentrations had short PFS .

Only 2 patients developed high titers of human anti-human antibody. These 2 patients maintained very low concentrations of ocaratuzumab and were amongst 3 total patients who demonstrated progressive disease in the study.

All patients had rapid and sustained B-cell depletion for at least 90 days after the last infusion. A retrospective analysis of B-cell recovery and response showed a direct correlation between time to B-cell recovery and PFS duration. Patients with prolonged B-cell depletion stayed in remission longer than patients who recovered their circulating B-cells more quickly.

In conclusion, clinical efficacy was seen across a wide range of serum concentrations of ocaratuzumab, suggesting significant potency of the drug even at low serum concentration levels. Despite all patients having low-affinity FcγRIIIa polymorphisms, the overall response rate was 32% with a median PFS of 38 weeks. Although a weekly dose of 375 mg/m^2 for 4 doses was used in this trial, lower doses of ocaratuzumab, such as 100 mg/m^2 given once weekly for 4 doses, may potentially be effective.

There are no relevant conflict of interests to disclose.

STUDY SUMMARY

- 50 patients with relapsed/refractory CD20+ follicular lymphoma were given 4 weekly IV doses of 375 mg/m^2 of ocaratuzumab
- 44 patients completed the study (i.e. completed the response assessment visit 9 weeks after the 4th infusion – Day 84)
- Patients who responded were monitored until disease progression
- Serum ocaratuzumab concentrations were determined with an ELISA and CD19+ B-cell counts were determined with FACS
- Pharmacokinetics of ocaratuzumab were determined using NONMEN (version VII)

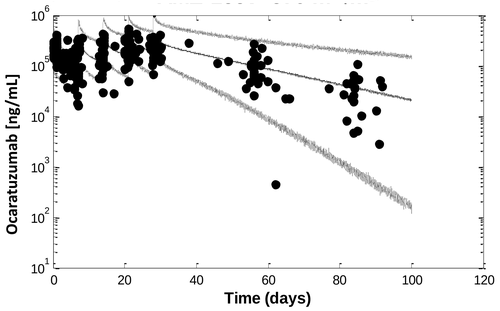
Table 1. Characteristics of the 50 Patients enrolled in the 375 mg/m^2 cohort

Characteristic	Dose = 375 mg/m^2 (N = 50)
Age (y), median (range)	61 (39 – 83)
FCγRIIIa Genotype	
Val/Phe	22
Phe/Phe	28
No. of prior systemic treatments, median (range)	2.0 (1 – 9)

POPULATION PK OF 50 PATIENTS IN THE 375 mg/m^2 COHORT

- Pharmacokinetics of ocaratuzumab is best described and well-estimated by a 2-compartment model with dose-dependent clearance (Figure 1 and Table 2)
- The half-life of ocaratuzumab is 18.6 days, similar to rituximab

Figure 1. Population pharmacokinetic model for 375 mg/m^2 ocaratuzumab



- To determine the final PK model, 7 covariates were tested: body surface area (BSA), total body weight, lean body weight, body mass index, gender, age, and the genotype of the FcγRIII receptor
- The only covariate retained in the final model was the effect of BSA on V1 (statistically significant) in order to reduce the inter-patient variability of V1 (reduction of 9.6%)

Table 2. Population pharmacokinetic parameter estimates of ocaratuzumab in patients treated with 375 mg/m^2 ocaratuzumab

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Clearance		
Parameter for CL at 375 mg/m2 (L/day)	0.26 (7.6)	45.9% (23.6)
Volume of Distribution		
Parameter for V1 (L)	2.99 (5.5)	34.1% (34.2)
Parameter for V2 (L)	3.31 (11.1)	50.0% (57.4)
Inter compartmental Clearance		
Parameter for Q (L/day)	0.94 (9.4)	

Abbreviations: SEE = standard error of the estimate; CL = clearance; V1 = volume of distribution in compartment 1; V2 = volume of distribution in compartment 2; Q = inter compartmental clearance

INDIVIDUAL PATIENT PK

- There was significant variation in serum ocaratuzumab concentration (Table 3)
- There was no correlation between serum ocaratuzumab concentration at Day 28 (1 week after last infusion) and PFS (Figures 2 & 3)
- Only 2 patients developed high titers of human anti-human antibodies (HAHA) and they also had low serum concentrations of ocaratuzumab and were among the 3 total patients who progressed (Table 3)

Table 3. Range of Serum Ocaratuzumab Concentration at Day 28, 1 week after last infusion

Ocaratuzumab Concentration at Day 28				
* 11	168,205	216,974	282,357	CR
* 2625	175,572	219,337	284,743	PR
19,141	178,897	226,087	299,115	SD
44,417	189,753	228,600	311,631	PD
68,362	190,249	230,879	342,268	* HAHA
121,963	204,256	231,046	349,601	
135,431	213,271	251,889	353,775	
138,452	213,942	256,770	370,129	
160,176	214,895	258,145	409,055	

Figure 3. There was no correlation between the serum concentration of ocaratuzumab 1 week after the last infusion and PFS

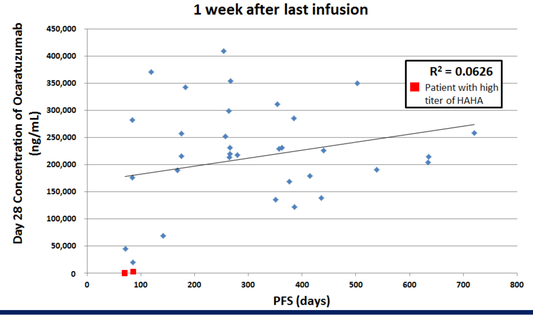
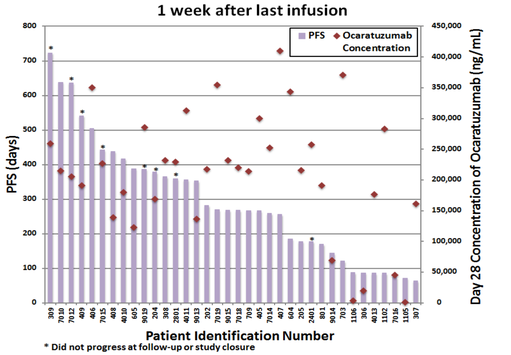
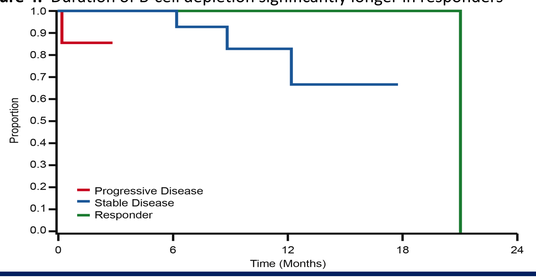


Figure 3. Clinical efficacy was seen across a wide range of serum ocaratuzumab concentration



- All patients demonstrated rapid B-cell depletion; however, the 2 patients who had high titers of HAHA and progressed recovered their B-cells faster than patients with stable disease and responders (Figure 4)

Figure 4. Duration of B-cell depletion significantly longer in responders



CONCLUSION

- Ocaratuzumab, a 3rd-generation anti-CD20 monoclonal antibody with high ADCC across all FcγRIIIa genotypes, has the potential to be active at low serum concentrations
- Despite variation in the clearance of ocaratuzumab, most patients have enough active drug at 4 weekly doses of 375 mg/m^2 to receive clinical benefit
- Only BSA had a statistically significant influence on the PK of ocaratuzumab
- Unlike other anti-CD20 monoclonal antibodies, faster clearance of ocaratuzumab was not correlated with faster disease progression
- Only 2 patients developed high titers of HAHA and also had the 2 most rapid clearances of ocaratuzumab, suggesting the presence of neutralizing HAHA

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This analysis was conducted by MENTRIK Biotech, LLC