Pharmacokinetic and Pharmacodynamic Analysis of Ocaratuzumab in 50 Patients with Relapsed Follicular Lymphoma and Low-Affinity FcγRIllα (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 FcγRIllα (CD16a) receptor on effector cells. It demonstrates 13-fold higher affinity for CD20 and 6-fold higher antibody-dependent cellular toxicity compared to rituximab.

In a Phase II study, 50 patients received IV ocaratuzumab at 375 mg/m² for 4 doses, the standard dosing schedule of rituximab. The median age (range) was 61 (39-83) years, and the median number of prior therapies (range) was 2 (1-3). Two patients were rituximab naive.

This abstract describes the pharmacokinetics (PK) and pharmacodynamics of ocaratuzumab. The steady-state concentration of ocaratuzumab was reached by the 3rd 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 0.25 L/day. The terminal alpha half-life for the central and peripheral compartments were 3.15 L and 3.31 L respectively, which corresponds to a terminal half-life of approximately 25 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 short PFS and some patients with high concentrations had short PFS.

Two only patients developed high titers of human anti-human antibodies (HAHA) and also had the 2 most rapid clearances of ocaratuzumab, suggesting the presence of neutralizing HAHA antibodies (Figure 1 and Table 2). There was no correlation between the serum concentration of ocaratuzumab and progression free survival (PFS) (Figure 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).

In conclusion, clinical efficacy was seen across a wide range of serum concentrations of ocaratuzumab. 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%). 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/m² ocaratuzumab.
- 44 patients 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 NLSA and CD19+ B-cell counts were determined with FACS.
- Pharmacokinetics of ocaratuzumab were determined using NONMEM (version VII). There were no relevant conflict of interests to disclose.

Table 1. Characteristics of the 50 Patients Enrolled in the 375 mg/m² Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>N (N = 50)</td>
</tr>
<tr>
<td>Age (y), median (range)</td>
</tr>
<tr>
<td>FCγRIllα Genotype</td>
</tr>
<tr>
<td>No. of prior systemic treatments, median (range)</td>
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Figure 1. Population pharmacokinetic model for 375 mg/m² 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 FcγRIllα 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%).

INDIVIDUAL PATIENT PK
- There was significant variation in serum ocaratuzumab concentration (Table 3).
- There was no correlation between serum ocaratuzumab concentration at Day 28 and progression free survival (PFS) as some patients with low concentrations had short PFS and some patients with high concentrations had short PFS.
- 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

<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Estimate</th>
<th>Inter-Parameter Variance (%SEE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/day)</td>
<td>0.94 (9.4)</td>
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</tr>
<tr>
<td>V1 (L)</td>
<td>10.2 (10.1)</td>
<td></td>
</tr>
<tr>
<td>V2 (L)</td>
<td>1.56 (16.0)</td>
<td></td>
</tr>
<tr>
<td>FcγRIllα Genotype</td>
<td>0.94 (9.4)</td>
<td></td>
</tr>
<tr>
<td>No. of prior systemic</td>
<td>3.94 (9.4)</td>
<td></td>
</tr>
<tr>
<td>treatments, median</td>
<td>2.0 (1 - 9)</td>
<td></td>
</tr>
</tbody>
</table>

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 standard deviations and progressed recovered their B-cells faster than patients with stable disease and responders (Figure 4).

CONCLUSION
- Ocaratuzumab, a 3rd generation anti-CD20 monoclonal antibody with high ADC specificity across all FcγRIllα genotypes, has the potential to be active at low serum concentrations.
- Despite the variation in the clearance of ocaratuzumab, most patients have shown enough activity at 4 weekly doses of 375 mg/m² 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.

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

- For more information, e-mail info@mentrik.com
- This analysis was conducted by MENTRIK Biotech, LLC

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