Population Pharmacokinetics of Obinutuzumab (GA101) in Patients with Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma (NHL)

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BACKGROUND

- Obinutuzumab (GA101) is a novel, humanized type II anti-CD20 monoclonal antibody with a glycoengineered Fc region, which facilitates induction of enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) and direct cell death.
- Approved in the US for patients with CLL in conjunction with chlorambucil based on a Phase 3 study with PFS endpoint and hazard ratio of 0.39 vs RTX.
- The aim of the population PK analysis was to characterize the PK properties of GA101 following IV administration in CLL and NHL patients and to identify covariate factors that influence its disposition.

METHODS

Data

- 678 patients from 4 Phase I - III studies contributed 12,634 serum concentrations. Of them:
  - 50.4% with CLL, 42.2% B-cell lymphoma (BCL), 4.4% diffuse large B-cell lymphoma (DLBCL), 2.9% Mantle cell lymphomas (MCL)
  - 57.1% males, average (range) age 65.7 years (22–89)
- Various flat (weight-independent) GA101 dosing regimens:
  - 50- 2000 mg weekly for 4 weeks, or
  - 400 - 1600 mg every 21 or 28 days for 6-8 cycles,
  - some regimens with additional doses on days 8 and 15 of cycle 1 and/or
  - with possibility to switch to higher dose arms
  - As monotherapy or in combination with CHOP, FC or chlorambucil
- GA101 is administered by IV infusion at a maximum rate of 400 mg/h

Modeling

- Nonlinear mixed-effects modeling was performed using NONMEM 7.2.0 with Monte Carlo importance sampling expectation-maximization assisted by mode *a posteriori* estimation (IMPMAP) method.
- The full model approach was used for covariate model development. Multiple covariates chosen based on mechanistic plausibility, exploratory analysis and scientific interest were simultaneously added to model parameters.
- Tested covariates: sex, body weight, age, diagnosis (CLL, BCL, DLBCL or MCL), and tumor size at baseline (BSIZ). Other covariates: normalized creatinine clearance, presence of anti-drug antibodies, and B-cell count at baseline (that was confounded with diagnosis) were evaluated by diagnostic plots.

RESULTS

The final population PK model:

- 2-compartment model with time-dependent clearance:

  $CL = CL_{inf} + CL_t, \quad CL_t = CL_T \cdot \exp(-k_{des} t)$

- Steady-state PK parameters typical for a monoclonal antibody (Table 1)
- CL_t declined with the half-life of 19 days (in CLL patients with BSIZ > 1750 mm^2), and steady-state is reached after approximately 4 months of dosing
- CL_{inf} and CL_T depended on diagnosis. Compared to patients with CLL:
  - 17% lower for BCL, 17% lower for DLBCL, and 75% higher for MCL
- Decline in time-dependent clearance CL_t depended on diagnosis and BSIZ:
  - k_{des} was 108% higher for NHL compared with CLL,
  - k_{des} was 165% higher for BSIZ < 1750 mm^2
- CL_{inf}, CL_T, Vc, Vp, and Q increased with body weight as power functions:
  - CL_{inf}, CL_T with close to allometric power coefficient 0.615 (95% CI: 0.437 – 0.794)
  - Vc with smaller power coefficient: 0.383 (95% CI: 0.293 – 0.474)
  - Vp, and Q with fixed power coefficients of 1 and 0.75, respectively

RESULTS

- CL_{inf}, CL_T, and Vc higher in males, 22%, 49%, and 18% respectively
- GA101 PK was independent of age, renal function or anti-drug antibodies (detected in 17 patients during follow up).

Table 1: Parameter Estimates of the Final Model

Parameter	Estimate	%RSE	Parameter	Estimate	%RSE	Shrinkage
k_{des} (1/day)	0.0359	10.8	$CL_{T,DIS23}$=$CL_{inf,DIS23}$	0.834	3.54	
CL_T (L/day)	0.231	8.43	$CL_{T,DIS4}$ =$CL_{inf,DIS4}$	1.75	17	
CL_{inf} (L/day)	0.0828	3.37	$k_{des,BSIZ<1750}$	2.65	11.9	
V_1 (L)	2.76	1.38	ω^2_{kdes}	CV=127%	7.95 [b]	15.4%
V_2 [a] (L)	1.01	4.47	ω^2_{CLT}	CV=95.3%	11.1 [b]	21.6%
Q (L/day)	1.29	11.5	ω^2_{CLinf}	CV=39.9%	7.12 [b]	11%
$CL_{inf,WT} = CL_{T,WT}$	0.615	14.8	ω^2_{V1}	CV=18.5%	9.03 [b]	10.8%
$V_{1,WT}$	0.383	12.1	ω^2_{V2}	CV=60.1%	10.6 [b]	32.6%
$CL_{T,SEX}$	1.49	9.7	ω^2_{Q}	CV=94.3%	17.5 [b]	52.2%
$CL_{inf,SEX}$	1.22	3.6	ω^2_{EPS}	CV=52.3%	10 [b]	0.1%
$V_{1,SEX}$	1.18	1.83	σ^2_{prop}	CV=17.8%	4.52 [b]	1.8 %
$k_{des,NHL}$	2.08	12.3	σ^2_{add} (μg/mL)^2	SD=0.165	69.1 [b]	

CL_{inf}, non-specific time-independent clearance; CL_T, initial value of time-dependent clearance; k_{des}, decay coefficient of time-dependent clearance; ω^2_{EPS}, variance of inter-individual error on proportional residual error. P_{COV}, effect of covariate COV on parameter P, where DIS23 is B-cell lymphoma and diffuse large B-cell lymphoma; DIS4 is mantle cell lymphoma; BSIZ is the baseline tumor size (mm^2).

Figure 1. Prediction-Corrected Visual Predictive Check

The lines show median (red), and the 5th and 95th percentiles (**blue**) of the observed prediction-corrected concentrations. The shaded regions show the 90% confidence intervals on these quantities obtained by simulations.

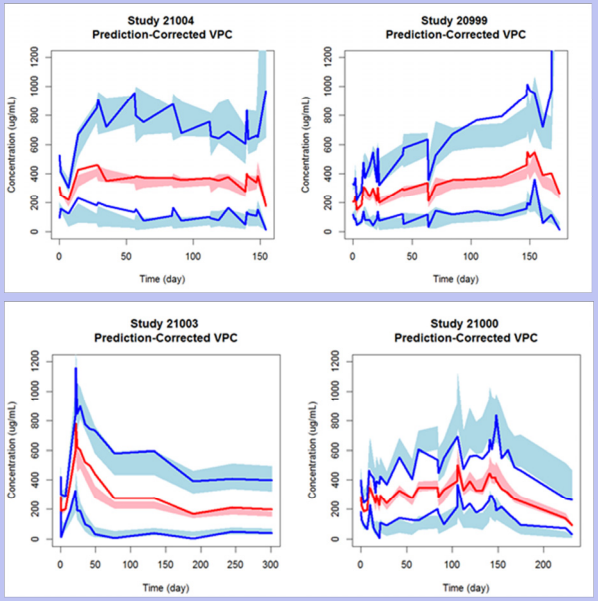
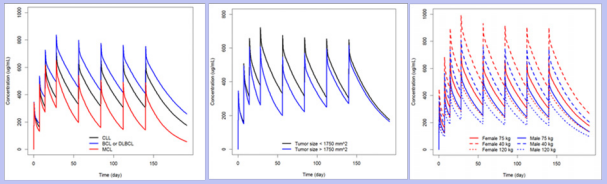


Figure 2. Effects of covariates on GA101 Concentrations

Population predictions for typical subjects with specific combinations of covariate values. Concentration time courses were simulated following 1000 mg IV doses on days 0, 8, 15, 28, 56, 84, 112, and 140.



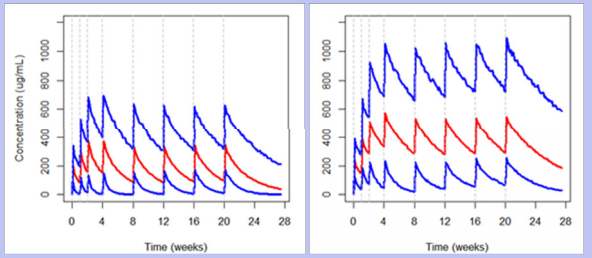
Diagnosis
Female,75 kg, BSIZ < 1750 mm^2

Baseline tumor load
Female,75 kg, with CLL

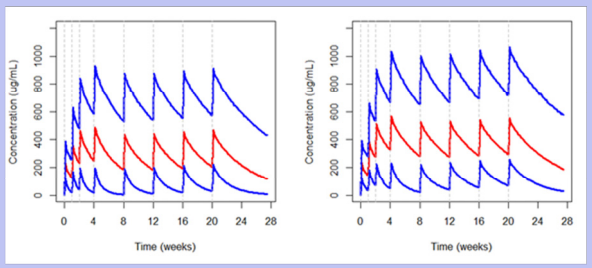
Weight and Sex
CLL, BSIZ < 1750 mm^2

Figure 3. Model-Based Simulations, by Disease

Each subject from the analysis data set was used to create 100 simulated subjects with the same covariates but different individual random effects. Concentration time courses were simulated following1000 mg IV doses on days 0, 8, 15, 28, 56, 84, 112, and 140. Residual variability was included. Once-a-day sampling was assumed. Medians (red), and 5th and 95th percentiles (blue) of the simulated concentrations are plotted.



MCL **DLBCL**



CLL **BCL**

CONCLUSIONS

- GA101 PK is consistent with other monoclonal antibodies targeting B-cells.
- The PK is consistent with target-mediated CL (with higher CL for higher tumor burden and higher CD20 expression) that decreases with elimination of target cells.
- GA101 CL is higher in patients with MCL and CLL (leukemic diseases with large amount of CD20 expressing cells in peripheral circulation) compared to BCL and DBCL (lymphatic diseases with less target in circulation).
- For patients with CLL, the differences in steady-state exposure due to differences in body weight and gender were within 30%. The expected differences in exposure for the proposed 1000 mg IV dosing regimen do not warrant any dose adjustment based on gender and body weight.