# Population Pharmacokinetics of Obinutuzumab (Gazyva) in Patients with Chronic Lymphocytic Leukemia (CLL), Follicular Lymphoma (FL), Other Indolent Non-Hodgkin's Lymphoma (iNHL) Subtypes, Diffuse Large B-cell Lymphoma (DLBCL), and Mantle Cell Lymphoma (MCL)

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## BACKGROUND

- Obinutuzumab (Gazyva, GA101) is a humanized type II anti-CD20 monoclonal antibody with a glycoengineered Fc region. A population PK model for patients with CLL and NHL was established earlier [1].
- Approved for treatment of CLL in combination with chlorambucil. The current work supported the registration in FL.
- The aim of the analysis was to update the model with new data of patients with FL, DLBCL and MCL, and to identify covariates of GA101 exposure.

## METHODS

### Data

- 961 patients from 6 Phase I - III studies contributed 16,301 serum concentrations:
  - 36% with CLL, 49% iNHLL (of them 87% FL), 14% DLBCL, 2% MCL
  - 57% males, average (range) age 64 years (22–89)
- Various flat (weight-independent) dosing regimens
  - As monotherapy or in combination with cyclophosphamide/ doxorubicin/ vincristine (CHOP), fludarabine/cyclophosphamide (FC), bendamustine (BENDA), or chlorambucil (chemo type was correlated with disease type)
  - Administered by IV infusion at a maximum rate of 400 mg/h

### Modeling

- Nonlinear mixed-effects modeling was performed using NONMEM 7.3.0 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.
- Diagnostics plots and predictive check procedures were used for model evaluation.
- Sensitivity analyses were performed for iNHL, FL, or DLBCL by refitting the model to the data of those diseases.

## RESULTS

The final model was 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 were typical for a monoclonal antibody (Table 1).
- $CL_{inf}$, Vc, and Vp increased with body weight; $CL_{inf}$, Vc, and $CL_T$ were higher in males, 18%, 19%, and 45% respectively. $CL_{inf}$ decreased with age and serum albumin (ALB). $CL_{inf}$ and $CL_T$ increased with baseline tumor size (TS), leading to initially lower exposure in patients with high TS.
  - For patients with iNHL and DLBCL, differences in steady-state exposure due to demographics and TS were within 35% for respective dosing regimens
- $CL_t$ declined with the half-life of 6.3 days. Thus, CL declined to $CL_{inf}$ after a month of dosing.
  - For the proposed dosing regimens (1000 mg IV Q3W or Q4W with additional doses on Days 8 and 15 of cycle 1), drug concentrations reach steady-state levels after cycle 1.
- $CL_{inf}$, $CL_T$, and $k_{des}$ depended on diagnosis:
  - $CL_{inf}$ was 47%, 107%, and 38% higher for CLL, MCL, and SLL, compared to iNHL or DLBCL.
  - $CL_T$ was 125% and 180% higher for CLL and MCL compared to other tumor types.
  - $k_{des}$ was lower ($t_{1/2}$=21 day) in MZL.
  - Simulations of iNHL dosing regimen indicated that at the end of Induction (Cycle 6), $AUC_\tau$ and $C_{trough}$ were 15-18% higher in patients with MZL and 27-36% lower in patients with SLL, compared to FL. Steady-state exposure during Maintenance was nearly identical for MZL and FL, but was 33-50% lower for SLL.
- $k_{des}$ was higher with concomitant FC ($t_{1/2}$= 2.4 days), and lower with BENDA (10.7 days) or CHOP (20.4 days).
  - However, more frequent dosing when administered with CHOP (Q3W) prevented lower drug exposures.
- PK did not depend on prior CD20+ tumor therapy, or renal or hepatic function.
- Anti-drug antibodies (20 patients, non-neutralizing) did not influence drug levels.

**Table 1. Parameter Estimates of the Final Model**

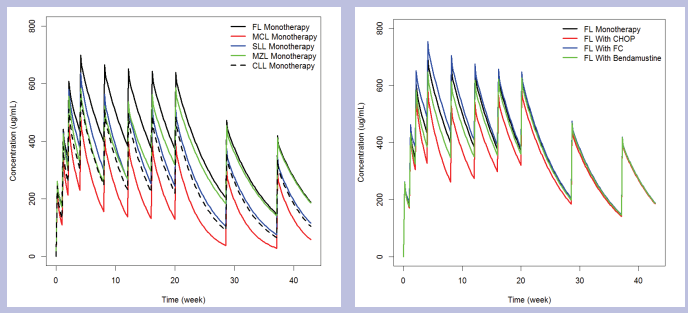
| Parameter | Estimate | %RSE | Parameter | Estimate | %RSE | Shrinkage |
|---|---|---|---|---|---|---|
| $k_{des}$ (1/day) | 0.11 | 7.2 | $CL_{T,MCL}$ | 2.80 | 40.0 | |
| $CL_T$ (L/day) | 0.154 | 9.12 | $CL_{inf,CLL}$ | 1.47 | 3.68 | |
| $CL_{inf}$ (L/day) | 0.0742 | 2.67 | $CL_{inf,MCL}$ | 2.07 | 18.3 | |
| $V_1$ (L) | 2.72 | 1.22 | $CL_{inf,SLL}$ | 1.38 | 11.5 | |
| $V_2$ (L) | 1.23 | 3.95 | $k_{des,CHOP}$ | 0.309 | 14.1 | |
| Q (L/day) | 1.32 | 11.4 | $k_{des,BENDA}$ | 0.591 | 14.4 | |
| $CL_{inf,WT}$ | 0.639 | 14.5 | $k_{des,FC}$ | 2.64 | 33.0 | |
| $V_{1,WT}$ | 0.378 | 10.1 | $\omega^2_{kdes}$ | CV=90.6% [a] | 8.56 [b] | 25.6% |
| $V_{2,WT}$ | 1.08 | 14.5 | $\omega^2_{CLT}$ | CV=110% [a] | 19.7 [b] | 26.9% |
| $CL_{T,SEX}$ | 1.45 | 10.0 | $\omega^2_{CLinf}$ | CV=44.6% [a] | 7.16 [b] | 6.1% |
| $CL_{inf,SEX}$ | 1.18 | 3.51 | $\omega^2_{V1}$ | CV=18.5% [a] | 7.01 [b] | 10.7% |
| $V_{1,SEX}$ | 1.19 | 1.54 | $\omega^2_{V2}$ | CV=47.9% [a] | 12.1 [b] | 39.3% |
| $CL_{T,TS}$ | 0.351 | 15.4 | $\omega^2_{Q}$ | CV=97.8% [a] | 17.8 [b] | 50.2% |
| $CL_{inf,TS}$ | 0.09 | 18.2 | $\omega^2_{EPS}$ | CV=47.3% [a] | 8.02 [b] | 2.4% |
| $CL_{inf,ALB}$ | -0.682 | 16.7 | $\sigma_L$ | 1.77 | 9.72 | |
| $CL_{inf,AGE}$ | -0.241 | 29.3 | $\sigma_H$ | 0.111 | 3.78 | |
| $k_{des,MZL}$ | 0.299 | 25.6 | $\sigma^2_{50}$ (μg/mL)$^2$ | 8.26 | 14.9 | |
| $CL_{T,CLL}$ | 2.25 | 13.6 | where residual error was described by: | $\ln C_{ij} = \ln \hat{C}_{ij} + \left(\sigma_L - (\sigma_L - \sigma_H)\cdot\frac{\hat{C}_{ij}}{\sigma_{50}+\hat{C}_{ij}}\right)\cdot\exp(\eta_i)\cdot\varepsilon_{ij}$ | | |

a. Computed as sqrt($\omega^2$); b. %RSE for the $\omega^2$ estimate

$CL_{inf}$ = time-independent clearance; $CL_T$ = initial value of time-dependent clearance; $k_{des}$ = decay coefficient of time-dependent clearance; $\omega^2_{EPS}$ = variance of inter-individual error on residual error. $P_{COV}$, effect of covariate COV on parameter P. Reference values of covariates: FL or DLBCL, female, WT=75 kg, AGE=65 years, ALB=40 g/L, TS=3000 mm$^2$.

**Figure 1. Typical Predictions following iNHL Dosing Regimen for Patients with Different Tumor Types and Patients with FL on different Concomitant Chemotherapies**

Population predictions for typical subjects following 1000 mg IV doses administered at 0, 7, 14, 28, 56, 84, 112, 140 days, and then at 200 and 260 days.




## DISCUSSION / CONCLUSIONS

- Higher clearance in CLL and MCL is consistent with higher levels of target cells in circulation compared to iNHL and DLBCL, where malignant cells are mostly in harder-to-reach tissues. Also, leukemic (liquid) nature of CLL and MCL allows easier access to target cells compared to lymphomas.
- Clearance in MCL was higher than in CLL, despite lower peripheral B-cell counts in MCL. This is likely due to the significantly higher expression of CD20 receptors on B-cells in MCL compared with CLL patients.
- Similar $CL_{inf}$ for SLL and CLL is consistent with similarity these diseases.
- Higher $CL_{inf}$ and $CL_T$ in MCL compared to CLL despite lower peripheral B-cell counts is likely due to significantly higher expression of CD20 on B-cells.
- Lower $k_{des}$ in MZL is likely due to a deeper pool of B cells compared to other types of iNHL, with a more restricted drug access to the tumor.
- FC co-administration, being an agressive treatment, is expected to lead to faster elimination of tumor cells and consequently to higher $k_{des}$.
- Lower $k_{des}$ with CHOP and BENDA could be related to differences between patient populations (chemos were not randomized) or additional co-medications (different for different chemos).
- The updated model described GA101 PK for different tumor types and concomitant chemotherapies.

[1] E. Gibiansky, L. Gibiansky, D. Carlile, C. Jamois, V. Buchheit, N. Frey, Population Pharmacokinetics of Obinutuzumab (GA101) in Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma and Exposure-Responses in CLL, CPT:PSP (2014) 3, e144; doi:10.1038/psp.2014.42