Poster No. 1198

Population Pharmacokinetics (popPK) and Exposure-Response Analyses for Glofitamab in Relapsed/Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (NHL): Confirmation of Efficacy and CRS Mitigation in Patients with Step-Up Dosing

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Disclosures

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Key takeaways

- PopPK and exposure-response (E-R) models previously investigated (Djebli N, et al. Blood 2019) suggested benefits of step-up dosing
- Updated models and emerging data confirmed that the 2.5/10/30mg step-up dosing regimen maximizes efficacy while minimizing CRS

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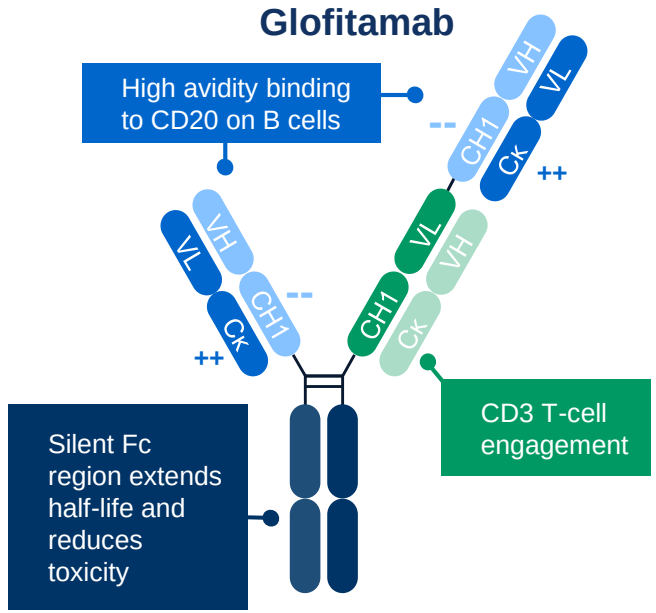
Background

- **Glofitamab** is a T-cell-engaging bispecific full-length antibody with unique 2:1 molecular configuration that comprises two binding regions for CD20 (on the surface of B cells) and one for CD3 (on the surface of T cells)
- In an ongoing Phase I dose-escalation study (NP30179; NCT03075696), glofitamab showed high and durable complete response (CR) rate and manageable safety at fixed doses ≥0.6mg in R/R NHL[1]
- PopPK and E-R relationships for glofitamab indicated step-up dosing would mitigate cytokine release syndrome (CRS) while maximizing efficacy[2]



Here, we present updated popPK and E-R, including data from patients receiving step-up dosing.

Clinical cut-off: October 1, 2020.

1. Dickinson M, et al. 25th EHA Congress, June 11–14, 2020 (Presentation S241); 2. Djebli N, et al. Blood 2019;134:3799.

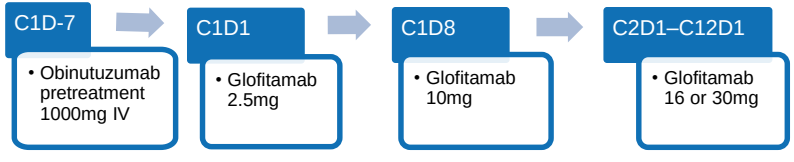
NP30179 is an ongoing Phase I dose-escalation study in patients with R/R NHL

Key inclusion criteria

- Age ≥18 years
- ≥1 prior therapy
- ≥1 measurable lesion
- Adequate hematological and liver function
- ECOG PS ≤1

Treatment

- 1000mg obinutuzumab 7 days prior to glofitamab
- Glofitamab IV step-up doses on C1D1 and D8 and at target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg)
- Q3W for up to 12 cycles



Methods

- Serial and sparse glofitamab, and sparse obinutuzumab PK data were used to develop a popPK model
- Physiologically relevant covariates were investigated for their influence on glofitamab PK
- Obinutuzumab concentration-time profiles were constructed, using the established obinutuzumab popPK model,[1] to estimate glofitamab RO% in the presence of obinutuzumab competing for CD20 receptors over time[2]

$$\text{Glofitamab RO\%} = \frac{[\text{Glofitamab}]*100}{[\text{Glofitamab}]+Kd_{\text{Glofitamab}}*\left(1+\frac{[\text{Obinutuzumab}]}{Kd_{\text{Obinutuzumab}}}\right)}$$

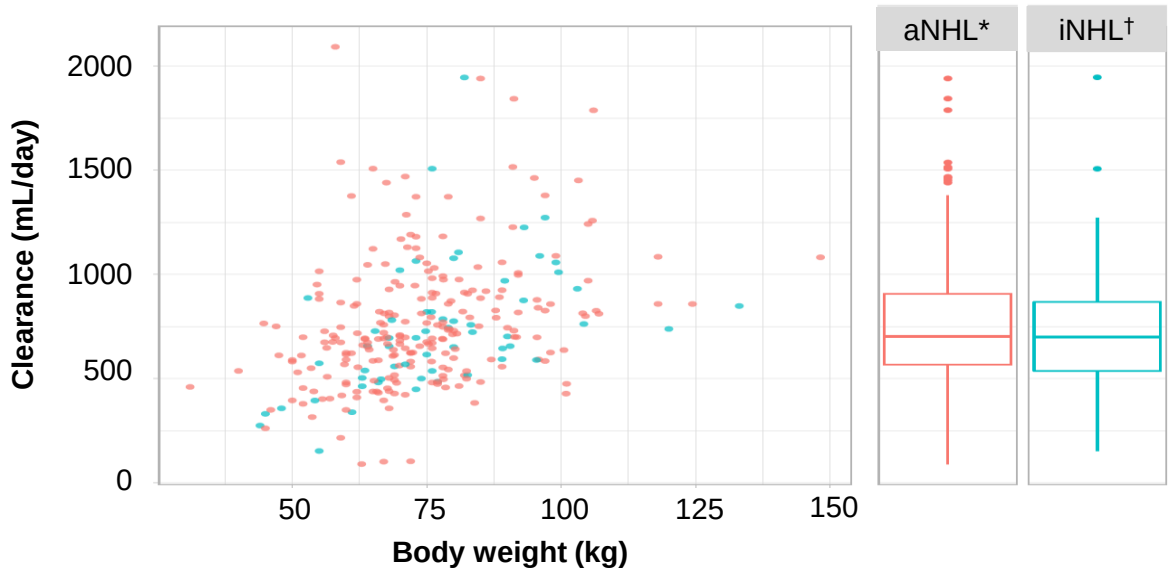
- E-R relationship between glofitamab Average RO% (AvgRO%) over the first 24 hours and CRS, with a focus on grade (Gr) ≥2 CRS (ASTCT criteria[3]) was investigated in patients with indolent (iNHL) and aggressive NHL (aNHL)
- E-R relationships between glofitamab time-averaged RO% up to C3D1 (first response assessment), and complete response rate were characterized in aNHL patients who reached C3D1

*[Glofitamab] and [Obinutuzumab] are glofitamab and obinutuzumab serum concentrations; $Kd_{Glofitamab}$ and $Kd_{Obinutuzumab}$ are the *in vitro* equilibrium dissociation constants (both are 4 nM).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; Q3W, once every 3 weeks; RO%, receptor occupancy.

1. Gibiansky E, et al. CPT Pharmacometrics Syst Pharmacol 2014;3:e144;
2. Salahudeen MS & Nishtala PS. Saudi Pharm J 2017;25:165–75;
3. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Glofitamab PK were comparable in patients with iNHL and aNHL

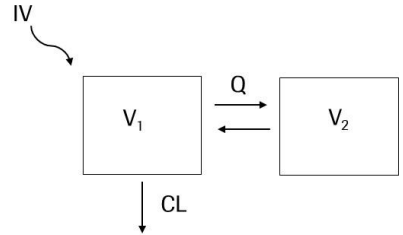
Scatterplot of estimated individual clearance versus body weight (left) and box plot of clearance by aNHL/iNHL (right)



*aNHL includes DLBCL, MCL, MZL, PMBCL, Richter's transformation, and transformed FL; †iNHL includes FL grade 1–3A.

CL, clearance; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PMCBL, primary mediastinal large B-cell lymphoma; Q, inter-compartment clearance; V1, central compartment; V2, peripheral compartment.

- The popPK analysis included 290 iNHL and aNHL patients with ≥1 PK sample (total samples = 6512)
- Glofitamab PK were best described using a two-compartment PK model with linear clearance



- Body weight was retained using theory-based allometric scaling on volumes and clearances ($p<0.001$). However, no clinically meaningful impact was observed
- No other investigated covariate was shown to influence glofitamab PK

Parameters were well estimated using a glofitamab popPK model

- Glofitamab volume of distribution from the central compartment (V1) approximates plasma volume
- Glofitamab clearance (CL) from the central compartment appears slightly higher than that of a typical IgG1 antibody[1]
- All popPK parameters were associated with low standard error of estimate (RSE)% values:
  - 0.28–1.62% for fixed-effect parameters
  - 4.05–28.4% for random-effect parameters

PK parameters	Unit	Estimate	RSE* (%) [shrinkage (%)]	Bootstrap median [2.5th and 97.5th percentile]
Fixed effects				
CL	mL/day	672	1.62 [NA]	670 [621;708]
Q	mL/day	959	0.280 [NA]	924 [753;1110]
V1	mL	3410	0.874 [NA]	3420 [3130;3620]
V2	mL	3410	0.686 [NA]	3290 [2730;3900]
Random effects (IIV)				
CL	CV%	42.8	9.34 [6.80]	42.3 [34.2;51.5]
Q	CV%	76.8	15.6 [27.2]	76.3 [33.1;97.5]
V1	CV%	52.5	28.4 [2.70]	51.4 [29.9;77.4]
V2	CV%	76.7	11.0 [18.5]	77.0 [58.2;103]
Covariate effects				
Effect of WT on CL and Q	–	0.75[a]	–	0.75
Effect of WT on V1 and V2	–	1[a]	–	1
Error model				
σ (proportional)	%	27.6	4.05 [5.90]	28.5 [26.5;31.1]

Bootstrap with 1000 simulations showed the model to be robust and confirmed high precision of the parameters estimated

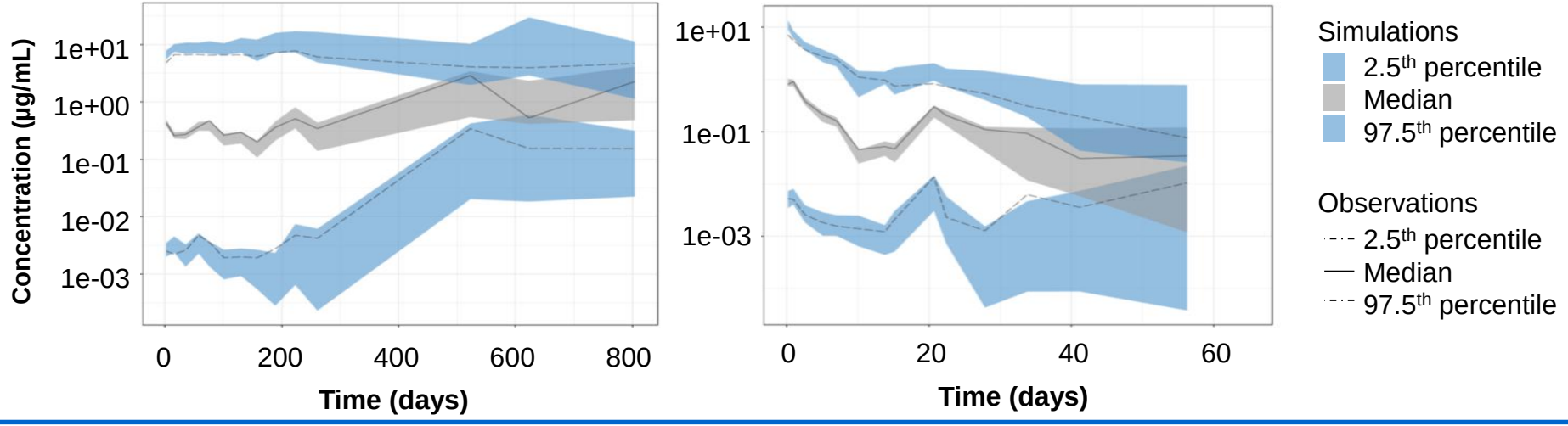
[a]Allometric coefficients: fixed. CV, coefficient of variation; Ig, immunoglobin; IIV, inter-individual variability; NA, not available; RSE, relative standard errors; WT, body weight; σ, residual error.

1. Bai S, et al. Clin Pharmacokinet 2012;51:119–35.

The glofitamab popPK model was qualified using visual predictive check (VPC)[1]

- The popPK model revealed no trend for apparent over- or under-prediction of glofitamab concentrations across a wide dose range
- The qualified popPK model was subsequently used to estimate individual glofitamab RO% for investigation in E-R analyses

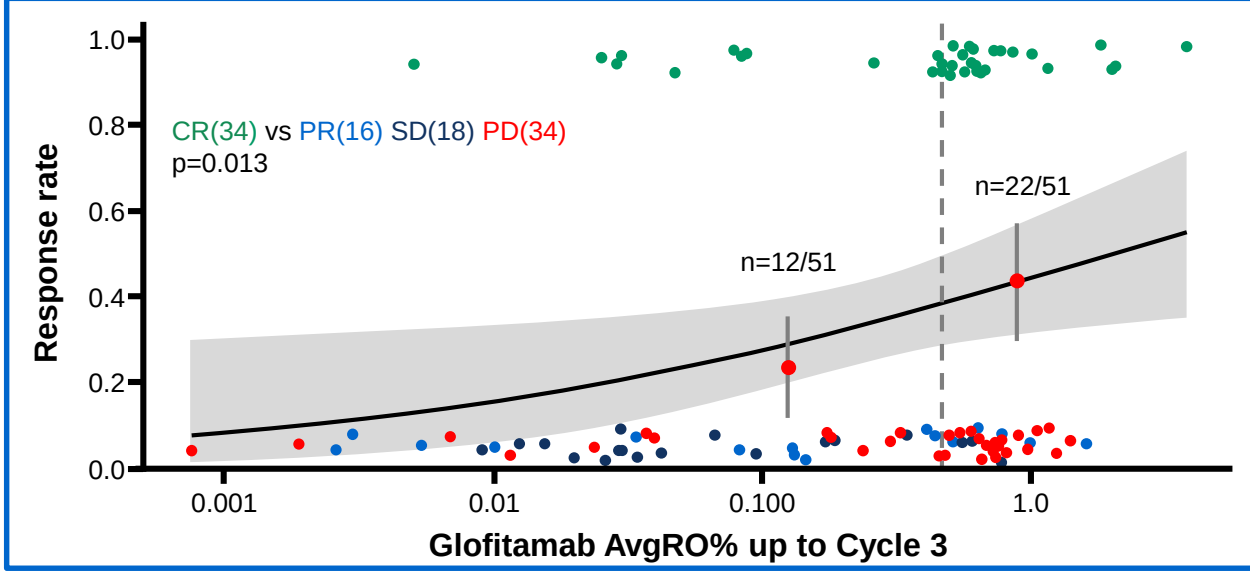
VPC across all doses from the glofitamab popPK model versus time (left panel) and time after last dose (right panel)



1. Bergstrand M, et al. AAPS J 2011;13:143–51.

Efficacy: positive E-R relationship with glofitamab AvgRO% in aNHL patients

Probability of CR versus glofitamab AvgRO% up to Cycle 3 in aNHL patients (N=102)



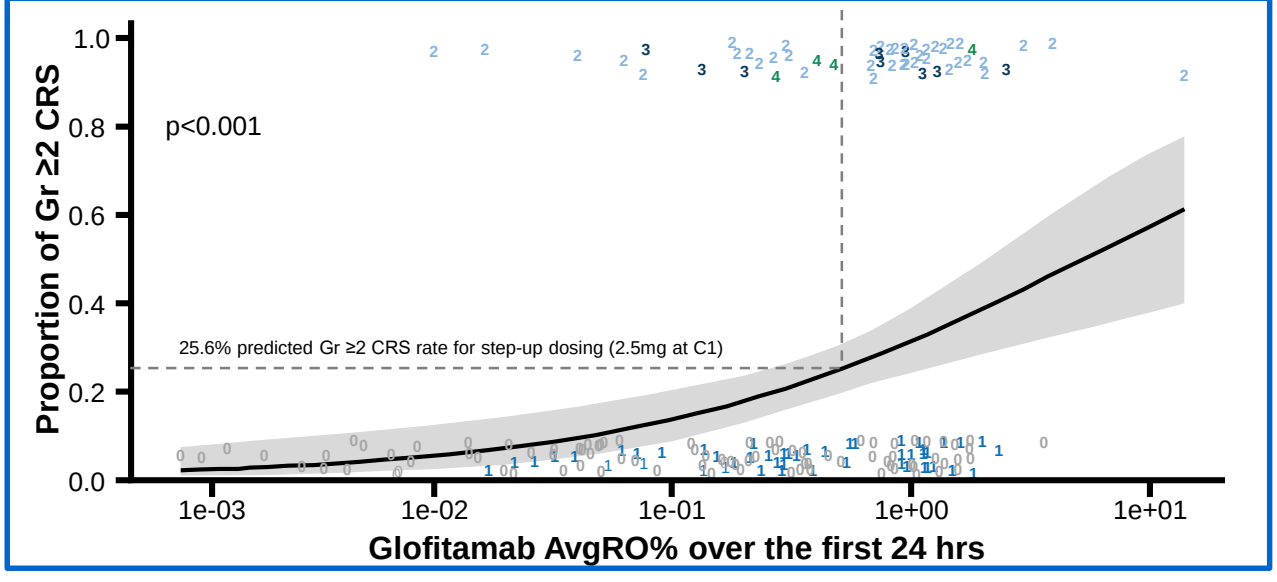
Dots illustrate the observed individual patient response coloured by achieved response. The proportion of responders (red dots) and associated 95% CIs (black vertical solid lines) are provided in lowest and highest AvgRO% groups, respectively (separated by the vertical dashed line at 0.495%). The black line shows the logistic regression. Grey shaded regions=95% CI for the logistic regression. The p-value is obtained from the Chi squared test using ANOVA function of R, comparing the model to the null model. AIC, Akaike information criterion.
CI, confidence interval; CRR, complete response rate.

- E-R analysis showed that patients with a higher AvgRO% at C3D1 demonstrated a higher CR rate, indicating that a 30mg dose should allow for greater efficacy
- Projections using this E-R analysis predict a median predicted CR rate of 43.8% (34.3–55.0%) in aNHL patients receiving 2.5/10/30mg step-up dosing
- In comparison, clinical data from aNHL patients receiving 2.5/10/16 and 2.5/10/30mg step-up dosing demonstrated a complete metabolic response rate of 53.6% (n=28)[1]

1. Hutchings M, et al. ASH 62nd Annual Meeting Meeting & Exposition, December 5–8, 2020 (oral 403).

Grade ≥2 CRS*: positive relationship with glofitamab AvgRO% in iNHL and aNHL patients

Probability of occurrence of Gr ≥2 CRS* versus glofitamab AvgRO% over the first 24 hours in iNHL and aNHL patients (N=264)



- Based on the exposure-safety model:
  - With a 10mg glofitamab dose at C1 (16mg thereafter), a Gr ≥2 CRS rate of 31.2% (25.4–36.9%) was predicted; in line with the incidence reported clinically[1]
  - Step-up dosing (2.5mg at C1), the resulting AvgRO% over the first 24 hrs corresponded to a Gr ≥2 CRS rate of 25.6% (20.0–30.6%)
  - Clinical data demonstrated a Gr ≥2 CRS rate of 23.0% following the 2.5mg glofitamab dose (n=50)[2]

*ASTCT criteria[3]. Numbers illustrate the observed individual patient CRS event and associated grade. Black line=logistic regression; grey shaded regions=95% CI for the logistic regression. P-value is obtained from the Chi squared test using ANOVA function of R, comparing the model to the null model. AIC, Akaike information criterion.

1. Dickinson M, et al. 25th EHA Congress, June 11–14, 2020 (Presentation S241);
2. Hutchings M, et al. ASH 62nd Annual Meeting Meeting & Exposition, December 5–8, 2020 (oral 403);
3. Lee DW, et al. Biol Blood Marrow Transplant. 2019;25:625–38.

Conclusions

Glofitamab popPK and exposure-response relationships for efficacy/safety were validated, including confirmatory safety data from step-up dosing patients

These models and emerging clinical data confirm that in NHL patients, the step-up dosing regimen allowed repeat doses of 30mg glofitamab to maximize efficacy while minimizing the risk of increased CRS at the first administration

These models are being developed further to support optimal biological-dose selection of glofitamab, both as monotherapy and in combination with other agents

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