Integrated Population Modeling of Loncastuximab Tesirine (Lonca) Exposure in B-cell Non-Hodgkin Lymphoma (B-NHL)

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INTRODUCTION

- Despite new therapies, prognosis is poor for patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL, e.g. diffuse large B-cell lymphoma [DLBCL]) who have inadequate response to salvage chemotherapy, are ineligible for autologous stem cell transplantation (ASCT), or who relapse post-ASCT; therefore, new treatments are needed[1–3]
- Loncastuximab tesirine (ADCT-402; Lonca) is an antibody (Ab) drug conjugate comprising a humanized monoclonal Ab directed against B-cell antigen CD19, conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin (SG3199) via a linker[4]
  - After binding to CD19 antigen on tumors, Lonca is internalized, its linker is cleaved, and PBD is released to form persistent DNA interstrand cross-links, causing tumor cell death[4]
- A first-in-human, dose-finding Phase 1 study in R/R B-NHL (NCT02669017)[5,6] identified the recommended Lonca dose (150 µg/kg every 3 weeks [Q3W] for 2 cycles, followed by 75 µg/kg Q3W thereafter), which was subsequently used in the Phase 2 study in R/R DLBCL (NCT03589469)[7,8]

STUDY OBJECTIVES

- To use data from the Phase 1 and Phase 2 studies to develop a population pharmacokinetic (PPK) model to characterize the pharmacokinetics (PK) of the Lonca dosing regimen and evaluate exposure covariates
- This PPK model was also used to investigate the exposure–response relationship; AACR e-poster 1367[9]

METHODS

Creation of Initial Dataset and Exploratory Analysis

- An integrated PPK model was used to describe drug concentrations in serum from 328 patients with R/R B-NHL (DLBCL [n=284], non-DLBCL [n=44]) of:
  - Total antibody (tAb; 5,241 samples)
  - Lonca PBD-conjugated Ab (cAb; 5,301 samples)
  - SG3199: Unconjugated warhead SG3199 (239 samples)

Structural PK Model Selection and Base PPK model

- Four 2-compartment structural models were assessed:
  - Linear (starting point; Phase 1 data only as a wider dosing range was used)
  - Linear with time-dependent clearance
  - Michaelis-Menten
  - Michaelis-Menten with time-dependent clearance

Covariate Screening

- Stepwise forward selection was used to assess the influence of selected covariates, and those significant at 0.005 level (>7.88 change in objective function value) were considered for inclusion in a full PPK model
- Model reduction steps further eliminated covariates from the full model (0.001 level); SG3199 was then added

Final Model Building and Validation

- The final integrated PPK model was evaluated by diagnostic goodness-of-fit plots, and validated by visual-predictive checks (VPC) and bootstrap analysis
- The effects of baseline covariates (**Table 1**) on Lonca PPK were assessed via covariate model building or subsequent Forest plot analysis, using the final PPK model

Table 1. Baseline Covariates Tested

Category	Covariates
Demographics	Body weight (kg); BSA (m^2); sex; age (continuous variable and for <65 years, ≥65 years, <75 years, and ≥75 years); race
Laboratory parameters	CRCL[a] (mL/min); albumin (g/L); ALT (U/L); AST (U/L); ALKP (U/L); TBIL (µmol/L); and LDH (U/L)
Drug formulation	Lyophilized; liquid
Immunogenicity	Presence or absence of ADAs (any time or pre-dose)
Disease characteristics	Disease subtype (DLBCL, non-DLBCL); ECOG status; tumor size (bulky[b], not bulky); total sum of area (cm^2); and lymphocyte count[c] (10^9 cells/L)
Concomitant medication	P-glycoprotein inhibitor
Hepatic function	Normal (TBIL ≤ ULN, and AST ≤ ULN); mild impairment (TBIL ≤ ULN and AST > ULN or ULN < TBIL ≤ 1.5×ULN) or moderate[d] impairment (1.5×ULN < TBIL ≤ 3×ULN)
Renal function	Normal (CRCL ≥ 90 mL/min); mild impairment (60 ≤ CRCL < 90 mL/min), moderate impairment (30 ≤ CRCL < 60 mL/min); or severe[e] impairment (15 ≤ CRCL < 30 mL/min)

ADA, antibody drug antibodies; ALKP, alkaline phosphatase; ALT, alanine amino transferase; AST, aspartate amino transferase; BSA, body surface area; CRCL, creatinine clearance; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; TBIL, total bilirubin; ULN, upper limit of normal

[a]Patient CRCL was calculated from baseline plasma/serum creatinine, age, sex and body weight using the Cockcroft-Gault equation; [b]Defined based on investigator report of subtype X (size exclusion criteria were included in the Phase 2 study, but that did not have to be documented); [c]The Phase 1 trial had CD19 expression data in US patients only and the Phase 2 trial did not collect CD19 expression data; therefore, lymphocyte count was used as a surrogate; [d]The moderate category of hepatic impairment was merged with the mild category, and there were no patients with severe hepatic impairment; [e]The severe category of renal impairment was merged with the moderate category.

- Covariates were potentially clinically relevant if they contributed to >30% change from the reference population at Cycle 1 C_{avg}

Statistical Methods

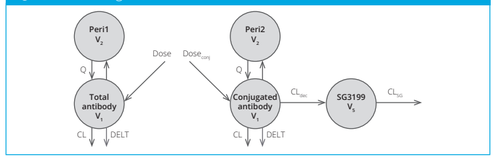
- Between-subject variability (BSV; assumed to be normally distributed, with mean of zero, and variance of ω^2)
- Between-occasion variability (BOV; modeled to describe cycle variability)
- Residual variability (described using an additive error term on the log scale)

RESULTS

Final Integrated PPK model of Lonca tAb and cAb

- Concentration–time data of tAb and cAb were best characterized by a 2-compartment linear model (**Figure 1**) with a time-dependent clearance component that decreased until steady-state was reached by ~15 weeks (Cycle 5)

Figure 1. Final Integrated PPK model of Lonca tAb and cAb



cAb, Lonca pyrrolobenzodiazepine (PBD)-conjugated Ab; CL, linear clearance; CL_{dec}, deconjugation clearance; CL_{SG}, elimination clearance of metabolite SG3199; DELT, time-dependent clearance; $Dose_{cmt1}$, f*Dose, where f is the fraction of tAb that is conjugated; Peri1, peripheral compartment 1; Peri2, peripheral compartment 2; PPK, population pharmacokinetic; Q, intercompartmental clearance; tAb, total antibody; V_1, volume of distribution in the central compartment; V_2, volume of distribution in the peripheral compartment; V_3, volume of distribution for metabolite SG3199.

PPK Parameter Estimates of the Final Covariate Model

- Parallel linear clearance was 0.218 L/day (BSV, 44.9%; **Table 2**)
- Estimated volume of distribution of the central compartment (V_1) was 3.86 L (BSV, 31.8%)
- Estimated typical half-life at steady-state of Lonca cAb was ~20.6 days by ~15 weeks

Table 2. PPK Parameter Estimates of the Final Covariate Model of tAb and Lonca cAb

Parameters	Symbol	Estimate (% RSE)	Symbol (BSV)	BSV
CL (L/day)	**θ1**	**0.218 (8.6)**	η1	**44.9 (9.7)**
WT on CL	θ10	0.438 (45.5)	—	—
ECOG on CL	θ13	0.275 (44.2)	—	—
ALBU on CL	θ14	-0.406 (83.7)	—	—
SEX on CL	θ20	-0.170 (45.5)	—	—
V_1 (L)	θ2	**3.86 (4.1)**	η2	**31.8 (9.7)**
WT on V_1	θ15	0.539 (25.9)	—	—
SEX on V_1	θ21	-0.0792 (69.1)	—	—
CL_{dec} (L/day)	θ3	0.0441 (11)	η3	89.4 (6.4)
V_2 (L)	θ4	3.53 (fixed)	η4	54 (12.1)
DELT (L/day)	θ5	0.117 (18.1)	η5	149.4 (13)
PTST on DELT	θ18	11.45 (28.9)	—	—
ALBU on DELT	θ28	-7.18 (11.4)	—	—
Q (L/day)	θ6	1.16 (fixed)	η6	129.6 (12.2)
K_{des} (1/day)	θ7	0.0347 (16.2)	η7	97.3 (25.7)
SEX on K_{des}	θ23	0.652 (69.5)	—	—
BOV of CL	η8	**25.7 (fixed)**	—	—
BOV of V_1	η11	**32.7 (fixed)**	—	—
BOV of CL_{dec}	η14	57.1 (fixed)	—	—
BOV of V_2	η17	24.9 (fixed)	—	—
ADD ERR1 (% CV)	θ8	21.1 (0.5)	—	—
ADD ERR2 (% CV)	θ9	22.2 (0.5)	—	—

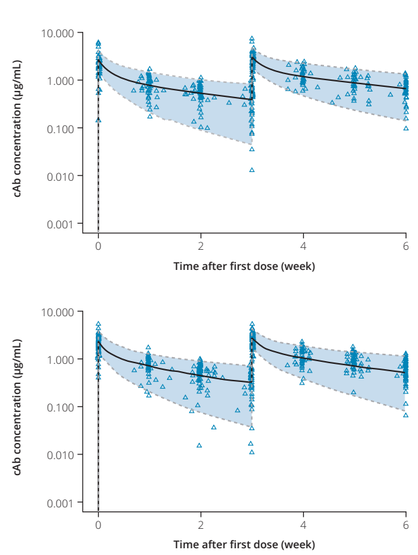
ADD ERR1, additive error of PBD-conjugated Ab on a log scale; ADD ERR2, additive error of tAb on a log scale; ALBU, albumin; BSV, between-subject variability; BOV, between-occasion variability; cAb, Lonca pyrrolobenzodiazepine (PBD)-conjugated Ab; CL, linear clearance; CL_{dec}, deconjugation clearance; CV, coefficient of variation; DELT, time-dependent clearance; DELT*exp(-K_{des}*t), partially time-dependent clearance; ECOG, Eastern Cooperative Oncology Group; K_{des}, first-order rate for decrease; PBD, pyrrolobenzodiazepine; PPK, population pharmacokinetic; PTST, disease subtype; Q, intercompartmental clearance; % RSE, % relative standard error; tAb, total antibody; V_1, volume of distribution in the central compartment; V_2, volume of distribution in the peripheral compartment; WT, body weight.

The objective function value = - 15096.39. Condition number = 104.24. Condition number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate. The typical values (TV) of PK parameters, $TVCL = 0.218 \cdot (WT/78.0)^{0.438} \cdot (ALB/40.0)^{0.406} \cdot ECOG_{CL} \cdot SEX_{CL}$, where $ECOG_{CL}$ is a shift factor of 1 for ECOG = 1 patients, and 1 + 0.275 for ECOG>0 patients, and SEX_{CL} is a shift factor of 1 for male patients, and 1 – 0.17 for female patients. $TVV_1 = 3.86 \cdot (WT/78.0)^{0.539} \cdot SEX_{V1}$, where SEX_{V1} is a shift factor of 1 for male patients and 1 – 0.0792 for female patients. $TVDELT = 0.117 \cdot (ALBU/40.0)^{7.18} \cdot PTST_{DELT}$, where $PTST_{DELT}$ is a shift factor of 1 for DLBCL patients, and 1 + 11.45 for non-DLBCL patients, and $TVK_{des} = 0.0347 * SEX_{Kdes}$, where SEX_{Kdes} is a shift factor of 1 for male, and 1 + 0.652 for female.

Validation of the Final PPK Model

- VPC analysis for cAb, which was similar in males and females (**Figure 2**), showed that the model adequately described the data (most observations were within 95% confidence intervals of model-predicted values)
- Bootstrap analysis demonstrated good model stability[10]
- No bias was observed in conditional weighted residuals or individual weighted residuals with respect to time- or population-predicted concentrations for Lonca cAb[10]

Figure 2. Visual Predictive Check Plots of the Final PPK model — Model-predicted and cAb Serum Concentrations in (A) Females and (B) Males during Weeks 0–6 of Treatment



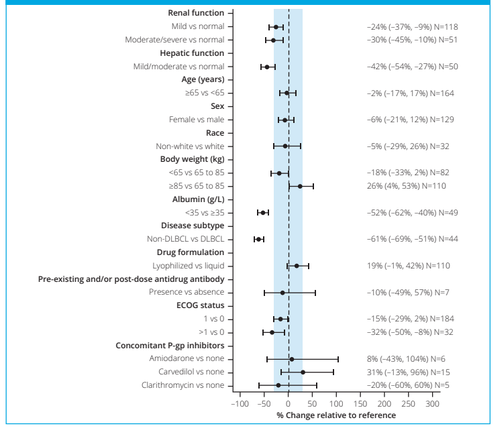
cAb, Lonca pyrrolobenzodiazepine (PBD)-conjugated Ab; PPK population pharmacokinetic.

Solid black line of figure represents the median-predicted values. Dashed gray line represents the model-predicted 95% confidence interval. Blue triangles represent observed PK data. Data shown for the first 6 weeks of treatment, representing the first 2 cycles at 150 µg/kg every 3 weeks.

Covariate Analyses

- Body weight, age, sex, race, renal impairment, drug formulation, antidrug Ab, and use of concomitant P-glycoprotein inhibitors did not significantly influence cAb exposure metrics (**Figure 3**)
- cAb Cycle 1 C_{avg} was lower for patients with:
  - Low albumin vs normal albumin
  - Non-DLBCL vs DLBCL
  - Mild/moderate hepatic impairment vs normal hepatic function
  - ECOG scores of >1 vs ECOG score of 0

Figure 3. Forest Plot of Covariate Analyses on Percent Change vs Reference Value of Model-Predicted cAb Cycle 1 C_{avg}



cAb, Lonca pyrrolobenzodiazepine (PBD)-conjugated Ab; C_{avg}, average serum concentration; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; P-gp, P-glycoprotein.

CONCLUSIONS

- PPK of Lonca was well described by a 2-compartment model with linear and time-dependent clearance
- PPK modeling predictions revealed lower cAb exposure in patients with low albumin and mild/moderate hepatic impairment
  - Dose adjustment is not recommended for these patients, as an increase in dose to offset the decreased exposures may lead to undue toxicities
- PPK modeling predictions also showed lower cAb exposure for ECOG status >1, and in non-DLBCL vs DLBCL, but this is likely due to the small sample size for patients with ECOG status >1 (n=32) and non-DLBCL patients (n=44), respectively
- PPK modeling suggested rapid attainment of steady-state exposure for a Lonca dosing regimen of 150 µg/kg Q3W for two cycles; dose reduction from Cycle 3 onwards maintained the same level of steady-state exposure
- These data support the recommended dosing regimen of Lonca

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