Elucidating Exposure-Response (Safety and Efficacy) of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Containing Antibody Drug Conjugate, for Recommended Phase 2 Dose Determination in Patients with Relapsed or Refractory Non-Hodgkin Lymphoma

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INTRODUCTION

- ADCT-402 (loncastuximab tesirine [Lonca-T]) is an antibody drug conjugate composed of a humanized CD19-specific IgG1 antibody (Ab) stochastically conjugated to tesirine, a pyrrolobenzodiazepine (PBD) dimer cytotoxin via a cleavable maleimide linker.
- A two-part Phase 1 dose-escalation trial of heavily pretreated patients with B-cell non-Hodgkin lymphoma is ongoing to assess the safety and tolerability of Lonca-T 15 to 200 µg/kg administered every 3 weeks (q3w) by intravenous infusion (NCT02669017):
  - Part 1: to define a maximum tolerated dose and dose for part 2
  - Part 2: to assess safety and tolerability at the part 1–recommended dose.
- Interim safety and efficacy data of Lonca-T are presented in a separate oral presentation (Abstract 187).
- Here, we present pharmacokinetic (PK) data elucidating the relationship between drug exposure and response in terms of safety and efficacy.

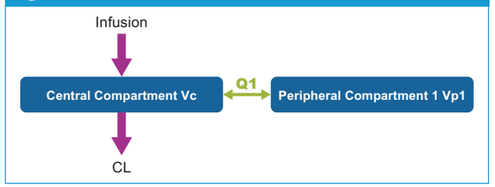
STUDY OBJECTIVES

- To model the dose and PK exposure of Lonca-T as drivers of safety (treatment-emergent adverse events [TEAEs]) and efficacy (reduction in tumor size) for the recommended Phase 2 dose.

STUDY DESIGN

- Concentrations of PBD-conjugated Ab in serum were determined using a validated electrochemiluminescence immunoassay.
- Data were analyzed by population PK methodology using NONMEM (version 7.3, first-order conditional estimation).
  - The base PK analysis employed the log-transformed both sides approach with a 2-compartment open model and zero-order infusion rate (**Figure 1**).
- Area under the curve (AUC) values were estimated from individual patient Bayesian post hoc predictions.
- The influence of various covariate factors on PK variability was assessed and included age, gender, race, body surface area (BSA), body mass index, weight, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine clearance, and hemoglobin (Hb).
- PK exposure trends with maximum severity of early (Cycle 1) and later (all cycles) TEAEs for any grade TEAEs, anemia, platelets, neutrophils, Hb, fatigue, edema, and pleural effusion were graphically explored.
- Apparent trends were quantitatively assessed with logistic regression relating the probability of the following binary outcome variables with AUC and demographic factors (age, sex, weight, BSA, and maximum Eastern Cooperative Oncology Group status):
  - Grade ≥3 maximum severity TEAE
  - Grade ≥3 platelet decrease
  - Grade ≥1 edema or pleural effusion.
- Associations of dose and PK with maximum change from baseline tumor size were determined to identify potential relationships between exposure and activity (at least 50% reduction; complete response and partial response).

Figure 1. Pharmacokinetic structural model



CL, systemic clearance; Q1, intercompartmental clearance; Vc, central volume of distribution; Vp1, peripheral volume of distribution.

RESULTS

Patient characteristics

- Data for 77 patients (53 men, 24 women), comprising 1138 observations, were included in the population PK model (**Table 1**).

Table 1. Patient characteristics in the pharmacokinetic analysis (n=77)

Patient characteristic	Mean (SD)	Median (min, max)
Dose, µg/kg	144 (60.0)	150 (14.7, 205.0)
Age, years	64.3 (12.8)	66 (24, 85)
Weight, kg	86.3 (23.2)	83.9 (42.1, 160.0)
Body mass index,[a] kg/m^2	28.9 (7.33)	28.1 (17.6, 46.4)
Body surface area,[a] m^2	1.95 (0.364)	2.02 (1.36, 2.75)
Albumin, g/dL	4.03 (0.445)	4.0 (2.9, 5.0)
Alanine aminotransferase, IU/L	21.4 (12.2)	19.0 (5.0, 72.0)
Aspartate aminotransferase, IU/L	26.1 (14.5)	22.0 (11.0, 82.0)
Bilirubin, µM/L	8.1 (5.25)	6.8 (2.9, 32.5)
Creatinine clearance,[a] mL/min	96.5 (43.6)	84.0 (27.6, 269.0)
Hemoglobin, g/L	116 (13.5)	115 (80, 148)

[a]Included data from 76 patients.
SD, standard deviation.

Final population PK model

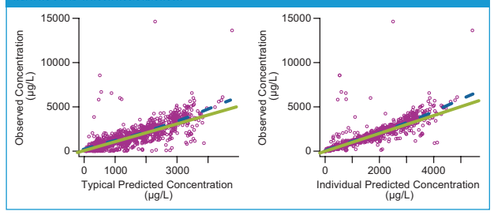
- Final population PK model parameters are provided in **Table 2**.
- There was a strong correlation between observed and estimated serum drug concentrations (**Figure 2**, **Figure 3**).
- Exposure and associated magnitude of intersubject variability increased with dose (data not shown):
  - Apparent terminal half-life values were long but moderately variable
  - Modest drug accumulation was seen with repeated dosing.
- BSA significantly affected volume of distribution (**Table 2**).
- No other significant covariates were identified.

Table 2. Final pharmacokinetic model parameters

Parameter (units)	Typical value	SE (CV%)
CL (L/hr)	0.0155	15.5
Vc (L)	4.37	2.1
Q (L/hr)	0.0322	36
Vp (L)	5.41	37
Residual error (CV%)	41.8	0.5
SHARE	0.102	31
Effect of BSA on Vc	1.69	5.2
Effect of BSA on Vp	7.86	21.4
IIV CL	81.9	17.6
IIV Q1	177	11.4
IIV Vp	144	12.6

BSA, body surface area; CL, systemic clearance; CV, coefficient of variation; IIV, interindividual variability of respective pharmacokinetic term; Q1, intercompartmental clearance; SE, standard error; Vc, central volume of distribution; Vp, peripheral volume of distribution.

Figure 2. Population pharmacokinetic-predicted versus observed concentrations



Open symbols represent data, solid green line represents line of identity or unity, and blue dashed line represents loess smooth.

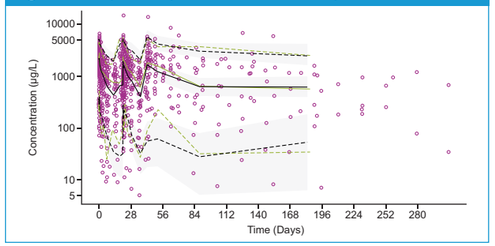
Relationship between exposure and safety

- Increased exposure (AUC) of PBD-conjugated Ab was associated with probability of Grade ≥3 platelet decrease in Cycle 1 (p=0.0067) and any TEAE Grade ≥3 during Cycle 1 and all cycles (both; p=0.031) (**Figure 4**, **Table 3**):
  - For any TEAEs Grade ≥3, men appeared to be more sensitive than women (**Figure 4F**).
- A visual trend of increased AUC with probability of Grade ≥1 edema or pleural effusion was apparent (**Figure 4E**).

Relationship between exposure and efficacy

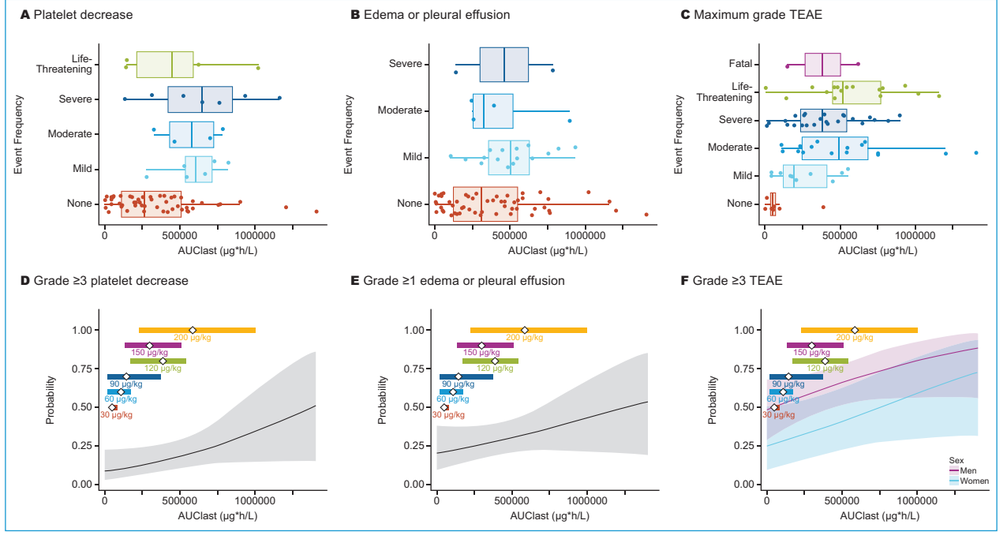
- Increased dose of Lonca-T was significantly associated with increased probability of objective response (p=0.0439) (**Figure 5**).
- Increased exposure (AUC) of PBD-conjugated Ab was significantly associated with increased probability of objective response (p=0.0292).

Figure 3. Population pharmacokinetic visual predictive check



Open symbols represent observed data. Black lines denote median (solid) and 5th and 95th percentiles (dashed) of simulated concentrations. Green lines denote median (solid) and 5th and 95th percentiles (dashed) of observed concentrations. Shaded regions denote 95% confidence intervals on simulation values.

Figure 4. Box plots **(A–C)** and predicted probability curves **(D–F)** for significant or clinically relevant TEAEs based on Lonca-T PBD-conjugated Ab exposure (AUC)



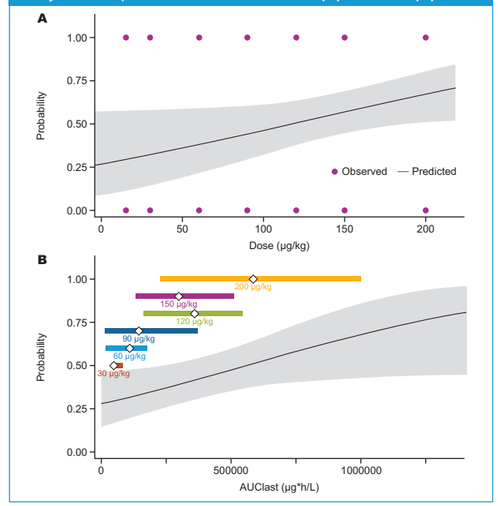
Bottom panels: Graphics depict the mean (black line) and 95% confidence interval (ribbon) predicted probability. Width of horizontal bars denote the 10th and 90th percentiles of individual-predicted AUC values with median (black diamond) in serum for respective dose groups.
Ab, antibody; AUC, area under the curve; Lonca-T, loncastuximab tesirine; PBD, pyrrolobenzodiazepine; TEAE, treatment-emergent adverse event.

Table 3. Predicted probabilities of significant or clinically relevant safety measures

		Dose cohort (µg/kg)	15	30	60	90	120	200
		Median predicted AUC (µg*h/L)[a]	14820	31850	68060	124100	245400	517000
Potential relationships identified	Model parameters	p-value[b]	Mean predicted probability					
Platelet decrease Grade ≥3 Cycle 1[c]	AUC Cycle 1	0.0067	0.006	0.006	0.007	0.011	0.023	0.11
Platelet decrease Grade ≥3 all cycles	Mean AUC	0.068	0.086	0.089	0.093	0.10	0.12	0.18
Edema/pleural effusion Grade ≥1 all cycles	Mean AUC	0.18	0.18	0.18	0.19	0.21	0.24	0.33
TEAE Grade ≥3 Cycle 1[c]	AUC Cycle 1	0.031	0.074	0.078	0.086	0.10	0.14	0.26
TEAE Grade ≥3 all cycles	Mean AUC, gender=M	0.031	0.49	0.49	0.50	0.53	0.57	0.66
TEAE Grade ≥3 all cycles	Mean AUC, gender=F	0.031	0.25	0.26	0.27	0.28	0.32	0.41

[a]Based on individual predicted value for respective dose cohort. [b]Overall significance of model with predictors versus intercept alone. [c]Based on Cycle 1 observations and AUC.
AUC, area under the curve; TEAE, treatment-emergent adverse event.

Figure 5. Predicted probability (with 95% confidence interval) of objective response versus Lonca-T dose **(A)** and AUC **(B)**



Both panels: Graphics depict the mean (black line) and 95% confidence interval (ribbon) predicted probability. Bottom panel: Width of horizontal bars denote the 10th and 90th percentiles of individual-predicted AUC values with median (black diamond) in serum for respective dose groups.
AUC, area under the curve; Lonca-T, loncastuximab tesirine.

CONCLUSIONS

- The PK profile of PBD-conjugated Ab after administration of Lonca-T was described using a linear 2-compartment model.
- BSA was a significant covariate of volume of distribution.
  - It is unclear if body size–based dosing is appropriate but will be investigated further when more data are available.
- Significant positive correlations were observed between PBD-conjugated Ab exposure (AUC) and incidence of Grade ≥3 TEAEs (Cycle 1 and all cycles), and Grade ≥3 platelet decrease in Cycle 1:
  - Frequency of Grade ≥3 TEAEs were higher with protracted doses; limiting the number of cycles administered will control the rate of severe adverse events
  - For severe adverse events, men may be more sensitive than women
  - A relevant trend was apparent between AUC and Grade ≥1 edema or pleural effusion.
- Interim efficacy assessment indicated significant dose-response and exposure-response relationships for Lonca-T when administered with a q3w schedule.
- Since this trial is ongoing, other pending data will be incorporated when available.

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