ADCT-402 (loncastuximab tesirine [Lonca-T]) is an antibody drug conjugate composed of a humanized CD30-specific IgG1 antibody (Ab) stoichiometrically conjugated to a pyrrolobenzodiazepine (PBD) dimer cytotoxin via a clickable 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 model and zero-order infusion rate (Figure 1).
- Area under the curve (AUC) values were estimated from individual patient Bayesian predictions.
- The influence of various covariates on PK variability was assessed and included age, gender, race, body surface area (BSA), body mass index, weight, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, mean arterial pressure, systolic blood pressure, and creatinine clearance, and hematocrit (Ht).
- PK exposure trends with maximum severity of early (Cycle 1) and late (Cycle 1 and all later cycles) TEAEs for any grade TEAEs, anemia, platelets, leukocytes, Ht, 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 severity TEAEs
- Grade ≥3 study-cohort

- 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 interindividual 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.
- Ht significantly affected volume of distribution (Table 2).
- No other significant covariates were identified.

**RESULTS**

**Patient characteristics**

- Data for 77 patients (53 men, 24 women), comprising 113 observations, were included in the PK analysis (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Median (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.3 (12.0)</td>
<td>60 (24, 85)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>88.2 (12.7)</td>
<td>90 (58-180)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.3 (7.73)</td>
<td>28.1 (17.6, 45.4)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0.16 (0.44)</td>
<td>0.2 (0.1, 0.7)</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>4.0 (4.45)</td>
<td>4.0 (2.9, 5.1)</td>
</tr>
<tr>
<td>Alanine transaminase, IU/L</td>
<td>21.4 (12.2)</td>
<td>20.0 (15.7, 69.0)</td>
</tr>
<tr>
<td>Aspartate transaminase, IU/L</td>
<td>28.1 (14.5)</td>
<td>22.0 (11.5, 32.0)</td>
</tr>
<tr>
<td>Bilirubin, µmol/L</td>
<td>8.1 (5.25)</td>
<td>8.6 (3.29, 32.5)</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>85.3 (43.5)</td>
<td>84.1 (27.3, 205.0)</td>
</tr>
<tr>
<td>Hematocrit, g/dL</td>
<td>116.1 (13.5)</td>
<td>115.3 (28.1, 44.6)</td>
</tr>
</tbody>
</table>

**Table 1. Patient characteristics in the pharmacokinetic analysis**

**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 limiting the number of cycles administered will control the rate of adverse events.
- For some adverse events, may be more sensitive than women.
- A relevant trend was apparent between AUC and Grade 1 edema or pleural effusion.
- Interindividual assessment indicated significant dose-response and exposure-responses relationships for Lonca-T when administered with a q3w schedule.
- Since this trial is ongoing, other pending data will be incorporated when available.

**Disclosures**

- The authors have the following financial disclosures: ADC Therapeutics; Celgene.
- Authors have indicated no financial conflicts with industry or any other organizations.

**References**


**Figure 1. Pharmacokinetic structural model**

- Concentrated on the predominant drug exposure and concentration in serum during the 14-day dosing period.
- Dose, µg/kg: 30, 60, 90, 120, 150, 200
- Time, days: 0, 1, 2, 7, 14

**Figure 2. Population pharmacokinetic-predicted versus observed concentrations**

- Predicted concentrations represent data, with green triangles representing the mean predicted AUC values with median (black diamond) in serum for respective dose groups.
- Observed concentrations (µg/L) were determined at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, and Cycle 9.

**Figure 3. Population pharmacokinetic visual predictive check**

- Both panels: Graphics depict the mean (solid black line) and 95% confidence interval (ribbon) predicted median (black diamond) and 5th and 95th percentiles of population pharmacokinetic parameters (CL, Vc, Q1) and observed concentrations.
- AUC: area under the curve; BSA: body surface area; CL: systemic clearance; ECOG: Eastern Cooperative Oncology Group; IIV: interindividual variability; ov: observed; pred: predicted; Q1: intercompartmental clearance; SE: standard error; Vc: central volume of distribution; Vp: apparent terminal half-life.

- Figure 4. Box plots (A–C) and predicted probability curves (D–F) for significant or clinically relevant TEAEs based on Lonca-T dose.
- Dose (µg/kg) shown on x-axis of each box plot.
- Probability (p-value) and sample size (N) shown on y-axis.
- TEAE: treatment-emergent adverse event; AUC: area under the curve; CL: systemic clearance; ECOG: Eastern Cooperative Oncology Group; IIV: interindividual variability; ov: observed; pred: predicted; Q1: intercompartmental clearance; SE: standard error; Vc: central volume of distribution; Vp: apparent terminal half-life.

- Table 2. Predicted probabilities of significant or clinically relevant safety measures

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

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<th>Dose (µg/kg)</th>
<th>15</th>
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<th>60</th>
<th>90</th>
<th>120</th>
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<tr>
<td>Probability</td>
<td>0.001</td>
<td>0.003</td>
<td>0.0001</td>
<td>0.000001</td>
<td>0.0000001</td>
<td>0.00000001</td>
</tr>
</tbody>
</table>

- Table 4. Mean predicted AUC values with median (black diamond) in serum for respective dose groups.

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

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

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<td>0.00000001</td>
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</table>

- Table 6. Mean predicted AUC values with median (black diamond) in serum for respective dose groups.

- Table 7. Predicted probability with 95% confidence interval of objective response versus Lonca-T dose (A) and AUC (B).

- Figure 6. Predicted probability with 95% confidence interval of objective response versus Lonca-T dose (A) and AUC (B).

- Table 8. Mean predicted AUC values with median (black diamond) in serum for respective dose groups.

- Table 9. Predicted probability with 95% confidence interval of objective response versus Lonca-T dose (A) and AUC (B).

- Figure 7. Predicted probability with 95% confidence interval of objective response versus Lonca-T dose (A) and AUC (B).

- Table 10. Mean predicted AUC values with median (black diamond) in serum for respective dose groups.

- Table 11. Predicted probability with 95% confidence interval of objective response versus Lonca-T dose (A) and AUC (B).

- Figure 8. Predicted probability with 95% confidence interval of objective response versus Lonca-T dose (A) and AUC (B).

- Table 12. Mean predicted AUC values with median (black diamond) in serum for respective dose groups.