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Relationship Between Exposure and Safety/Efficacy of Loncastuximab Tesirine in B-cell Non-Hodgkin Lymphoma

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INTRODUCTION

- 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)[1]
- Single-agent Lonca showed antitumor activity and had a favorable safety profile in Phase 1[2,3] (NCT02669017; overall response rate [ORR]: 45.6%)[3] and Phase 2 (NCT03589469; LOTIS-2, ORR: 48.3%)[4,5] studies in relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) and R/R diffuse large B-cell lymphoma (DLBCL), respectively
- Encouraging antitumor activity in patients with high-risk characteristics was also observed[3,4]
- The dosing regimen was established in the Phase 1 study: 150 µg/kg every 3 weeks (Q3W) for 2 cycles, followed by 75 µg/kg Q3W thereafter for up to 1 year until disease progression, unacceptable toxicity, or other discontinuation criteria

STUDY OBJECTIVE

- To explore the efficacy and safety exposure–response relationship for Lonca PBD-conjugated Ab (cAb) using a validated population pharmacokinetic (PPK) model; AACR e-poster 1366[6]

METHODS

PPK Modeling

- A pooled Phase 1 and Phase 2 PPK model of total antibody (tAb) and cAb data was used to generate individual cAb exposure metrics, including average serum concentration (C_{avg}), peak concentration (C_{max}), and trough concentration (C_{min})
  - Efficacy population: 284 patients with DLBCL
  - Safety population: 328 patients with NHL (all patients)

Efficacy: ORR, Overall Survival (OS), Progression-free Survival (PFS) and Duration of Response (DoR)

- The primary efficacy endpoint was ORR (modeled using multivariate logistic regression based on the exposure metrics selected from the exploratory analysis); a univariate logistic regression analysis was performed to assess ORR in association with cAb exposure
- In the exploratory analysis, the relationship between cAb exposure and OS, PFS and DoR (for patients with complete response or partial response) was evaluated by time-to-event Kaplan–Meier analysis (a univariate analysis) and log rank test, stratified by quartiles of the selected estimated exposure metrics
- A Cox proportional hazard regression model was used for base and final models for OS, and to further evaluate selected exposure–response relationship
- Baseline covariates tested are shown in **Table 1**

Safety

- Univariate logistic regression was used to evaluate the effects of cAb exposure on treatment-emergent adverse events (TEAEs) ≥Grade 2
- Pre-specified TEAEs included decreased neutrophil levels, edema-effusion, fatigue, liver function test abnormalities, pain, decreased platelet count, skin and nail reactions, and increased gamma-glutamyltransferase (GGT) levels (defined as increase from the upper limit of normal)
  - Grade ≥2 increased GGT was selected for further analysis using multivariate logistic regression

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 (white, other); BMI (kg/m^2)
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)
Immunogenicity	Presence or absence of ADAs (any time or pre-dose)
Disease characteristics	Disease subtype (DLBCL, non-DLBCL); selected high-risk[b] phenotype, non-high-risk phenotype; ECOG status; tumor size (bulky[c], not bulky); total sum of area (cm^2); and lymphocyte count[d] (10^9 cells/L); elapsed time of initial diagnosis (months)
Prior medication	Prior chemotherapy response, prior stem cell therapy
Concomitant medication	P-glycoprotein inhibitor; dexamethasone; rituximab
Hepatic function	Normal (TBIL ≤ ULN, and AST ≤ ULN); mild impairment (TBIL ≤ ULN and AST > ULN or ULN < TBIL ≤ 1.5×ULN) or moderate[e] 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[f] impairment (15 ≤ CRCL <30 mL/min)
Study	Phase 1[2,3], Phase 2[4,5]

ADA, antibody drug antibodies; ALKP, alkaline phosphatase; ALT, alanine amino transferase; AST, aspartate amino transferase; BMI, Body Mass Index; 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]Double-hit, triple-hit, primary mediastinal, transformed, double expressor, and triple expressor lymphoma: 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.

RESULTS

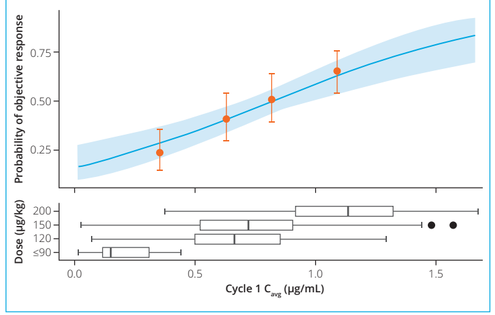
Exposure/Covariates and Efficacy Outcomes

- Significant positive associations (univariate analysis) between cAb Cycle 1 C_{avg} (exposure) and ORR (p=3.21 x 10^{-6}; **Figure 1**), OS (p=0.0016), and PFS (p=0.0000466), but not DoR (p=0.678), were observed

ORR

- ORR was 23.9%, 40.8%, 50.7%, and 64.8% for patients in Quartile 1 (Q1), Q2, Q3, and Q4 of cAb Cycle 1 C_{avg}, respectively
- In the final multivariate logistic regression analysis, cAb Cycle 1 C_{avg} (p=0.000035), baseline tumor sum of area (continuous variable; based on 2014 Lugano Classification[7]; p=0.0000813), and disease phenotype (selected high-risk characteristics [N=84; double-hit, triple-hit, primary mediastinal, transformed, double expressor, and triple expressor lymphoma] vs other [N=200]) (p=0.0122) were predictors of ORR

Figure 1. Observed and Model-Predicted ORR from the Univariate Logistic Regression Base Model by cAb Cycle 1 C_{avg}, and Distribution of Dose Levels



cAb, Lonca pyrrolobenzodiazepine (PBD)-conjugated Ab; C_{avg}, average concentration, ORR, overall response rate.

Solid orange circles (vertical line segments) represent the observed objective response rate (95% CI) for each quartile of Cycle 1 C_{avg}. Solid blue line (shaded blue area) represents the predicted objective response rate (95% CI) using individual patient level Cycle 1 C_{avg}. The quartile (Q) ranges for Cycle 1 C_{avg} were: Q1 (0.0120–0.504 µg/mL), Q2 (0.506–0.723 µg/mL), Q3 (0.727–0.941 µg/mL), and Q4 (0.943–1.68 µg/mL).

OS

- Baseline albumin, bulky disease, and mild/moderate hepatic function had a significant effect on OS (**Table 2**)
- OS improved with increasing cAb Cycle 1 C_{avg} (**Figure 2**)
- Patients in the higher quartiles of cAb Cycle 1 C_{avg} generally had better OS than those in the lower quartiles, suggesting an exposure–response relationship
- Median OS was not reached in Q4
- Estimates from the final Cox proportional hazards model for OS showed that mortality risk was:
  - Decreased by 4.76% for every 0.1 µg/mL increase in Cycle 1 C_{avg}
  - Increased by 7.67% for every 1 g/L decrease in baseline albumin, 213% with bulky tumor, and 90% with mild/moderate hepatic impairment

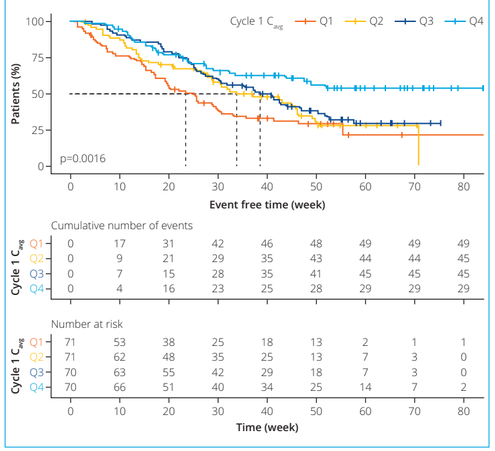
Table 2. Parameter Estimates from the Final Cox Proportional Hazards Model for OS with Cycle 1 C_{avg} cAb

Predictor	Predictor statistic	HR (95% CI)	P-value	HR P05: median (95% CI)	HR P95: median (95% CI)
Cycle 1 C_{avg} (µg/mL)	0.722 (0.148–1.299)	0.614 (0.379–0.994)	0.0472	1.323 (1.003–1.746)	0.755 (0.572–0.997)
Baseline albumin (g/L)	40 (31–48)	0.929 (0.899–0.960)	1.1E-5	1.937 (1.442–2.600)	0.554 (0.426–0.721)
Hepatic function	Mild/ moderate impairment: normal (n=44:237)	1.901 (1.293–2.797)	0.0011	N/A	N/A
Bulky disease	Bulky: other (n=26:256)	3.135 (2.013–4.882)	4.31E-7	N/A	N/A

cAb, Lonca pyrrolobenzodiazepine (PBD)-conjugated Ab; C_{avg}, average serum concentration; CI, confidence interval; HR, hazard ratio; N/A, not applicable; OS, overall survival; P05, 5th percentile; P95, 95th percentile.

Likelihood ratio test, p-value <0.001. Median (P05–P95) is presented for continuous predictors and count of comparator: reference is provided for categorical predictors under Predictor statistic.

Figure 2. Kaplan–Meier Plot for The Final Model of OS by Cycle 1 C_{avg} of cAb (Exposure Quartiles Q1–Q4)



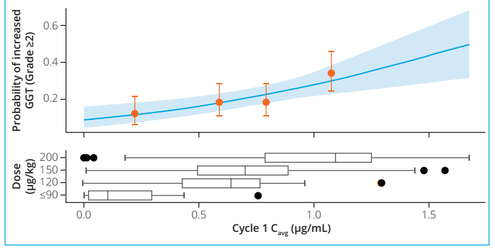
cAb, Lonca pyrrolobenzodiazepine (PBD)-conjugated Ab; C_{avg}, average serum concentration OS, overall survival; Q, quartile.

Solid lines represent the Kaplan–Meier survival curves for quartile groups of cAb exposure. Right-censoring is indicated by the vertical ticks on the survival curves. Median event-free times, if reached, are indicated with black dashed lines. Log rank test was used to test for significant differences between Kaplan–Meier curves (p<0.05). The quartile (Q) ranges for Cycle 1 C_{avg} were: Q1 (0.0120–0.504 µg/mL), Q2 (0.506–0.723 µg/mL), Q3 (0.727–0.941 µg/mL), and Q4 (0.943–1.68 µg/mL).

Exposure/Covariates and Safety Outcomes

- Grade ≥2 TEAEs for increased GGT (**Figure 3**), as well as liver function test abnormalities, consistently showed significant relationships with cAb C_{avg} and C_{min} for Cycles 1–3 (p<0.05)
- Despite biochemical abnormalities in laboratory tests, no clinically significant liver toxicity was observed
- Grade ≥2 skin and nail reactions showed significant relationships with cAb C_{avg} and C_{min} for Cycles 1–2 (p<0.05)

Figure 3. Observed and Predicted Probability of Increased GGT of ≥ Grade 2 from the Univariate Logistic Regression Base Model by Cycle 1 C_{avg}, and the Distribution of Dose Levels



C_{avg}, average concentration; C_{min}, trough concentration; GGT, gamma-glutamyltransferase.

Solid orange circles (vertical line segments) represent the observed proportion of patients (95% CI) with increased GGT of ≥ Grade 2 for each quartile of Cycle 1 C_{avg}. Solid blue line (shaded blue area) represents the predicted probability (95% CI) of increased GGT of ≥ Grade 2 from a univariate logistic regression using individual patient level Cycle 1 C_{avg}. The quartile (Q) ranges for Cycle 1 C_{avg} were: Q1 (0.0120–0.462 µg/mL), Q2 (0.463–0.700 µg/mL), Q3 (0.702–0.918 µg/mL), and Q4 (0.919–1.68 µg/mL).

- Grade ≥2 pain showed a significant relationship for cAb Cycle 1 C_{max} only (p<0.05)
- Multivariate logistic regression analysis for cAb showed odds of Grade ≥2 increased GGT were higher for:
  - Every 1 µg/mL increase in Cycle 1 C_{avg} (by 273%; p=0.00181)
  - Non-white patients (by 175%; p=0.0172)
  - Every 1 U/L increase in baseline ALT (by 2%; p=0.00554)
  - Patients with bulky tumor (by 169%; p=0.0255)
  - Patients with prior chemotherapy response (best overall response of complete response or partial response vs other; by 312% p=0.00683)

CONCLUSIONS

- Higher Lonca exposure in Cycle 1 resulted in significantly improved OS, PFS, and ORR, but not DoR and, as expected, increased probability of Grade ≥2 TEAEs, including increased GGT
- Low baseline albumin, mild/moderate hepatic impairment, and bulky disease were associated with poorer survival:
  - Bulky disease is a known risk factor for poorer response to treatment[8]
  - The greater risk of death in patients with low baseline albumin or mild/moderate hepatic impairment may reflect a more fragile health state for these patients

Acknowledgments

The authors would like to thank and acknowledge the participating patients and their families, and all study co-investigators and research coordinators. This study is sponsored by ADC Therapeutics. http://clinicaltrials.gov/show/NCT02669017 and http://clinicaltrials.gov/show/NCT03589469. Editorial support was provided by Susan Brackenridge, PhD, and Sally Hassan, PhD, of Fishawack Communications Ltd, part of Fishawack Health, funded by ADC Therapeutics.

Disclosures

Brian Hess has had a consulting/advisory role for ADC Therapeutics, an advisory role for Bristol-Myers Squibb and AstraZeneca, and has served on the speaker's bureau of AstraZeneca. **Weiyun Ai** had an advisory role for Acrotech Biopharma, ADC Therapeutics, BeiGene, Kymera Therapeutics, and Nurix Therapeutics, and received research funding from Nurix Therapeutics. **Willian Townsend** had a consulting/advisory role for Celgene, Gilead, and Roche; served on the speaker's bureau of Celgene, Gilead, and Roche; received honoraria from Celgene, Gilead, Roche; received consulting fees from Celgene, Gilead, and Roche; and received travel fees from Roche. **David Ungar** and **Joseph Boni** are employees of ADC Therapeutics and own stock in the company. **Lori Liao** and **Sam Liao** are employees of Pharmax Research, a company hired by ADC Therapeutics to perform modeling and simulations for this study. **Xiaoyan Zhang** is a former employee of ADC Therapeutics.

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