A Clinical Quantitative Systems Pharmacology Framework Describing Loncastuximab Tesirine Distribution and to Explore Patient Outcomes From the LOTIS-2 Clinical Trial in Patients With B-cell Lymphomas

Kiersten Utsey,[1] Eric Jordie,[1] Tim Knab,[1] Katharina Wilkins,[1] Masoud Nickaeen,[1] Serafino Pantano,[2] Francesca Zammarchi,[3] Danilo Cucchi,[3] Karin Havenith,[3] Joseph P. Boni[4,*]

[1]Metrum Research Group, Simsbury, CT, USA; [2]ADC Therapeutics, SA, Épalinges, Switzerland; [3]ADC Therapeutics, London, UK; [4]ADC Therapeutics America, Murray Hill, NJ, USA

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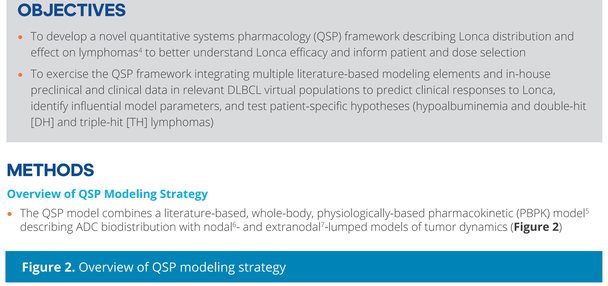
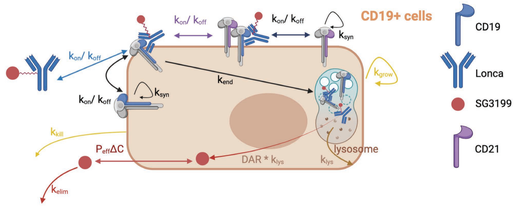


DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; Lonca, loncastuximab tesirine; PBD, pyrrolobenzodiazepine dimer; PBPK, physiological-based pharmacokinetic; QSP, quantitative systems pharmacology.

INTRODUCTION

- B-lymphocyte antigen CD19 has been clinically validated as a therapeutic target for the treatment of B-cell malignancies
- Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is an antibody–drug conjugate (ADC) comprising an anti-CD19 antibody conjugated to a pyrrolobenzodiazepine dimer cytotoxin (**Figure 1**)
- Lonca targets CD19 cell-surface antigens in most malignant B cells and is indicated for treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after ≥2 systemic treatments[1]

Figure 1. Receptor-mediated endocytosis of the ADC



- The tumor is composed of CD19+ and CD19-/low cells, expressing high/low amounts of surface CD19 antigens
- Binding of the ADC-CD19 complex with CD21 inhibits the drug's internalization[2]
- Diffusion of the payload into neighboring cells leads to bystander cell killing
- Payload has a short half-life and is eliminated in the extracellular space[3]

OBJECTIVES

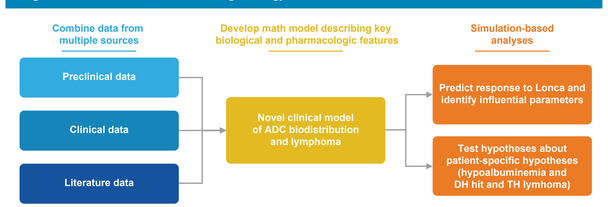
- To develop a novel quantitative systems pharmacology (QSP) framework describing Lonca distribution and effect on lymphomas[4] to better understand Lonca efficacy and inform patient and dose selection
- To exercise the QSP framework integrating multiple literature-based modeling elements and in-house preclinical and clinical data in relevant DLBCL virtual populations to predict clinical responses to Lonca, identify influential model parameters, and test patient-specific hypotheses (hypoalbuminemia and double-hit [DH] and triple-hit [TH] lymphomas)

METHODS

Overview of QSP Modeling Strategy

- The QSP model combines a literature-based, whole-body, physiologically-based pharmacokinetic (PBPK) model[5] describing ADC biodistribution with nodal[6]- and extranodal[7]-lumped models of tumor dynamics (**Figure 2**)

Figure 2. Overview of QSP modeling strategy

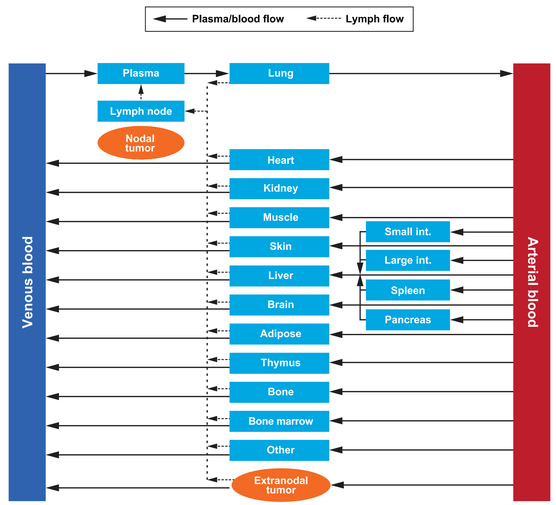


ADC, antibody–drug conjugate; DH, double-hit; QSP, quantitative systems pharmacology; TH, triple-hit.

Overview of QSP Modeling Strategy (continued)

- The model is a system of ordinary differential equations that describe key processes of Lonca activity in a tumor, including binding of Lonca to CD19, internalization of the Lonca:CD19 complex, degradation of Lonca resulting in release of the cytotoxic payload, and subsequent killing of the tumor cell
- This model was parameterized using literature data and preclinical data for Lonca, including cytotoxicity, tumor cell doubling time, binding affinities, drug-to-antibody ratios, and internalization data
- A virtual population was generated from patients enrolled in the LOTIS-2 clinical trial (NCT03589469). The model was used to predict individual clinical observations (**Figure 2**) for model parameters and covariates affecting response (**Figure 3**), including the following:
  - Initial tumor size/location
  - Body weight
  - Hypoalbuminemia (as neonatal Fc receptor [FcRn] expression)
  - Growth and Lonca-induced death rates of tumor cells
  - Lonca internalization rate into cells
  - Payload diffusion rate out of cells
  - Fraction and surface density (molecules/cell) of CD19+ cells from pretreatment tumor biopsies
  - DH/TH lymphoma disease phenotypes

Figure 3. QSP model describing ADC biodistribution and tumor dynamics



ADC, antibody–drug conjugate; int., intestine; QSP, quantitative systems pharmacology.

- A whole-body PBPK model describes the ADC biodistribution
- A lymphoma tumor model with nodal and extranodal lesions captures tumor dynamics
  - Nodal tumor: concentration of ADC in the lymph fluid drives tumor growth inhibition in an FcRn-independent manner
  - Extranodal tumor: concentration of ADC in the interstitial space drives tumor growth inhibition via FcRn-dependent and FcRn-independent disposition into the compartment

Simulation Setup

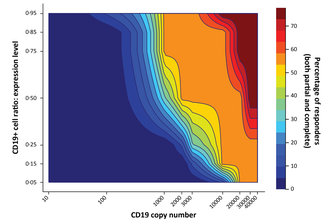
- A virtual population was generated from patients enrolled in the LOTIS-2 clinical trial
- 567 simulations were performed by scanning CD19+ expression levels, CD19 antigen surface densities per tumor cell, initial tumor mass, and tumor location using regular phase 2 dosing (150 µg/kg every 3 weeks, followed by 75 µg/kg every 3 weeks) (**Figure 4**)
- Response was determined by comparing the area under the curve (AUC) of the tumor volume dynamics against the AUC of a stable disease scenario (initial tumor volume multiplied by total simulation duration)

RESULTS

Identifying CD19+ Expression Level and Surface Density Threshold for Response

- Analyses illustrated the following:
  - CD19 expression level (fraction of CD19+ cells in tumor assessed by immunohistochemistry [IHC]) alone is a poor predictor of response to Lonca
  - CD19 surface density in addition to expression level improves response prediction
  - As predictedf from in vitro study, patients respond to Lonca with tumor cell surface densities as low as 1000 molecules/cell (**Figure 4**), below the recent threshold identified for CAR T-cell therapies[8]

Figure 4. QSP model-generated Lonca heat map profile of CD19+ cell ratio of expression (proportion of the tumor cells that were CD19+) versus CD19 surface density and response

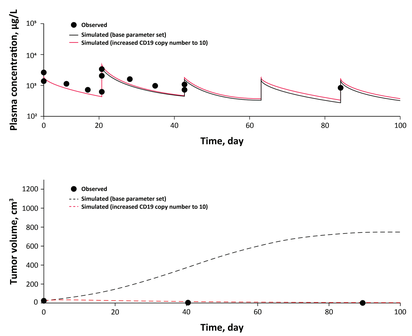


QSP, quantitative systems pharmacology.

Identifying CD19+ Expression Level and Surface Density Threshold for Response (continued)

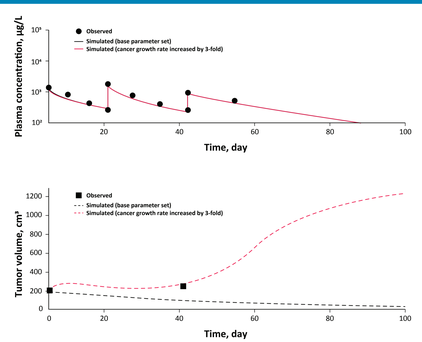
- Responses were seen in patients across all levels of CD19 expression, including patients with undetectable CD19 expression. Projections of QSP-model simulations to individual observations enabled the evaluation of how influential parameters affected outcome hypotheses (**Figure 5**)
- Predicted influence of covariates on LOTIS-2 patient-level outcomes indicated that DH/TH lymphomas are more aggressive, with growth rates 2 to 3 times higher than less-aggressive phenotypes (**Figure 6**), and patients with hypoalbuminemia have reduced plasma exposure, which was well described through the systemic reduction in FcRn expression levels (**Figure 7**)

Figure 5. Simulation of patient with undetectable CD19 expression



- Observation: Patient has ≈0% CD19+ cells in the tumor by IHC but has a complete response to Lonca
- Model Explanation: A small (undetectable) density of surface antigens per CD19-/low tumor cell is sufficient to describe response

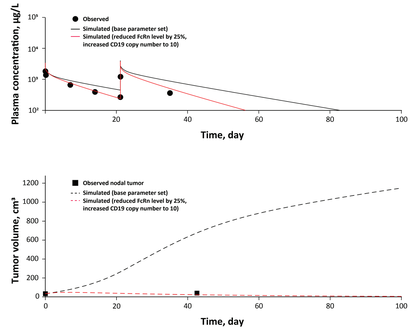
Figure 6. Simulation of a patient with DH lymphoma



DH, double hit.

- Observation: Patient has a high percentage of CD19+ cells in the tumor by IHC but has no response to Lonca
- Model explanation: DH DLBCL has a faster cancer growth rate than less aggressive phenotypes[9]

Figure 7. Simulation of a patient with hypoalbuminemia and low levels of CD19 expression



- Observation: Patient with hypoalbuminemia has enhanced clearance and reduced plasma exposure to Lonca but responded to therapy, despite having ≈0% CD19+ cells in the tumor by IHC
- Model explanation: Patient has a reduced systemic FcRn expression level[10,11] and has sufficient (small) levels of surface antigens per CD19-/low cells

CONCLUSIONS

- A novel QSP framework integrating PBPK modeling with tumor dynamics was developed using literature and in-house data
- By employing a virtual population reflecting patients treated with Lonca, it is possible to evaluate indication, clinical population selection, influence of clinical study covariates, disease phenotypes, and CD19 expression levels on clinical responses

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Disclosures

K Utsey: employee of Metrum Research Group. **E Jordie:** employee of Metrum Research Group. **T Knab:** employee of Metrum Research Group. **K Wilkins:** employee of Metrum Research Group. **M Nickaeen:** employee of Metrum Research Group. **S Pantano:** employee of and current equity holder at ADC Therapeutics SA, a publicly traded company. **F Zammarchi:** employee of and current equity holder at ADC Therapeutics SA, a publicly traded company. **D Cucchi:** employee of and current equity holder at ADC Therapeutics SA, a publicly traded company. **K Havenith:** employee of and current equity holder at ADC Therapeutics SA, a publicly traded company. **J Boni:** employee of and current equity holder at ADC Therapeutics SA, a publicly traded company.

*Contact information

Joseph P. Boni, PhD: Joe.Boni@adctherapeutics.com

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