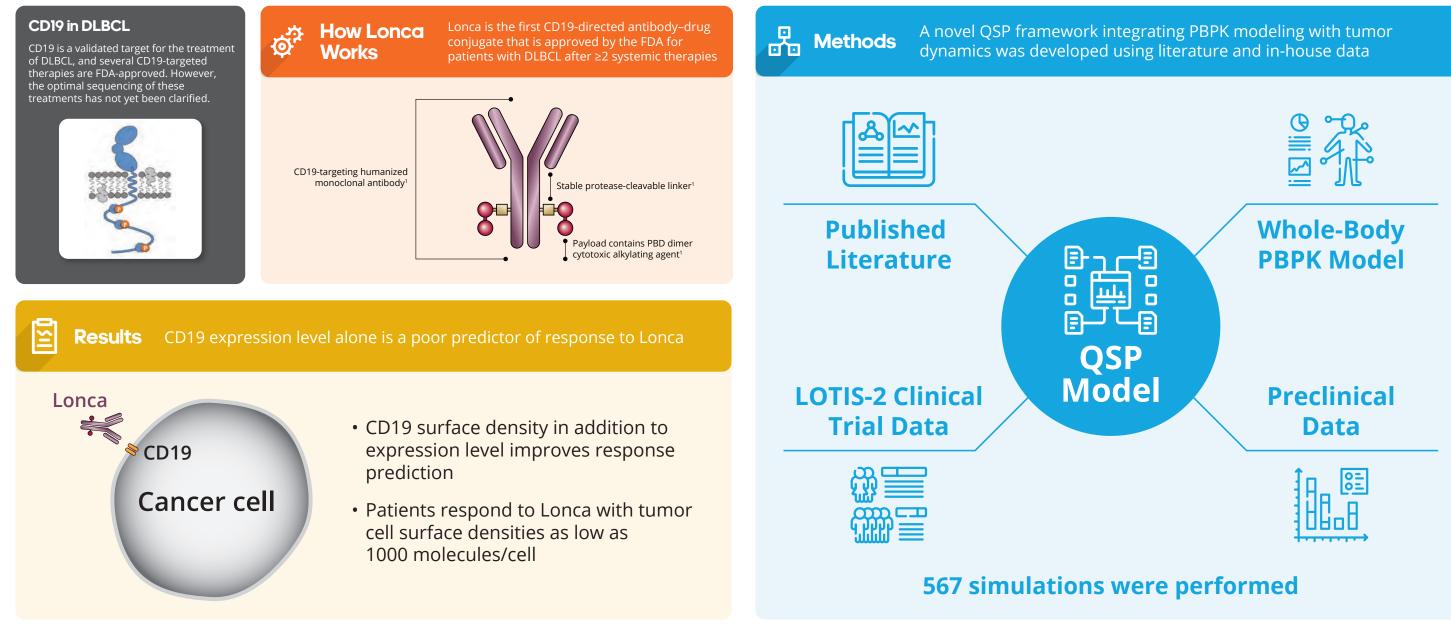# A Clinical Quantitative Systems Pharmacology Framework Describing Loncastuximab Tesirine Distribution and to Explore Patient Outcomes From the LOTIS-2 Clinical Trial in Patients With B-cell Lymphomas

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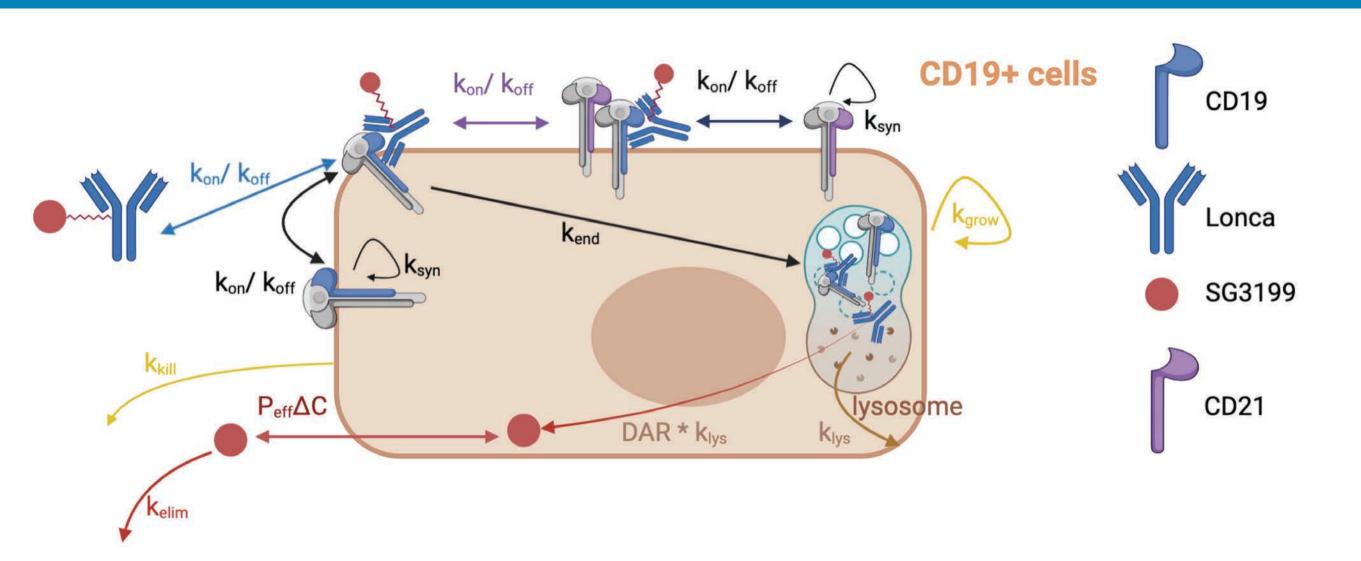
[1]Metrum Research Group, Simsbury, CT, USA; [2]ADC Therapeutics, SA, Épalinges, Switzerland; [3]ADC Therapeutics, London, UK; [4]ADC Therapeutics America, Murray Hill, NJ, USA

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.

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
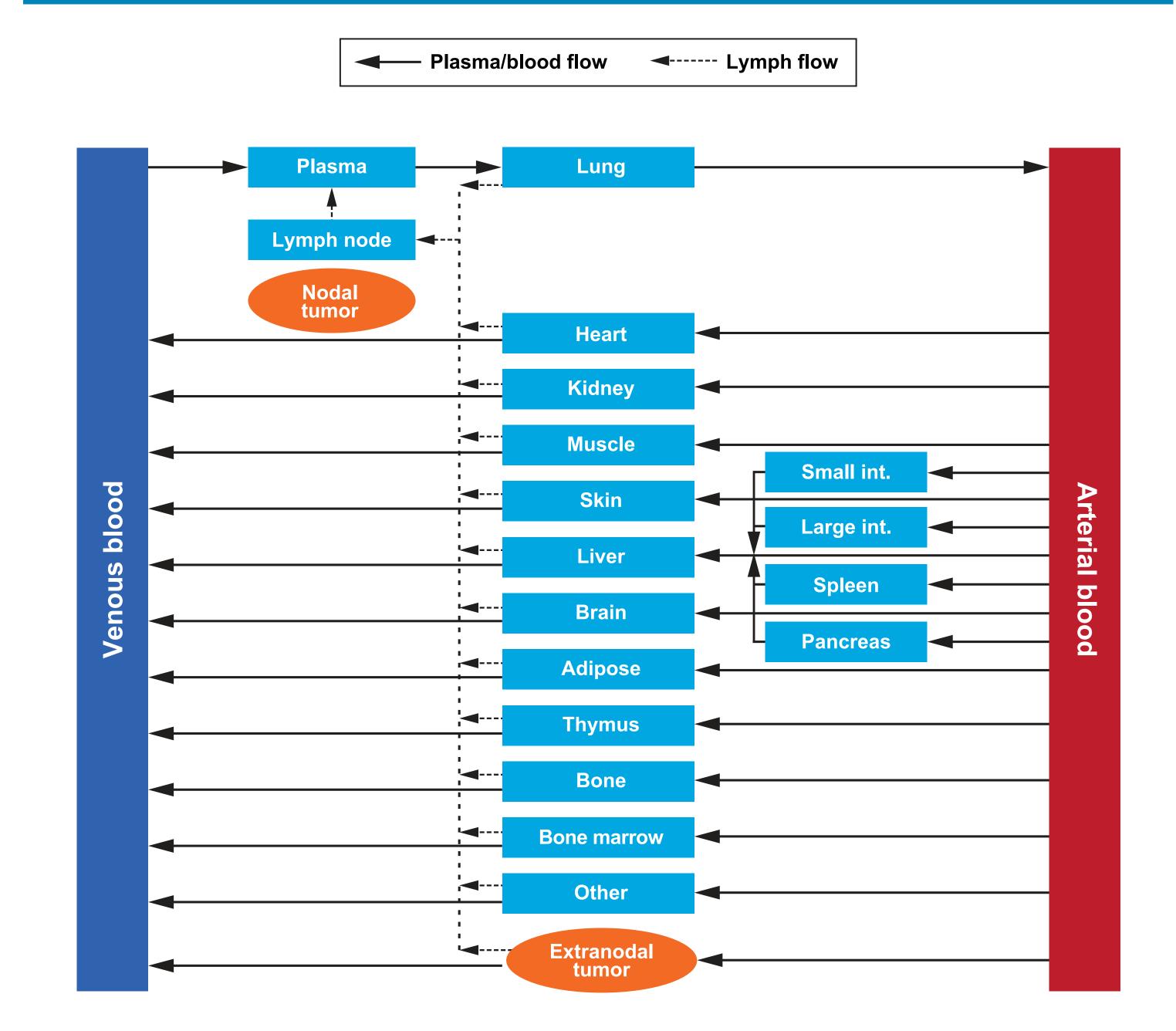
Overview of QSP Modeling Strategy

- 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
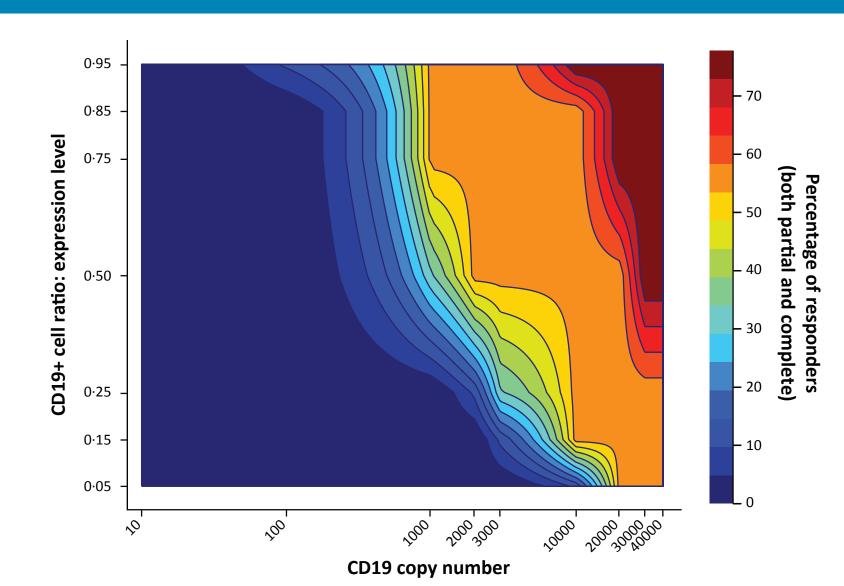
Simulation Setup

- 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
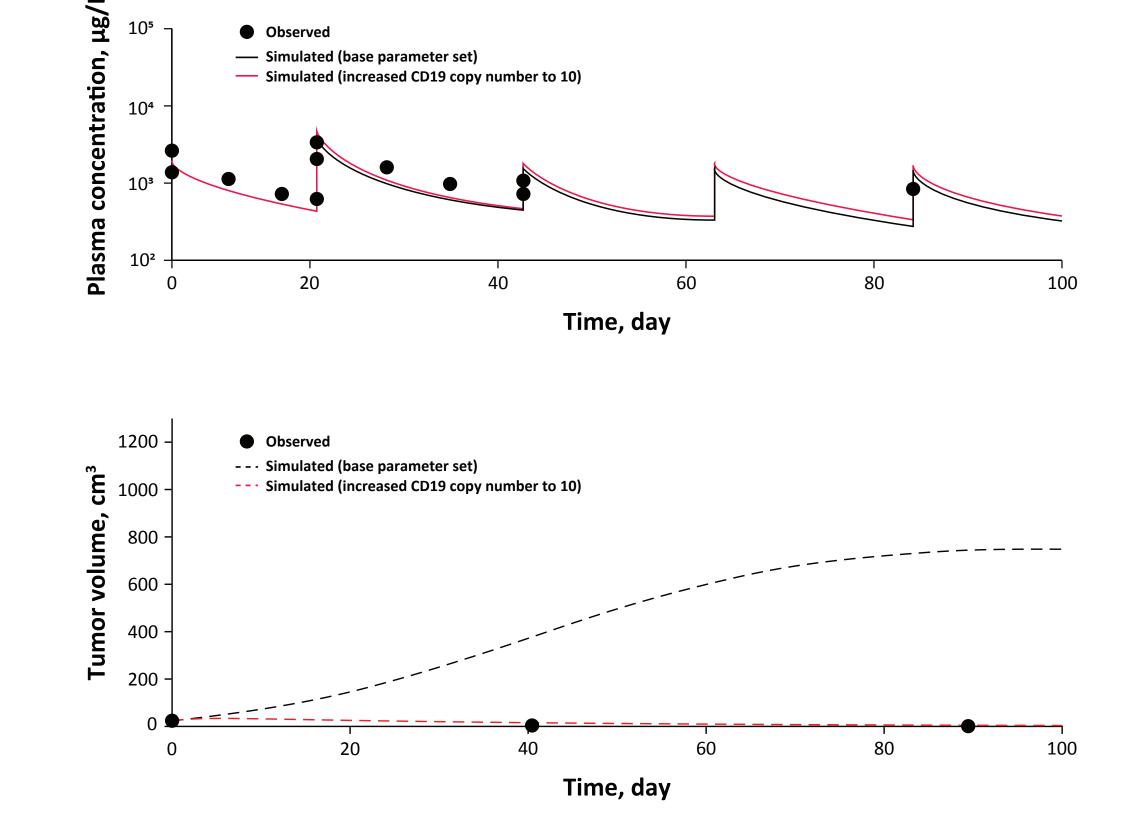

QSP, quantitative systems pharmacology.

Identifying CD19+ Expression Level and Surface Density Threshold for Response (continued)
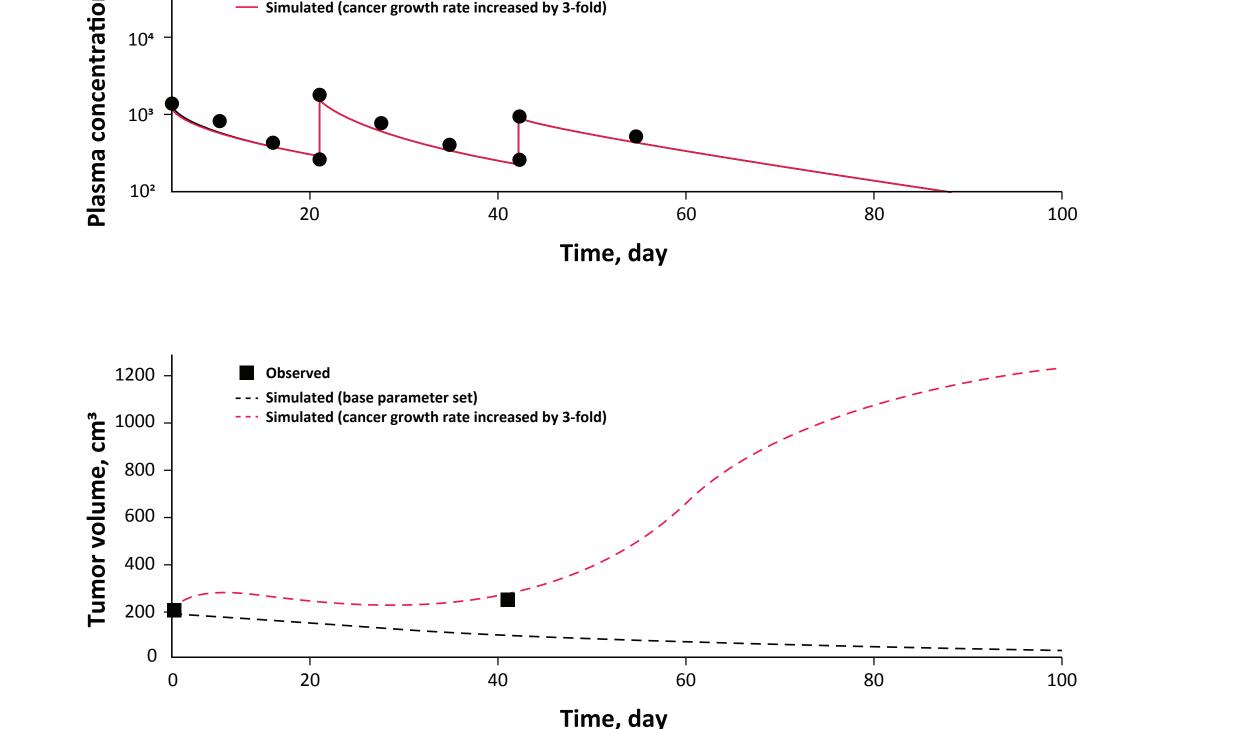
- Responses were seen in patients across all levels of CD19 expression, including patients with undetectable CD19 expression. Projections of QSP-model simulations to individual observations enabled the evaluation of how influential parameters affected outcome hypotheses (**Figure 5**)
- Predicted influence 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**)

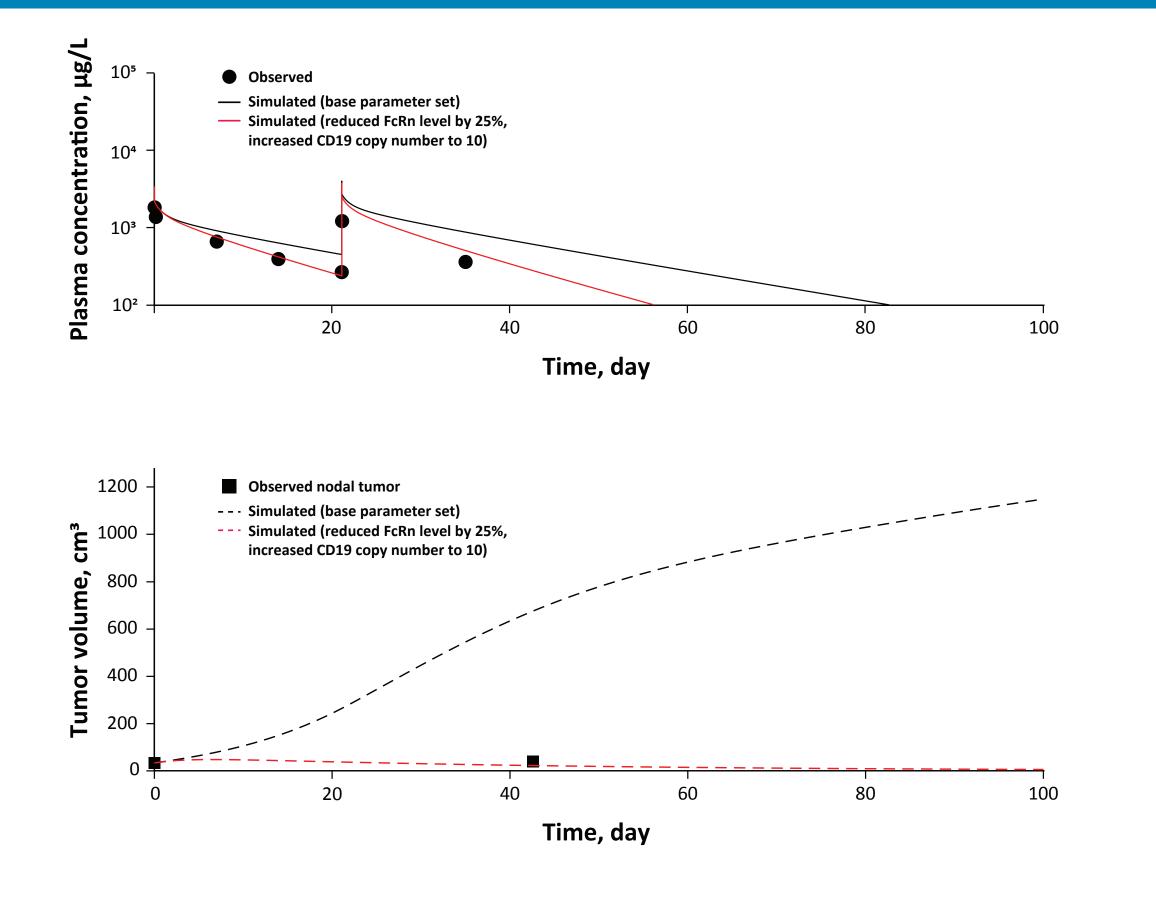### Figure 5. Simulation of patient with undetectable CD19 expression

- 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

References
1. ZYNLONTA®. Prescribing information. ADC Therapeutics SA. 2022.
2. Ingle, GS, et al. *Br J Haematol.* 2008;140(1):46-58.
3. Hartley, JA, et al. *Sci Rep.* 2018;8(1):10479.
4. Caimi, PF, et al. *Blood.* 2022;140 (Suppl 1):9548-9550.
5. Jones, HM, et al. *CPT Pharmacometrics Syst Pharmacol.* 2019;8(10):738-747.
6. Káhári, L, et al. *J Clin Invest.* 2019;129(8):3086-3102.
7. Lindauer, A, et al. *CPT Pharmacometrics Syst Pharmacol.* 2017;6(1):11-20.
8. Spiegel, JY, et al. *Nat Med.* 2021;27(8):1419-1431.
9. Pemmaraju, N, et al. *Proc (Bayl Univ Med Cent).* 2014;27(2):125-127.
10. Pyzik, M, et al. *Front Immunol.* 2019;10:1540.
11. Pyzik, M, et al. *Proc Natl Acad Sci U.S.A.* 2017;114(14):E2862-E2871.