ABCL-366

Quantitative Systems Pharmacology Model Predicts Combination Activity of CD19-Targeted Loncastuximab Tesirine Co-Dosed With a CD20/CD3 T-cell Bispecific (Epcoritamab) in Diffuse Large B-cell Lymphoma

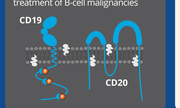
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By employing PBPK-QSP modeling, combination treatments can be evaluated to explore hypotheses for further clinical investigation

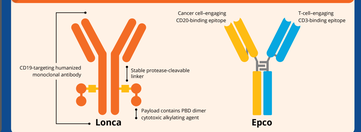
CD19 and CD20 in DLBCL

CD19 and CD20 are clinically validated therapeutic targets for the treatment of B-cell malignancies

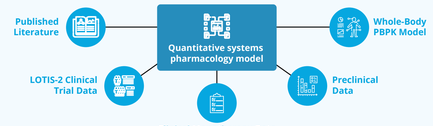


Potential Lonca/bsAb combination therapy

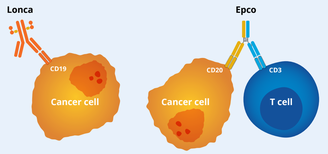
Lonca and Epco target different B-cell surface antigens and could provide synergistic efficacy



Methods A validated and published Lonca mPBPK model was combined with a published PBPK model of T-cell bsAbs and adapted to describe Epco to simulate combination therapies (Lonca + Epco) and monotherapy of each agent



Results Modeled results predicted that combination therapy with Lonca + Epco promoted substantially more tumor growth inhibition compared with either agent alone



- Increased doses of Lonca in combination treatment were predicted to have limited additional therapeutic benefit
- Additional cycles of combination treatment were predicted to increase tumor growth inhibition

bsAb, bispecific antibody; DLBCL, diffuse large B-cell lymphoma; Epco, epcoritamab; Lonca, loncastuximab tesirine; mPBPK, minimal physiologically-based pharmacokinetic; P, phosphate group; PBD, pyrrolobenzodiazepine; PBPK, physiologically-based pharmacokinetic; QSP, quantitative systems pharmacology.

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KEY MESSAGES

- By the end of cycle (C) 3, loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) + epcoritamab (Epco) was predicted to promote substantially more tumor growth inhibition (TGI) than Epco or Lonca alone
- While increased doses of Lonca, from 90 to 150 µg/kg, in combination therapy had limited further therapeutic benefit, additional treatment cycles of the Lonca + Epco combination treatment were predicted to increase the extent of tumor regression
- Simulations suggested that the Lonca dose could be decreased to improve tolerability
- These results are comparable to predictions for Lonca in combination with other bispecific antibodies[1] (bsAbs; Lonca + mosunetuzumab [Mosun] or glofitamab [Glofit])
- Response from Lonca + Epco codosing was predicted to be less affected by suppressed T-cell counts at baseline compared with Epco alone. This feature may enhance responsiveness in cases of moderate T-cell counts; however, clinical testing is needed to explore these findings

INTRODUCTION

- CD19 and CD20, B-lymphocyte surface antigens, are clinically validated therapeutic targets for the treatment of B-cell malignancies[2,3]
- Lonca is an antibody–drug conjugate comprising an anti-CD19 antibody conjugated to a pyrrolobenzodiazepine dimer cytotoxin that is approved as monotherapy for heavily pretreated patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)[4]
- Epco is a CD20 × CD3 T-cell–engaging bsAb that redirects T cells to eliminate malignant B cells[5]
- Epco targets a different B-cell surface antigen than Lonca; hence, combining Lonca with Epco is expected to result in efficacy beyond that of either administered as a monotherapy
- Previously, a novel physiologically-based pharmacokinetic (PBPK)–quantitative systems pharmacology (QSP) model was developed[6] and validated with Lonca monotherapy clinical observations in patients with R/R DLBCL[7]

OBJECTIVE

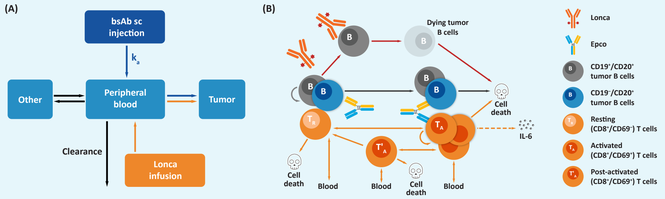
- To ascertain optimal Lonca + Epco administration and to understand important determinants of exposure leading to the optimal dosing regimen in the context of potential CD19 expression heterogeneity

METHODS

Model Construction

- The Lonca QSP model was based on the previously validated and published Lonca PBPK-QSP model.[6,7] This model was reduced in physiological complexity to be compatible with a published QSP model for T-cell–dependent bsAbs[8] while maintaining the core functionality of predicting tumor dynamics after Lonca and/or Epco treatment (**Figure 1**)

Figure 1. (A) Integrated Epco and Lonca PK QSP model and (B) depiction of Lonca and Epco mechanisms of action implemented in the tumor compartment



bsAb, bispecific antibody; Epco, epcoritamab; IL-6, interleukin 6; Lonca, loncastuximab tesirine; PK, pharmacokinetic; QSP, quantitative systems pharmacology; SC, subcutaneous.

- The following assumptions were made for integrating the pharmacokinetic-pharmacodynamic (PKPD) models:
  - Lonca or Epco can induce healthy and malignant B-cell killing
  - The tumor is composed of T cells and malignant B cells
  - Tumor volume is based on malignant B-cell count
  - T cells can enter or leave the tumor as with other tissues
  - $CD19^{-low}/CD20^{+}$ B cells account for tumor heterogeneity from cells insensitive to Lonca treatment

TGI Modeling

- The following approved bsAb dosing regimens were used to model prototypical patient administration (**Figure 2**)
  - Epco: subcutaneous (SC) administration of 0.16 mg on C1D1, 0.8 mg on C1D8, 48 mg on C1D15, 48 mg on C1D22, 48 mg Q1W for C2 to C3, 48 mg on D1 and D15 for C4 to C9, and 48 mg Q4W from C10 onward
  - Mosun: intravenous (IV) administration of 1 mg on C1D1, 2 mg on C1D8, 60 mg on C1D15, 60 mg on C2D1, and 30 mg Q3W from C3 onward
  - Glofit: IV administration of 2.5 mg on C1D8 following obinutuzumab pretreatment on C1D1, 10 mg on C1D15, and 30 mg Q3W for C2 onward
- The following dosing regimens outlined in the LOTIS-7 protocol were used to model population-based responses (**Figure 3** and **Figure 4**)
  - Epco: SC administration of 0.16 mg on C1D1; 0.8 mg on C1D8; 48 mg on C1D15; 48 mg on D1, D8, and D15 during C2-3; and 48 mg Q3W from C4 onward
  - Mosun: SC administration of 5 mg on C1D1, 45 mg on C1D8, 45 mg on C1D15, and 45 mg Q3W from C2 onward
  - Glofit: same as approved regimen
  - Lonca: IV administration given Q3W at the following doses:
    - 150 µg/kg for 2 doses followed by 75 µg/kg
    - 120 µg/kg for 2 doses followed by 75 µg/kg
    - 90 µg/kg

Virtual Population Variability Used to Model Population-Based Responses

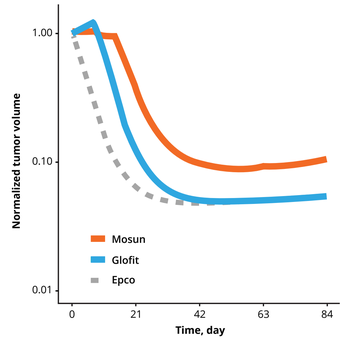
- The following assumptions and ranges were used to describe potential responses to Lonca + Epco combination therapy:
  - ≥80% of the tumor cells are $CD19^{+}/CD20^{+}$; the remaining tumor cells are $CD19^{-low}/CD20^{+}$
  - $CD19^{-low}/CD20^{+}$ tumor cells have 0 to 1 CD19 epitope per cell, resulting in varied susceptibility to Lonca from completely insensitive to somewhat sensitive
  - The Lonca-induced maximum killing rate of $CD19^{+}/CD20^{+}$ tumor cells varied by ±10%
  - Initial tumor volume = 1 to 10 mL
  - Malignant B-cell proliferation rate = 0.0 to 0.15 day^{-1}

RESULTS

QSP Modeling of Lonca + Epco

- Epco monotherapy was predicted to have similar TGI to Glofit monotherapy and superior TGI compared with Mosun and predicted to plateau by C2, following their approved dosing regimens, respectively (**Figure 2**). This is consistent with clinical observations[9]

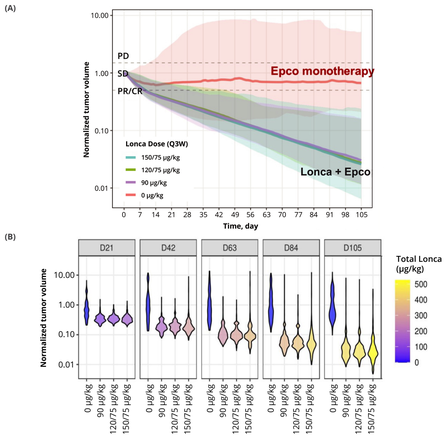
Figure 2. Long-term tumor growth inhibition of Epco, Mosun, and Glofit monotherapy in a prototypical patient[a]



[a]Initial tumor volume of 49.5 mL, doubling every 23 days.
Epco, epcoritamab; Glofit, glofitamab; Mosun, mosunetuzumab.

- Virtual population modeling results for Lonca + Epco indicated that the addition of Lonca outperformed and showed greater depth of response than Epco alone (**Figure 3A**)
- For any given dose cycle, the TGI provided by Lonca + Epco combination therapy was independent of both the individual dose level and the total (cumulative) amount of Lonca administered to that point (**Figure 3B**)
  - Increased TGI was predicted with additional dose cycles, independent of Lonca dose levels
  - QSP model predictions suggest that increased antitumor activity of Lonca + Epco combination therapy compared with Epco monotherapy may not be observed immediately. However, the additional benefit of combination therapy becomes more pronounced as the efficacy of Epco monotherapy stagnates while the combination therapy is predicted to result in continued benefit with increased dose cycles

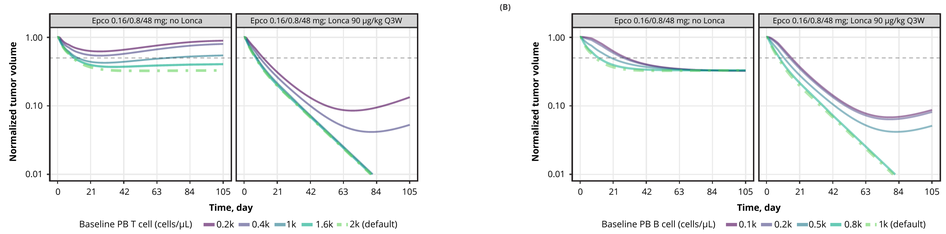
Figure 3. (A) Population-based simulations for tumor growth inhibition of Lonca + Epco[a] versus Epco[a] monotherapy and (B) tumor growth inhibition of Lonca + Epco[a] by total cumulative Lonca dose



[a]Epco dosed uniformly according to LOTIS-7 protocol.
CR, complete response; D, day; Epco, epcoritamab; Lonca, loncastuximab tesirine; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease.

- As patients with DLBCL may present with low T-cell counts,[10] the effect of baseline T-cell count was evaluated. In a simulation for a prototypical patient that is less sensitive to Lonca, the model predicted a substantial reduction in Epco monotherapy activity while combination therapy was unaffected when the T-cell count was reduced by as much as 50% (**Figure 4A**)
- A reduction in B-cell count by as much as 20% in a prototypical patient that is less sensitive to Lonca was predicted to have limited impact on combination therapy, while any amount of B-cell reduction was predicted to have minimal impact on Epco monotherapy activity (**Figure 4B**)

Figure 4. Impact of reduced (A) T-cell count and (B) B-cell count on Epco monotherapy (left) and Lonca + Epco combination therapy (right)[a]



[a]The tumor represented here had an initial volume of 7.5 mL with 80% $CD19^{+}/CD20^{+}$ and 20% $CD19^{-}/CD20^{+}$ tumor B cells and a doubling time of 27 days. The dashed line represents the separation between responders and nonresponders.
Epco, epcoritamab; Lonca, loncastuximab tesirine; PB, peripheral blood; Q3W, every 3 weeks.

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Disclosures

Y Li: employee of Metrum Research Group. **AK Wilkins:** employee of Metrum Research Group. **J Davis:** employee of Metrum Research Group. **T Knab:** employee of Metrum Research Group. **K Russo:** employee and a current equity holder at ADC Therapeutics SA. **C Keir:** employee and current equity holder at ADC Therapeutics SA. **JP Boni:** was an employee of ADCT Therapeutics SA at the time of the study and is a current equity holder at ADC Therapeutics SA.

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