T-077

Quantitative Systems Pharmacology Modeling of Loncastuximab Tesirine Combined With Mosunetuzumab and Glofitamab Helps Guide Dosing for Patients With DLBCL

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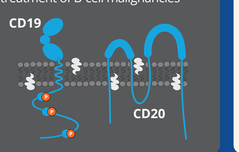
By employing PBPK-QSP modeling, combination treatments can be evaluated to explore hypotheses for further clinical investigation

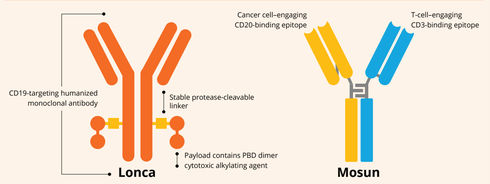
CD19 and CD20 in DLBCL

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

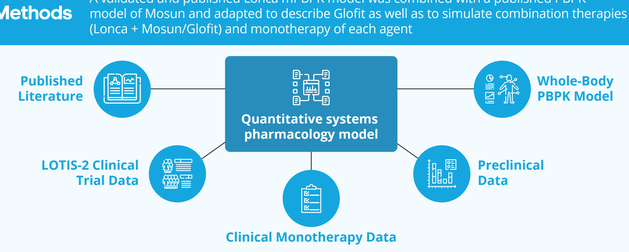


Potential Lonca/bsAb combination therapy

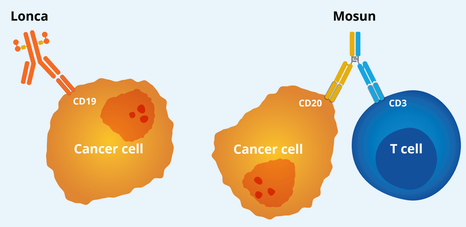
Lonca and Mosun/Glofit target different B-cell surface antigens and could provide synergistic efficacy



Methods A validated and published Lonca mPBPK model was combined with a published PBPK model of Mosun and adapted to describe Glofit as well as to simulate combination therapies (Lonca + Mosun/Glofit) and monotherapy of each agent



Results Modeled results predicted that combination therapy with Lonca + Mosun or Lonca + Glofit promoted substantially more tumor growth inhibition compared with any of these agents 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
- The ongoing LOTIS-7 clinical study (NCT04970901) evaluates the safety and anticancer activity of Lonca in combination with both Glofit and Mosun

bsAb, bispecific antibody; DLBCL, diffuse large B-cell lymphoma; Glofit, glofitamab; Lonca, loncastuximab tesirine; Mosun, mosunetuzumab; mPBPK, minimal physiologically-based pharmacokinetic; PBD, pyrrolobenzodiazepine; PBPK, physiologically-based pharmacokinetic; QSP, quantitative systems pharmacology.

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CONCLUSIONS

- Substantially more tumor growth inhibition (TGI) was predicted to occur at the end of cycle 3 (C3) of loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) + mosunetuzumab (Mosun) combination therapy and at the end of C4 of Lonca + glofitamab (Glofit) than with any of these agents alone
- Increased doses of Lonca in combination therapy regimens were predicted to have limited additional benefit to TGI; however, additional cycles of combination therapy were predicted to enhance TGI
- Simulations suggest that Lonca doses could be reduced to allow for improved tolerability for longer periods of time, up to the point of maximal benefit, although clinical testing is needed to explore these findings
- The ongoing LOTIS-7 clinical study (NCT04970901) evaluates the safety and anticancer activity of Lonca + Mosun and Lonca + Glofit

INTRODUCTION

- CD19 and CD20, B-lymphocyte surface antigens, are clinically validated therapeutic targets for the treatment of B-cell malignancies[1,2]
- 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)[3]
- Mosun and Glofit are CD20 × CD3 T-cell–engaging bispecific antibodies (bsAbs) that redirect T cells to eliminate malignant B cells[4,5]
  - Mosun and Glofit both target a different B-cell surface antigen than Lonca; hence, combining Lonca with either of these bsAbs is expected to result in efficacy beyond that of 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

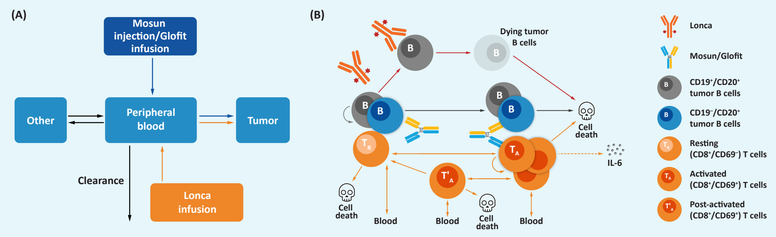
- To ascertain optimal Lonca + Mosun and Lonca + Glofit administration and to understand important determinants of exposure leading to the optimal dosing regimen in the context of potential CD19 expression heterogeneity

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 of Mosun[8] while maintaining the core functionality of predicting tumor dynamics during Lonca monotherapy (**Figure 1**)

Figure 1. (A) Integration of Mosun subcutaneous administration into the PK-QSP model and (B) depiction of the QSP model for Lonca + Mosun/Glofit combination therapy



The following parameters were used to model Mosun subcutaneous administration: bioavailability = 0.7; absorption rate = 0.26 day^{-1}.
Glofit, glofitamab; IL-6, interleukin 6; Lonca, loncastuximab tesirine; Mosun, mosunetuzumab; PK, pharmacokinetics; QSP, quantitative systems pharmacology.

- The following assumptions were made for integrating the PKPD models:
  - Lonca or Mosun/Glofit can induce tumor B-cell killing, though Lonca-killed tumor B cells would linger in the "dying" state. The rate for removing dying tumor B cells was modulated to account for different surface CD19 copy numbers
  - The tumor is composed of T cells and malignant B cells (i.e., no healthy B cells)
  - Tumor volume is calculated based on the tumor B-cell number (the total of tumor B cells and dying tumor cells)
  - T cells can enter or leave the tumor as they enter or leave other tissues

TGI Modeling of a Virtual DLBCL Patient Population

- Virtual populations were created by resampling (prevalence weighting) from a larger virtual cohort, such that monotherapy tumor responses matched reported clinical observations from 3 respective clinical trials, as previously described.[9] A virtual cohort of 20,000 subjects was generated by Latin hypercube sampling with 5 key parameters specifying:
  - Initial tumor volumes: 0.1 to 100 mL
  - Malignant B-cell proliferation rates: 0.01 to 0.05 day^{-1}
  - CD19$^{-/Low}$ fraction: 0 to 10%
  - Lonca-induced maximal cell killing rate on CD19$^{-/Low}$ cells: 0.01 to 0.07 day^{-1}
  - Apoptotic transition rate: 0.01 to 0.05 day^{-1}
- Prevalence weights were computed by matching simulated tumor responses to Mosun and Lonca monotherapy treatments from the approved regimen to their corresponding clinical observations.[10,11] Prevalence weights were then assigned via quadratic programming, and a virtual population of 500 patients was created by resampling with proportional frequencies (**Table 1**)

Table 1. Observed versus simulated patient response rates to Mosun, Glofit, and Lonca monotherapy treatments

	Mosun		Lonca		Glofit (predictions)	
Response	Sims	Obs	Sims	Obs	Sims	Obs
CR	18.63	20	28.05	29	33.83	33
PR	19.06	17	32.33	29	13.28	15
SD	7.92	7	16.71	17	38.97	
PD	54.39	56	22.91	25	13.92	

CR, complete response; Obs, observations; PD, progressive disease; PR, partial response; SD, stable disease; Sims, simulations.
Response classifications are based on guidelines.[12]
Mosun clinical data from n = 129 aggressive-non-Hodgkin lymphoma (NHL) patients.[10]
Lonca clinical data from n = 145 R/R DLBCL patients.[11]
Glofit clinical data from n = 127 aggressive-NHL patients,[13] held out for predictive validation.

- Lonca was given every 3 weeks (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
- Mosun 5 mg on cycle 1 day 1 (C1D1), 45 mg on C1D8, 45 mg on C1D15, and 45 mg Q3W for C2 onward
- Glofit 2.5 mg on C1D8 following obinutuzumab pretreatment on C1D1, Glofit 10 mg on C1D15, and Glofit 30 mg Q3W for C2 onward

TGI Modeling Parameters for a Prototypical Patient

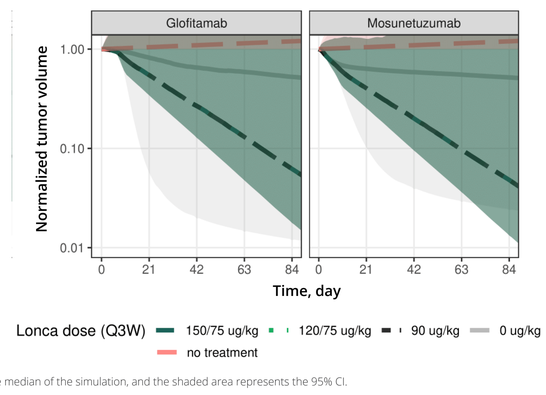
- Initial tumor volume = 49.5 mL
- The tumor was composed of 100% CD19^{+}/CD20^{+} malignant B cells
- Initial T-cell:B-cell ratio in tumor = 0.06
- Tumor B-cell proliferation rate = 0.03 day^{-1} (tumor doubling time ≈ 23 days)
- Tissue B cells and T cells were pre-equilibrated, and no depletion was assumed

RESULTS

QSP Modeling of Lonca + bsAbs

- Virtual population pharmacodynamic modeling results for Lonca + Mosun and Lonca + Glofit (**Figure 2**) both indicated that the addition of Lonca outperformed and showed greater depth of response than either of these bsAbs alone
  - Both simulations indicated that TGI potential was independent of Lonca dosage

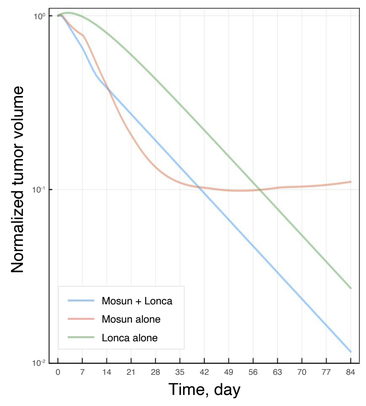
Figure 2. Virtual population simulations of tumor volume change to Lonca + Mosun/Glofit combination therapy versus its corresponding monotherapy or control



The solid represents the median of the simulation, and the shaded area represents the 95% CI.
Q3W, every 3 weeks.

- Tumor volume reduction with Mosun monotherapy was predicted to plateau after day 28, whereas Lonca + Mosun combination therapy was predicted to continue to provide TGI (**Figure 3**). Similar results were observed for Glofit monotherapy compared with Lonca + Glofit combination therapy (data not shown)

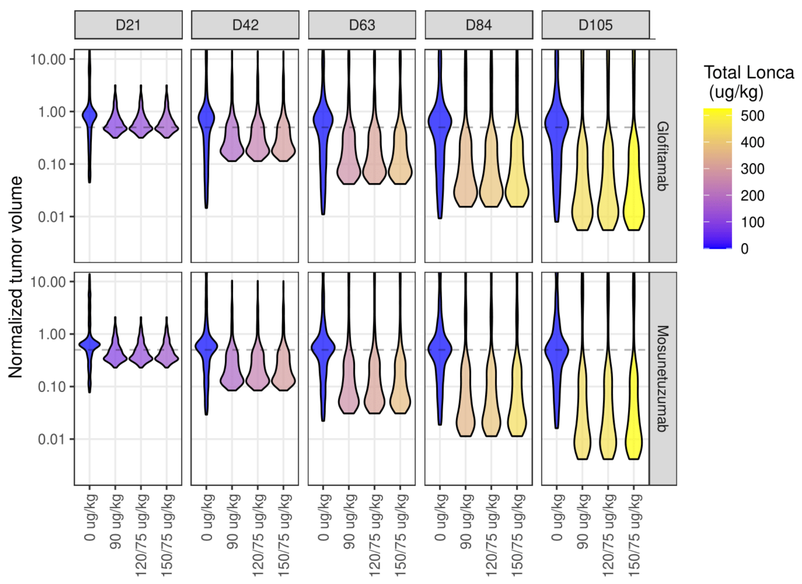
Figure 3. Long-term tumor dynamics in response to Lonca + Mosun versus Lonca or Mosun monotherapy in a prototypical patient receiving both at their prescribed doses



Prototypical patient received Mosun doses of 5 mg on C1D1, 45 mg on C1D8 and C1D15, followed by 45 mg Q3W, and/or Lonca doses of 150 µg/kg for the first 2 cycles, followed by 75 µg/kg Q3W. This patient's tumor was homogeneous (100% CD19^{+}/CD20^{+}).
C, cycle; D, day; Lonca, loncastuximab tesirine; Mosun, mosunetuzumab; Q3W, every 3 weeks.

- When examined by the total dosage of Lonca received, the TGI provided by Lonca + bsAb combination therapy was predicted to increase with additional cycles of Lonca while being independent of the Lonca dosage level (**Figure 4**)

Figure 4. Virtual population simulations of tumor volume response to Lonca + Mosun/Glofit by total cumulative Lonca dose



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Disclosures

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

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References

1. Bailly S, et al. *Hematol Oncol*. 2022;40(4):505-517.
2. Salles G, et al. *Adv Ther*. 2017;34(10):2232-2273.
3. ZYNLONTA® (loncastuximab tesirine-lpyl). Package insert. ADC Therapeutics; 2022.
4. Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065.
5. Dickinson MJ, et al. *N Engl J Med*. 2022;387(24):2220-2231.
6. Utsey K, et al. *Clin Pharmacol Drug Dev*. 2023;12(12):123-125.
7. Caimi PF, et al. *eJHaem*. 2023:1-8. Epub ahead of print.
8. Hosseini I, et al. *NPJ Syst Biol Appl*. 2020;6(1):28.
9. Gadkar K, et al. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(5):235–249.
10. Caimi PF, et al. *Haematologica*. 2024;109(4):1184-1193.
11. Budde LE, et al. *J Clin Oncol*. 2022;40:481–491.
12. Cheson BD, et al. *J Clin Oncol*. 2007;25:579–586.
13. Hutchings M, et al. *J Clin Oncol*. 2021;39(18):1959–1970.