First in Human Population PKPD Modeling and Simulation of CUE-101 PK

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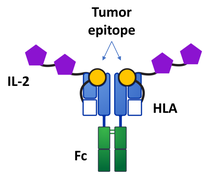
Background

- Immuno-STATs™ are modular T cell engagers engineered to selectively activate tumor-antigen specific CD8+ T cells via targeted delivery of cytokines.
- Each CUE-100 series Immuno-STAT molecule is comprised of a bivalent peptide-HLA complex on an Fc framework with 4 molecules of an attenuated interleukin-2 (IL-2) variant (Quayle 2020; Seidel 2021):



- CUE-101, the first Immuno-STAT in clinical trials, contains a peptide epitope derived from the HPV16 E7 protein, and 4 molecules of attenuated human IL-2 to activate HPV16-specific CD8+ T cells for the treatment of HPV16+ cancers.
- CUE-102, the second Immuno-STAT in clinical trials, is 99% sequence identical to CUE-101 but contains a peptide epitope derived from the Wilms' Tumor 1 protein, an oncofetal antigen that is expressed in numerous cancer types.
- Both CUE-101 and CUE-102 continue to demonstrate favorable safety, tolerability and meaningful clinical benefit in patients in their respective ongoing Phase 1 trials.
- In this study, preliminary pharmacokinetic (PK) and pharmacodynamic (PD) data from study CUE-101-01 were used to generate a population PK/PD model for CUE-101. This model was then used to simulate exposure following alternative dose levels of CUE-101.
- Given the similarity of these two drug candidates, exploratory PK modeling was also performed integrating the distinct exposure datasets of CUE-101 and CUE-102.

Study Design: CUE-101-01

- Study CUE-101-01 (NCT03978689) is a first-in-human, open label, dose escalation and expansion study of CUE-101 monotherapy in second line and CUE-101 combination therapy with pembrolizumab in first line patients with HPV16+ recurrent/metastatic HNSCC.
- Study objectives include determination of safety and tolerability, PK, antitumor responses, immune responses, immunogenicity, and blood-based biomarkers of monotherapy and/or combination treatment.
- The trial consists of 4 parts: (A) CUE-101 monotherapy dose escalation (0.06 - 8 mg/kg), (B) CUE-101 monotherapy dose expansion/confirmation, (C) combination dose escalation, and (D) combination dose expansion/confirmation.
- PK modeling and PK/PD modeling of the monotherapy biomarker dataset was focused on patients from Parts A, B, & C since Part D remains ongoing.
- CUE-101 is administered intravenously over one hour every 3 weeks.

PK Modeling Methods

- NONMEM 7.5 was used for all analyses.
- Serum concentrations of CUE-101 were determined using a validated hybrid capture LC/MS/MS assay that simultaneously measures two unique peptides from CUE-101.
- CUE-101 exposure data was collected over multiple cycles in Parts A, B, and C of the ongoing trial. CUE-101 monotherapy doses ranged from 0.06 mg/kg to 8 mg/kg in Parts A and B for a total of 49 subjects, and CUE-101 doses ranged from 1 mg/kg to 4 mg/kg in combination with 200 mg pembrolizumab in Part C for a total of 9 subjects as of the data cut-off for this analysis.
- Approximately 18.5% of the PK data were below the limit of quantification (BLQ) of the method (< 10 ng/ml). Method M3 was applied to handle such data as it generates the least biased results compared to other known methods used to handle BLQ data.
- Different structural models (1, 2 and 3 compartment) were evaluated based on the trends that were observed in the preliminary concentration-time plots, and each was evaluated using standard goodness-of-fit plots.
- Clearance, intercompartmental clearance and volume parameters were allometrically scaled to a median body weight of 77.7 kg, with a fixed exponent of ¾ for clearance and intercompartmental clearance, and 1 for volume of distribution.
- The predictive performance of the final PK model was evaluated using posterior predictive checks (PPC). In this analysis, AUC (0 to infinity) and Cmax obtained from cycle 1 were used as this cycle included the highest number of samples post-dose.

CUE-101 PK Model Results & Simulations

- Both 2-compartment and 3-compartment models were fit to the concentration-time data. These models are depicted in **Figure 1**.
- The 3-compartment model best described the data according to the evaluation methods utilized in this study. The Akaike information criterion (AIC) estimates were 457.847 and -41.619 for the 2- and 3-compartment models, respectively. The lower AIC value for the 3-compartment model suggests that it provides a significantly better fit to the data.
- The PPC of AUC (0 to infinity) and Cmax of the 3-compartment PK model are shown in **Figure 2**. No major systematic discrepancies between the simulated and the observed AUC (0 to infinity) and Cmax were apparent.
- **Table 1** summarizes the parameters of the 3-compartment model.

Figure 1: Diagrams of the pharmacokinetic models tested: (A) 2-compartment model (B) 3-compartment model

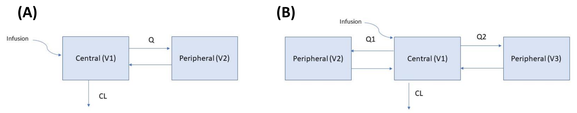


Figure 2: (A) Posterior Predictive Check (PPC) using dose normalized AUC (0 to infinity) as the PK statistic. (B) PPC using dose normalized Cmax as the PK statistic. Red and blue dashed vertical lines represent simulated and observed values of the PK statistics, respectively. From left to right the lines are located at the 5th, 50th, and 95th percentiles of each PK statistic.

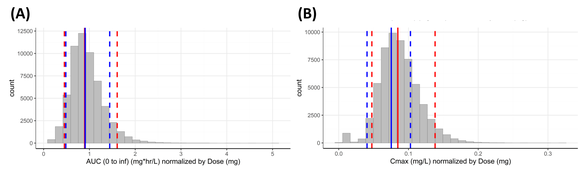


Table 1: Summary of parameters for the 3-compartment model for CUE-101

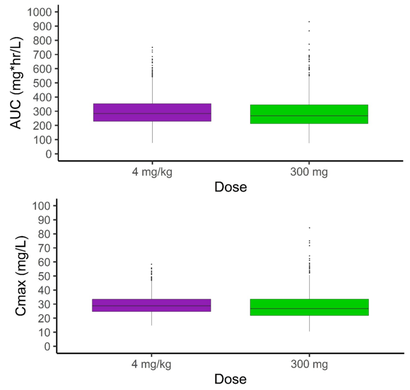
Structural model parameters	Estimate	%RSE	IIV on PK parameters (%CV)	%RSE
CL (L/h)	1.10	0.656	31.8	0.836
Vd1 (L)	8.18	0.393	22.6	3.67
Q1 (L/h)	3.17	0.792	38.6	6.61
Vd2 (L)	20.54	0.625	34.5	5.71
Q2 (L/h)	0.08	2.25	60.7	23.9
Vd3 (L)	22.03	0.626	35.4	15.5
D (hours)	1.04	9.80	0.248	539
Residual error (SD)	**%RSE**	-	-	-
0.362	5.39	-	-	-

CL: Clearance (scaled to 77.7 kg), **Vd1:** Central volume of distribution (scaled to 77.7 kg), **Q2:** Inter-compartmental clearance between Vd1 and Vd2 (scaled to 77.7 kg), **Vd2:** Peripheral volume of distribution 1 (scaled to 77.7 kg), **D:** Duration of infusion, **Q2:** Inter-compartmental clearance between Vd2 and Vd3 (scaled to 77.7 kg), **Vd3:** Peripheral volume of distribution 2 (scaled to 77.7 kg), **%RSE**: Relative standard error, **IIV:** Inter-individual variability, **%CV:** Coefficient of variation as a percentage, **SD:** Standard deviation.

Comparison of Fixed vs. Weight-based Dosing on CUE-101 Exposure

- Fixed doses ranging from 50-700 mg were simulated from the PK model and compared to weight-based doses of 0.5-4 mg/kg.
- **Figure 3** shows that a fixed dose of 300 mg provides nearly identical exposure (as estimated by AUC and Cmax) to 4 mg/kg.

Figure 3: Comparison of simulated AUC and Cmax values from a weight-based dose of 4 mg/kg and a fixed dose of 300 mg CUE-101



PKPD Modeling Methods

- PD biomarkers evaluated in this preliminary study included frequency of Natural Killer (NK) and T regulatory cells (Tregs) in peripheral blood mononuclear cells (PBMCs), serum levels of Interleukin 6 (IL-6), Interferon gamma (IFNγ), Tumor Necrosis Factor alpha (TNFα), and absolute counts of eosinophils and lymphocytes.
- Patients enrolled in Part C were excluded from this analysis as the combination therapy (pembrolizumab) confounds analysis of immune-related effects of CUE-101.
- Attempts were made to fit these data to a variety of indirect response models, but the sparse nature of the data resulted in poor convergence.
- Therefore, drug exposure (measured as AUC or Cmax) for each patient versus the highest observed post-dose biomarker value (corrected for baseline by subtraction of pre-dose values) using the data from all cycles were used to assess the drug exposure-response relationship using the following equation:

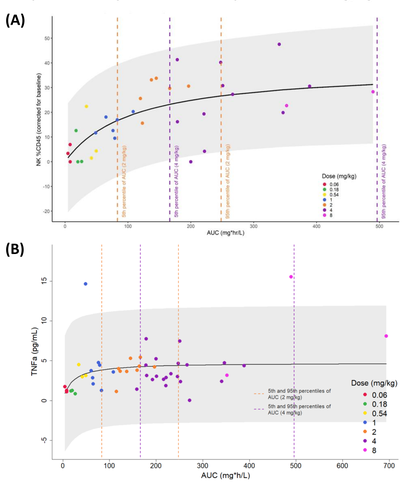
$$\text{Response} = \frac{AUC_i\,(or\ Cmax_i) * Emax}{AUC_i(or\ Cmax_i) + EC50}$$

where AUC is the area under the curve for the individual "i", Cmax is the maximum concentration for the individual "i", Emax is the maximum estimated response, and EC50 is the estimated AUC exposure that produces 50% response.

CUE-101 PKPD Model Results

- The Emax model was the most suitable model to characterize the drug exposure-response data based on fit to the data and the parameter estimates
- Maximum increase of NK cell frequency showed the best relationship with CUE-101 exposure relative to the other tested biomarkers. The maximum response to CUE-101 plateaus at exposures associated with doses of 4 mg/kg, although there is some overlap with exposures associated with the 2 mg/kg dose **(Figure 4A)**.
- The relationship between the maximum response of TNFα serum concentration and CUE-101 exposure was similar to that observed for NK cell frequency but showed less dynamic range across exposures **(Figure 4B)**.
- The other biomarkers evaluated either showed no relationship in scatterplots and models were not fit (e.g., change in Treg frequency), or models were fit that exhibited similar trends but with less meaningful responses in relation to CUE-101 exposure.

Figure 4: Observed maximum (A) NK cell (%CD45) frequency and (B) serum TNFα level following CUE-101 treatment, corrected for baseline, versus measured AUC (drug exposure) for each patient. Observed data = filled circles. The black curve line = predicted response. Gray area = the 90% prediction band. Dotted vertical lines = 5th and 95th percentiles of AUCs simulated from 2- and 4 mg/kg doses, respectively.



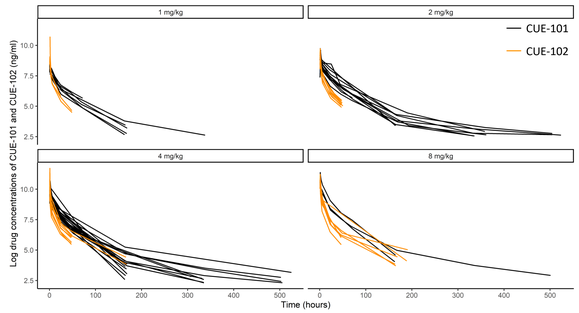
Study Design: CUE-102-01

- Study CUE-102-01 (NCT05360680) is a first-in-human, open label, dose escalation and expansion study of CUE-102 monotherapy in subjects with WT1+, recurrent/metastatic cancers.
- Study objectives include determination of safety and tolerability, PK, antitumor responses, immune responses, immunogenicity, and blood-based biomarkers of monotherapy treatment.
- The trial consists of 2 parts: (A) CUE-102 monotherapy dose escalation (1 - 8 mg/kg) and (B) CUE-102 monotherapy dose expansion/confirmation.
- CUE-102 is administered intravenously over one hour every 3 weeks.

Integrated Modeling of CUE-101 & CUE-102 PK

- The preliminary drug concentration-time profile for CUE-102 showed similar exposure trends compared to CUE-101 across doses of 1, 2, 4, and 8 mg/kg (shown for cycle 1 in **Figure 5**).
- To test the PK similarity between these two drugs, preliminary CUE-102 data were incorporated into the 3-compartment PK model for CUE-101 and model re-fitting was performed.
- The 3-compartment PK model for CUE-101 provided a good fit to CUE-102 data as indicated by the basic goodness of fit plot (**Figure 6**) and the similar and precise parameter estimates of the 3-compartment model (**Table 2**).
- The current population PK modeling analysis suggests that CUE-101 and CUE-102 share similar PK properties in patients.

Figure 5: Log concentration of CUE-101 and CUE-102 over time following first dose



Note: The validated bioanalytical method for CUE-102 was developed with a higher lower limit of quantitation relative to the CUE-101 bioanalytical method.

Figure 6: Observed drug conc. of CUE-101 and CUE-102 vs predicted (individual)

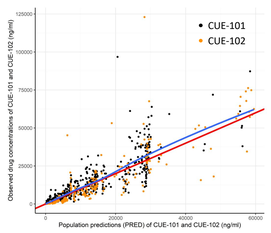


Table 2: Summary of parameters for the 3-compartment model for CUE-101 and CUE-102

Structural model parameters	Estimate	%RSE	IIV on PK parameters (%CV)	%RSE
CL (L/h)	1.42	0.774	49.3	0.449
Vd1 (L)	8.02	0.384	24.8	0.561
Q1 (L/h)	3.01	0.653	39.0	12.8
Vd2 (L)	24.34	0.558	42.1	16.9
Q2 (L/h)	0.06	2.47	73.4	5.45
Vd3 (L)	26.90	0.964	65.9	1.46
D (hours)	1.04	15.6	2.63	5.22
Residual error (SD)	**%RSE**	-	-	-
0.377	4.68	-	-	-

CL: Clearance (scaled to 77.4 kg), **Vd1:** Central volume of distribution (scaled to 77.4 kg), **Q2:** Inter-compartmental clearance between Vd1 and Vd2 (scaled to 77.4 kg), **Vd2:** Peripheral volume of distribution 1 (scaled to 77.4 kg), **D:** Duration of infusion, **Q2:** Inter-compartmental clearance between Vd2 and Vd3 (scaled to 77.4 kg), **Vd3:** Peripheral volume of distribution 2 (scaled to 77.4 kg). **%RSE**: Relative standard error, **IIV:** Inter-individual variability, **%CV:** Coefficient of variation as a percentage, **SD:** Standard deviation.

Conclusions

- CUE-101 disposition was best described by a 3-compartment PK model with elimination from the central compartment. Clearance of CUE-101 is relatively low (1.10 L/hr for a 70 kg individual), with the volumes of distribution suggesting that there is some distribution into peripheral tissues.
- PK simulations examining the suitability of CUE-101 to be given by fixed doses support that a fixed dose of 300 mg would match the exposures seen at 4 mg/kg.
- Both the maximum increase of NK cell frequency and the maximum increase of TNFα serum concentration demonstrate a relationship with CUE-101 exposure. For both biomarkers the effect of CUE-101 appears to level off at exposures associated with the 4 mg/kg dose, suggesting that a 4 mg/kg CUE-101 dose results in a maximum PD effect.
- Preliminary analysis of CUE-102 exposure in patients demonstrates comparability to that observed with CUE-101, consistent with the preclinical experience with both molecules across multiple species (data not shown). The CUE-101 PK model provides a good fit to the CUE-102 exposure data.
- The similarity in the PK profiles of CUE-101 and CUE-102 support an opportunity to rapidly develop additional drug candidates from the CUE-100 series of Immuno-STATs by leveraging the similarity of their core pharmacologic properties.

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