Tisagenlecleucel (CTL019) Model-Based Cellular Kinetic Analysis of Chimeric Antigen Receptor (CAR) T Cells to Characterize the Impact of Tocilizumab on Expansion and to Identify Correlates of Cytokine Release Syndrome Severity

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Introduction

- Tisagenlecleucel (CTL019) is an autologous immunotherapy
  - A patient's own T cells are reprogrammed with a transgene encoding a CD19-specific CAR
- Cytokine release syndrome (CRS) is the most common toxicity associated with CAR T-cell therapy and is an on-target toxicity[1,2]
  - CRS occurs following tisagenlecleucel cell activation and expansion
  - Severe CRS has been successfully managed with tocilizumab (anti–interleukin-6 [IL-6] receptor antibody) therapy and corticosteroids[3]
  - Model-based methods to characterize the impact of IL-6 inhibition on tisagenlecleucel expansion have not been previously reported
- A previous noncompartmental analysis (NCA) showed that higher tumor burden at enrollment correlated with greater peak transgene level and higher-grade CRS[4,5]
  - Patients with higher tumor burden and concurrently higher transgene expansion often require tocilizumab
  - NCA showed that the exposure in patients who required tocilizumab is greater than the exposure in patients who did not require tocilizumab, suggesting that tocilizumab has little to no impact on expansion in a high-transgene expanding group
  - The change in CAR T-cell kinetics after a patient received a tocilizumab dose were not examined
- A population cellular kinetics model was used to characterize CAR T-cell kinetics before and after tocilizumab and corticosteroid therapy to determine whether these treatments impact the expansion of CAR T cells

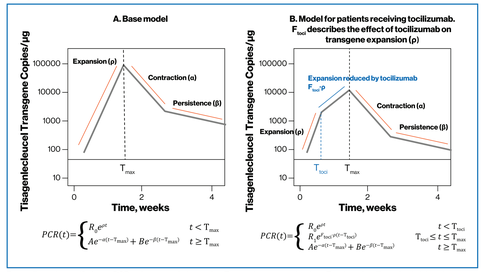
Methods

- Two phase 2 studies of B-cell acute lymphoblastic leukemia (ALL) in pediatric and young adult patients were used for this analysis: NCT02435849 (ELIANA) and NCT02228096 (ENSIGN)
  - ELIANA is an ongoing global trial that, at the time of data cutoff, included 62 patients from 10 countries
  - ENSIGN is a US multicenter trial that enrolled a total of 29 patients
  - The 2 trials have near-identical enrollment and treatment protocols, allowing data to be pooled for analysis
- Patients received a single dose of tisagenlecleucel
  - The median weight-adjusted dose was 3.1×10^6 transduced viable T cells per kg (range, 0.2 to 5.4×10^6 cells/kg)
  - The median total dose of transduced viable T cells was 1.0×10^8 (range, 0.03 to 2.6×10^8 cells)
  - Patient outcomes from interim analyses have been previously reported[3,6]
- Tisagenlecleucel levels were measured in peripheral blood samples of 90 patients (ELIANA, n = 61; ENSIGN, n = 29) by quantitative polymerase chain reaction (qPCR) using transgene-specific primers and reported as transgene copies per microgram of genomic DNA

Results

- A novel population cellular kinetic model to characterize tisagenleleucel was based on a model previously developed to quantify T-cell turnover[7]

Figure 1. Mathematical Model for Maximal Tisagenlecleucel Expansion



F_{toci}, tocilizumab-specific factor; PCR, polymerase chain reaction; T_{max}, peak concentration time ; T_{toci}, time of tocilizumab administration.

- In the base model, cells proliferate at a rate (ρ), at time (t_{max}), proliferation stops, and the CAR T cells initially contract at a rate (α), followed by a more gradual decline at rate (β) (**Figure 1A**)
  - α is thought to correspond to apoptotic cell death that occurs following a typical T-cell immune response
  - β is thought to correspond to a more gradual decline of the memory T cells
- For patients who received tocilizumab, the model allowed for a possible reduction in the expansion rate by multiplying ρ by a tocilizumab-specific factor (F_{toci}) (**Figure 1B**)
- F_{toci} < 1 indicates a slower rate of expansion after the comedication administration
- The effect of steroids was modeled in a similar fashion using a steroid-specific factor (F_{ster})

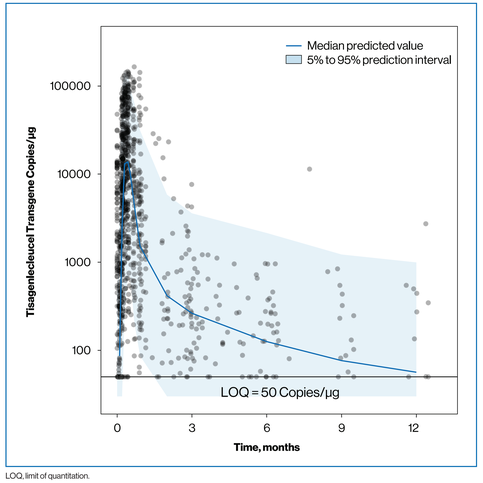
Table 1. Mathematical Model Parameters

Parameter	Units	Parameter Estimate	Relative Standard Error, %	Intersubject Variability, ω^2
Foldx[a]	—	3900	30	2.4
T_{max}	Days	9.3	4.2	0.38
C_{max}	DNA copy/µg	24000	20	0.65
α	1/day	0.16	11	0.91
FB[b]	—	0.0079	15	0.80
β	1/day	0.0032	23	0.86
F_{toci}	—	1.2	7.5	—
F_{ster}	—	1	9	—

C_{max}, peak concentration; F_{ster}, steroid-specific factor; F_{toci}, tocilizumab-specific factor; T_{max}, peak concentration time.
[a]Foldx is the fold expansion and it is computed by the equation foldx = $\exp(\rho T_{max})$. [b]FB corresponds to the fraction of tisagenlecleucel transcripts that is expressed by memory-like cells.

- The impact on peak concentration (C_{max}) by study, sex, race, presence of Down syndrome, prior hematopoietic stem cell transplant, fludarabine-based lymphodepletion therapy, tisagenlecleucel product transfection efficiency, and administration of tocilizumab, corticosteroids, and tisagenlecleucel were explored using a full covariate model
  - No impact of other intrinsic and extrinsic factors on C_{max} were identified
- Six parameters had random effects when fitting the population model, meaning that they were log-normally distributed across the population with variance (ω^2): C_{max}, T_{max}, α, β, foldx, and FB (**Table 1**)
  - Foldx corresponds to the fold expansion of qPCR from baseline up until C_{max} and is given by: foldx = $\exp(\rho \cdot T_{max})$
  - FB corresponds to the fraction of transgene that may be representative of memory-like cells that decline gradually at rate β
- For the base model, the terms R_0, A, and B in the equations above were computed as follows to ensure continuity: $R_0 = C_{max}/foldx$; $A = C_{max} \cdot (1\text{-}FB)$; $B = C_{max} \cdot FB$
- When patients receive tocilizumab, $R_0 = C_{max}/foldx$; $R_1 = C_{max}/foldx \cdot e^{\rho \cdot T_{toci}}$; $C_{max} = C_{max}/foldx \cdot e^{\rho \cdot T_{toci}} \cdot e^{F_{toci} \rho \cdot (T_{max} - T_{drug})}$; $A = C_{max} \cdot (1\text{-}FB)$; $B = C_{max} \cdot FB$
- When patients receive both tocilizumab and corticosteroids, the effect on the expansion rate of both drugs is given by the product $F_{toci} \cdot F_{ster}$

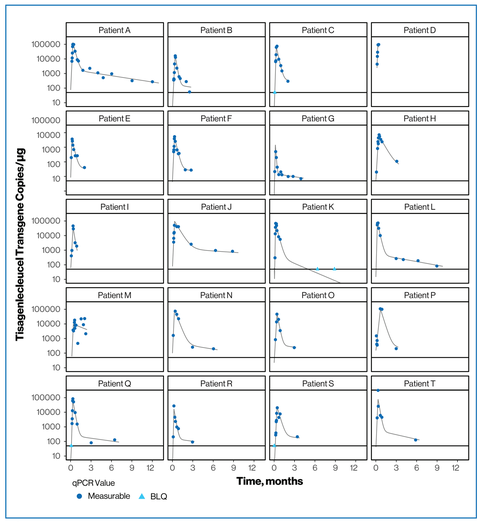
Figure 2. Visual Predictive Check of the Model Simulation Compared With the Data



LOQ, limit of quantitation.

- The model described the data well (**Figures 2 and 3**)
- Using the model, the initial doubling time (ln 2/ρ) was 0.78 days, the initial rate of decline (ln 2/α) was 4.3 days, and the terminal half-life (ln 2/β) was 220 days
  - Given the limited follow-up of some patients, the terminal half-life should be interpreted with caution

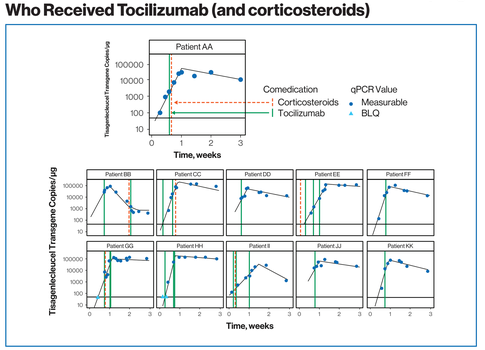
Figure 3. Individual Fits for a Representative Set of Patients Over 12 Months



BLQ, below limit of quantitation; qPCR, quantitative polymerase chain reaction.
Profiles are a subset of data included in the analyses and are reflective of the overall model fitting.

- The model-estimated C_{max} of tisagenlecleucel in patients who required tocilizumab was 2-fold higher than in those who did not require tocilizumab
  - This is consistent with the finding that there is 1.4-fold higher C_{max} in patients with grade 3/4 CRS (P = .006)[4]
- The effect of tocilizumab or corticosteroid comedication on the expansion rate of tisagenlecleucel was F_{toci} = 1.09 (90% CI, 0.81-1.26) and F_{ster} = 1.0 (90% CI, 0.85-1.31)
- No impact on the rate of expansion could be detected
- Individual plots for 11 patients with rich qPCR sampling (≥ 6 qPCR samples in the first 2 weeks and who received their first tocilizumab or steroid dose on day 6 or before) show continued tisagenlecleucel expansion after tocilizumab and corticosteroids (**Figure 4**)

Figure 4. Individual Fits for Patients With Rich qPCR Sampling Who Received Tocilizumab (and corticosteroids)



BLQ, below limit of quantitation; qPCR, quantitative polymerase chain reaction.

Conclusions

- This work represents the first model-based analysis of a CAR T-cell therapy
- The model consistently described aggregate data and individual patient data for the cellular kinetics of tisagenlecleucel
- Patients with higher peak transgene levels were more likely to receive tocilizumab, consistent with prior results based on NCA[4]
- No effect of tocilizumab and corticosteroids on the rate of expansion was observable

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Disclosures

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