

**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW**

Application Number	BLA125643
Submission Date	3/31/2017
Compound	Axicabtagene ciloleucel
Applicant	Kite Pharma
Dosing regimen (route of administration)	A target of 2×10^6 anti-CD19 CAR T cells/kg body weight (range: [REDACTED] (b) (4) [REDACTED] cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T cells.
Indication	Adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT)
Primary PM Reviewer	Chao Liu, Ph.D.
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Signature

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1 SUMMARY OF FINDINGS

- A higher axicabtagene ciloleucel expansion rate and slower declining rate was associated with greater probability of CRS onset and exacerbation. With the same axicabtagene ciloleucel changing rate, a greater axicabtagene ciloleucel concentration was associated with higher probability of CRS onset.
- Patients who had no response to the axicabtagene ciloleucel treatment tended to show a lower exposure (AUC) of axicabtagene ciloleucel at the first month.
- There was no adequate evidence showing that greater axicabtagene ciloleucel persistence was associated with lower risk of disease relapse.

1.1 Consulted Questions

The purpose of this review is to address the following key questions.

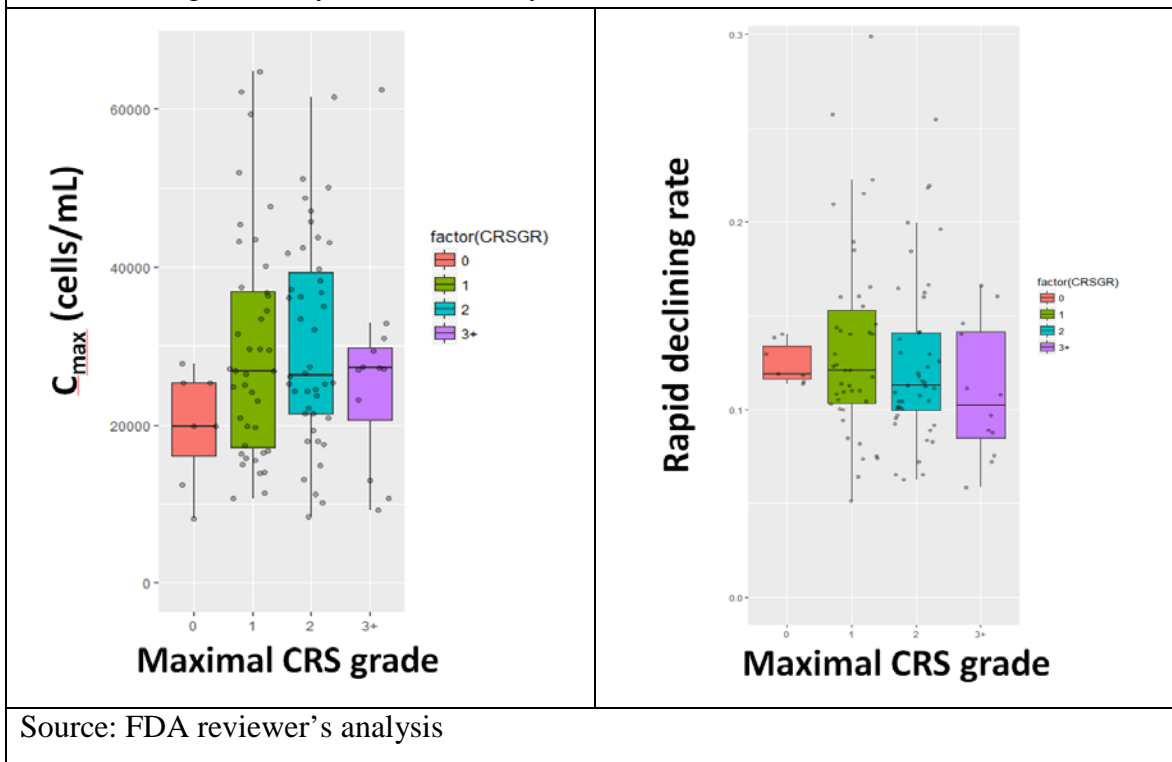
1.1.1 What are the PK characteristics of axicabtagene ciloleucel based on population PK analysis?

A population PK model was developed to characterize the axicabtagene ciloleucel kinetics, where the PK was described by exponential growth followed by biexponential decline. The axicabtagene ciloleucel reached peak concentration at the 5th day post treatment. After then, axicabtagene ciloleucel underwent biexponential decline. The half-lives of the rapid decline (α) and slow decline (β) phases were 3.3 days and 173 days, respectively. An impact of tocilizumab therapy on the rate of expansion was not detected. None of the other covariates explored (including corticosteroid dosing) were confirmed to have an effect.

1.1.2 What is the relationship between axicabtagene ciloleucel kinetics and adverse events?

Cytokine Release Syndrome (CRS) and neurotoxicity were two major types of adverse event in this analysis. For CRS, a positive relationship between axicabtagene ciloleucel concentration and changing rate (expansion as being positive and declining as being negative) was identified. According to the analysis at the subject level, a trend of greater maximal concentration of axicabtagene ciloleucel was associated with the maximal toxicity grade of CRS (**Figure 1**). In addition, slower axicabtagene ciloleucel declining rate was associated with more severe CRS in terms of the maximal toxicity grade.

Figure 1: Comparison of Predicted axicabtagene ciloleucel C_{\max} /rapid declining rate with the maximal grade of cytokine release syndrome



Source: FDA reviewer's analysis

To further quantify the longitudinal relationship between CAR-T and CRS, a first order Markov model was developed to explore the time course of CRS and its relationship with longitudinal axicabtagene ciloleucel exposure. In the first order Markov model, it was assumed that the probability of moving to the following state (grade of adverse event) in the next day depends only on the present state of CRS at the current day and not on the previous states. The following statistically significant relationships between CRS status change and CAR-T kinetics were identified:

- A higher axicabtagene ciloleucel expansion rate was associated with higher probability of CRS onset and exacerbation coming up (**Table 3**).
- A greater declining rate of axicabtagene ciloleucel was associated with higher likelihood of CRS remission in the coming time interval.
- For patients with similar axicabtagene ciloleucel changing rate, greater axicabtagene ciloleucel concentration was associated with higher probability of CRS onset.

With regards to 1) the biological mechanism of CRS and 2) the positive feedback between CRS and axicabtagene ciloleucel kinetics, the causality of the axicabtagene ciloleucel exposure upon CRS should be interpreted with caution.

For neurotoxicity, a Markov model was also developed to explore the time course of neurotoxicity and its relationship with longitudinal axicabtagene ciloleucel exposure. The following statistically significant relationships between neurotoxicity status change and axicabtagene ciloleucel kinetics were identified:

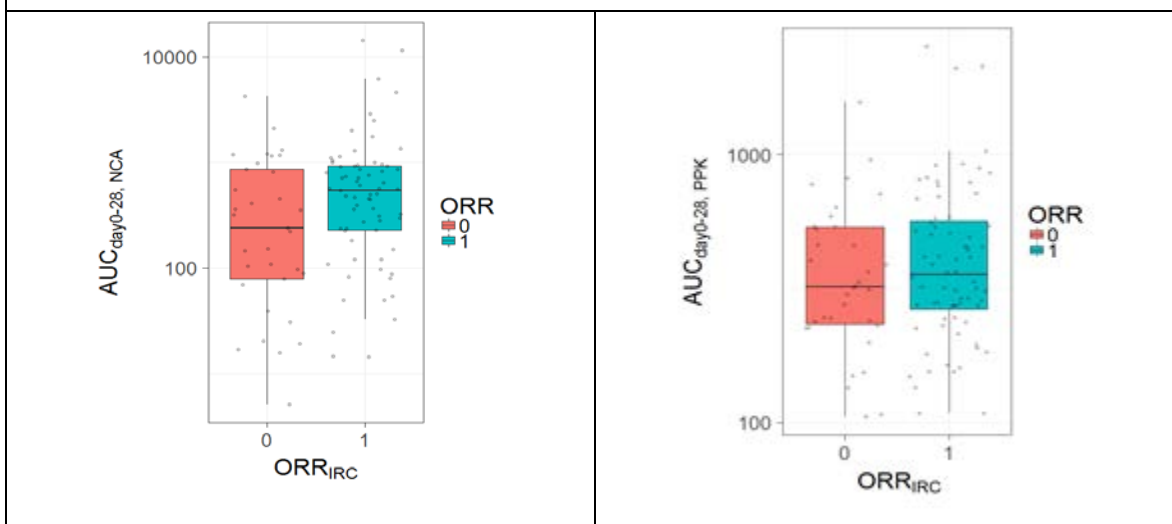
- Axicabtagene ciloleucel number showed a stronger association with neurotoxicity onset and exacerbation compared to CRS. A subject with higher axicabtagene ciloleucel concentration has greater risk of neurotoxicity onset/exacerbation (**Table 4**).
- For patients with similar axicabtagene ciloleucel concentration, a subject who has greater CAR-T expansion rate or slower declining rate tend to show greater risk of neurotoxicity onset or exacerbation

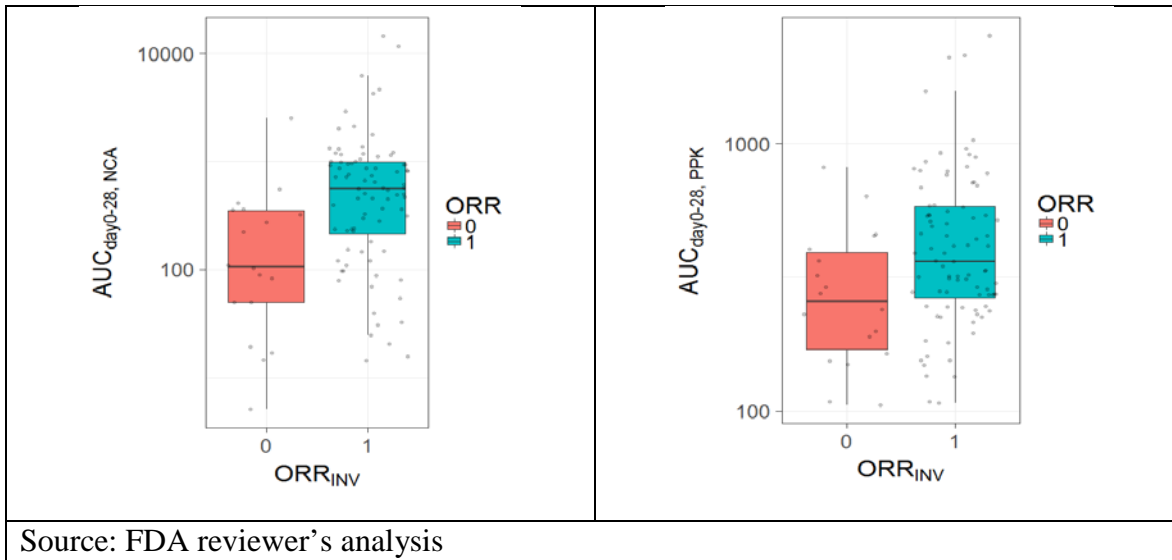
1.1.3 What is the relationship between CAR-T kinetics and efficacy?

Axicabtagene ciloleucel exposure v.s. response:

Two endpoints were chosen: 1) Overall Response Rate per Independent Review Committee (ORR_{IRC}); 2) Overall Response Rate per Investigators (ORR_{INV}). The graphical exploration suggested that patients who had response to the CAR-T treatment tended to show a greater AUC from day 0 to day 28, according to both observed and PPK model predicted CAR-T kinetics (Figure 2). The association between ORR and axicabtagene ciloleucel exposure were more significant for investigator assessed ORR (ORR_{INV}).

Figure 2: Higher axicabtagene ciloleucel exposure at the first month was associated with ORR





Multivariate logistic regression was performed to screen factors associated with overall response rate. About 80 factors measured at baseline were screened.

- For ORR_{INV} , number of prior therapies for study disease and the level of amyloid A were negatively associated with disease response. In addition, patients with higher AUC at the first month showed greater probability of response (Table 7).
- For ORR_{IRC} , none of the factors showed statistically significant correlation with this endpoint. There was a trend that greater AUC at the first month post treatment was correlated with disease response as the graphical analysis showed. The lack of statistical significance could be due to the limited sample size in the analysis (Table 7).

Axicabtagene ciloleucel persistence v.s. duration of response (DOR)

The relationship between axicabtagene ciloleucel persistence and DOR was assessed by PK parameters at subject level, as well as longitudinal axicabtagene ciloleucel exposure. The DOR per independent review (IRC) was employed in the analysis. For subject-level analysis, multivariate Cox proportional hazard model was employed to assess the correlation between axicabtagene ciloleucel PK parameters (e.g. declining rate) and hazard. T cell declining rates (rapid and slow) were not associated with duration of response.

The longitudinal Cox model assessed the relationship between time-varying axicabtagene ciloleucel concentration/slope and its relationship with the risk of relapse/death. Based on the current data collected, the evidence was not strong enough to support the hypothesis that the risk of relapse was associated with lower CAR-T number at the time of disease progression.

Axicabtagene ciloleucel kinetics v.s. progression free survival (PFS):

The longitudinal Cox model was employed where the whole time course of axicabtagene ciloleucel concentration and changing rate (slope) were included in the analysis. A trend that greater hazard (risk of disease progression, relapse and death) associated with lower CAR-T number was suggested. In this analysis, the average concentration of CAR-T over 2 weeks prior to each time interval provided the best data description.

Axicabtagene ciloleucel kinetics v.s. overall survival (OS):

The relationship between CAR-T kinetics and overall survival was explored using a time-varying Cox proportional hazards model. There is a trend that lower axicabtagene ciloleucel concentration is associated with higher risk of death. However, these results should be interpreted with caution because most of the PK profile was extrapolated at the time of death or censoring.

In summary, a trend that non-responders had slower CAR-T expansion and greater exposure at the first month was observed. On the other hand, there were no evident relationship between T cell persistence and disease relapse.

1.1.3 Dose the co-medication of tocilizumab or corticosteroid impact the CAR-T cell expansion?

No. The impact of the co-medication of tocilizumab and corticosteroid was evaluated by the population PK analysis. The model assessed whether the CAR-T cell expansion rate changed following tocilizumab or corticosteroid administration. The impact of the co-medication of tocilizumab and corticosteroid upon CAR-T expansion is mild and not statistically significant. It should be highlighted that patients who ever received tocilizumab or corticosteroid showed greater AUC as compared with the ones who did not receive them. This may not be evidence that concomitant medication affects the CAR-T cell expansion, because patients who received these drugs tended to have more severe CRS, which leads to greater CAR-T cell expansion.

2 RESULTS OF REVIEWER'S ANALYSIS

2.1 Introduction

The reviewer initiated an independent analysis to investigate the consulted questions by the review team, which mainly focused on describing the pharmacokinetics of CAR-T, as well as the relationship between CAR-T kinetics and safety or efficacy endpoints.

2.2 Objectives

- Develop a population PK model to describe the axicabtagene ciloleucel kinetics
- Investigate where there are changes in the rate of axicabtagene ciloleucel transgene expansion after tocilizumab or corticosteroids are given.
- Develop a longitudinal CRS model and assess the relationship with CAR-T kinetics
- Develop survival models for DOR, EFS and OS, and assess the relationship with time course of CAR-T.
- Evaluate other factors at subject level which may be associated with CRS, ORR, EFS, DOR and OS.

2.3 Population PK analysis

2.3.1 Data

This analysis includes data from two studies: ZUMA-1 and 09-C-0082. Because 1) nonlinear mixed effect modeling methods are designed to work with sparse data and 2) the purpose was to characterize the cellular kinetics, all patients with cellular kinetic data were included in this analysis, regardless of whether the patients had available primary efficacy endpoint evaluated.

Table 1: Summary of Studies included in Population PK Analysis

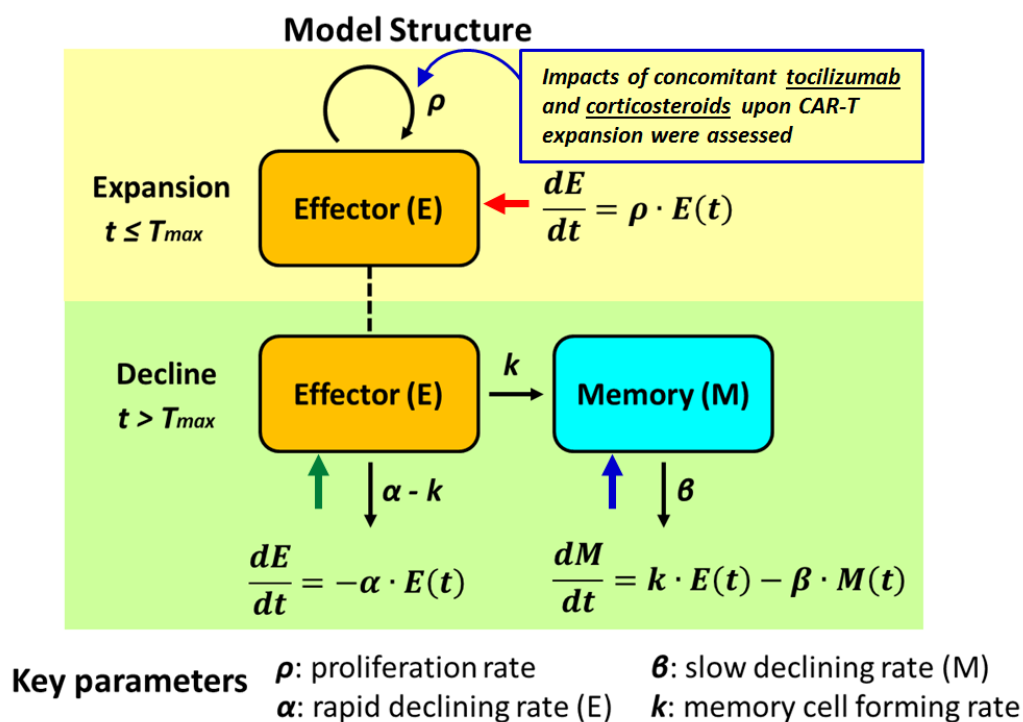
	KTE-C19-101 (ZUMA-1)	NCI 09-0082
Phase	1/2	1
Study design	Open-label safety and efficacy; multicenter	Open-label safety and feasibility dose escalation; single center
Study population	Refractory DLBCL, PMBCL, and TFL Phase 1: DLBCL, PMBCL, and TFL Phase 2: Cohort 1: DLBCL Cohort 2: PMBCL and TFL	Relapsed/refractory NHL (DLBCL, PMBCL, TFL, FL, MCL) and CLL Cohorts 11 through 14: DLBCL, TFL, and PMBCL
Analysis population	Phase 1 N = 7 Phase 2, Cohorts 1 and 2 N = 101	Cohorts 11 through 14 N = 13
Study objectives	Phase 1: Primary: To evaluate the safety of axicabtagene ciloleucel regimens Phase 2: Primary: To evaluate the efficacy of axicabtagene ciloleucel as measured by ORR in subjects with aggressive NHL; namely DLBCL, PMBCL, and TFL Secondary: To assess the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints	Primary: To determine safety and feasibility of the administration of cryopreserved anti-CD19 CAR T cells following a nonmyeloablative conditioning chemotherapy regimen in subjects with B-cell malignancies Secondary: To determine the in vivo survival of the anti-CD19 CAR T cells and to determine whether the treatment regimen can cause regression of B-cell malignancies

Source: Applicant's summary of clinical pharmacology studies

2.3.2 Model structure

The cellular kinetic profile showed that the axicabtagene ciloleucel cells undergo an exponential expansion at rate ρ until time T_{max} , followed by a bi-exponential decline at rates α (initial slope) and β (terminal slope). The structural model that describes this profile was based on a published model that was used to describe the murine immune response to an infection by listeria monocynogenes or lymphocytic choriomeningitis virus, where similar profiles were observed [1].

Figure 3: Structure of the population PK model



2.3.3 Results

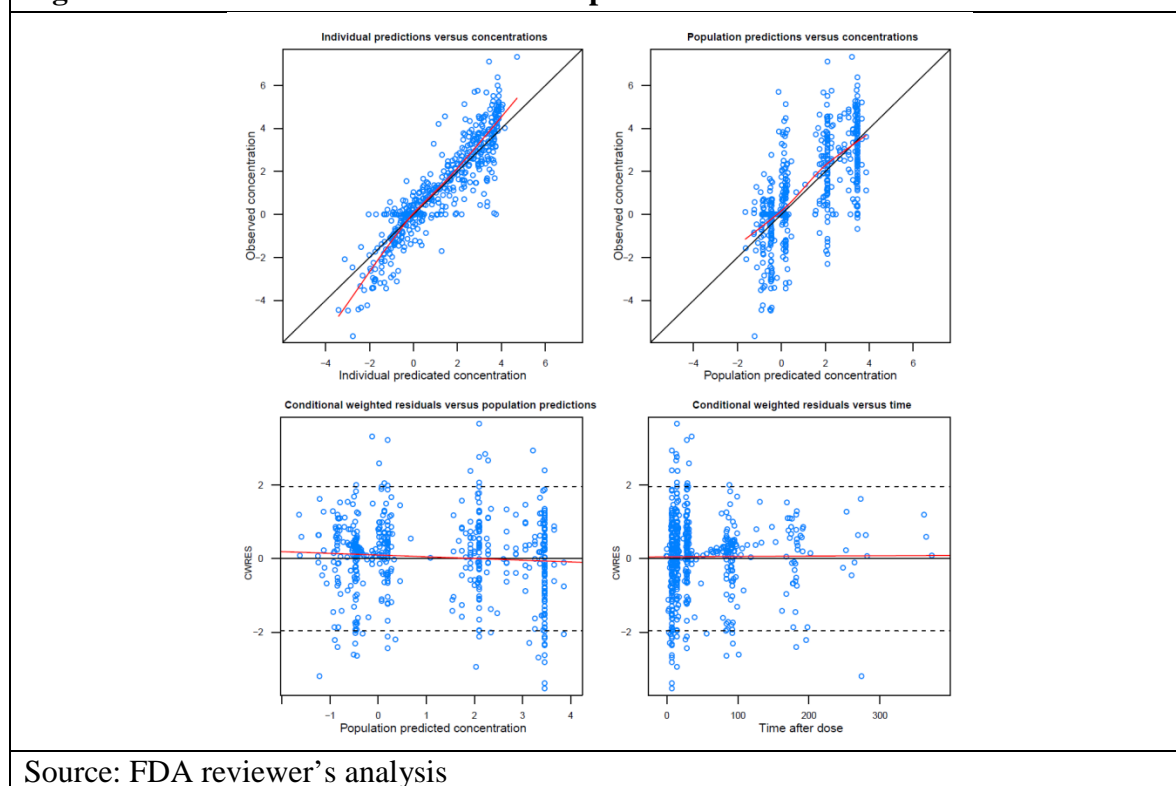
The final model parameters are provided in **Table 2**. The α and β half-lives was computed by using equation $\ln(2)/\text{rate}$ and it was found that $t_{1/2-\alpha} = 3.3$ days and $t_{1/2-\beta} = 173$ days. The $t_{1/2-\beta}$ estimate however should be interpreted with caution as the median follow-up time was only 93 days.

Table 2: Parameter estimates of the final population PK model

Parameter	Description	Estimate
C_{\max}	Maximal axicabtagene ciloleucel concentration (cells/ μ L)	48.2
FB	Fraction of axicabtagene ciloleucel that decline slowly	0.018
F_{toci}	Tocilizumab effect on expansion rate	0.96
F_{ster}	Corticosteroids effect on expansion rate	0.92
α	Rapid decline rate (day^{-1})	0.21
β	Gradual decline rate (day^{-1})	0.004
Foldx	Fold expansion from baseline	50.9
T_{\max}	Time of maximal axicabtagene ciloleucel concentration (day)	4.92

Source: FDA reviewer's population PK analysis

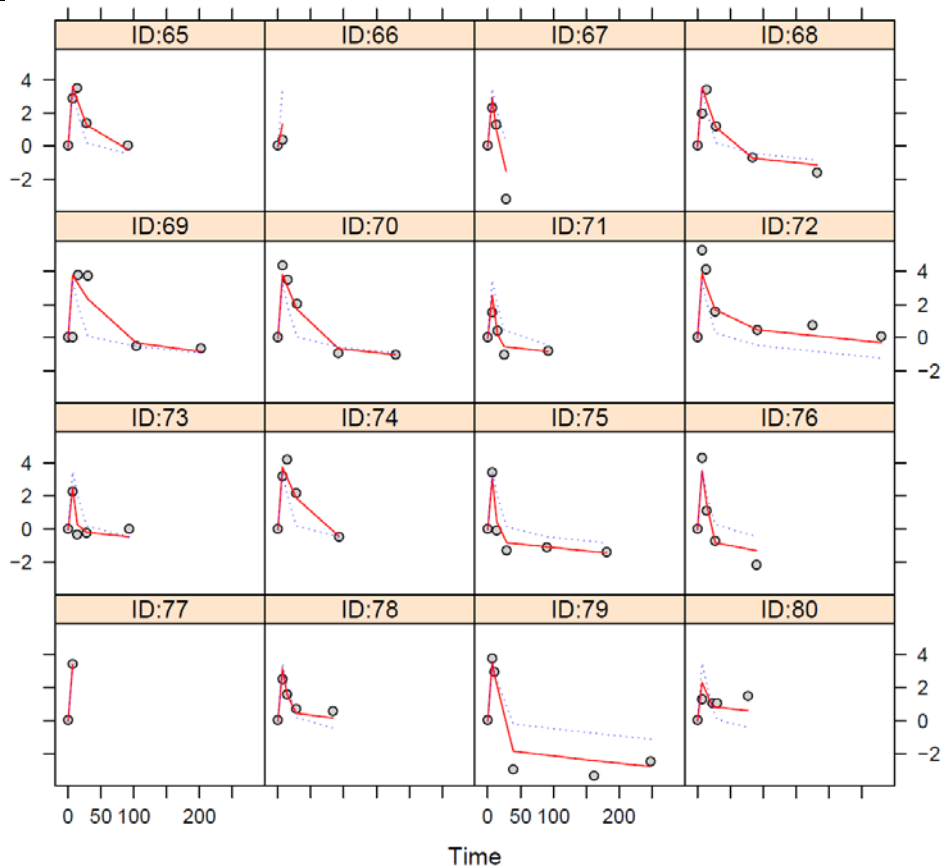
The diagnostic plots for the PPK model are provided in **Figure 4**. The individual plot shows the predicted tumor size based on post-hoc parameters is able to capture the observed axicabtagene ciloleucel concentration reasonably well. Conditional weighted residuals versus predicted axicabtagene ciloleucel PK or time demonstrated no clear trends or biases.

Figure 4: Goodness of Fit Plots for the Population PK Model

Source: FDA reviewer's analysis

The individual plot shows the predicted axicabtagene ciloleucel PK based on *post-hoc* parameters is able to capture the observed axicabtagene ciloleucel PK reasonably well (Figure 5).

Figure 5: Axicabtagene ciloleucel PK (log scale) versus Time by ID



Source: FDA reviewer's analysis

Patients that received tocilizumab had a 2-fold higher $AUC_{\text{day 0-28}}$. This is thought to be because patients with greater axicabtagene ciloleucel expansions/slower declines are more likely to develop Grade 3 and 4 cytokine release syndrome and therefore are more likely to require tocilizumab therapy. An impact of tocilizumab therapy on the rate of expansion was not detected. None of the other covariates explored (including corticosteroid dosing) were confirmed to have an effect. However, care should be taken when interpreting the lack of effect of tocilizumab or corticosteroids. PK data during the T cell expansion phase were relatively limited, which may not be adequate to fully detect the impact of concomitant medication upon T cell kinetics.

2.3.4 Longitudinal exposure-CRS Model

The longitudinal exposure-CRS analyses were based on data from Study ZUMA-1. The CRS were treated as ordered categorical (grades 0, 1/2, 3/4/5), and an extension of the proportional odds model was used to describe the probability and severity of CRS over time. (Figure 6)

Figure 6: Data structure for CAR-T kinetics vs. longitudinal CRS

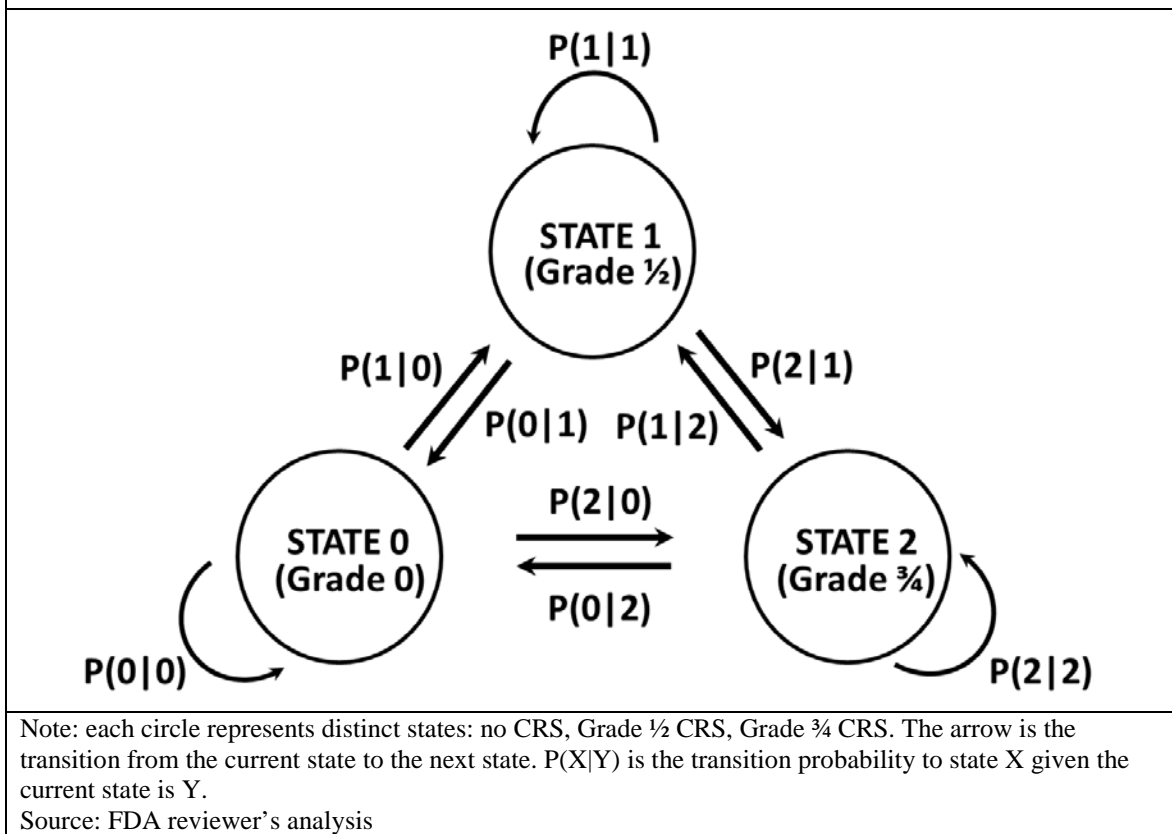


Note: The round dots represent the observed CAR-T concentration; the dashed lines are model predicted CAR-T kinetics; the color areas are the time intervals where AE occurred, different AE grades are represented by distinct colors: green, 1st grade AE; blue, 2nd grade AE; orange, 3rd grade AE; red, 4th grade AE; purple, 5th grade AE.

Source: FDA reviewer's analysis

The extension included a first-order Markov model to condition the probability of transition between different severities based on the preceding one. This accounts for the likely association between the severity of the adverse effects between one time point and another. Logit transformations were used to constrain the estimated probabilities to values between 0 and 1, and the function describing the probability of transition from state $s^{(n)}$ to grade $s^{(m)}$ for the i^{th} patient at the j^{th} time interval was given the structure shown in Figure 7.

Figure 7: Model structure for CAR-T kinetics vs. longitudinal adverse events



The logit model was of the form:

$$\text{Logit}\left(P_{(ijs^{(m)}|s^{(n)})}\right) = \log\left(\frac{P_{(ijs^{(m)}|s^{(n)})}}{1 - P_{(ijs^{(m)}|s^{(n)})}}\right) = f_{s^{(m)}|s^{(n)}} + \eta_i$$

$$f_{s^{(m)}|s^{(n)}} = B_{s^{(m)}|s^{(n)}} + \beta_{1|s^{(n)}} \cdot \log(CART) + \beta_{2|s^{(n)}} \cdot SLP_{\log(CART)}$$

where $P_{(ijs^{(m)}|s^{(n)})}$ is the transition probability from $s^{(n)}$ to $s^{(m)}$. $B_{s^{(m)}|s^{(n)}}$ is a baseline logit from state $s^{(n)}$ to $s^{(m)}$, $\beta_{1|s^{(n)}} \cdot \log(CART)$ is the effect of log-transformed CAR-T concentration modeled as being linear; $\beta_{2|s^{(n)}} \cdot SLP_{\log(CART)}$ the effect of CAR-T changing rate at logarithm scale. η is the subject-specific random effect. The parameter estimates, precision of the estimate, and 95% confidence interval for sponsor's model are shown in the Table 3:

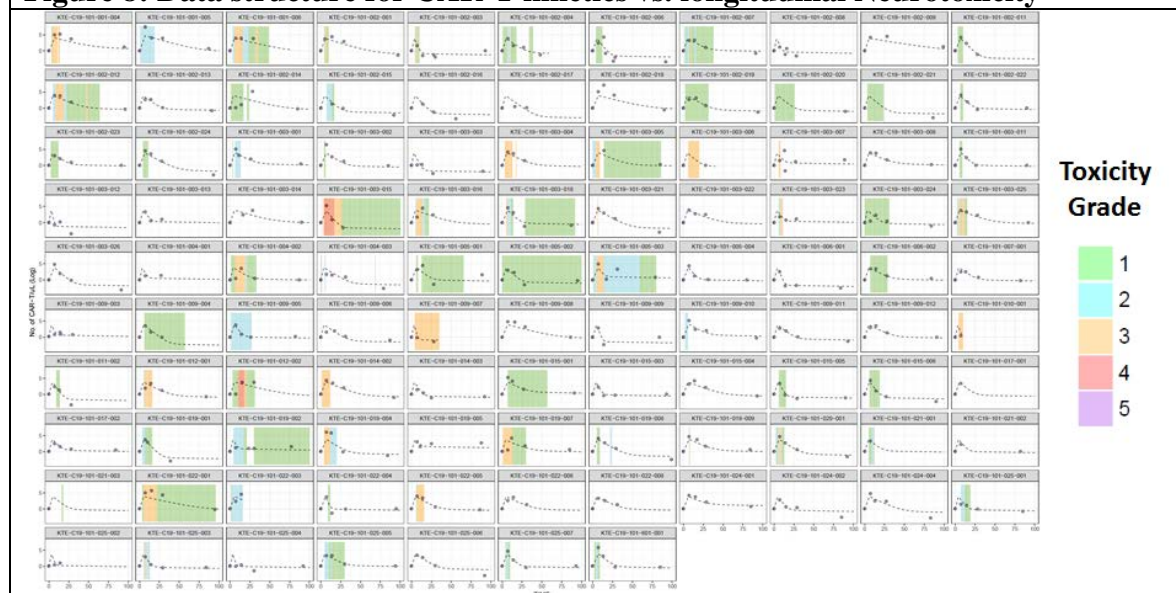
Table 3: Parameter estimates for Markov exposure - CRS model

Parameter	Estimate	Relative SE	95% CI
$B_{1 0}$	-6.75	6.90%	-7.669 - -5.831
$B_{2 0}$	-1.48	14.50%	-1.899 - -1.061
$B_{1 1}$	2.38	10.30%	1.898 - 2.862
$B_{2 1}$	-6.26	6%	-6.993 - -5.527
$B_{1 2}$	1.74	7.90%	1.47 - 2.01
$B_{2 2}$	-0.181	44.80%	-0.34 - -0.022
$\beta_{slp 0}$	5.62	17.80%	3.66 - 7.58
$\beta_{slp 1}$	1.33	18%	0.862 - 1.798
$\beta_{slp 2}$	1.47	31.20%	0.57 - 2.37
$\beta_{CAR-T 0}$	0.629	14.90%	0.445 - 0.813
$\beta_{CAR-T 1}$	-0.199	44.40%	-0.372 - -0.026
$\beta_{CAR-T 2}$	0 FIX	—	—

2.3.5 Longitudinal exposure-Neurotoxicity Model

The longitudinal exposure-neurotoxicity analyses were conducted based on data from Study ZUMA-1. All AEs related with neurotoxicity were treated as ordered categorical (grades 0, 1/2, 3/4/5). The AE toxicity grade was determined by highest score of neuro-related AEs at each day (**Figure 8**).

Figure 8: Data structure for CAR-T kinetics vs. longitudinal Neurotoxicity



Note: The round dots represent the observed CAR-T concentration; the dashed lines are model predicted CAR-T kinetics; the color areas are the time intervals where AE occurred, different AE grades are represented by distinct colors: green, 1st grade AE; blue, 2nd grade AE; orange, 3rd grade AE; red, 4th grade AE; purple, 5th grade AE.

Source: FDA reviewer's analysis

Similar to the analysis for E-R for CRS analysis, an extension of the proportional odds model with first-order Markov model was used to describe the probability and severity of neurotoxicity over time. The parameter estimates, precision of the estimate, and 95% confidence interval for sponsor's model are shown at Table 4:

Table 4: Parameter estimates for Markov exposure – neurotoxicity model

Parameter	Estimate	Relative SE	95% CI
$B_{1 0}$	-6.91	4.20%	-7.473 - -6.347
$B_{2 0}$	-1.77	15.30%	-2.301 - -1.239
$B_{1 1}$	2.15	18%	1.393 - 2.907
$B_{2 1}$	-8.45	5.90%	-9.428 - -7.472
$B_{1 2}$	2.87	10.10%	2.302 - 3.438
$B_{2 2}$	-1	23.70%	-1.465 - -0.535
$\beta_{slp 0}$	1.92	24.20%	1.011 - 2.829
$\beta_{slp 1}$	1.61	37.60%	0.422 - 2.798
$\beta_{slp 2}$	0 FIX	—	—
$\beta_{CAR-T 0}$	1.17	8.50%	0.975 - 1.365
$\beta_{CAR-T 1}$	0.611	25.40%	0.307 - 0.915
$\beta_{CAR-T 2}$	0 FIX	—	—

2.3.6 Longitudinal exposure-TTE (time to event) Analysis

FDA reviewer developed Cox proportional hazards models to evaluate the relationship between CAR-T exposure and multiple time to event efficacy endpoints, including progression free survival (PFS), overall survival (OS), and duration of response (DOR), based on the data collected from ZUMA-1. Various CAR-T time-varying exposure measures were evaluated as shown in the Table 5.

Table 5: Time-varying axicabtagene ciloleucel exposure metrics in the TTE analysis

Exposure Metrics	Definition
Cavg1D	Average CAR-T concentration over prior one day at each day
Cavg1W	Average CAR-T concentration over prior one week at each day
Cavg10D	Average CAR-T concentration over prior ten days at each day
Cavg2W	Average CAR-T concentration over prior two weeks at each day
Cavg3W	Average CAR-T concentration over prior three weeks at each day
Cavg4W	Average CAR-T concentration over prior four weeks at each day
Cavg6W	Average CAR-T concentration over prior six weeks at each day
CavgT	Average CAR-T concentration from the first exposure to each day

The Cox model was specified as:

$$h(t, X'_{ex}(t)) = h_o(t) \cdot \exp(\beta_{ex2} \cdot X'_{ex}(t))$$

where $X_{ex}(t)$ is the CAR-T exposure measure which may vary with t, β_{ex2} represents the slope of CAR-T concentration or changing rate. The selection of the time-varying CAR-T exposure metrics as shown in Table 5 was based on Akaike information criterion (AIC) and biological plausibility. Both linear and log-linear models were estimated. The model parameter estimates for these models are illustrated at Table 6.

Table 6: Parameter Estimates for Exposure - TTE Model

Endpoint	Parameter	Scale	Estimate	SE	P-value
DOR	β_{cavg4w}	Linear	0.9	0.421	0.032
	$\beta_{slp(CAR-T)}$		321	131	0.014
	β_{cavg1w}	Logarithm	-0.462	0.233	0.047
	$\beta_{slp(CAR-T)}$		48.9	52.6	0.353
PFS	β_{cavg2w}	Linear	-0.161	0.076	0.034
	$\beta_{slp(CAR-T)}$		0.0005	0.079	0.079
	$\beta_{cavg10d}$	Logarithm	-0.336	0.148	0.023
	$\beta_{slp(CAR-T)}$		1.668	2.225	0.454
OS	β_{cavg2w}	Linear	-0.175	0.141	0.212
	$\beta_{slp(CAR-T)}$		-0.079	0.127	0.534
	$\beta_{cavg10d}$	Logarithm	-0.189	0.193	0.328
	$\beta_{slp(CAR-T)}$		4.440	3.689	0.229

2.3.7 Regression analysis at subject level for ORR, DOR, PFS and OS

About 80 factors were screened for the regression analysis. Due to the relevantly large number of covariates, univariate analysis was performed to minimize the impact of missing values. The factors selected will serve as the candidates for the following multivariate analysis. ORR was treated as dichotomous and analyzed using logistic model. Time to event endpoints like PFS, DOR or OS were analyzed using Cox proportional hazard model.

In the univariate analysis, the significance level was selected at 0.05 and no overall type I error control was performed at this stage. It is important to note that this is an exploratory analysis based on a small number of patients. The goal of the analysis is to identify some associations that may warrant further exploration.

Based on the covariates selected in the univariate analysis, multivariate analysis was performed to reduce the redundancy of the covariates selected. Stepwise selection was

performed out of the candidate covariates as chosen in the univariate analysis. The selection was based on AIC, a tradeoff between the accuracy of the predicted outcomes and the number of independent variables included in the model, and biological plausibility. The model parameter estimates for these models are shown in Table 7.

Table 7: Parameter Estimates for Regression Analysis

Endpoint	Covariate	Estimate	SE	P-value
ORR _{IRC}	—	—	—	—
ORR _{INV}	No. of prior chemotherapy regimen	-0.691	0.249	0.005
	Amyloid A	-1.845E-09	8.1E-10	0.023
DOR	Presence of B symptoms	1.576	0.568	0.005
	Splenic involvement	1.83	1.022	0.073
PFS	Amyloid A	-1.26E-09	4.53E-10	0.005
	Bcl6 alterations/overexpression	-1.18	0.329	0.0003
	IL2 receptor alpha	5.99E-05	2.36E-05	0.011
OS	IL2 receptor alpha	5.98E-05	2.84E-05	0.0356
	International Prognostic Index (IPI)	0.38	0.23	0.09
	No. of prior chemotherapy regimen	0.39	0.15	0.007
	IL10	0.059	0.021	0.0058
	IL12	1.57	0.618	0.011
	VEGFD	5.75E-04	3.38E-04	0.0885

FDA reviewer's comments: As sample size was very limited and no overall alpha was adjusted, this analysis may have low power and high probability of type I error. Thus, these results from regression analysis should be interpreted with caution.

3 REFERENCES

[1] De Boer RJ, Perelson, AS. Quantifying T lymphocyte turnover. *Journal of Theoretical Biology*, 327, 45-87, 2013.