Poster
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Prediction of Early Onset Cytokine Release Syndrome and Neurologic Events after Axicabtagene Ciloleucel in Large B-Cell Lymphoma Based on Machine Learning Algorithms

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BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of adult patients with relapsed/refractory large B-cell lymphoma (LBCL) after ≥2 prior lines of systemic therapy[1]
- In the ZUMA-1 (NCT02348216) multicenter, single-arm, registrational, Phase 1/2 study of axi-cel in patients with refractory LBCL, with a median follow-up of 27.1 months (n=101; pivotal Cohorts 1+2)[2]:
  - 83% Objective response rate (58% complete response rate) was seen
  - Grade ≥3 cytokine release syndrome (CRS) and neurologic events (NEs) were reported in 11% and 32% of patients, respectively
- In the long-term follow-up analysis of ZUMA-1 recently presented here at ASH 2021, the 5-year overall survival rate was 43% after a median follow-up of 63 months[3]
- CRS and NEs associated with CAR T-cell therapy required inpatient management in ZUMA-1, per protocol[4]
- Some axi-cel–treated patients have early, while others have late onset of CRS and NEs,[5] warranting distinct monitoring and management approaches
- Several exploratory safety management cohorts were added to ZUMA-1 to minimize treatment-related toxicity
  - Cohort 4, which evaluated levetiracetam (anticonvulsant) prophylaxis and earlier corticosteroid and tocilizumab (anti–interleukin-6 receptor antibody) intervention, demonstrated a reduced incidence of Grade ≥3 CRS and NEs[6]
  - Cohort 6, which assessed the impact of adding prophylactic corticosteroids to the Cohort 4 toxicity management regimen, demonstrated no cases of Grade ≥3 CRS, delayed CRS onset, and generally similar NE toxicity compared with pivotal Cohorts 1+2[7]

OBJECTIVE

- To develop a predictive signature for early onset acute toxicities (within 3–4 days after axi-cel) based on machine learning algorithms from ZUMA-1 data, which could facilitate toxicity management in a real-world setting

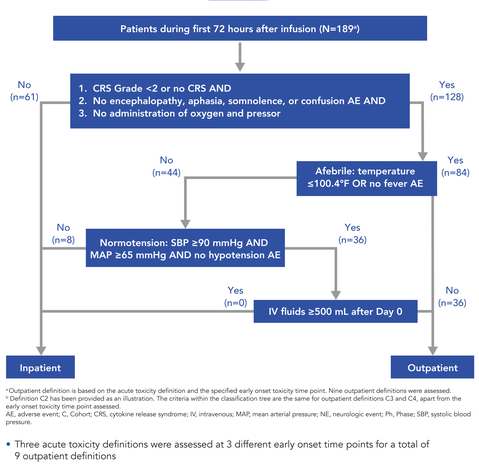
METHODS

- This post hoc analysis included patients from ZUMA-1 Phase 1 and Phase 2 Cohorts 1, 2, 4, and 6
  - Testing and training
    - Cohorts 1, 2, and 4
  - Validation
    - Data from patients from ZUMA-1 Phase 2 Cohort 6[7] were included to validate the best-performing model generated using training data
  - Patients in Phase 1 and Phase 2 Cohorts 1 and 2 had ≥2 years of follow-up; patients in Cohort 4 and Cohort 6 had ≥6 months of follow-up

Figure 1. Outpatient Definitions

Definition[a]	Early Onset Toxicity Time Point	Acute Toxicity Definition	No. of Patients Meeting Outpatient Definition (n [%])	
			Ph1 and Ph2 C1, 2, and 4 (N=149)	Ph2 C6 (N=40)
A2	Day 0 to 2	Patients with worst Grade ≤1 CRS and no NEs	88 (59)	37 (93)
A3	Day 0 to 3		72 (48)	33 (83)
A4	Day 0 to 4		57 (38)	26 (65)
B2	Day 0 to 2	Patients with no CRS or NEs	41 (28)	34 (85)
B3	Day 0 to 3		31 (21)	27 (68)
B4	Day 0 to 4		23 (15)	15 (38)
C2	Day 0 to 2	**Definition C** (see schematic) Patients identified by AE, vital signs, and intervention	84 (56)	36 (90)
C3	Day 0 to 3		64 (43)	32 (80)
C4	Day 0 to 4		50 (34)	24 (60)

Definition C2[b]

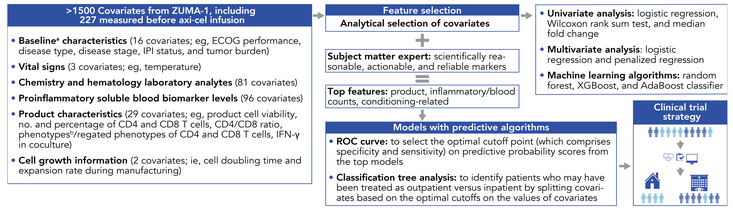


[a] Outpatient definition is based on the acute toxicity definition and the specified early onset toxicity time point. Nine outpatient definitions were assessed.
[b] Definition C2 has been provided as an illustration. The criteria within the classification tree are the same for outpatient definitions C3 and C4, apart from the early onset toxicity time point assessed.
AE, adverse event; C, Cohort; CRS, cytokine release syndrome; IV, intravenous; MAP, mean arterial pressure; NE, neurologic event; Ph, Phase; SBP, systolic blood pressure.

- Three acute toxicity definitions were assessed at 3 different early onset time points for a total of 9 outpatient definitions

METHODS *(continued)*

Figure 2. Outpatient Data and Predictive Strategy



[a] The baseline value is defined as the last value measured prior to conditioning chemotherapy. [b] Phenotypes include the number and percentage of naïve memory T cells, central memory T cells, effector T cells, effector memory T cells, naïve + central memory T cells, effector + effector memory T cells.
Axi-cel, axicabtagene ciloleucel; ECOG, Eastern Cooperative Oncology Group; IFN, interferon; IPI, International Prognostic Index; ROC, receiver operating characteristic.

- For the model development, patient data were randomly divided into training (70%) and testing (30%) sets
- Machine learning algorithms were applied to 3 categories of covariates:
  - Clinical (eg, tumor-related [lactate dehydrogenase level, burden], disease stage, blood cell counts, analytes related to cells [hemoglobin], and analytes related to metabolic status)
  - Mechanistic (eg, product attributes and inflammatory blood biomarkers)
  - Hybrid category that integrated both clinical and mechanistic covariates

RESULTS

Table 1. Summary of Clinical Covariates With Predictive Potential at Baseline and Day 0 and Clinical Model Performance

Patient/Tumor Characteristics	Blood Chemistry		Blood Cells		Inflammatory Markers
	Altered Disease-Related Metabolic and Hematologic State				Inflammatory State
Baseline	Baseline	Day 0	Baseline	Day 0	Day 0
Bulky disease	Urate	Albumin	RBCs	RBCs	Ferritin
	Calcium		WBCs	Hemoglobin	
	Phosphate		Neutrophils		
	Creatinine		Basophils		
	Chloride				
	LDH				

Outpatient Definition	A2	B2	C2	A3	B3	C3	A4	B4	C4
Training AUC	0.990	0.887	0.929	0.861	1.000	0.855	1.000	0.978	1.000
Testing AUC	0.659	0.636	0.657	0.624	0.673	0.583	0.690	0.757	0.699

Covariates that are positively and negatively associated with all 9 outpatient definitions are shown in blue and red, respectively. Covariates that had different association directions across the 9 outpatient definitions are shown in black. Baseline assessments were those last collected prior to conditioning chemotherapy, and Day 0 assessments were those collected prior to axi-cel infusion on the day of infusion. Models that make predictions that are 100% correct have AUC values equal to 1.
AUC, area under the curve; LDH, lactate dehydrogenase; RBC, red blood cell; WBC, white blood cell.

Table 2. Summary of Hybrid Covariates With Predictive Potential at Baseline and Day 0 and Hybrid Model Performance

Product Attributes	Patient/Tumor Characteristics	Blood Chemistry		Blood Cells		Inflammatory Markers	
"Fit" Product	Altered Disease-Related Metabolic and Hematologic State					Inflammatory State	
	Baseline	Baseline	Day 0	Baseline	Day 0	Baseline	Day 0
Cell viability	Bulky disease	Urate	Albumin	RBCs	RBCs	IL-17	IL-15
		Calcium		WBCs	Hemoglobin		CCL2
		Phosphate		Neutrophils			Ferritin
Total cells		Creatinine		Basophils			
		Chloride					
		LDH					

Outpatient Definition	A2	B2	C2	A3	B3	C3	A4	B4	C4
Training AUC	0.930	0.948	0.757	0.945	0.988	0.879	0.831	1.000	0.897
Testing AUC	0.716	0.779	0.715	0.712	0.684	0.647	0.777	0.748	0.668

Covariates that are positively and negatively associated with all 9 outpatient definitions are shown in blue and red, respectively. Covariates that had different association directions across the 9 outpatient definitions are shown in black. Baseline assessments were those last collected prior to conditioning chemotherapy, and Day 0 assessments were those collected prior to axi-cel infusion on the day of infusion. Models that make predictions that are 100% correct have AUC values equal to 1.
AUC, area under the receiver operating characteristic curve; CCL, chemokine ligand; IL, interleukin; LDH, lactate dehydrogenase; RBC, red blood cell; WBC, white blood cell.

Table 3. Summary of Hybrid Covariates With Predictive Potential at Baseline and Day 0 and Performance of Minimalistic Hybrid Model and Minimalistic Mechanistic Model

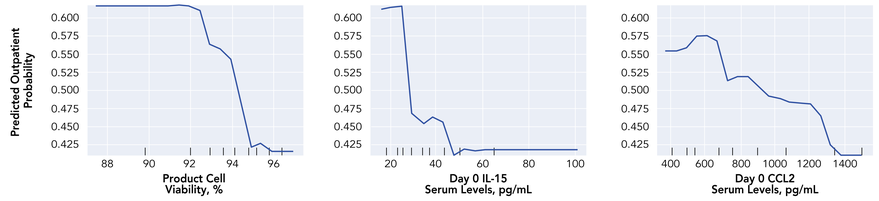
Product Attributes	Blood Chemistry	Blood Cells	Inflammatory Markers
Baseline	Baseline	Day 0	Day 0
Cell viability	Urate	RBCs	IL-15
	Calcium		CCL2

Model	Outpatient Definition	A2	B2	C2	A3	B3	C3	A4	B4	C4
Minimalistic hybrid model (6 covariates)	**Training AUC**	0.867	0.914	0.839	0.854	0.873	0.785	0.899	1.000	0.903
	Testing AUC	0.737	0.669	0.633	0.736	0.688	0.770	0.741	0.878	0.638
Minimalistic mechanistic model (Cell viability + IL-15 + CCL2)	**Training AUC**	0.963	0.864	0.695	0.803	0.998	0.773	0.790	0.859	0.860
	Testing AUC	0.719	0.736	0.609	0.750	0.757	0.766	0.808	0.752	0.620

Covariates that are positively and negatively associated with all 9 outpatient definitions are shown in blue and red, respectively. Baseline assessments were those last collected prior to conditioning chemotherapy, and Day 0 assessments were those collected prior to axi-cel infusion on the day of infusion. Models that make predictions that are 100% correct have AUC values equal to 1.
AUC, area under the receiver operating characteristic curve; CCL, chemokine ligand; IL, interleukin; RBC, red blood cell.

- Multivariate analysis and machine learning algorithms led to several comparable predictive models for early onset CRS or NEs (best-performing models with receiver operating characteristic (ROC). ROC AUC >0.8 in training and >0.7 in testing; **Tables 1–3**)
- The covariates in best-performing models included product cell viability, centrally measured Day 0 (pre–axi-cel treatment) IL-15 and CCL2 serum levels and locally measured blood cell counts, blood chemistry analytes, tumor burden, and serum lactate dehydrogenase level (**Tables 1–3**)
- Minimalistic hybrid model (6 covariates) and minimalistic mechanistic model (Cell viability + IL-15 + CCL2) performed comparably with larger models (**Table 3**)

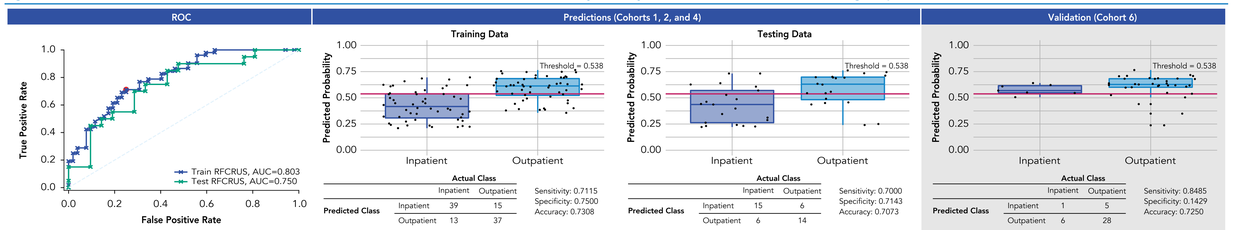
Figure 3. Three Mechanistic Covariates Using Outpatient Definition A3 Were All Positively Associated With Early Onset Toxicities



Covariate	Estimated Coefficient	Associated *P* Value
Product cell viability	–.225	.0068
Day 0 IL-15 serum levels	–.00549	.568
Day 0 CCL2 serum levels	–.00134	.0307

Partial dependence plot is based on random forest analysis. Estimated coefficients and P values are from logistic regression.
CCL, chemokine ligand; IL, interleukin.

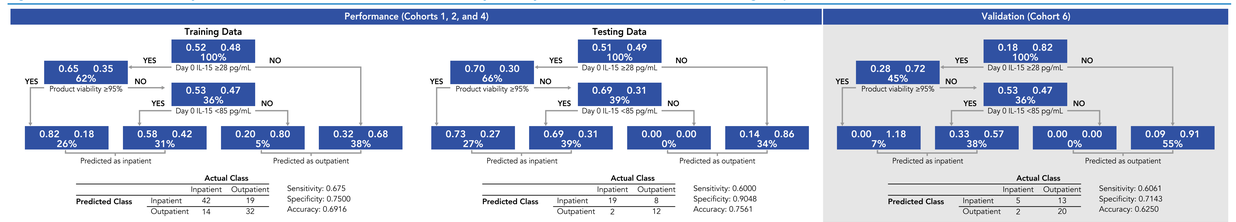
Figure 4. ROC and Cutoff Selection on Predicted Score From a 3-Covariate Model (Product Cell Viability and Day 0 IL-15 and CCL2 Serum Levels) Using Outpatient Definition A3



The red dot on the ROC plot represents the corresponding sensitivity and specificity in training. The true positivity rate (sensitivity) was 0.7115, and the false positive rate (1-specificity) was 0.2500.
CCL, chemokine ligand; IL, interleukin; ROC, receiver operating characteristic.

- A 3-covariate mechanistic model (product cell viability and Day 0 interleukin-15 [IL-15] and CCL2 serum levels) based on outpatient definition A3 performed comparably (ROC AUC >0.7 in testing) to larger best-performing models

Figure 5. Classification Tree Analysis From a 3-Covariate Model (Product Cell Viability and Day 0 IL-15 and CCL2 Serum Levels) Using Outpatient Definition A3



CCL, chemokine ligand; IL, interleukin.

- Classification trees of training and testing datasets with splitting based on Day 0 IL-15 and product cell viability showed a potential to categorize patients by early versus late onset of toxicities (specificity ≥0.75 in training and testing)
- Models based on data from Cohort 6 did not recapitulate performance of those models optimized using data from ZUMA-1 Phase 1 and Phase 2 Cohorts 1, 2, and 4 (**Figure 4** and **Figure 5**)

CONCLUSIONS

- Machine learning algorithms applied to covariates measured before axi-cel infusion yielded predictive models for early onset CRS or NEs that can be used for toxicity prediction, monitoring, and management
- High performing hybrid (ie, integrated mix of clinical and mechanistic covariates) or mechanistic models corroborated the importance of T-cell viability (product cell fitness) and conditioning-related elevation of factors (IL-15 and CCL2) in influencing toxicities
- Although the validation on Cohort 6 (prophylactic and earlier utilization of corticosteroids and/or tocilizumab) did not entirely recapitulate the performance of the best-performing models generated on previous cohorts where patients were managed differently, the overall analysis confirmed the importance of covariates uncovered in this study, paving the way for predictive algorithms in the real-world setting

REFERENCES

1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2021.
2. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42.
3. Jacobson C, et al. ASH 2021. Poster #1764.
4. Locke FL, et al. *Mol Ther*. 2017;25:285-295.
5. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544.
6. Topp M, et al. *Blood*. 2019;134(suppl_abstr):243.
7. Oluwole OO, et al. *Br J Haematol*. 2021;194:690-700.

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