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Predictors and implications of renal injury after CD19 chimeric antigen receptor T-cell therapy

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AUTHOR CONTRIBUTIONS
AB, VG, IJ and RS designed the study concept, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AB, VG, JF, SD, IJ and RS contributed to the acquisition, analysis or interpretation of the data. AB, AG and RS drafted the manuscript. AB, RS, AG, JF and SD handled the statistical analysis. IJ and RS were involved insupervision. All authors critically reviewed the manuscript.

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ABSTRACT

Chimeric Antigen Receptor (CAR) T cells targeting CD19 induce durable remissions in patients with relapsed or refractory non-Hodgkin lymphoma (NHL), but many patients experience treatment-related toxicity. Cytokine release syndrome and immune effector cell-associated neurologic syndrome are extensively characterized. However, limited data exist on the burden, predictors, and implications of acute kidney injury (AKI) after CAR T cell therapy.

On initial screening of the FDA adverse event reporting system, we identified a disproportionately high rate of renal adverse events among nearly 6,000 CAR T adverse event reports, suggesting it is clinically important in this patient population. In a subsequent single-center analysis of 399 NHL patients treated with CD19 CAR T cells, we found a substantial burden of AKI after CAR T infusion (10% and 5% of any grade and grade ≥2 AKI) with pre-renal causes being predominant (72%). Evolution to chronic kidney disease was rare, however, 3 patients required hemodialysis. Importantly, patients experiencing cytokine release syndrome and/or neurotoxicity as well as those with low serum albumin and high inflammatory cytokines, including IL-6 and TNF-alpha, were more likely to develop AKI. While pre-CAR T renal dysfunction was not associated with adverse outcomes, patients developing post-CAR T AKI had lower overall survival compared to their counterparts.

Our findings indicate that renal dysfunction is a common toxicity of CAR T cell therapy with meaningful prognostic impact. Notably, the link between systemic inflammation and renal dysfunction, suggests that readily available biomarkers may inform on renal injury risk after CAR T cell therapy.

INTRODUCTION

Chimeric Antigen Receptor (CAR) T cells targeting CD19 induce durable remissions in patients with relapsed or refractory non-Hodgkin lymphoma (NHL), including large B cell lymphoma (LBCL) and mantle cell lymphoma (MCL).[1-15] Following a series of pivotal phase 1-2 multicenter clinical trials, four CD19 CAR T cell products, axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), and brexucabtagene autoleucel (brexu-cel), received FDA approval for NHL in the third-line setting or later,[1-10] paving the way for follow-up studies in the second-line.[11-14] Three phase 3 randomized controlled trials separately compared CD19 CAR T cell therapy to prior standard of care high dose chemotherapy with autologous stem cell transplant (auto-HCT) in LBCL patients with relapsed or refractory disease less than 12 months after completion of first-line chemoimmunotherapy.[11-13,15] Among these, the ZUMA-7 and TRANSFORM studies demonstrated improved median event-free survival in the CAR T cell arm relative to auto-HCT, leading to FDA approval of axi-cel and liso-cel in this setting.[16-17] Indications for CAR T cell therapy in lymphoma were further extended after the phase 2 PILOT study showed impressive efficacy of liso-cel in LBCL patients with significant medical comorbidities including chronic kidney disease (CKD), leading to its expanded approval as second-line therapy for transplant-ineligible patients.[14]

Despite these major therapeutic advances, many patients experience treatment-related toxicity.[1-14] Cytokine release syndrome (CRS), immune effector cell-associated neurologic syndrome (ICANS), and immune effector cell-associated hematologic toxicity are extensively characterized.[18-21] However, limited data exist on the burden, predictors, and implications of acute kidney injury (AKI) after CAR T cell therapy. Among the seminal trials investigating the use of CD19 CAR T cell therapy in lymphoma patients who relapse after two or more lines of therapy, only the TRANSCEND study extended eligibility to patients with CKD grade 3.[2-5] Thus, our understanding of

lymphoma outcomes and toxicities in patients with pre-existing kidney disease is otherwise limited to small retrospective studies.[22-24]

Here we describe a global pharmacovigilance analysis of nearly 6,000 CD19 CAR T cell recipients in addition to the largest single retrospective analysis to date of 399 NHL patients with normal and reduced baseline renal function who received CD19 CAR T cell therapy at our institution. We evaluated AKI incidence, etiologies, and clinical consequences in addition to CAR T cell-related outcomes and toxicities. Additionally, we analyzed pre-lymphodepletion, pre-infusion, and post-infusion laboratory values to determine predictors of AKI within 100 days after CAR T cell infusion.

METHODS

FAERS analysis

To further assess the association between CD19 CAR T cell therapy and AKI we queried the FDA adverse event reporting system (FAERS), a global post-marketing surveillance program, which includes voluntary and mandatory safety reports submitted by healthcare professionals, consumers, and manufacturers. The database was screened for reports of commercial CD19 CAR T cell products (axi-cel, tisa-cel, liso-cel, and brexu-cel) as the primary etiology of a given AE between January 1, 2017, and September 30, 2022. Patients under 18 years old were excluded. We applied an algorithm to eliminate suspected duplicate reports of the same drug-AE pair with different case numbers by screening for identical values in four key fields: age, sex, event date, and country of occurrence. AKI outcome definition included the ”Preferred Terms” in the “Acute renal failure” Standardized MedDRA Query (version 25.1) with manual validation by the authors.[25]

We performed a disproportionality analysis to compare the reporting of AKI events following CD19 CAR T cell therapy with all other oncological patients from the database. The age-and-sex-adjusted reporting odds ratio (adj.ROR) and the lower bound of the information component 95% credibility interval (IC_{025}) were used to detect significant disproportionate reporting. A lower bound

of the adj.ROR 95% confidence interval (CI) greater than one and a positive IC_{025} value were used as thresholds for signal detection. To mitigate indication and reporting biases, we conducted sensitivity analyses using different comparator groups, including the full database, hemato-oncological patients, and patients with lymphoid malignancies. [26-27]

MSK cohort population

We performed a single-center real-world retrospective study to analyze baseline and dynamic changes in renal function in adult patients with relapsed or refractory NHL treated with CD19 CAR T cells at Memorial Sloan Kettering Cancer Center (MSK) between April 28, 2016 and December 31, 2023. Axi-cel, tisa-cel, liso-cel, and brexu-cel were given mostly as standard therapy. Additionally, some patients received liso-cel under the TRANSCEND NHL 001 study (NCT02631044). Our cohort did not include patients on hemodialysis or renal transplant recipients. Patient data were entered and stored in a REDCap database.[28] This research was approved by the Institutional Review Board committee and conducted in accordance with the Declaration of Helsinki.

Definitions

Estimated glomerular filtration rate (eGFR) was calculated via the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation[29] and was based on serum creatinine just prior to lymphodepletion. Chronic kidney disease grading was tiered by the Kidney Disease Improving Global Outcomes (KDIGO) definitions. AKI was defined by serum creatinine between day 0 and day 100 using KDIGO criteria (supplementary methods). For AKI assessment, disease relapse or progression, anti-cancer treatment after CAR T cells, and death were considered competing events. EMR charts of all cases of AKI were individually reviewed by a board-certified nephrologist to adjudicate each cause of AKI. Renal recovery was defined as a return in creatinine to baseline range within 90 days. Otherwise, patients were considered as having progressed to

CKD. CRS and ICANS were graded according to ASTCT guidelines.[30] Detailed statistical methods and formulas are described in supplementary methods.

RESULTS

Global pharmacovigilance analysis

To evaluate the extent to which renal injury impacts patients with lymphoid malignancies who are treated with CD19 CAR T cell therapy, we interrogated the FDA adverse event reporting system (FAERS) database containing more than 7,000,000 cases. 5,912 patients received CD19 CAR T cells, including 3,526 axi-cel, 1,780 tisa-cel, 178 liso-cel, and 428 brexu-cel (**Table 1**; **Figure 1A**). CD19 CAR T cell recipients were a median (IQR) age of 62 (51-69). The main indications for treatment were NHL (n=4,127 [88%]) and ALL (n=536 [11%]). Reports mostly originated from the Americas (74%).

We identified 211 (3.6%) reports of AKI for which CD19 CAR T cell therapy was considered the primary etiology. AKI cases were mostly reported in NHL patients (n=179 [91%]). Age, sex, event year, CD19 CAR T type, and indication did not differ significantly between AKI and other CD19 CAR T cell safety events. Concurrent CRS was reported more frequently by patients who developed AKI relative to those who did not (n=136 [64%] vs. n=2,838 [50%], respectively, p<0.001). AKI events occurred at a median time of 2.5 (1-8) days post-infusion. Patients who developed AKI following treatment had a higher reported fatality rate compared to other CD19 CAR T safety events (n=104 [49%] vs. n=1,250 [23%], p<0.001) (**Table 1**).

Importantly, AKI reporting was significantly higher in patients treated with CD19 CAR T cells compared to all other cancer patients in the FAERS database (adj.ROR= 1.72 [1.34−2.20], IC_{025}= 0.19). To mitigate indication and reporting biases, we conducted sensitivity analyses by using different comparator groups. The association between CD19 CAR T cell treatment and increased reporting of AKI remained significant when compared to the entire FAERS database (adj.ROR=

2.40 [1.87−3.07], IC_{025}=0.47), patients with hematologic malignancies (adj.ROR= 1.44 [1.20−1.73], IC_{025}=0.27), and patients with lymphoid malignancies (adj.ROR= 1.39 [1.16−1.67], IC_{025}=0.24) (**Figure 1B**).

Overall, this pharmacovigilance analysis highlights AKI as a frequently reported adverse event among patients receiving CD19 CAR T cell therapy. However, limitations inherent to pharmacovigilance data prevent a precise determination of true incidence and risk factors of AKI.

MSK cohort baseline characteristics

To gain insight into the prevalence, etiology, and implications of AKI, we studied 399 patients (**Table 2**) diagnosed with NHL (84% LBCL, 11% MCL, and 5% non-LBCL) who underwent CAR T cell therapy at our institution. Among these patients, the median age was 66 years and CAR T cell products included 46% axi-cel, 20% tisa-cel, 29% liso-cel, and 5% brexu-cel.

Before lymphodepleting chemotherapy, typically initiated five days prior to CAR T cell infusion, patients exhibited a median eGFR of 94 mL/min (IQR: 75-101). Most patients (55%) had a normal eGFR (≥90 mL/min; grade 0-1 CKD), followed by 35% with grade 2 CKD (eGFR 60-89 mL/min) and 10% with grade 3 CKD (eGFR 30-59 mL/min). Older age was associated with baseline CKD grade 2-3 relative to normal eGFR ($p < 0.001$). Pre-CAR T cell Karnofsky Performance Scale, number of pre-apheresis treatment lines, and prior hematopoietic stem cell transplantation did not significantly differ across CKD groups (**Table 2**).

Given that suboptimal lymphodepletion chemotherapy dosing has been associated with differences in outcomes and toxicities in CD19 CAR T cell-treated patients,[31-32] we calculated total fludarabine dosing. Patients with decreased renal function received lower doses of fludarabine ($p = < 0.001$), ranging from a median total dose of 72 mg/m^2 (IQR 60-76) in stage 3 CKD to 88 mg/m^2 (IQR 80-91) in patients with normal eGFR. We also used an established pharmacokinetic (PK) model to measure fludarabine exposure, using total fludarabine dose and serum creatinine, age, and weight on the first day of lymphodepletion.[32-33] Among 330 patients (143 axi-cel, 18 brexu-cel, 101 liso-cel,

68 tisa-cel) who received fludarabine as part of lymphodepletion, exposure by area under the curve (AUC) was higher on average in patients with lower eGFR (p value inevaluable since eGFR is a variable in the PK calculation model; **Table 2**).

MSK cohort clinical and toxicity outcomes

At a median follow-up time of 24 months, patients in the cohort experienced a median progression-free survival (PFS) of 12 months (95% CI, 8.6 - 18 months) and a median overall (OS) of 36 months (95% CI, 23 months – not reached) (**Figure S1**). CAR T cell-related adverse effects occurred at a similar frequency to previously published seminal clinical trials.[1-14] Grade 0-1 CRS occurred in 243 (61%) patients versus 156 (39%) who experienced grade ≥2 CRS. The median duration of CRS was 5 days, and 192 (48%) patients required Tocilizumab infusion. Grade 0-1 ICANS occurred in 322 (81%) patients relative to 77 (19%) with grade ≥2 symptoms. The median duration of ICANS was 5 days, and 150 (38%) patients required steroids. Overall, 62 (16%) patients were admitted to the ICU after CAR T cell infusion. Significant hematologic toxicity was also observed in the cohort with 287 (74%) patients experiencing severe neutropenia (absolute neutrophil count < 500) with a median duration of 10 days and 95 (25%) patients with severe thrombocytopenia (platelets < 20,000) with a median duration of 21 days (**Table S1**).

In a cause-specific Cox regression model, surrogates for disease burden,[34] including elevated pre-lymphodepletion lactate dehydrogenase (LDH) and the need for systemic bridging therapy (treatment given between apheresis and infusion), were associated with OS and PFS. Pre-lymphodepletion eGFR, however, was not associated with OS, PFS, CRS grade ≥2, ICANS grade ≥2, or neutropenia (**Table S2, Table S3, Table S4, Table S5, Table S6**). Thus, baseline renal function was not significantly associated with efficacy or toxicity endpoints.

Clinical burden of AKI after CD19 CAR T cell therapy

Between CAR T cell infusion (day 0) and day 100, excluding patients who experienced disease relapse and/or received additional anti-cancer treatment, the cumulative incidence of any AKI and grade ≥2 AKI were 10% (39 patients) and 4.8% (19 patients), respectively (**Figure 2A** and **2B**). The median time to any AKI was 9 days, whereas the median time to grade 2+ AKI was 7 days. The trajectory of creatinine and eGFR for all patients over 12 months following CAR T cell infusion is depicted (**Figure S2A** and **S2B**).

Of the 39 patients who experienced an AKI, 28 (71.8%) were attributed to pre-renal factors, including 14 cases that occurred concurrently with CRS. Eight (20.5%) AKI events were considered intra-renal etiology, including 5 cases occurring with CRS-induced hemodynamic compromise, 1 case occurring with TLS, and 2 cases associated with acute tubular necrosis. Three (7.7%) cases of AKI were linked to hydronephrosis (**Figure 2C**). Continuous renal replacement therapy (CRRT) was initiated in 3 patients for AKI due to hemodynamic instability stemming from CRS. Three patients (7.7%) died of CRS-induced shock in the ICU and 20 (51.2%) patients died from complications of lymphoma progression after resolution of AKI. Other causes of death included progression of lung cancer (2.6%), COVID and a pulmonary embolism (2.6%), acute myocardial infarction (2.6%), and unknown (5.1%). Eight (20.5%) patients are alive as of August 2024. Among evaluable AKI patients, 1 patient progressed to CKD with serum creatinine remaining over 1.5-fold higher than baseline at the end of follow-up.

The potential contribution of medications to renal injury was also considered. Among the 39 patients who experienced AKI, 31 (79.5%) received potentially nephrotoxic drugs within 1 week prior to onset of AKI (**Table S7**). Furosemide administration within 7 days of AKI onset was observed in 12 (30.8%) patients of which 9 AKI events were pre-renal etiology, 5 of which occurred in the setting of CRS. The most frequent exposure was vancomycin in 19 patients (48.7%), though serum troughs exceeded the maximum therapeutic range (20 mg/L) in only 6 patients (serum concentrations of 25, 45, 21.4, 24.6, 21.6, 40 mg/L), among which two patients had post-renal AKI

cause and three patients had concurrent CRS, including one patient who experienced resolution of AKI with fluid resuscitation. Among the 10 patients (25.6%) who received vancomycin concurrently with piperacillin-tazobactam, a combination that has been associated with increased risk of renal injury,[35] only 1 patient experienced an intra-renal AKI event, suggesting that antibiotic exposure was not a significant cause of renal injury in our cohort.

Risk factors for AKI

We first evaluated biomarkers predictive of renal injury prior to administration of lymphodepleting chemotherapy, occurring about 5 days prior to CAR T cell infusion. Clinical characteristics of event-free AKI versus non-AKI patients are shown (**Table S8**). In a univariable cause-specific Cox regression, baseline lower hemoglobin and albumin levels and higher log transformed ferritin, CRP, and log transformed LDH levels were associated with developing any AKI (**Table 3**). Incidence of AKI stratified by high versus low pre-lymphodepletion laboratory values, including LDH, albumin, ferritin, and hemoglobin is shown (**Figure 3A-D**). Importantly, no association was detected between baseline eGFR and developing renal injury, consistent with a prior study.[24] Furthermore, neither the use of systemic bridging therapy nor specifically bridging platinum therapy were significantly associated with developing any AKI. In a multivariable model, using stepwise regression of significant covariates, serum albumin level prior to lymphodepletion remained a significant risk factor for AKI (HR 0.15 [95% CI 0.07 – 0.32], $p < 0.001$; **Table 3**).

Since fludarabine-based conditioning regimens were previously shown to be a risk factor for AKI after allo-HCT,[36] we used the fludarabine PK model to further investigate the potential impact of disparate fludarabine exposures across patients in our cohort. Fludarabine exposure by AUC, either as a continuous or categorical variable (high 18-25 versus low 0-18 mgh/L), was not significantly associated with developing any grade AKI in a cause specific regression model (**Table 3**).

Since systemic inflammation has been linked to adverse CAR T cell outcomes,[37] we evaluated biomarkers of inflammation just prior to CAR T cell infusion (day 0). At this timepoint, higher serum CRP, TNF-alpha, and log-transformed IL-6 and IL-10 were significantly associated with developing AKI. Serum log transformed IL-6 (HR 1.74 [95% CI 1.18 – 2.56], p = 0.008) and TNF-alpha (HR 2.23 [95% CI 1.54 – 3.23], p = <0.001) on day 0 remained significant in a multivariable model with stepwise addition of inflammatory biomarker covariates (**Table 4**). Thus, elevations of pre-infusion cytokines IL-6 and TNF-alpha are significant risk factors for AKI.

Since inflammatory markers are dynamic, we modeled them longitudinally between days 0 to 30 using GEE models adjusting for time from CAR T infusion. When modeling markers individually, while adjusting for time, age, and costimulatory domain, elevations in log-transformed serum ferritin, CRP, TNF-alpha, and IL-10, but not LDH, were individually associated with decreased eGFR on average (**Figure 4A**). Serum log-transformed TNF-alpha remained significant on multivariate analysis (estimate -6.98 [95% CI -10.29 - -3.67], p < 0.001; **Figure 4B**). Trends in post-infusion eGFR stratified by categorized TNF-alpha serum levels over time is shown (**Figure S3**).

We also considered the potential impact of infectious complications on renal injury between Day 0 and Day 100. Among patients who did not experience a disease-related event, bacteremia occurred in 6 (15%) patients prior to the AKI event relative to 18 (7.3%) patients without AKI. As a time-dependent covariate, bacteremia was significantly associated with AKI (HR 2.78 [95% CI 1.07 – 7.23], p = 0.036. Viral infections were also associated with AKI (20.5% versus 14%; HR 4.52 [95% CI 1.93 – 10.6], p < 0.001; **Table S9**).

Finally, since systemic inflammation, CRS, and ICANS are potentially linked,[37] we studied the impact of CRS and ICANS, as time-dependent covariates, on AKI. Any grade CRS (HR 2.59 [95% CI 1.13 – 5.97], p = 0.025) and any grade ICANS (HR 3.07 [95% CI 1.53 – 6.16], p = 0.002) were significantly associated with AKI. Tocilizumab administration was also associated with increased

AKI risk (HR 4.05 [95% CI 1.94 – 8.46], p = <0.001). Overall, our findings suggest that systemic inflammation is a prominent risk factor for AKI in patients receiving CAR T cell therapy.

Implications of AKI

To compare disease-related outcomes of patients in the cohort, we calculated PFS and OS in patients who developed AKI compared to those who did not. Univariable Cox regression analysis using AKI as a time-dependent covariate demonstrated that patients who developed any AKI through day 100 experienced significantly lower PFS (HR 2.63 [95% CI 1.79-3.87]; P < 0.001) and OS (HR 3.36 [95% CI 2.25-5.00]; P < 0.001). Among patients who developed grade ≥2 AKI, there was also significantly lower PFS (HR 3.14 [95% CI 1.89-5.24]; P < 0.001) and OS (HR 4.18 [95% CI 2.49-7.02]; P < 0.001). To further investigate this difference, we analyzed AKI as a time-dependent covariate in a cox regression model for neutropenia and did not find a significant association (**Table S6**). Thus, lymphoma patients who experience renal injury after CD19 CAR T cell therapy have inferior survival, which is not driven by neutropenia.

DISCUSSION

Renal injury, while recognized as a complication of cancer treatments, remains underexplored in the context of CAR T cell therapy, a transformative approach in oncology. Addressing this gap, our study harnesses both global and institutional data sources to shed light on kidney dysfunction following CAR T cell therapy. Through a detailed pharmacovigilance analysis of nearly 6,000 adverse event reports from the FDA's database for patients treated with CAR T, we uncovered a disproportionately high incidence of AKI in comparison to other treatments. Our examination of a cohort of 399 lymphoma patients, the largest group studied to date, revealed that AKI is a prevalent issue, affecting 10% of patients. Significantly, our analysis pinpointed cytokines associated with systemic inflammation as key contributors to the development of AKI. The observation that patients with post-infusion renal injury faced reduced overall survival highlights the

importance of preemptive strategies to mitigate this risk, emphasizing the importance of understanding and addressing renal toxicity in the era of CAR T cell therapy.

Consistent with our previously published retrospective series of 46 adult patients with NHL treated with CD19 CAR T cells,[22] we find that most AKI events after CAR T cell infusion are grade 1 and that most patients recover from these events within 3 months. Median time to any AKI was 9 days in our cohort, relative to 2.5 days in our pharmacovigilance analysis, likely reflecting heterogenous AKI definitions in the FAERS database. In contrast to a recently published analysis,[24] we include LBCL patients treated with liso-cel, which is crucial due to the expanded use of this product in patients with baseline renal dysfunction. Our large and diverse patient cohort includes patients with other lymphoma subtypes including MCL, which historically necessitates aggressive upfront platinum-containing chemotherapy regimens followed by auto-HCT in a subset of patients. The study shows that baseline renal dysfunction leading into CAR T cell therapy is not associated with differences in survival or toxicity outcomes, though this may reflect the small number of patients with stage 3 CKD in our cohort.

Our analysis demonstrates that readily available biomarkers reflecting physiological reserve, disease burden, and systemic inflammation may inform on renal injury risk. Intriguingly, we are the first to determine that hypoalbuminemia is strongly associated with risk of AKI after CAR T cell therapy. Low serum albumin is frequently seen in patients with critical illness and is considered a negative acute phase reactant.[38] In the setting of elevated serum cytokines, increased albumin clearance due to higher capillary permeability and decreased albumin production at the transcriptional level can occur.[38] Thus, baseline systemic inflammation as reflected by decreased albumin and increased CRP, ferritin, TNF-alpha, and/or IL-6 may predispose to increased renal toxicity after CAR T cell infusion. Our observation that post-infusion serum TNF-alpha levels, but not LDH levels, are associated with AKI suggests that inflammatory cytokines, rather than the direct impact of tumor lysis, are important in developing nephrotoxicity. Our finding that TLS was

observed in only 1 patient is consistent with this. We also find that patients who develop any grade CRS or ICANS, including those experiencing or being treated for high grade toxicity, are at increased risk for AKI. Therefore, inflammation prior to and after CAR T cell infusion are important predictors of renal injury. Bacteremia occurred in 15% of patients prior to AKI, though nearly half of AKI events occurred in the setting of CRS, suggesting stronger contribution of CAR T cells relative to sepsis-induced cytokine release.

Weaknesses of the study include the retrospective nature of the analysis and inability to profile all medication exposures across the cohort. Since drug-induced renal injury typically occurs just prior to AKI, broad comparison of nephrotoxin exposures between AKI and non-AKI patients is likely to enrich for non-culprit drugs that may not be temporally linked to renal injury. Furthermore, non-AKI patients lack a clear reference point for this comparison. Administration of nephrotoxic drugs within 7 days prior to AKI was observed in patients, though pre-renal causes were the most frequent mechanism of injury in this group, suggesting a contribution of transient hypoperfusion rather than drug-induced pathogenesis. Additionally, PK modeling was used to address the potential impact of fludarabine exposure differences across patients in the cohort, and we did not find an association with AKI.

The association between renal injury and subsequent mortality suggests that AKI is a clinically and prognostically significant complication that is worthy of prospective analysis in future cellular therapy trials. Our finding that patients with baseline renal dysfunction have similar disease outcome and toxicity supports broadening CAR T cell patient eligibility to include patients with lower baseline eGFR. In fact, one group recently published on the successful and safe administration of lymphodepleting chemotherapy and CD19 CAR T cells in lymphoma patients with pre-existing ESRD.[39] With the recent approval of liso-cel in transplant-ineligible patients, CAR T cell therapy is now being considered feasible in patients with significant medical comorbidities.[14]

We anticipate that a growing number of patients with CKD will undergo CAR T cell therapy, therefore, our understanding of therapy-associated risks in this population is crucial.

Significant challenges remain in predicting and preventing CAR T cell therapy-associated toxicities, yet our study supports the use of readily measured and potentially clinically actionable inflammatory biomarkers to inform on renal injury risk after CAR T cell infusion. The use of steroids has been shown to decrease serum cytokines in older patients prior to the initiation of chemotherapy,[40] thus patients with baseline hypoalbuminemia and elevated serum cytokine levels may benefit from additional therapy prior to CAR T cell infusion to optimize renal injury risk. Although risk mitigation strategies will require further validation, we advocate for adequate hydration and appropriate avoidance of nephrotoxic agents as able in CAR T cell recipients, especially those with AKI risk factors.

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TABLES

Table 1: Characteristics of CD19 CAR T reports in the FDA adverse event reporting system by acute kidney injury reporting status

	AKI (n=211)	Other CAR T reports (n=5,701)	P value
Reporting region[1]			
Americas	149/200 (74.50)	4,010/5,433 (73.81)	0.464
Europe	39/200 (19.50)	1,140/5,433 (20.98)	
Asia	10/200 (5.00)	179/5,433 (3.29)	
Australia	2/200 (1.00)	104/5,433 (1.91)	
Reporter			
Health professional	185/199 (92.96)	4,936/5,379 (91.76)	0.635
Consumer/Lawyer	14/199 (7.04)	443/5,379 (8.24)	
Event year			
2017-2018	33/175 (18.86)	675/3,441 (19.62)	0.538
2019-2020	74/175 (42.29)	1,569/3,441 (45.60)	
2021-2022[2]	68/175 (38.86)	1,197/3,441 (34.79)	
Age, years			
Median (IQR)	62 (54-70)	62 (51-69)	0.439
Sex			
Female	66/190 (34.74)	1,686/4,510 (37.38)	0.508
Male	124/190 (65.26)	2,824/4,510 (62.62)	
Product			
Axi-cel	116/211 (54.98)	3,410/5,701 (59.81)	0.577
Tisa-cel	71/211 (33.65)	1,709/5,701 (29.98)	
Brexu-cel	17/211 (8.06)	411/5,701 (7.21)	
Liso-cel	7/211 (3.32)	171/5,701 (3.00)	
Indication			
NHL	179/197 (90.86)	3,948/4,499 (87.75)	0.215
ALL	16/197 (8.12)	520/4,499 (11.56)	
Other	2/197 (1.02)	31/4,499 (0.69)	
Concurrent CRS	136/211 (64.45)	2,838/5,701 (49.78)	<0.001
Time to AE onset, days			
Median (IQR)	2.5 (1.0-	4.0 (1.0-	0.009

	8.0)	10.0)	
Outcome			
Hospitalization[3]	104/211 (49.29)	1,959/5,369 (36.49)	<0.001
Life-threatening	48/211 (22.75)	427/5,369 (7.95)	<0.001
Death	104/211 (49.29)	1,250/5,369 (23.28)	<0.001

[1]Among CD19 CAR T recipients from the Americas, 4,095 were from the United States (AKI, n =143; non-AKI, n=3,952). [2]Only cases reported before September 30, 2022, were included. [3]Denotes that the adverse event was the cause of inpatient admission or, if it occurred during hospitalization, was the cause of delayed discharge. All values are n/N (%) unless otherwise indicated. P values were calculated with the Bonferroni correction for multiple comparisons.

Abbreviations: AKI = acute kidney injury; CAR T = chimeric antigen receptor T cells; Axi-cel = axicabtagene ciloleucel; Tisa-cel = tisagenlecleucel; Brexu-cel = brexucabtagene autoleucel; Liso-cel = lisocabtagene maraleucel; NHL = non-Hodgkin lymphoma; ALL = Acute lymphoblastic leukemia; IQR = Interquartile range

Table 2: MSK cohort patient characteristics by baseline renal function

CHARACTERISTIC	OVERALL, N =399[1]	EGFR >=90, N = 220[1]	EGFR 60-89, N = 140[1]	EGFR <60, N = 39[1]	P VALUE[2]
Pre-CAR T Age	66 (56, 73)	61 (51, 68)	70 (63, 77)	72 (65, 76)	<0.001
Sex					0.075
Male	260 (65%)	153 (70%)	81 (58%)	26 (67%)	
Female	139 (35%)	67 (30%)	59 (42%)	13 (33%)	
Pre-CAR T KPS					0.11
>=90	124 (31%)	77 (35%)	39 (28%)	8 (21%)	
<90	274 (69%)	142 (65%)	101 (72%)	31 (79%)	
Unknown	1	1	0	0	
Ethnicity					0.4
Hispanic or Latino	26 (6.8%)	12 (5.7%)	10 (7.5%)	4 (11%)	
Not Hispanic or Latino	354 (93%)	197 (94%)	123 (92%)	34 (89%)	
Unknown	19	11	7	1	
Race					0.089
Asian	35 (9.1%)	26 (12%)	7 (5.3%)	2 (5.3%)	
Black or African American	16 (4.2%)	6 (2.8%)	8 (6.0%)	2 (5.3%)	
Other	16 (4.2%)	10 (4.7%)	3 (2.3%)	3 (7.9%)	
White	316 (83%)	170 (80%)	115 (86%)	31 (82%)	
Unknown	16	8	7	1	
NHL broad classification					0.6
LBCL	335 (84%)	186 (85%)	119 (85%)	30 (77%)	
Mantle cell lymphoma	44 (11%)	22 (10%)	15 (11%)	7 (18%)	
Non-LBCL	20 (5.0%)	12 (5.5%)	6 (4.3%)	2 (5.1%)	
NHL transformation origin					0.42
de novo LBCL	210 (53%)	124 (57%)	68 (49%)	18 (46%)	
transformed tFL	77 (19%)	39 (18%)	32 (23%)	6 (15%)	
Other primary	42 (11%)	21 (9.6%)	15 (11%)	6 (15%)	
Unknown/ not applicable	70	36	25	9	
Double or triple hit					0.057
Not double or triple hit	258 (70%)	142 (70%)	86 (68%)	30 (77%)	
Double or triple hit	47 (13%)	27 (13%)	20 (16%)	0 (0%)	
Unknown/ not applicable	94	51	34	9	
Cell of origin					0.6
GCB	165 (43%)	94 (45%)	59 (43%)	12 (32%)	
non-GCB	157 (41%)	83 (39%)	57 (42%)	17 (45%)	
Unknown/ not applicable	77	43	24	10	
Prior treatment lines	3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.5
Unknown	6	4	2	0	
Prior treatment lines (category)					0.5
<=3 lines	256 (65%)	146 (68%)	88 (64%)	22 (56%)	
4-5 lines	89 (23%)	48 (22%)	31 (22%)	10 (26%)	
6+ lines	48 (12%)	22 (10%)	19 (14%)	7 (18%)	
Unknown	6	4	2	0	
Previous auto-HCT	77 (19%)	45 (21%)	22 (16%)	10 (26%)	0.3
Previous allo-HCT	19 (4.8%)	11 (5.0%)	4 (2.9%)	4 (10%)	0.14
Primary refractory disease	146 (37%)	89 (40%)	47 (34%)	10 (26%)	0.2
Unknown	3	0	3	0	
Bridging type					0.5
no bridging	86 (22%)	44 (20%)	35 (25%)	7 (18%)	

non-systemic bridging	65 (16%)	40 (18%)	17 (12%)	8 (21%)	
systemic bridging	248 (62%)	136 (62%)	88 (63%)	24 (62%)	
CAR T product					0.006
Axi-cel	183 (46%)	117 (53%)	54 (39%)	12 (31%)	
Brexu-cel	23 (5.8%)	11 (5.0%)	7 (5.0%)	5 (13%)	
Liso-cel	115 (29%)	58 (26%)	48 (34%)	9 (23%)	
Tisa-cel	78 (20%)	34 (15%)	31 (22%)	13 (33%)	
CAR T costimulatory domain					0.015
CD28	206 (52%)	128 (58%)	61 (44%)	17 (44%)	
41BB	193 (48%)	92 (42%)	79 (56%)	22 (56%)	
Lymphodepletion					0.6
Flu/Cy	343 (86%)	192 (87%)	117 (84%)	34 (87%)	
Bendamustine	56 (14%)	28 (13%)	23 (16%)	5 (13%)	
Total fludarabine dose (mg/m^2)	86 (74, 90)	88 (80, 91)	79 (72, 89)	72 (60, 76)	<0.001
Unknown	57	29	23	5	
Predicted fludarabine AUC (mgh/L)	15.75 (13.95, 17.51)	14.71 (13.30, 16.35)	17.03 (15.07, 18.88)	17.72 (15.58, 20.29)	N/A
Unknown	69	36	28	5	
Predicted fludarabine AUC (mgh/L) category					N/A
0 – 18	266 (81%)	179 (97%)	69 (62%)	18 (53%)	
18 – 25	64 (19%)	5 (2.7%)	43 (38%)	16 (47%)	
Unknown	69	36	28	5	
Pre-CAR T disease response					0.6
CR	40 (10%)	21 (9.5%)	15 (11%)	4 (10%)	
PR	130 (33%)	79 (36%)	41 (29%)	10 (26%)	
SD/PD	229 (57%)	120 (55%)	84 (60%)	25 (64%)	
LDH range pre-LD					0.4
normal	242 (61%)	134 (61%)	81 (58%)	27 (69%)	
elevated	157 (39%)	86 (39%)	59 (42%)	12 (31%)	
CRP pre-LD	0.6 (0.4, 2.7)	0.7 (0.3, 3.4)	0.6 (0.4, 1.8)	0.6 (0.3, 1.9)	0.4
Unknown	71	41	27	3	
Ferritin pre-LD	196 (71, 525)	181 (71, 550)	187 (69, 465)	302 (97, 576)	0.2
Unknown	73	42	28	3	

[1]Median (IQR); n (%)
[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

Abbreviations: CAR T = chimeric antigen receptor T cell; KPS = Karnofsky Performance Scale; NHL = non-Hodgkin lymphoma; LBCL = large B cell lymphoma; tFL = transformed follicular lymphoma; GCB = germinal center B-cell; Axi-cel = axicabtagene ciloleucel; Tisa-cel = tisagenlecleucel; Brexu-cel = brexucabtagene autoleucel; Liso-cel = lisocabtagene maraleucel; Flu/Cy = fludarabine and cyclophosphamide; auto-HCT = autologous stem cell transplant; allo-HCT = allogeneic stem cell transplant; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; AUC = area under the curve (for drug exposure over time); pre-LD = pre-lymphodepletion; LDH = lactate dehydrogenase; CRP = C reactive protein. N/A (not applicable) indicates that the we are unable to obtain p value since eGFR is in the PK calculation model.

Table 3: Cox-regression analysis for pre-lymphodepletion predictors of acute kidney injury

	Univariable			Multivariable		
CHARACTERISTIC[1]	**HR[1,2]**	**95% CI[1,2]**	**P VALUE[1]**	**HR[1,2]**	**95% CI[1,2]**	**P VALUE[1]**
Pre-CAR T Age	1.01	0.99, 1.04	0.3			
Pre-CAR T KPS			0.2			
>=90	—	—				
<90	1.56	0.74, 3.29				
Baseline eGFR			0.063			
eGFR >=90	—	—				
eGFR 60-89	0.48	0.23, 1.02				
eGFR <60	0.37	0.09, 1.54				
Bridging type			0.3			
no bridging	—	—				
non-systemic bridging	1.84	0.58, 5.78				
systemic bridging	2.05	0.79, 5.31				
Platinum exposure			0.5			
not exposed	—	—				
exposed	1.35	0.60, 3.06				
Predicted fludarabine AUC (mgh/L)	0.90	0.78, 1.03	0.11			
Predicted fludarabine AUC (mgh/L) category			0.1			
0 – 18	—	—				
18 – 25	0.42	0.13, 1.37				
CAR T product			0.2			
Axi-cel	—	—				
Brexu-cel	1.80	0.61, 5.31				
Liso-cel	0.60	0.25, 1.44				
Tisa-cel	1.41	0.65, 3.05				
Hgb	0.76	0.64, 0.90	0.001	1.05	0.84, 1.31	0.7
LDH	2.00	1.41, 2.83	<0.001	1.58	0.92, 2.73	0.11
Albumin	0.15	0.08, 0.26	<0.001	0.15	0.07, 0.32	<0.001
CRP	1.08	1.02, 1.14	0.024	0.96	0.89, 1.04	0.3
Ferritin	1.39	1.09, 1.78	0.008			

[1] LDH and Ferritin were log transformed
[2] HR = Hazard Ratio, CI = Confidence Interval

Abbreviations: CAR T = chimeric antigen receptor T cell; Axi-cel = axicabtagene ciloleucel; Tisa-cel = tisagenlecleucel; Brexu-cel = brexucabtagene autoleucel; Liso-cel = lisocabtagene maraleucel; Flu/Cy = fludarabine and cyclophosphamide; pre-LD = pre-lymphodepletion; Hgb = hemoglobin; LDH = lactate dehydrogenase; CRP = C reactive protein; AUC = area under the curve (for drug exposure over time); pre-lymphodepletion indicates lab value obtained prior to initiating lymphodepleting chemotherapy, in most cases 5 days prior to CAR T cell infusion.

Table 4: Cox-regression analysis for pre-infusion predictors of acute kidney injury

	Univariable			Multivariable		
CHARACTERISTIC[1]	**HR[12]**	**95% CI[12]**	**P VALUE[1]**	**HR[12]**	**95% CI[12]**	**P VALUE[1]**
Hgb	0.68	0.55, 0.84	<0.001			
LDH	2.54	1.76, 3.66	<0.001			
Albumin	0.19	0.11, 0.34	<0.001			
CRP	1.09	1.05, 1.14	<0.001			
Ferritin	1.00	1.00, 1.00	0.015	1.00	1.00, 1.00	0.8
Fibrinogen	0.54	0.17, 1.70	0.3			
TNF-alpha	2.75	1.98, 3.83	<0.001	2.23	1.54, 3.23	<0.001
IL-10	1.82	1.39, 2.38	<0.001			
IL-6	1.89	1.43, 2.50	<0.001	1.74	1.18, 2.56	0.008

[1] LDH, Ferritin, TNF-alpha, and IL6 were log-transformed
[2] HR = Hazard Ratio, CI = Confidence Interval

Abbreviations: Hgb = hemoglobin; LDH = lactate dehydrogenase; CRP = C reactive protein; pre-infusion indicates day 0 lab value just prior to CAR T cell infusion.

FIGURE LEGENDS

Figure 1: Study flowchart and disproportionality analysis of CAR T-related adverse events. (A) Flowchart of the FDA adverse event reporting system (FAERS) data retrieval process. Reports without a defined primary suspected drug for a given AE and suspected duplicated reports were excluded. (B) Disproportionality analysis of CD19 CAR T-related acute kidney injury (AKI) events compared to the full FAERS database, cancer patients, hemato-oncological patients, and patients with lymphoid malignancies. A positive lower bound of the information component 95% credibility interval ($IC_{025} > 0$) and a lower limit of the ROR 95% confidence interval above 1 are the conventional thresholds for significant signal detection.

Abbreviations: AKI = acute kidney injury; CAR-T= chimeric antigen receptor T cells; CI = confidence interval; FAERS = FDA adverse event reporting system; IC = information component; NHL= non-Hodgkin lymphoma; adj.ROR = age-and sex-adjusted reporting odds ratio.

Figure 2: Cumulative incidence and etiologies of acute kidney injury. The cumulative incidence of AKI at any grade (A) and grade ≥2 AKI (B) up to Day 100 are shown. Shaded regions correspond to 95% confidence intervals. Disease relapse or progression, change in treatment, and death were considered competing events. Causes of AKI in the MSK cohort are displayed according to category as adjudicated by a nephrologist (C). Cases of CRS and TLS that occurred during the time of AKI are also listed.

Abbreviations: AKI = acute kidney injury; CAR T = chimeric antigen receptor T cell; CRS = cytokine release syndrome; TLS = tumor lysis syndrome

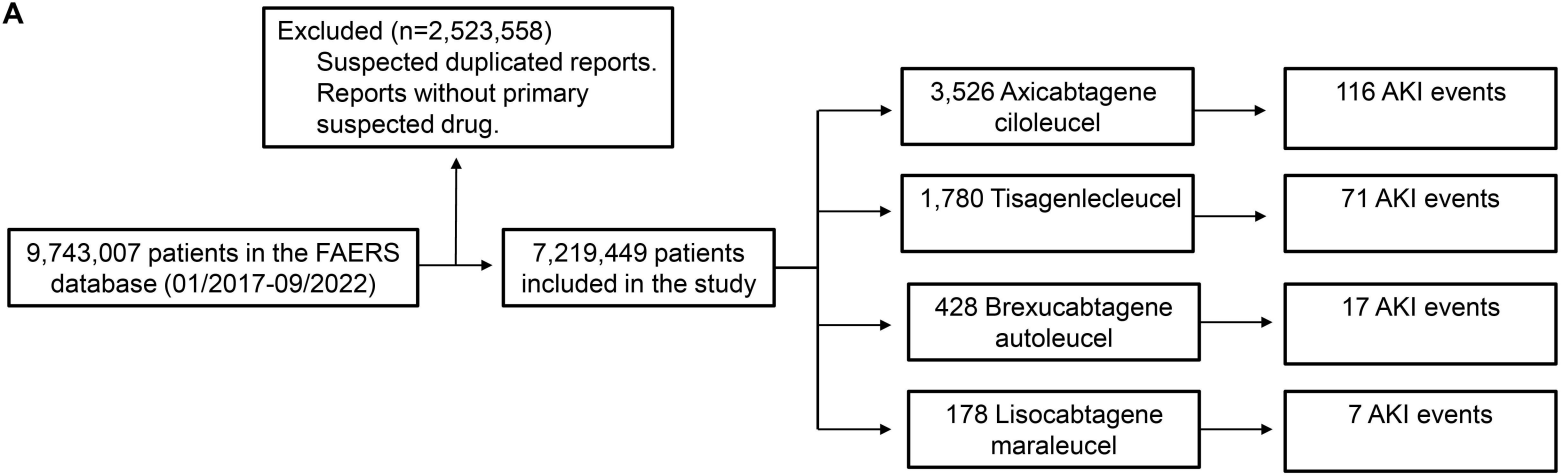
Figure 3: Incidence of any acute kidney injury by pre-lymphodepletion laboratory values. Cumulative incidence of AKI was stratified according to pre-lymphodepletion LDH (A) above the upper limit of normal 250 U/L (grey) versus below 250 U/L (orange), albumin (B) above the upper limit of normal 3.9 g/L (grey) versus ≤ 3.9 g/L (orange), log-transformed ferritin (C) above the upper limit of normal 415 ng/mL (grey) versus ≤ 415 ng/mL (orange), and hemoglobin above 10.4 g/dL (grey) are compared to patients with hemoglobin ≤ 10.4 g/dL (orange). Shaded regions represent 95% confidence intervals.

Abbreviations: AKI = acute kidney injury; CAR T = chimeric antigen receptor T cell; U/L = units per liter; g/L = grams per liter; ng/mL = nanograms per milliliter; g/dL = grams per deciliter

Figure 4: GEE model for longitudinal association of post-infusion predictors of eGFR. All generalized estimating equation (GEE) models are adjusted for age at infusion, costimulatory domain of the CAR product, and the time from CAR T infusion using a linear and quadratic term. Associations of various biomarkers on eGFR (log-transformed) were analyzed from the time of CAR T cell infusion to day +30. Single biomarker per model (A) and multivariable biomarker (B) analyses of the indicated laboratory parameters are shown. Ferritin, CRP, TNF-alpha, LDH, IL-10, and IL-6 were log-transformed.

Figure 1

A



B

	Total reports n	AKI reports n (%)	adj.ROR (95% CI)	IC_{025}
CAR−T	5,912	211 (3.57)		
Comparator group				
Entire FAERS database	7,214,143	161,717 (2.24)	2.40 (1.87−3.07)	0.47
Cancer patients	1,358,051	36,786 (2.71)	1.72 (1.34−2.20)	0.19
Hemato−oncological patients	424,746	10,860 (2.56)	1.44 (1.20−1.73)	0.27
Lymphoid malignancies patients	354,820	9,236 (2.60)	1.39 (1.16−1.67)	0.24

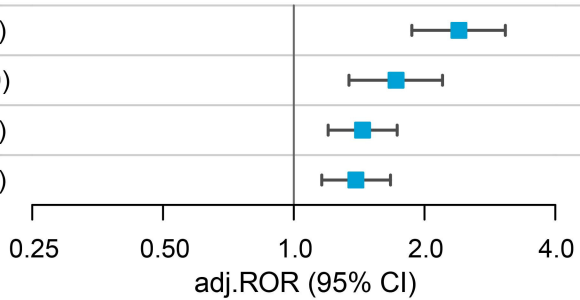


Figure 2

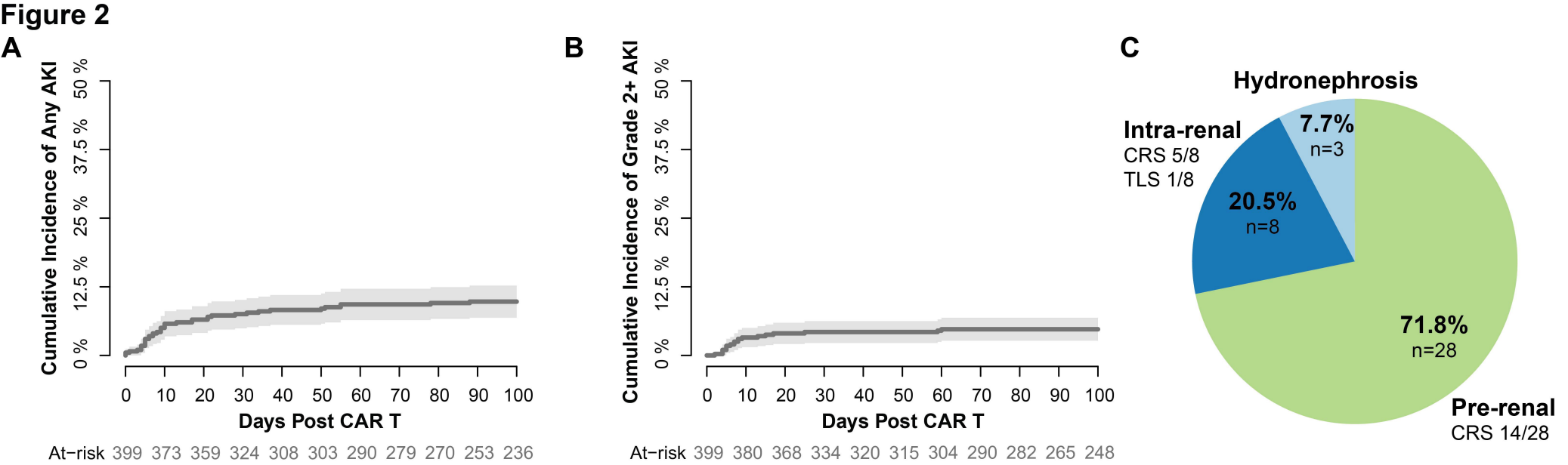

A
Cumulative Incidence of Any AKI
0 %
12.5 %
25 %
37.5 %
50 %
0 10 20 30 40 50 60 70 80 90 100
Days Post CAR T
At−risk 399 373 359 324 308 303 290 279 270 253 236
B
Cumulative Incidence of Grade 2+ AKI
0 %
12.5 %
25 %
37.5 %
50 %
0 10 20 30 40 50 60 70 80 90 100
Days Post CAR T
At−risk 399 380 368 334 320 315 304 290 282 265 248
C
Hydronephrosis
7.7%
n=3
Intra-renal
CRS 5/8
TLS 1/8
20.5%
n=8
71.8%
n=28
Pre-renal
CRS 14/28

Figure 3

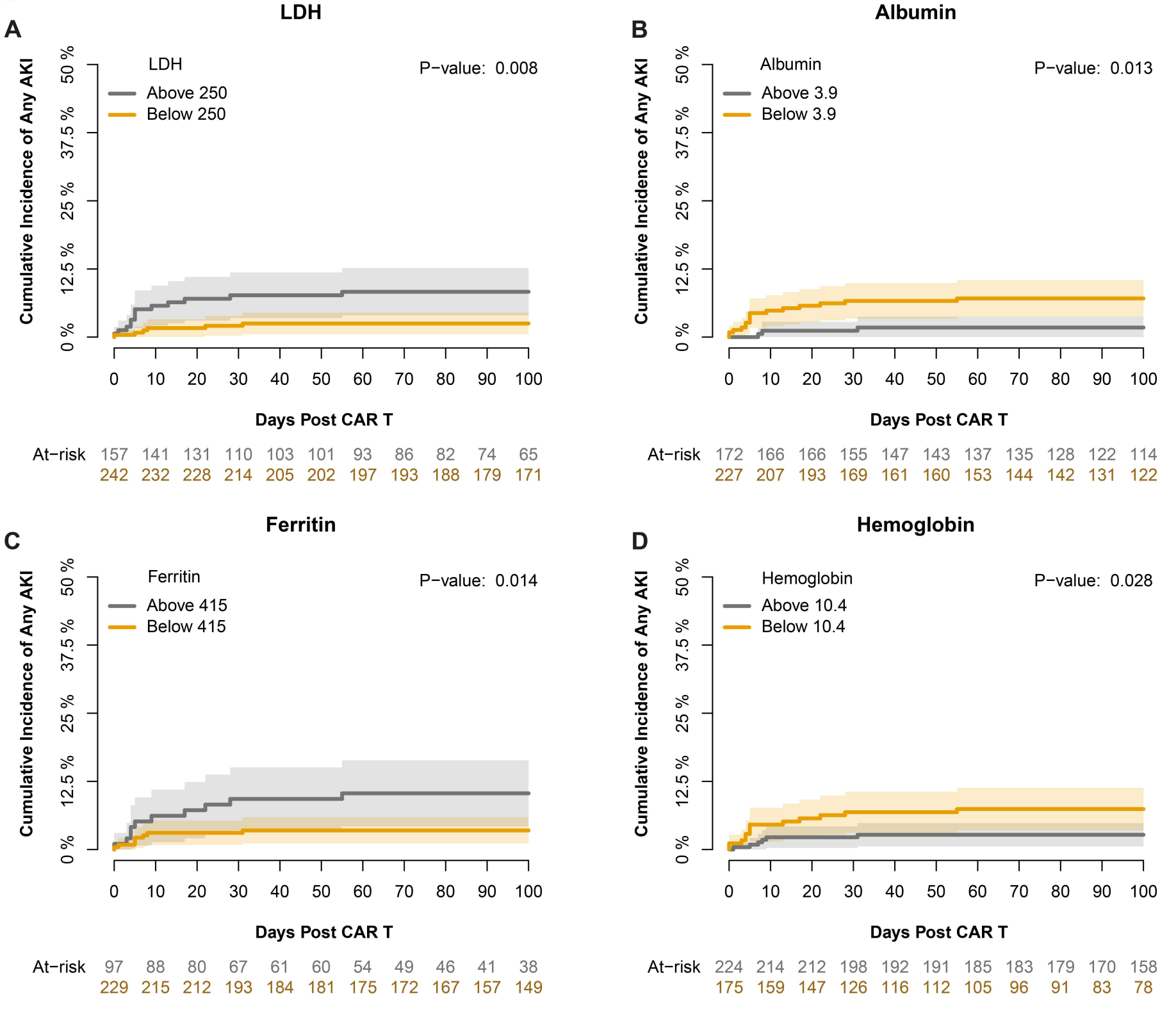
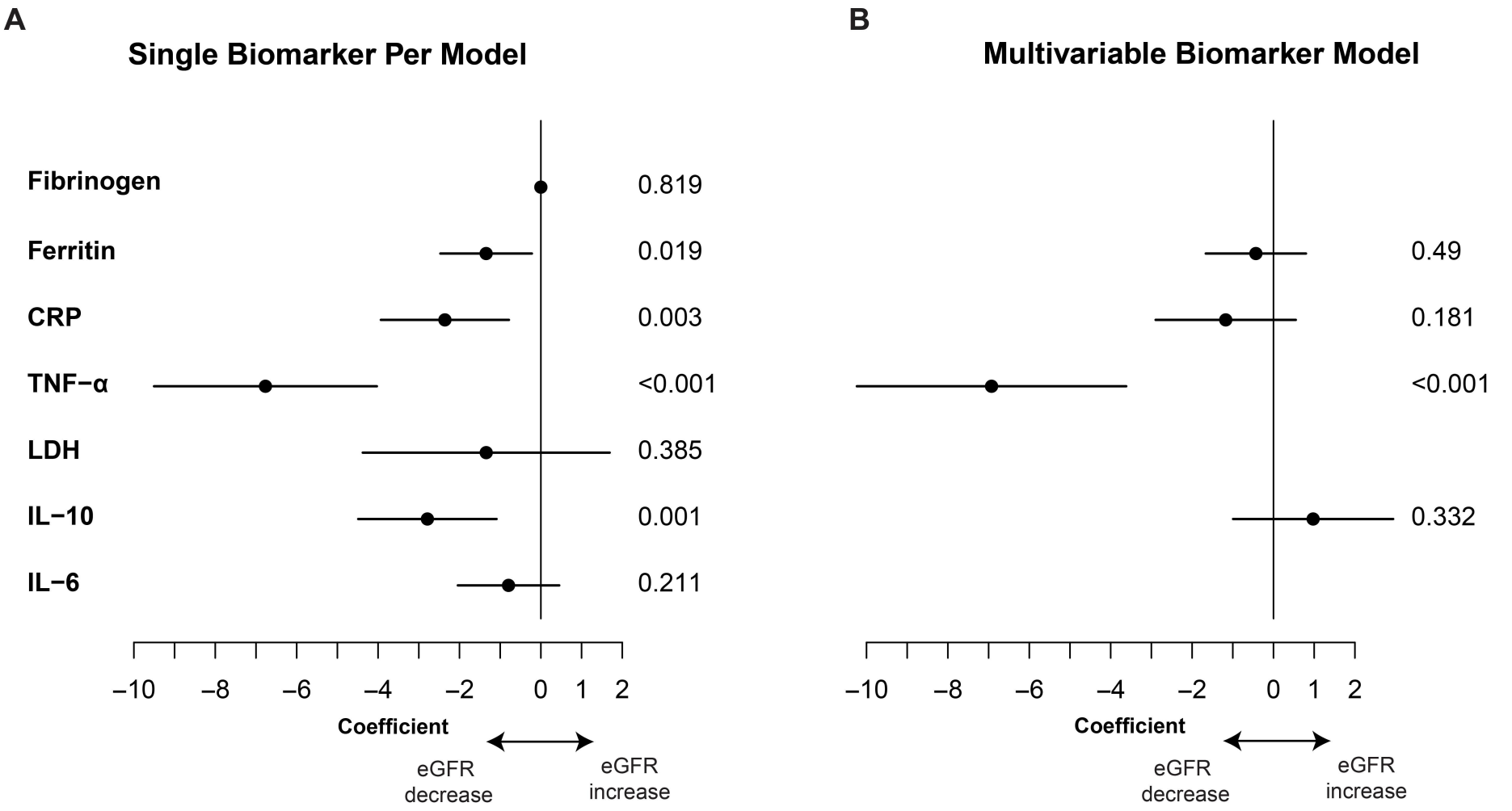

A
LDH
LDH
Above 250
Below 250
P−value: 0.008
Cumulative Incidence of Any AKI
0 %
12.5 %
25 %
37.5 %
50 %
0 10 20 30 40 50 60 70 80 90 100
Days Post CAR T
At−risk 157 141 131 110 103 101 93 86 82 74 65
242 232 228 214 205 202 197 193 188 179 171
B
Albumin
Albumin
Above 3.9
Below 3.9
P−value: 0.013
Cumulative Incidence of Any AKI
0 %
12.5 %
25 %
37.5 %
50 %
0 10 20 30 40 50 60 70 80 90 100
Days Post CAR T
At−risk 172 166 166 155 147 143 137 135 128 122 114
227 207 193 169 161 160 153 144 142 131 122
C
Ferritin
Ferritin
Above 415
Below 415
P−value: 0.014
Cumulative Incidence of Any AKI
0 %
12.5 %
25 %
37.5 %
50 %
0 10 20 30 40 50 60 70 80 90 100
Days Post CAR T
At−risk 97 88 80 67 61 60 54 49 46 41 38
229 215 212 193 184 181 175 172 167 157 149
D
Hemoglobin
Hemoglobin
Above 10.4
Below 10.4
P−value: 0.028
Cumulative Incidence of Any AKI
0 %
12.5 %
25 %
37.5 %
50 %
0 10 20 30 40 50 60 70 80 90 100
Days Post CAR T
At−risk 224 214 212 198 192 191 185 183 179 170 158
175 159 147 126 116 112 105 96 91 83 78

Figure 4


A
Single Biomarker Per Model
Fibrinogen
Ferritin
CRP
TNF−α
LDH
IL−10
IL−6
0.819
0.019
0.003
<0.001
0.385
0.001
0.211
−10
−8
−6
−4
−2
0
1
2
Coefficient
eGFR decrease
eGFR increase
B
Multivariable Biomarker Model
0.49
0.181
<0.001
0.332
−10
−8
−6
−4
−2
0
1
2
Coefficient
eGFR decrease
eGFR increase

Supplementary Methods, Tables and Figures

KDIGO criteria for AKI: Grade 1, 1.5- to <2-fold above baseline; grade 2, 2- to <3-fold above baseline; grade 3, 3-fold above baseline. Urine output decrease, though part of KDIGO criteria, was not included in our study.

Statistical analysis: Descriptive statistics, such as median and interquartile range (IQR) for continuous variables and percentages for categorical variables, are indicated in each table. Fisher's exact test or x^2 test was used to evaluate the association between categorical variables. The Wilcoxon rank-sum test or Kruskal-Wallis test was used to assess differences in a continuous variable between or among patient groups. Univariable and multivariable logistic regression and Cox regression models were constructed to evaluate associations with outcomes. Generalized estimating equations (GEE) examined the longitudinal association between inflammatory biomarkers and eGFR over the first 30 days post-CAR T cell infusion. Certain biomarkers, along with eGFR, were log-transformed based on the observed skewness in these variables over time. GEE models estimated the individual association of each biomarker while only adjusting for time post-CAR T infusion, the costimulatory domain of the CAR product, and age at infusion. Based on these results, a multivariable model was constructed and included factors that were significant at the 0.05 level. In all models, time was modeled using both a linear and quadratic term. All tests were two-sided with a significance level of p-value<0.05. Data processing and statistical analyses were performed in R statistical software.

Formulas: For chemotherapy dose analysis, body surface area (BSA) was calculated by the DuBois method: $BSA\ (m^2) = Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$.

Table S1: CAR T cell therapy complications

Characteristic	N = 399[1]
Max CRS	
0	106 (27%)
1	137 (34%)
2	130 (33%)
3	17 (4.3%)
4	8 (2.0%)
5	1 (0.3%)
Duration of CRS (days)	5.0 (3.0, 7.0)
Unknown	110
Max ICANS	
0	287 (72%)
1	35 (8.8%)
2	27 (6.8%)
3	41 (10%)
4	8 (2.0%)
5	1 (0.3%)
Duration of ICANS (days)	5 (2, 10)
Unknown	295
Tocilizumab use	192 (48%)
Steroid use	150 (38%)
ICU admission	62 (16%)
Unknown	1
Severe neutropenia post CAR T	
No	97 (25%)
Yes	287 (74%)
ANC < 500 pre-LD	3 (0.8%)
Unknown	12
Neutropenia duration (days)	10 (7, 17)
Unknown	123
Severe thrombocytopenia (<20K) post CAR T	
no	280 (73%)
yes	95 (25%)
PLT < 20K pre-LD	6 (1.6%)
Unknown	18
Thrombocytopenia duration (days)	21 (7, 32)
Unknown	336

[1]n (%); Median [Range]

Table S2: Predictors of Overall Survival

Characteristic	N	HR[1]	95% CI[1]	P value
Pre-CAR T Age	399	1.02	1.01, 1.03	0.004
Pre-CAR T KPS	398			0.018
>=90		—	—	
<90		1.53	1.06, 2.19	
eGFR (categorized)	399			0.4
eGFR >=90		—	—	
eGFR 60-89		1.27	0.91, 1.77	
eGFR <60		1.07	0.64, 1.78	
eGFR (continuous)	399	1.00	0.99, 1.00	0.5
LDH (pre-LD)	399			<0.001
normal		—	—	
elevated		3.60	2.61, 4.98	
Bridging	399			0.005
no		—	—	
yes		1.74	1.16, 2.62	
Bridging type	399			<0.001
no bridging		—	—	
non-systemic bridging		0.75	0.39, 1.45	
systemic bridging		2.04	1.35, 3.08	
CAR T Product	399			0.4
Axi-cel		—	—	
Brexu-cel		1.20	0.60, 2.40	
Liso-cel		1.13	0.77, 1.66	
Tisa-cel		1.39	0.94, 2.06	
CAR T costimulatory domain	399			0.2
CD28		—	—	
4-1BB		1.22	0.90, 1.66	

[1]HR = Hazard Ratio, CI = Confidence Interval

Table S3: Predictors of Progression Free Survival

Characteristic	N	HR[1]	95% CI[1]	P value
Pre-CAR T Age	399	1.00	0.99, 1.01	0.4
Pre-CAR T KPS	398			0.068
>=90		—	—	
<90		1.32	0.97, 1.79	
eGFR (categorized)	399			0.6
eGFR >=90		—	—	
eGFR 60-89		1.07	0.80, 1.43	
eGFR <60		0.85	0.54, 1.36	
eGFR (continuous)	399	1.00	1.00, 1.01	0.6
LDH (pre-LD)	399			<0.001
normal		—	—	
elevated		2.53	1.93, 3.32	
Bridging	399			0.1
no		—	—	
yes		1.31	0.94, 1.83	
Bridging type	399			<0.001
no bridging		—	—	
non-systemic bridging		0.73	0.44, 1.21	
systemic bridging		1.50	1.07, 2.10	
CAR T Product	399			0.010
Axi-cel		—	—	
Brexu-cel		0.80	0.42, 1.53	
Liso-cel		0.81	0.57, 1.13	
Tisa-cel		1.53	1.09, 2.13	
CAR T costimulatory domain	399			0.5
CD28		—	—	
4-1BB		1.09	0.83, 1.43	

[1]HR = Hazard Ratio, CI = Confidence Interval

Table S4: Predictors of CRS Grade ≥2

Characteristic	N	OR[1]	95% CI[1]	P value
Pre-CAR T Age	399	1.00	0.98, 1.01	0.8
Pre-CAR T KPS	398			0.6
>=90		—	—	
<90		1.12	0.73, 1.74	
eGFR (categorized)	399			>0.9
eGFR >=90		—	—	
eGFR 60-89		1.08	0.70, 1.66	
eGFR <60		1.13	0.55, 2.24	
eGFR (continuous)	399	1.00	0.99, 1.01	0.7
LDH (pre-LD)	399			>0.9
normal		—	—	
elevated		0.98	0.65, 1.48	
Bridging	399			0.7
no		—	—	
yes		1.11	0.68, 1.83	
Bridging type	399			0.4
no bridging		—	—	
non-systemic bridging		0.81	0.40, 1.58	
systemic bridging		1.20	0.73, 2.00	
CAR T Product	399			<0.001
Axi-cel		—	—	
Brexu-cel		1.57	0.66, 3.95	
Liso-cel		0.20	0.11, 0.35	
Tisa-cel		0.70	0.41, 1.20	
CAR T costimulatory domain	399			<0.001
CD28		—	—	
4-1BB		0.35	0.23, 0.52	

[1]OR = Odds Ratio, CI = Confidence Interval

Table S5: Predictors of ICANS Grade ≥2

Characteristic	N	OR[1]	95% CI[1]	P value
Pre-CAR T Age	399	1.01	0.99, 1.03	0.4
Pre-CAR T KPS	398			0.030
>=90		—	—	
<90		1.89	1.06, 3.54	
eGFR (categorized)	399			0.2
eGFR >=90		—	—	
eGFR 60-89		0.75	0.42, 1.30	
eGFR <60		1.57	0.70, 3.33	
eGFR (continuous)	399	1.00	0.99, 1.01	0.7
LDH (pre-LD)	399			0.047
normal		—	—	
elevated		1.66	1.01, 2.75	
Bridging	399			0.033
no		—	—	
yes		2.07	1.06, 4.46	
Bridging type	399			0.011
no bridging		—	—	
non-systemic bridging		1.07	0.38, 2.87	
systemic bridging		2.37	1.20, 5.15	
CAR T Product	399			<0.001
Axi-cel		—	—	
Brexu-cel		2.73	1.11, 6.65	
Liso-cel		0.32	0.15, 0.62	
Tisa-cel		0.39	0.17, 0.81	
CAR T costimulatory domain	399			<0.001
CD28		—	—	
4-1BB		0.30	0.17, 0.52	

[1]OR = Odds Ratio, CI = Confidence Interval

Table S6: Predictors of Neutropenia

Characteristic[1]	N	HR[2]	95% CI[2]	P value
Pre-CAR T Age	373	1.00	0.99, 1.01	0.7
Pre-CAR T KPS	372			0.2
>=90		—	—	
<90		1.19	0.92, 1.55	
eGFR (categorized)	373			0.2
eGFR >=90		—	—	
eGFR 60-89		1.27	0.99, 1.64	
eGFR <60		1.20	0.80, 1.79	
eGFR (continuous)	373	1.00	0.99, 1.00	0.3
LDH (pre-LD)	373			0.001
normal		—	—	
elevated		1.50	1.18, 1.90	
Bridging	373			0.2
no		—	—	
yes		1.21	0.90, 1.62	
Bridging type	373			0.043
no bridging		—	—	
non-systemic bridging		0.92	0.62, 1.37	
systemic bridging		1.31	0.97, 1.77	
CAR T Product	373			0.004
Axi-cel		—	—	
Brexu-cel		0.73	0.43, 1.25	
Liso-cel		0.89	0.67, 1.17	
Tisa-cel		0.55	0.39, 0.77	
CAR T costimulatory domain	373			0.016
CD28		—	—	
4-1BB		0.75	0.59, 0.95	
AKI[3]	276	1.24	0.58, 2.63	0.60

[1]Patients with neutropenia before CAR T infusion were removed from the analysis

[2]HR = Hazard Ratio, CI = Confidence Interval

[3]Time-dependent covariate: outcome is neutropenia

Table S7: Etiology and Nephrotoxic Drug Exposure Among Patients Experiencing AKI

Patient ID	Adjudicated AKI Cause	Drugs within 1 week prior to AKI
1	Hydronephrosis	(1) Vancomycin - max level 25 (2) Norepinephrine (3) Piperacillin-Tazobactam
51	Pre-renal - CRS	(1) Vancomycin - max level 18 (2) Piperacillin-Tazobactam
60	Pre-renal	(1) Vancomycin - max level 16 (2) Furosemide (3) Piperacillin-Tazobactam
63	Pre-renal	(1) Vancomycin - max level 14.6
74	Pre-renal	None
82	Pre-renal	(1) Vancomycin - 1 dose, no level (2) Furosemide (3) Piperacillin-Tazobactam
91	Pre-renal - CRS	(1) Vancomycin - 1 dose, no level (2) Piperacillin-Tazobactam
96	Pre-renal	None
101	Pre-renal - CRS	(1) Vancomycin - 1 dose, no level (2) Furosemide
103	Pre-renal - CRS	(1) Vancomycin - max level 16 (2) Furosemide (3) Piperacillin-Tazobactam
108	Pre-renal - CRS	(1) Vancomycin - max level 12.7 (2) Norepinephrine (3) Piperacillin-Tazobactam
109	Pre-renal - CRS	(1) Vancomycin - max level 45 (2) Furosemide
112	Pre-renal - CRS	None
127	Pre-renal	(1) NSAIDs
138	Pre-renal - CRS	(1) Piperacillin-Tazobactam
149	Pre-renal	(1) Furosemide
150	Pre-renal	(1) IV contrast
175	Intra-renal / ATN	(1) Vancomycin – max level 21.4
279	Intra-renal - CRS	(1) Vancomycin - max level 24.6 (2) Furosemide (3) Piperacillin-Tazobactam
290	Intra-renal - CRS / managed for TLS	(1) Rasburicase – 2 doses for TLS
291	Pre-renal	None
292	Intra-renal	(1) Vancomycin – 3 doses, no level (2) NSAIDs
293	Pre-renal - CRS	(1) Piperacillin-Tazobactam
299	Hydronephrosis	None
308	Pre-renal - CRS	(1) Vancomycin – 1 dose, no level (2) Furosemide (3) Piperacillin-Tazobactam
399	Hydronephrosis	(1) Vancomycin – max level 21.6
423	Pre-renal	None
436	Pre-renal	(1) Furosemide (2) Foscarnet
437	Intra-renal - CRS	(1) Vancomycin – max level 40
615	Intra-renal - CRS	(1) Piperacillin-Tazobactam
664	Pre-renal - CRS	(1) Vancomycin – max level 12.7
670	Pre-renal - CRS	(1) Piperacillin-Tazobactam
707	Pre-renal	(1) IV contrast
738	Pre-renal - CRS	(1) Vancomycin – max level 8.6 (2) Piperacillin-Tazobactam (3) Furosemide

740	Intra-renal / ATN	(1) Piperacillin-Tazobactam (2) Foscarnet (3) Furosemide (4) IV contrast
757	Pre-renal	None
764	Pre-renal - CRS	(1) Piperacillin-Tazobactam
804	Intra-renal - CRS	(1) Vancomycin – max level 15.3 (2) Furosemide (3) IV contrast
860	Pre-renal	None

Abbreviations: CRS = cytokine release syndrome; TLS = tumor lysis syndrome

Table S8: Baseline Clinical Characteristics of Event-Free AKI versus non-AKI Patients

CHARACTERISTIC	OVERALL, N = 399[1]	EVENT-FREE AND NO AKI, [2] N = 245[1]	AKI GRADE 1, N = 20[1]	AKI GRADE ≥2, N = 19[1]
Pre-CAR T Age	66 (56, 73)	66 (56, 72)	62 (54, 72)	70 (59, 77)
Sex				
Male	260 (65%)	145 (59%)	15 (75%)	16 (84%)
Female	139 (35%)	100 (41%)	5 (25%)	3 (16%)
Pre-CAR T KPS				
>=90	124 (31%)	87 (36%)	5 (25%)	4 (21%)
<90	274 (69%)	157 (64%)	15 (75%)	15 (79%)
Ethnicity				
Hispanic or Latino	26 (6.8%)	14 (6.0%)	2 (12%)	1 (5.9%)
Not Hispanic or Latino	354 (93%)	221 (94%)	15 (88%)	16 (94%)
Unknown	19	10	3	2
Race				
Asian	35 (9.1%)	25 (11%)	4 (21%)	1 (5.6%)
Black or African American	16 (4.2%)	9 (3.8%)	2 (11%)	0 (0%)
Other	16 (4.2%)	11 (4.6%)	1 (5.3%)	0 (0%)
White	316 (83%)	192 (81%)	12 (63%)	17 (94%)
Unknown	16	8	1	1
NHL broad classification				
LBCL	335 (84%)	197 (80%)	19 (95%)	14 (74%)
Mantle cell lymphoma	44 (11%)	30 (12%)	1 (5.0%)	5 (26%)
Non-LBCL	20 (5.0%)	18 (7.3%)	0 (0%)	0 (0%)
NHL transformation origin				
de novo LBCL	210 (53%)	121 (50%)	12 (60%)	9 (47%)
transformed tFL	77 (19%)	48 (20%)	7 (35%)	1 (5.3%)
Other primary	42 (11%)	24 (9.9%)	0 (0%)	4 (21%)
Unknown/ not applicable	70	52	1	5
Double or triple hit				
Not double or triple hit	258 (70%)	154 (68%)	15 (79%)	9 (50%)
Double or triple hit	47 (13%)	26 (11%)	3 (16%)	4 (22%)
Unknown/ not applicable	94	65	2	6
Cell of origin				
GCB	165 (43%)	102 (43%)	11 (58%)	8 (44%)
non-GCB	157 (41%)	90 (38%)	7 (37%)	5 (28%)
Unknown/ not applicable	77	53	2	6
Prior treatment lines	3 (2, 4)	3 (2, 4)	3 (2, 4)	2 (2, 3)
Unknown	6	5	1	0
Prior treatment lines (category)				
<=3 lines	256 (65%)	155 (65%)	11 (58%)	15 (79%)
4-5 lines	89 (23%)	60 (25%)	4 (21%)	2 (11%)
6+ lines	48 (12%)	25 (10%)	4 (21%)	2 (11%)
Unknown	6	5	1	0
Previous auto-HCT	77 (19%)	51 (21%)	2 (10%)	1 (5.3%)
Previous allo-HCT	19 (4.8%)	11 (4.5%)	0 (0%)	2 (11%)
Primary refractory disease	146 (37%)	74 (31%)	7 (35%)	13 (68%)
Unknown	3	3	0	0
Bridging type				
no bridging	86 (22%)	59 (24%)	3 (15%)	2 (11%)
non-systemic bridging	65 (16%)	49 (20%)	5 (25%)	2 (11%)

systemic bridging	248 (62%)	137 (56%)	12 (60%)	15 (79%)
CAR T product				
Axi-cel	183 (46%)	106 (43%)	12 (60%)	6 (32%)
Brexu-cel	23 (5.8%)	16 (6.5%)	0 (0%)	4 (21%)
Liso-cel	115 (29%)	83 (34%)	5 (25%)	2 (11%)
Tisa-cel	78 (20%)	40 (16%)	3 (15%)	7 (37%)
CAR T costimulatory domain				
CD28	206 (52%)	122 (50%)	12 (60%)	10 (53%)
41BB	193 (48%)	123 (50%)	8 (40%)	9 (47%)
Lymphodepletion				
Flu/Cy	343 (86%)	212 (87%)	18 (90%)	16 (84%)
Bendamustine	56 (14%)	33 (13%)	2 (10%)	3 (16%)
Total fludarabine dose (mg/m^2)	86 (74, 90)	86 (73, 90)	87 (82, 90)	78 (73, 89)
Unknown	57	34	2	3
Predicted fludarabine AUC (mgh/L)	15.75 (13.95, 17.51)	16.17 (14.46, 17.63)	14.25 (13.74, 15.90)	15.44 (13.82, 17.04)
Unknown	69	39	3	5
Predicted fludarabine AUC (mgh/L) category				
0 – 18	266 (81%)	161 (78%)	15 (88%)	13 (93%)
18 – 25	64 (19%)	45 (22%)	2 (12%)	1 (7.1%)
Unknown	69	39	3	5
Pre-CAR T disease response				
CR	40 (10%)	37 (15%)	1 (5.0%)	0 (0%)
PR	130 (33%)	90 (37%)	6 (30%)	2 (11%)
SD/PD	229 (57%)	118 (48%)	13 (65%)	17 (89%)
LDH range pre-LD				
normal	242 (61%)	178 (73%)	9 (45%)	6 (32%)
elevated	157 (39%)	67 (27%)	11 (55%)	13 (68%)

[1]Median (IQR); n (%)
[2]Event-free indicates patients who did not experience disease relapse, change of cancer treatment, or death

Abbreviations: CAR T = chimeric antigen receptor T cell; KPS = Karnofsky Performance Scale; NHL = non-Hodgkin lymphoma; LBCL = large B cell lymphoma; tFL = transformed follicular lymphoma; GCB = germinal center B-cell; Axi-cel = axicabtagene ciloleucel; Tisa-cel = tisagenlecleucel; Brexu-cel = brexucabtagene autoleucel; Liso-cel = lisocabtagene maraleucel; Flu/Cy = fludarabine and cyclophosphamide; auto-HCT = autologous stem cell transplant; allo-HCT = allogeneic stem cell transplant; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; AUC = area under the curve (for drug exposure over time); pre-LD = pre-lymphodepletion; LDH = lactate dehydrogenase; CRP = C reactive protein.

Table S9: Infectious Complications in Event Free AKI versus non-AKI Patients

Characteristic[1]	Event N[1]	HR[12]	95% CI[12]	p-value[1]
Bacteremia	39	2.78	1.07, 7.23	0.036
Viral Infection	39	4.52	1.93, 10.6	<0.001

[1]Time-dependent Covariates; only includes infections post CAR T cell infusion between Day 0 and Day 100.

[2]HR = Hazard Ratio, CI = Confidence Interval

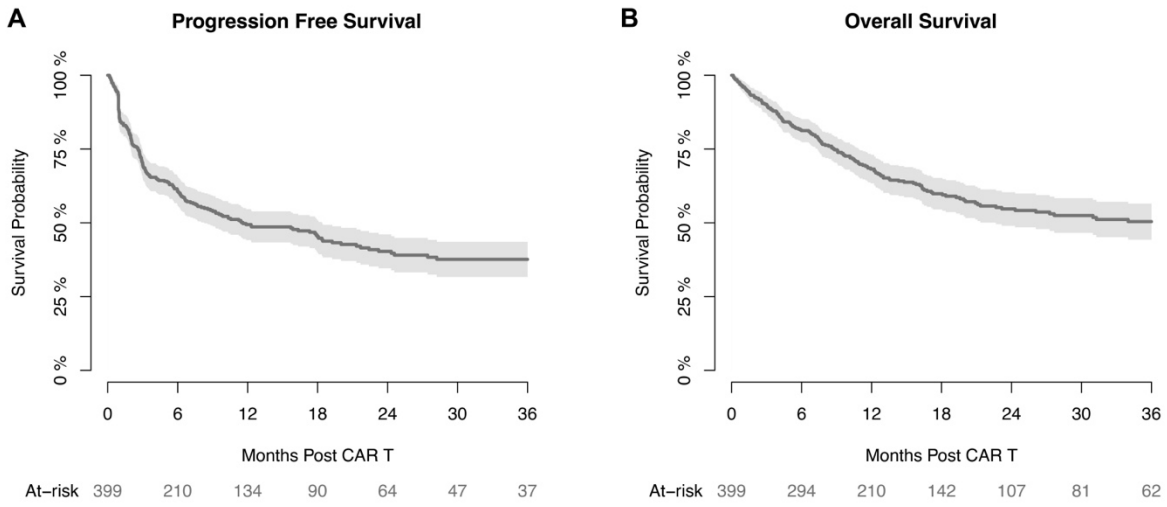


Figure S1: Overall clinical outcomes of the MSK cohort. (A) Progression free survival (PFS) and (B) overall survival (OS) is shown in patients across the MSK cohort. Shaded areas indicate the 95% confidence interval.

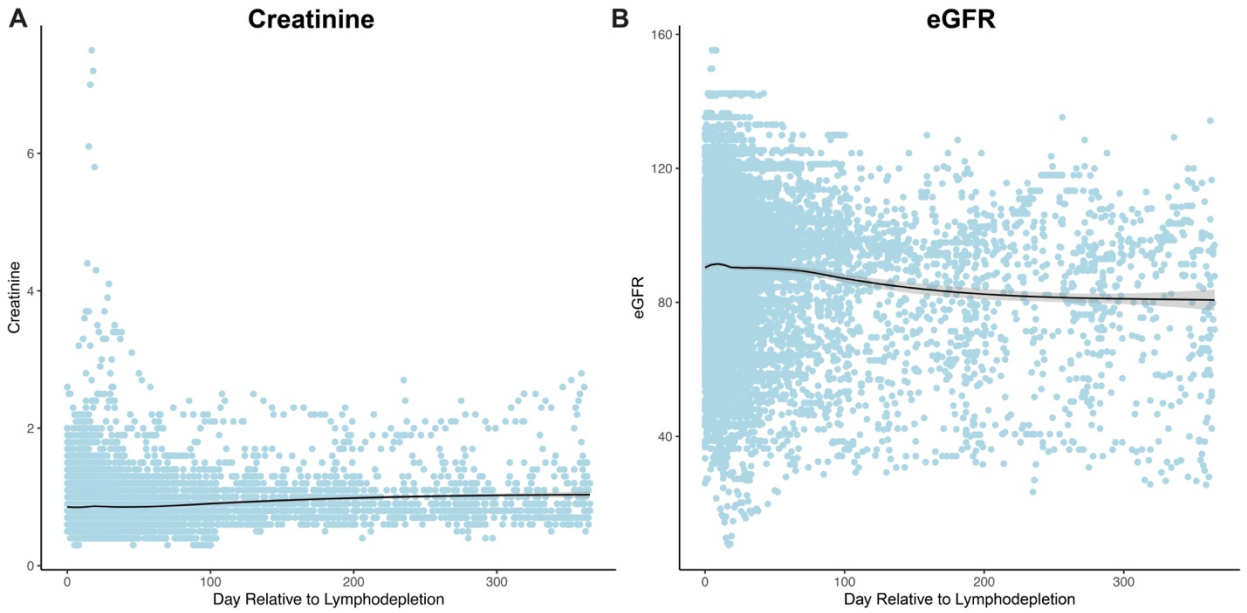


Figure S2: Trajectory of renal function across all patients. Serum creatinine (A) and estimated glomerular filtration rate (eGFR; B) are plotted over 360 days relative to the time of lymphodepletion. Mean values (black lines) along with 95% confidence bands were estimated using local polynomial smoothing.

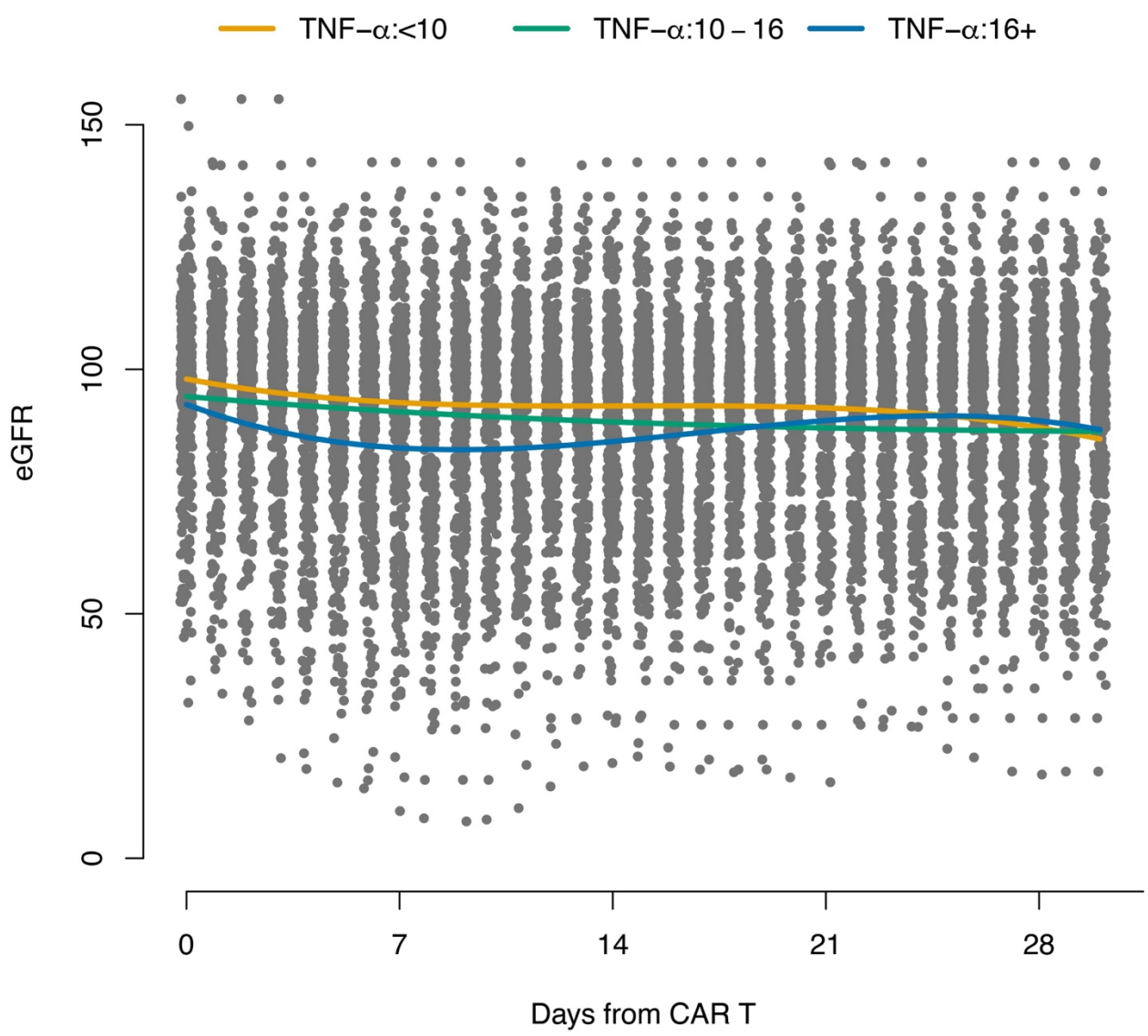


Figure S3: Trajectory of patient estimated glomerular filtration rate (eGFR) by TNF-alpha levels. Median eGFR curves are shown in the first 30 days after CAR T cell infusion, stratified by serum TNF-alpha levels: <10 pg/mL (orange), 10-16 pg/mL (green), and >16 pg/mL (blue).