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

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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

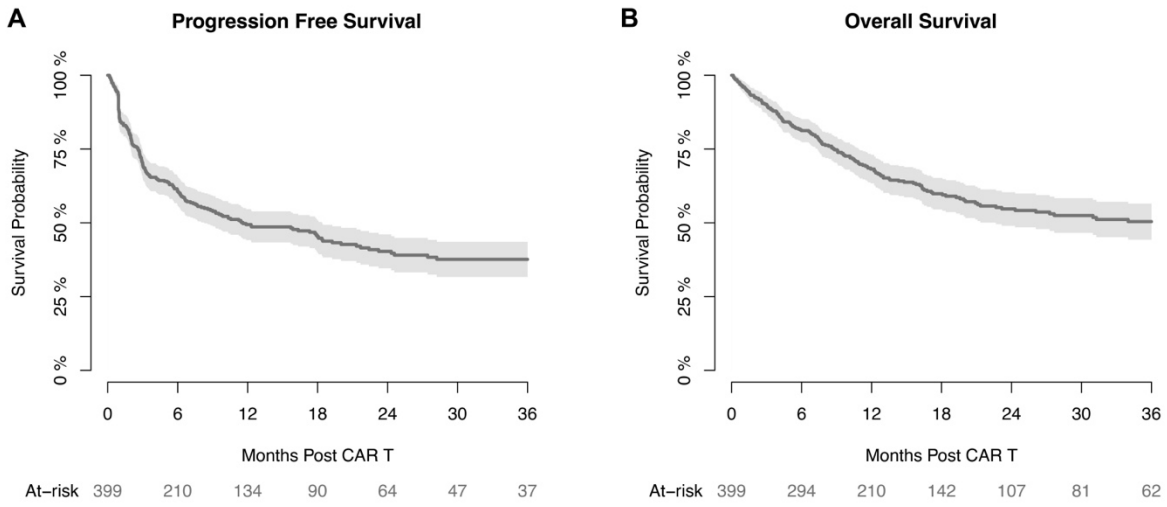

Figure S1: Overall clinical outcomes of the MSK cohort. (A) Progression free survival (PFS) and (B) overall survival (OS) is shown in patients across the MSK cohort. Shaded areas indicate the 95% confidence interval.

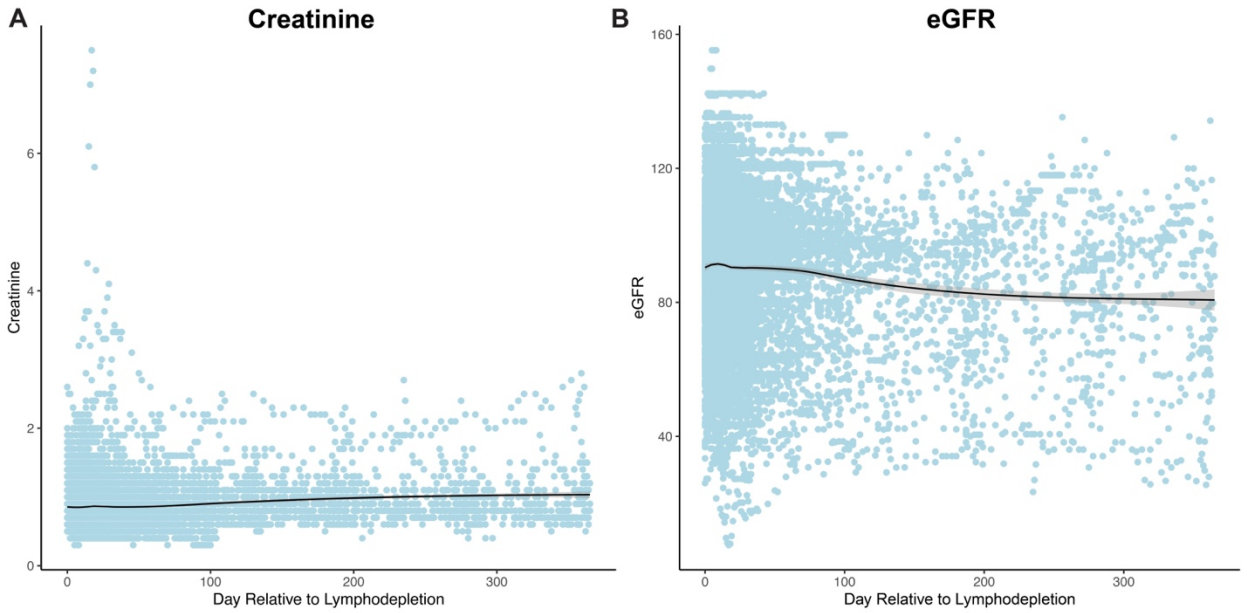

Figure S2: Trajectory of renal function across all patients. Serum creatinine (A) and estimated glomerular filtration rate (eGFR; B) are plotted over 360 days relative to the time of lymphodepletion. Mean values (black lines) along with 95% confidence bands were estimated using local polynomial smoothing.

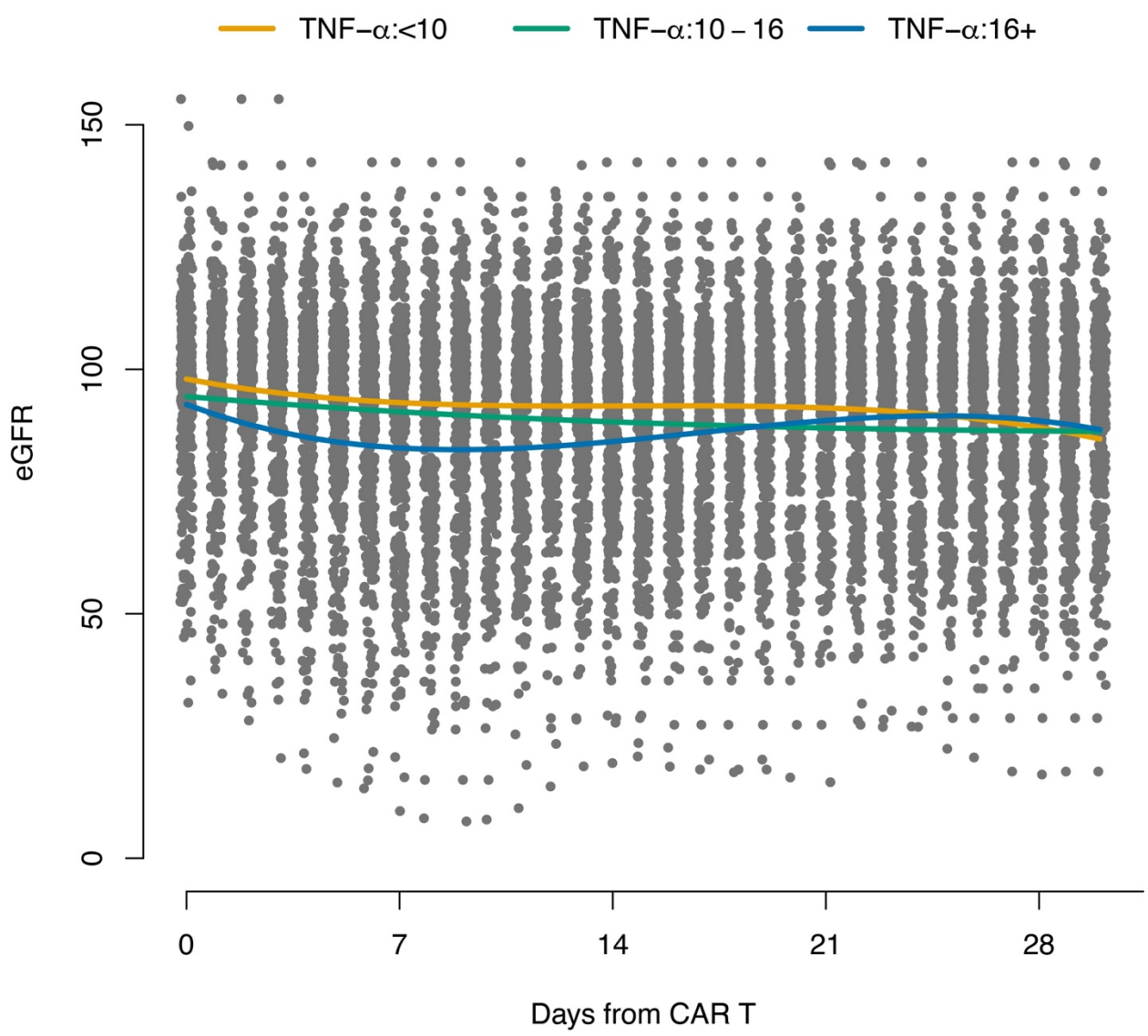

Figure S3: Trajectory of patient estimated glomerular filtration rate (eGFR) by TNF-alpha levels. Median eGFR curves are shown in the first 30 days after CAR T cell infusion, stratified by serum TNF-alpha levels: <10 pg/mL (orange), 10-16 pg/mL (green), and >16 pg/mL (blue).