Supplemental Material

Cortazar *et al.* Clinical Features and Outcomes of Immune Checkpoint Inhibitor-associated AKI: a multicenter study

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Supplemental Appendix – Data collected on cases

Data collected from each case included age; gender; race; comorbidities, including pre-existing autoimmune disease; baseline serum creatinine (SCr), defined as the value immediately preceding initiation of ICPi therapy; malignancy type; ICPi regimen; occurrence of extrarenal immune-related adverse events (irAEs) prior to or concomitant with ICPi-AKI; concomitant use of tubulointerstitial nephritis-causing medications, including proton pump inhibitors, antibiotics, and nonsteroidal anti-inflammatory drugs within 2 weeks preceding the diagnosis of ICPi-AKI; longitudinal SCr values; urinalysis, urine microscopy, and quantification of proteinuria at the time of AKI; need for renal replacement therapy; glucocorticoid regimen; alternative immunosuppressants administered; and survival status at last follow-up. We also collected pathology reports from all patients who underwent a kidney biopsy. We classified the degree of interstitial fibrosis/tubular atrophy and glomerulosclerosis as none/mild (0-25%), moderate (26-50%), or severe (>50%). We also collected data on the presence of granulomatous features and tissue eosinophilia. Patients were considered to have tissue eosinophilia if the pathologist noted that eosinophils comprised a prominent component of the interstitial infiltrate.

Collaborating Institution (# patients contributed)	
Brigham and Women's Hospital/Dana Farber Cancer Institute (14)	Boston, MA
Columbia University Medical Center (7)	New York, NY
Duke University (6)	Durham, NC
Johns Hopkins University (3)	Baltimore, MD
Massachusetts General Hospital (13)	Boston, MA
Mayo Clinic (11)	Rochester, MN
MD Anderson Cancer Center (13)	Houston, TX
Memorial Sloane Kettering Cancer Center (20)	New York, NY
University of Alabama Birmingham (5)	Birmingham, AL
University of California, Los Angeles (3)	Los Angeles, CA
University of Miami (3)	Miami, FL
University of Pennsylvania (5)	Philadelphia, PA
University of Toronto (8)	Toronto, ON
University of Virginia (6)	Charlottesville, VA
University of Washington (5)	Seattle, WA
Vanderbilt University (1)	Nashville, TN
Washington University in Saint Louis (7)	Saint Louis, MO
Yale University (8)	New Haven, CT

Supplemental Table 1. Collaborating institutions. Eighteen total institutions contributed to patients to the study.

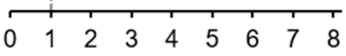
Year of ICPi initiation	Cases (*n*=138)	Control (*n*=276)
2011-2012	10 (7.2)	4 (1.4)
2013-2014	17 (12.3)	20 (7.2)
2015-2016	45 (32.6)	144 (52.2)
2017-2018	66 (47.8)	108 (39.1)

Supplemental Table 2. ICPi initiation by year, cases vs. controls

Variable	Biopsied (*n*=60)	Non-biopsied (*n*=78)	P Value
Age at ICPi initiation (yrs)	64 (58-73)	69 (60-75)	0.047
Female, n (%)	21 (35)	34 (44)	0.38
Race, n (%)			0.90
White	50 (83)	66 (85)	
Black	4 (7)	6 (8)	
Asian	1 (2)	2 (3)	
Comorbidities, n (%)			
Hypertension	30 (50)	47 (60)	0.30
Diabetes	9 (15)	14 (18)	0.82
CHF	0 (0)	3 (4)	0.26
COPD	2 (3)	4 (5)	0.70
Cirrhosis	0 (0)	2 (2.6)	0.51
Baseline SCr (mg/dL)	0.94 (0.80-1.34)	0.91 (0.80-1.20)	0.34
Baseline eGFR (ml/min)	74 (55-91)	72 (55-88)	0.92
CKD, n (%)	19 (32)	25 (32)	1.00
CKD IV, n (%)	4 (7)	5 (6)	1.00
Autoimmune Disease, n (%)	11 (18)	6 (8)	0.07
Malignancy, n (%)			0.88
Melanoma	20 (33)	29 (37)	
Lung	15 (25)	21 (27)	
Genitourinary	10 (17)	13 (17)	
Other	15 (25)	15 (19)	
Proton pump inhibitor, n (%)	33 (55)	42 (54)	1.00
ICPi[1], n (%)			
Anti-CTLA-4	19 (32)	25 (32)	1.00
Anti-PD-1	56 (93)	71 (91)	0.76
Anti-PD-L1	5 (8)	5 (6)	0.75
Combo anti-CTLA-4 + anti-PD-1/ PD-L1	18 (30)	21 (27)	0.71

Supplemental Table 3. Baseline characteristics of biopsied and non-biopsied patients with ICPi-AKI. [1]Denotes all ICPis ever received. Abbreviations: Combo, combination; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICPi, immune checkpoint inhibitor; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; SCr, serum creatinine.

Variable	Odds Ratio (95% CIs) for ICPi-AKI among biopsied patients (*n*=60) Univariate	Multivariable	Forest Plot
Age (per 10 yrs)	0.97 (0.78–1.19)	0.77 (0.59–1.01)	
Female	0.88 (0.49–1.579	0.81 (0.47–1.54)	
Prior auto-immune disease	1.84 (0.86–3.92)	1.90 (0.84–4.26)	
eGFR (per 30 ml/min decline)	1.73 (1.21–2.49)	2.41 (1.55–3.76)	
PPI use	2.44 (1.39–4.31)	2.93 (1.59–5.39)	
Combination ICPi therapy	2.95 (1.53–5.69)	3.96 (1.92–8.16)	



Supplemental Table 4. Risk factors for ICPi-AKI among biopsied patients. The multivariable model was adjusted for all covariates listed in the table. Abbreviations: ICPi, immune checkpoint inhibitor; PPI, proton pump inhibitor.

Concomitant Nephrotoxins	*n* (%)
Cisplatin	0 (0)
VEGF/TKI[1]	7 (5)
Other[2]	2 (1)

Supplemental Table 5. Concomitant chemotherapeutic nephrotoxins. This table shows the number of patients who received cisplatin, a VEGF/TKI agent, or other potentially nephrotoxic chemotherapeutic agents with 2 weeks prior to ICPi-AKI. Data were available for the entire cohort (*n*=138). [1]Alectinib (*n*=1), bevacizumab (*n*=2), bosutinib (*n*=1), crizotinib (*n*=1), osimertinib (*n*=1), and vemurafenib (*n*=1); [2]Carboplatin (*n*=1), dabrafenib (*n*=1). Abbreviations: VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor.

Histologic Feature	*n* (%)
Granulomatous Features	11 (20)
Tissue Eosinophilia	32 (57)
Interstitial Fibrosis/Tubular Atrophy[1]	
None/Mild	43 (80)
Moderate	9 (17)
Severe	2 (4)
Glomerulosclerosis	
None/Mild	47 (84)
Moderate	5 (9)
Severe	4 (7)

Supplemental Table 6. Histologic features of biopsied patients with TIN. *n*=56.
[1]54 patients with available data on interstitial fibrosis/tubular atrophy. Abbreviations: TIN, tubulointerstitial nephritis.

Treatment Variable	All (*n*=119)	Biopsied (*n*=53)	Not Biopsied (*n*=66)	P Value
SCr at GC initiation (mg/dL)	3.01 (2.25–4.48)	3.19 (2.53–5.11)	2.81 (2.13–3.97)	0.13
Required RRT at GC initiation, n (%)	3 (3)	3 (6)	0 (0)	0.09
Treatment delay[1] (days)	3 (0–8)	6 (2–14)	2 (0–6)	<0.001
Received IV pulse GC, n (%)	36 (30)	15 (28)	21 (32)	0.69
Grams of solumedrol	1.00 (0.38–2.03)	0.75 (0.44–1.75)	1.50 (0.38–2.75)	0.98
Initial daily oral GC dose (mg of prednisone)	60 (60–80)	60 (60–61)	60 (60–90)	0.63
Days at initial oral GC dose	7 (5–12)	7 (5–12)	7 (5–11)	0.38
Days at > 20 mg oral prednisone	28 (16–47)	28 (20–47)	30 (14–44)	0.25
Cumulative oral GC dose in first 2 weeks (mg of prednisone)	780 (600–980)	790 (665–951)	780 (570–980)	0.50
Days of oral GC	63 (32–107)	69 (42–102)	54 (28–94)	0.02
Received non-GC immuno-suppressant[2], n (%)	11 (9)	7 (13)	4 (6)	0.21
Nadir SCr after treatment[3] (mg/dL)	1.40 (1.08–1.73)	1.47 (1.09–1.81)	1.39 (1.05–1.64)	0.39

Supplemental Table 7. Treatment of ICPi-AKI, stratified by biopsy status. Data are shown as median (interquartile range) and *n* (%). [1]Denotes time from doubling of SCr to initiation of GCs. [2]Non-GC immunosuppression included mycophenolate mofetil (*n*=7), rituximab (*n*=2), cyclophosphamide (*n*=1), and eculizumab (*n*=1). [3]Defined as the lowest value achieved within 3 months following the AKI episode (excluding values obtained during RRT). Abbreviations: GC, glucocorticoids; RRT, renal replacement therapy; SCr, serum creatinine.

Age/ Sex	Cancer Type	ICPi Regimen	Biopsy Findings	Alternative Immuno-suppression	Renal Recovery Status	6 Month Survival Status
58F	GBM	Pembro		MMF	Partial	Deceased
64F	Liver	Nivo		Rituximab	Complete	Alive
75M	Melanoma	Ipi+Nivo	TIN	MMF	Partial	Deceased
41M	Squamous cell lung	Nivo	Pauci-Immune GN	Rituximab	Complete	Deceased
51F	Melanoma	Ipi+Nivo+ Pembro	TIN	MMF, Infliximab	Partial	Alive
57M	Melanoma	Ipi+Nivo	Anti-GBM GN	Cyclophosphamide	None	Alive
54M	Squamous cell lung	Pembro		MMF	Complete	Alive
56F	Melanoma	Pembro + Durvalumab		Plasma Exchange, Eculizumab	Partial	Deceased
63M	RCC	Nivo	TIN	MMF	Partial	Alive
66M	RCC	Nivo	TIN	MMF	Partial	Alive
63M	Melanoma	Nivo	TIN	MMF	Partial	Alive

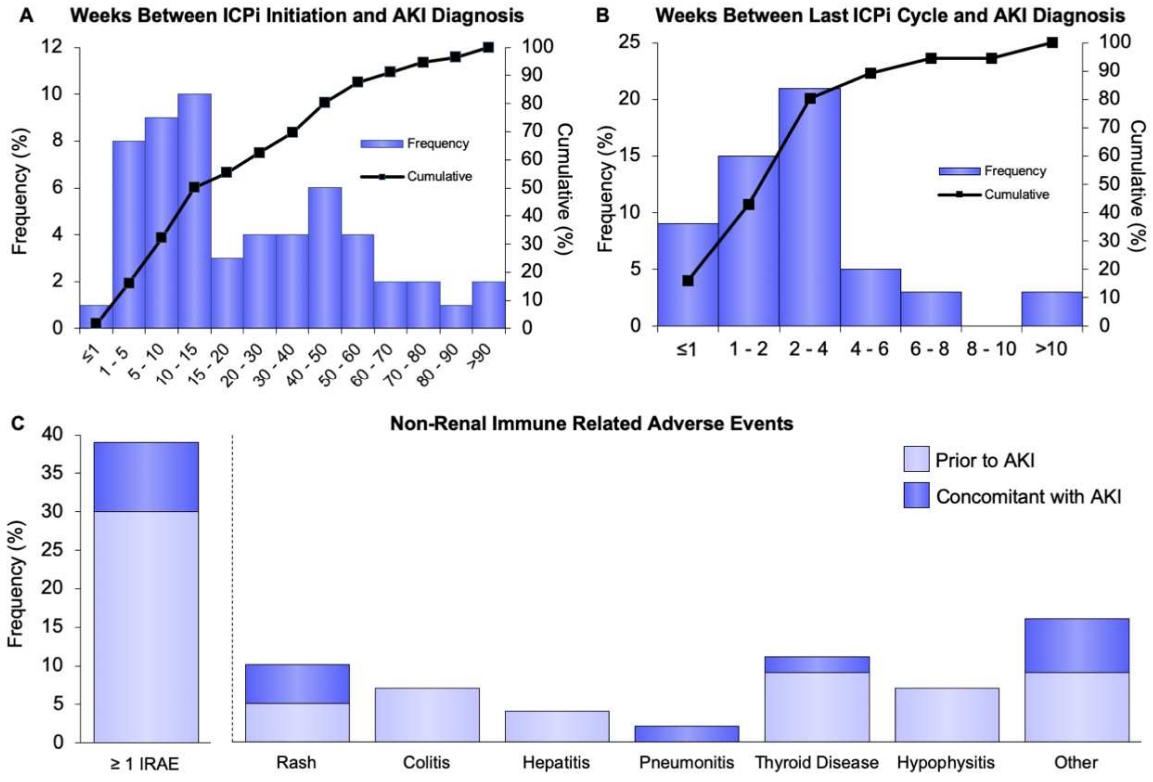
Supplemental Table 8. Clinical features of patients receiving immunosuppression in addition to steroids (*n*=11). Patients with glomerular disease received the immunosuppressant as initial therapy concomitantly with steroids, while patients with biopsy-proven or suspected TIN received the immunosuppressant for resistant disease. Abbreviations: F, female; GBM, glioblastoma multiforme; GC, glucocorticoids; GN, glomerulonephritis; Ipi, Ipilimumab; M, male; MMF, mycophenolate mofetil; Nivo, Nivolumab; Pembro, Pembrolizumab; RCC, renal cell carcinoma; TIN, tubulointerstitial nephritis.

Drug	Univariate Odds Ratio (95% CI)
Antibiotic	1.87 (0.59–5.90)
NSAID	2.02 (0.89–4.58)
PPI	1.14 (0.58–2.27)

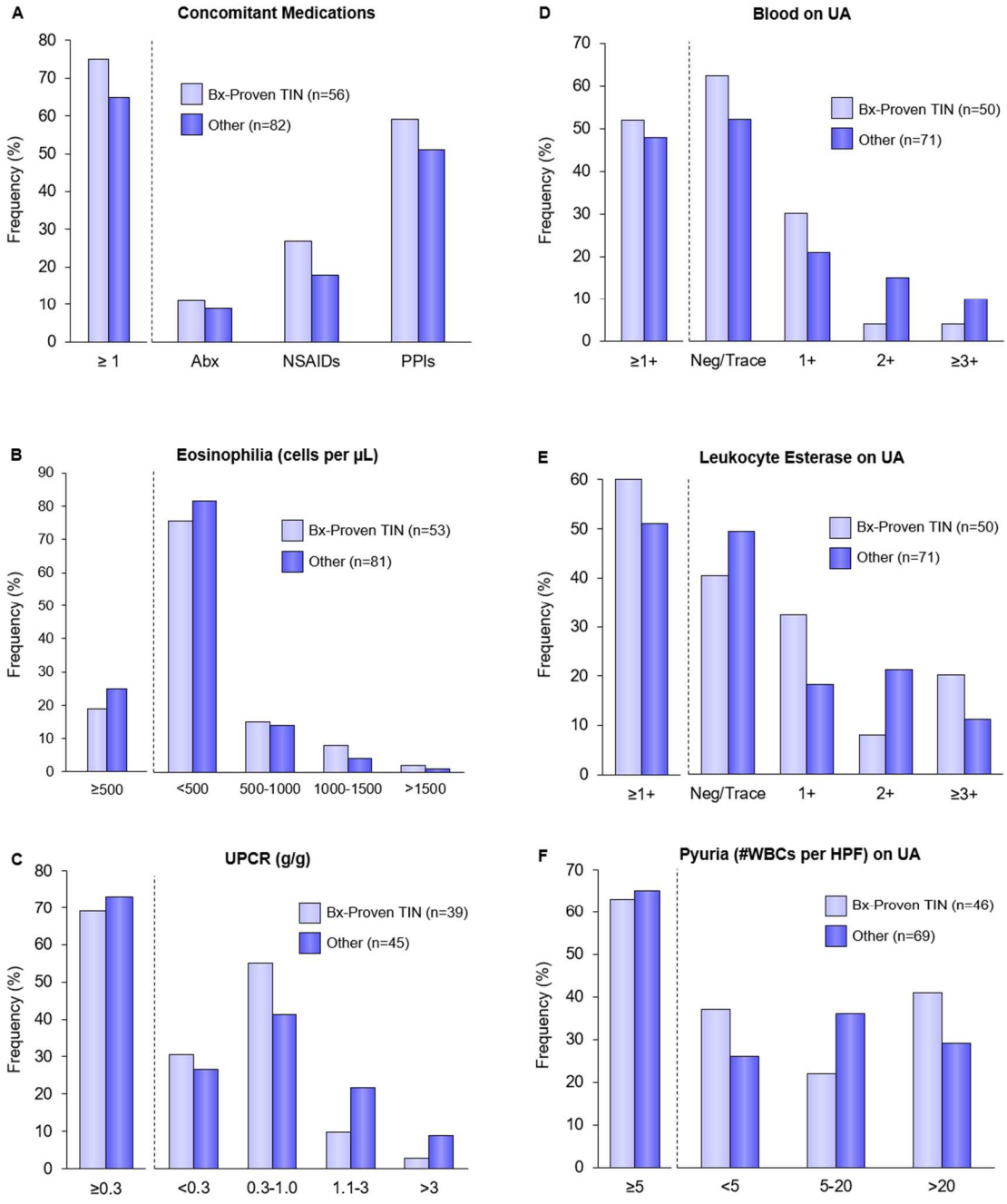
Supplemental Table 9. **Odds ratios for complete renal recovery according to concomitant potential TIN-causing medications.** Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; TIN, tubulointerstitial nephritis.

Histologic Feature	Univariate Odds Ratio (95% CI)
Granulomatous TIN	1.73 (0.46-6.56)
Tissue Eosinophilia	1.01 (0.34-2.98)
Moderate/Severe IFTA	0.47 (0.12-1.74)
Moderate/Severe GS[1]	1.69 (0.40-7.10)

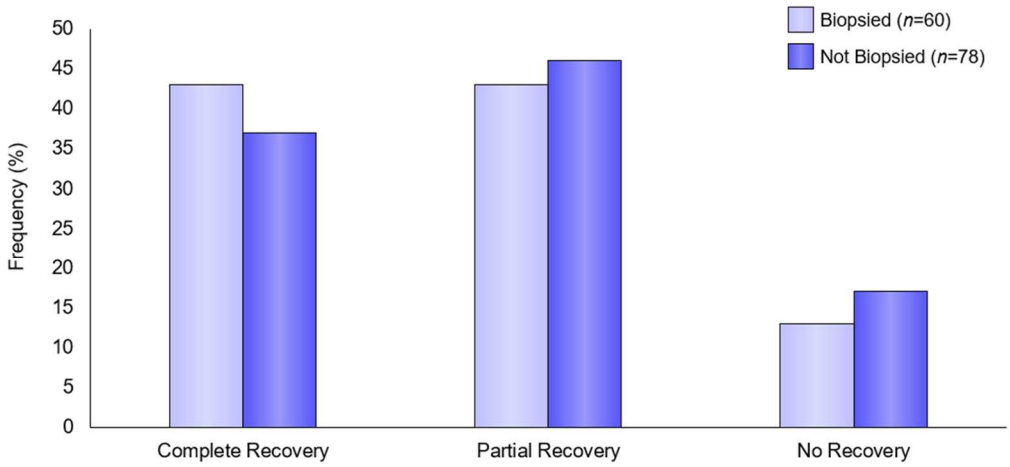
Supplemental Table 10. **Odds ratios for complete renal recovery according to histologic features in patients with TIN.** [1]Sum of global and segmental glomerulosclerosis.
Abbreviations: GS, glomerulosclerosis; IFTA, interstitial fibrosis and tubular atrophy.



Supplemental Figure 1. Clinical features of ICPi-AKI in patients with biopsy-proven TIN (*n*=56).

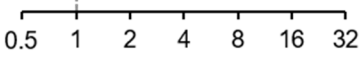


Supplemental Figure 2. Clinical features of ICPi-AKI in patients with and without biopsy-proven TIN. Panel A shows the frequency of concomitant potential TIN-causing medications taken within two weeks preceding ICPi-AKI in patients with and without biopsy-proven TIN. Panels B, C, D, E, and F show the distribution of eosinophilia, proteinuria, hematuria, leukocyte esterase, and pyuria, respectively, in patients with and without biopsy-proven TIN. For all analyses, chi-square testing demonstrated similar distributions between biopsy-proven vs. non-biopsy-proven TIN. Abbreviations: Abx, antibiotic; Bx, biopsy; HPF, high-power field; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; TIN, tubulointerstitial nephritis; UA, urinalysis; UPCR, urine protein-to-creatinine ratio; WBCs, white blood cells.

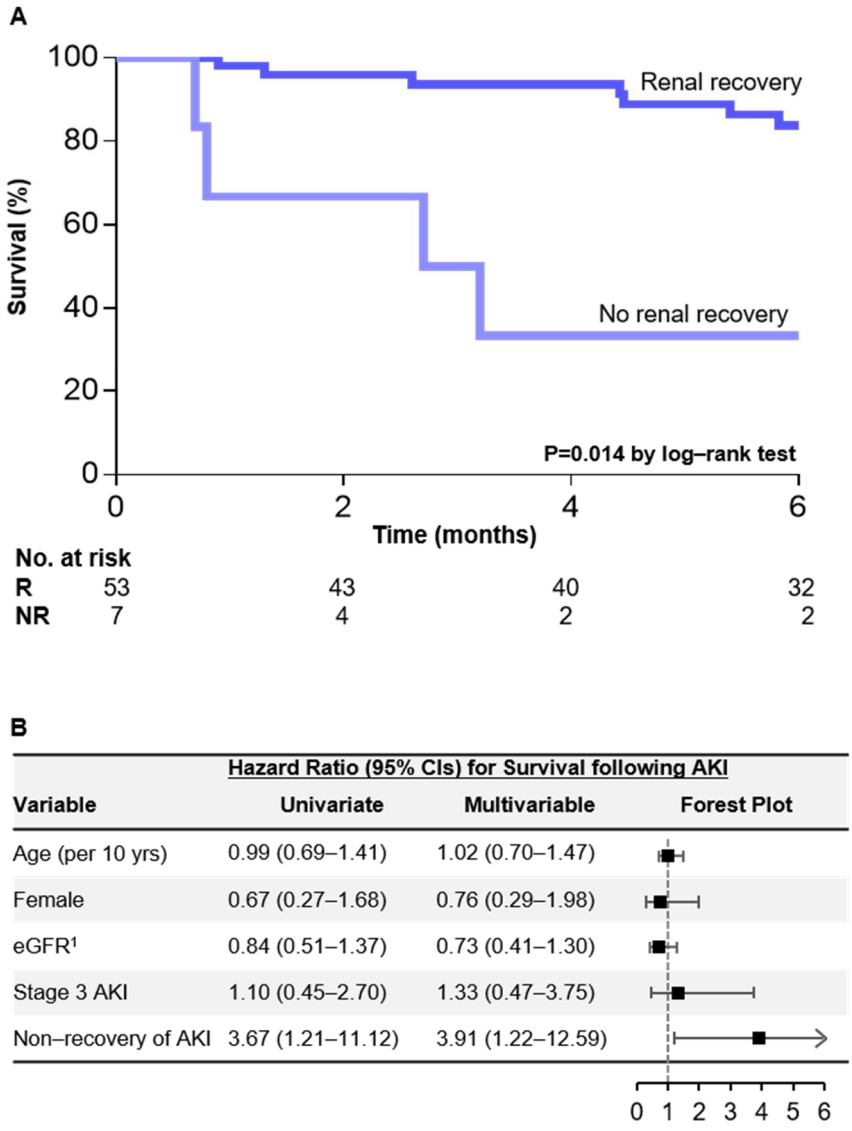


Supplemental Figure 3. Renal recovery following ICPi-AKI among biopsied versus non-biopsied patients. The frequency of complete, partial, and no renal recovery following an episode of ICPi-AKI was similar in biopsied versus non-biopsied patients.

Variable	Odds Ratios (95% CIs) for Complete Renal Recovery among biopsied patients (*n*=60)		
	Univariate	Multivariable	Forest Plot
Age (per 10 yrs)	0.84 (0.53–1.33)	0.98 (0.57–1.69)	
Female	0.97 (0.33–2.83)	0.77 (0.24–2.55)	
Combination ICPi therapy[1]	1.47 (0.48–4.46)	1.04 (0.30–3.64)	
Fold increase in baseline SCr	0.86 (0.69–1.08)	0.81 (0.64–1.04)	
Concomitant Drug[2]	5.37 (1.35–21.41)	5.88 (1.32–26.17)	
Treated with glucocorticoids	2.07 (0.37–11.63)	1.72 (0.25–11.96)	



Supplemental Figure 4. Factors associated with renal recovery following ICPi-AKI among biopsied patients. Univariate and multivariable adjusted odds ratios (and 95% CIs) for achievement of complete renal recovery in biopsied patients only (*n*=60). [1]Combination ICPi therapy refers to treatment with both an anti-CTLA-4 and an anti-PD-1/PD-L1 antibody. [2]Refers to concomitant use of potential TIN-causing medications, including antibiotics, NSAIDs, and PPIs within 2 weeks prior to the diagnosis of ICPi-AKI. Concomitant irAE with AKI was not included in the model due to being a perfect predictor of failure to achieve complete renal recovery among biopsied patients. Abbreviations: CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; irAE, immune-related adverse event; NSAID, nonsteroidal anti-inflammatory drug; PD-1, programmed cell death 1 protein; PD-L1, programmed death-ligand 1; PPI, proton pump inhibitor; RRT, renal replacement therapy; SCr, serum creatinine.



Supplemental Figure 5. Renal recovery status predicts overall survival in biopsied-only patients (*n*=60). Panel A shows Kaplan-Meier 6-month survival curves, stratified by renal recovery status, starting at the time of development of ICPi-AKI. Panels B shows univariate and multivariable adjusted hazard ratios for 6-month mortality. [1]Refers to per 30 ml/min/1.73m^2 decline. Abbreviations: NR, no recovery; R, recovery.