Immune checkpoint inhibitors acute kidney injury

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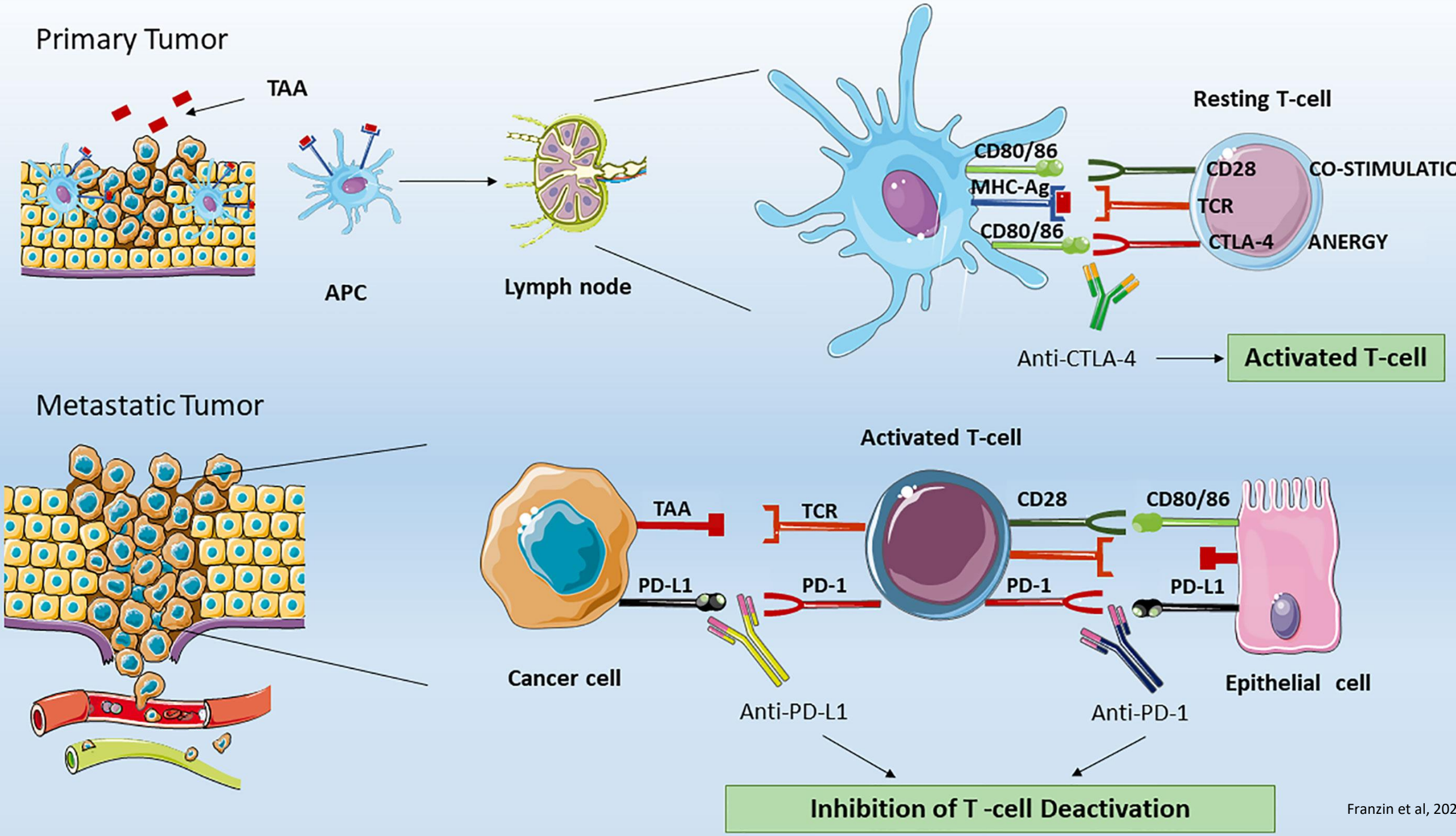
Outline

1. ICI mechanisms of action
2. Prevalence of ICI AKI
3. Mechanisms of ICI AKI
4. Clinical features
5. Histology
6. Treatment
7. Outcomes
8. Special populations: SOT

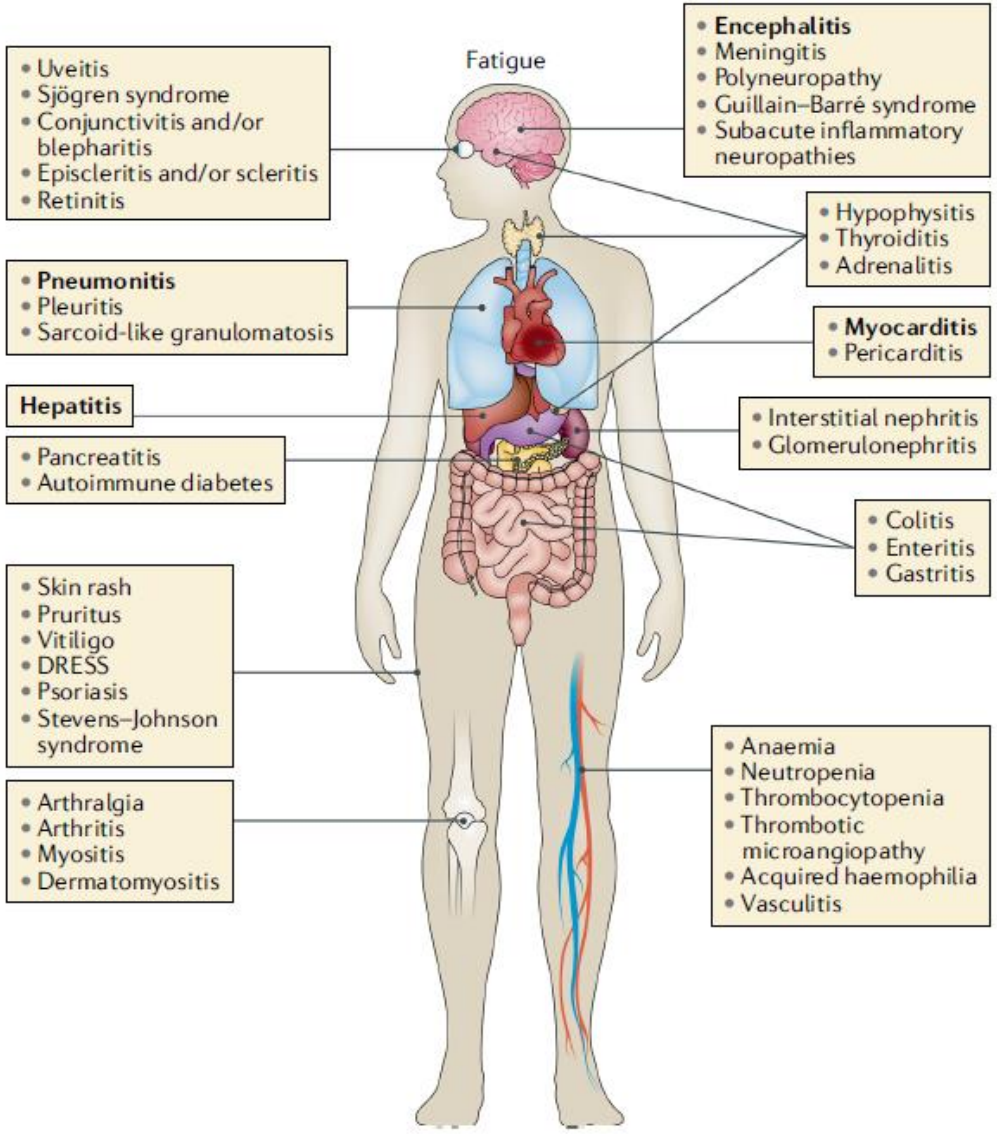
Immune checkpoint inhibitors

- Monoclonal antibodies against immune checkpoints
- Unleash the « brake » againts cancer immunity
- Used for different cancer types.
- Remarkable survival benefit



Franzin et al, 2020

Immune related adverse events



- 60% develop irAE
- Common irAE are associated with clinical response

Martins F A et al. Nat Rev Clin Oncol 2019:16:563-580.

Definition of AKI

System	Grade	Description
CTCAE	Grade 1	Higher than ULN to 1.5× ULN
	Grade 2	>1.5–3.0× baseline; >1.5–3.0× ULN
	Grade 3	>3.0× baseline; >3.0–6.0× ULN; hospitalization indicated
	Grade 4	>6.0× ULN; life-threatening consequences; RRT indicated
	Grade 5	Death
KDIGO	Stage 1	Increase in SCr of ≥0.3 mg/dl within 48 h or 1.5–1.9× baseline
	Stage 2	Increase in SCr to 2–2.9× baseline
	Stage 3	Increase in Cr to 3× baseline or to ≥4.0 mg/dl or initiation of RRT

CTCAE, Common Terminology Criteria for Adverse Events; ULN, upper limit of normal; SCr, serum creatinine.

CTCAE doesn't take into account baseline sCr , but **upper limit of normal** which could be a bias in patient with oncological disease and sarcopenia.

What is the frequency & etiology of AKI and what are its risk factors in patients on checkpoint inhibitors?

CJASN
Clinical Journal of American Society of Nephrology

Cohort

1016 patients

61% male

Mean eGFR 82 mL/min

Follow-up 12 months

Acute kidney injury 17%

Sustained AKI (≥ 3 days) 8%

Checkpoint inhibitor related AKI 3%

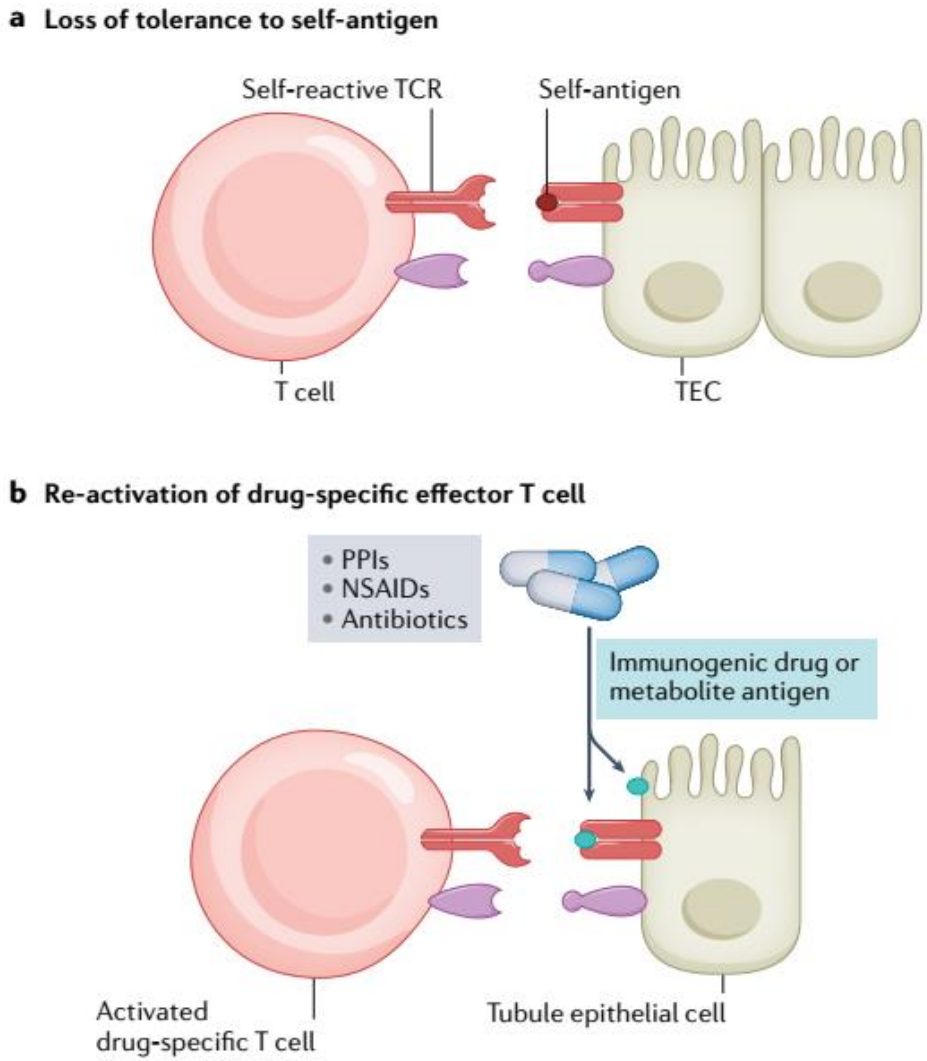
Proton Pump Inhibitors → Hazard ratio

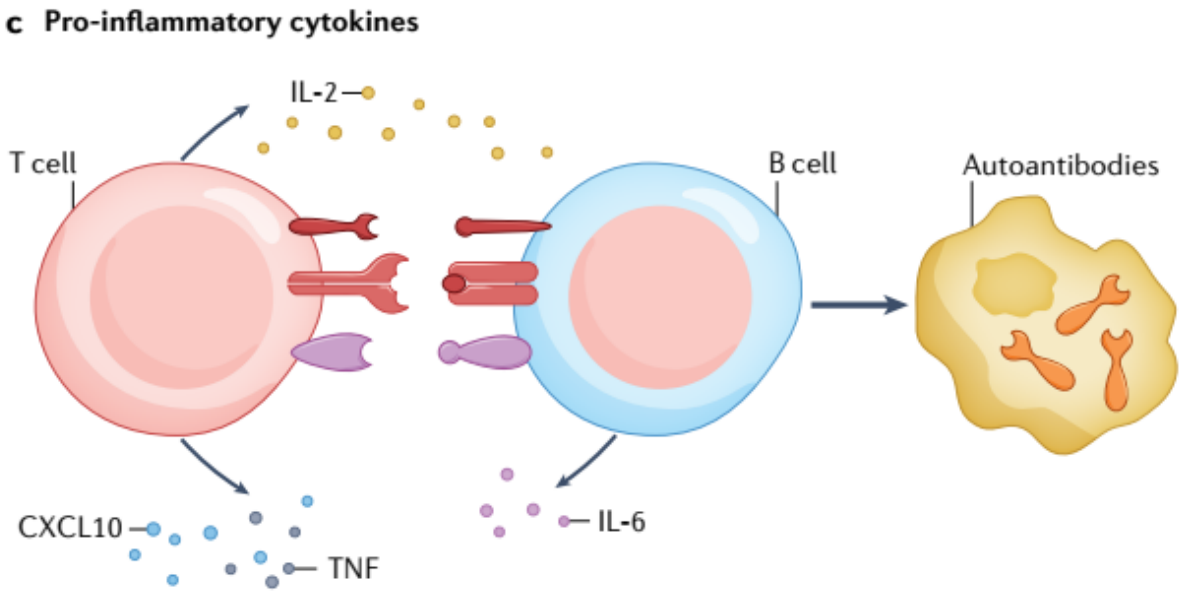
Sustained AKI (≥ 3 days)	Checkpoint inhibitor related AKI
2.85	2.24
95%CI 1.34-6.08	95%CI 0.96-5.21

Conclusions: AKI is common in patients receiving checkpoint inhibitors, and the causes are heterogeneous. Proton pump inhibitor therapy is a risk factor for sustained AKI.

Harish Seethapathy, Sophia Zhao, Donald Chute, Leyre Zubiri, et al. ***The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors.*** CJASN doi: 10.2215/CJN.00990119. **Visual Abstract by Pablo Garcia, MD**

ICI and renal toxicity





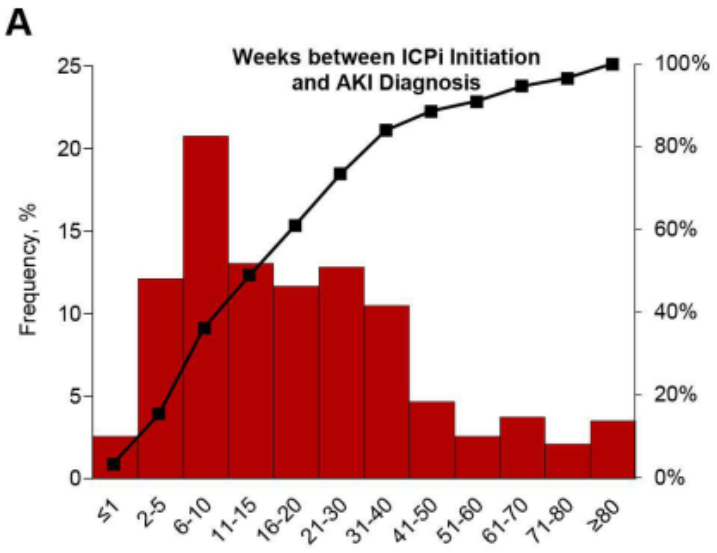
Sprangers B et al. Nat Rev Nephrol 2022;18(12):794-805.

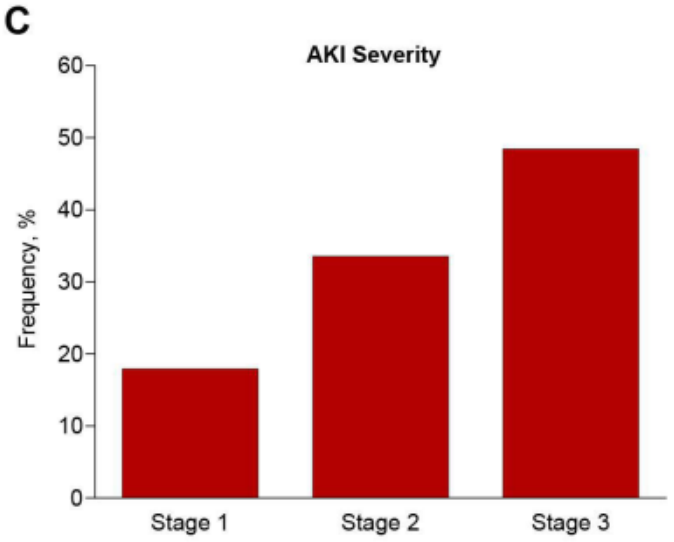
ICI-AKI: clinical characteristics

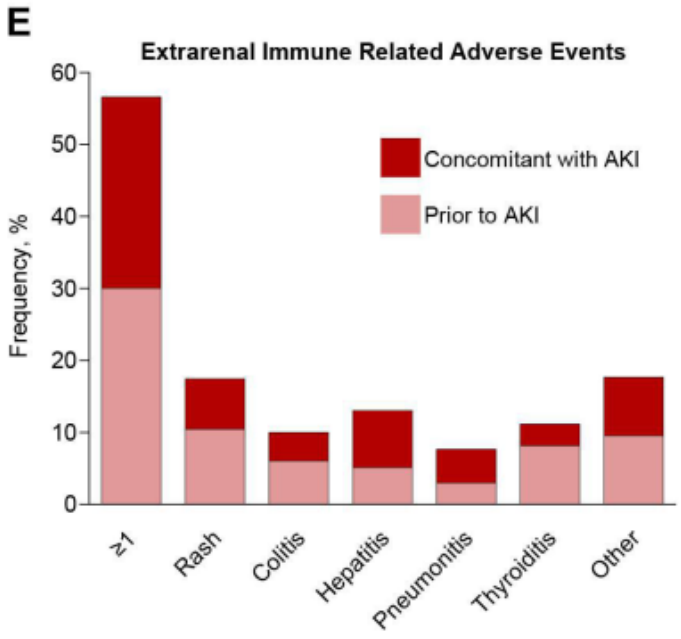
Variable	ICPi-AKI (n=429)	No ICPi-AKI (n=429)	P value
Age at ICPi initiation, years, median (IQR)	68 (59–75)	65 (58–73)	0.02
Male, n (%)	266 (62.0)	251 (58.5)	0.32
Race, n (%)			0.99
White	351 (81.8)	350 (81.6)	
Black	27 (6.3)	24 (5.6)	
Asian	21 (4.9)	21 (4.9)	
Other/unknown	30 (7.0)	34 (7.9)	
Baseline SCr, mg/dL, median (IQR)	0.97 (0.80–1.21)	0.88 (0.73–1.07)	<0.001
Baseline eGFR,*(mL/min per 1.73 m^2			
Median (IQR)	73 (57–90)	83 (66–97)	<0.001
Autoimmune disease, n (%)	42 (9.8)	56 (13.1)	0.16
Extrarenal irAE,† n (%)	201 (46.9)	123 (28.7)	<0.001
Malignancy, n (%)			0.01
Melanoma	104 (24.2)	93 (21.7)	
Lung	126 (29.4)	133 (31.0)	
Genitourinary	100 (23.8)	70 (16.7)	
Other	99 (23.6)	133 (31.7)	
ICPi class, n (%)			
Anti-CTLA-4	103 (24.0)	95 (22.1)	0.57
Anti-PD-1	347 (80.9)	355 (82.8)	0.54
Anti-PD-L1	42 (9.8)	30 (7.0)	0.18
Combo anti-CTLA-4+ anti-PD-1/PD-L1	99 (23.1)	75 (17.5)	0.05

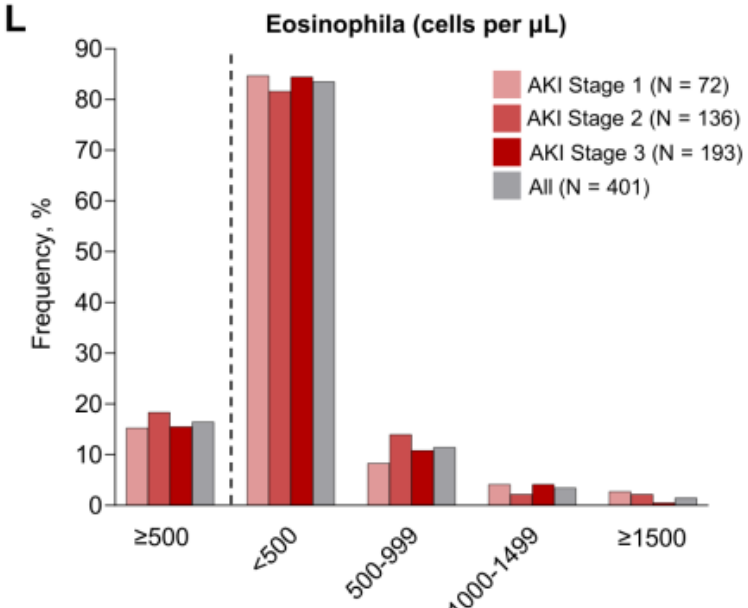
Gupta S et al. J Immunother Cancer 2021;9(10):e003467.

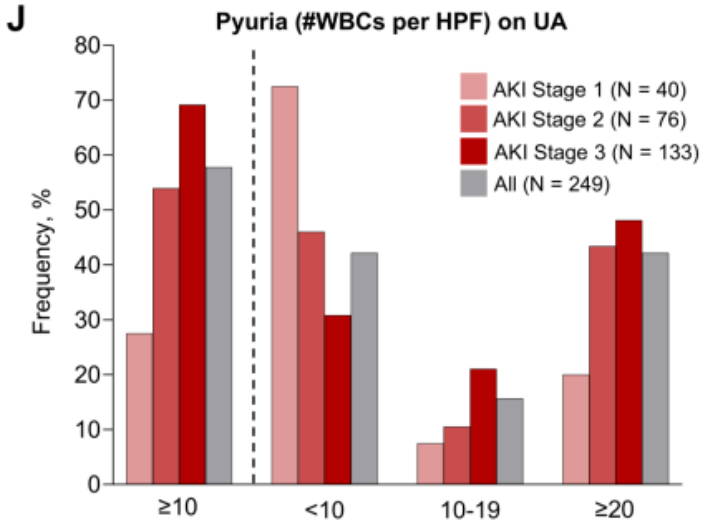
ICI-associated AKI

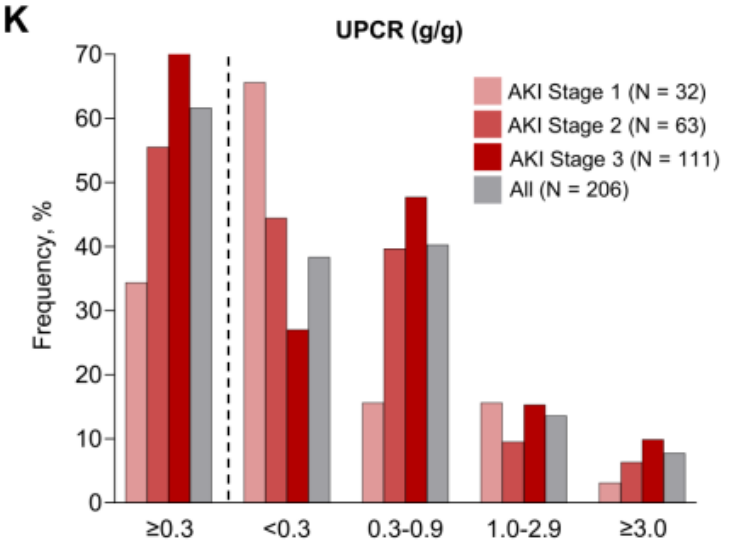












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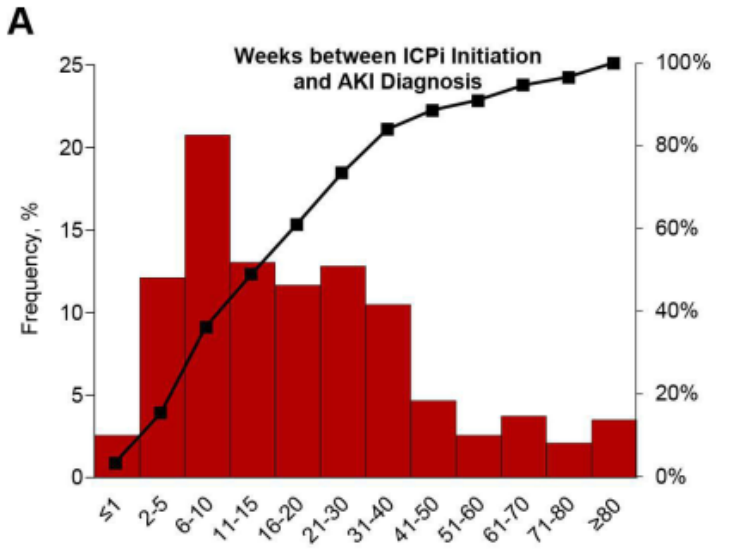
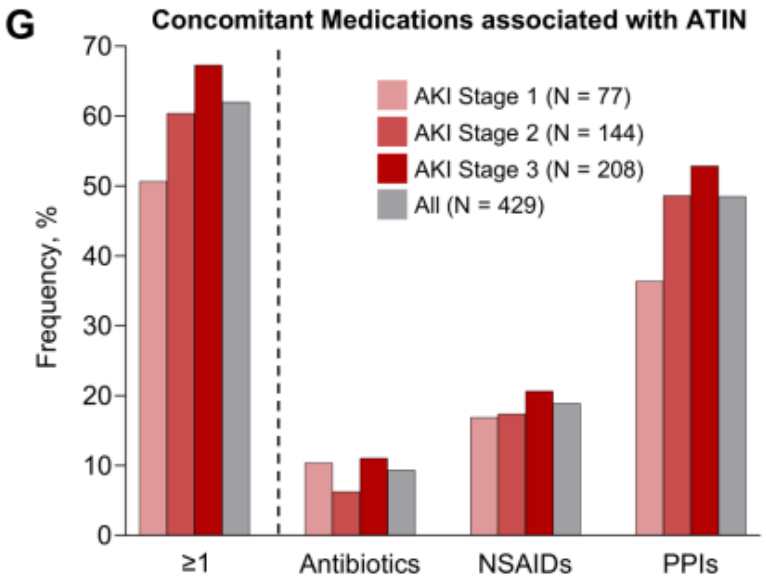
ICI-associated AKI





Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years)	1.17 (1.04-1.31)	1.05 (0.92-1.21)
Male sex	1.16 (0.88-1.52)	1.15 (0.86-1.53)
Combination ICPi therapy	1.42 (1.01-1.98)	1.30 (0.90-1.87)
Baseline eGFR (ml/min/1.73m^2)		
≥90 (REF)	1	1
60-89	1.54 (1.13-2.10)	1.36 (0.95-1.94)
45-59	2.48 (1.59-3.87)	2.23 (1.35-3.68)
<45	1.92 (1.74-4.89)	2.62 (1.47-4.65)
PPI use*	2.55 (1.92-3.40)	2.40 (1.79-3.23)
Prior or concomitant extrarenal irAEs**	2.19 (1.65-2.91)	2.07 (1.53-2.78)

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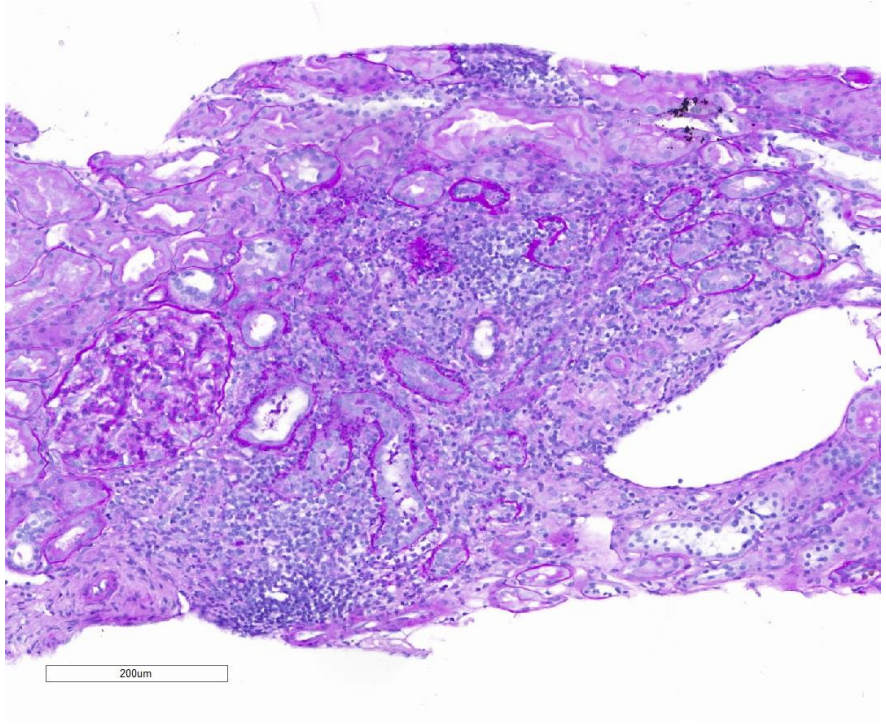
Histology

- Acute tubulointerstitial nephritis (ATIN) is the most common observation in ICI related AKI, histologically indistinguishable from ATIN secondary to other drugs
- ATIN affects **> 90% of patients who undergo biopsy**
- Infiltrate is predominantly composed of lymphocytes, with varying degrees of plasma cells, eosinophils and neutrophils
- Further characterization of the lymphocyte infiltrate shows a predominance of **CD3+ T lymphocytes**
- Non-ATIN patterns of damage likely cause < 10% of all ICI induced AKI
- Pauci-immune glomerulonephritis / vasculitis (27%), podocytopathies (20%) and C3 glomerulopathy (11%) are the most common non-ATIN manifestation of ICI toxicity
- ICIs may reactivate preexisting autoimmune diseases



(Kidney Int 2016;90:638) (J Am Soc Nephrol 2020;31:435)

Glomerular disease < ICI

- Rare
- No standarised treatment
- Exclusion diagnosis

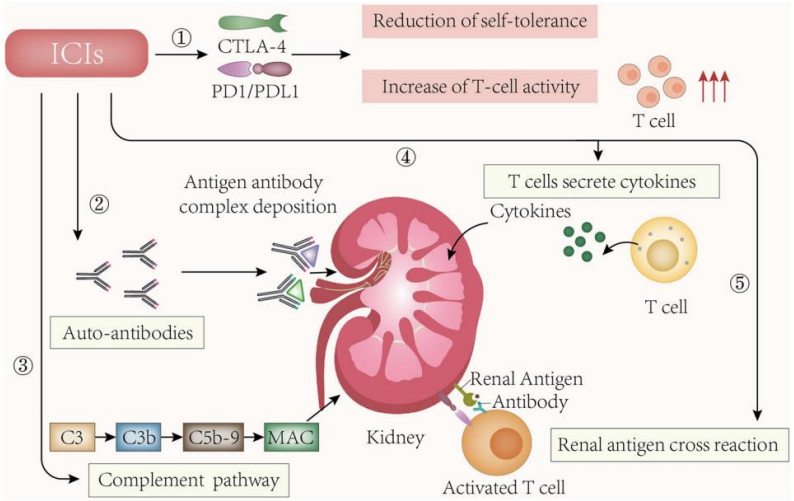


Figure 1. Potential mechanisms of ICIs induced glomerular diseases. ICIs: immune checkpoint inhibitors; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; PD1: programmed death 1 protein; PDL1: programmed death-ligand 1; MAC: membrane attack complex. Nonspecific activation of the immune system, induce the production of autoimmune antibodies and antibody-antigen complexes deposit in the kidney, increase proinflammatory cytokines/chemokines in kidney tissue; cross-reactivity between anti-tumor T cells and antigens is induced on healthy cells, and form membrane attack complex by complement alternative pathway are potential mechanisms of ICIs induced glomerular diseases.

Table 1. Characteristics of reported patients with glomerular disease associated with ICIs.

Characteristics	N (%)
Total number	53
Sex	
Male	35 (76.1%)
Femal	11 (23.9%)
Not available	7
Tumor types	
Melanoma	16 (32.6%)
Non-small cell lung cancer	13 (26.5%)
Renal cell carcinoma	6 (12.2%)
Gastrointestinal cacer	3 (6.1%)
Lymphoma	3 (6.1%)
Others	8 (16.3%)
Not available	4
ICIs therapy	
Anti- PD1 antibodies	35 (71.4%)
Nivolumab	18 (36.7%)
Pembrolizumab	15 (30.6%)
Tislelizumab	1 (2.0%)
SHR-1210	1 (2.0%)
Anti-PDL1 antibodies	2 (4.1%)
Durvalumab	2 (4.1%)
Anti-CTLA4 antibodies	4 (8.1%)
Ipilimumab	3 (6.1%)
Tremelimumab	1 (2.0%)
Combination treatments	8 (16.3%)
Not available	4
Renal pathology	
Pauci-immune GN	15 (28.3%)
ANCA positive	4 (7.5%)
ANCA negative or undetected	11 (20.8%)
Podocytopathies	14 (26.4%)
MCD	12 (22.6%)
FSGS	2 (3.8%)
Immune-complex GN	10 (18.9%)
IgA nephropathy	6 (11.3%)
Others	4 (7.5%)
AA amyloidosis,	4 (7.5%)
Membranous nephropathy	4 (7.5%)
C3 glomerulopathy	4 (7.5%)
Anti-glomerular basement membrane GN	2 (3.8%)
Treatment	
ICIs discontinued	42 (89.4%)
Steroids	41 (87.2)%
High dose methylprednisolone	11 (23.4%)
Cyclophosphamide	2 (4.3%)
Rituximab	7 (14.9%)
Mycophenolate	3 (6.4%)
Infliximab	2 (4.3%)
Tocilizumab	1 (2.1%)
TNFα-block	1 (2.1%)
RRT/plasmapheresis	9 (19.1%)
Not available	6
Outcomes	
Complete or partial remission	41 (91.1%)
No progression	4 (8.9%)
Not available	8

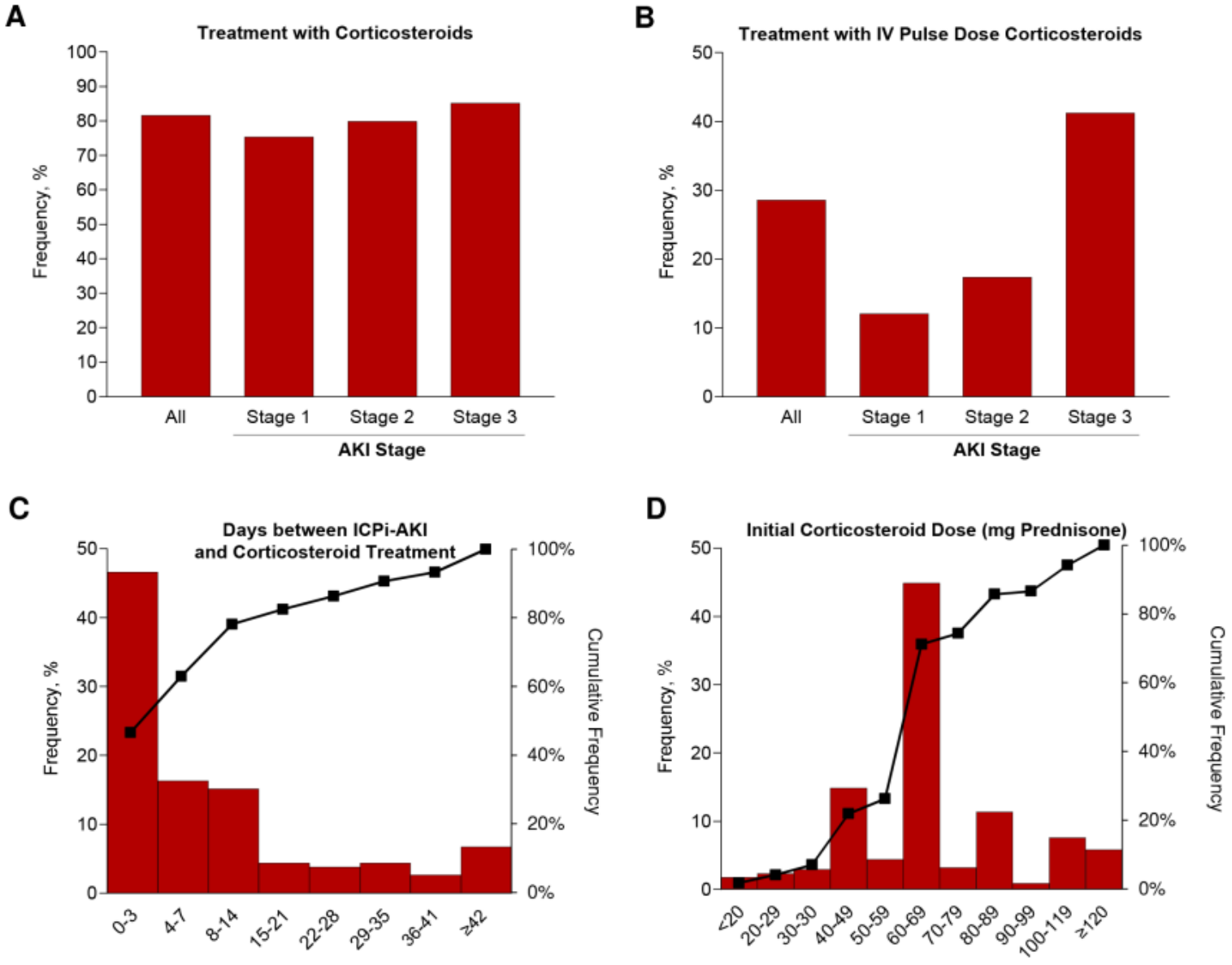
ANCA: antinuclear cytoplasmic antibody, GN: glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; RRT: renal replacement therapy.

He X, et al Ren Fail. 2022

Management and treatment of ICI AKI

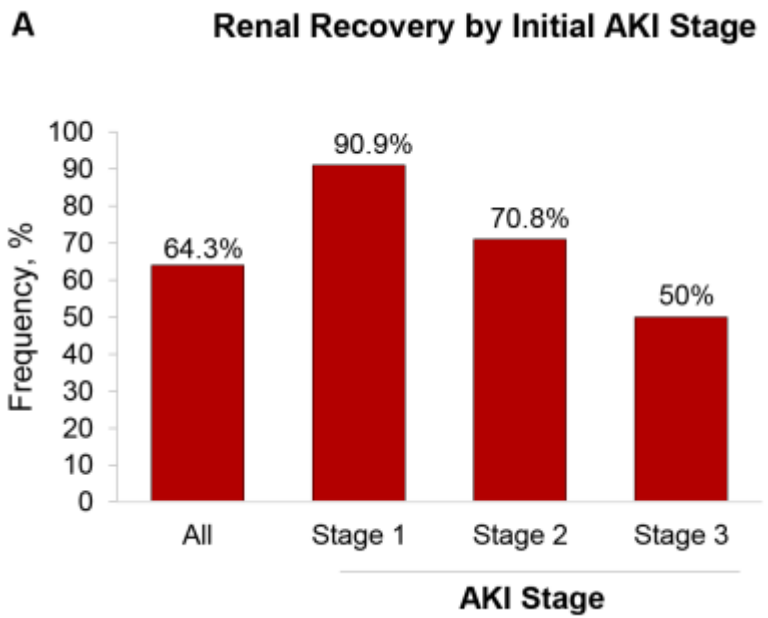
- Management of ICI AKI is similar to drug-AIN
  1. Stop offendig drug
  2. Start corticosteroid therapy (0.5-1 mg/kg/day) if AKI grade 2 or more

ICI-associated AKI: treatment



Gupta S et al. J Immunother Cancer 2021;9(10):e003467.

ICI-associated AKI: renal outcome



Gupta S et al. J Immunother Cancer 2021;9(10):e003467.

Management and treatment of ICI AKI

- Management of ICI AKI is similar to drug-AIN
  1. Stop offendig drug
  2. Start corticosteroid therapy (0.8-1 mg/kg/day) if AKI grade 2 or more

  Is there a second line treatment if corticosteroids fail or patient is corticodependent?

  1. MMF
  2. Infliximab

Infliximab in corticosteroid resistant or relapsing disease?

Case series of 10 patients

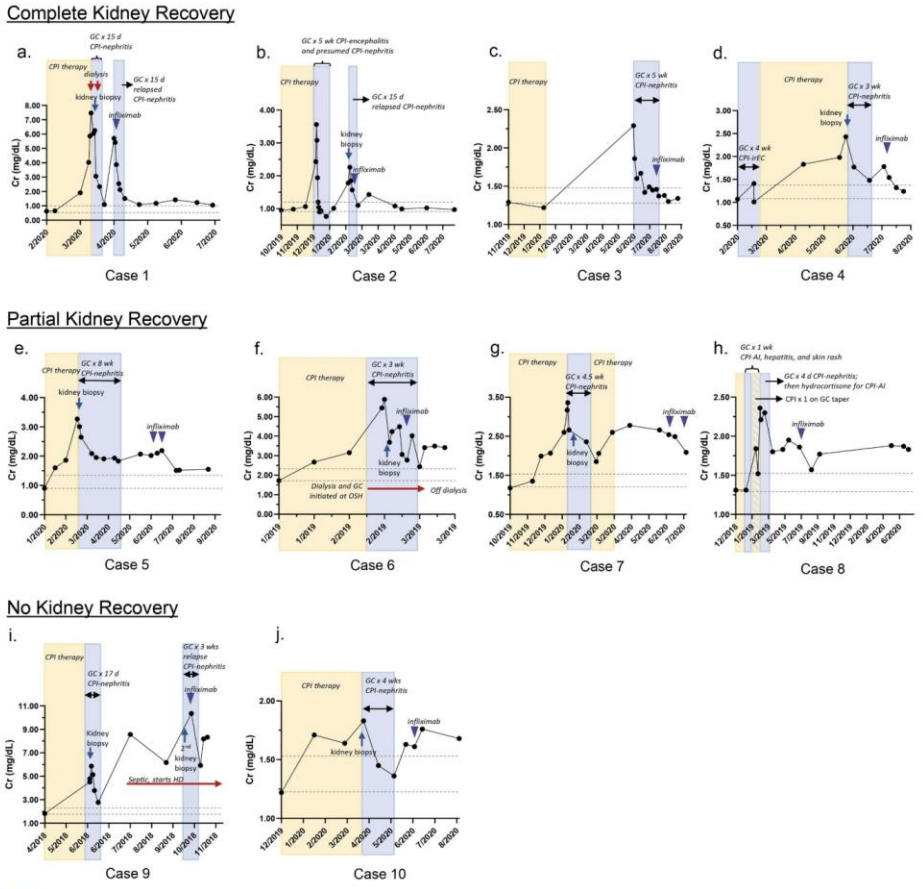


Figure 1. Time course of events and response to treatment. Panels A-D: Cases 1–4 with complete kidney recovery. Panels E-H: Cases 5–8 with partial kidney recovery. panels I-J: Cases 9–10 no kidney recovery. yellow: checkpoint inhibitor (CPI) therapy. CPI dosing regimens are provided in Table 1. Blue: glucocorticoid (GC) therapy. Purple triangle: infliximab (5 mg/kg IV). Dotted black line represents creatinine level to < 0.35 mg/dL above baseline; complete renal recovery.

Better respons if early administration of anti-TNF-a

2 pts had no recovery by had CKD with IFTA 40%

Lin JS, et al. Oncoimmunology. 2021

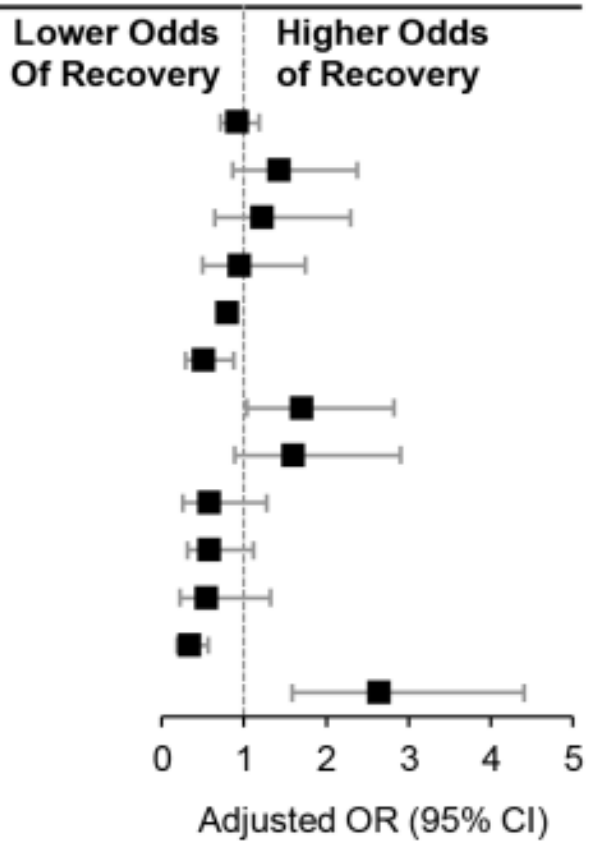
<table>
<tr><th rowspan="2">Treatment</th><th rowspan="2">Stage/ Grade [a]</th><th colspan="4">Guidelines</th></tr>
<tr><th>ASCO</th><th>NCCN</th><th>SITC</th><th>ESMO</th></tr>
<tr><td rowspan="4">ICIs interruption</td><td>1</td><td>NO</td><td rowspan="2">NO</td><td>NO</td><td>NO</td></tr>
<tr><td>2</td><td>NO, but if worsening, YES.</td><td colspan="2" rowspan="2">YES</td></tr>
<tr><td>3</td><td colspan="2" rowspan="2">YES</td></tr>
<tr><td>4</td></tr>
<tr><td rowspan="4">Corticosteroids (prednisone) or additional immunosuppression</td><td>1</td><td colspan="2">NO</td><td rowspan="4">The first-line treatment for ICI-TIN is glucocorticoids. If ineffectiveness, infliximab or mycophenolate mofetil.</td><td>NO</td></tr>
<tr><td>2</td><td colspan="2">Initial dose of 0.5-1 mg/kg/d, if worsening, increase to 1-2 mg/kg/d.</td><td>If worsening, initial oral dose of 0.5-1 mg/kg.</td></tr>
<tr><td>3</td><td colspan="2" rowspan="2">Initial dose of 1-2 mg/kg/d, if worsening, consider additional immunosuppression.</td><td rowspan="2">If worsening, initiate intra-venous methyl-prednisolone 1-2 mg/kg.</td></tr>
<tr><td>4</td></tr>
<tr><td rowspan="4">ICIs rechallenge</td><td>1</td><td rowspan="2">YES</td><td rowspan="2">If improved to ≤Grade 1, YES.</td><td>YES</td><td rowspan="2">If improved to ≤Grade 1, YES</td></tr>
<tr><td>2</td><td rowspan="3">NA</td></tr>
<tr><td>3</td><td colspan="2" rowspan="2">NO</td><td>NA</td></tr>
<tr><td>4</td></tr>
<tr><td rowspan="4">Others</td><td>1</td><td>SCr monitoring</td><td>SCr and urine protein monitoring</td><td rowspan="4">• Concomitant medications known to cause ICI-ATIN interruption
• Nephrology consultation
• If the lack of specific clinical features of ICI-AKI, renal biopsy.</td><td rowspan="4">• Other causes assessment
• Other nephrotoxic drugs interruption
• Personalized renal biopsy</td></tr>
<tr><td>2</td><td rowspan="3">• Nephrology consultation
• Other causes assessment</td><td>Nephrology consultation</td></tr>
<tr><td>3</td><td rowspan="2">Renal biopsy</td></tr>
<tr><td>4</td></tr>
</table>

[a]Nephrotoxicity can be graded using the CTCAE scale and can also be graded with the KDIGO) criteria.

ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; SITC, Society for Immunotherapy of Cancer; ESMO, European Society for Medical Oncology; ICIs, immune checkpoint inhibitors; ICI-TIN, immune checkpoint inhibitor-associated acute tubulointerstitial nephritis; ICI-AKI, immune checkpoint inhibitor-associated acute kidney injury; NA, not available; SCr, serum creatinine.

ICI-associated AKI: renal outcome

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years)	1.10 (0.92-1.34)	0.92 (0.71-1.18)
Male sex	1.80 (1.18-2.75)	1.43 (0.86-2.38)
White	1.57 (0.93-2.67)	1.22 (0.64-2.30)
Combination Therapy	1.65 (0.98-2.77)	0.94 (0.50-1.75)
Baseline eGFR (per 10 points)	0.74 (0.66-0.82)	0.79 (0.69-0.91)
Lung cancer	0.38 (0.25-0.60)	0.51 (0.29-0.87)
Concomitant ATIN-causing medication*	1.50 (0.98-2.29)	1.70 (1.03-2.82)
Concomitant extrarenal irAEs**	2.01 (1.20-3.39)	1.60 (0.88-2.90)
≥2+ Blood on urinalysis	0.49 (0.26-0.90)	0.58 (0.26-1.28)
≥2+ Leukocyte esterase on urinalysis	0.42 (0.24-0.73)	0.58 (0.31-1.12)
≥1 g/g UPCR	0.40 (0.20-0.81)	0.54 (0.22-1.32)
Stage 3 AKI	0.30 (0.20-0.47)	0.33 (0.19-0.57)
Treated with corticosteroids***	2.27 (1.48-3.48)	2.64 (1.58-4.41)



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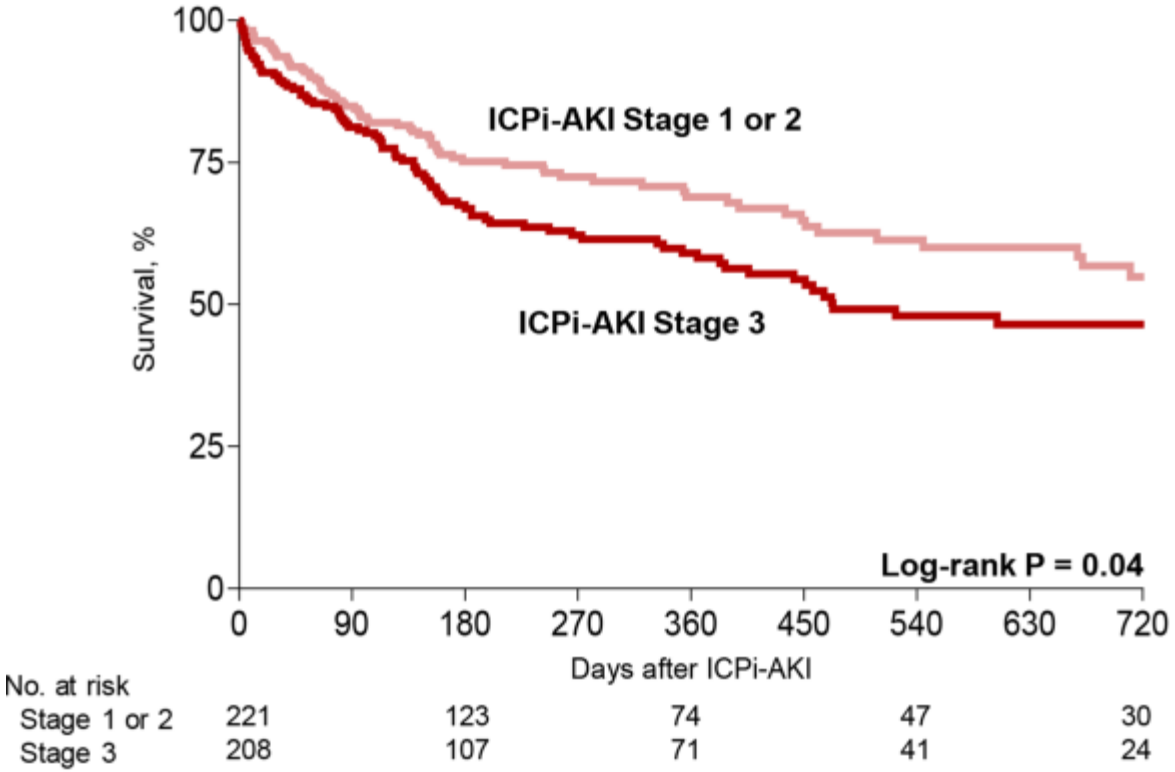
ICI-associated AKI: patient outcome



Variable	Adjusted HR (95% CI)
Stage 3 AKI (vs. stage 1 or 2 AKI)	1.39 (0.97-1.99)
Age (per 10 years)	1.01 (0.86-1.21)
Male sex	1.08 (0.75-1.54)
White	1.05 (0.64-1.70)
Lung cancer	1.13 (0.74-1.71)
Concomitant ATIN-causing medication*	0.90 (0.64-1.28)
Prior or concomitant extrarenal irAE**	0.91 (0.65-1.28)
Combination ICPi therapy	1.31 (0.87-1.96)
Baseline eGFR (ml/min/1.73m^2)	
≥90 (REF)	1
60-89	1.09 (0.67-1.78)
45-59	1.32 (0.72-2.41)
<45	1.90 (1.03-3.49)
Treatment with corticosteroids***	0.92 (0.64-1.32)

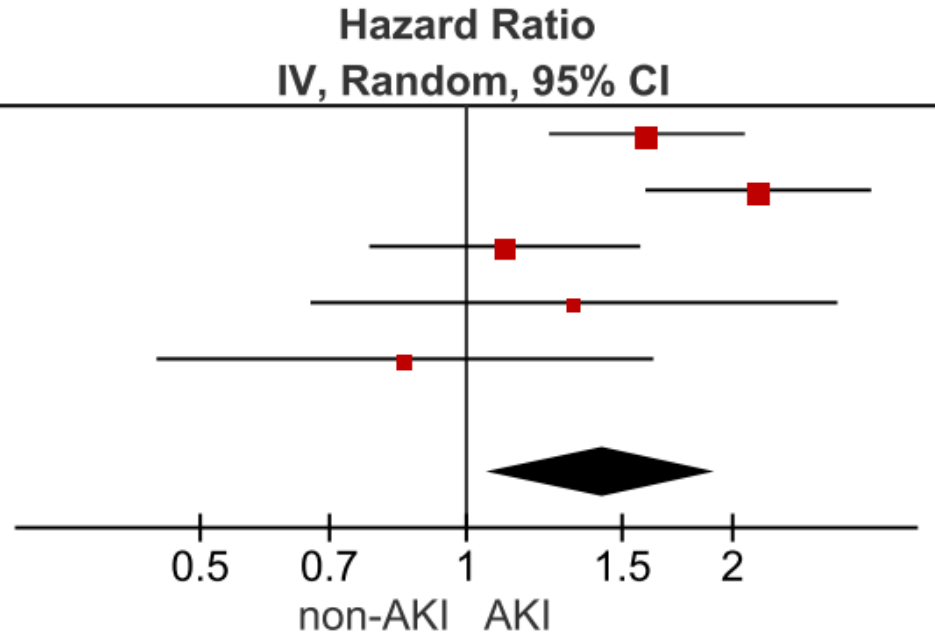
Gupta S et al. J Immunother Cancer 2021;9(10):e003467.

ICI-associated AKI: patient outcome

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Garcia-Carro 2021	0.47	0.13	26.8%	1.60 [1.24, 2.06]
Koks 2021	0.76	0.15	25.2%	2.14 [1.59, 2.87]
Meraz-Munoz 2020	0.1	0.18	22.8%	1.11 [0.78, 1.57]
Seethapathy 2020	0.28	0.35	12.2%	1.32 [0.67, 2.63]
Shimamura 2021	-0.16	0.33	13.1%	0.85 [0.45, 1.63]
Total (95% CI)			**100.0%**	**1.42 [1.05, 1.92]**

Heterogeneity: Tau² = 0.07; Chi² = 11.68, df = 4 (P = 0.02); I² = 66%

Test for overall effect: Z = 2.31 (P = 0.02)



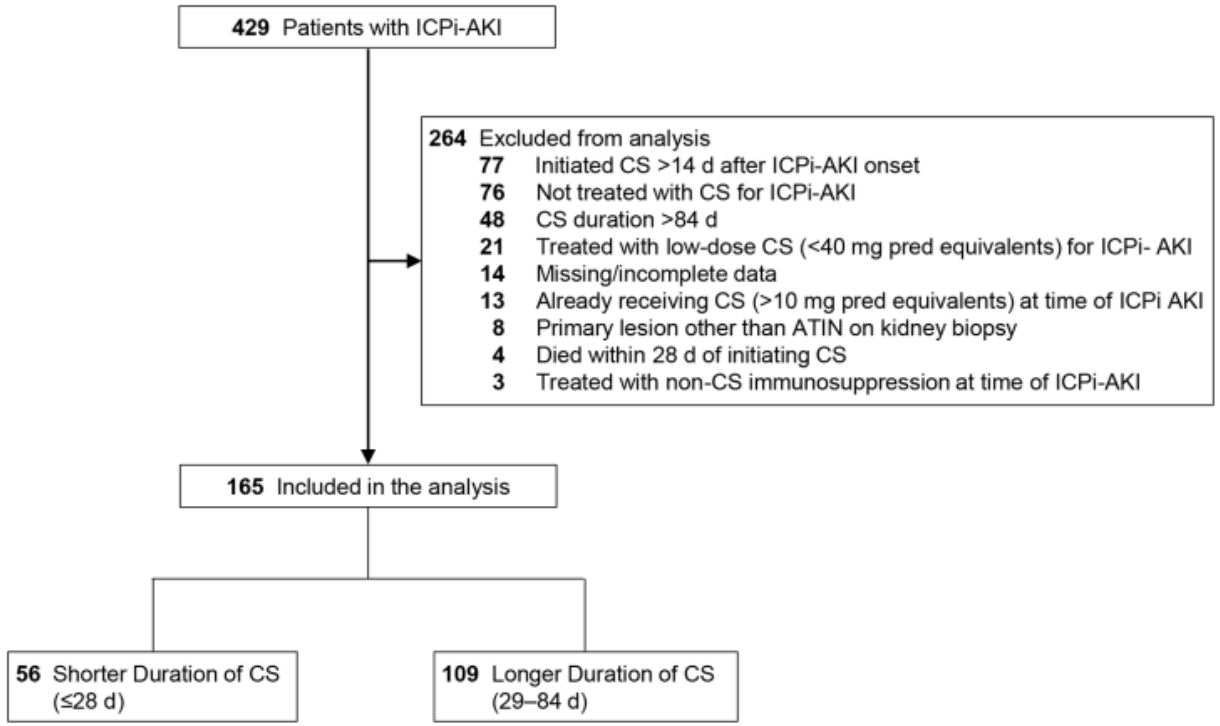
AKI stage 1 or 2 vs AKI stage 3 : HR 1.35 [0.99, 1.83]

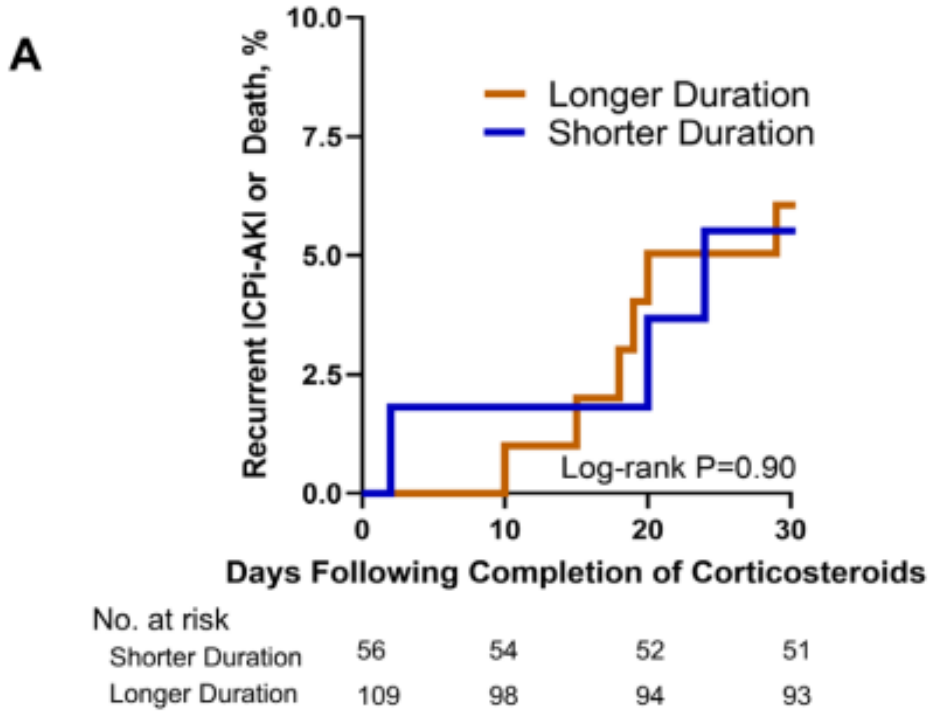
Renal recovery vs no renal recovery : HR 2.93 [1.41, 6.08]

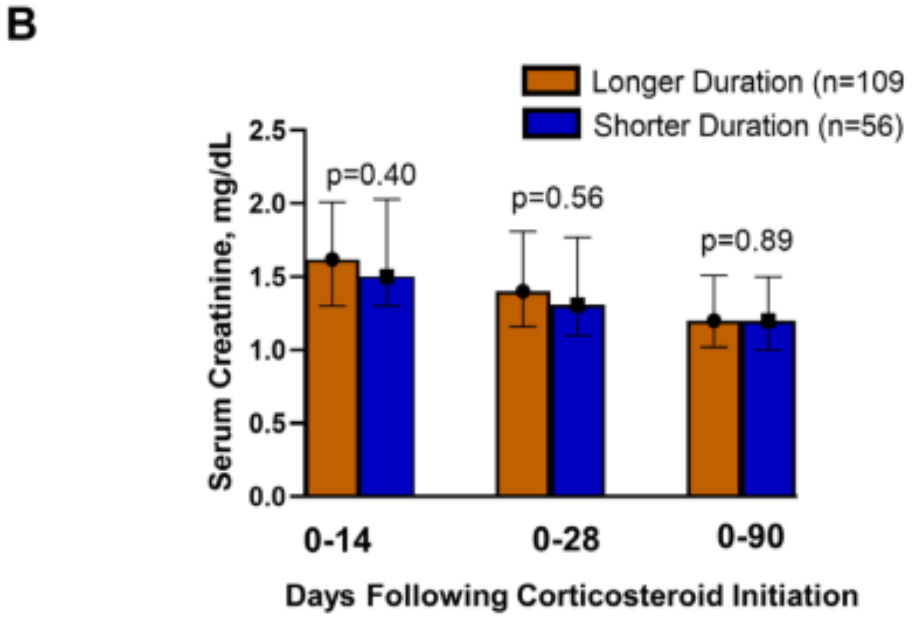
Of note: mortality 46-72% during 25-37 weeks of FU

Garcia-Carro C et al. Clin Kidney J 2023;16(5):773-775.
Kanbay M et al. Clin Kidney J 2023;16(5):817-826.

ICI-AKI: duration of CS







Gupta S et al. J Immunother Cancer 2021;10(9):e005646.

What about rechallenge?

- The mechanism of ICI-AKI is likely different from other causes of drug-induced ATIN. It seems that in ICI-AKI, the ICI is an **indirect cause of ATIN**(making rechallenge possible) whereas in 'traditional'drug-induced ATIN the drug is the direct culprit and rechallenge will often result in recurrence of ATIN.
- Cortazar study
  - 31 of 138 pts (22%) with ICI AKI were rechallenged
  - 24 (**77**%) did not develop AKI and 7 (23%) did develop AKI
  - Outcomes in the 7 that did develop AKI:
    - 1 (14%) no recovery
    - 1 (14%) partial recovery
    - 5 (71%) complete recovery
- Gupta study
  - 121 of 429 pts (28%) with ICI AKI were rechallenged
  - 101 (**83,5**%) did not develop AKI and 20 (16,5%) did develop AKI
  - Recurrent ICI-AKI:
    - 4 (20%) AKI stage 1, 8 (40%) AKI stage 2 and 8 (40%) AKI stage 3
    - Renal recovery in 12 of 20 (60%) of patients
    - No difference whether CS were given at rechallenge or not
    - Increased mortality in patients without renal recovery

Increased Th1 and cytotoxic T cells mediated by IFNg and TNFa

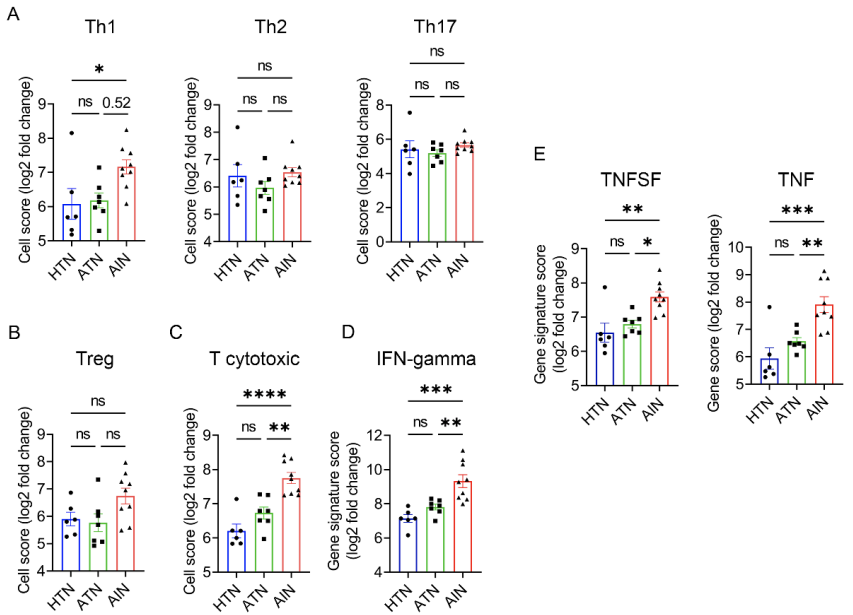


Figure 4. Identification, abundance and function of the different T cell subsets in kidney biopsies of patients with ICI-AIN, ATN and HTN. Specific gene signatures were used to determine cell score. **A.** Abundance of T helper subsets, Th1, Th2 and Th17 **B.** Treg and **C.** cytotoxic T cells score was determined and compared between three groups. Data represents cell score (log2 fold change) geometric mean ± SEM for different groups. The p values were determined using Tukey's multiple comparisons test *p<0.05, **p<0.01, ***p<0.0005, **** p<0.0001 (adj p value). Gene signature score for T cell effector function mediated by **D.** IFN-γ (*IFNG, STAT1, CCR5, CXCL9, CXCL10, CXCL11, IDO1, PRF1, GZMA, HLA-DRA*) and **E.** TNF superfamily (TNFSF) and TNF expression was calculated and compared for the three groups. Data represents the gene signature score (log2 fold change) ± SEM for different groups and Tukey's multiple comparison test was used for statistical analysis, *p<0.05, **p<0.01, ***p<0.0005, (adj p value).

Singh et al, JCI 2022

Cytokines and Immune Cell Phenotype in Acute Kidney Injury Associated With Immune Checkpoint Inhibitors

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

- Prospective cohort Mayo Clinic
- Kidney injury biomarkers, T cell cytokines & immune cell phenotype were measured
- Patients with AKI on ICI therapy N = 24
- 2021 - 2022

Outcomes

ICI, immune checkpoint inhibitors

Increase in CD4 memory, T helper, dendritic cells & IL-2, IL-10 & TNF- α in AKI-ICI compared to AKI-other ($p < 0.05$)

	AKI – ICI N=14 Median (IQR)	P value	AKI – Other N=10 Median (IQR)
Urine cytokines	N = 14		N = 10
TNF-α (ng/g)	4.8 (3.23, 6.89)	0.010	1.95 (1.29, 2.51)
	IL-10, IL -2 – significantly increased in AKI – ICI		
Kidney tissue	N = 4		N = 4
CD4 Memory T cells	3.10 (1.77, 5.39)	0.021	0.25 (0.11, 0.40)
	T helper, Dendritic cells – significantly increased in AKI – ICI		

KI REPORTS
Kidney International Reports

Farooqui N et al, 2022

Visual abstract by:
Mythri Shankar, MD, DNB
@nephromythri

Conclusion: Specific T-cell responses and their respective cytokines may be indicative of AKI associated with ICI therapy and may help to differentiate AKI-ICI from AKI-other. Urine TNF-α is a promising biomarker for AKI-ICI, which is most often caused by AIN, and TNF-α pathway may serve as a potential target for therapeutic intervention.

Bilan à minima

Suspicion de toxicité rénale immuno-médiée si élévation de la sCr entre 1 semaine après la 1ère dose et jusqu'à 12 mois après la dernière dose d'un ICI

Bilan minimal

- Biologie avec numération de formule sanguine complète
- EMU (recherche de leucocytes et hématies dans les urines)
- Spot urinaire (protéine, albumine, créatinine, Na, urée)

Envisager une IRA non liée à un ICI

- Echographie rénale à la recherche d'une cause obstructive
- Infection/sepsis urinaire
- Présence de néphrotoxiques:
  - Médication (antibiotiques, IPP, AINS, etc.)
  - Chimiothérapie néphrotoxique
  - Produit de contraste
  - Complément alimentaire

IRA immuno-médiée ?

NON → Initier les traitements appropriés en fonction de l'étiologie

OUI → Prise en charge selon la classification KDIGO

ICI: inhibiteur de point de contrôle immunitaire, sCr : créatinine sérique, EMU : examen microscopique des urines, IRA : insuffisance rénale aigue

IRA immuno-médiée

Grade 1
- sCr < 1.5x baseline*
- Oligurie < 0.5mL/kg/h pendant 6-12h

→ Suspendre l'ICI et les autres néphrotoxiques

→ Amélioration sCr endéans 7 jours

OUI → Si reprise de l'immunothérapie, suivi à chaque cycle de la fonction rénale (sCr, EMU, spot urinaire avec rapport protéine/créatinine)

NON → Absence d'amélioration ou aggravation sCr:
- Discuter la biopsie rénale
- Suivre protocole Grades 2-3

Grade 2
- sCr entre 1.5-3x baseline*
- Oligurie < 0.5mL/kg/h pendant > 12h.

Grade 3
- sCr > 3x baseline*
- Oligurie < 0.3 mL/kg/h pendant > 24h ou anurie pendant 12h

→ Suspendre l'immunothérapie et **commencer les corticostéroïdes**: Medrol 0,5-1 mg/kg/jour
- **Biopsie rénale à réaliser** endéans les 3 jours après l'instauration des stéroïdes (même si sédiment inactif) et adaptation du traitement en fonction du diagnostic histologique
- Suivi clinico-biologique rapproché avec analyses hebdomadaires pour suivre la réponse aux stéroïdes (sCr, EMU, rapport protéine urinaire/créatinine)

* Créatininémie (sCr) en baseline correspond à la créatininémie avant l'initiation de l'immunothérapie en dehors de tout épisode infectieux ou de prise de néphrotoxique

Néphrite interstielle (NIA)*

Diagnostic de NIA avec ou sans NTA associée
- Protéinurie non glomérulaire
- Leucocyturie

- Medrol 0,5-1 mg/kg/j
- Si amélioration de la sCr, diminuer progressivement les doses sur 3 à 6 semaines.
- Analyses hebdomadaires (en ambulatoire) pendant le traitement aux stéroïdes.

Amélioration sCr à 5-7 jours ?

OUI

- Reprise de l'immunothérapie après la fin de la réduction des stéroides **et** un retour à la créatininémie baseline.
- Poursuivre le suivi de la fonction rénale de façon hebdomadaire durant le traitement par ICI pour s'assurer de la stabilité de la sCr durant l'ICI
- A l'arrêt des ICI, poursuivre le suivi de la fonction rénale jusqu'à 6 mois après la dernière dose

NON

- Ajout d'IFX 5 mg/kg IV en une dose unique
- Augmenter la dose de Medrol jusqu'à 1-2 mg/kg/j durant 7 jours puis diminuer progressivement sur 2 semaines après la dose d'IFX
- Si contre-indication à l'IFX ou absence de réponse, ajout de MMF 500 mg 2x/j et augmenter la dose sur 2 semaines jusqu'à 1000 mg 2x/j pendant un maximum de 3 mois, à adapter selon la réponse
- Reprise immunothérapie si stabilisation de la sCr après la fin de la réduction des corticostéroides

* Concerne 80-90% des formes de toxicité rénale immuno-médiée
NIA: néphrite interstitielle aiguë, NTA: nécrose tubulaire aiguë, ICI: inhibiteur de checkpoint immunitaire, IFX : infliximab, MMF: mycophénolate mophetil

Glomérulonéphrite (GN)

Diagnostic de GN
- Présence d'une hématurie et d'une protéinurie glomérulaire

Considérer les diagnostics différentiels de GN
- Anamnèse en faveur de maladie de système (connectivite, vascularite, etc.)?
- Bilan biologique : FAN, anti-dsDNA, FR, C3, C4, ANCA, anti-GBM, hépatite B et C, VIH, électrophorèse sérique des protéines
- Discuter la biopsie rénale

Prise en charge thérapeutique
- Suspendre l'immunothérapie et discuter du rechallenge avec néphrologue (cf infra)
- Commencer le Medrol à dose de 1mg/kg/j (dose maximale de 80 mg/j) durant 7 jours avant d'adopter un schéma dégressif en fonction de la réponse
- Adopter une approche multidisciplinaire et discuter de l'ajout de RTX 375 mg/m² IV 1x/semaine pour 4 doses ou 1000 mg IV 1x/ 2 semaines pour 2 doses

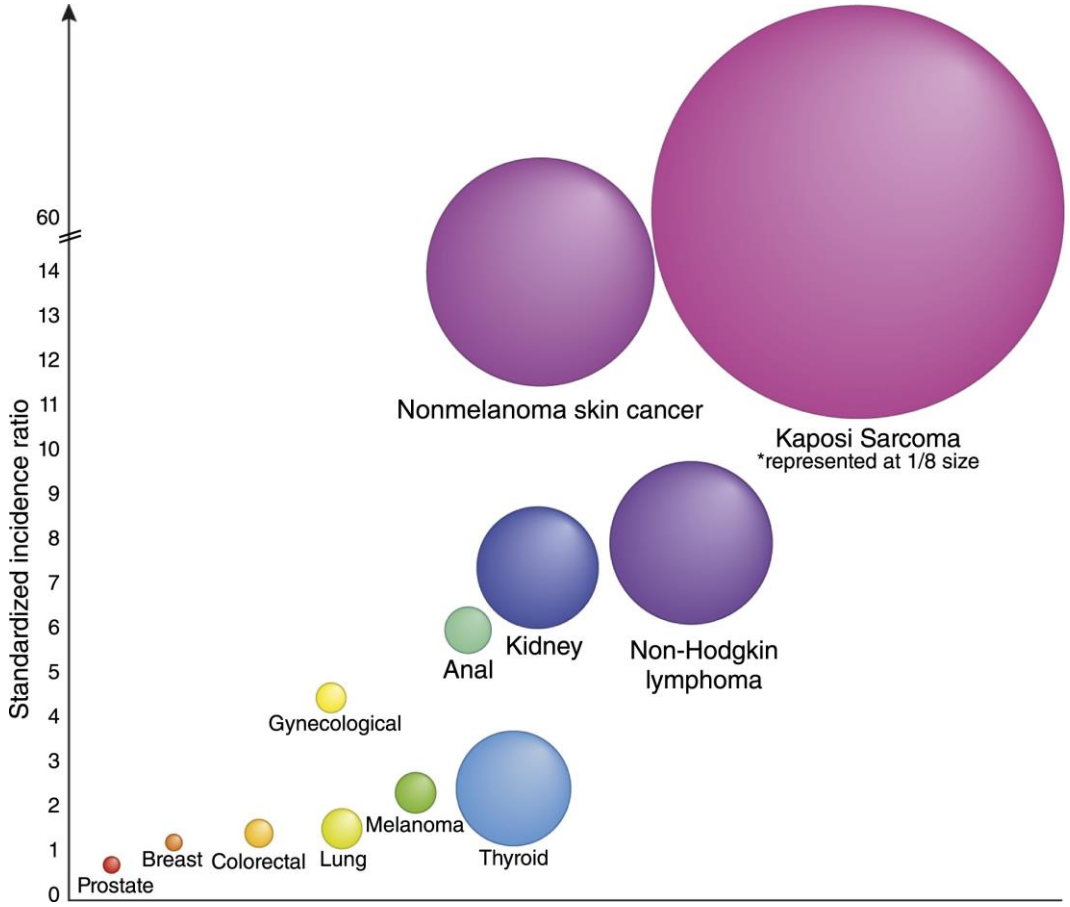
GN : glomérulonéphrite, RTX : rituximab

Special patient population

- Solid organ transplant recipients

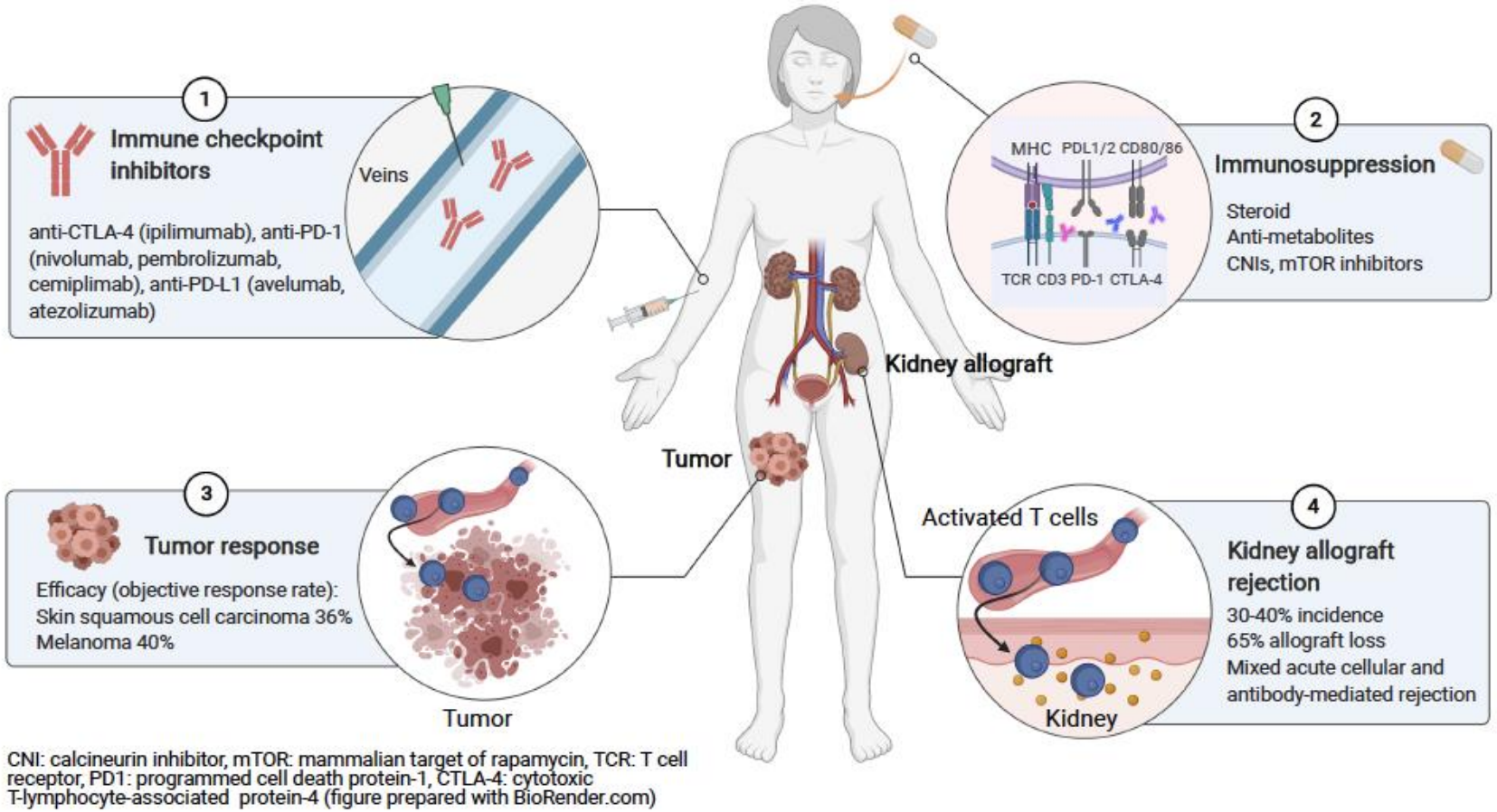
Cancer incidence in kidney transplantation

- Overall incidence of cancer 2 to 4 fold higher than the general population
- Higher risk of metastasis and death compared to the general population
- Third cause of death with functional graft



Au et al, Nature Reviews Nephrology 2018
Rosales et al, Int J Cancer 2020
Francis et al, Journal of Onco-Nephrology, 2020.
Al Adra, CJASN 2022

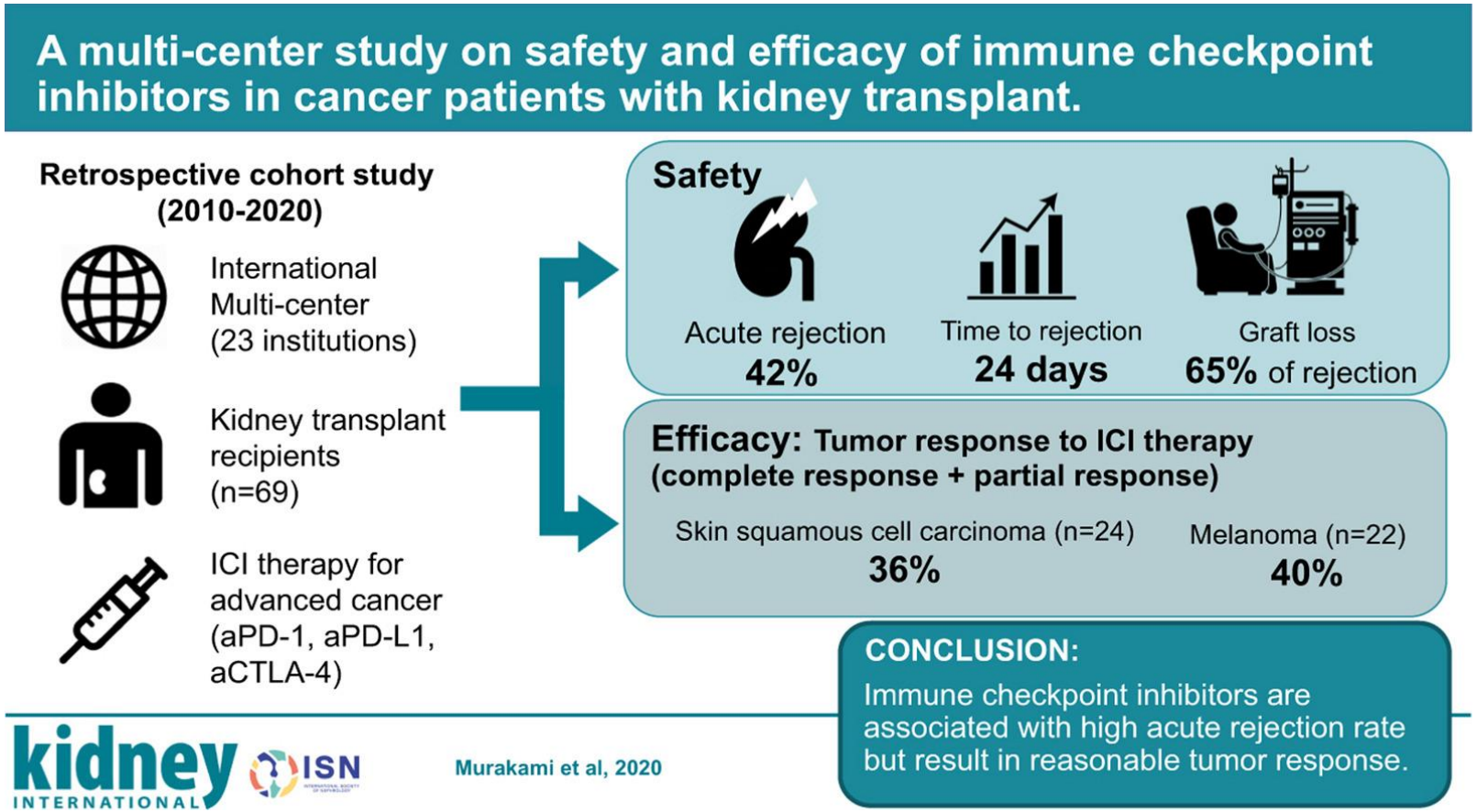
But in transplantation? What do we know?



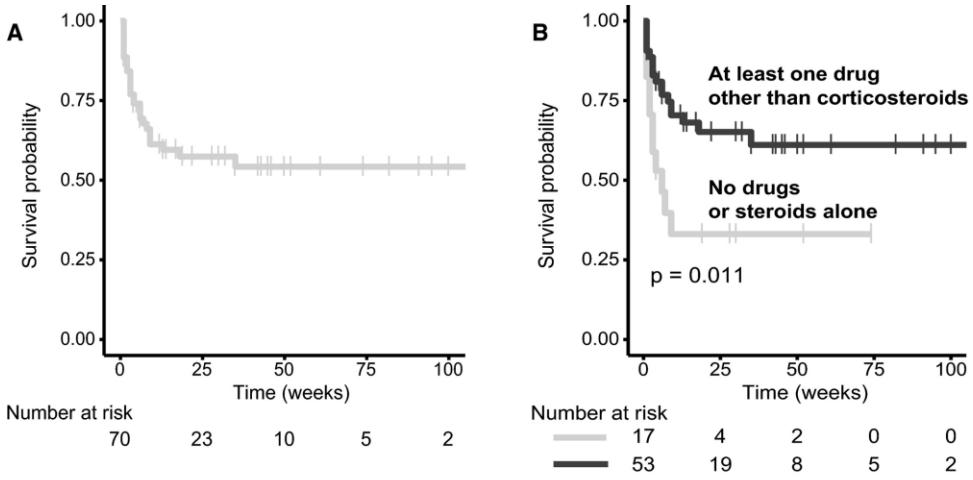
CNI: calcineurin inhibitor, mTOR: mammalian target of rapamycin, TCR: T cell receptor, PD1: programmed cell death protein-1, CTLA-4: cytotoxic T-lymphocyte-associated protein-4 (figure prepared with BioRender.com)

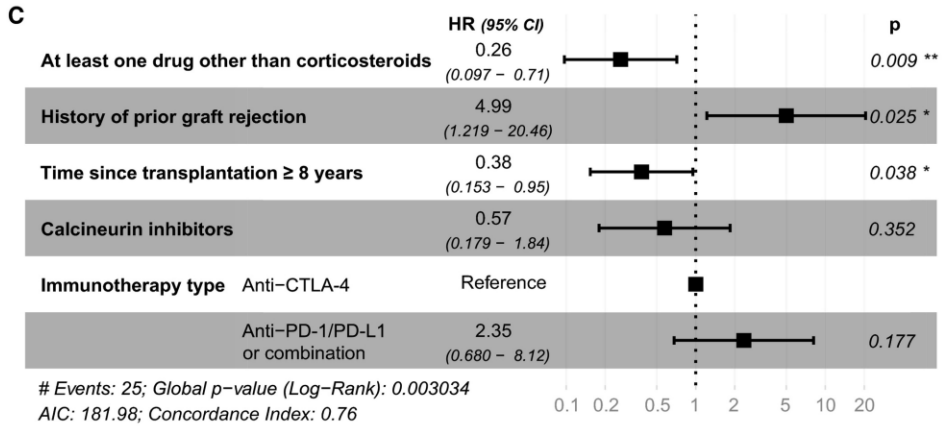
Murakami, Abudayyeh, Kidney News (2021)

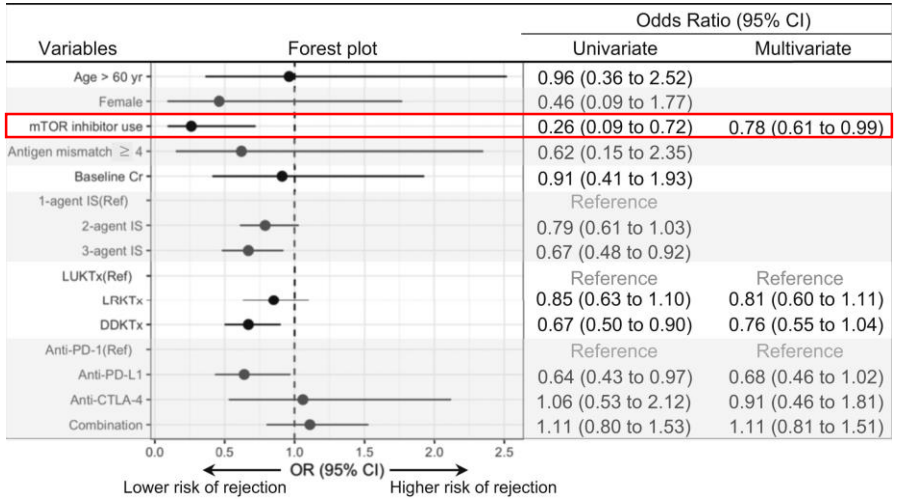
What do we know?



Factors associated with graft rejection







Murakami et al, Kidney international 2020
D'Izargny-Gargas et al, AJT 2020

Prospective clinical trials for kidney transplant recipients treated with immune checkpoint inhibitors.

Study	Nivolumab in tx patients	Tacrolimus and ICI	CONTRAC-1
Cancer type	Any cancers (incurable, metastatic solid tumors)	Skin cancers (Melanoma, cSCC, BCC, Merkel cell carcinoma)	cSCC
Transplant	Kidney	Kidney	Kidney
ICI	Nivolumab*	Nivolumab +/- Ipilimumab	Cemiplimab
Immunosuppression	Keep the same dose	Tac (2-5 ng/ml), pred 5 mg/day	mTORi + dynamic pred
Patient #	17	8	12
Rejection	2 (11.7%)	2 (25%)	0 (0%)
ORR (CR+PR)	53%	33%	45%
Registry	ANZCTR CA209-993ISR	NCT03816332	NCT03565783
Primary institution	Royal Adelaide Hospital, multicenter Australia	Johns Hopkins Hospital, multicenter USA	Dana Farber Cancer Institute USA
Reference	Lancet Oncol (2022)	J Clin Oncol (2024)	J Clin Oncol (2024)

Tx: transplant, ICI: immune checkpoint inhibitor, cSCC: cutaneous squamous carcinoma, BCC: basal cell carcinoma, ORR: objective response rate, CR: complete response, PR: partial response, mTORi: mammalian target of rapamycin

Van Meerhaeghe T, et al CKJ 2024

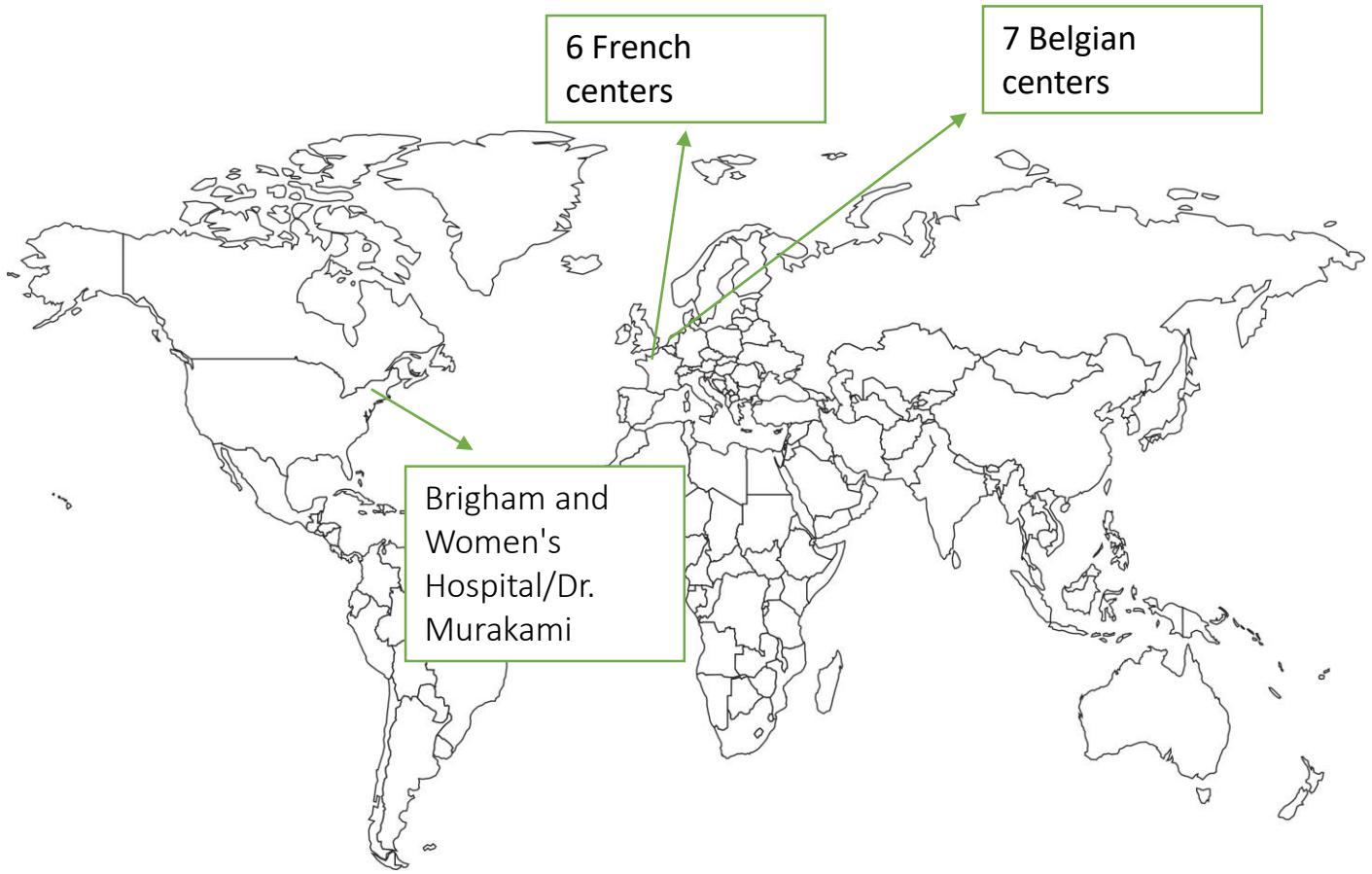
High unmet medical need

Immune checkpoint inhibitors in renal transplant recipients
ICIR

Tess Van Meerhaeghe, MD, Hôpital Erasme, Brussels

Promoteur: Pr Alain Le Moine

ICIR: multicentric and exploratory study



Inclusion criteria

KTR suffering from cancer, treated with ICI

Aim of the study

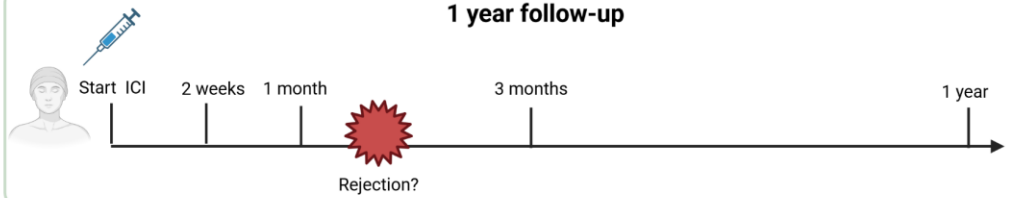
Creation of a **registry** and **biobank** composed of blood, urine and tissue of ICI treated kidney transplant recipients

To better understand graft rejection in this context and predict the risk of rejection and tumoral response.

Immune checkpoint inhibitors in renal transplant patients

Inclusion of patients and longitudinal follow-up with blood, urine and tissu sampling

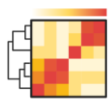
1 year follow-up



Analyses with omics technologies

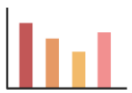
Blood and urine

Transcriptome



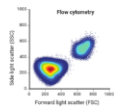
Gene expression whole blood Nanostring

Proteome



Serum and urine cytokine and chemokine expression

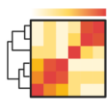
Immune phenotyping



PBMC

Kidney tissue

Transcriptome

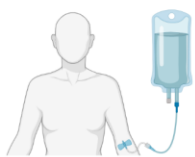


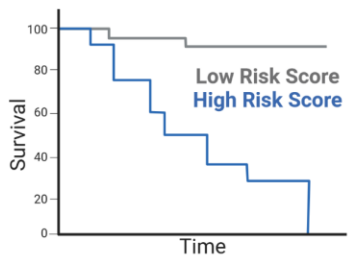
Gene expression tissue during rejection

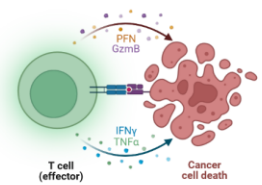
Multiplex Immunohistochemistry

MILAN

Data acquisition







Objectives

- Mecanisms of rejection in this particular situation
- Biomarkers of rejection
  - Can we predict rejection ?
- Biomarkers of tumoral response
  - Can we predict tumoral response?

Baseline characteristics	KTR n = 12
Age (mean) in years	67,9
Male sex (%)	5 (41.7%)
Type of cancer	8 Skin Ca (66.7%): • 6 SCC • 1 melanoma • 1 Merkell cell Ca 1 RCC (8.3%) 1 lung (8.3%) 1 gastric (8.3%) 1 colon (8.3%)
Mean time from Tx to ICI initiation (in years)	12
Immunosuppression **CTC alone** **CTC + mTORi** **CTC + TAC** **TAC + mTORi** **CTC + TAC + MMF** **CTC + TAC + mTORi**	 2 (16.7%) 5 (41.7%) 1 (8.3%) 1 (8.3%) 1 (8.3%) 2 (16.7%)
Type of ICI used	4 cemiplimab (33.3%) 5 pembrolizumab (41.7%) 1 nivolumab (8.3%) 1 avelumab (8.3%) 1 nivo + durvalumab (8.3%)
Rejection rate	3 (25%)
Time to rejection	19 days
Histology	1 TCMR grade IB (tubulitis grade 3) 2 TCMR grade III (transmural arteritis)
Treatment	2 transplantectomies 1 treatment with corticosteroids
Tumor response **Complete response (CR)** **Progressive disease (PD)** **unknown**	 5 (41.7%) 5 (41.7%) 2 (16.6%)

Merci pour votre attention

- Questions?