Brigham and Women's Hospital
Founding Member, Mass General Brigham

Acute Kidney Injury Related to Immune Checkpoint Inhibitors

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Director, Onco-Nephrology Program
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- Clinical focus: Onconephrology
- Research focus: Nephrotoxicity of Cancer Therapies

Disclosures

- Research funding from BTG International, AstraZeneca, Janssen
- Research funding from NIDDK (K23DK125672 and R03DK141708)
- Consultant for Secretome, Proletariat Therapeutics, BTG, Mersana Therapeutics, Alexion, MediBeacon
- Speaker fees from Springer Inc.
- Advisory Board for Orion Pharma
- President Emeritus and Founder of American Society of Onconephrology

Objectives

*To explain key risk factors for immune checkpoint inhibitor-associated acute kidney injury (ICI-AKI)

*To recognize the complexities associated with diagnosing and managing ICI-AKI

Case

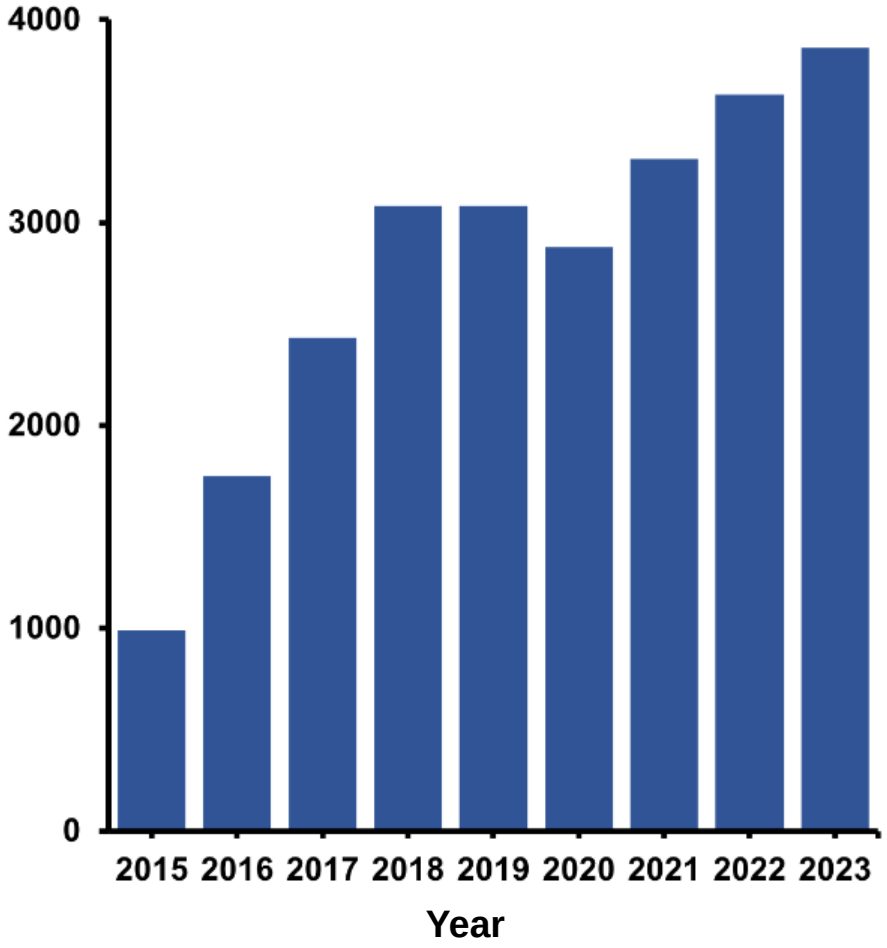
63 y.o. female with adenocarcinoma of lung with metastases to the brain, thoracic lymph nodes, and bone, on treatment with pembrolizumab and pemetrexed maintenance therapy, who presented to onconephrology for evaluation and management of AKI

Case

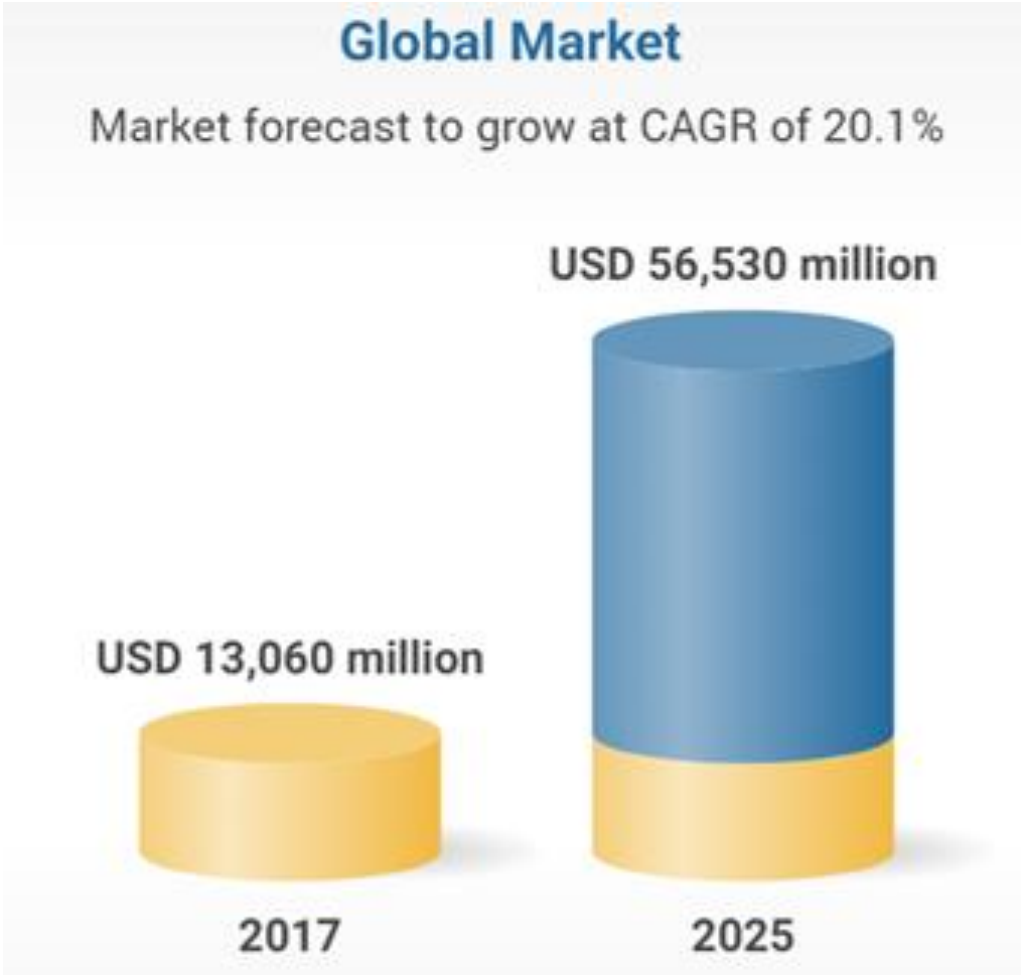
- Previously on carboplatin/pemetrexed/pembrolizumab, and then transitioned to pemetrexed, pembrolizumab maintenance
- SCr rose from a baseline of 0.7 mg/dl prior to starting all therapy to 1.4 mg/dl
- Urinalysis negative for blood, protein, white blood cells, red blood cells
- Was previously taking non-steroidal anti-inflammatory drugs regularly
- No immune-related adverse events while on immunotherapy
- History of proton pump inhibitor use

What is the next step???

The Rise of Immune Checkpoint Inhibitors (ICIs)



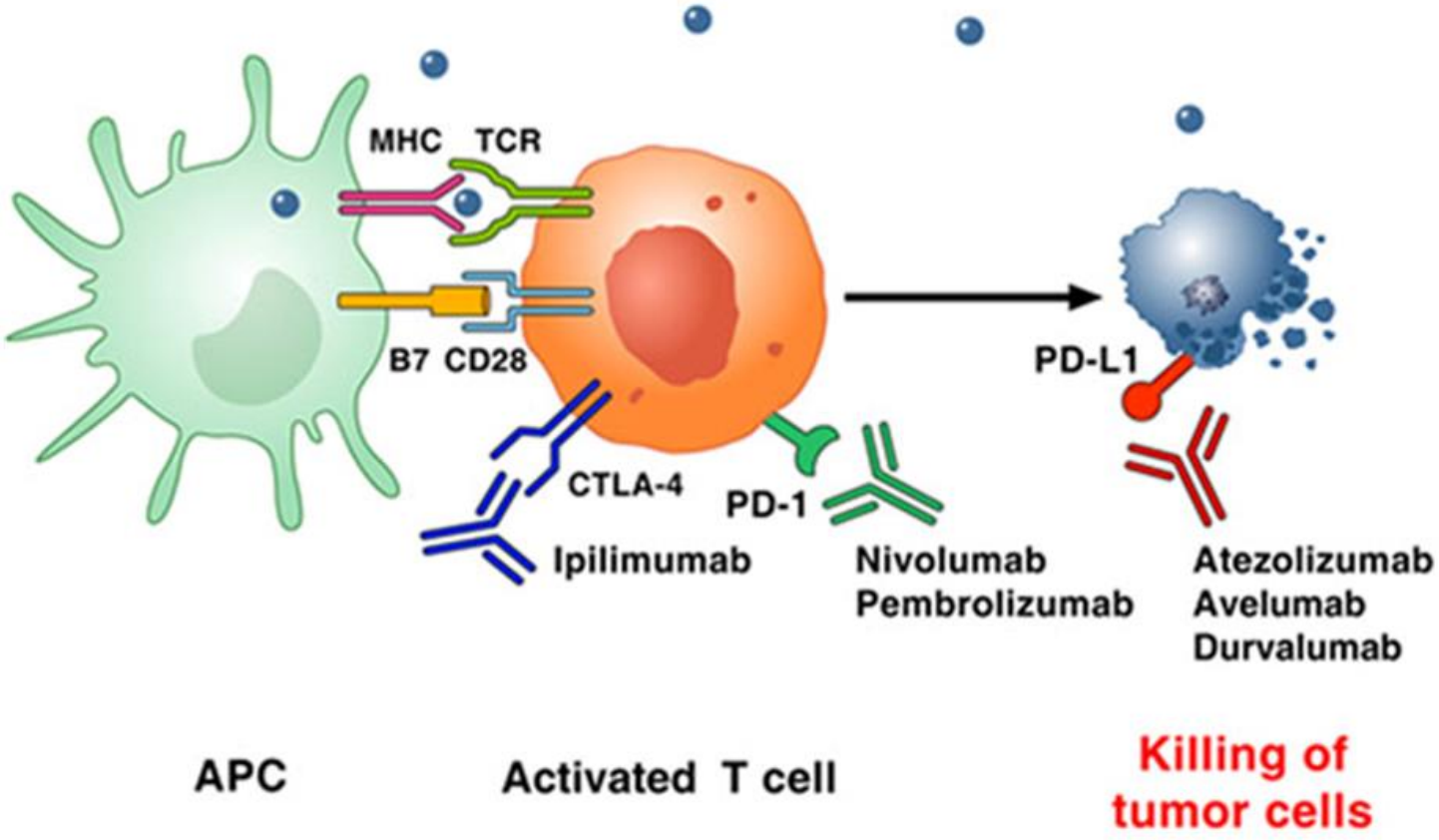
Patients Initiated on ICIs at BWH/DFCI and MGH



https://www.cancerresearch.org/en-us/scientists/immuno-oncology-landscape/

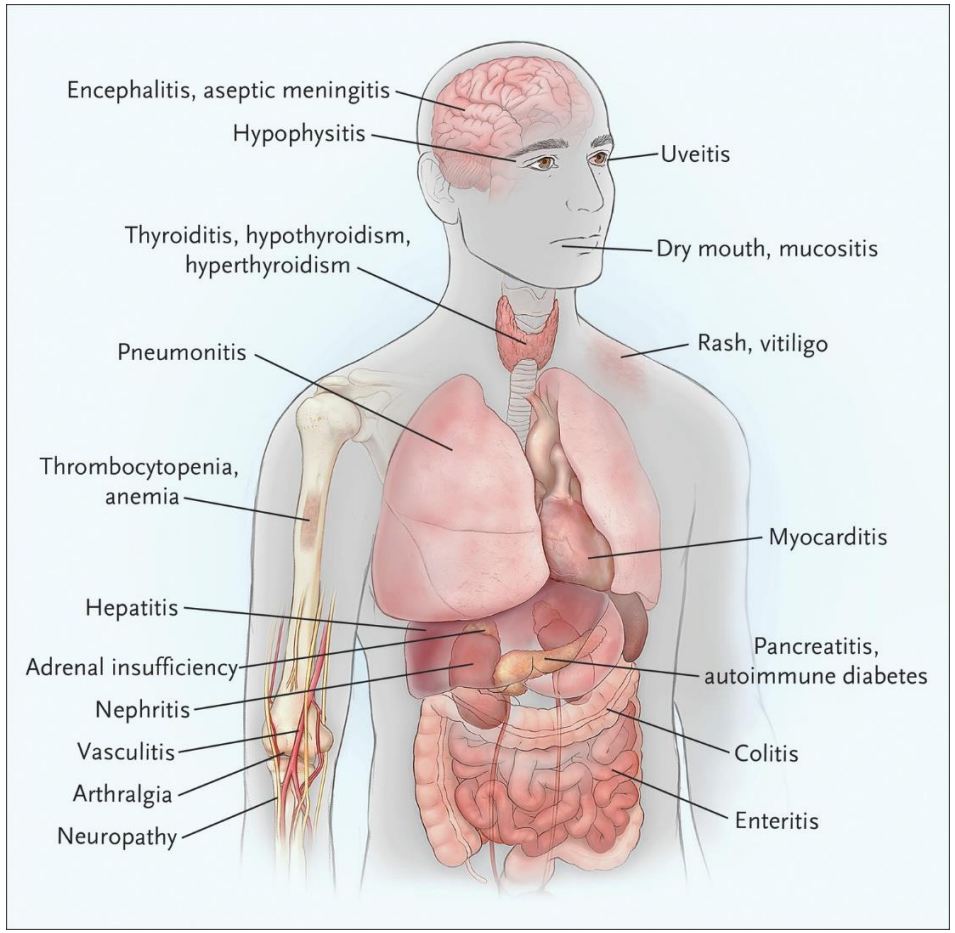
Mechanism of Action of ICIs

- **Block immune inhibitory checkpoints and release "brakes" on immune system**
- **Release of cytolytic molecules like tumor necrosis factor-α, granzyme B, interferon-γ**



Varricchi, Galdiero, Tocchetti, Circulation, 2017

ICI-AKI is one of several “Immune-related Adverse Events (irAEs)”



Postow et al., N Engl J Med, 2018

Histologic Features of ICI-AKI: Initial Case Series

kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

clinical investigation www.kidney-international.org

Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors

see commentary on page 474

Frank B. Cortazar[1], Kristen A. Marrone[2], Megan L. Troxell[3], Kenneth M. Ralto[4], Melanie P. Hoenig[4], Julie R. Brahmer[2], Dung T. Le[2], Evan J. Lipson[2], Ilya G. Glezerman[5], Jedd Wolchok[5], Lynn D. Cornell[6], Paul Feldman[7], Michael B. Stokes[8], Sarah A. Zapata[9], F. Stephen Hodi[10], Patrick A. Ott[10], Michifumi Yamashita[11] and David E. Leaf[12]

***n*=13 (ATIN in 12/13)**

AJKD
Case Report

Association of Acute Interstitial Nephritis With Programmed Cell Death 1 Inhibitor Therapy in Lung Cancer Patients

Anushree C. Shirali, MD,[1] Mark A. Perazella, MD,[1] and Scott Gettinger, MD[2]

***n*=6 (ATIN in 6/6)**

18/19 (95%) with ATIN

Histologic Features of ICI-AKI: Beyond ATIN

SHORT REPORT Open Access

Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience

Omar Mamlouk[1], Umut Selamet[2], Shana Machado[1], Maen Abdelrahim[3], William F. Glass[4], Amanda Tchakarov[4], Lillian Gaber[5], Amit Lahoti[6], Biruh Workeneh[6], Sheldon Chen[6], Jamie Lin[6], Noha Abdel-Wahab[7,8], Jean Tayar[8], Huifang Lu[8], Maria Suarez-Almazor[8], Nizar Tannir[9], Cassian Yee[10], Adi Diab[10†] and Ala Abudayyeh[6*†]

Retrospective study of all patients treated with ICIs at MD Anderson between 2008–2018 who were biopsied for AKI (*n*=16 out of 6412 treated patients)

Mamlouk et al., J Immunother Cancer, 2019

Histologic Features of ICI-AKI: Beyond ATIN

ATIN (*n*=14)

Pauci-immune GN (*n*=3; only 1 had +ANCA)

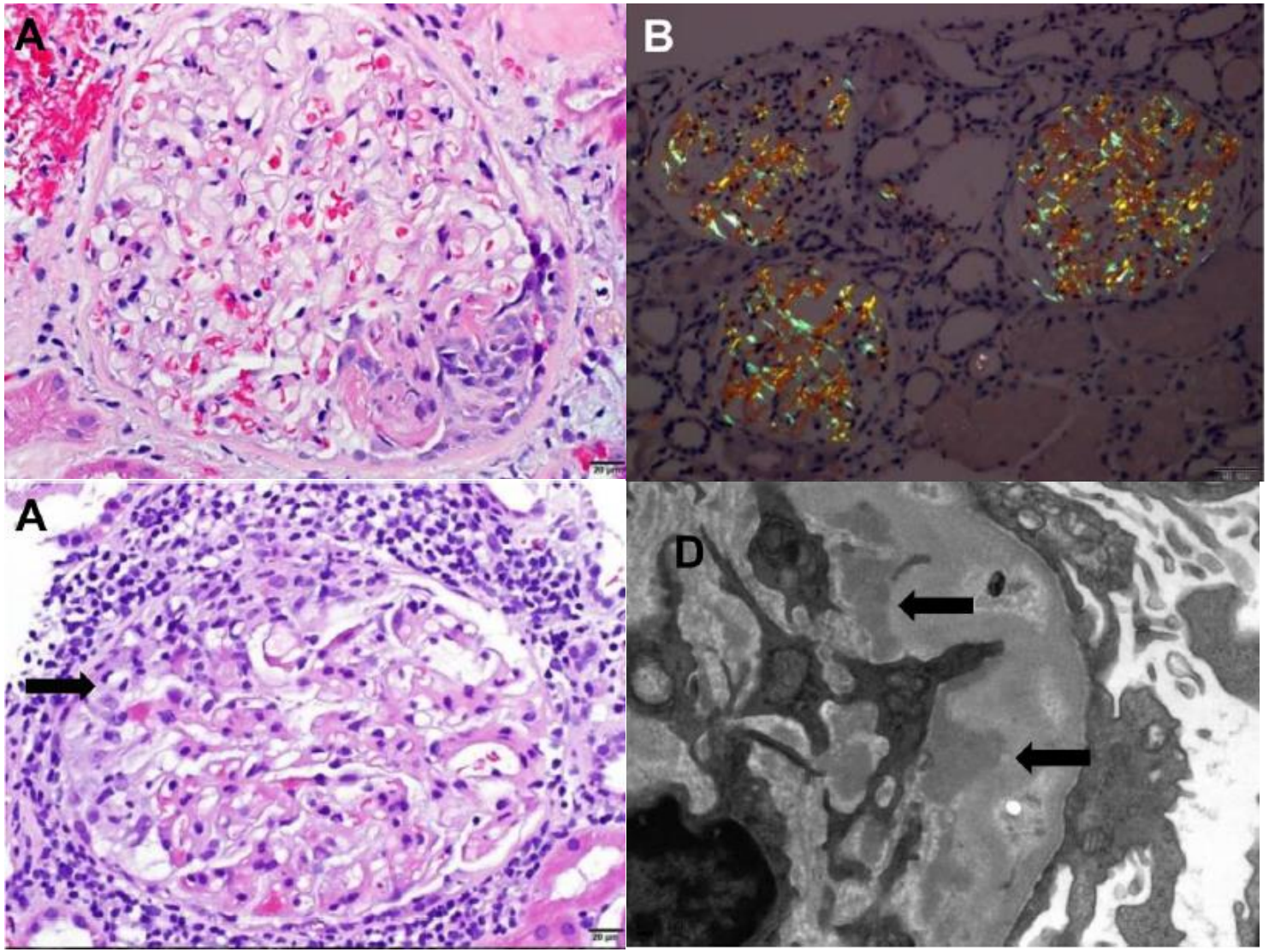
AA amyloid (*n*=1)

IgAN (*n*=2)

MN (*n*=1; anti-PLA2R neg)

C3GN (*n*=1)

Secondary FSGS (*n*=1)



Mamlouk et al., J Immunother Cancer, 2019

AKI is common in patients receiving ICIs, but how much is true ICI-AKI?

The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors

Harish Seethapathy,[1] Sophia Zhao,[1] Donald F. Chute,[1] Leyre Zubiri,[2] Yaa Oppong,[1] Ian Strohbehn,[1] Frank B. Cortazar,[1] David E. Leaf,[3] Meghan J. Mooradian,[2] Alexandra-Chloé Villani,[4,5] Ryan J. Sullivan,[2] Kerry Reynolds,[2] and Meghan E. Sise[1]

Patients who received ICI therapy at MGH between 2011 and 2016 with baseline and follow-up SCr available (**N=1016**)

~15% incidence of any AKI

'Sustained AKI' (**N=82 patients**)
110 episodes of sustained AKI

8% incidence of sustained AKI (any etiology)

ICI-related
(41 episodes; **N=30** patients)

3% incidence of ICI-AKI

Hemodynamic AKI/ATN
(57 episodes)

AKI of undetermined cause
(9 episodes)

Urinary tract obstruction (3 episodes)

Seethapathy et al., Clin J Am Soc Nephrol, 2019

ICI-AKI: Major Consequences, Yet Key Questions Remained Unanswered

ICI-AKI can lead to:

- Discontinuation of ICI therapy
- Irreversible loss of kidney function
- Prolonged courses of immunosuppression

Existing data largely limited to single-center case series

Limited data on safety of rechallenge

Cortazar et al., KI, 2016;
Manohar et al., NDT, 2019;
Seethapathy et al., CJASN, 2019;
Meraz-Muñoz et al., JITC, 2020;
Cortazar et al., JASN, 2020

Journal for ImmunoTherapy of Cancer

Acute kidney injury in patients treated with immune checkpoint inhibitors

Multicenter international study
429 patients with ICI-AKI
30 sites
10 countries

Gupta et al., J Immunother Cancer, 2021

Data Collection

Detailed data on **429 patients diagnosed with ICI-AKI between 2012-2020, from 30 sites across 10 countries:**

- Demographics and comorbidities
- Concomitant treatment with nephrotoxic medications
- Prior/concomitant extrarenal irAEs
- Laboratory and biopsy data
- Treatments for ICI-AKI
- Outcomes: renal recovery, ICI-rechallenge, survival

Gupta et al., J Immunother Cancer, 2021

Definitions

Criteria for ICI-AKI
Criteria 1: Increase in SCr ≥ 100% from baseline OR treatment with RRT
Criteria 2: Increase in SCr ≥50% from baseline AND at least one of the following:
1) ATIN on biopsy
2) ICI held for at least one cycle
3) Treatment with corticosteroids

Gupta et al., J Immunother Cancer, 2021

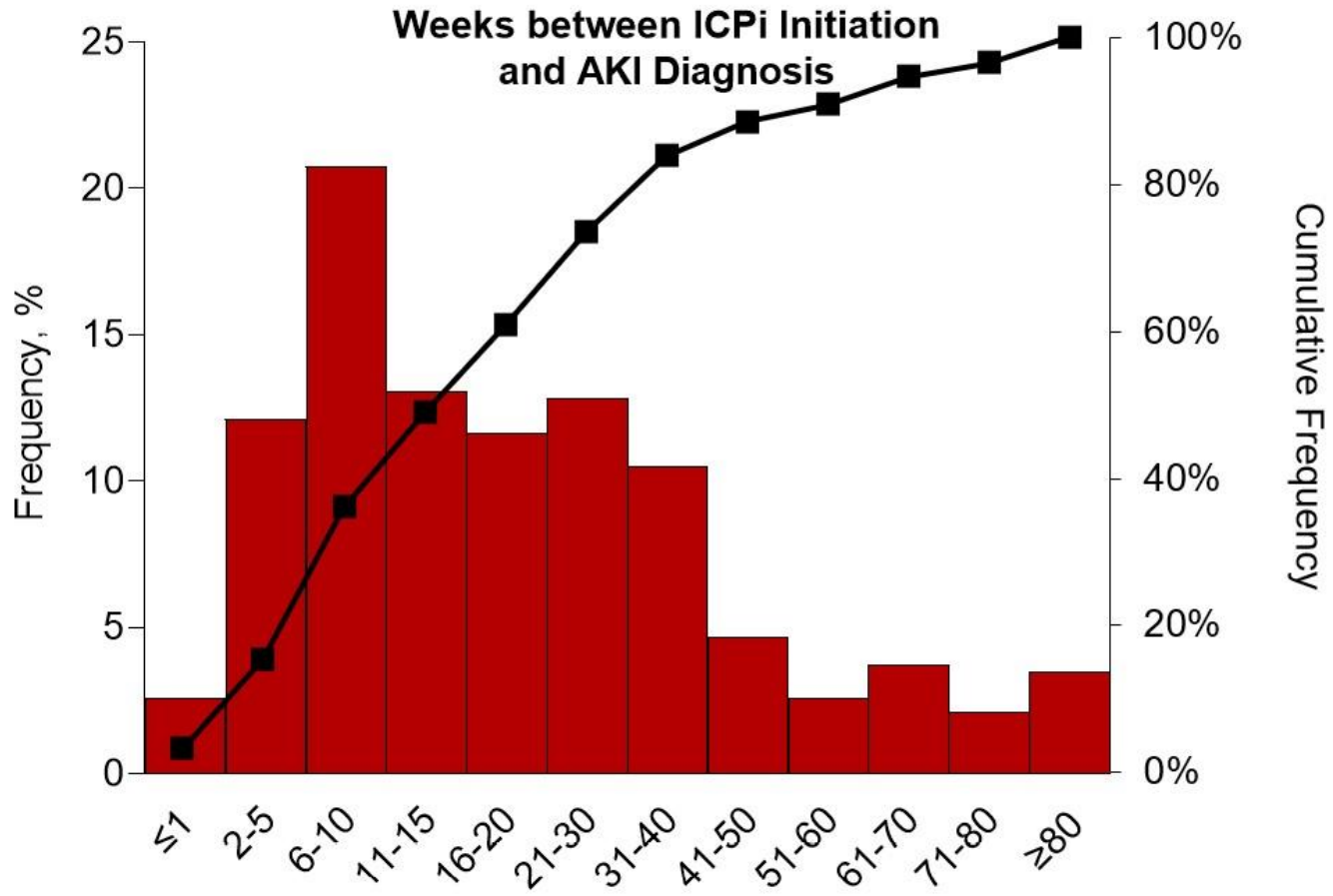
Definitions

Control Patients: received ICIs contemporaneously but did not develop ICI-AKI

Renal Recovery: nadir SCr ≤1.5 times the baseline value within 90 days following ICI-AKI

Gupta et al., J Immunother Cancer, 2021

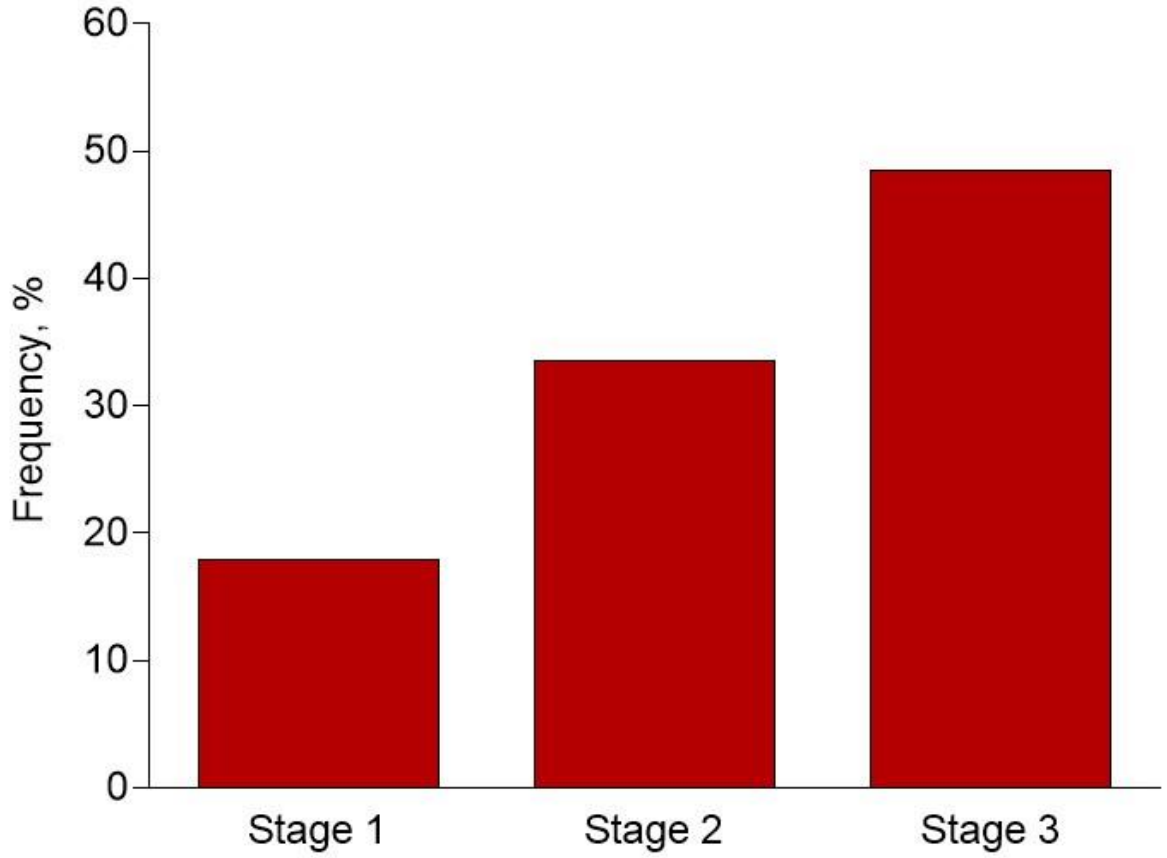
Timing of ICI-AKI



***ICI-AKI developed at a median of 16 weeks (IQR, 8-32) after ICI initiation**

Gupta et al., J Immunother Cancer, 2021

Severity of ICI-AKI

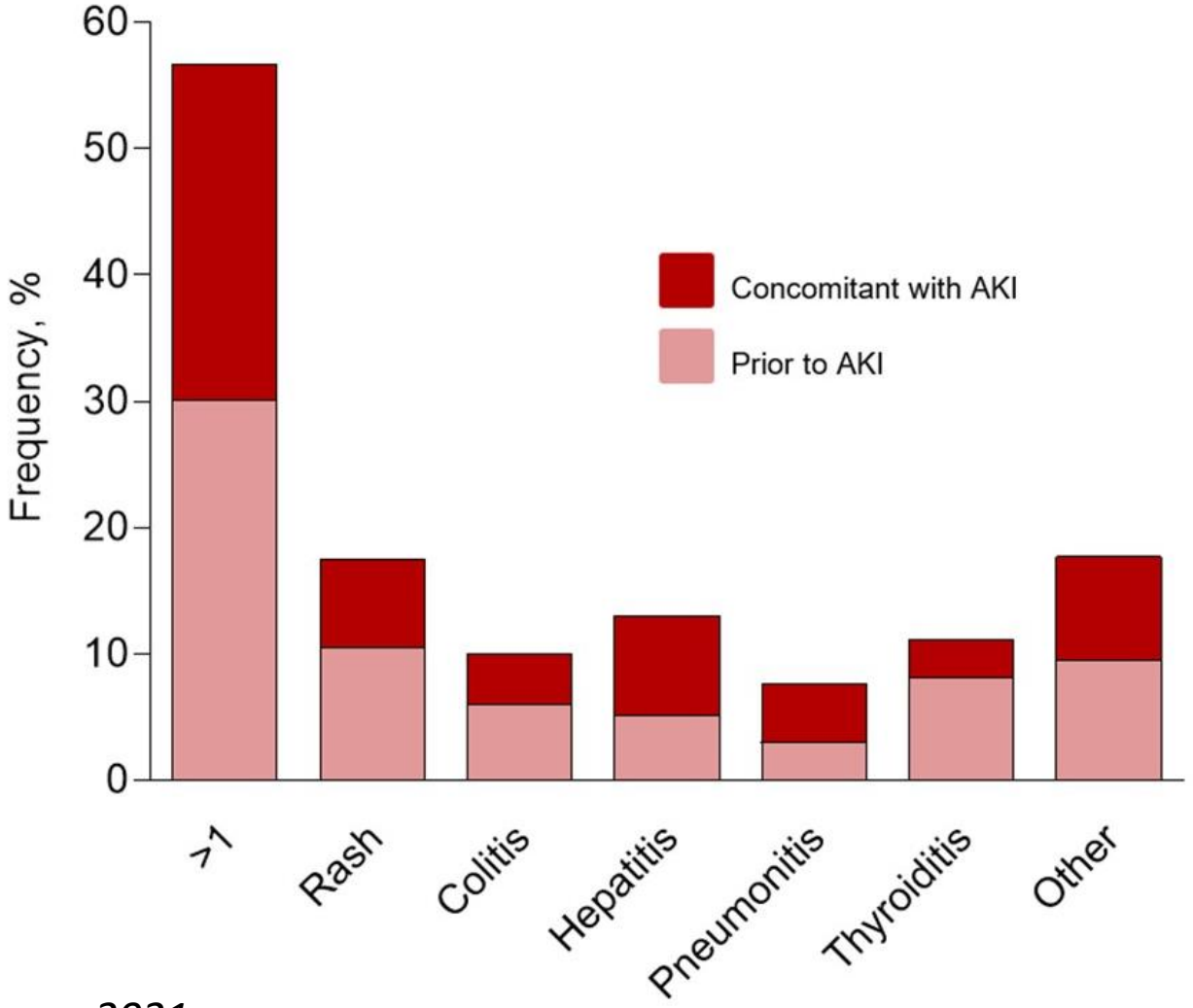


- **77 patients (18%) had stage 1**
- **144 (34%) had stage 2**
- **208 (49%) had stage 3, including 33 who received RRT (8% overall)**

Gupta et al., J Immunother Cancer, 2021

Extrarenal Immune-Related Adverse Events

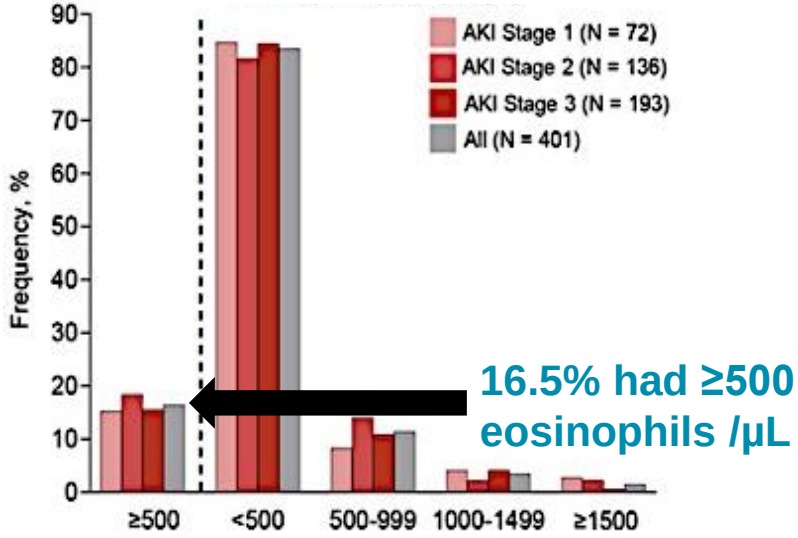
Extrarenal irAEs in 243 (57%) patients



Gupta et al., J Immunother Cancer, 2021

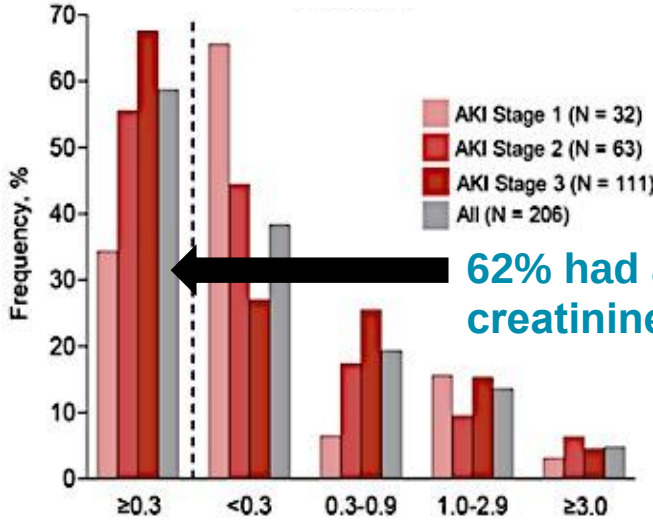
Can We Diagnose ICI-AKI Based on Clinical or Laboratory Features?

Eosinophilia



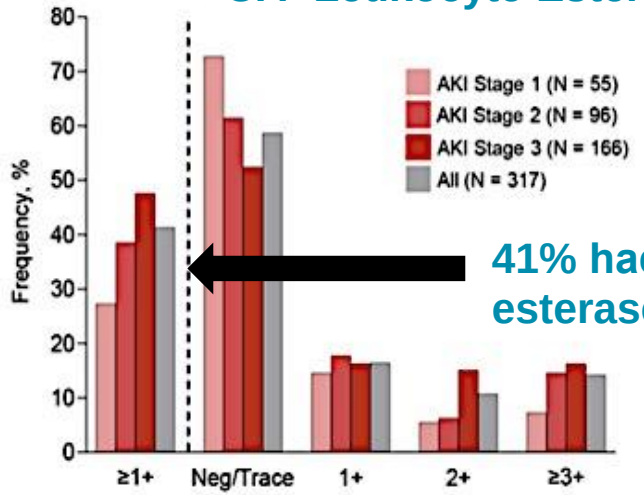
16.5% had ≥500 eosinophils /µL

Urine Protein/Creatinine



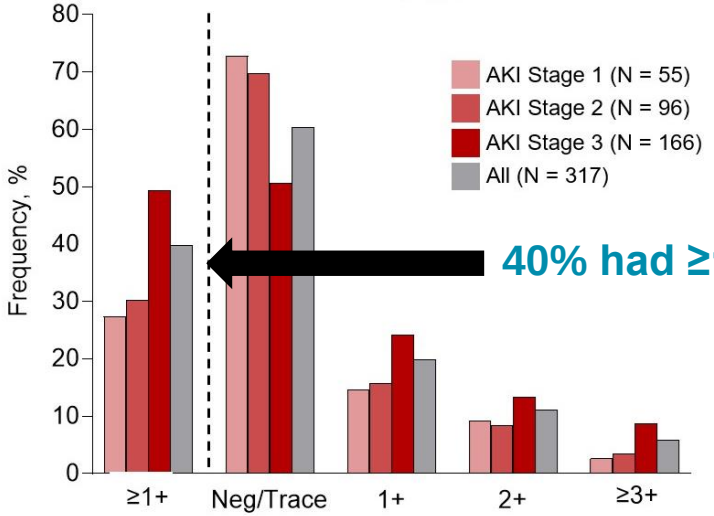
62% had a urine protein-to-creatinine ratio ≥0.3 g/g

UA- Leukocyte Esterase



41% had ≥1+ leukocyte esterase on urinalysis

UA- Blood

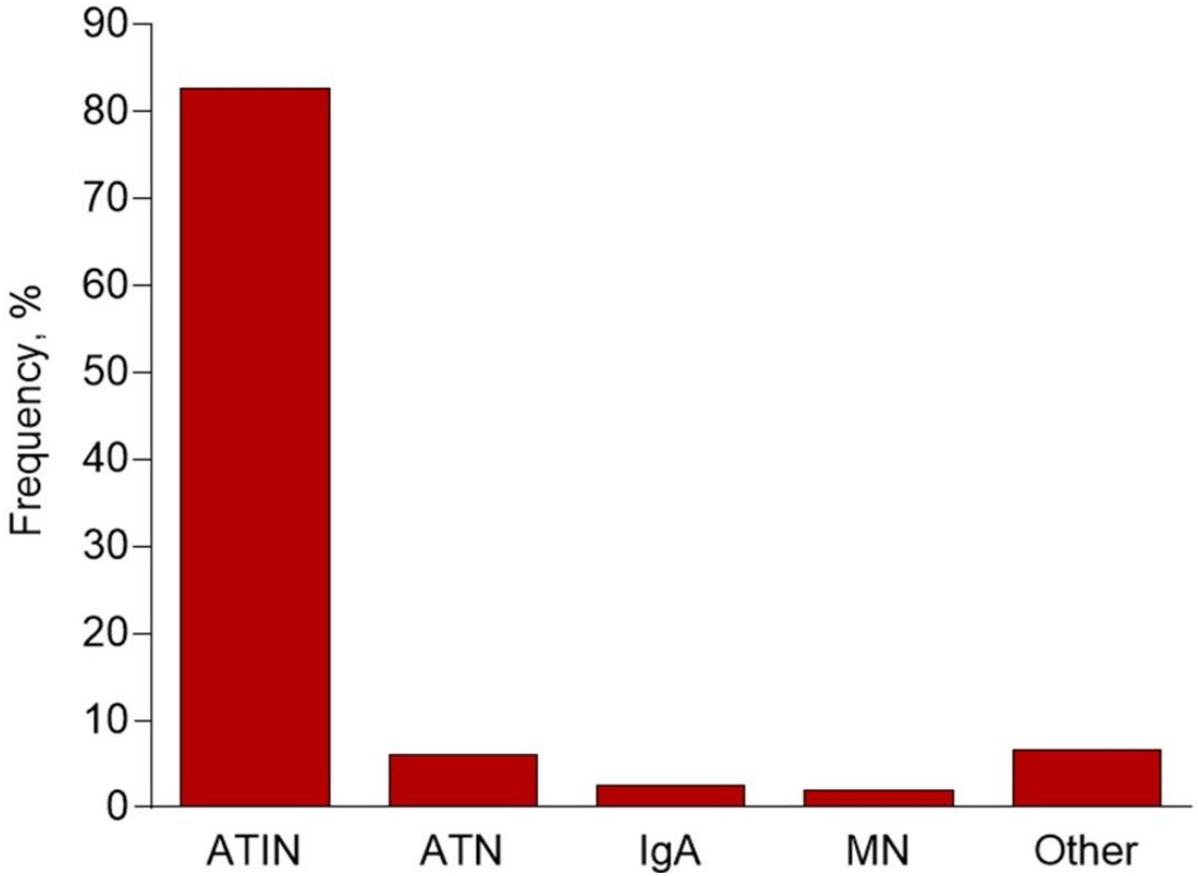


40% had ≥1+ blood on urinalysis

Gupta et al., J Immunother Cancer, 2021

Pathologies on Biopsy

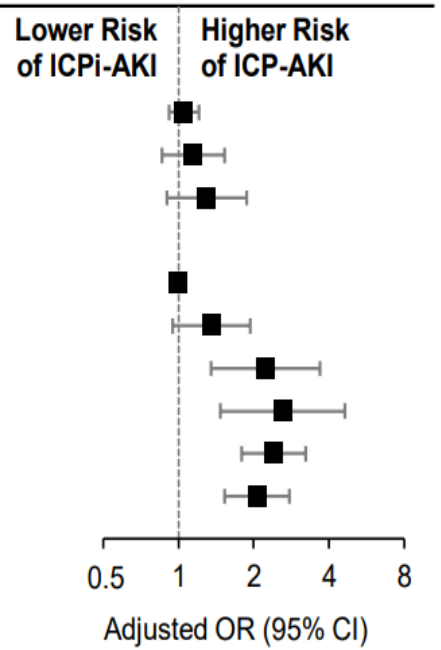
ATIN in 125/151 (83%) of biopsied patients

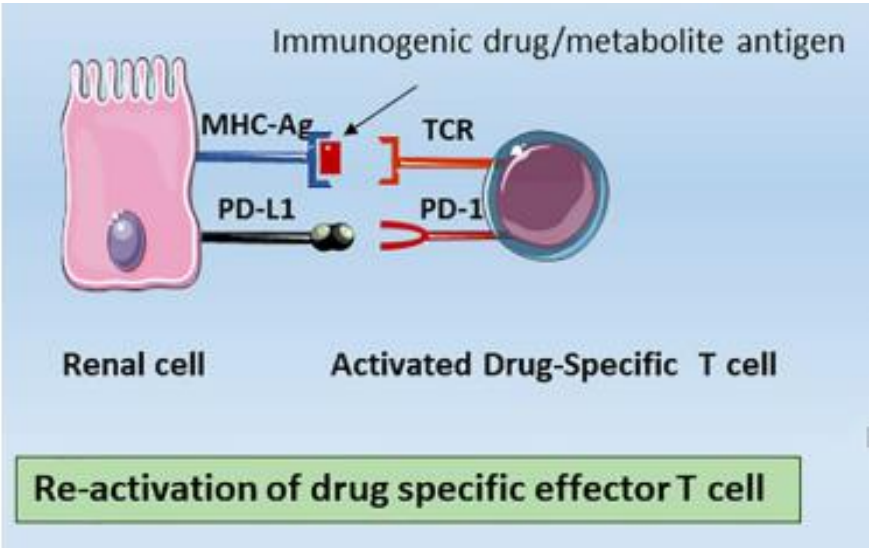


Gupta et al., J Immunother Cancer, 2021

Risk Factors for ICI-AKI: Why Onconephrologists Dislike PPIs

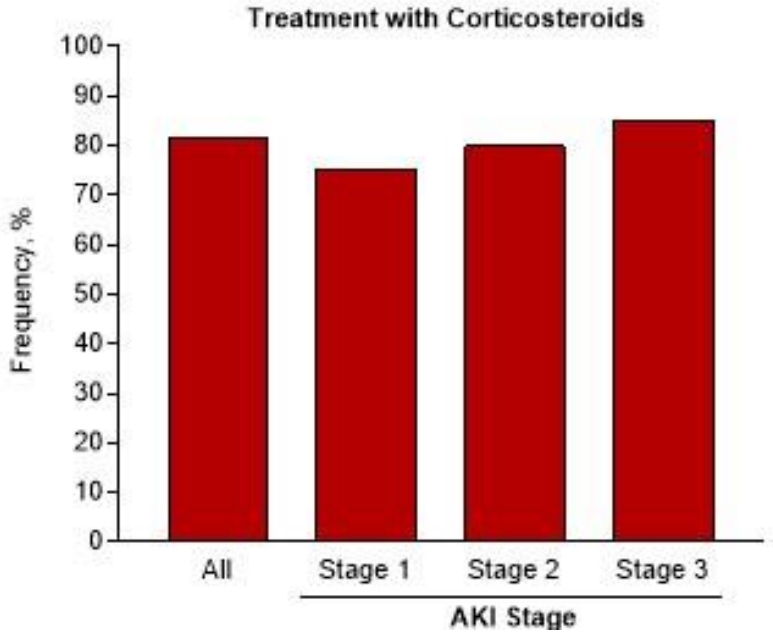
Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years)	1.17 (1.04-1.31)	1.05 (0.92-1.21)
Male sex	1.16 (0.88-1.52)	1.15 (0.86-1.53)
Combination ICPi therapy	1.42 (1.01-1.98)	1.30 (0.90-1.87)
Baseline eGFR (ml/min/1.73m^2)		
≥90 (REF)	1	1
60-89	1.54 (1.13-2.10)	1.36 (0.95-1.94)
45-59	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)

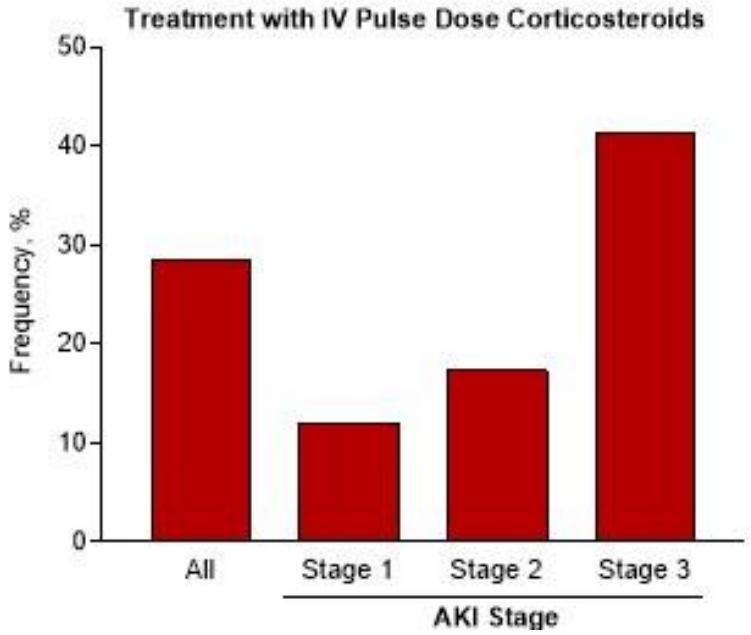




Gupta et al., J Immunother Cancer, 2021
Franzin et al., Front in Immunology, 2020

Treatment with Corticosteroids



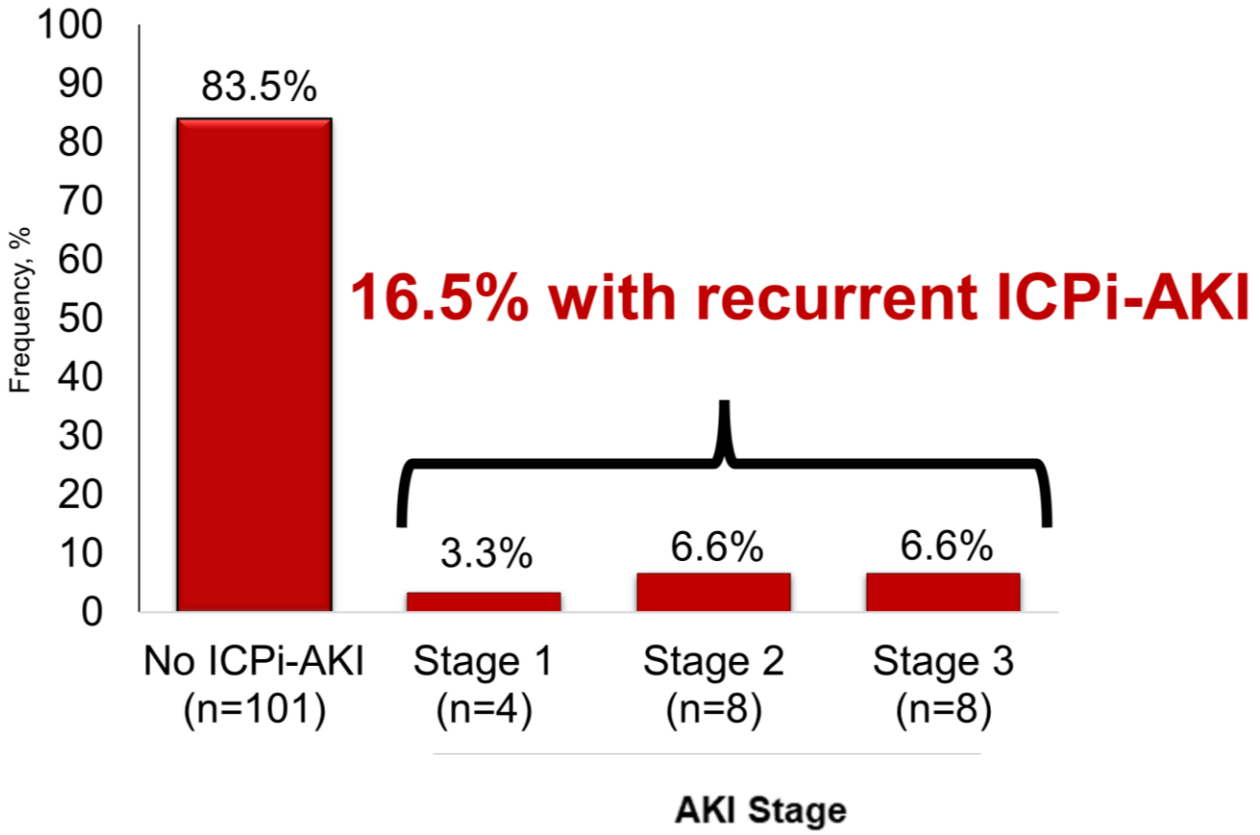


350 (82%) patients were treated with steroids, of whom 100 received IV pulse dose steroids

Gupta et al., J Immunother Cancer, 2021

Recovery and Rechallenge

- Renal recovery in 276 patients (64.3%)
- Early treatment with corticosteroids is associated with a higher odds of renal recovery
- Of 121 patients rechallenged, fewer than 1 in 5 patients had recurrent ICI-AKI after rechallenge



Gupta et al., J Immunother Cancer, 2021

Back to Our Case

Previously on carboplatin/pemetrexed/pembrolizumab, and then transitioned to pemetrexed, pembrolizumab maintenance
SCr rose from a baseline of 0.7 mg/dl prior to starting all therapy to 1.4 mg/dl
Urinalysis negative for blood, protein, WBCs, RBCs
Was previously taking NSAIDs regularly
No immune-related adverse events while on immunotherapy
History of proton pump inhibitor use

What is the next step???

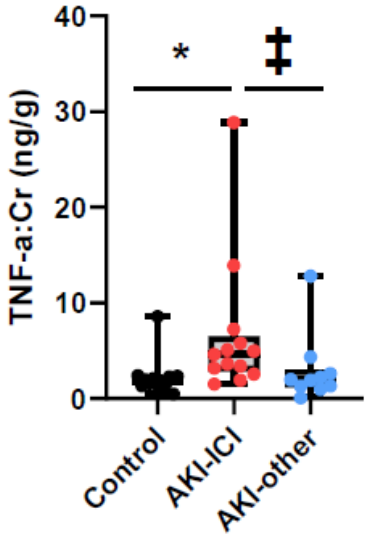
Biopsy:
*Hematuria, proteinuria (particularly albuminuria), +serologies
*__Those receiving combination therapy__
*ANY concern for alternative cause

No biopsy
*Solitary kidney/history of nephrectomy
*Anticoagulation
*No obvious alternative cause
*Frailty; patient preference

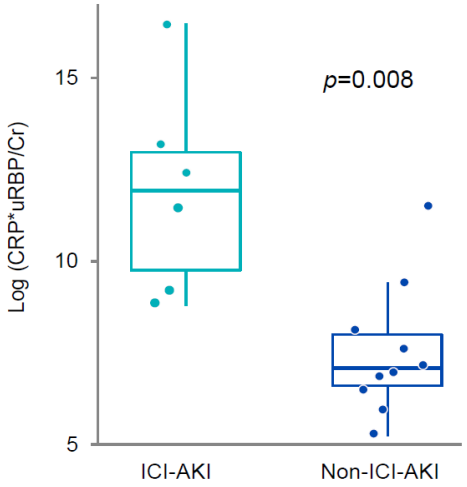
Novel Biomarkers of ICI-AKI

Urine Biomarkers

TNF-α

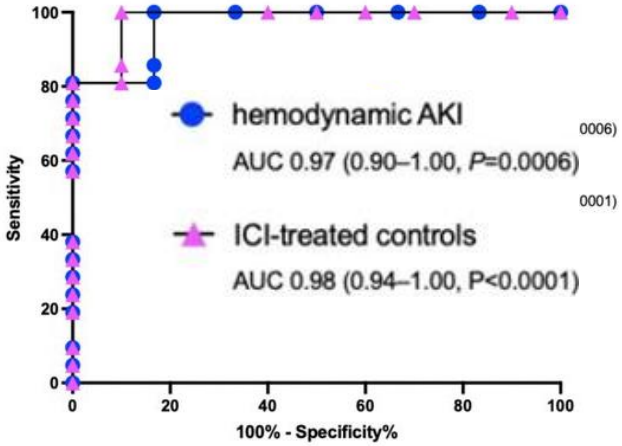


Retinol-binding Protein/Cr*CRP

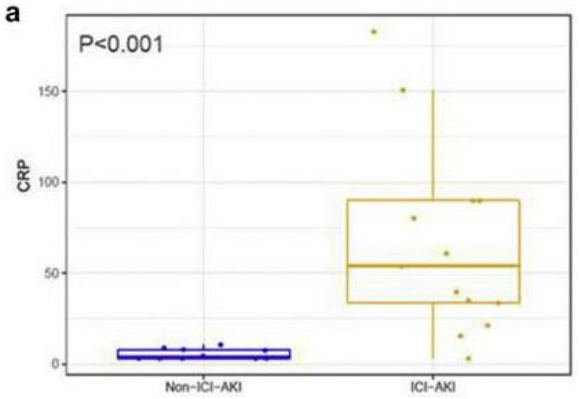


Serum Biomarkers

Soluble IL-2R



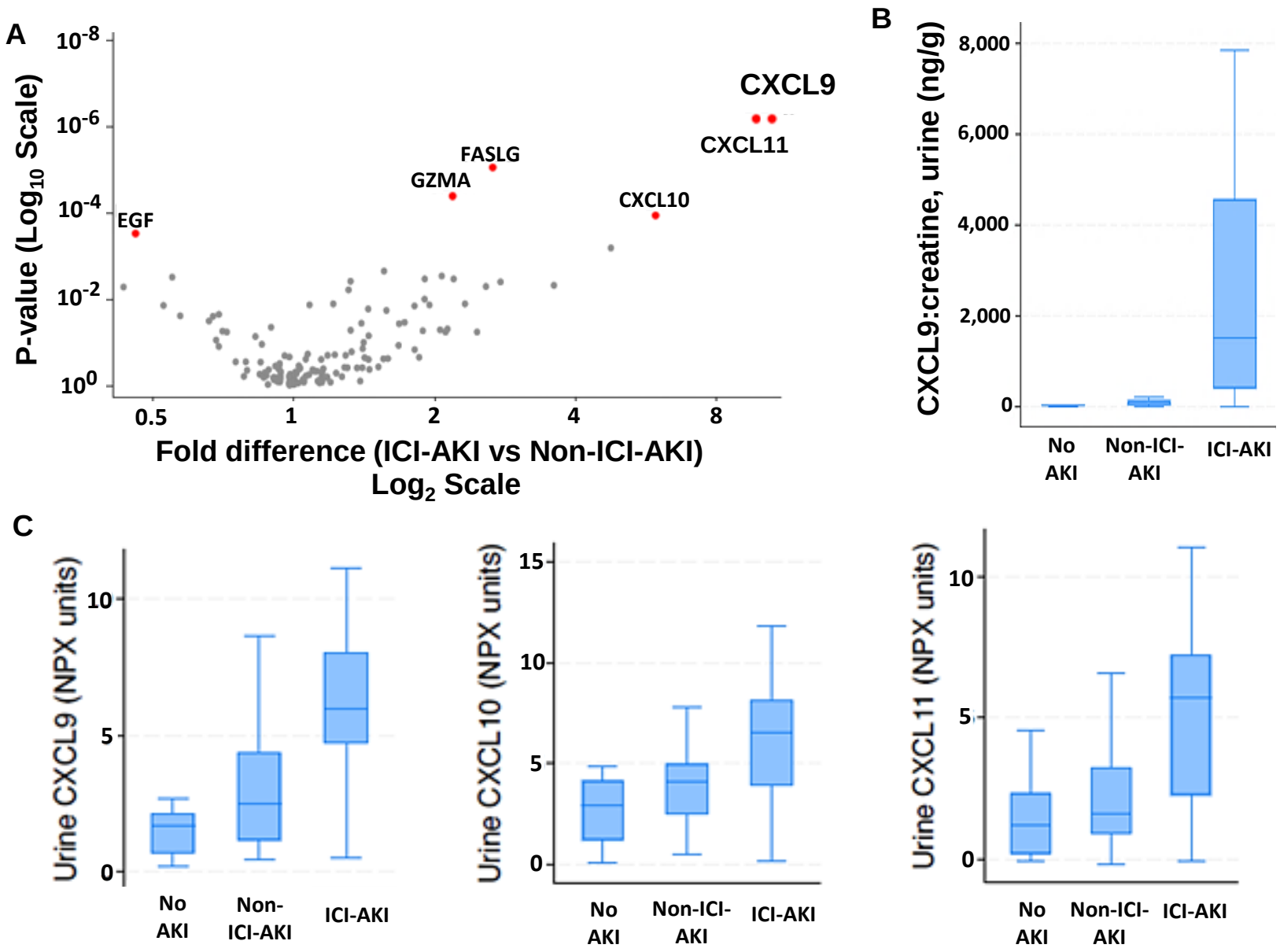
C Reactive Protein (CRP)



Moledina DG et al. J Clin Invest. 2023.
Sise ME et al. J Immunother Cancer. 2023.

Farooqui et al. KI Reports. 2022
Isik B et al. KI Reports. 2021.
Courtesy of Abhijat Kitchlu

Novel Biomarkers of ICI-AKI: Urinary CXCL-9



Gupta et al., Accepted, KI

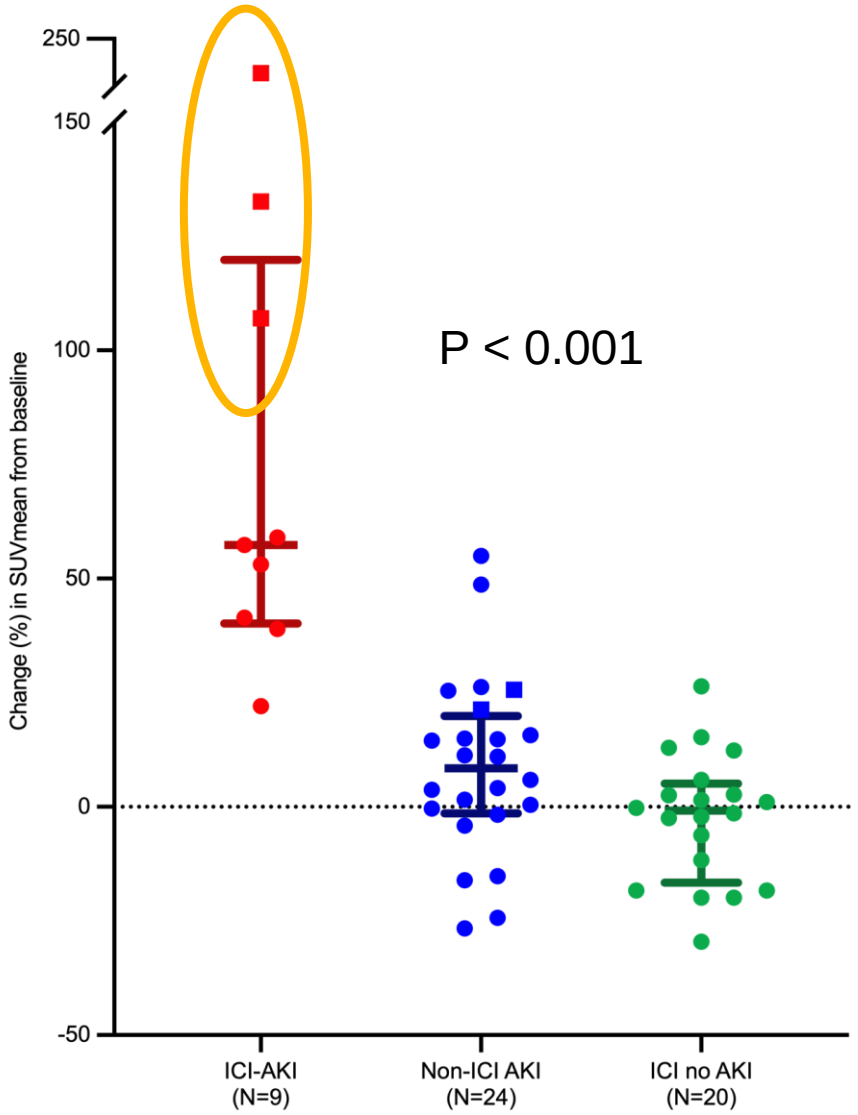
Beyond Urinary and Blood-Based Biomarkers…

F^{18}-FDG PET imaging as a diagnostic tool for immune checkpoint inhibitor–associated acute kidney injury

Shruti Gupta,[1,2,3] Olivia Green-Lingren,[1] Sudhir Bhimaniya,[3,4] Aleksandra Krokhmal,[4] Heather Jacene,[3,4] Marlies Ostermann,[5] Sugama Chicklore,[6] Ben Sprangers,[7,8] Christophe M. Deroose,[9] Sandra M. Herrmann,[10] Sophia L. Wells,[1] Sarah A. Kaunfer,[1] Jessica L. Ortega,[1] Clara García-Carro,[11] Michael Bold,[12] Kevin L. Chen,[13] Meghan E. Sise,[3,14] Pedram Heidari,[15] Wai Lun Will Pak,[16] Meghan D. Lee,[14] Pazit Beckerman,[17] Yael Eshet,[18] Raymond K. Hsu,[19] Miguel Hernandez Pampaloni,[20] Arash Rashidi,[21] Norbert Avril,[22] Vicki Donley,[21] Zain Mithani,[23] Russ Kuker,[24] Muhammad O Awiwi,[25] Mindy X. Wang,[26] Sujal I. Shah,[27] Michael D. Weintraub,[3,28] Heiko Schoder,[29] Raad B. Chowdhury,[1,2,3] Harish Seethapathy,[3,14] Kerry L. Reynolds,[3,30] Maria Jose Soler,[31] Ala Abudayyeh,[26] Ilya Glezerman,[16] and David E. Leaf[1,3]

Published August 8, 2024 - More info

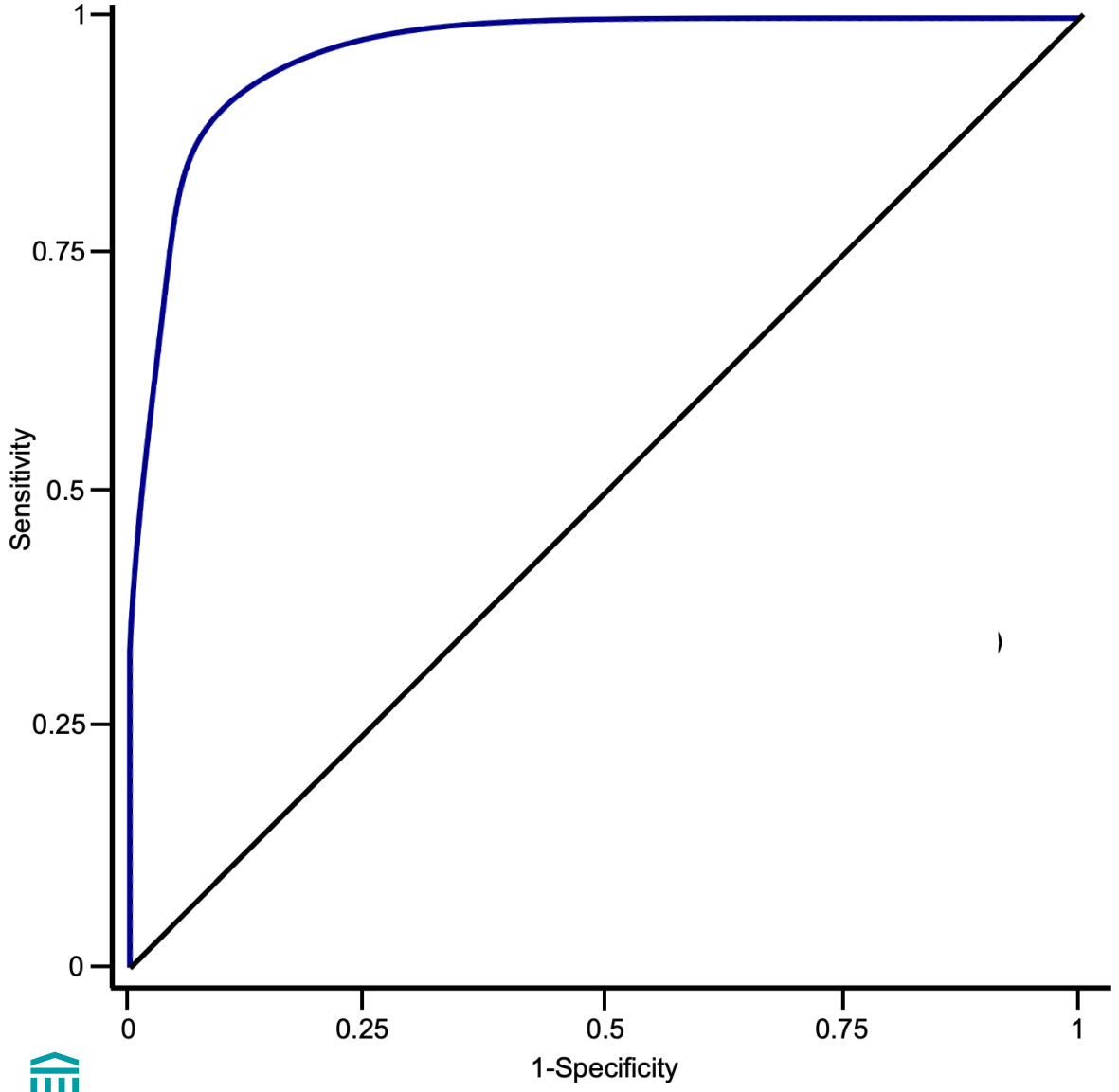
FDG-PET/CTs: Percentage change in SUV_{mean} from baseline to the time of AKI



- ICI-AKI: the **SUV_{mean} increased by a median of 57.4% (IQR, 40.3 to 119.8) from baseline to follow-up**
- AKI from non-ICI causes: SUV_{mean} increased by 8.5% (IQR, 1.4 to 19.9)
- Controls without AKI: SUV_{mean} decreased by 0.8% (IQR, -16.6 to 5.1)

Gupta et al., J Clin Invest, 2024

AUC for Differentiation of ICI-AKI from Controls

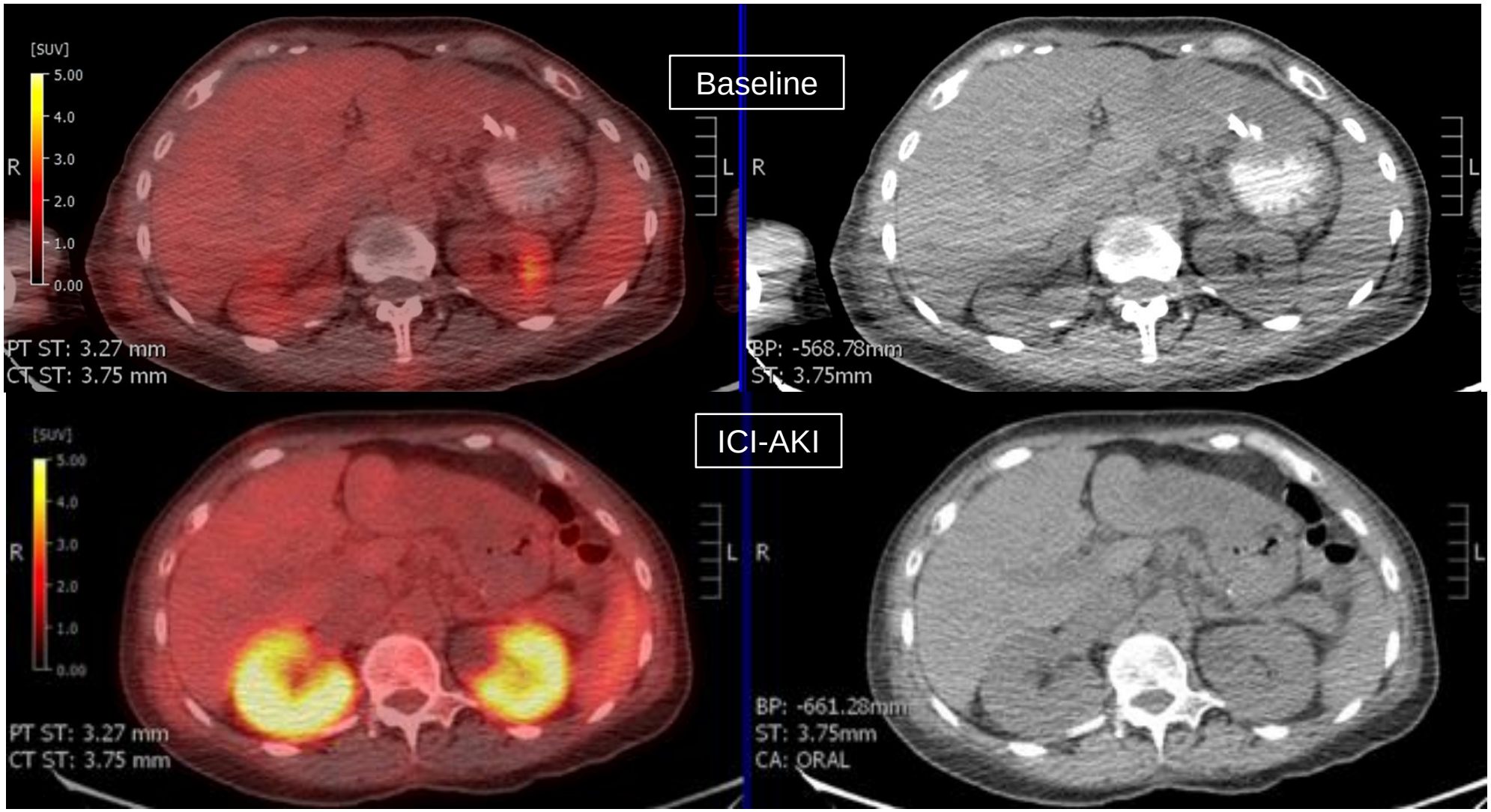


AUC 0.97 (95% CI, 0.93-1.00)

AUC unchanged after a sensitivity analysis where we excluded patients in the control group if they were receiving AIN-causing medications

Gupta et al., J Clin Invest, 2024

Representative Image of a Baseline and Follow-Up PET-CT



Case Follow-Up

63 y.o. female with adenocarcinoma of lung with metastases to the brain, thoracic lymph nodes, and bone, on treatment with pembrolizumab and pemetrexed maintenance therapy, who presented to onconephrology for evaluation and management of AKI

Case Follow-Up

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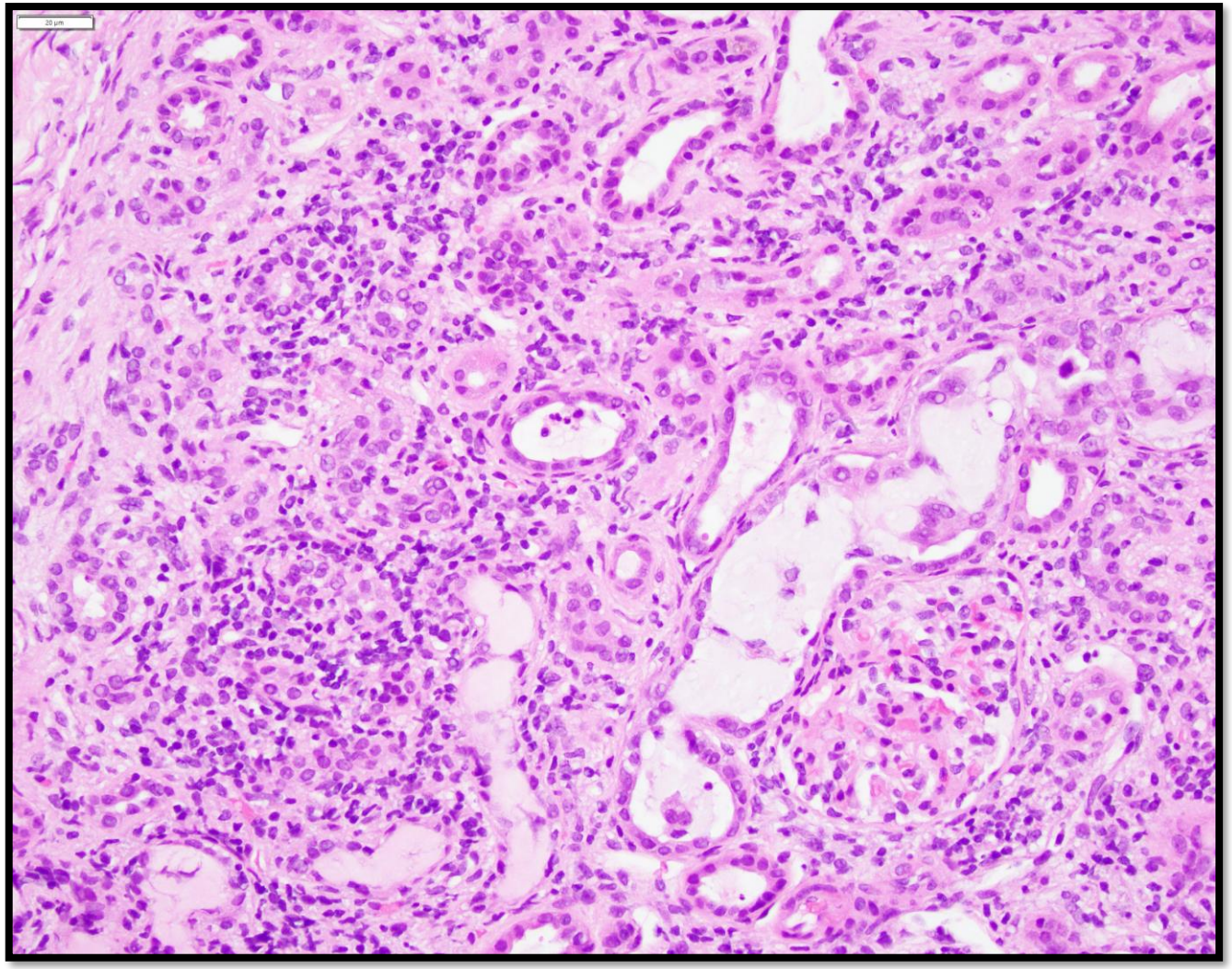
SCr rose from a baseline of 0.7 mg/dl prior to starting all therapy to 1.4 mg/dl
Urinalysis negative for blood, protein, WBCs, RBCs
Was previously taking NSAIDs regularly
No immune-related adverse events while on immunotherapy
History of proton pump inhibitor use

Case Follow-Up

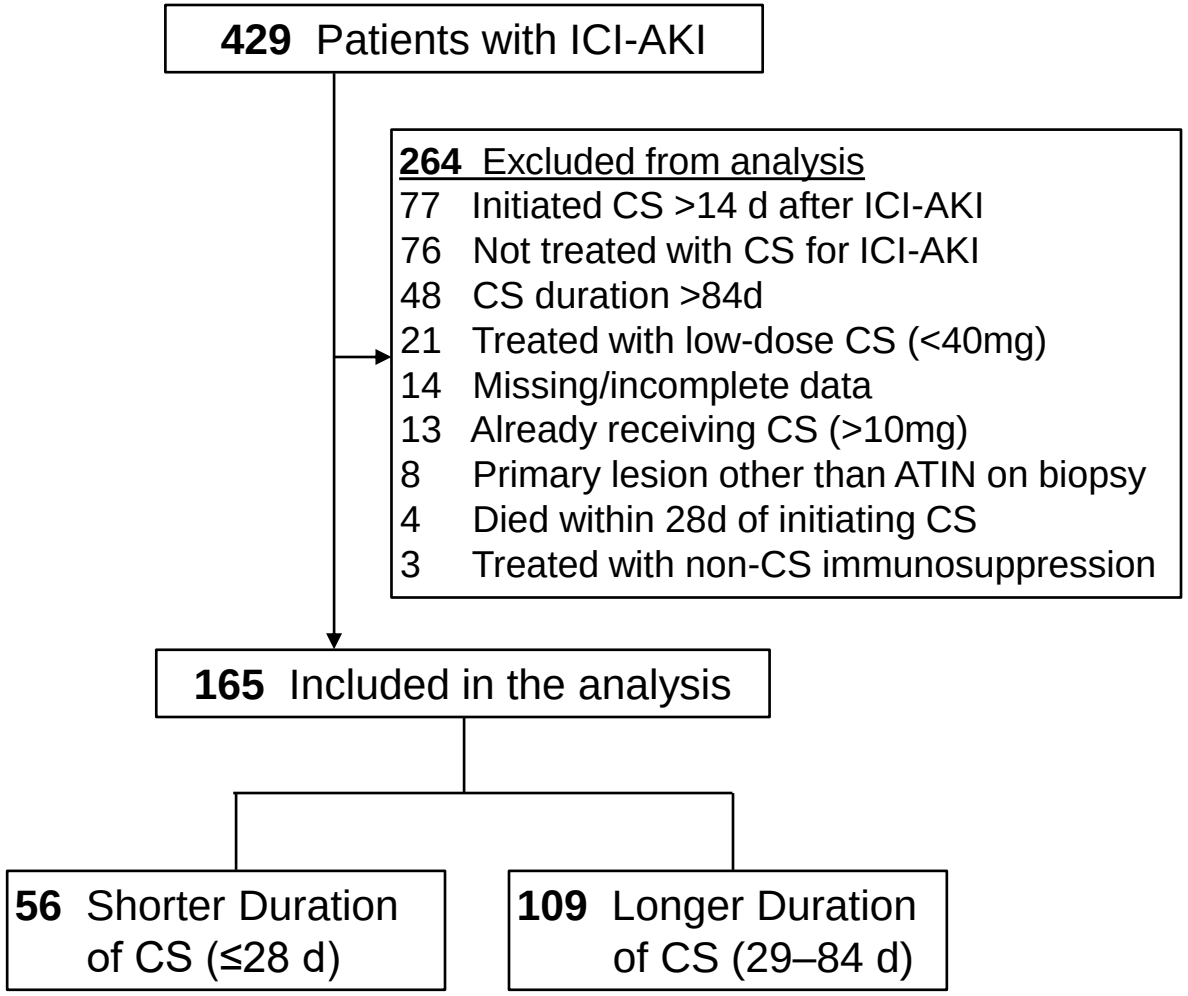
Decision was made to pursue a kidney biopsy….

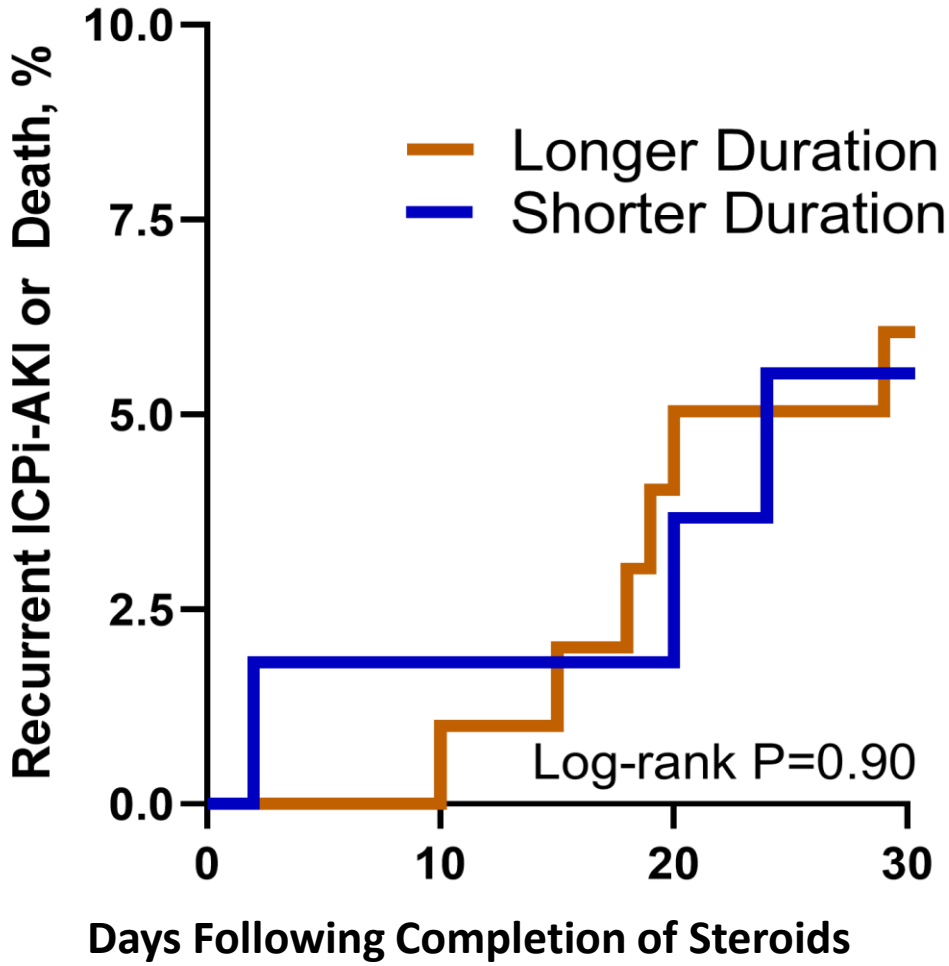


Case Follow-Up

- Started on prednisone 1 mg/kg while awaiting biopsy
- Slow improvement in kidney function with return of serum creatinine to 0.95 mg/dl
- Successfully rechallenged, OFF proton pump inhibitor, and without recurrence of ICI-AKI

Treatment of ICI-AKI with Steroids: How Long is Enough?





Gupta et al., J Immunother Cancer, 2022

Special Populations

- Kidney Transplant
- Underlying Autoimmune Diseases

A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant.

Retrospective cohort study (2010-2020)

International Multi-center (23 institutions)

Kidney transplant recipients (n=69)

ICI therapy for advanced cancer (aPD-1, aPD-L1, aCTLA-4)

Safety

Acute rejection **42%**

Time to rejection **24 days**

Graft loss **65%** of rejection

Efficacy: Tumor response to ICI therapy (complete response + partial response)

Skin squamous cell carcinoma (n=24) **36%**

Melanoma (n=22) **40%**

CONCLUSION:

Immune checkpoint inhibitors are associated with high acute rejection rate but result in reasonable tumor response.

kidney INTERNATIONAL ISN

Murakami et al, 2020

Original Reports | Skin Cancer

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Cemiplimab for Kidney Transplant Recipients With Advanced Cutaneous Squamous Cell Carcinoma

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- Phase 1 study of cemiplimab for kidney transplant recipients with metastatic SCC (n=12)
- After cross-taper to an mTOR inhibitor and pulsed dose corticosteroids, patients received cemiplimab intravenously once every 3 weeks for up to 2 years and were assessed for response every 8 weeks.
- Primary end point was the rate of kidney rejection
- No kidney rejection or loss was observed
- Response was observed in 5 of 11 evaluable patients, including 2 with durable responses

Autoimmune Disease

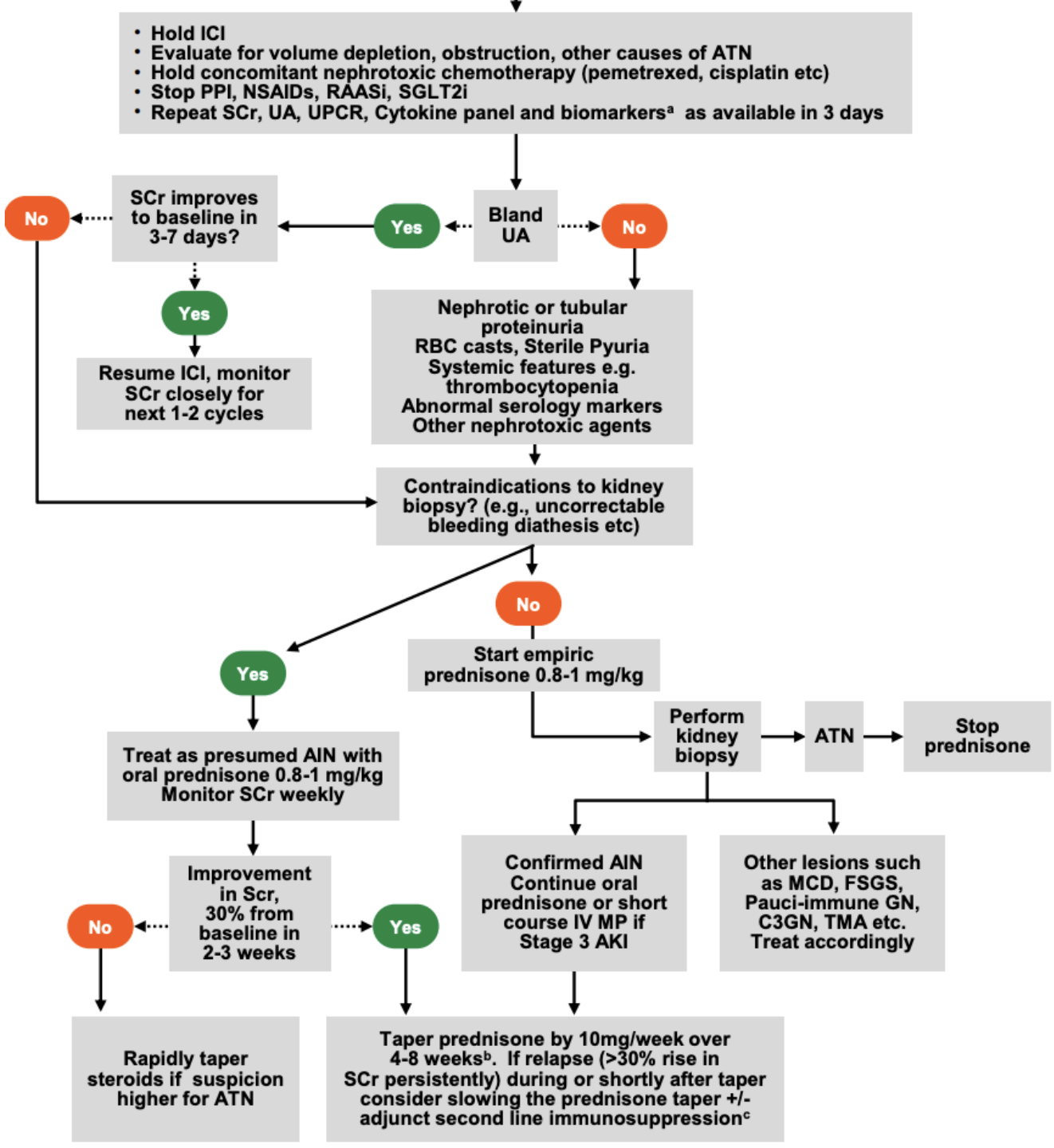
- ICI use is feasible in patients with pre-existing autoimmune disorders who develop cancer, though disease activity, level of immunosuppression, and the extent of organ damage and function should be considered

- AIM-NIVO trial underway

ICI-AKI Position Statement

Expert panel consensus recommendations for diagnosis and management of ICI-AKI

American Society of Onconephrology



Herrmann SM , Abudayyeh A, Gupta S, et al. Kidney Int. 2024.

Question #1: Which of the Following is not Known to Be a Risk Factor for ICI-AKI?

A. Proton pump inhibitor use
B. Allopurinol use
C. Lower Baseline eGFR
D. Extrarenal immune-related adverse events

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Question #2: Which of the Following is the Most Common Pathology on Kidney Biopsy in a Patient with ICI-AKI?

A. Acute tubular injury
B. IgA nephropathy
C. Acute tubulointerstitial nephritis
D. Thrombotic microangiopathy

Question #2: Which of the Following is the Most Common Pathology on Kidney Biopsy in a Patient with ICI-AKI?

A. Acute tubular injury

B. IgA nephropathy

C. Acute tubulointerstitial nephritis

D. Thrombotic microangiopathy

Question #3: A 65 y/o patient with metastatic melanoma is referred to you for the evaluation of AKI. He has been treated with nivolumab for the past 4 months. He has not had any known exposure to proton pump inhibitors, and he has no history of any extrarenal irAEs. His SCr has risen from a prior baseline of 1.0 to 1.5 mg/dl. He is found to have 2+ blood and 2+ protein on urinalysis. A 24-hour urine protein collection reveals 2.4 g of proteinuria, of which 2 g is albuminuria. Renal US shows normal-sized kidneys and no evidence of obstruction. On examination of his urine sediment, he has 10-12 non-dysmorphic RBCs per hpf.

What is your next step in the management of this patient?

A. Empiric treatment with corticosteroids
B. Empiric treatment with rituximab
C. Perform a kidney biopsy
D. Continue immunotherapy since the AKI is not severe
E. Check a soluble IL2 receptor, and if elevated, start corticosteroids

What is your next step in the management of this patient?

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- Leaders and founding members of the American Society of Onconephrology
- My husband and my 2 daughters (oldest wants to be a kidney doctor!)

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