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

Acute Kidney Injury Related to Immune Checkpoint Inhibitors

Shruti Gupta MD, MPH
Director of Onconephrology, BWH/DFCI
Division of Renal Medicine, Department of Medicine
Brigham and Women's Hospital and Dana-Farber Cancer Institute
Assistant Professor of Medicine
Harvard Medical School

Shruti Gupta MD, MPH

University of Virginia School of Medicine
Medicine Residency @ MGH
Nephrology Fellowship @ BWH/MGH
Assistant Professor of Medicine @ HMS
Director, Onco-Nephrology Program
@ DFCI/BWH

- 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 BTG, Mersana Therapeutics, Alexion, MediBeacon
- Speaker fees from BTG Inc.
- 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

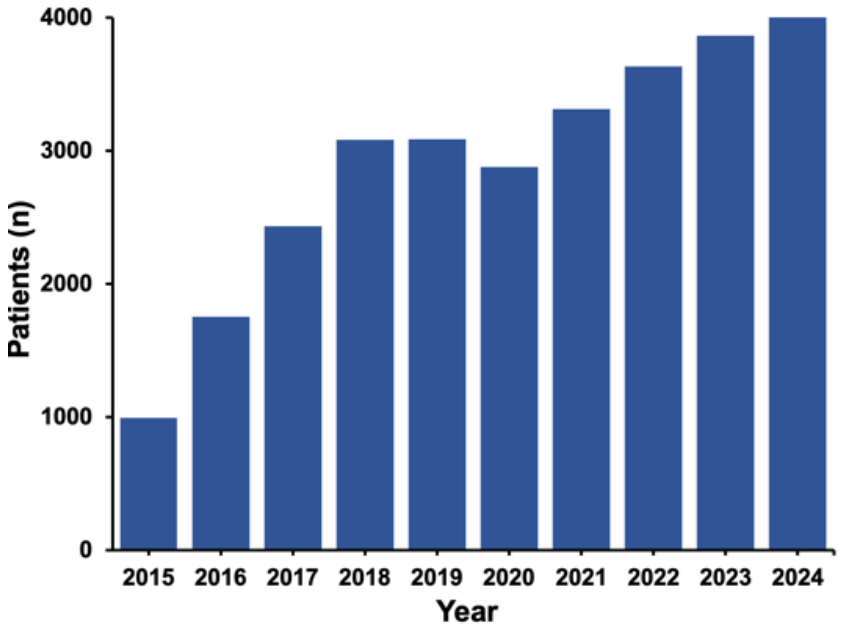
63 y.o. female with adenocarcinoma of lung with metastases to the brain, thoracic lymph nodes, and bone, on treatment with pembrolizumab and pemetrexed maintenance therapy, who presented to onconephrology for evaluation and management of AKI

Case

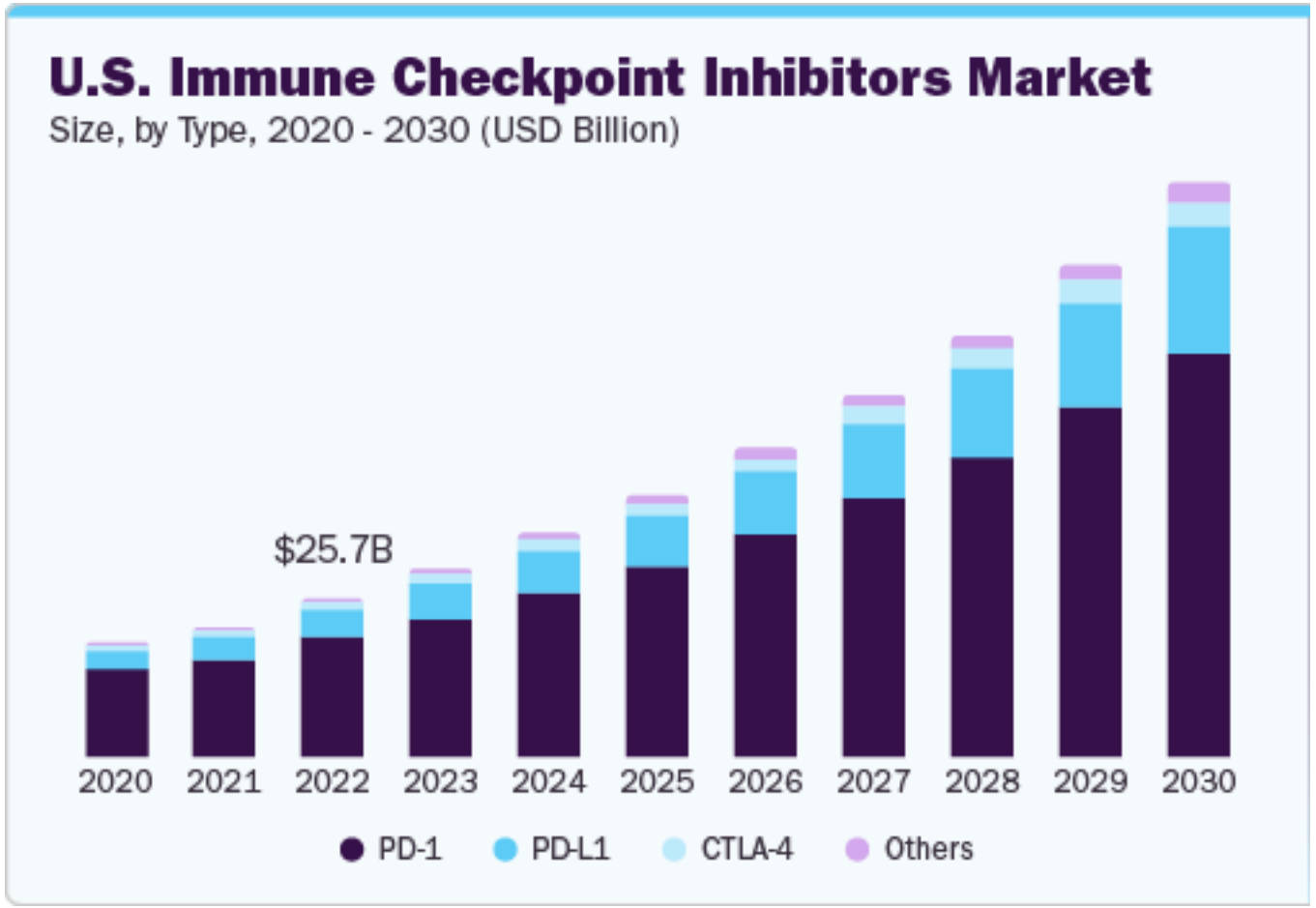
- Previously on carboplatin/pemetrexed/pembrolizumab, and then transitioned to pemetrexed, pembrolizumab maintenance
- SCr rose from a baseline of 0.7 mg/dl prior to starting all therapy to 1.4 mg/dl
- Urinalysis negative for blood, protein, white blood cells, red blood cells
- Was previously taking 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)

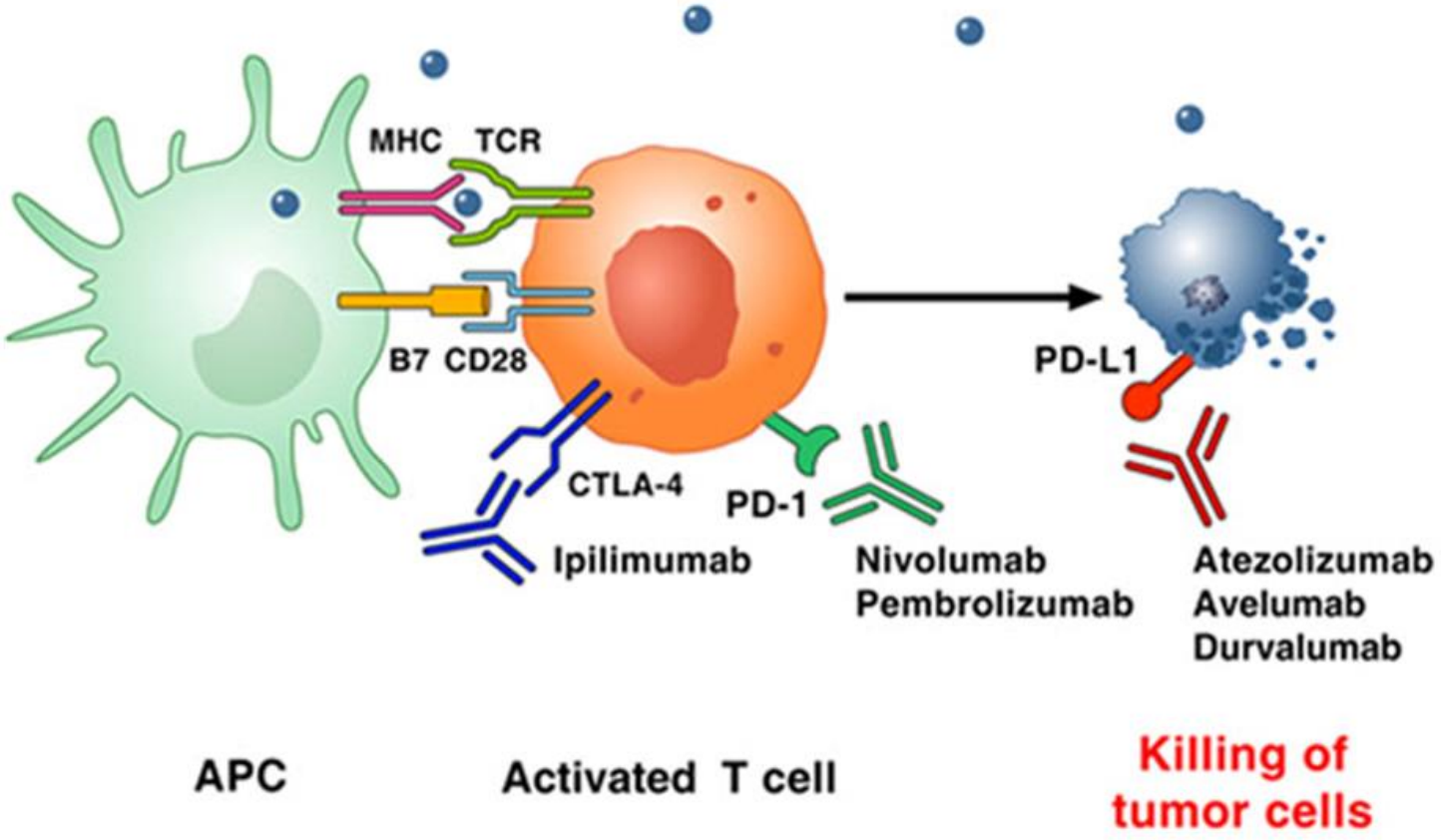


Patients Initiated on ICIs at BWH/DFCI and MGH



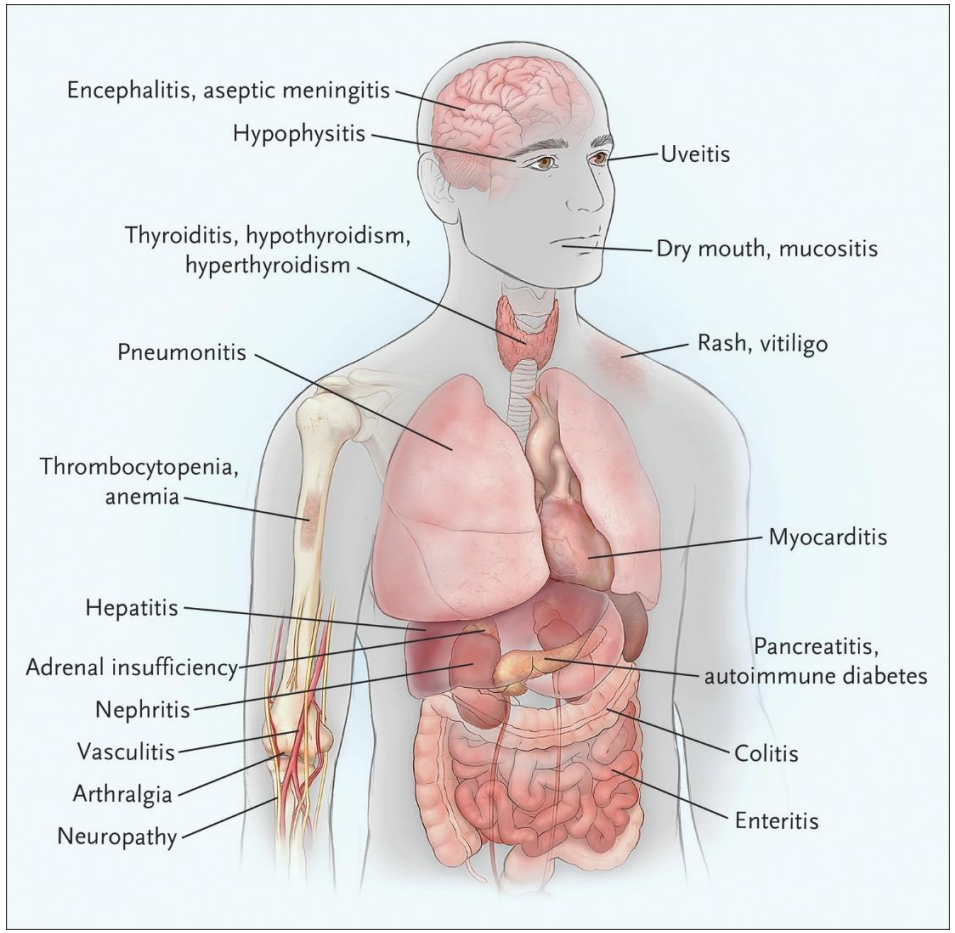
Mechanism of Action of ICIs

- **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

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

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

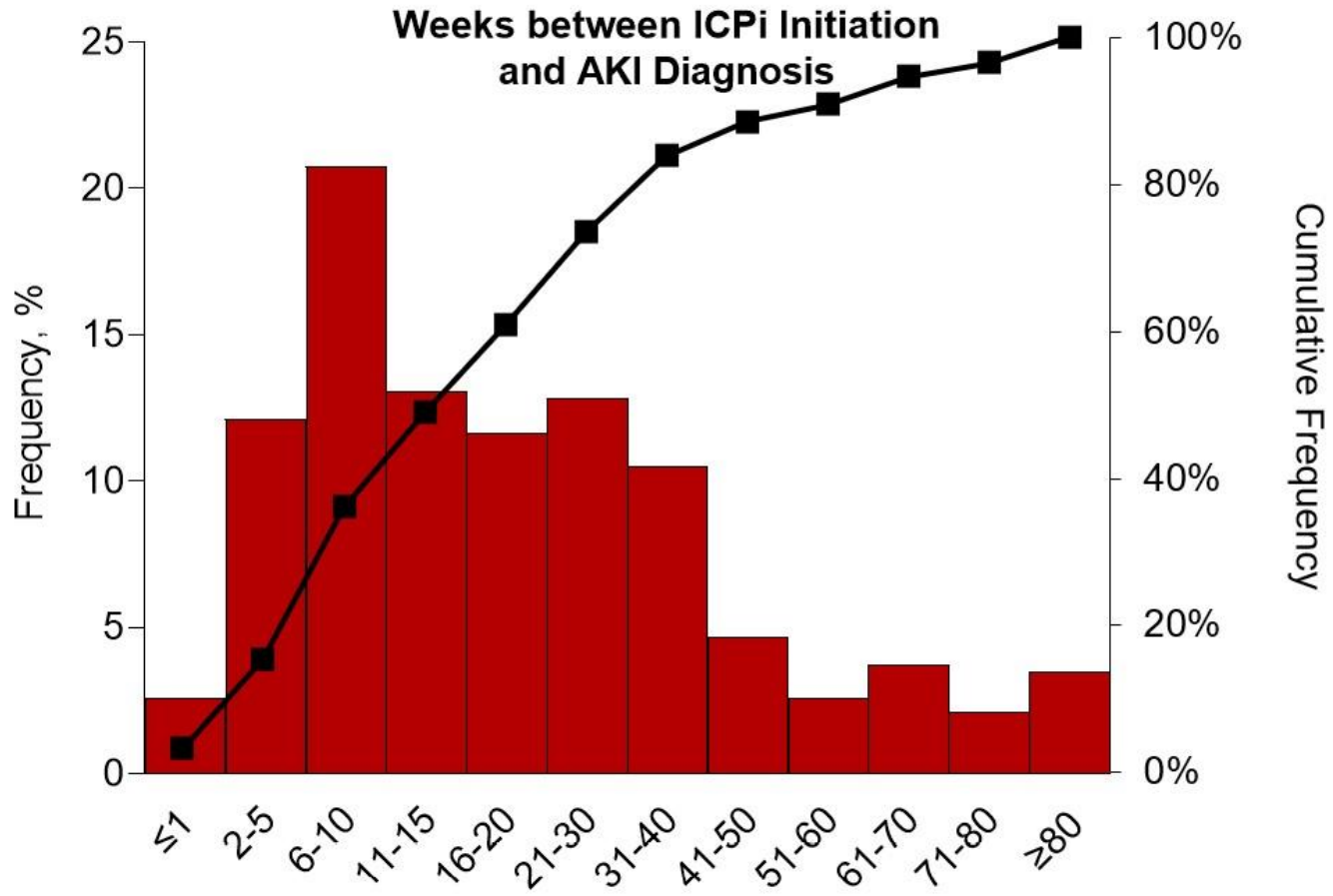
Gupta et al., J Immunother Cancer, 2021

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

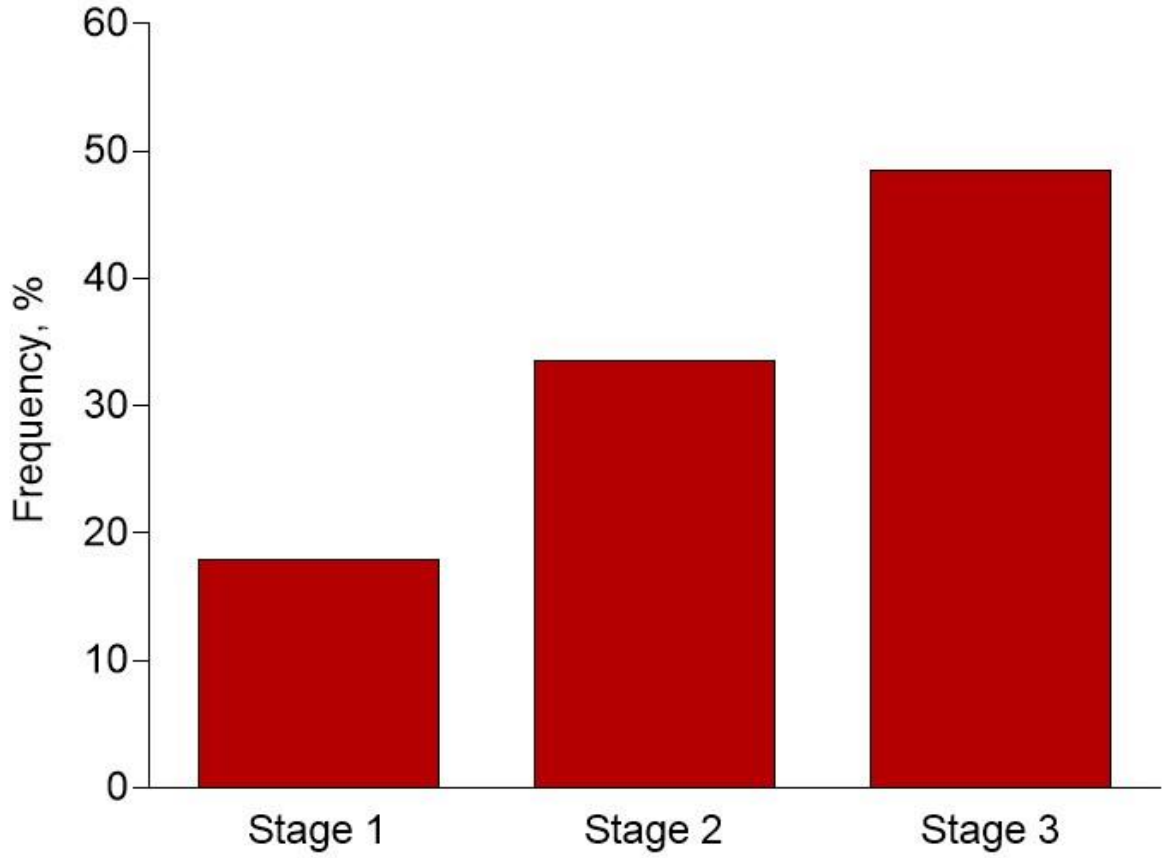
Timing of ICI-AKI



***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

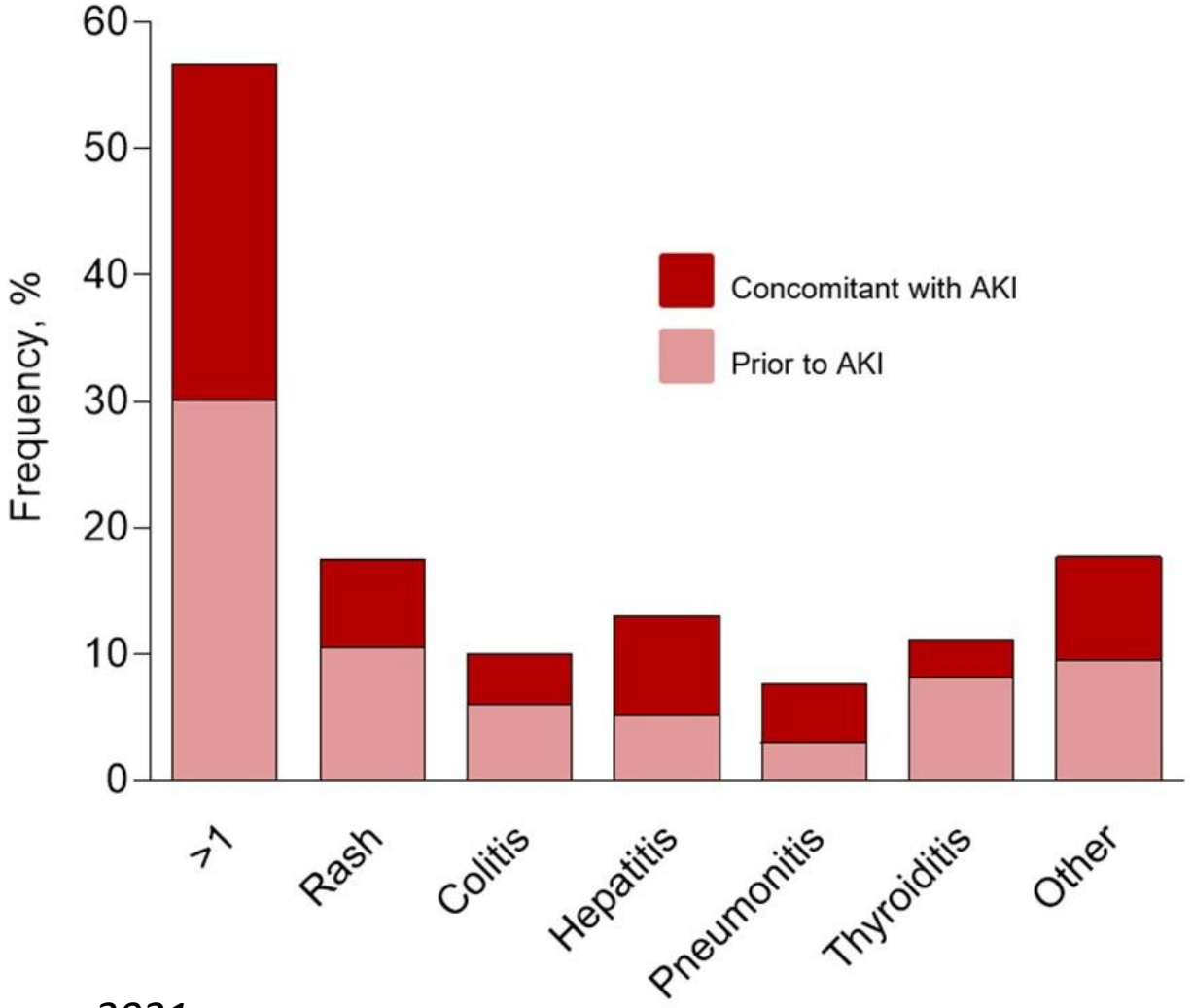


- 77 patients (18%) had stage 1
- 144 (34%) had stage 2
- 208 (49%) had stage 3, including 33 who received RRT (8% overall)

Gupta et al., J Immunother Cancer, 2021

Extrarenal Immune-Related Adverse Events

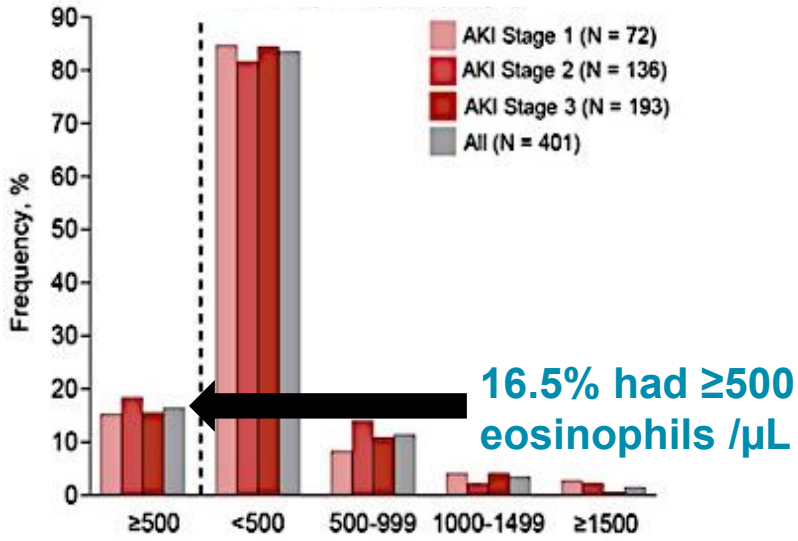
Extrarenal irAEs in 243 (57%) patients



Gupta et al., J Immunother Cancer, 2021

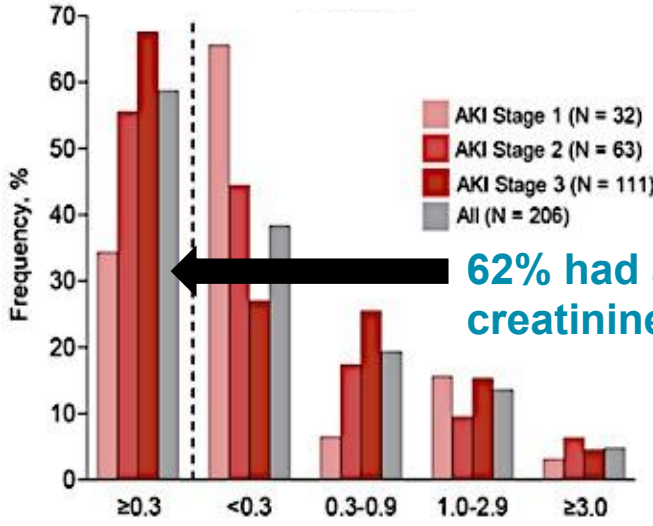
Can We Diagnose ICI-AKI Based on Clinical or Laboratory Features?

Eosinophilia



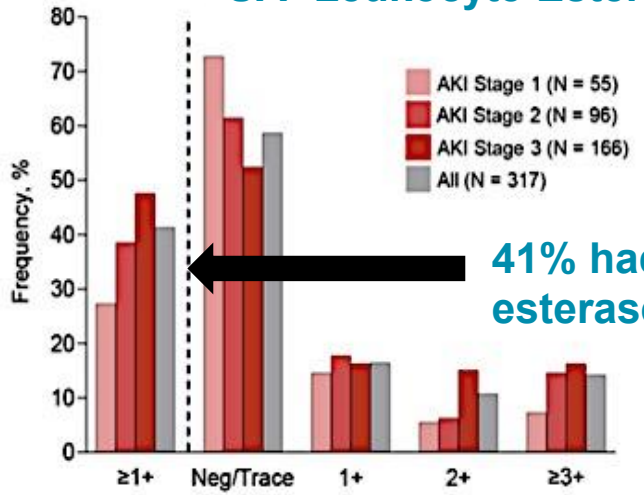
16.5% had ≥500 eosinophils /µL

Urine Protein/Creatinine



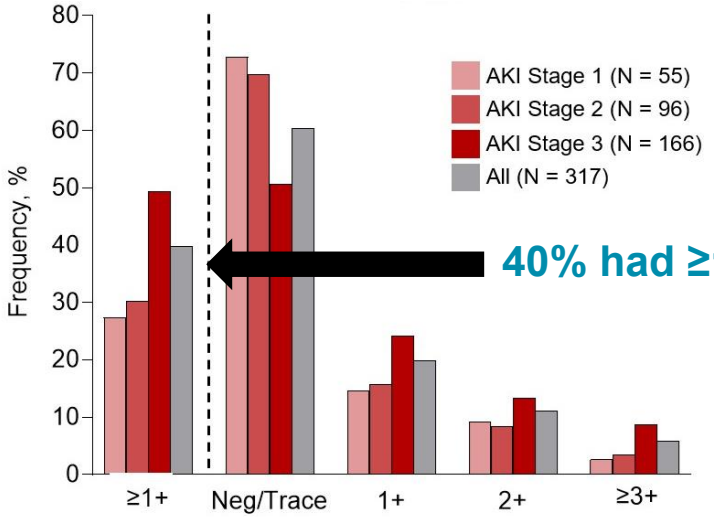
62% had a urine protein-to-creatinine ratio ≥0.3 g/g

UA- Leukocyte Esterase



41% had ≥1+ leukocyte esterase on urinalysis

UA- Blood

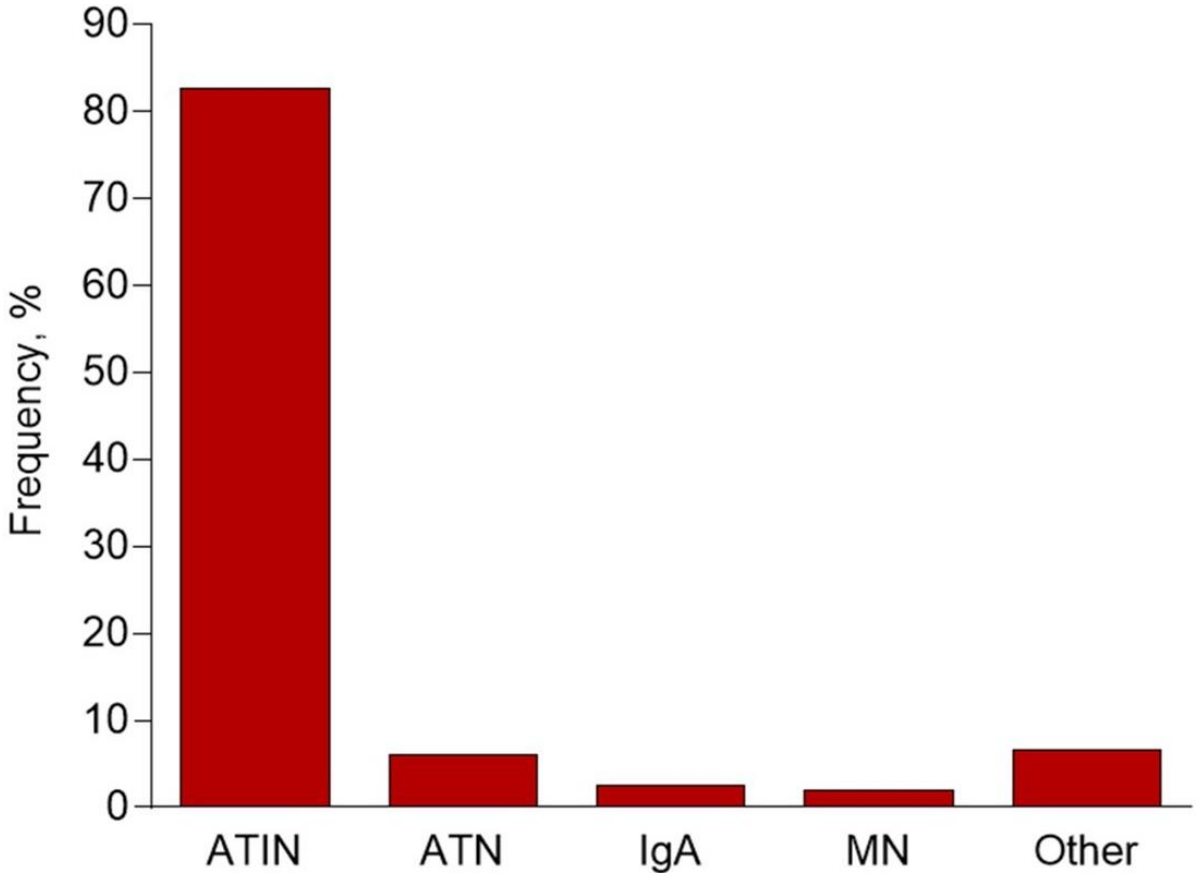


40% had ≥1+ blood on urinalysis

Gupta et al., J Immunother Cancer, 2021

Pathologies on Biopsy

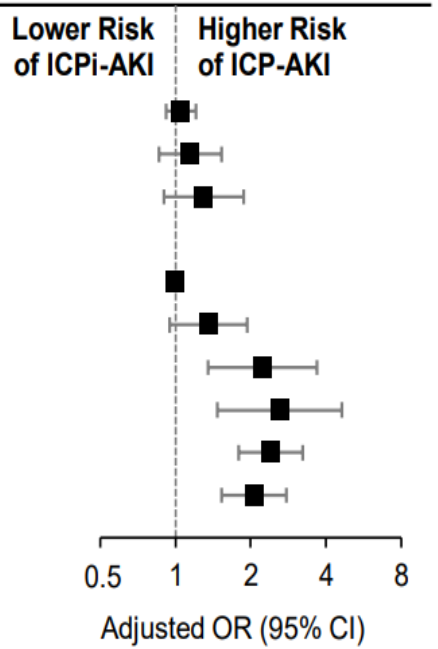
ATIN in 125/151 (83%) of biopsied patients

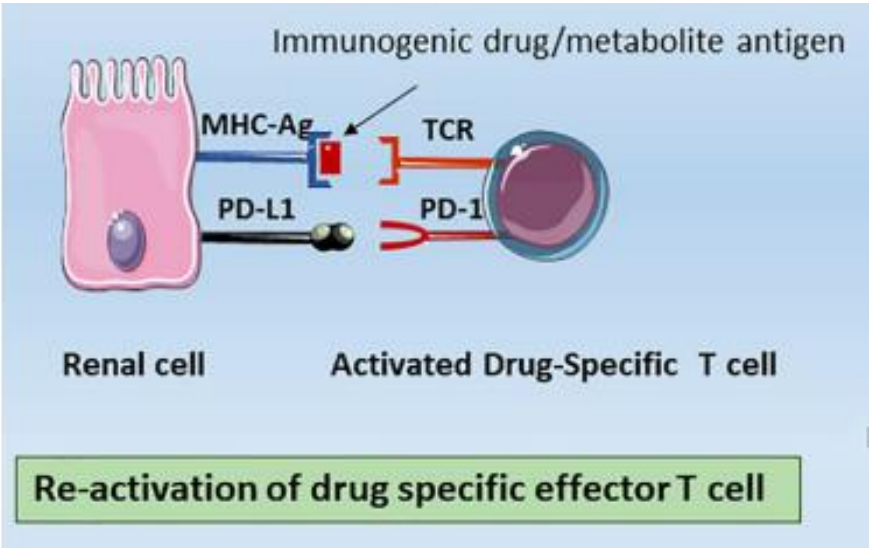


Gupta et al., J Immunother Cancer, 2021

Risk Factors for ICI-AKI: Why Onconephrologists Dislike PPIs

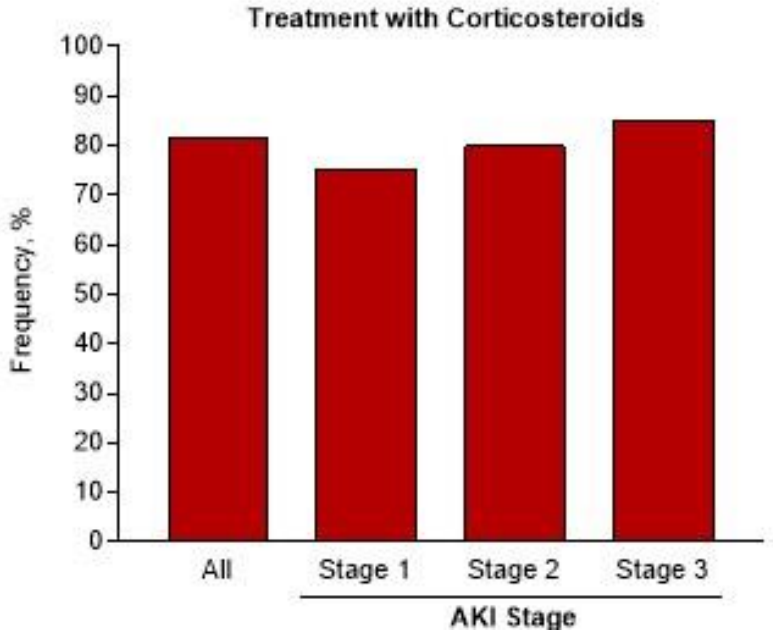
Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years)	1.17 (1.04-1.31)	1.05 (0.92-1.21)
Male sex	1.16 (0.88-1.52)	1.15 (0.86-1.53)
Combination ICPi therapy	1.42 (1.01-1.98)	1.30 (0.90-1.87)
Baseline eGFR (ml/min/1.73m^2)		
≥90 (REF)	1	1
60-89	1.54 (1.13-2.10)	1.36 (0.95-1.94)
45-59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

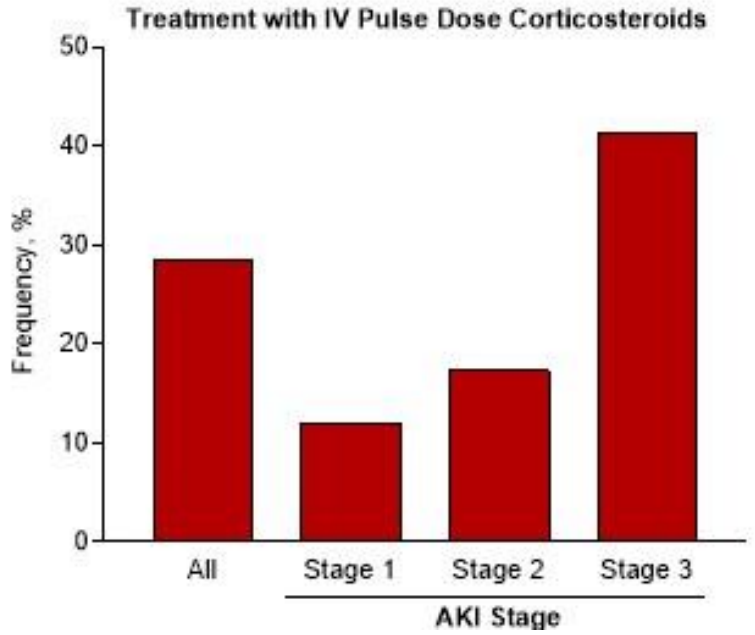




Gupta et al., J Immunother Cancer, 2021
Franzin et al., Front in Immunology, 2020

Treatment with Corticosteroids



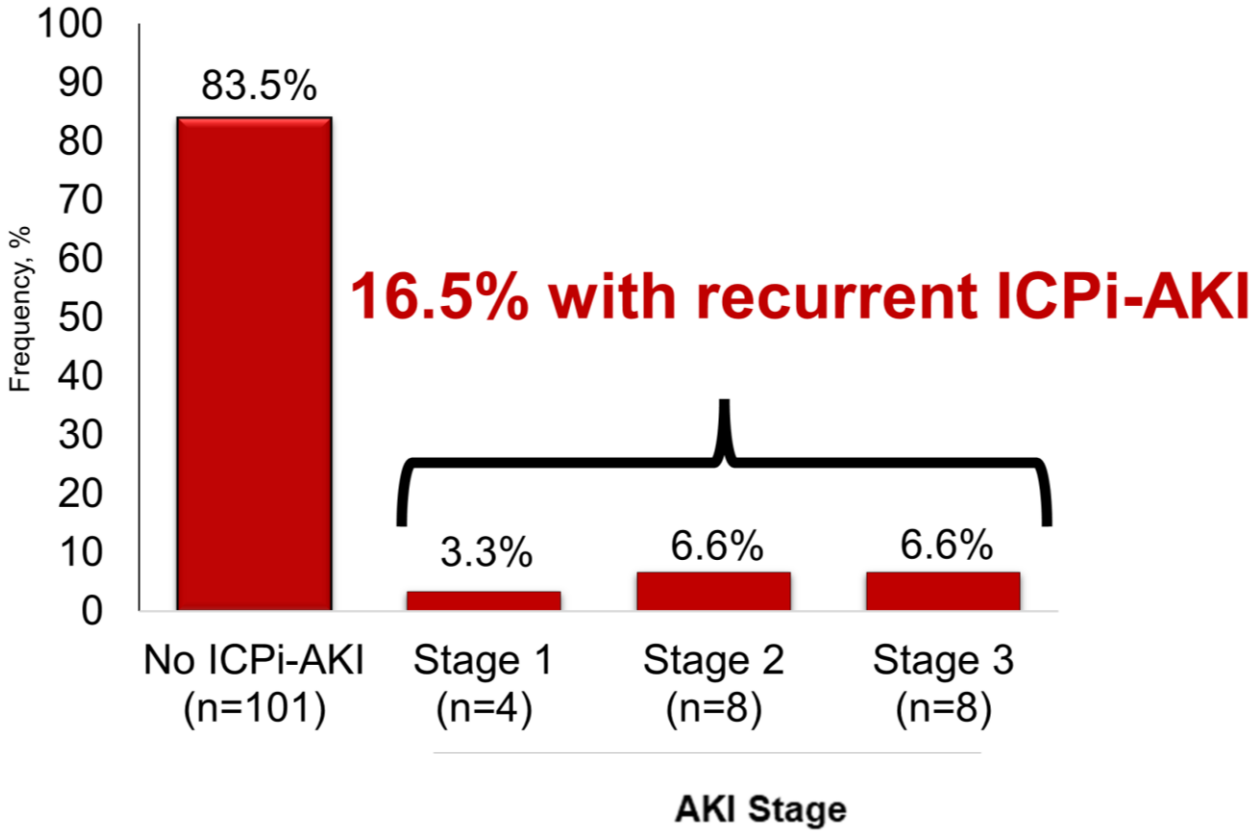


350 (82%) patients were treated with steroids, of whom 100 received IV pulse dose steroids

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

Urinary CXCL9 in immune checkpoint inhibitor-associated acute interstitial nephritis

kidney INTERNATIONAL
ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort

116 participants from 3 major U.S. cancer centers

- **38** with biopsy-confirmed ICI-AIN
- **36** with non-AIN-AKI
  - **18** biopsy-proven non-AIN
  - **16** clinically-adjudicated non-AIN
  - **2** with obstruction
- **25** ICI-treated (no AKI)
- **17** non-ICI treated cancer controls

Methods

Discovery →
Proteomics:
1) Olink Target 96 Immuno-Oncology Panel
2) Olink Target 96 Inflammation Panel

Validation →
Modified sandwich electrochemi-luminescence immunoassay for CXCL9

Gupta et al., Kidney International, 2025

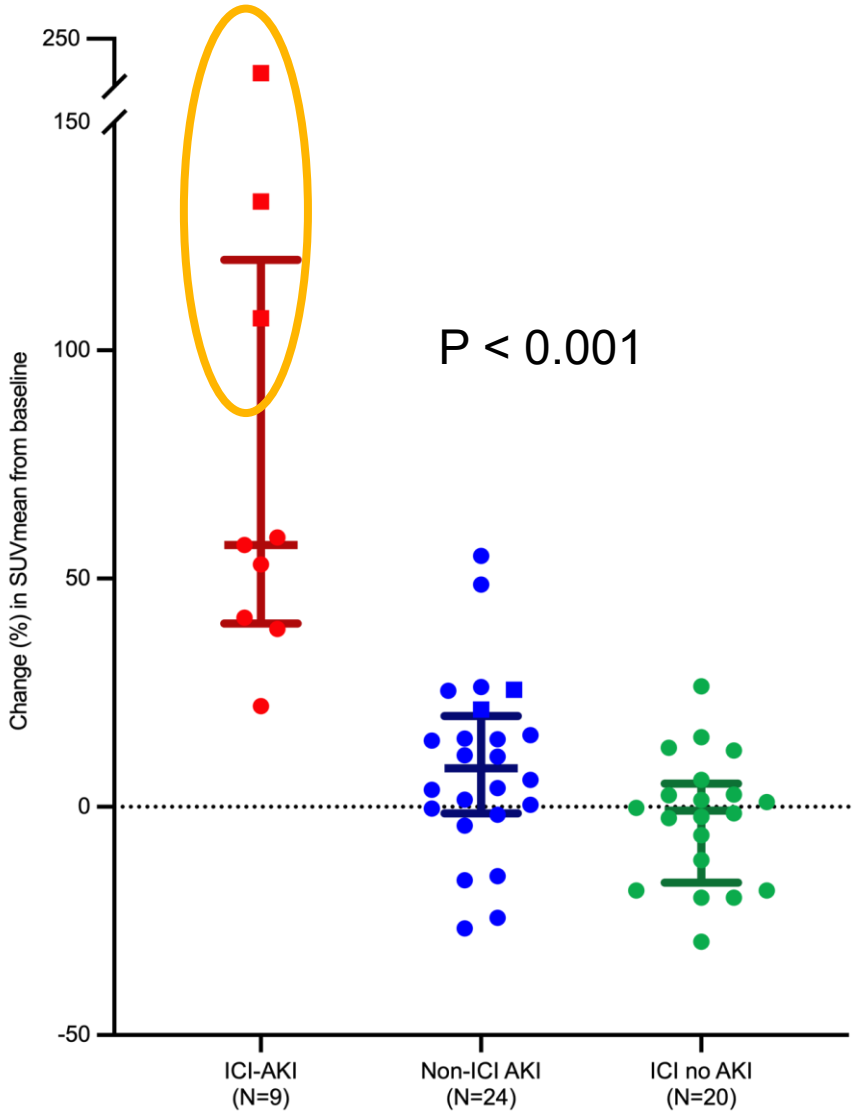
Beyond Urinary and Blood-Based Biomarkers…

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

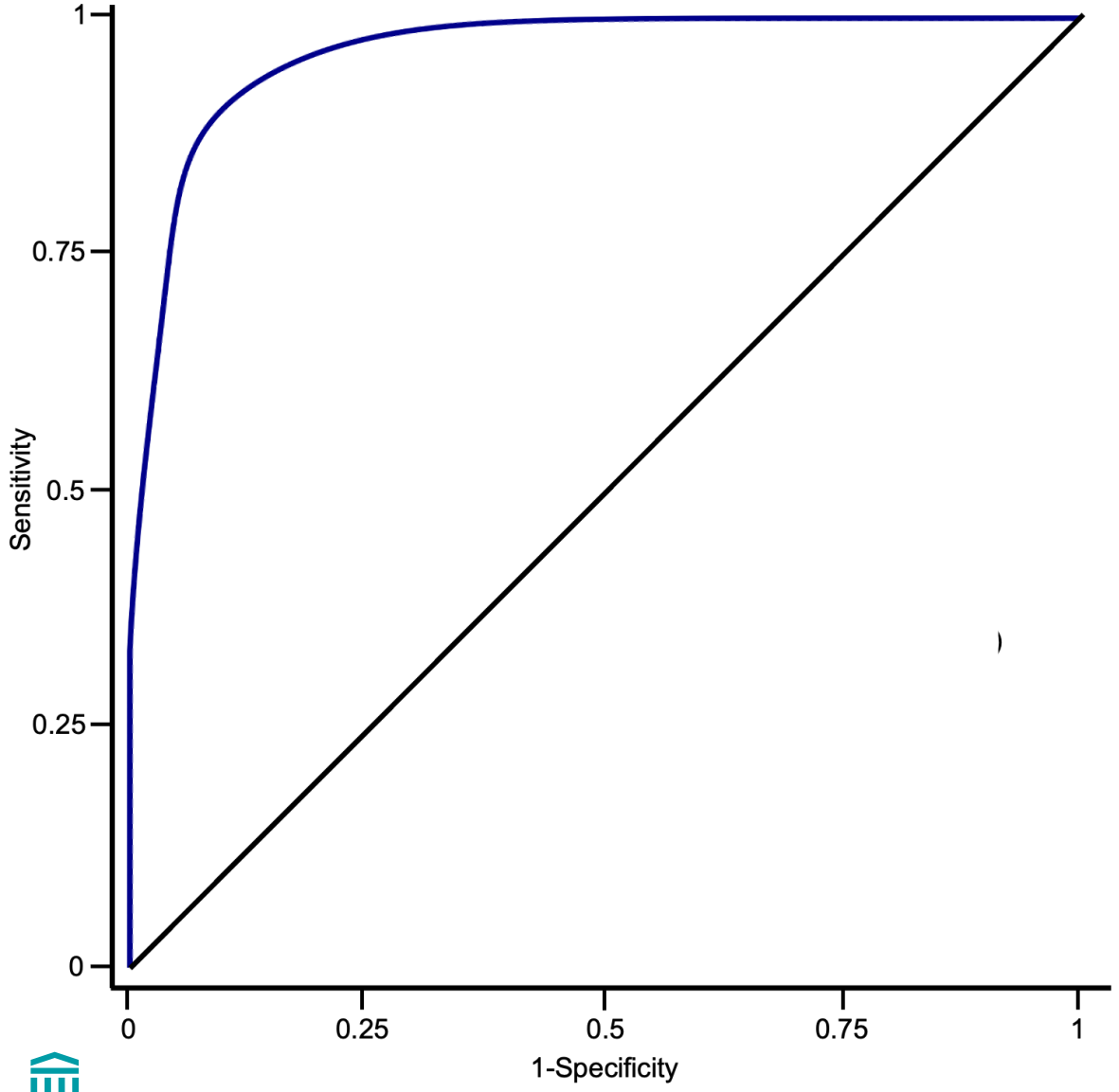
FDG-PET/CTs: Percentage change in SUV_{mean} from baseline to the time of AKI



- 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

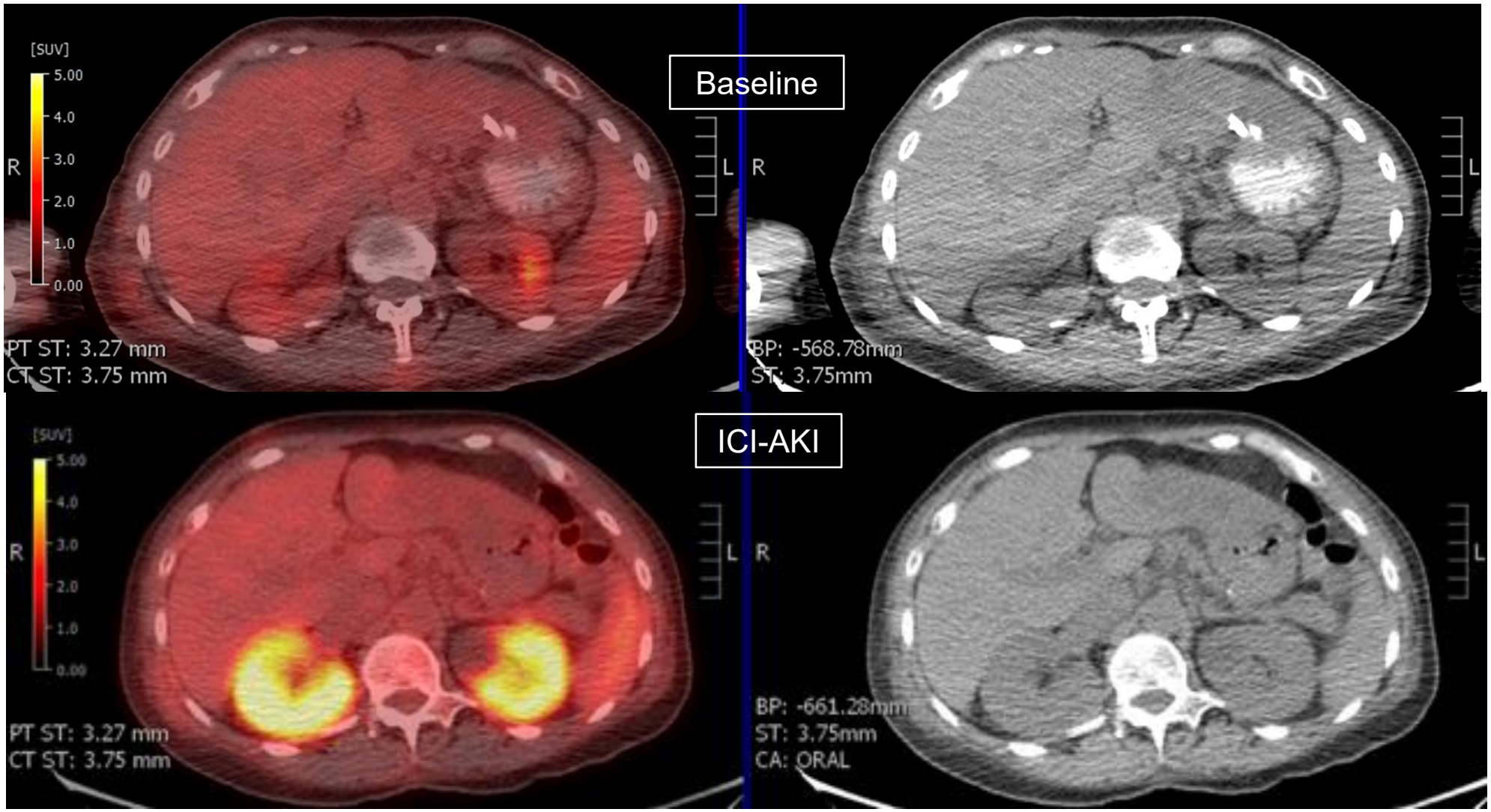


AUC 0.97 (95% CI, 0.93-1.00)

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

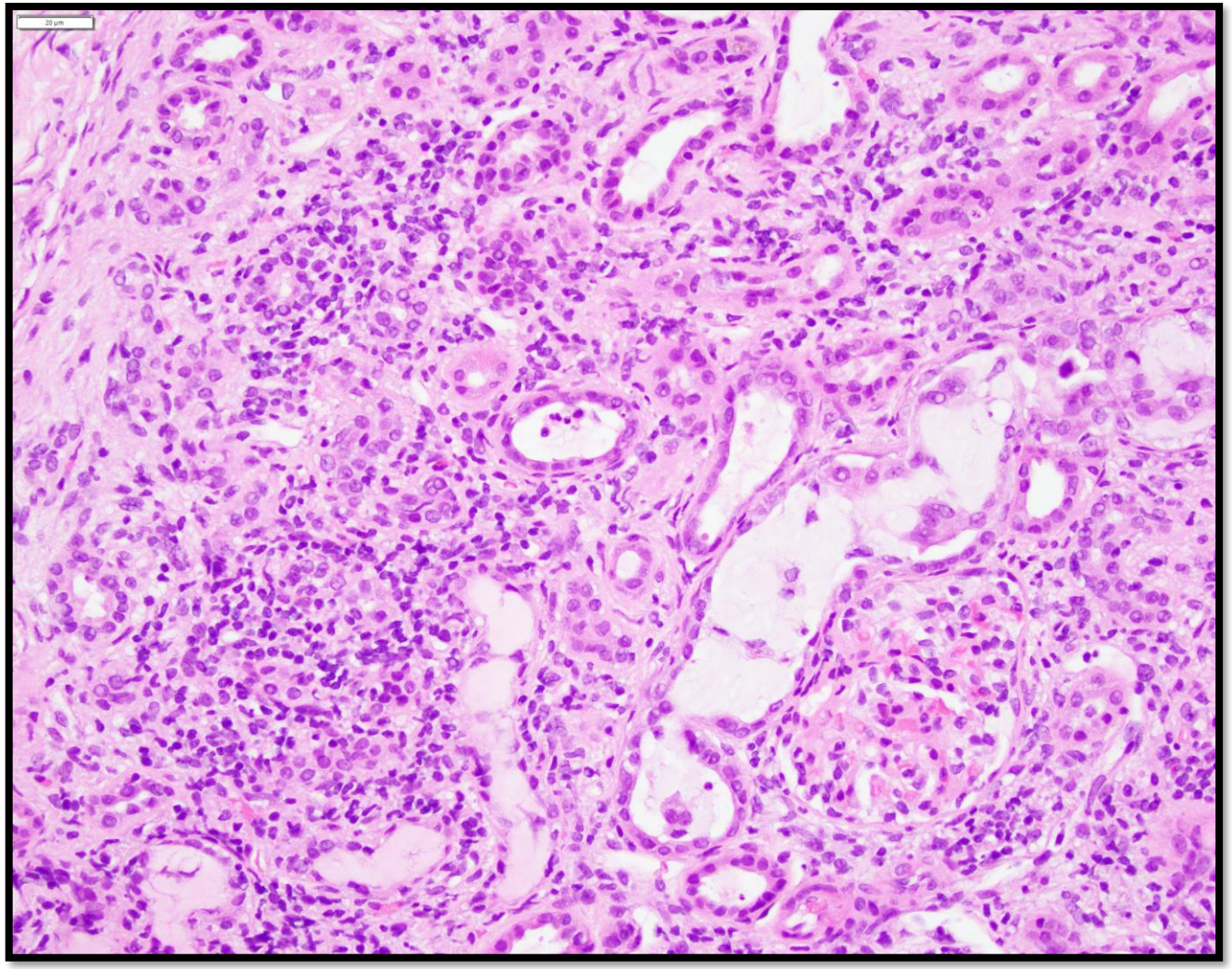
63 y.o. female with adenocarcinoma of lung with metastases to the brain, thoracic lymph nodes, and bone, on treatment with pembrolizumab and pemetrexed maintenance therapy, who presented to onconephrology for evaluation and management of AKI

Case Follow-Up

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

Case Follow-Up

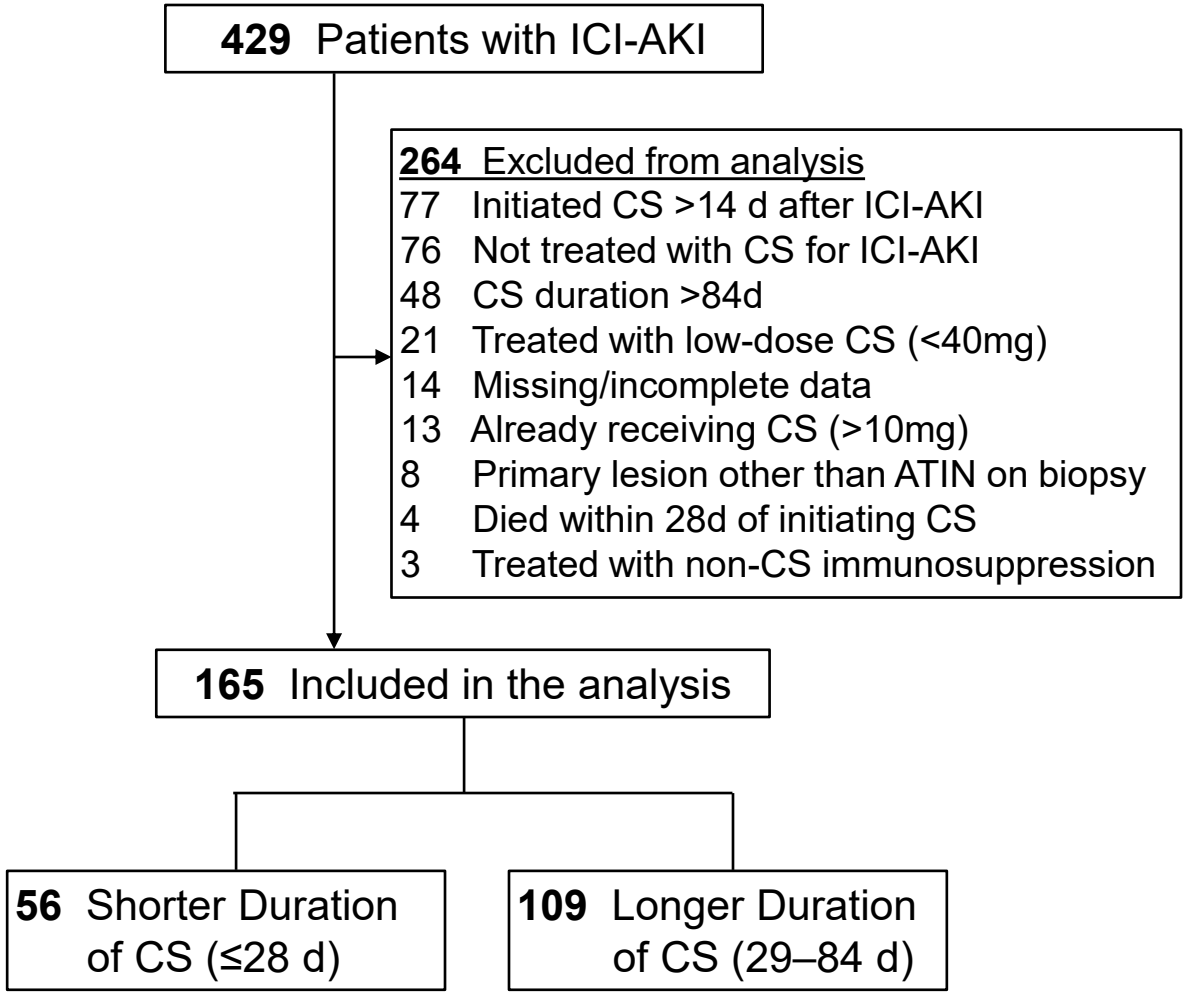
Decision was made to pursue a kidney biopsy….

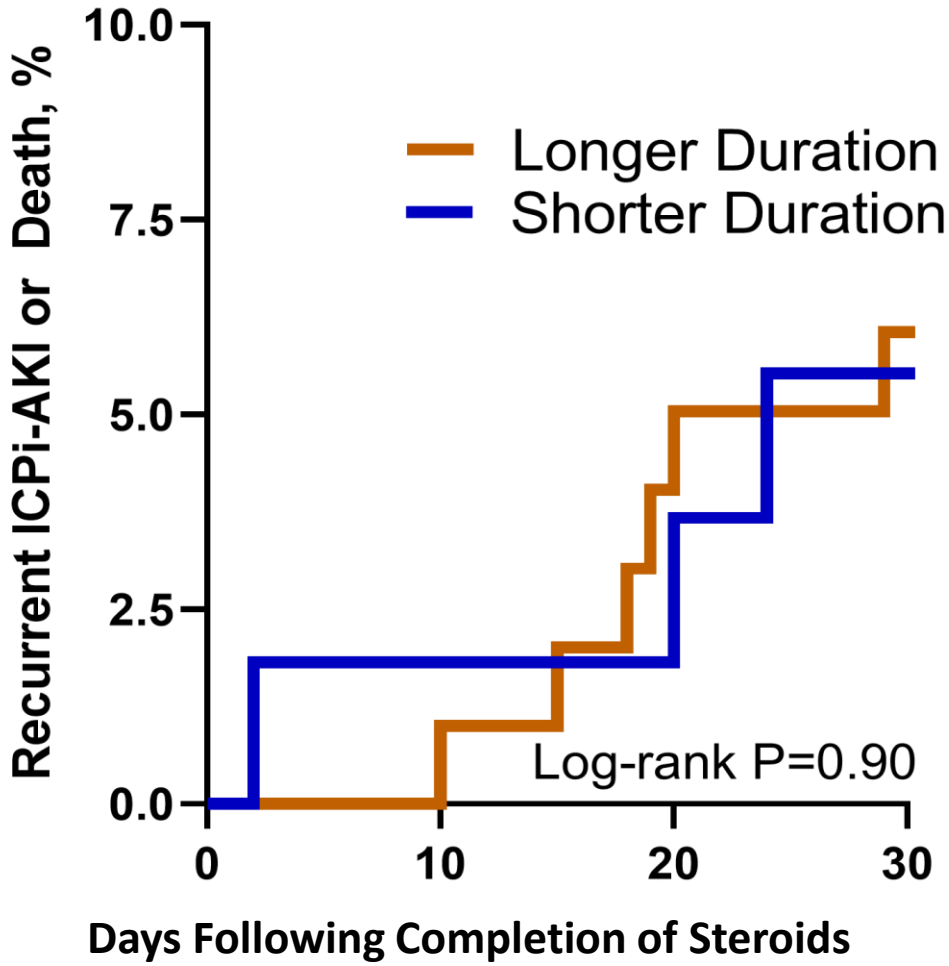


Case Follow-Up

- 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

Infliximab for Grade III/ IV ICI Nephritis
Clinical and Translational Evidence

ISN
INTERNATIONAL SOCIETY OF NEPHROLOGY

MD Anderson Cancer Center

January 2022 - October 2024

Patients who received ICI, developed stage III/ IV AKI, and had AIN on kidney biopsy n=55

Treated with steroids only n=27

Treated with Steroids and Infliximab n=28

No baseline differences between the 2 groups

Time to renal response (TTR) was significantly improved in patients exposed to infliximab within 30 days of starting steroids compared to steroids-only

Duration of renal response (DORR) was longer in infliximab group *(only in univariate analysis)*

No differences seen in Cancer progression-free survival (CFS)

Immune expression was higher in drug- and ICI-AIN compared to controls

Elevated TNF-α expression in drug and ICI-AIN correlated with renal response

ICI, Immune Checkpoint Inhibitor; AIN, Acute Interstitial Nephritis

KI REPORTS
Kidney International Reports

Youssef N et al, 2025

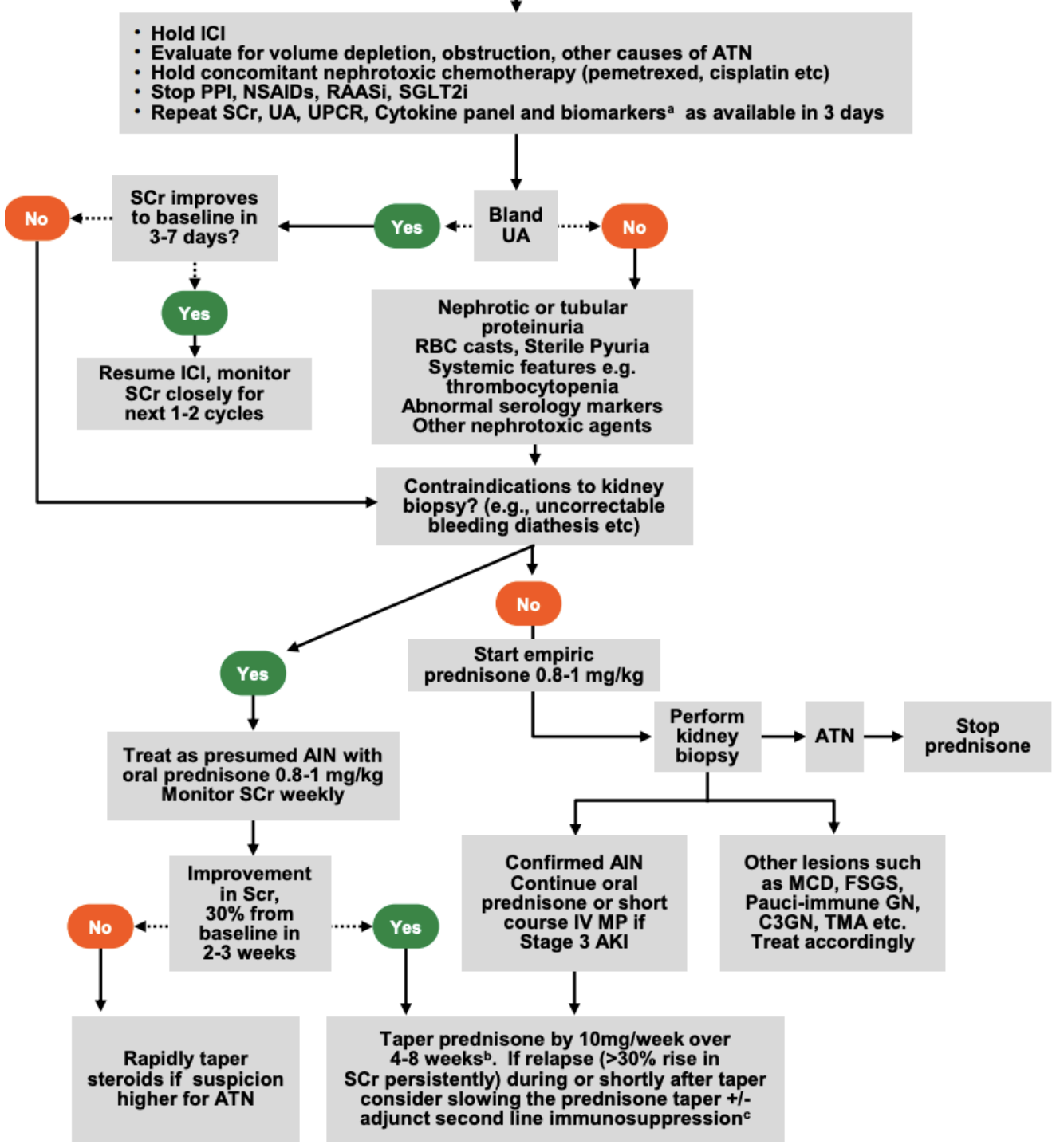
Visual abstract by:
Edgar Lerma, MD, FISN
@edgarvlermamd

Conclusion Infliximab use may offer a therapeutic advantage over steroids alone in stage III/ IV ICI AIN.

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

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

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 urinary CXCL9, and if elevated, start corticosteroids

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 urinary CXCL9, and if elevated, start corticosteroids

Acknowledgements

- Co-PI of ICI-AKI consortium, Dr. David E. Leaf
- Collaborators at all of our sites around the world
- My small but might lab (shrutiGkidney.org)
- Leaders and founding members of the American Society of Onconephrology
- My husband and my 2 daughters (oldest wants to be a kidney doctor!)

References

1) Gupta S, Short SA, Sise M. Acute kidney injury in patients treated with immune checkpoint inhibitors. J Immunother Cancer. 2021;9:e003467.
2) Sise ME, Wang Q, Seethapathy H, Moreno D, Harden D, Smith RN, Rosales IA, Colvin RB, Chute S, Cornell LD, Herrmann S, Fadden R, Sullivan RJ, Yang N, Barmettler S, Wells SL, Gupta S, Villani AC, Reynolds K, Farmer J. Soluble and Cell-Based Markers of Immune Checkpoint Inhibitor Associated Nephritis. J Immunother Cancer. 2023; 11(1): e006222.
3) Cortazar FB, Marrone KA, Troxell ML. Clinicopathological features of acute kidney injury and checkpoint inhibitors. Kidney Int 206;90:638-47.
4) Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. Am J Kidney Dis 2016;68:287-91.
5) Isik B, Alexander MP, Manohar S. Biomarkers, clinical features, and rechallenge for immune checkpoint inhibitor renal immune-related adverse events. Kidney Int Rep 202;6:1022-31.
6) Mamlouk O, Selamet U, Machado S, et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: a single-center experience. J Immunotherapy Cancer 2019;7.
7) Seethapathy J, Zhao S, Chute DF. The incidence, causes, and risk factors for acute kidney injury in patients receiving immune checkpoint inhibitors. Clin Journ Amer Soc Neph. 2019; 14(12): 692-700.
8) Herrmann SM, Abudayyeh A, Gupta S, et al. Diagnosis and Management of Immune Checkpoint Inhibitor-Associated Nephrotoxicity: A Position Statement from the American Society of Onco-nephrology. Kidney Int. 2024; 107(1):21-32.
9) Gupta S,* Green-Lingren O,* Bhimaniya S,* et al. F18-FDG PET imaging as a diagnostic tool for immune checkpoint inhibitor-associated acute kidney injury. J Clin Invest. 2024; 134(18).
10) Gupta S, Garcia-Carro C, Prosek JM, et al. Shorter versus Longer Corticosteroid Duration and Recurrent Immune Checkpoint Inhibitor-Associated AKI. J Immunother Cancer. 2022; 10(9):e005646.
11) Gupta S,* Strohbehn IA,* Wang Q, et al. Acute Kidney Injury in Patients Receiving Pembrolizumab Combination Therapy versus Pembrolizumab Monotherapy for Advanced Lung Cancer. Kidney Int. 2022;102(4): 930-935.