

Beyond Biopsy: Biomarkers and Treatments for ICI-AKI

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Onconeurology Symposium

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Financial Disclosures

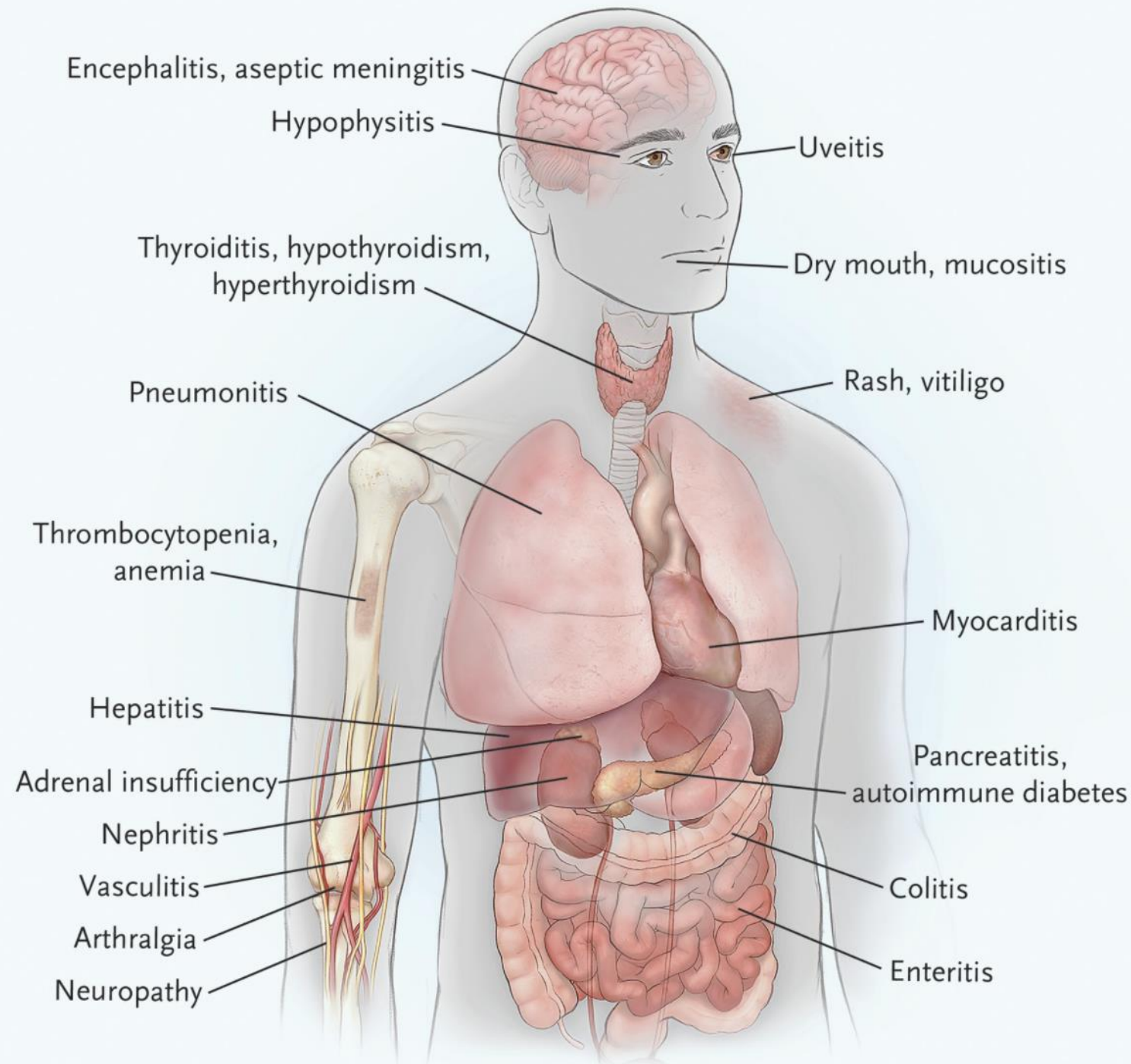
- Research funding: Angion, Otsuka, Gilead, Cabaletta, Novartis, Roche, Merck, Astra Zeneca, Amgen
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- Data safety monitoring committee member for Alpine Immune Sciences/Vertex.
- Paid editorial work: NEJM clinician, Kidney International Reports
- Speaker: Curio, TD Cowen, ReachMD/ Medintelligence, Autoimmune Hepatitis Association

OUTLINE

1. Diagnosis of immunotherapy-induced AIN (ICI-AIN)
2. Existing and novel biomarkers of ICI-AIN
3. Treatment of ICI-AIN

Immune-related adverse events

- Affects >85% of patients receiving ICIs
- The most common toxicities occur at barrier sites, including the gastrointestinal mucosa, liver, skin, and lungs



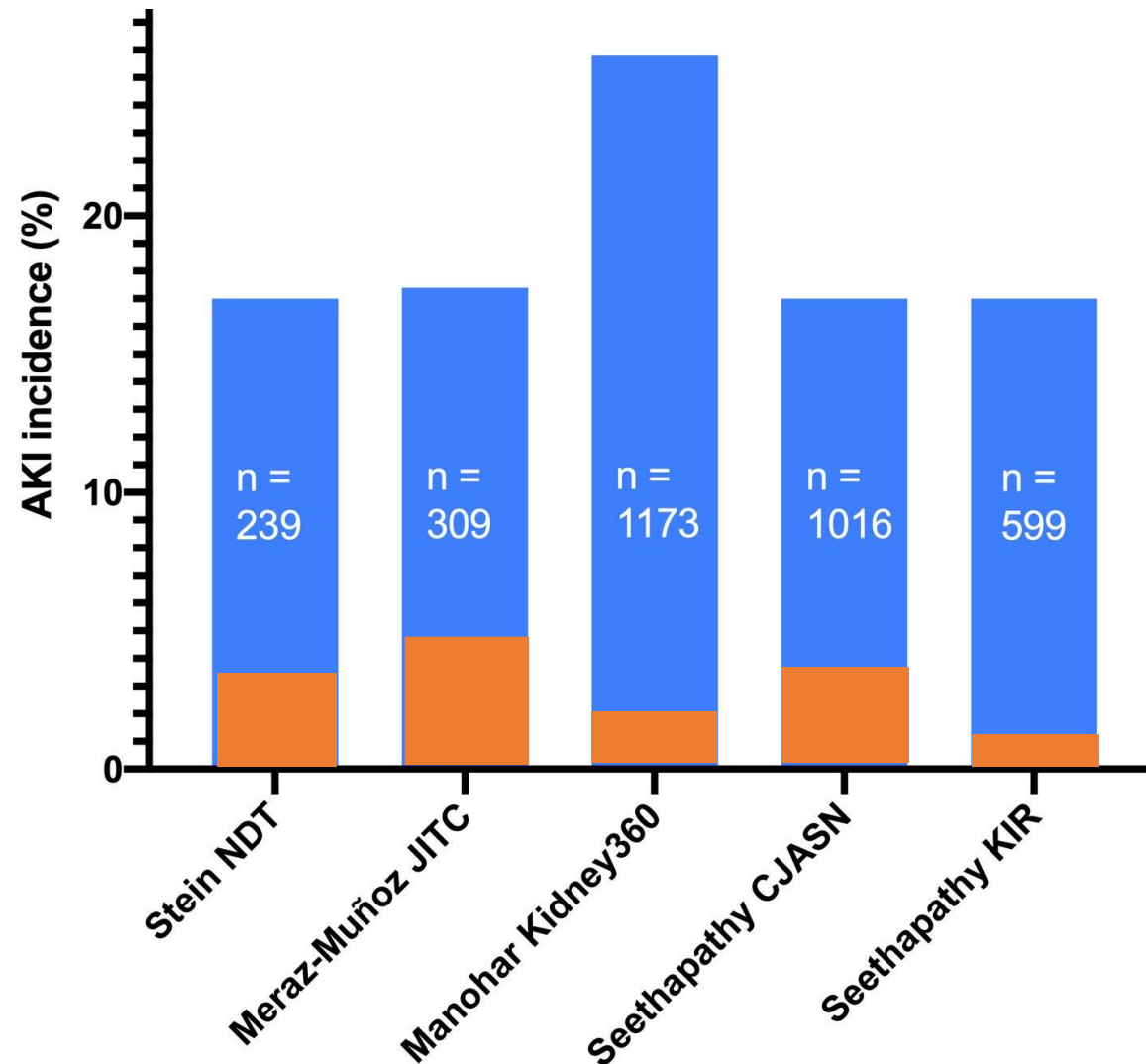
Over one-third of patients with cancer qualify for an ICI

2011	2014
March 25, 2011 Ipi for unresectable or metastatic melanoma	September 4, 2014 Pembro for unresectable or metastatic melanoma
	December 23, 2014 Nivo for unresectable or metastatic melanoma

2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
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Overall AKI vs. ICI-AKI



Dehydration / Pre-renal azotemia

Septic/ischemic ATN

Nephrotoxic ATN

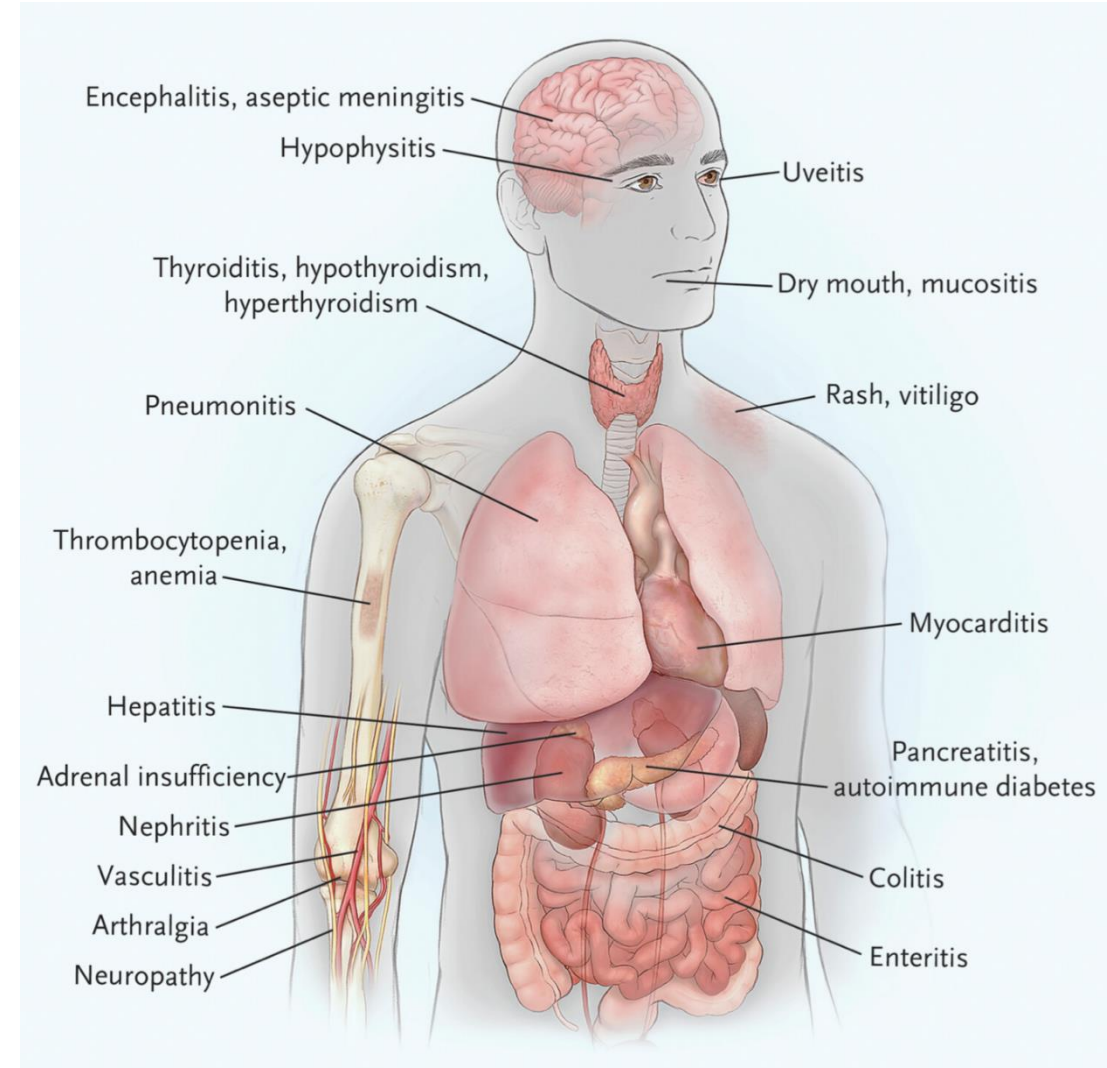
Urinary obstruction

AIN

- 2-3% w PD1 monotherapy
- 5% with CTLA4/PD1 combo
- 1% with PDL1 – atezo, durva, avelumab

Typical presentation of ICI-AIN

- Mean 3-4 months after starting ICIs, but can be as early as 2-3 weeks
- Approximately half have concurrent immune related adverse events
- Nonspecific urinary findings
~25%-40% lack pyuria



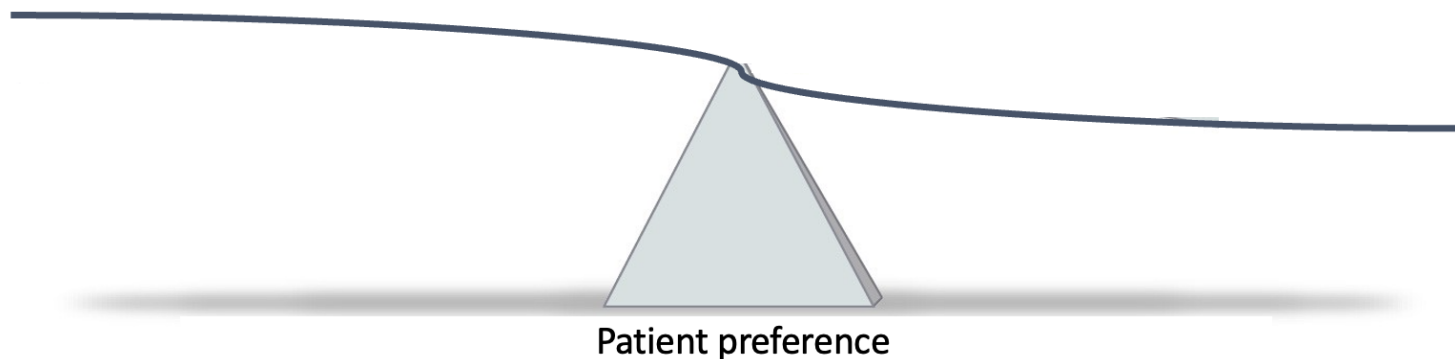
Does the patient need a kidney biopsy?

Factors favoring kidney biopsy

- Clinical syndrome suggests an alternative cause
 - Hematuria
 - Proteinuria > 1 gram
 - +Anca or other serology
- Receiving other nephrotoxic chemotherapies
 - Platin, pemetrexed, VEGF/TKIs
- Cancer-related factors: Newly starting therapy, melanoma

Factors favoring empiric treatment

- Looks like AIN
 - No significant proteinuria or low grad tubular proteinuria
 - WBC casts/leukocyturia
- Taking other AIN meds (PPI, NSAIDS, abx)
- No other hemodynamic disturbances
- High risk biopsy (anticoagulation, single kidney, patient frailty)



Trends: Combination Therapy, Earlier Stage of Disease

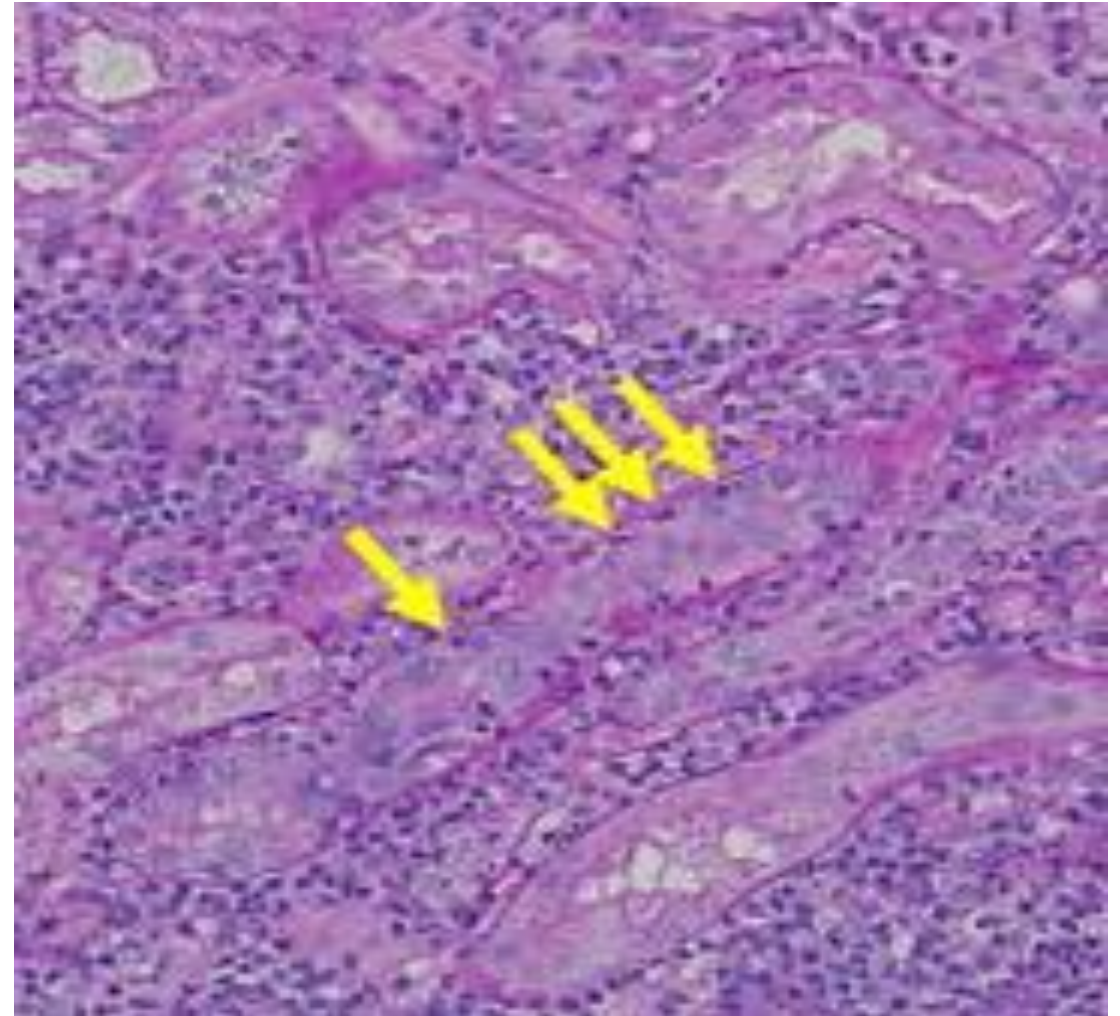
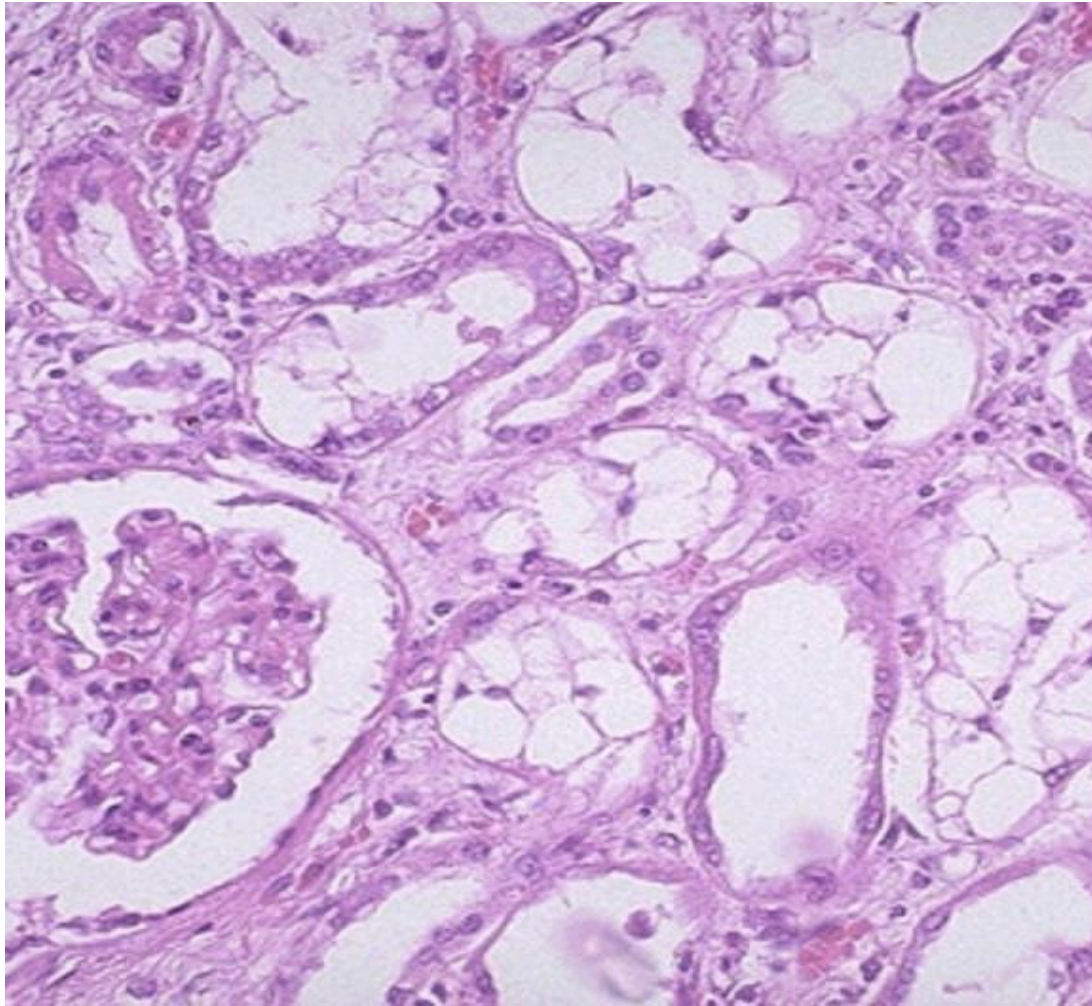
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Tale of two cases

- 71 yo male with presenting 4 weeks after cycle 1 of pembrolizumab for metastatic melanoma
- Scans showed progressive disease
- Scheduled for ipi/nivo but on arrival had creatinine 1.1 -- > 2.1mg/dL, hypotensive (SBP 90s), metabolic disarray, LFT abnormalities, and neutropenia.
- Hydrated but creatinine continued to rise
- UA: 20-50 WBCs
- Renal consult: "WBC casts. Start prednisone"
- 74 yo female presenting 3 weeks after cycle 1 of pemetrexed/carboplatinum/pembrolizumab presenting with rise in creatinine from 1.5 → 3.0mg/dL in the setting of diarrhea and poor PO intake.
- Other PMH: CKD baseline creatinine 1.5 with DM and HTN
- UA: Bland < 10 WBC
- No other manifestations of irAEs. Creatinine rose to 5.0mg/dL and she underwent kidney biopsy

Tale of two cases

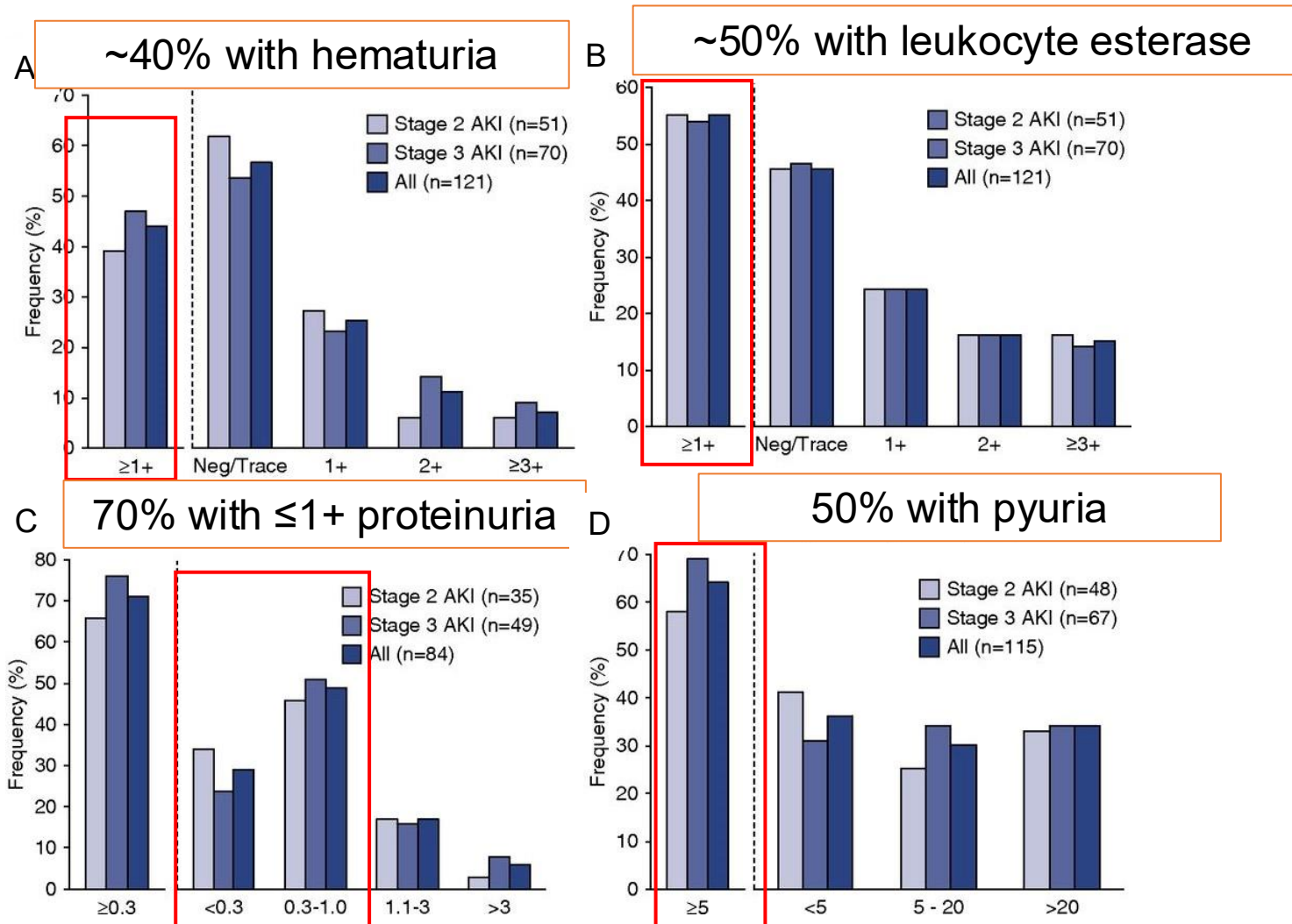


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Need for non-invasive diagnosis

Urinalysis findings in ICPI –AIN are non-specific



Cortazaar JASN 2020

WBC casts have low sensitivity for AIN diagnosis and unknown specificity



Microscopy Finding	N=21	%
White blood cells	12	57.1%
White blood cell casts	3	14.3%
Red Blood cells	10	47.6%
RTE cells	3	14.3%
RTE casts	3	14.3%
Granular casts	13	61.9%
Hyaline casts	18	85.7%
At least 1 of these	20	95.2%

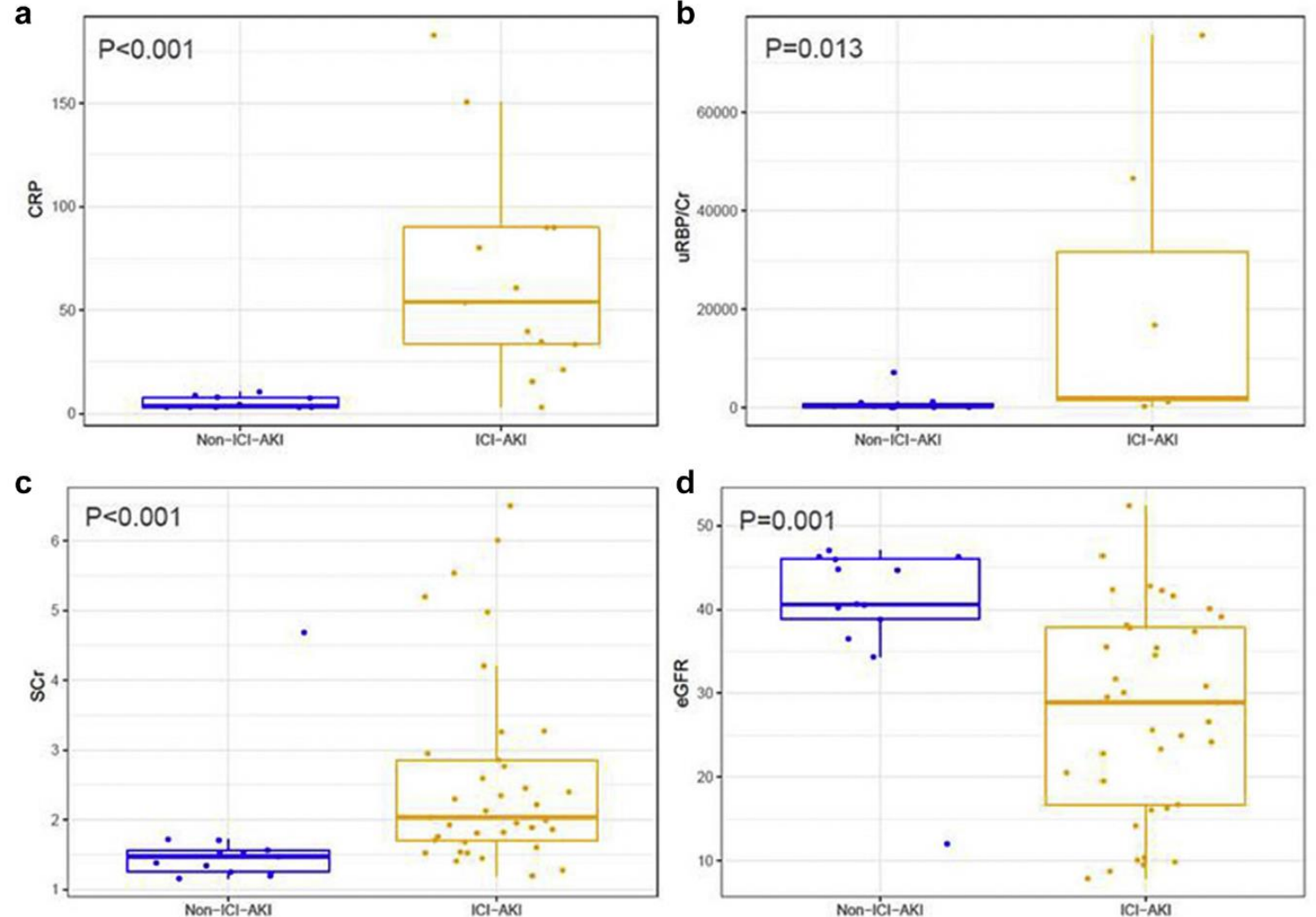
Similar WBC cast rate from Muriithi et al (4%)

Caveat: patients with WBC casts may receive presumptive AIN diagnosis and not undergo a biopsy

WBC casts are rare in AIN

Can clinically available biomarkers identify AIN

- 37 patients with ICI-AKI and 13 non-ICI-AKI controls (at least stage 1 AKI)
 - 34 received steroids



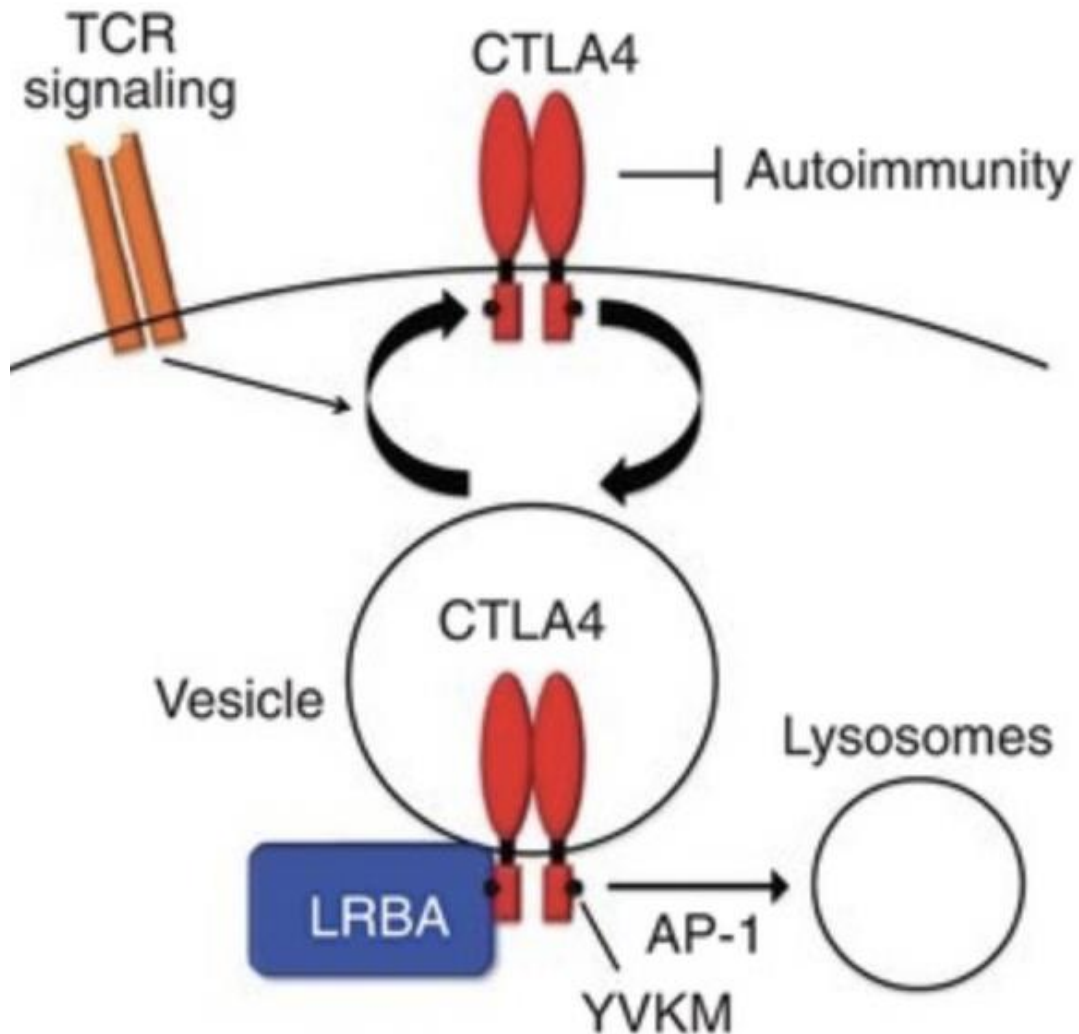
Goal: Find non-invasive biomarkers of ICI-AIN

Targeted vs. Untargeted approaches

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Targeted vs. Untargeted approaches

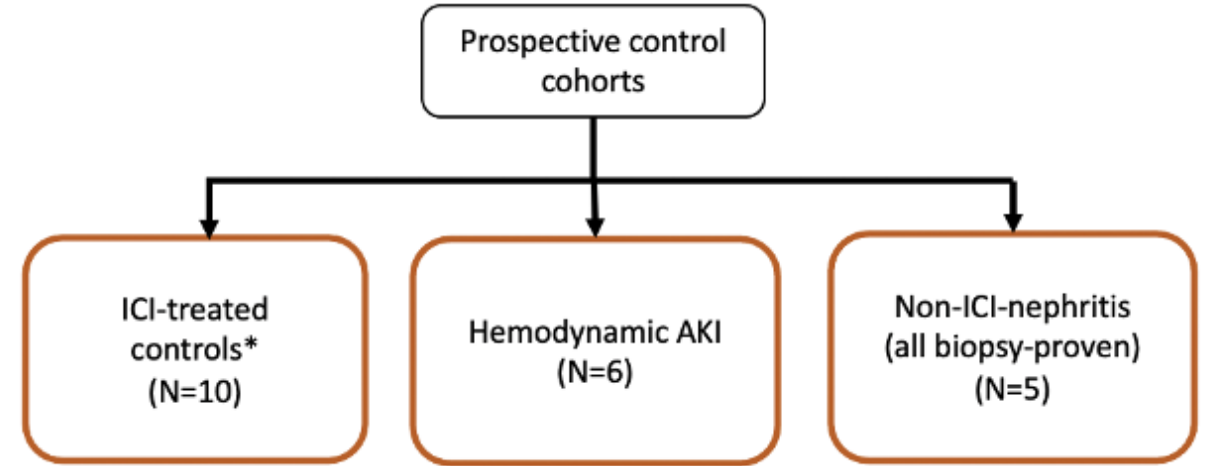
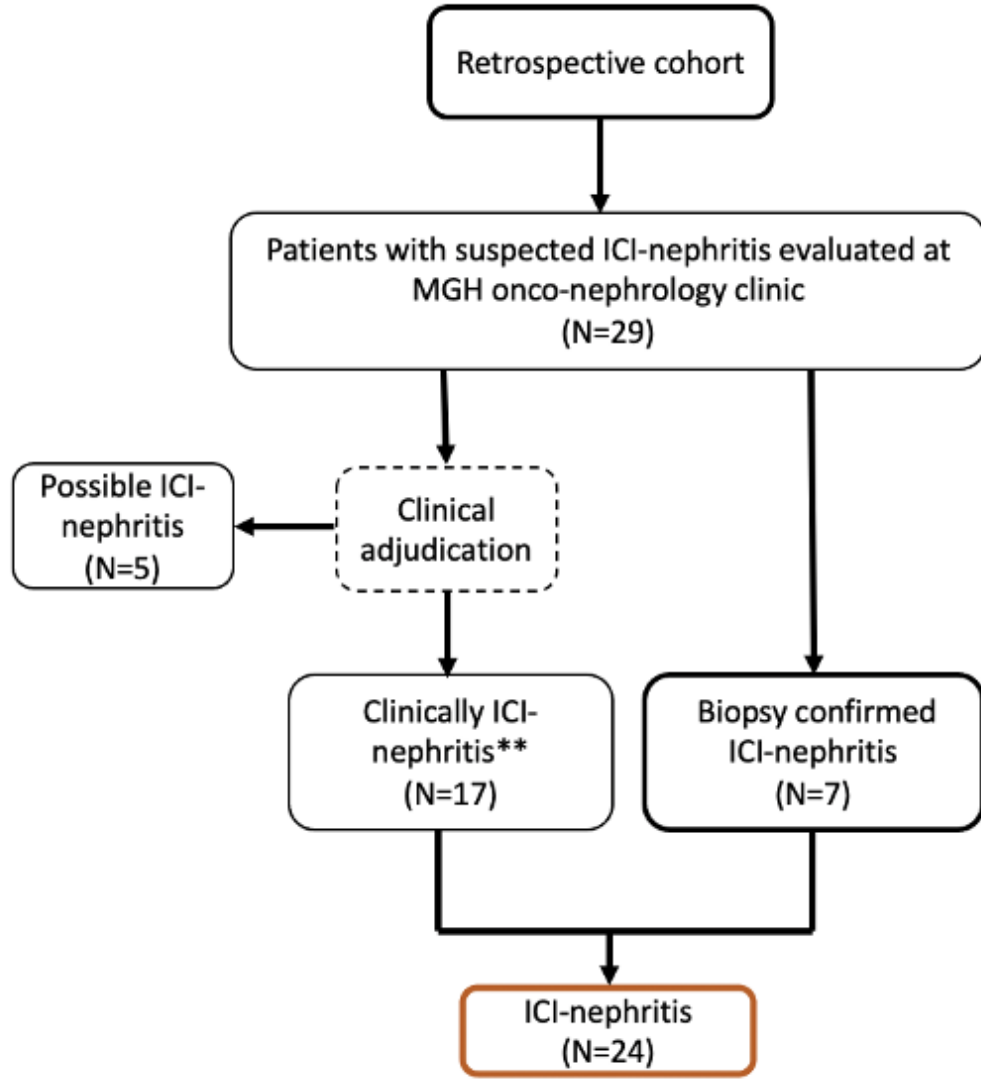
Targeted Approach



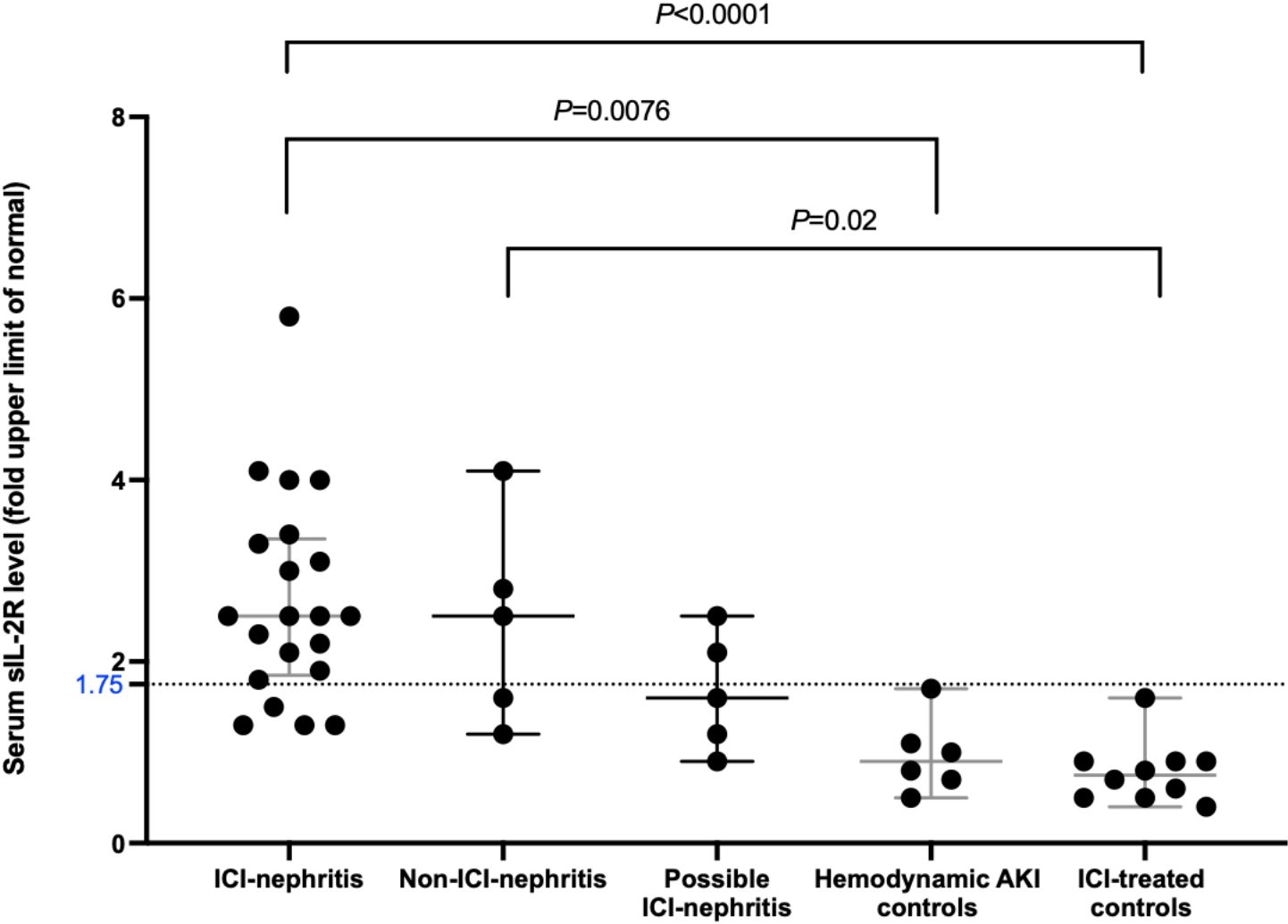
Dr. Jocelyn Farmer

“Test markers of congenital CTLA4 deficiency”

CTLA4 deficiency is a rare inborn error of immunity due to germline loss-of-function mutations in *CTLA4* or its regulators (eg, *LRBA* and *DEF6*). CTLA4 deficiency causes constitutive and pathologic T cell that drives end-organ autoinflammatory disease



Serum sIL2R is elevated in ICI-AIN



Quest (reference range 532-1891 pg/mL)
ARUP laboratories (reference range 175.3-858.2 pg/mL)

Figure 3. Diagnostic performance of sIL-2R serum level for ICI-nephritis

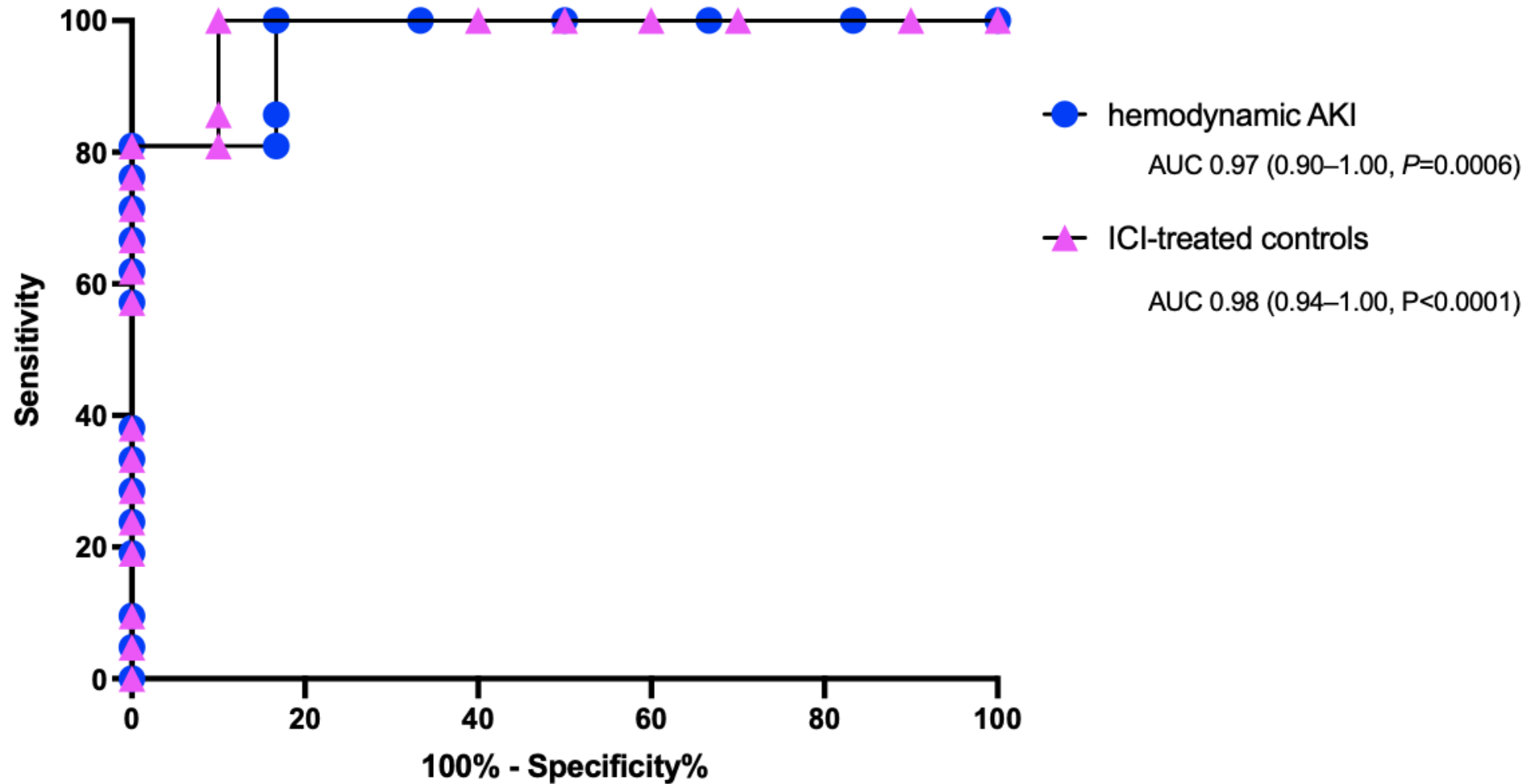
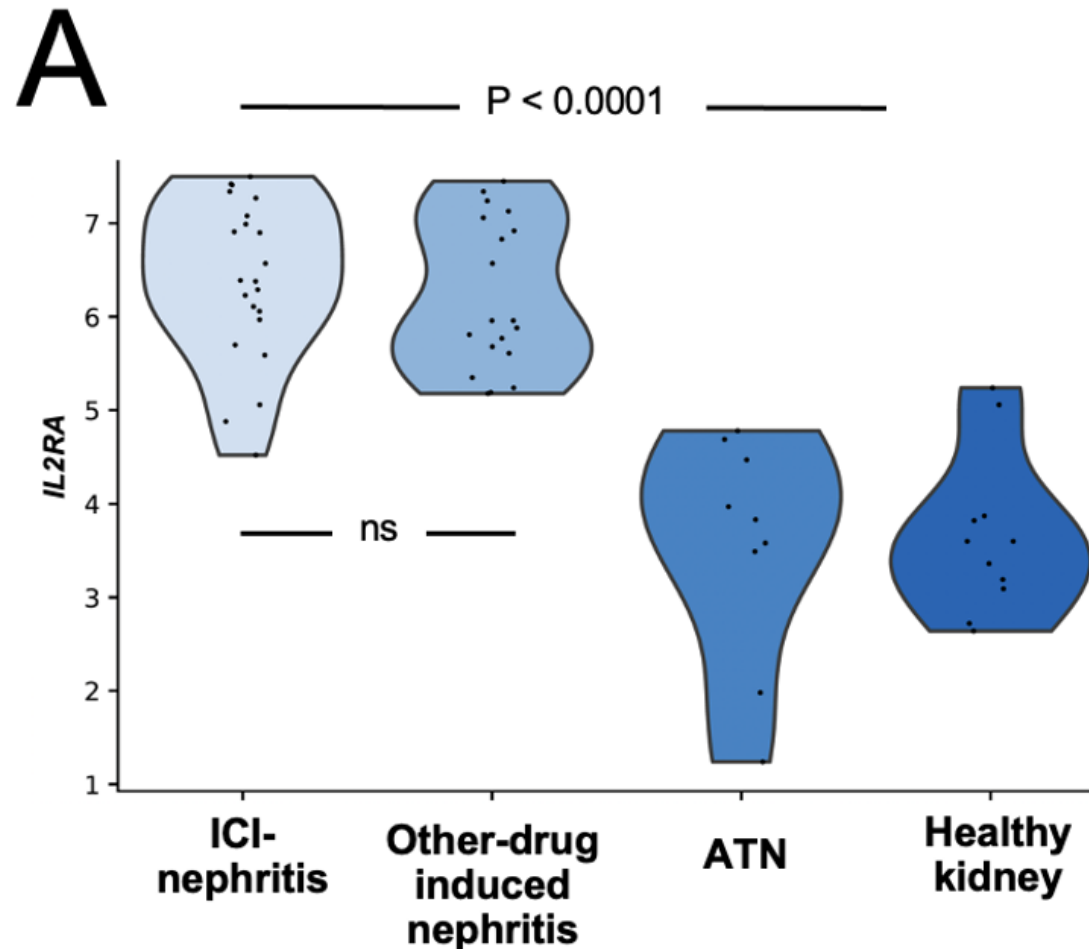


Figure 3. Receiver operating characteristic (ROC) curve, comparing ICI-nephritis cases and ICI-treated controls (pink triangles) or hemodynamic AKI controls (blue circles), respectively.

IL2R-alpha gene expression is elevated in ICI-AIN kidney biopsy tissue



Dr. Bob Colvin

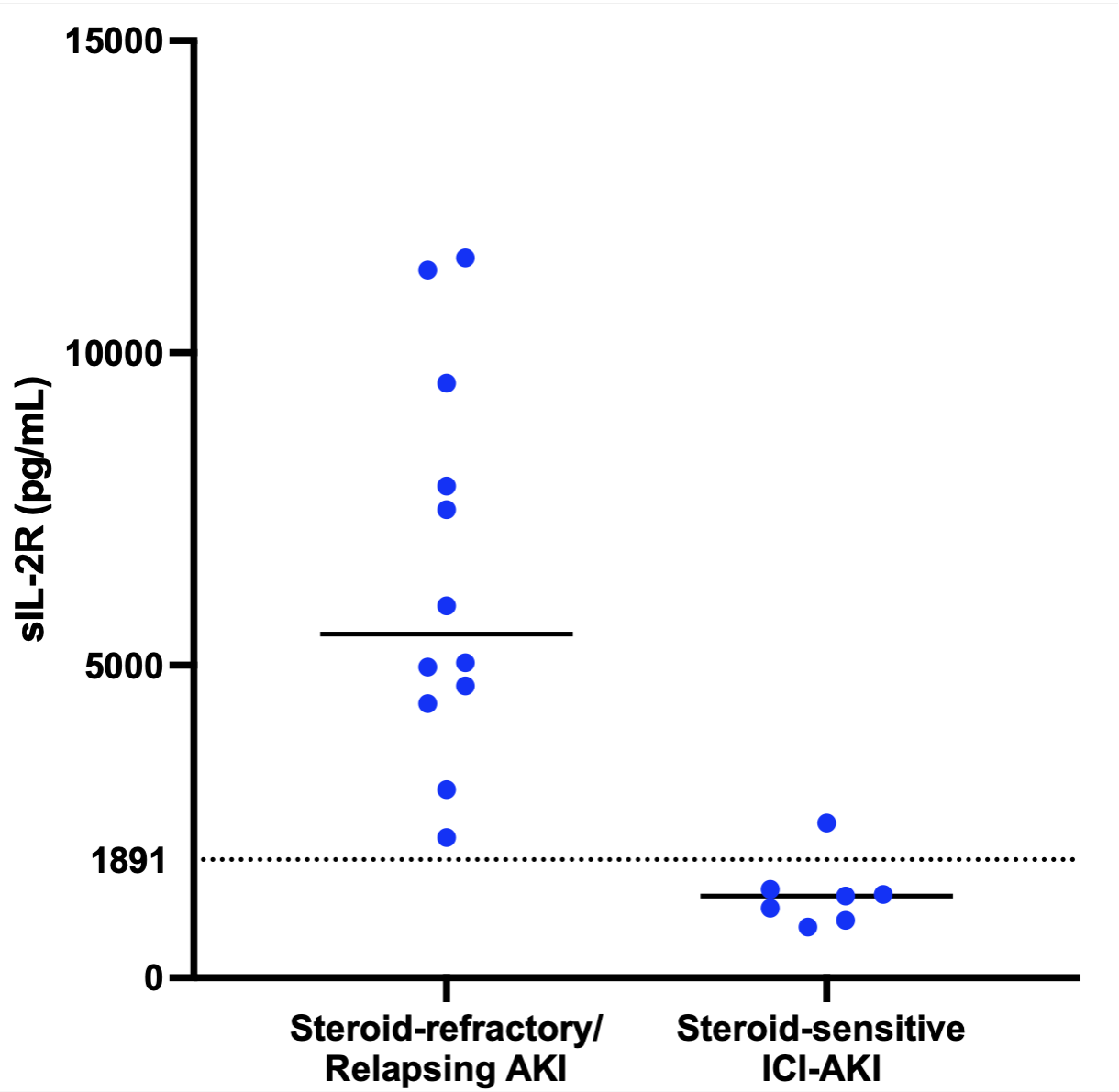


Dr. Ivy Rosales

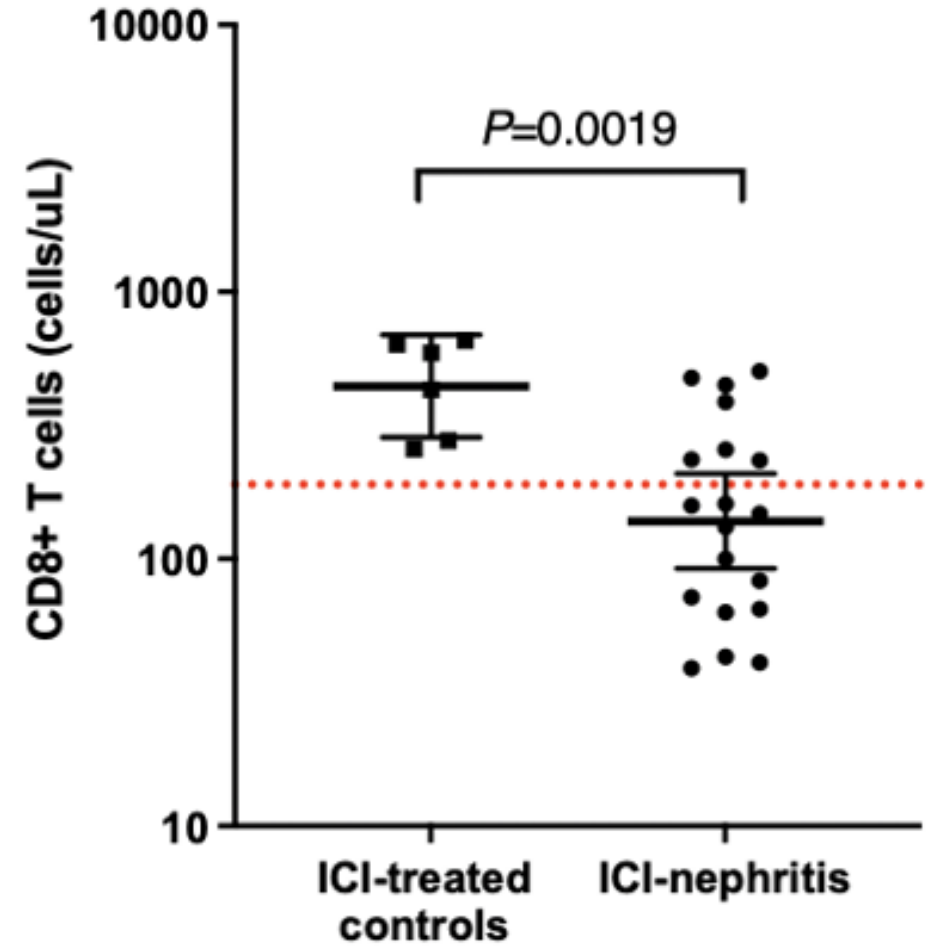
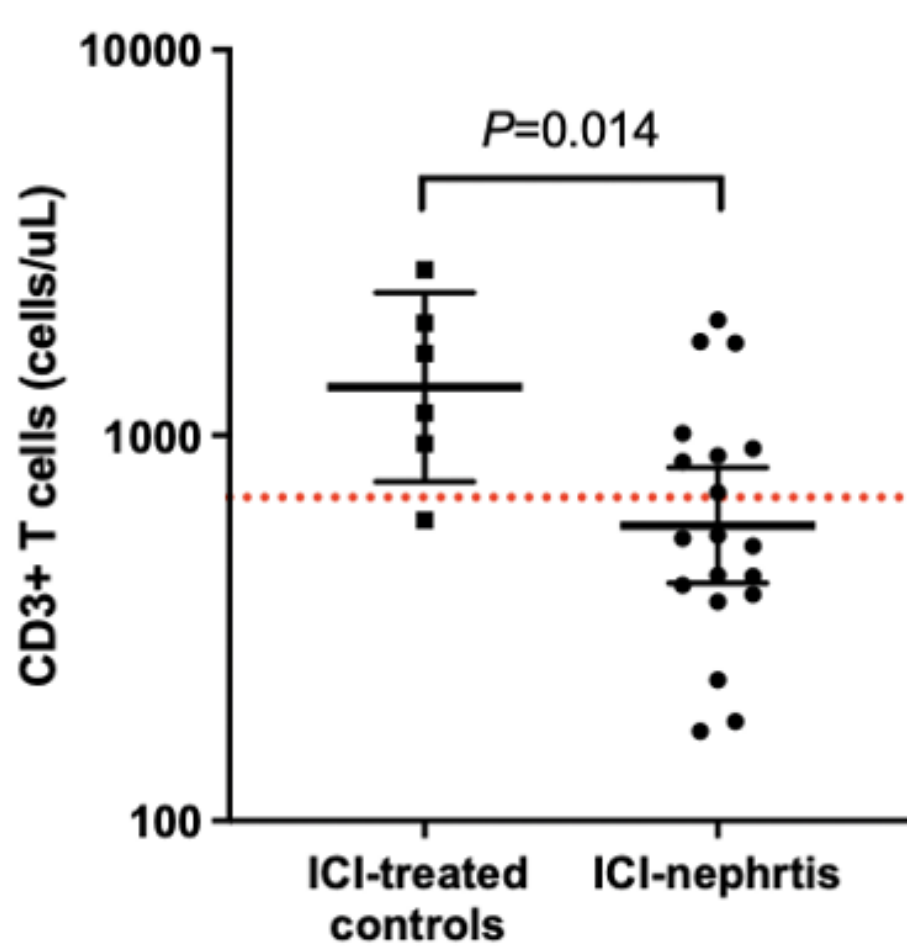


Dr. Neal Smith

Soluble IL2R after steroids may predict response

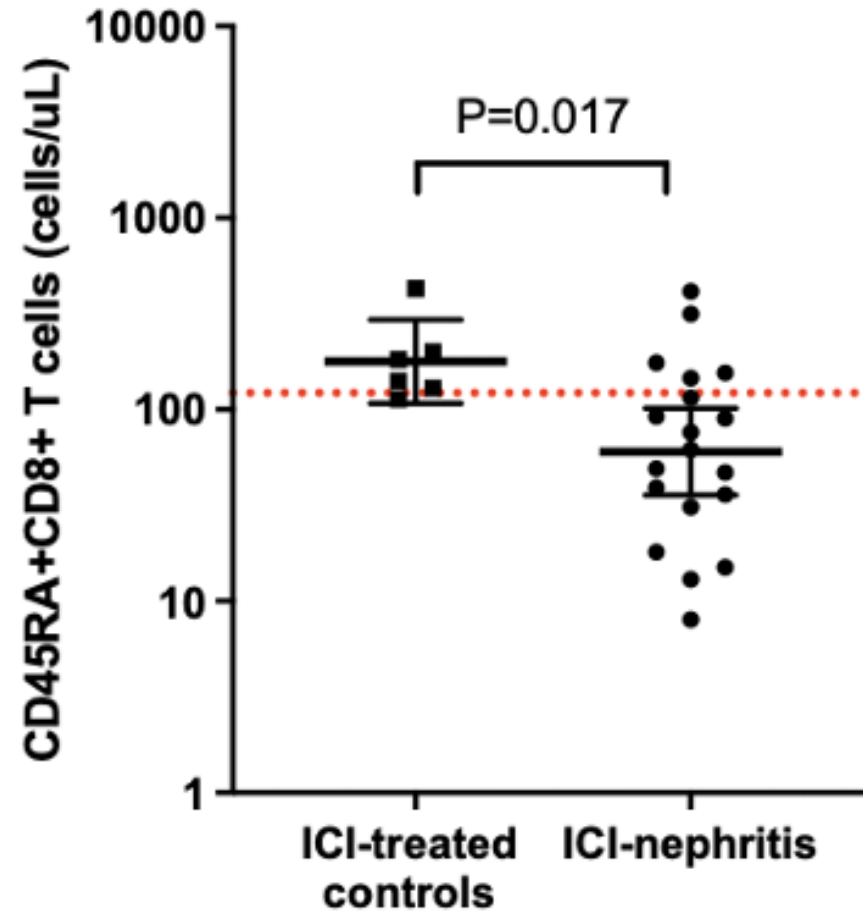


Low circulating total and CD8+ T cells



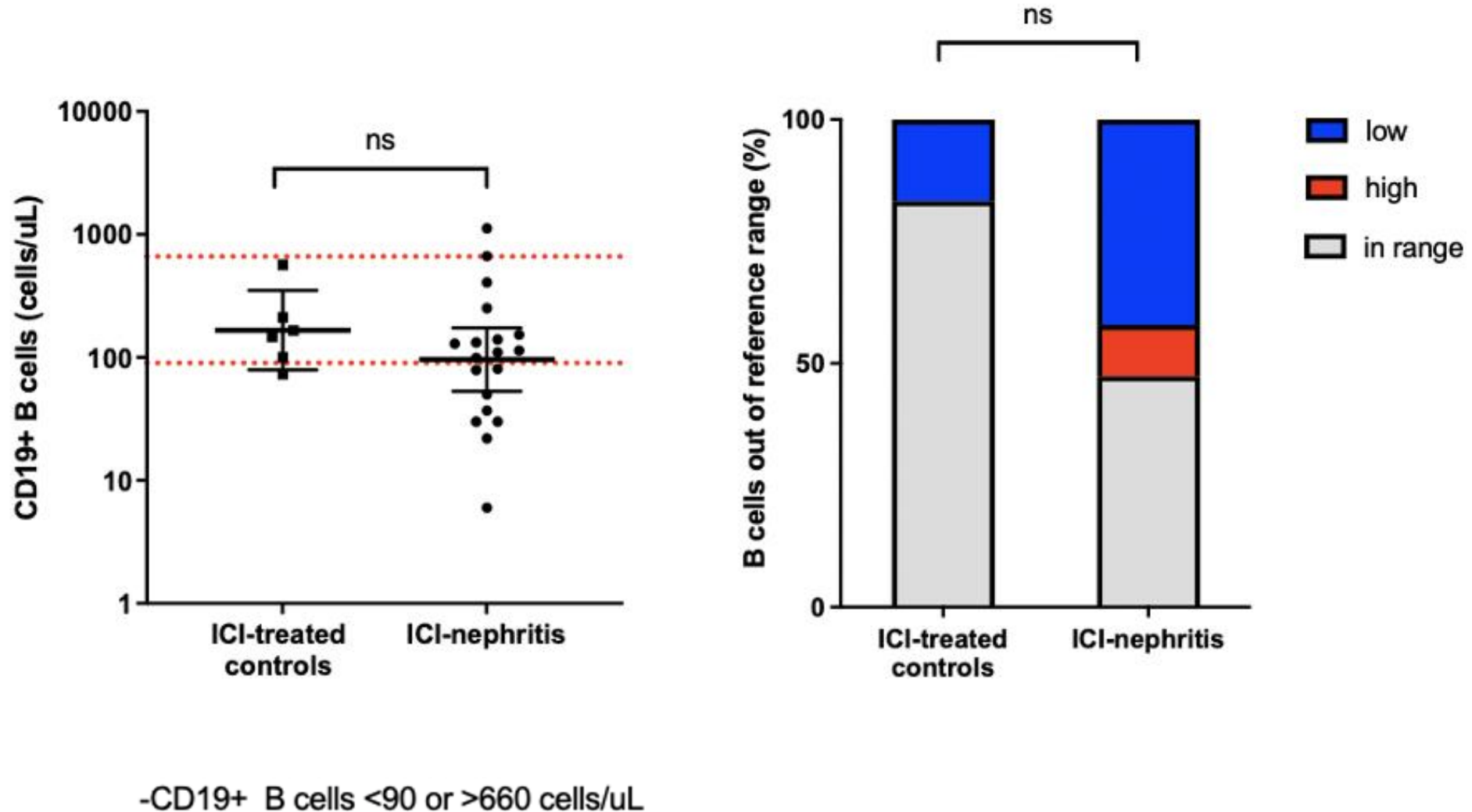
-CD8+ T cells < 190 cells/uL

Low circulating naïve CD8+ T cells

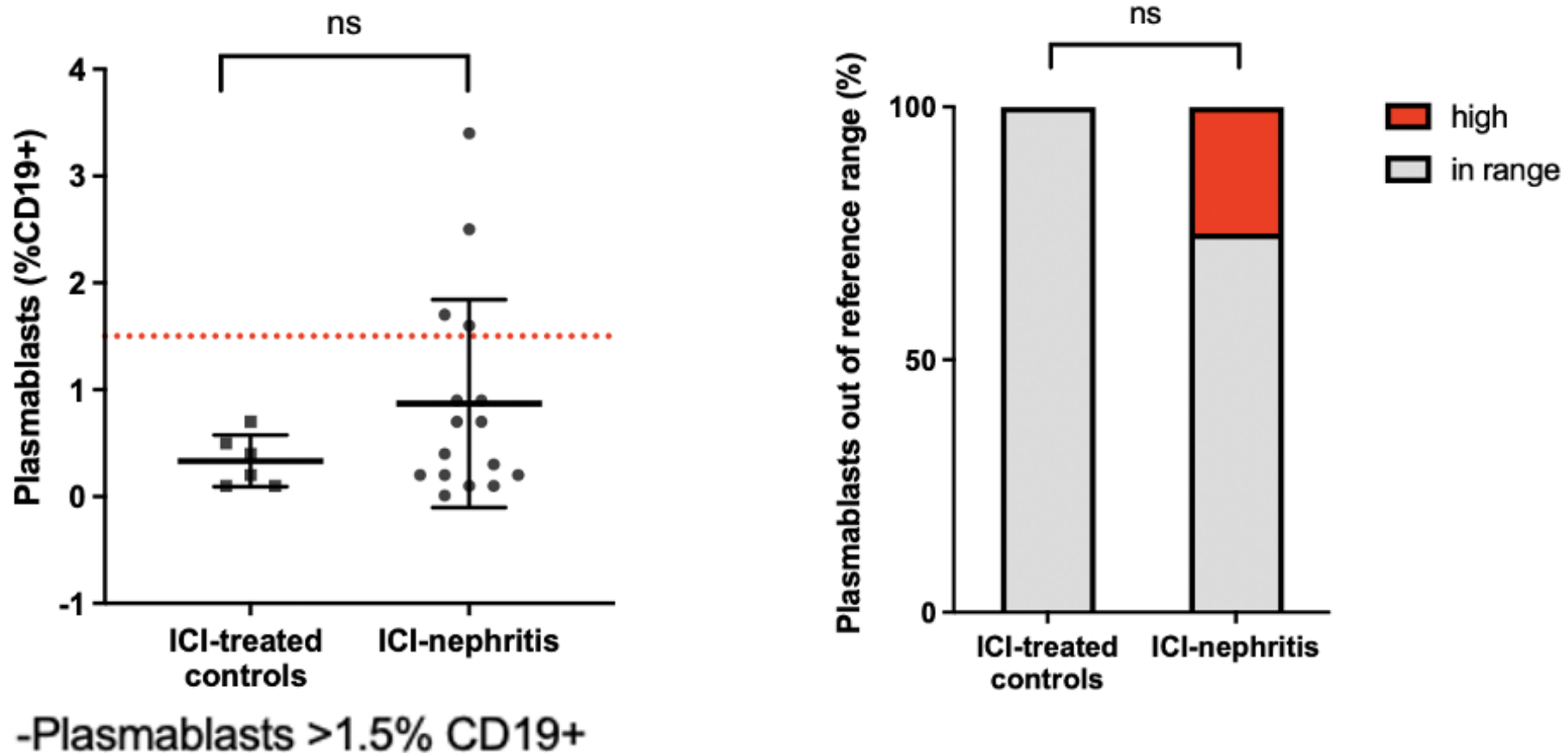


-CD8+CD45RA+ <122 cells/uL

B cell dysregulation - low or high B cells

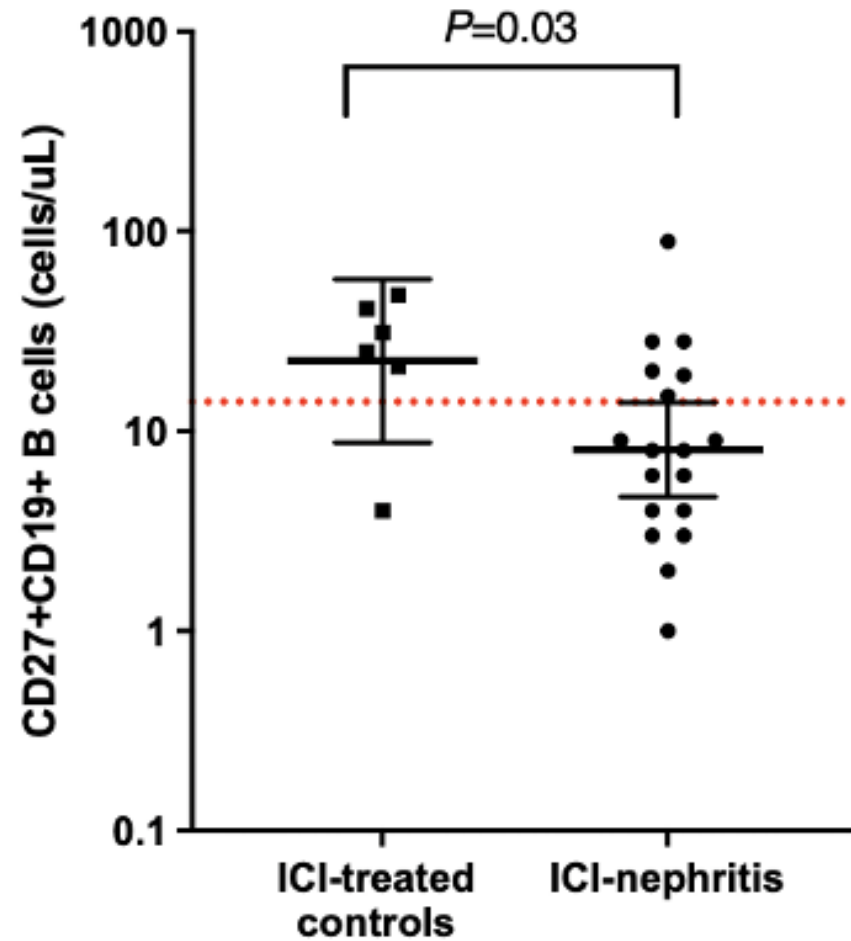


B cell dysregulation - Plasmablast expansion



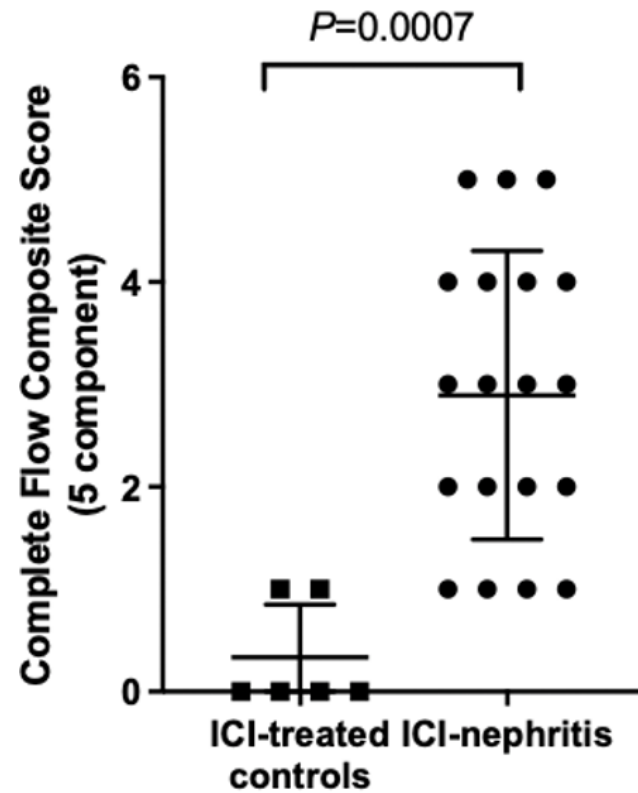
One quarter of patients demonstrated plasmablast expansion (defined by CD19+CD20-CD27+CD38+) consistent with B cell activation in peripheral blood plasmablasts

Low circulating memory B cells

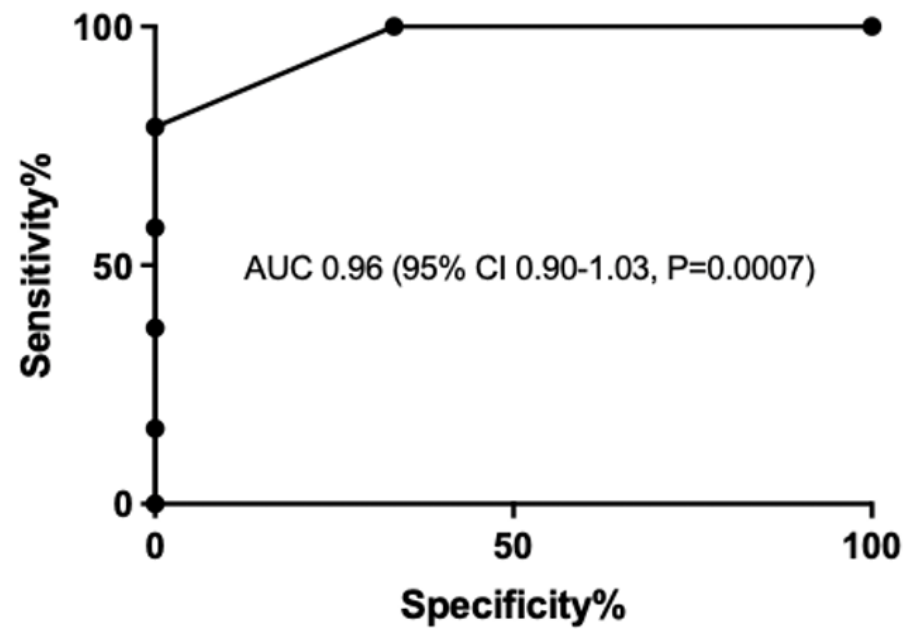


-CD19+CD27+ <20.5 cells/uL

Composite flow cytometry score (5 components)



ROC of 5 component composite flow cytometry score

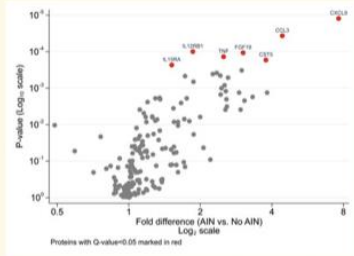


Components of score:

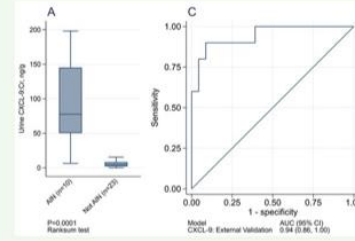
- CD8+ T cells < 190 cells/uL
- CD19+ B cells <90 or >660 cells/uL
- CD8+CD45RA+ <122 cells/uL
- CD19+CD27+ <20.5 cells/uL
- Plasmablasts >1.5% CD19+

Urine CXCL9 identified in an untargeted approach

Highly multiplexed proteomics identified CXCL9 as a biomarker for acute interstitial nephritis (AIN)

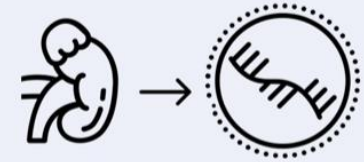


Internal and external validation of CXCL9 using sandwich immunoassay



ROC analysis with external validation
AUC=0.94

Higher kidney tissue expression of CXCL9 in those with AIN



Participants with biopsy confirmed diagnosis
Discovery Cohort

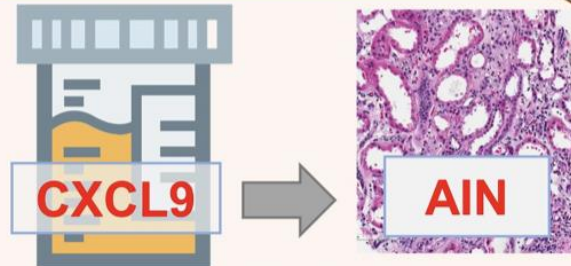
- Yale AIN study

Validation Cohorts

- Mt. Sinai
- C-PROBE

Tissue Expression

- MGH



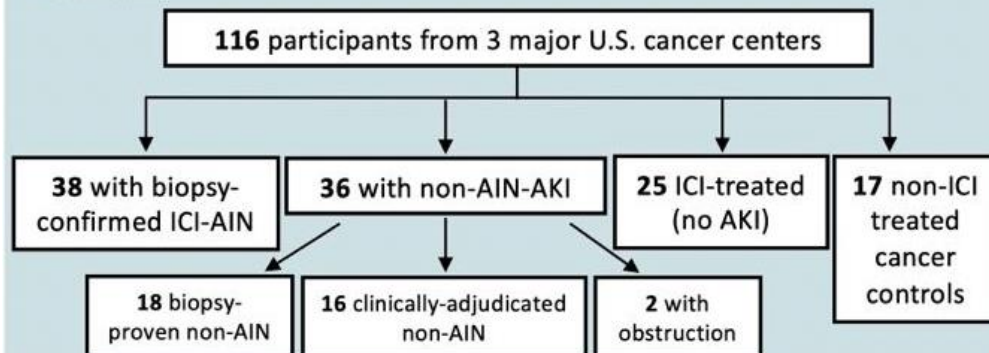
Urine CXCL9 is a
diagnostic biomarker of
acute interstitial nephritis

Urinary CXCL9 in immune checkpoint inhibitor-associated acute interstitial nephritis

kidney
INTERNATIONAL



Cohort



Methods



Discovery

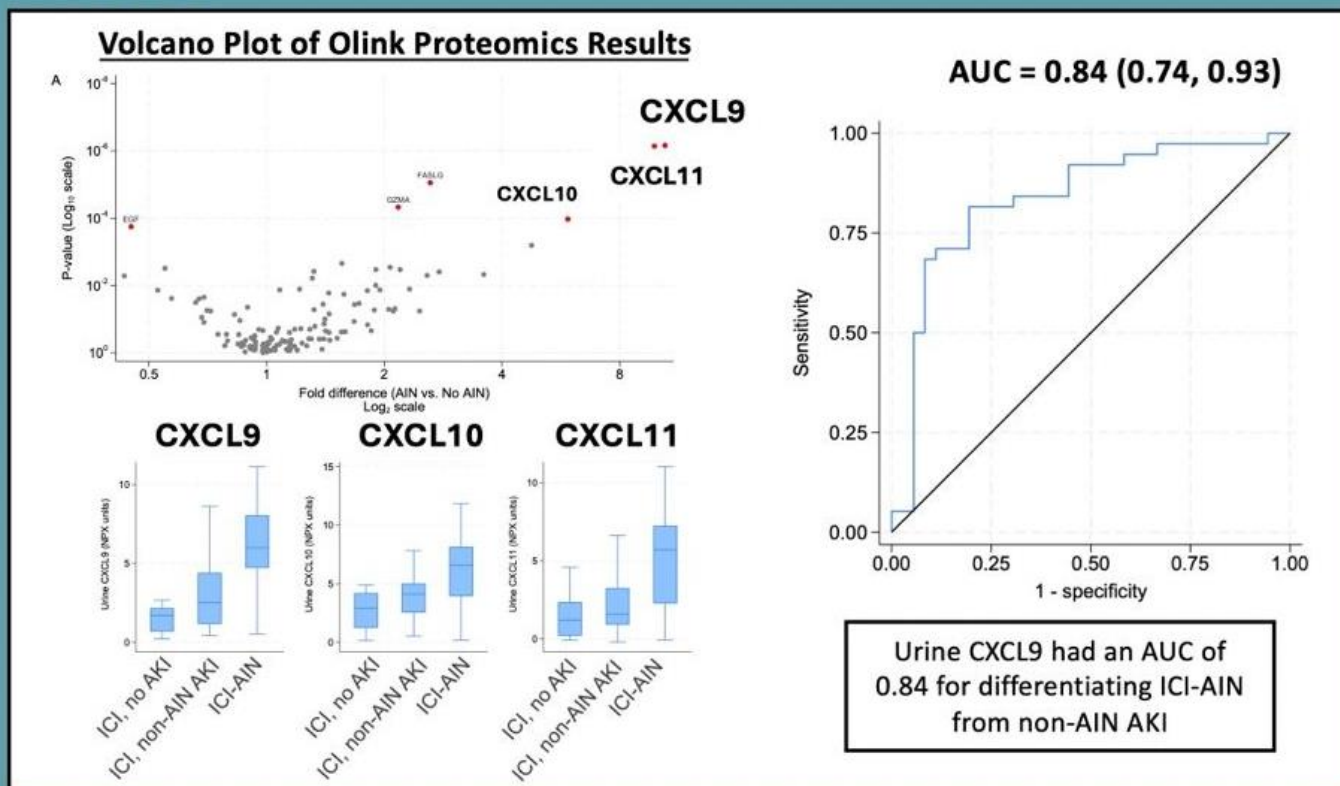
Proteomics:

- 1) Olink Target 96 Immuno-Oncology Panel
- 2) Olink Target 96 Inflammation Panel

Validation

Modified sandwich electrochemiluminescence immunoassay for CXCL9

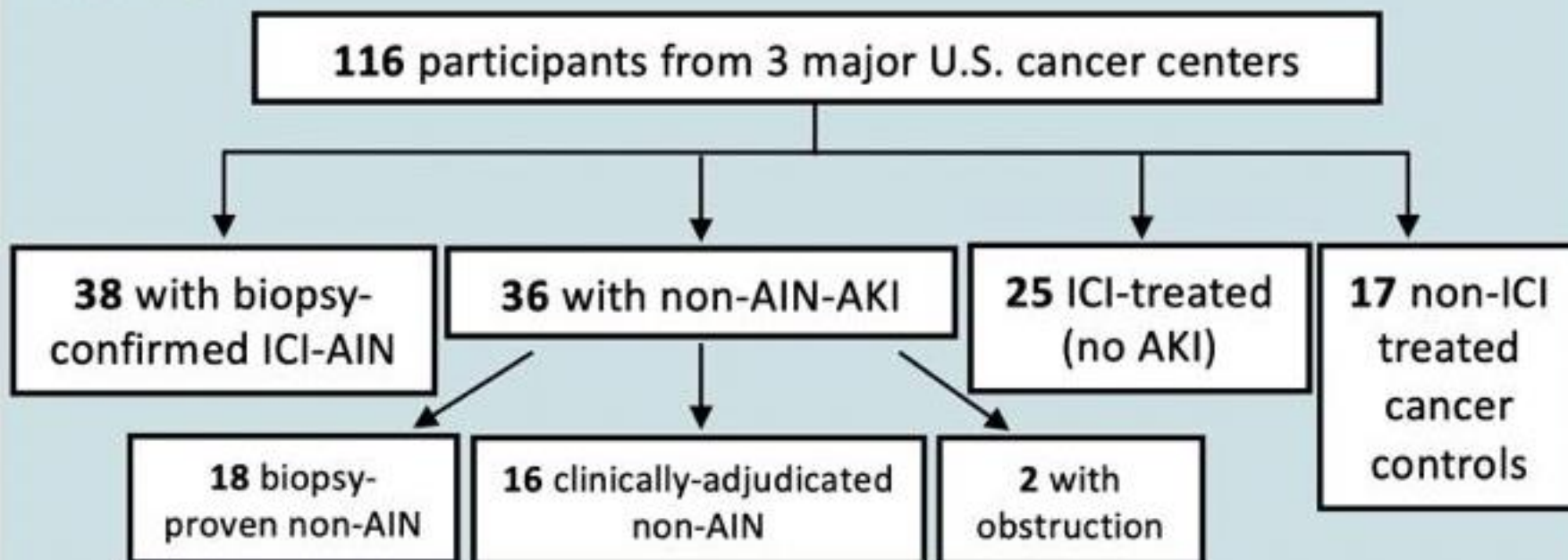
Outcomes



CONCLUSION: Interferon- γ -induced chemokines, specifically CXCL9, CXCL10 and CXCL11, are the key urine proteins differentiating AIN-AKI from controls. CXCL9 provides high discrimination for ICI-AIN.

Gupta and Mistry et al., 2025

Cohort



Methods



Discovery



Proteomics:

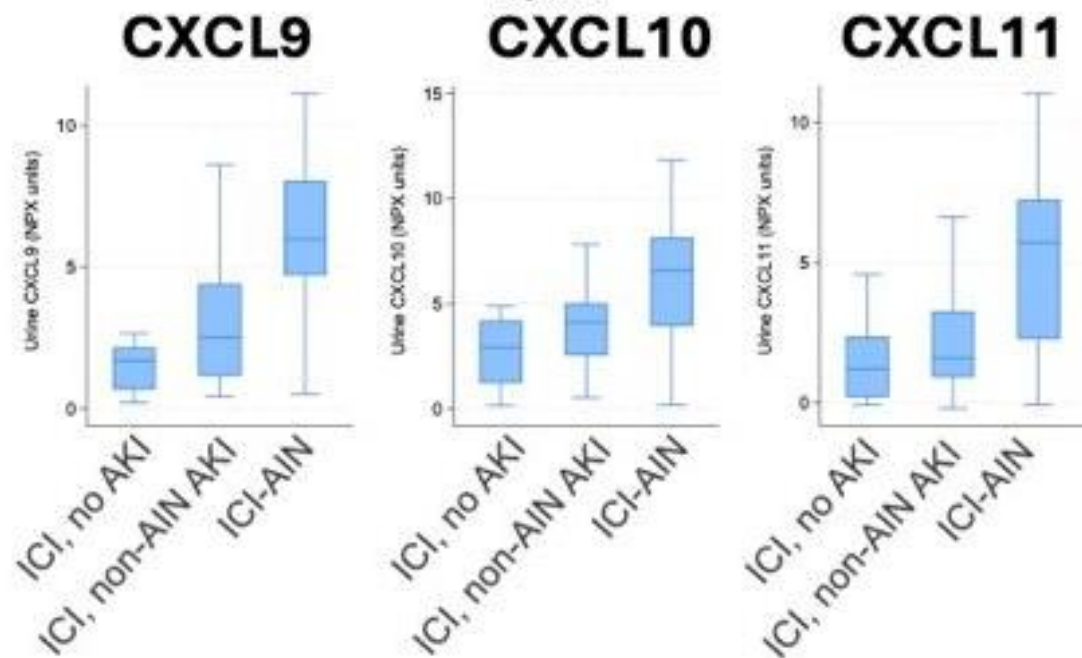
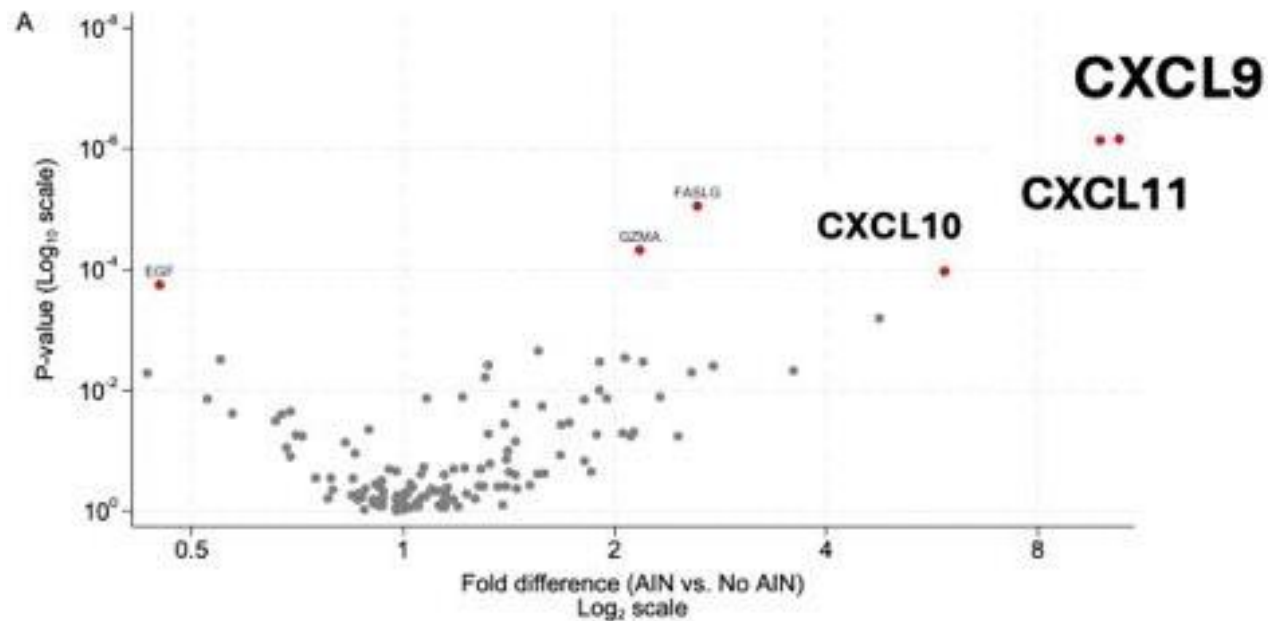
- 1) Olink Target 96 Immuno-Oncology Panel
- 2) Olink Target 96 Inflammation Panel

Validation

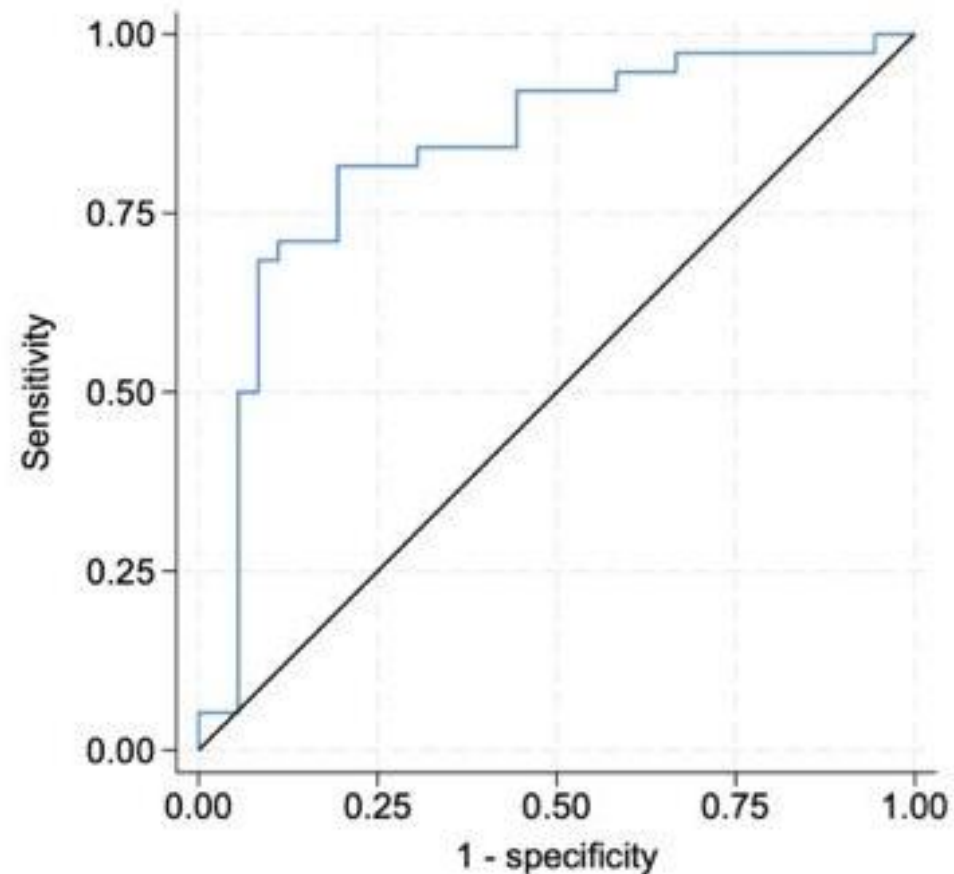


Modified sandwich electrochemi-luminescence immunoassay for CXCL9

Volcano Plot of Olink Proteomics Results



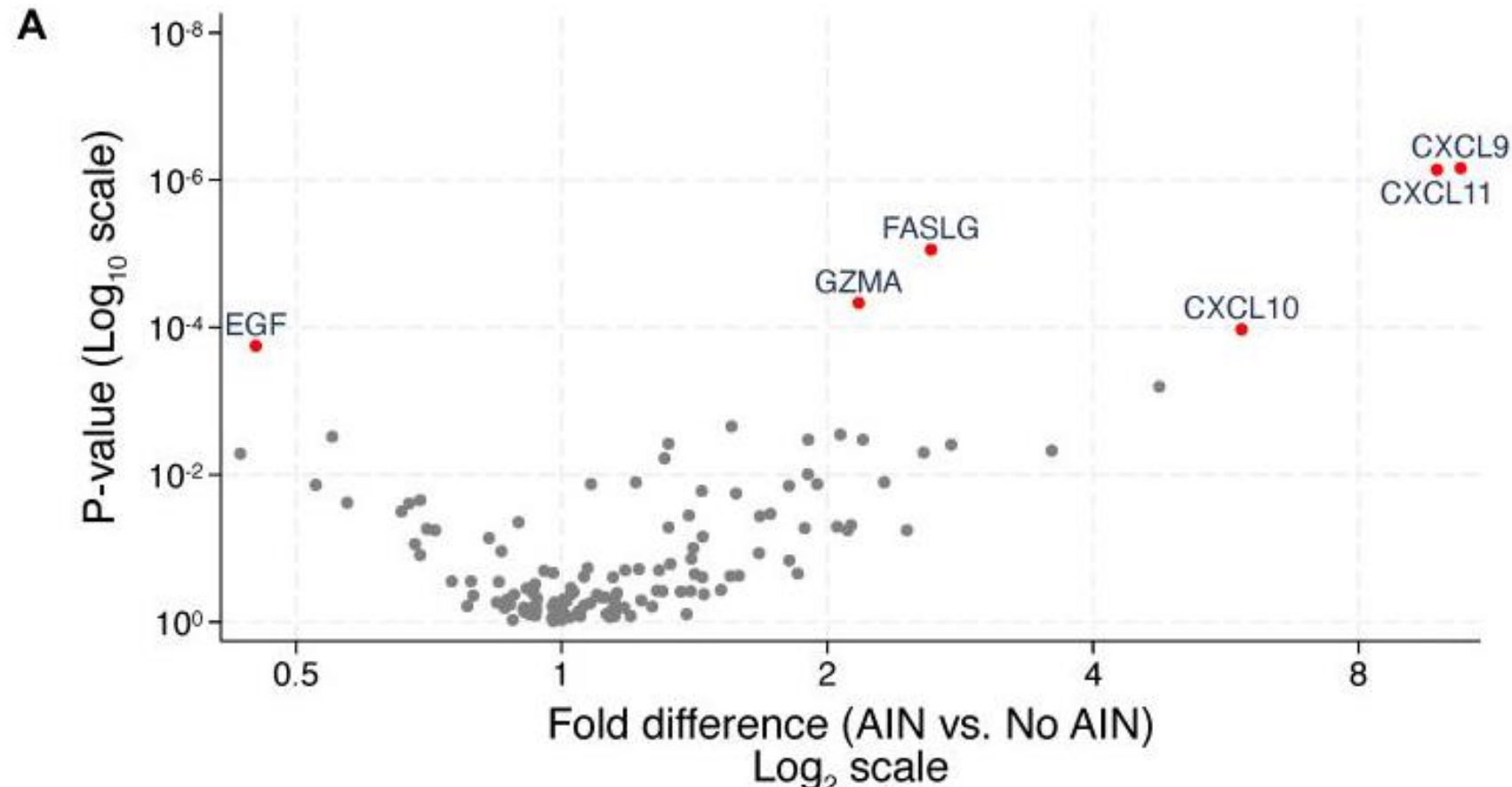
AUC = 0.84 (0.74, 0.93)



Urine CXCL9 had an AUC of
0.84 for differentiating ICI-AIN
from non-AIN AKI

Urinary CXCL9 in immune checkpoint inhibitor-associated acute interstitial nephritis

Volcano plot – differential expression/abundanc of IFN-gamma stimulated chemokines as most differentially (CXCL9, CXCL10, and CXCL11) in AIN vs. controls

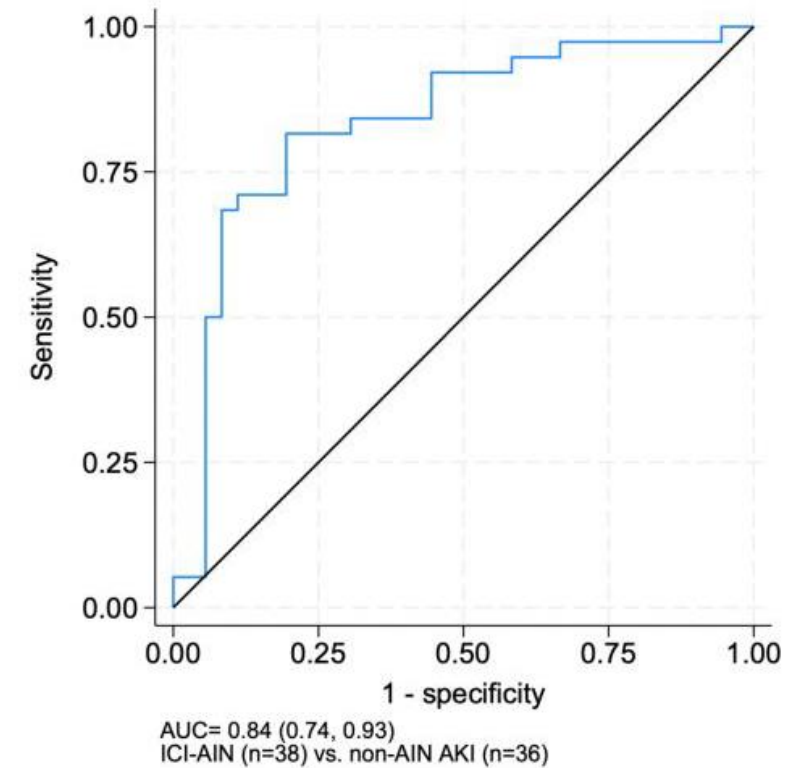
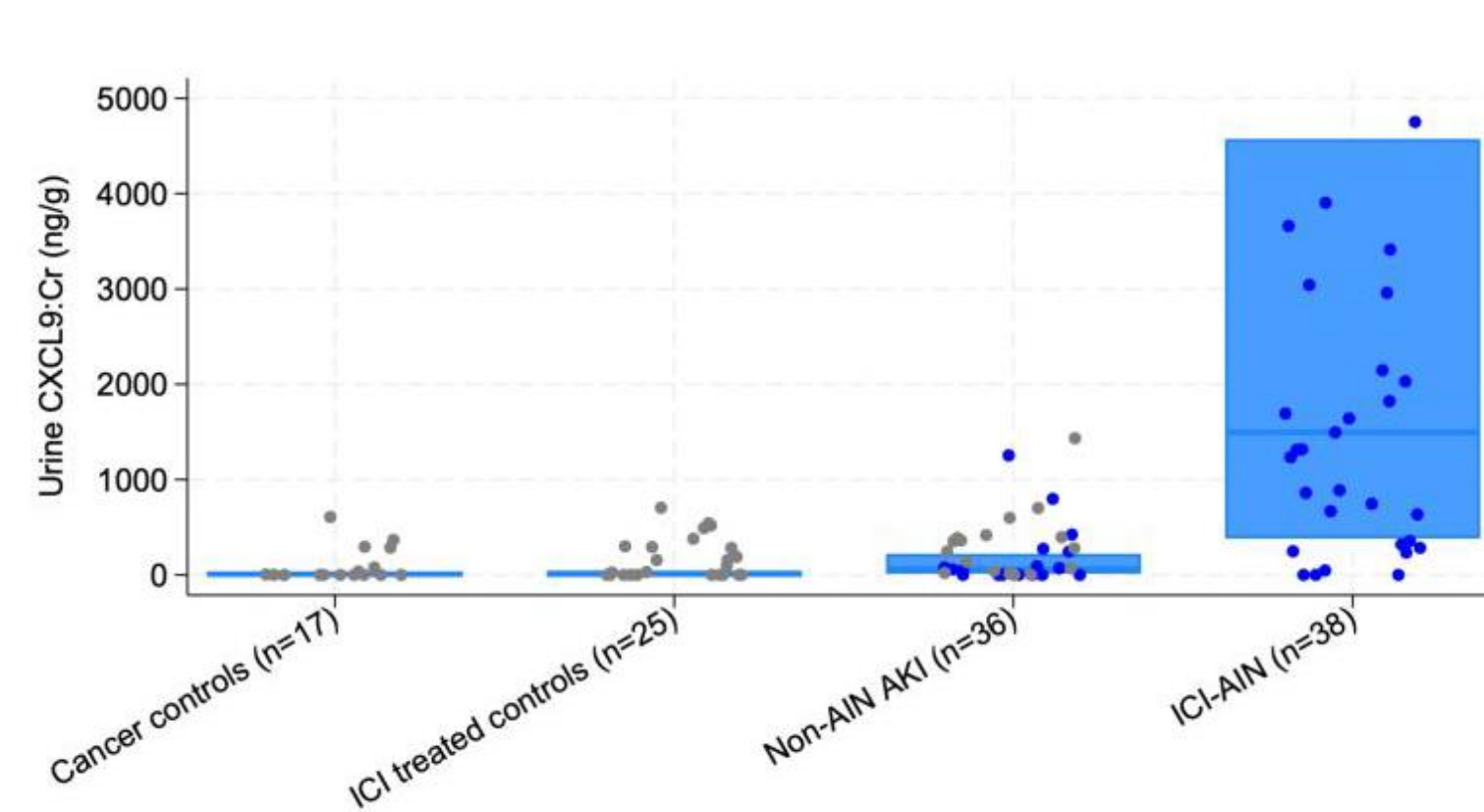


Urinary CXCL9 in immune checkpoint inhibitor-associated acute interstitial nephritis

kidney
INTERNATIONAL



CXCL9 by immunoassay



Research goals for diagnosing ICI-AIN

1. Step 1: Find disease biomarkers of ICI-AIN to limit the need for biopsy
2. Step 2: Work together to validate these prospectively



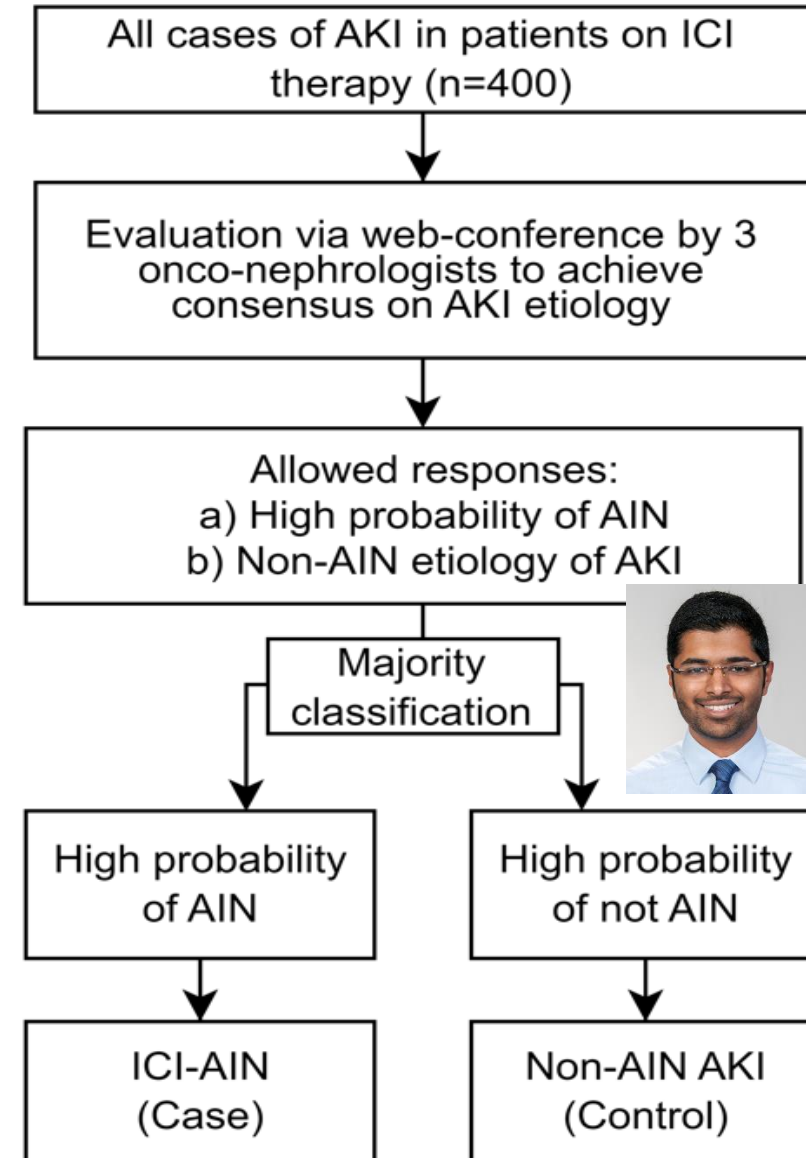
Yale: Dennis Moledina



JHU: Chirag Parikh



MGB: Shruti



Management

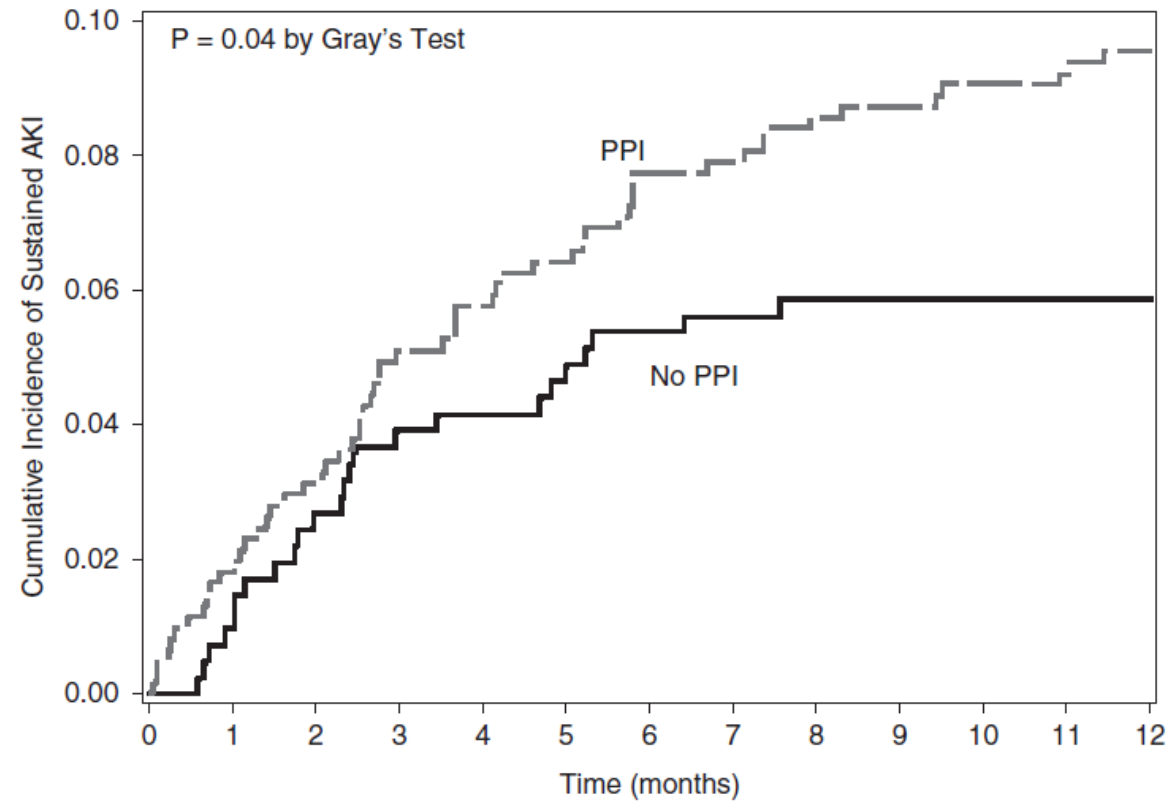
Management

- Withhold immune checkpoint inhibitor
- Stop all other meds that could provoke AIN
 - PPI to H2 blocker
 - Stop/switch antibiotics
 - Ask about NSAIDS
- High dose steroids, 1mg/kg per day prednisone equivalent Consider intravenous methylprednisolone if creatinine > 4 mg/dL, hospitalized, or needing RRT
- Begin steroid taper once creatinine is < 1.5 times baseline
- If using prolonged steroids – avoid trimethoprim/sulfamethoxazole and ppi

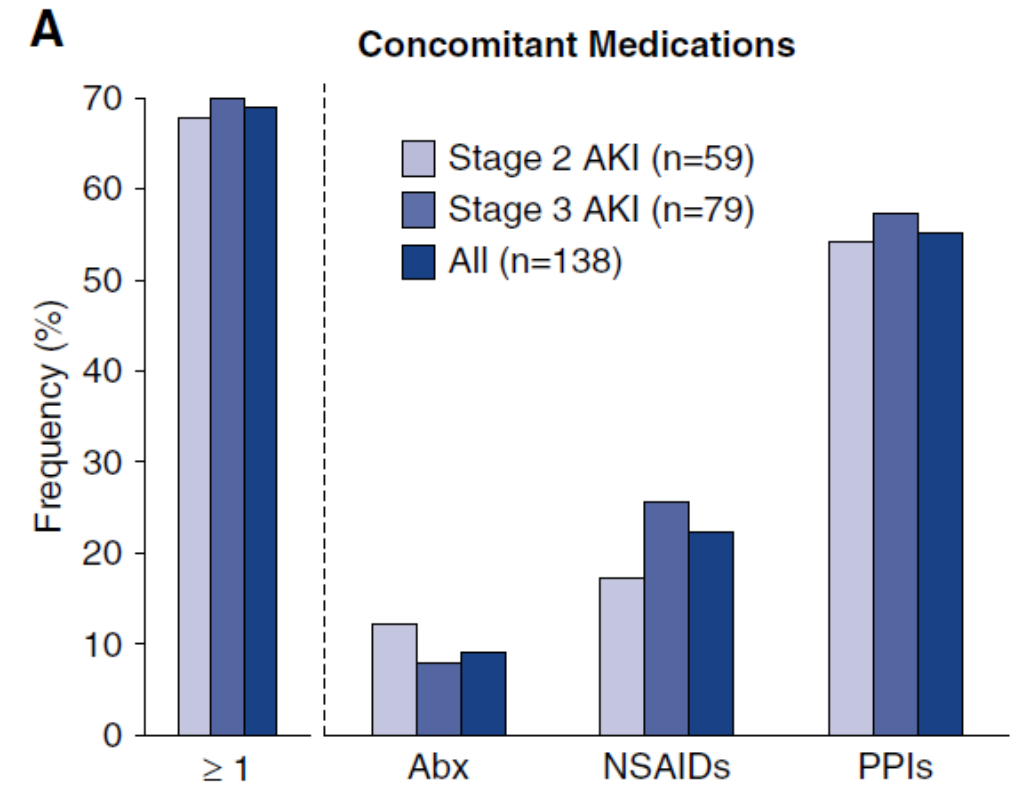
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- If using prolonged steroids – avoid trimethoprim/sulfamethoxazole
- Multicenter study suggest median time to 10mg is 6 weeks

Risk factors – other AIN meds



Seethapathy and Sise CJASN 2019



Cortazar and Leaf. JASN 2020

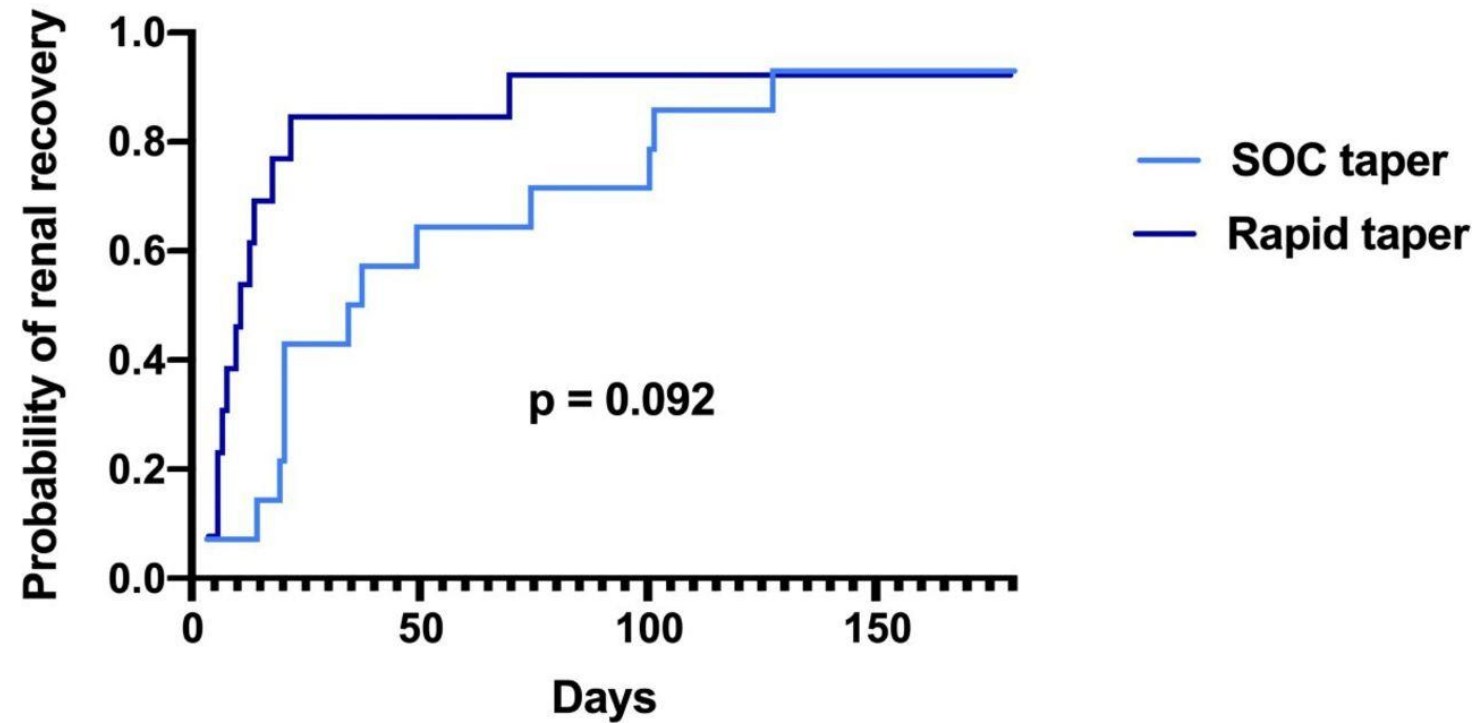
Management

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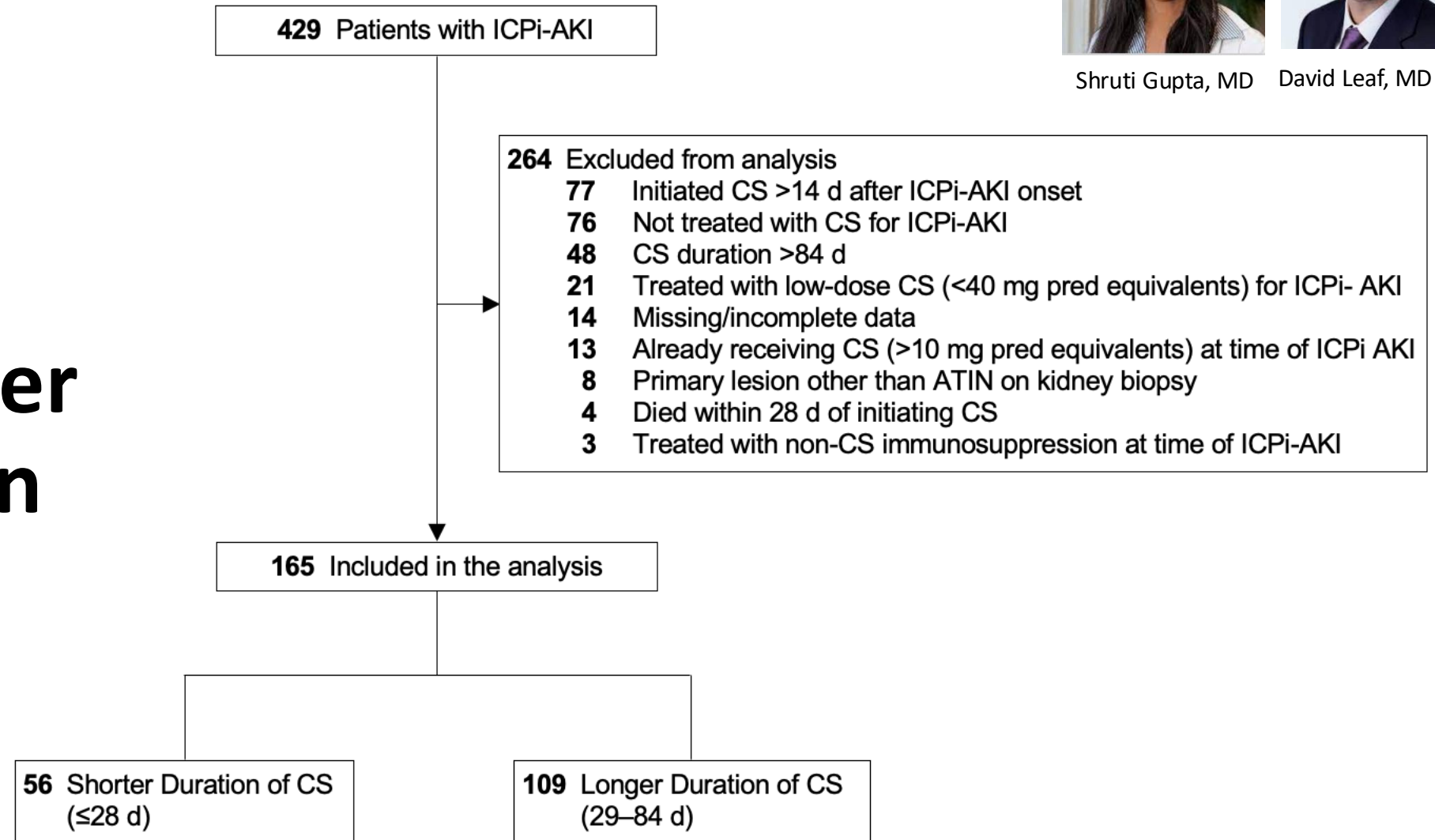
Rapid Taper Protocol

- Begin prednisone 1mg/kg/day (In hospitalized patients, consider 1-3 days of intravenous methylprednisolone)
- Repeat creatinine in 5-7 days
- Provided creatinine is improving by $\geq 25\%$ then rapidly taper prednisone 40mg x 3 days, 30mg x 3 days, 20mg x 3 days, 10mg daily.
- Repeat creatinine every 7 days and continue taper as long as creatinine continues to decline. If the creatinine rises, restart 60mg day and taper over 4-6 weeks.

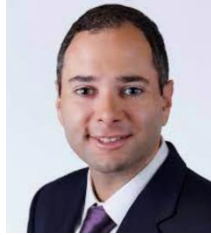
Renal Recovery



Multicenter validation

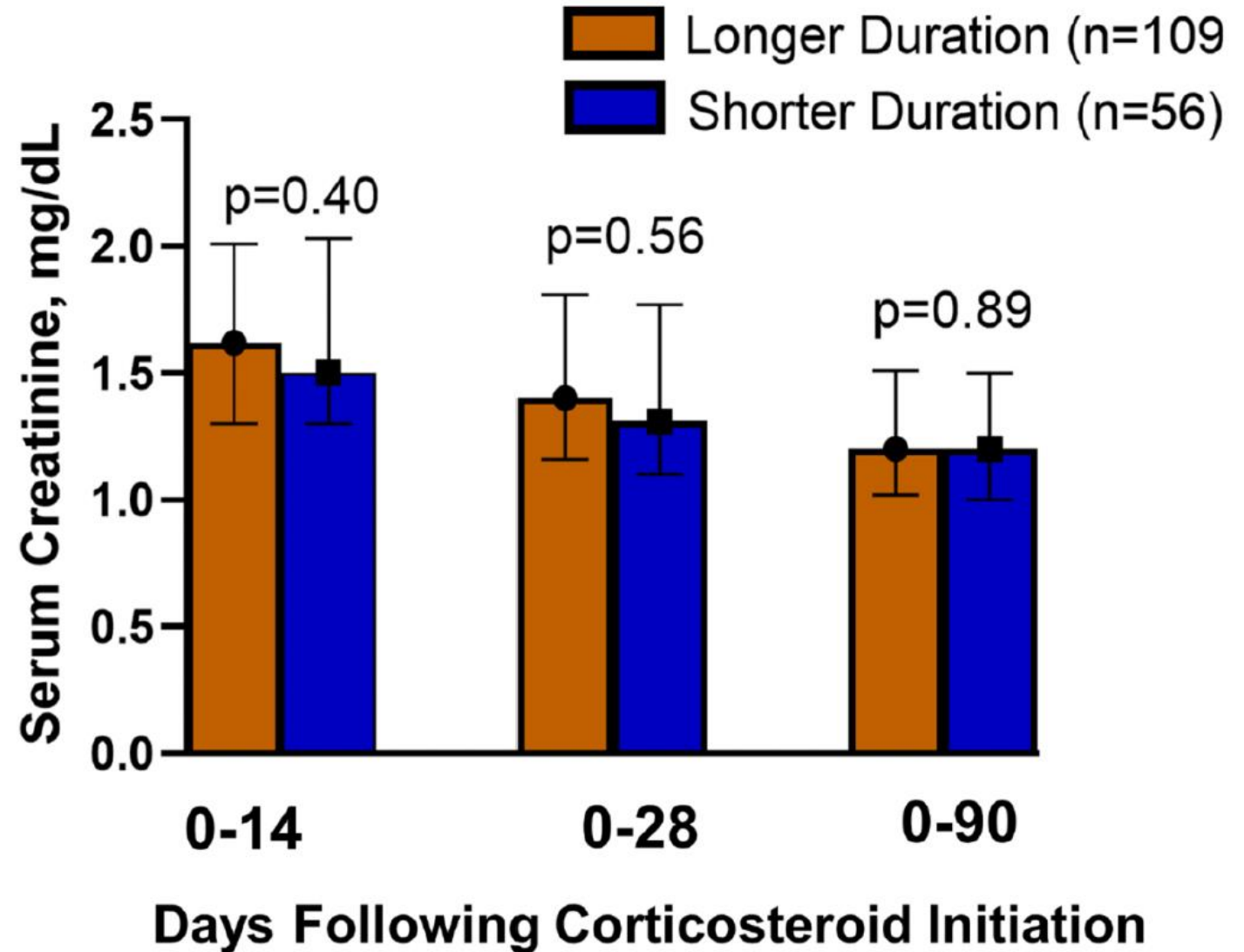


Shruti Gupta, MD

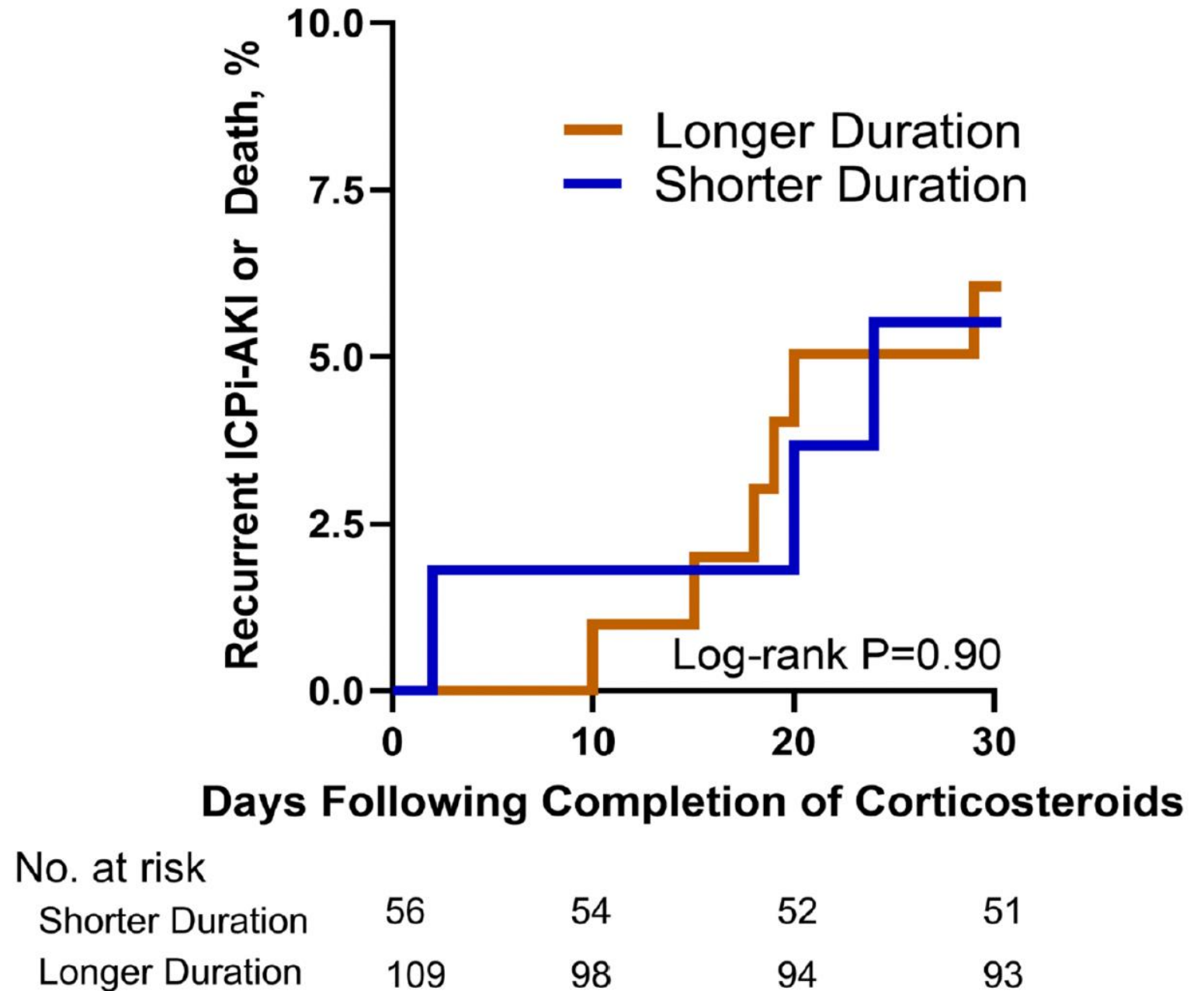


David Leaf, MD

**No
difference in
recovery**



**No
difference in
AKI relapse**

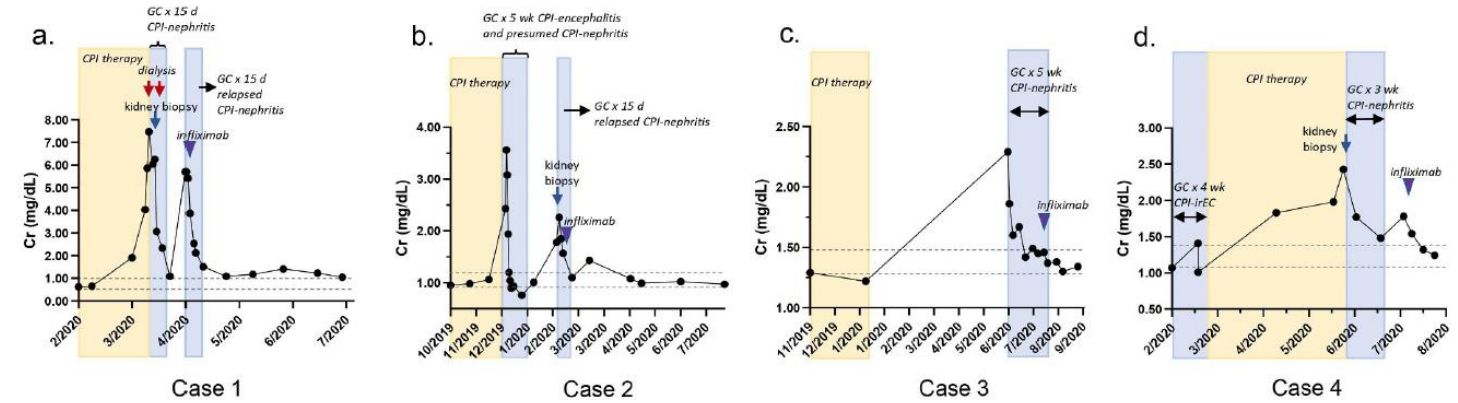


Infliximab* for relapsing or difficult to treat ICI-AKI

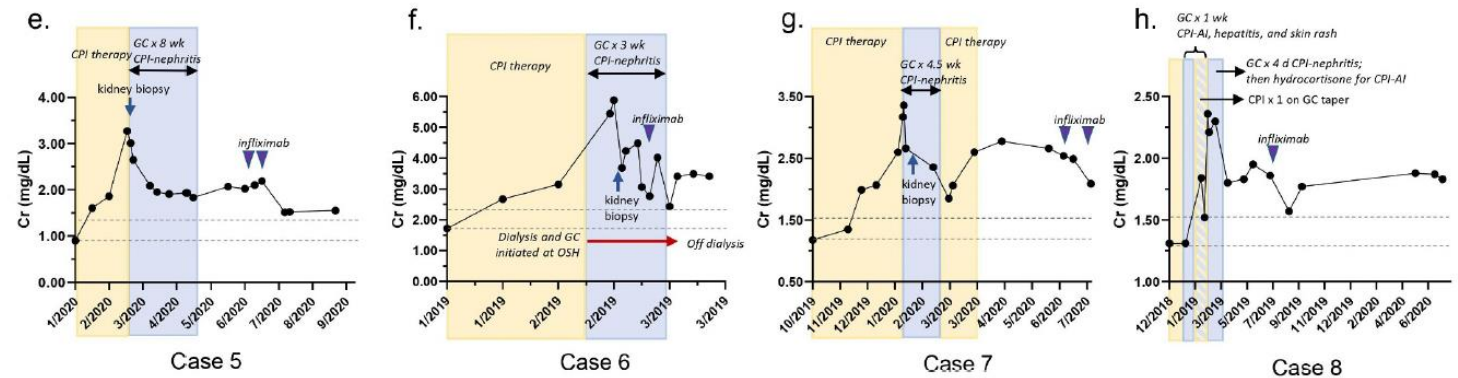
*off label

Other off label options: MMF, ruxolitinib

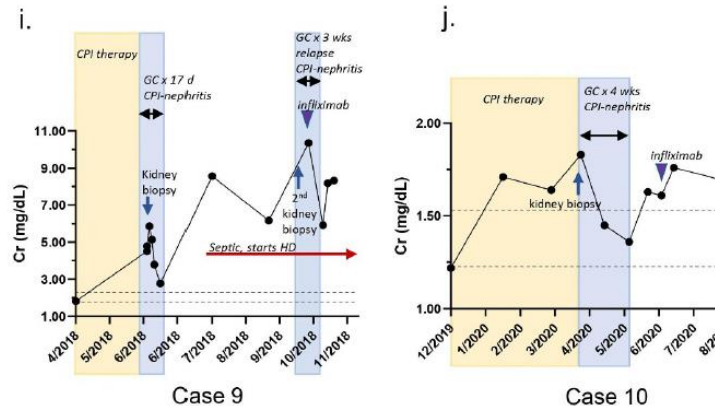
Complete Kidney Recovery



Partial Kidney Recovery



No Kidney Recovery



Infliximab for Grade III/ IV ICI Nephritis

Clinical and Translational Evidence



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

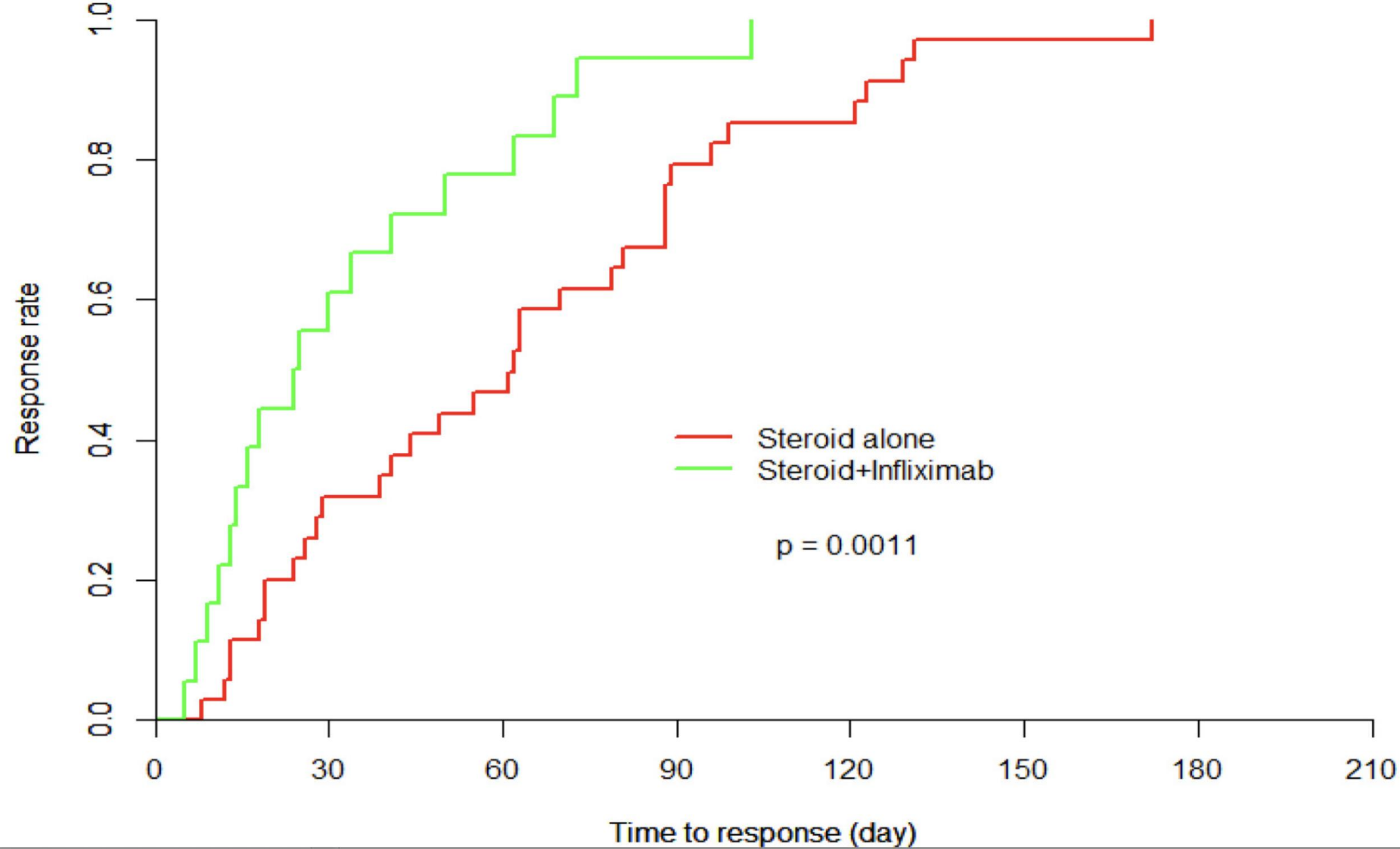
ICI, Immune Checkpoint Inhibitor; AIN, Acute Interstitial Nephritis

KI REPORTS
Kidney International Reports

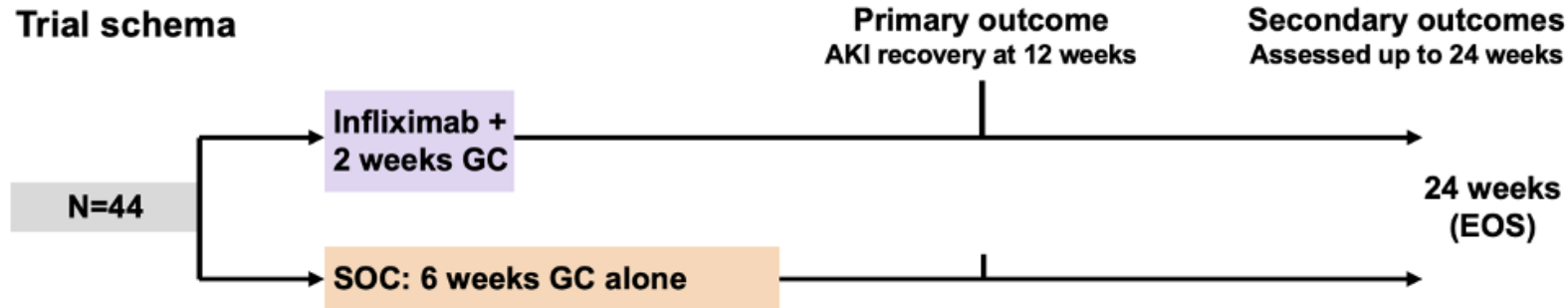
Youssef N et al, 2025

Visual abstract by:
Edgar Lerma, MD, FASN
X @edgarvlernamd

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



NCT07683975



This is a **two-arm, open-label randomized pilot clinical trial**.

After a brief run-in period, where all patients receive 1 week of prednisone at 1 mg/kg/day, patients will be randomly assigned to one of two treatment arms in a 1:1 ratio.

- **Arm 1** will receive infliximab 5mg/kg IV x 1 along with prednisone 1mg/kg/day x 2 weeks.
- **Arm 2** will receive prednisone 1mg/kg/day x 2 weeks (maximum 100mg/day) followed by a 4-week taper, during which prednisone will be tapered by 0.2mg/kg/day per week.

Follow-up will be until week 24.

Primary outcome: AKI recovery at 12 weeks

Management

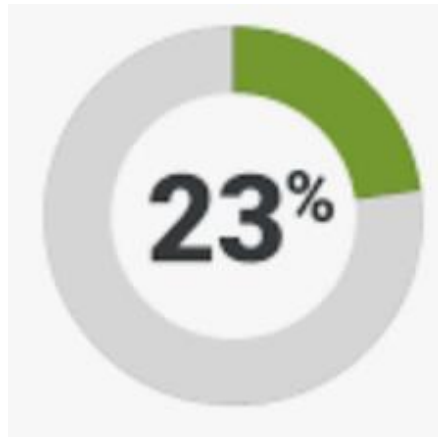
- Withhold immune checkpoint inhibitor
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- Begin steroid taper once creatinine is < 1.5 times baseline
- If using prolonged steroids – avoid trimethoprim/sulfamethoxazole
- Multicenter study suggest median time to 10mg is 6 weeks

ICI Rechallenge after AKI

Cortazar and Leaf, JASN, 2020

31 of the 138 patients (22%) with ICI-AKI
were rechallenged
~2mo after AKI

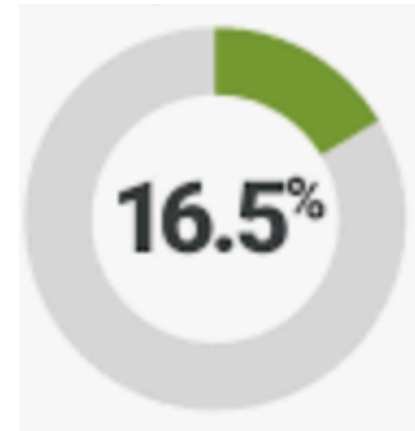
7 (23%) developed recurrent ICI-AKI



Gupta and Leaf, JITC, 2021

121 of the 429 patients (28.2%) with ICI-AKI
were rechallenged
~2mo after AKI

20 (16.5%) developed recurrent ICI-AKI



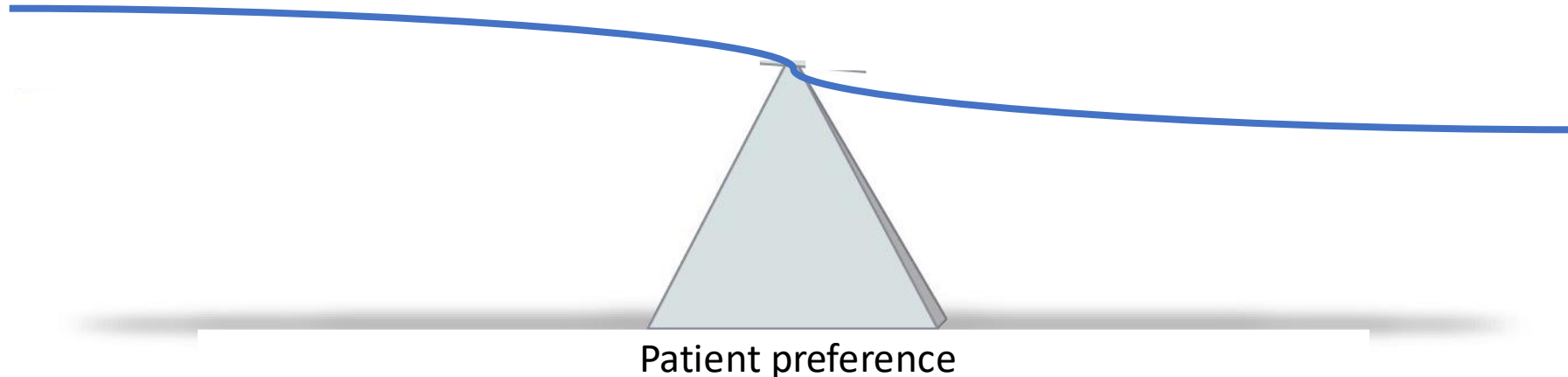
Considerations for speed of steroid taper and ICI rechallenge

Factors favoring quick taper and ICI rechallenge

- No other severe irAEs (myocarditis, myositis, pneumonitis, hepatitis, neurologic irAE)
- AKI recovers quickly with steroids
- Other AIN-triggers can be discontinued
- AIN > Other immune-mediated glomerulonephritis
- Newly starting therapy
- Melanoma and ICI sensitive tumors (microsatellite unstable)

Factors favoring longer steroid course and avoiding ICI rechallenge

- AKI slowly recovering
- **Adjuvant therapy** with long expected life expectancy



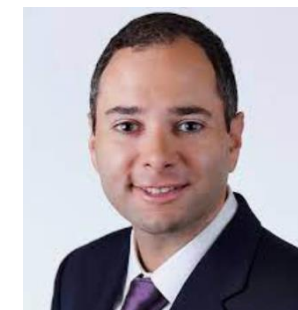
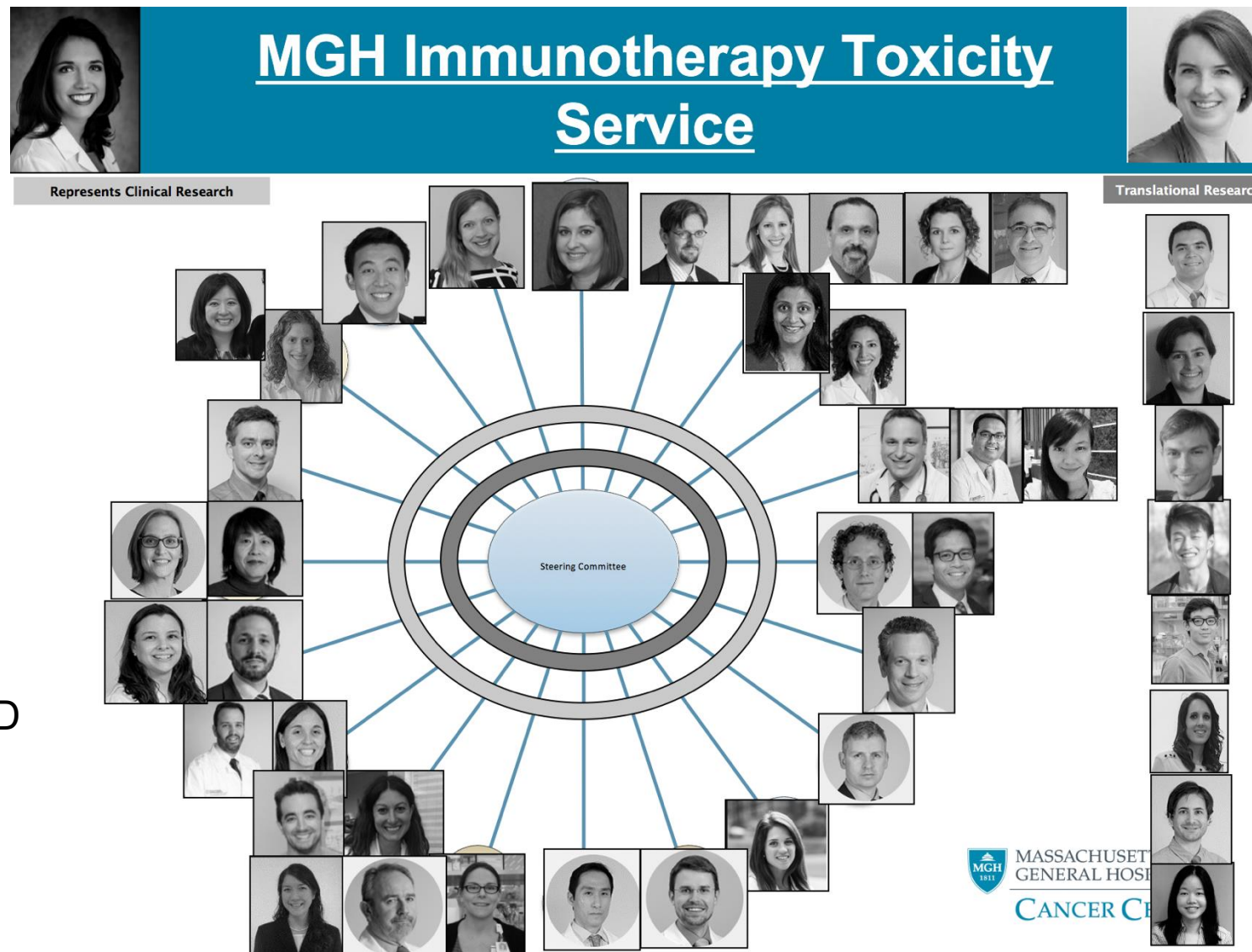
Trends: Combination Therapy, Earlier Stage of Disease

2011	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
March 25, 2011 Ipi for unresectable or metastatic melanoma	September 4, 2014 Pembro for unresectable or metastatic melanoma	October 1, 2015 Nivo + Ipi for melanoma (BRAF V600 wild-type)	May 16, 2016 Nivo for cHL	February 1, 2017 Nivo for urothelial carcinoma	February 16, 2018 Durva for unresectable NSCLC	February 15, 2019 Pembro in adjuvant melanoma	January 8, 2020 Pembro for high-risk bladder cancer	January 22, 2021 Nivo + Cabozantinib for RCC	March 4, 2022 Nivo + Chemo for NSCLC	January 26, 2023 Pembro for NSCLC	January 12, 2024 Pembro + chemoRT for stage III-IVA cervical cancer	March 19, 2025 Pembro for HER2+ gastric/GI adenocarcinoma w/ PD-L1 (CPS ≥1)
	December 23, 2014 Nivo for unresectable or metastatic melanoma	October 2, 2015 Pembro for NSCLC	May 17, 2016 Atezo for urothelial carcinoma	March 14, 2017 Pembro for cHL	April 16, 2018 Nivo + Ipilimumab for RCC	March 8, 2019 Atezo + Nab-Taxol for TNBC	March 11, 2020 Nivo + Ipi for HCC	February 2, 2021 Cemil for advanced basal cell carcinoma	March 18, 2022 Nivo + Relatib for melanoma	February 9, 2023 Dostar for endometrial cancer	March 5, 2024 Nivo + Gem/Cis for urothelial carcinoma	
		October 9, 2015 Nivo for second line NSCLC	August 4, 2016 Pembro for SCCHN	March 22, 2017 Avelu for MCC	June 12, 2018 Pembro for cervical cancer	March 18, 2019 Atezo + Carbo/Etop in SCLC	March 30, 2020 Durva + Etoposide + Carbo or Cisplatin for ES-SCLC	February 22, 2021 Cemil for NSCLC	March 21, 2022 Pembro for endometrial carcinoma	March 22, 2023 Retifan for MCC	June 14, 2024 Durva + Chemo for dMMR endometrial cancer	
		October 28, 2015 Ipi for melanoma with complete resection	October 17, 2016 Atezo for NSCLC	April 30, 2017 Durva for urothelial carcinoma	June 13, 2018 Pembro for PMBCL	April 11, 2019 Pembro for stage 3 NSCLC	May 15, 2020 Nivo + Ipi for NSCLC	March 22, 2021 Pembro + Chemo for esophageal carcinoma	May 27, 2022 Ipi + Nivo for esophageal SCC	April 3, 2023 Enfort + Pembro for urothelial carcinoma	June 17, 2024 Pembro + Chemo for endometrial carcinoma	
		November 13, 2015 Nivo for second line squamous NSCLC	October 24, 2016 Pembro for first line NSCLC	May 8, 2017 Avelu for urothelial carcinoma	July 10, 2018 Nivo + Ipi for MSI-H	April 19, 2019 Pembro + Axitinib for RCC	May 18, 2020 Atezo for NSCLC	April 16, 2021 Nivo + Chemo for gastric cancer	May 27, 2022 Nivo + Chemo for esophageal SCC	July 31, 2023 Dostar + Chemo for endometrial cancer	August 1, 2024 Dostar + Chemo for endometrial cancer	
		November 23, 2015 Nivo for RCC	November 9, 2016 Nivo for SCCHN	May 9, 2017 Pembro for non-squamous NSCLC	August 17, 2018 Nivo for SCLC	May 14, 2019 Avelu + Axitinib for 1st line RCC	May 25, 2020 Nivo + Ipi + Chemo for NSCLC	April 22, 2021 Dostar for endometrial cancer	September 2, 2022 Durva for bile duct cancer	October 13, 2023 Nivo for stage IIB/IIC melanoma	August 15, 2024 Durva + Chemo for resectable NSCLC	
		December 18, 2015 Pembro for unresectable melanoma		May 17, 2017 Pembro for urothelial carcinoma	August 20, 2018 Pembro + Platinum in 1st line, NSCLC	June 10, 2019 Pembro for metastatic HNSCC	May 29, 2020 Atezo + Beva for untreated HCC	May 5, 2021 Pembro + Chemo for gastric cancer	October 21, 2022 Treme + Durva for HCC	October 16, 2023 Pembro + Chemo for resectable NSCLC	September 12, 2024 Atezo + Hyaluronidase SC	
				May 22, 2017 Pembro for colorectal cancer and other solid tumor	November 9, 2018 Pembro in HCC	June 17, 2019 Pembro for metastatic SCLC	June 10, 2020 Nivo for esophageal squamous cell	May 20, 2021 Nivo for esophageal	November 8, 2022 Cemip + Chemo for NSCLC	October 27, 2023 Toripa + Gem/Cis for NPC	September 17, 2024 Pembro + Chemo for malignant pleural mesothelioma	
				August 1, 2017 Nivo for colorectal cancer	December 6, 2018 Atezo + Beva + Taxol + Carbo for NSq NSCLC	July 30, 2019 Pembro for esophageal squamous cell	June 16, 2020 Pembro for TMB-H	July 21, 2021 Pembro + lenvatinib for endometrial cancer	November 10, 2022 Treme + Durva + Chemo for NSCLC	October 31, 2023 Pembro + Chemo for bile duct cancer	October 3, 2024 Nivo + Chemo for resectable NSCLC	
				September 22, 2017 Pembro for gastric cancer	December 19, 2018 Pembro in merkel	September 17, 2019 Pembro + Lenvatinib for endometrial carcinoma	June 24, 2020 Pembro for cutaneous squamous cell carcinoma	July 27, 2021 Pembro + Chemo for breast cancer	December 15, 2023 Pembro + enfortumab vedotin-cjfv for urothelial cancer	November 16, 2023 Pembro + Chemo for gastric cancer	December 4, 2024 Durva for LS-SCLC	
				December 20, 2017 Nivo for metastatic melanoma with complete resection		September 27, 2019 Pembro for endometrial carcinoma	June 29, 2020 Pembro for colorectal cancer	August 17, 2021 Dostar for all dMMR tumor	December 27, 2024 Nivo + hyaluronidase-mhy for SC injection for solid tumors		December 13, 2024 Cosibellmab for cutaneous SCC	
						December 3, 2019 Atezo + Beva + Taxol + Carbo for NSq NSCLC	June 30, 2020 Avelu for bladder cancer	August 19, 2021 Nivo for urothelial cancer				
							July 30, 2020 Atezo + Cobimetinib + Vemurafenib in melanoma	October 13, 2021 Pembro for cervical cancer				
							October 2, 2020 Nivo + Ipi for mesothelioma	October 15, 2021 Atezo for NSCLC				
								November 17, 2021 Pembro for RCC				
								December 3, 2021 Pembro for Stage IIB/IIC Melanoma				
							November 13, 2020 Pembro + Chemo for advanced breast cancer					

**113 FDA
APPROVED
INDICATIONS
AS OF
MARCH 2025**

Sise Lab:

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Leyre Zubiri, MD
Si Yuan Khor, MD
Jiaxuan Lyu, MD
Harish Seethapathy, MD
Sophia Zhao, MD, PhD



David Leaf, MD



Shruti Gupta, MD



Dennis Moledina, MD

Thank you!

Email questions to msise@mgb.org