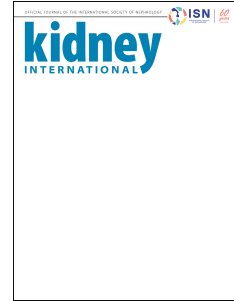


Journal Pre-proof



Diagnosis and Management of Immune Checkpoint Inhibitor-Associated Nephrotoxicity: A Position Statement from the American Society of Onco-nephrology

Sandra M. Herrmann, Ala Abudayyeh, Shruti Gupta, Prakash Gudsoorkar, Nattawat Klomjit, Shveta S. Motwani, Sabine Karam, Verônica T. Costa E Silva, Sheikh B. Khalid, Shuchi Anand, Jaya Kala, David E. Leaf, Naoka Murakami, Arash Rashidi, Rimda Wanchoo, Abhijat Kitchlu

PII: S0085-2538(24)00724-5

DOI: <https://doi.org/10.1016/j.kint.2024.09.017>

Reference: KINT 4005

To appear in: *Kidney International*

Received Date: 7 June 2024

Revised Date: 9 September 2024

Accepted Date: 13 September 2024

Please cite this article as: Herrmann SM, Abudayyeh A, Gupta S, Gudsoorkar P, Klomjit N, Motwani SS, Karam S, Costa E Silva VT, Khalid SB, Anand S, Kala J, Leaf DE, Murakami N, Rashidi A, Wanchoo R, Kitchlu A, Diagnosis and Management of Immune Checkpoint Inhibitor-Associated Nephrotoxicity: A Position Statement from the American Society of Onco-nephrology, *Kidney International* (2024), doi: <https://doi.org/10.1016/j.kint.2024.09.017>.

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Diagnosis and Management of Immune Checkpoint Inhibitor-Associated Nephrotoxicity: A Position Statement from the American Society of Onco-nephrology

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Manuscript Word Count: 4247

Abstract Word Count: 148

Tables: 2 Figures: 3 Boxes: 2

Short title: Immune checkpoint inhibitor nephrotoxicity

Keywords: immune checkpoint inhibitors, acute kidney injury, acute interstitial nephritis, immune-related adverse event

Abstract

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer and are now the backbone of therapy for several malignancies. However, ICIs can cause a spectrum of renal immune-related adverse events including acute kidney injury (AKI), most commonly manifesting as acute interstitial nephritis (AIN), though glomerular disease and electrolyte disturbances have also been reported. In this position statement by the American Society of Onco-nephrology (ASON), we summarize the incidence and risk factors for ICI-AKI, pathophysiological mechanisms and clinicopathological features of ICI-AKI. We also discuss novel diagnostic approaches and promising biomarkers for ICI-AKI. From expert panel consensus, we provide clinical practice points for the initial assessment and diagnosis of ICI-AKI, management and immunosuppressive therapy, and consideration for re-challenge with ICI following AKI episodes. In addition, we explore ICI use in special populations such as kidney transplant recipients and propose key areas of focus for future research and clinical investigation.

Introduction

Immune checkpoint inhibitors (ICIs) have dramatically transformed the landscape of cancer therapy since they were first introduced in 2011. There are currently 10 ICIs that are used for over 20 different cancer types (**Supplementary Table S1**), with new indications and combinations continuing to emerge rapidly for both the adjuvant and neoadjuvant settings. While ICIs are highly effective at activating the immune system and inducing durable tumor responses, they are also associated with autoimmune toxicities, termed immune-related adverse events (irAEs). Acute kidney injury (AKI) directly attributed to ICIs (ICI-AKI) is a well-recognized toxicity that can occur in patients receiving these therapies. ICI-AKI has important repercussions, as it can lead to discontinuation of potentially life-saving therapy and prolonged courses of immunosuppression. ICI-AKI most commonly presents as ICI-associated acute interstitial nephritis (ICI-AIN),¹⁻⁴ though other kidney-related complications can occur, including glomerular diseases, and other electrolyte abnormalities.^{2,5-7} Over the last decade, our understanding of the incidence, clinical features, and risk factors for ICI-AKI has grown considerably, and data has emerged regarding management approaches and outcomes. In this position statement by the American Society of Onconephrology (ASON), we summarize the epidemiology, pathophysiological mechanisms and clinicopathological features of ICI-AKI. We also discuss novel diagnostic approaches, including promising biomarkers and imaging studies.^{3,8,9} We provide clinical practice points for: 1) the initial assessment and diagnosis of ICI-AKI; 2) management and immunosuppressive therapy; and 3) consideration for re-challenge with ICI following AKI episodes. These clinical practice points reflect the consensus of the ASON Position Statement Committee, which convened a core group of international content experts on ICI-AKI. At present, the current state of evidence pertaining to ICI-AKI (i.e., primarily observational cohorts and series) does not allow for graded recommendations from evidence synthesis. However, the presented clinical practice points were derived from an iterative, consensus approach based on the expert opinions of the ASON Position

Statement panel. Lastly, we explore ICI use in special populations such as kidney transplant recipients, discuss existing knowledge gaps, and propose key areas of focus for future research and clinical investigation.

Pharmacokinetics and AKI Pathophysiology

ICIs are primarily humanized or human immunoglobulin G1 (IgG1) kappa or IgG4 kappa¹⁰ with molecular weights between 140-150 kDa.¹¹ Due to their large size, they have a small volume distribution and linear clearance.¹² Kidney and liver dysfunction do not affect ICI clearance, and they are not dialyzable.¹³ Half-life is long and ranges from 7 to 27 days.^{12,14} ICIs disrupt the normal immune regulatory checkpoints, leading to an activation of T cells against tumor cells. This can inadvertently target kidney tissue, leading to an enhanced immune response and causing kidney inflammation and injury (**Figure 1**). Molecular mimicry between antigens expressed in tumor cells and renal tubular cells may also contribute to AKI.^{14,15} Additionally, the production of autoantibodies and the formation of immune complexes can further exacerbate renal damage in the context of ICI therapy.^{14,16}

Epidemiology: Incidence and Risk Factors for AKI During ICI therapy

Overall, the incidence of AKI from any cause in patients receiving ICI therapy can be as high as 17%^{3,4,17}; however, AKI directly attributed to the ICI, or ICI-AKI, is estimated to be 3%–5%.^{1,3,4,18,19} Notably, among patients undergoing combination therapy with anti-T-lymphocyte-associated antigen 4 (CTLA-4) and anti-programmed death-1 (PD-1) the incidence of ICI-AKI is the highest reaching up to 5%,^{16,20} while with PD-1 inhibitor monotherapy, the reported incidence is approximately 2%.²¹ The lowest incidence rate of ICI-AKI is with anti-programmed death-1 ligand

(PD-L1) being less than 1%.²² Of note, most of the data collected on ICI-AKI incidence is based on retrospective diagnoses and the true incidence may be higher and the clinical course may be milder if all AKI were considered. Other causes of AKI, including volume depletion, obstructive AKI and acute tubular injury likely comprise a significant proportion of AKI that is not due to kidney immune-related adverse events. Risk factors identified for ICI-AKI include chronic kidney disease (CKD) at baseline, combination treatment with anti-CTLA-4 and anti-PD-1 or anti-PD-L1 agents, prior or concomitant extrarenal immune-related adverse events (irAEs) and concomitant use of AIN-associated drugs such as proton pump inhibitors (PPI).^{1,17,18} Of these, concomitant use of PPI remains a common and potentially modifiable risk factor.^{3,17,20} One meta-analysis showed that among patients on ICI treatment who were concomitantly receiving PPIs, the risk of AKI was significantly higher compared to non-PPI use, with a pooled OR of 1.84 (95% confidence interval [CI]: 1.16 - 2.90).²³ The mechanism is unclear, but it is postulated that PPIs activate T cells that become latent over time, and exposure to ICIs leads to the reactivation of these T cells, loss of tolerance, and ICI toxicity.^{15,20,24} Another postulated mechanism is that PPIs may result in the formation of drug-associated haptens that are transported to kidney and metabolized by tubular epithelial cells (**Figure 1**). Antigen-antibody complexes and/or metabolites may then be presented to dendritic cells located in kidney interstitial tissue, leading to subsequent T-cell-mediated immune responses.²⁵

DIAGNOSIS OF ICI-AKI

Clinical Features and Renal Pathologies in ICI-AKI

The median time between ICI initiation and ICI-AKI onset is typically between 14-16 weeks, though this is variable, with some patients developing ICI-AKI as early as 1 week after ICI initiation, and others more than 1 year later.^{1,3,18} With respect to ICI-AKI severity, nearly 50% of patients develop stage 3 AKI, and of these 16% (8% overall) require renal replacement therapy.

Prior or concomitant extrarenal irAEs occur in 57% of the cases, most commonly skin and gastrointestinal.¹ Clinical features of ICI-AKI, including serum and urine laboratory studies, are non-specific. Hematuria and pyuria are found in 40% and 60%, respectively; however, only 17% demonstrate significant eosinophilia (≥ 500 eosinophils/ μl). About 60% have a urine protein-to-creatinine ratio ≥ 0.3 g/g.

ICI-AIN is the most common kidney pathology and accounts for approximately 90% of cases in the largest published multicenter cohort.¹ Though rare, several glomerular diseases have been described in multiple case reports and series.^{5,26} A systematic review of 45 biopsy-proven cases of glomerular disease found that the most common types of glomerular lesions were pauci-immune glomerulonephritis/renal vasculitis (27%), podocytopathies including minimal change disease and FSGS (24%), and C3GN (11%).²⁶ Other forms of glomerulonephritis have been reported less frequently, including IgA nephropathy, immune complex glomerulonephritis, AA amyloidosis, membranous nephropathy, anti-glomerular basement membrane disease, and thrombotic microangiopathy.^{5,26-29} To date, the overall incidence of glomerular disease associated with ICI therapy remains unclear.³⁰

Electrolytes Abnormalities

ICI use can lead to multiple electrolyte abnormalities (**Table 1**) among which hyponatremia is the most common.³⁰ While data from randomized control trials (RCTs) report a relatively low incidence of 1-9%,^{21,31} real-world retrospective reports suggest a much higher percentage of 54-60%.^{2,7} Various mechanisms have been proposed, with the most common being the syndrome of inappropriate antidiuresis (though it may be challenging to determine whether this is mediated by malignancy versus therapy).² Other etiologies are mostly associated to immune-induced endocrinopathies such as hypophysitis, adrenalitis and thyroiditis.^{24,30} Endocrinopathies are rarely reversible and require long-term therapy. Hypokalemia is the second most reported electrolyte

abnormality⁷, and can result from gastrointestinal losses in the setting of colitis,³² or renal losses due to proximal or distal renal tubular acidosis.^{6,33,34} ICI-related hypercalcemia is the third most common reported electrolyte abnormality noted in a recent query of the FDA Adverse Event Reporting System database.⁷ Four potential reported mechanisms were considered: endocrine disease-related, sarcoid-like granuloma, humoral hypercalcemia due to parathyroid-related hormone and hyper-progressive disease following ICI initiation.^{35,36} It is important to note, however, that these reported mechanisms may not be necessarily directly related to ICI use. Finally, hypocalcemia was found to be relatively frequent in patients on PD-1 inhibitors with a pooled incidence rate of hypocalcemia at 1%,^{21,31} with hypoparathyroidism as the possible underlying mechanism. This could occur either because of immune-mediated damage or in response to calcium-sensing receptor-activating antibodies.³⁰

Biomarkers

Currently, there are few clinically available biomarkers that can aid in the diagnosis of kidney-related immune-related adverse events. A single-center study from the Mayo Clinic evaluated 52 patients with AKI during ICI therapy. A total of 37 patients met clinical criteria or biopsy-proven ICI-AIN. Patients with ICI-AIN had 10-fold higher median serum C-reactive protein (CRP) concentrations and urine retinol binding protein-to-creatinine ratio compared with 10 controls with AKI due to other causes.³ In a similar comparison, Sise et al. found that soluble interleukin-2 receptor (sIL2R) may help to discriminate patients with ICI-AIN (n = 24) from non-ICI-treated patients with AKI due to hemodynamic causes (n = 6) and ICI-treated controls without AKI (n = 10).⁹ sIL2R performed better than flow cytometry-based measures of T and B cells (e.g., absolute CD8 T cell counts). However, both sIL2R and CRP are nonspecific markers of inflammation and can be elevated in the presence of extra-renal irAEs, and potentially other inflammatory states.

Both these studies require replication and external validation in larger series. Furthermore, other promising biomarkers that are not yet clinically available have been reported to be elevated in the urine of patients with biopsy-proven AIN, including tumor necrosis factor- α (TNF- α), interleukin-9 (IL-9), and CXC motif ligand 9 (CXCL-9).³⁷ One prospective pilot study from Mayo Clinic involving 24 patients with ICI-AKI found that median urinary TNF- α levels were approximately 2-times higher in patients with ICI-AIN as compared to patients with non-ICI AKI, with an area under the curve (AUC) of 0.81 (95% CI 0.61-1.00).⁸ In the largest study to date assessing urinary biomarkers in drug-induced AIN, Moledina et al. found that CXCL-9 was 7.5-fold higher among patients with AIN, and the AUC for CXCL-9 was 0.94 (0.86–1.00) for diagnosing AIN overall. However, only two patients in this study had ICI-AIN. Therefore, these findings need to be tested in a larger cohort of patients with ICI-AKI.³⁸

In addition to urine and serum biomarkers, histological stains may be helpful in the diagnosis of ICI-AIN. One study showed that positive PD-L1 staining in tubular epithelial cells may help differentiate PD-1-related AIN from AIN due to other causes.³⁹ In another study using imaging mass cytometry, it was observed that the abundance of specific T cells such as CD4+ memory T cells, T helper cells, and dendritic cells may aid in differentiating AKI caused by ICI-AIN versus acute tubular necrosis/injury (ATN/ATI).⁸ However, all these studies require further validation before broader clinical use.

Imaging

Data are emerging on the use of positron emission tomography (PET) to diagnose ICI-AKI non-invasively. Specifically, case reports initially described increased cortical F¹⁸-fluorodeoxyglucose (FDG) uptake in patients with ICI-AKI.⁴⁰⁻⁴³ However, the diagnosis of ICI-AKI in all but one case was clinical and not biopsy-proven.⁴³

A single-center case series of 14 patients with biopsy-proven disease, with paired PET-CT scans at baseline and at the time of ICI-AKI, found the mean FDG standardized uptake value (SUV_{mean}) in the kidney parenchyma increased from 3.4 to 4.4 ($P = 0.051$).⁴⁴ However, some patients in this series had biopsies reporting ATN (without concomitant AIN). Moreover, there was no control group to assess whether similar increases in SUV would have been observed in patients with AKI from alternative etiologies.

To address these limitations, a recent multicenter study of 53 patients was conducted, consisting of 9 patients with ICI-AKI, 24 with AKI from non-ICI causes, and 20 ICI-treated patients but without AKI.⁴⁵ Among those with ICI-AKI, the SUV_{mean} increased by a median of 57.4% from baseline to follow-up. In contrast, it increased by only 8.5% in patients with AKI from non-ICI causes and was unchanged in patients receiving ICIs without AKI with an AUC for the differentiation of ICI-AKI from the control groups based on change in SUV_{mean} was 0.97.

Although these data suggest that PET-CT could aid in diagnosing ICI-AKI noninvasively, larger studies are needed to confirm these findings before routine use of PET-CT can be endorsed. The accuracy of this measurement is complicated by several confounding factors, including time to imaging after FDG injection, burden of metastatic disease taking up FDG, dose of FDG injected, and fasting state.

Indications for Kidney Biopsy

The gold standard for the diagnosis of ICI-AIN or ICI-associated glomerular diseases is a kidney biopsy. While certain guidelines may have different recommendations regarding kidney biopsy and initiating empiric glucocorticoids, if there is a lack of alternative causes of AKI (which cannot be completely ruled out without a kidney biopsy),^{46,47} we recommend that kidney biopsy should be strongly considered and performed in ICI-treated patients who develop Kidney Disease:

Improving Global Outcomes (KDIGO) stage 2 or 3 AKI (where feasible, and on a case-by-case basis, after risk and benefits are discussed with patient). We only would suggest foregoing kidney biopsy if there were a more plausible alternative etiology for the AKI (e.g., obstructive uropathy or pre-renal causes that respond rapidly to initial management) or an absolute contraindication to performing a kidney biopsy) (See **Table 2** for comparison). Kidney biopsy is particularly important when patients are receiving more than one nephrotoxic anti-neoplastic agent (e.g., platinum-based therapy, pemetrexed, gemcitabine), therefore AIN cannot be differentiated from ATN/ATI or other entities like thrombotic microangiopathy without a biopsy.⁴⁸ Patients who develop stage 1 AKI should be evaluated for reversible causes of AKI, such as prerenal azotemia, urinary obstruction, or drug-induced injury from agents other than ICIs, and ICI therapy should be held until AKI has resolved. Patients with persistent stage 1 AKI, especially those with associated renal tubular acidosis, unexplained proteinuria or hematuria, or other persistent electrolyte abnormalities, should be referred to nephrology for consultation and consideration of a kidney biopsy (**Box 1, Figure 2**).⁶

Box. 1: Clinical Practice Points for Diagnosis and Initial Assessment of ICI-AKI

Diagnosis and Assessment of Suspected ICI-AKI

- All patients with AKI during ICI therapy should undergo history and physical examination (including volume status assessment) to evaluate for etiology of kidney injury. Urinalysis and microscopy (assessing for pyuria and white blood cell casts), complete blood count, electrolytes, urine albumin-to-creatinine ratio, urine protein-to-creatinine ratio, and abdominal imaging (to rule out hydronephrosis) should be obtained.

- All patients with suspected ICI-associated AKI with stage 2 or greater severity should be referred to a nephrologist for further assessment and shared management with oncology clinicians.
- Kidney biopsy should be strongly considered when feasible in ICI-treated patients who develop stage 2 or 3 AKI, if alternative causes are ruled-out (e.g., obstructive uropathy or pre-renal causes that responded rapidly to initial management) and there is no absolute contraindication (e.g. patient's preferences or increased bleeding risk). This is particularly important when patients are receiving more than one nephrotoxic anti-neoplastic agents (e.g. platinum-based chemotherapy, pemetrexed or vascular endothelial growth factor-inhibitors), have poor initial response to glucocorticoids therapy, or have urine studies suggestive of glomerular disease (e.g., red blood cell casts, high-grade proteinuria). In patients for whom kidney biopsy is not feasible or absolute contraindications exist, an empiric course of glucocorticoids may be considered (see Management section below).

MANAGEMENT

Treatment of ICI-AKI

The treatment of ICI-AKI depends upon the severity and histopathological subtype of injury (i.e., if injury is known to be caused by AIN versus glomerular pathology). All patients require immediate cessation of drugs that are known to cause AIN (e.g., non-steroidal anti-inflammatory drugs, PPI, antibiotics) and a comprehensive evaluation for alternative causes of AKI. The optimal management is uncertain, with some recommending a pause in further ICI therapy, while others advocating for its continuation. Arguments in favor of continuing ICI therapy include the absence

of studies demonstrating the benefits of interrupting ICI alone and the known prolonged effects of immunotherapy even after discontinuation.⁴⁹ However, in practice, some justify holding ICI to eliminate a persistent trigger for inflammation until the evaluation is complete and a kidney function trend is established.²⁴

For patients with stage 2 AKI or higher severity and strong clinical suspicion of ICI-AKI, immediate cessation of ICI therapy is advised, followed promptly by a plan for a kidney biopsy and the initiation of glucocorticoids (**Box 2, Figure 2**). It is important to treat patients as soon as ICI-AKI is suspected without waiting for results of the biopsy, as earlier initiation of glucocorticoids (within 3 days) is more than twice as likely to be associated with kidney recovery compared to delayed initiation, and this, in turn, is associated with increased overall survival.^{1,50} Additional immunosuppressants are generally needed for patients with glomerulonephritis on kidney biopsy. We recommend starting prednisone at a dose of 0.8-1 mg/kg for ICI-AKI.¹⁹ We suggest not exceeding a prednisone dose above 60-80 mg daily depending on the patient's body habitus in most patients. Patients with AKI requiring kidney replacement therapy (KRT) at the diagnosis may be treated with intravenous pulse methylprednisolone 0.5–1 g daily for up to 3 days before the beginning of prednisone, although this practice has not been systematically evaluated in this population. The total duration of glucocorticoid treatment is variable but ranges from 6-8 weeks in most studies, with taper starting after the first to second week, if kidney function improves with glucocorticoid therapy.²⁴ One retrospective study suggested that shorter glucocorticoid taper duration (<28 days) may result in comparable outcomes to longer tapers. This practice may be considered only in patients without severe ICI-AKI that are likely to benefit from shorter duration of immunosuppressive therapy.⁵¹ These findings require confirmation by prospective, randomized studies that include patients with biopsy-proven ICI-AIN, as ICIs have variable half-lives and this may potentially influence the optimal duration of glucocorticoid taper.^{14,15} Among patients with biopsy proven-AIN with relapsing ICI-AKI after adequate treatment with glucocorticoids, addition

of a TNF- α inhibitor, such as infliximab 5 mg/kg, can be considered as a one-time dose or monthly, as needed, if AKI persists.^{1,52,53} The rationale for use of TNF- α blockade as a glucocorticoid-sparing agent is based upon the expert opinion of the authors and previous case-series and warrants further investigation.⁵³

Limited data exists to guide treatment of steroid-refractory ICI-AIN. If a kidney biopsy was not part of the initial diagnosis, then confirmation of the histopathological diagnosis should be obtained, where possible. In the largest retrospective study that included 22 patients treated with alternate immunosuppressants, 11 patients received mycophenolate mofetil (5 recovered), 5 received infliximab (3 recovered) and 2 received tocilizumab (1 recovered).¹ Recent case series suggest that infliximab can be an efficacious treatment for relapsing or refractory ICI-AIN.⁵³ We advise against the use of azathioprine, cyclophosphamide, or cyclosporine in ICI-AIN due to a lack of supporting data. Appropriate prophylaxis for pneumocystis jirovecii pneumonia is advised for patients receiving glucocorticoid therapy (equivalent prednisone dose >20 mg/daily for over 4 weeks), infliximab or other non-glucocorticoid immunosuppressants. Avoiding AIN-associated antibiotics such as sulfa-containing drugs is preferable. We also would recommend the use of H2 blockade instead of PPIs for those patients requiring gastrointestinal prophylaxis.

Among patients who develop glomerulonephritis, in addition to stopping drugs that may cause vasculitis (e.g., hydralazine), we suggest using non-steroidal immunosuppressive therapy, such as rituximab, in combination with glucocorticoids. Rituximab targets pathogenic B-cells, reducing chemokine production and limiting endothelial injury. This appears to impact the irAE without interfering with anti-neoplastic effects of ICI.^{54,55} In a series of five patients diagnosed with ICI-induced renal vasculitis, treatment with rituximab resulted in partial to complete kidney recovery and no vasculitis relapse.⁵⁶ No specific treatment exists for concurrently occurring TMA, although similar rituximab-based regimens have been used with limited success.^{29,57} Use of complement blockade may be a viable treatment option in moderate to severe cancer drug-induced TMA, but

only with evidence of abnormal activation of alternate complement pathway or genetically identified complement pathway disorder.⁵⁸ In a recent study, TMA in the setting of ICIs was associated with the lowest rate of kidney function recovery.²⁹

Box. 2: Clinical Practice Points for Management and Immunosuppression for ICI-AKI

Management of ICI-AKI

- Patients with suspected ICI-AKI should have ICI agents held after discussion with oncology.
- Patients with suspected ICI-AKI should have immediate cessation of drugs that are typically associated with AIN and may potentiate risk during ICI therapy (e.g., NSAIDs, PPI, antibiotics)
- Patients with AKI stage 2 or higher with biopsy-proven or strong clinical suspicion of ICI-AKI, should be promptly started on glucocorticoids (preferably within 3 days, as this is more likely to be associated with renal recovery). We suggest prednisone 0.8- 1 mg/kg equivalent daily (with maximum dose of 60-80 mg daily) in patients with stage 2-3 AKI. In patients with stage 3 AKI or dialysis-requirement, consider use of methylprednisolone 0.5-1g IV daily for up to 3 days followed by prednisone 0.8-1 mg/kg equivalent daily. Duration of glucocorticoids will depend on the acuity of the initial insult and kidney function trend, but generally requires 4-8 weeks of tapering therapy. The tapering can start as early as 1-2 weeks post glucocorticoid therapy if kidney function starts to improve. However, we recommend slowing the taper if serum creatinine increases while decreasing the steroids.

- Prophylaxis of pneumocystis jirovecii pneumonia should be considered for patients on high doses of glucocorticoid therapy for over 4 weeks (preferably not using antibiotics that are known to cause AIN (e.g. Trimethoprim-sulfamethoxazole). In cases of relapsing or refractory ICI-AKI use of glucocorticoid sparing agents such as infliximab can be considered.
- Treatment of glomerular disease associated with ICI therapy should be guided by multidisciplinary expert discussion and should be based on the specific glomerular disease present (as described in the main text).

Rechallenge with ICI

We recommend that rechallenge be considered once ICI-AKI resolves (and kidney function is close to baseline) on a case-by-case basis after joint discussions between oncology and nephrology. ICI rechallenge can be performed with or without low dose of glucocorticoids (prednisone 5-10 mg daily) depending on the severity of initial ICI-AKI and if other extra-renal irAEs are observed. The rationale for this recommendation stems from the largest study to date of patients with ICI-AKI, which included 429 patients with ICI-AKI, 121 of whom (28.2%) were rechallenged, of whom 48.8% were receiving low-dose glucocorticoids at the time of rechallenge. Of the 121 patients who were re-challenged, 42 (34.7%) patients had an initial stage 3 ICI-AKI prior to rechallenge, yet the rate of ICI-AKI recurrence was only 16%.¹ While the existing retrospective data on ICI rechallenge may be susceptible to selection bias, rechallenging patients with ICI after ICI-AKI may be reasonable for most patients. When ICI-AKI does recur, most patients respond to treatment with glucocorticoids.^{1,3}

We suggest carefully assessing patients' suitability and safety for ICI rechallenge, considering various factors such as the AKI severity, the specific type of kidney injury (AIN vs GN), the presence of concomitant AIN-associated drugs (e.g., PPI, NSAIDs, and antibiotics) that may be discontinued prior to re-challenge, the response to immunosuppressive therapy (complete, partial, or none), the cancer treatment goal (curative or palliative), whether the patient has a native or transplanted kidney, and the availability of alternative treatment options. Typically, patients experiencing mild to moderate AKI stage 1-2, exhibiting classic symptoms of AIN or having a biopsy proven ICI-AIN, and demonstrating a positive response to treatment (with serum creatinine levels returning to or nearing baseline) are deemed suitable for ICI rechallenge. This recommendation holds true regardless of other variables, provided there are no significant concomitant extra-renal toxicities (e.g., myocarditis) posing greater risks.⁵⁹

Among patients who have partial or no recovery (or dialysis dependence) from their initial episode of ICI-AKI or other complicating factors, the decision to rechallenge needs to be individualized. Among those who did not have a kidney biopsy for initial diagnosis, obtaining histopathological confirmation of diagnosis and understanding the pattern and severity of injury may be required to plan optimal modifications in treatment, for example, adding other immunosuppressants in a patient with glomerulonephritis triggered by ICI-AKI prior to rechallenge.

Patients who developed AKI with dual ICI therapy are generally rechallenged with anti-PD-1 agents alone.⁵⁹ To date, there are only observational studies supporting the concomitant use of glucocorticoids or other immunosuppressants (or switching ICI type/agent) to reduce the rate or severity of recurrence.^{1,3} Rechallenge in the setting of glomerulonephritis after effective treatment with rituximab has also been reported.⁶⁰ However, there are only observational studies which may be prone to selection bias, and therefore prospective studies, i.e. randomized clinical trials, are in need in this area.

Box. 3: Clinical Practice Points for Re-challenge with ICI Therapy After ICI-AKI*Re-challenge with ICI Therapy*

- If re-challenge with ICI therapy is indicated, this should be considered after multidisciplinary discussion with patient in a shared decision-making framework. Re-challenge should be considered for the majority of patients who demonstrate good response to ICI therapy (or have malignancy generally suspected to be responsive to immunotherapy, e.g. melanoma), those who did not have severe or life-threatening immune-related adverse events, those with mild or fully recovered AKI, or those with limited alternative therapeutic options.
- Potential precipitants for AIN (e.g., PPIs, NSAIDs, antibiotics) should be held prior to re-challenge. There may be consideration for low-dose prednisone (e.g. prednisone 5-10 mg daily) at the time of re-challenge for those who undergo early re-challenge (i.e., within 8 weeks of AKI) or those with severe initial AKI events, on a case-by-case basis.

ICI use in Kidney Transplant Recipients.

Kidney transplant recipients (KTR) experience 3-10-fold higher risk of cancer post-transplant due to long-term immunosuppression, and cancer is a leading cause of death in KTR.⁶¹ Using ICIs in KTR is challenging due to the concerns for acute kidney allograft rejection and the efficacy concerns in the setting of concurrent use of immunosuppression. Immune checkpoints (including PD-1 and CTLA-4) may have critical roles in maintaining transplant allograft tolerance. Thus, while ICIs are intended to enhance tumor immunity, they may alter existing allograft tolerance. Following

the initial case reports of kidney transplant recipients receiving CTLA4 and PD-1 inhibitors,^{62,63} several cohort studies and meta-analyses estimated the risk of acute allograft rejection rate as high as 30-40%.^{21,64,65,66} Both pure T-cell mediated rejection (TCMR) and mixed antibody-mediated rejection (ABMR) are common, and 65% resulted in allograft failure requiring dialysis. Mammalian target of rapamycin (mTOR) inhibitor use and being on more than two immunosuppressants are associated with a lower risk of rejection.⁶⁵ Immunosuppression strategies with the dual aims of avoiding allograft rejection and maintaining the tumor response represents an unmet need. An index case report suggested a combination of mTOR inhibitor and dynamic steroid use as an effective immunosuppression regimen for these goals.⁶⁷ Three prospective trials studied the safety and efficacy of ICI in KTR (**Supplementary Table S2**).⁶⁸⁻⁷⁰ Maintaining immunosuppression or using the combination of tacrolimus and glucocorticoid therapies led to a 10-25% rejection rate.^{68,69} In the CONTRAC-1 study, where the combination of mTOR inhibitor and dynamic glucocorticoids was used in 12 KTR with metastatic cutaneous squamous cell carcinoma treated with cemiplimab, there was no acute rejection with an objective response rate of 45%.⁷⁰ Mechanisms of allograft rejection in ICI are currently under investigation. The particular importance of mTOR pathway and pre-existing allospecific CD8 T cells in ICI-associated rejection has been suggested, but requires further elucidation.^{71,72} Overall, more data is needed to investigate the optimal immunosuppression regimen for balancing allograft tolerance and anti-tumor responses for KTR.

ICI use in Patients with Advanced CKD and End Stage of Kidney Disease (ESKD)

The mechanism of ICI clearance is through proteolytic degradation and receptor-mediated endocytosis which allows its use in patients with advanced CKD or ESKD.^{24,73} Therefore, there is no contraindication for its use in patients with significant impairment of renal function. Prior case

reports and series have suggested that ICIs are safe to use in patients with ESKD with similar incidence of immune-related adverse events as compared with the general population.^{13,74} However, close monitoring is warranted, especially in patients with CKD as the development of AKI may lead CKD progression⁷⁵ and increased mortality.^{76,77}

Gaps and Future Directions

Several non-invasive markers show promise for ICI-AKI, including urinary cytokines such as CXCL9, TNF- α , INF- γ , IL-2, and IL-9^{8,37,38,49} however, these markers have not yet been validated in large scale studies. Additionally, studies on tertiary lymphoid signatures (TLS) and immune cell phenotype of the kidney tissue microenvironment in patients with ICI-AIN may help distinguish ICI-AKI and AKI from other causes.^{5,8,26,78} In addition to sensitive and specific biomarkers, there is also a need to understand the mechanistic underpinnings of ICI-AKI with animal models. While observational studies suggest a shorter duration of glucocorticoid treatment may be safe,⁵¹ these findings need to be confirmed with randomized clinical trials. Additionally, while most cases of ICI-AIN respond to glucocorticoids, the role of steroid-sparing agents (e.g., infliximab, tocilizumab) as either up-front immunosuppression, adjunct or salvage therapy should also be explored. Robust data is also lacking in kidney transplant patients with regards to the risk-benefit evaluation of using ICI and optimization of immunosuppressive medications.

Box. 4: Identified Priorities for Research Related to ICI-AKI*Future Research Priorities*

- The role of additional non-invasive approaches with ICI-AKI diagnosis, including use of serum and urine biomarkers requires additional investigation. Similarly, use of imaging studies, e.g. FDG-PET imaging needs to be tested in larger studies
- Use of second-line immunosuppression as glucocorticoids-sparing agents require further assessment for efficacy for kidney recovery, impact on cancer outcomes and additional safety/tolerability outcomes
- Larger prospective studies are needed to guide consideration of re-challenge with ICI therapy, including patient selection, risk of recurrent AKI and impact on cancer outcomes

Conclusions

As the use of ICI therapies continues to grow, it is critical that oncologists and nephrologists be aware of their complications and how to manage kidney irAEs. Despite promising non-invasive biomarkers studies emerging in the literature, these need validation in larger studies. Therefore, kidney biopsy continues to be the gold standard for the diagnosis of ICI-AKI. The mainstay of therapy remains glucocorticoids in most cases, but steroid-sparing agents such as infliximab may be necessary for refractory or relapsing cases. We recommend that rechallenge be considered in selected patients after AKI recovery, in whom ICI treatment is considered the optimal cancer

therapy by oncologists, and in the absence of more severe systemic irAEs (e.g., myocarditis or severe cytokine release syndrome). Medications associated with ICI-AIN should be stopped if possible. Further studies are needed to establish the ideal duration of glucocorticoid prophylaxis in patients with ICI-AKI undergoing re-challenge. In addition, prospective studies to determine the role of glucocorticoid prophylaxis for the prevention of ICI-AIN during rechallenge are needed.

Disclosure Statement

A.A., S.M., V.T.S., S.B.K., N.K., N.M. have nothing to disclose.

A.K. administers funds from Amgen and Janssen Inc. to support the University Health Network Onco-Nephrology Fellowship Program.

S.H. has received research support from Mayo Clinic intramural career development K2R award and by Mayo CCaTS grant number UL1TR002377.

S.G. was a scientific coordinator for the ASCEND trial (GlaskoSmithKline), served as a consultant for Secretome, Proletariat Therapeutics, and Alexion, received speaker fees from Springer Inc., and received research support from BTG International, GE Healthcare, AstraZeneca, and NIH NIDDK (K23DK125672).

D.E.L. received research support from BioPorto, BTG International, Metro International Biotech LLC, Renibus Therapeutics, Inc., and Alexion Pharmaceuticals, has served as a consultant for Sidereal Therapeutics, Casma Therapeutics, MexBrain, Entrada Therapeutics, CardioRenal Systems, Inc., and Alexion Pharmaceuticals, and serves as a Co-Chair of a Safety Monitoring Committee for EMD Serono Research and Development Institute, Inc.

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S.A. served as a consultant for Traverre Therapeutics, Vera Therapeutics, Mendara Inc. She has received research support from NIH (R01DK127138, R21MD019394, U01AI169477) and Abbott Laboratory and Ascend Laboratory provided assay materials for work conducted under U01AI169477.

Acknowledgments/Funding Support

No specific funding was received for the preparation of this manuscript.

Authors' Contributions

A.K. and S.H. were mutually involved in the planning, outline.

and writing. All the authors contributed on writing the original manuscript and design of graphics. A.K and S.H. edited all the revisions of the manuscript.

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Figures and legends

Figure 1: Pathogenesis and risk factors of immune checkpoint inhibitor-induced acute kidney injury

Pathogenesis of ICI-AKI: At the lymph node level, the CTLA4 acts as an immune checkpoint by competing co-stimulatory signal between CD80/86 and CD28. In peripheral tissue, PD-1/PD-L1 pathway plays a key role in regulating tissue inflammatory responses by effector T cells that recognize antigens in peripheral tissues. Activated antigen-experienced T cells increase their levels of PD-1 and continue to express it in tissues. Tumor cells express PD-L1 to avoid host immune surveillance, which decreases the activity of T cells and limits cytotoxic killing of tumor cells. Similarly, LAG3 interacts with several known ligands that can inhibit T cell function including MHC class II. LAG3 is also working as peripheral immune checkpoint and can work synergistically with PD-1/PD-L1 axis. Activated T/B cells may have off-site side effects mediating direct tubulointerstitial or glomerular kidney injury. Putative risk factors for ICI-AKI include dual ICI therapy, concurrent or prior irAEs, baseline CKD and AIN inducing drugs (e.g. PPI, NSAIDs, etc.) Injured cells produce proinflammatory cytokines, which can recruit inflammatory cells and induce fibroblast proliferation related to tubular cell damage (i.e. AIN) and further kidney injury (i.e. CKD, ESKD).

Abbreviations: irAEs: immune-related adverse events; ICI: immune checkpoint inhibitors; GFR: glomerular filtration rate; AIN; acute interstitial nephritis; PPI: proton pump inhibitors; NSAIDs; non-steroids anti-inflammatory drugs; DC, dendritic cell; CTLA-4, cytotoxic T lymphocyte-associated protein-4; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-associated ligand-1; T-cell, T lymphocyte; TCR, T cell receptor CD-28, cluster of differentiation-28; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; Ag-antigen; CD-28, cluster of differentiation-28; CD 80/86, cluster of differentiation 80/86

AKI: acute kidney injury; CKD: chronic kidney disease; acute tubular necrosis (ATN). EKSD: end-stage kidney disease

Figure 2: Clinical approach to acute kidney injury in patients receiving treatment with immune checkpoint inhibitors

Abbreviations: ICI, immune checkpoint inhibitor; AKI, acute kidney injury; ATN, acute tubular necrosis; GN, glomerular disease; PPI, proton pump inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, Sodium-glucose Cotransporter-2 Inhibitors; SCr, serum creatinine; UA, urinalysis; UPCR, urine protein to creatinine ratio; RBC, red blood cell; AIN, acute interstitial nephritis; MP: methylprednisolone; MCD, minimal change disease; FSGS: focal segmental glomerulosclerosis; C3GN, C3 glomerulonephritis; TMA, thrombotic microangiopathy

- a. Consider checking clinically available biomarkers (e.g., serum C-reactive protein, urine retinol binding protein-to-creatinine ratio, sIL-2R levels)
- b. Taper prednisone by 10 mg/week if SCr improves after the first week of treatment
- c. Second line immunosuppression: e.g., Mycophenolate mofetil, infliximab

Tables:

Table 1: Electrolyte and acid-base disorders related to immune checkpoint inhibitors use

Electrolyte disorder	Estimated Incidence	Postulated mechanisms	Suggested Workup
Hyponatremia ^{2,7,21,31 30}	9-62%	- Adrenalitis - Thyroiditis - SIAD^a	TSH ACTH Cosyntropin stimulation test
Hypokalemia ⁷	Unknown 19% of all electrolytes disturbances reported in FAERS database 19%	- Thyroiditis - ACTH-dependent Cushing's syndrome - Colitis induced diarrhea^a - Renal tubular acidosis	TSH ACTH
Hypercalcemia ^{7,30,35,36,79-81}	0.7-15%	- Thyroiditis* -Hypophysitis -Tumor pseudohyperprogression - Sarcoidosis-like granuloma - Immune-related PTHrP	TSH ACTH 1,25OH vitamin D PTH-rp
Hypocalcemia ^{7,21,82}	1	- Auto-immune hypoparathyroidism^a -Tumor lysis syndrome	PTH
Hypophosphatemia ^{7,83,84}	2-3 %	- Hyperparathyroidism	PTH
Hyperphosphatemia ³⁰	Unknown	- Tumor Lysis Syndrome^a -Hypoparathyroidism	
Hypernatremia ⁸⁵	Unknown	- Arginine Vasopressin deficiency	Copeptin Desmopressin challenge test Urine and serum osmolality Urine volume
Renal tubular acidosis ^{6,86}	Unknown	-Auto-immune process causing tubule-interstitial injury	Urine pH Urine anion gap Urine ammonium ABG

Abbreviations: ACTH, adrenocorticotrophic hormone; ABG: arterial blood gas; PTH, parathyroid hormone; SIAD, syndrome of inappropriate diuresis; TSH, thyroid stimulating hormone.

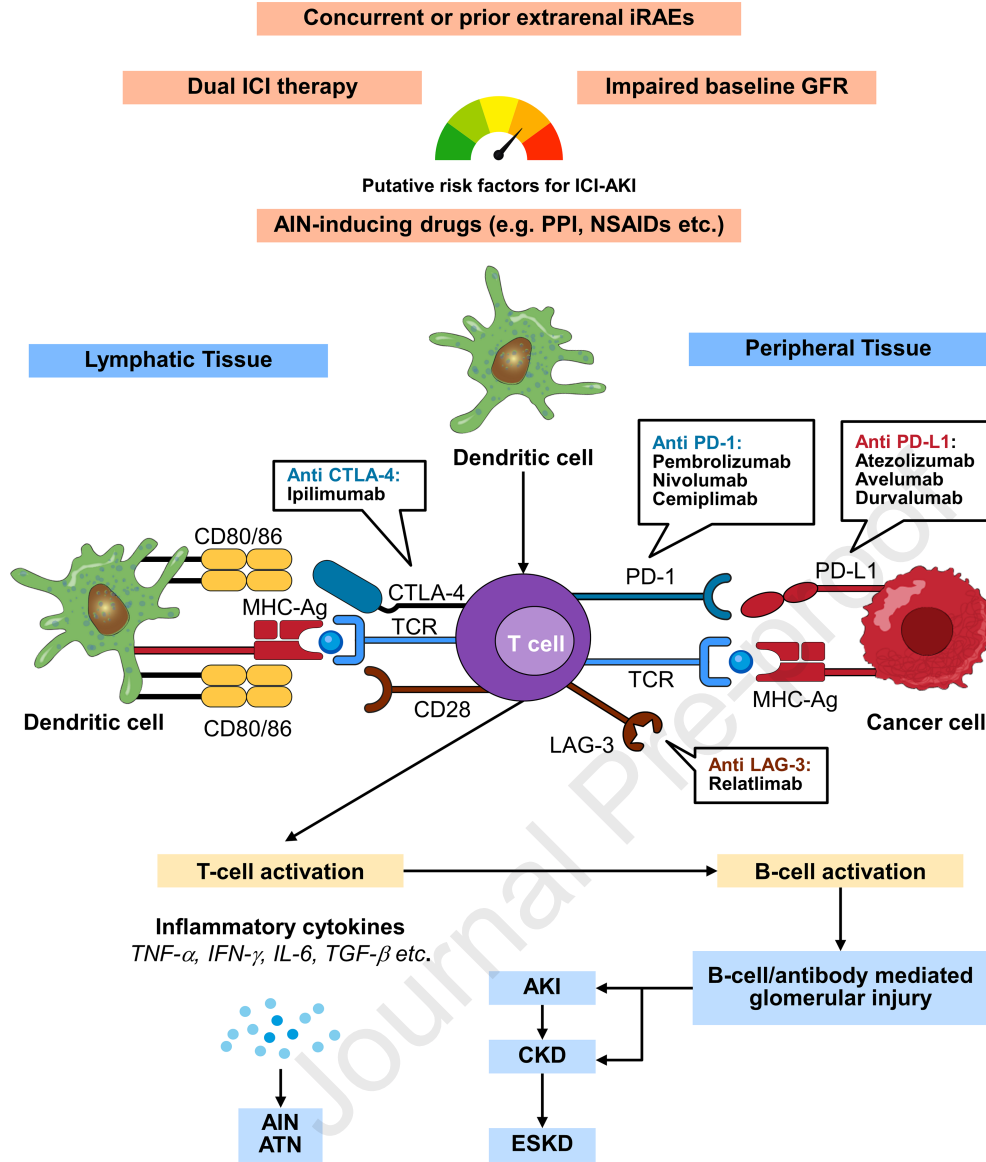
^aMost common etiologies are indicated in bold.

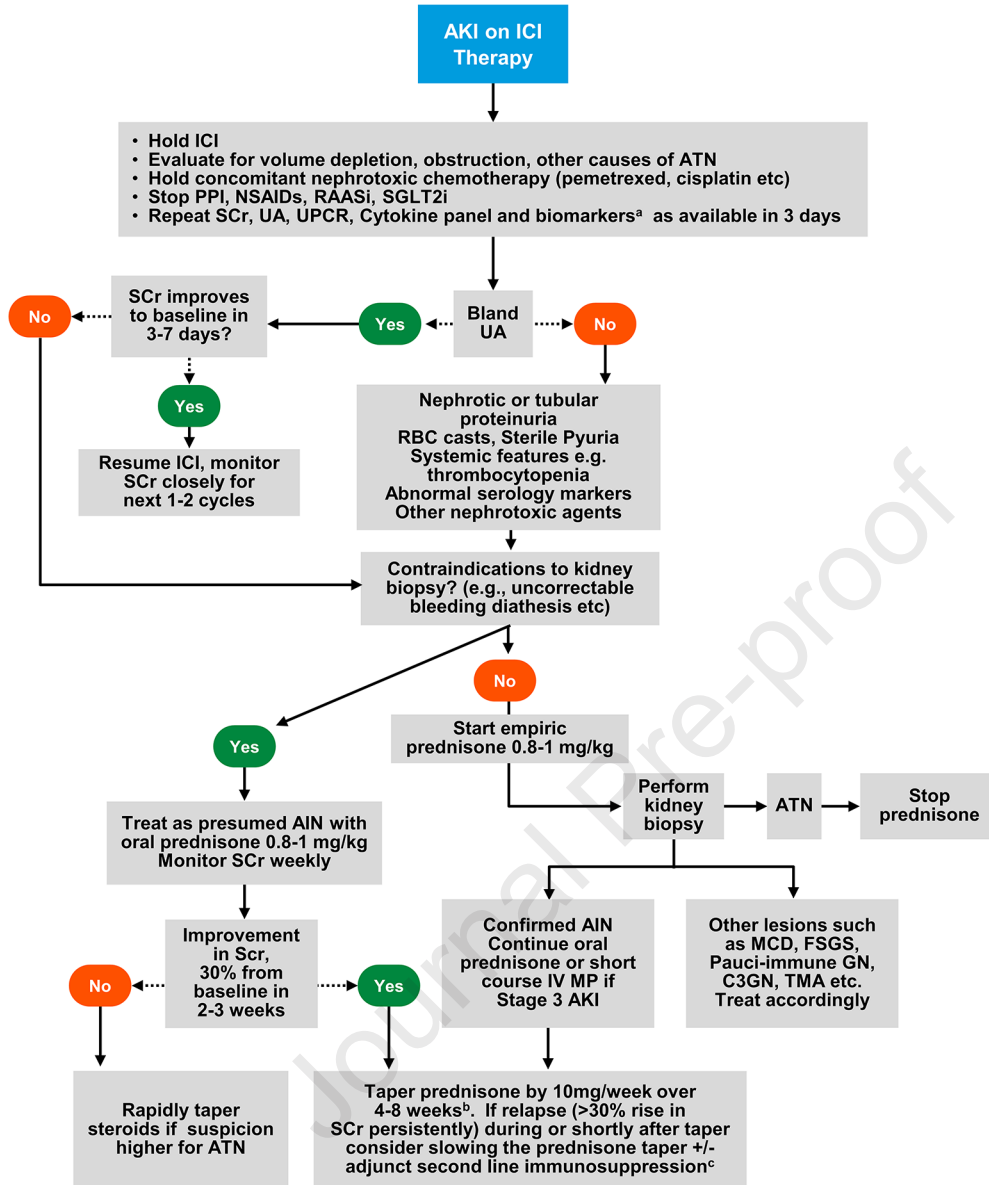
Table 2. Differences regarding when to perform kidney biopsy in patients with ICI-AKI based on oncology and nephrology society guidelines:

ASCO Guidelines	NCCN Guidelines	ASON Position Statement
Recommend foregoing kidney biopsy and initiate glucocorticoids if lack of alternative cause of AKI	Recommend consideration of a kidney biopsy for CTCAE ^a grade ≥ 2 or higher (i.e., elevation of SCr >1.5 times or higher from baseline)	Recommend kidney biopsy for KDIGO AKI stage 2 and 3 if there are no absolute contraindications, particularly when a plausible alternative etiology for AKI exists (e.g., use of other nephrotoxic agents like platinum therapy, VEGF inhibitors), urine studies are suggestive of active glomerular disease, there is concern for RTA, or there is persistent elevated SCr ≥ 1.5 times baseline despite conservative management (e.g., IV fluids)

Abbreviations: ASCO: American Society of Clinical Oncology; ASON: American Society of Onco-Nephrology; CTCAE: Common terminology criteria for adverse events; ICI-AKI: Acute kidney injury-associated with immune checkpoint inhibitors; IV: intravenous; KDIGO: Kidney Disease Improving: Global Outcomes; NCCN: National Comprehensive Cancer Network; RTA: Renal tubular acidosis; SCr; serum creatinine; VEGF: Vascular endothelial growth factor.

^aCTCAE: US National Cancer Institute (NCI) uses this to collect standardized treatment-related data about adverse events to help evaluate new cancer therapies.





Patients with ICI-AKI should be considered for ICI rechallenge following stabilization of kidney function in a shared decision-making framework with the patient and multidisciplinary team, including oncology and nephrology. ICI re-challenge considerations may include extent of renal recovery, other available treatment options, and patient preference