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**Renal adverse effects of Immune Checkpoints Inhibitors in clinical practice:
ImmuNoTox (INT) study.**

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Keyword: Checkpoint inhibitors; adverse renal events; IRAEs; acute kidney injury

Abstract: (249 words)

Background/objectives: Acute Kidney Injury induced by Checkpoint Inhibitors therapies (CPI-induced AKI) is an uncommon but severe Immune Related Adverse Event (IRAE). The aim was to describe the epidemiology, risks factors, clinical, and laboratory characteristics of these renal AE in a real-life cohort treatment.

Design/participants: Consecutive patients undergoing a CPI therapy at the *Hôpital Lyon Sud* from January 2015 to July 2017 were included. A systematic retrospective analysis of medical files was performed, monthly serum creatinine levels, associated treatments, and occurrence of other IRAEs data were collected. AKI episodes explained by classic AKI etiologies (pre-renal, obstructive, septic) were excluded from the analysis.

Results: CPI-induced AKI incidence was 3.7% (13/352), and appeared to be time-dependent (7.7% (11/143) for patients with >3 months of CPI exposure), ranging from 1 to 16 months. All cases with available histology were acute tubulointerstitial nephritis, with poor urinary sediment. The severity of AKI was mild (stage 1 in 50% of cases), with no need for renal-replacement therapy. Although CPI-induced AKI patients had more frequently other IRAEs (77% vs 39%), this was not associated with a greater risk of AKI. Pre-existing chronic kidney disease (defined as an estimated glomerular filtration rate <60mL/min) was not associated with a greater risk of CPI-induced AKI. Treatments of CPI-induced AKI were heterogeneous, with discontinuation of CPIs, and inconstant systemic corticosteroid therapy.

Conclusion: The monitoring of renal function and early identification of AKI during CPIs treatment is essential. The optimal management of CPI-induced AKI remains unclear and requires a close collaboration between the oncology and nephrology departments.

Clinical Relevancy Statement:

Immune checkpoint inhibitors (CPIs) have dramatically improved patient outcomes in different malignant contexts such as melanoma, non-small cell lung cancers (NSCLC), or urologic cancers. Usually well-tolerated, CPIs are however associated with immune related adverse events (IRAEs). Among them, acute kidney injury (AKI) is uncommon, and not well-described. Following the exponential increase in the prescription of CPIs, previously uncommon cases of IRAE (such as AKI) became of common occurrence in referral centers. Data regarding the epidemiology, risk factors, or management of CPI-induced AKI are currently lacking or can be discordant. Data regarding CPI-induced AKI, in a large real-life cohort were reported herein.

INTRODUCTION:

Immune checkpoint inhibitors (CPI) such as anti PD-(L)1 or anti CTLA-4 lead to the restoration of anti-tumor immunity. They are largely used for the treatment of several solid malignancies (such as advanced melanoma, advanced non-small cells and small cells lung cancer, or urologic cancers) [1]. The toxicity profiles of CPI are very heterogeneous and depend on their type as well as on their association with other CPI, chemotherapy, or a targeted therapy. Among CPI toxicities, Immune Related Adverse Events (IRAEs) are secondary to non-specific activation of the immune system. Every organ can be involved [2], the most frequent are the skin, the liver, and the digestive tract. In randomized clinical trials, single agent CPI were globally well tolerated as grade ≥ 3 IRAEs occurred in less than 15% of patients treated with an anti PD-(L)1 and in less than 40% of patients treated with an anti CTLA-4 [3]. Rarely, IRAEs are life threatening as they can induce severe immune-related renal adverse events that impose the treatment to be discontinued.

The exact incidence of renal adverse events is uncertain and ranges from 0.4% [4] to 29% [5] depending on studies. These estimated incidences mostly rely on large meta-analyses of controlled, randomized clinical trials [2,6] that included highly selected patients, which is hardly a reflection of real life conditions, and for which there was no specific renal outcome as primary or secondary endpoints. Only three 'real life' studies (retrospective studies including consecutive treated patients) [7–9] investigating CPI-induced acute kidney injury (AKI) were performed. In these studies, the incidence of AKI was respectively 17, 16.5, and 17%, but only 3, 3.9, and 3.3% of AKI could be attributed to the CPI therapy itself.

The most common manifestation of renal adverse event associated with CPI therapy is CPI-induced AKI [10] with histological description of acute interstitial nephritis (AIN)

[11]. Less frequently, glomerular lesions (such as minimal change disease [12–14], immune complex glomerulonephritis [15], pauci-immune glomerulonephritis [16], membranous nephropathy [16], IgA nephropathy [17]), thrombotic microangiopathy [11], acute tubular necrosis have been described, or even ionic disturbance [18–20] without AKI.

The clinical presentation of CPI-induced AKI is usually non-specific, with inconstant leucocyturia, mild or no proteinuria, and variable setting of occurrence. As of today, no specific risk factors have been identified, but concomitant treatment with medications known to induce allergic AIN (such as proton-pump inhibitors [PPIs] or non-steroidal anti-inflammatory drugs [NSAID]) are thought to trigger CPI-induced AKI [21]. The optimal management of AKI during CPI treatment remains unclear, the use of systemic corticosteroid therapy, as well as CPI discontinuation, are favored even though the level of proof is low for this recommendation [22]. The renal outcome is variable, and the risk-benefit ratio of the subsequent reintroduction of the same or another CPI is uncertain. In this context, the ImmuNoTox (INT) study was conducted, it is a retrospective monocentric study including patients treated with either an anti CTLA-4, anti PD-1, or anti PD-L1 CPI, which aimed at 1- describing their specific renal tolerance in a large, real life treatment cohort and 2- assessing the risk factors that might contribute to CPI-induced AKI.

PATIENTS AND METHODS:

Population:

Data from all patients treated with CPI therapy in the dermatology, oncology, or pneumology departments at the *Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre Bénite*, France from January 2015 to July 2017 were retrospectively analyzed.

Considered CPIs were anti CTLA-4 antibodies (Ipilimumab), anti PD-1 antibodies (Nivolumab or Pembrolizumab), and anti PD-L1 antibodies (Avelumab, Atezolizumab or Durvalumab).

This study was approved by a national ethical research committee “Ile de France II” in October 2017 (IRB registration #00001072) and registered on clinicaltrials.gov (NCT03316417). The *Comission nationale de l’informatique et des libertés* (CNIL, French national commission for the protection of digital information) gave a positive opinion for the study. Patients were informed of the nature of the collected data and their right to retract from the study by an individual letter of information.

Inclusion criteria:

All consecutives adult patients (≥ 18 year-old) treated with CPI were included, except those for whom no serum creatinine value (neither at baseline nor during follow-up) was available. The follow-up period corresponded to the duration of the CPI treatment, until its discontinuation for either tumoral progression, IRAEs requiring treatment modification and/or discontinuation, or death.

Data collection:

Demographic data, medical history, clinical, laboratory, and histological data at presentation were collected from medical files. CPI treatment characteristics, co-medications, and the cumulated volume of iodinated contrast agent were also reported. The co-medications were grouped into medications known to alter renal hemodynamic (renal HD drug i.e. diuretics and renin-angiotensin system [RAS] blockers) and medications historically known to induce allergic AIN (i.e. proton pump inhibitors [PPIs], non-steroidal anti-inflammatory drugs [NSAIDs] and fluindione).

CKD was defined by an estimated glomerular filtration rate (eGFR) < 60mL/min using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula adjusted on body surface area (BSA), described as more suitable for cancer patients [23,24], who are commonly sarcopenic.

Information about the occurrence of extra renal IRAEs (hepatic, cutaneous, endocrine, gastrointestinal, neurologic, pulmonary, cardiac, rheumatologic, hematologic IRAEs defined by the CTCAE v5.0) was also collected.

Outcomes:

The primary outcome was the incidence of CPI-induced AKI. AKI was defined as a serum creatinine (SCr) level 1.5-fold higher than baseline, measured by enzymatic method (Roche, France) with calibrators defined by an isotope-dilution mass spectrometry and according to the v5.0 Common Terminology Criteria for Adverse Events (CTCAE) [25]. The SCr level before the first injection defined the baseline SCr level. AKI were divided in three severity groups based on the magnitude of the SCr level increase, according to KDIGO clinical practice guidelines: 1.5 – 1.9 fold from baseline SCr (AKI stage 1), 2 – 2.9 fold from baseline SCr (AKI stage 2), and over 3 fold from baseline SCr (AKI stage 3). Based on the clinical history, laboratory analysis, ultrasound imaging, evident drug nephrotoxicity, and histological analysis when available, AKI events were classified by two independent nephrologists (ME and CT) as either CPI-induced (if no other potential cause of AKI was identified) or non CPI-induced. If there was a discrepancy in opinion between both nephrologists, a third independent nephrologist was consulted (ENC). All non CPI-induced AKI were excluded from the final analysis.

Secondary outcomes were the assessment of pre-specified baseline characteristics, risk factors, and treatments against the development of AKI during CPI therapy. Additionally, the cases of nephrologist-confirmed CPI-related nephrotoxicity were reported and characterized (in terms of clinical, laboratory and histological presentations, severity, reversibility). AKI management was studied, including the use of a systemic corticosteroid regimen or not. SCr level 3 months after the initial episode was also recorded, and the reversibility of AKI was defined as a SCr level elevation less than 1.3-fold from the baseline after 3 months.

Statistical analysis:

Characteristics of patients were expressed as count (percentage) or median [interquartile range, IQR] because variables were not normally distributed (tested using the D'Agostino-Pearson test). The two groups were compared using the Mann and Whitney test for quantitative variables and the Fisher exact test for the qualitative ones. A univariate regression was performed to evaluate the relationship between all measured baseline characteristics and AKI episodes. Age, baseline eGFR, and others IRAE were chosen *a priori* as variables of interest for the multivariate regression analysis. In addition, baseline variables with a P value < 0.1 in the univariate analysis were included in the multivariate regression. Covariates were expressed as OR [95%CI] (odds ratio [95% confidence interval]). The analysis was carried out using the R software v4.0, R Foundation for Statistical Computing, Vienne, Austria and GraphPad Prism 8.0.1 for Windows, San Diego, California USA. A p-value < 0.05 was retained for statistical significance.

RESULTS:

Patients:

Data from 352 patients (**Figure 1**) were collected; there were 223 males and the sex ratio M/F was 1.73, their median [IQR] age was 67 [57 - 76] years (**Table 1**). In the whole cohort, 300 (85.2%) patients were treated with anti PD-1, 10 (2.8%) with anti PD-L1, 38 (10.8%) with anti CTLA-4 monotherapy (Ipilimumab), and 4 (1.2%) with a combination of anti PD-1 and anti CTLA-4 (Nivolumab and Ipilimumab). A total of 189 (53.7%) patients suffered from advanced melanoma, 142 (40.3%) patients were treated for advanced non-small cells lung cancer, and the remaining patients (n=21; 6%) were treated for urologic cancers (renal or urothelial carcinoma).

AKI incidence:

A total of 14 CPI-induced AKI occurred in 13 patients, corresponding to an incidence of 3.7% appearing at a median (range) time of 148 (35 – 480) days. There were 4 cases of AKI excluded from the CPI-induced AKI group, as another likely cause of AKI was found: 1 case of septic shock associated with glycopeptide accumulation, 1 case of septic shock alone, 1 case of manifest pre-renal AKI associated with diarrhea, and 1 case of obstructive pyelonephritis (**Figure 1**). The clinical features of patients from the CPI-induced AKI group are described in **Table 2**. CPI-induced AKI were attributed to anti PD-1 agents in 13/300 (4.3%) patients (9/230, 3.9% treated with Nivolumab and 4/70, 5.7% treated with Pembrolizumab). No CPI-induced AKI was recorded in patients treated with anti CTLA-4 agents or anti PD- L1 agents alone, or with a combined therapy. The incidence of AKI according to therapy and underlying cancer is described in **Figure 2**. The median (range) SCr peak level was 2.1 (1.3 – 5.0) mg/L. The severity of kidney failure was predominantly mild to

moderate: 6 (43%) patients presented with AKI stage 1, 5 (36%) with AKI stage 2, and 3 (21%) with stage 3. No patient required renal-replacement therapy.

Identification of risk factors for AKI

In the CPI-induced AKI group, there was significantly more extra renal IRAE (n=10/13, 77%, pneumonia in one patient, thyroiditis in 5 patients, colitis in 2 patients, skin rash in 2 patients, and hepatitis in 5 patients) compared to the other group (p=0.0088, **Table 1**), however extra renal IRAE was not significantly associated with a greater risk of AKI (**Table 3**). The use of the vitamin K antagonist fluindione (historically well known to induce allergic AIN) was significantly associated with a greater risk of developing AKI in the multivariate analysis (OR=6.40, 95%CI [1.42; 26.08]; p=0.01; **Table 3**).

Interestingly, pre-existing CKD (identified in 68 (19%) patients, 21 (31%) of whom had an eGFR < 45mL/min) was not an associated risk factor of developing CPI-induced AKI (OR = 1.27, 95%CI [0.22; 5.112]; p=0.72). Likewise, the overall incidence of IRAEs in CKD patients (17.5%) was not higher than the one of non-CKD patients (45%). The etiology of CKD was “undetermined nephropathy” in 41/68 (60%) patients, the others were hypertensive nephropathy (12/68, 18%), diabetic nephropathy (8/68, 12%), drug-induced nephropathy (4/68, 6%), and consequences of sepsis-induced ATN (3/68, 4%). No patient had an identified auto-immune cause of CKD, although it was not an exclusion criterion. Some other patients had auto-immune disease, but without associated CKD.

There was no type of primary tumor that was associated with a greater risk of AKI compared to other types of tumor (**Table 3**).

To study the impact of CPI treatment duration on AKI occurrence, two subgroups of patients with different time exposure (i.e. ≤ 3 months, and > 3 months) were formed. The CPI-induced AKI incidence was 0.96% (2/209) for the ≤ 3 months subgroup, and 7.7% (11/143) for the > 3 months subgroup ($p < 0.01$), suggesting an exposure-time-dependent risk to develop AKI.

Renal outcomes in the CPI-induced AKI group:

Urinary analysis was available for 8 of the 14 patients with CPI-induced AKI. The proteinuria/creatininuria ratio was < 50 mg/mmol in all cases. Significant leucocyturia ($> 30/\text{mm}^3$) was found in 7/14 cases, and eosinophiluria in none. One patient presented with microscopic hematuria. The median [IQR] baseline eGFR was 71.6 [60 – 87.5] mL/min, and 3 patients had pre-existing CKD (**Table 2**).

Histological features:

Kidney biopsies were performed in 6/14 patients from the CPI-induced AKI group, with histological findings compatible with the diagnosis of tubulo-interstitial nephritis in all cases (**Figure 3**). A total of 5 patients had a typical allergic AIN. The cellular infiltrates were polymorphic, with a predominance of CD3+ cells. Infiltrates of eosinophil polymorphonuclear leukocytes were present in 2 cases. One patient had an isolated acute tubular necrosis; 2 patients had associated tubulitis. No patient had glomerular injury or acute vascular lesions.

*Treatment management and reversibility (**Table 2**):*

Patients with AKI were managed according to the practice in place in the care center (i.e. treatment decision in multidisciplinary meeting, and tight collaboration between the referent oncologist and the nephrologist).

Among the AKI+ patients, 7/14 (50%) were treated with systemic corticosteroid (CS) therapy. CS regimens in the present cohort were all oral prednisone, with heterogeneous doses (0.5 mg/kg/day for 4 of them, 1 mg/kg/day for 2 patients, and 2mg/kg/day for 1 patient). All patients discontinued CPI therapy at AKI diagnosis.

CPI treatment was reintroduced for 5 patients (patients 5, 6, 7, 8, and 12) with the same drug, with no recurrence of AKI for patients 5, 6, 8, and 12. For patient 7, the CPI treatment with Nivolumab was restarted after AKI resolution, and AKI reoccurred 4 weeks later. A repeated kidney biopsy confirmed the relapse of CPI-induced AKI. In the particular case of patient 12, AKI was treated by discontinuing PPI treatment, with no associated CS therapy. Pembrolizumab was then reintroduced without recurrence of AKI.

DISCUSSION:

A low overall incidence of 3.7% of CPI-induced AKI was reported herein. These data are consistent with those from the available literature, as it was 2.1% [6] and between 0.7% and 6% [19] in 2 meta-analysis of randomized clinical trials (RCTs) with renal follow-up, and 3.8% in a retrospective review of IRAEs cases [26]. Three recent real life studies reported an incidence of 3% [7] and 3.8% [8] of CPI-induced AKI in North American patients, and of 3.3% [9] in European patients. The present study corroborates these results and allows a reliable measure of incidence of CPI-induced AKI in the studied population. A comparable degree of severity (mild to moderate) was also reported herein.

Although the use of PPIs has been described in previous studies as a risk factor of CPI-induced AKI [7,21,27], it was not found as a significant risk factor for developing AKI in the present study. However, the particular case of patient 12 (for whom baseline renal function was restored after PPI discontinuation only, with no associated CS therapy) shows that these medications have to be closely monitored. Surprisingly, in the present cohort, the co-medication with fluindione (an indanedione-derived vitamin K antagonist, well-known to induce allergic AIN [28]) was found associated with a high risk of developing CPI-induced AKI. These discordant data suggest that CPI-induced AKI is an immunological disease that could be, in some cases but not all, triggered by medications.

Despite the higher proportion of extra-renal IRAEs among patients from the CPI-induced AKI group, there were not found significantly associated with a greater risk of developing AKI. This description of CPI-induced AKI often associated with extra-renal IRAE has been previously described by Meraz-Munoz *et al.* [8]. This could be surprising considering that IRAEs are commonly described as more often “single-site” than “multiple-site” [29]. IRAEs are described as resulting from an aberrant immune-self response elicited by CPI. “Single-site” IRAEs could be explained by the reactivation of a resting “tissue-specific” auto-reactive T-cell clone, or by similarity between tumoral antigen and organ antigen [30]. If CPI-induced AKI are in future studies confirmed as “multiple-site” IRAEs, it will suggest a different underlying pathophysiological mechanism, such as a global/multi-organ loss of tolerance. The explanation for a global loss of tolerance induced by CPIs remains largely understood. It is therefore of utmost importance to closely monitor renal function in patients who previously presented with extra renal IRAEs. In the present cohort, the clinical and laboratory findings associated with CPI-induced AKI were poor, and

there was no case of acute glomerulopathy, as previously reported [11]. Glomerular injuries have however been reported in other studies [16], but remain uncommon [12,13,15], which has been confirmed in a large multicentric retrospective cohort study [31] describing anecdotic glomerulonephritis, and commonly acute interstitial nephritis. However, oncologic patients are indeed already at high nephrological risk because of other nephrotoxic medications, comorbidities, risk of paraneoplastic syndrome with renal involvement. In the absence of contraindication, we therefore recommend a systematic kidney biopsy in case of AKI during CPI treatment.

Surprisingly, all cases of AKI in the present study occurred in patients under anti PD-1 treatment. Contrary to some data in the literature [26], there was herein no case of AKI in patients under anti CTLA-4 or anti PD-1 + anti CTLA-4 treatment, whereas the incidence of AKI has been reported to be higher for the combination treatment compared to each treatment alone [11]. This is probably due to a lack of statistical power in the present study as only a minority of patients was treated with these CPI regimens.

The results presented herein also suggest that patients with eGFR < 60mL/min were not prone to more AKI or IRAE than patients with no preexisting CKD, even though they were treated with the same posology of CPI agents. The efficacy and safety of CPI were, to our knowledge, not evaluated in case of pre-existing CKD. These data encourage the use of these molecules in the CKD population without any delay nor dose adaptation, but with a close monitoring. Moreover, the basal eGFR was significantly lower in AKI+ patients compared to AKI- patients, but still > 60mL/min without marker of kidney damage, which can be explained by the significantly higher age of patients in the AKI+ group compared to patients in the AKI- group [32].

The present study has some limitations. First, data were collected only during CPI treatment, although IRAE can occur later after CPI treatment [33], which resulted in a lack of follow-up of patients who potentially developed AKI following CPI withdrawal, especially since CPIs have relatively long half-lives. This could result in an underestimation of the incidence of CPI-induced AKI. Second, many reports have suggested that IRAEs could be associated with an increased overall survival and progression-free survival [29,34,35], and we do not describe here the oncological outcome of our patients. This is an important topic, but the present study was not designed to analyze it. Third, the low incidence of CPI-induced AKI in the present cohort did not allow sufficient statistical strength in the analysis. Finally, the present study was not designed to evaluate the effects of previous therapies, nor to determine the AKI incidence follow after CPI discontinuation, although it may have a longer-term impact on AKI [36,37].

CPI-related AKI is a severe, life-threatening IRAE, and usually implicates treatment discontinuation [10]. Renal recovery after CPI-induced AKI is inconstant, as described in the present cohort, and coherent with previous data [7,8,11,21]. The present study did not allow to assess specific treatment regimens and their efficiency because of its retrospective design. Moreover, the statistical power was too low to assess the safety of CPI therapy reintroduction after a first episode of AKI, either with the same or with another molecule. This issue of CPI treatment reintroduction is quite arduous, with a subtle balance between the risk of terminal kidney disease in case of AKI recurrence and the risk of oncologic progression in case of prolonged cessation. The possibility to resort to another immune checkpoint inhibitor is not yet evaluated. Therefore, facing the lack of large therapeutic studies investigating the question of management of CPI-induced AKI, the decision of reintroduction of CPI molecule must

be discussed in specialized centers with an expertise in the management of these rare cases of IRAEs. A very tight collaboration between nephrologists and oncologists is of the essence.

Proceeding to a systematic description of renal adverse events under CPI treatment remains mandatory in order to improve the understanding of the underlying mechanisms. Nowadays, this adverse event still seems uncommon, but the rapidly increasing use of double checkpoint blockade raises concerns about a sharp rise in their absolute number in the near future.

Disclosures:

All the authors have no conflict of interest to disclose

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Tables

Table 1: Characteristics of the population at baseline

	Whole cohort (n=352)					CPI-induced AKI (n=13)			Others* (n=339)			p	
DEMOGRAPHIC													
Age, years (median [IQR])	67 [57 – 76]					77 [69 – 82]			67 [56.5 - 75]			0.0028	
BMI, kg/m ² (median [IQR])	23 [20 – 27]					24 [22 – 31]			23 [20 – 27]			0.51	
Sex ratio (M/F)	223/129=1.7					7/6=1.2			216/123=1.7			0.56	
TREATMENT													
Molecule	Nivo = 230	Pembro = 70	Ipi = 38	Ipi+Nivo = 4	Anti PL-L1 = 10	Nivo = 9	Pembro = 4	Nivo = 221	Pembro = 66	Ipi = 38	Ipi + Nivo = 4	Anti PD-L1 = 10	
Nb of injections (median [IQR])	5 [4 – 17]	7 [4 – 19]	4 [3 - 4]	3 [2 - 4]	4 [2 - 7]	14 [8 - 15]	9 [7 – 11.5]	5 [4 - 17]	7 [4 - 20]	4 [3 - 4]	3 [2 - 4]	4 [2 - 7]	NA
Duration, months (median [IQR])	3 [2 – 9]	5 [2 – 14]	2 [1 - 3]	2 [1 -3]	3 [2.75 – 4]	7 [4 - 10]	6.5 [5 -9.5]	3 [2 - 8]	5 [2 - 14]	2 [1 - 3]	2 [1 -3]	3 [2.75 – 4]	NA
Cumulate dose, mg/kg (median [IQR])	15 [12 – 51]	14 [8 – 38]	12 [9 – 12]	NA	NA	42 [24 – 45]	18 [14.5 – 23]	15 [12 – 51]	14 [8 – 40]	12 [9 – 12]	NA	NA	NA
COMORBIDITIES													
Basal eGFR, mL/min (median [IQR])	82 [67 – 98]					71.6 [60 - 87.5]			83 [67 – 98]			0.032	
Basal creatinine, mg/L (median [IQR])	0.88 [0.75 - 1.0]					0.97 [0.72 - 1.2]			0.88 [0.75 - 1.0]			0.67	
Nb of CKD (eGFR<60mL/min), n (%)	68 (19%)					3 (21%)			65 (18%)			0.72	
Diabetes, n (%)	47 (13%)					3 (23%)			44 (13%)			0.39	
High blood pressure, n (%)	112 (32%)					8 (62%)			104 (31%)			0.03	
EXTRA-ONCOLOGIC MEDICATIONS													
Allergic AIN drug (all), n (%)	224 (64%)					11 (85%)			213 (63%)			0.14	
- PPIs	160 (45%)					8 (62%)			152 (45%)			0.27	
- NSAIDs	47 (13%)					3 (23%)			44 (13%)			0.39	

- Fluindione	24 (7%)	4 (31%)	20 (6%)	0.0079
Renal HD drug (all), n (%)	141 (40%)	9 (64%)	132 (39%)	0.041
- Diuretics	57 (16%)	3 (23%)	54 (16%)	0.45
- RAS inhibitors	89 (25%)	6 (46%)	83 (24%)	0.10
OTHER				
IRAE ≥ 1 (% IRAE (+)), n (%)	143 (41%)	10 (77%)	133 (39%)	0.0088
Cumulate iode, (median [IQR])	150 [100 – 357]	350 [150 – 520]	150 [100 – 350]	0.3

Abbreviations: IQR, interquartile range; M, male; F, female; Nb, number; NA, non available; AKI, Acute Kidney Injury; eGFR, estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; AIN, Acute Interstitial Nephritis; PPIs, Proton Pump Inhibitors; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; HD, Hemodynamic; IRAE, Immune related Adverse Events; Nivo, Nivolumab; Pembro, Pembrolizumab; Ipi, ipilimumab; Anti PD-L1, anti protein death – ligand 1

“Allergic AIN drug” refers to drugs known to induce allergic acute interstitial nephritis (PPIs, Nonsteroidal anti-inflammatory drugs, and Fluindione). “Renal HD drug” refers to drugs known to alter renal hemodynamic (diuretics and renin-angiotensine system [RAS] inhibitors). All quantitative values are expressed as median [IQR].

* The group ‘Others’ refers to patients either without AKI or with non-CPI-induced AKI.

Table 2: Clinical features of CPI-induced AKI patients

Patient	Sex/ Age	Malignancy	Molecule and cumulative dose	SCr/eGFR – SCr peak	AKI stage	Proteinuria	RBC	WBC	Other IRAE	Days before AKI	Histologic diagnosis (Y/ N)	Treatment	Reversibility (Y/N) – SCr +M3
1	M / 63	Epidermoid pulmonary cancer	Nivolumab 42mg/kg	1.14/88 – 1.87	1	0	1	6	Thyroidis	180	N	CS 2mg/kg	N – 1.71
2	M / 66	Pulmonary adenocarcinom	Nivolumab 123mg/kg	1.20/76 – 2.07	1	0	0	0	None	480	Y	CS 1mg/kg	N – 2.05
3	M / 68	Melanoma	Pembrolizumab 16mg/kg	1.02/89 – 1.87	1	0	0	0	Thyroidis	147	Y	CS 0.5mg/kg	N – 1.64
4	M / 69	Pulmonary adenocarcinom	Nivolumab 24mg/kg	1.24/70 – 2.09	1	NA	NA	NA	Thyroidis	120	N	None	NA (death)
5	M / 70	Melanoma	Pembrolizumab 10mg/kg	0.97/87 – 1.62	1	NA	NA	NA	Hepatic	90	N	None	Y – 0.98
6	F / 74	Melanoma	Nivolumab 153 mg/kg	0.67/71 – 1.3	2	NA	NA	NA	Hepatic / skin	270	N	None	Y – 0.67
7	F / 77	Melanoma	Nivolumab 45mg/kg	0.78/77 – 1.60	2	21	34	18	Hepatic / skin / thyroidis / colitis	60	Y	CS 0.5mg/kg	Y – 0.96
7bis	F / 77	Melanoma	Nivolumab 45mg/kg	0.78/77 – 1.98	2	14	55	0	Hepatic / skin / thyroidis / colitis	150	Y	CS 1mg/kg	N – 1.39

8	F / 79	Pulmonary adenocarcinoma	Nivolumab 45mg/kg	0.63/72 – 1.43	2	NA	NA	NA	Thyroiditis	120	N	None	Y – 0.65
9	M / 82	Epidermoid pulmonary cancer	Nivolumab 6mg/kg	0.61/99 – 2.31	3	NA	NA	NA	None	35	N	None	NA (death)
10	M / 85	Melanoma	Nivolumab 27mg/kg	1.22/56 – 2.59	2	11	91	0	Hepatic	150	Y	CS 0.5mg/kg	N – 2.27
11	F / 85	Melanoma	Pembrolizumab 20mg/kg	0.72/66 – 2.88	3	0	0	0	Hepatic / Skin	180	Y	CS 0.5mg/kg	N – 1.15
12	F / 89	Melanoma	Pembrolizumab 32mg/kg	0.86/44 – 4.98	3	33	326	61	None	155	N	STOP PPIs	Y – 1.01
13	F / 81	Urothelial carcinoma	Nivolumab 6mg/kg	1.22/30 – 3.18	2	NA	NA	NA	pneumonitis	45	N	None	NA (death)

Abbreviations: M, Male; F, Female; NA, Non Available; SCr, serum creatinine; eGFR, estimate Glomerular function rate (BSA-adjusted CKD-EPI); RBC, Red Blood cell; WBC, White Blood Cells; IRAE, immune related Adverse Events; AKI, Acute Kidney Injury; CS, corticosteroid. Doses of corticosteroids are given in prednisone-equivalent, and all patients received here oral prednisone.

Units: age in years; SCr in mg/dL; eGFR in mL/min; Proteinuria in mg/mmol; RBC in el.mm³; WBC in el./mme³; AKI in days

Table 3
Risk factors for AKI in patients receiving CPIs

Variable	OR	(95%CI)	P value
Univariate analysis			
Age	1.08	[1.03; 1.15]	0.006
Male gender	0.66	[0.22; 2.11]	0.47
Baseline eGFR	0.98	[0.95; 1.00]	0.091
Melanoma as primary tumor	0.97	[0.26; 3.44]	0.99
NSCPC as primary tumor	1.06	[0.30; 4.22]	0.99
Urothelial cancer as primary tumor	0.90	[0.12; 40.2]	1
Duration of CPIs	1.03	[0.96; 1.08]	0.33
Other IRAE	2.34	[0.73; 7.21]	0.14
Cardiovascular disease	1.18	[0.35; 3.62]	0.77
Diabetes	2.00	[0.44; 6.85]	0.30
High blood pressure	3.60	[1.17; 12.16]	0.028
RAS inhibitors	2.64	[0.83; 8.18]	0.088
PPIs	1.97	[0.64; 6.63]	0.24
Diuretics	1.58	[0.35; 5.36]	0.50
NSAIDs	2.01	[0.44; 6.88]	0.30
Fluindione	7.09	[1.80; 23,92]	0.002
Cumulated iode	1.00	[1.00; 1.00]	0.67
Antibiotics	0.85	[0.23; 2.68]	0.80
Multivariate analysis			
Age	1.06	[0.99; 1.13]	0.10
Duration of CPIs	1.02	[0.95; 1.08]	0.57

Baseline eGFR	0.98	[0.95; 1.01]	0.15
Other IRAE	2.15	[0.61; 7.44]	0.22
High blood pressure	1.83	[0.54; 6.74]	0.34
Use of Fluidone	6.40	[1.42; 26.08]	0.01

Abbreviations: AKI, acute kidney injury; CPI, immune checkpoint inhibitors; OR, odd ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; IRAE, immune related adverse events; RAS inhibitors, renin angiotensin system inhibitors; PPIs, proton pump inhibitors; NSAIDs, non steroidal anti inflammatory drugs.

Figures:

Figure 1; Flow chart

Abbreviations: AKI, acute kidney injury; CPIs, immune checkpoints inhibitors

Figure 2; Incidence of AKI

A/ Incidence of AKI for each molecule used B/ Incidence of AKI by cancer type

Abbreviations: NSCLC, non-small cells lung cancer

Figure 3; Renal biopsy from patient 7

Described elementary lesions are shown by arrows

A/ PAS stain Gx10: nodular interstitial inflammation, without granuloma B/ Masson's trichrome stain Gx40: massive infiltration of inflammatory mononuclear cells (lymphocytes)

C/ Masson's trichrome Gx40: tubulitis and severe acute tubular necrosis D/ PAS stain Gx40: cell infiltrate composed by both lymphocytes and many plasma cells.

Supplementary figure:

Supplementary Figure 1; Kinetic of serum creatinine in patients with CPI-induced AKI

Each curve represents each patient with CPI-induced AKI. The first value represents the baseline creatinine level.

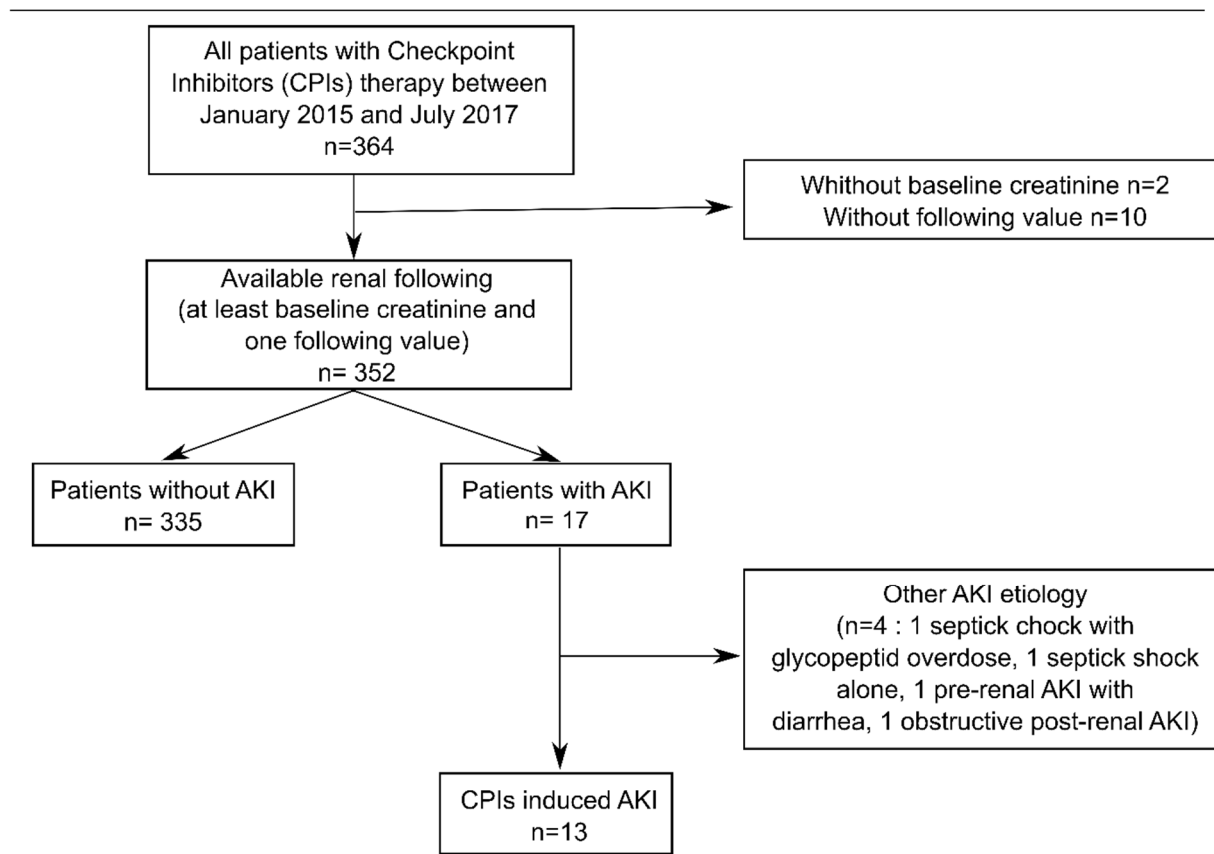


Figure 1 – Flow chart

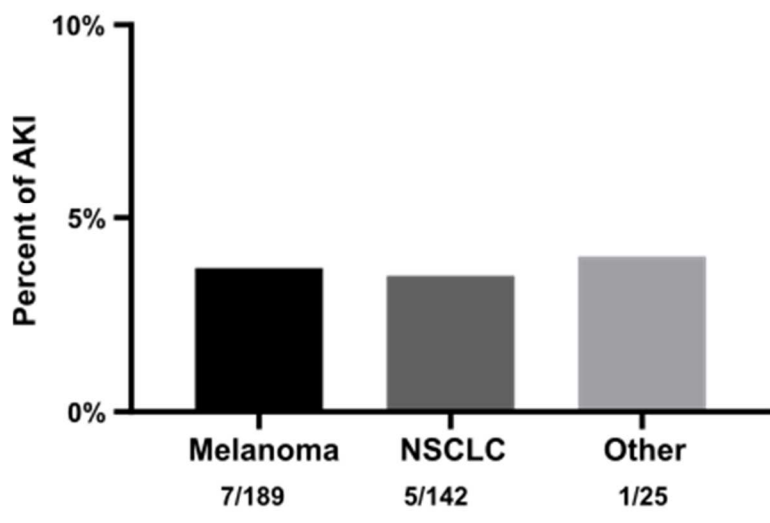
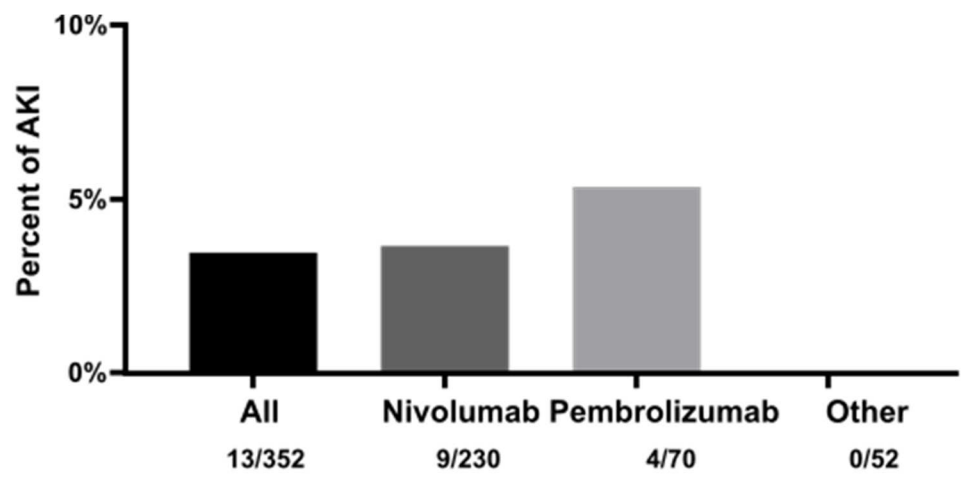


Figure 2 – Incidence of AKI

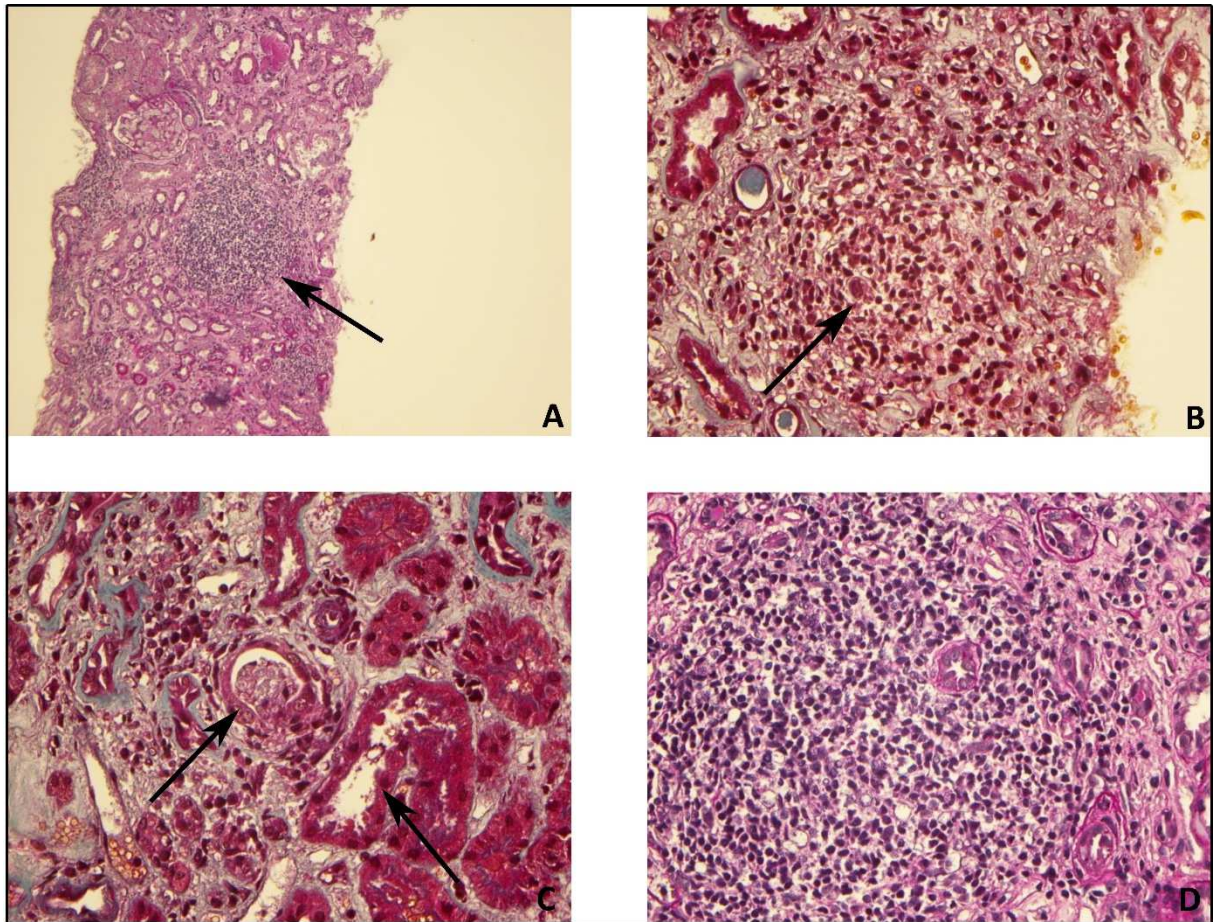


Figure 3 – Renal biopsy from patient n°7

Graphical abstract:

Renal adverse events of Immune Checkpoints Inhibitors in clinical practice : ImmuNoTox study
M.Espi, C.Teuma, E.Novel-Catin, D.Maillet, P.J.Souquet, S.Dalle, L.Koppe, D.Fouque, 2020

