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Effets secondaires rénaux chez les patients traités par immunothérapie par anti-PD1 pour mélanome métastatique : étude réalisée en vie réelle dans une cohorte de 239 patients

Claire Stein

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Aix-Marseille Université

Effets secondaires rénaux chez les patients traités par immunothérapie par anti-PD1 pour mélanome métastatique : étude réalisée en vie réelle dans une cohorte de 239 patients

T H È S E A R T I C L E

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DE MARSEILLE

Le 21 Juin 2019

Par Madame Claire STEIN

Née le 30 octobre 1991 à Marseille 06eme (13)

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 LECHEVALLIER Eric (PU-PH)
 ROSSI Dominique (PU-PH)

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TABLE OF CONTENTS

TITLE, AUTHORS and AFFILIATIONS	2
ABSTRACT	3
1. INTRODUCTION	4
2. METHODS & PATIENTS	4
a. Patients screening.....	4
b. Data collection	5
c. Definitions	5
d. Statistical analysis	5
e. Ethics approval	6
3. RESULTS	6
a. Patients	6
b. Renal adverse events	6
c. Overall survival and risk factors for death	7
d. Occurrence of AKI in surviving patients	10
e. Composite primary outcome (AKI or death)	11
f. Immune related adverse events (IrAEs)	12
4. DISCUSSION	13
5. CONCLUSION	16
6. REFERENCES	18
a. Tables and figures legend	18
b. Abbreviations	27

Renal adverse events in patients treated with anti-PD1 for advanced melanoma: a real-life study in a monocentric cohort of 239 patients.

Claire Stein¹, Stéphane Burtey¹⁻², Julien Mancini³, Marion Pelletier¹, Marion Sallée¹⁻², Philippe Brunet¹⁻², Philippe Berbis⁴, Jean Jacques Grob⁵, Stéphane Honoré⁶, Caroline Gaudy⁵, Noémie Jourde-Chiche¹⁻²

¹AP-HM, Centre de Néphrologie et Transplantation Rénale, Hôpital de la Conception, Marseille, France

²Aix-Marseille Univ, INSERM 1263, INRA 1260, C2VN, Marseille, France

³AP-HM, Santé Publique, Hôpital de la Timone, Marseille, France

⁴AP-HM, Centre de Dermatologie et de Vénéréologie, Hôpital Nord, Marseille, France

⁵AP-HM, Centre de Dermatologie et de Vénéréologie et Cancérologie Cutanée, Hôpital de la Timone, Marseille, France

⁶AP-HM, Onco-Pharmacie, Hôpital de la Timone, Marseille, France

Corresponding author :

Pr Noémie JOURDE-CHICHE

Centre de Néphrologie et Transplantation Rénale, Hôpital de la Conception, AP-HM, Marseille, France

Email : noemie.jourde@ap-hm.fr Phone : +33 4 91 38 30 42 Fax : +33 4 91 38 32 06

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ABSTRACT:

Background: The development of immune checkpoints inhibitors has been a turning point in the treatment for advanced melanoma, but their use is associated with immune-related adverse events (IrAEs). Renal IrAEs have rarely been reported with the anti-programmed death receptor-1 (anti-PD1) antibodies Nivolumab and Pembrolizumab. We aimed to evaluate the incidence of acute kidney injury (AKI) in a monocentric real-life cohort of patients treated with anti-PD1 for advanced melanoma.

Methods: Retrospective collection of clinical charts and comprehensive biological data of all the patients treated for an advanced melanoma in the University Hospital of Marseille (France) with Nivolumab or Pembrolizumab between 2014 and 2018. Patients treated with Ipilimumab were excluded. Acute kidney injury (AKI) was defined by the rise in creatinine at least 1.5 times from baseline or upper limit of normal. Overall survival, survival without AKI, and impact of AKI on survival were analyzed. Risk factors for death and for AKI were identified.

Results: 239 were included. The median overall survival was 13.4 months. During the follow-up, 41 (17%) patients had at least one episode of AKI (grade 1-2 for most patients) and one of them required emergency dialysis. Patients with AKI were more likely to display baseline Chronic Kidney Disease (CKD), to be treated with RAAS inhibitor, to have received ipilimumab prior to anti-PD1 therapy and they had received more cycles and higher cumulated doses of anti-PD1 than patients without AKI. The main cause of AKI was pre-renal, and only 4 patients (1.7%) developed an acute interstitial nephritis (AIN); 8% of patients developed a chronic kidney disease (CKD). Extra-renal IrAEs were more frequent (52% of patients). The occurrence of AKI did not impact overall survival. In multivariate analysis, the overall mortality was lower in overweight and obese patients (respectively, HR= 0.61 (p=0.015) and HR=0.52 (p=0.04)) and higher in patients treated with Proton Pump Inhibitors (PPI) (HR=1.825, p=0.005) or corticosteroids (HR=1.593, p=0.043).

Conclusion: AKI is not rare in patients treated with anti-PD1 for advanced melanoma, but is mostly pre-renal with only 1.7% of patients with a characteristic renal IrAE. Survival is not altered by AKI in this population with a poor vital prognosis. Overweight and obesity were protective in this cohort whereas treatments with PPI and corticosteroids were associated with impaired survival.

1 - INTRODUCTION

Melanoma is a cutaneous malignancy responsible for 1783 deaths in France in 2017 (1). Its incidence has increased in the past years and about 132 000 new cases are diagnosed each year worldwide according to the World Health Organization. The development of immune checkpoints inhibitors has been a turning point in the treatment for advanced melanoma, in particular with the use of ipilimumab (anti-CTLA4) and anti-PD1 antibodies (2,3). The anti-PD1 antibodies Nivolumab and Pembrolizumab are IgG4 humanized antibodies directed against the programmed death receptor-1 protein. They were approved by the FDA in 2014 (4) and later in Europe (2015) for the treatment of advanced, unresected or metastatic melanoma. In comparison with Ipilimumab, they have shown a better and longer efficiency with less side effects in clinical trials (5–8). More recently they were also approved as an adjuvant therapy for stage III high risk resected melanoma (9,10). The aim of immunotherapy is to restore the natural anti-tumoral response of the immune system. Thus, by unbalancing the immune system, they can be responsible for immune related adverse events (IrAEs) which are described as side effects related to a supposed immunological effect of the drugs (11,12). Among these IrAEs, renal adverse events were rare in clinical trials, but their incidence in real life could be higher than previously reported (13).

The aim of this study was to determine the incidence of renal adverse events in a real-life cohort of patients treated with anti-PD1 for advanced melanoma, to identify the causes of acute kidney injury (AKI) and to evaluate the impact of AKI on overall survival. As secondary endpoints, we aimed to identify risk factors for mortality and for AKI in this population, and to report the overall incidence of IrAEs.

2 – METHODS & PATIENTS

a - Patients' screening: We retrospectively screened, from the onco-pharmacological database of our institution (Assistance Publique-Hôpitaux de Marseille), all patients treated by immune checkpoints inhibitors from January 2014 to February 2018. We selected patients for whom the indication was “melanoma”, aged > 18 years, treated with Nivolumab or Pembrolizumab. Treatment indications were stage IV melanoma or unresected stage III melanoma according to the American Joint Committee on Cancer classification. We excluded

patients included in clinical trials comprising a protocol therapy versus placebo, as well as patient treated with Ipilimumab. We obtained an initial cohort of 343 patients (**Figure 1**).

b- Data collection: For every patient, clinical data collected included: age, gender, body mass index (BMI), comorbidities (diabetes, hypertension, dyslipidemia, smoking, history of auto immune disease, hemopathy, chronic kidney disease (CKD)), and baseline prescribed medications (non-steroidal anti-inflammatory drugs (NSAID), renin-angiotensin-aldosterone system (RAAS) inhibitors, allopurinol, diuretics, corticosteroids, proton pump inhibitor (PPI)). These data were collected from their digital medical records. Data concerning the immunotherapy were collected from the Onco-pharmacological database: number of line, name of the immune checkpoints inhibitor, cumulated doses (mg), number of cycles. Serum creatinine ($\mu\text{mol/L}$) and estimated glomerular filtration rate (eGFR) (using the CKD-EPI or MDRD formula) were collected from the hospital laboratory and the patient's personal laboratory.

c- Definitions: AKI was defined by a rise in serum creatinine of at least 1.5 times from baseline or upper limit of normal. The grade of injury was defined according to the National Cancer Institute Common Terminology Criteria for adverse event (1). CKD was defined as a baseline eGFR $<60\text{ml/min}/1,73\text{m}^2$ using the CKD-EPI or MDRD formula. Causes of AKI were classified as obstructive (post-renal), pre-renal, and intrinsic. Intrinsic AKI, documented by renal biopsy in some patients, comprised acute interstitial nephritis (AIN), acute tubular necrosis (ATN), glomerular diseases and vascular diseases. Hemopathy was defined as any type of blood disease (benign or malignant) at any status (active or remission). Auto-immune disease was defined as any type of illness that occurs when the body tissues are attacked by its own immune system. Extra-renal IrAEs were defined as auto-immune-like side effects associated with the immunotherapy (included side effects affecting the skin, the gastrointestinal tract, the endocrine system, the lung, the articular system and others). The last follow-up was the date of death or the last visit of the patient.

d- Statistical analysis: To describe the population, we used effectives and percentages for qualitative variables, means, medians and interquartile range for continuous variables. The association between qualitative variables was performed using Fisher's exact tests and the comparisons of continuous variables were performed using Mann-Whitney tests. To analyze

overall survival, AKI-free survival, and a composite outcome merging the two events, the Kaplan-Meier method was used to estimate the median survival and its 95% Confidence interval (CI). We used a log-rank test for univariate comparison of survival and Cox regression models to estimate hazard ratio (HR) and 95% CI. Then multiple Cox regression model was used to test the effect of covariates after adjustment for potential confounders. The effect on overall survival of the occurrence of AKI was tested considering it as a time-dependent covariate. A p-value of 5% or lower was considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Inc., New York, USA) except the effect of AKI (time-dependent covariate) tested using the rms package for R 3.5.2 (The R Foundation for Statistical Computing Platform, Vienna, Austria).

e - Ethics approval: This retrospective study was approved by the institutional review board of the Assistance Publique-Hôpitaux de Marseille (AP-HM, approval number 2018-84) prior to any data collection.

3 - RESULTS

a - Patients:

We analyzed retrospectively 239 of the 343 patients. Among the 104 patients who were excluded (**Figure 1**): 73 had a combination therapy comprising anti-PD1 and Ipilimumab (n=28), an IDO inhibitor (n=29), Urelumab (n=9), Talimogene (n=5), Dabrafenib (n=1), or an anti-LAG3 antibody (n=1); 17 patients were treated by anti-PD1 for an indication other than melanoma; 1 patient was included in a clinical trial of anti-PD1 versus placebo; 5 were followed-up in another center; finally, 8 patients were excluded for a lack of data. The baseline characteristics of the 239 patients analyzed are summarized in **Table 1**. The median follow-up was 352 days from the first day of treatment to the last follow-up.

b - Renal adverse events:

At least one episode of acute kidney injury (AKI) occurred in 41/239 patients (17%). Of these 41 patients, 9 (22%) suffered from CKD prior to the initiation of the immunotherapy. Baseline characteristics of these 41 patients, and comparison with patients who did not develop AKI, are summarized in **Table 2**. Patients with AKI were more likely to display baseline CKD

($p=0.0071$), to be treated with RAAS inhibitor ($p=0.0362$), to have received ipilimumab prior to anti-PD1 therapy ($p=0.0030$) and they had received more cycles ($p<0.0001$) and higher cumulated doses ($p=0.0037$) of anti-PD1 than patients without AKI.

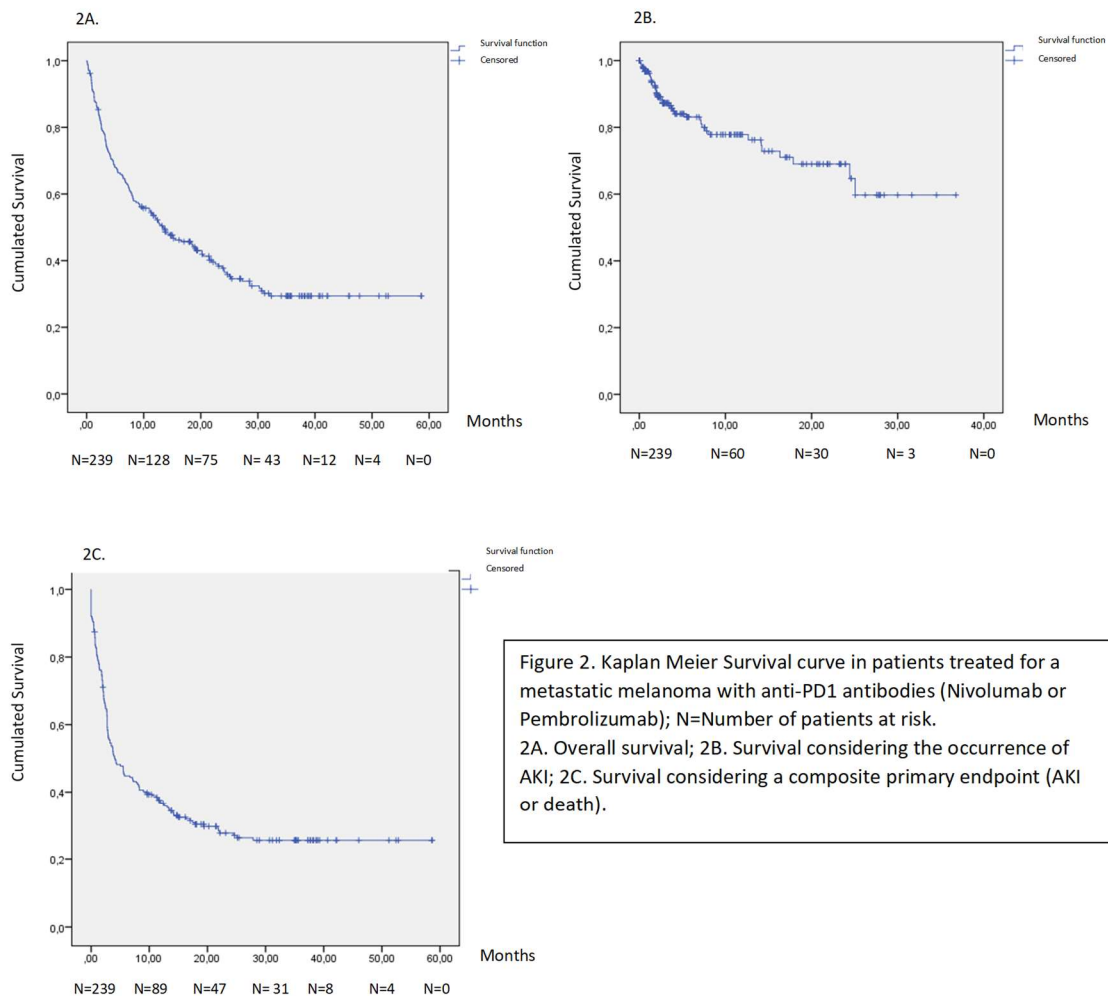
The median follow-up in the 41 patients with AKI was 588 days (IQR [209;822]). The interval from the initiation of anti-PD1 antibodies to the occurrence of AKI ranged from 3 to 763 days, with a median of 65 days (IQR [41;218]). Because only surviving patients could develop AKI, further analysis on the risk factors for AKI were analyzed in patients censored for death.

A unique episode of AKI occurred in 25/239 (10.5%) patients, while 16/239 (6.7%) had at least 2 episodes. Only the first episode of AKI was studied for every patient (included diagnosis and medical management when available). Most patients presented non-severe AKI: grade 1 for 25/41 (61%), grade 2 for 12/41 (29%). Only 2 (5%) patients developed a grade 3 AKI, and 2 (5%) a grade 4 AKI which required emergency dialysis in 1 patient. The causes of AKI could be determined for 22 patients: 11 were pre-renal AKI; 4 were related to a supposed acute interstitial nephritis (AIN), among which 1 was confirmed by a kidney biopsy; 4 were consistent with acute tubular necrosis (ATN); 1 had nephrosclerosis lesions on kidney biopsy; 2 were related to urinary tract obstruction. The cause of AKI remained undetermined in 19 cases.

The medical management of AKI required discontinuation of the anti-PD1 therapy in 11/41 patients, including 4 cases where immunotherapy was not reintroduced. A course of corticosteroid was administered to 7 patients. At the end of the immunotherapy, 20 patients had developed CKD (stage 3 of the KDIGO classification for 17). Among the 9 patients with prior CKD, only one, who displayed stage 4 CKD (diabetic kidney disease and unique congenital kidney) before immunotherapy, reached end-stage renal disease (ESRD) and started chronic dialysis 1 month after the last injection of anti-PD1.

c - Overall survival and risk factors for death

The median overall survival in the 239 patients (**Figure 2A**) was 13.4 months (95%CI: 8.3-18.5). One hundred and fifty-three (64%) patients died during the study period. Importantly, the occurrence of AKI (when considered as a time-dependent covariate) did not impact overall survival with a hazard ratio of 1.26 ($p=0.32$).



In univariate analysis, overall survival was not influenced by gender ($p=0.761$), by age at the beginning of treatment (≥ 65 versus < 65 years, $p=0.830$), by comorbidities such as CKD ($p=0.740$), diabetes ($p=0.854$), hypertension ($p=0.188$), by treatment with non-steroidal anti-inflammatory drugs (NSAID) ($p=0.448$), allopurinol ($p=0.934$), diuretics ($p=0.585$), RAAS inhibitors ($p=0.524$), or by the type of anti PD1 (Nivolumab versus Pembrolizumab, $p=0.805$).

On the contrary, overall survival differed according to the number of line of anti-melanoma therapy (first line or more), to the BMI (<18.5 vs $18.5-24.9$ vs $25-29.9$ vs ≥ 30 kg/m²) and to the baseline prescription of proton pump inhibitors (PPI) and corticosteroids, as shown in **Figure 3**.

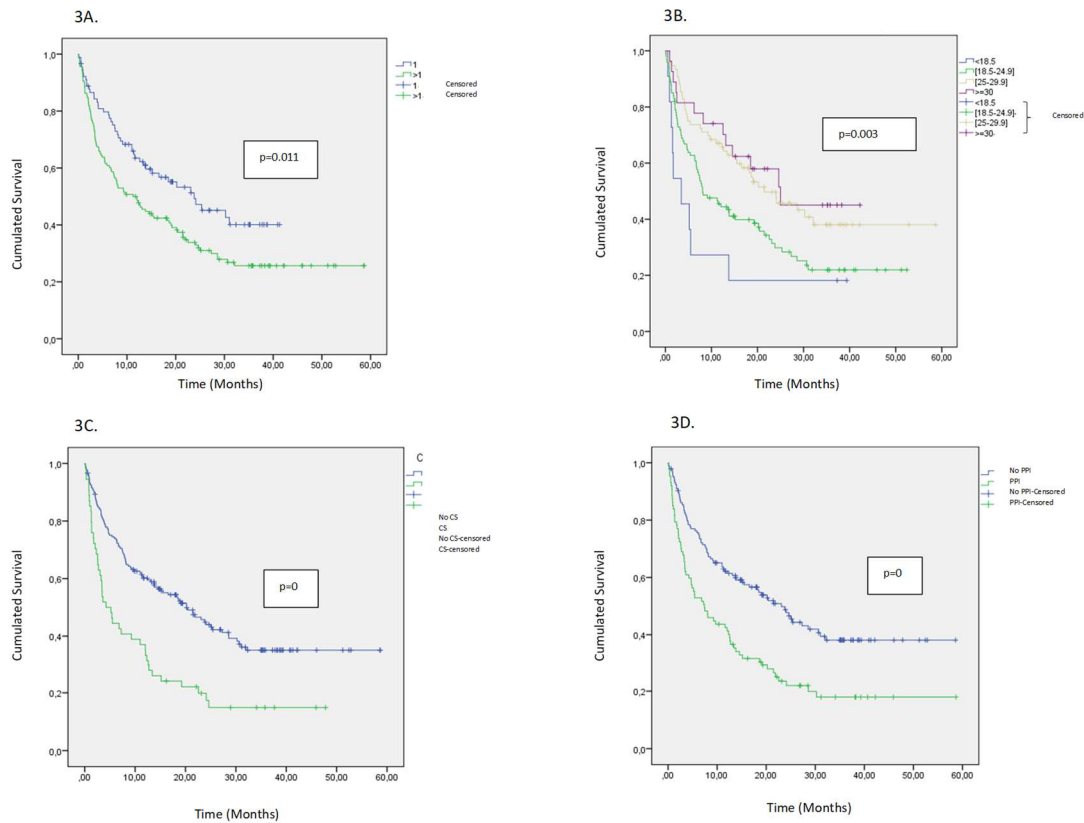


Figure 3. Kaplan Meier overall survival curve in patients treated for a metastatic melanoma with anti-PD1 antibodies (Nivolumab or Pembrolizumab), univariate Cox regression analysis: 3A. Anti-PD1: line number of treatments. 3B. BMI. 3C. Corticosteroids as a baseline treatment. 3D. PPI as a baseline treatment.

In univariate analysis, treatment with anti-PD1 antibodies as a second line at least was associated with an increased risk of mortality compared to treatment with anti-PD1 as a first line therapy (HR=1.58, 95%CI: 1.11-2.25, p=0.012). There was a lower risk of mortality in patients with a BMI 25-29.9 kg/m² (p=0.008) or with a BMI >30 kg/m² (p=0.027) compared to patients with a normal BMI 18.5-24.9 kg/m². Treatment with PPI and corticosteroids at baseline was associated with an increased risk of mortality, with respectively HR=1.95 (95%CI: 1.41-2.71, p<0.0001) for PPI, and HR=2.15 (95%CI: 1.51-3.06, p<0.001) for corticosteroids.

In multivariate analysis, after adjustment for gender, age and number of lines of treatment, overweight and obesity (BMI 25-29.9 kg/m² and BMI >30 kg/m² respectively) were still identified as protecting factors with a lower risk of mortality compared to patients with a normal BMI, with HR= 0.61 (95%CI: 0.409-0.909, p=0.015) for overweight and HR=0.52 (95%CI: 0.279-0.971, p=0.04) for obese patients. As well, when adjusted with gender, age, number of lines and BMI, treatment with PPI and corticosteroids at baseline were still identified as

independent risk factors of mortality, with respectively HR = 1.825 (95%CI: 1.196-2.783, p=0.005) for PPI and HR=1.593 (95%CI: 1.015-2.501, p=0.043) for corticosteroids. Finally, treatment with anti-PD1 antibodies as a second line at least, when adjusted, was not statistically significant anymore.

d - Occurrence of AKI in surviving patients

In patients censored for death, the mean survival without AKI (**Figure 2B**) was 26.4 months (95%CI: 23.5-29.2). Survival without AKI was not influenced by gender (p=0.869), age (\geq 65 vs < 65 years, p=0.211), comorbidities such as diabetes (p=0.138), hypertension (p=0.210), treatment with NSAID (p=0.293), allopurinol (p=0.149), diuretics (p=0.148), type of anti-PD1 antibody (p=0.948), BMI (p=0.982) or the number of lines of treatment (p=0.951). Baseline treatment with RAAS inhibitors (**Figure 4A**) and previous chronic kidney disease (**Figure 4B**) were associated with reduced survival without AKI. Baseline treatment with corticosteroids (**Figure 4C**) and PPI (**Figure 4D**) were also associated with a reduced survival without AKI in univariate analysis. There was a 2.8-fold increase in the risk of AKI in patients with previous CKD (HR 2.82, 95% CI: 1.34-5.91, p=0.006) and a 2-fold increase in the risk of AKI in patients treated with RAAS inhibitors (HR 1.98, 95%CI: 1.07-3.66, p=0.031).

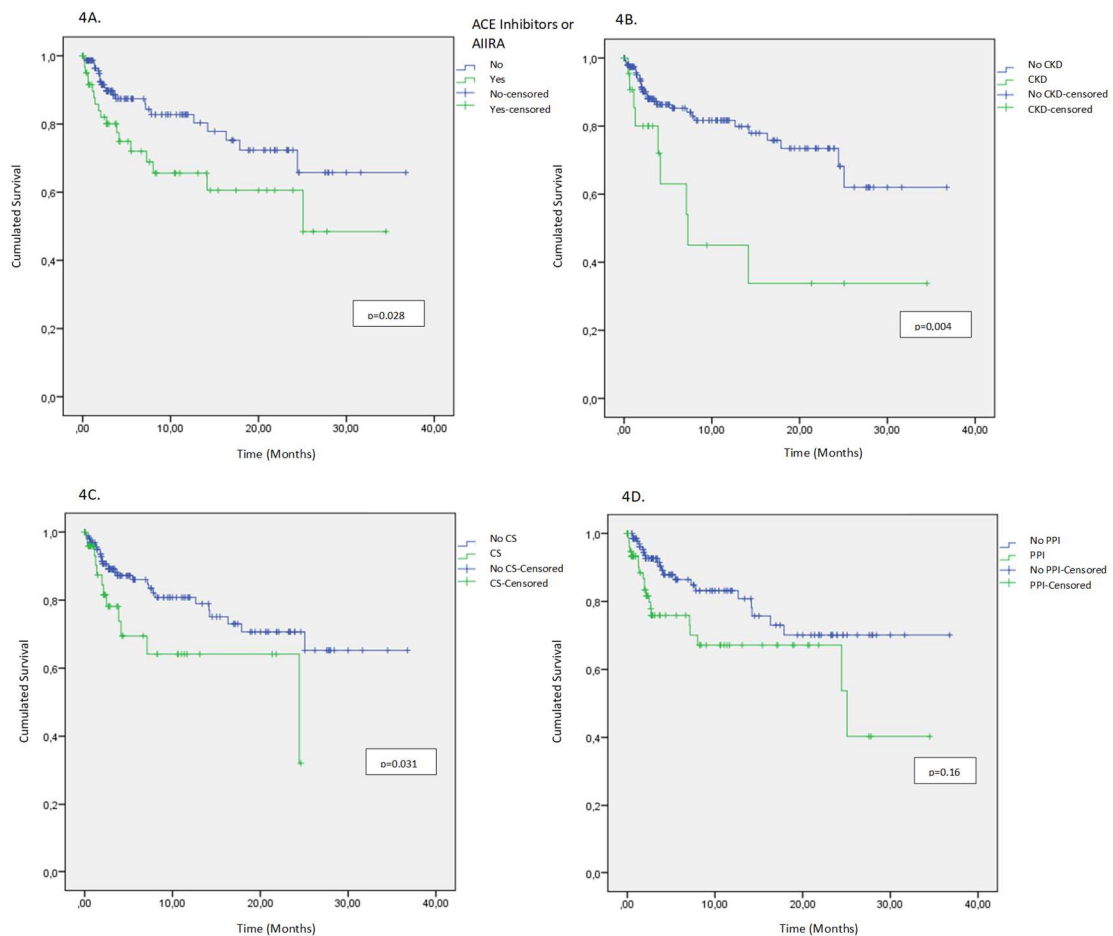


Figure 4. Kaplan Meier survival curve considering the occurrence of AKI in patients treated for a metastatic melanoma with anti-PD1 antibodies (Nivolumab or Pembrolizumab), univariate Cox regression analysis: 4A. ACE inhibitors or AIIRA. 4B. Chronic kidney disease 4C. Corticosteroids as a baseline treatment 4D. PPI as a baseline treatment

e - Composite primary outcome (AKI or death)

When considering a composite primary outcome (AKI or death), the median survival without AKI (**Figure 2C**) was 4 months (95%CI: 2.5-5.6). The number of lines of treatment (1 versus ≥ 2 , $p=0.017$) (**Figure 5A**), the BMI $<25\text{kg}/\text{m}^2$ ($p=0.002$ vs BMI 25-29.9 and $p=0.044$ vs BMI >30) (**Figure 5B**), and the baseline treatment with corticosteroid ($p<0.0001$) (**Figure 5C**) or PPI ($p<0.0001$) (**Figure 5D**) were identified as risk factors for this composite outcome in the univariate cox regression analysis.

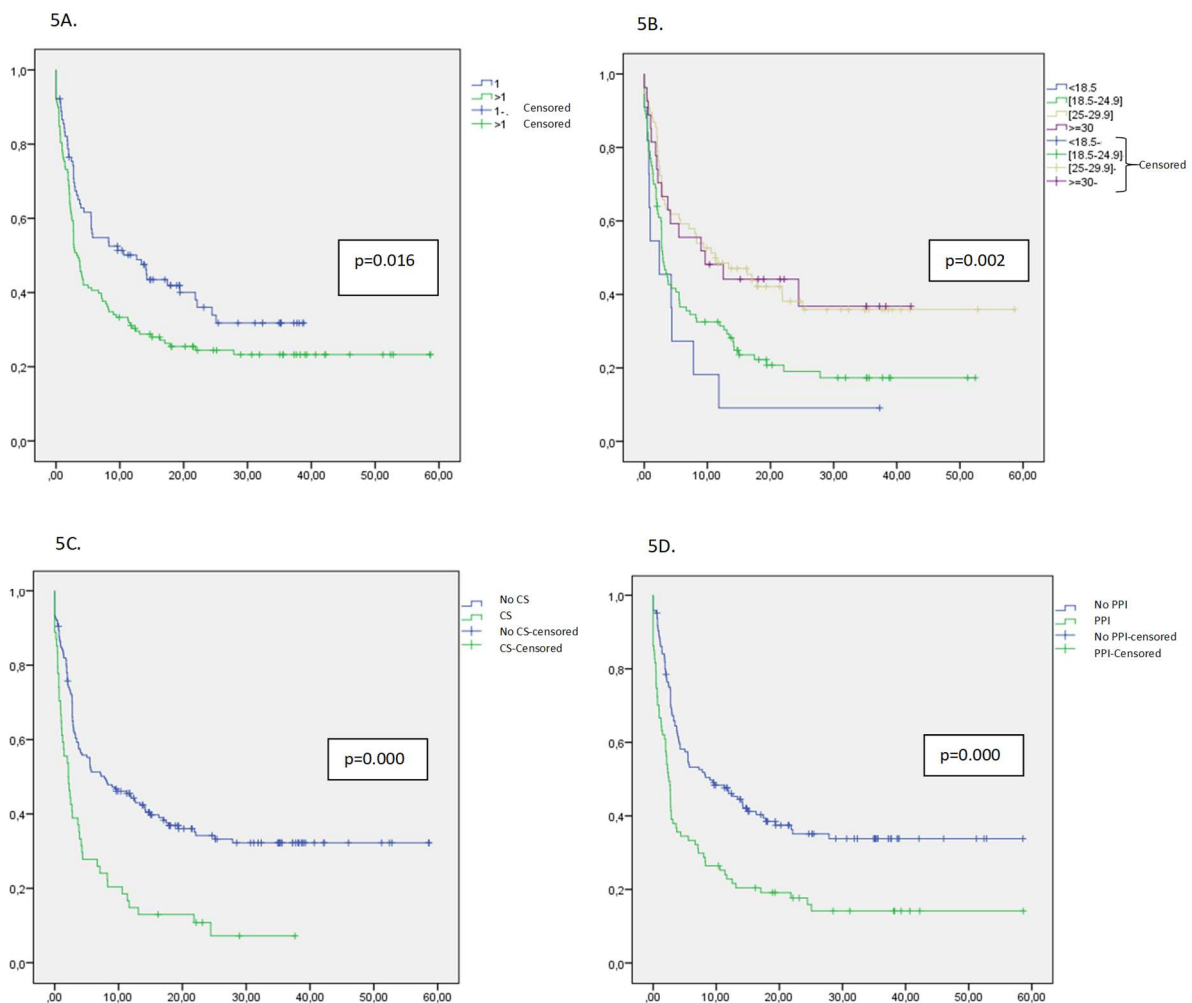


Figure 5. Kaplan Meier survival curve considering a composite primary outcome (AKI or death) in patients treated for a metastatic melanoma with anti-PD1 antibodies (Nivolumab or Pembrolizumab), univariate Cox regression analysis: 5A. Anti-PD1: line number of treatments. 5B. BMI. 5C. Corticosteroids as a baseline treatment 5D. PPI as a baseline treatment

f - Immune related adverse events (IrAEs):

Data concerning extra-renal adverse events were available for 225/239 patients from the cohort. Among them, 117 (52%) presented at least one extra-renal immune related adverse event (IrAE). The 3 most common IrAEs were cutaneous (32%), gastro-intestinal (25.8%) and endocrine (12%). Other IrAEs were respiratory (4.4%), and rheumatological (4%). Skin reactions comprised pruritus (22.7% of patients), vitiligo (13.3%) and rash (6.7%). Gastro-intestinal side effects comprised diarrhea (19.6% of patients) and colitis (3.1%). Endocrine disorders comprised thyroiditis, hypophysitis and diabetes mellitus. Among the 41 patients who developed AKI, 29 (72.5%; one missing data) also presented an extra-renal IrAE.

4 - DISCUSSION

In this monocentric cohort of 239 patients treated for advanced melanoma by anti-PD1 immunotherapy, the median overall survival was 13.4 months. The main objective of this work was to determine the real-life incidence of AKI in this population, and to evaluate the impact of AKI on survival and organ damage (CKD). While AKI occurred in 17% of patients, most episodes were non-severe (grade 1 or 2), with only one patient requiring emergency dialysis, and only 8.8% of patients from the cohort ended-up with CKD. The main identified cause of AKI was pre-renal, and acute interstitial nephritis occurred in 4 patients only (1.7%). Patients treated with RAAS blockers, and patients with baseline CKD, were more likely to experience an episode of AKI. Importantly, the occurrence of AKI did not impact overall survival in this population. Independent risk factors for death were normal BMI (versus overweight or obese patients), and the baseline prescription of proton-pump inhibitors (PPI) and corticosteroids. Of note, non-renal immune-related adverse events occurred in 52% of patients from this cohort.

The incidence of AKI in the present cohort, although higher than that reported in anti-PD1 clinical trials in advanced melanoma (<3% for Nivolumab (5,6,9) and 2-7% for Pembrolizumab (7,8)), is in accordance with other real life cohorts, with unselected patients (13–15). In this retrospective study, all laboratory data, which comprised a systematic dosage of serum creatinine, were analyzed. This allowed a sensitive detection of AKI, taking into account asymptomatic and mild episodes of AKI. Moreover, 10% of patients suffered from CKD prior to the beginning of immunotherapy, which was a risk factor for AKI, as previously reported (16).

Limited data is available in the literature to evaluate the safety and efficacy of immunotherapy in patients with CKD. Herz et al. described a small cohort of patients with a stage 3 CKD treated for metastatic melanoma, without further deterioration of their kidney function (17). One case of accelerated decline in renal function was reported in a CKD patient treated for lung adenocarcinoma with Nivolumab, but he had previously received a combined chemotherapy regimen comprising cisplatin (18).

The most common pathological lesions described in the literature for renal IrAEs related to anti-PD1 are acute interstitial nephritis (AIN) (19,20) and lupus-like immune complex

glomerulonephritis (21,22). IgA nephropathy (23) and nephrotic syndrome due to focal segmental glomerulosclerosis (24) have also been reported with Nivolumab, and more recently AIN associated with glomerular lesions (25). Apart from these renal IrAEs, common causes of AKI are also encountered in patients treated with anti-PD1, like acute tubular necrosis (ATN) (26), pre-renal and obstructive AKI. Pre-renal AKI was the main cause of AKI in the present cohort, possibly favored by gastro-intestinal IrAEs (diarrhea and colitis).

In the literature, the time range of AKI onset in patients treated with anti-PD1 is wide, ranging from 2 days (27) to 10 months, usually between 3-6 months (13,15,19,21). Delayed AKI, occurring after the last dose of anti-PD1, has also been described (13,19). In the present cohort, the interval from initiation of anti-PD1 antibodies to AKI was broad as well, ranging from 3 to 763 days, with a median of 65 days.

Regarding the medical management of AKI (grade 2 and more), oral corticosteroid therapy and discontinuation of immunotherapy are currently recommended in patients with no evidence of pre-renal AKI or urinary obstruction (28). The FDA recommends to monitor patients for elevated serum creatinine prior to and periodically during the treatment with anti-PD1, and to administer corticosteroids at a dose of 1-2 mg/kg/day (prednisone equivalent) followed by corticosteroid taper for life-threatening (grade 4) serum creatinine elevation, or a dose of 0.5-1 mg/kg/day (prednisone equivalent) followed by corticosteroid taper for severe (grade 3) or moderate (grade 2) serum creatinine elevation. Immunotherapy should be permanently discontinued in case of grade 4 AKI, and withheld for grade 3 and 2 AKI (29).

Median overall survival of patients from the present cohort was comparable with that reported in clinical trials (5–8). Age was not associated with survival, as previously described (30). An improved survival was observed in overweight and obese patients, as described in a meta-analysis published in 2018 (31). In this meta-analysis, obesity was associated with a 36% reduction in mortality in patients treated for metastatic melanoma, in particular in male patients treated with immunotherapy or targeted therapy (versus chemotherapy) (31). Several hypotheses have been raised to explain this potential protective effect of obesity. The metabolic and immune dysfunction associated with obesity could be responsible for a chronic stimulation and dysregulation of T cells (32). This chronic inflammatory state of obese patients could modify their response to immunotherapy (33), as could their particular gut microbiome (34–37).

Another interesting finding of this work is that baseline treatments with PPI (37.5% of patients) and corticosteroids (23.3% of patients) were associated with a reduced survival.

The possible deleterious effect of PPI in patients treated with anti-PD1 for melanoma has been suggested once before, in the abstract of a retrospective study of 140 patients treated with ipilimumab alone or in combination with nivolumab (38). The authors suggested that the reduced survival benefit of anti-PD1 observed with PPI might be related to modified inflammatory and immune responses (38). No such association of PPI prescription with mortality was observed in two others retrospective studies, conducted in patients with different types of cancers (21% with melanoma) (39,40) treated with anti-PD1 or PDL-1 therapy (39) or anti-CTLA-4 (40). The proportion of patients treated with PPI in clinical trials from the literature is not notified, and no analysis was conducted regarding their potential association with outcomes. The association of PPI with mortality observed in the present work could be biased, PPI being potentially prescribed to more fragile patients, or to patients treated with corticosteroids. In this study, 76% of the patients treated with corticosteroids had PPI as a baseline treatment as well and 47% of them treated with PPI had corticosteroids, so it could be possible that these two factors are mutually dependant. Yet, this work calls for the evaluation of PPI therapy in future clinical trials of immunotherapy, at least in patients treated for melanoma.

The worse outcome of patients treated with corticosteroids has not been reported before in melanoma, but has been observed in patients treated with immunotherapy for non-small-cell lung cancer (NSCLC). Thus, Arbour et al. reported in 2018 that the use of corticosteroids at the initiation of PDL-1 blockade was associated with worse outcomes in two independent cohorts of patients treated for NSCLC (41). The same negative impact was described in patients exposed to corticosteroids during the first cycle of nivolumab (42). In the present cohort, almost a quarter of patients were receiving corticosteroids at the beginning of anti-PD1 therapy, with a wide range of doses. Although corticosteroids may reduce the immune activation on which relies the efficacy of immunotherapy, these patients could also have presented a more severe melanoma, or a lower tolerance to treatment. Indeed, the two main indications for corticosteroids in this cohort were: brain metastasis (69%) and/or a history of a previous IrAE (64%, mostly related to Ipilimumab). The specific effect of corticosteroids on the outcome of patients treated with anti-PD1 for advanced melanoma is thus uncertain, and this question will not be answered with this work.

Non-renal IrAEs, although frequently reported in medical charts of patients from the present cohort (52%) may have been underestimated in this work, due to its retrospective nature. In clinical trials, IrAEs occurred in 78% of patients treated with Pembrolizumab (10) and 74-97% of patients treated with Nivolumab (5,9). As reported in the literature, skin reactions were the most common IrAEs, followed by diarrhea (11). A past history or current flare of extra-renal IrAE has been described as a risk factor for immunotherapy-related AIN (19), and could warrant a closer monitoring of renal function in these patients. Here, because episodes of AKI were mostly pre-renal, we suggest that extra-renal IrAEs, especially gastro-intestinal, should lead to the suspension of other drugs favoring AKI, such as RAAS inhibitors or diuretics. This study was not meant to test whether non-renal IrAEs could be a predictor for better outcome, as described recently in the literature (43,44). True renal IrAE (e.g., acute interstitial nephritis) was a rare event (1.7%), and globally, AKI did not impact overall survival.

The main strength of this study is its comprehensiveness regarding baseline characteristics and renal follow-up. Although it was a retrospective work, few data were missing. The systematic longitudinal gathering of serum creatinine, from the hospital laboratory and from the patients' laboratory, as part of the close monitoring of immunotherapy, allowed the detection of every episode of AKI in this cohort. Another strength of this work is its focus on patients with advanced melanoma, who displayed few comorbidities, as opposed to patients with broncho-pulmonary cancers for instance, in whom associated cardio-vascular burden could have been a confounding factor on the occurrence of AKI. The main limitation of this study is that not all episodes of AKI were treated with the intervention of a nephrologist, and that in many cases, the cause of AKI remained uncertain.

5 - CONCLUSION

In this real-life cohort study of patients treated with Nivolumab or Pembrolizumab for advanced melanoma, 17% of patients experienced at least one episode of AKI, but only 1.7% of patients had a characteristic renal irAE. The occurrence of AKI did not influence overall survival in this population with a poor vital prognosis, and CKD was not a problematic burden. Overweight and obesity were protective in this cohort. Treatments with PPI and corticosteroids were associated with impaired survival. The proper role of PPI and corticosteroids on patients' outcome remains an unanswered question. The growing use of

anti-PD1 in less severe forms of melanoma in the future could also unveil a long-term impact of AKI episodes.

Conflict of interest: None

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Tables and figures legends:

- Table 1. Baseline characteristics of the final cohort of 239 patients (NA: not available, missing data).
- Table 2. Baseline characteristics of the two groups: AKI versus control (NA: not available, missing data).
- Figure 1. Flowchart
- Figure 2. Kaplan Meier Survival curve in patients treated for a metastatic melanoma with anti-PD1 antibodies (Nivolumab or Pembrolizumab); N=Number of patients at risk. 2A. Overall survival; 2B. Survival considering the occurrence of AKI; 2C. Survival considering a composite primary endpoint (AKI or death).
- Figure 3. Kaplan Meier overall survival curve in patients treated for a metastatic melanoma with anti-PD1 antibodies (Nivolumab or Pembrolizumab), univariate Cox regression analysis: 3A. Anti-PD1: line number of treatments. 3B. BMI. 3C. Corticosteroids as a baseline treatment. 3D. PPI as a baseline treatment.
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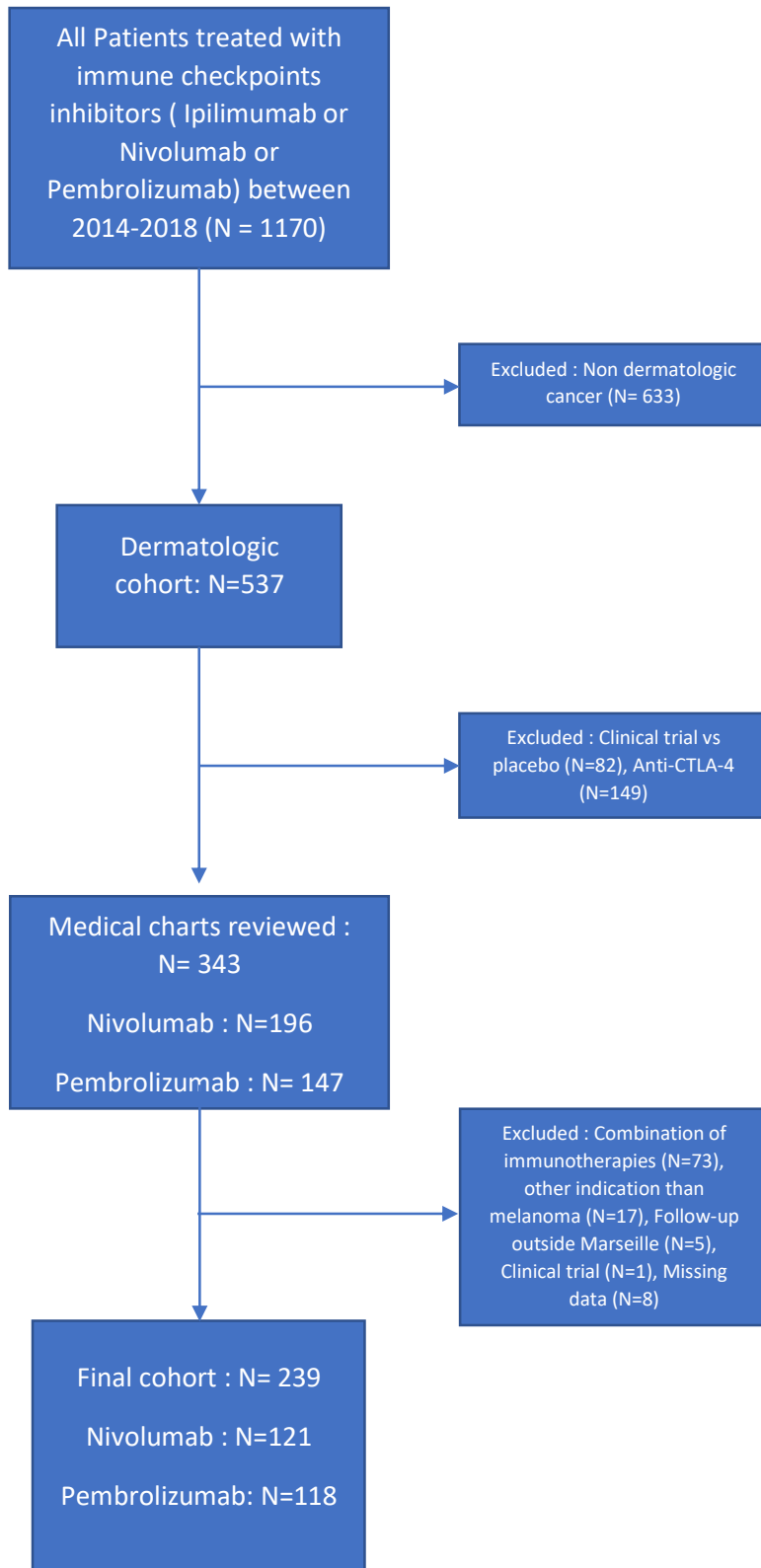


Figure 1. Flowchart

Table 1: Baseline characteristics of the final cohort of 239 patients (NA: not available, missing data).

	N = 239
Gender :	
- Male	132/239 (55.2%)
- Female	107/239 (44.8%)
Age (years) :	
- Mean (range)	66.2 (23-89)
- Median [IQR]	68 [58.5;77]
BMI (kg/m ²) :	
- Mean (range)	25 (16-47)
- Median [IQR]	24 [22;27]
Hypertension	98/232 (42%) NA : 7/239 (2.9%)
Diabetes	27/233 (11.6%) NA : 6/239 (2.5%)
Dyslipidemia	55/233 (23.6%) NA : 6/239 (2,5%)
Autoimmune Disease	34/233 (14.6%) NA : 6/239 (2.5%)
Hemopathy	10/233 (4.3%) NA : 6/239 (2.5%)
Chronic Kidney Disease (CKD)	23/239 (9.6%)
CKD stage III	22/23
CKD stage IV	1/23
Serum creatinine (μmol/L)	
- Mean (range)	79 (35-261)
- Median [IQR]	75 [66 ;86]
eGFR (ml/min/1,73m ²)	
- Mean (range)	82 (22-127)
- Median [IQR]	84 [70 ;94,25]
Smoking	81/226 (36%) NA : 13/239 (5.4%)
RAAS inhibitor	68/232 (29.3%) NA : 7/239 (2.9%)
PPI (Proton Pump Inhibitor)	86/232 (37%) NA : 7/239 (2.9%)
Allopurinol	2/232 (0.9%) NA : 7/239 (2.9%)
NSAID	12/231 (5.2%) NA : 8/239 (3.3%)
Diuretics	35/232 (15.1%) NA : 7/239 (2.9%)
Corticosteroid	54/232 (23.3%) NA : 7/239 (2.9%)
Corticosteroid daily dose (mg)	
- Mean (range)	45 (5-240)
- Median [IQR]	40 [20;42.5]
Melanoma staging (AJCC)	
- IIIB	2/239 (0.8%)
- IIIC	13/239 (5.4%)
- IV	224/239 (93.7%)
Anti-PD1 used	
- Nivolumab	121/239 (50.6%)
- Pembrolizumab	118/239 (49.4%)
N cycles of anti-PD1	
- Mean (range)	16 (1-76)
- Median [IQR]	8 [4;22.5]
Cumulated doses of anti-PD1 (mg) :	
- Mean (range)	3117 (80-16980)

- Median [IQR]	1420 [622.5;4272.5]
Previous lines of treatment:	
- Targeted therapy	82/230 (35.6%) <i>MD : 9/239 (3.8%)</i>
- Ipilimumab	60/229 (26.2%) <i>MD : 11/239 (4.6%)</i>

Table 2. Baseline characteristics of the two groups: AKI versus control (NA: not available, missing data).

	AKI Group (N=41)	No AKI Group (N=198)	p
Gender:			
- Male	18/41 (44%)	109/198 (55%)	0.2296
- Female	23/41 (56%)	89/198 (45%)	
Age (years):			
- Mean (range)	68.3 (40-86)	65.7 (23-89)	0.2226
- Median [IQR]	71 [61;77]	68 [57.2;77]	
BMI (kg/m2):			
- Mean (range)	25 (18-38)	25 (16-47)	0.5480
- Median [IQR]	25 [22.7;27.2]	24 [22;27]	
Hypertension	21/40 (52.5%) NA: 1/41 (2.4%)	77/192 (40.1%) NA: 6/198 (3%)	0.1623
Diabetes	7/40 (17.5%) NA: 1/41 (2.4%)	20/193 (10.4%) NA: 5/198 (2.5%)	0.2739
Dyslipidemia	7/40 (17.5%) NA: 1/41 (2.4%)	48/193 (24.9%) NA: 5/198 (2.5%)	0.4142
Autoimmune Diseases	10/40 (25%) NA: 1/41 (2.4%)	24/193 (12.4%) NA: 5/198 (2.5%)	0,050
Hemopathy	2/41 (4.9%) NA: 0/41 (0%)	8/192 (4,2%) NA: 6/198 (3%)	0.69
CKD	9/41 (22%)	14/198 (7.1%)	0.0071
- CKD stage III	8/9	14/14	
- CKD stage IV	1/9	0/14	
Smoking	16/40 (40%) NA: 1/41 (2.4%)	65/186 (35%) NA: 12/198 (6%)	0.5875
RAAS inhibitors	18/41 (44%) NA: 0/41 (0%)	50/191 (26.2%) NA: 7/198 (3.5%)	0.0362
PPI (Proton Pump Inhibitor)	20/41 (49%) NA: 0/41 (0%)	67/191 (35.1%) NA: 7/198 (3.5%)	0.1116
Allopurinol	1/41 (2.4%) NA: 0/41 (0%)	1/191 (0.5%) NA: 7/198 (3.5%)	0.3228
NSAID	4/41 (9.7%) NA: 0/41 (0%)	8/190 (4.2%) NA: 8/198 (4%)	0.2337
Corticosteroid	12/41 (29.3%) NA: 0/41 (0%)	42/191 (22%) NA: 7/198 (3.5%)	0.3149
Corticosteroid daily dose (mg):			
- Mean (range)	28.4 (10-40)	46.8 (5-240)	0.1227
- Median [IQR]	20 [20;40]	40 [20;60]	
Diuretics	10/40 (25%) NA: 1/41 (2.4%)	25/191 (13.1%) NA: 7/198 (3.5%)	0.0859
Melanoma staging (AJCC) :			
- IIIB	0 (0%)	2/198 (1%)	0,7267
- IIIC	3/41 (7.3%)	10/198 (5%)	
- IV	38/41 (92.7%)	186/198 (94%)	
Anti-PD1 used :			
- Nivolumab	22/41 (53.7%)	99/198 (50%)	0.7328
- Pembrolizumab	19/41 (46.3%)	99/198 (50%)	
N cycles of anti-PD1:			
- Mean (range)	24 (1-67)	14.2 (1-76)	<0,0001
- Median [IQR]	17 [7;40]	7 [4;19.75]	
Cumulated doses of anti-PD1 (mg):			
- Mean (range)	4678 (95-14660)	2717 (80-16980)	0.0037
- Median [IQR]	2820 [1300;9940]	1245 [571.2;3396.5]	

Previous lines of treatment:			
- Targeted therapy	11/39 (28.2%) NA: 2/41 (4.9%)	71/191 (37.2%) NA: 7/198 (3%)	0.3599
- Ipilimumab	17/38 (44.7%) NA: 3/41 (7.3%)	43/190 (22.6%) NA: 8/198 (4%)	0.0030

Abbreviations

Anti-PD1	Anti-Programmed Death receptor-1
AKI	Acute Kidney Injury
IrAEs	Immune-related Adverse Events
ICI	Immune Checkpoints Inhibitors
FDA	Food and Drug Administration
OS	Overall Survival
BMI	Body Mass Index
CKD	Chronic Kidney Disease
NSAID	Non-Steroidal Anti-Inflammatory Drugs
RAAS	Renin-Angiotensin-Aldosterone System Inhibitor
PPI	Proton Pump Inhibitor
eGFR	Estimated Glomerular filtration Rate
AIN	Acute Interstitial Nephritis
ATN	Acute Tubular Necrosis
CI	Confidence Interval
HR	Hazard Ratio
IQR	Inter quartile Range
ESRD	End-Stage Renal Disease
NSCLC	Non-Small-Cell Lung Cancer

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans **aucune discrimination selon leur état ou leurs convictions**. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas **usage de mes connaissances contre les lois de l'humanité**.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai **jamais leur confiance** et **n'exploiterai pas le pouvoir hérité** des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. **Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers** et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.