Safe Anti-PD-1 Re-challenge with Antibody Switching after immune-related adverse events: Brief Communication

ABSTRACT

Aims: To evaluate the safety of rechallenge with a different anti-PD-1 antibody after an immune-related adverse event (irAE) that has prompted the discontinuation of anti-PD-1 therapy. **Patients & Methods:** We describe two patients with metastatic melanoma who developed potentially disabling and early irAEs following anti-PD-1 treatment. Therapy was discontinued and toxicities resolved with corticosteroids. **Results:** Rechallenge switching to an alternative anti-PD-1 antibody did not lead to a new or recurrent irAE. **Conclusions:** Switching to a different anti-PD-1 antibody when resuming therapy after an irAE might be a safe strategy and warrants further investigation. Structural and biological differences between antibodies might explain the different safety outcomes.

SUMMARY POINTS

- Generally, immune checkpoint inhibitors (ICI) are recommended to be permanently discontinued after a grade 3-4 immune-related adverse event (irAE), according to most guidelines.
- Rechallenge with the reintroduction of the same ICI class or the same molecule after a clinically significant irAE is a difficult clinical decision that merits careful balance of risks and benefits, particularly in patients who did not obtained a clinical benefit yet.
- Due to their biological and structural differences, a switch of anti-PD-1 antibody (e.g. nivolumab to pembrolizumab or *viceversa*) might be a safe approach to consider if rechallenge with anti-PD-1 therapy is planned.
- Further investigation (prospective randomized trials or real-world data collected into registries) regarding the optimal approach on how reintroducing ICI after development of severe irAEs is warranted.

TEXT

Programmed cell death-1 (PD-1) blockade has become a cornerstone of cancer treatment in multiple tumor types [1]. Safety is characterized by the emergence of immune-related adverse events (irAEs) that can be severe, disabling and lead to therapy discontinuation [2]. Most clinical trials did not allow immune checkpoint inhibitors (ICI) resumption after a severe irAE. However, re-introduction of ICI is currently becoming a “real-world” scenario for oncologists facing these situations. Here, we report two cases in which switch and re-challenge with an alternative anti-PD-1 antibody following an irAE does not recapitulate the same or a new irAE and allows treatment continuation.

Case Presentations

Case 1 is a 66-year-old male with no relevant past medical history diagnosed with stage IV-M1c (0), BRAF wild-type cutaneous melanoma with bone, soft tissue, lymph nodes and liver metastases. Treatment with nivolumab 3 mg/kg iv 2-weekly was started and the patient was admitted 24 hours after the first infusion because of fever of 39ºC. Ceftriaxone was initiated. During admission serum creatinine increased gradually up to 2.05 mg/dL (0.3 – 1.3) with no signs of dehydration and a normal spontaneous urine balance. A urine analysis showed the presence of 15-20% eosinophils. A renal ultrasound scan (US) showed no abnormalities. No known nephrotoxic drugs were involved. After 3 days, blood and urine culture were negative, and antibiotics discontinued. Because of the suspicion of an immune-related nephritis, a kidney biopsy was performed, and the patient was started on methylprednisolone 1mg/kg iv daily. Two days later, creatinine improved to 1.64 mg/dL and the patient was

discharged on tapering doses of prednisone. A kidney biopsy demonstrated an acute tubule-interstitial nephritis with focal inflammatory infiltrates without immune-mediated complexes evidenced by immunofluorescence (Figure 1). Nivolumab was discontinued due to the histological confirmation nephritis associated with a grade 2 creatinine increased according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Three weeks later, serum creatinine level was within the normal range and corticosteroids were discontinued. During the following month, the patient required bone radiotherapy and a surgical fixation of the head of the left femur due to a bone metastasis. A CT scan performed 12 weeks after the only dose of nivolumab given showed a partial response which was maintained over 6 months with no anti-PD-1 treatment. At disease progression, the patient was concerned to receive the same anti-PD-1 and agreed to anti-PD-1 retreatment with pembrolizumab (2 mg/kg iv every 3 weeks). At anti-PD-1 resumption the patient had no symptoms or laboratory value abnormalities and was on no immunosuppression. He received 3 doses of pembrolizumab 3-weekly over the course of 10 weeks with no evidence of adverse events (Figure 2 A), but unfortunately treatment was discontinued due to progressive disease and he was transitioned to hospice care.

Case 2 is a 68-year-old woman with no relevant past medical history who was diagnosed with a stage IV uveal melanoma. Staging PET-CT scan showed lung and lymph node metastases and no liver metastases. Blood tests prior to treatment showed no abnormalities. First-line treatment with pembrolizumab 2 mg/kg iv every 3 weeks was started. Prior to the second dose, blood tests

showed a grade 3 transaminitis (aspartate aminotransferase, AST 211 U/L and alanine aminotransferase, ALT 215 U/L, normal range 5 – 40), according to CTCAE v5.0, with bilirubin within normal range. Serologic tests for hepatitis B and C were negative. An abdominal US ruled out liver metastases and bile duct alterations. Prednisone 1 mg/kg/day *po* was initiated and pembrolizumab interrupted. Four weeks later, AST and ALT were within normal range and steroids were withdrawn. Re-challenge with anti-PD-1 was considered and agreed with the patient a switch to nivolumab. The patient initiated nivolumab 3mg/kg iv 2-weekly, two weeks after the last dosing of corticosteroids; and received a total of 6 doses of nivolumab over the course of 12 weeks with an excellent tolerance (Figure 2 B). Restaging imaging showed progressive disease, no liver metastases were described. Subsequently, she received a second line of therapy with anti-CTLA-4 monotherapy for four doses without further progression. She developed a hypophysitis and no other irAEs.

Discussion

Published guidelines of irAE management by different groups and widely recognized societies are based on the algorithms developed during the conduct of clinical trials with ICIs and expert consensus[3-5]. Generally, these guidelines recommend the permanent discontinuation of ICI following a grade 3-4 irAE. Resuming ICIs after a potential life-disabling irAEs requires a thorough discussion with the patient to balance the risk-benefit ratio for a recurrent or new severe and permanent decline in organ function. A recent review describes three possible ways of retreating patients with ICIs after a severe irAE: a class switch from anti-PD-(L)1 to anti-CTLA-4 therapy or vice versa; a rechallenge

with the reintroduction of the same class agent, or the same molecule and ICI resumption concomitantly with immunosuppressive therapy[6]. Limited data are available on any of these strategies and although interesting reports have been published, the lack of clinical trials makes that rechallenge with ICI still remains an open debate and it is not accurately addressed in clinical guidelines.

A class switch of ICI is a feasible option for melanoma patients, for whom both anti-PD-1 and anti-CTLA-4 therapies are approved. A retrospective analysis from Menzies *et al* [7] that included 67 melanoma patients who discontinued ipilimumab due to severe irAEs (86% grade≥ 3) were subsequently treated with anti-PD-1. Thirty-four percent of patients develop new/different irAEs with anti-PD-1 and 21% had grade 3-4 irAEs suggesting a potential overlap in susceptibility to severe irAEs. Another study assessed the safety of ipilimumab following failure of anti-PD-1 therapy[8]. Globally, 35% of patients receiving ipilimumab after anti-PD-1 developed grade 3-4 irAEs. When considering the sequencing from one class of ICI to another, the relatively long half-life of the agents and the duration of receptor occupancy of peripheral blood T cells, can be important considerations as class switching may be equivalent to giving these agents combined with a possibly higher chance of inducing irAEs.

Resuming ICIs de-escalating to a single-based anti-PD-1 therapy after an irAE secondary to anti-CTLA-4 and anti-PD-1 combination can be considered for selected patients with appropriate monitoring thus 50% of rechallenged patients develop recurrent or distinct irAEs, most frequently grade 1-2 events; and, 30% of patients discontinue the resumed anti-PD-1 due to irAEs of any grade[9].

However, it is unclear which is the optimal approach in case of anti-PD-1 monotherapy interruption due to a potentially life-disabling irAE. In a retrospective study of lung cancer patients from Santini and colleagues[10], 38 patients were retreated with anti-PD-(L)1 monotherapy after discontinuation due to toxicity, including 14 (37%) and 24 (63%) patients who had received an anti-PD-1 plus anti-CTLA-4 combination and an anti-PD-(L)1 single agent, respectively. The first irAE was grade 1-2 in 25 (66%) patients and grade 3-4 in 13 (34%) patients. Among the re-challenged population, 10 (26%) patients had a recurrence of the initial irAE and 10 (26%) patients a distinct irAE, which were severe (grade 3-4) in 8 out of 20 cases (40%). The majority of the new/recurrent irAEs occurred early and were manageable; however, 2 treatment-related deaths occurred. Following retreatment, 5 patients (13%) experienced a partial response. Similarly, Simonaggio *et al*[11] recently published a retrospective study of anti-PD-(L)1 re-challenge following a grade 2 or higher irAE in 40 patients with a broad spectrum of cancers who discontinued ICI. Patients had received anti-PD-1 as monotherapy (65%), anti-PD-1 combined with anti CTLA-4 (10%) or combined with another agent (7.5%); anti-PD-L1 monotherapy (12.5%) or anti-PD-L1 combined with other drug (2.5%). In their report, among the 40 patients retreated with anti-PD-(L)1, the same irAE (42.5%) or a new irAE (12.5%) occurred in 22 patients (55%) with no increase in severity. Interestingly, an early onset and the need for hospitalization due to the severity of the initial irAE leading to ICI interruption was linked to a higher likelihood of a recurrent or new irAE with re-challenge. Neither of these studies detail whether the patients were retreated with the same anti-PD-(L)1 or if they were switched to an alternative anti-PD-(L)1 antibody. Both studies suggest that rechallenge

with anti-PD-(L)1 in patients with different cancers is acceptable with close monitoring, and permanent discontinuation of ICI a reasonable option in those cases where an objective response has been achieved.

Another retrospective study from Abu-Sbeih *et al*[12] assessed specifically the safety of ICI resumption in 167 patients with different cancers after immune-mediated diarrhea and colitis (IMDC) following ICI therapy. Patients had received anti-CTLA-4 (28%), anti-PD-(L)1 (47%) and combination with anti-CTLA-4 and anti-PD-1 (25%).135 and 32 patients resumed anti-PD-(L)1 and anti-CTLA-4 therapy, respectively, most frequently because of continued therapy. IMDC recurred in 57 patients (34%) overall, mostly grade 1-2 in severity; 43 patients (32%) after anti-PD-(L)1 and in 14 patients (44%) following anti-CTLA-4 resumption; 82% required immunosuppressive therapy for recurrent IMDC, and all required permanent discontinuation of ICI therapy. This analysis suggests that resumption of ICI after IMDC in many patients can be considered, especially anti-PD-1/L1.

Case reports have also described successful rechallenge with the same class agent but different molecule in different scenarios. Swami *et al*[13] retreated a patient with atezolizumab (anti-PD-L-1) after nivolumab (anti-PD-1) discontinuation due to persistent polyarthritis that required corticosteroids and methotrexate. Symptoms improved and immunosuppressant requirements decreased suggesting that a switch from anti-PD-1 to anti-PD-L1 or *viceversa* can be a safe, hypothetically thanks to a differential expression of PD-1 and PD-L1/2 across different cell types. In the case reported by Lepir *et al*[14], a patient was initially treated with nivolumab showing progressive disease and a switch to pembrolizumab was decided. The patient experienced a partial

response and the authors proposed that pharmacodynamics differences between these antibodies might be responsible of this phenomenon.

Lastly, some authors support the strategy of rechallenge with concurrent immunosuppression[6, 15, 16], although limited data is available. In a recent retrospective study, ICIs were restarted after IMDC resolution, concomitantly with vedolizumab, an $\alpha4\beta7$ integrin inhibitor that blocks T cell trafficking to the gut, and only one out of eight patients had recurrence of irAEs compared to three out of six who did not receive vedolizumab[17]. Similarly, Badran *et al*[18] resumed concurrent ICIs (pembrolizumab; ipilimumab; ipilimumab and nivolumab, or cemiplimab) and anti-TNFα therapy (infliximab) in a cohort of 5 patients with different malignancies who developed immune-related colitis refractory to corticosteroids. All patients were able to continue ICI therapy without recurrence of symptoms. Concurrent immunosuppressants and ICI therapy did not seem to impact negatively on tumor control and was associated with a better side effect profile. An ongoing phase I clinical trial (NCT03293784)[19] is evaluating the safety and tolerability of treating metastatic melanoma with ICIs combined with either infliximab or certolizumab, a similar anti-TNFα agent, to avoid the onset of irAEs.

Herein we report two cases of safe re-challenge following clinically significant irAE by switching the anti-PD-1 antibody. On presentation with symptoms, patients 1 and 2 were initiated on corticoid therapy for irAEs and achieved a good control. The decision to resume ICI after irAEs carries a risk of relapse of the same or a new irAE, as discussed earlier, and is often done on an individual

basis. We suggest that anti-PD-1 antibody switching might be considered in patients who develop severe or disabling irAEs early in their immunotherapy course where additional immunotherapy is likely to provide a benefit, and where other treatment alternatives are either unavailable or have a low likelihood of providing benefit. Because some toxicities are deemed too serious (e.g. neurologic toxicities, severe pneumonitis or cardiac events) to resume any immune therapy, clinicians should use critical judgement and caution in resuming or switching anti-PD-1 in patients with life-threatening irAEs. Prospective data will be necessary, however, to clearly define toxicities where anti-PD-1 switching might be both safe and lead to improved tumor outcomes.

Nivolumab and pembrolizumab are both IgG4 kappa with high affinity and specificity against PD-1[20]. Both antibodies have overlapping indications for the treatment of solid tumors and they have never been compared in a face-to-face clinical trial. However, structural and biological differences exist among them. First, whereas pembrolizumab is an engineered humanized antibody, nivolumab is fully human. The strength with which an antibody binds the target molecule also differs among them: while nivolumab affinity measured as K_D (equilibrium dissociation constant) is 3.06 pM, pembrolizumab K_D is 29 pM. Moreover, the epitope regions, where the different antibodies bind to PD-1, are not identical. Pembrolizumab shows a much greater overlap with the PD-L1 binding site than nivolumab and there is practically no overlap between the binding sites, dominated by interactions with the PD-1 N-loop in the case of nivolumab and the PD-1 CD loop in the case of pembrolizumab[20-23]. All these distinctive characteristics might generate slight differences in their clinical

efficacy and safety profile. We postulate that these biological and structural differences, together with a hypothetical intrinsic genetic tendency for toxicity of each individual, might trigger a particular immune response to a specific antibody leading to an early onset and severe irAE. Epitope prediction analysis and/or antigen-antibody reactivity tests in patient tissue[24] might help to elucidate our findings and hypothesis.

Randomized studies have shown that patients treated with combination ipilimumab and nivolumab and who experience clinically significant irAEs have high response rates and excellent clinical outcomes with observation alone [25, 26]. Thus, many patients with ongoing stable or responding disease may not need to resume ICI therapy. However, patients who experience a severe or life-disabling irAE early while on anti-PD-1 therapy may benefit from anti-PD-1 switching when a dramatic progressive disease or a rapid clinical response have not yet been shown. Certainly, we cannot rule out that resuming the same anti-PD-1 agent might have achieved a similar outcome. Prospective data will be necessary to clearly define populations where is both safe and leads to improved tumor outcomes.

Our experience helps provide evidence of the safety of anti-PD-1 switching and we propose this may promote the initiation of prospective or collaborative retrospective studies to examine the impact of resuming the same anti-PD-1 antibody or switching to a different anti-PD-1 on both irAEs and antitumor activity.

In conclusion, this report provides our experience in resuming anti-PD-1 therapy following a potentially disabling and early onset irAE by antibody switching. We postulate that disparities in antibody properties such as class, recognition of different epitope region or affinity might be responsible of the clinical success of this approach. We believe that this strategy warrants further investigation, either in the context of a clinical trial or by collecting the experience from additional centers. In addition, it might be a strategy to consider especially if no further effective treatments are available and no clinical benefit has not yet been obtained.

REFERENCES

1. Xin Yu J, Hodge JP, Oliva C, Neftelinov ST, Hubbard-Lucey VM, Tang J. Trends in clinical development for PD-1/PD-L1 inhibitors. *Nat. Rev. Drug Discov.* 19(3), 163-164 (2020).
2. Wang DY, Johnson DB, Davis EJ. Toxicities Associated With PD-1/PD-L1 Blockade. *Cancer J.* 24(1), 36-40 (2018).
3. Brahmer JR, Lacchetti C, Schneider BJ *et al*. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J. Clin. Oncol.* 36(17), 1714-1768 (2018).
4. Puzanov I, Diab A, Abdallah K *et al*. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J. Immunother. Cancer* 5(1), 95 (2017).
5. Haanen J, Carbonnel F, Robert C *et al*. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 29(Suppl 4), iv264-iv266 (2018).

   *Clinical guidelines for immune-related adverse events management from the European Society of Medical Oncology
6. Haanen J, Ernstoff M, Wang Y *et al*. Rechallenge patients with immune checkpoint inhibitors following severe immune-related adverse events: review of the literature and suggested prophylactic strategy. *J. Immunother. Cancer* 8(1), (2020).

   **A review of retrospective data of rechallenge patients with immune-checkpoint inhibitors after severe immune-related adverse events. The authors also suggest a prophylactic strategy for reintroduction of therapy in combination with immunosupressors
7. Menzies AM, Johnson DB, Ramanujam S *et al*. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann. Oncol.* 28(2), 368-376 (2017).
8. Bowyer S, Prithviraj P, Lorigan P *et al*. Efficacy and toxicity of treatment with the anti-CTLA-4 antibody ipilimumab in patients with metastatic

melanoma after prior anti-PD-1 therapy. *Br. J. Cancer* 114(10), 1084-1089 (2016).

9. Pollack MH, Betof A, Dearden H *et al*. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. *Ann. Oncol.* 29(1), 250-255 (2018).

10. Santini FC, Rizvi H, Plodkowski AJ *et al*. Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC. *Cancer Immunol. Res.* 6(9), 1093-1099 (2018).

11. Simonaggio A, Michot JM, Voisin AL *et al*. Evaluation of Readministration of Immune Checkpoint Inhibitors After Immune-Related Adverse Events in Patients With Cancer. *JAMA Oncol.* doi:10.1001/jamaoncol.2019.1022 (2019).

    **A retrospective study of rechallenge immune-checkpoint inhibitors in cancer patients who discontinued due to immune-related adverse events. A total of 31 patients were rechallenged with anti-PD-(L)1 monotherapy after anti-PD-(L)1 single agent treatment.

12. Abu-Sbeih H, Ali FS, Naqash AR *et al*. Resumption of Immune Checkpoint Inhibitor Therapy After Immune-Mediated Colitis. *J. Clin. Oncol.* 37(30), 2738-2745 (2019).

13. Swami U, Lenert P, Furqan M, Abu Hejleh T, Clamon G, Zhang J. Atezolizumab after Nivolumab-Induced Inflammatory Polyarthritis: Can Anti-PD-L1 Immunotherapy Be Administered after Anti-PD-1-Related Immune Toxicities? *J. Thorac. Oncol.* 13(6), e102-e103 (2018).

14. Lepir T, Zaghouani M, Roche SP *et al*. Nivolumab to pembrolizumab switch induced a durable melanoma response: A case report. *Medicine (Baltimore)* 98(2), e13804 (2019).

15. Martins F, Sykiotis GP, Maillard M *et al*. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. *Lancet Oncol.* 20(1), e54-e64 (2019).

16. Esfahani K, Elkrief A, Calabrese C *et al*. Moving towards personalized treatments of immune-related adverse events. *Nat. Rev. Clin. Oncol.* 17(8), 504-515 (2020).

17. Abu-Sbeih H, Ali FS, Wang X *et al*. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis. *J. Immunother. Cancer* 7(1), 93 (2019).
18. Badran YR, Cohen JV, Brastianos PK, Parikh AR, Hong TS, Dougan M. Concurrent therapy with immune checkpoint inhibitors and TNFalpha blockade in patients with gastrointestinal immune-related adverse events. *J. Immunother. Cancer* 7(1), 226 (2019).
19. Montfort A, Filleron T, Virazels M *et al*. Combining Nivolumab and Ipilimumab with Infliximab or Certolizumab in Patients with Advanced Melanoma: First Results of a Phase Ib Clinical Trial. *Clin. Cancer Res.* 27(4), 1037-1047 (2021).
20. Fessas P, Lee H, Ikemizu S, Janowitz T. A molecular and preclinical comparison of the PD-1-targeted T-cell checkpoint inhibitors nivolumab and pembrolizumab. *Semin. Oncol.* 44(2), 136-140 (2017).
    **A molecular, preclinical and early clinical comparison of nivolumab and pembrolizumab anti-PD-1 antibodies.
21. Lee JY, Lee HT, Shin W *et al*. Structural basis of checkpoint blockade by monoclonal antibodies in cancer immunotherapy. *Nat. Commun.* 7 13354 (2016).
22. Tan S, Zhang H, Chai Y *et al*. An unexpected N-terminal loop in PD-1 dominates binding by nivolumab. *Nat. Commun.* 8 14369 (2017).
23. Na Z, Yeo SP, Bharath SR *et al*. Structural basis for blocking PD-1-mediated immune suppression by therapeutic antibody pembrolizumab. *Cell Res.* 27(1), 147-150 (2017).
24. Jing Y, Liu J, Ye Y *et al*. Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. *Nat. Commun.* 11(1), 4946 (2020).
25. Postow MA, Chesney J, Pavlick AC *et al*. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N. Engl. J. Med.* 372(21), 2006-2017 (2015).
26. Larkin J, Chiarion-Sileni V, Gonzalez R *et al*. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N. Engl. J. Med.* 381(16), 1535-1546 (2019).

FIGURES

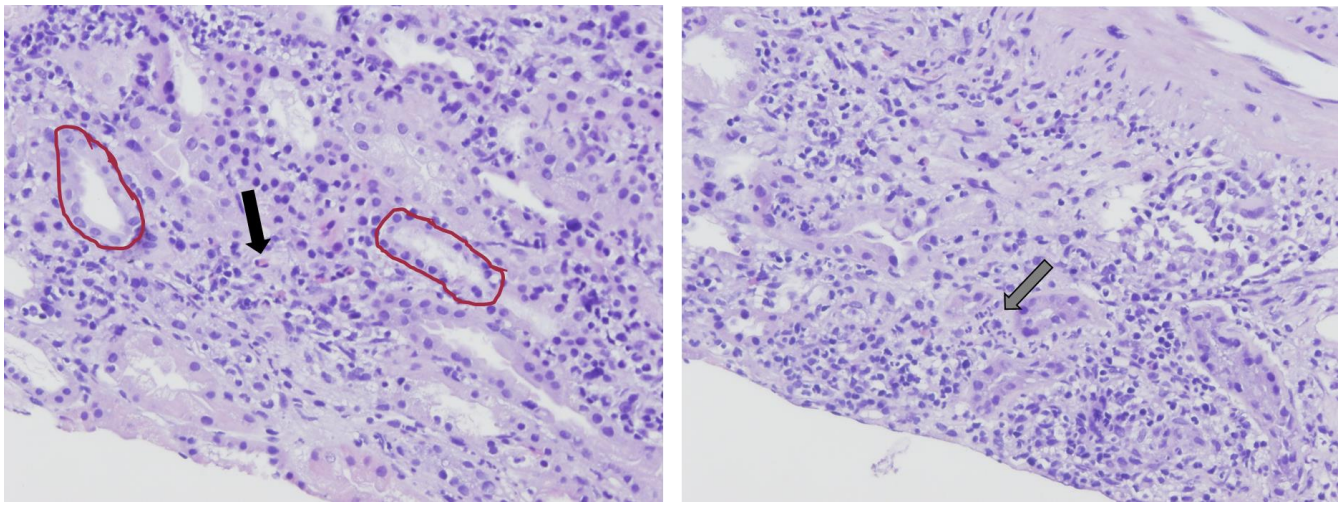

Figure 1. Percutaneous renal biopsy (hematoxylin-eosin stain) with acute tubule-interstitial nephritis. Acute tubulitis (red line, left panel) with mixed focal inflammatory lymphocytic (grey arrow, right panel), neutrophilic and eosinophilic (black arrow, left panel) infiltrates. Multiple immunofluorescence assays, including C3, C4, IgA, IgG, IgM and fibrinogen were negative.

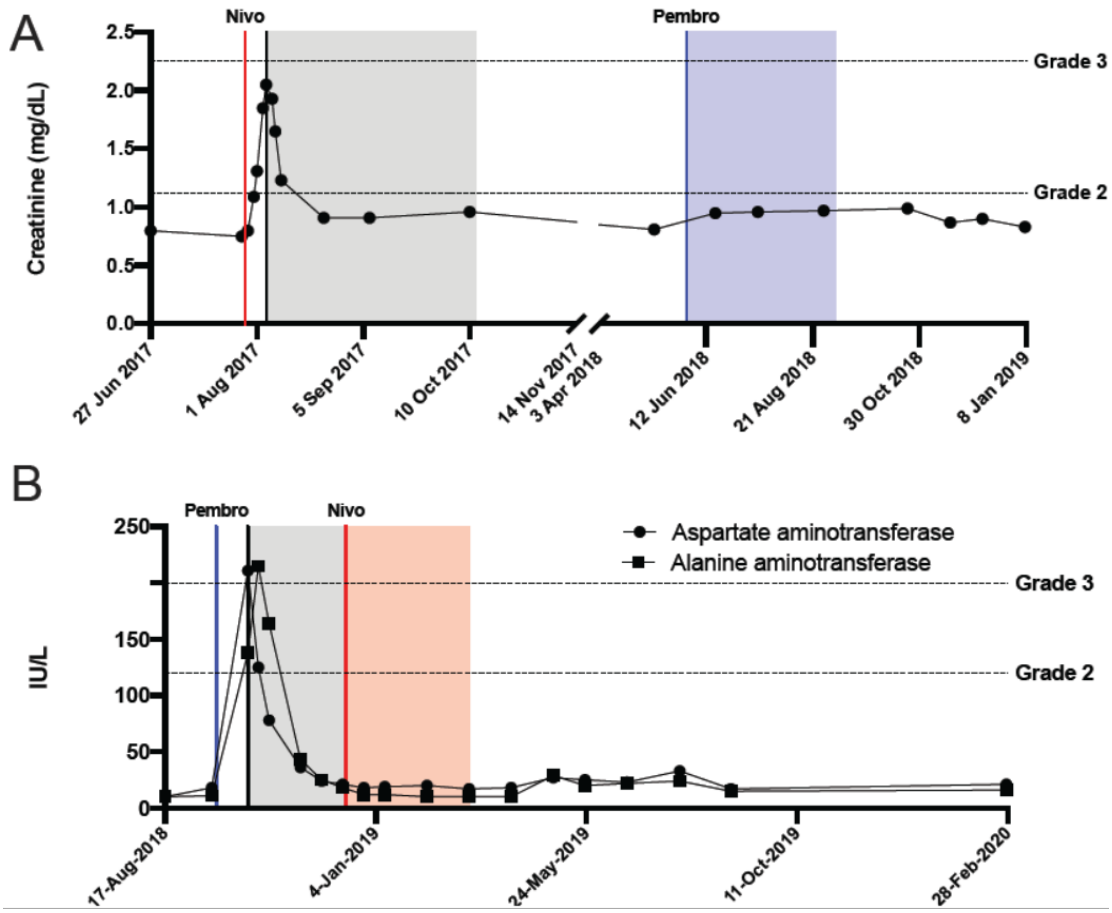

Figure 2. Patients timelines showing treatments and immune-related adverse events. Red line and shade, Nivolumab treatment; blue line and shade, Pembrolizumab treatment; gray shade, corticosteroids treatment.
A, serum creatinine levels of patient 1
B, serum aspartate and alanine aminotransferase of patient 2

TABLES

Table 1. Retrospective studies evaluating rechallenge with anti-PD-(L)1 following an irAE

Study	Number of patients rechallenged	Tumor type	Initial ICI target	ICI at rechallenge	Initial irAE	irAE at rechallenge	Recurrent irAE	New irAE	ORR	Anti-PD-(L)1 to anti-PD-(L)1	irAE at rechallenge anti-PD-(L)1 to anti-PD-(L)1
Menzies *et al* [7]	67	Melanoma	Ipilimumab	Anti-PD-1	Grade 3-4: 86%	25 (67%) Grade 3-4: 21%	2 (3%)	23 (34%)	40%	-	-
Pollack *et al* [9]	80	Melanoma	Anti-CTLA-4 + anti-PD-1	Anti-PD-1	Grade 2: 31% Grade 3-4: 69%	40 (50%) Grade 1-2: 65% Grade 3-5: 35%	14 (18%)	9 (11%)	70%	-	-
Santini *et al* [10]	38	NSCLC	PD-(L)1: 24 (63%) PD-(L)1 + CTLA-4: 14 (37%)	Anti-PD-(L)1	Grade 1-2: 66% Grade 3-4: 34%	20 (53%) Grade 1-2: 60% Grade 3-4: 40%	10 (26%)	10 (26%)	13%	24 (63%)	NR
Simonaggio *et al* [11]	40	Melanoma (28%), lung (15%), lymphoma (15%), colorectal (15%), other (27%)	PD-1: 26 (65%) PD-L1: 5 (12.5%) PD-1 + CTLA-4: 4 (10%) PD-(L)1 combination: 4 (10%)	Anti-PD-(L)1	Grade 2: 47.5% Grade 3-4: 52.5%	22 (55%) Grade 2: 38% Grade 3-4: 62%	17 (42.5%)	5 (12.5%)	35% (3 patients not evaluated)	31 (77.5%)	NR

Abu-Sbeih *et al* [12]	167*	Melanoma (54%), NSCLC (16%), genitourinary (10%), other (20%)	PD-(L)1: 79 (47%) CTLA-4: 47 (28%) PD-1 + CTLA-4: 41 (25%)	Anti-CTLA-4 (19%) Anti-PD-(L)1 (81%)	Grade 3-4: 35.5%†	NR	34 (34%) Grade 1-2: 89% Grade 3-4: 10.5%	NR	NR	71 (42.5%)	26 (37%)

ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event; ORR, objective response rate; NSCLC, non-small cell lung cancer; NR, not reported.
*Rechallenge because of cancer progression or relapse in 48 patients (29%).
†This study only included immune-related diarrhea and colitis.