638 PLASMA PROTEOME ANALYSIS IN PATIENTS WITH IMMUNE CHECKPOINT INHIBITORS RELATED ARTHRITIS AND PNEUMONITIS

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Background Immune checkpoint inhibitors (ICIs) have resulted in unprecedented advances in the treatment of cancer. By disinhibiting the immune system, they enhance anti-tumor immunity, but provoke off-target inflammatory and immune-related adverse events (irAEs) which can seriously impact morbidity and mortality. The exact immunobiology of irAEs is not completely understood, but may involve specific immune pathways. To date, there is no validated biomarker test to predict the development of irAEs in patients treated with ICIs.

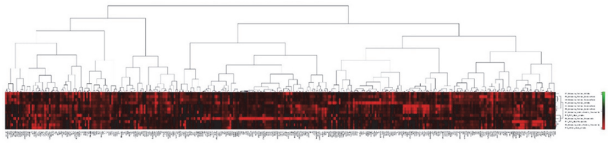
Methods To identify possible biomarkers of irAEs, we performed in-depth proteomic profiling of blood samples obtained from cancer patients receiving ICIs. The plasmas were processed with Hu-14 immuno-depletion column (Agilent Technologies) and the samples were labeled with TMT (Thermo Scientific). The proteins were next pre-fractionated with HPLC, trypsin digested and analyzed by nanoAQUITY LC coupled Synapt G2-Si ion-mobility mass spectrometry (WATERS).

Results A total of 12 patients were enrolled in the study; all were receiving anti-programmed cell death-1 (PD-1) agents. Cancer types included melanoma (n=9), renal cell carcinoma (n=2), and non-small cell lung cancer (n=1). Eight patients had irAEs with active toxicity symptoms at blood draw (4 with pneumonitis-irAE and 4 with arthritis-irAE); 6 of those patients were receiving corticosteroids (ranging from 5 to 60 mg/d), and 1 was receiving tocilizumab (an anti-IL-6 receptor antibody). Four patients who completed a minimum of one year of anti-PD1 treatments without irAEs were enrolled as control group. Median time from ICI initiation until blood draw was 16 months (range, 4–31) among patients with irAEs and 23 months (range, 17–28) among controls.We identified 925 protein gene products from 2.5 million mass spectra that can cover 107 dynamic range of plasma proteins. Among them, 19 proteins showed statistically significant differences between patients with and without irAEs ($P<0.05$) (figure 1). Nine proteins including CFB, CLEC3B, ITIH4, HPX, RARRES2, TF, OAF, MYL12A, and MYL12B were significantly upregulated in patients with irAEs; MYL12A and MYL12B are known to be elevated in airway inflammation of lung tissues. While, 10 other proteins including APOC4, AVPR2, B9D1, DPEP2, JCHAIN, LINC00238, PLG, RAB40C, TCF4, and ZFP30 were significantly downregulated in patients with irAEs (figure 2).

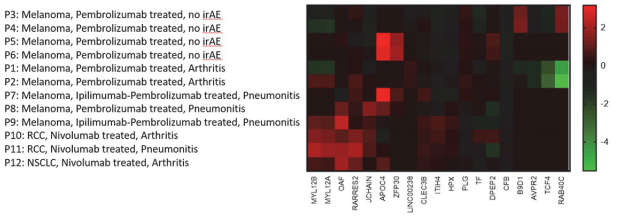
Conclusions In-depth plasma proteome analysis identified possible biomarkers of adverse events modulated by ICI treatment. We plan a prospective validation cohort study of melanoma patients initiating treatment with ICIs to further evaluate the potential clinical utility of the identified biomarkers and their association with immune toxicity, and tumor response to ICI therapy.

Ethics Approval The study was approved by The Institutional Review Board at The University of Texas MD Anderson Cancer Center, approval number PA16-0928

Consent Written informed consent was obtained from all patients who agreed to participate in the study



Abstract 638 Figure 1 Unsupervised clustering of plasma proteome after ICIs
337 proteins were quantified from at least 8 out of total 12 patients and clustered after Loess normalization.
Patient 1 (P1): Melanoma, Pembrolizumab treated, Arthritis (irAE), Patient 2 (P2): Melanoma, Pembrolizumab treated, Arthritis (irAE), Patient 3 (P3): Melanoma, Pembrolizumab treated, No irAE, Patient 4 (P4): Melanoma, Pembrolizumab, no irAE, Patient 5 (P5): Melanoma, Pembrolizumab treated, no irAE, Patient 6 (P6): Melanoma, Pembrolizumab treated, no irAE, Patient 7 (P7): Melanoma, Ipilimumab-Pembrolizumab treated, Pneumonitis (irAE), Patient 8 (P8): Melanoma, Pembrolizumab, Pneumonitis (irAE), Patient 9 (P9): Melanoma, Ipilimumab-Pembrolizumab treated, Pneumonitis (irAE), Patient 10 (P10): RCC, Nivolumab, Arthritis (irAE), Patient 11 (P11): Renal Cell Carcinoma (RCC), Nivolumab, Pneumonitis (irAE), P12: Non-Small Cell Lung Carcinoma (NSCLC), Nivolumab, Arthritis (irAE).



Abstract 638 Figure 2 Heatmap of circulating plasma proteins showed significance
Nineteen proteins showed statistically significant differences between patients with and without irAEs

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639 IMMUNE-RELATED THYROID DYSFUNCTION IN PATIENTS WITH EXISTING THYROID DYSFUNCTION

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Background Thyroid dysfunction is a well known side effect of immune checkpoint blockade (ICB) and is one of the most common causes of immune-related adverse events (IRAE).[1–9] The incidence varies with each individual therapy but generally estimated to be in the range between 6–18% per one study. Hypothyroidism and thyroiditis are the most common manifestations. Initial hyperthyroidism followed by hypothyroidism is another manifestation. Hypothyroidism is more common with an incidence of 10% whereas hyperthyroidism has an incidence of 5%. Less is known about the incidence of worsening thyroid dysfunction in patients with pre-existing thyroid dysfunction treated with ICB.

Methods A retrospective analysis was collected on 370 patients who received immunotherapy from April 2015 to April 2019. Of those, 212 had abnormal thyroid function tests. We analyzed a subgroup of these patients who had baseline thyroid dysfunction for worsening thyroid dysfunction after they were given ICB. Fifty-three patients were included in the analysis and had an abnormal baseline TSH at the start of immunotherapy. Type of immunotherapy, worst TSH, duration between initiation of immunotherapy to worst TSH, treatment type, and grade of abnormality as per Immune Checkpoint Inhibitor Related

Adverse Events Common Terminology Criteria for Adverse Events (IRAE-CTCAE) were also recorded. Analysis was done for patients to compare likelihood of worsening TSH resulting in change in treatment for thyroid disorder.

Results Of the identified patients (N=53) with abnormal TSH screening values outside of the institution's normal reference range 0.35 - 4.95 uIU/ml, 45.7% (N=16) were hypothyroid and 54.3% (N=19) were hyperthyroid at baseline. Of those who were hypothyroid, 50% (N=8) had worsening TSH and 50% (N=8) had unchanged TSH during treatment. Of those who were hyperthyroid, 31.6% (N=6) had unchanged TSH, 52.6% (N=10) had worsened TSH, and 15.8% (N=3) had normalization of TSH compared to baseline. Overall 26.4% had worsening and of those 11.3% required treatment change.

Conclusions Thyroid dysfunction is one of the most common IRAE's associated with immune checkpoint inhibitors. Little is known about the impact of immunotherapy on patients with existing thyroid dysfunction. Patients who have underlying thyroid dysfunction are at an increased risk for worsening thyroid dysfunction with the use of ICB but though not unduly above the risk general population. Of those with change, only a modest percentage required an alteration of their endocrine therapy. Of interest, our data suggests a potential increased risk in patients with baseline hyperthyroidism compared to hypothyroidism which may be clinically relevant.

Ethics Approval The study was approved by ECU Brody School of Medicine Institution's Ethics Board, approval number 19-000710.

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640 CHARACTERIZING SEVERE ACUTE KIDNEY INJURY IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background Renal immune-related adverse events (irAEs), are relatively rare in patients treated with immune checkpoint inhibitors (ICIs). This retrospective analysis characterizes the etiology of severe acute kidney injury (AKI) in patients treated with ICIs at the University of California, San Diego.

Methods The electronic medical record was used to identify all patients with an estimated glomerular filtration rate (eGFR) <15 mL/hr who received ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab between 1/2000 and 1/2019. Patients with baseline eGFR < 15 mL/hr or who experienced an eGFR decline to <15 mL/hr prior to ICI initiation were excluded. Extracted data included serum creatinine, eGFR, ICI dose, urinalysis, renal ultrasound, clinical documentation of both ICI-related nephritis and other suspected causes of AKI. These data were analyzed to determine cause of AKI and possible relation to ICI.

Results 46 patients who received ICI therapy and subsequently developed an AKI with eGFR <15 mL/hr were identified. Three of these 46 patients (6.5%) had AKIs partially or predominately attributed by the clinician to ICI therapy (table 1). Characteristics of ICI-related AKI for these patients are summarized in (table 2). AKI onset occurred 32–110 days after ICI initiation. All three patients exhibited proteinuria, pyuria, and hematuria on urinalysis with negative urine cultures, but none underwent confirmatory renal biopsy. Only one patient had urine eosinophils checked, which was negative. Two (66%) of these patients received high-dose corticosteroids with subsequent complete eGFR recovery. Neither of these two patients required renal replacement therapy. One patient (33%) declined corticosteroid treatment due to concomitant multiorgan failure. An additional four (8.7%) patients developed multifactorial AKIs with other concurrent IRAEs that were treated with corticosteroids, but were not formally diagnosed with ICI-related AKI.

Abstract 640 Table 1 AKI etiologies in ICI-treated patients

AKI etiology	Percentage of patients
Pre-renal (including hepatorenal, cardiorenal)	28.2
Post-obstructive	19.6
Intrinsic renal	
ICI-related	**6.5**
Multifactorial with concomitant IRAE	**8.7**
Sepsis/septic shock	13.0
Non-ICI medications	4.3
Iodinated contrast	4.3
Other/unclear	15.2

Abstract 640 Table 2 Patient characteristics in ICI-related AKI

Malignancy	ICI therapy	Day of AKI onset	Nadir eGFR (mL/min)	Urinalysis	irAE treatment	Renal recovery
Hepatocellular Carcinoma	Nivolumab	110	7	2+ protein 0-2 WBC/hpf 6-10 RBC/hpf No casts	Prednisone (1 mg/kg with 90-day taper)	Yes-baseline eGFR
Melanoma	Ipilimumab	39	15	3+ protein 11-20 WBC/hpf 6-10 RBC/hpf Granular casts	Declined treatment	No
Undifferentiated neuroendocrine carcinoma	Nivolumab	32	8	1+ protein 21-50 WBC/hpf >50 RBC/hpf Muddy casts	Prednisone (1 mg/kg with 60-day taper)	Yes-baseline eGFR

Conclusions In our cohort, 6.5% of patients who develop AKI after receiving ICI therapy experienced immune-related nephritis. A further 8.7% of patients experienced other irAEs with AKI, suggesting that the true prevalence of immune-related nephritis is likely underdiagnosed. Notably, 84.8% of patients who develop AKI after ICI therapy have a non-ICI-related etiology, and no patient in our cohort of 46 patients underwent renal biopsy, highlighting the need for blood-based biomarker development for immune-related nephritis.