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Publication Date

2020-08-01

DOI

10.1016/j.ejca.2020.05.005

Peer reviewed

HHS Public Access

Author manuscript

Eur J Cancer. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Eur J Cancer. 2020 August ; 135: 211–220. doi:10.1016/j.ejca.2020.05.005.

Survivorship in immune therapy: Assessing toxicities, body composition and health-related quality of life among long-term survivors treated with antibodies to programmed death-1 receptor and its ligand

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Abstract

Aim: Antibodies to programmed death-1 receptor and its ligand (anti–PD-1/PD-L1) produce durable responses in many cancers. However, the long-term effects of anti–PD-1/PD-L1 blockade are not well defined. We identified the toxicities, health outcomes and health-related quality of life (HRQoL) amongst long-term survivors treated with anti–PD-1/PD-L1.

Methods: We assessed 217 patients who received anti–PD-1/PD-L1 for melanoma, renal cell carcinoma or non–small-cell lung carcinoma between 2009 and 2017, with survival greater than two years after treatment. Patient and tumour characteristics, immune-related adverse events (irAEs), cardiometabolic parameters (glucose, blood pressure, body mass index [BMI]), body composition (using automated body composition analyser, computed tomography and Slice-o-matic software) and HRQoL outcomes were tracked.

Results: Among the included patients, most were men (70.3%) and at anti–PD-1/PD-L1 initiation had an average age of 61.0 years and median BMI of 28.5. Median overall survival was

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Conflict of interest statement

D.B.J. reports serving on advisory boards for Array Biopharma, BMS, Incyte, Jansen, Merck and Novartis; receiving research funding from BMS and Incyte and receiving travel support from Genentech. K.E.B. reports receiving research funding from LCFA-IASLC-BMS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.05.005.

not reached; 33 (15.2%) died during the follow-up primarily from progressive cancer (n = 28). At the last follow-up, most patients' Eastern Cooperative Oncology Group performance status was 0 (38%) or 1 (41%). There was no difference in blood pressure, glucose or BMI from baseline to two years after treatment initiation. Body composition showed increased adiposity (p = 0.05), skeletal muscle mass (p = 0.03) and skeletal muscle gauge (p = 0.04). We observed chronic irAEs at the last follow-up including hypothyroidism (10.6%), arthritis (3.2%), adrenal insufficiency (3.2%) and neuropathy (2.8%). New diagnoses of type 2 diabetes (6.5%) and hypertension (6.0%) were observed, with uncertain relationship to anti–PD-1/PD-L1. Patient-reported outcomes compared favourably with cancer and general populations, although younger age (p = 0.003) and need for subsequent therapy (p = 0.03) were associated with worse HRQoL outcomes.

Conclusion: Durable responses to anti–PD-1/PD-L1 therapy and favourable HRQoL outcomes are encouraging. Chronic events may be more common than previously thought although no clear chronic adverse cardiometabolic effects were observed.

Keywords

Anti–PD-1; Checkpoint inhibitors; Melanoma; Renal cell carcinoma; Lung cancer; Toxicities; Survivorship; Quality of life; Pembrolizumab; Nivolumab; Ipilimumab

1. Introduction

Antibodies to programmed death-1 receptor and its ligand (anti–PD-1/PD-L1) are transforming the landscape of cancer care. These agents are now approved in 17 different cancer types as single agents and in combination with chemotherapy, tyrosine kinase inhibitors and other immunotherapies [1,2]. Approximately half of all patients with metastatic cancer are now eligible to receive these therapies, with many more approvals expected [1].

In contrast to other therapies for metastatic solid tumours, anti–PD-1/PD-L1 is often associated with durable responses which may even amount to cures in some patients [2]. In addition, these agents are being increasingly used in patients treated with curative intent surgery (e.g. patients with resected stage III melanoma treated with nivolumab or pembrolizumab) or chemotherapy and radiation (e.g. patients with stage III lung cancer treated with durvalumab after completion of chemoradiation) [3,4]. Thus, a growing population of cancer survivors treated with anti–PD-1/PD-L1 is now emerging.

Despite this expanding cohort, the long-term effects of anti–PD-1/PD-L1–based therapies are not well defined. Most toxicities, specifically immune-related adverse events (irAEs), are acute in nature and resolve with glucocorticoid therapy [5,6]. However, a growing body of literature has demonstrated that persistent toxicities may occur, particularly those affecting the endocrine glands, joints, peripheral nerves and lungs [7-10]. The incidence and morbidity of these more chronic events are not well characterised. In addition, emerging data have implicated immune activation in a variety of other processes including atherosclerosis, hypertension, diabetes and depression, and it remains unclear how the PD-1/PD-L1 blockade affects these immune-related processes [11-14]. Herein, we have assessed a large cohort of patients treated with anti–PD-1/PD-L1 to identify the long-term immune toxicities, health

outcomes, body composition metrics and health-related quality of life (HRQoL) affecting long-term survivors.

2. Materials and methods

2.1. Patients

After obtaining institutional review board approval, we extracted clinical data from the electronic medical record for patients at Vanderbilt University Medical Center treated with anti–PD-1/PD-L1 for the period of October 2009 to August 2017; the follow-up occurred through September 2019. Patients were included if they had ≥24 months of evaluable follow-up from the first anti–PD-1/PD-L1 dose until the date of the last follow-up. Patients were eligible for inclusion if they had received at least one dose of anti–PD-1/PD-L1 (nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, or combination ipilimumab and nivolumab), irrespective of dose, indication (melanoma, NSCLC, or RCC) or setting (clinical trial or commercially available). Patients who received prior or subsequent anticancer therapies were included.

2.2. Study design

We assessed anti–PD-1/PD-L1 efficacy in terms of overall survival (OS), defined as the time of treatment initiation to time of death from any cause, and progression-free survival (PFS) as defined by Response Evaluation Criteria in Solid Tumours 1.1 criteria. We collected data on patient demographics, acute irAEs (including grade and involved organ system), chronic irAEs (toxicities that persisted after discontinuing anti–PD-1/PD-L1, including those that persisted until the last follow-up) and treatment for irAEs. Side-effects characteristic of and attributed to subsequent therapies or cancer-related symptoms were identified but were not considered related to anti–PD-1/PD-L1 treatment. Baseline vital signs and laboratory values including cardiometabolic parameters (body mass index [BMI], blood pressure, random glucose), Eastern Cooperative Oncology Group (ECOG) performance status and comorbidities were also tracked. Cardiometabolic data were also collected at approximately two years after treatment initiation for comparison with baseline. Cardiometabolic data taken from the date of treatment initiation and approximately 2 years after treatment initiation were compared. Comorbidities and ECOG performance status from the last recorded follow-up were tracked to compare with pre-treatment data. In addition, we recorded response to treatment, disease progression, radiotherapy requirements and development of radiation necrosis. We also assessed new comorbidities diagnosed after immunotherapy initiation that are not classically associated with immune therapy in a descriptive fashion (e.g. coronary artery disease, hypertension).

To collect patient-reported outcomes, we used the Functional Assessment of Cancer Therapy: General (FACT-G), Impact of Event Scale - Revised (IES-R) and National Comprehensive Cancer Network (NCCN) Distress Thermometer (DT). Patient demographics and tumour characteristics were compared with the patient-reported outcome measures to assess for a relationship. Specifically, age, gender, baseline ECOG performance status, progression status, response to anti–PD-1/PD-L1, receipt of CNS radiation,

requirement of subsequent therapy, cancer types and development of irAEs were compared within each patient-reported outcome metric.

2.3. Body composition measurements

We assessed change over time in body composition, including muscle and fat composition using cross-sectional imaging. Computed tomography (CT) scans obtained before treatment and at 12 months or greater from treatment start were analysed using Slice-o-matic (Tomovision V 5.0) and ABACS (automated body composition analyser using CT) software according to previously established methods [15]. Briefly, patient scans were viewed using AGFA IMPAX software (version 6.6.1.3525), and the L3 level was identified by researchers. Axial, cross-sectional images at the L3 level were then uploaded to Slice-o-matic and automatically segmented into muscle tissue, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) using ABACS automatic segmentation software. This software identifies muscle tissue as tissue with a radiodensity between −29 and + 150 Houndsfield units (HU). Given that the radiodensity of organs also falls within this range, software incorporates knowledge of L3 muscle shape to avoid erroneously labelling organs as muscle tissue [16]. Once muscle tissue was identified, SAT is defined as the tissue lying outside the border of the defined muscle area with a radiodensity between −190 and −30 HU, and VAT is defined as the tissue lying inside the border of the defined muscle area with a radiodensity between −150 and −50 HU. This software has been previously validated through comparison with manual segmentation and was found to have excellent concordance [20]. Skeletal muscle index (SMI) was used to normalise muscle area for height and was calculated as follows: [skeletal muscle area (in cm^2)]/[height (m^2)]. Total adipose tissue index (TATI) was used to normalise adipose tissue for height and was calculated as follows: [subcutaneous adipose tissue area (cm^2) + visceral adipose tissue area (cm^2)]/[height (m^2)]. Skeletal muscle gauge (SMG) incorporates both muscle area and muscle density and has been shown previously to be strongly correlated with patient outcomes including toxicity and functional status [17]. SMG was measured in arbitrary units and was calculated as follows: (SMI cm^2/m^2):*(skeletal muscle density in HU).

2.4. Statistics

Categorical and continuous variables were summarised by percentages and means. OS and PFS were estimated using the Kaplan-Meier method and compared between groups by the log-rank test; patients were censored at the last available follow-up. Body composition metrics were compared from pre-treatment to follow-up using the paired t-test. For continuous self-reported outcomes (FACT-G and IES-R), univariable linear regression was used for continuous predictors, and the Wilcoxon rank-sum test (two groups) or Kruskal-Wallis rank sum test (greater than two groups) was used for categorical predictors. The Wilcoxon signed-rank test was used for comparison between correlated FACT-G well-being scores. Ordinal logistic regression was used for ordinal self-reported outcomes (NCCN). A two-sided p-value of <0.05 was considered significant. Pearson correlation was calculated between self-reported outcomes. All analyses were performed using R, version 3.6.1.

3. Results

3.1. Patients

We identified 907 patients treated with anti–PD-1/PD-L1 between October 2009 and August 2017 and 217 survived for at least 24 months with evaluable follow-up. Among these 217 patients, most were men (70.3%), and the average age upon starting treatment with anti–PD-1/PD-L1 was 61.0 years. Most patients were treated for melanoma (n = 135, 62.2%), while 44 and 38 were treated for RCC and NSCLC, respectively. The checkpoint inhibitors used were pembrolizumab (39.2%), nivolumab (32.7%), nivolumab with ipilimumab (18.9%), atezolizumab (8.8%) and avelumab (0.5%). Most patients had a baseline ECOG performance status of 0 (43.8%) or 1 (46.5%). One hundred twenty patients (55.3%) had received prior systemic therapy that included chemotherapy and molecularly targeted therapy (largely BRAF/MEK inhibitors or multikinase inhibitors). Most patients had a partial (59.0%) or complete (12.9%) response to anti–PD-1/PD-L1, while 10.1% had primary progression of disease and 18.0% had stable disease. Patient characteristics and demographics are summarised in Table 1.

3.2. Response to therapy and survival

The median OS and PFS were not reached (Fig. 1A and B). PFS was superior for melanoma and NSCLC compared with RCC (p = 0.01); OS was similar between groups although non-significantly better in melanoma (p = 0.08) (Fig. 2A and B). Eighty-six patients (39.6%) required subsequent systemic therapy (Table 1). At the last follow-up, most patients had an ECOG performance status of zero (38.3%) or one (41.0%) (Supplementary Table A). In addition, most patient's ECOG performance status remained stable (41.0%), increased by one (17.1%) or decreased by one (17.1%) at their last follow-up compared with initiation of anti–PD-1/PD-L1 (Supplementary Table B). Thirty-three (15.2%) patients died at the last follow-up and 28 died from progression of their primary malignancy, whereas three died without progression due to CNS radiation necrosis, multiple myeloma and gastrointestinal bleed, respectively, and two died of other causes in the setting of slowly progressive disease (heart failure partly related to BRAF/MEK inhibition and bleeding from the bronchopleural fistula at least partly related to radiation).

3.3. Acute immune-related toxicities

Acute toxicities (those that developed during treatment) related to anti–PD-1/PD-L1 treatment developed in 65.0% of the population, most commonly in patients with melanoma (71.1%). Most events were grade I/II (45.2%), while 13.4% had grade III/IV toxicities. Of all acute toxicities, 35.5% required corticosteroid treatment and 4.6% needed additional immunosuppressive therapy (e.g. infliximab). The most commonly recorded acute toxicities were dermatitis (18.4%), thyroiditis (12.9%), arthritis (9.7%), pneumonitis (9.2%) and hepatitis (7.4%) (Table 2). No difference in OS was observed between patients with acute toxicities vs. those without them (P = 0.37).

3.4. Chronic immune-related toxicities

We also tracked irAEs that were persistent at the last follow-up. Toxicities were considered chronic if they were definitely or probably related to anti–PD-1/PD-L1 therapy and still present after treatment cessation. Chronic toxicities were more common in patients treated with ipilimumab/nivolumab (49%) vs. those treated with monotherapy (26%). The most common chronic toxicity was thyroiditis/hypothyroidism (10.6%). Other chronic effects observed in a smaller subset of patients included arthritis (3.2%), adrenal insufficiency (3.2%), neuropathy (2.8%), pneumonitis (1.8%), dermatitis (1.0%), type I diabetes (0.8%) and dysphagia (0.5%) (Table 3). Of the three patients with chronic pneumonitis, two had persistent grade II shortness of breath or wheezing and one was asymptomatic with only radiographic changes. In patients with chronic neuropathy, two had pain (grade II) while four had sensory changes. No difference in OS was observed among patients with chronic toxicities vs. those without them. No fatal late toxicities were observed (with the possible exception of one case of fatal radiation necrosis, see next subsection).

3.5. New comorbidities and ongoing management

Given emerging data surrounding aberrant immune function and numerous human diseases, we sought to determine if new health conditions were noted after anti–PD-1/PD-L1 therapy and recorded all new comorbidities present at the last follow-up. These comorbidities were included if they were not present at the baseline evaluation and not clearly related to anti–PD-1/PD-L1 therapy. The most frequently developed new comorbidities were gastroesophageal reflux disease (9.7%), type II diabetes (6.5%), hypertension (6.0%) and depression (6.0%). Of note, there was no difference in the rate of developing new comorbidities based on the receipt of prior corticosteroids for irAEs (35/77 comorbidities with prior corticosteroids vs 58/140 comorbidities with no prior steroids, $p = 0.57$). A summary of all comorbidities that developed is displayed in Table 4.

Studies have suggested that immune therapy may potentiate radiation necrosis in patients receiving both radiation therapy and immune checkpoint inhibitors [18]. A subset of patients received radiotherapy after starting anti–PD-1/PD-L1 therapy. Of the 139 patients that received radiation treatment, 44 (31.7%) had cerebral radiotherapy and 11 (25.0%) subsequently developed radiation necrosis. One patient developed chronic neurologic symptoms secondary to radiation necrosis from whole brain and stereotactic radiation and ultimately died from progressive radiation necrosis despite multiple courses of steroids and surgical interventions (Supplementary Table C).

3.6. Cardiometabolic parameters

In view of the number of patients who developed cardiovascular comorbidities and literature suggesting chronic cardiovascular effects of the PD-1/PD-L1 blockade, we investigated the long-term changes to blood pressure, random glucose and BMI. There were no statistically significant differences in baseline blood pressure, BMI or random glucose compared with two years after starting anti–PD-1/PD-L1 therapy in these 217 patients. Increased systolic blood pressure neared statistical significance, with an average increase of 2.1 mmHg from baseline to two years (paired t-test $p = 0.09$) (Supplementary Table D).

3.7. Body composition measurements

Next, we assessed body composition changes over time. Total adiposity increased from baseline to 12+ months (mean TATI 140.1 vs. 144.1, paired t-test p = 0.05). Measures of muscle mass also increased on therapy, including SMI (47.05 vs. 47.72, p = 0.03) and SMG (1653.9 vs. 1671, p = 0.04). These differences remained significant after adjusting for BMI, gender, age and prior therapy (Supplementary Table E).

3.8. Patient-reported outcomes

In addition to clinical outcomes, we sought to assess the HRQoL and psychosocial well-being through patient-reported outcomes and used the following instruments: FACT-G, IES-R and NCCN DT. The sample size was 114, 115 and 94 patients for FACT-G, IES-R and NCCN DT, respectively. Notably, there was no difference in scores based on gender, baseline ECOG performance status, tumour type, receipt of radiotherapy, progression on anti–PD-1/PD-L1 therapy or development of chronic irAEs. In contrast, younger age (p = 0.0007) and the need for subsequent therapy (p = 0.03) were associated with lower (worse) FACT-G scores. In addition, the presence of acute toxicities was associated with worse NCCN DT scores (p = 0.019) but not with other instruments (Supplementary Fig. A-B). Within FACT-G, physical, social, and emotional well-being scores were all higher than functional well-being (p = 0.005, p < 0.001, p < 0.001). In addition, interestingly, scores on different survey measures had only modest correlation with each other (Supplementary Fig. C-E).

To assess whether a minority of patients were particularly adversely affected in a fashion not captured by the median, we specifically assessed patients who were in the lowest 10% of FACT-G scores (n = 11) in an exploratory fashion. The average age of this group was 56 years, lower than that of the overall cohort. Of note, 63.6% of these patient progressed on anti—PD-1/PD-L1 during the follow-up and 91% developed acute toxicities with 63.6% requiring treatment with corticosteroids. In addition, 91% of these patients developed new comorbidities between starting anti–PD-1/PD-L1 and their last follow-up. We assessed for possible drivers of poor QoL in these patients and identified possible causes in ten of eleven patients (Supplementary Table F). Of these, three had bothersome, chronic symptoms from subsequent therapies, three had significant cancer-related complications, four had substantial medical or psychological comorbidities predating their treatment and two had chronic anti–PD-1–related symptoms. These latter two developed chronic anti–PD-1–related arthritis (and painful compression fracture occurring while on steroids) and persistent rash and fatigue from anti–PD-1, respectively.

4. Discussion

To our knowledge, this is the largest, most comprehensive analysis of patients with prolonged survival after anti–PD-1/PD-L1 therapy. In this select population, most patients experienced favourable anticancer outcomes and had an excellent performance status at the last follow-up. Although most patients had acute irAEs related to anti–PD-1/PD-L1 therapy, a smaller subset developed chronic toxicities, primarily endocrinopathies or rheumatologic toxicities. Cardiometabolic parameters were not significantly different from baseline to the

24-month follow-up, and patient-reported outcomes were excellent although were influenced by age and subsequent therapies.

Although acute toxicities from anti–PD-1/PD-L1 therapy have been the focus of much research in recent years, the long-term consequences of the immune checkpoint blockade are only beginning to be elucidated, and the incidence of long-term toxicities has not been defined [19-23]. Chronic endocrine dysfunction (which seems largely related to destruction of hormone producing cells rather than ongoing inflammation) and rheumatologic conditions are the most well-validated chronic toxicities [22]. More recently, signals of long-term effects on the lung parenchyma (from pneumonitis) and augmentation of radiation therapy effects have been suggested in small studies [23,24]. Our study corroborated these findings, showing that endocrine and rheumatologic complications occurred most often among long-term survivors (13.8% and 3.2%). Other infrequent but clinically relevant events included radiation necrosis (with one fatality), pneumonitis, chronic painful neuropathies and dermatitis. Thus, we show that chronic irAEs are fairly common and may produce substantial symptoms in a small minority of patients.

A growing body of literature has implicated chronic immune dysregulation in numerous common medical problems, including atherosclerosis, heart failure, hypertension, diabetes, Alzheimer disease and many others [19,25-28]. The implications of sustained removal of these key nodes of self-tolerance (PD-1/PD-L1 ± CTLA-4) on these processes have not been explored in patients. A subset of patients did develop cardiac, neurologic and metabolic diagnoses after treatment (including 6.5% and 6% who developed hypertension and diabetes), though no obvious signals of increased blood pressure, BMI or random glucose were noted across the full cohort. On the other hand, body composition analysis did detect a small but statistically significant increase in muscle and fat composition from baseline to greater than one year on treatment. This may be due to improved health status overall after control of acute, cancer-related symptoms. Ultimately, large national or international databases and case–control studies will be needed to establish any causal links.

Overall HRQoL and factors affecting HRQoL have not been well defined in long-term survivors. In this long-term surviving population, we observed excellent scores; the FACT-G (82) exceeded the average scores both for patients with cancer (79) and the average population (80) as recorded in some studies; this observation was similar for the NCCN DT [29,30]. Although we sought to identify factors that correlated with worse scores, we only observed that the need for additional therapies (which have their own side-effects) and, surprisingly, younger age correlated with inferior scores. Of interest, the presence of chronic events did not predict worse scores, suggesting that either (1) most toxicities do not impair HRQoL or (2) more robust, immunotherapy-specific instruments are needed to capture the spectrum of events. However, we did identify a subset of patients with particularly low scores. Although several had chronic irAEs which may have contributed to their lower HRQoL scores, pre-existing comorbidities, cancer-related complications or subsequent treatments seemed to have stronger adverse influences on HRQoL.

Our study also provides more evidence that patients who survive more than two years have excellent outcomes with further follow-up; only 15% of patients died of their disease during

the study period. We also identified an intriguing population of patients who had initial disease progression but still experienced long-term survival. While this was largely due to good responses to subsequent therapy, a subset experienced mixed responses to anti–PD-1/PD-L1 with prolonged benefit after local therapy on the progressing lesion(s).

This study has limitations. The retrospective nature introduces the potential for confounding bias. Furthermore, while two years is a relatively long follow-up given the recent approval of anti–PD-1/PD-L1 therapies, definitive characterisation of the effects of anti–PD-1 on other chronic conditions will require more prolonged follow-up and much larger sample sizes (with either case–control designs or systematic evaluations before therapy and with long-term follow-up) for definitive causal analyses. Finally, while we did not observe differences with blood pressure and random glucose, these were from real-world, clinically obtained data; physiologic or molecular measurements (e.g. glucose tolerance tests) may demonstrate more subtle changes. Still, the lack of clinically apparent changes over time represents important data points.

The durable response of anti–PD-1/PD-L1 therapy in treating metastatic cancer continues to be encouraging. Chronic events may be more common than previously thought and cause morbidity in a meaningful minority of patients. No obvious long-term cardiometabolic signals were identified in this study, however, and patients generally reported excellent HRQoL scores and had improvements in skeletal muscle metrics. Further research is required to better define long-term sequalae associated with the checkpoint blockade.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by NCCN Young Investigators Award (D.B.J.), ACS Institutional Research Grant (D.B.J.), NIH K23 CA204726 (D.B.J.), NIH R01CA227481 (D.B.J.), NIH K12CA090625 (K.E.B.), NIH R38HL143619 (A.C.Y.) and NIH K08 CA234225-01 (G.R.W.).

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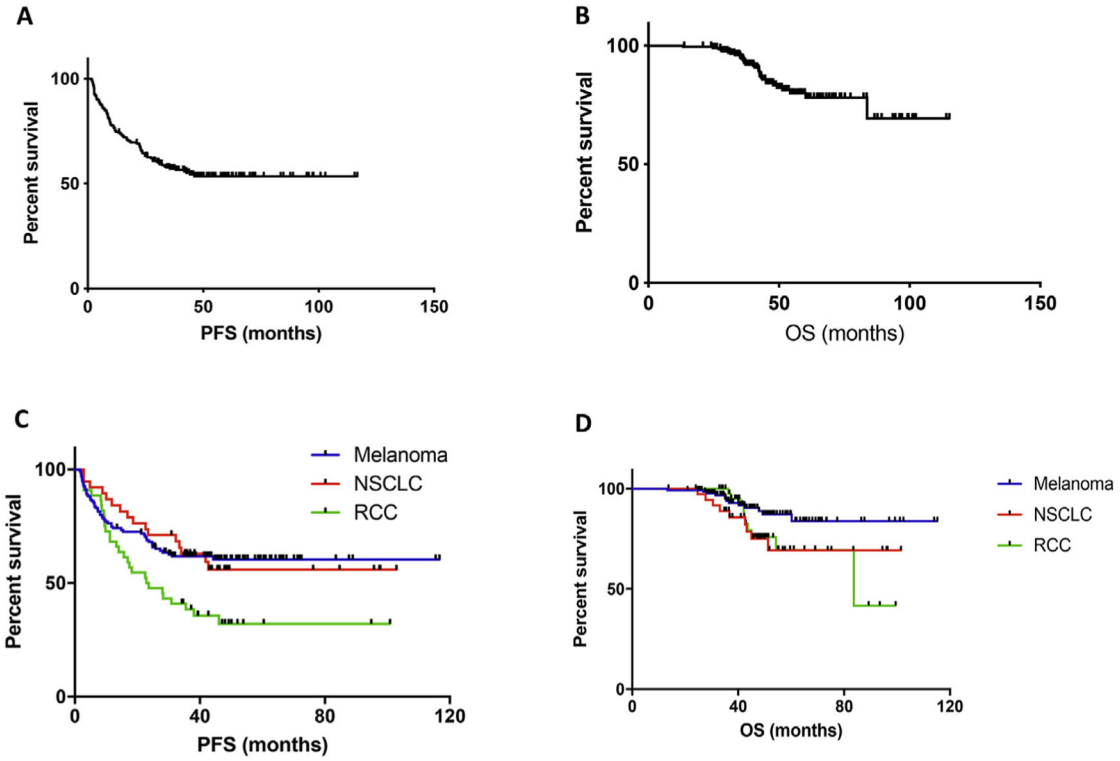

Fig. 1.

A) Progression-free survival, all patients. Median not reached. (B) Overall survival, all patients. (C) PFS by tumour type. PFS was superior for melanoma and NSCLC compared with RCC (p = 0.012) (D) OS by tumour type. PFS, progression-free survival; OS, overall survival.

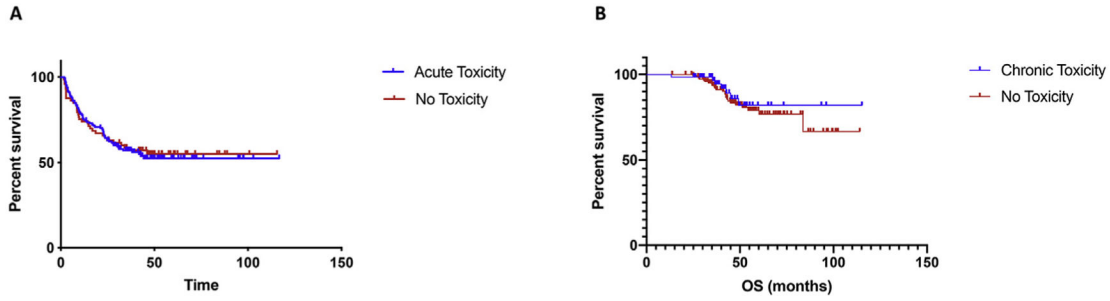

Fig. 2.

A) Overall survival in patients with acute irAEs. (B) Overall survival in patients with chronic irAEs. irAEs, immune-related adverse events.

Table 1

Patient demographics.

	Melanoma (n = 135)	RCC (n = 44)	NSCLC (n = 38)	Total (n = 217)
Gender (male)	95 (70.3%)	36 (81.8%)	21 (55.3%)	152 (70.0%)
Age at start of therapy	60	65	62	61
Baseline ECOG				
ECOG 0	68 (50.37%)	15 (34.09%)	12 (31.58%)	95 (43.78%)
ECOG 1	53 (40.74%)	24 (54.55%)	24 (63.16%)	101 (46.54%)
ECOG 2	2 (1.48%)	2 (4.55%)	1 (2.63%)	5 (2.30%)
Checkpoint inhibitor				
Pembrolizumab	80 (59.26%)	3 (6.82%)	2 (5.26%)	85 (39.17%)
Nivolumab	17 (12.59%)	24 (54.55%)	30 (78.95%)	71 (32.72%)
Ipilimumab + nivolumab	36 (26.67%)	1 (2.27%)	4 (10.53%)	41 (18.89%)
Avelumab	0	1 (2.27%)	0	1 (0.46%)
Atezolizumab	2 (1.48%)	15 (34.09%)	2 (5.26%)	19 (8.76%)
Best response to therapy				
Complete response	21 (15.56%)	3 (6.82%)	4 (10.53%)	28 (12.90%)
Partial response	82 (60.74%)	24 (54.55%)	22 (57.89%)	128 (58.99%)
Stable disease	19 (14.07%)	12 (27.27%)	8 (21.05%)	39 (17.97%)
Progressive disease	13 (9.63%)	5 (11.36%)	4 (10.53%)	22 (10.14%)
Prior therapy	58 (42.96%)	31 (70.45%)	31 (81.58%)	120 (55.30%)
Prior targeted therapy	53 (39.26%)	28 (63.64%)	1 (2.63%)	82 (37.79%)
Prior chemotherapy	1 (0.74%)	3 (6.82%)	18 (47.37%)	22 (10.14%)
Prior chemotherapy and targeted therapy	4 (8.62%)	0	12 (31.58%)	16 (7.37%)
Subsequent therapy	46 (34.07%)	27 (61.36%)	13 (34.21%)	86 (39.63%)
Subsequent targeted therapy	42 (91.30%)	27 (61.36%)	6 (15.79%)	75 (34.56%)
Subsequent chemotherapy	0	0	3 (7.89%)	3 (1.38%)
Subsequent chemotherapy and targeted therapy	4 (8.70%)	0	4 (10.53%)	8 (3.69%)

ECOG, Eastern Cooperative Oncology Group.

Table 2

Acute toxicities that developed from anti–PD-1 therapy.

	Melanoma (n = 135)	RCC (n = 44)	NSCLC (n = 38)	Total (n = 217)
Developed acute toxicity	96 (71.11%)	20 (45.45%)	25 (65.79%)	141 (64.98%)
Type of toxicity				
Adrenal insufficiency	5 (3.70%)	2 (4.55%)	1 (2.63%)	8 (3.69%)
Anaemia	0	0	2 (5.26%)	2 (0.92%)
Arthritis	16 (11.85%)	3 (6.82%)	2 (5.26%)	21 (9.68%)
Atrial fibrillation	1 (0.74%)	0	0	1 (0.46%)
Bell’s palsy	1 (0.74%)	0	0	1 (0.46%)
Colitis	17 (12.59%)	0	0	17 (7.83%)
Cytokine release	1 (0.74%)	0	0	1 (0.46%)
Dermatitis	31 (22.96%)	4 (9.09%)	5 (13.16%)	40 (18.43%)
Diabetic ketoacidosis	1 (0.74%)	0	0	1 (0.46%)
Dysuria	5 (3.70%)	2 (4.55%)	1 (2.63%)	8 (3.69%)
Encephalitis	1 (0.74%)	0	0	1 (0.46%)
Hepatitis	14 (10.37%)	2 (4.55%)	0	16 (7.36%)
Hypophysitis	7 (5.19%)	1 (2.27%)	2 (5.26%)	10 (4.61%)
ITP	1 (0.74%)	0	0	1 (0.46%)
Mucositis	3 (2.22%)	0	1 (2.63%)	4 (1.84%)
Myocarditis	1 (0.74%)	0	0	1 (0.46%)
Neuropathy	4 (2.96%)	1 (2.27%)	0	5 (2.30%)
Ocular myasthenia	0	0	1 (2.63%)	1 (0.46%)
Pancreatitis	1 (0.74%)	1 (2.27%)	0	2 (0.92%)
Peritonitis	0	1 (2.27%)	0	1 (0.46%)
Pericardial effusion	2 (1.48%)	0	0	2 (0.92%)
Pneumonitis	14 (10.37%)	2 (4.55%)	4 (10.53%)	20 (9.22%)
Pruritis without rash	5 (3.70%)	0	3 (7.89%)	8 (3.69%)
Thyroiditis	17 (12.59%)	5 (11.36%)	6 (15.79%)	28 (12.90%)
Uveitis	1 (0.74%)	0	0	1 (0.46%)
Worst toxicity grade				

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	Melanoma (n = 135)	RCC (n = 44)	NSCLC (n = 38)	Total (n = 217)
Grade I/II	72 (53.33%)	14 (31.82%)	12 (31.58%)	98 (45.16%)
Grade III/IV	21 (15.56%)	4 (9.09%)	4 (10.53%)	29 (13.36%)
Required steroids for toxicity	58 (42.96%)	10 (22.73%)	9 (23.68%)	77 (35.48%)
Required other immunosuppressants	9 (6.67%)	0	1 (2.63%)	10 (4.61%)

anti–PD-1, antibodies to programmed death-1 receptor.

Table 3

Chronic effects that developed from anti–PD-1 therapy.

	Melanoma (n = 135)	**RCC (n = 44)**	**NSCLC (n = 38)**	**Total (n = 217)**
Adrenal insufficiency	6 (4.44%)	0	1 (2.63%)	7 (3.23%)
Arthritis/arthralgias	6 (4.44%)	1 (2.27%)	0	7 (3.23%)
Dermatitis	2 (1.48%)	0	0	2 (0.92%)
Diabetes	0	2 (4.54%)	0	2 (0.80%)
Dysphagia	1 (0.74%)	0	0	1 (0.46%)
Hypothyroidism	12 (9.45%)	6 (13.64%)	4 (10.52%)	22 (10.14%)
Neuropathy	4 (2.96%)	1 (2.27%)	1 (2.63%)	6 (2.76%)
Pneumonitis	3 (2.22%)	1 (2.27%)	0	4 (1.84%)

anti–PD-1, antibodies to programmed death-1 receptor.

Table 4

Comorbidities that developed after anti–PD-1 therapy.

Comorbidity	Melanoma (n = 135)	RCC (n = 44)	NSCLC (n = 38)	Total (n = 217)
Cardiovascular				
Atrial fibrillation	2 (1.48%)	1 (2.27%)	0	3 (1.38%)
Carotid stenosis	1 (0.74%)	0	0	1 (0.46%)
Congestive heart failure	3 (2.22%)	2 (4.55%)	0	5 (2.30%)
Coronary artery disease	4 (2.96%)	2 (4.55%)	0	6 (2.76%)
Hyperlipidaemia	3 (2.22%)	1 (2.27%)	0	4 (1.84%)
Hypertension	8 (5.93%)	3 (6.82%)	2 (5.26%)	13 (5.99%)
Peripheral vascular disease	1 (0.74%)	1 (2.27%)	0	2 (0.92%)
Endocrine				
Diabetes (type 2)	8 (5.93%)	3 (6.82%)	2 (5.26%)	13 (5.99%)
Adrenal insufficiency	1 (0.74%)	2 (4.55%)	3 (7.89%)	6 (2.76%)
SIADH	0	1 (2.27%)	0	1 (0.46%)
Gastrointestinal				
Gastric reflux	10 (7.41%)	5 (11.36%)	6 (15.79%)	21 (9.68%)
Genitourinary				
Benign prostatic hyperplasia	3 (2.22%)	3 (6.82%)	0	6 (2.76%)
Erectile dysfunction	3 (2.22%)	0	0	3 (1.38%)
Prostate cancer	1 (0.74%)	0	0	1 (0.46%)
Musculoskeletal				
Arthritis	2 (1.48%)	0	0	2 (0.92%)
Osteoporosis	1 (0.74%)	0	0	1 (0.46%)
Neurologic				
Dementia	1 (0.74%)	0	0	1 (0.46%)
Migraine	0	1 (2.27%)	0	1 (0.46%)
Seizures	0	1 (2.27%)	0	1 (0.46%)
CVA	0	1 (2.27%)	0	1 (0.46%)
Ocular				
Cataracts	2 (1.48%)	1 (2.27%)	0	3 (1.38%)

Comorbidity	Melanoma (n = 135)	RCC (n = 44)	NSCLC (n = 38)	Total (n = 217)
Corneal dystrophy	1 (0.74%)	0	0	1 (0.46%)
Conjunctivitis	1 (0.74%)	0	0	1 (0.46%)
Pulmonary				
COPD/emphysema	0	2 (4.55%)	0	2 (0.92%)
Sleep apnoea	2 (1.48%)	2 (4.55%)	2 (5.26%)	6 (2.76%)
Asthma	1 (0.74%)	2 (4.55%)	0	3 (1.38%)
Psychiatric				
Anxiety	5 (3.70%)	2 (4.55%)	3 (7.89%)	10 (4.61%)
Depression	10 (7.41%)	3 (6.82%)	0	13 (5.99%)
Insomnia	1 (0.74%)	1 (2.27%)	0	2 (0.92%)
Renal				
Chronic kidney disease	0	3 (6.82%)	0	3 (1.38%)
Renal cell carcinoma	1 (0.74%)	0	0	1 (0.46%)
Other				
Breast cancer	0	0	1 (2.63%)	1 (0.46%)
Leukaemia	3 (2.22%)	0	0	3 (1.38%)
Lymphoedema	2 (1.48%)	0	0	2 (0.92%)

anti–PD-1, antibodies to programmed death-1 receptor.