RESEARCH

Immune checkpoint inhibitors, endocrine adverse events, and outcomes of melanoma

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Abstract

Objective: Immune checkpoint inhibitors (ICI) can cause endocrine adverse events. However, endocrine AEs could be related to better treatment outcomes. Our aim was to investigate whether this holds true in a real-world setting of metastatic melanoma patients.
Design: A retrospective single-institution study.
Methods: We included 140 consecutive metastatic melanoma patients treated with ICI between January 2012 and May 2019. We assessed the endocrine toxicity and the best possible treatment outcomes from electronic patient records, including laboratory parameters and radiological images.
Results: Of the treated patients, 21 patients (15%) were treated with ipilimumab, 46 (33%) with nivolumab, 67 (48%) with pembrolizumab, and 6 (4%) with combination therapy (ipilimumab + nivolumab). Endocrine AEs appeared in 29% (41/140) patients. Three patients had two different endocrine AEs. Thyroid disorders were the most common: 26% (36/140), followed by hypophysitis: 4% (5/140). Three subjects (2%, 3/140) were diagnosed with autoimmune diabetes. Three patients had to terminate treatment due to endocrine toxicity. Radiological manifestations of endocrine AEs were found in 16 patients (39%, 16/41). Endocrine toxicity was associated with significantly better treatment outcomes. Median progression-free survival (8.1 months, range 5.1–11.1 months vs 2.7 months, range 2.4–3.0 months, $P < 0.001$), and median overall survival (47.5 months, range 15.5–79.5 months vs 23.7 months, range 15.3–32.1 months, $P = 0.035$) were longer for patients experiencing endocrine AEs.
Conclusions: The higher number of endocrine AEs suggest that regular laboratory monitoring aids in AE detection. Endocrine AEs in metastatic melanoma may correlate with better treatment outcomes.

Key Words
- CTLA-4
- endocrine adverse event
- immune checkpoint inhibitor
- PD-1
- toxicity

Endocrine Connections (2022) **11**, **e210562**

Introduction

Treatment outcomes of metastatic melanoma significantly improved after the introduction of immune checkpoint inhibitors (ICIs). By binding to their ligands, they prevent inhibitory signals, enhance the proliferation of T-cells, and activate T-cells to attack cancer cells. ICIs used to treat metastatic melanoma include anticytotoxic T-lymphocyte-associated protein-4 (CTLA-4) MAB, ipilimumab (1) and antiprogrammed cell death protein 1 (PD-1) MAbs,

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https://doi.org/10.1530/EC-21-0562

nivolumab and pembrolizumab (2, 3). In addition, a more effective, but toxic, combination treatment with nivolumab and ipilimumab is also used (4).

Oncologists, familiar with chemotherapy-induced toxicities, encountered new adverse events (AE) induced by immunotherapy. ICIs can generate autoimmune-like reactions towards one or multiple organs, including the gastrointestinal tract, skin, and endocrine glands (5). These AEs are classified as immune-related AEs (irAEs) and their seriousness varies from transient laboratory findings to life-threatening conditions requiring immediate diagnosis and treatment (6, 7).

Endocrine AEs are the third most common AEs of ICIs including thyroiditis, hypophysitis, and autoimmune diabetes (8). The frequency of endocrine AEs varies with different ICIs; hypophysitis is characteristic of ipilimumab, while thyroiditis is more common with nivolumab and pembrolizumab (9). Ipilimumab causes thyroiditis in 0–7.4% of the treated patients, while PD-1 inhibitors induce them in 0–19.2% of treated patients, respectively. The incidence of ipilimumab-induced hypophysitis varies between 0 and 17.4% and is dose-dependent. In contrast, the incidence of hypophysitis with PD-1 inhibitors has been reported to be 0.9–1.2%. Furthermore, combination therapy with ipilimumab and nivolumab causes endocrinopathies more frequently than with monotherapies; even up to 50% of patients treated with combination therapy experience endocrine AEs (10).

Numerous algorithms exist for the assessment and management of endocrine AEs (7, 9, 10). With the increasing use of ICIs even in the adjuvant setting, endocrine AEs will emerge as a challenge for treating physicians (11). Still, despite the possible difficulties in diagnosing and managing endocrinopathies, there are signs that endocrine AEs may be connected to better treatment responses translating into improved overall survival (OS) (12, 13). At the same time, endocrine AEs may be permanent and require lifelong medication (8). These findings encouraged us to analyse our real-world (RW) data of metastatic melanoma patients treated with ICIs. Our aim was to evaluate whether better treatment outcomes with endocrinopathies could be reproduced in a RW patient population.

Materials and methods

Ethical approval

Approval for this study was received from the independent Institutional Review Board (IRB) and Ethics Committee (EC) of Helsinki University Hospital. Due to the retrospective nature of this study, informed consent was waived. All methods were performed in accordance with the institutional guidelines and regulations. Data were anonymized for statistical analyses and handled in a manner that meets the EU General Data Protection Regulation 2016/679 (GDPR) on data protection.

Patients

The study data consist of medical reports as well as laboratory and imaging results. We included a total of 140 consecutive metastatic melanoma patients treated at the Comprehensive Cancer Centre of Helsinki University Hospital between January 2012 and May 2019 with immunotherapy. The ICI treatment was either anti-PD-1 (nivolumab or pembrolizumab) or anti-CTLA-4 monotherapy (ipilimumab), or a combination of ipilimumab and nivolumab.

The criteria for starting ICI treatment included unresectable stage III or IV metastatic melanoma, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, no active autoimmune disease or unstable other serious illness, as well as no active brain metastases. Each treatment plan was approved by a multidisciplinary meeting before treatment initiation.

We collected the following data from the patient records: patient age at treatment initiation, sex, and ECOG performance status. Furthermore, we listed the characteristics of metastatic disease, including possible brain metastases and the American Joint Committee on Cancer stage at treatment initiation (version 8) (14). We also reviewed previous treatments given for metastatic melanoma. We recorded the duration of immunotherapy and scaled the best possible treatment outcome according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (15). We thoroughly investigated all AEs caused by immunotherapy. We recorded the duration and severity of AEs using Common Terminology Criteria for Adverse Events version 5.0 (16).

Before treatment initiation, a standard spectrum of laboratory tests was taken including whole blood cell count (WBC), sodium, potassium, calcium, creatinine, glomerular filtration rate, aspartate and alanine aminotransferases (ALT), bilirubin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), C-reactive protein (CRP), thromboplastin time, creatine kinase, albumin, albumin-corrected calcium, amylase, fasting glucose, and troponin-I. Thyroid function was measured with thyroid-stimulating hormone (TSH), free thyroxine

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(fT4), free triiodothyronine (fT3), and thyroid antibodies: TSH receptor antibodies (TSHRAb), thyroid peroxidase antibodies (TPOAb), and antithyroglobulin antibodies. Before treatment initiation, we also monitored other hormones including testosterone, oestradiol, cortisol, prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and adrenocorticotrophic hormone (ACTH). All laboratory tests were analysed at the central laboratory of Helsinki University Hospital with in-house methods. A whole-body CT and a brain MRI or a brain CT were performed prior to treatment initiation as well.

Before each treatment cycle, we measured WBC, CRP, sodium, potassium, calcium, creatinine, ALT, ALP, bilirubin, LDH, albumin corrected calcium, amylase, TnI, fasting glucose, TSH, fT4, and cortisol. If symptoms indicating endocrinopathies or other AEs occurred, additional laboratory tests were taken, and symptom-oriented imaging was performed.

Ipilimumab monotherapy was given at a dose of 3 mg/kg every 3 weeks for a maximum of four cycles. Nivolumab was administered at a dose of 3 mg/kg q2w to 36 patients (26%), at a flat dose of 240 mg q2w (3 patients, 2%), or at a flat dose of 480 mg (7 patients, 5%) q4w. Pembrolizumab was administered at a dose of 2 mg/kg q3w (48 patients, 34%) or at a flat dose of 200 mg q3w (19 patients, 14%), respectively. Four doses of combination therapy were given at a dose of 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab q3w followed by nivolumab 3 mg/kg q2w.

The treatment response was evaluated with a whole-body CT and a brain CT or a brain MRI. The scans were conducted every 12 weeks, or earlier, if signs of progression or AEs occurred. The patients received ICI treatment until progression or severe toxicity. The treatment was terminated if treatment response remained stable in two subsequent CTs taken 8 weeks apart. In addition, a pilot study of a limited duration anti-PD-1 therapy for patients with melanoma was conducted at Helsinki University Hospital between November 2015 and March 2017 (17). These 38 study patients were all included in our data.

We categorized endocrine AEs as thyroid dysfunction, hypophysitis, and autoimmune diabetes (18). Thyroid dysfunction included primary hypothyroidism, thyrotoxicosis, and transient thyrotoxicosis followed by hypothyroidism (thyroiditis). Hypothyroidism was defined as an increased TSH concentration above the upper normal limit and a fT4 concentration under the lower normal limit and thyrotoxicosis as a suppressed TSH concentration and a fT4 concentration above the upper normal limit. Thyroiditis, that is transient thyrotoxicosis followed by hypothyroidism, was encountered in many ICI-treated patients and was defined as a transition from suppressed TSH levels to increased levels, accompanied by corresponding changes of fT4 levels. Hypophysitis was defined as deficiencies in anterior pituitary hormones, that is ACTH, TSH, and gonadotropins, and their corresponding end-organ hormone concentrations. Autoimmune diabetes was characterized as a new onset of type 1 diabetes following the use of ICIs.

Two of our designated radiologists (HL or MJ) assessed the radiological images of patients with endocrine AEs and evaluated the treatment response by RECIST criteria. We categorized radiological changes as slight, moderate, or severe. We evaluated the change in the size of the thyroid and pancreas as compared in the CT and or MRI scans.

Finally, we reviewed the measures used to treat endocrine AEs including medication, hospitalization, and possible treatment cessation.

Statistical analysis

All statistical analyses were performed with SPSS Statistics® version 27. Descriptive statistics were presented as counts (*n*) and proportions (%). Follow-up was the time between treatment initiation and the last follow-up day or death. Progression-free survival (PFS) and OS were calculated using the Kaplan–Meier method and the log-rank test. PFS after ICI treatment was calculated from the treatment initiation date to disease progression, death, or the last follow-up, whichever occurred first. OS was calculated from the treatment initiation to death or the last follow-up. Student's *t*-test was used to compare two groups for parametric continuous variables and the Mann–Whitney *U* test for non-parametric continuous variables. For comparisons of more than two groups, we used the Kruskal–Wallis test. All tests were two-sided and $P < 0.05$ was considered significant. The date of data cut-off was 20 May 2021.

Results

Altogether 140 patients with metastatic melanoma were treated with ipilimumab, anti-PD-1 treatment, or the combination of ipilimumab + nivolumab between January 2012 and May 2019 at Helsinki University Hospital. The median follow-up time was 23.5 months (range 0.6–95.8 months). Out of 140 patients, 21 were treated with ipilimumab, 46 with nivolumab, 67 with pembrolizumab,

Table 1 Background characteristics of all patients and the patient subgroups treated with different immune checkpoint inhibitors (ICI): nivolumab (nivo), pembrolizumab (pembro), ipilimumab (ipi), and nivolumab + ipilimumab (nivo+ipi). Data are presented as median (range) or as n (%). Some patients had many lines of chemotherapy.

Variable	All patients	Nivo	Pembro	Ipi	Nivo + ipi
n	140	46	67	21	6
Male	75 (54%)	21 (46%)	40 (60%)	11 (52%)	3 (50%)
Female	65 (46%)	25 (54%)	27 (40%)	10 (48%)	3 (50%)
Age (years)	65 (29–84)	66 (32–84)	65 (31–80)	58 (29–76)	50 (37–69)
ECOG PS					
0	80 (57%)	25 (54%)	46 (69%)	8 (38%)	1 (17%)
1	60 (43%)	21 (46%)	21 (31%)	13 (62%)	5 (83%)
LDH					
≤ULN	71 (51%)	23 (50%)	36 (54%)	7 (33%)	4 (67%)
>ULN	69 (49%)	23 (50%)	31 (46%)	14 (67%)	2 (33%)
$BRAF^{V600}$	54 (39%)	16 (35%)	2 (3%)	4 (19%)	2 (33%)
NRAS	27 (19%)	8 (17%)	19 (28%)	0 (0%)	0 (0%)
Disease stage					
Stage III	3 (2%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)
Stage IV M1a (0)	10 (7%)	4 (9%)	5 (8%)	1 (5%)	0 (0%)
Stage IV M1a (1)	17 (12%)	3 (7%)	8 (12%)	6 (29%)	0 (0%)
Stage IV M1b (0)	7 (5%)	1 (2%)	4 (6%)	1 (5%)	1 (17%)
Stage IV M1b (1)	22 (16%)	8 (17%)	11 (16%)	3 (14%)	0 (0%)
Stage IV M1c (0)	42 (30%)	15 (33%)	21 (31%)	4 (19%)	2 (33%)
Stage IV M1c(1)	24 (17%)	11 (24%)	8 (12%)	5 (24%)	0 (0%)
Stage IV M1d (0)	10 (7%)	3 (7%)	5 (8%)	1 (5%)	1 (17%)
Stage IV M1d (1)	5 (4%)	1 (2%)	2 (3%)	0 (0%)	2 (33%)
Brain metastases	15 (11%)	4 (9%)	7 (10%)	1 (5%)	3 (50%)
Lines of treatment					
None	113 (81%)	41 (89%)	58 (87%)	10 (48%)	4 (67%)
One	17 (12%)	4 (9%)	8 (12%)	3 (14%)	2 (33%)
Two or more	10 (7%)	1 (2%)	1 (1%)	8 (38%)	0 (0%)
Prev. treatments					
BRAFi ± MEKi	10 (7%)	2 (4%)	2 (3%)	4 (19%)	2 (33%)
Chemotherapy	27 (19%)	3 (7%)	7 (10%)	7 (33%)	0 (0%)
Prior hypothyr.	19 (14%)	2 (4%)	14 (21%)	3 (14%)	0 (0%)

BRAFi, BRAF inhibitor; $BRAF^{V600}$, $BRAF^{V600}$ mutation-positive melanoma; ECOG PS, Eastern cooperative oncology group performance status; LDH, lactate dehydrogenase; MEKi, MEK inhibitor; NRAS, NRAS mutation-positive melanoma; Prev. treatments, previous treatments; Prior hypothyr., prior hypothyreosis; ULN, upper limit of normal.

and 6 with ipilimumab–nivolumab combination therapy. Further patient characteristics are listed in Table 1.

Before the first treatment, 4 patients (3%) had positive TSH receptor antibodies (TRAbs), 17 patients (12%) had a borderline level of TSHRAbs, and 7 patients (5%) had elevated TPOAbs. Prior to ICI treatment, 19 patients (14%) had primary hypothyroidism and were on levothyroxine treatment. None of the patients with a previous diagnosis of hypothyroidism encountered ICI-related thyroid endocrinopathy. Furthermore, two of our patients with ICI-related autoimmune diabetes had a specific HLA class II allele DQB1*03, which is associated with an increased risk of type 1 diabetes (19).

Out of the treated patients, 111 (79%) had AEs. The patients tended to have multiple AEs, as there were 319 AEs in total. Endocrine AEs counted for 14% of all AEs (44/319). Three patients had two endocrine AEs. There were seven grade 3–4 endocrine AEs, but no deaths related to endocrinopathies. In comparison, there were 44 grade 3–4 other AEs, and in two patients, death was possibly related to ICI treatment in addition to unclear infection. Both patients suffered from acute kidney failure after ICI treatment.

Thyroiditis was the most common endocrine AE (26%, 36/140), followed by five cases of hypophysitis (4%, 5/140). The endocrine AEs required medication in 50% of the cases (22/44). Three patients had to discontinue treatment due to endocrine AE (7%, 3/44). In comparison, other irAEs in general caused treatment cessation in 25 out of 111 patients (23%). All AEs, endocrine AEs, and medication to endocrine AEs are summarized in Table 2.

The median time to the first occurrence of an endocrine AE was 6.4 weeks (range 0–41.3 weeks), whereas the median time to the first occurrence of other AEs was shorter;

Table 2 Treatment-related adverse events (AEs) of all patients and the patient subgroups treated with different immune checkpoint inhibitors (ICI): nivolumab (nivo), pembrolizumab (pembro), ipilimumab (ipi), and nivolumab + ipilimumab (nivo+ipi). Data are presented as *n* (%). Three patients had two endocrine AEs and multiple patients had more than one other AEs.

Variable	All patients	Nivo	Pembro	Ipi	Nivo + ipi
Any AE in total	319	100	148	50	21
Any AE/patient	111 (79%)	35 (76%)	53 (79%)	18 (86%)	5 (83%)
Grade 3–4	44 (31%)	11 (24%)	16 (24%)	12 (57%)	5 (83%)
Led to cessation	25 (23%)	7 (15%)	13 (19%)	4 (19%)	1 (17%)
End. AE in total	44 (31%)	11 (24%)	27 (40%)	3 (14%)	3 (50%)
End. AE/patient	41 (29%)	10 (22%)	25 (37%)	3 (14%)	3 (50%)
Grade 3–4	7 (16%)	2 (4%)	5 (7%)	0 (0%)	0 (0%)
Led to cessation	3 (7%)	0 (0%)	3 (5%)	0 (0%)	0 (0%)
Required med.	22 (50%)	6 (13%)	14 (21%)	1 (5%)	1 (17%)
Levothyroxine	11 (25%)	4 (9%)	6 (9%)	1 (5%)	0 (0%)
Carbimazole	2 (5%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)
Prednisone	9 (21%)	1 (2%)	7 (11%)	0 (0%)	1 (17%)
Hydrocortisone	5 (11%)	1 (2%)	4 (6%)	0 (0%)	0 (0%)
Methylpredn.	2 (5%)	1 (2%)	0 (0%)	0 (0%)	1 (17%)
Insulin	3 (7%)	1 (2%)	2 (3%)	0 (0%)	0 (0%)
Thyroid AE	36 (82%)	9 (20%)	22 (33%)	2 (10%)	3 (50%)
Grade 3–4	3 (7%)	1 (2%)	2 (3%)	0 (0%)	0 (0%)
Hypothyroidism	8 (22%)	2 (4%)	4 (6%)	1 (5%)	1 (17%)
Grade 3–4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thyrotoxicosis	14 (39%)	2 (4%)	9 (13%)	1 (5%)	2 (33%)
Grade 3–4	1 (3%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Thyrotoxicosis f. by hypot.	14 (39%)	5 (11%)	9 (13%)	0 (0%)	0 (0%)
Grade 3–4	2 (6%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)
Hypophysitis	5 (11%)[a]	1 (2%)	3 (5%)	1 (5%)	0 (0%)
Grade 3–4	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Autoimmune d.	3 (7%)	1 (2%)	2 (3%)	0 (0%)	0 (0%)
Grade 3–4	3 (7%)	1 (2%)	2 (3%)	0 (0%)	0 (0%)

[a]Two males/three females; hypopituitarism due to impaired ACTH/cortisol (*n* = 3), gonadotropin/testosterone (*n* = 1), TSH/T4 (*n* = 1) secretion.
AE, adverse event; autoimmune d., autoimmune diabetes; end. AE, endocrine AE; required med., required medication; thyrotoxicosis f. by hypot., thyrotoxicosis followed by hypothyroidism.

2.7 weeks (range 0–106.9 weeks). The first endocrine AE appeared earlier with anti-PD-1 treatment (median time 6.4 weeks; range 0–41.3 weeks) than with ipilimumab (median time 13.4 weeks; range 6.1–17.4 weeks) or with combination treatment (median time 8.7 weeks; range 2.7–8.7 weeks). On average, the first endocrine AE occurred after the third infusion (range 1–12) and the second after the seventh infusion (range 6–9). The mean duration of the first endocrine AE was 8.7 weeks (range 0–170) and 29.8 weeks (range 0.6–170.0) for the first other AE, respectively.

The hormone levels of patients with endocrine AEs were closely monitored and they varied widely between the patients. No specific pattern could be found. In general, most hormonal changes were transient. However, fluctuations were typical and resolved after 64–304 days.

CT scans were systematically performed to evaluate response. The most prominent radiological findings were usually detectable only after the endocrinological disorder had been identified based on laboratory tests. Radiological changes of the pituitary gland could not be reliably assessed in patients with hypocortisolism due to the varying imaging modalities (MRI, CT). However, CT manifestations of the thyroid and/or pancreas were found in 14 patients with thyroiditis and in 2 patients with diabetes. As our radiologist (HL) reviewed the scans retrospectively, a reduction in thyroid size could be detected in the treatment response CT scans in half of the patients developing hypothyroidism. In addition, 8 of the 14 patients with thyrotoxicosis had visual changes of the thyroid: three patients had a slight decline in thyroid size, whereas 5 patients had a more distinct decline in thyroid size. The pancreas decreased slightly in size in two of the patients developing autoimmune diabetes (Fig. 1). The radiological manifestations of endocrine AEs did come with a delay and were more obvious retrospectively, and were not related to better treatment responses.

The overall response rate (RR) was 39%. Complete response (CR) was achieved by 27 patients (19%) and

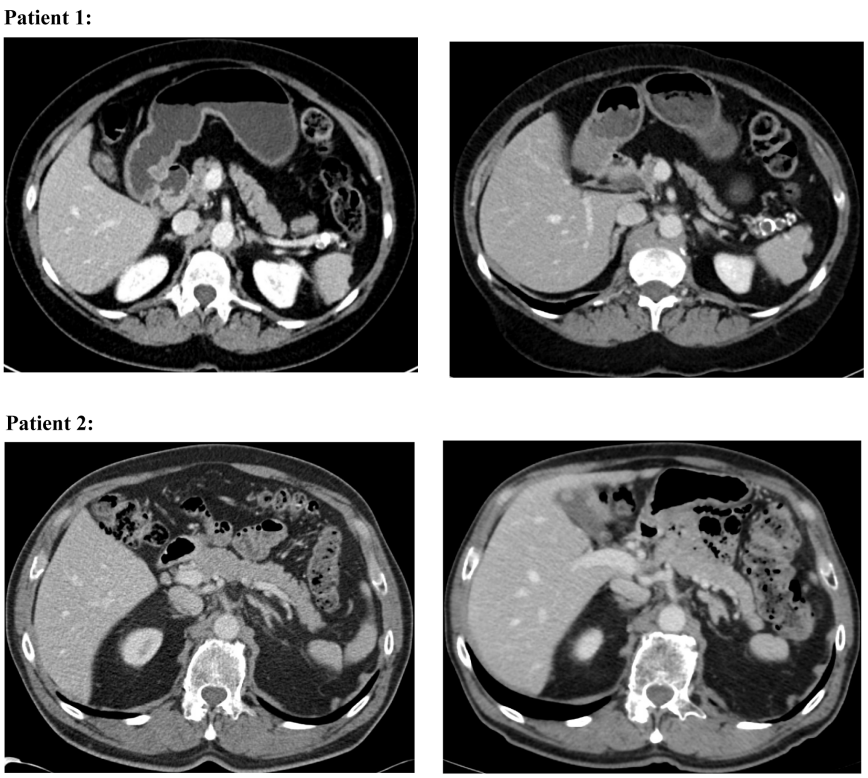

Figure 1
The reduction of pancreas in two of the patients developing autoimmune diabetes. The second patient had such extensive metastases in the pancreas that the reduction of the pancreas was hard to capture in a picture.

28 (20%) patients had partial response (PR) as the best response. The best treatment response was stable disease (SD) in 20 patients (14%), whereas 65 (46%) had progressive disease (PD). RR of nivolumab was 46% (11 CR, 10 PR), and 45 % with pembrolizumab (15 CR, 15 PR). The limited duration anti-PD-1 treatment RR was slightly lower than with unlimited anti-PD-1 treatment (42%, 5 CR, 11 PR). Compared to anti-PD-1 treatments, the RR rate with ipilimumab was lower, 14% (1 CR, 2 PR) as well as with combination treatment (RR 14%, no CR, 1 PR). The treatment responses with the limited duration of anti-PD-1 treatment consisted of 5 CR, 11 PR, 6 SD, and 16 PD. The median duration of unlimited anti-PD-1 treatment was 2.4 months (range 0–72.3 months) and 3.0 months (range 0–6.0 months) for the limited anti-PD-1 treatment, respectively.

At data cut-off on 20 May 2021, 23 patients (16%) were still responding and 55 patients (39%) were alive. In addition, 11 patients (8%) were still on treatment at data cut-off. Toxicity led to treatment termination in 28 patients (20%). For 64 patients (46%), treatment was terminated due to progression. According to the present treatment protocol, the treatment was stopped due to stabilized response for 9 (6%) patients. Within the local pilot study with limited anti-PD-1 treatment duration, the treatment was stopped for 27 patients at 6 months (19%) (17). One patient (1%) switched from pembrolizumab q3w to nivolumab q4w due to better patient compliance.

We found that RR was better in patients experiencing endocrine AEs (Fig. 2). The overall RR for patients with endocrine AEs was 56% compared to 32% for patients without endocrine AEs.

For all patients, median PFS was 3.1 months (range 0.4–73.0 months) and median OS was 23.5 months (range 0.56–95.8 months). Both PFS and OS were longer in patients with endocrine AEs than without (Fig. 3). Median OS for patients with endocrine AEs was 47.5 months (range 15.5–79.5 months) and 23.7 months (range 15.3–32.6 months) for patients without endocrine AEs. Furthermore, median PFS for patients with endocrine AEs was 8.1 months (range 5.1–11.1 months) and 2.7 months without endocrine AEs (range 2.4–3.0 months).

There was no significant difference between groups with or without endocrine AEs regarding age, sex, baseline LDH or CRP, baseline level of eosinophils or lymphocytes or their change after the first infusion, baseline thyroid antibodies whether abnormal or normal, or ECOG performance status tested with Student's *t*-test, the Mann–Whitney *U* test, or the Kruskal–Wallis test.

We conducted a landmark analysis at 1, 2, 3, and 4 months and the effect was minimal on the difference

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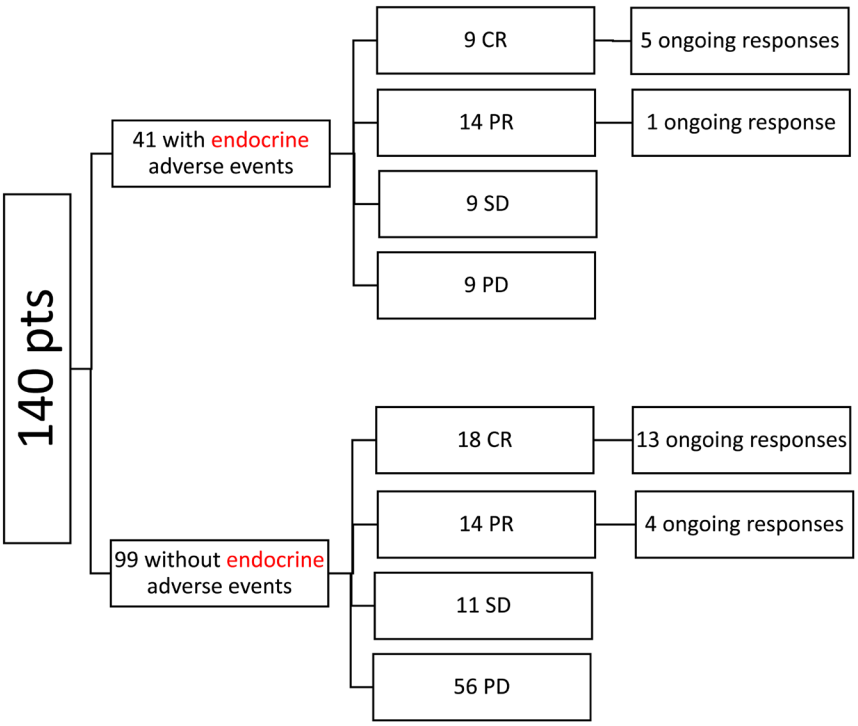

Figure 2
Treatment responses in patients with and without endocrine adverse events. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

between PFS and OS with patients experiencing endocrine AEs vs patients without them.

Discussion

Our results suggest that endocrine AEs are related to longer median PFS and OS. There were no deaths due to endocrine AEs. Generally, ICI-related endocrine AEs were quite manageable and rarely caused treatment termination.

Our centre has a policy of a close and consistent laboratory monitoring of patients receiving ICI. This enables us to detect endocrine AEs at an early point, prevent them from escalating, and timely initiate substitution treatment. Frequent laboratory monitoring thus allows for more accurate diagnosis of AEs.

The main limitation of our study is related to the retrospective collection of data, which can cause missing information and uncertainty. This data reflects a single tertiary centre experience. However, all melanoma cases of the Southern part of Finland with a catchment area of 2.2 million inhabitants are referred to our centre for treatment. Furthermore, 38 patients were treated within a pilot study with a limited anti-PD-1 treatment duration (17), which could have reduced the incidence of endocrine AEs due to shorter exposure time.

In a systematic literature review evaluating the toxicity and clinical outcome of IO-therapy, 36 studies with different cancer types were included (20). Out of 22 studies comprising 4413 melanoma patients, 21 found a positive correlation between irAEs and treatment outcome supporting our findings. The authors also speculated if a certain immunogenic phenotype could explain this finding. There were similar findings with non-small cell lung cancer (NSCLC) patients faring better with endocrine AEs.

In addition, a large systematic meta-analysis comprising 8452 patients evaluated the association between irAEs of anti-PD-1 therapy and clinical outcomes in patients with NSCLC (21). A significant correlation between improved OS with patients experiencing irAEs was again found, and a subgroup of patients with endocrine irAEs had a reduced risk of death, supporting our findings. Although the patients in these two studies represent different tumour types with different demographic features and risk factors, the finding seems valid, since anti-PD-1-therapy is widely used in both patient groups, and a similar correlation between irAEs and OS was observed in both studies.

In contrast to other published data, we report a greater number of endocrine AEs, presumably due to our frequent laboratory monitoring and recognizing and categorizing all abnormal hormonal laboratory results as endocrine AEs (22, 23, 24, 25). In two prospective trials with 177 (22) and 339 (23) metastatic melanoma patients, respectively, the incidence and kinetics of endocrinopathy by immunotherapy drugs were lower than in our study.

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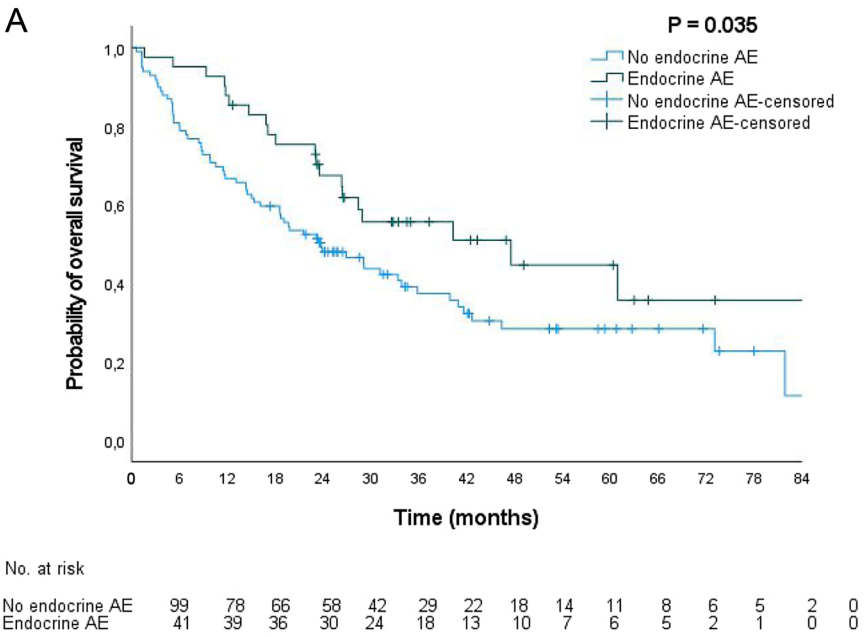

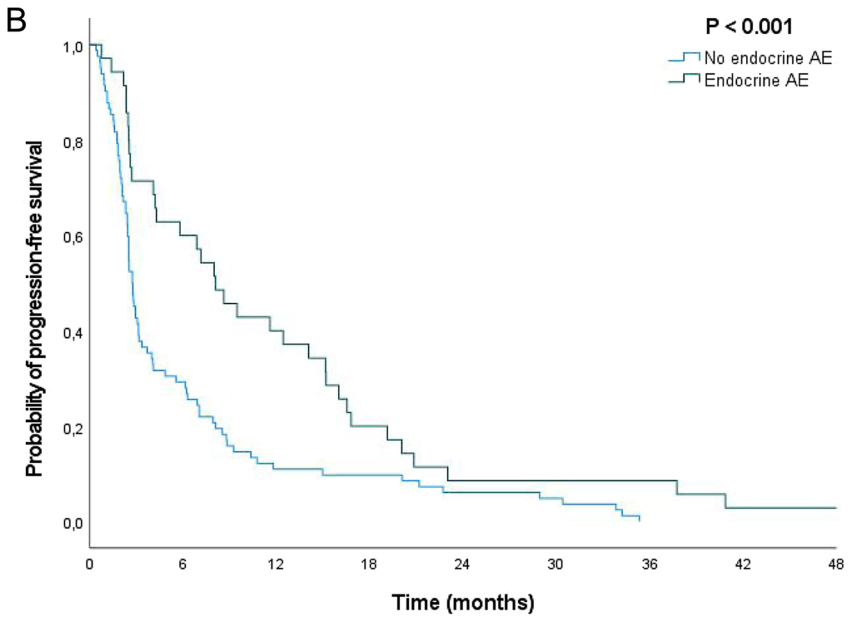

Figure 3
Kaplan–Meier curves of (A) overall survival and (B) progression-free survival in patients with- and without endocrine adverse events (AE).

In another study with 99 advanced melanoma patients treated with pembrolizumab, the incidence of thyroid irAEs was slightly higher (17.1% vs 14% and 3%), but still a bit lower than in our study (25.7%) (24). However, in a prospective trial with 52 advanced melanoma patients, treated with four doses of ipilimumab followed by nivolumab or pembrolizumab at disease progression, the incidence of thyroid dysfunction was 13.5% with ipilimumab, and 24.1% with PD-1 inhibitors, more in line with our findings (25). Also, another retrospective analysis comprising 1246 patients treated with ICI and a median follow-up of 11.3 months found that a number of patients (42%) developed an ICI-associated thyroid irAE (26).

Of note, clinical trials with a high number of ICIs and metastatic melanoma present endocrine AEs varyingly. For instance, the classification of thyroid disorders is heterogeneous and has been reported as decreased or increased TSH, or as hypothyroidism, thyrotoxicosis, and thyroiditis. Sometimes studies even report both the

abnormal hormonal findings as well as the diagnosed conditions as separate AEs in one patient (27). In contrast, we classified all thyroid laboratory abnormalities as thyroid endocrine AEs.

In contrast to our findings, a greater number of abnormal imaging results as manifestations of endocrine AEs have been reported. Radiological abnormalities in the pituitary gland of metastatic melanoma patients with hypophysitis treated with ipilimumab have been found in as much as 77% (26). Furthermore, a case series of follow-up scans showed that up to 90% of the radiological changes caused by ipilimumab may resolve (28). In contrast to our findings, a significant association between radiological abnormalities and treatment responses was seen in a retrospective study of metastatic melanoma patients undergoing anti-CTLA-4 therapy (29).

We did not detect a connection between endocrine AEs or thyroid AEs in subjects characterized by increased thyroid autoantibodies prior to ICI treatment. According to our study, hypothyroidism is often transient, and therefore, substitution therapy with levothyroxine should be withheld until necessary. We also found that transient thyrotoxicosis is much more common than persistent hyperthyroidism. Similar observations were recently reported among patients with ICI-induced thyroid AEs (30).

Endocrine AEs do not usually present with prior or even early radiological manifestations, but in some cases, radiological findings mainly in the development of type I diabetes are prominent and support the diagnosis. The oncologist should therefore consult both the radiologist and the endocrinologist, and preferentially establish multidisciplinary teams to ensure adequate diagnosis and treatment of possibly endocrine AEs.

Increased toxicity has been found to correlate to improved treatment outcomes in other cancers as well. It is well known that skin toxicities of cetuximab and panitumumab in metastatic colorectal cancer correlate with a better prognosis (31) supporting the observation that also endocrine irAEs could correlate with a better response to ICI treatment. Patients with endocrine irAEs faring better on ICI treatment may be due to a competent immune status translating into a generalized ICI-induced immune activation. Earlier, it has been shown that the improved outcome can be maintained despite the use of corticosteroids to treat irAEs (32).

ICI treatment itself and possible endocrine AEs may cause significant impairments to health-related quality of life (33). Nowadays, however, endocrine irAEs can be well managed with the help of various algorithms and through multidisciplinary teamwork. Since the prognosis of melanoma patients has improved significantly and patients live longer, future research should take the quality of life of melanoma patients with irreversible endocrine AEs into consideration. Furthermore, it would be essential to find valid predictive biomarkers identifying the risk for endocrine AEs (34). The long-term effects on fertility of young patients and hypophysitis are unknown, and need to be studied.

The increasing use of ICI in the adjuvant setting may through development of endocrine irAEs cause lifelong consequences and medication. ICI treatments are expensive and especially the care of treatment-related type I diabetes increases costs, raising the question of cost-effectiveness (35). In addition, longer treatment times and increasing use of combination treatments may result in a greater possibility of endocrine AEs (9).

Solely, the diagnosis of metastatic melanoma creates a burden to a patient, let alone having to deal with lifelong treatment-related sequelae. On one hand, endocrine AEs can result in permanent hormone deficiencies requiring lifelong substitution therapies, but on the other hand, endocrine AEs seem to be related to longer PFS and OS. Based on our results, a systematic laboratory and patient follow-up are highly recommendable during ICI treatment as well as a close multidisciplinary teamwork with oncologists, endocrinologists, and radiologists in order to secure timely diagnosis and treatment of irAEs (36).

Declaration of interest

Micaela Hernberg reports personal fees from BMS, MSD, Novartis. Siru Mäkelä has had a paid consulting or advisory role with MSD and BMS. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This study was funded by Helsinki University Hospital Research Fund (Grant number Y1018XMH07 to M H and TYH2019254 to C S-J). Open access funded by Helsinki University Library.

Acknowledgement

The authors would like to thank Timo Muhonen for the valuable guidance with landmark analysis.

References

1 Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, *et al.* Improved

survival with ipilimumab in patients with metastatic melanoma. *New England Journal of Medicine* 2010 **363** 711–723. (https://doi.org/10.1056/NEJMoa1003466)
2 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *New England Journal of Medicine* 2015 **372** 320–330. (https://doi.org/10.1056/NEJMoa1412082)
3 Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, Hodi FS, Schachter J, Pavlick AC, Lewis KD, *et al.* Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet: Oncology* 2015 **16** 908–918. (https://doi.org/10.1016/S1470-2045(15)00083-2)
4 Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New England Journal of Medicine* 2015 **373** 23–34. (https://doi.org/10.1056/NEJMoa1504030)
5 Velasco G de, Je Y, Bossé D, Awad MM, Ott PA, Moreira RB, Schutz F, Bellmunt J, Sonpavde GP, Hodi FS, *et al.* Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunology Research* 2017 **5** 312–318. (https://doi.org/10.1158/2326-6066.CIR-16-0237)
6 Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, Postow MA & Wolchok JD. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Annals of Oncology* 2015 **26** 2375–2391. (https://doi.org/10.1093/annonc/mdv383)
7 Majem M, García-Martínez E, Martinez M, Muñoz-Couselo E, Rodriguez-Abreu D, Alvarez R, Arance A, Berrocal A, de la Cruz-Merino L & Lopez-Martin JA. SEOM clinical guideline for the management of immune-related adverse events in patients treated with immune checkpoint inhibitors (2019). *Clinical and Translational Oncology* 2020 **22** 213–222. (https://doi.org/10.1007/s12094-019-02273-x)
8 Iglesias P. Cancer immunotherapy-induced endocrinopathies: clinical behavior and therapeutic approach. *European Journal of Internal Medicine* 2018 **47** 6–13. (https://doi.org/10.1016/j.ejim.2017.08.019)
9 Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE & Tolaney SM. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncology* 2018 **4** 173–182. (https://doi.org/10.1001/jamaoncol.2017.3064)
10 González-Rodríguez E, Rodríguez-Abreu D & Spanish Group for Cancer Immuno-Biotherapy (GETICA). Immune checkpoint inhibitors: review and management of endocrine adverse events. *Oncologist* 2016 **21** 804–816. (https://doi.org/10.1634/theoncologist.2015-0509)
11 Herrscher H & Robert C. Immune checkpoint inhibitors in melanoma in the metastatic, neoadjuvant, and adjuvant setting. *Current Opinion in Oncology* 2020 **32** 106–113. (https://doi.org/10.1097/CCO.0000000000000610)
12 Das S & Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *Journal for ImmunoTherapy of Cancer* 2019 **7** 306. (https://doi.org/10.1186/s40425-019-0805-8)
13 Suo A, Chan Y, Beaulieu C, Kong S, Cheung WY, Monzon JG, Smylie M, Walker J, Morris D & Cheng T. Anti-PD1-induced immune-related adverse events and survival outcomes in advanced melanoma. *Oncologist* 2020 **25** 438–446. (https://doi.org/10.1634/theoncologist.2019-0674)
14 Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, Lazar AJ, Faries MB, Kirkwood JM, McArthur GA, *et al.* Melanoma staging: evidence-based changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA: A Cancer Journal for Clinicians* 2017 **67** 472–492. (https://doi.org/10.3322/caac.21409)
15 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, Oosterom AT van, Christian MC, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute* 2000 **92** 205–216. (https://doi.org/10.1093/jnci/92.3.205)
16 *Common Terminology Criteria for Adverse Events (CTCAE) Version 5*. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2017.
17 Mäkelä S, Kohtamäki L, Laukka M, Juteau S & Hernberg M. Limited-duration anti-PD-1 therapy for patients with metastatic melanoma. *Acta Oncologica* 2020 **59** 438–443. (https://doi.org/10.1080/0284186X.2020.1716388)
18 Stelmachowska-Banaś M & Czajka-Oraniec I. Management of endocrine immune-related adverse events of immune checkpoint inhibitors: an updated review. *Endocrine Connections* 2020 **9** R207–R228. (https://doi.org/10.1530/EC-20-0342)
19 Jacobi T, Massier L, Klöting N, Horn K, Schuch A, Ahnert P, Engel C, Löffler M, Burkhardt R, Thiery J, *et al.* HLA class II allele analyses implicate common genetic components in type 1 and non-insulin-treated type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** 105.e245–e254. (https://doi.org/10.1210/clinem/dgaa027)
20 Cortellini A, Buti S, Agostinelli V & Bersanelli M. A systematic review on the emerging association between the occurrence of immune-related adverse events and clinical outcomes with checkpoint inhibitors in advanced cancer patients. *Seminars in Oncology* 2019 **46** 362–371. (https://doi.org/10.1053/j.seminoncol.2019.10.003)
21 Zhao Z, Wang X, Qu J, Zuo W, Tang Y, Zhu H & Chen X. Immune-related adverse events associated with outcomes in patients with NSCLC treated with anti-PD-1 inhibitors: a systematic review and meta-analysis. *Frontiers in Oncology* 2021 **11** 708195. (https://doi.org/10.3389/fonc.2021.708195)
22 Scott ES, Long GV, Guminski A, Clifton-Bligh RJ, Menzies AM & Tsang VH. The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. *European Journal of Endocrinology* 2018 **178** 173–180. (https://doi.org/10.1530/EJE-17-0810)
23 Kassi E, Angelousi A, Asonitis N, Diamantopoulos P, Anastasopoulou A, Papaxoinis G, Kokkinos M, Giovanopoulos I, Kyriakakis G, Petychaki F, *et al.* Endocrine-related adverse events associated with immune-checkpoint inhibitors in patients with melanoma. *Cancer Medicine* 2019 **8** 6585–6594. (https://doi.org/10.1002/cam4.2533)
24 Filette J de, Jansen Y, Schreuer M, Everaert H, Velkeniers B, Neyns B & Bravenboer B. Incidence of thyroid-related adverse events in melanoma patients treated with pembrolizumab. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 4431–4439. (https://doi.org/10.1210/jc.2016-2300)
25 Guaraldi F, La Selva R, Samà MT, D'Angelo V, Gori D, Fava P, Fierro MT, Savoia P & Arvat E. Characterization and implications of thyroid dysfunction induced by immune checkpoint inhibitors in real-life clinical practice: a long-term prospective study from a referral institution. *Journal of Endocrinological Investigation* 2018 **41** 549–556. (https://doi.org/10.1007/s40618-017-0772-1)
26 Widmann G, Nguyen VA, Plaickner J & Jaschke W. Imaging features of toxicities by immune checkpoint inhibitors in cancer therapy. *Current Radiology Reports* 2016 **5** 59. (https://doi.org/10.1007/s40134-017-0256-2)
27 Karimian Z, Mavoungou S, Salem JE, Tubach F & Dechartres A. The quality of reporting general safety parameters and immune-related adverse events in clinical trials of FDA-approved immune checkpoint inhibitors. *BMC Cancer* 2020 **20** 1128. (https://doi.org/10.1186/s12885-020-07518-5)
28 Tirumani SH, Ramaiya NH, Keraliya A, Bailey ND, Ott PA, Hodi FS & Nishino M. Radiographic profiling of immune-related adverse events

in advanced melanoma patients treated with ipilimumab. *Cancer Immunology Research* 2015 **3** 1185–1192. (https://doi.org/10.1158/2326-6066.CIR-15-0102)

29 Bronstein Y, Ng CS, Hwu P & Hwu WJ. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. *American Journal of Roentgenology* 2011 **197** W992–W1000. (https://doi.org/10.2214/AJR.10.6198)

30 Brancatella A, Lupi I, Montanelli L, Ricci D, Viola N, Sgrò D, Antonangeli L, Sardella C, Brogioni S, Piaggi P, *et al.* Management of thyrotoxicosis induced by PD1 or PD-L1 blockade. *Journal of the Endocrine Society* 2021 **5** bvab093. (https://doi.org/10.1210/jendso/bvab093)

31 Petrelli F, Ardito R, Ghidini A, Zaniboni A, Ghidini M, Barni S & Tomasello G. Different toxicity of cetuximab and panitumumab in metastatic colorectal cancer treatment: a systematic review and meta-analysis. *Oncology* 2018 **94** 191–199. (https://doi.org/10.1159/000486338)

32 Petrelli F, Signorelli D, Ghidini M, Ghidini A, Pizzutilo EG, Ruggieri L, Cabiddu M, Borgonovo K, Dognini G, Brighenti M, *et al.* Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancers* 2020 **12** 546. (https://doi.org/10.3390/cancers12030546)

33 O'Reilly A, Hughes P, Mann J, Lai Z, Teh JJ, Mclean E, Edmonds K, Lingard K, Chauhan D, Lynch J, *et al.* An immunotherapy survivor population: health-related quality of life and toxicity in patients with metastatic melanoma treated with immune checkpoint inhibitors. *Supportive Care in Cancer* 2020 **28** 561–570. (https://doi.org/10.1007/s00520-019-04818-w)

34 Nakamura Y. Biomarkers for immune checkpoint inhibitor-mediated tumor response and adverse events. *Frontiers in Medicine* 2019 **6** 119. (https://doi.org/10.3389/fmed.2019.00119)

35 Copley-Merriman C, Stevinson K, Liu FX, Wang J, Mauskopf J, Zimovetz EA & Chmielowski B. Direct costs associated with adverse events ofsystemic therapies for advanced melanoma. *Medicine* 2018 **97** e11736. (https://doi.org/10.1097/MD.0000000000011736)

36 Illouz F, Briet C, Cloix L, Le Corre Y, Baize N, Urban T, Martin L & Rodien P. Endocrine toxicity of immune checkpoint inhibitors: essential crosstalk between endocrinologists and oncologists. *Cancer Medicine* 2017 **6** 1923–1929. (https://doi.org/10.1002/cam4.1145)

Received in final form 23 December 2021
Accepted 11 January 2022
Accepted Manuscript published online 11 January 2022