Title: Thyroid Abnormalities following the use of CTLA-4 and PD-1 Inhibitors in the treatment of melanoma

Short Title: Thyroid abnormalities following Immune Checkpoint Inhibitors in Melanoma

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Abstract

Context

Checkpoint inhibitors are emerging as important cancer therapies, but are associated with a high rate of immune side effects, including endocrinopathy.

Objective

To determine the burden of thyroid dysfunction in patients with melanoma treated with immune checkpoint inhibitors and describe the clinical course.

Design and Patients

Consecutive patients with melanoma treated with either Ipilimumab, Nivolumab, Pembrolizumab or the combination of Ipilimumab and Nivolumab were identified . Baseline thyroid function tests were used to exclude those with pre-existing thyroid abnormalities, and thyroid function tests during treatment used to identify those with thyroid dysfunction.

Results

Rates of overt thyroid dysfunction were in keeping with the published Phase 3 trials. Hypothyroidism occurred in 13.0% treated with a PD-1 inhibitor and 22.2% with a combination of PD-1 inhibitor and Ipilimumab. Transient subclinical hyperthyroidism was observed in 13.0% treated with a PD-1 inhibitor, 15.9% following a PD-1 inhibitor, and 22.2% following combination treatment with investigations suggesting a thyroiditic mechanism rather than Graves' disease, and a high frequency of subsequent hypothyroidism. Any thyroid abnormality occurred in 23.0% following Ipilimimab, 39.1% following a PD-1 inhibitor and 50% following combination treatment.Abnormal thyroid function was more common in female patients.

Conclusion

Thyroid dysfunction occurs commonly in patients with melanoma treated with immune checkpoint inhibitors, with rates, including sub-clinical dysfunction, occurring in up to 50%.

Introduction

Immune checkpoint inhibitors have been approved as treatment options for melanoma in both the advanced and, more recently, adjuvant settings. Ipilimumab was the first agent to demonstrate an overall survival advantage in patients with metastatic disease [1, 2]. It is a monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4) that blocks an inhibitory signal to T cells, thereby prolonging a stimulated immune response against tumour cells. The Food and Drug Administration (FDA) approved ipilimumab for use in the adjuvant setting after a large study demonstrated improved recurrence-free survival compared to placebo in patients with resected Stage III disease [3]. There is also a survival benefit when ipilimumab is used in resected Stage III disease [4]. Newer agents such as pembrolizumab and nivolumab have superseded the use of ipilimumab as a monotherapy in metastatic disease, with improvements in both response rate and survival [5, 6]. These checkpoint inhibitors are antibodies against the programmed death protein-1 (PD-1), upregulated on activated T cells. By interrupting PD-1 binding to its ligand, PD-L1, there is an increase in effector T cell activity in the tumour microenvironment. In addition to being more effective, pembrolizumab and nivolumab have a lower rate of adverse events than ipilimumab. Arguably the most potent checkpoint-inhibitor treatment strategy for advanced melanoma is the combination of ipilimumab with nivolumab. Although we await the overall survival data from the Checkmate-067 Phase III study, numerically the combination has the highest response rate and longest progression free survival compared with nivolumab or ipilimumab monotherapy[6]. The price of such efficacy is a higher rate of toxicity.

Autoimmune side effects are frequently described, and endocrinopathy is a common toxicity. Ipilimumab has been associated with hypopituitarism, presumed due to a hypophysitis, in between 10 to 15%[7, 8]. Both hyperthyroidism due to Graves' disease and hypothyroidism have also been described following ipilimumab treatment[9, 10]. PD-1 inhibitors have also been reported to commonly result in thyroid dysfunction, with hypothyroidism occurring in between 7 and 16% in clinical trials (with higher rates in those treated with a combination of nivolumab and ipilimumab) [11]. Hyperthyroidism has also been described after treatment with PD-1 inhibitors[12]. Supplementary Table 1 summarises the reported incidence of thyroid abnormalities in the key trials of these drugs in melanoma.

Here, we describe a single centre experience of thyroid abnormalities in patients with melanoma treated with immune checkpoint inhibitors. We describe a systematic analysis of thyroid function abnormalities following treatment with the PD-1 inhibitors nivolumab or pembrolizumab, anti-CTLA-4 inhibitor ipilimumab, or combination of ipilimumab and nivolumab, as well as a detailed analysis of hyperthyroidism occurring after use of ipilimumab, nivolumab, pembrolizumab and the combination of ipilimumab with nivolumab.

Patients and Methods

Subjects

We retrospectively reviewed the records of patients with melanoma treated with the PD-1 inhibitors nivolumab or pembrolizumab, or the CLTA-4 inhibitor ipilimumab at the Royal Marsden, either as part of published trials, as part of a compassionate use program, or routine care, as mono or combination therapy. Patients with treatment-induced hypopituitarism, abnormal thyroid function prior to receiving the immunotherapy drug, or without availability of baseline thyroid function tests were excluded. Thyroid function was measured at baseline before treatment. Serum TSH and free T4 (FT4) were then measured every 2-4 weeks as mandated by trial protocols or routine clinical practice. Results of thyroid function tests during treatment were collected from the electronic record. For patients who developed hypothyroidism results of additional tests including thyroid antibodies and treatment with thyroxine were also collected.

Secondly patients with melanoma treated with an immune checkpoint inhibitor who developed hyperthyroidism (either sub-clinical or clinically overt) were identified by review of clinical records. Serial thyroid function tests were collected to determine the time course of thyroid dysfunction, as well as results of thyroid peroxidase antibodies, results of Tc99 pertechnate uptake scans and need for treatment with beta blockers, anti-thyroid drugs and thyroxine. We also recorded the need for corticosteroid treatment for other immune related toxicities in the hyperthyroid cohort.

Three cohorts were identified of consecutively treated patients in the given date ranges.

Ipilimumab

143 patients were identified treated between March 2011 and June 2014. 6 patients were excluded due to a diagnosis of hypopituitarism, and 11 were excluded due to abnormal thyroid function tests at baseline, leaving 126 patients included in the study.

PD-1 Inhibitors

67 patients were identified treated between May 2013 and December 2014. 13 were excluded due to abnormal baseline thyroid function, and a further 8 due to no baseline thyroid function tests being available, leaving 46 patients included in the study. 28 received Pembrolizumab and 18 Nivolumab.

Ipilimumab and Nivolumab Combination

22 patients were identified, treated between August 2013 and December 2015. 3 were excluded due to abnormal thyroid function at baseline, and 1 excluded as no follow up data was available. One patient developed secondary adrenal insufficiency presumed due to hypophysitis, but had a low FT4 and an elevated serum TSH so was included, leaving 18 patients included in the study.

Laboratory Tests

Serum TSH, FT4 and Thyroid Peroxidase antibodies were measured using an Abbott Architect method. Reference ranges were serum TSH 0.49-4.67 mU/L and FT4 9.1-23.8 pmol/L.

Hypothyroidism was defined as a FT4 below the reference range, whilst hyperthyroidism was defined as a FT4 above the reference range. Sub-clinical hypothyroidism and hyperthyroidism were defined as a serum TSH above or below

the reference range respectively with a normal FT4. Where patients had an initial hyperthyroid phase (overt or sub-clinical) before becoming hypothyroid, they were included in the hyperthyroid groups for analysis of initial serum TSH changes, but the hypothyroid group for other comparisons. A single abnormal result, as above, was used to categorise patients.

Thyroid Uptake scans

Planar images were obtained at 20 minutes following intravenous administration of 80 MBq Tc-99m Pertechnetate using a Low Energy High Resolution Collimator on Philips Brightview (Eindhoven, The Netherlands) or Siemens Symbia T6 (Erlangen, Germany) gamma cameras. The 20-minute thyroid uptake value was calculated as follows: counts within a region of interest (ROI) drawn around the thyroid gland were corrected for background counts and converted to measurements of activity using a pre-measured gamma camera sensitivity factor. This measurement of thyroid activity was compared to the injected activity following decay correction to account for the time interval between injection and imaging, with the normal uptake function range taken to be 0.4 to 4.0% of the injected activity.

Statistics

Descriptive statistics are presented as mean +/- standard deviation. Comparisons between groups were made with either a t test or ANOVA with Dunn's Multiple comparison test for TSH comparisons, with significance levels of $p<0.05$. Chi-squared test was used for categorical analysis. Times to events are presented as median with interquartile range.

Results

Thyroid Abnormalities following treatment with Ipilimumab

Of the 126 included patients treated with Ipilimumab, 1 developed primary hypothyroidism whilst 8 (6%) developed sub-clinical hypothyroidism. 20 (16%) developed sub-clinical hyperthyroidism, none of whom required treatment. Thus overall, 23% of patients had some degree of thyroid dysfunction. Clinical details of those with abnormal thyroid function are summarised in Supplementary Table 2. The mean age in those with normal thyroid function was 56.7 years (+/- 15.2) and 59.0 years(+/- 13.5) in those with abnormal thyroid function, but this was not significant (p=0.45). The one patient with hypothyroidism developed an abnormal serum TSH 63 days after treatment, and those with sub-clinical hypothyroidism had a median time of 65 days (26-90) to first abnormal serum TSH, whilst the sub-clinical hyperthyroidism group developed an abnormal serum TSH a median of 50 days (36-111) after treatment. The distribution of thyroid function at time of the most extreme TSH are shown in Figure 1 (a and b).

Thyroid Abnormalities following treatment with PD-1 Inhibitors

Of the 46 included patients, 6 (13%) developed primary hypothyroidism, with a further 6 (13%)sub-clinical hypothyroidism. 6 patients (13%) developed sub-clinical hyperthyroidism. Of the patients with hypothyroidism, 2 had an initial sub-clinical hyperthyroid phase, one of whom was already taking a beta blocker for supraventricular tachycardia, and neither required anti-thyroid drugs. Clinical details of those with thyroid abnormalities (categorised according to final thyroid status) are summarised in Supplementary Table 3. Thus 39% of patients demonstrated some degree of thyroid dysfunction. Mean age in those with normal thyroid function was

55.3 years (+/- 12.1) and 59.8 years (+/- 13.2) in those with abnormal thyroid function (p=0.23).

In those with hypothyroidism, the median time to an abnormal serum TSH was 32 days (25-57) whilst the peak serum TSH was reached in a median of 81 days (58-107). In those with sub-clinical hypothyroidism, the median time to first abnormal serum TSH was 66 days (38-74). In those with sub-clinical hyperthyroidism the median time to first abnormal serum TSH was 57 days (25-127) with the nadir serum TSH being reached at 64 days (28-197). The distribution of thyroid function at time of the most extreme TSH is shown in Figure 1(c and d).

In the hypothyroid cohort, 5 patients started thyroxine with a median time to treatment of 126 days (80-320). Thyroid peroxidase antibodies were tested in one patient, and were positive.

Thyroid Abnormalities following treatment with Ipilimumab and Nivolumab combination.

Of the 23 included patients treated with the combination of Ipilimumab and a PD-1 inhibitor nivolumab, 4 patients (22.2%) developed hypothyroidism, 1 of whom had a preceding episode of hyperthyroidism, and 2 had preceding sub-clinical hyperthyroidism, none of whom needed anti-thyroid drugs, and 2 of whom were treated with thyroxine. One patient (5.6%) had sub-clinical hypothyroidism, and a further 4 patients (22.2%) had sub-clinical hyperthyroidism without subsequent hypothyroidism. Thus overall 50% of patients had thyroid abnormalities. Clinical details are summarised in Supplementary Table 4 (according to final thyroid status).

Mean age in those with normal thyroid function was 54.3 years (+/- 15.16) and 63.4 years (+/- 7.9) in those with thyroid abnormalities but this was not significant

(p=0.13). The distribution of thyroid function at time of the most extreme TSH are shown in Figure 1 (e and f). Due to the smaller numbers no further analysis was performed.

Pooled Analysis

Overall 190 patients with melanoma treated with Ipilimumab, a PD-1 inhibitor or combination were included, of whom 56 (29.5%) developed thyroid abnormalities. This is summarised in Table 1, grouping patients by their final thyroid status (ie those with transient hyperthyroidism who developed subsequent hypothyroidism and are grouped in the hypothyroid cohort). There was a trend to those with thyroid abnormalities being older with a mean age of 60.0 years (+/- 12.6) compared to a mean age of 56.2 years (+/- 14.5) in those with normal thyroid function, however this did not reach statistical significance (p= 0.09). There was a significant gender difference, with 23% of male patients developing thyroid abnormalities compared to 38.3% of female patients (p=0.022). Taking the most extreme thyroid results, hypothyroid patients had a mean serum TSH of 26.4 +/- 31.54 mU/L with mean free T4 of 9.6 +/- 5.9 pmol/L. The mean serum TSH in the sub-clinical hypothyroid group was 7.7 +/- 3.9 mU/l with mean free T4 of 12.6 +/- 1.6 pmol/L, whilst the subclinical hyperthyroid group had a mean serum TSH of 0.26 +/- 0.1 mU/L with free T4 of 15.3 +/1 3.0 pmol/L.

Next we compared thyroid function at baseline in those whose thyroid function remained normal compared to those who developed thyroid dysfunction (Figure 2). Notably, the pre-treatment serum TSH was significantly higher at 3.1 mU/l (+/- 1.3) in those who went on the develop hypothyroidism and 2.5 mU/l (+/- 1.1) in those with subsequent sub-clinical hypothyroidism than in those whose thyroid function

remained normal at 1.7 mu/l (+/- 1.0) or who developed only sub-clinical hyperthyroidism without progression to hypothyroidism at 1.6 mU/l (+/- 0.9).

Hyperthyroidism following immune checkpoint inhibitors

Next we identified a total of 6 patients who had received either monotherapy with a PD-1 inhibitor or ipilimumab or a combination of nivolumab with ipilimumab for melanoma and developed hyperthyroidism, all investigated with thyroid uptake scans. (Three patients were also included in the above cohorts). Clinical details of the 6 patients are summarised in Table 2. The mean age was 64 years (+/- 12.7) and there were 4 males and 2 females. The mean serum TSH at baseline was 2.0 mU/l+/- 1.2 with a mean baseline FT4 of 12.9 pmol/l +/- 3.8. The median time to an abnormal TSH in this cohort was 18 days (11-22) with a median time to nadir TSH of 35 days (25-57). All patients had an undetectable TSH at the nadir. Thyroid peroxidase antibodies were checked in 4 patients, and were positive in three. All patients had thyroid uptake scans and all showed reduced uptake in keeping with a thyroiditis (3 had undetectable uptake). Of note all patients had had previous contrast enhanced CT scans with an interval between last CT and the uptake scan ranging from 21 to 71 days (median 42).

Beta blockers were required in 4 out of 6 patients to control symptoms of hyperthyroidism but no patients received antithyroid drugs. 4 out of the 6 patients went on to develop hypothyroidism with a median time to starting thyroxine therapy of 291 days (91-436). Two patients returned to normal thyroid function without needing thyroxine therapy. Interestingly both required high dose corticosteroids for

treatment of other autoimmune related toxicities (colitis and hepatitis) and were the only patients with hyperthyroidism to receive corticosteroids.

Discussion

We have described a high rate of thyroid abnormalities in patients with melanoma treated with immune checkpoint inhibitors, including a high rate of sub-clinical thyroid abnormalities. Overall 29.5% of patients developed thyroid abnormalities, with the lowest rate of 23% in those treated with ipilimumab, and the highest of 50% of those treated with combination therapy. Thyroid abnormalities were more common in female patients. Whilst the majority of abnormalities did not require treatment, this still poses a resource burden in terms of need for follow up and repeat measurement of thyroid function. It is notable that a subset of patients who develop hypothyroidism have a transient initial hyperthyroid phase (often subclinical), highlighting the need for careful recognition and follow up of those with thyroid abnormalities.

The rate of hypothyroidism following treatment with a PD1 inhibitor was in line with that reported in clinical trials with nivolumab and pembrolizumab [5, 6, 11], with 5 out of 46 (11%) evaluable participants developing frank hypothyroidism requiring thyroxine replacement, as well as those of a recent review of patients treated with pembrolizumab [13] Notably two of these had an initial period of hyperthyroidism before subsequently developing hypothyroidism. Thyroid dysfunction can occur early after initiating treatment with a PD-1 inhibitor, with a median onset of just over 4 weeks. We also report a high rate of sub-clinical thyroid dysfunction, with both reductions and elevations in serum TSH, with normal free FT4 levels, without progression to overt thyroid dysfunction. Although the mean first abnormal TSH was

higher in the cohort that developed hypothyroidism than the sub-clinical group, the wide range and occurrence of an initial hyperthyroid phase in two out of 5 patients who went on to become hypothyroid means than all patients with abnormal thyroid function test need close follow up to differentiate clinically significant from sub-clinical thyroid dysfunction.

In order to determine the aetiology of the thyroid dysfunction, we examined in detail a cohort of 6 patients who developed hyperthyroidism after treatment with immune checkpoint inhibitors (nivolumab, ipilimumab or the combination of nivolumab and ipilimumab). All had a completely suppressed serum TSH after treatment and all 6 had thyroid uptake scans showing reduced or absent uptake. 4 out of 6 went on to develop hypothyroidism. This supports a destructive thyroiditis rather than Graves' disease as the cause of the hyperthyroidism. This is in keeping with a previous report [12] where 6 patients with hyperthyroidism following a PD-1 inhibitor were identified, and none had detectable TSH receptor antibodies. Thyroid uptake scans were not performed in that study. In our cohort, thyroid peroxydase antibodies were checked in 4 participants and were positive in three, supporting but not proving an autoimmune aetiology for the thyroiditis. A potential confounding factor is that, as would be typical for patients with metastatic disease, all had received intravenous iodinated contrast material as enhancement for CT scans prior to scintigraphy (the interval between the scans ranged from 21 to 71 days). Whilst guidelines suggest that that iodinated contrast material can interfere with Sodium Iodide thyroid scans for up to two months, there is evidence that this limitation does not pertain to the Pertechnetate scans used in the patients included in this study [14]. [15]. Thus the results of thyroid uptake scans support a thyroiditis as the aetiology of the thyroid dysfunction.

It is of interest that of the two participants with hyperthyroidism who required high dose systemic corticosteroids for management of other immune related toxicities, neither went on to become hypothyroid. Thus we speculate that immunosuppressive therapy may prevent the development of hypothyroidism in those with thyroiditis following immune checkpoint inhibitors. This is in contrast to the situation in ipilimumab induced hypophysitis, where high dose steroids have not been shown to reverse pituitary dysfunction[16]. Whilst it is not clear that immunosuppressive treatment would be justified to prevent hypothyroidism, many patients do develop more than one immune mediated toxicity and hence may require corticosteroids for non-thyroid indications.

Identification of patients at risk of thyroid dysfunction would aid in directing follow up. It is notable that patients who went on to develop hypothyroidism (either overt or sub-clinical) had a higher mean serum TSH prior to treatment than those with normal thyroid function on treatment or sub-clinical hyperthyroidism. This raises the possibility that these patients may have had mild thyroid dysfunction prior to treatment, that predisposed to development of hypothyroidism. Indeed, as thyroid antibodies were not available for most patients, either before or during immunotherapy treatment, we cannot rule out pre-existing sub-clinical Hashimoto thyroiditis.

Our study does have certain limitations. As it was a retrospective study we did not have thyroid antibody results in all patients with abnormal thyroid function, so we cannot prove an autoimmune aetiology. In particular, it is notable that the cohort of patients treated with ipilimumab who developed a low serum TSH on treatment had a wide range of FT4 levels within the normal range, whilst those treated with a PD-1

inhibitor had higher FT4 levels (Figure 1 b and d). Although patients with overt hypopituitarism were excluded, we cannot rule out the possibility that some of these had a mild hypophysitis with TSH deficiency rather than sub-clinical hyperthyroidism, possibly over-estimating the rate of primary thyroid abnormalities in these patients. Similarly, the one patient treated with ipilimumab who developed a low FT4 had only a mildly elevated TSH, that was lower than the mean in those with sub-clinical hypothyroidism. This is difficult to explain and it is possible that this patient had a mixed picture with co-existent pituitary dysfunction. Nevertheless this does give an accurate assessment of the range of thyroid abnormalities encountered in patients with melanoma treated with immune checkpoint inhibitors.

In summary, endocrinologists need to be aware of the high risk of thyroid dysfunction in patients treated with immune checkpoint inhibitors. In particular hyperthyroidism appears to be frequently caused by a thyroiditis (despite case reports of Grav's' disease) not requiring anti-thyroid drugs and with a high frequency of development of subsequent hypothyroidism.

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FIGURES AND TABLES

Figure 1: Distribution of thyroid function at the time of the most extreme TSH. (a) and (b) ipilimumabtreated patients (c) and (d) programmed death receptor-1 inhibitor-treated patients and (e) and (f) those treated with combination of ipilimumab and nivolumab. (a), (c) and (e) show the distribution of TSH and (b), (d) and (f) that of free T4. All graphs show mean ± SEM.

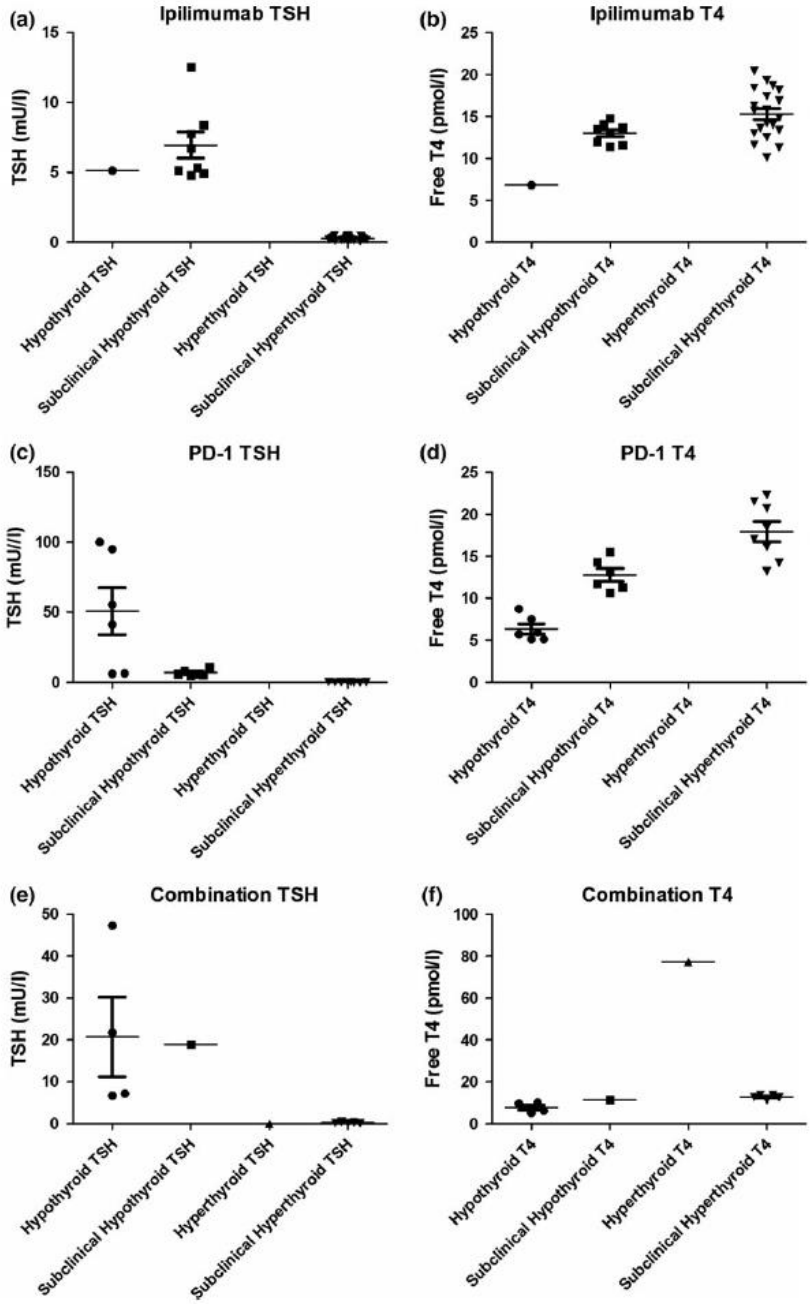

Figure 2: Baseline TSH according to thyroid status. Whiskers represent 5th–95th centile, *P < 0.05 (compared to normal).

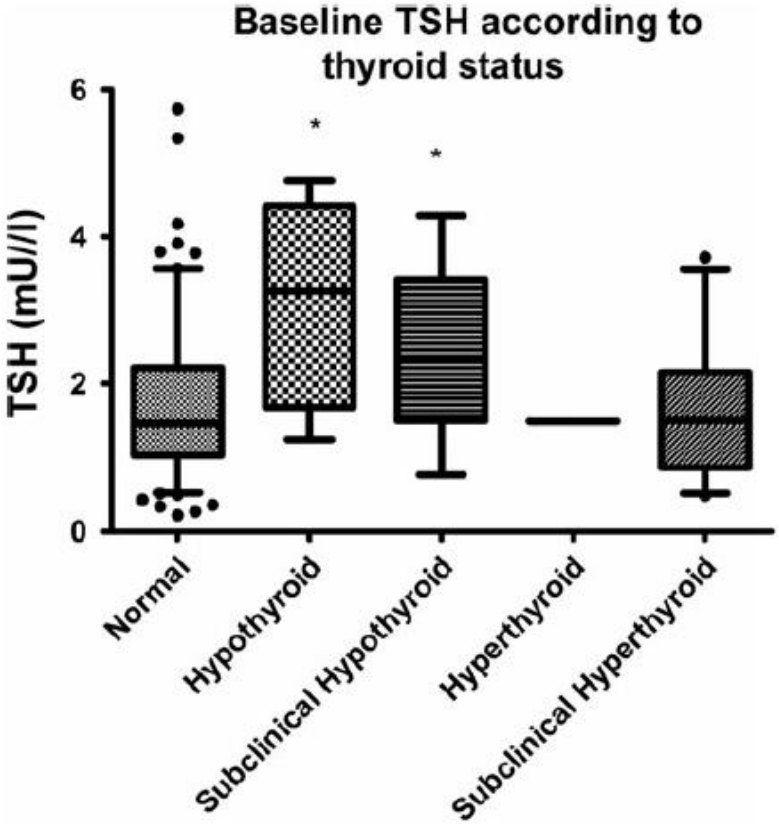

Table 1: Summary of all thyroid abnormalities

	Ipilimumab	PD-1	Combination	Combined
Total number of patients treated (included)	126	46	18	190
Primary hypothyroidism	1 (0·8%)	6 (13·0%)	4 (22·2%)	11 (5·8%)
Subclinical hypothyroidism	8 (6·4%)	6 (13·0%)	1 (5·6%)	15 (7·9%)
Primary hyperthyroidism	0	0	0	0
Subclinical hyperthyroidism	20 (15·9%)	6 (13·0%)	4 (22·2%)	30 (15·8%)
All thyroid dysfunction	29 (23·0%)	18 (39·1%)	9 (50%)	56 (29·5%)

PD-1, programmed death receptor-1.

Table 2: Clinical details of patients with hyperthyroidism following immunotherapy drugs

				Baseline thyroid function		Thyroid function at nadir TSH			Thyroid function at peak TSH		Investigations			Treatment				
	Drug	Gender	Age	TSH	T4	TSH	T4	Time to nadir (days)	TSH	T4	TPO Ab	Uptake scan (20 minutes uptake value)	Beta-blocker	Carbimazole / PTU	Thyroxine	Time to starting thyroxine (days)	Other therapies	CT to uptake scan (days)
1	Nivo	M	71	1·68	12·1	<0·03	20·7	72	6·4	5·9	151·8	0·10%	Y	N	Y	126		21
2	Pembro	M	59	3·72	10·8	<0·03	21·5	27	95·0	<5·1	ND	0·04	N	N	Y	466		31
3	Combo	M	60	1·49	10·4	<0·03	>77·2	19	6·7	6·2	ND	0	Y	N	N		Prednisolone for Colitis	29
4	Combo	F	61	0·35	20·6	<0·03	61·2	27	45·6	6·7	9·8	0·19	Y	N	Y	455		52
5	Ipi	M	86	1·75	11·2	<0·03	21·5	42	7·4	8·7	329·3	0	N	N	Y	79		71
6	Combo	F	49	3·03	12·5	<0·03	30·5	52			0·4	0	Y	N	N		Methyprednisolone for Hepatitits	59

Serum TSH in mU/l and free T4 in pmol/l. TPO antibody titre expressed as kU/l. Time to nadir TSH and starting thyroxine are dated from starting the immunotherapy drug. Reference ranges were serum TSH 0·49–4·67 mU/l and free T4 9·1–23·8 pmol/l, TPO antibdoes 0–5·6. Normal value for 20-minutes thyroid uptake value 0·4–4%.
Nivo, nivolumab; Pembro, pembrolizumab; Ipi, ipilimumab; Combo, ipilimumab and nivolumab.