

# Thyroid Dysfunctions Due to Immune Checkpoint Inhibitors: A Review

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**Aim:** Immune checkpoint inhibitors are anti-cancer drugs associated with adverse events that result from releasing the immune system against self-antigens while attacking cancer cells. Thyroid dysfunctions are among the most common associated adverse events.

**Materials and Methods:** We conducted a systematic search of the literature in 2 databases: PubMed and Medline. Articles that reported thyroid adverse events of immune checkpoint inhibitors were reviewed. Thyroid disorders include hyperthyroidism and hypothyroidism and are most commonly seen with programmed cell death protein 1 and programmed death-ligand 1 inhibitors.

**Conclusions:** Thyroid disorders are common side effects seen with check point inhibitors and are treated, depending on the clinical situation, by adequate hormonal replacement, thionamides, corticosteroids or observation only. The use of high dose corticosteroids has not been established as a treatment of thyroid toxicities. Thyroid function tests screening should be a part of baseline laboratory testing of all patients undergoing treatment with immune checkpoint inhibitors.

**Keywords:** immune check point inhibitors, thyroid dysfunction, anti-PD1, anti-PDL1

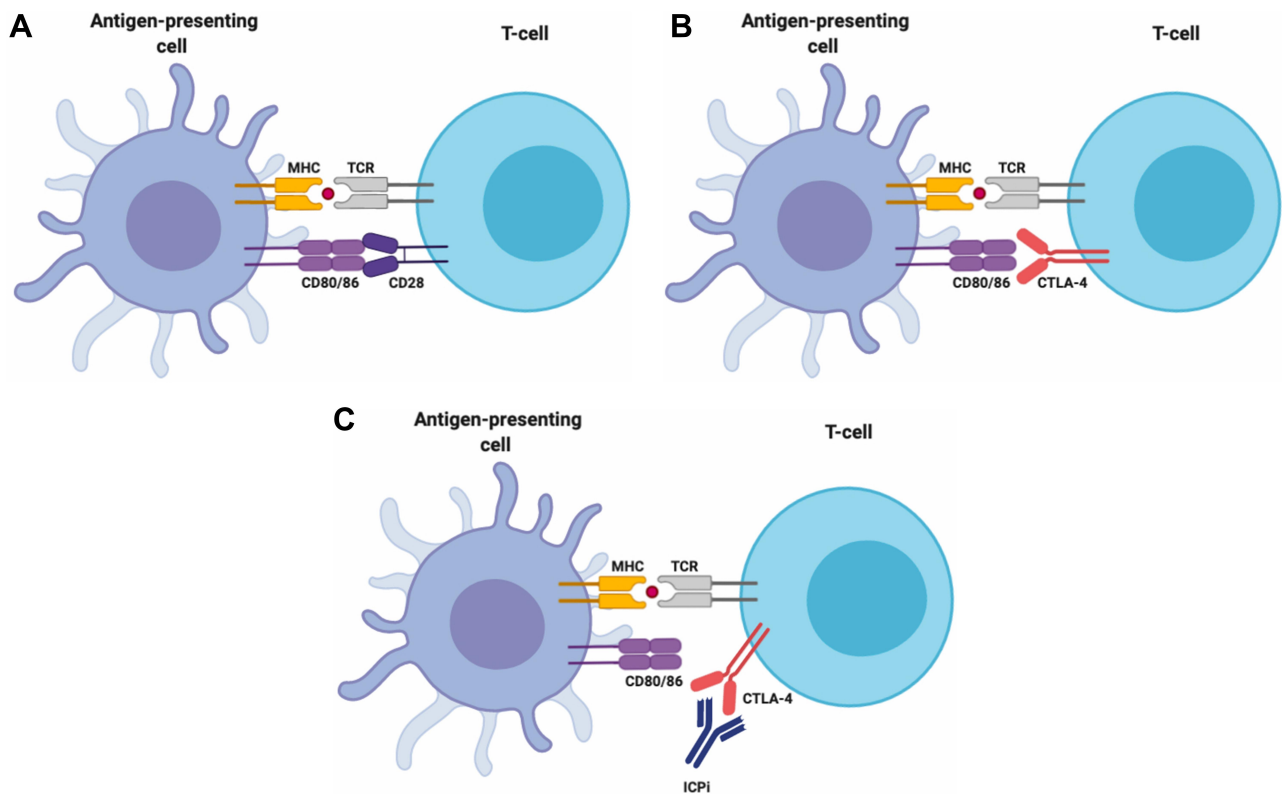
## Prospectus

Immune checkpoint inhibitors are anti-cancer medications with wide range use in different types of cancer. The mechanism of action of these drugs results in some new types of adverse events related to the immune system. Thyroid dysfunctions are among the common adverse events observed. The increase in the use of immune checkpoint inhibitors and the improved survival of patients treated by these medications make the identification of these side effects more common. In fact, these disorders can affect the quality of life of the patients, and might be life-threatening in some cases if not promptly recognized and treated. The aim of this review is to summarize the current knowledge of the thyroid side effects of immune checkpoint inhibitors and their prevention, diagnose and treatment.

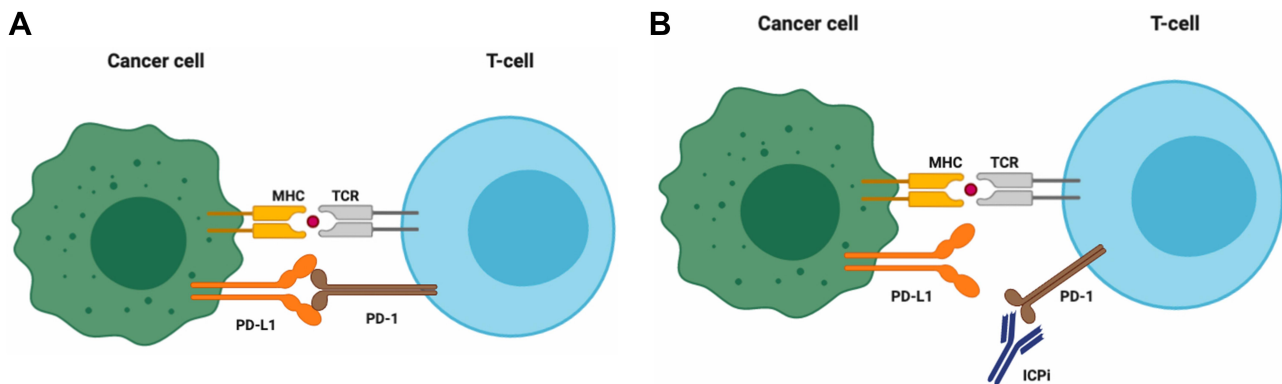
## Introduction

Over the recent years, the use of immune checkpoint inhibitors (ICPi) has improved the management and prognosis of many solid tumors.<sup>1</sup> These drugs are monoclonal antibodies that block immune checkpoints that are present on the surface of T-cells to ensure immune self-tolerance, resulting in an increase of the T-cells ability to attack the cancer cells<sup>2</sup> (Figures 1 and 2).

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**Figure 1** CTLA-4 pathway: **(A)** T cell activation in response to the tumor-associated antigen requires 2 signals. The first signal is achieved when the major histocompatibility complex (MHC) on the surface of the antigen-presenting cell (APC) recognizes the T-cell receptor (TCR) of the T cell. The second signal is the binding of CD80/86 (also known as B7) on the APC cell with the CD28 receptor on the T cell. This will lead to the activation of the immune response against the tumor cells. **(B)** CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4), a homolog of CD28, is a checkpoint present on T cells that limits proliferative response of activated T-cell by competing with CD28 for its ligand CD80/86. This inhibition will interrupt the second signal. **(C)** Monoclonal antibodies against CTLA-4 block CTLA-4 and will lead to T-cell activation and proliferation against the tumor cells.



**Figure 2** PD-1 - PD-L1 pathway: **(A)** PD-1 is a checkpoint present on the surface of T cells. When PD-1 binds to its ligands, PD-L1/2 present on APC and cancer cells, this will result in the inhibition of T cell activity in favour of tumor survival. **(B)** Monoclonal antibodies against PD-1 or PDL-1/2 will lead to the activation of the immune response against the tumor cells.

Currently, seven ICPI are approved for the treatment of different solid tumors: a cytotoxic T-lymphocytes associated protein 4 (CTLA-4) inhibitor Ipilimumab;<sup>3</sup> three programmed cell death protein (PD-1) inhibitors: Nivolumab,<sup>4</sup> Pembrolizumab<sup>5</sup> and Cemiplimab;<sup>6</sup> and three programmed death-ligand 1 (PD-L1) inhibitors:

Atezolizumab,<sup>7</sup> Avelumab<sup>8</sup> and Durvalumab.<sup>9</sup> Table 1 summarizes the different ICPI and their clinical indications.

ICPI are associated with immune-related adverse events (irAEs), that result from unleashing the immune system against self-antigens while attacking neoplastic

**Table 1** Summary of Immune Checkpoint Inhibitors and Their Clinical Indications

Drug (Trade Name)	ICPi Class	Indications
Ipilimumab (Yervoy)	CTLA-4 inhibitor	Melanoma
Nivolumab (Opdivo)	PD-1 inhibitor	Melanoma Non small cell lung cancer Renal cell carcinoma Hodgkin lymphoma Head and neck squamous cell carcinoma Urothelial Carcinoma Colorectal Cancer Hepatocellular carcinoma Small cell lung cancer
Pembrolizumab (Keytruda)	PD-1 inhibitors	Melanoma Non small cell lung cancer Head and neck squamous cell carcinoma Hodgkin Lymphoma Urothelial Cancer Gastric or GEJ Cancer Cervical Cancer Hepatocellular carcinoma Merkel Cell Carcinoma Renal cell carcinoma Small cell lung cancer Esophageal carcinoma Endometrial cancer
Cemiplimab (Libtayo)	PD-1 inhibitors	Cutaneous Squamous Cell Carcinoma
Atezolizumab (Tecentriq)	PD-L1 inhibitors	Urothelial Carcinoma Non-squamous NSCLC Small cell lung cancer Breast cancer
Avelumab (Bavencio)	PD-L1 inhibitors	Merkel Cell Carcinoma Urothelial Cancer Renal cell carcinoma
Durvalumab (Imfinzi)	PD-L1 inhibitors	Bladder Cancer NSCLC Small cell lung cancer
Combination (Ipilimumab+ Nivolumab)	CTLA-4 inhibitor + PD-1 inhibitor	Melanoma RCC Colorectal Cancer

**Abbreviations:** GEJ, gastro esophageal junction cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

cells.<sup>10</sup> Endocrine diseases are among the most common associated IrAEs, involving the pituitary gland, the thyroid gland, the pancreas, the adrenal gland and the parathyroid glands.<sup>11–13</sup>

The aim of this review is to describe the incidence, pathogenesis, clinical manifestations and guidelines on the management and screening of thyroid disorders associated with ICPI.

## Search Strategy

We conducted a systematic search of the literature in 2 databases: Medline and PubMed. Articles that reported thyroid adverse events of immune checkpoint inhibitors were reviewed. We used the following keywords or corresponding Medical Subject Heading terms: “ipilimumab,” “nivolumab,” “pembrolizumab,” “atezolizumab,” “Cemiplimab” “Avelumab” “Durvalumab” “CTLA-4 inhibitors” “ PD-1

inhibitors” “PDL-1 inhibitors” “immune checkpoint inhibitors” “hypothyroidism” “hyperthyroidism” “thyroiditis” “Graves” “Hashimoto” “thyroid dysfunction” “thyroiditis” “thyroid disease”. We also reviewed references of published trials and review articles.

## Thyroid Disorders

Thyroid dysfunction under ICPI can present as thyrotoxicosis or hypothyroidism.<sup>14</sup> The incidence of thyroid dysfunction differs between different ICPI classes. In a meta-analysis of 37 studies, the predicted incidence of hyperthyroidism was estimated to be 3.2% with PD1-inhibitors and 8.0% with combination therapy.<sup>13</sup> The median time to onset of hyperthyroidism is reported to be around 21 days in combination therapy and 47 days in monotherapy with PD1-inhibitors.<sup>13–15</sup> For hypothyroidism, the incidence estimated by the same meta-analysis<sup>11</sup> was higher with combination therapy 13.2%, and 7% with PDL-1 inhibitors alone. Median time to onset is comparable between the 2 regimens with 63 days in combination therapy and 70 days in PD-1 inhibitors monotherapy.<sup>16</sup>

The pathogenesis of thyroid disorders under ICPI is not completely known. Data from observational studies suggest that thyroid dysfunction induced by ICPI is due to a silent destructive thyroiditis that can evolve either to hypothyroidism or euthyroidism.<sup>17</sup> However, few cases of thyrotoxicosis are due to Graves’ disease and have been described in the literature.<sup>18</sup>

In a case series study of nivolumab-induced thyroiditis, PD-L1 and PD-L2 were found in normal thyroid glands, which could possibly implicate that the administration of PD-1 inhibitors can disrupt the interaction between the PD-1 on the T-cells and the PDL-1/2 on the thyrocytes, leading to T-cell activation against the thyroid.<sup>19</sup>

The association between thyroid dysfunction due to ICPI and the presence of thyroid antibodies is not fully elucidated. In a study by Osorio et al anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin were positive in 80% of patients with thyroid dysfunction due to pembrolizumab, while these antibodies were present in only 8% of patients without thyroid dysfunction ( $P < 0.0001$ ).<sup>20</sup>

In a recent case report of immunotherapy-induced thyroiditis, thyroid biopsy was performed in a woman with metastatic melanoma on nivolumab and ipilimumab who presented with hyperthyroidism. Unique features including abundant clusters of necrotic cells, lymphocytes and CD163-positive histiocytes were described.<sup>21</sup>

Data from a recent prospective cohort study of patients with ICI-induced thyroiditis showed T lymphocyte-

mediated process with intra-thyroidal predominance of CD8<sup>+</sup> and CD4<sup>-</sup>CD8<sup>-</sup> T lymphocytes.<sup>22</sup>

The clinical presentation of thyroid dysfunction with ICPI is similar to that of the general population, with thyrotoxicosis presenting with tachycardia, weight loss, fatigue and diarrhea and hypothyroidism presenting with bradycardia, weight gain, fatigue and constipation.<sup>24</sup> These symptoms are not specific and might be overshadowed by the symptoms of the underlying neoplasm.<sup>16</sup> The diagnosis of thyroid dysfunction due to immunotherapy is based on TSH and Free T4 levels to differentiate primary from central thyroid dysfunction. Total T3 measurement is necessary in cases of thyrotoxicosis. The interpretation of these levels should be done with caution due to the confounding factors in cancer therapy (steroids use, iodine contrast injection and non-thyroid illness) that might affect the hypothalamic-pituitary-thyroid axis.<sup>24</sup> TSH elevation might be observed with cortisol deficiency without having true hypothyroidism.

In the setting of thyrotoxicosis, and when the etiology is uncertain, thyroid scintigraphy should be performed, since it can be a useful tool into distinguishing thyroid disruption from hyperfunction.<sup>23</sup> The interpretation of this imaging modality should also be done with caution, especially in the setting of iodine injection.<sup>24</sup> In inflammatory thyroiditis, doppler ultrasound of the thyroid is not routinely recommended but may help in the diagnosis by showing hypovascularization of the parenchyma.<sup>24</sup>

Since thyrotoxicosis is usually transient and self-limited, it is reasonable to monitor patients in this phase closely and manage them symptomatically, with beta blockers if needed.

Corticosteroids are the mainstay of the treatment of subacute thyroiditis and should be used when the symptoms of thyrotoxicosis are severe.<sup>12</sup> Thionamides should be used when the diagnosis of Graves disease is established.<sup>12,24</sup>

The management of hypothyroidism depends on the degree of TSH elevation and the severity of symptoms.<sup>12</sup> Adrenal insufficiency should be ruled out before the start of hormonal replacement to avoid adrenal crisis that could be lifethreatening.<sup>12</sup> Hormonal replacement with levothyroxine at a dose of 1–1.6mcg/kg/day (depending on the age and comorbidities) is the mainstay of the treatment.<sup>21</sup> When the TSH below 10 mU/L, the decision on hormonal replacement should be evaluated on an individual basis (depending on the presence of symptoms or antibodies).<sup>12</sup> Some experts recommend measuring anti-TPO in the setting of a high TSH between 5 and 10 mU/L to guide the decision for treatment.<sup>24</sup> However, a TSH persistently higher than 10 mU/L or any level of TSH elevation in the presence of symptoms

**Table 2** Thyroid Disorders Induced by ICPI Therapy – Screening and Monitoring Recommendations in Guidelines

Guidelines	Hormonal Screening	Monitoring After Thyroid Disorder
American Society of Clinical Oncology (ASCO) 2018	Screening during immunotherapy: TSH and free T4: every 4–6 weeks from the start of therapy or as needed for case detection in symptomatic patients	<b>For hypothyroidism:</b> TSH every 6–8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low  During immunotherapy: TFTs (at least TSH) every 6 weeks (or as needed for symptoms) After immunotherapy: TFTs annually (or as indicated by symptoms) <b>For hyperthyroidism:</b> TSH and free T4 every 2 to 3 weeks until it is clear whether there will be persistent hyperthyroidism or hypothyroidism.
European Society for Medical Oncology (ESMO) 2017	Screening before the first immunotherapy course: TSH, free T4, T3* During immunotherapy: <b>Anti-CTLA4</b> (including combination with anti-PD-1)  · TFTs every cycle  · TFTs 4–6 weeks after cycle 4 <b>Anti-PD-1/Anti-PD-L1</b>  · TFTs every cycle for first 3 months · TFTs every second cycle thereafter (in case of 2-weekly schedule)	N/A
French Society of Endocrinology (SFE) 2018	Screening before the first immunotherapy course: TSH Systematic screening for anti-TPO or anti-TSH-receptor antibody is not recommended. During immunotherapy: <b>First 3–6 months:</b> TSH before each course <b>Second 6 months:</b> TSH every 2 months <b>After 12 months:</b> Screening may be performed in case of clinical symptoms of thyroid dysfunction.	<b>For hypothyroidism:</b> During immunotherapy: TSH every 3 months After immunotherapy: Levothyroxine can be progressively withdrawn under monitoring of clinical status and TSH. <b>For hyperthyroidism:</b> N/A
Society for Immunotherapy of Cancer (SITC) 2017	Screening before the first immunotherapy course: TSH and free T4 During immunotherapy: Before each cycle TSH and free T4	<b>For hypothyroidism:</b> TSH and free T4 after 6–8 weeks of treatment initiation. After identification of the appropriate maintenance dose: TSH and free T4 every year (or sooner if patient's status changes) <b>For hyperthyroidism:</b> Monitor closely with regular symptom evaluation and free T4 testing every 2 weeks.

**Note:** \*T3: only in case of suspicion of abnormal thyroid gland function, but with normal FT4.

are indications for treatment. Patients with severe symptoms or signs of myxedema require admission for IV therapy.<sup>12</sup> The discontinuation of therapy in the setting of thyroid disorders is not necessary except in cases of severe symptoms when therapy should be temporarily held and can be resumed once symptoms improve.<sup>12,24–27</sup> The need for thyroid replacement seems permanent as the recovery of the thyroid gland has not been described.<sup>20,27,28</sup> We recommend monitoring TSH and FT4 every 4 to 6 weeks starting from the initiation of treatment or from when the patient's symptoms are suggestive of thyroid dysfunction.<sup>12</sup>

The recommendations for screening and monitoring of thyroid disorders in the setting of ICPI use are summarized in Table 2.

## Conclusion

The use of ICPI in cancer treatment is currently increasing and will continue to increase in the future. This newly introduced modality of treatment is challenging for all specialists, including internists, oncologists and endocrinologists, due to the various patterns of adverse effects. Thyroid disorders are among the common side effects seen and should be adequately treated.

The use of corticosteroids has not been established as a treatment of thyroid toxicities, however, the available studies are limited by their retrospective nature and small sample size. Some studies have suggested a positive correlation between the development of various endocrine side effects, including thyroid abnormalities, and clinical cancer response<sup>18,20,29</sup>; however, larger prospective studies are needed to confirm this correlation.

It is not well understood why some patients are more prone than others to develop thyroid side effects. More investigations and research are needed to identify risk factors for these side effects and possibly tailor the treatment patients accordingly.

Finally, thyroid function tests including TSH and Free T4 and anti-TPO antibodies screening should be a part of baseline laboratory testing of all patients undergoing treatment with immune checkpoint inhibitors. Patients should be educated about immunotherapy and the clinical profile of possible immune-related thyroid dysfunction adverse events.

## Abbreviations

Anti-TPO, thyroid peroxidase antibodies; CTLA-4, cytotoxic T-lymphocytes associated protein 4; ICPI, immune checkpoint inhibitors; IrAEs, immune-related adverse

events; PD-1, programmed cell death protein; PDL-1, programmed death-ligand 1; PDL-2, programmed death-ligand 2; TRAb, TSH receptor antibodies; TSH, thyroid-stimulating hormone; TFT, thyroid function test.

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