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Annales d'Endocrinologie xxx (2018) xxx–xxx

Annales d'Endocrinologie
Annals of Endocrinology

Consensus

Expert opinion on thyroid complications in immunotherapy

Frederic Illouz[a,*,1], Delphine Drui[b,1], Philippe Caron[c,2], Christine Do Cao[d,2]

[a] *Department of Endocrinology, Diabetes and Nutrition, Reference Centre of Rare Thyroid and Hormonal Receptors Disease, Hospital of Angers, 49933 Angers cedex 09, France*
[b] *Department of Endocrinology, Institut du Thorax, CHU de Nantes, 44000 Nantes, France*
[c] *Service d'Endocrinologie, Maladies Métaboliques, Nutrition, CHU de Toulouse, Hôpital Larrey, TSA 30030, 31059 Toulouse cedex 9, France*
[d] *Service d'Endocrinologie, CHRU de Lille, Hôpital Huriez, 59037 Lille cedex, France*

Abstract

Thyroid pathologies are the most common forms of endocrinopathy under anticancer immunotherapy. Frequency ranges from 3% to 22% for hypothyroidism and 1% to 11% for thyrotoxicosis. Risk is higher with anti-PD-1 than anti-CTLA-4 treatment and higher again with associated treatment. Pathophysiology mainly consists in silent inflammatory thyroiditis, which accounts for the usual presentation of transient thyrotoxicosis followed by hypothyroidism. Therapeutic strategy usually consists in monitoring with or without symptomatic treatment in case of thyrotoxicosis, and levothyroxine replacement therapy in case of symptomatic hypothyroidism or TSH > 10 mIU/L. Screening for dysthyroidism should be systematic ahead of treatment and before each immunotherapy injection for the first 6 months, then at a lower rhythm. It comprises clinical assessment and TSH assay. Onset of thyroid dysfunction should not interrupt immunotherapy, being mainly transient, easy to treat and mild. Teamwork between oncologists and endocrinologists improves screening and management, so as better to accompany the patient during treatment.

Keywords: Dysthyroidism; Thyrotoxicosis; Hypothyroidism; Immunotherapy; Anti-PD1; Anti-CTLA-4

1. Recommendations

R1: Diagnosis of dysthyroidism under immunotherapy is based on plasma TSH assay, as clinical signs are poorly specific.

R2: The most frequent etiological diagnosis in dysthyroidism under immunotherapy is silent inflammatory thyroiditis.

R2a. In case of thyrotoxicosis, anti-TSH-receptor antibody assay, thyroid scintigraphy and Doppler ultrasound can be performed in case of diagnostic doubt between iatrogenic thyroiditis and other hyperthyroid diagnoses, notably in case of severe thyrotoxicosis.

R2b. In case of hypothyroidism with < 10 mIU/L TSH elevation, anti-TPO antibody assay can clarify indications for levothyroxine replacement therapy but, therapeutically, is less contributive when TSH ≥ 10 mIU/L.

R3: Thyrotoxicosis severity is assessed by clinical impact and free T4 elevation. Hypothyroidism severity is assessed by clinical impact and TSH elevation.

R4: Onset of thyroid dysfunction does not contraindicate continuation of immunotherapy. In case of severe thyrotoxicosis or hypothyroidism, immunotherapy may be interrupted but should never be definitively contraindicated. In case of severe orbitopathy, immunotherapy should be interrupted, with resumption assessed on a case-by-case basis.

R5: Treatment strategy for thyroid dysfunction under anticancer immunotherapy should be discussed between the endocrinologist and the immunotherapy prescriber.

R5a: In asymptomatic thyrotoxicosis, clinical and biological monitoring may be implemented. In symptomatic thyrotoxicosis, β-blocker therapy is recommended if not contraindicated. Antithyroid drugs may be considered in Graves' disease.

R5b: Treatment for immunotherapy-induced hypothyroidism is based on levothyroxine, and:

DOIs of original articles: https://doi.org/10.1016/j.ando.2018.07.002, https://doi.org/10.1016/j.ando.2018.07.008, https://doi.org/10.1016/j.ando.2018.07.006, https://doi.org/10.1016/j.ando.2018.07.001, https://doi.org/10.1016/j.ando.2018.07.003, https://doi.org/10.1016/j.ando.2018.07.004, https://doi.org/10.1016/j.ando.2018.07.005
* Corresponding author.
E-mail address: frillouz@chu-angers.fr (F. Illouz).
[1] Co-first authors.
[2] Co-senior authors.

https://doi.org/10.1016/j.ando.2018.07.007
0003-4266/

- should be applied if TSH > 10mIU/L;
- should be considered in case of TSH 5–10 mIU/L on 2 assays associated with either clinical symptomatology or presence of anti-TPO antibodies.

Levothyroxine therapy may begin at 1–1.6 μg/kg/day, but should be adapted according to age, comorbidities and survival expectancy. Such adaptation is as in other forms of hypothyroidism.

R6: Before the first anticancer immunotherapy injection, systematic screening for pre-existing thyroid dysfunction by TSH assay is recommended. Systematic pre-treatment screening for antithyroid autoimmunity by anti-TPO or anti-TSH-receptor antibody assay is not recommended.

R7: During anticancer immunotherapy, TSH should be monitored to screen for dysthyroidism, before each course for the first 3-6 months then every 2 months for the next 6 months or in case of suggestive symptoms. After 12 months' immunotherapy, screening may be performed in case of clinical symptoms of thyroid dysfunction.

R8: In hypothyroidism, normal thyroid function may recover, but is unpredictable. Thyroid replacement therapy should be continued throughout the immunotherapy. During levothyroxine therapy, monitoring is based on TSH assay, performed every 3 months. On termination of immunotherapy, levothyroxine can be progressively withdrawn under monitoring of clinical status and TSH.

R9: Pre-existing treated thyroid pathology or dysfunction does not contraindicate immunotherapy. Onset of thyroid dysfunction secondary to one immunotherapy molecule (anti-CTLA-4, anti-PD-1 or anti-PD-L1) does not contraindicate introducing another.

2. Epidemiology

Thyroid pathologies are the most frequent endocrine side-effects under anticancer immunotherapy. Although reports are numerous, epidemiological data are vitiated by heterogeneity in screening procedures, follow-up time, expression of results, molecules used in monotherapy or association and type of tumor. Data from large-scale oncologic clinical trials are discrepant and often underestimate thyroid side-effects, as their primary objective is to assess the efficacy of the immunotherapy and screening for thyroid dysfunction, which is often poorly symptomatic, is not systematic. Hypothyroidism rates vary between 3% and 22% and thyrotoxicosis rates between 1% and 11% [1–10]. Frequency is greater in more recent reports, testifying to improvement in screening [1,2,11–13]. In a recent meta-analysis of 38 randomized trials, mainly prior to 2016, risk of dysthyroidism was greater under anti-PD-1 than anti-CTLA-4, whatever the type of tumor. Risk was dose-dependent for anti-CTLA-4 (especially above a threshold of 10 mg/kg), unlike for anti-PD-1 [14]. Some specific studies subsequently provided more precise and standardized analysis of thyroid side-effects of immunotherapy [15–19]: overall incidence of thyrotoxicosis ranged from 3% to 16% and hypothyroidism from 6% to 13%, notably according to therapeutic class and sequence and whether subclinical forms were counted. All studies agreed that risk of dysthyroidism was greater in combined anti-PD-1 and anti-CTLA-4 therapy [2,3,5,6,20,21], and incidence could be as high as 50% (22% thyrotoxicosis and 28% hypothyroidism) if subclinical forms were included [18,19].

3. Pathophysiology

The pathophysiology of thyroid dysfunction under anticancer immunotherapy is not completely known, but mainly involves silent inflammatory thyroiditis, which in turn involves T-cell cytotoxicity. Thyroiditis is diagnosed in the phase of thyrotoxicosis, which is often transient, or of subclinical or clinical hypothyroidism, which are 2 stages of the same nosologic entity. Characteristics are closer to those of postpartum silent thyroiditis than of autoimmune thyroiditis unrelated to pregnancy, in which pathophysiology involves antithyroid antibody cytotoxicity. Natural killer (NK) cells have been implicated, as they increase in number in thyroiditis under anti-PD-1; low expression of CTLA-4 by circulating lymphocytes might explain the lower rate of dysthyroidism under anti-CTLA-4 treatment. Other mechanisms are also possible, perhaps involving PD-1 and PD-L1 in thyroid tissue, as thyroid dysfunction is not systematically of autoimmune origin [15,16,19].

4. Diagnosis

4.1. Positive diagnosis

Clinical symptoms of thyroid dysfunction under anticancer immunotherapy are poorly specific. Signs of hypothyroidism (fatigue, weight gain, bradycardia, slow transit) or thyrotoxicosis (fatigue, nervousness, weight loss, palpitations) may be confused with those of the cancer. Diagnosis is based on TSH assay compared with pre-treatment value to rule out pre-existing dysthyroidism. TSH elevation confirms diagnosis of hypothyroidism and low values confirm thyrotoxicosis. However, results are to be taken with caution in this context of cancer; it is important to ensure that there is no iodine saturation related to contrast medium injection, and no glucocorticoid treatment liable to impact the hypothalamic-pituitary-thyroid axis, and to rule out TSH concentration reduction by a non-thyroid condition such as low T3/T4 syndrome. Along with these precautions in interpreting results, it should be borne in mind that anti-CTLA-4 and, to a lesser degree, anti-PD-1 molecules can induce hypophysitis and thyrotropin deficiency, which may lower TSH levels (associated with low or lowered free T4 concentration).

R1: Diagnosis of dysthyroidism under immunotherapy is based on plasma TSH assay, as clinical signs are poorly specific.

Please cite this article in press as: Illouz F, et al. Expert opinion on thyroid complications in immunotherapy. Ann Endocrinol (Paris) (2018), https://doi.org/10.1016/j.ando.2018.07.007

5. Etiologic diagnosis

Dysthyroidism under immunotherapy mainly implicates "silent inflammatory" thyroiditis, typically comprising a thyrotoxicosis phase followed by hypothyroidism [15,16,19,23]. Presentation can also be less typical: spontaneously resolving thyrotoxicosis and recovery of euthyroidism, or primary hypothyroidism; however, these atypic forms may simply be truncated, with a very transient thyrotoxicosis phase that gets overlooked, or a hypothyroidism phase that goes undetected.

Onset of Graves' disease without associated orbitopathy was reported in 2 cases [24,25]. Conversely, a few cases of orbitopathy without thyroid involvement were reported under ipilimumab and nivolumab [26–29].

Thus, in case of thyrotoxicosis, Graves' disease has to be ruled out by screening for anti-TSH-receptor antibodies. Thyroid scintigraphy is relatively non-contributive to etiological diagnosis, as interpretation can be biased by iodine overload, notably of iatrogenic origin; it should be performed only in case of diagnostic uncertainty. While 18FDG-PET can help diagnose "inflammatory" thyroiditis, by showing thyroid hypermetabolism, it is not recommended as a routine examination. Thyroid Doppler ultrasound has not been assessed; in case of doubt, it may help diagnose inflammatory thyroiditis, by showing hypovascularization of the thyroid parenchyma.

In case of hypothyroidism, findings of antithyroid antibodies at diagnosis are variable [15,16,18,19,22]. Anti-TPO antibodies should be assayed to diagnose lymphocytic thyroiditis, although positive findings do not affect treatment strategy in clinical hypothyroidism; in subclinical hypothyroidism (TSH < 10 mIU/L), positive findings may indicate levothyroxine replacement therapy.

R2: The most frequent etiological diagnosis in dysthyroidism under immunotherapy is silent inflammatory thyroiditis.

R2a. In case of thyrotoxicosis, anti-TSH-receptor antibody assay, thyroid scintigraphy and Doppler ultrasound can be performed in case of diagnostic doubt between iatrogenic thyroiditis and other hyperthyroid diagnoses, notably in case of severe thyrotoxicosis.

R2b. In case of hypothyroidism with < 10 mIU/L TSH elevation, anti-TPO antibody assay can clarify indications for levothyroxine replacement therapy but, therapeutically, is less contributive when TSH 10 mIU/L.

6. Severity of hypothyroidism and of thyrotoxicosis

Immunotherapy side-effect severity is usually assessed on the Common Terminology Criteria for Adverse Events (CTCAE), intended to grade adverse effects occurring during trials and to guide therapy by deciding whether to continue, adapt or terminate a given treatment. Dysthyroidism is generally moderate or asymptomatic, graded 1 or 2 on clinical trials, with fewer than 1% of severe cases, graded 3 or 4 [1–10,14]. However, there have been reports of acute episodes of dysthyroidism ranging from severe thyrotoxicosis up to thyroid storm, and 1 case of myxedema coma aggravating the patient's already precarious health status [15,30–32].

CTCAE grading is mainly used in therapeutic trials, and seems poorly adapted for management of immunotherapy-induced dysthyroidism. Severity should be graded according to clinical symptoms and to free T4 concentration in thyrotoxicosis or TSH concentration in hypothyroidism: a hormonal parameter needs to supplement the CTCAE's clinical criteria, even if thresholds are difficult to set. Treatment strategy should be guided by this clinical/hormonal association, which is not the same as the CTCAE itself.

Pre-treatment dysthyroidism or onset under immunotherapy, regardless of severity, do not contraindicate introduction or continuation of immunotherapy. In case of severe thyrotoxicosis, immunotherapy may in some cases be postponed, and may be interrupted or definitively terminated in case of severe orbitopathy.

R3: Thyrotoxicosis severity is assessed by clinical impact and free T4 elevation. Hypothyroidism severity is assessed by clinical impact and TSH elevation.

R4: Onset of thyroid dysfunction does not contraindicate continuation of immunotherapy. In case of severe thyrotoxicosis or hypothyroidism, immunotherapy may be interrupted but should never be definitively contraindicated. In case of severe orbitopathy, immunotherapy should be interrupted, with resumption assessed on a case-by-case basis.

7. Treatment of thyroid dysfunction

7.1. Thyrotoxicosis

Treatment depends on clinical severity and etiologic diagnosis, and should be determined conjointly by the endocrinologist and the oncologist or organ specialist.

The Summary of Product Characteristics (SPC) for the various immunotherapy molecules advise corticosteroid treatment for acute thyroid inflammation, but this strategy needs to be reconsidered in the light of recent findings [33–36]. There is no evidence that steroid use limits thyrotoxicosis or shortens the thyrotoxicosis phase. Thyrotoxicosis is usually transient, consisting in release of thyroid hormones that have already been produced. Simple monitoring can suffice in subclinical forms. In symptomatic thyrotoxicosis, beta-blockers should be initiated if not contraindicated [37–40]. Corticotherapy should be considered in clinically severe thyrotoxicosis.

Antithyroid drugs are reserved for very rare cases of Graves' disease. Orbitopathy is managed as in Graves' orbitopathy, following the EUGOGO group guidelines [41].

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7.2. Hypothyroidism

Hypothyroidism is usually of secondary onset after the thyrotoxicosis phase of "silent inflammatory thyroiditis". There are no specific guidelines on iatrogenic hypothyroidism under immunotherapy; thus, indications for replacement therapy in subclinical hypothyroidism are based on general recommendations regarding hypothyroidism [42]. However, the decision to implement replacement therapy should take account of general health status, comorbidity and especially cardiovascular comorbidity, and the severity of the hypothyroidism.

Thyroid hormone replacement is appropriate in clinical hypothyroidism associating TSH elevation on 2 assays and low fT4, or TSH > 10 mIU/L. Implementation follows the usual modalities, taking account of age and comorbidities.

In subclinical hypothyroidism, replacement therapy may be considered in case of TSH concentration 5–10 mIU/L on 2 assays, associated with clinical symptomatology or antithyroid antibodies suggesting risk of aggravation.

It should be noted that onset of hypothyroidism under anti-PD-1 has sometimes been reported to be associated with better overall or progression-free survival [16,43,44], although this may amount to a marker of efficacy rather than an effect of dysthyroidism [45,46]; exposure bias cannot be ruled out, as responders were treated longer than non-responders, leaving them more time to develop hypothyroidism.

R5: Treatment strategy for thyroid dysfunction under anticancer immunotherapy should be discussed between the endocrinologist and the immunotherapy prescriber.

R5a: In asymptomatic thyrotoxicosis, clinical and biological monitoring may be implemented. In symptomatic thyrotoxicosis, β-blocker therapy is recommended if not contraindicated. Antithyroid drugs may be considered in Graves' disease.

R5b: Treatment for immunotherapy-induced hypothyroidism is based on levothyroxine, and:

- should be applied if TSH > 10mIU/L;
- should be considered in case of TSH 5–10 mIU/L on 2 assays associated with either clinical symptomatology or presence of anti-TPO antibodies.

Levothyroxine therapy may begin at 1–1.6 μg/kg/day, but should be adapted according to age, comorbidities and survival expectancy. Such adaptation is as in other forms of hypothyroidism.

8. Screening and monitoring in thyroid dysfunction

8.1. Pre-treatment assessment

Pre-treatment assessment of thyroid function is necessary to rule out pre-existing dysthyroidism. It should be based on TSH assay; fT4 assay may be contributive, given the risk of hypophysitis under certain immunotherapies (especially when using anti-CTLA-4).

The predictive value of pre-treatment findings of antithyroid antibodies for onset of dysthyroidism is controversial. Osorio, assessing patients receiving pembrolizumab, found antithyroid antibodies in 80% of those showing hypothyroidism (with antibodies appearing during the thyrotoxicosis phase in 60% of cases) versus only 8% of those without [16]; however, these findings were not subsequently confirmed [15,18,19]. Thus, although thyroid autoimmunity seems to be associated with the development of thyroid dysfunction, the predictive value of antithyroid antibodies remains to be proven.

R6: Before the first anticancer immunotherapy injection, systematic screening for pre-existing thyroid dysfunction by TSH assay is recommended. Systematic pre-treatment screening for antithyroid autoimmunity by anti-TPO or anti-TSH-receptor antibody assay is not recommended.

8.2. Follow-up

In oncologic efficacy trials, endocrine toxicity is reported globally, without distinguishing time to onset between different thyroid dysfunctions [1–3,13,14]. SPC recommendations setting out screening strategy for endocrine side-effects are mainly based on these efficacy studies, in which definitions of tolerance are imprecise [33–36]; they have never been updated, and specify neither monitoring frequency nor the assays to be performed. Given the small number of clinical trials, there is no consensus on rates and modalities of monitoring; recommendations range from no systematic screening to monitoring every 1 to 8 weeks for the first 3 months of treatment [37,38,40,47–52].

Recommendations for monitoring frequency can be based on 6 descriptive studies [15–18,22,23]. Onset of thyrotoxicosis can be early, in the 3rd week (2nd course), especially in a context of thyroiditis with secondary hypothyroidism [15–18]. Onset of hypothyroidism is later, at 6-10 weeks, especially when secondary to thyrotoxicosis [15–18,22,23]. In combined treatments, onset seems to be earlier, at a median 3 weeks [23]. Time to onset of thyroid dysfunction under ipilimumab monotherapy is not known.

These data may guide frequency of monitoring, but a TSH control should also be systematic in case of onset of suggestive clinical signs.

8.3. Progression of thyroid dysfunction

Thyrotoxicosis is almost always transient, apart from the extremely rare cases of Graves' disease. Outcome of hypothyroidism after termination of immunotherapy is unknown. Clinical follow-up studies usually reported need for hormonal

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R7: During anticancer immunotherapy, TSH should be monitored to screen for dysthyroidism, before each course for the first 3–6 months then every 2 months for the next 6 months or in case of suggestive symptoms. After 12 months' immunotherapy, screening may be performed in case of clinical symptoms of thyroid dysfunction.

replacement in case of thyrotoxicosis followed by hypothyroidism, but did not specify whether withdrawal was attempted [15,18–19]. In a recent study, 4 out of 7 patients showed spontaneous normalization of thyroid function after an episode of thyrotoxicosis without hypothyroidism phase, while the other 3 patients developed true secondary hypothyroidism [19]. A retrospective study, in which thyroid hormone assessment was not systematic or regular, reported spontaneous resolution of subclinical hypothyroidism in 6 out of 21 patients [17]. It is thus preferable to continue replacement therapy throughout immunotherapy. Once the equilibrium dose has been determined, dose adaptation is based on 3-monthly TSH assay. Progressive withdrawal from replacement therapy may be attempted at termination of immunotherapy.

R8: In hypothyroidism, normal thyroid function may recover, but is unpredictable. Thyroid replacement therapy should be continued throughout the immunotherapy. During levothyroxine therapy, monitoring is based on TSH assay, performed every 3 months. On termination of immunotherapy, levothyroxine can be progressively withdrawn under monitoring of clinical status and TSH.

8.4. Predictive factors for onset of thyroid dysfunction under anticancer immunotherapy

Predictive factors for onset of thyroid dysfunction under immunotherapy are poorly known. Morganstein et al. suggested that pre-treatment plasma TSH level might predict onset of hypothyroidism even when within the normal range [18]. A significant association between antithyroid antibodies and risk of dysthyroidism was reported in some studies but not others, and is a matter of debate [15,16,18,19,22]. As stated above, while thyroid autoimmunity seems to be associated with the development of thyroid dysfunction, it is not clear that the presence of antibodies prior to immunotherapy is in itself a risk factor. Risk seems unrelated to age; an extra risk for female gender is controversial (18,19).

Combined or sequential association of ipilimumab and anti-PD-1 increases risk of thyroid dysfunction [2,3,5,6,20,21], especially if the interval between the two is less than 4 weeks [15]. Thyroid dysfunction is dose-dependent for anti-CTLA-4, unlike anti-PD-1 and anti-PDL-1.

Silent inflammatory thyroiditis may occur in euthyroid patients but it can also worsen an existing hypothyroidism, increasing thyroxine requirements [19]. Conversely, a few cases of thyrotoxicosis necessitating interruption of thyroxine therapy were reported in hypothyroid patients [17]. Mechanisms may include:

- real aggravation of hypothyroidism due to thyroid follicle lesions;
- increased levothyroxine requirements due to impaired absorption, perhaps related to concomitant digestive disorder;
- increased levothyroxine requirements due to accelerated thyroid hormone metabolism. Such pre-treatment thyroid disorder does not contraindicate immunotherapy, but requires monitoring during treatment.

R9: Pre-existing treated thyroid pathology or dysfunction does not contraindicate immunotherapy. Onset of thyroid dysfunction secondary to one immunotherapy molecule (anti-CTLA-4, anti-PD-1 or anti-PD-L1) does not contraindicate introducing another.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The text was read over and commented on by Pr. Goichot, Pr. Klein, Pr. Groussin, Dr. Abeillon and Dr. Cugnet, whom the authors especially thank for their criticisms and suggestions.

References

[1] Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–35.
[2] Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey C, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345–56.
[3] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
[4] Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908–18.
[5] Weber JS, Gibney G, Sullivan RJ, Sosman JA, Slingluff Jr CL, Lawrence DP, et al. Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. Lancet Oncol 2016;17:943–55.
[6] Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab

alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 2016;17:1558–68.
[7] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823–33.
[8] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.
[9] Gulley JL, Rajan A, Spigel DR, Iannotti N, Chandler J, Wong DJL, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. Lancet Oncol 2017;18:599–610.
[10] Patel MR, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol 2018;19:51–64.
[11] Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015;16:257–65.
[12] Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018, http://dx.doi.org/10.1056/NEJMoa1801946 [Epub ahead of print].
[13] Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant Pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018, http://dx.doi.org/10.1056/NEJMoa1802357 [Epub ahead of print].
[14] Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol 2018;4:173–82.
[15] de Filette J, Jansen Y, Schreuer M, Everaert H, Velkeniers B, Neyns B, et al. Incidence of thyroid-related adverse events in melanoma patients treated with pembrolizumab. J Clin Endocrinol Metab 2016;101:4431–9.
[16] Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol 2017;28:583–9.
[17] Villa NM, Farahmand A, Du L, Yeh MW, Smooke-Praw S, Ribas A, et al. Endocrinopathies with use of cancer immunotherapies. Clin Endocrinol (Oxf) 2018;88:327–32.
[18] Morganstein DL, Lai Z, Spain L, Diem S, Levine D, Mace C, et al. Thyroid abnormalities following the use of cytotoxic T-lymphocyte antigen-4 and programmed death receptor protein-1 inhibitors in the treatment of melanoma. Clin Endocrinol (Oxf) 2017;86:614–20.
[19] Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, Withers S, et al. Pembrolizumab-induced thyroiditis: comprehensive clinical review and insights into underlying involved mechanisms. J Clin Endocrinol Metab 2017;102:2770–80.
[20] Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006–17.
[21] Long GV, Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, McNeil CM, et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. Lancet Oncol 2017;18:1202–10.
[22] Orlov S, Salari F, Kashat L, Walfish PG. Induction of painless thyroiditis in patients receiving programmed death 1 receptor immunotherapy for metastatic malignancies. J Clin Endocrinol Metab 2015;100:1738–41.
[23] Lee H, Hodi FS, Giobbie-Hurder A, Ott PA, Buchbinder EI, Haq R, et al. Characterization of thyroid disorders in patients receiving immune checkpoint inhibition therapy. Cancer Immunol Res 2017;5:1133–40.
[24] Azmat U, Liebner D, Joehlin-Price A, Agrawal A, Nabhan F. Treatment of ipilimumab induced graves' disease in a patient with metastatic melanoma. Case Rep Endocrinol 2016;2016:2087525.
[25] Gan EH, Mitchell AL, Plummer R, Pearce S, Perros P. Tremelimumab-induced graves hyperthyroidism. Eur Thyroid J 2017;6:167–70.
[26] Min L, Vaidya A, Becker C. Thyroid autoimmunity ophthalmopathy related to melanoma biological therapy. Eur J Endocrinol 2011;164:303–7.
[27] McElnea E, Ní Mhéalóid A, Moran S, Kelly R, Fulcher T. Thyroid-like ophthalmopathy in a euthyroid patient receiving ipilimumab. Orbit 2014;33:424–7.
[28] Borodic GE, Hinkle D. Ipilimumab-induced orbital inflammation resembling graves disease with subsequent development of systemic hyperthyroidism from CTLA-4 receptor suppression. Ophthal Plast Reconstr Surg 2014;30:83.
[29] Campredon P, Imbert P, Mouly C, Grunenwald S, Mazières J, Caron P. Severe inflammatory ophthalmopathy in a euthyroid patient during Nivolumab treatment. Eur Thyroid J 2018;7:84–7.
[30] McMillen B, Dhillon MS, Yong-Yow S. A rare case of thyroid storm. BMJ Case Rep 2016;2016:10.
[31] Yu C, Chopra IJ, Ha E. A novel melanoma therapy stirs up a storm: ipilimumab-induced thyrotoxicosis. Endocrinol Diabetes Metab Case Rep 2015;2015:140092.
[32] Khan U, Rizvi H, Sano D, Chiu J, Hadid T. Nivolumab induced myxedema crisis. J Immunother Cancer 2017;5:13.
[33] http://ec.europa.eu/health/documents/community-register/2017/20170824138672/anx_138672_fr.pdf.
[34] http://ec.europa.eu/health/documents/community-register/2018/20180118139835/anx_139835_fr.pdf.
[35] http://ec.europa.eu/health/documents/community-register/2017/20171019139076/anx_139076_fr.pdf.
[36] http://ec.europa.eu/health/documents/community-register/2017/20170918138675/anx_138675_fr.pdf.
[37] Illouz F, Briet C, Cloix L, Le Corre Y, Baize N, Urban T, et al. Endocrine toxicity of immune checkpoint inhibitors: essential crosstalk between endocrinologists and oncologists. Cancer Med 2017;6:1923–9.
[38] Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol 2017;13:195–207.
[39] Puzanov I, Diab A, Abdallah K, Bingham CO, 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) toxicity management working group. J Immunother Cancer 2017;5:95–123.
[40] 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;21:804–16.
[41] Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 european thyroid association/european group on graves' orbitopathy guidelines for the management of graves' orbitopathy. Eur Thyroid J 2016;5:9–26.
[42] Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the american association of clinical endocrinologists and the american thyroid association. Thyroid 2012;22:1200–35.
[43] Kim HI, Kim M, Lee SH, Park SY, Kim YN, Kim H, et al. Development of thyroid dysfunction is associated with clinical response to PD-1 blockade treatment in patients with advanced non-small cell lung cancer. Oncoimmunology 2017;7:e1375642.
[44] Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol 2018;4:374–8.
[45] Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune related adverse events and association with outcomes. Clin Cancer Res 2016;22:886–94.
[46] Judd J, Zibelman M, Handorf E, O'Neill J, Ramamurthy C, Bentota S, et al. Immune-related adverse events as a biomarker in non-melanoma patients treated with programmed cell death 1 inhibitors. Oncologist 2017;22:1232–7.

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[47] Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139–40.
[48] Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev 2016;44:51–60.
[49] Joshi MN, Whitelaw BC, Palomar MT, Wu Y, Carroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. Clin Endocrinol (Oxf) 2016;85:331–9.
[50] Hamnvik OP, Larsen PR, Marqusee E. Thyroid dysfunction from antineoplastic agents. J Natl Cancer Inst 2011;103:1572–87.
[51] Iglesias P. Cancer immunotherapy-induced endocrinopathies: clinical behavior and therapeutic approach. Eur J Intern Med 2018; 47:6–13.
[52] Hannen J, Carbonnel F, Robert C, Kerr K, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines. Ann Oncol 2017;28:119–42 (suppl 4)iv.

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