Incidence of thyroid dysfunctions during treatment with nivolumab for non-small cell lung cancer: Retrospective study of 105 patients

Pauline Campredon 1, Céline Mouly 1, Amélie Lusque 2, Laurence Bigay-Game 3, Emilie Bousquet 3, Julien Mazières 3, Philippe Caron 1

1. CHU Larrey, Department of endocrinology and metabolic diseases, 31059 Toulouse, France
2. Institut Claudius-Regaud, IUCT-O, Department of statistics, 31100 Toulouse, France
3. CHU Larrey, Pulmonology department, Toulouse, France

Correspondence:
Philippe Caron, CHU Larrey, Cardiovascular and Metabolic Unit, Department of Endocrinology and Metabolic Diseases, ISA 30030, 24, chemin de Pouvourville, 31059 Toulouse cedex, France.
caron.p@chu-toulouse.fr

Keywords
Incidence
Nivolumab
Thyrotoxicosis
Hypothyroidism
Thyroiditis

Summary
Introduction > Immunotherapy is a standard not only in second line but also in first line treatment in patients with non-small cell lung cancer (NSCLC) and other tumors. Thyroid dysfunctions are the most common endocrine toxicities.

Objective > To determine the incidence of thyroid dysfunctions during treatment with a PD-1 monoclonal antibody (nivolumab) in patients with NSCLC.

Methods > Retrospective study of patients treated with nivolumab for NSCLC between May 2015 and December 2016; euthyroidism within the 3 months preceding immunotherapy; monitoring of thyroid function tests until stopping nivolumab, death or February 2017. Patients treated with levothyroxine, amiodarone or another immunotherapy were excluded.

Results > Among 183 patients treated, 105 fullfilled the inclusion criteria (72 males, median age: 61 years [range: 41-80]). Fifteen patients (14.3%) experienced a thyroid dysfunction, among them, compared to the “control” group (n = 90), we found more females (53.3% vs. 27.8%; P = 0.07), and younger patients (median age: 56 years vs. 62 years; P = 0.02). Thirteen patients had thyrotoxicosis (median onset: 8 weeks), and then hypothyroidism was observed in 5 patients. Isolated hypothyroidism was rare (n = 2) and late (median: 30 weeks). Three patients had anti-TPO antibodies. Three patients discontinued immunotherapy transiently due to thyroid dysfunctions. After a median follow-up of 9 months [95% CI, 7.5-10.3], one patient (6.7%) in the “thyroid dysfunctions” group and 30 patients (33.3%) in the “control” group died, with a trend toward a higher overall survival in the “thyroid dysfunctions” group (HR: 0.16 [95% CI, 0.02-1.15]; P = 0.07).

Conclusion > Thyroid dysfunctions (isolated thyrotoxicosis, biphasic thyroiditis and hypothyroidism) were common, and required patients with NSCLC to be screened during nivolumab therapy.
**Mots clés**
Incidences
Nivolumab
Thyrotoxicose
Hypothyroïdie
Thyroidite

**Résumé**

**Incidence des effets indésirables thyroïdiens chez les patients ayant un cancer bronchique non à petites cellules au cours d’un traitement par nivolumab**

**Introduction**
L’immunothérapie par le nivolumab (anticorps monoclonal anti-PD-1) représente un traitement de 1ère et 2ème ligne des formes avancées du cancer bronchique non à petites cellules (CBNPC) en particulier. Les dysthyroidies en sont les toxicités endocriniennes les plus fréquentes. Objectif : Déterminer l’incidence des dysthyroidies lors d’un traitement par nivolumab pour un CBNPC.

**Méthodes**
Étude rétrospective de patients ayant débuté un traitement par nivolumab entre mai 2015 et décembre 2016 pour un CBNPC, euthyroidiens dans les 3 mois précédant l’immunothérapie, suivis jusqu’à arrêt du nivolumab, au décès ou en février 2017. Étaient exclus les patients traités par lévothyroxine, amiodarone ou une autre immunothérapie.

**Résultats**
Parmi 183 patients traités, 105 ont été inclus (72 hommes, âge médian : 61 ans [minimum-maximum : 41-80]). Quinze patients (14,3 %) ont eu une dysthyroidie ; parmi eux, comparés au groupe témoin (n = 90), il y avait plus de femmes (53,3 % vs 27,8 %; p = 0,07), et des sujets plus jeunes (âge médian : 56 ans vs 62 ans ; p = 0,02). Treize patients ont eu une thyrotoxicose (médiane d’apparition : 8 semaines), suivie d’une hypothyroïdie chez 5 patients. L’hypothyroïdie isolée était rare (n = 2) et tardive (médiane : 30 semaines). Trois patients avaient des anticorps anti-TPO. Trois patients ont stoppé l’immunothérapie transitoirement en lien avec la dysthyroidie. Après un suivi médian de 9 mois [IC 95 % 7,5-10,3], un patient (6,7 %) est décédé dans le groupe dysthyroidie et 30 patients (33,3 %) dans le groupe témoin, avec une tendance à une meilleure survie globale dans le groupe dysthyroidie (HR : 0,16 [IC 95 % 0,02-1,15] ; p = 0,07).

**Conclusion**
Les dysthyroidies, thyrotoxicose ou hypothyroïdie biphasique, sont fréquentes et imposent leur dépistage lors d’un traitement par nivolumab.

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**What was known?**
- Frequency of endocrine adverse events during immunotherapy of patients with metastatic melanomas and non-small cell lung cancer.
- Thyroid disorders are frequently observed with anti-PD-1 monoclonal antibody treatment.

**What this study adds?**
- Clinical description of thyroid dysfunctions during nivolumab treatment.
- Discuss treatment modalities of thyroid dysfunctions associated with nivolumab treatment.

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**Introduction**

Immunotherapy is a standard not only in second line but also in first line treatment in patients with non-small cell lung cancer (NSCLC) and other tumors. They act by affecting the anti-tumor immune response. This modulation goes through direct actions at the checkpoints of the immune cycle, such as CTLA-4 and PD-1. Studies have highlighted multisystemic adverse events linked to immunotherapies (gastrointestinal, cutaneous, respiratory, neurological, ocular). Multiple endocrine disorders have also been described. Anti-CTLA-4 monoclonal antibodies (ipilimumab) preferentially exhibit a pituitary toxicity with hypophysitis as the primary consequence. The incidence continues to vary up to 25% [1-3]. Thyroid disorders are second in terms of frequency, with an incidence of 2 to 4% [1,3,4]. Adrenal disorders are much less frequent. Anti-PD-1 monoclonal antibodies (nivolumab, pembrolizumab) have demonstrated their efficacy in randomized
controlled clinical trials on improving survival rates in patients with metastatic melanomas and NSCLC [1-5]. The most frequent endocrine disorders related to this treatment were thyroid diseases, up to 28% described, particularly thyroiditis [1,3,5-8]. Less than 1% hypophysitis are described and adrenal disorders are very rare [7,9]. Faced with the increasingly widespread use of anti-PD-1 monoclonal antibodies, it is important to study the incidence of thyroid disorders during anti-PD-1 therapy, and to establish diagnostic and therapeutic strategies.

Our primary objective was to report the incidence of thyroid dysfunctions during nivolumab treatment in patients with pre-treated advanced NSCLC. The secondary objectives were to describe all cases of thyroid disorder (clinical, biological and management) in a real life study, and to evaluate overall survival and progression-free survival according to the onset of thyroid dysfunctions.

**Methods**

**Patients**

The records of patients seen in the Pneumology Department of the Centre Hospitalier Universitaire-Larrey and at Institut Universitaire du Cancer, Toulouse, France and treated with nivolumab for a pre-treated advanced NSCLC, were the subject of a retrospective analysis.

The inclusion criteria were adult patients hospitalized between May 2015 and December 2016, treated for an advanced NSCLC with nivolumab, having normal thyroid function test (free T4, free T3, TSH) before initiation of immunotherapy, and a systematic monitoring of the thyroid function before each intravenous nivolumab infusion (3 mg/kg) every two weeks until the end of treatment, death or February 6, 2017. Patients had a thoracic CT scan every 3 months with evaluation of the indication of nivolumab treatment.

Exclusion criteria included patients with an abnormal TSH level in the 3 months prior to nivolumab treatment, ongoing treatment with either levothyroxine or amiodarone, a combination with another immunotherapy, have no thyroid function tests within the 3 months prior to the start of immunotherapy, and finally patients who have received only one nivolumab infusion

Two groups of patients could be formed, the “thyroid dysfunctions” group included patients with at least one abnormal TSH level after the first infusion of nivolumab and the “control” group when TSH levels were in the normal range throughout the nivolumab treatment.

A central hypothyroidism was eliminated based on the concomitant dosage of T4/T3 in patients with a low TSH level.

**Primary endpoint**

In order to meet the main objective, we defined three subgroups of patients in the “thyroid dysfunctions” group:

- "Isolated thyrotoxicosis" subgroup with a decrease of TSH < 0.1 μU/mL, transient or permanent (persistent until the end of the study), with no increase of TSH level during monitoring;
- "Biphasic thyroiditis" subgroup with transient thyrotoxicosis, with a decrease of TSH < 0.1 μU/mL, followed by hypothyroidism with an increase of TSH level above the patient’s usual laboratory reference range;
- "Isolated hypothyroidism" subgroup with an increase of TSH level, above the patient’s usual laboratory reference range (i.e. greater than 4 μU/mL) and not preceded by a thyrotoxic phase, transient or permanent at the end of the study.

Hypothyroidism is transient when the increase of TSH level is followed by a spontaneous return to the normal level (or after stopping treatment with levothyroxine). It is permanent when the increase of TSH lasts more than 3 months or requires a long-term treatment with levothyroxine.

**Secondary endpoints**

In order to meet secondary objectives, we studied the general data about patients and their thyroid disorders, the management of thyroid disorders with specific treatment and discontinuation of anti-PD-1, and reasons of withdrawal of treatment. Finally, we studied overall survival and progression-free survival according to the patients groups.

**Clinical and biological analysis**

For each patient, we have collected clinical data (age, sex, smoking status, personal and family history of thyroid dysfunction), thyroid function tests (TSH, free T4, free T3). These tests were performed in usual patient’s laboratory, in real life condition. At the time of diagnosis we have collected the presence of thyroid antibodies (anti-thyroglobulin, anti-thyroperoxidase, anti-receptor of TSH).

**Statistical analysis**

The data were summarized by frequency and percentage for categorical variables and by median and range for continuous variables. The Chi2 or Fisher’s exact test was used to compare categorical variables, and the Kruskal-Wallis test was used for continuous variables.

All survival times were calculated from the initiation of immunotherapy and estimated by the Kaplan-Meier method with 95% confidence intervals (CI), using the following first event definitions: progression or death from any cause for progression-free survival (PFS) and death from any cause for overall survival (OS). As recommended in the literature, the impact of thyroid dysfunction on survival was evaluated using two analysis to minimize the bias inherent to the "guarantee time": the Cox proportional hazards model with time-dependent covariate and a sensitivity Landmark analysis at 3-months (excluding patients who died or progressed in the first 3-months).
Tests were two-sided and P-values < 0.05 were considered significant. Statistical analyses were conducted using Stata®, version 13.

Results
We studied the records of 183 patients hospitalized between May 2015 and December 2016. We excluded from the analysis: patients with an abnormal pre-therapy TSH level, treated with levothyroxine, ongoing treatment with amiodarone, with no pre-therapy TSH level, and who had received a single infusion of nivolumab (figure 1). The median age of the excluded patients was 63 years (range: 30–84 years), with 57.7% males. We analyzed the data of 105 patients. The median age of the included patients was 61 years (range: 41–80 years). The percentage of males was 68.6%. There was no significant difference in terms of age and sex between the included and excluded populations. Thyroid dysfunctions and control groups were similar in the disease’s severity. Eighty percent of patients had a disease at stage IV in thyroid dysfunctions group vs. 82.2% in control group. WHO performance status was also similar, 85.7% patients had WHO stage 0 or I in thyroid dysfunctions group vs. 91.1% in control group (P = 0.62).

Thyroid dysfunctions
Among the 105 patients included, 15 had thyroid dysfunctions, thus an incidence of 14.3%. Two patients had isolated hypothyroidism, including one transient and one permanent; 5 patients developed a biphasic thyroiditis, and 8 patients had an isolated thyrotoxicosis. Nine patients had transient thyroid dysfunctions and 6 had permanent thyroid dysfunctions. Nine patients were asymptomatic (figure 2).

The median time period between introduction of nivolumab therapy and the onset of thyroid dysfunctions was 1.8 months after the first infusion (range: 0.5–10.3 months).

Description of the 2 groups of patients
The two groups of patients differed, the “thyroid dysfunctions” group was significantly younger (P = 0.02) and there were more female compared to “control” group. All studied parameters between the two groups are in AppendixBAnnex 1.

The duration of nivolumab therapy was longer in the "thyroid dysfunctions" group (5.7 months after the first injection, range: 1.3–14.1) compared to the "control" group (2.1 months, range: 0.5–15.2; P = 0.48). In thyroid dysfunctions group, 7 patients (46.7%) discontinued nivolumab because they had a progression of the disease, and 1 patient (6.7%) for a pulmonary toxicity. In control group, 53 patients (58.9%) discontinued nivolumab therapy because they had a progression of the disease, 3 patients (3.3%) for toxicity (ophthalmic, digestive and diabetes), 2 (2.2%) for toxicity (dermatologic and digestive) and cancer progression, 9 died (10%) and 2 drop out (2.2%).

Autoimmunity
At the time of diagnosis of their thyroid dysfunction only 11 of the 15 patients had their thyroid autoimmunity evaluated: 3 patients had positive anti-TPO antibodies (20%) whereas they appeared to be negative for the 8 others; no patient had anti-TSH receptor antibody.

Secondary objectives
In the “thyroid dysfunctions” group, 3 patients with thyrotoxicosis received corticosteroids, and 2 of these 3 patients developed hypothyroidism. Of 15 patients, 9 patients had grade
1 thyroid disorder, 6 patients had grade 2 thyroid disorder. No patient had grade 3 or 4 thyroid disorder (Table I).

Nivolumab treatment was withdrawn in 3 patients due to onset of thyroid disorders; for these three patients, the discontinuation was transient during 14 days, 2 and 6 months, respectively. Patients who discontinued 2 and 6 months, had grade 2-thyroid disorder, and developed hypothyroidism during discontinuation.

**Survival analysis**

In the “thyroid dysfunctions” group, 7 patients (46.7%) experienced a disease progression during nivolumab therapy compared to 55 patients (61.1%) in the “control group” (Appendix BAnnex 2). After a median follow-up of 9 months (95% CI, 7.5–10.3), one patient (6.7%) from the “thyroid dysfunctions” group and 30 patients (33.3%) in the “control” group died. The overall survival and progression-free survival at 6 months were respectively 80.5% [95% CI, 70.7–87.3%] and 44.3% [95% CI, 34.3–53.7%] for the overall population. The presence of thyroid dysfunctions seemed to be associated with a better overall survival (HR based on Cox model with time-dependent covariate: 0.16, 95% CI, 0.02–1.15; P = 0.069). The sensitivity Landmark analysis was performed in 52 patients alive and without progression at 3-months to compare overall survival between patients with or without thyroid dysfunction in the first 3 months. This analysis also indicated a trend to a better overall survival in patients with thyroid dysfunctions (figure 3). The median progression-free survival rate was 3.8 months (95% CI, 2.1–6.7). However, the presence of a thyroid dysfunction did not appear to be a significant parameter with an HR of 0.78 (95% CI, 0.35–1.73; P = 0.540).

**Discussion**

This retrospective study highlighted an incidence of 14.3% for thyroid dysfunctions during treatment with nivolumab in patients with an advanced NSCLC. This incidence is in agreement with data from the literature: in NSCLC of stage III/IV, 14.3% of endocrine diseases were described in 35 patients, without exact incidence of thyroid toxicities [10]. Thyroid dysfunction was reported in 19.5% of patients treated by nivolumab for NSCLC [11] and with an incidence close to 17% of thyroid dysfunction among patients treated by pembrolizumab in patients with melanomas [8].

In randomized controlled trials evaluating nivolumab in NSCLC, incidence of hypothyroidism was 6 to 7% with anti-PD-1 treatment, whereas thyrotoxicosis was reported for 1 to 6% of these patients treated with nivolumab for NSCLC [12–14]. No endocrine toxicities of grade 3 or 4 were reported. In a large meta-analysis assessing anti-PD-1 therapy the relative risk of developed hypothyroidism and thyrotoxicosis was, respectively, 6.8 and 3.4 [7].

Whereas the incidence rate of reported thyroid dysfunctions was less than 10% in the first studies assessing the efficacy of nivolumab [11,15,16], recent studies which specifically assess the incidence of endocrine adverse effects report a higher frequency, given the fact that these thyroid dysfunctions are asymptomatic or pauci-symptomatic. Indeed, the most recent
### TABLE I
Cases of nivolumab induced thyroid disorders

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<th>TSH (µUI/mL) (Phase 2: biphasic thyroiditis)</th>
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studies highlight incidence even higher than 10%, up to more than 20% [6,11].

In our study, incidence of isolated hypothyroidism, isolated thyrotoxicosis and biphasic thyroiditis were respectively 1.9%, 7.6% and 4.8%. The most common form of thyroid side effects was thyroiditis. Thyrotoxicosis was most often asymptomatic or pauci-symptomatic. After the onset of thyrotoxicosis, a diffuse increase of 18-FDG uptake by the thyroid gland has been observed, compatible with the inflammatory nature of thyroiditis [8]. A recent study described with an other anti-PD-1

<table>
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<td>12</td>
<td>48 H</td>
<td>asthenia</td>
<td>0</td>
<td>BB, ATS, LT</td>
<td>Yes (2 months)</td>
<td></td>
<td>Thyrotoxicosis</td>
<td>20</td>
</tr>
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<td>13</td>
<td>54 F</td>
<td>0</td>
<td>0</td>
<td>Corticosteroid</td>
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<td></td>
<td>Progression</td>
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<tr>
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<td>Asthenia, weight loss</td>
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<tr>
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<td>64 F</td>
<td>Hair loss</td>
<td>Thrombopenia</td>
<td>LT</td>
<td>No</td>
<td></td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

0: absent; ND: not done; N: normal; LT: levothyroxine; BB: beta-blockers; ATS: anti-thyroid drugs; TPO: thyroid peroxidase; TG: thyroglobulin; IRAEs: ImmuneRelated Adverse Events.

*Patient had levothyroxine treatment at the time of corticosteroid decrease.

Figure 3
Overall survival and thyroid dysfunctions; landmark analysis at 3 months
(pembrolizumab) that 64% of patients with thyroid disorders have diffuse increased 18-FDG uptake of the thyroid gland [15]. We proposed that only symptomatic treatment could be indicated in the thyrotoxicosis phase. No Graves’ disease was described in our patients. Corticosteroids should be discussed in case of severe forms, given that corticosteroids could prevent the efficiency of immunotherapy, and that thyrotoxicosis are mostly asymptomatic and transient. There are no evidence that immunotherapy should be stopped in relation to thyroid disorders in most patients. Monitoring of thyroid function is essential, because hypothyroidism frequently occurs after a thyrotoxic phase. Symptoms of hypothyroidism are less specific and may be confused with the symptoms rather usual in patients seen in oncology setting (asthenia, fatigue, constipation, etc.). Substitutive treatment by levothyroxine allows a rapid improvement of symptoms. In this retrospective study, the treatment of thyroid dysfunctions and discontinuation of nivolumab therapy were reported in the first patients, but the current strategy would be now different, based on a symptomatic treatment with β blockers for the thyrotoxic phase or substitutive levothyroxine treatment in case of symptomatic and persistent hypothyroidism, and on exceptional discontinuation of nivolumab treatment in case of severe (grade 3–4) or comorbid thyroid dysfunctions.

A study reported the significant presence of anti-thyroid antibodies prior to immunotherapy in patients who developed thyroid dysfunctions during treatment with pembrolizumab compared to the control group (80% vs. 8%, P < 0.0001), suggesting that their presence may be a predictive marker for the onset of thyroid dysfunctions [16]. Anti-TPO antibodies are present in 8–15% of normal adults, more frequent in women than in men, increasing usually with ageing. The pathophysiological mechanisms of thyroid disorders involved not only cellular immunity, but also humoral immunity. The modulation of humoral immunity during a treatment with anti-PD-1 monoclonal antibodies is both dependent and independent on T cells [17–19]. An increased autoimmunity in knockout mice for PD-1 was highlighted in two studies [20,21], however PD-1 knockout mice do not develop thyroiditis. Moreover, PD-L1 and PD-L2 are expressed in normal thyroid tissue, and blockage of the PD-1 pathway in tissues expressing PD-L1 and PD-L2 could enhance local immune activity suggesting that nivolumab treatment reduce immune tolerance and leads to the development of thyroiditis. In our study, we did not observe the association between the presence of anti-TPO antibodies and the onset of thyroid dysfunctions. This may be due to a non-systematic test of anti-thyroglobulin antibodies and absence of monitoring anti-TPO antibodies during nivolumab therapy.

In the course of immunotherapies, a correlation was reported between the onset of secondary adverse events and the overall survival rate. An increase in the overall survival rate had been shown in patients treated by nivolumab with a cutaneous adverse event (rash or vitiligo) [22]. A longer median overall survival was reported in patients who developed hypophysitis during treatment with anti-CTLA-4 antibodies for a metastatic melanoma [23]. It has been described with other anti-PD-1 monoclonal antibody (pembrolizumab) in NSCLC that patients with thyroid dysfunctions had a better overall survival than those in the group who did not develop it [16]. In our study, a not statistically significant tendency toward improvement of the overall survival was observed in the “thyroid dysfunctions” group. Patients in “thyroid dysfunctions” group were significantly younger with female predominance. Younger age and female gender have been demonstrated to be good prognostic factors for overall survival in NSCLC. The occurrence of thyroid dysfunctions is not a reason to stop immunotherapy with anti-PD-1 monoclonal antibodies in patients with NSCLC.

The strengths of this study are the number of patients in the studied groups, patients included were free of thyroid dysfunctions before initiating immunotherapy and utmost a systematic monitoring of the thyroid function tests during nivolumab treatment.

The limitation of the study is its retrospective nature, with missing data for patients of the 2 groups, the duration of the study was a year and a half; by the end of the study, most patients with thyroid dysfunctions were in the thyrotoxic phase, but an extended monitoring could reveal a shift into hypothyroidism within the scope of thyroiditis. We have included only patients with no thyroid disease, therefore incidence of thyroid dysfunction is possibly underestimated. Difference in the duration of nivolumab therapy between both groups could affect the result, but discontinuation of nivolumab was mostly linked with disease progression and not with thyroid toxicity.

**Conclusion**

The incidence of thyroid dysfunctions during treatment with nivolumab was 14.3% in patients with NSCLC. Immunotherapy is a turning point landmark in the treatment of various cancers. Given the expanding use of immunotherapy, even as a first line treatment, oncologists will be increasingly faced with these endocrine toxicities. Thus, these adverse effects and particularly thyroid disorders deserve to be properly screened and treated. In the meantime, specific studies should be designed in order to understand the mechanisms implicated in their pathophysiology.

**Ethical approval**

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee (AC-2013-1955, CPP Sud-Ouest et Outre-mer I).
Informed consent

All patients were included in this study and in IMMUNO-PREDICT study (ClinicalTrials.gov ID: NCT02827344) after informed consent.

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References


