

# Immune-related Thyroid Dysfunction (irTD) in Non-small Cell Lung Cancer (NSCLC) Correlates With Response and Survival

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**Abstract.** *Background:* There is no clear information on the proportion of patients who need therapy for immune-related thyroid dysfunction (irTD) or who need to delay, omit, or discontinue immunotherapy. Furthermore, it is not well known whether irTD correlates with better outcomes or not. *Patients and Methods:* We conducted a retrospective study in patients with metastatic non-small cell lung cancer (NSCLC) treated with anti-PD1 or anti-PD-L1. *Results:* Our study enrolled 75 patients, 25.3% of them developed immune-related thyroid dysfunction. Three patients delayed a course of immunotherapy due to irTD, 2 patients omitted a course and 1 patient permanently discontinued. In patients with irTD compared with those without irTD the ORR was 42.1% vs. 7.1% ( $p<0.001$ ), DCR was 78.9% vs. 32.1% ( $p<0.001$ ); mPFS was 15.7 vs. 3.6 months ( $p<0.001$ ) and mOS was 18.6 months vs. 5.1 months ( $p<0.001$ ). *Conclusion:* Immune-related thyroid dysfunction has a mild impact on the immunotherapy treatment program. The occurrence of irTD correlates with more favorable response and survival.

Immune-checkpoint inhibitors monoclonal antibodies against cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) have been proved to be an effective strategy in various types of cancer and the use of

these drugs alone or in combination is increasing in clinical practice. Two anti-PD-1 antibodies [Nivolumab (1-3) and Pembrolizumab (4-7)], two anti-PD-L1 [Atezolizumab (8-9) and Durvalumab (10)] and one anti-CTLA-4 [Ipilimumab (3)] have shown efficacy in lung cancer and are currently used in various countries, with different approval guidelines and costs. CTLA-4 and PD-1 are both inhibitory receptors expressed on the surface of T-cells which, following the binding with their respective ligands (CD 80/CD86 and PD-L1/PD-L2), induce the inhibition of lymphocyte activity, playing a central role in the regulation of the immune response. CTLA-4 works as a brake signal and mainly regulates the amplitude of the early stages of activation of T-cells (11). On the other hand, PD-1 specifically limits the activity of T-cells in peripheral tissues, at the time of an inflammatory response to infection and limits autoimmunity (12). Ultimately, both of these checkpoints lead to a reduction in the activity of T-cells. PD-L1 is a molecule also expressed by various types of cancer and the PD-1/PD-L1 binding that inhibits the activity of T-lymphocytes is a loophole used by cancer cells to evade the immune response, so the use of drugs that block the activity of these inhibitory checkpoints can release the anticancer activity of T-cells and enhance the immune response (13, 14). However, immune checkpoints play a key role in maintaining immune self-tolerance and their blockade increases immune-related adverse event (irAE), that can occur in various organs but most frequently affect skin, colon, liver, lungs and endocrine organs (15). Endocrine gland diseases are among the most frequent complications of immune checkpoint inhibitors, including: thyroid dysfunction, insulin-deficient diabetes mellitus, hypophysitis and primary adrenal insufficiency (16, 17). In particular, immune-related thyroid dysfunction (irTD) has an incidence ranging between 5% and 25%, being higher in combinations of anti-PD-1 and anti-CTLA-4 (10, 18-21).

The pathogenesis of thyroid dysfunction under immune checkpoint inhibitors (ICIs) is still uncertain. Some authors hypothesize a destructive thyroiditis mediated by autoreactive T

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cells against the thyroid gland (22), others argue that a mechanism of acute inflammation and destruction of the thyroid gland mediated by anti-thyroid antibodies is at the basis of thyroid dysfunction and hypothesize a role of PD-1 in the modulation of humoral immunity (23). In a case series study the authors found that normal thyroid tissue expresses PD-L1 and PD-L2, which suggest that PD-1 blockade reduces immune tolerance even in normal thyroid tissue and this favors the development of thyroiditis (24). In the prospective study a positive correlation was found between positive TgAb and/or TPOAb at baseline and the development of destructive thyroiditis (25). However, some cases of isolated hypothyroidism (22) and thyrotoxicosis due to Graves' disease have been described under ICIs (26). Although the incidence of thyroid dysfunction is known, and it is known how to treat these patients, until now there is no clear evidence on the proportion of patients who need therapy for irTD, and the need to delay, omit or interrupt immunotherapy has not been established. Furthermore, few studies mostly with limited cases have shown a favorable correlation between the onset of immune-related thyroid dysfunction during therapy with PD-1/PD-L1 blockade and outcome in non-small cell lung cancer (23, 27-35).

## Patients and Methods

**Study design.** We conducted a monocentric retrospective study in patients with metastatic non-small cell lung cancer (NSCLC) treated with anti-PD1 nivolumab (3 mg/kg every 2 weeks or 240 mg every 2 weeks) or pembrolizumab (2 mg/kg every 3 weeks or 200 mg every 3 weeks), and anti-PD-L1 atezolizumab (1,200 mg every 3 weeks). The primary endpoint was to identify the incidence and severity of irTD in "real life" and the percentage of patients requiring discontinuation, omission or delay of immunotherapy. Secondary endpoints included overall response rate (ORR), defined as percentage of patients who have achieved partial or complete response from immunotherapy according to RECIST 1.1 (36) and iRECIST (37) when applicable; disease control rate (DCR), defined as the proportion of patients who have achieved complete or partial response and stable disease (SD) for at least 8 weeks from the start of immunotherapy; progression-free survival (PFS), defined as the time from the start of immunotherapy to the first progression according to RECIST 1.1 and iRECIST criteria, and overall survival (OS), defined as the survival period from the start of immunotherapy and the time of the patient's death or the last follow-up. The severity of adverse events (AEs) was graded using CTCAE v5.0 (38) and also evaluating the values of thyroid hormones (TSH, FT4, T3/FT3). Our study was approved by the Ethics Committee of the Lazio 1 (approval number 700/CE).

**Inclusion/exclusion criteria.** Inclusion criteria were: a) patients aged 18 years or older, b) histologically confirmed non-small cell lung cancer, c) at least two courses of immunotherapy completed, d) absence of thyroid dysfunction at the start of immunotherapy, and e) at least two dosages of thyroid hormones (TSH, FT4, T3/FT3) after the start of immunotherapy. Exclusion criteria were: a) previous thyroid dysfunction, b) administration of less than two courses of immunotherapy, and c) less than two dosages of thyroid hormones.

Table I. Patient baseline characteristics.

Patient characteristics	
Patients n=75	
Median age, years (range)	69 (37-82)
Age, number (%)	
<70	41 (54.7)
≥70	34 (45.3)
Gender	
Male	49 (65.0)
Female	26 (35.0)
PS ECOG	
0-1	70 (93.3)
2	5 (0.7)
Histology	
Squamous	20 (26.7)
Adenocarcinoma	52 (69.3)
NSCLC	3 (4.0)
Pretreated	
Yes	63 (84.0)
No	12 (16.0)
ICIs	
Nivolumab	55 (73.3)
Pembrolizumab	12 (16.0)
Atezolizumab	8 (10.7)

PS: Performance status; ECOG: Eastern Collaborative Oncology Group; ICIs: immune-checkpoint inhibitors.

**Thyroid dysfunction.** The thyroid dysfunction categories were divided into four groups: hypothyroidism, sub-clinical hypothyroidism, hyperthyroidism and sub-clinical hyperthyroidism. The definitions of these categories are in agreement with the American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and European Thyroid Association (ETA) (39-41).

**Data collection.** The clinico-pathological features of patients were obtained retrospectively from medical records, as well as data on the treatment performed and results achieved. The result of the thyroid hormones was obtained from patients records or from an electronic archive.

**Statistical analysis.** Statistical analysis was performed using SPSS v. 23 (IBM, Armonk, NY, USA). Kaplan-Meier curves for PFS and OS were performed with SPSS. Multivariate analysis was performed using the Cox Regression Hazard Model method. A value of  $p < 0.05$  was considered statistically significant for all tests. Pearson correlation coefficient and linear regression analysis were used to correlate irTD with response rate and survival.

## Results

**Patient characteristics.** From July 2015 to April 2020, 85 patients were included. Patient characteristics are summarized in Table I. Ten patients were excluded because of pre-existent thyroid dysfunction. Seventy-five patients were evaluable for analysis (intention-to-treat, ITT). 49 were male and 26 female, their median age was 69 years (range=37-82),

Table II. Multivariate analysis of progression-free survival and overall survival in intention to treat population (ITT), using the Cox Regression Hazard Model.

Variable	PFS (months)	HR (95% CI)	p-Value	OS (months)	HR (95% CI)	p-Value
Age						
<70	4.4	0.77	0.311	5.9	0.82	0.453
≥70	5.0	(0.46-1.28)		9.8	(0.48-1.39)	
Gender						
Male	4.4	1.17	0.577	8.5	1.16	0.602
Female	4.9	(0.68-2.02)		7.4	(0.66-2.03)	
Histology						
Squamous	4.4	0.87	0.637	6.20	0.85	0.586
Non-squamous	5.0	(0.49-1.54)		8.50	(0.48-1.51)	
irTD						
Yes	15.7	0.25	<0.001	18.6	0.24	<0.001
No	3.6	(0.13-0.52)		5.10	(0.12-0.52)	

irTD: Immune-related thyroid dysfunction; PFS: progression-free survival; OS: overall survival.

performance status was ECOG 0-1 in 70 patients and 2 in 5 patients, while the prevalent histology was adenocarcinoma (52 patients), followed by squamous (20 patients) and non-small cell NOS (3 patients). Sixty-three patients (84%) were pretreated with chemotherapy (CT) and 12 (16%) were CT naïve. Fifty-five patients received nivolumab, 12 received pembrolizumab and 8 received atezolizumab. The median number of courses was 8 (range=2-75). Median duration of follow-up was 6.24 months (range=3.36-40.8).

**Thyroid dysfunction.** A thyroid dysfunction (TD) of any grade was found in 19/75 patients (25.3%), after a median of 5 cycles of therapy (range=1-42, median days 76, range=29-733). Central TD was excluded in all patients. Fifteen patients were treated with nivolumab and 4 patients with pembrolizumab. No TD was observed in the 8 patients treated with atezolizumab. Five patients (6.7%) developed hypothyroidism (G2 in 4 and G3 in 1 patient) and hormone replacement with levothyroxine was needed. Four patients (5.3%) experienced hyperthyroidism and three were treated with the anti-thyroid drug methimazole because of G2 hyperthyroidism. The other patient after a phase of mild hyperthyroidism lasting about three months had spontaneous normalization of thyroid hormone values. One of these patients developed thyroiditis with G2 hyperthyroidism followed by G2 hypothyroidism and was treated for both dysfunctions. Other TD were subclinical hyperthyroidism in 7 patients (9.3%), none of these required antithyroid drugs, and subclinical hypothyroidism in 4 patients (5.3%), one of these received levothyroxine. The therapeutic decision for thyroid dysfunction was made with the collaboration of an endocrinologist.

**Omission or delay or discontinuation for thyroid dysfunction.** Three patients (4%) delayed a treatment course due to thyroid dysfunction (hypothyroidism for 2 and hyperthyroidism for 1

patient). Two patients (2.6%) omitted a course because of hypothyroidism and 1 patient (1.3%) permanently discontinued treatment due to G3 hypothyroidism.

**Response rate and survival.** In the intention to treat population (ITT), overall response rate (ORR) was 16% (PR 12 patients) and disease control rate (DCR) was 44% (PR 12 patients, SD 21 patients). The median progression-free survival was 4.9 months (range=3.3-6.5) and the median overall-survival was 8.3 months (range=3.9-12.6). The 12-months PFS and OS rates were 24.7% and 34.7%, respectively. In the multivariate analysis for survival, a favorable and statistically significant correlation was highlighted for the presence of thyroid dysfunction; no significant differences were found for any of the other variables (age, sex, histology). These results are shown in Table II.

In patients who developed immune-related thyroid dysfunction *vs.* patients who did not, overall-response rate was 42.1% (8/19 PR) *vs.* 7.1% (4/56 PR) (HR=0.36; 95% CI=0.12-0.47,  $p<0.001$ ), while no complete response was detected; disease-control rate was 78.9% (8 PR and 7 SD) *vs.* 32.1% (4 PR and 14 SD) (HR=0.42; 95% CI=0.24-0.73,  $p<0.001$ ) respectively; mPFS was 15.7 months *vs.* 3.6 months (HR=0.25; 95% CI=0.13-0.52,  $p<0.001$ ) and mOS was 18.6 months *vs.* 5.1 months (HR=0.24; 95% CI=0.12-0.52,  $p<0.001$ ). The 12-month PFS rates was 47.4% *vs.* 16.1% (HR=0.32; 95% CI=0.09-0.53,  $p<0.005$ ) and 12-month OS was 65.4% *vs.* 23.2% (HR=0.41; 95% CI=0.22-0.68,  $p<0.001$ ).

## Discussion

The typical clinical presentation of irTD is thyroiditis with or without thyrotoxicosis, which subsequently resolves or progresses to hypothyroidism. However, some case of

isolated hypothyroidism and Graves' disease are described. Diagnosis is based on thyroid hormone and antibody values as symptoms may be confused with those of cancer.

*Pathogenesis of thyroid dysfunction and presentation.* The pathogenesis of TD is still uncertain. The most accredited hypothesis is that there is an immune-mediated destructive thyroiditis (22-24), however this does not clarify the cases of isolated hypothyroidism and thyrotoxicosis due to Graves' disease reported in the literature (22, 26). In our study five out of seven patients with subclinical hyperthyroidism and one with mild hyperthyroidism had spontaneous normalization of thyroid hormones after a median of 88 days. In the other two cases, subclinical hyperthyroidism persisted till the last thyroid hormone tests. This trend is suggestive for thyroiditis with transient hyperthyroidism. Only in two patients with subclinical hyperthyroidism, TgAb and TPoAb were performed and both were elevated. In one patient with hyperthyroidism followed by hypothyroidism we found high TPoAb values. Also, in this case the clinical course and the antibody allowed the identification of thyroiditis. In the other two cases of hyperthyroidism, the unavailability of antibodies (TgAb, TPoAb and TRAb) did not allow to identify thyroiditis or Graves' disease. In a case of hypothyroidism, we detected normal values of the antibodies, suggesting an isolated hypothyroidism. On the contrary in another case, TPoAb were elevated: that is indicative of hypothyroidism following thyroiditis. In the other two cases of overt hypothyroidism and four cases of subclinical hypothyroidism we don't have sufficient data to comment about the cause.

*Incidence of immune-related thyroid dysfunction.* Overall, the TD incidence of 25.3% (hypothyroidism and hyperthyroidism of any grade were equal to 12% and 13.3%, respectively) found in our retrospective analysis is higher than that reported by Barroso-Sousa *et al.* (20) in a recent meta-analysis of 38 randomized trials involving various solid tumors. The latter estimates the incidence of any grade of hypothyroidism at 7% (CI=3.9-12.3,  $p=0.0089$ ) in patients treated with anti-PD-1 and 3.9% (CI=1.7-8.4,  $p=0.9861$ ) in those treated with anti-PD-L1, while hyperthyroidism of any grade was found in 3.2% (CI=1.7-5.7,  $p=0.0438$ ) in patients who received anti-PD-1 and 0.6% (CI=0.2-1.8,  $p=0.0653$ ) in those treated with PD-L1. Concerning non-small cell lung cancer, similar incidence of TD (21%) was observed by Osorio *et al.* (23), a higher incidence (32.7%) was reported by Kim *et al.* (28). Other authors report lower incidence: Herbst *et al.* (42) found hypothyroidism and hyperthyroidism of any grade in 8.2% and 4.7%, respectively, in 682 patients treated with pembrolizumab, while Garon *et al.* (43) observed hypothyroidism and hyperthyroidism of any grade in 6.9% and 1.8%, respectively, in 495 patients treated with pembrolizumab. An even lower incidence was reported with nivolumab by Gettinger *et al.* (44): the hypothyroidism

rate was equal to 5.8% and hyperthyroidism to 1.9%. In our retrospective study, the majority of patients (55) were treated with nivolumab, while the other 20 patients with pembrolizumab (12) or atezolizumab (8). The absolute preponderance of patients treated with nivolumab, due to the different time of approval, indication and reimbursement by the Italian Regulatory Agency, does not allow for any statistical comparison between the three groups. However, one third (33.3%) of the patients treated with pembrolizumab and more than a quarter (27.3%) of the patients treated with nivolumab experienced irTD, while no cases were detected in the 8 patients treated with atezolizumab. This is in agreement with the meta-analysis data by Barroso-Sousa *et al.* (20) reporting a higher incidence of irTD with anti-PD1 compared to anti-PD-L1. We observed that the onset of the irTD from the start of immunotherapy occurred after a median of 5 courses (range=1-42) and a median of 76 days (range=29-733). Other authors also reported a wide range of onset time, for example Chang *et al.* (45) in the anti-PD-1 monotherapy group reported a median time to onset of thyrotoxicosis of 47 days (range=14-447 days) and hypothyroidism of 70 days (range=27-475).

*Discontinuation, omission or delay of immunotherapy due to thyroid dysfunction.* In our opinion, the clinical impact of mild thyroid dysfunction, though frequent, is not relevant, whereas its severity could lead to a change in treatment program and the need of replacement or anti-thyroid therapy. In our analysis 42.1% of patients with thyroid dysfunction required levothyroxine replacement therapy (5 patients because of G2-G3 hypothyroidism) or treatment with the antithyroid drug methimazole (3 patients due to G2 hyperthyroidism). Only one patient with irTD had permanently discontinued treatment due to G3 hypothyroidism (5.3%), two patients omitted an immunotherapy course (10.5%) and only three patients (15.8%) delayed a cycle of immunotherapy due to thyroid dysfunction. So irTD in our study was moderate and had a mild impact on immunotherapy treatment, in fact six patients with irTD (31.6%) had to change their planned courses and only one of them had to permanently discontinue it. Other studies report a lower incidence. In the study of Osorio *et al.* (23) all patients with thyroid dysfunction required thyroid replacement but none of these had to delay or discontinue pembrolizumab. Maekura *et al.* (46) report that three of five patients with hypothyroidism required levothyroxine replacement, but none discontinued treatment. In the study of Peirò *et al.* (35) 17 of 73 patients (23.3%) had TD and two patients with thyrotoxicosis (7 patients) had temporary discontinuation of nivolumab, while no patient with hypothyroidism (10 patients) discontinued treatment.

The limited number of cases of these studies do not allow definitive conclusions, but our study and others agree that discontinuation of treatment for thyroid dysfunction is uncommon. We believe that early initiation of hormone



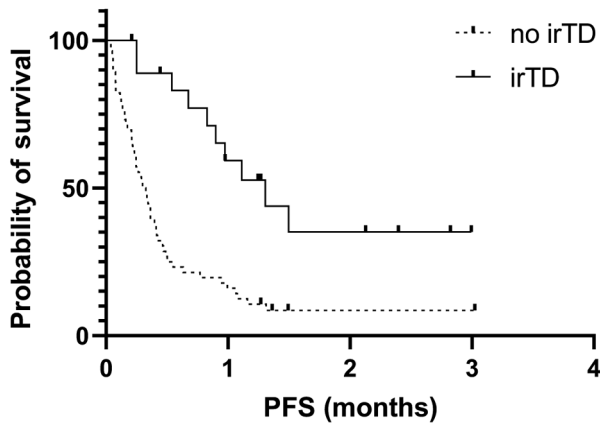


Figure 1. Kaplan-Meier estimates of progression-free survival for patients with or without immune-related thyroid dysfunction (irTD).

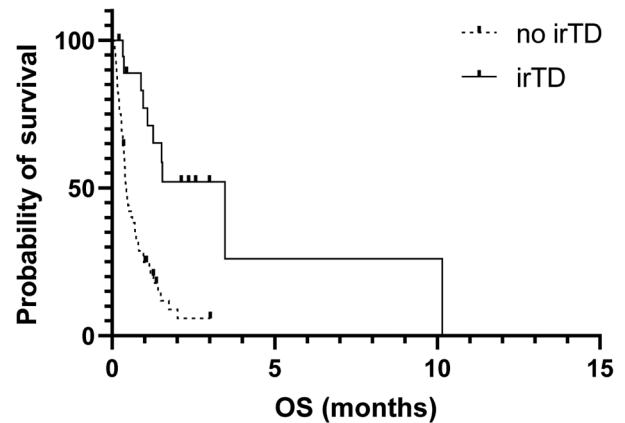


Figure 2. Kaplan-Meier estimates of overall survival for patients with or without immune-related thyroid dysfunction (irTD).

replacement or antithyroid drugs has significantly reduced omission, delay, or definitive interruption of immunotherapy.

**Correlation between thyroid dysfunction and outcome.** In our study another relevant aspect is that the onset of irTD is only factor that showed a favorable and significant correlation with survival in the ITT population at multivariate analysis. Patients with irTD achieved a 6-fold higher response rate (HR=0.36,  $p<0.001$ ) compared to those without, and reduced the risk of progression and death by 75% (HR=0.25,  $p<0.01$ ) and 76% (HR=0.24,  $p<0.01$ ), respectively (Figure 1 and Figure 2). Other authors show a favorable correlation of thyroid dysfunction with the response rate and survival: Osorio *et al.* (23) studied 51 patients with advanced NSCLC treated with pembrolizumab and reported OS significantly longer in those who developed thyroid dysfunction (TD) than those without TD (mOS 40 vs. 14 months, HR=0.29; 95% CI=0.09–0.94,  $p=0.029$ ); Kim *et al.* (28) in 58 patients with stage IV non-small cell lung cancer treated with anti PD-1 also demonstrated that in the TD group PFS (median 118.0 vs. 61.0 days, log-rank  $p=0.014$ ) and OS (median 118.0 vs. 71.0 days, log-rank  $p=0.025$ ) were longer than in euthyroid group. They also showed that TD was an independent prognostic factor for OS and PFS; Sato *et al.* (29) in 38 patients treated with Nivolumab for advanced NSCLC observed higher ORR (63.6% vs. 7.4%,  $p<0.01$ ) and longer PFS (median: not reached vs. 49 days,  $p<0.001$ ) in patients with or without irAE respectively. In this study six patients had TD; Grangeon *et al.* (30), in a large retrospective study analyzed 270 patients with advanced NSCLC who received (anti PD-L1 or anti PD-1) and showed that in patients who have experienced irTD (19.6%), compared with those without irTD, PFS (median 8.05 vs. 2.59 months,  $p=0.05$ ) and OS (median not reached vs. 18.2 months,  $p=0.01$ ) where

significantly longer; Koyama *et al.* (32), in 132 patients treated with nivolumab or pembrolizumab found that median PFS was significantly longer in NSCLC patients with irTD than in those without irTD (8.8 vs. 1.8 months,  $p=0.012$ ). In this study, the incidence of irTD was higher in TTF-1 negative patients than in those positive, besides in the TTF-1-negative NSCLC group, there was a significant difference in median PFS between patients with and without irTD: 10.3 months; 95% CI=2.1–not reached (NR) months vs. 2.4 months; 95% CI=1.7–3.8 months;  $p=0.030$  respectively. The authors suggest that TTF-1 expression could be correlate with irTD and anti-PD-1 efficacy. Ferreira *et al.* (33) in a retrospective study analyzed 161 patients treated with immune checkpoint inhibitors for various malignancies and observed that in patients with TD, the response rate and overall survival were significantly higher than the control group (ORR 58.6% vs. 34.2%,  $p=0.015$ ; OS 3.27 vs. 1.76 years,  $p=0.030$ ); Zhou *et al.* (34) in 191 patients treated with anti-PD-1 for non-small cell lung cancer also observed a significantly more favorable progression-free survival and overall survival in patients who developed thyroid dysfunction versus those who did not (PFS 10.4 vs. 5.5 months,  $p<0.001$ ; OS 16.8 vs. 11.1 months,  $p<0.001$ ). Also, Peirò *et al.* (35) showed that TD was associated with better overall survival in the NSCLC subgroup [HR=0.4 (95% CI=0.17–0.94);  $p=0.035$ ].

So, the results of our study agree with other studies that the onset of immune-related thyroid dysfunction during PD-1 blockade in non-small cell lung cancer correlates with more favorable response and survival.

The reason why immune-related thyroid dysfunction correlates with the outcome of PD-1/PD-L1 blockade is not known. It has been hypothesized that healthy tissues express antigens identical or similar to those expressed by the tumor,

thus immune checkpoint inhibitors in addition to enhancing the activity of the immune system against cancer can also determine an aggression of healthy tissues that share the same or similar tumor antigens (47). Normal thyroid tissue expresses PD-L1 and PD-L2, which suggest that PD-1 blockade reduces immune tolerance even in normal thyroid tissue (24). Other authors suggest that TTF-1 expression could be correlate with irTD and anti-PD-1 efficacy (32). We hypothesize that the onset of irTD during check point inhibitors is a sign of increased activity and predictive of efficacy of the treatment, therefore in our opinion is not surprising that survival outcomes are better in patients who experienced irTD, as evidenced in our and other studies. However, this can be argued in non-small cell lung cancer but has to be verified in other cancers, in malignant melanoma for example hypothyroidism or hyperthyroidism were not associated with a better survival (48).

*Limitations and strengths of the study.* Our study is a retrospective and monocentric study, and our sample is not large even if it is superior to that of other studies on the topic. In most cases the antibodies (TgAb, TPoAb and TRAb) were not available, consequently in some cases of irTD we don't have sufficient data to identify the cause. We also do not know if a pre-existing and unknown thyroid autoimmunity has favored thyroid dysfunction as reported by other studies. Our study also has strengths: we limited the study only to patients with non-small cell lung cancer treated with anti-PD-1/PD-L1 monotherapy, thus we eliminated confounding factors related to different types of cancer and combination therapy; the data relating to the objectives of the study are adequate.

## Conclusion

The incidence of irTD found in our retrospective analysis concerning patients with non-small cell lung cancer treated with PD-1/PD-L1 blockade is high (25.3%), but it is similar to that of other studies. The onset of the irTD from the start of immunotherapy occurred quite early after a median of 76 days but it can appear after several months. We found that if irTD is promptly treated has a mild impact on the immunotherapy program. In our study only a small number of patients needed discontinuation, omission or delay of immunotherapy. Also, in our analysis as already reported by other studies, the occurrence of irTD correlates with the best outcomes like a higher overall-response rate and disease-control rate and also a better survival.

We hypothesize that the onset of irTD during check point inhibitors is a sign of increased activity and predictive of efficacy of the treatment in non-small cell lung cancer.

However, larger case studies are needed to confirm the correlation of immune-related thyroid dysfunction and

efficacy of treatment with anti-PD-1/PD-L1 and to clarify the mechanisms of the association of thyroid dysfunction and better outcome.

## Conflicts of Interest

The Authors have no conflicts of interest to disclose.

## Authors' Contributions

Conception: Chillelli MG. Data curation: Chillelli MG, Giron Berrios JR and Signorelli C. Collection and assembly of data: All Authors. Formal analysis and interpretation: Giron Berrios JR, Chillelli MG, Signorelli C and Ruggeri EM. Manuscript writing: Chillelli MG, Giron Berrios JR, Signorelli C and Ruggeri EM. Financial support: All Authors. All Authors have read and approved the final manuscript.

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