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ORIGINAL ARTICLE

Thyroid dysfunction induced by immune checkpoint inhibitors is associated with a better progression-free survival and overall survival in non-small cell lung cancer: an original cohort study

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Abstract

Background The objective of this study was to investigate the association between the onset of TD and treatment efficacy in NSCLC patients who initiated anti-PD-1 blockade (Nivolumab®) and to assess the impact of TD severity and subtype on nivolumab efficacy.

Materials and methods This study was performed at a referral oncology center between July 20, 2015 and June 30, 2018. Patients with histologically confirmed stage IIIB/IV NSCLC in progression after one or two lines of treatment and who initiated Nivolumab were included. Thyroid function (TSH ± fT4, fT3) was monitored and patients were classified according to TD status [TD(+) versus TD(−)], severity [moderate thyroid dysfunction: TSH level between 0.1 and 0.4 or 4.0 and 10 mIU/L and severe thyroid dysfunction: TSH ≤ 0.1 or ≥ 10mUI/L) and subtype (isolated hypothyroidism, isolated hyperthyroidism and hyperthyroidism then hypothyroidism)]. Clinical endpoints were overall survival (OS) and progression-free survival (PFS).

Results Among 194 eligible patients, 134 patients (median age, 63 yo; 70.1% male) were included. Forty (29.9%) patients were classified in TD(+) and had a longer OS of 29.8 months (95% CI 18.8-NR) versus 8.1 months (95% CI 5.5–11.5) in TD(−) group ($p < 0.001$). PFS was also longer (8.7 months (95% CI 5.3–15.1) in TD(+) versus 1.7 months (95% CI 1.6–1.9) in TD(−) group ($p < 0.001$). In Cox proportional hazards analysis, TD remained an independent predictive factor of OS/PFS. Severity and subtype of TD were not correlated with OS/PFS.

Conclusions This study suggested that TD induced by Nivolumab appears to be an independent predictive factor of survival, irrespective of TD severity and subtype.

Keywords Non-small cells lung cancer · Immune checkpoint inhibitors · PD-1 blockade · Thyroid dysfunction · Prognosis

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, good clinical practice and relevant french regulations regarding ethics and data protection. living patients were informed and gave their non-opposition to participate in the study. the study (29BRC19.0228) was approved by our university hospital's institutional review board (B2019CE48).

Consent for publication

All authors contributed to drawing up the manuscript and approved this version.

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Introduction

In the recent years, a better understanding of the immunological mechanisms involved in oncogenesis has led to the development of immune checkpoint inhibitors (ICI). Nivolumab is a human IgG4 immunoglobulin, which belongs to the ICI anti-programmed cell death 1 (anti-PD-1) family. Phase III trials (CHECKMATE 017 and CHECKMATE 057) of non-small cell lung cancer (NSCLC) patients treated with nivolumab vs. docetaxel demonstrated a significant higher overall survival (OS) in patients who had nivolumab therapy [1, 2]. Nivolumab marketing authorization as a second-line treatment for advanced NSCLC (grades IIIB and IV) was obtained in France in 2015 [3, 4].

ICIs are associated with a new spectrum of toxicity known as immune-related adverse events (IRAEs). One of the most common ICI-induced IRAEs are endocrine IRAEs [5, 6]. The latter include disorders such as ICI-induced diabetes, hypophysitis and thyroid dysfunction (TD). The association between immunotherapy efficacy and the onset of IRAEs is debated across the literature with conflicting results. Most of these studies were in melanoma patients. The association between skin-IRAEs (e.g. vitiligo) and improvement of survival outcomes [e.g. OS, progression-free survival, (PFS)] is reported in melanoma patients [7–9]. However, TD does not seem to be associated with patient's outcomes in melanoma patients [10]. To date, there is a paucity of literature on the onset of TD as a predictive factor in NSCLC. In NSCLC, the incidence of TD differed across the literature ranging from 4–12% in earlier [1, 2, 11–13] to 21–35.5% in more recent and more specific studies [14–17] and up to 50% in those with combined regimens of immune checkpoints inhibitors [18]. Thyroid function monitoring is now recommended by dosing of TSH and T4L before treatment initiation, then before each cycle of treatment during the first three to six months [19–21].

There is a need for predictors of ICI treatment response (i.e. ICI clinical benefit). To date, despite its technical and methodological limitations, PD-L1 expression level seems to be the only reliable metric in prediction of ICI clinical benefit [22, 23]. Active research for new metrics predictors of cancer treatment response has given rise to biological parameters, such as tumor mutational load, microsatellite instability, tumor-infiltrating lymphocytes [24], most of which cannot be readily used in routine practice. On the other hand, emerging clinical metrics, such as Lung Immune Prognostic Index (LIPI) score, an inflammation marker, can be easily used [25].

Several studies have already addressed the question of the association between IRAEs and response to anti-PD1 immunotherapy in the NSCLC. Haratani et al. found an association between the occurrence of IRAEs and the overall response rate in patients treated with nivolumab [26]. Hasan Ali et al. found an association between skin effects and response in patients treated with nivolumab [27].

Regarding TD induced by ICI, several studies reported an association between TD and response to anti-PD-1 in patients treated with pembrolizumab [14] and nivolumab [16, 17].

We hypothesized that the ICI-induced TD in NSCLC patients treated with nivolumab was associated with better treatment efficacy (i.e. survival outcomes). We further studied the impact of severity and sub-type of TD on survival outcomes.

Materials and methods

This was an observational, retrospective and monocentric study, conducted at the University Hospital of Brest from July 20, 2015, to June 30, 2018.

Population

Patients were screened using the Chimio® software (Computer Engineering, Paris, France) according to indication and treatment, i.e. keywords: "Lung/bronchus", "Nivolumab".

Inclusion criteria were: patients ≥ 18 years old with a cytologically/histologically confirmed locally advanced (stage IIIB) or metastatic (stage IV) NSCLC with progressive disease (PD); to undergo Nivolumab as second or more line of therapy.

Exclusion criteria were: primary tumor other than lung cancer; history of total thyroidectomy or previous treatment with levothyroxine or thyroid dysfunction before Nivolumab initiation; no thyroid function monitoring during Nivolumab treatment and missing data; patients who expressed their opposition to participate in the study.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and relevant French regulations regarding ethics and data protection. Living patients were informed and gave their non-opposition to participate in the study. The study (29BRC19.0228) was approved by our university hospital's institutional review board (B2019CE48).

Cohort characteristics

The following patient characteristics were retrieved from medical records: age, gender, smoking status (absent, current or former), WHO performance index, tumor characteristics (histology, genetic alteration, staging, history of brain metastasis), prior radiotherapy treatment, prior systemic lines

(defined by the number of chemotherapy/immunotherapy regimens used before Nivolumab treatment).

We also recorded data on PD-L1 expression in tumor, LDH levels and the lymphocyte-to-neutrophil ratio (dNLR) summarized in the LIPI score (Lung immune prognostic index). The latter distinguishes three prognosis categories: good (normal LDH, dNLR < 3), intermediate (abnormal LDH or dNLR > 3) and poor (abnormal LDH and dNLR > 3).

Treatment schedule and morphological monitoring

Nivolumab (3 mg/kg) was administered by IV infusion for 30 min every 2 weeks until PD, unacceptable toxicity, or death. Tumor evaluation by computed tomodensitometry (CT) and/or magnetic resonance imaging (MRI) was performed every 2 months until PD according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or immune (i)RECIST 1.1 criteria.

Thyroid function screening and classification of thyroid dysfunction

Thyroid function screening was performed before (< 3 months) and during treatment with Nivolumab according to ESMO Guidelines for each cycle and then every 6 weeks after cycle 4 [19]. Thyroid function test (TFT) including TSH, free T4 (fT4), free T3 (fT3) were measured by immunochemiluminescence (Centaur XPT Siemens). Antithyroid antibodies (Abs) including anti-thyroid peroxidase antibodies (TPOAb), TSH receptor antibodies (TRAbs) were measured by immunofluorescence (Kryptor Thermo Fischer Brahms). Reference laboratory values were: TSH, 0.4–4.0 mIU/L; fT4, 11.5–22.7 pmol/L; fT3, 3.5–6.5 pmol/L; TPOAb, < 60 kIU/L and TRAb, < 1.8U/L.

Given that most of TD was asymptomatic, we did not use CTCAE criteria for the classification of TD. The following abnormalities of thyroid function tests were taken into consideration:

1. Patients with abnormalities of TSH level were classified in the group "Thyroid Dysfunction+" (TD(+)) and those with normal TSH level were classified in the group "Thyroid Dysfunction" (TD(−)). In case of normal TSH with an isolated abnormality of peripheral hormone fT4 and/or fT3, the patient was classified in the "Thyroid Dysfunction" group (TD(−))
2. According to the level of peripheral thyroid hormones (i.e. fT3 and fT4): subclinical and overt thyroid dysfunctions were defined as an abnormal TSH level, without and with at least one abnormality of the peripheral hormones (fT3, fT4), respectively.
3. According to TSH level: thyroid dysfunction was regarded as moderate with TSH level range of 0.1–0.4 mIU/L or 4.0–10 mIU/L and severe with TSH level range of ≤ 0.1 mUI/L or ≥ 10 mUI/L
4. According to thyroid dysfunction subtype, patients were classified into 3 following categories: isolated hypothyroidism, isolated hyperthyroïdism and hyperthyroidism followed by hypothyroidism (hyper/hypothyroidism).

Clinical endpoints

Patients were followed up until the occurrence of the primary endpoints or until January 1, 2019. The Co-primary clinical endpoints were OS and progression-free survival (PFS) according to TD(+) and TD(−). The secondary clinical endpoints were objective response rate (ORR), disease control rate (DCR) and duration of response according to TD(+) and TD(−). We also performed a subgroup analysis according to the severity and subtype of thyroid dysfunction.

OS was defined as the time from the first administration of nivolumab until death. PFS was defined as the time from the first administration of nivolumab until PD or death, whichever came first. The ORR was defined as either partial or complete response. DCR was defined as the percentage of patients who achieved complete response, partial response and stable disease. The duration of response was defined as the time between the first objective response and PD. A response beyond the 12-month timepoint was regarded as a prolonged response.

Statistics

Quantitative variables were expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR), according to their distribution. They were compared using a non-parametric Mann–Whitney *U* test. Categorical variables were expressed as percentages and compared using a Chi-square test (or Fisher's exact test). The survival analysis was carried out using the Kaplan–Meier curves and the log-rank test to compare OS and PFS between the two groups. A Cox proportional hazard regression model was used for multivariable analysis to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and PFS, using a backward stepwise selection of variables according to their clinical relevance or if $p < 0.2$ in univariable analysis. All statistical tests were two-sided and $p < 0.05$ indicated a statistically significant difference. All analyses were performed on XLSTAT 2019.2.2.

Results

Population and patients characteristics

Among the 194 eligible patients, 60 were excluded. One hundred thirty-four (69.1%) were finally included in the study from July 20, 2015 to June 30, 2018. Flowchart of the study is illustrated in Fig. 1.

The mean age was 62.5 years (SD: 8.9). Ninety-four patients (70.1%) were male and 97.7% of patients were current or former smokers. The WHO performance score was 0 or 1 for 77.3% of patients. Patient's pathological subtypes were: squamous cell carcinoma (26.1%), adenocarcinoma (71.6%) and undifferentiated carcinoma (2.2%). Among them, 93.3% of them had a stage IV disease. Brain metastasis was reported in 29.1% of patients. Nivolumab was prescribed in second-line for 75.4% of patients, at least in third-line for others. Half of the patients had already been treated with radiotherapy (51.5%) and 3% had previously received another immunotherapy treatment. PD-L1 status was known in 44 patients (32.8%), with expression > 5% in 22.7% of them. The LIPI score was good in 28% of patients, intermediate in 40.8% and poor in 31.2%. Mean Pre-Nivolumab TSH level was 1.70 mIU/L (SD: 0.98). The patient's characteristics are presented in Table 1.

Thyroid dysfunction (+) and thyroid dysfunction (−) groups

Among the 134 patients included, 40 (29.9%) presented with at least one TSH abnormality during follow-up and were assigned to the TD(+) group. Seventy-four patients (70.1%) had no abnormal thyroid function (i.e. normal values of TSH, fT4 and fT3) and 20 patients had isolated abnormalities of fT4 and/or fT3 values and were assigned to the TD(−) group. The median time before the onset of TD was 54 days (IQR 36–104).

There was no significant between group difference in age, sex, WHO performance index, smoking status, past treatment regimens, PD-L1 expression and pre-nivolumab TSH level. However, there was a non-significant difference in histological subtype of cancer [squamous cell carcinoma: 40% in TD(+) vs. 20.2% in TD(−),$p = 0.055$]. The two groups were significantly different in tumor stage [stage IIIb: 15% in TD(+) vs. 3.2% in TD(−),$p = 0.012$] and in LIPI score [good LIPI score: 41.2% in TD(+) vs. 20.3% in TD(−),$p = 0.039$].

The characteristics of the TD(+) and TD(−) groups are presented in Table 1. Non-thyroid IRAEs occurred more frequently in TD(+) patients than TD(−) patients (67.5% vs. 39.4%, $p = 0.003$). In addition, EGFR ($n = 1$) mutation, ROS ($n = 1$) and ALK ($n = 1$) translocation were observed in TD (−) patients.

Thyroid dysfunction (+) severity and subtypes

In the TD(+), 12 patients (30%) had subclinical and 28 (70%) overt thyroid dysfunction (70%). Subclinical TD included 5 patients with isolated thyrotoxicosis, 7 patients with isolated hypothyroidism and no patient with hyper/hypothyroidism. Overt thyroid dysfunction included 7 patients with isolated thyrotoxicosis, 12 patients with isolated hypothyroidism and 9 patients with hyper/hypothyroidism. According to the TSH level, TD was classified as

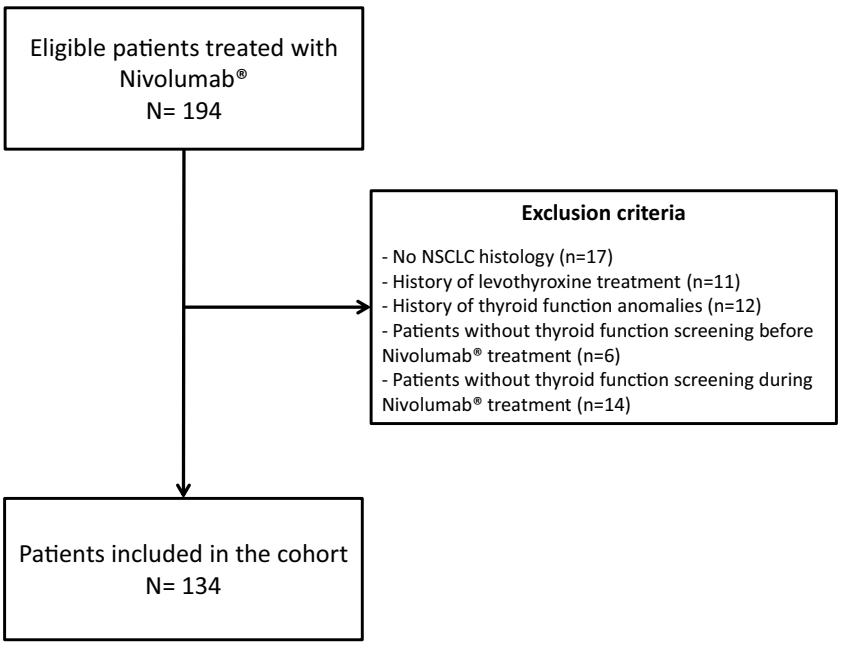

Fig. 1 Flowchart of the study

Table 1 Patients characteristics

Characteristics	Total $n=134$	TD(+) $n=40$	TD(−) $n=94$	p value (TD(+) vs TD(−)
Patients				
Age				
Mean ± SD	62.5 ± 8.9	63.2 ± 9.2	62.2 ± 8.8	0.561
≥ 70 years old (%)	26 (19.4)	8 (20)	18 (19.1)	0.909
Sex. male (%)	94 (70.1)	27 (67.5)	67 (71.3)	0.662
Smoking ($n=131$) (%)				
Current or former smoker	128 (97.7)	39 (100)	89 (96.7)	0.254
WHO Performance Score ($n=119$) (%)				
0–1	92 (77.3)	33 (86.8)	59 (72.8)	0.089
≥ 2	27 (22.7)	5 (13.2)	22 (27.2)	
Tumor				
Pathologic subtypes (%)				
Squamous cells carcinoma	35 (26.1)	16 (40)	19 (20.2)	
Non-squamous cells carcinoma	96 (71.6)	23 (57.5)	73 (77.7)	0.055
Undifferentiated	3 (2.2)	1 (2.5)	2 (2.1)	
Stage (%)				
IIIB	9 (6.7)	6 (15)	3 (3.2)	**0.012**
IV	125 (93.3)	34 (85)	91 (96.8)	
Brain metastasis (%)	39 (29.1)	12 (30)	27 (28.7)	0.882
Tumoral PD-L1 expression ($n=44$) (%)				
≤ 5%	34 (77.3)	11 (73.3)	23 (79.3)	0.654
> 5%	10 (22.7)	4 (26.7)	6 (20.7)	
Past regimens				
Number of regimens (%)				
1	101 (75.4)	33 (82.5)	68 (72.3)	
2	26 (19.4)	5 (12.5)	21 (22.3)	0.409
≥ 3	7 (5.2)	2 (5)	5 (5.3)	
Radiotherapy (%)	69 (51.5)	20 (50)	49 (52.1)	0.822
Other ICI (%)	4 (3)	1 (2.5)	3 (3.2)	0.830
Best therapeutic response ($n=120$) (%)				
Partial or complete response (%)	27 (22.5)	6 (16.2)	21 (25.3)	
Stable disease	45 (37.5)	15 (40.5)	30 (36.1)	0.546
Progression	48 (40)	16 (43.2)	32 (38.6)	
Biology				
LIPI score (dNLR > 3 et LDH > ULN) ($n=93$) (%)				
0: good	26 (28)	14 (41.2)	12 (20.3)	
1: intermediate	38 (40.9)	14 (41.2)	24 (40.7)	**0.039**
2: poor	29 (31.2)	6 (17.6)	23 (39)	
Pre-Nivolumab TSH level(mIU/L) Mean ± SD	1.70 ± 0.98	1.90 ± 1.06	1.61 ± 0.94	0.126

dNLR; derived neutrophil/leukocyte-lymphocyte ratio; ICI: immune checkpoint inhibitors; LIPI: lung immune prognostic index; PD-L1: programmed cell death ligand 1; TD(+): thyroid dysfunction (+) group

moderate in 19 patients and severe in 21 patients. Three patients required a temporally discontinuation of the Nivolumab treatment due to transient treatment-induced hyperthyroidism. According to CTCAE classification, there was no grade 4–5 thyroid IRAE.

Survival and response to Nivolumab treatment in TD (+) and TD (−) groups

The median follow-up was 10.4 months. In the entire cohort, median OS was 12.2 months (IQR 4.3–29.1) and median

PFS was 2 months (IQR 1.6–9.1). The ORR was 23.1% and the DCR was 40.3%. A prolonged response was observed in 11.2% of patients.

At the database lock, 89 patients (66.4%) had died: 15 patients in the TD(+) (37.5%) and 74 patients (78.7%) in the TD(−) group ($p < 0.001$). The median OS in TD(+) group was significantly longer than in TD(−) group: 29.8 months (95% CI 18.8-not reached) vs. 8.1 months (95% CI 5.5–11.5), respectively ($p < 0.001$) (Fig. 2a). In multivariable analysis, the occurrence of a TD remained an independent factor associated with better OS (HR = 0.32 [0.16; 0.62]; $p < 0.001$; Table 2).

During Nivolumab therapy, 27 (67.5%) of TD(+) patients vs. 85 (90.4%) of TD(−) had progressive disease. The median PFS in TD(+) group was significantly longer than in TD(−) group [8.7 months (95% CI 5.3–15.1) vs. 1.7 months (95% CI 1.6–1.9), $p < 0.001$] (Fig. 2b). In multivariable analysis, the occurrence of a TD remained an independent predictive factor associated with better PFS (HR = 0.36 [0.21; 0.62]; $p < 0.001$; Table 2).

ORR in the TD(+) group was 47.5% versus 12.8% in the TD(−) group ($p < 0.001$). DCR in the TD(+) group was 70% versus 27.7% in the TD(−) group ($p < 0.001$). Median treatment duration was longer in TD(+) versus TD(−) group [5.5 months (IQR 3–13.5) versus 1 month (IQR: 1–3) respectively; $p < 0.001$]. A prolonged response was observed in 20% of patients with the occurrence of TD and 7.4% of patients without ($p = 0.035$). However, the median duration of response did not differ statistically between the TD(+) and TD(−) groups [15.4 months (IQR: 10.1–21.3)

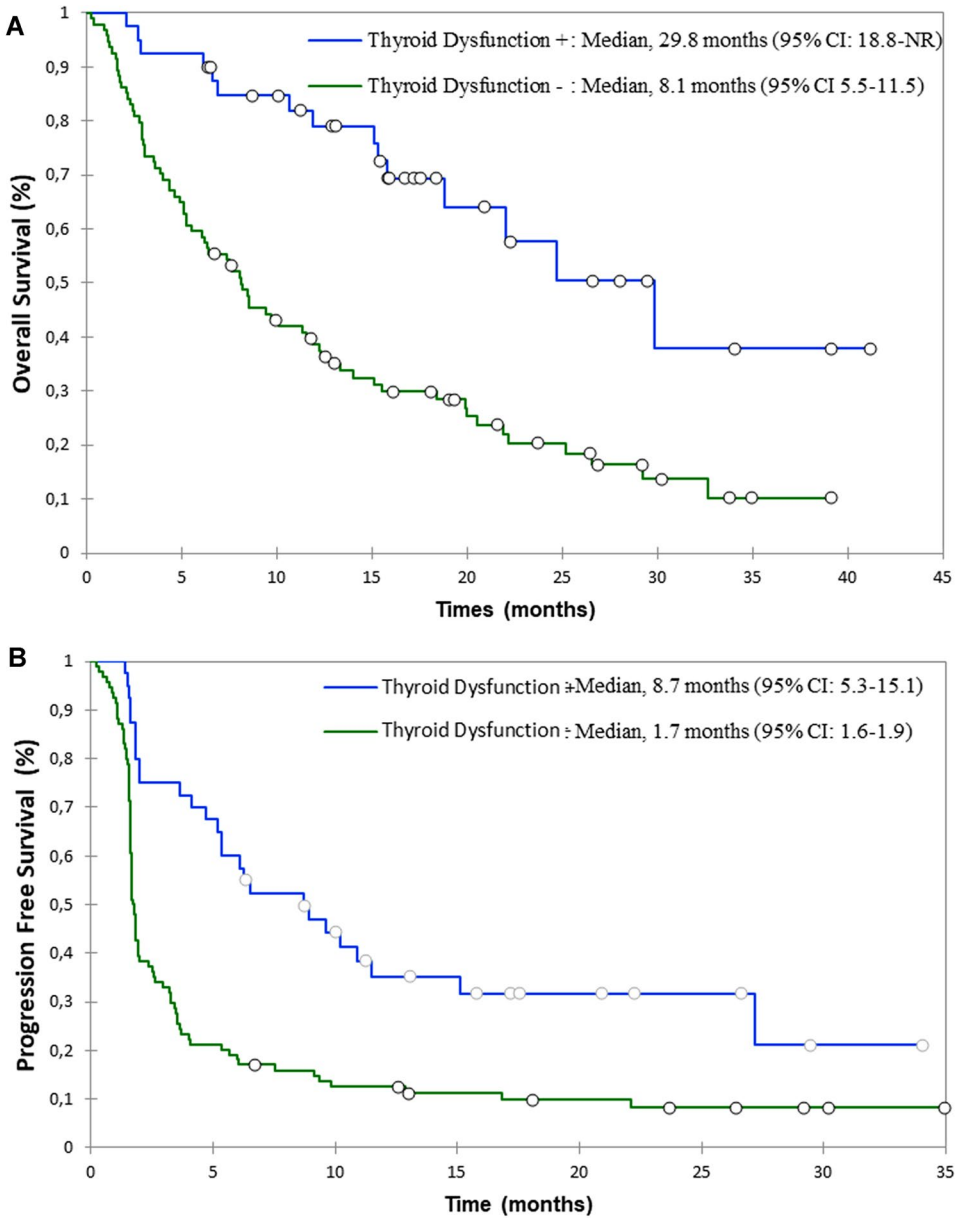

Fig. 2 OS (**a**) and PFS (**b**) in patients according to in TD(+) ad TD(−) group

Table 2 Univariate and multivariate analyses using Cox regression for overall survival and progression-free survival according to thyroid dysfunction and others characteristics of the cohort

	Overall survival		Progression-free survival	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Univariate				
Sex (male)	1.07 [0.64; 1.78]	0.788	1.24 [0.78; 1.96]	0.366
Age > 70 ans	1.02 [0.64; 1.61]	0.944	0.9 [0.59; 1.36]	0.611
WHO Performance Score ≤ 1	0.42 [0; 0.69]	**< 0.001**	0.64 [0.4; 1.02]	0.063
Current or former smoker	1.27 [0.4; 4.02]	0.685	1.94 [0.61; 6.2]	0.261
Squamous cell carcinoma positive	0.99 [0.6; 1.62]	0.971	0.9 [0.59; 1.38]	0.638
Stade IIIB positive	0.38 [0.12; 1.19]	0.096	0.49 [0.21; 1.12]	0.089
Brain metastasis positive	0.7 [0.43; 1.13]	0.141	0.74 [0.49; 1.13]	0.164
Number of past regimens (≥ 3)	0.63 [0.38; 1.05]	0.075	0.8 [0.52; 1.23]	0.304
History of others ICI (%)	1.54 [0.56; 4.2]	0.402	1.26 [0.46; 3.44]	0.647
Radiotherapy positive	0.96 [0.63; 1.46]	0.858	1.21 [0.83; 1.75]	0.315
PD-L1 expression > 5%	1.1 [0.4; 2.97]	0.858	1.1 [0.47; 2.55]	0.825
LIPI score (poor prognosis)	1.82 [1.06; 3.13]	**0.029**	1.59 [0.99; 2.56]	0.056
Non-thyroid IRAEs positive	0.32 [0; 0.55]	**< 0.001**	0.4 [0; 0.61]	**< 0.001**
TD (+)	0.45 [0; 0.69]	**< 0.001**	0.44 [0; 0.64]	**< 0.001**
Multivariate				
WHO Performance Score ≤ 1	0.33 [0.17; 0.64]	**< 0.001**	0.37 [0.2; 0.69]	**0.002**
Non-thyroid IRAEs positive	–	–	0.43 [0.26; 0.72]	**0.001**
TD (+)	0.32 [0.16; 0.62]	**< 0.001**	0.36 [0.21; 0.62]	**< 0.001**

Bold indicates *p* value < 0.05

ICI: immune checkpoint inhibitors; IRAEs: immune related adverse; LIPI: lung immune prognostic index; events; PD-L1: programmed cell death ligand 1; PS: performance score; TD(+): thyroid dysfunction (+) group

and 9.6 months (IQR 6.9–18.7), respectively, $p = 0.330$]. In subgroup analysis, median OS and PFS did not differ according to the severity and subtype of TD (Fig. 3). ORR and DCR also did not differ according to the severity and subtype of TD (Table 3).

Discussion

Our study showed that patients who experienced a TD induced by nivolumab in second or third-line treatment of advanced NSCLC have a better response and a longer survival irrespective of TD severity and subtype.

These results highlighted a statistically significant association between nivolumab-induced thyroid IRAEs and nivolumab efficacy. The occurrence of TD under nivolumab treatment was a predictor of clinical benefit (i.e. response and OS). Median OS and PFS were longer in TD(+) vs. TD(−): 29.8 months vs. 8.1 months ($p < 0.001$) and 8.7 months vs. 1.8 months ($p < 0.001$), respectively. The differences observed were greater than those reported by Kim et al. [16] [median OS:3.9 vs. 2.3 months ($p = 0.025$); median PFS: 3.9 vs. 2 months ($p = 0.014$) in patients with and without thyroid dysfunction, respectively]. This can be explained by the between-study difference in the stage of NSCLC (IV in Kim et al. vs. IIIb/IV in our study) and the median follow-up time (89 days in Kim et al. study vs. 10.4 months in our study) [16]. Our results were comparable with those of Yamauchi et al. (median OS: "not reached" vs. 14.2 months ($p = 0.025$); median PFS: 5.8 vs. 2.3 months ($p = 0.01$) in NSCLC patients with and without TD, respectively) [17].

Cox proportional multivariable analysis showed that the nivolumab-induced TD and a WHO performance index ≤ 1 were the only two independent protective factors of a longer OS. The latter was consistent with the literature [28, 29]. Our study found additional helpful data on WHO performance correlation and PFS. In line with other studies, the nivolumab-induced non-thyroid IRAEs were associated with PFS in our study [26, 30, 31]. However, other potential prognostic factors, such as the level of PD-L1 expression and LIPI-score, were not independently associated with OS and PFS in our study. We did not take into account the time duration between nivolumab onset and TD onset in our multivariate Cox model. This could lead to a potential bias as patients with bad prognosis have shorter life expectancy to present with IRAEs [32, 33]. However, given our median 54-day time before the onset of TD and the exclusion of patients without TFTs during follow-up, such potential bias might have less impact on our results, in particular in

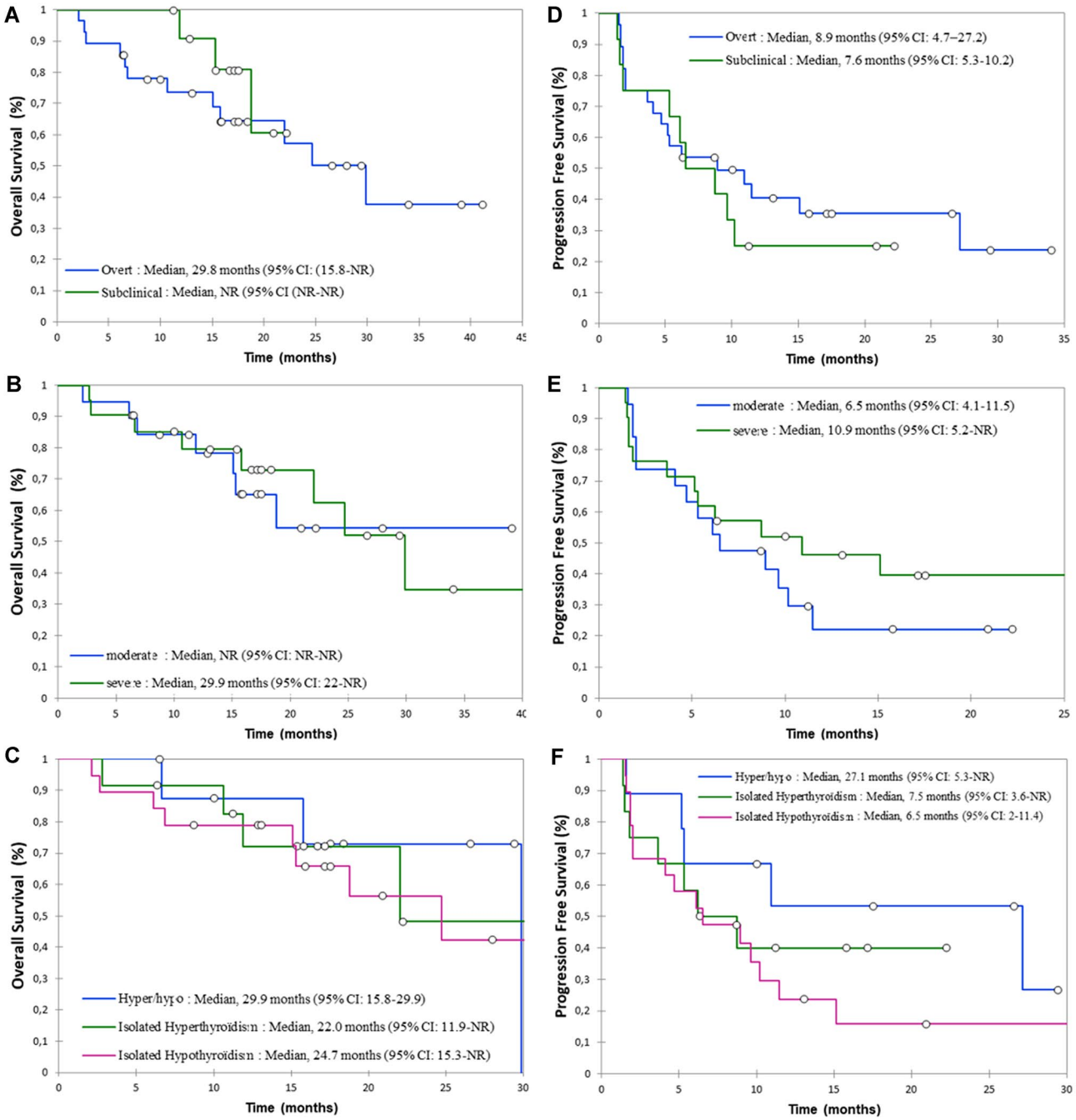

Fig. 3 OS and PFS according to thyroid dysfunction subgroups: subclinical and overt thyroid dysfunction (**a**), moderate and severe thyroid dysfunction (**b**), isolated hypothyroidism, isolated hyperthyroidism and hyper/hypo (**c**) for OS and subclinical and overt thyroid dysfunction (**d**), moderate and severe (**e**), isolated hypothyroidism, isolated hyperthyroidism and hyper/hypo (**f**) for PFS

regard with OS. However, given the association between the nivolumab-induced non-thyroid IRAEs and a longer PFS, further research is warranted to obtain the time duration between nivolumab and non-thyroid IRAEs onset. Finally, stage IIIb and a good LIPI score were more frequent in the TD(+) group. However, these two parameters were not associated with OS and PFS in the multivariate analysis.

One of the strengths of our study was the evaluation of a single anti-PD1 drug (i.e. nivolumab) efficacy in NSCLC according to nivolumab-induced TD subtype and severity. To our knowledge, the study by Kim et al. was the only one previously assessing the association between PD-1 blockade drugs (i.e. pembrolizumab and nivolumab) efficacy and PD-1 blockade-induced TD severity in a subgroup

Table 3 Overall response and disease control rate to Nivolumab according to severity and subtype of thyroid dysfunction

	Overall response rate $n=(\%)$		Disease control rate $n=(\%)$	
		p value		p value
Severity fT3/fT4 levels				
Subclinical	5/12 (41.7)	0.629	7/12 (58.3)	0.292
Overt	14/28 (50)		21/28 (75.0)	
Severity TSH levels				
Moderate	10/19 (52.6)	0.536	12/19 (63.2)	0.369
Severe	9/21 (42.9)		16/21 (76.2)	
Subtype				
Isolated hypothyroidism	9/19 (47.4)	0.820	12/19 (63.2)	0.365
Isolated hyperthyroidism	5/12 (41.7)		8/12 (66.7)	
Hyper/hypothyroidism	5/9 (55.6)		8/9 (88.9)	

of patients with NSCLC [16]. This study demonstrated an improvement in OS and PFS in case of overt TD compared to subclinical TD ($p=0.016$ and 0.026, respectively) [16]. The latter results were not confirmed by the results of our study of a larger population and a longer follow-up. Finally, this is the first study assessing specifically the predictive value of TD according to its subtype in NSCLC. Our results show a trend towards an improvement in OS and tumor response in case of thyroiditis but without significance.

TD was defined as at least one abnormal TSH level during nivolumab therapy. Isolated laboratory abnormalities in fT3 and/or fT4 were not regarded as TD in our study. We believe that such anomalies should be considered as equivocal and could be linked to central causes or other drugs effects. With these criteria, the incidence of TD in our cohort was 29.9% and was similar to studies assessing specifically TD in patients with NSCLC (32.7% in Kim et al. study and 29.1% in Yamauchi et al. study [16, 17]). It is important to note that despite the retrospective nature of our study, only a few patients were excluded due to missing TD screening [no thyroid function screening before nivolumab ($n=6$) or during nivolumab treatment ($n=14$)]. Moreover, patients who did not undergo thyroid function monitoring during Nivolumab® treatment could be regarded as patients with hyperprogressive disease dying before the 2nd or 3rd cycle. This could have led to an overestimation of OS and PFS in our cohort. However, the prognosis and therapeutic response of our cohort were consistent with those of the phase III clinical trials [1, 2] and real-life studies [34, 35].

Understanding the underlying mechanisms of IRAEs and the pathophysiology of the therapeutic response can help at finding optimal predictive factors of immunological agents efficacy. In melanoma patients who received ICI including anti-PD-1 treatment, the skin IRAEs are correlated with survival and therapeutic response [7–9]. This association is thought to be caused by shared antigens between melanoma cells and normal melanocytes [5]. This embryological reasoning can also be hypothesized for the thyroid-IRAEs in NSCLC. Indeed, embryologically, lung and thyroid tissues differentiate from the endoderm. Thyroid transcription factor-1 (TTF-1) controls embryonic development of the thyroid and lung and is expressed in both organs [36, 37]. Koyama et al. study assessed the association between TTF-1 expression in the tumor, thyroid dysfunction occurrence, therapeutic response and survival. TD was associated with therapeutic response and survival but surprisingly the incidence of TD was lower in TTF-1-positive than TTF-1-negative NSCLCs (9% vs. 20%, $p=0.08$). Furthermore, PFS was longer (10.3 months) in patients with TTF-1-negative NSCLC with TD compared to those with TTF-1-positive NSCLC with and without TD and TTF-1-negative NSCLC without TD (4.2, 1.4 and 2.4 months, respectively) [38]. Further assessments of the pathophysiology (or mechanism) of ICI therapeutic response in NSCLC are warranted.

There are some limitations to this study. This is a retrospective and monocentric study and our sample size was potentially not sufficient for subgroup analysis in patients with TD. In addition, even though TFTs were performed almost systematically, Abs assays were often missing in our cohort. Given that the Abs could be negative at the time of diagnosis, this limitation may not have affected our results [39]. We chose not to screen for TD according to the results of morphological and functional explorations (i.e., ultrasonography and thyroid scintigraphy). The latter are not systematically performed in all TD subtypes and are mainly done to differentiate iatrogenic thyroiditis and other diagnoses of hyperthyroidism, especially in the case of severe thyrotoxicosis [21]. We can concur with the need for such morphological and functional explorations to better understand ICI-induced TD especially in diagnosis of thyroiditis.

In conclusion, our study showed that nivolumab-induced TD is associated with improvement of OS and response rate in patients with stage IIIb/IV NSCLC irrespective of TD severity and subtype. However, the potential underlying mechanism of such TD remains unclear. Moreover, our findings need to be further confirmed prospectively. Altogether, further relevant, larger randomized studies are needed.

Author contributions VK, NR are the guarantor of the study. PT, CJ, NR designed the study. PT realized the analysis. PT, CJ, ZA drafted the manuscript. PT, CJ, NR, ZA did the interpretation of data. NR, ZA, GC, GQ, RD, VK revised the manuscript for intellectual content.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest in this work.

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