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Immune Checkpoint Inhibitor Induced Thyroid Dysfunction is a Frequent Event Post-Treatment in NSCLC

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Abstract

Introduction: Thyroid dysfunction is the most frequent endocrine immune related adverse event (irAE) in non-small cell lung cancer (NSCLC), typically arising 3–6 months into immune checkpoint inhibitor (ICI) therapy, but arising after ICI cessation, in some cases. Due to limited post-treatment adverse event reporting requirements on ICI trials, the incidence of ICI-induced thyroid dysfunction arising after therapy is unclear. We investigated ICI-induced thyroid dysfunction in a cohort of 294 NSCLC patients, with a specific focus on the post-treatment setting.

Methods: Retrospective analysis of ICI-induced thyroid dysfunction (clinically acted upon or laboratory only) was performed in 294 UCLA NSCLC patients treated 2012–2018. Clinically acted upon thyroid dysfunction was defined as thyroid diagnosis documentation and/or thyroid medication administration. Laboratory only dysfunction was defined as abnormal thyroid labs in the absence of clinical action. Timing of thyroid dysfunction relative to ICI treatment and thyroid monitoring patterns were also assessed.

Results: 82% (241/294) of ICI treated NSCLC patients had thyroid labs during treatment. Of these 241 patients, 13% (31/241) had clinically acted upon thyroid dysfunction prior to, 8% (18/241) during, and 4% (9/241) after ICI. Most patients, 66% (159/241), did not have thyroid labs after ICI, but in the 53 patients with labs and no prior clinical dysfunction, 17% (9/53) developed clinical dysfunction after ICI. In these 9 patients, median time from ICI initiation to dysfunction was 253 days. Two patients with post-treatment laboratory only dysfunction were observed.

Conclusions: ICI-induced thyroid dysfunction arising post-treatment appears more common than previously appreciated, warranting additional evaluation.

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Keywords

Non-Small Cell Lung Cancer (NSCLC); Immune related adverse events (irAE); Thyroid Dysfunction; Immune Checkpoint Inhibitor (ICI); Anti-PD-(L)1 Therapy

1. Introduction

The emergence of anti-programmed cell death protein 1 (PD-1)/anti-programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) has revolutionized treatment of this disease [1–4]. However, with the increased use of ICIs in NSCLC, a new class of adverse events has emerged, termed immune related adverse events (irAEs). irAEs are thought to be a result of non-specific immune activation and most commonly affect the skin, liver, gastrointestinal tract, and endocrine systems [5–7]. Importantly, the most frequent endocrine irAEs associated with anti-PD-(L)1 therapy is thyroid dysfunction, which can manifest in a variety of manners [8–13]. While patients with active auto-immune conditions were excluded from the clinical trials that led to ICI approval in NSCLC, patients with hypothyroidism that was stable on hormone replacement were not excluded from these studies [1, 2, 14].

Thyroid dysfunction can be asymptomatic or may be accompanied by a variety of non-specific symptoms including fatigue, weight gain, cold intolerance, constipation.[15]. Owing to its non-specific presentation, symptoms alone are unreliable for diagnosis. Instead, evaluation of laboratory values including Thyroid Stimulating Hormone (TSH), free Thyroxine 4 (fT4), and Triiodothyronine (T3) is relied upon to make the diagnosis [16]. If left untreated, thyroid dysfunction can profoundly affect a patient's quality of life, as well as his or her ability to tolerate anti-cancer therapy [17–19]. However, thyroid dysfunction can be effectively treated with prompt medical intervention, so timely detection and treatment of thyroid dysfunction is imperative [18, 20–22].

The detection of ICI induced thyroid dysfunction is complicated by the fact that ICI induced endocrinopathies can have a delayed onset, with occurrences of ICI associated hypothyroidism typically occurring three to six months after the initiation of anti-PD-(L)1 therapy [23, 24]. This has likely led to a general underreporting of ICI induced thyroid dysfunction on clinical trials, since patients are typically only followed for AE occurrence for 30 days after treatment cessation [23, 25, 26]. Further, although many electronic health records (EHRs) are structured such that patients receiving ICI containing treatment regimens have thyroid laboratory values assessed at baseline and with every cycle, post-ICI thyroid monitoring is not mandatory[27]. These factors suggest that the incidence of ICI-induced thyroid dysfunction in the post-treatment setting may be greatly underrecognized, underreported, and undertreated in patients with NSCLC.

Although ICI induced thyroid dysfunction is a well-recognized phenomena in NSCLC, no prior study has specifically evaluated the incidence of thyroid dysfunction arising after completion of ICI therapy, nor the adequacy of thyroid monitoring in the post-treatment setting. Thus, we hypothesized that the incidence of ICI induced thyroid dysfunction after treatment is higher than currently appreciated. To evaluate this hypothesis, we investigated

the adequacy of thyroid function monitoring and incidence of thyroid dysfunction both during and after ICI therapy in a cohort of 294 NSCLC patients treated with an ICI, in the absence of concurrent chemotherapy, at The University of California, Los Angeles (UCLA) between May 2012 and December 2018.

2. Methods

2.1 Patients

We retrospectively evaluated the medical records of NSCLC patients treated at UCLA with an ICI, in the absence of concurrent chemotherapy, between May 2012 and December 2018. An ICI was defined as an anti-PD-(L)1 monoclonal antibody either alone or in combination with an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody. Patients who were treated with an ICI plus chemotherapy were excluded to avoid confounding our analysis with chemotherapy induced toxicity. Patients without at least one set of thyroid labs obtained during treatment, defined as a TSH with reflex total triiodothyronine (T3), total thyroxine (T4), and/or free T4 from the same blood draw, were excluded. The remaining patients were then assessed for clinically acted upon thyroid dysfunction arising before, during, or after ICI.

2.2 Clinical Management Definitions

Clinically acted upon thyroid dysfunction was defined as either a thyroid gland disease diagnosis (hypothyroidism or hyperthyroidism) by ICD-9/10 codes and/or documentation of a thyroid directed medication prescription (e.g levothyroxine) in the electronic health record (EHR). Further, clinically acted upon thyroid dysfunction was considered to be pre-existing if it occurred prior to the date of first ICI administration, to have occurred during ICI if it arose between the first and last date of ICI administration, and after ICI therapy if it arose after date of last ICI administration. For patients treated sequentially with multiple ICIs, classification of thyroid dysfunction timing was based on first ICI administered. For patients with clinically acted upon thyroid dysfunction during or after ICI, we also evaluated whether they required beta blocker therapy for symptom management and whether these patients had orbitopathies related to their thyroid disease. Clinically acted upon thyroid dysfunction during and after ICI was further characterized as either central or peripheral based upon pre-existing guidelines for diagnosing thyroid dysfunction based on laboratory abnormalities, a distinction that was confirmed by an endocrinologist (Dr. Rettinger) [28, 29].

2.3 Thyroid Abnormality Definitions

To assess for ICI induced thyroid dysfunction that was not clinically acted upon, those patients without clinically acted upon thyroid dysfunction were subsequently evaluated for abnormal paired thyroid lab values. We defined an instance of abnormal paired thyroid lab values as an abnormal TSH with either an abnormal total T3, total T4, or free T4 on a single blood draw. Due to the unclear significance of a single abnormal set of lab values, we further restricted our analysis to patients who had persistently abnormal thyroid lab values. Persistence was defined as abnormal paired thyroid lab values for at least two consecutive blood draws for which TSH plus total T3, total T4, or free T4 were out of range.

(Supplementary Figure 1) Grading of adverse events in patients with clinically acted upon thyroid dysfunction was retrospectively determined via CTCAE V5.

2.4 Timing of Clinically Acted Upon Thyroid Dysfunction in Relation to ICI Therapy

To assess the timing of clinically acted upon thyroid dysfunction in relation to ICI therapy we reported the median number of days from the administration of the first dose of ICI therapy to the first instance of (1) an abnormal TSH lab value, (2) an abnormal TSH plus paired total T3, total T4, or free T4, and (3) clinically acted upon thyroid dysfunction. For patients whose thyroid dysfunction was clinically acted upon after ICI treatment, we also reported the median number of days from the administration of the last dose of ICI therapy to the occurrence of these same three variables.

2.5 Definitions of Clinical Follow Up

An evaluation of oncology follow-up post-ICI therapy was performed. Oncology follow-up was defined as an appointment with an oncologist occurring at a date following the last cycle of ICI, which did not include the end of treatment assessment for patients on a clinical trial. Adequacy was reported as a percentage of patients with such a follow-up appointment. In a secondary analysis, patients who did not survive after ICI treatment were excluded. Survival was defined as the patient being alive at least two months after the last dose of ICI. For patients with no documented follow-up appointments, we ascertained whether these patients had been seen by a non-UCLA oncologist prior to or after being treated with ICI. For those patients with EHR documentation of outside oncologists, efforts were made to request records of appointments and subsequent thyroid lab testing from the outside oncologist. (Supplementary Figure 2)

3.6 Adequacy of Thyroid Monitoring and Post-ICI Oncology Follow-Up

We assessed the adequacy of thyroid laboratory monitoring during and after ICI therapy, as well as oncology follow-up post-ICI treatment, in our patient population. IRB approval was obtained for all relevant analyses, including use of the EHR to manually extract thyroid lab values and oncologist appointment dates. Adequacy of thyroid function assessment was ascertained for two timepoints: (a) during ICI treatment and (b) after ICI treatment. Adequacy of thyroid function assessment during ICI was calculated by dividing the number of times thyroid function labs were drawn over the total number of cycles of ICI given. This value was converted to a percentage and reported as an average. Adequacy of thyroid lab evaluation after ICI was calculated by dividing the number of times thyroid function tests were drawn over the number of months elapsed since the last cycle of ICI treatment. This value was also reported as an average. ICI cycle was defined as a discrete administration of an ICI followed by treatment free interval. Cycle numbers were identified via documentation in the EHR. For patients treated with ICI on clinical trial, efforts were also made to obtain paper records of thyroid function testing from the trial. Of note, patients who received an ICI on a clinical trial, but for whom paper records could not be located to document their thyroid function while on trial, were deemed to have insufficient data for adequacy of thyroid analysis while on ICI, rather than deemed to not have adequate monitoring during ICI, and excluded from further analyses.

3.7 Rationale for Thyroid Lab Testing in Patients After ICI Cessation

In the patients without clinically acted upon thyroid dysfunction before/during ICI therapy who had at least one set of thyroid labs evaluated after ICI, we sought to evaluate the rationale for thyroid lab evaluation after ICI in two manners. First, we searched each patient's EHR for symptoms known to be associated with thyroid dysfunction, such as "fatigue", "weight loss", "weight gain", "cold intolerance", and/or "heat intolerance," to asses if such symptoms were present at the time of thyroid lab evaluation and may have prompted evaluation. Second, we manually reviewed all medical provider notes corresponding to the date(s) thyroid labs were obtained to ascertain whether a reason was stated by the provider for ordering thyroid function tests.

2.8 Statistical Analysis

A univariate Cox proportional hazards approach was taken to analyze if patient factors such as gender (male, female), race (White, Asian, Other), smoking status (smoker, non-smoker, smoking status unknown), and ICI regimen type (Durvalumab/Tremelimumab, Nivolumab, Nivolumab/Ipilimumab, Pembrolizumab, or Other) affected time to event (thyroid dysfunction) in the 210 patients without pre-existing thyroid dysfunction. Time to event was defined in two different ways since some patients had events during (n=18) and some after ICI treatment (n=9): 1) time to clinically acted upon thyroid dysfunction for patients who had the event during ICI treatment, whereas patients who did not have clinically acted upon thyroid dysfunction during ICI treatment were censored at their end-of-treatment time and 2) time to clinically acted upon thyroid dysfunction during or after ICI treatment whereas patients without either of these two events were censored at the end of their treatment time.

A univariate logistic regression analysis was performed to evaluate how factors such as gender (male, female), race (White, Asian, Other), smoking status (smoker, non-smoker, smoking status unknown), or ICI regimen type (Durvalumab/Tremelimumab, Nivolumab, Nivolumab/Ipilimumab, Pembrolizumab, or Other) affected likelihood of having clinically acted upon thyroid dysfunction only during (n=18), only after (n=9), or either during or after ICI (n=27). This analysis was performed for the 210 patients without pre-existing thyroid dysfunction and done in three ways: 1) likelihood of event occurring during ICI, 2) likelihood of event occurring after ICI, and 3) likelihood of event occurring during or after ICI. Statistical analyses were performed using IBM SPSS V27, Armonk NY and p-values <0.05 were considered statistically significant.

3. Results

3.1 Clinically Acted Upon Thyroid Dysfunction

Of the 294 NSCLC patients identified at UCLA treated with ICI, in the absence of concurrent chemotherapy, 241 had at least one set of thyroid labs obtained during treatment. These 241 patients were used for all subsequent analyses of thyroid evaluation adequacy. Demographics of these patients are shown in Table 1. Of note, a disproportionate number of patients with nonsquamous NSCLC [78% (189/241)] were present in our data set and the majority of patients were treated with ICI on a clinical trial, 84% (203/241). Nearly half

of patients were treatment naïve (44%, 107/241) and never smokers (45%, 108/241). The most common ICI received was single agent pembrolizumab in 50% (122/241) of patients, followed by nivolumab in 20% (49/241), and nivolumab/ipilimumab in 11% (27/241). The majority, 58% (140/241) of patients self-identified as White, non-Hispanic.

These 241 patients were then further subdivided into three categories: (A) Patients with pre-existing clinically acted upon thyroid dysfunction prior to ICI (n=31, 13%), (B) Patients with clinically acted upon thyroid dysfunction first arising during ICI (n=18, 8%), and (C) Patients without clinically acted upon thyroid dysfunction prior to or during ICI (n=192, 80%). Of note, 97% (30/31) of the patients with pre-existing thyroid dysfunction were receiving thyroid supplementation therapy prior to ICI administration. Clinically acted upon thyroid dysfunction that arose during ICI therapy was observed in 8% (18/241) of patients, with thyroid directed therapy initiated during ICI in 94% (17/18) of these patients. After ICI, 4% (9/241) of patients developed clinically acted upon thyroid dysfunction, 67% (6/9) of whom received thyroid hormone replacement after ICI (Table 2A). None of the patients with clinically acted upon thyroid dysfunction during or after ICI required beta blocker therapy for symptom management. The most common thyroid gland disease diagnosis prior to, during, or after ICI in patients was hypothyroidism. Specifically, 96% (22/23) of patients with a thyroid gland diagnosis prior to ICI had hypothyroidism, while 89% of the diagnoses made during ICI (16/18), and 67% after ICI (6/9), were hypothyroidism. (Table 2B). In the nine patients with post-ICI thyroid dysfunction, none had orbitopathies related to their thyroid disease. Of the 18 patients with clinically acted upon thyroid dysfunction during ICI therapy, 15 patients had peripheral hypothyroidism and 1 had peripheral hyperthyroidism. For 2 patients we were unable to determine central vs peripheral thyroid dysfunction because they were treated on a clinical trial and we were not able to review the paper lab results.. Of the 9 patients with clinically acted upon thyroid dysfunction occurring after ICI therapy, 6 patients had peripheral hypothyroidism and 1 had peripheral hyperthyroidism. For 2 patients we were unable to determine central vs peripheral thyroid dysfunction because they were treated on a clinical trial and we were not able to review the paper lab results. (Supplementary Table 1).

3.2 Adequacy of Thyroid Lab Evaluation and Oncology Follow-up After ICI

During ICI, thyroid labs were evaluated at a similar rate for patients receiving therapy on a clinical trial, 73% of ICI cycles had a concurrent thyroid lab evaluation, or as standard of care, 79% of cycles. However, after the last cycle of ICI only 34% (82/241) of patients had at least one set of thyroid labs evaluated. In these 82 patients, thyroid labs were evaluated at an average of 0.96 times/month (Supplementary Table 2). Given these findings, we next assessed whether patients saw an oncologist after completion of ICI therapy to evaluate how this impacted thyroid lab surveillance.

Seventy-two percent (173/241) of patients had oncology follow up after completion of ICI therapy. In these patients with post-ICI oncology follow up, 47% (81/173) had at least one set of thyroid labs evaluated after ICI (Table 3A). Conversely, in the 68 patients without oncology follow-up, only one had thyroid labs evaluated after ICI. Since patient death could be one reason for the lack of oncology follow-up and/or thyroid lab evaluation after ICI,

we next assessed the number of patients who were alive at least 2 months after last ICI administration. Of the original 241 patients identified, 63 died within 2 months of last dose of ICI (37 within one month and 26 between one and two months), leaving 178 patients that were still alive at least 2 months after last ICI administration. In these 178 surviving patients, 59% (105/178) did not have at least one set of thyroid labs evaluated after ICI despite the fact that 64% (67/105) of these patients did have oncology follow-up after ICI (Table 3B).

3.3 Incidence of Clinically Acted Upon Thyroid Dysfunction After ICI

As discussed above, 4% (9/241) of patients developed clinically acted upon thyroid dysfunction after ICI. However, the majority of the 241 patients in our analysis did not undergo laboratory monitoring for the occurrence of thyroid dysfunction after ICI. This likely under-represents the number of patients developing thyroid dysfunction after ICI. To more accurately assess the incidence of post-ICI thyroid dysfunction, we restricted our analysis to the 53 patients that had at least one set of thyroid labs evaluated after ICI and did not have clinically acted upon thyroid dysfunction that arose before or during ICI therapy. In these patients, 17% (9/53) first developed clinically acted upon thyroid dysfunction after ICI cessation (Table 4). Finally, since subsequent systemic anti-cancer therapy could be the cause of thyroid dysfunction arising after ICI, we evaluated the post-ICI clinical course in these 9 patients. This analysis did not identify a clear relationship between the therapeutic agents received after ICI and thyroid toxicity in any of these nine patients (Supplementary Table 3). As such, we hypothesize that ICI therapy led to the development of post-ICI clinically acted upon thyroid dysfunction in these patients. In these 9 patients with clinically acted upon thyroid dysfunction after treatment with ICI, 2 patients had a grade 1 adverse event, 6 patients had a grade 2 event, and 1 patient had grade 3 event requiring hospitalization for profound hypothyroidism.

3.4 Rationale for Thyroid Lab Testing in Patients After ICI Cessation

In the 53 patients without clinically acted upon thyroid dysfunction before/during ICI therapy who had at least one set of thyroid labs evaluated after ICI, we sought to evaluate the rationale for thyroid lab evaluation after ICI. Our analysis revealed that symptoms concerning for thyroid dysfunction prompted evaluation in 6% (3/53) of patients, while an explicit reason for thyroid lab testing post-ICI was present in the EHR for 32% (16/50) of the remaining patients. In these 19 patients with identifiable rationale for thyroid lab evaluation in the post-ICI setting, 16% (3/19) had clinically acted upon thyroid dysfunction identified after ICI. Similarly, in the 34 patients with thyroid labs evaluated after ICI, but no identifiable rationale for evaluation, 18% (6/34) had clinically acted upon thyroid dysfunction arising after ICI.

3.5 Timing of Thyroid Dysfunction in Relation to ICI Therapy

Next, we evaluated the timing of thyroid dysfunction in relation to ICI therapy. In patients with clinically acted upon thyroid dysfunction that occurred during ICI therapy, the median number of days from first ICI dose to abnormal TSH was 43, with clinical action occurring at a median of 96 days. In patients who had clinically acted upon thyroid abnormalities that first occurred after ICI, the median number of days from first ICI dose to an abnormal TSH was 182 days and the median number of days to clinical action was 253. Furthermore, these

patients had an abnormal TSH a median of 64 days after their last dose of ICI and a median of 126 days elapsed from last dose of ICI to clinical action for their thyroid dysfunction (Table 5).

3.6 Thyroid Laboratory Abnormalities Arising in Patients without Clinically Acted Upon Thyroid Dysfunction

Since we previously showed that patients frequently develop ICI induced thyroid dysfunction that is not clinically acted upon,[19] we sought to evaluate the occurrence of thyroid laboratory abnormalities in the 183 patients without clinically acted upon dysfunction. In these 183 patients, 15% (28/183) had laboratory evidence of thyroid dysfunction, defined as an abnormal TSH with either an abnormal total T3, total T4, or free T4 on a single blood draw. Four patients experienced laboratory only abnormalities prior to ICI treatment, 22 during treatment, and 2 after treatment (Table 6). Due to the unclear significance of a single thyroid laboratory abnormality, we further restricted our analysis to only include patients that had persistently abnormal thyroid laboratory abnormalities that were not clinically acted upon. We found that 11 patients fulfilled this definition, two who exhibited persistent dysfunction prior to ICI therapy, eight with persistent dysfunction during ICI, and one with persistent dysfunction after ICI (Supplementary Table 4).

3.7 Factors Impacting Clinically Acted Upon Thyroid Dysfunction

A Cox proportional hazards analysis was performed to assess how factors such as gender, race, smoking status, and ICI regimen influenced time to clinically acted upon thyroid dysfunction. There was no statistically significant difference in time to event when comparing time to clinically acted upon thyroid dysfunction for gender, race, smoking, or ICI regimen type ($p>0.05$) (Supplementary Table 8). Further, a univariate logistic regression analysis was performed to assess how these same factors influenced the likelihood of having clinically acted upon thyroid dysfunction during or after ICI therapy. No statistically significant difference in likelihood of having an event was found when comparing gender, race, smoking status, or ICI regimen ($p>0.05$) (Supplementary Table 9).

4. Discussion

This single-center, retrospective analysis evaluating the longitudinal occurrence of ICI induced thyroid dysfunction in NSCLC patients found that more than half of patients, 66% (159/241), did not have thyroid function laboratory values assessed after cessation of therapy. In the 53 patients without evidence of pre-existing thyroid dysfunction who had thyroid values assessed after therapy, 17% (9/53) developed clinically meaningful thyroid dysfunction after ICI. These findings are striking and suggest that ICI induced thyroid dysfunction after therapy cessation is not being appropriately monitored for in NSCLC and, as a result, may be occurring at a much higher rate than currently appreciated.

The rate of ICI induced clinically acted upon thyroid dysfunction during therapy in our analysis, 8% overall (7% hypothyroidism), is consistent with prior reports. Specifically, on the Checkmate-057 and KEYNOTE-001 trials, ICI induced thyroid dysfunction was identified in 11% and 12% of patients, respectively, while hypothyroidism was reported at a

rate of 7% in both trials (Checkmate-057: 19/287 patients, KEYNOTE-001: 34/495 patients) [2, 3, 30]. Importantly, the slightly higher rates of all-cause thyroid dysfunction observed on these trials can likely be accounted for by the fact that these percentages are inclusive of isolated TSH abnormalities, which did not meet the definition for clinically acted upon thyroid dysfunction in the current study. Thus, the observed congruence between the rate at which we retrospectively identified clinically meaningful ICI induced thyroid dysfunction during therapy and the rate previously reported on trial, suggests our definition of clinically acted upon ICI induced thyroid dysfunction is an appropriate one.

As ICI trials typically only require short irAE follow-up reporting after therapy cessation, 30 days on both Checkmate-057 and KEYNOTE-010, little is currently known about the rate of ICI induced thyroid dysfunction post-treatment [3, 30]. Specifically, Couey *et al.* showed that median duration of AE reporting on ICI trials is 90 days, but median off-treatment interval to delayed immune-related events (DIRE), defined as any irAEs occurring after 90 days, was 6 months [23, 30]. Further, Guaraldi *et al.* found that ICI related thyroid dysfunction occurs much later in patients receiving PD-1 inhibitors, mean 151 days after initiation, compared to 45 days in those receiving CTLA-4 inhibitors [24]. For ICI-related thyroid dysfunction secondary to hypophysitis, thyroid dysfunction would be expected to persist without spontaneous recovery even at a time significantly after the inciting event, in contrast to thyroiditis. Our data shows that in patients who first experienced clinically acted upon thyroid dysfunction after ICI, the median time to an abnormal TSH after initiation of ICI treatment was 182 days and thyroid function was not clinically acted upon until a median of 253 days. We also found that significant time can elapse between last dose of ICI and the development of clinically meaningful thyroid dysfunction, as it took a median of 64 days from last ICI dose to an abnormal TSH and a median of 126 days until thyroid dysfunction was acted upon. Taken together these findings suggest that limited post-trial reporting periods may be underrepresenting the true incidence of ICI-induced thyroid dysfunction due to delayed onset of these irAEs after cessation of therapy.

In our study, we found that 4% (9/241) of patients developed clinically acted upon thyroid dysfunction after cessation of ICI therapy. However, we believe this number grossly underestimates the true incidence of ICI induced thyroid dysfunction because the majority of the 241 patients analyzed, 66% (159/241), did not have thyroid function tests evaluated after discontinuation of ICI therapy. Thus, we restricted our subsequent analyses to include only those patients who (1) did not have a history of clinically acted upon thyroid dysfunction identified prior to or during ICI, since these patients had already developed thyroid abnormalities before end of treatment and (2) had at least one set of thyroid labs evaluated after ICI therapy, since post-treatment ICI induced thyroid dysfunction can only be accurately recognized if a clinician is evaluating thyroid function laboratory values after therapy cessation. In this more restrictive population of 53 patients, we found that 17% (9/53) developed clinically meaningful thyroid dysfunction after ICI therapy and that none of these 9 patients were treated with subsequent anti-cancer therapies that were likely to cause the observed thyroid abnormalities.

Since patients experiencing symptoms suspicious for thyroid dysfunction may have been preferentially tested for dysfunction after treatment, we also evaluated the rate at which

concerning symptoms, or an explicit reason for testing, was documented in the EHR and found that this occurred in only about one-third of patients. Even more striking was the fact that the rate of post-ICI clinically acted upon thyroid dysfunction in patients with an explicit reason for testing, 16%, was lower than the rate identified in the approximately two-thirds of patients without documented rationale for testing, 18%. Thus, we do not think preferential testing of symptomatic patients explains the significant level of thyroid dysfunction identified after ICI. Taken together, these findings suggest that the risk of developing ICI induced thyroid dysfunction post-treatment in NSCLC is significant, underscoring the need for continued thyroid monitoring after cessation of therapy.

One potential explanation for the low rate of thyroid evaluation observed after ICI in our analysis is the mature nature of our data set. Specifically, approximately one-third, 37% (89/241), of patients included in our evaluation were enrolled on the KEYNOTE-001 trial at UCLA, as early as 2012, when little was known of the potential toxicities of pembrolizumab in NSCLC [2]. Thus, it is feasible that when these patients came off trial, the treating oncologists were not aware that ICI-related thyroid dysfunction can manifest many months after cessation of therapy. Another potential explanation for this finding is patient death shortly after ICI therapy resulting in lack of subsequent monitoring, but this does not seem to be the primary force driving this observation, since only 41% (73/178) of patients who survived at least 2 months after last dose of ICI had subsequent thyroid lab evaluation. Furthermore, of these 73 patients, 20 had clinically acted upon thyroid dysfunction either before or during ICI therapy. Thus, only 29% (53/178) of these patients without clinically acted upon thyroid dysfunction before or during ICI therapy had subsequent thyroid lab evaluation.

Because not all patients who had thyroid lab abnormalities due to ICI treatment experienced clinically acted upon dysfunction, we sought to characterize the thyroid function test abnormalities present in patients who did not have clinically meaningful thyroid dysfunction identified prior to, during, or after ICI therapy. Of these 183 patients, 15% (28/183) had laboratory evidence of thyroid dysfunction and of these 28 patients, 11 patients had persistent thyroid function test abnormalities in two or more consecutive blood draws. These results suggest that even with adequate thyroid function monitoring during ICI therapy, a subset of patients are developing ICI induced thyroid dysfunction that is not being clinically acted upon.

One potential mechanistic explanation for the incidence of thyroid dysfunction after ICI therapy cessation is the observation that although the serum half-life of anti-PD-1 antibodies ranges from 12–20 days, pharmacodynamic experiments show that the occupancy of PD-1 receptors with anti-PD-1 antibodies is >70% even 2 months or more after the initial dose of anti-PD-1 [31]. Thus, anti-PD-1 antibodies may continue to cause irAEs even after the unbound antibody has been cleared from patient serum. Another potential mechanistic explanation for the delayed onset of irAEs is the observation that ICIs induce T-cell receptor (TCR) expansion by increasing the number of unique rearranged TCR V-β sequences, as well as B-cell mediated autoantibody production [13, 32–35]. Thus, it is possible that continued rearrangement of TCR sequences induced by ICI therapy eventually leads to the development of self-reactive TCRs. The timing of irAEs would therefore be dependent

on when a rearrangement results in a TCR that recognizes self. However, a definitive mechanism for thyroid dysfunction following ICI therapy has yet to be elucidated, which is a clear weakness of this study since we cannot definitively know that the instances of clinically acted upon thyroid dysfunction identified are a result of ICI therapy or ICI independent. That said, as discussed above, the rate of clinical dysfunction during ICI is consistent with prior reports and ICI induced thyroid dysfunction first arising after cessation of therapy, is a well characterized phenomenon [2, 3, 23, 24]. Rather than serving as a mechanistic evaluation of post-treatment ICI induced thyroid dysfunction, or a definitive evaluation of causation, the purpose of this study is to shed light on an important clinical observation, namely that a substantial proportion of ICI treated NSCLC patients appear to be developing thyroid dysfunction after therapy with no clear alternative explanation.

As such, our study's central findings have important clinical implications. If the number of NSCLC patients developing new onset ICI induced thyroid dysfunction after cessation of therapy is truly in the range of 17%, there is an urgent need to more rigorously evaluate thyroid function post-ICI. Even if the rate of ICI induced thyroid dysfunction is half, 8.5%, or even a quarter, 4.25%, of the rate observed in this study, the lack of thyroid lab monitoring after ICI therapy in more than half of NSCLC patients is unacceptable. Although the ICI induced endocrinopathies are often irreversible, they can be easily diagnosed and treated with hormone replacement therapy, materially improving patient quality of life [36]. However, if physicians are not routinely checking thyroid labs post-ICI, as our study suggests, they cannot accurately identify and treat post-ICI thyroid dysfunction. Ample evidence suggests that thyroid dysfunction following ICI can occur many months after cessation of therapy, emphasizing the importance of prolonged post-treatment monitoring [23, 24, 37]. Therefore, it is of high importance to diagnose these abnormalities when present to optimize decision-making in patient management.

Important limitations of this analysis include the narrow scope of cancers represented (NSCLC), the single-center setting, the limited number of patients evaluated, and underrepresentation of certain patient demographics In addition, we were unable to employ other diagnostic modalities for thyroid function evaluation, such as thyroid ultrasound, due to the retrospective nature of our data set. Our data set was skewed towards white, non-smoking, lung adenocarcinoma patients treated on a clinical trial. However, our statistical analyses revealed that factors such as gender, race, smoking status, and ICI therapy regimen were not associated with either clinically acted upon thyroid dysfunction occurrence or timing of such an event. Of note, although most of the patients analyzed received ICIs on trial, there was no difference between frequency of thyroid function testing between patients receiving ICIs on clinical trials compared to standard of care. Additionally, the data presented herein is from a single center, restricted to patients treated by a limited number of investigators, and retrospectively obtained. It is possible the inadequacy of thyroid function testing after ICI may be due to a system-wide lack of awareness of irAEs following ICI therapy, but this seems unlikely since the investigators included have been utilizing ICIs in NSCLC since 2012, three years prior to regulatory approval.[4] Additionally, UCLA Health system implements best practices across disciplines, including thyroid function testing with every cycle of ICI administration, albeit with no inherent best practice for evaluation after cessation of therapy. Future studies will evaluate longitudinal occurrence of

ICI induced endocrinopathies across tumor types, in a much larger patient population, as well as functional translational assays and imaging modalities such as thyroid ultrasound to identify mechanisms underlying occurrence. Finally, we chose to exclude patients who received concurrent chemoimmunotherapy from this study to limit the potential confounding effects of chemotherapy on thyroid function but since chemoimmunotherapy is standard of care in NSCLC, it will be important for future studies to evaluate the effects of combined therapy on the development of thyroid dysfunction in the post-treatment setting.

5. Conclusion

In conclusion, our retrospective analysis suggests that post-ICI induced thyroid dysfunction is more common in NSCLC than previously recognized. However, our data suggests that the majority of ICI treated NSCLC patients are not receiving adequate post-ICI thyroid monitoring. As such, many cases of ICI induced thyroid dysfunction that occur post-treatment are likely going undiagnosed, compromising patient care. Taken together, these findings underscore the need for more frequent thyroid function monitoring in ICI treated NSCLC patients after completion of therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

AL reports the following: (1) Employment Company: Boston Scientific Immediate family member (wife) (2) Stock (<5% equity) Company: Boston Scientific Immediate family member (wife) (3) Commercial Research Grants Daiichi Sankyo Calithera Biosciences AstraZeneca Dracen Pharmaceuticals WindMIL (4) Consultant/Advisory Board AstraZeneca Bristol-Myers Squibb Leica Biosystems Jazz Pharmaceuticals Novocure Pfizer MorphoSys Oncocyte.

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References

[1]. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, Sakai H, Albert I, Vergnenegre A, Peters S, Syrigos K, Barlesi F, Reck M, Borghaei H, Brahmer JR, O'Byrne KJ, Geese WJ, Bhagavatheeswaran P, Rabindran SK, Kasinathan RS, Nathan FE, Ramalingam SS, Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer, N Engl J Med 381(21) (2019) 2020–2031. [PubMed: 31562796]

[2]. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn M-J, Felip E, Lee J-S, Hellmann MD, Hamid O, Goldman JW, Soria J-C, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki

GM, Roach C, Emancipator K, Gandhi L, Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer, 10.1056/NEJMoa1501824 (2015).

[3]. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr., Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR, Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer, 10.1056/NEJMoa1507643 (2015).

[4]. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR, Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer, N Engl J Med 373(2) (2015) 123–35. [PubMed: 26028407]

[5]. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, Izzeddine H, Marabelle A, Champiat S, Berdelou A, Lanoy E, Texier M, Libenciuc C, Eggermont AM, Soria JC, Mateus C, Robert C, Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination, Nat Rev Clin Oncol 13(8) (2016) 473–86. [PubMed: 27141885]

[6]. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA, National Comprehensive Cancer N, Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline, J Clin Oncol 36(17) (2018) 1714–1768. [PubMed: 29442540]

[7]. N. National Comprehensive Cancer, Management of Immunotherapy-Related Toxicities Version 3.2021, 2021. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. (Accessed 7/6/2021 2021).

[8]. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, Rodriguez C, Cambridge L, Rizvi H, Wolchok JD, Merghoub T, Rudin CM, Fish S, Hellmann MD, Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer - ScienceDirect, Ann Oncol 28(3) (2017) 583–589. [PubMed: 27998967]

[9]. de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B, A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors, Horm Metab Res 51(3) (2019) 145–156. [PubMed: 30861560]

[10]. Carter Y, Sippel RS, Chen H, Hypothyroidism after a cancer diagnosis: etiology, diagnosis, complications, and management, Oncologist 19(1) (2014) 34–43. [PubMed: 24309982]

[11]. Patel NS, Oury A, Daniels GA, Bazhenova L, Patel SP, Incidence of Thyroid Function Test Abnormalities in Patients Receiving Immune-Checkpoint Inhibitors for Cancer Treatment, The Oncologist 23(10) (2018) 1236–1241. [PubMed: 29769383]

[12]. Wang PF, Chen Y, Song SY, Wang TJ, Ji WJ, Li SW, Liu N, Yan CX, Immune-Related Adverse Events Associated with Anti-PD-1/PD-L1 Treatment for Malignancies: A Meta-Analysis, Front Pharmacol 8 (2017) 730. [PubMed: 29093678]

[13]. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, Lambotte O, Mariette X, Prat A, Suárez-Almazor ME, Immune-related adverse events of checkpoint inhibitors, Nature Reviews Disease Primers 6(1) (2020) 38.

[14]. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu TE, Badin F, Ready N, Hiltermann TJN, Nair S, Juergens R, Peters S, Minenza E, Wrangle JM, Rodriguez-Abreu D, Borghaei H, Blumenschein GR Jr., Villaruz LC, Havel L, Krejci J, Corral Jaime J, Chang H, Geese WJ, Bhagavatheeswaran P, Chen AC, Socinski MA, CheckMate I, First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer, N Engl J Med 376(25) (2017) 2415–2426. [PubMed: 28636851]

[15]. Leng O, Razvi S, Hypothyroidism in the older population, Thyroid Res 12 (2019) 2. [PubMed: 30774717]

[16]. LeFevre ML, Force USPST, Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement, Ann Intern Med 162(9) (2015) 641–50. [PubMed: 25798805]

[17]. Hartmann K, Thyroid Disorders in the Oncology Patient, J Adv Pract Oncol 6(2) (2015) 99–106. [PubMed: 26649243]

[18]. Winther KH, Cramon P, Watt T, Bjorner JB, Ekholm O, Feldt-Rasmussen U, Groenvold M, Rasmussen AK, Hegedus L, Bonnema SJ, Disease-Specific as Well as Generic Quality of Life Is Widely Impacted in Autoimmune Hypothyroidism and Improves during the First Six Months of Levothyroxine Therapy, PLoS One 11(6) (2016) e0156925. [PubMed: 27257805]

[19]. Lisberg A, Tucker DA, Goldman JW, Wolf B, Carroll J, Hardy A, Morris K, Linares P, Adame C, Spiegel ML, Wells C, McKenzie J, Ledezma B, Mendenhall M, Abarca P, Bornazyan K, Hunt J, Moghadam N, Chong N, Nameth D, Marx C, Madrigal J, Vangala S, Shaverdian N, Elashoff DA, Garon EB, Treatment Related Adverse Events Predict Improved Clinical Outcome in NSCLC Patients on KEYNOTE-001 at a Single Center, Cancer Immunol Res (2018).

[20]. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA, 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis, Thyroid 26(10) (2016) 1343–1421. [PubMed: 27521067]

[21]. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM, American R Thyroid Association Task Force on Thyroid Hormone, Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement, Thyroid 24(12) (2014) 1670–751. [PubMed: 25266247]

[22]. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH, 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism, European Thyroid Journal 7(4) (2018) 167–186. [PubMed: 30283735]

[23]. Couey MA, Bell RB, Patel AA, Romba MC, Crittenden MR, Curti BD, Urba WJ, Leidner RS, Delayed immune-related events (DIRE) after discontinuation of immunotherapy: diagnostic hazard of autoimmunity at a distance, Journal for ImmunoTherapy of Cancer 7(1) (2019) 165. [PubMed: 31269983]

[24]. Guaraldi F, La Selva R, Samà MT, D'Angelo V, Gori D, Fava P, Fierro MT, Savoia P, Arvat E, Characterization and implications of thyroid dysfunction induced by immune checkpoint inhibitors in real-life clinical practice: a long-term prospective study from a referral institution, J Endocrinol Invest 41(5) (2018) 549–556. [PubMed: 29043574]

[25]. Abdel-Wahab N, Suarez-Almazor ME, Frequency and distribution of various rheumatic disorders associated with checkpoint inhibitor therapy, Rheumatology (Oxford) 58(Suppl 7) (2019) vii40–vii48. [PubMed: 31816084]

[26]. Michot JM, Lappara A, Le Pavec J, Simonaggio A, Collins M, De Martin E, Danlos FX, Ammari S, Cauquil C, Ederhy S, Barreau E, Belkhir R, Berdelou A, Lazarovici J, Chanson P, Izzedine H, Seferian A, Le Pajolec C, Baldini C, Martin-Romano P, Mariette X, Robert C, Besse B, Hollebecque A, Varga A, Laghouati S, Mateus C, Voisin AL, Soria JC, Massard C, Marabelle A, Champiat S, Lambotte O, The 2016–2019 ImmunoTOX assessment board report of collaborative management of immune-related adverse events, an observational clinical study, Eur J Cancer 130 (2020) 39–50. [PubMed: 32172197]

[27]. Davies M, Duffield EA, Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events, Immunotargets Ther 6 (2017) 51–71. [PubMed: 28894725]

[28]. Kumar V AA, Aster JC, Robbins SL, Cotran RS, The Endocrine System. In: Kumar V, Abbas AK, Aster JC, Robbins SL, Cotran RS. Robbins and Cotran pathologic basis of disease. 9th ed., Elsevier/Saunders, Philadelphia, PA, United States 2015.

[29]. Jameson JL, Mandel SJ, Weetman AP, Disorders of the Thyroid Gland, in: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J (Eds.), Harrison's Principles of Internal Medicine, 19e, McGraw-Hill Education, New York, NY, 2014.

[30]. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, Molina J, Kim J-H, Arvis CD, Ahn M-J, Majem M, Fidler MJ, de Castro G, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB, Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, The Lancet 387(10027) (2016) 1540–1550.

[31]. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, Stankevich E, Pons A, Salay TM, McMiller TL, Gilson MM, Wang C, Selby M, Taube JM, Anders R, Chen L, Korman AJ, Pardoll DM, Lowy I, Topalian SL, Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates, J. Clin. Oncol 28(19) (2010) 3167–3175. [PubMed: 20516446]

[32]. Weinmann SC, Pisetsky DS, Mechanisms of immune-related adverse events during the treatment of cancer with immune checkpoint inhibitors, Rheumatology 58(Supplement_7) (2019) vii59–vii67. [PubMed: 31816080]

[33]. Robert L, Tsoi J, Wang X, Emerson R, Homet B, Chodon T, Mok S, Huang RR, Cochran AJ, Comin-Anduix B, Koya RC, Graeber TG, Robins H, Ribas A, CTLA4 blockade broadens the peripheral T-cell receptor repertoire, Clin Cancer Res 20(9) (2014) 2424–32. [PubMed: 24583799]

[34]. Oh DY, Cham J, Zhang L, Fong G, Kwek SS, Klinger M, Faham M, Fong L, Immune Toxicities Elicted by CTLA-4 Blockade in Cancer Patients Are Associated with Early Diversification of the T-cell Repertoire, Cancer Res 77(6) (2017) 1322–1330. [PubMed: 28031229]

[35]. Peiffert M, Cugnet-Anceau C, Dalle S, Chikh K, Assaad S, Disse E, Raverot G, Borson-Chazot F, Abeillon-du Payrat J, Graves' Disease during Immune Checkpoint Inhibitor Therapy (A Case Series and Literature Review), Cancers (Basel) 13(8) (2021).

[36]. Nogueira E, Newsom-Davis T, Morganstein DL, Immunotherapy-induced endocrinopathies: assessment, management and monitoring, Ther Adv Endocrinol Metab 10 (2019) 2042018819896182. [PubMed: 31903179]

[37]. Ryder M, Callahan M, Postow MA, Wolchok J, Fagin JA, Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution, Endocrine-Related Cancer 21(2) (2014) 371–381. [PubMed: 24610577]

Table 1.

Demographics of 241 pts with Advanced NSCLC Treated at UCLA with an Immune Checkpoint Inhibitor (ICI) in the Absence of Concurrent Chemotherapy

	N = 241
Age-Year	
Median	67
Range	26–91
Gender – no (%)	
Female	125 (52%)
Male	116 (48%)
Race/Ethnicity	
White, non-Hispanic	140 (58%)
Asian	36 (15%)
Hispanic	13 (5%)
Black/African American	8 (3%)
American Indian	8 (3%)
Other	36 (15%)
Previous Lines of Therapy – no. (%)	
0	107 (44%)
1–3	97 (40%)
≥3	37 (15%)
ICI Regimen Received by 5 or More Patients in UCLA Cohort * – no. (%)	
Pembrolizumab	122 (50%)
Nivolumab	49 (20%)
Nivolumab/Ipilimumab	27 (11%)
Other regimen[1]	17 (7%)
Durvalumab/Tremelimumab	11 (5%)
Avelumab	8 (3%)
Durvalumab	7 (3%)
ICI on Clinical Trial vs. SOC[a] * – no. (%)	
Clinical Trial	203 (84%)
SOC	38 (16%)
Smoking Status – no. (%)	
Ever	130 (54%)
Never	108 (45%)
Unknown	3 (1%)
Histology – no. (%)	
Squamous Cell Carcinoma	42 (17%)
Nonsquamous	189 (78%)

	N = 241
NSCLC unspecified histology	10 (4%)

[a] SOC: standard of care

[b] PD-L1: programmed death ligand 1

[*] ICI Agent Received and Clinical Trial vs SOC was determined by the first ICI agent the patient received.

[1] Six patients received atezolizumab containing regimens, 1 patient received an avelumab containing regimen, 1 patient received cemiplimab, 6 patients received nivolumab containing regimens, 1 patient received a pembrolizumab containing regimen, 1 patient received utomilumab, 1 patient received a durvalumab containing regimen

Table 2A.

Clinically Acted Upon Thyroid Dysfunction in ICI Treated UCLA NSCLC Patients

Occurrence of Thyroid Dysfunction in Relation to ICI Therapy	Thyroid Diagnosis or Medication Administered [N=241 (% patients)]
A) Pre-Existing Thyroid Dysfunction	**31/241 (13%)**
Diagnosis Documented	23 (10%)
Thyroid Medication Administered	30 (12%)
B) Thyroid Dysfunction Arising During ICI	**18/241 (8%)**
Diagnosis Documented	18 (8%)
Thyroid Medication Administered	17 (7%)
C) Thyroid Dysfunction Arising After ICI	**9/241 (4%)**
Diagnosis Documented	9 (4%)
Thyroid Medication Administered	6 (3%)

*One patient with a thyroid diagnosis did not receive a thyroid medication and eight patients with a history of thyroid medication were not given a formal diagnosis.

Table 2B.

Clinically Acted Upon Thyroid Dysfunction in ICI Treated UCLA NSCLC Patients Stratified by Diagnosis

Occurrence of Thyroid Dysfunction in Relation to ICI Therapy	Thyroid Diagnosis [N=241 (% patients)]
A) Pre-Existing Thyroid Dysfunction	**31/241 (13%)**
Hypothyroidism	22 (9%)
Hyperthyroidism	1 (1%)
No diagnosis, but medication administered*	8 (3%)
B) Thyroid Dysfunction During ICI	**18/241 (8%)**
Hypothyroidism	16 (7%)
Hyperthyroidism	2 (1%)
C) Thyroid Dysfunction After ICI	**9/241 (4%)**
Hypothyroidism	6 (2%)
Hyperthyroidism	3 (1%)

*Eight patients that received a thyroid medication did not have a formal thyroid diagnosis in the documented in the electronic health record.

Table 3A.

Medical Oncology Follow Up After Cessation of ICI Therapy

	Percentage of Patients (n=241)
Patients with medical oncology follow-up after cessation of ICI therapy	72% (173/241)
Patients without medical oncology follow-up after cessation of ICI therapy	28% (68/241)

Table 3B.

Medical Oncology Follow Up After Cessation of ICI Therapy in Patients Surviving at Least 2 Months after ICI Completion

	Percentage of Patients (n=178)
Patients alive at least 2 months after cessation of ICI therapy with medical oncology follow-up after ICI	78% (139/178)
Patients alive at least 2 months after cessation of ICI therapy without medical oncology follow-up after ICI	22% (39/178)

Table 4A.

Analysis of Thyroid Laboratory Evaluation in ICI Treated NSCLC Patients After Completion of ICI Therapy

	Percentage of patients (Total n=241)
No thyroid labs obtained after ICI	66% (159/241)
≥1 set of thyroid labs obtained after ICI	34% (82/241)
≥1 set of thyroid labs obtained after ICI AND No evidence of clinically acted upon thyroid dysfunction prior to or during ICI therapy	22% (53/241)

Table 4B.

Incidence of Newly Diagnosed Clinically Acted Upon Thyroid Dysfunction After Cessation of ICI Therapy in Patients with ≥1 Set of Thyroid Labs Obtained after ICI

	Percentage of patients (Total n=53)
Clinically acted upon dysfunction arising after ICI in Patients with ≥1 Set of Thyroid Labs Obtained after ICI	17% (9/53)

Table 5.

Timing of Thyroid Abnormalities in Patients with Clinically Acted Upon Thyroid Abnormalities with Respect to ICI Administration

Thyroid Dysfunction Arising During ICI Therapy	
A) Median Number of Days to Abnormal TSH From First Dose of ICI	43
Median Number of Days to Clinically Acted Upon Thyroid Dysfunction From First Dose of ICI	96
Thyroid Dysfunction Arising After ICI Therapy	
A) Median Number of Days to Abnormal TSH From First Dose of ICI[1]	182
Median Number of Days to Clinically Acted Upon Thyroid Dysfunction From First Dose of ICI[*]	253
B) Median Number of Days to Abnormal TSH From Last Dose of ICI	64
Median Number of Days to Clinically Acted Upon Thyroid Dysfunction From Last Dose of ICI	126

[1]For patients with multiple lines of ICI therapy, the date of the first dose was counted from the first line of treatment with an ICI.

[*]Median number of days to clinically acted upon thyroid dysfunction was determined using the date of thyroid associated diagnosis in EHR, or thyroid directed medication prescription, whichever came first chronologically.

Table 6.

Occurrence of Thyroid Abnormalities in Relation to ICI therapy in Patients without Clinically Acted Upon Thyroid Dysfunction*

Patients with Thyroid Laboratory Only Abnormalities	Thyroid Diagnosis [N=183 (% patients)]
A) Thyroid Lab Abnormality First Arising Before ICI	**4/183 (2%)**
Hypothyroidism	2 (1%)
Hyperthyroidism	2 (1%)
B) Thyroid Lab Abnormality First Arising During ICI	**22/183 (12%)**
Hypothyroidism	9 (5%)
Hyperthyroidism	9 (5%)
Euthyroid Sick Syndrome	4 (2%)
C) Thyroid Lab Abnormality First Arising After ICI	**2/183 (1%)**
Hypothyroidism	1 (0.5%)
Hyperthyroidism	1 (0.5%)

*Thyroid abnormalities defined by a single blood draw yielding a TSH and either total T3, total T4, or free T4 that were out of range.