HHS Public Access

Author manuscript

Cancer Immunol Immunother. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Cancer Immunol Immunother. 2022 August ; 71(8): 1795–1812. doi:10.1007/s00262-021-03128-7.

Associations between immune-related thyroid dysfunction and efficacy of immune checkpoint inhibitors – A systematic review and meta-analysis

Yee-Ming Melody Cheung, MBBS[1,2], **Wei Wang, PhD**[3,4], **Bradley McGregor, MD**[5], **Ole-Petter Riksfjord Hamnvik, MBBCh, BAO, MMSc**[1]

[1]Division of Endocrinology, Diabetes, and Hypertension, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA 02115, USA

[2]Department of Medicine, Endocrine Unit, Austin Hospital, The University of Melbourne, Victoria, Australia

[3]Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, USA

[4]Division of Sleep Medicine, Harvard Medical School, Boston, USA

[5]Department of Medical Oncology, Dana-Farber Cancer Institute, and Harvard Medical School, Boston, MA 02215, USA

Abstract

BACKGROUND: There is growing evidence suggesting that the occurrence of immune-related adverse events (irAEs) may be a predictor of immune checkpoint inhibitor (ICI) efficacy. Whether this association extends to all irAEs or just those within particular organs/systems is yet to be resolved. As immune-related thyroid dysfunction (thyroid irAE) is one of the most commonly reported irAEs, this study aims to summarize the available data and determine if thyroid irAE is a surrogate marker for improved cancer outcomes during ICI therapy.

METHODS: PubMed, EMBASE and Cochrane Library were searched up to July 1st 2021 for studies assessing the relationship between thyroid irAE development during ICI therapy and

Address all correspondence and request for reprints to: Ole-Petter Riksfjord Hamnvik, Division of Endocrinology, Diabetes, and Hypertension, Department of Medicine, Brigham and Women's Hospital, 221 Longwood Ave, RFB-2, Boston, MA 02115, ohamnvik@bwh.harvard.edu.

AUTHOR CONTRIBUTIONS

Yee-Ming Melody Cheung had substantial contribution in the conception and design of the manuscript, along with its methodology. She also conducted the statistical analyses and was primarily responsible for drafting the manuscript. She was one of two reviewers responsible for the review and selection of studies for both the systematic review and meta-analysis, as well as for the extracting of data from the selected studies.

Wei Wang had substantial contribution in overseeing and supervising all statistical analyses performed for the meta-analysis. She also contributed to the revisions of the manuscript.

Bradley McGregor had substantial contribution in the drafting and revisions of the manuscript.

Ole-Petter Riksfjord Hamnvik had substantial contribution in the conception and design of the manuscript, along with its methodology. He also contributed to the drafting and revisions of the manuscript. He was one of two reviewers responsible for the review and selection of studies for both the systematic review and meta-analysis, as well as for the extracting of data from the selected studies. He also provided supervision and oversight of the project.

All authors have given approval for this version of the manuscript to be published.

Author disclosures/competing interests

The authors (YC, BM, WW and OH) do not have any disclosures or conflicts of interest

cancer outcomes. Outcome measures of interest include overall survival (OS) and progression free survival (PFS). Sub-group analyses based on cancer type and adjustment for immortal time bias (ITB) were also performed.

RESULTS: Forty-seven studies were included in the systematic review. Twenty-one studies were included in the OS meta-analysis whilst 15 were included in the PFS meta-analysis. Development of thyroid irAE during ICI therapy was associated with improved OS and PFS (OS: HR 0.52, CI 0.43-0.62, p<0.001; PFS: HR 0.58, CI 0.50-0.67, p<0.001). Sub-group analyses involving non-small cell lung cancer populations and studies where ITB was accounted for, observed similar results (HR 0.37, CI 0.24-0.57, p<0.001) and (HR 0.51, CI 0.39-0.69, p<0.001), respectively.

CONCLUSION: Despite the heterogeneity and biases identified, the evidence does suggest that the development of thyroid irAE is associated with anti-tumor effects of ICIs and therefore, can be used as a surrogate marker for clinical response.

Keywords

autoimmune thyroiditis; autoimmune thyroid dysfunction; overall survival; progression free survival; objective response rate

INTRODUCTION

Immune checkpoint inhibitors (ICI) such as inhibitors of programmed cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), have been studied and shown to improve cancer outcomes in a variety of clinical settings, including in locally advanced and metastatic cancer.[1–4] However, by blocking the usual inhibitory signal to the immune system, immune-related adverse events (irAEs) are common. The thyroid has proven to be particularly vulnerable, with immune-related thyroid dysfunction (thyroid irAE) being one of the most frequently described irAEs.[5,6]

Whilst there is growing evidence suggesting that the development of irAEs signifies an enhanced T cell-mediated immunoreaction and therefore, a potentially more efficacious ICI response,[7–10] it remains debated as to whether this relationship extends to all irAEs or only to those that develop within certain organs/systems. Results to date from studies investigating thyroid irAE and cancer outcomes are mixed, with significant heterogeneity between study design, study populations and the methods in which immortal time bias (ITB) is accounted for.

ITB is a key element in determining the effective association between clinical outcomes and a time-dependent variable.[11] It describes the phenomenon where patients who die or whose disease progresses earlier are less likely to develop an outcome, whilst those patients that stayed in the study for a longer time interval have a theoretically increased risk of experiencing an outcome, therefore resulting in a bias. Unfortunately, a significant proportion of the studies investigating the effects of thyroid irAE on cancer outcomes do not account for ITB. A robust review taking into consideration ITB, heterogeneity as well as other potential biases, is therefore required to thoroughly examine and evaluate these studies. We performed a systematic review and meta-analysis (including a sub-group

analysis of studies that accounted for ITB) to determine if the presence of thyroid irAE in patients after the use of ICIs is associated with improved treatment efficacy and cancer outcomes.

METHODS

Search strategy and inclusion criteria

This study is registered with the International Prospective Register of Systematic Reviews, number CRD42021259904. We followed the PRISMA guidelines and employed the Population-Intervention-Comparator-Outcome-Study Design framework to structure the research question and its corresponding literature search.

We searched PubMed, EMBASE and Cochrane Library for studies published up until the 1st of July 2021. The key terms included ("thyroid" "thyroid dysfunction" OR "hypothyroid" OR "hyperthyroid" OR "thyroiditis" OR "immune related adverse event" OR "endocrine") AND ("nivolumab" OR "pembrolizumab" OR "durvalumab" OR "avelumab" OR "atezolizumab" OR "ipilimumab" OR "tremelimumab" OR "cemiplimab" OR "camrelizumab" OR "sintilimab" OR "tislelizumab" OR "toripalimab" OR "PD-1" OR "PD-L1" OR "CTLA-4") AND ("progression free survival" OR "objective response rate" OR "overall survival" OR "survival").

Selection process

Two review authors (YC, OH) independently screened titles and abstracts identified using the above search strategy for eligible studies. The citations of relevant studies were also screened for additional eligible studies.

The predetermined inclusion criteria for the systematic review were:

1. Full text, peer reviewed articles
2. Articles in English
3. The reporting of the correlation between thyroid irAE or endocrine irAEs and treatment outcome during ICI therapy (at least one of: OS or PFS).
4. Studies that only evaluated endocrine irAEs must include a breakdown of the endocrinopathies developed so as to determine the proportionate contribution of thyroid dysfunction to overall cancer outcomes, or specify that thyroid irAE made up the majority of endocrine irAEs.

The additional inclusion criteria for the meta-analysis were:

1. The reporting of OS or PFS outcome data specific to thyroid irAE (as the meta-analysis examines the association of thyroid irAE with cancer outcomes, having outcome data for just immune-related endocrine adverse events was not sufficient to be included in the meta-analysis)

2. The reporting of both hazard ratio (HR) and confidence intervals (CI) for OS or PFS specific to thyroid irAE (studies that only reported an isolated p value, HR or CI were excluded as analyses were unable to be performed)

For both the systematic review and the meta-analysis we excluded reviews, case reports, guidelines, editorials and letters to the editor, and those published as conference abstracts only. Final eligibility and inclusion were determined by the agreement of both reviewers.

Studies included

The electronic literature search identified 2788 citations in PubMed, 789 in EMBASE and 170 in Cochrane Library. After removal of duplicate copies and studies that did not meet the requirements of the inclusion criteria, 101 were retrieved for more detailed, full text evaluation. Fifty-nine studies that passed the initial citation screening were then excluded after full text screening leaving 42 studies that satisfied the systematic review inclusion criteria. After manually reviewing the citations of relevant publications, a further five studies were included in the systematic review.

Twenty-one studies met the criteria to be included in the OS meta-analysis, whilst 15 fulfilled the inclusion criteria for the PFS meta-analysis (Figure 1).

Data extraction and collection

Data were extracted by the same two reviewers, and entered into a pre-designed data-extraction form within Microsoft Excel version 2019 (Microsoft Corporation, Seattle, Washington, USA). Variables collected included: primary disease site, number of participants, study design, type of ICI, percentage of patients developing thyroid irAE, median time to onset of thyroid irAE, biochemical severity of thyroid irAE, number of deaths, OS and PFS in patients with and without thyroid irAE, and whether ITB was accounted for. Of note, there were no overlapping datasets within the studies included in the meta-analysis.

Quality assessment

The Cochrane risk-of-bias tool for non-randomised trials was used to assess the design, conduct and reporting of the included studies.[12]. Studies were classified as low, moderate, serious, critical or unclear risk.

Statistical analysis

Both fixed and random effects model meta-analyses were performed. The generic inverse-variance weighted method was used to estimate overall effect size from the final set of studies reporting OS and/or PFS data in patients with and without thyroid irAE. I^2 statistics were used to estimate the proportion of the variability of the results attributed to heterogeneity rather than sampling error. I^2 levels of 25% or less correspond to a low heterogeneity.[13,14] Given the relatively small size of our final study set along with the moderate levels of heterogeneity identified between the studies included, we have chosen to report all our results based on the random effects model.[15]

Begg funnel plots[16] and Egger's test[17] were performed to detect publication bias. For both tests, significant publication bias was considered when $p<0.05$.

Sub-group analyses were also performed to investigate the effects primary cancer type and ITB have on the development of thyroid irAE during ICI therapy and potential cancer treatment outcomes.

RESULTS

Forty-seven studies were included in the systematic review, 21 studies were included in the OS meta-analysis and 15 were included in the PFS meta-analysis. All 47 studies included were in the setting of advanced or metastatic malignancies. The most common cancers studied were non-small cell lung cancer (NSCLC) followed by melanoma. PD-1 inhibitors were the most commonly prescribed ICI followed by combination therapy (PD-1/PD-L1 inhibitor with a CTLA-4 inhibitor). Forty-one of the 47 studies were retrospective in nature, whilst 6 were prospective. The pooled patient population was 19,115, with the population of individual studies ranging from 40 to 6596 participants. The incidence of thyroid irAE was between 1 to 37.5%. The specifics of each study are summarized in table 1.

Systematic review

Data review according to outcome—Of the 47 studies, 34 were positive[5,18–50] meaning they observed a correlation between thyroid irAE/endocrine irAEs and either a longer OS or PFS. Thirteen studies did not find a statistically significant association between the development of thyroid irAE/endocrine irAEs and ICI efficacy.[6,51–62]

Thirty-one studies observed a significant association between the occurrence of thyroid irAE/endocrine irAE and a longer OS,[5,18,20,21,23–33,35,38–42,44–50,57,63,64] whilst eleven did not.[6,22,51–54,56,58,60–62] Five studies did not include correlations between immune-related endocrine or thyroid dysfunction and OS as an endpoint.[36,43,55,57,59]

Nineteen studies were positive for a longer PFS,[5,18,21,22,24–29,33,36,42,43,46,48,49,55,64] whilst eleven were negative.[6,20,31,45,51,52,55,57,59,60,65] Seventeen studies did not report correlations between endocrine irAE/thyroid irAE and PFS as an endpoint.[23,30,32,35,38–41,47,50,53–56,61–63]

Data review according to type of irAE—Eighteen studies evaluated thyroid irAE exclusively.[5,18,20,26–28,30,31,33,38,41,45–48,52,56,57] Thirteen studies evaluated irAEs in general, but also provided details on thyroid irAE.[6,21,23,39,42,44,49,53,54,59,60,62,64] Sixteen studies evaluated endocrine irAEs where the majority of adverse events were due to thyroid dysfunction.[22,24,25,29,32,35–37,40,43,50,51,55,58,60,61,63] In these 16 studies, 57-91% of the endocrine irAEs were reported as thyroid-related.

Twenty-two [5,18,20,21,23,26–28,30,31,33,38,39,41,42,44–49,64] of the 31 studies that specifically included details of thyroid irAE were positive,[5,18,20,21,23,26–28,30,31,33,38,39,41,42,44–49,52,54,56,57,59,60,62,64] and seven were

negative[6,52–54,56,57,66] Of those that reported on endocrine irAEs, twelve out of 16 studies were positive[22,24,25,29,32,35–37,40,43,50,63] and four were negative.[51,55,58,61]

Data review according to primary tumor—Thirty-three studies evaluated NSCLC/lung populations.[5,6,18,20–28,30,31,33,37–39,41–43,45,47–49,51–53,57,58,60,61,64] Seventeen studies evaluated populations containing only NSCLC [6,18,20–27,48,49,51–53,60,64] (n=4300). Twelve of these 17 studies were positive,[18,20–27,48,49,64] while five were negative.[6,51–53,60] Sixteen studies evaluated NSCLC/lung together along with a mix of other cancers.[5,28,30,31,33,37–39,41–43,45,47,57,58,61] Fourteen of these 16 studies were positive while two were negative.[5,28,30,31,33,37–39,41–43,45,47,57,58] For the majority of these 'mixed cancer' studies, NSCLC remained the predominant primary cancer type.

Thirteen of the 47 studies did not include NSCLC/lung participants as part of their cohort.

Eight studies evaluated participants exclusively with a diagnosis of melanoma (n=2921),[29,36,44,46,54,56,62,63] Of these eight studies, three had negative findings,[54,56,62] and five had positive associations[19,29,36,46,65] with either OS or PFS. Two studies exclusively evaluated participants with renal cell carcinoma (n=441),[32,59] while one study exclusively evaluated participants with urothelial cancer[40] (n=97). All three studies were associated with positive findings. The remaining two studies exclusively investigated populations with head and neck cancers[35,55] (n=197). One was associated with a longer OS[35] whilst the other was a negative study.[55]

The reported incidence of thyroid irAE during ICI monotherapy in the studies comprising non-NSCLC/non-lung populations when compared to studies comprising NSCLC/lung populations were 1-22.6% and 6.2-32.7%, respectively.

Data review according to ICI type—The majority of studies included patients treated with PD-1 inhibitors. Eleven studies evaluated patients treated with nivolumab alone,[5,22,24,26,29,30,32,35,48,52,55] one evaluated patients with nivolumab ± peptide vaccination,[54] five evaluated patients treated with pembrolizumab alone,[20,36,40,64,67] thirteen evaluated patients treated with either nivolumab or pembrolizumab[6,18,25,27,28,31,33,45,49,51,53,58,62] and eight included patients treated with a mix of PD-1/PD-L1 inhibitors or ipilimumab.[21,23,37,38,42,50,56,57] Seven studies included patients where a PD-1/PD-L1 was used in combination with a CTLA-4 inhibitor (combination therapy),[37,43,44,46,47,59,61] two studies evaluated patients treated exclusively with PD-L1 inhibitors[39,41] and one study included patients treated with a combination of PD-1/PD-L1 combined with chemotherapy.[60] Finally, one study included participants treated with ipilimumab after a course of nivolumab.[63] Of the studies where treatment included PD-1 inhibitor monotherapy, 22 were positive and six were negative.[51–53,55,58,62] The two studies[39,41] that evaluated patients treated exclusively with PD-L1 inhibitors were both positive. All seven studies that included patients treated with combination therapy were either positive, or observed a longer OS/PFS that did not reach statistical significance.[43,44,46,47,59–61] The study that evaluated patients treated with nivolumab ± peptide vaccination[54] along with the study that included patients treated with PD-1/PD-L1 combined with chemotherapy, [60] were both negative.

Data review according to biochemical severity—Six studies[5,30,33,46,48,49] conducted sub-group analyses on thyroid irAE based on biochemical severity (subclinical vs. overt hyperthyroidism and hypothyroidism, where overt is defined as biochemical evidence of an abnormal thyroid stimulating hormone [TSH] and free triiodothyronine [fT3] or free thyroxine [fT4] levels whilst subclinical is defined as an abnormal TSH with normal fT3 and fT4 levels). All six studies did not observe a statistically significant correlation between the development of subclinical thyroid states and improved clinical outcomes.

Data review according time to onset of thyroid irAE—Twenty-one studies reported the time to onset of thyroid irAE post ICI treatment.[18,20,26,28–31,33,38,41,44–49,52,54,56,57,61] The earliest median time to onset of thyroid irAE reported was 3.3 weeks whilst the latest was 30 weeks.[52] Ten studies reported time to onset based on the type of thyroid irAE (ie hyperthyroidism vs hypothyroidism)[20,28,30,31,41,45,46,49,57,61] and five differentiated between subclinical and overt thyroid irAE.[28,33,46,49,61] Overt disease along with thyrotoxicosis/hyperthyroidism appeared to occur earlier, whilst subclinical thyroid irAE and hypothyroidism appeared to develop later.

Data review according to ITB—Twenty-five of the 47 studies addressed the confounding effects of ITB.[5,22–25,30–33,36,39,42,51,53,54,57,59–61,63,64] Eighteen of these 25 studies employed landmark analyses[5,22–25,29,32,47,51,53,54,57,59,60,62–64] whilst 7 utilized an extended cox model with time-varying covariates.[30,31,33,36,39,42,47] Two studies performed both landmark and an extended cox model with time-varying covariates as part of their analyses.[47,54] After excluding the 22 studies that did not account for ITB, 17 studies were positive[5,22–25,30–33,36,39,42,47,59,60,63,64] and eight were negative.[51–54,57,59,61,62]

Meta-analysis

Overall survival—Twenty-one studies (n=12,158) fulfilled the criteria for inclusion in the OS meta-analysis.[5,18,20,21,28,30,31,33,38,39,41,42,44–48,51,52,60,61] Thyroid irAE occurrence was significantly associated with longer OS (HR 0.52, CI 0.43-0.62, p <0.001) (Figure 2). Moderate level heterogeneity was detected (I^2=56.8%, p=0.0007). Further sub-group analyses were conducted based on primary cancer type and whether ITB was accounted for. In the seven studies where NSCLC was the only cancer evaluated, patients that developed thyroid irAE appeared to have longer OS (HR 0.37, CI 0.24-0.57, p<0.001) than individuals that did not develop thyroid irAE. Heterogeneity between studies was low (I^2=0%, p=0.8009) (Figure 3A). There were too few studies assessing other cancer types to perform sub-group analyses. Finally, nine studies that accounted for ITB had sufficient data provided to perform a sub-group analysis. In these studies, thyroid irAE was again, associated with longer OS (HR, 0.51, CI 0.39-0.69, p<0.001), (I^2=64.2%, p=0.0044) (Figure 3B).

Progression-free survival—Fifteen studies (n=3,284) fulfilled the inclusion criteria to be included in the PFS meta-analysis.[5,18,20,21,28,31,33,42,45,46,48,51,52,59,60] Thyroid irAE occurrence was significantly associated with longer PFS (HR 0.58, CI 0.50-0.67, p<0.001) (Figure 4) and heterogeneity between studies was low (I^2 =0%, p=0.881). Sub-group analyses were not performed due to the small number of studies available for analysis.

Publication bias

Using the Cochrane risk-of-bias tool, the risk of bias within studies was primarily adjudicated as being 'moderate or serious' due to the limitations inherent to a retrospective design. The majority of studies did conduct multivariate analyses, but only 53% accounted for ITB.

Publication bias was also assessed using the Begg funnel plot and Egger's test. The funnel plot for OS did not display evident asymmetry (p=0.13). However, Egger's test was significant for publication bias (p<0.001). The funnel plot for PFS on the other hand, did not show asymmetry (p=0.151) and Egger's test was also not suggestive of publication bias (p=0.06).

As small-sized studies can commonly contribute to publication bias, we performed a sub-analysis where only OS studies with population sizes ≥100 were included. The results of the Begg funnel plot (p=0.40) and Egger's test (p <0.0001) remained consistent with publication bias despite the exclusion of these smaller studies.

DISCUSSION

While there have been multiple systematic reviews and meta-analyses assessing the incidence of irAEs and their associations with clinical outcomes,[7,68–72] to our knowledge, this is the first to specifically review and evaluate the potential correlations between the development of thyroid irAE and cancer outcomes.

The results of our meta-analysis suggests that the presence of thyroid irAE appears to be inversely associated with the oncological benefits of ICI therapy, where a net benefit in OS and PFS is observed in spite of developing an irAE.

The studies that did not observe a correlation between cancer outcomes and the development of thyroid irAE were often performed in small[51,52,60] or populations with high levels of comorbidities (older age ≥70 years, Charlson Comorbidity Index score ≥3 and Eastern Cooperative Oncology Group Performance Status ≥2).[53] This raises the possibility that population size as well as high mortality rates may be contributing factors to these negative studies.

In addition, a number of the negative studies were performed in mixed[57–59] or non-NSCLC/lung cohorts,[54–56,59,62] suggesting that the effects of thyroid irAE on cancer outcomes may also be potentially dependent on the primary cancer type. This is supported by the findings of two mixed cancer cohort studies where longer OS was observed in individuals that developed thyroid irAE, but this association was then lost in a sub-group analysis of individuals with melanoma.[5,47] It is unknown why thyroid irAEs would be associated with survival in only some cancers. One possible explanation would be the presence of shared antigens between certain cancers and the thyroid, although this has not been proven. Alternatively, there may be sex-associated molecular differences in the immune components of cancers. Studies have shown a divergent sex-bias of immune features between lung cancers and melanoma (i.e., higher tumor mutation burden and neoantigen load in males

with melanoma vs. higher stimulatory/inhibitory immune checkpoints in females with lung cancer),[73] which could lead to an apparent association with cancers that are more or less common in men vs. women. Further studies investigating the sex-associated molecular differences in immunotherapy response, however, are required.

The correlation between the development of thyroid irAE and improved cancer outcomes however, appeared to only be significant in individuals who develop overt rather than subclinical thyroid dysfunction. Although we acknowledge that this correlation is based on a small number of studies, this is not a surprising finding as severity of irAEs has previously been described as an independent favorable predictor of OS and PFS.[40]

Furthermore, given the large number of studies included in our review that did not account for ITB, it is possible that an artificial inflation of the correlation between thyroid irAE and clinical outcomes is observed. However, our sub-group analysis (involving only studies that accounted for ITB) did observe a significant association between thyroid irAE and longer OS, suggesting a legitimate association.

The association between thyroid irAE and cancer outcomes has potential relevant clinical implications. Unlike most other irAEs which commonly result in serious sequelae, ICI interruption and cessation, thyroid irAE is considered a relatively safe irAE. Furthermore, current guidelines recommend and encourage the continuation of ICI therapy in the setting of thyroid irAEs.[74] The majority of patients tend to present with mild symptoms and can be managed with close monitoring and where appropriate, levothyroxine therapy.[75] Thyroid irAE is therefore more likely to have continued clinical benefits when compared with other irAEs. Also, although most thyroid irAE tend to occur around or after the time of when the tumors are first evaluated for response to ICI therapy via computed tomography scans (6 to 8 weeks post ICI initiation), overt thyroid irAE can occur as early as 3 weeks after ICI commencement. In these circumstances, it would be somewhat reassuring if thyroid function tests (TFTs) already demonstrate overt thyroid irAE. TFTs should therefore be considered in all patients undergoing ICI therapy due to the high rates of thyroid irAE in this population, but can also be used to complement other clinical findings in assessing the likelihood of clinical response.

Our study has several limitations. Firstly, the majority of data collected were from retrospective studies, which can lead to various biases including information, selection as well potential biases in outcome measurements. Secondly, heterogeneity was detected between studies. While this is not surprising given endocrine/thyroid irAE were not the primary outcomes of interest for many of the included studies, significant heterogeneity can inherently impact the reliability of comparisons made between studies. Two studies in our systematic review reported results which were undoubtedly outside of the expected ranges (i.e., a thyroid irAE incidence of 1% and a median time to isolated overt hypothyroidism of 30 weeks), and could therefore also contribute to heterogeneity. However, only one study[52] was included in our meta-analysis, and it had a relatively small contribution to the overall effect size for both the OS (weight 0.82%) and PFS (weight 1.89%) meta-analyses. Similarly, while we included the one study which had the unique treatment regimen of PD-1/PD-L1 therapy in combination of chemotherapy as part of our meta-analysis, this

study also had a relatively small impact on the overall effect size for both the OS (weight 1.54%) and PFS (weight 4.14%) meta-analyses.

Publication bias was also identified and is likely a consequence of reporting bias. There appeared to be selective outcome reporting with an evidently larger number of published studies reporting on a positive association between thyroid irAE and OS compared with a negative association. Selective analysis reporting was also present and contributed to a number of negative studies being excluded from our meta-analysis due to insufficient reporting of data (i.e., HR and CI). These biases can lead to a potential overestimation of the association between thyroid irAE and clinical outcomes. Further prospective studies that report on both the positive and negative associations between thyroid irAE and ICI therapy outcomes are therefore required to validate our findings. Additionally, ICI doses were not evaluated in this review. This is because the ICI regimens within studies were complex and could not be summarized without the risk of over-simplification and the introduction of further biases.

Finally, our study population was heavily skewed towards patients treated for advanced NSCLC. Similarly, the vast majority of the patients were treated with PD-1 inhibitors, thus it would be difficult to generalize our study's findings to the general cancer population treated with any ICIs.

CONCLUSIONS

As the use of ICIs continue to expand, thyroid irAE will be increasingly encountered in clinical practice. Although deficiencies and biases remain within the current literature, the evidence does suggest that the development of thyroid irAE is associated with anti-tumor effects of ICIs and therefore, can be used as a surrogate marker for clinical response. Additional prospective studies are needed to further validate the correlation between thyroid irAE and clinical outcomes, particularly in different primary cancer sites and ICI types, as well as the role biomarkers such as TFTs may have in clinical practice.

FUNDING

This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or National Institutes of Health

REFERENCES

1. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. : Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 377:1345–1356, 2018
2. Antonia SJ, Villegas A, Daniel D, et al. : Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 377, 2017
3. Borghaei H, Paz-Ares L, Horn L, et al. : Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 373:1627–39, 2015 [PubMed: 26412456]
4. Overman MJ, McDermott R, Leach JL, et al. : Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 18:1182–1191, 2017 [PubMed: 28734759]

5. Yamauchi I, Yasoda A, Matsumoto S, et al. : Incidence, features, and prognosis of immune-related adverse events involving the thyroid gland induced by nivolumab. PLoS One 14:e0216954, 2019 [PubMed: 31086392]
6. Shankar B, Zhang J, Naqash AR, et al. : Multisystem Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors for Treatment of Non-Small Cell Lung Cancer. JAMA Oncol 6:1952–1956, 2020 [PubMed: 33119034]
7. Zhou X, Yao Z, Yang H, et al. : Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med 18:87, 2020 [PubMed: 32306958]
8. Hussaini S, Chehade R, Boldt RG, et al. : Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors - A systematic review and meta-analysis. Cancer Treat Rev. 2020 Dec 3;92:102134. Cancer Treat Rev 92:102134 [PubMed: 33302134]
9. Cortellini A, Buti S, Agostinelli V, et al. : A systematic review on the emerging association between the occurrence of immune-related adverse events and clinical outcomes with checkpoint inhibitors in advanced cancer patients. Semin Oncol 45:362–371, 2019
10. Fujii T, Naing A, Rolfo C, et al. : Biomarkers of response to immune checkpoint blockade in cancer treatment. Crit Rev Oncol Hematol 130:108–120, 2018 [PubMed: 30196907]
11. Gleiss A, Oberbauer R, Heinze G: An unjustified benefit: immortal time bias in the analysis of time-dependent events. Transpl. Int 31:125–13, 2018 [PubMed: 29024071]
12. Sterne JAC, Hernán MA, Reeves BC, et al. : ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 355; i4919; doi:10.1136/bmj.i4919., 2016 [PubMed: 27733354]
13. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–58, 2002 [PubMed: 12111919]
14. Higgins JP, Thompson SG, Deeks JJ, et al. : Measuring inconsistency in meta-analyses. BMJ 327:557–60, 2003 [PubMed: 12958120]
15. DerSimonian R, Kacker R: Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 28:105–14, 2007 [PubMed: 16807131]
16. Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–101, 1994 [PubMed: 7786990]
17. Egger M, Davey Smith G, Schneider M, et al. : Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–34, 1997 [PubMed: 9310563]
18. Kim HI, Kim M, Lee SH, et al. : Development of thyroid dysfunction is associated with clinical response to PD-1 blockade treatment in patients with advanced non-small cell lung cancer. Oncoimmunology. Oncoimmunology 7:e1375642, 2017 [PubMed: 29296533]
19. Fujisawa Y, Yoshino K, Otsuka A, et al. : Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab. J Dermatol Sci 88:225–231, 2017 [PubMed: 28736218]
20. Osorio JC, Ni A, Chaft JE, et al. : Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol 28:583–589, 2017 [PubMed: 27998967]
21. Grangeon M, Tomasini P, Chaleat S, et al. : Association Between Immune-related Adverse Events and Efficacy of Immune Checkpoint Inhibitors in Non-small-cell Lung Cancer. Clin Lung Cancer. Clin Lung Cancer 30:201–207, 2019
22. Haratani K, Hayashi H, Chiba Y, et al. : Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. JAMA Oncol 4:374–378, 2018 [PubMed: 28975219]
23. Owen DH, Wei L, Bertino EM, et al. : Incidence, Risk Factors, and Effect on Survival of Immune-related Adverse Events in Patients With Non-Small-cell Lung Cancer. Clin Lung Cancer 19::e893–e900, 2018 [PubMed: 30197259]
24. Ricciuti B, Genova C, De Giglio A, et al. : Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. J Cancer Res Clin Oncol 145:479–485, 2019 [PubMed: 30506406]

25. Cortellini A, Chiari R, Ricciuti B, et al. : Correlations Between the Immune-related Adverse Events Spectrum and Efficacy of Anti-PD1 Immunotherapy in NSCLC Patients. Clin Lung Cancer 20:237–247.e1, 2019 [PubMed: 30885550]
26. Funazo TY, Nomizo T, Ozasa H, et al. : Clinical impact of low serum free T4 in patients with non-small cell lung cancer treated with nivolumab. Sci Rep 9:17085, 2019 [PubMed: 31745135]
27. Koyama J, Horiike A, Yoshizawa T, et al. : Correlation between thyroid transcription factor-1 expression, immune-related thyroid dysfunction, and efficacy of anti-programmed cell death protein-1 treatment in non-small cell lung cancer. J Thorac Dis 11:1919–1928, 2019 [PubMed: 31285885]
28. Lei M, Michael A, Patel S, et al. : Evaluation of the impact of thyroiditis development in patients receiving immunotherapy with programmed cell death-1 inhibitors. J Oncol Pharm Pract 25:1402–1411, 2019 [PubMed: 30782080]
29. Maeda T, Yoshino K, Nagai K, et al. : Development of endocrine immune-related adverse events and improved survival in advanced melanoma patients treated with nivolumab monotherapy. Eur J Cancer 115:13–16, 2019 [PubMed: 31082687]
30. Peiró I, Palmero R, Iglesias P, et al. : Thyroid dysfunction induced by nivolumab: searching for disease patterns and outcomes. Endocrine 64:605–613, 2019 [PubMed: 30805887]
31. Sakakida T, Ishikawa T, Uchino J, et al. : Clinical features of immune-related thyroid dysfunction and its association with outcomes in patients with advanced malignancies treated by PD-1 blockade. Oncol Lett 18:2140–2147, 2019 [PubMed: 31423288]
32. Verzoni E, Cartenì G, Cortesi E, et al. : Real-world efficacy and safety of nivolumab in previously-treated metastatic renal cell carcinoma, and association between immune-related adverse events and survival: the Italian expanded access program. J Immunother Cancer 7:99, 2019 [PubMed: 30944023]
33. Basak EA, van der Meer JWM, Hurkmans DP, et al. : Overt Thyroid Dysfunction and Anti-Thyroid Antibodies Predict Response to Anti-PD-1 Immunotherapy in Cancer Patients. Thyroid 307, 2020
34. Cortellini A, Friedlaender A, Banna GL, et al. : Immune-related Adverse Events of Pembrolizumab in a Large Real-world Cohort of Patients With NSCLC With a PD-L1 Expression ≥ 50% and Their Relationship With Clinical Outcomes. Clin Lung Cancer 21:498–508.e2, 2020
35. Economopoulou P, Kotsantis I, Papaxoinis G, et al. : Association of autoimmunity with survival in patients with recurrent/metastatic head and neck squamous cell carcinoma treated with nivolumab. Oral Oncol 111:105013, 2020 [PubMed: 32977184]
36. Eggermont AMM, Kicinski M, Blank CU, et al. : Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol 6:519–527, 2020 [PubMed: 31895407]
37. España S, Pérez Montes de Oca A, Marques-Pamies M, et al. : Endocrine adverse events related to immune-oncology agents: retrospective experience of a single institution. Transl Lung Cancer Res 9:103–110, 2020 [PubMed: 32206558]
38. Lima Ferreira J, Costa C, Marques B, et al.: Improved survival in patients with thyroid function test abnormalities secondary to immune-checkpoint inhibitors Cancer Immunol Immunother doi:10.1007/s00262-020-02664-y., 2020
39. Kelly K, Manitz J, Patel MR, et al. : Efficacy and immune-related adverse event associations in avelumab-treated patients. J Immunother Cancer 8:e001427, 2020 [PubMed: 33219092]
40. Kijima T, Fukushima H, Kusuhara S, et al. : Association Between the Occurrence and Spectrum of Immune-Related Adverse Events and Efficacy of Pembrolizumab in Asian Patients With Advanced Urothelial Cancer: Multicenter Retrospective Analyses and Systematic Literature Review. Clin Genitourin Cancer S1558-7673:30163-4, 2020
41. Kotwal A, Kottschade L, Ryder M: PD-L1 Inhibitor-Induced Thyroiditis Is Associated with Better Overall Survival in Cancer Patients. Thyroid 30:177–184, 2020 [PubMed: 31813343]
42. Maillet D, Corbaux P, Stelmes JJ, et al. : Association between immune-related adverse events and long-term survival outcomes in patients treated with immune checkpoint inhibitors. Eur J Cancer 132:61–70, 2020 [PubMed: 32334337]

43. Bai R, Li L, Chen X, et al. : Correlation of Peripheral Blood Parameters and Immune-Related Adverse Events with the Efficacy of Immune Checkpoint Inhibitors. J Oncol 10;2021:9935076, 2021 [PubMed: 34335763]
44. Frelau A, Jali E, Campillo-Gimenez B, et al. : Prognostic impact of thyroid dysfunctions on progression-free survival in patients with metastatic melanoma treated with anti-PD-1 antibodies. Melanoma Res 31:208–217, 2021 [PubMed: 33904517]
45. Luongo C, Morra R, Gambale C, et al. : Higher baseline TSH levels predict early hypothyroidism during cancer immunotherapy. J Endocrinol Invest 44:1927–1933, 2021 [PubMed: 33576954]
46. Muir CA, Clifton-Bligh RJ, Long GV, et al. : Thyroid immune-related adverse events following immune checkpoint inhibitor treatment. J Clin Endocrinol Metab Apr 20:dgab263. doi:10.1210/clinem/dgab263. Epub ahead of print., 2021
47. Street S, Chute D, Strohbehn I, et al. : The positive effect of immune checkpoint inhibitor-induced thyroiditis on overall survival accounting for immortal time bias: a retrospective cohort study of 6596 patients. Ann Oncol 32:1050–1051, 2021 [PubMed: 34020034]
48. Thuillier P, Joly C, Alavi Z, et al. : 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. Cancer Immunol Immunother doi:10.1007/s00262-020-02802-6., 2021
49. Zhou Y, Xia R, Xiao H, et al. : Thyroid function abnormality induced by PD-1 inhibitors have a positive impact on survival in patients with non-small cell lung cancer. Int Immunopharmacol 91, 2020
50. Al Ashi SI, Thapa B, Flores M, et al. : Endocrine Toxicity and Outcomes in Patients With Metastatic Malignancies Treated With Immune Checkpoint Inhibitors. J Endocr Soc 5:bvab100, 2021 [PubMed: 34195529]
51. Ahn BC, Pyo KH, Xin CF, et al. : Comprehensive analysis of the characteristics and treatment outcomes of patients with non-small cell lung cancer treated with anti-PD-1 therapy in real-world practice. J Cancer Res Clin Oncol 145:1613–1623, 2019 [PubMed: 30911841]
52. Campredon P, Mouly C, Lusque A, et al. : Incidence of thyroid dysfunctions during treatment with nivolumab for non-small cell lung cancer: Retrospective study of 105 patients. Presse Med 48:e199–e207, 2019 [PubMed: 31005502]
53. Ksienski D, Wai ES, Croteau N, et al. : Efficacy of Nivolumab and Pembrolizumab in Patients With Advanced Non-Small-Cell Lung Cancer Needing Treatment Interruption Because of Adverse Events: A Retrospective Multicenter Analysis. Clin Lung Cancer 20:e97–e106, 2019 [PubMed: 30337270]
54. Freeman-Keller M, Kim Y, Cronin H, et al. : Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes. Clin Cancer Res 22:886–94, 2016 [PubMed: 26446948]
55. Matsuo M, Yasumatsu R, Masuda M, et al. : Relationship between immune-related adverse events and the long-term outcomes in recurrent/metastatic head and neck squamous cell carcinoma treated with nivolumab. Oral Oncol 101:104525, 2020 [PubMed: 31863963]
56. Al Mushref M, Guido PA, Collichio FA, et al. : THYROID DYSFUNCTION, RECOVERY, AND PROGNOSIS IN MELANOMA PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS: A RETROSPECTIVE REVIEW. Endocr Pract 26:36–42, 2020 [PubMed: 31461358]
57. D'Aiello A, Lin J, Gucalp R, et al. : Thyroid Dysfunction in Lung Cancer Patients Treated with Immune Checkpoint Inhibitors (ICIs): Outcomes in a Multiethnic Urban Cohort. Cancers (Basel) 13:1464, 2021 [PubMed: 33806774]
58. Rubino R, Marini A, Roviello G, et al. : Endocrine-related adverse events in a large series of cancer patients treated with anti-PD1 therapy. Endocrine May 25. doi:10.1007/s12020-021-02750-w. Epub ahead of print, 2021
59. Paderi A, Giorgione R, Giommoni E, et al. : Association between Immune Related Adverse Events and Outcome in Patients with Metastatic Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors. Cancers (Basel) 13:860, 2021 [PubMed: 33670634]

60. Morimoto K, Yamada T, Takumi C, et al. : Immune-Related Adverse Events Are Associated With Clinical Benefit in Patients With Non-Small-Cell Lung Cancer Treated With Immunotherapy Plus Chemotherapy: A Retrospective Study. Front Oncol 11, 2021
61. Lui DTW, Lee CH, Tang V, et al. : Thyroid Immune-Related Adverse Events in Patients with Cancer Treated with anti-PD1/anti-CTLA4 Immune Checkpoint Inhibitor Combination: Clinical Course and Outcomes. Endocr Pract S1530-891X(21)00030-6, 2021
62. Holstead RG, Kartolo BA, Hopman WM, et al. : Impact of the development of immune related adverse events in metastatic melanoma treated with PD −1 inhibitors. Melanoma Res 31:258–263, 2021 [PubMed: 33904518]
63. Fujisawa Y, Yoshino K, Otsuka A, et al. : Retrospective study of advanced melanoma patients treated with ipilimumab after nivolumab: Analysis of 60 Japanese patients. J Dermatol Sci 89:60–66, 2018 [PubMed: 29079332]
64. Cortellini A, Friedlaender A, Banna GL, et al. : Immune-related Adverse Events of Pembrolizumab in a Large Real-world Cohort of Patients With NSCLC With a PD-L1 Expression ≥ 50% and Their Relationship With Clinical Outcomes.\. Clin Lung Cancer 21:498–508.e2, 2020 [PubMed: 32680806]
65. Frelau A, Jali E, Campillo-Gimenez B, et al. : Prognostic impact of thyroid dysfunctions on progression-free survival in patients with metastatic melanoma treated with anti-PD-1 antibodies. Melanoma Res 31:208–217, 2021 [PubMed: 33904517]
66. Paderi A, Giorgione R, Giommoni E, et al. : Association between Immune Related Adverse Events and Outcome in Patients with Metastatic Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors. Cancers (Basel) 13, 2021
67. Lisberg A, Tucker DA, Goldman JW, et al. : Treatment-Related Adverse Events Predict Improved Clinical Outcome in NSCLC Patients on KEYNOTE-001 at a Single Center. Cancer Immunol Res 6:288–294, 2018 [PubMed: 29382669]
68. de Filette J, Andreescu CE, Cools F, et al. : A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors. Horm Metab Res 51:145–156, 2019 [PubMed: 30861560]
69. Park R, Lopes L, Saeed A: Anti-PD-1/L1-associated immune-related adverse events as harbinger of favorable clinical outcome: systematic review and meta-analysis. Clin Transl Oncol 23:100–109, 2021 [PubMed: 32495269]
70. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. : Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. JAMA Oncol 4:173–182, 2018 [PubMed: 28973656]
71. Hussaini S, Chehade R, Boldt RG, et al. : Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors - A systematic review and meta-analysis. Cancer Treat Rev 92, 2021
72. Cortellini A, Buti S, Agostinelli V, et al. : A systematic review on the emerging association between the occurrence of immune-related adverse events and clinical outcomes with checkpoint inhibitors in advanced cancer patients. Semin Oncol 46:362–371, 2019 [PubMed: 31727344]
73. Ye Y, Jing Y, Li L, et al. : Sex-associated molecular differences for cancer immunotherapy. Nat Commun 11:1779, 2020 [PubMed: 32286310]
74. Network NCC: NCCN Guidelines Version 4.2021 Management of Immune Checkpoint Inhibitor-Related Toxicity https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf, 2021
75. Chang LS, Barroso-Sousa R, Tolaney SM, et al. : Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. Endocr Rev 40:17–65, 2019 [PubMed: 30184160]

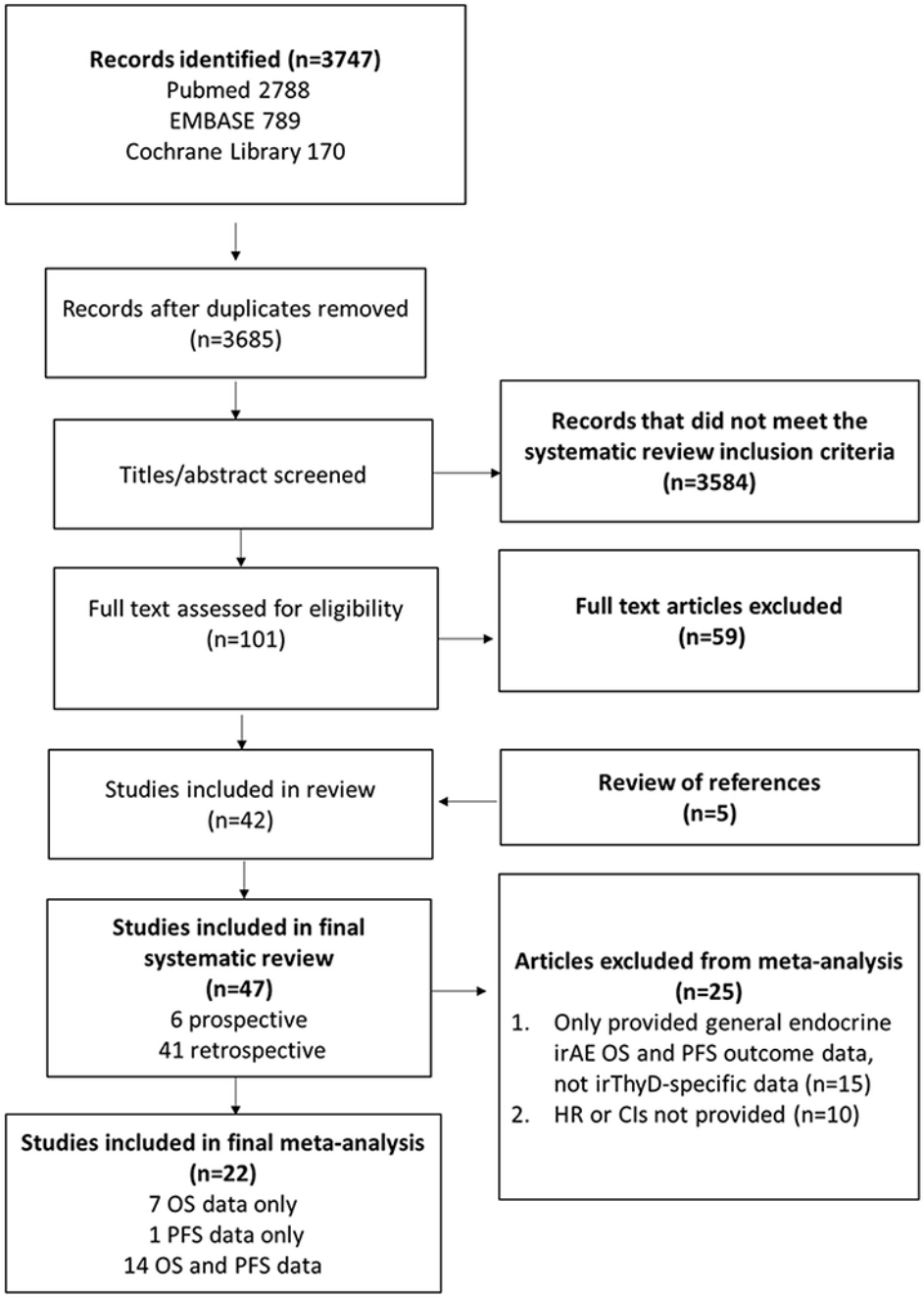

Figure 1:

Study selection flowchart

Confidence interval (CI), hazard ratio (HR), immune related adverse effects (irAE), immune related thyroid dysfunction (thyroid irAE), number (n), odds ratio (OR), overall survival (OS), progression free survival (PFS)

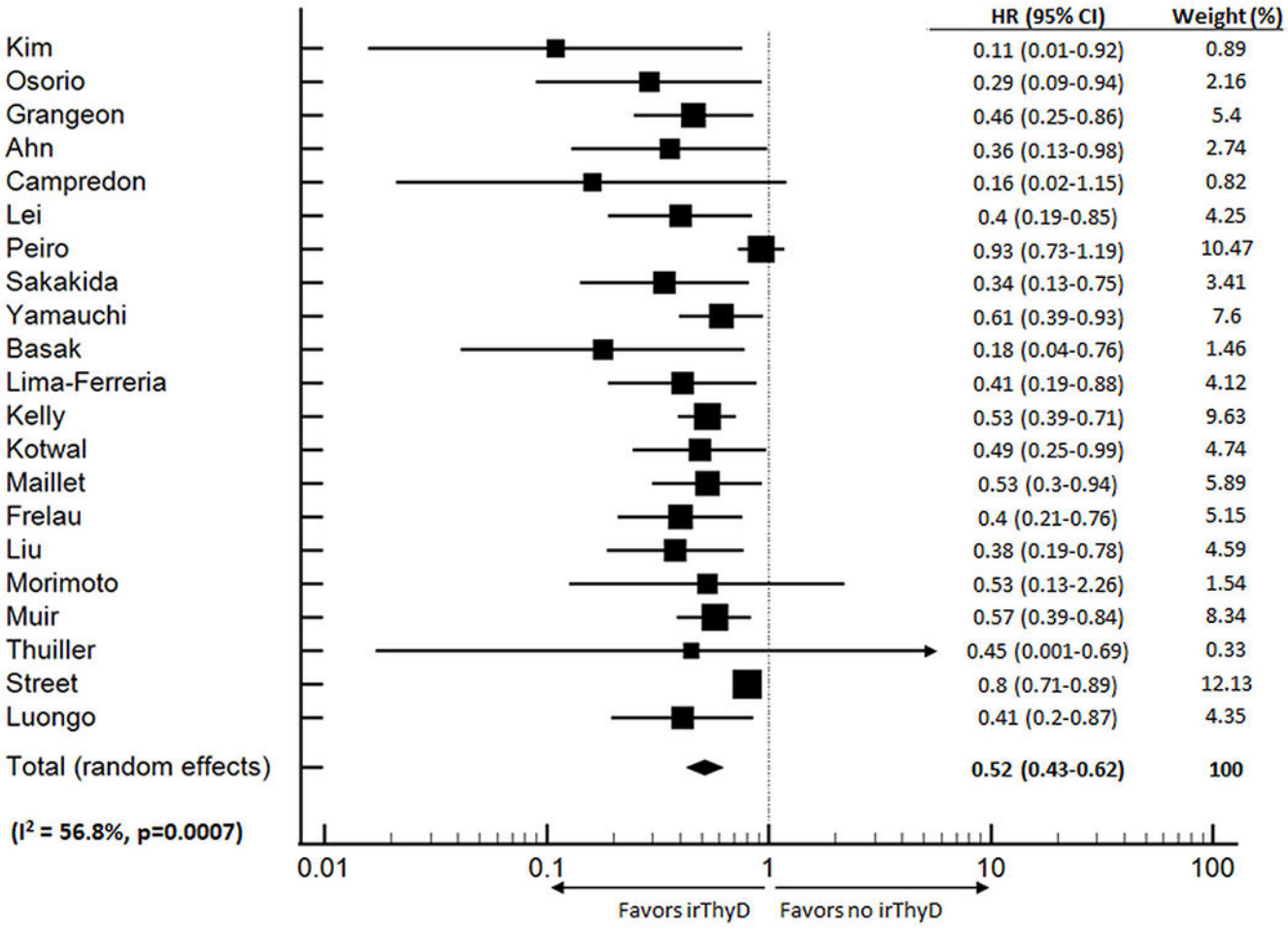

Figure 2:

Forest Plot (random effects model) of the association between thyroid irAE development and overall survival

The size of the squares indicates the weight of each study.

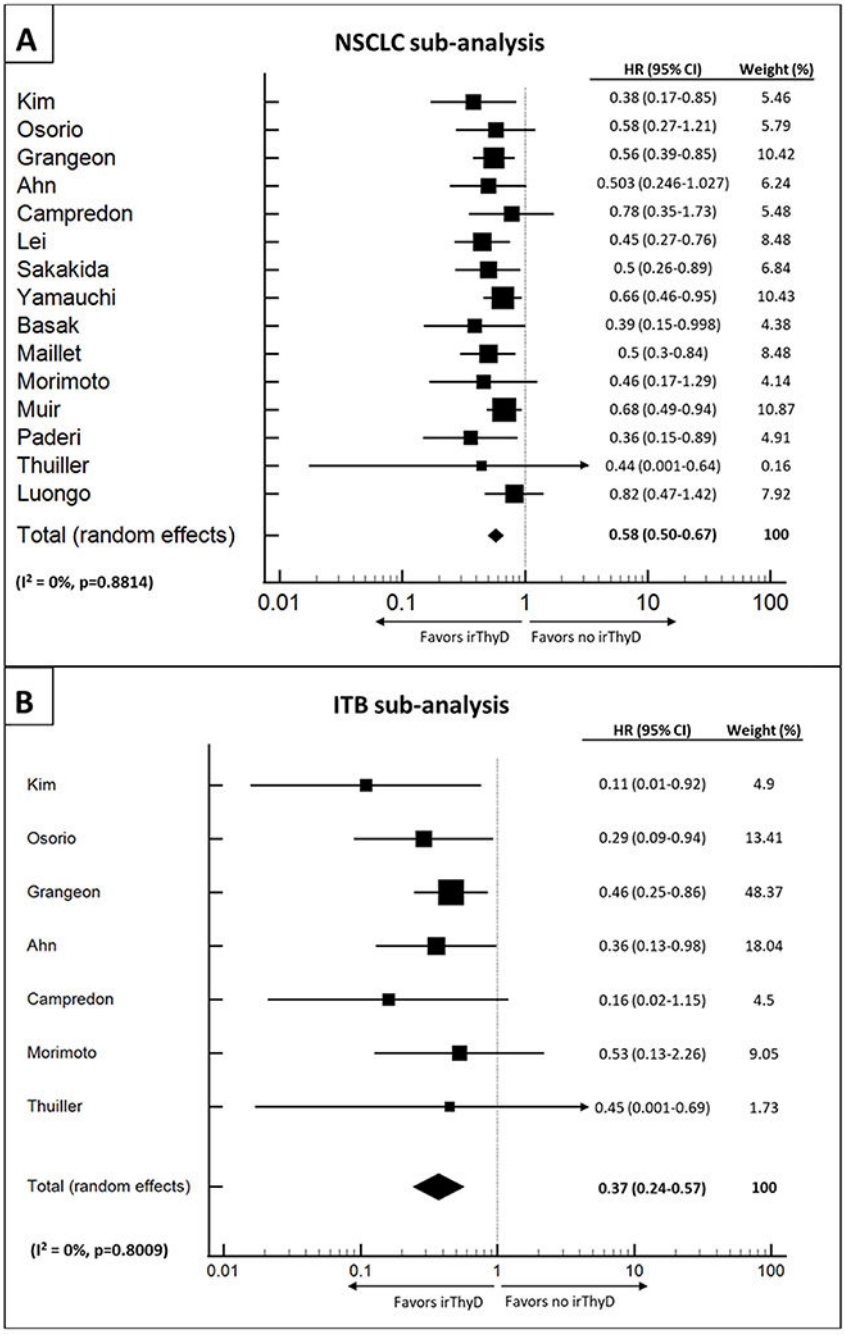

Figure 3:

Forest Plots (random effects model) between thyroid irAE development and overall survival in individuals with NSCLC (panel A) and when ITB is accounted for (panel B)

The size of the squares indicates the weight of each study.

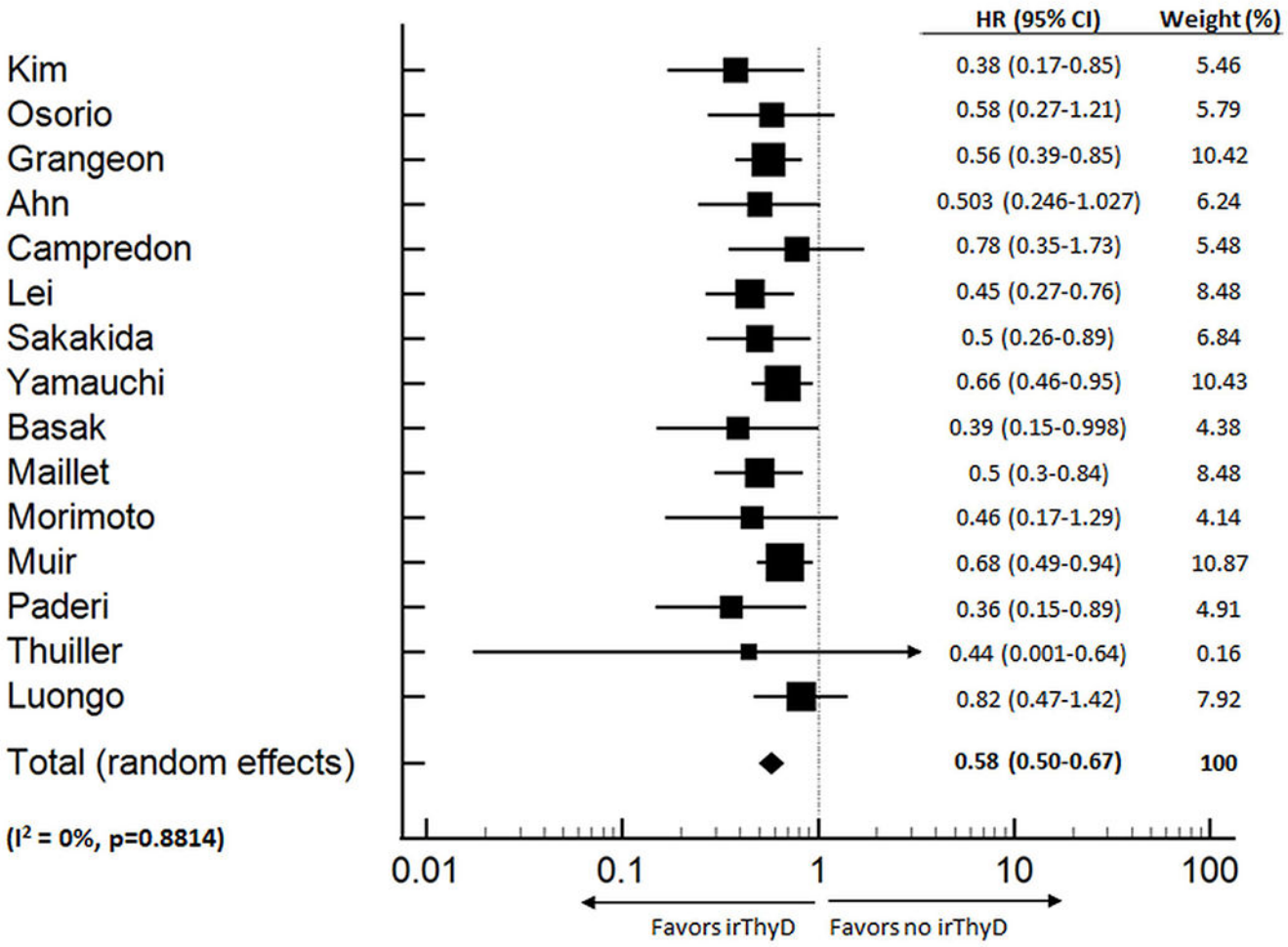

Figure 4:

Forest Plot (random effects model) of the association between thyroid irAE development and progression free survival

The size of the squares indicates the weight of each study.

Table 1:

Systematic review of the studies evaluating the correlation between the development of immune-related thyroid dysfunction and clinical outcomes secondary to immune checkpoint inhibitors

Number	Reference	Study type	Primary tumor site	Treatment	N=	ITB	irAE of interest	Outcomes (thyroid irAE vs. no thyroid irAE)			Summary
								OS	PFS	Positive/ Negative study	
1	Freeman-Keller et al (2016)[54]	Retrospective	Melanoma	Anti-PD-1 ± peptide vaccination (nivolumab + peptide vaccine or nivolumab alone)	148	Yes	General, thyroid	NS	Not reported	Negative	Non-significant OS for endocrinopathies, including thyroid irAE
2	Kim et al (2017)[18]	Retrospective	NSCLC	Anti-PD-1 (nivolumab or pembrolizumab)	58	No	Thyroid	118 vs. 71 days, **(p=0.025)** Adjusted HR 0.11, **(p=0.041)**	118 vs. 61 days, **(p=0.014)** Adjusted HR 0.38, **(p=0.018)**	Positive	thyroid irAE was an independent predictive factor for favorable outcome
3	Fujisawa et al (2017)[63]	Retrospective	Melanoma	CTLA-4 post PD-1 (ipilimumab post nivolumab)	60	Yes	General, endocrine	Adjusted RR 0.22, **(p=0.015)**	Not reported	Positive	Endocrine irAEs were significant factors associated with survival
4	Osorio et al (2017)[20]	Prospective	NSCLC	Anti-PD-1 (pembrolizumab)	51	No	Thyroid	40 vs 14 months, HR 0.29, **(p=0.029)**	NS	Positive	OS was significantly longer in patients who developed thyroid irAE
5	Grangeon et al (2018)[21]	Retrospective	NSCLC	Anti-PD-1 or anti-PD-L1 (not specified)	270	No	General, thyroid	NR vs 18.2 months, HR 0.46, **(p=0.01)**	8.05 vs. 2.59 months, HR 0.56, **(p=0.005)**	Positive	thyroid irAE was correlated with better clinical outcomes
6	Haratani et al (2018)[22]	Retrospective	NSCLC	Anti-PD-1 (nivolumab)	134	Yes	General, endocrine	NS	Adjusted HR 0.237, **(p=0.02)**	Positive	Endocrine irAEs were correlated with better PFS, but not OS
7	Owen et al (2018)[23]	Retrospective	NSCLC	Anti-PD-1 or anti-PD-L1 (nivolumab, pembrolizumab, atezolizumab)	91	Yes	General, thyroid	NR vs. 6.5 months, **(0.018)** 3-month landmark NR vs. 16.2 months, **(p=0.0296)**	Not reported	Positive	thyroid irAE was correlated with longer OS

Number	Reference	Study type	Primary tumor site	Treatment	N=	ITB	irAE of interest	Outcomes (thyroid irAE vs. no thyroid irAE)			Summary
								OS	PFS	Positive/ Negative study	
8	Ricciuti et al (2018)[24]	Retrospective	NSCLC	Anti-PD-1 (nivolumab)	195	No	General, endocrine	Adjusted HR 0.45, **(p=0.001)**	Adjusted HR 0.59, **(p=0.011)**	Negative	Endocrine irAEs were correlated with better clinical outcomes
9	Ahn et al (2019)[51]	Retrospective	NSCLC	Anti-PD-1 (nivolumab or pembrolizumab)	155	Yes	General, endocrine	NR vs. 12.58 months, **(p=0.037)** Adjusted HR NS	NS	Negative	Endocrine irAEs were not identified as significant positive predictive factors of better clinical outcomes
10	Campredon et al (2019)[52]	Retrospective	NSCLC	Anti-PD-1 (nivolumab)	105	Yes	Thyroid	NS	NS	Positive	A non-statistically significant tendency toward improvement of the overall survival was observed in the thyroid irAE group
11	Cortellini et al (2019)[25]	Retrospective	NSCLC	Anti-PD-1 (nivolumab or pembrolizumab)	559	Yes	General, endocrine	Adjusted HR 0.55, **(p=0.0044)**	Adjusted HR 0.63, **(p=0.0084)**	Positive	Endocrine irAEs correlated with improved ORR and PFS and improved OS
12	Funazo et al (2019)[26]	Retrospective	NSCLC	Anti-PD-1 (nivolumab)	111	No	Thyroid	Low fT4: NR vs. 556 days HR 0.139, **(p=0.020)**	Low fT4: NR vs. 67 days HR 0.297, **(p=0.010)**	Positive	In the patients with advanced NSCLC, low fT4 after nivolumab treatment was associated with significantly longer PFS and OS
13	Koyama et al (2019)[27]	Retrospective	NSCLC	Anti-PD1 (nivolumab or pembrolizumab)	132	No	Thyroid	NR vs. 14.1 months, **(p=0.011)**	9.8 vs. 1.8 months, **(p=0.012)**	Negative	thyroid irAE was correlated with better OS and PFS in NSCLC patients
14	Ksienski et al (2019)[53]	Retrospective	NSCLC	Anti-PD-1 (nivolumab or pembrolizumab)	254	Yes	General, thyroid	NS	Not reported	Positive	thyroid irAE was not correlated with OS after nivolumab or pembrolizumab treatment
15	Lei et al (2019)[28]	Retrospective	Melanoma, RCC, NSCLC	Anti-PD-1 (nivolumab or pembrolizumab)	103	No	Thyroid	NR vs. 12.9 months, HR	10.1 vs. 3.7 months HR	Positive	thyroid irAE was correlated with better

Number	Reference	Study type	Primary tumor site	Treatment	N=	ITB	irAE of interest	Outcomes (thyroid irAE vs. no thyroid irAE)			Summary
								OS	PFS	Positive/ Negative study	
								0.40, **(p=0.014)**	0.45, **(p=0.002)**		clinical outcomes OS, PFS and ORR
16	Maeda et al (2019)[29]	Retrospective	Melanoma	Anti-PD-1 (nivolumab)	73	Yes	General, endocrine	20-week landmark **(p=0.27)**	20-week landmark **(p=0.07)**	Positive	Endocrine irAEs were correlated with better clinical outcomes
17	Peiro et al (2019)[30]	Prospective	Majority NSCLC, melanoma, lymphoma	Anti-PD-1 (nivolumab)	73	No	Thyroid	NSCLC & TD: HR, 0.4, **(p=0.035)**	Not reported	Positive	In patients with NSCLC, nivolumab-induced thyroid dysfunction appears to be correlated with better OS
18	Sakakida et al (2019)[31]	Retrospective	Majority NSCLC, melanoma, lymphoma, RCC, head and neck, gastric, urothelial	Anti-PD-1 (nivolumab or pembrolizumab)	174	Yes	Thyroid	156 vs. 59 weeks, HR 0.34, **(p=0.01)** Adjusted HR 0.42, **(p=0.04)**	66 vs 27 weeks, HR 0.50, **(p=0.02)** Adjusted HR NS	Positive	thyroid irAE was an independent prognostic factor for longer OS
19	Verzoni et al (2019)[32]	Prospective	RCC	Anti-PD-1 (nivolumab)	398	Yes	General, endocrine	1-year OS 92.3% **(p = 0.001)**	Not reported	Negative	Endocrine irAEs were correlated with improved OS
20	Yamauchi et al (2019)[5]	Retrospective	Lung, melanoma, others	Anti-PD-1 (nivolumab)	200	Yes	Thyroid	16.1 vs. 13.6 months, HR 0.61, **(p = 0.022)** Lung & TD: NR vs.14.2 months, HR 0.51 CI 0.27-0.92, **(p=0.025)** Melanoma & TD: NS	4.9 vs. 2.9 months, HR 0.66 **(p = 0.023)** Lung &TD: 5.8 vs.2.3 months, HR 0.55 CI 0.33-0.88, **(p=0.012)** Melanoma & TD: 3.3 vs 4.1 months, HR 0.94 CI 0.41-2.00, (p=0.885)	Positive	thyroid irAE related to good prognosis in lung cancer but might be inconclusive in melanoma
21	Al Mushref et al (2020)[56]	Retrospective	Melanoma	Anti-PD-1 or CTLA-4 (ipilimumab,	186	No	Thyroid	NS	Not reported	Positive	Thyroid irAEs did not appear to be associated with change in survival

Number	Reference	Study type	Primary tumor site	Treatment	N=	ITB	irAE of interest	Outcomes (thyroid irAE vs. no thyroid irAE)			Summary
								OS	PFS	Positive/ Negative study	
				pembrolizumab or nivolumab)							
22	Basak et al (2020)[33]	Prospective	Melanoma, NSCLC, RCC	Anti-PD-1 (nivolumab or pembrolizumab)	168	Yes	Thyroid	1-year OS rates 94 vs. 59%, HR 0.18, **(p=0.020)**	1-year PFS rates 64 vs. 34%, HR 0.39, **(p=0.050)**	Positive	thyroid irAE is associated with improved OS and PFS
23	Cortellini et al (2020)[64]	Retrospective	NSCLC w PD-L1 expression >50%	Anti-PD-1 (pembrolizumab)	1010	Yes	General, thyroid	Adjusted HR 0.30, **(p<0.0001)**	Adjusted HR 0.40, **(p<0.0001)**	Positive	Endocrine irAEs were significantly related to improved OS, PFS and ORR
24	Economopoulou et al (2020)[35]	Retrospective	Head and neck	Anti-PD-1 (nivolumab)	89	No	General, endocrine	**(p=0.014)**	Not reported	Positive	The development of endocrine irAEs is a predictor of improved survival in patients with advanced HNSCC treated with nivolumab.
25	Eggermont et al (2020)[36]	RCT (secondary analysis)	Melanoma	Anti-PD-1 (Pembrolizumab)	1011	Yes	General, endocrine	Not reported	HR 0.34, **(p=0.03)**	Positive	Occurrence of endocrine irAEs were associated with a longer PFS in the pembrolizumab arm
26	Espana et al (2020)[37]	Retrospective	NSCLC, melanoma, urothelial	Anti-PD-1 +/ − anti-CTLA-4 or anti-CTLA-4 (pembrolizumab, nivolumab, atezolizumab, ipilimumab or combination therapy)	188	No	Endocrine	NR vs. 31.4 months **(p=0.001)** Adjusted HR 0.42, **(p=0.008)**	56.7 vs. 27.7 months, **(p=0.008)**	Positive	Endocrine irAEs were significantly associated with improved OS and PFS
27	Lima-Ferreira et al (2020)[38]	Retrospective	Melanoma, NSCLC, lymphoma, urothelial and head and neck	Anti-PD-1 or anti-CTLA-4 (pembrolizumab, nivolumab or ipilimumab)	161	No	Thyroid	3.26 vs. 1.76 years, **(p=0.030)**	Not reported	Positive	Primary and central thyroid dysfunction can be a predictive clinical biomarker of a better response to ICI across several neoplasms

Number	Reference	Study type	Primary tumor site	Treatment	N=	ITB	irAE of interest	Outcomes (thyroid irAE vs. no thyroid irAE)			Summary
								OS	PFS	Positive/ Negative study	
28	Kelly et al (2020)[39]	Prospective	Majority NSCLC	Anti-PD-L1 (avelumab)	1783	Yes	General, thyroid	HR 0.53, CI **0.39-0.71**	Not reported	Positive	thyroid irAE was significantly associated with improved OS
29	Kijima et al (2020)[40]	Retrospective	Urothelial	Anti-PD-1 (pembrolizumab)	97	No	General, endocrine	**(p=0.04)**	Not reported	Positive	Endocrine irAEs were associated with increased ORR and longer OS
30	Kotwal et al (2020)[41]	Retrospective	Lung (85%), Uroepithelial, Merkel cell, prostate, penis	Anti-PD-L1 (atezolizumab or avelumab)	91	No	Thyroid	NR vs 9.8 months, **(p=0.027)** Adjusted HR 0.49, CI 0.25-0.99, **(p=0.034)**	Not reported	Negative	thyroid irAE appears to be associated with improved OS
31	Maillet et al (2020)[42]	Retrospective	Melanoma, NSCLC, RCC, urothelial	Anti-PD-L1 or anti-CTLA-4 (not specified)	410	Yes	General, thyroid	HR 0.53, CI **0.3-0.94**	HR 0.5, CI **0.3-0.84**	Negative	thyroid irAE is correlated with better OS and PFS
32	Matsuo et al (2020)[55]	Retrospective	Head and neck squamous cell	Anti-PD-1 (nivolumab)	108	No	General, endocrine	Not reported	NS	Positive	No correlation between endocrine irAEs and clinical outcomes
33	Shankar et al (2020)[6]	Retrospective	NSCLC	Anti-PD-1, anti-PD-L1 (not specified)	623	No	General, thyroid	NS	NS	Positive	No correlation between thyroid irAE and clinical outcomes observed
34	Al Ashi et al (2021)[50]	Retrospective	NSCLC, melanoma, RCC, bladder	Anti-PD-1 anti-PD-L1 or anti-CTLA-4 (nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab or ipilimumab)	551	No	Endocrine	Adjusted HR 0.56, CI 0.42-0.76, **p<0.001**	Not reported	Negative	The development of endocrine irAEs was associated with a longer OS
35	Bai et al (2021)[43]	Retrospective	Lung, melanoma, esophageal, urothelial, gastric	Anti-PD-1, anti-PD-L1 or combination therapy (not specified)	103	No	General, endocrine	Not reported	13.3 vs. 4.13 months **(p=0.01)**	Positive	Endocrine irAEs were associated with better PFS

Number	Reference	Study type	Primary tumor site	Treatment	N=	ITB	irAE of interest	Outcomes (thyroid irAE vs. no thyroid irAE)			Summary
								OS	PFS	Positive/ Negative study	
36	D'Aiello et al (2021)[57]	Retrospective	NSCLC, SCLC	Anti-PD-1 or anti-PD-L1 (pembrolizumab, nivolumab, durvalumab or atezolizumab)	205	Yes	Thyroid	Not reported	NS	Negative	There were no observed differences in PFS between those that developed thyroid irAE and those that did not
37	Frelau et al (2021)[44]	Retrospective	Melanoma	Anti-PD-1 +/− CTLA-4 or CTLA-4 (pembrolizumab or nivolumab or combination therapy)	110	No	General, thyroid	43.9 vs. 9.8 months, **(p=0.0021)** Adjusted HR 0.4, 95% CI **0.21-0.76, (p=0.005)**	18.1 vs. 3.9 months, **(p=0.0085)** NS	Negative	thyroid irAE appeared to be associated with better OS
38	Holstead et al (2021)[62]	Retrospective	Melanoma	Anti-PD-1 (nivolumab or pembrolizumab)	87	Yes	General, thyroid	NS	Not reported	Positive	There appeared to be a trend towards better OS in individuals with endocrine irAEs
39	Lui et al (2021)[61]	Retrospective	HCC, lung, breast, melanoma, RCC, CC pancreas, colorectal, gastric, NET	Anti-PD-1/anti-CTLA-4 combination therapy (nivolumab/ pembrolizumab and ipilimumab)	103	Yes	Endocrine	17.9 vs.5.7 months **(p<0.001)** Adjusted HR 0.34, 95% CI 0.17-0.71, **(p=0.004)** 3-month landmark: HR 0.42, CI 0.13-1.36, (p=0.135)	Not reported	Negative	thyroid irAE may have prognostic significance in individuals with advanced cancer and combination therapy
40	Luongo et al (2021)[45]	Retrospective	NSCLC, melanoma, RCC	Anti-PD-1 (nivolumab or pembrolizumab)	96	No	Thyroid	HR 0.41, CI 0.2-0.87, **p=0.0197**	NS	Positive	thyroid irAE was associated with an improved 2-year OS when compared to euthyroid patients
41	Morimoto et al (2021)[60]	Retrospective	NSCLC	Anti-PD-1 or anti-PD-L1 combined with chemotherapy	70	No	General, thyroid	NS	HR 0.46, CI 0.17-1.29, (p=0.14)	Negative	Endocrine irAEs were associated with a trend towards improved PFS
42	Muir et al (2021)[46]	Retrospective	Melanoma	Anti-PD-1 +/− CTLA-4 or CTLA-4 (ipilimumab,	1246	No	Thyroid	Adjusted HR 0.57, 95% CI	Adjusted HR 0.68, 95% CI	Negative	Overt thyrotoxicosis appeared to be associated with

Number	Reference	Study type	Primary tumor site	Treatment	N=	ITB	irAE of interest	Outcomes (thyroid irAE vs. no thyroid irAE)			Summary
								OS	PFS	Positive/ Negative study	
				pembrolizumab or nivolumab or combination therapy)				0.39-0.84, **(p=0.005)**	0.49-0.94, **(p=0.02)**		better OS and PFS. No association was observed for hypothyroidism
43	Paderi et al (2021)[59]	Retrospective	RCC	Anti-PD-1 +/− CTLA-4 (nivolumab or combination therapy)	43	Yes	General, thyroid	Not reported	Adjusted HR 0.34 CI 0.13-0.87, **(p=0.025)** 16-week landmark (p=0.160)	Positive	At the 16-week landmark analysis, thyroid irAE showed a trend towards improved PFS
44	Rubino et al (2021)[58]	Retrospective	NSCLC, melanoma	Anti-PD-1 (pembrolizumab or nivolumab)	251	No	General, endocrine	NS	NS	Positive	Endocrine irAEs were not associated with OS or PFS
45	Street et al (2021)[47]	Retrospective	Melanoma, breast, gastrointestinal, genitourinary, head and neck, hematologic, neurologic, thoracic	Anti-PD-1, anti-PD-L1 or CTLA-4 or combination therapy (not specified)	6596	Yes	Thyroid	Adjusted HR 0.8, CI 0.71-0.89), **(p=<0.001)**	Not reported	Positive	Thyroid irAE was associated with improved OS even after accounting for immortal time biases
46	Thuillier et al (2021)[48]	Retrospective	NSCLC	Anti-PD-1 (nivolumab)	194	No	Thyroid	29.8 vs. 8.1 months, **(p<0.001)** Adjusted HR 0.32, **(p<0.001)**	8.7 vs. 1.7 months, **(p<0.001)** Adjusted HR = 0.36 **(p<0.001)**	Positive	thyroid irAE appeared to be correlated with better OS, PFS and ORR
47	Zhou et al (2021)[49]	Retrospective	NSCLC	Anti-PD-1 (pembrolizumab or nivolumab)	191	No	General, thyroid	16.8 vs. 11.1 months, **(p< 0.001)**	10.4 vs. 5.5 months, **(p<0.001)**	Positive	thyroid irAE appeared to be correlated with better OS and PFS

Cholangiocarcinoma (CC), complete response (CR), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), hazards ratio (HR), head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma (HCC), immune checkpoint inhibitor (ICI), immune-related adverse event (irAE), immune-related thyroid dysfunction (thyroid irAE), number (N), non-small cell lung cancer (NSCLC), not reached (NR), not significant (NS), overall survival (OS), programmed cell death receptor 1 (PD-1), programmed cell death ligand (PD-L1), progression-free survival (PFS), renal cell carcinoma (RCC), small cell lung cancer (SCLC), 95% confidence interval (CI), thyroid dysfunction (TD)