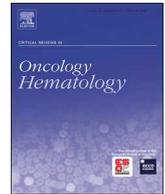




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## Tyrosine kinase inhibitors and immune checkpoint inhibitors-induced thyroid disorders

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## ABSTRACT

Recently, tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICPIs) have emerged as new classes of anticancer therapies. Although generally considered less toxic than cytotoxic chemotherapy, these new drugs can cause significant unanticipated side effects including thyroid dysfunction. This review provides a literature assessment of thyroid dysfunctions induced by TKI and ICPIs. We intend to define for these two classes the frequency of thyroid involvement, the potential mechanisms that result in this toxicity, the clinical-biological impact and the therapeutic management. Detection of thyroid dysfunction requires monitoring of TSH, in combination with free T4 if needed and, depending on the clinical impact and the kinetics of biological abnormalities, starting symptomatic treatment of hyperthyroidism and/or correcting hypothyroidism.

## 1. Introduction

The development of molecular biology and cancer immunology has brought drastic changes in anticancer therapies in recent years (DiMasi and Grabowski, 2007). In addition to conventional cytotoxic chemotherapy, new therapeutic approaches are now available, based 1/ on the molecular profile of the tumor - such as tyrosine kinase inhibitors (TKIs) which, according to their action profile, block certain self-induced signals from the tumor cell (this is the concept of personalized medicine); and 2/ on the lifting of the immune-tolerance barriers to cancer by means of immune checkpoint inhibitors (ICPIs).

TKIs are classified as targeted therapies because of their mode of action. They bind competitively to the ATP binding sites of tyrosine kinases, whether they are membrane receptor tyrosine kinases or cytosolic protein tyrosine kinases. The kinome defines the set of tyrosine kinase proteins in a cell. TKIs thus block some of these proteins that play a key role in cell signaling and whose activity is deregulated in cancers. As deregulated pathways tend to promote energy metabolism and cancer cell survival, thus TKIs can restore control of cell proliferation. The spectrum of activity of these TKIs is extremely variable from one molecule to another (inhibition of one to several tyrosine kinases). Some TKIs have also been designed to preferentially inhibit

angiogenesis and to limit the metastatic spread of cancer cells (Arora and Scholar, 2005; Krause and Van Etten, 2005) (Fig. 1). These compounds might hence exhibit toxicity against highly vascularized organs like thyroid gland. TKIs are now used in metastatic kidney cancers, gastrointestinal stromal tumors (GIST), chronic myeloid leukemias, acute lymphoblastic leukemias, some sarcomas, hepatocellular carcinomas, certain bronchial cancers, medullary thyroid cancer and differentiated thyroid cancer refractory to iodine-131.

The principle of immunotherapy against solid cancer is to amplify the adaptive cytotoxic T-cell-mediated antitumor immune reaction (Fig. 1). One effective strategy currently used is blocking some immune inhibitory “checkpoints” like PD1 (Programmed Cell Death 1), PDL1 (Programmed Cell Death Ligand 1) or CTLA4 (Cytotoxic T lymphocyte antigen-4) preventing them to blunt T-cell proliferation and activation against tumor cells (Brahmer et al., 2012; Topalian et al., 2012). Three families of ICPIs are currently marketed: anti-CTLA4 (ipilimumab, tremelimumab), anti-PD1 (nivolumab, pembrolizumab) and anti-PDL1 (avelumab, atezolizumab, durvalumab). These molecules have improved the survival of cancer patients but are accompanied by autoimmune side effects, manifested by various tissue inflammatory reactions, especially in the thyroid (Arora and Scholar, 2005; Brahmer et al., 2012; Eggermont et al., 2016; Gharwan and Groninger, 2016;

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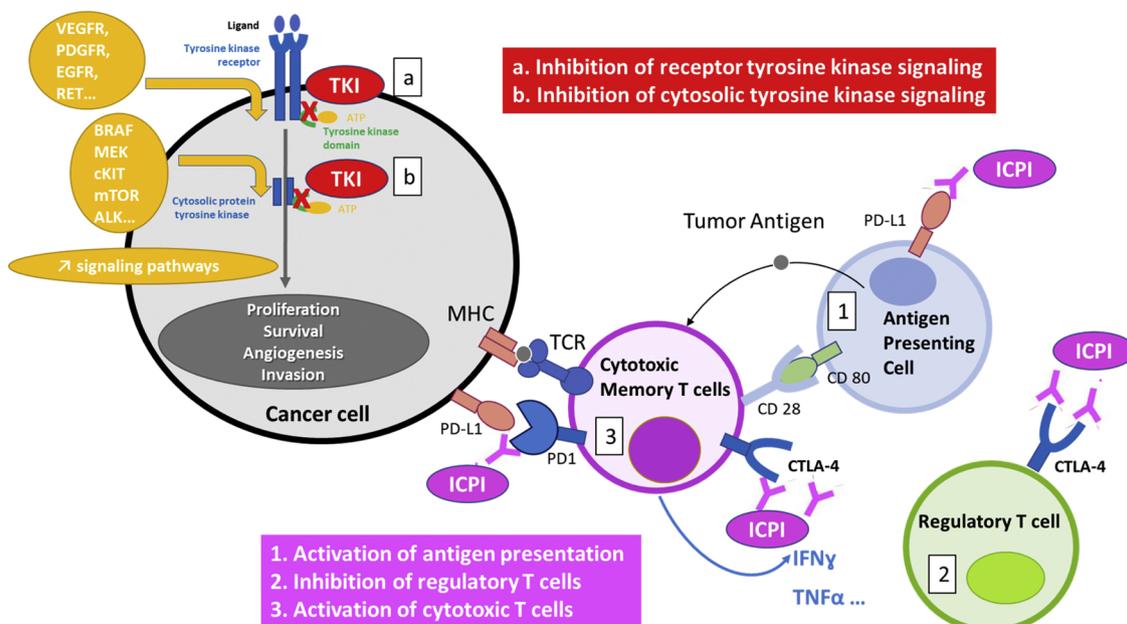


Fig. 1. Mechanisms of action of TKIs and ICPIs. Adapted from (Orlov et al., 2015).

TKIs block the activation of proteins involved in the signaling pathways of cell survival and angiogenesis (a,b). ICPIs block the action of immune tolerance effectors (1, 2) and induce the recruitment of cytotoxic T lymphocytes (3).

TKI: Tyrosine Kinase Inhibitor, symbolized by

ICPI: Immune Checkpoint Inhibitor (Anti-PD-1, Anti-PDL1, Anti-CTLA-4), symbolized by

ALK: Anaplastic lymphoma kinase, ATP: Adenosine triphosphate, B-RAF: B-Rapidly Accelerated Fibrosarcom, CD: Cluster of differentiation, CKIT: C-kit receptor, CTLA-4: Cytotoxic T Lymphocyte-Associated Antigen-4, EGFR: Endothelial Growth Factor Receptor, INFγ: Interferon gamma, MEK: Mitogen-activated Extracellular signal regulated Kinase, MHC: Major Histocompatibility Complex, mTOR: mechanistic target of rapamycin, PDGFR: Platelet Derived Growth Factor Receptor, PD1: Programmed cell Death-1, PDL1: Programmed Death-Ligand 1, RET: Rearranged during Transfection, TCR: T Cell Receptor, TNFα: Tumor Necrosis Factor-alpha, VEGFR: Vascular Endothelial Growth Factor Receptor.

Krause and Van Etten, 2005; Topalian et al., 2012).

The thyroiditis induced by these therapies occurs at varying frequencies and can be manifested by biological hyper- or hypothyroidism depending on when the thyroid disorder is recognized or both successively. Cooperation between endocrinologist and oncologist generally enables the continuation of anti-cancer therapy and the supervision of symptomatic treatment of dysthyroidism.

This article provides a comprehensive assessment of the literature relating to the thyroid side effects of TKIs and ICPIs.

## 2. Thyroid dysfunction associated with TKIs and ICPIs is common and benign (Table 1)

The prevalence of thyroid dysfunction (hypo- or hyperthyroidism) related to a TKI or ICPI varies considerably from about 3.1% to 100% depending on the type of molecule, the dose administered, the types of thyroid monitoring and the recording accuracy of these events (see Table 1 and Table 2) (Abdel-Rahman and Fouad, 2014; Barroso-Sousa et al., 2018b, 2018a; Boutros et al., 2016; de Filette et al., 2016; Delivanis et al., 2017; Fallahi et al., 2014; Gharwan and Groninger, 2016; Kim et al., 2010; Morganstein et al., 2017; Orlov et al., 2015; Pani et al., 2017; Sznol et al., 2017; Torino et al., 2009). Given the frequency of this iatrogenic dysthyroidism, it should be noted that the prevalence of clinical hypothyroidism in the general population is between 0.2% and 5.3% in Europe and between 0.3% and 3.7% in the United States, while the prevalence of clinical hyperthyroidism is similar in Europe and the United States (0.7% versus 0.5%) (Taylor et al., 2018). These figures depend of course on the definition used and the population studied (iodine-deficient or not) but illustrate the causality of these treatments in the thyroid dysfunctions identified.

The quality of report of thyroid toxicity induced by TKIs or ICPIs depends on the rigor of clinical trials that were not designed to evaluate

the frequency of thyroid side effects. Indeed, these studies list sometimes established or incipient hypothyroidism, sometimes variations of thyroid stimulating hormone (TSH) or increase in thyroid hormone therapy, sometimes global endocrine effects. In addition, the pattern of monitoring the thyroid biological parameters differed from one trial to another. Finally, the studies rarely detail previous or concomitant treatments, such as interferon, amiodarone, radiation therapy to the neck and brain, corticosteroid therapy and repeated iodine contrast injection for CT scan, which can also modify the thyroid function or thyrotropic hormone regulation. Moreover, the gradation of thyroid toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) scale used in oncology describes the outcome of the thyroid disorder but does not make it possible to decide on the treatment to be initiated. This specific management will depend on the amplitude of variations in the TSH/free T4 levels, the clinical impact, and the transient or permanent nature of dysthyroidism. In general, hospitalization is not required (grade 3) and the indication of symptomatic treatment of thyrotoxicosis or correction of hypothyroidism (grade 2) is not in itself a criterion of severity.

The probability of developing TKI-induced dysthyroidism depends on the patient's background (risk is higher in female and older patient groups), the existence of associated thyroid disorder, the duration of TKI exposure and the molecule (Beukhof et al., 2017; Funakoshi and Shimada, 2013; Illouz et al., 2009; Lechner et al., 2018). On the other hand, the type of cancer treated does not seem to be a factor modifying the risk of thyroid side effects.

Thus, TKI-induced thyroid toxicity involves mainly compounds targeting VEGFR1-3 (Vascular Endothelial Growth Factor Receptor) or PDGFR (Platelet Derived Growth Factor Receptor) such as sunitinib, sorafenib, axitinib and vandetanib unlike other TKI such as nilotinib, imatinib and dasatinib that do not target angiogenic receptors (Table 1) (Abdel-Rahman and Fouad, 2014; Kim et al., 2010). But this

**Table 1**  
Frequency and presentation of dysthyroidism during TKI therapy (number of patients with thyroid dysfunction/number of patients in the study).

Name of TKI Targeted tyrosine kinases Indications	References	Thyrotoxicosis	Transient Hypothyroidism	Definitive Hypothyroidism	Thyrotoxicosis then hypothyroidism	Dysthyroidism (within each study) minimum/maximum frequency	Dysthyroidism (all studies) main frequency
<b>Axitinib</b> (VEGFR 1-3, PDGFR, C-Kit) CCRCC	(Ohba et al., 2013)	5/6 (83%)	5/6 (83%)	ND	4/6 (66.6%)	6/6 (100%)	<b>137-157 / 580 (15.5-23.6%)</b>
	(Ueda et al., 2013)	ND	69/355 (19.4%)	ND	ND	69/355 (19.4%)	
	(Hutson et al., 2013)	ND	39/189 (20.6%)	ND	ND	39/189 (20.6%)	
	(Karam et al., 2014)	ND	17/24 (70.8%)	ND	ND	17/24 (70.8%)	
	(Daimon et al., 2012)	0/6	6/6 (100%)	ND	ND	6/6 (100%)	
	(Mukohara et al., 2010)	5/12 (41.7%)	7/12 (58.3%)	ND	3/12 (25%)	9/12 (75%)	
	(Tomita et al., 2011)	20/64 (31.3%)	31/64 (48.4%)	ND	ND	31-51/64 (48.4-79.7%)	
	(Motzer et al., 2013a)	ND	72/359	ND	ND	72/359 (20%)	
	(Kim et al., 2010)	2/10 (20%)	4/10 (40%)	1/10 (10%)	1/10 (10%)	6/10 (60%)	
	<b>Dasatinib</b> (BCR-ABL, Src, C-Kit, EphR) Acute lymphoblastic leukemia	(Kim et al., 2010)	1/8 (12.5%)	1/8 (12.5%)	0/8	0/8	
(de Groot et al., 2007)		ND	ND	9/15 (60%)	ND	9/15 (60%)	
(de Groot et al., 2005)		ND	7/8* (87.5%)	ND	ND	7/8 (87.5%)	
<b>Nilotinib</b> (BCR-ABL, C-Kit, LCK, EphA3,8, DDR1, DDR2, PDGFR, MAPK11, ZAK) CML	(Kim et al., 2010)	18/55 (32.7%)	6/55 (10.9%)	ND	5/55 (9.09%)	25/55 (45.4%)	<b>25/55 (45.40%)</b>
	(Motzer et al., 2013b)	ND	67/554 (12.1%)	ND	ND	67/554 (12.1%)	
<b>Pazopanib</b> (VEGFR-1-3, PDGFR, C-Kit) CCRCC, Sarcoma	(Matrana et al., 2013)	ND	17/112 (15.2%)	ND	ND	17/112 (15.2%)	<b>84/666 (12.6%)</b>
	(Pani et al., 2017)	1/25 (4%)	ND	11/25 (44%)	1/25 (4%)	11/25 (44%)	
<b>Regorafenib</b> (VEGFR 1-3, PDGFR, KIT, RET, FGFR 1-2, TIE2, DDR2, Thk2A, Eph2A, RAF-1, BRAF, SAPK2, PTK5) CCRCC, GIST, HCC	(Bruix et al., 2013)	ND	15/36 (41.7%)	ND	ND	15/36 (41.7%)	<b>26/61 (42%)</b>
	(Tamaskar et al., 2008)	1/39 (2.6%)	7/39 (17.9%)	ND	ND	(41.7-44%)	
<b>Sorafenib</b> (VEGFR 1-2, RET, PDGFR, C-KIT, RAF) CCRCC, HCC, Follicular thyroid Carcinoma refractory to Radioactive iodine	(Clement et al., 2008)	1/23 (4.3%)	7/23 (30.4%)	ND	ND	8/23 (34.8%)	<b>149-160/1455 (10.2-11%)</b>
	(Riesbeck et al., 2011)	ND	8/31 (25.8%)	ND	ND	8/31 (25.8%)	
	(Ueda et al., 2013)	ND	29/355 (8.2%)	ND	ND	29/355(8.2%)	<b>7.3-82.6%</b>
	(Hutson et al., 2013)	ND	7/96 (7.3%)	ND	ND	7/96 (7.3%)	
	(Miyake et al., 2010)	11/69 (15.9%)	46/69 (66.7)	ND	ND	46-57/69 (66.7-82.6%)	
	(Daimon et al., 2012)	0/12	6/12 (50%)	ND	ND	6/12 (50%)	
	(Kudo et al., 2018)	ND	8/475 (16.8%)	ND	ND	8/475 (16.8%)	
	(Motzer et al., 2013a)	ND	29/355 (8.2%)	ND	ND	29/355 (8.2%)	

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**Table 1** (continued)

Name of TKI Targeted tyrosine kinases Indications	References	Thyrototoxicosis	Transient Hypothyroidism	Definitive Hypothyroidism	Thyrototoxicosis then hypothyroidism	Dysthyroidism (within each study) minimum/maximum frequency	Dysthyroidism (all studies) main frequency
<b>Sunitinib</b> (VEGFR-2, PDGFR, c-KIT, RET, CSF-1R, FLT3) CCRCC, GIST, pancreatic NET	(Desai et al., 2006) (Rini et al., 2007) (Schoeffski et al., 2006) (Wong et al., 2007) (Mannavola et al., 2007) (Wolter et al., 2008) (Shinohara et al., 2011) (Riesenbeck et al., 2011) (Daimon et al., 2012) (Fallahi et al., 2014) (Rini et al., 2008) (Motzer et al., 2013b) (Motzer et al., 2012) (Akaza et al., 2015) (Coelho et al., 2016) (Gore et al., 2009) (Kappers et al., 2011) (Sabatier et al., 2012)	10/42 (23.8%) 10/66 (15.1%) 6/33 (18.2%) 3/40(7.5%) ND 3/59 (5.1%) 4/17 (23.5%) ND	7/42 (16.7%) 46/66 (69.7%) 15/33 (45.4%) 21/40 (52.5%) 17/24 (70.8%) 16/59 (27.1%) 9/17 (52.9%) 8/52 (15.4%)	15/42 (35.7%) ND ND ND ND ND ND ND	6/42 (14.3%) ND ND ND ND ND 4/17 (23.5%) ND	26/42 (61.9%) 46-56/66 (69.7-84.8%) 15-21/33 (45.4-63.6%) 21-24/40 (52.5-60%) 17/24 (70.8%) 16-19/59 (27.1-32.2%) 9-13/17 (52.9-76.4%) 8/52 (15.4%)	1318-1349/7532 (17.5-17.9%)
<b>Vandetanib</b> (VEGFR-2-3, RET, BRK, TIE2, EphA2, Src) Medullary thyroid cancer *	(Robinson et al., 2010) (Wells et al., 2012) (Lodish et al., 2015)	ND ND ND	2/17* (11.8%) 11/4/231* (49.3%) 10/11* (91%)	ND ND ND	ND 11/4/231* (49.3%) (11.8-91%)	2/17* (11.8%) 11/4/231* (49.3%) (11.8-91%)	126/259 (48.60%)
<b>Cabozantinib</b> (VEGFR-1-3, RET, MET, KIT, TRKB, FLT-3, AXL, ROS1, TYRO3, MER & TIE-2) CCRCC, Medullary thyroid cancer*	(Yavuz et al., 2014) (Pisciandaro et al., 2018) (Rabinowitz et al., 2018) (Choueiri et al., 2015) (Schlumberger et al., 2017) (Choueiri et al., 2018)	5/29 (17.2%) ND ND ND ND ND	21/29 (72.4%) 4/17 (13.8%) 4/8 (50%) 67/331 (20.2%) 26/214 (12.1%) 18/78 (23.1%)	11/29 (37.9%) ND ND ND ND ND	3/29 (10.3%) ND ND ND ND ND	27/29 (93.1%) 4/17 (23.5%) 4/8 (50%) 67/331 (20.2%) 26/214 (12.1%) 18/78 (23.1%) (12.1-93.1%)	146/677
<b>Lenvatinib</b> (VEGFR1-3, FGFR1-4, PDGFRα, KIT & RET) Follicular thyroid Carcinoma refractory to Radioactive iodine *, CCRCC (in association with everolimus)	(Koyama et al., 2018) (Kudo et al., 2018) (Motzer et al., 2015) (Yamada et al., 2011) (Schlumberger et al., 2016) (Ikeda et al., 2017)	0/5 ND ND ND ND ND	4/5 (80%) 78/476 (16.4%) 19/52 (36.5%) 7/27* (25.9%) 12/59* (20.3%) 10/46 (21.7%)	ND ND ND ND ND ND	ND ND ND ND ND ND	4/5 (80%) 78/476 (16.4%) 19/52 (36.5%) 7/27* (25.9%) 12/59 (20.3%) 10/46 (21.7%) (16.4-80%)	126/665 (18.9%)

CCRCC: Clear Cell Renal Cell Carcinoma, CML: Chronic Myeloid Leukemia, FGFR: Fibroblast Growth Factor Receptors, GIST: Gastro-Intestinal Stromal Tumor, HCC: Hepatocellular carcinoma, HL: Hodgkin's Lymphoma, HNSCC: Head and Neck Squamous Cell Carcinoma, ND: Non determined, NET: Neuroendocrine Tumor, NSCLC: Non-Small Cell Lung Cancer, PDGFR: Platelet Derived Growth Factor Receptor, TKI: Tyrosine Kinase Inhibitor, UC: Urothelial Carcinoma, VEGFR: Vascular Endothelial Growth Factor Receptors, \*: Increased doses of levothyroxine after total thyroidectomy.

**Table 2**  
Thyroid effects of different types of immunotherapy (number of patients with thyroid dysfunction/number of patients in the study).

Class of ICPI Name of ICPI Indications	References	Thyrototoxicosis	Transient Hypothyroidism	Definitive Hypothyroidism	Thyrototoxicosis then Hypothyroidism	Dysthyroidism (within each study)	Dysthyroidism (all studies)
Anti-CTLA4 <u>Ipilimumab</u> Melanoma/NSCLC	(Eggermont et al., 2016) (Robert et al., 2015) (Larkin et al., 2015) (Wolchok et al., 2017) (Hodi et al., 2016) (McDermott et al., 2013) (Postow et al., 2015) (Morganstein et al., 2017)	ND 6/256 (2.3%) 3/311 (2.7%) 3/311 (2.7%) 0/46 ND 0/46 20/126 (15.8%)	ND ND ND ND ND ND ND	48/471 (10.2%) 2/256 (0.8%) 13/311 (11.7%) 14/311 (12.6%) 6/46 (1.3%) 2/131 (1.5.3%) 7/46 (15.2%) 9/126 (7.1%)	ND ND ND ND ND ND ND ND	48/471 (10.2%) 8/256 (3.1%) 13/311 (11.7%) 14/311 (12.6%) 6/46 (1.3%) 2/131 (15.3%) 7/46 (15.2%) 29/126 (23%)	<b>127/1698 (7.4%)</b>
Anti-PD-1 <u>Nivolumab</u> Melanoma/NSCLC/ CRC/CC/HL/HNSCC/UC	(Borghaei et al., 2015) (Larkin et al., 2015) (Weber et al., 2015) (Ferris et al., 2016) (Wolchok et al., 2017) (Brahmer et al., 2015) (Antonia et al., 2016a,b)	4/287 (1.4%) 13/313 (4.1%) 5/268 (1.9%) 2/236 (0.8%) 14/313 (4.5%) ND 2/98 (2%)	ND ND ND ND ND ND ND	17/287 (5.9%) 27/313 (8.6%) 16/268 (6%) 9/236 (3.8%) 33/313 (10.5%) 5/131 (3.8%) 3/98 (3.1%)	ND 2/313 (0.6%) ND ND ND ND ND	17-21/287 (5.9-7.3%) 40/313 (12.8%) 16-21/268 (6-7.8%) 9-11/236 (3.8-4.7%) 33-47/313 (10.5-15%) 5/131 (3.8%) 3/98 (3.1%)	<b>133-158/1656 (8-9.5%)</b>
<u>Pembrolizumab</u> Melanoma/NSCLC/ CRC/CC/HL/HNSCC/UC/MSI + Cancers	(Robert et al., 2015) (Ribas et al., 2016) (Reck et al., 2016) (Bellmunt et al., 2017) (Garon et al., 2015) (Robert et al., 2015) (de Filette et al., 2016) (Delvantis et al., 2017) (Osorio et al., 2017)	17/278 (6.1%) 15/655 (2.3%) 12/154 (7.8%) 10/266 (3.8%) 9/495 (1.8%) ND 12/99 (12.1%) 7/93 (7.5%) 8/48 (16.7%)	ND ND ND ND ND ND 0/99 1/93 (1.1%) 0/48	25/278 (9%) 49/655 (7.5%) 14/154 (9.1%) 17/266 (6.4%) 34/495 (6.9%) 32/357 (9%) 15/99 (15.2%) 8/93(8.6%) 10/48 (20.8%)	ND ND ND ND ND ND 9/99 (9.1%) 3/93 (3.2%) 6/48 (12.5%)	42/278 (15.1%) 49- 64/655 (7.5-9.8%) 14-26/124 (9.1-21%) 17-27/266 (6.4-10.2%) 34-43/495 (6.9-8.7%) 32/357 (9%) 17/99 (17.2%) 13/93(14%) 12/48 (25%) <b>(7.5-25%)</b>	<b>230-283/2415 (9.5-11.7%)</b>
Anti-PDL1 <u>Atezolizumab</u> UC	(Fehrenbacher et al., 2016) (Peters et al., 2017) (Balar et al., 2017) (Atezolizumab, p.i)	ND ND ND 42/2616 (1.6%)	ND ND ND ND	9/142 (6.3%) 33/659 (5%) 8/119 (6.7%) 120/2616 (4.6%)	ND ND ND ND	9/142 (6.3%) 33/659 (5%) 8/119 (6.7%) 120-162/2616 (4.6-6.2%) <b>(4.6-6.7%)</b>	<b>170-212/3536 (4.8-6%)</b>
<u>Avelumab</u> Merkel Carcinoma	(Gulley et al., 2017) (Avelumab, 2017)	ND 8/1738 (0.5%)	ND ND	11/184 (6%) 90/1738 (5.2%)	ND ND	11/184 (6%) 98/1738 (5.6%) <b>(5.6-6%)</b>	<b>119/2024 (5.9%)</b>
<u>Durvalumab</u> UC ADDIN	(Antonia et al., 2016a,b) (Powles et al., 2017) (Durvalumab, 2017)	ND 10/191 (5.2%) 1/1417 (0.07%)	ND ND ND	10/102 (9.8%) 136/1417 (9.6%)	ND ND ND	10/102 (9.8%) 10-20/191 (5.2-10.5%) 136-137/1417 (9.6%) <b>(5.2-10.5%)</b>	<b>156-167/1608 (9.1-9.7%)</b>

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**Table 2 (continued)**

Class of ICPI Name of ICPI Indications	References	Thyrototoxicosis	Transient Hypothyroidism	Definitive Hypothyroidism	Thyrototoxicosis then Hypothyroidism	Dysthyroidism (within each study)	Dysthyroidism (all studies)
Immunotherapy combinations <i>Nivolumab + Ipilimumab</i>	(Larkin et al., 2015)	31/313 (10%)	ND	47/313 (15%)	12/313 (3.8%)	66/313 (21.1%)	173-226/947 (18.3-23.9%)
Melanoma	(Wolchok et al., 2017)	35/313 (11.1%)	ND	53/313 (16.9%)	ND	53-88/313 (16.9-28.1%)	
	(Hodi et al., 2016)	4/94 (4.3%)	ND	16/94 (17%)	ND	16-20/94 (17-21.3%)	
	(Antonia et al., 2016a,b)	10/115 (8.7%)	ND	14/115 (12.2%)	ND	14-24/115 (12.2-20.9%)	
	(Postow et al., 2015)	4/94 (4.3%)	ND	15/94 (16%)	ND	15-19/94 (20.2%)	
	(Morganstein et al., 2017)	4/18 (22.2%)	ND	5/18 (27.7%)	3/18 (16.7%)	9/18 (50%)	(12.2-50%)

CCRCC: Clear Cell Renal Cell Carcinoma, HL: Hodgkin Lymphoma, HNSCC: Head and Neck Squamous Cell Carcinoma, ICPI: Immune Checkpoint Inhibitor, MSI +: Microsatellite instability, ND: Non determined, NSCLC: Non-Small Cell Lung Cancer, P.I: Prescribing Information, UC: Urothelial Carcinoma.

observation requires a cautious interpretation given the small number of subjects in some studies using TKIs. By contrast, thyroid dysfunction has not been reported *in vivo*, with treatments such as monoclonal antibodies directing against VEGF (bevacizumab and aflibercept) though reduction of thyroid perfusion may occur (van der Veldt et al., 2013) nor with TKIs targeting EGFR (Epidermal Growth Factor Receptor) (cetuximab and panitumumab), ALK (Anaplastic Lymphoma Kinase) and MEK (Mitogen-activated Protein Kinase Kinase).

Iatrogenic thyroid disorder related to TKIs is mainly caused by destructive thyroiditis, probably due to vascular damage. A thyrotoxic phase is often reported first after a median treatment duration of 6 weeks (1–70 weeks), then hypothyroidism occurs after a median duration of 22 weeks (1–135) (Abdel-Rahman and Fouad, 2014; Kim et al., 2010). Most cases of hyperthyroidism are brief (nearly 80%) and almost always of grade 1 or 2 (98–100% of patients) (Bianchi et al., 2013; Kim et al., 2010). Hyperthyroidism affects an average of 15.8% of patients undergoing TKI therapy (Abdel-Rahman and Fouad, 2014; Fallahi et al., 2014; Illouz et al., 2009; Kim et al., 2010; Ohba et al., 2013; Torino et al., 2009) and corresponds rather to a state of transient thyrotoxicosis, most often subclinical (Table 1). The occurrence of hypothyroidism is late and prolonged (Table 1), easy to recognize and therefore reported more frequently (18% of cases). In a recent meta-analysis, the relative risk of hypothyroidism was 3.59 [95% CI: 2.40–5.38; p < 0.0001] (Abdel-Rahman and Fouad, 2014). TKI-induced hypothyroidism may persist when treatment is discontinued (Beukhof et al., 2017; Illouz et al., 2009; Wolter et al., 2008).

Thyroid dysfunction is also a major side effect of ICPIs. It occurs in 3.1–25% of patients treated with ICPI as monotherapy, affecting an average 20% of patients receiving multiple ICPI combinations (Table 2). The risk of hyperthyroidism and hypothyroidism is higher in patients treated with anti-PD1 versus anti-PD-L1 and anti-CTLA-4 (Barroso-Sousa et al., 2018a) (Table 2). When a combination of immunotherapy is prescribed, the risk of thyroid toxicity is roughly double than in monotherapy. Schematically, the dysthyroidism under ICPI occurs between the 2nd and the 4th cycle, but there have been cases of dysthyroidism reported up to 3 years after the initiation of treatment (de Filette et al., 2016) (Table 3). When a combination of ICPI is prescribed, dysthyroidism usually appears in the first cycle (de Filette et al., 2016). The risk of developing thyroid disorder depends, as for TKIs, on the patient’s background (female predominance and in the elderly), the existence of associated thyroid disorder, the exposure time and the combination with another ICPI (Porta et al., 2016). It is not formally established that a high titer of anti-thyroperoxidase (TPO-Abs) or anti-thyroglobulin (Tg-Abs) antibodies, or that TSH levels at the high end of the normal range before the prescription of immunotherapy are associated with an increased risk of thyroid toxicity.

Some studies have shown a statistical correlation between the occurrence of thyroid dysfunction when prescribing TKIs or ICPIs and a better prognosis in progression-free survival and overall survival. (Beukhof et al., 2017; Osorio et al., 2017; Pani et al., 2017; Riesenbeck et al., 2011; Schmidinger et al., 2011). This can be explained by the anti-angiogenic effect of TKIs or the immune-mediated effects of immunotherapy involving both cancer and thyroid. Therefore, the thyroid function could serve as an indirect “sensor” for the effect of TKIs or ICPIs (Makita and Iiri, 2013). However, there is an analytical bias because surviving patients will have more time to develop treatment-related toxicity than those who die early.

### 3. Pathophysiology of thyroid side effects induced by TKIs and ICPIs (Fig. 2)

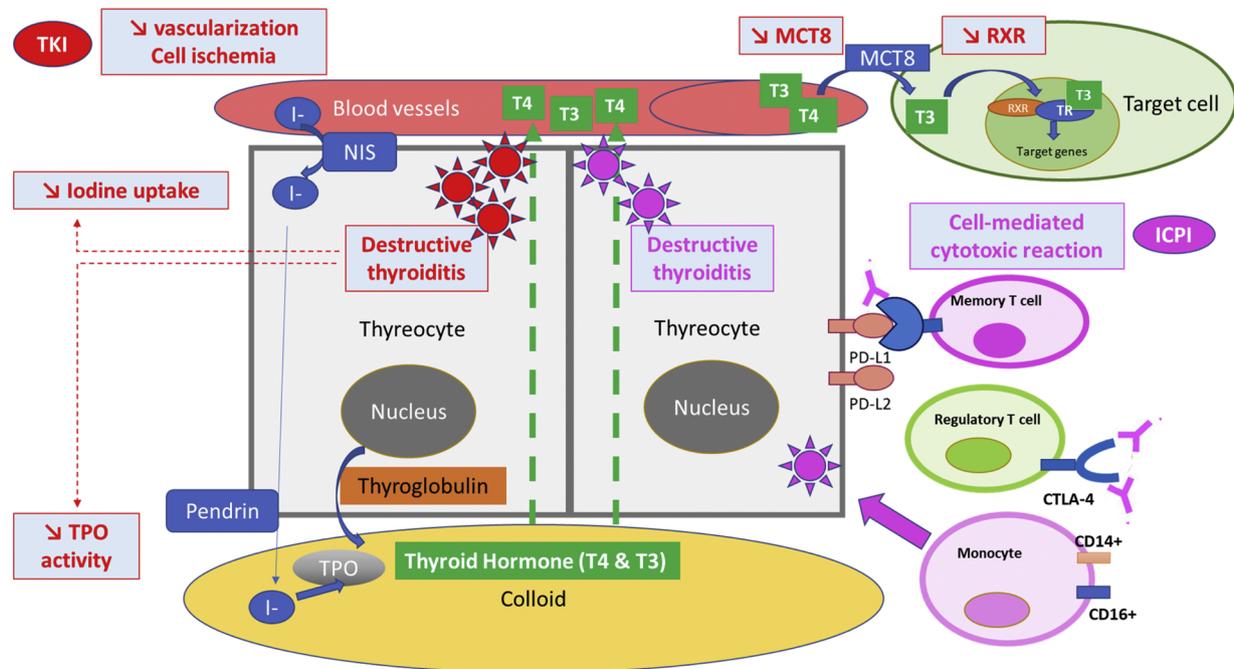
The cumulative clinical experience of recent years and the basic studies have led to a better understanding of the mechanisms of thyroid dysfunction. Schematically, we may consider that the iatrogenic thyroiditis of TKIs is linked to vascular damage and the iatrogenic thyroiditis of ICPIs is based on an inflammatory mechanism by autoimmune

**Table 3**

Median time in months to occurrence of hyperthyroidism as well as hypothyroidism according to the immunotherapy molecule (Eggermont et al., 2016; Jaafar et al., 2018; Morganstein et al., 2017).

Class of ICPI	Anti-CTLA4	Anti-PD1	Anti-PDL1			
Name of ICPI	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Avelumab	Durvalumab
Hyperthyroidism	1.64 (1.18–3.64)	0.76–1.48 (0.03–14.2)	1.4 (0.03–22)	3.2 (1.4–5.8) in UC 4.9 (0.69–31) in NSCLC	2.8 (0.49–13)	1.41 (0.46–2.33)
Hypothyroidism	2.13 (0.85–2.96)	2-3 (0.03–22)	3.5 (0.03–19)	5.4 (0.69–11.3) in UC 4.8 (0.49–31) in NSCLC		1.38 (0.49–7.85)

ICPI: Immune Checkpoint Inhibitor, NSCLC: Non-Small Cell Lung Cancer, UC: Urothelial Carcinoma.



**Fig. 2.** The pathophysiological mechanisms of dysthyroidism under TKIs and ICPI therapy.

Tyrosine Kinase Inhibitor (TKI), Immune Checkpoint Inhibitor (ICPI)

CD: Cluster of differentiation, CTLA-4: Cytotoxic T Lymphocyte-Associated Antigen-4, I-: Iodine, NIS: Sodium-iodide symporter, MCT8: Monocarboxylate transporter 8, PDL1-2: Programmed death-ligand 1–2, TPO: Thyroperoxidase, RAR: Retinoic acid receptor, TR: Thyroid hormone receptor.

reaction. Additional pathophysiological hypotheses have been put forward to explain the worsening hypothyroidism of the thyroidectomized subject, involving alteration of the transport and metabolism of thyroid hormones with certain TKIs.

Sunitinib-induced thyroid toxicity has been the most studied clinical model for 10 years. Desai et al, have conducted a prospective study with 42 patients treated by sunitinib. Persistent primary hypothyroidism occurred in 15 (36%) patients. Six of 15 (40%) hypothyroid patients had suppressed TSH concentrations before developing hypothyroidism suggesting induced thyroiditis through a destructive mechanism (Desai et al., 2006). Such biphasic thyroiditis pattern was reported from 3 to 87.4 to 66.6 % of cases (Table 1). First, thyrotoxicosis is reported, accompanied by a transient increase in thyroglobulin associated with TKI-induced cell lysis, and then hypothyroidism develops secondarily. This sequence is repeated at each cycle when an intermittent on/off pattern is prescribed. When several cycles of treatment are performed, a decreased vascularization of the thyroid parenchyma is reported with thyroid hypotrophy which will eventually be responsible for permanent hypothyroidism if the treatment is prolonged. (Desai et al., 2006; Kappers et al., 2011; Makita and Iiri, 2013; Sato et al., 2010). The thyroiditis reported with anti-angiogenic TKIs is therefore the consequence of devascularization of the thyroid vesicles, which represent the functional units of the thyroid. The vascularization abnormalities and the resulting cellular hypoxia are related to capillary regression

mediated by the anti-VEGFR effect (Cao, 2014; Kamba et al., 2006; Kappers et al., 2011; Makita et al., 2010; Yang et al., 2013). There is both functional and structural damage. Indeed, VEGF-A/VEGFR2 signaling is directly involved in all fenestrated capillaries (which allows the introduction of iodine and the secretion of thyroid hormones through the endothelial cells) and in the trophic development of the thyroid tissue, according to the work conducted in murine models (Jang et al., 2017). Therefore blocking this signaling pathway also leads to a decreased synthesis of thyroid hormones (Cao, 2014; Kamba et al., 2006; Kitajima et al., 2012; Makita et al., 2010; Mannavola et al., 2007; Yang et al., 2013). Other intra-thyroid mechanisms have been suspected in the occurrence of hypothyroidism under TKI, such as the inhibition of iodine uptake by thyrocytes and the inactivation of thyroperoxidase (Liwanpo et al., 2014; Mannavola et al., 2007; Salem et al., 2008; Simonides et al., 2008; Wong et al., 2007). These hypotheses were subsequently invalidated because this functional impairment was a logical consequence of the ischemia and tissue damage induced by TKI. Regarding the central nervous system, it is also assumed that some TKIs, by decreasing the production of nitric oxide, could decrease the secretion of TRH by the paraventricular nucleus of the hypothalamus and thus decrease the secretion of TSH by the thyrotrophic pituitary cells (Ohba et al., 2013). TKIs also have effects on the peripheral metabolism of thyroid hormones regardless of their own thyroid toxicity. In thyroidectomized patients treated with TKIs, there is an increased

demand for thyroid hormone. Indeed, TKIs such as sunitinib or sorafenib increase the activity of type 3 deiodinase (as evidenced by the decrease in T3/T4 and T3/rT3 ratios) resulting in hypothyroidism because of lower tissue availability of the active hormone T3, locally inactivated in T2 or rT3 (Abdulrahman et al., 2010; Beukhof et al., 2017; Kappers et al., 2011). Finally, other TKIs such as imatinib, bosutinib and dasatinib, but also sunitinib, can inhibit the transporter of MCT8 thyroid hormones (monocarboxylate transporter) across the plasma membrane, reducing the supply of T3 to peripheral tissues but also centrally, in the thyrotropic cell (Braun et al., 2012). Thyroid hormones exert their action by binding to specific nuclear receptors that are heterodimerized with a retinoic acid receptor. Sunitinib, by binding to retinoic acid receptors, could prevent this heterodimerization and thus inhibit the expression of target genes (Shu et al., 2016). Sunitinib also has immunostimulatory properties by inhibiting the expression of CTLA4 and PD1 on CD4+ and CD8+ T cells. If this cytotoxic lymphocyte activation is beneficial for tumor control, it can be exercised against healthy tissues, affecting organs such as the thyroid, on the ICPI toxicity model detailed below (Ozao-Choy et al., 2009).

The pathophysiological conception of dysthyroidism linked to immunotherapy is still likely to evolve with the emergence of new research (Angell et al., 2018; Delivanis et al., 2017). A mechanism of silent lymphocytic thyroiditis that in its clinical presentation is similar to the postpartum thyroiditis, at the time of physiological reactivation of the immune system, is currently assumed (Iwatani et al., 1988). Similarly, in the patient under ICPI therapy, following the amplification of the adaptive immune response, a cell-mediated cytotoxic immune reaction occurs linked to mature NK (Natural killers) cells, T helper CD4+ cells and cytotoxic CD8+ T cells (Delivanis et al., 2017). Unlike the typical autoimmune diseases for example, ICPI-related iatrogenic autoimmune disorders are accompanied by a decrease in some immunosuppressive cells and an increase in HLA-DR expression on the surface of CD14+CD16+ monocytes (Delivanis et al., 2017). Some researchers have suggested that thyroiditis induced by pembrolizumab may be related to monocytic activation induced by this overexpression of HLA-DR. These monocytes would infiltrate the thyroid tissue after recognition of antigens similar to the tumor antigens and exert their cytotoxic action, explaining why the first phase of thyrotoxicosis is contemporaneous with an increase in thyroid volume, before returning to normal or before a possible evolution towards hypothyroidism. The analysis of a thyroid fine needle aspiration cytology carried out in a patient with thyroiditis receiving combined treatment with nivolumab and ipilimumab, had in fact numerous necrotic cells and plenty of CD163 histiocytes and lymphocytes (Angell et al., 2018). Other arguments support the hypothesis of a cytotoxic cell-mediated response rather than the induction of humoral immunity: 1/ pembrolizumab - which gives thyroid toxicities - is an IgG4 antibody, an immunoglobulin subclass that is not associated with antibody or complement-mediated cytotoxicity (Davies and Sutton, 2015); 2/ TPO-Abs do not seem to have a pathogenic role for the ICPI-induced dysthyroidism (Delivanis et al., 2017); 3/ in classical autoimmune thyroiditis (Graves' disease, Hashimoto's thyroiditis), the circulating anti-TPO and Tg-Abs levels correlate with T-cell infiltration into the thyroid gland (Huber et al., 2002; Yoshida et al., 1978), which does not seem the case for the thyroiditis induced by ICPIs.

For the issue of thyroid disorder 2–5 times more common with anti-PD1/PDL1 compared to anti-CTLA4, two explanations are proposed. This difference could be related to the strong expression of PDL1 and PDL2 in healthy thyroid tissue, making it a preferred target for cytotoxic T cells and, in addition, to the weak CTLA4 expression in circulating lymphocytes and intra-thyroid lymphocytes (Delivanis et al., 2017; Yamauchi et al., 2017). On the other hand, particular genetic backgrounds could increase the susceptibility to autoimmune toxicities related to ICPI. An HLA typing predisposing to autoimmune thyroid disorders also seems to promote the occurrence of thyroiditis under ICPI therapy (Jacobson et al., 2008; Menconi et al., 2008; Nada and

Hammouda, 2014). The role of certain polymorphisms of CTLA4 and PD1 has also been mentioned, but this hypothesis is not confirmed (Han et al., 2006; Orlov et al., 2015; Tomer, 2010).

#### 4. Description of thyroid disorders

##### A Clinical presentation

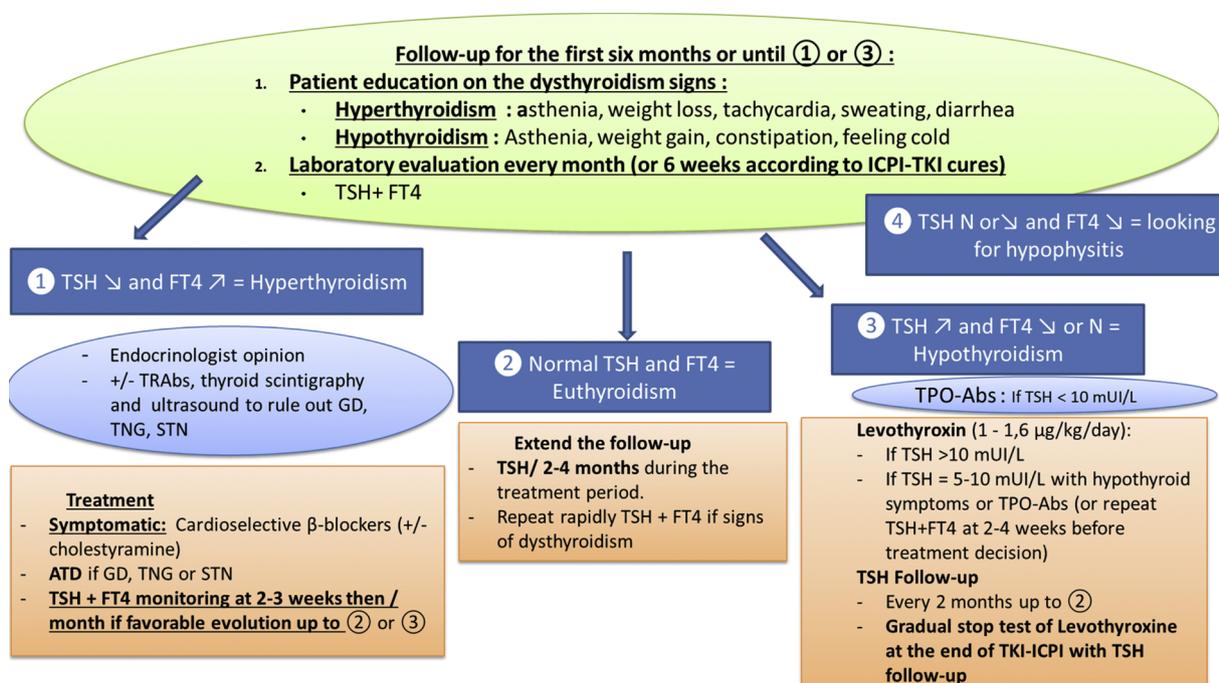
The clinical presentation of the thyroid disorder is varied. Two situations are encountered. Indeed, these disorders can occur in a healthy thyroid (strictly normal thyroid function and morphology) or in a patient with a preexisting known or unknown thyroid disease: nodular thyroid disease, nodular goiter, autoimmune thyroiditis with or without thyroid dysfunction. It will be necessary to discern the toxicity inherent to the anti-cancer treatment from the potential baseline thyroid condition. The classic presentation of dysthyroidism associated with TKIs or ICPIs is silent thyroiditis. This thyroiditis begins with a phase of thyrotoxicosis secondary to thyroid vesicles destruction releasing the stock of available thyroid hormones and thyroglobulin into the bloodstream. Clinical manifestations may be absent or minor and go unnoticed, or may cause palpitations, tachycardia, heat intolerance, weight loss, irritability, sleep disorders, or asthenia. Thyrotoxicosis may also be reported in hypothyroid patients prior to the initiation of ICPIs or TKIs (Villa et al., 2018). Genuine thyrotoxicosis storms have rarely been described; they are often secondary to a combination between several ICPIs (McMillen et al., 2016). In the phase of thyrotoxicosis, there is a return to euthyroidism preceded or not by a transition to hypothyroidism that is sometimes not reversible. As for conventional thyroiditis, it is considered that 50% of these patients will progress to permanent hypothyroidism secondary to the destruction of thyroid follicles. In the hypothyroid phase, patients also have few symptoms, inconsistently complaining of weight gain, chills, constipation, and fatigability or reporting these symptoms to their neoplastic disease. The transition between the thyrotoxicosis and hypothyroidism phases seems much faster and earlier with ICPIs (shorter form of thyrotoxicosis) than with TKIs.

In patients treated with sunitinib using a discontinuous schedule, TSH increases at the end of the 4 weeks of the ON phase (treatment intake) and returns to normal at the end of the 2 weeks of the OFF phase (treatment discontinuation). After several treatment cycles, the rate of TSH increases in stages at the end of the OFF phase: the initially intermittent hypothyroidism becomes permanent (Illouz et al., 2009). Sometimes hypothyroidism is the initial mode of revelation without previous thyrotoxicosis. Hypothyroidism can sometimes be severe if diagnosed late as reported under treatment with nivolumab (Khan et al., 2017). The risk of permanent hypothyroidism seems greater under TKI therapy especially as accompanied by thyroid atrophy.

Finally, rare cases of Graves' disease without expression of anti-RTSH antibodies (TRAbs) or orbitopathies without hyperthyroidism have been described (imatinib, sorafenib, ipilimumab, tremelimumab and pembrolizumab) (Azmat et al., 2016; Borodic et al., 2011; de Filette et al., 2016; Eroukhanoff et al., 2016; Gan et al., 2017; Konca Degertekin et al., 2012).

- What biological and morphological assessments should be made?

The symptoms and physical signs of dysthyroidism under TKI and ICPI therapy are often discrete. Paraclinical evaluation is essential to establish the diagnosis of iatrogenic thyroiditis and eliminate a differential diagnosis by listing the patient's co-morbidities and confounding factors (nutritional status, treatments, injections of iodinated contrast agents). During the thyrotoxicosis phase, TSH is low and free T4 increased (or normal in cases of subclinical hyperthyroidism). During this phase, TRAbs are often absent - they are measured only when there is diagnostic doubt with Graves' disease. During the hypothyroid phase, TSH is high and free T4 is low (or normal in cases of subclinical



**Fig. 3.** Treatment of dysthyroidism.

ATD: Synthetic antithyroid drug, GD: Grave's disease, ICPI: Immune checkpoint inhibitor STN: Solitary Toxic Nodule, TKI: Tyrosine Kinase Inhibitor, TNG: Toxic Nodular Goiter, TPO-Abs: anti-thyroid peroxidase antibodies, TRAbs: anti-thyrotropin receptor antibodies, we: weeks.

hypothyroidism). The measurement of TPO-Abs will only be performed if the TSH level rises moderately, between 5 and 10 mIU/L to argue the benefit of a levothyroxine supplementation from the outset. During this phase, TPO-Abs and/or Tg-Abs are present, but generally low (25% of patients under TKI therapy and in 50 to 67% of cases under immunotherapy). They usually occur after the prescription of these anti-cancer drugs and their presence is associated with thyroid dysfunction in 80% of cases (de Filette et al., 2016; Kobayashi et al., 2018; Osorio et al., 2017). As a reminder, in the case of lowered TSH associated with a low or normal free T4 in a patient treated with immunotherapy and especially with anti-CTLA4, a complete assessment of the pituitary function is recommended to rule out hypophysitis with corticotropin deficiency (measure the cortisol levels every 8 h and ACTH if cortisol levels are low) or combined thyrotropic deficiency.

The thyroid gland has a different ultrasound appearance in thyroiditis under TKI and ICPI therapy. Indeed, under ICPI therapy we can see first a transient hyperechoic thyroid hypertrophy and sometimes hypervascular hypertrophy, and then a hypoechoic appearance (Angell et al., 2018; Kobayashi et al., 2018). Under TKI therapy, a hypoechoic, heterogeneous appearance and decreased vascularization are initially observed by Doppler, then a progression to thyroid atrophy (this is the case for 89% of patients treated with sunitinib with hypothyroidism) (Pani et al., 2015).

In the phase of biological hyperthyroidism, in case of diagnostic doubt with Graves' disease or functional nodular dystrophy, a thyroid scintigraphy may be performed on endocrinology recommendations (checking for the absence of recent injection of iodinated contrast products which would give false negative results). This examination does not show a tracer uptake in the case of iatrogenic thyroiditis at the stage of lesion damage.

If an <sup>18F</sup>FDG PET/CT scan is performed for cancer monitoring, patients developing thyroiditis under immunotherapy will show an increased thyroid uptake of 18 FDG, in a diffuse manner, as described in common autoimmune thyroiditis (Hashimoto's thyroiditis, Graves' disease) (de Filette et al., 2016; Delivanis et al., 2017; Karantanis et al., 2007).

## 5. Therapeutic aspect (Fig. 3)

No predictor of the occurrence of dysthyroidism has been clearly identified to date for TKIs and for ICPIs. Thus, in order to better detect the occurrence of thyroid dysfunction, it is essential to teach the patient to recognize the symptoms of hypothyroidism and thyrotoxicosis, to provide this case history routinely during the oncology consultations. However, given the paucisymptomatic nature of these thyroid dysfunctions and their early onset after the initiation of TKIs or ICPIs, we suggest, as recently recommended by the French Society of Endocrinology, to measure the TSH/free T4 levels before starting treatment, and every 3–4 weeks during the first 6 months as changes in free T4 levels precede the changes in TSH by 3–6 weeks (Drui et al., 2018; Illouz et al., 2018). After this period, the laboratory tests may be conducted every 2–3 months, and simplified by the TSH measurement alone.

Screening for anti-thyroid autoimmunity (TPO-Abs, Tg-Abs, TRAbs) before initiation of TKIs or ICPIs is not recommended. A history of thyroid disorder does not contraindicate initiation of TKI or ICPI therapy. In hypothyroid patients in these classes of anti-cancer drugs, adjustment of the replacement therapy may be necessary; it will be performed in connection with the patient's endocrinologist.

The occurrence of thyroid dysfunction, usually grade 1 or 2, does not contraindicate the continuation of TKI or ICPI therapy.

During the thyrotoxicosis phase, a symptomatic treatment will be initiated including low-dose non-cardioselective β-blockers such as propranolol, in the absence of contraindication, in order to control cardiothyrosis and tremors (Drui et al., 2018; Illouz et al., 2018). Severe thyrotoxicosis may justify the addition of cholestyramine treatment for its chelation effect of thyroid hormones in the enterohepatic circulation. Based on current literature data, there is no evidence to support routine use of corticosteroids except in the case of Graves' orbitopathy (Bartalena et al., 2016). Treatment with synthetic antithyroid drugs will be initiated only in cases of Graves' disease, toxic nodular goiter or solitary toxic nodules detected during this monitoring.

Given the risk of progression to hypothyroidism in the weeks following thyrotoxicosis, regular monitoring of TSH and free T4 is required. Hyperthyroidism is almost always resolving, followed or not by a hypothyroidism phase. In the hypothyroid phase, the  $\beta$ -blocker treatment is of course discontinued and a supportive treatment with levothyroxine may be started. This treatment will only be prescribed if the TSH is greater than 10 mIU/L or between 5 and 10 mIU/L in symptomatic patients or those with elevated TPO-Abs (Drui et al., 2018; Illouz et al., 2018). In asymptomatic patients with TSH between 5 and 10 mIU/L, a second TSH + free T4 test may be performed every 2–4 weeks in order to avoid treating transient hypothyroidism or conversely, not to overlook worsening hypothyroidism that may deserve further hormone replacement. Classically, levothyroxine may be initiated at a dose of 1–1.6  $\mu\text{g}/\text{kg}/\text{day}$ , except in elderly patients or patients with cardiovascular co-morbidities who will start with lower intakes (25–50  $\mu\text{g}/\text{day}$ ) to be increased by levels of 12.5  $\mu\text{g}$ . A follow-up TSH test will be performed 6 weeks after the prescription of Levothyroxine.

Patients with already substituted hypothyroidism should have the TSH levels carefully monitored in order to adjust the levothyroxine doses if necessary.

## 6. Conclusion

In patients treated with TKIs or ICPIs, the thyroid toxicities are common and pauci-symptomatic at the beginning of their evolution but can lead to prolonged hypothyroidism that should not be ignored. Endocrinologists and oncologists must systematize the laboratory follow-up of the thyroid based on the logistical or monitoring constraints already imposed on the patient. At least the TSH + free T4 measurement should be proposed monthly for 6 months, and then have this monitoring expanded and simplified if there is no event or following the episode of thyroiditis, after the euthyroidism is restored with or without treatment. In both cases, even if the pathophysiological mechanisms involved are singular, giving in particular a clinical expression of different chronology depending on the nature of the immune or vascular damage, the resultant is destructive thyroiditis. It is typically manifested by a thyrotoxicosis phase (by definition insensitive to synthetic antithyroid drugs) whose transient symptoms can be treated with non-cardioselective  $\beta$ -blockers or even with cholestyramine. Then the patient may develop hypothyroidism, which is reversible in half of the cases, to be supplemented by Levothyroxine, depending on the intensity of the signs of hypometabolism and the elevation of TSH levels. The occurrence of thyroid dysfunction does not contraindicate the continuation of TKI or ICPI therapy.

Collaboration between oncologists and endocrinologists for diagnosis, treatment and therapeutic education will be essential to good management of these thyroid side effects.

## Author disclosure statement

The authors have no competing interests and nothing to disclose.

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