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THYROID DYSFUNCTIONS INDUCED BY IMMUNE CHECK-POINT INHIBITORS

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იმუნური მაკონტროლებელი მოლეკულების ინჰიბიტორებით გამოწვეული ფარისებრი ჯირკვლის დისფუნქციები

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რეზიუმე

იმუნური სისტემა კიბოს განვითარებისა და პროგრესირებისაგან იცავს ორგანიზმს. იმუნოთერაპიული მიდგომები, რომელიც სიმსივნის მიკროგარემოში დათრგუნული იმუნური უჯრედების ფუნქციას გაააქტიურებს, ბოლო ათეული წელია ინტენსიურად ინერგება კლინიკურ პრაქტიკაში. სამედიცინო საზოგადოების განსაკუთრებული ყურადღება მიიპყრო ავთვისებიანი სიმსივნეების იმუნოთერაპიამ ე.წ. Immune checkpoints inhibitors - იმუნური მაკონტროლებელი მოლეკულების ინჰიბიტორებით (ი.მ.მ.ი). ი.მ.მ.ი-ს ძირითადად წარმოადგენს ციტოტოქსიური T ლიმფოციტის ანტიგენ 4-ის (CTLA-4), უჯრედის დაპროგრამებული სიკვდილის პროტეინ 1-ის (PD-1), უჯრედის დაპროგრამებული სიკვდილის პროტეინის ლიგანდ 1-ის (PD-L1) საწინააღმდეგო მონოკლონური ანტისხეულები. ისინი T უჯრედებს სიმსივნური უჯრედების წინააღმდეგ ააქტიურებენ, თუმცა მთელ რიგ აუტოიმუნურ გვერდით ეფექტებს აღძრავენ, რომლებიც სამედიცინო ლიტერატურაში ცნობილია როგორც იმუნური გვერდითი მოვლენები. იმუნოთერაპიით გამოწვეული გვერდითი მოვლენები, ქიმიოთერაპიასთან ასოცირებული გვერდითი მოვლენებისგან განსხვავებით, ხასიათდებიან დაყოვნებული რეაქციით და გახანგრძლივებული მოქმედებით, რომელთა ეფექტური მართვა და აღმოფხვრა დამოკიდებულია მათ ადრეულ ამოცნობაზე.

წინამდებარე მიმოხილვა მიზნად ისახავს გაზარდოს ონკოლოგებისა და ენდოკრინოლოგების თეორიული და პრაქტიკული ცოდნა იმუნური მაკონტროლებელი მოლეკულების ინჰიბიტორებით გამოწვეული თირეოიდული დისფუნქციების შესახებ, კრიტიკულად გადაამუშაოს ამ პაციენტთა მართვის მიდგომები, რათა უზრუნველყოფილი იქნას ონკოპაციენტების სიცოცხლის ხარისხის გაუმჯობესება.

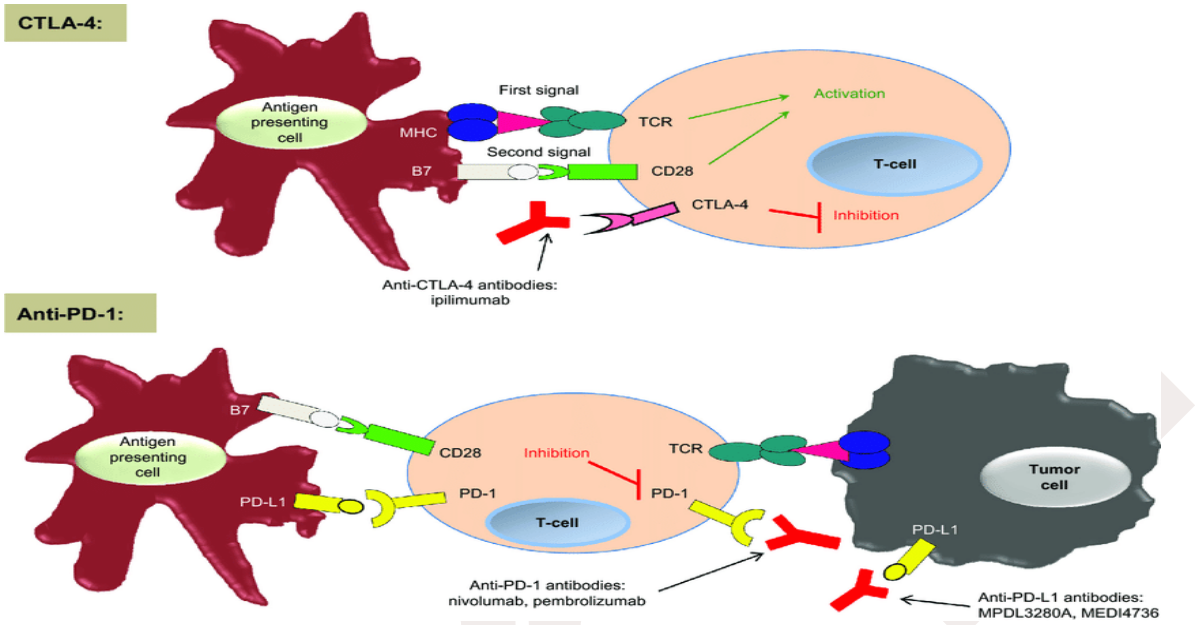
Introduction. Until recently, chemotherapy, radiation and surgery were considered the cornerstones of cancer treatment [1]. Advances in immunotherapy have revolutionized tumors treatment. Currently, the most widely used approach is the administration of targeted monoclonal antibodies (mAbs) directed against T cell activation [2].

Under homeostatic conditions, there is a balance between pro-inflammatory and anti-inflammatory signaling maintained by immune checkpoints [1]. These immune checkpoints are a set of inhibitory and stimulatory pathways that directly affect the function of immune cells. Malignant cells disrupt this balance by promoting an immunosuppressive state that favors immune evasion and tumor growth [1].

Cancer cells recruit or induce development of regulatory T cells (Tregs), downregulate tumor antigen expression, induce T cell tolerance and/or apoptosis and produce immune suppressive cytokines that stimulate inhibitory immune check-points. This leads to a unique and highly immunosuppressive tumor microenvironment (TME) [1]. In an attempt to overcome these immunosuppressive conditions, immune check-point inhibitors act by blocking the effects of selected inhibitory pathways [1]. The best described immune checkpoints are CTLA-4, PD-1, PD-L-1[1].

CTLA-4 is constitutively expressed by regulatory T cells and upregulated after T cells activation, acting as an "OFF" switch. CTLA-4 binds the B7 ligand on antigen presenting cell (APC). Binding CTLA-4, immune check-point inhibitor prevents it from binding with B7, and allows B7 to bind with CD28, in this way inducing the immune system to attack tumor cells [3].

PD-1 is present on T, B, and NK cells, and binds to PD-L-1, expressed by tumor cells, preventing apoptosis of the cell expressing PD-L-1 by the immune system. ICIs, that bind either PD-L-1 or PD-1, prevent this process [3].



Simplified concept of CTLA-4 and PD-1 immune checkpoints. Notes: In the priming phase, antigen-presenting cells present antigens to the T-cell. Two signals are required to initiate a T-cell response. CTLA-4 is upregulated after T-cell activation and inhibits the T-cell response. Anti-CTLA-4 antibodies bind to CTLA-4, turning off the 'inhibitory signal', thus resulting in an enhancement of T-cell function. In the effector phase, the PD-1 inhibitory receptor is expressed by the T-cell and, when it is engaged by its ligands PD-L1 and PD-L2, it serves to inhibit the T-cell response. Anti-PD-1 antibodies bind to PD-1, turning off the 'inhibitory signal' in the peripheral tissues and enhancing T-cell function. PD-1/PD-L1 interactions are complex, and this interaction is also involved in the priming phase. We have chosen to portray the main concepts for both of these immunologic checkpoints in this figure for simplicity. Abbreviations: CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte-associated antigen; MHC, major histocompatibility complex; PD, programmed cell death; TCR, T-cell receptor [4].

Currently FDA approved seven ICIs for the treatment of different solid tumors: CTLA-4 inhibitor – ipilimumab, PD-1 inhibitors – pembrolizumab, nivolumab and cemiplimab and PD-L-1 inhibitors – atezolizumab, avelumab and durvalumab [5,6]. Table-1 summarizes the different ICIs and their main clinical indications [1,5,7].

TUMOR	ANTI-PD-1			ANTI-PD-L1			ANTICTLA4
	PEMBROLIZUMAB	NIVOLUMAB	CEMIPLIMAB	ATEZOLIZUMAB	AVELUMAB	DURVALUMAB	IPILIMUMAB
MELANOMA				V	V	V	
NSCLC					V	V	V
HNSCC				V	V	V	V
RCC	V			V	V	V	V
UROTHELIAL							V
cHL		V		V	V	V	V
MSI-H		V		V	V	V	V
MCC	V	V		V		V	
CSCC			V				

NSCLC-non-small cell lung cancer, HNSCC- head and neck squamous cell carcinoma, RCC-renal cell carcinoma, cHL- classical Hodgkin's lymphoma, MSI-H - high microsatellite instability tumors, MCC- Merkel cell carcinoma, CSCC- cutaneous squamous cell carcinoma.

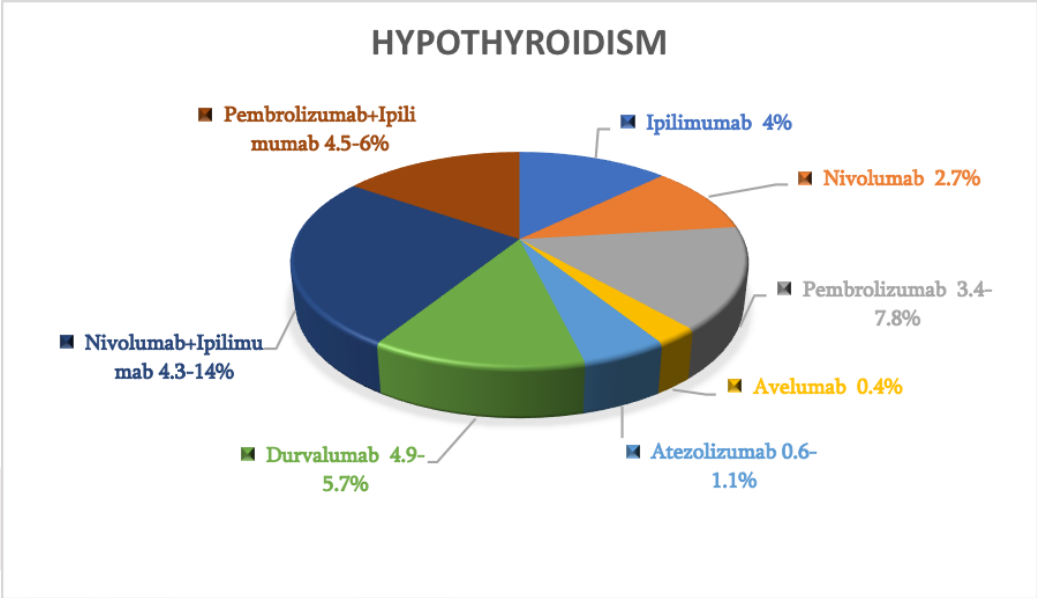
Immune inhibitory pathways have significant role in the maintenance of self-tolerance, therapeutic targeting of these pathways can lead to imbalances in immunologic tolerance, that manifest as immune-related adverse events (irAEs) [7]. A broad range of autoimmune toxicities have been reported [4]. Endocrine diseases are among the most common associated irAEs, especially immune related thyroid dysfunctions.

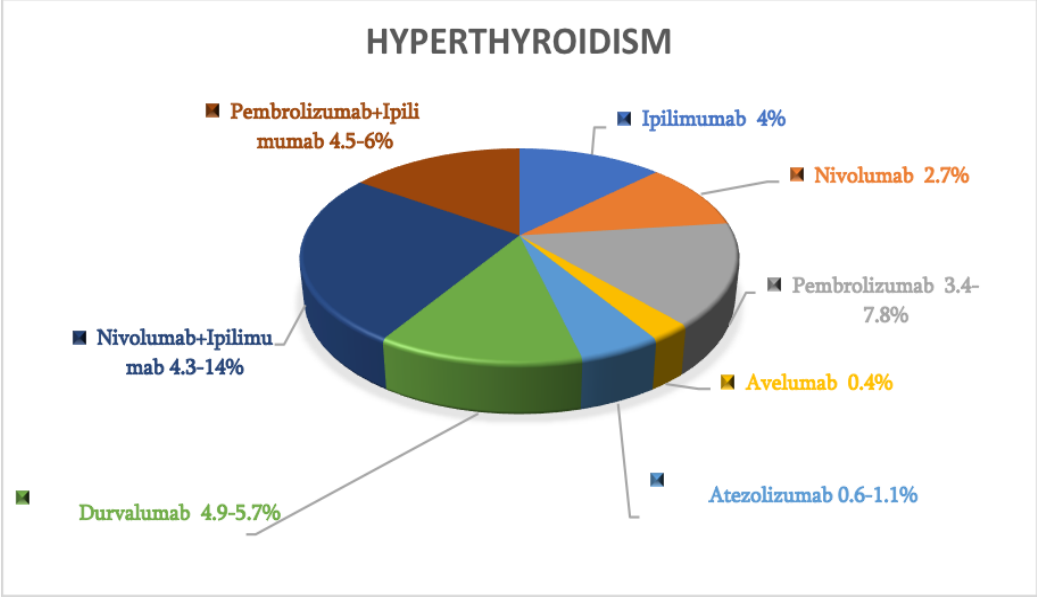
The main goal of this article is to describe and analyze the incidence, pathogenesis, clinical manifestations and guidelines on the management and screening of thyroid disorders associated with ICIs [5]. Thus, physicians and specialists involved in treating patients can easily identify and manage immune-related side effects.

Thyroid Disorders. The spectrum of thyroid disturbances under ICIs can present as thyrotoxicosis, hypothyroidism, painless thyroiditis, thyroid eye disease and occasionally sever form such as thyroid storm [3,5,8].

The incidence of thyroid disorders differs between different ICI classes [5]. Chart-1 represents reported frequencies of hypothyroidism (**%**) and hyperthyroidism (**%**) [7,9]. Thyroid dysfunctions are mostly provoked by anti-PD-1 or anti-PD-L-1 mAbs and incidence ranges from 4 to 19.5% [7].

Chart-1. Immune-related Hypothyroidism and Hyperthyroidism frequencies (%) under different ICIs.





The median time to onset of hyperthyroidism is reported to be around 21 days in combination therapy (CTLA-4 +PD-1/PD-L-1 inhibitors) and 75 days in monotherapy with PD-1 inhibitors [5, 10]. The predicted incidence of hypothyroidism was higher with combination therapy approximately 13% and 7% for PD-1 inhibitors alone [5,10]. However, immunotherapy is a "living drug" and the modulation of the adaptive immune response might persist for years, resulting in immune-related thyroid dysfunctions after cessation of treatment [11].

Although the etiology of immune-related thyroid disorders remains elusive, the knowledge that the antitumor immunity and the autoimmunity represents indistinguishable models of attack by T cells rationalizes the assumption that ICIs manipulating the T cells signaling toward unleashing the antitumor response, can exacerbate the autoimmunity [11]. But there are some data that provide support for a distinct pattern of immune-mediated thyroid destruction in autoimmune patients compared with PD-1 inhibitor (pembrolizumab) induced thyroiditis patients. In pembrolizumab-induced thyroiditis patients there was no detectable surface expression of PD-1 on T cells. On the contrary, PD-1 expression on T cells from autoimmune patients was not different than healthy volunteer controls. As such, whereas the role of PD-1 dependent T cell activation may contribute to T cell mediated destruction of the thyroid in pembrolizumab treated patients, the role of PD-1 in the autoimmune setting seems less likely, consistent with known antibody-mediated mechanism for the latter [12].

The clinical manifestations of either hypothyroidism (bradycardia, fatigue, weight gain, constipation, dry skin, cold intolerance) or thyrotoxicosis (tachycardia, fatigue, weight loss, palpitations, new onset atrial fibrillation, diarrhea, heat intolerance, excessive diaphoresis) may be misinterpreted as symptoms of the underlying malignancy [5,7,13]. The diagnosis of thyroid dysfunction due to ICI is based on TSH and FT4 levels to differentiate primary from central thyroid disorders [5] In case of thyrotoxicosis additionally total T3 is necessary to be measured [5] and complementary investigations are useful, in the case of severe thyrotoxicosis or an unfavorable evolution: TRAb assay, Ultrasound-Doppler, and iodine/99mTc scintigraphy should then be performed to distinguish thyroid disruption from hyperfunction [5,14].

The handling of immune-related thyroid disorders depends on the level of TSH and the severity of symptoms. In the absence of prospective data, these patients should be managed as per established guidelines based upon pooled clinical experience [15]. Table-2 depicts current guidelines for management of immune-related thyroid disorders [16,17].

Table-2. Management of immunotherapy-related hyperthyroidism and hypothyroidism.

ir Adverse Event	ASCO Clinical Practice Guidelines		SITC Clinical Practice Guidelines
Hypothyroidism	Grade1: TSH, 10 mIU/L and asymptomatic	Should continue ICI with close follow-up and monitoring of TSH, FT4	► Thyroid function (TSH, fT4) should be tested every 4–6 weeks during ICI treatment and should continue to be tested every 6–12 months following the conclusion of ICI treatment. ► Patients with elevated TSH and normal fT4 should receive repeat TSH
	Grade2: Moderate symptoms; able to perform ADL; TSH persistently. 10 mIU/L	May hold ICI until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist. 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal	

		TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICI therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable	and fT4 testing routinely, and if this pattern persists without hypothyroidism symptoms, then levothyroxine treatment should be considered. Levothyroxine should be administered to patients with hypothyroidism at 1.5–1.6 μg/kg/day for young, healthy patients, and should be administered at 25 or 50 μg/day for patients >65 years of age or with heart disease. ► Patients with symptoms of hypothyroidism and/ or with elevated TSH and low fT4 should be tested for morning cortisol to identify possible concurrent adrenal insufficiency. ► Patients with low TSH and normal fT4 should receive repeat TSH and fT4 testing routinely, and if symptoms of hyperthyroidism or high fT4 develop patients should be treated with beta-blockers. Patients with asthma or chronic obstructive pulmonary disease should be treated with cardio selective beta-blockers such as atenolol or metoprolol. ►
	Grade3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICI until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2	
	Additional considerations For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 mg/kg/d For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 mg Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase) Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated		
Hyperthyroidism	Grade1: Asymptomatic or mild symptoms	Can continue ICI with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism or hypothyroidism	

	Grade2: Moderate symptoms, able to perform ADL	Consider holding ICI until symptoms return to baseline Consider endocrine consultation b-Blocker (e.g., atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration for persistent hyperthyroidism (. 6 weeks) or clinical suspicion, work-up for Graves' disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves' disease	Patients with persistently low TSH and high fT4 should be evaluated for hyperthyroidism and Graves' disease etiology
	Grade3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICI until symptoms resolve to baseline with appropriate therapy Endocrine consultation b-Blocker (e.g., atenolol, propranolol) for symptomatic relief for severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU)	

Conclusion. As check-point blockade is becoming a standard of care and several combination therapy strategies enter clinical practice [9], increased awareness is imperative at any time during treatment with immune check-point inhibitors and long after treatment cessation. Severe symptoms indicative of thyroid dysfunction requires prompt intervention, while in case of non-severe and non-specific symptoms close monitoring is advocated [11]. The precise mechanism is not well understood why some patients are more prone than others to develop endocrinopathies by ICIs [5,18]. Therefore, further research and investigation are needed to identify the patients who are at risk for immune-related thyroid toxicity. A further step that should be followed is the identification of biomarkers which can indicate when is best to use the checkpoint inhibitors [19].

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THYROID DYSFUNCTIONS INDUCED BY IMMUNE CHECK-POINT INHIBITORS

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SUMMARY

The immune system is the core defense against cancer development and progression. Failure of the immune system to recognize and eliminate malignant cells plays an immense role in the pathogenesis of cancer. The paramount achievement in immunotherapy particularly – Immune Check-point Inhibitors (ICI) over the recent decade has brought about major paradigm shift in cancer treatment. ICIs, represented mainly by inhibitory monoclonal antibodies – anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) (ipilimumab), anti-programmed cell death protein 1 (PD-1-pembrolizumab/nivolumab/cemiplimab), Anti-PD-1 Ligand molecules (PD-L-1-atezolizumab/avelumab/durvalumab) reactivate the immune system against tumor cells but can also trigger a myriad of autoimmune side effects, termed immune-related adverse events (irAEs). Immunotherapy related adverse events typically have a delayed onset and prolonged duration compared to adverse events from chemotherapy, and its effective management depends on early recognition and prompt intervention with immune suppression and/or immunomodulatory strategies.

The present review aims to raise awareness about thyroid side effects of immune check-point inhibitors to physicians who are taking care of cancer patients and to specialists - mainly oncologists and endocrinologists who are urged to cooperate for the management of thyroid immunotoxicity.

Keywords: immune check-point inhibitors, thyroid side effects, anti-CTLA-4, anti-PD-1, anti-PD-L-1 monoclonal antibodies.