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Targeting PD-1/PD-L1 in Advanced Thyroid Cancer: Therapeutic Efficacy, Predictive Biomarkers, and Clinical Challenges

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Abstract

Context: Thyroid cancer is the most common endocrine malignancy and generally has a favorable prognosis. However, aggressive subtypes and advanced radioactive iodine-refractory disease remain associated with limited therapeutic options and poor outcomes. The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway has emerged as an important regulator of immune escape and a potential therapeutic target in advanced thyroid cancer.

Evidence Acquisition: This narrative review examines evidence on PD-1/PD-L1 pathway biology, interactions between this pathway and the thyroid tumor immune microenvironment, molecular regulation, clinical significance, therapeutic applications, mechanisms of resistance, and future perspectives.

Results: The PD-1/PD-L1 axis promotes immune evasion by suppressing T-cell activation, driving T-cell exhaustion, and establishing an immunosuppressive tumor microenvironment. PD-L1 expression is detectable across thyroid cancer subtypes, with the highest frequency reported in poorly differentiated and anaplastic carcinomas. The BRAF V600E mutation, mitogen-activated protein kinase pathway activation, PI3K/AKT signaling, inflammatory cytokines, and hypoxia contribute to PD-L1 regulation. Clinical responses to checkpoint blockade are heterogeneous, and the absence of validated predictive biomarkers remains a major obstacle. PD-L1 expression alone is insufficient for reliable patient selection.

Conclusions: Targeting the PD-1/PD-L1 pathway offers therapeutic potential for selected patients with advanced thyroid cancer. Further progress requires integrated biomarker strategies that combine tumor genomics, immune profiling, and microenvironmental characteristics, as well as a better understanding of resistance mechanisms and validation in thyroid-specific clinical trials.

Keywords: Thyroid Cancer, PD-1, PD-L1, Cancer Immunotherapy

1. Introduction

Differentiated thyroid carcinoma (DTC), comprising papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), accounts for approximately 90% of thyroid malignancies and generally has an excellent prognosis after surgery, radioactive iodine (RAI) therapy, and thyroid-stimulating hormone suppression. However, a subset of patients develops radioactive iodine-refractory disease, characterized by loss of iodine avidity, disease progression, and limited treatment options. In addition, poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC) are aggressive subtypes associated with rapid progression, resistance to standard therapy, and poor survival. Medullary thyroid carcinoma (MTC), which arises from parafollicular C cells rather than follicular epithelium, does not respond to RAI and requires systemic therapy in advanced disease (1-4). These therapeutic challenges have stimulated interest in alternative treatment modalities, including immunotherapy.

Cancer immunotherapy has transformed the management of several advanced malignancies by restoring the immune system's ability to recognize and

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eliminate tumor cells. Immune checkpoints are physiological mechanisms that maintain tolerance and prevent excessive immune activation; however, cancer cells can exploit these pathways to evade immune surveillance. Among these pathways, the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis is the most extensively investigated (5).

PD-1 is an inhibitory receptor expressed mainly on activated T lymphocytes, whereas PD-L1 is expressed on tumor cells, antigen-presenting cells, and stromal cells within the tumor microenvironment. Engagement of PD-1 by PD-L1 recruits the phosphatases SHP-1 and SHP-2, suppressing T-cell receptor signaling, reducing cytokine production, impairing cytotoxicity, and driving progressive T-cell exhaustion (6). Tumor cells thereby create an immunosuppressive environment that facilitates tumor growth and metastatic progression.

Increasing evidence indicates that thyroid cancer is immunologically active rather than an immune-desert malignancy. The thyroid tumor microenvironment contains tumor-associated macrophages, regulatory T cells, myeloid-derived suppressor cells, natural killer cells, dendritic cells, and tumor-infiltrating lymphocytes. The balance between immune activation and suppression influences tumor behavior and therapeutic response (7). In this context, dysregulation of the PD-1/PD-L1 pathway has emerged as an important mechanism of immune evasion.

PD-L1 expression has been reported across histological subtypes, although its frequency and clinical significance vary. In a large screening study of 407 primary thyroid cancers, tumoral PD-L1 was expressed in 6.1% of PTC, 7.6% of FTC, and 22.2% of ATC, illustrating both the subtype gradient and the comparatively low positivity rates obtained with stringent scoring (8). Molecular alterations commonly observed in thyroid cancer, including BRAF V600E, RAS mutations, RET rearrangements, and TERT promoter mutations, may influence PD-L1 regulation through mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT, and inflammatory cytokine signaling (9). PD-L1 expression therefore appears to reflect interactions among tumor genetics, cellular signaling, and immune pressure during tumor evolution.

Beyond its biological role, the PD-1/PD-L1 pathway has attracted attention as a potential diagnostic, prognostic, and predictive biomarker. Associations between PD-L1 expression and tumor size, extrathyroidal extension, lymph node metastasis, recurrence, and survival have been reported, but findings conflict across studies, largely because of differences in immunohistochemical methodology, antibody clones, scoring systems, and patient populations (10). The clinical utility of PD-L1 as a stand-alone biomarker therefore requires further validation.

Early clinical evidence suggests that selected patients with advanced thyroid cancer, especially those with aggressive or RAI-refractory disease, may benefit from checkpoint blockade. Nevertheless, responses remain variable, and resistance limits long-term success. Current research therefore focuses on predictive biomarkers and rational combinations with tyrosine kinase inhibitors, molecularly targeted agents, and radiotherapy (11, 12). Emerging checkpoints such as LAG-3, TIGIT, and TIM-3 may offer additional opportunities (13).

In this review, we discuss the molecular mechanisms underlying PD-1/PD-L1 regulation in thyroid cancer, the pathway's interaction with the tumor immune microenvironment, its clinical significance, current therapeutic evidence, and future perspectives. We integrate molecular insights with emerging clinical data to clarify the evolving role of PD-1/PD-L1 targeting in precision medicine for thyroid cancer. Finally, we discuss the mechanisms underlying tumor nonresponse to checkpoint inhibition.

2. The PD-1/PD-L1 Immune Checkpoint Pathway: Molecular Biology and Regulation

2.1. Structure and Physiological Function of PD-1/PD-L1 Signaling

PD-1, encoded by the PDCD1 gene on chromosome 2q37, is an inhibitory checkpoint receptor belonging to the CD28 family within the immunoglobulin superfamily. It is expressed primarily on activated CD4+ and CD8+ T lymphocytes and also on B cells, natural killer cells, and monocytes under inflammatory conditions (6, 14). Unlike stimulatory receptors, PD-1 negatively regulates immune activation and maintains peripheral tolerance (14).

PD-1 contains an extracellular immunoglobulin variable-like domain, a transmembrane region, and a cytoplasmic domain with two signaling motifs: an immunoreceptor tyrosine-based inhibitory motif and an immunoreceptor tyrosine-based switch motif. Ligand binding leads to phosphorylation of these motifs and recruitment of the Src homology region 2-containing phosphatases SHP-1 and SHP-2. These phosphatases inhibit T-cell receptor–associated signaling, including the PI3K/AKT and RAS/RAF/MEK/ERK pathways, thereby reducing T-cell proliferation, cytokine secretion, and cytotoxicity (15).

PD-L1 (B7-H1, CD274), encoded on chromosome 9p24.1, is the principal ligand of PD-1. Under physiological conditions, its expression is limited and contributes to immune homeostasis by protecting normal tissues from

immune-mediated injury. However, malignant cells can induce PD-L1 as an adaptive mechanism of immune escape; tumor-associated PD-L1 engages PD-1 on cytotoxic lymphocytes, resulting in functional exhaustion of tumor-specific T cells (14, 16).

2.2. PD-1/PD-L1-Mediated Immune Escape in Cancer

Tumor immune escape is a multistep process involving impaired antigen recognition, suppression of effector function, and the establishment of an immunosuppressive microenvironment. In most malignancies, PD-L1 is induced through two broad mechanisms. Intrinsic oncogenic signaling, notably via PI3K/AKT/mTOR and MAPK, directly increases PD-L1 transcription and surface expression. In contrast, interferon-gamma (IFN-gamma) released by activated T cells stimulates PD-L1 expression through the JAK/STAT pathway, creating a negative feedback loop that limits immune-mediated tumor destruction, a phenomenon known as adaptive immune resistance (17).

2.3. Relevance of PD-1/PD-L1 Biology to Thyroid Cancer

The regulation of PD-1/PD-L1 is particularly relevant in thyroid cancer because this malignancy is characterized by substantial genomic diversity and variable immune infiltration. Alterations affecting MAPK signaling, including BRAF mutations and RET rearrangements, may influence both PD-L1 expression and immune cell recruitment. Aggressive subtypes such as ATC also exhibit chronic inflammation, immune suppression, and increased checkpoint molecule expression, providing a biological rationale for checkpoint blockade (9). Because single-agent PD-1/PD-L1 inhibition has shown variable efficacy in thyroid cancer, integrating molecular profiling with immune characterization is likely to be a critical step toward precision immunotherapy.

3. The Tumor Immune Microenvironment of Thyroid Cancer and Its Interaction With the PD-1/PD-L1 Axis

3.1. The Immune Landscape of Thyroid Cancer

The tumor immune microenvironment is a critical determinant of cancer initiation, progression, metastasis, and treatment response. Tumor behavior is strongly influenced by dynamic interactions between cancer cells and the surrounding immune, stromal, and vascular compartments (18). In thyroid cancer, these interactions are particularly relevant because histologic subtypes exhibit distinct immune profiles, ranging from relatively immune-infiltrated differentiated tumors to highly immunosuppressive, aggressive malignancies, such as ATC.

The thyroid tumor microenvironment comprises tumor-infiltrating lymphocytes (TILs), tumor-associated macrophages (TAMs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), natural killer cells, dendritic cells, cancer-associated fibroblasts, and endothelial cells. The balance between antitumor activation and immunosuppression determines whether immune surveillance controls tumor growth or tumor cells escape elimination (19).

3.2. Tumor-Infiltrating Lymphocytes and T-Cell Exhaustion

CD8+ cytotoxic T cells are the primary effectors responsible for recognizing and eliminating malignant cells. CD8+ infiltration has been demonstrated in thyroid carcinomas, indicating that immune recognition occurs within the thyroid tumor microenvironment (11). Despite the presence of tumor-reactive lymphocytes, their antitumor activity is frequently impaired by checkpoint activation.

Chronic antigen exposure leads to T-cell exhaustion, characterized by reduced proliferative capacity, impaired cytokine secretion, decreased cytotoxicity, and increased expression of inhibitory receptors, including PD-1, TIM-3, LAG-3, and TIGIT (20). In thyroid cancer, increased PD-1 expression on TILs, together with PD-L1 expression on tumor or immune cells, may create an immunosuppressive feedback loop that prevents effective tumor clearance. The presence of exhausted T cells provides the biological rationale for PD-1/PD-L1 blockade, which can partially restore T-cell function by interrupting inhibitory signaling.

3.3. Tumor-Associated Macrophages and Immune Suppression

Macrophages are among the most abundant immune populations in solid tumors. In response to environmental signals, they acquire different phenotypes: classically activated M1 macrophages are proinflammatory and antitumoral, whereas alternatively activated M2-like macrophages promote tumor growth, angiogenesis, tissue remodeling, and immune suppression (21).

In thyroid cancer, particularly in aggressive subtypes, increased TAM infiltration has been associated with tumor invasion, lymph node metastasis, and reduced survival. TAMs contribute to immune escape by secreting immunosuppressive cytokines, such as IL-10 and TGF-beta, and expressing checkpoint ligands, including PD-L1 (22). Interactions between tumor cells and macrophages may create a positive feedback loop in which inflammatory mediators further stimulate PD-L1 expression.

3.4. Regulatory T Cells and Myeloid-Derived Suppressor Cells

Regulatory T cells maintain immune tolerance but may also facilitate tumor progression by suppressing antitumor immunity. Increased infiltration of CD4+CD25+FOXP3+ Tregs has been reported in thyroid cancer and is associated with immune suppression and disease progression (23). Tregs act through the secretion of immunosuppressive cytokines, metabolic disruption of effector T cells, and modulation of antigen-presenting cell function. They can also enhance PD-1/PD-L1-mediated escape by promoting an environment favorable to tumor survival.

MDSCs represent another major immunosuppressive population. They suppress T-cell activation through reactive oxygen species, nitric oxide, arginase-1, and immunosuppressive cytokines. Although MDSCs have been studied more extensively in other malignancies, emerging evidence indicates that they also contribute to immune dysfunction in advanced thyroid cancer (24).

3.5. Cancer-Associated Fibroblasts and Stromal Regulation of Immune Escape

Nonimmune stromal cells also shape tumor immunity. cancer-associated fibroblasts regulate extracellular matrix remodeling, invasion, angiogenesis, and immune cell recruitment. They promote immune evasion by producing chemokines that attract immunosuppressive cells and releasing factors such as TGF-beta that inhibit T-cell function. They may also indirectly enhance PD-L1 expression and contribute to checkpoint resistance (25). In aggressive thyroid cancer variants, stromal activation and fibrosis may create physical and biochemical barriers that limit immune cell infiltration.

4. Molecular Regulation of PD-L1 Expression in Thyroid Cancer

4.1. Overview

In thyroid cancer, PD-L1 expression is not simply a consequence of immune activation; rather, it reflects the integration of oncogenic signaling, inflammatory pathways, hypoxic stress, and epigenetic modification (26). Understanding these mechanisms is important because PD-L1 expression may influence tumor aggressiveness, immune escape, and responsiveness to checkpoint inhibitors. Several alterations that characterize thyroid carcinogenesis, particularly those affecting the MAPK and PI3K/AKT pathways, have been implicated in PD-L1 upregulation and may contribute to the immunosuppressive phenotype of advanced disease (Table 1).

4.2. BRAF V600E Mutation and PD-L1 Expression

BRAF V600E is the most frequent genetic alteration in PTC and a major driver of MAPK pathway activation. Constitutive stimulation of the RAF-MEK-ERK cascade promotes proliferation, invasion, epithelial-mesenchymal transition, and altered immune interactions (27).

Activated MAPK signaling can enhance PD-L1 transcription through downstream transcription factors, including AP-1 and STAT-related pathways. Several studies have reported higher PD-L1 expression in BRAF-mutated thyroid carcinomas than in BRAF wild-type carcinomas. BRAF V600E has also been linked to reduced major histocompatibility complex (MHC) class I expression, a mechanism of immune escape that is reversible in vitro with interferon or MEK inhibition (28). However, this association is not uniform: in a whole-section study of 126 PTCs, neither PD-L1 nor PD-1 expression correlated significantly with BRAF V600E immunoexpression (29).

4.3. MAPK Pathway Activation and Immune Checkpoint Regulation

The MAPK pathway is a central signaling network in thyroid carcinogenesis; alterations in BRAF, RAS, and RET result in persistent MAPK activation. Beyond its oncogenic role, MAPK signaling influences tumor immunity by regulating cytokine production, antigen presentation, and checkpoint expression. Activated ERK signaling enhances the transcriptional activity of factors involved in PD-L1 regulation (30). MAPK-driven PD-L1 expression may therefore represent a mechanism through which genetically altered tumor cells adapt to immune pressure, providing a rationale for combining MAPK pathway inhibitors with PD-1/PD-L1 blockade.

4.4. PI3K/AKT/mTOR Pathway

Alterations affecting the PI3K/AKT/mTOR pathway, including PIK3CA mutations, PTEN loss, and activation of downstream components, have been associated with increased PD-L1 expression across different histological types of thyroid cancer, predominantly follicular and anaplastic tumors (31). AKT/mTOR activation enhances PD-L1 expression through increased protein translation, stabilization of PD-L1 messenger RNA, and activation of transcriptional regulators. In thyroid cancer, these abnormalities are particularly relevant in advanced and poorly differentiated tumors, where they may contribute to both disease progression and immune resistance. Inhibition of this pathway could therefore enhance sensitivity to checkpoint blockade.

4.5. RET and RAS Alterations

Table 1. Molecular Mechanisms Regulating PD-L1 Expression in Thyroid Cancer [a]

Molecular Pathway / Alteration	Mechanism of PD-L1 Regulation	Association with Thyroid Cancer	Potential Therapeutic Implication
BRAF V600E mutation	Activates RAF-MEK-ERK signaling, leading to transcriptional activation of immune checkpoint-related genes and increased PD-L1 expression; also linked to reduced MHC class I expression.	Common in papillary thyroid carcinoma and associated with aggressive features such as extrathyroidal extension and lymph node metastasis; the correlation with PD-L1 is not uniform across studies.	Combination of BRAF/MEK inhibitors with PD-1/PD-L1 blockade may enhance immune response.
MAPK pathway activation (BRAF, RAS, RET alterations)	Persistent MAPK signaling promotes inflammatory cytokine production, tumor cell survival and checkpoint upregulation.	Central driver pathway in differentiated thyroid carcinoma.	MAPK inhibition may modify the tumor immune microenvironment and improve immunotherapy efficacy.
PI3K/AKT/mTOR pathway activation	Enhances PD-L1 translation and protein stability through downstream signaling and promotes immunosuppressive tumor behavior.	Frequently involved in advanced and poorly differentiated thyroid cancers.	Targeting PI3K/AKT/mTOR signaling may overcome immune resistance mechanisms.
IFN-gamma/JAK/STAT pathway	IFN-gamma released by activated T cells induces STAT1 and IRF-1 activation and PD-L1 transcription (adaptive immune resistance).	A major mechanism of PD-L1 induction in immune-infiltrated thyroid tumors.	Indicates that PD-L1 expression may reflect both immune activation and immune suppression.
HIF-1alpha / hypoxia signaling	Hypoxic stress induces HIF-1alpha binding to the PD-L1 promoter, increasing PD-L1 expression.	Relevant in aggressive thyroid cancers with necrosis, rapid growth and poor vascular organization.	Targeting hypoxia-related pathways may improve response to checkpoint blockade.
TERT promoter mutations	May indirectly promote immune escape through genomic instability and tumor evolution.	Associated with poorly differentiated and anaplastic thyroid carcinoma, especially when co-occurring with BRAF V600E.	May identify high-risk patients requiring novel therapeutic strategies.
Epigenetic and post-transcriptional regulation	DNA methylation, histone modification and chromatin remodeling influence CD274 transcription; specific microRNAs regulate PD-L1 mRNA stability and translation.	Contributes to tumor heterogeneity and variable PD-L1 expression; an emerging mechanism in thyroid cancer immune regulation.	Epigenetic therapies may enhance tumor immunogenicity; microRNAs are potential biomarkers or therapeutic targets.
Tumor-associated inflammatory cytokines (IL-6, TNF-alpha, TGF-beta)	Promote immune suppression and may indirectly enhance PD-L1 expression through inflammatory signaling networks.	Contribute to the immunosuppressive tumor microenvironment, especially in advanced disease.	Cytokine modulation may represent an additional immunotherapeutic strategy.

[a] Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; IFN-gamma, interferon-gamma; IRF-1, interferon regulatory factor-1; HIF-1alpha, hypoxia-inducible factor-1alpha.

RET rearrangements and RAS mutations are important molecular events in papillary and follicular thyroid carcinoma. Although their direct relationship with PD-L1 is less well established than that of BRAF, these oncogenic drivers may influence immune regulation through downstream signaling: RET activation stimulates both MAPK and PI3K/AKT, whereas RAS mutations may promote inflammatory signaling and alter the immune microenvironment (32). Further work is needed to determine whether RET- or RAS-driven thyroid cancers constitute distinct immunological subgroups with differential responses to PD-1/PD-L1 inhibitors; notably, in a phase 2 trial of dual checkpoint blockade, NRAS alterations were associated with worse outcomes (33).

4.6. TERT Promoter Mutations and Immune Escape

TERT promoter mutations are among the most significant molecular alterations associated with aggressive behavior in thyroid cancer. They enhance telomerase activity and contribute to tumor immortality, progression, and treatment resistance (34). Although the direct regulatory relationship between TERT alterations and PD-L1 remains under investigation, TERT-driven genomic instability and tumor evolution may promote immune escape. The coexistence of TERT promoter mutations with BRAF V600E is particularly associated with aggressive phenotypes, suggesting that these molecular subgroups may be candidates for immunotherapeutic approaches.

4.7. Cytokine Signaling, IFN-Gamma and Adaptive PD-L1 Expression

One of the best-characterized mechanisms of PD-L1 induction involves the IFN-gamma/JAK/STAT pathway. Binding of IFN-gamma to its receptor activates JAK1/JAK2, leading to phosphorylation and nuclear translocation of STAT1, which in turn induces interferon regulatory factor-1. interferon regulatory factor-1 binds regulatory regions of the CD274 promoter and enhances PD-L1 transcription (17, 35). This creates a paradoxical situation in which immune infiltration simultaneously indicates active antitumor immunity and promotes immune suppression. In thyroid cancer, understanding this balance may help identify patients more likely to respond to checkpoint blockade.

4.8. Hypoxia, Epigenetic and Post-Transcriptional Regulation

Hypoxia-inducible factor-1alpha (HIF-1alpha) binds hypoxia-responsive elements within the PD-L1 promoter and directly increases PD-L1 transcription (36). This

Table 2. PD-1/PD-L1 Expression and Biological Characteristics Across Thyroid Cancer Subtype [a]

Thyroid Cancer Subtype	PD-1/PD-L1 Expression Pattern	Major Molecular Features	Clinical Implications
Papillary thyroid carcinoma (PTC)	Detected in tumor cells and tumor-infiltrating immune cells; reported positivity varies widely (approximately 6 - 53%) according to antibody and threshold, and may increase in aggressive tumors.	Frequent BRAF V600E mutation, MAPK pathway activation, RET rearrangements; inflammatory signaling may contribute to PD-L1 induction.	Associated in some studies and in meta-analysis with extrathyroidal extension, lymph node metastasis and shorter disease-free survival. Potential role for immunotherapy in selected advanced cases.
Follicular thyroid carcinoma	Reported in a subset of cases (tumoral positivity approximately 7.6% in a large screening series); less extensively studied than PTC.	Frequent RAS mutations, PI3K/AKT pathway alterations, changes affecting thyroid differentiation.	Clinical significance remains uncertain. Further studies are needed to determine whether PD-L1 can predict immunotherapy response.
Medullary thyroid carcinoma (MTC)	Highly variable between series, from very low expression to positivity in roughly one quarter of tumors, with weak to moderate intensity.	RET mutations/rearrangements; activation of MAPK and PI3K/AKT signaling.	Associations with distant metastasis and recurrence are inconsistent, and no objective responses were seen in the small prospective medullary thyroid carcinoma cohort treated with dual checkpoint blockade. Predictive biomarkers require validation.
Poorly differentiated thyroid carcinoma	Increased PD-1 and PD-L1 expression compared with differentiated thyroid cancers.	Accumulation of aggressive molecular alterations including TERT promoter mutations, TP53 abnormalities, MAPK and PI3K pathway activation.	Biologically aggressive group with potential sensitivity to checkpoint inhibition; included with anaplastic thyroid carcinoma (ATC) in combination trials.
ATC	Highest frequency of PD-L1 expression among thyroid cancers, although reported rates range from about 20% to over 80% depending on methodology.	High genomic instability, frequent TP53 alterations, TERT promoter mutations, BRAF alterations, inflammatory tumor microenvironment.	Strongest rationale for PD-1/PD-L1 blockade. Combination with mutation-matched targeted therapy, multikinase inhibitors and radiotherapy has produced the longest survival reported to date in ATC.

[a] Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MAPK, mitogen-activated protein kinase; PDTC, poorly differentiated thyroid carcinoma; ATC, anaplastic thyroid carcinoma.

mechanism is particularly relevant in aggressive thyroid cancers, where hypoxia and necrosis are common. Epigenetic mechanisms also contribute: DNA methylation, histone modification, and chromatin remodeling influence CD274 transcription, and several microRNAs directly target CD274 mRNA and regulate PD-L1 protein abundance (37). Together, these layers of control help explain the marked intratumoral and intertumoral heterogeneity of PD-L1 expression observed in thyroid carcinoma.

5. PD-1/PD-L1 Expression Across Thyroid Cancer Subtypes

5.1. Overview of Expression Patterns

Thyroid cancer comprises a heterogeneous group of malignancies with distinct molecular profiles, biological behaviors, and outcomes. Although checkpoint activation is observed across subtypes, the extent and significance of PD-1/PD-L1 expression vary considerably according to differentiation status, genetic background, and the immune microenvironment (38). In general, aggressive variants such as PDTC and ATC show higher checkpoint expression than differentiated carcinomas, consistent with the concept that advanced tumors progressively acquire immune-escape mechanisms. Interpretation nevertheless remains difficult because of differences in immunohistochemical techniques, antibody clones, scoring criteria, and sampling. Reported positivity rates for the same subtype range from under 10% to over 80%, depending on the methodology (8, 10) (Table 2).

5.2. PTC

PTC accounts for approximately 80% of thyroid cancers. Despite its generally favorable prognosis, a subset of patients develops recurrent disease, lymph node metastasis, or radioiodine-refractory disease.

PD-L1 expression has been demonstrated in both tumor cells and tumor-infiltrating immune cells in PTC and has been associated with aggressive clinicopathological features, including extrathyroidal extension, lymph node metastasis, larger tumor size, and advanced stage (28). In a cohort of 398 patients with PTC, PD-L1 positivity was an independent predictor of shorter disease-free survival and was significantly associated with tumor recurrence (39).

Bai et al. examined the immunohistochemical expression of PD-L1, PD-1, and BRAF V600E in whole-tissue sections from 126 cases of primary PTC larger than 1 cm. PD-L1 was positive in 53.2% of cases, and its expression correlated positively with abundant TILs, background chronic lymphocytic thyroiditis, female sex, absence of psammoma bodies, and PD-1 expression. In multivariable logistic regression, abundant TILs, female sex, and absence of psammoma bodies were independent factors associated with PD-L1 expression. PD-1 expression was detected in TILs and correlated with abundant TILs, background chronic lymphocytic thyroiditis, and absence of stromal calcification; absence of stromal calcification was an

independent associated factor. Neither PD-L1 nor PD-1 expression correlated significantly with BRAF V600E expression (29).

The prognostic significance of PD-L1 in PTC remains contested. Some studies report an association between PD-L1 positivity and recurrence risk, whereas others find no independent prognostic value after adjustment for conventional clinicopathological factors (40). A systematic review and meta-analysis of PD-L1 immunoexpression in follicular epithelial-derived thyroid carcinoma found a significant association between PD-L1 positivity and shorter disease-free survival in PTC, whereas no such association was demonstrable in dedifferentiated tumors (anaplastic and poorly differentiated) (41). A second meta-analysis similarly linked high PD-L1 expression to tumor size of 2 cm or greater, recurrence, extrathyroidal extension, and concurrent thyroiditis (10). These inconsistencies underscore the need for standardized PD-L1 assessment and integration with additional biomarkers.

5.3. FTC

FTC accounts for approximately 10 - 15% of thyroid cancers and differs biologically from PTC in its tendency toward hematogenous rather than lymphatic dissemination. Fewer studies have investigated PD-1/PD-L1 in FTC. Available evidence indicates that PD-L1 is expressed in a subset of cases, with tumor positivity of 7.6% in one large screening series, but is generally less prominent than in aggressive variants (8).

The immune landscape of FTC remains poorly characterized. RAS mutations, PI3K/AKT pathway activation, and alterations affecting thyroid differentiation genes may influence tumor immunity and checkpoint expression. Further studies are required to determine whether PD-L1 can serve as a predictive biomarker for immunotherapy in advanced FTC.

5.4. MTC

MTC originates from parafollicular C cells and accounts for approximately 3 - 5% of thyroid malignancies. Because it does not respond to radioactive iodine, systemic treatment is particularly important in advanced disease.

Reported PD-L1 expression in MTC is highly variable, and its clinical significance remains uncertain. In the study by Bi et al., surgical specimens from 87 patients with MTC were examined immunohistochemically for PD-1 and PD-L1 expression in tumor cells and associated immune cells, using a threshold of more than 1% positive cells. PD-1 and PD-L1 were positive in 22 and 19 patients, respectively, and were coexpressed in 11. PD-L1 positivity correlated significantly with distant metastases at surgery (21.1% vs 1.5%, P = 0.007). Coexpression of PD-1 and PD-L1 was associated with advanced pathological TNM stage III/IV and distant metastases. No other clinicopathological or prognostic association was identified. The authors concluded that the PD-1/PD-L1 pathway is expressed in MTC and correlates with distant metastasis, supporting its potential as a therapeutic target (42).

Other series have reached different conclusions. In a cohort of 200 patients with MTC, PD-L1 expression was associated with structural recurrence and biochemical recurrence or persistent disease (43), whereas a retrospective immunohistochemical study of PD-L1 and TIM-3 found that neither marker was frequently expressed or associated with overall or progression-free survival (44). A further series reported very low PD-L1 expression in MTC (45). These discrepancies most likely reflect differences in antibody clones, scoring systems, and cohort composition and caution against assuming a uniform immunotherapeutic rationale in MTC.

MTC is frequently driven by alterations in the RET proto-oncogene, which may influence immune regulation through downstream signaling. Clinical evidence for PD-1/PD-L1 blockade in MTC remains very limited; in the only prospective trial to include an MTC cohort, no objective responses were observed among 7 patients treated with dual checkpoint blockade (33).

5.5. PDTC

PDTC is an intermediate entity between differentiated thyroid cancer and ATC, characterized by increased invasiveness, reduced differentiation, and limited treatment responsiveness. It displays several features associated with immune escape, including increased expression of checkpoint molecules, altered antigen presentation, and an immunosuppressive microenvironment. Higher PD-1 expression has been reported in PDTC than in differentiated carcinomas (38, 46), and PD-L1 positivity has been documented in a substantial proportion of PDTC cases in series that also examined anaplastic tumors (47). The coexistence of aggressive molecular alterations—TERT promoter mutations, TP53 abnormalities, and MAPK/PI3K pathway activation—may further promote immune resistance and disease progression.

5.6. ATC

ATC is the most aggressive form of thyroid cancer and is associated with an extremely poor prognosis, with a historically reported median survival of around 5 to 6 months despite multimodal therapy. Among thyroid cancer subtypes, it offers the strongest biological rationale

for checkpoint targeting: multiple studies report high PD-L1 expression in ATC tumor cells and immune infiltrates (48).

ATC is characterized by profound genomic instability, frequent TP53 alterations, TERT promoter mutations, and activation of multiple oncogenic pathways, accompanied by extensive inflammatory signaling and immune suppression—a microenvironment potentially responsive to checkpoint blockade.

Cantara et al. found that approximately 70 - 90% of ATC cases were PD-L1 positive, whereas normal thyroid tissue and differentiated carcinomas were negative (49). In a retrospective cohort of 16 patients, Chintakuntlawar et al. found PD-L1 expression on ATC tumor cells in most samples; high PD-1 expression was associated with worse overall survival (50). Reported positivity rates nevertheless vary widely, from around 20% to over 80%, depending on antibody clone, scoring method, and threshold (8, 47), with direct implications for the use of PD-L1 as a selection criterion.

Preclinical work supports combination approaches. In an immunocompetent orthotopic mouse model of ATC, combining the BRAF V600E inhibitor PLX4720 with an anti-PD-L1 or anti-PD-1 antibody markedly improved survival. Maximal tumor reduction was associated with increased numbers and cytotoxicity of CD8+ T cells and natural killer cells, an increase in predominantly M1-polarized tumor-associated macrophages, and a decrease in myeloid-derived suppressor-like cells (51). In a second murine study, lenvatinib monotherapy increased tumor-infiltrating macrophages, CD8+ T cells, regulatory T cells, and, most notably, polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs). Although both combination regimens further increased CD8+ T cells, only lenvatinib plus anti-PD-1 decreased PMN-MDSCs. This combination ameliorated lenvatinib-induced MDSC expansion and significantly improved its antitumor effect (52).

6. Clinical Significance of PD-1/PD-L1 in Thyroid Cancer: Prognostic Value, Diagnostic Utility, and Predictive Biomarker Potential

6.1. PD-L1 as a Prognostic Biomarker

Reliable biomarkers of tumor behavior and outcome remain a major unmet need in thyroid cancer. Conventional clinicopathological parameters, including tumor size, extrathyroidal extension, lymph node involvement, distant metastasis, and histological subtype, provide valuable prognostic information but do not fully capture the biological complexity of aggressive disease. Immune-related biomarkers such as PD-L1 have therefore attracted attention (53).

Increased PD-L1 expression has been reported in association with larger tumor size, extrathyroidal extension, lymph node metastasis, advanced stage, and recurrence, particularly in PTC (8, 39). Two independent meta-analyses support a prognostic signal: PD-L1 positivity was associated with shorter disease-free survival in PTC but not in dedifferentiated tumors (41), and with tumor size of 2 cm or greater, recurrence, extrathyroidal extension, concurrent thyroiditis, and late-stage disease in differentiated thyroid carcinoma (10).

The prognostic significance of PD-L1 nevertheless remains controversial. Some studies show that high PD-L1 expression is associated with reduced disease-free or overall survival, whereas others do not confirm an independent prognostic role after adjustment for established risk factors (40, 54). Discrepancies may be explained by differences in patient populations, tumor subtypes, antibody clones, staining thresholds, and whether tumor cells, immune cells, or both are scored. Although PD-L1 expression reflects important aspects of tumor biology, its role as a stand-alone prognostic biomarker in thyroid cancer remains uncertain.

6.2. Diagnostic Utility of PD-L1 in Thyroid Nodules

A smaller but growing body of literature has examined whether PD-L1 has diagnostic as well as prognostic value. In a study that applied PD-L1 immunocytochemistry to thyroid fine-needle aspiration material and matched histologic specimens, PD-L1 expression was significantly more frequent in papillary thyroid carcinoma than in benign nodules and was not observed in noninvasive follicular thyroid neoplasm with papillary-like nuclear features. PD-L1-expressing neoplasms were also enriched for BRAF V600E (55). These findings suggest that PD-L1 could contribute to the assessment of cytologically indeterminate nodules. However, its reported specificity is insufficient for stand-alone use, and prospective validation is required before it can be recommended for routine practice. Interpretation is further complicated by PD-L1 expression in autoimmune thyroid disease and chronic lymphocytic thyroiditis, which frequently accompanies PTC (29).

6.3. PD-L1 as a Predictive Biomarker for Immune Checkpoint Inhibition

PD-L1 immunohistochemistry is widely used to select patients with cancers such as non-small cell lung cancer, melanoma, and urothelial carcinoma, but its predictive value in thyroid cancer is not fully established (56).

Several factors complicate interpretation. First, PD-L1 expression is dynamic and may change in response to inflammatory signals, prior treatment, radiation, or targeted therapy. Second, PD-L1 alone does not capture the complexity of the tumor immune microenvironment: tumors with high PD-L1 expression may still be resistant because of immune exclusion, defective antigen presentation, or activation of alternative checkpoints (57).

Clinical data illustrate this challenge across different settings. In the phase 2 KEYNOTE-158 thyroid cohort, objective responses to pembrolizumab occurred regardless of PD-L1 status, with a response rate of 5.7% among PD-L1-negative tumors (58). In contrast, in the phase 2 spartalizumab study in ATC, all objective responses occurred in PD-L1-positive tumors, and the response rate increased with PD-L1 expression (59). Thus, PD-L1 status appears to be neither necessary nor sufficient to predict benefit, and additional biomarkers are required to improve patient selection.

6.4. Beyond PD-L1: Integrated Biomarker Strategies

Because PD-L1 alone performs poorly, attention has turned to composite biomarkers. Tumor mutational burden (TMB) predicts response to checkpoint blockade across cancer types (60). Tumor-agnostic analyses within KEYNOTE-158 showed that high microsatellite instability/mismatch repair deficiency and high TMB were associated with response; these analyses included patients from the thyroid cohort (58). Additional candidate markers include the density and spatial distribution of CD8+ T cells, T-cell-inflamed gene expression signatures, the composition of the myeloid compartment, and specific genomic alterations. For example, NRAS variants were associated with worse outcomes, whereas BRAF V600E did not influence response in a phase 2 trial of nivolumab plus ipilimumab (33). Prospective validation of integrated biomarker panels in thyroid-specific trials remains the principal outstanding requirement.

6.5. Limitations of PD-L1 Assessment

6.5.1. Immunohistochemical Variability

PD-L1 assessment is performed almost exclusively by immunohistochemistry; however, multiple antibody clones, scoring systems, and positivity thresholds have been used. Unlike cancers in which the tumor proportion score or combined positive score is standardized, thyroid cancer lacks universally accepted criteria, and this alone accounts for much of the between-study variation described in Section 5 (56).

6.5.2. Tumor Heterogeneity

PD-L1 expression shows considerable spatial and temporal heterogeneity; therefore, a single biopsy may not represent the tumor's PD-L1 status, particularly in heterogeneous malignancies such as ATC.

6.5.3. Dynamic Regulation

Because PD-L1 can be induced by immune pressure, notably through IFN-gamma signaling, PD-L1 status represents a dynamic state rather than a fixed tumor characteristic. These limitations underscore the need for integrated biomarker strategies that combine PD-L1 expression with molecular, immunological, and clinical parameters.

7. Therapeutic Landscape of PD-1/PD-L1 Blockade in Thyroid Cancer

7.1. Rationale for Immune Checkpoint Blockade

Immune checkpoint inhibitors (ICIs) have transformed cancer treatment by restoring antitumor immune activity and producing durable responses in melanoma, lung cancer, renal cell carcinoma, and head and neck cancers (61). These successes have stimulated research in thyroid cancer, where the rationale is based on PD-L1 expression in tumor cells and immune infiltrates, the presence of tumor-reactive lymphocytes, activation of inflammatory pathways, and increased checkpoint expression in aggressive subtypes. However, unlike highly immunogenic malignancies, thyroid cancer exhibits considerable heterogeneity in immune activation, which translates into variable responses.

7.2. PD-1 Blockade in Differentiated and Radioiodine-Refractory Thyroid Cancer

Most patients with DTC achieve excellent outcomes with conventional treatment, but a subset develops RAI-refractory disease characterized by progressive growth and limited treatment options.

The phase 1b KEYNOTE-028 study investigated pembrolizumab in patients with advanced PD-L1-positive solid tumors, including a cohort of 22 patients with advanced papillary or follicular thyroid cancer. Two patients achieved a partial response, yielding a confirmed objective response rate (ORR) of 9.1%. The 6-month progression-free survival rate was 58.7%, and the safety profile was manageable (62).

The larger phase 2 KEYNOTE-158 study evaluated pembrolizumab monotherapy in 103 patients with

previously treated papillary or follicular thyroid carcinoma, irrespective of PD-L1 status. The ORR was 6.8% (95% CI, 2.8 - 13.5), and the median duration of response was 18.4 months. Responses occurred regardless of PD-L1 expression, and approximately half of the enrolled patients were alive at 3 years (58). These results indicate that PD-1 blockade alone benefits only a small minority of patients with advanced DTC and reinforce the importance of biomarker-driven selection.

Dual-checkpoint blockade has also been tested. In a phase 2 nonrandomized trial, nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks) produced objective responses in 3 of 32 patients with RAI-refractory DTC (9.4%; 95% CI, 2.8 - 28.5). The study did not meet its primary endpoint in this population and does not support further investigation of dual blockade in unselected DTC, although the signal observed in the exploratory ATC cohort was considered worthy of further investigation (33).

7.3. Immune Checkpoint Inhibition in Medullary Thyroid Carcinoma

Prospective data on MTC are extremely limited. The exploratory MTC cohort in the nivolumab-plus-ipilimumab trial included 7 patients; no objective responses were reported (33). Given the variable and often low PD-L1 expression described in Section 5.4 and the availability of highly effective selective RET inhibitors for RET-altered disease, checkpoint blockade currently has no established role in MTC outside clinical trials.

7.4. Immune Checkpoint Inhibition in Anaplastic and Poorly Differentiated Thyroid Carcinoma

ATC provides the strongest rationale for immunotherapy, and the most substantial clinical progress has been made in this subtype.

Spartalizumab, an anti-PD-1 antibody, was evaluated in a phase 2 cohort of 42 patients with locally advanced or metastatic ATC. The ORR was 19% (95% CI, 8.6 - 34.1), including 3 complete responses (7%) and 5 partial responses (12%), with a favorable safety profile. This was the first trial to demonstrate that ATC responds to PD-1 blockade. All responses occurred in PD-L1-positive tumors, and the response rate increased with PD-L1 expression, in contrast to the pattern observed in differentiated disease (59).

Checkpoint blockade has also been investigated as part of first-line multimodal therapy. In a phase 2 study of pembrolizumab combined with chemoradiotherapy as initial treatment for ATC, initial locoregional responses were observed, but all 3 enrolled patients died within 6 months. Two deaths involved unexpected fatal pulmonary complications, prompting study closure (63). In the salvage setting, adding pembrolizumab to kinase inhibitor therapy at progression produced measurable clinical benefit in a subset of patients; median overall survival from the addition of pembrolizumab was 6.9 months (64).

The most striking results to date have come from combining checkpoint blockade with mutation-matched targeted therapy. In a phase 2 nonrandomized trial, 42 patients with unresectable or metastatic ATC received atezolizumab with genotype-directed therapy: vemurafenib plus cobimetinib for BRAF V600E-mutated tumors, cobimetinib for RAS- or NF1/2-altered tumors, and bevacizumab (or paclitaxel-based chemotherapy) for the remaining patients. Median overall survival was 18.2 months for the entire trial and 43.2 months in the BRAF V600E cohort, the longest overall survival reported to date for systemic therapy in ATC, compared with a historical benchmark of approximately 5 months (65). A retrospective analysis similarly found that adding a checkpoint inhibitor to dabrafenib plus trametinib in BRAF V600E-mutated ATC was associated with improved outcomes. Surgical resection of the primary tumor after initial BRAF-targeted therapy may provide further survival benefit in selected patients (66) (Table 3).

7.5. Combination Strategies

Combining checkpoint inhibitors with molecularly targeted therapy is a promising direction in thyroid cancer immunotherapy. The underlying concept is that targeted agents modify the tumor microenvironment, increase antigen presentation, enhance immune cell infiltration, and overcome resistance.

7.5.1. Combination with Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors, such as lenvatinib, sorafenib, and axitinib, are established treatments for advanced RAI-refractory thyroid cancer. In addition to their direct antitumor effects, they influence immune regulation by reducing immunosuppressive signaling and normalizing tumor vasculature. The preclinical basis for this approach is the lenvatinib work described in Section 5.6, in which anti-PD-1 therapy reversed lenvatinib-induced expansion of PMN-MDSCs (52).

Clinically, lenvatinib plus pembrolizumab has shown encouraging activity in aggressive thyroid cancer. In an initial retrospective series of patients with ATC and PDTC, the combination produced complete and long-lasting remissions in a substantial proportion of patients (67). The subsequent prospective phase 2 ATLEP trial, which included 27 patients with ATC and 8 with PDTC, met its primary endpoint, with an ORR of 34.3% at 3 months (68). A

Table 3. Clinical Studies Evaluating PD-1/PD-L1 Inhibitors in Thyroid Cancer [a]

Study / Drug	Design and phase	Patient Population	Treatment Strategy	Main Findings	Clinical Significance
Mehnert et al., KEYNOTE-028 (pembrolizumab) (62)	Phase 1b, nonrandomized	22 patients with advanced PD-L1-positive papillary or follicular thyroid cancer	Pembrolizumab monotherapy	ORR 9.1% (2 partial responses); 6-month PFS 58.7%; manageable safety profile	First clinical evidence supporting PD-1 blockade in selected thyroid cancer patients
Oh et al., KEYNOTE-158 (pembrolizumab) (58)	Phase 2, single-arm, multicohort	103 patients with previously treated advanced papillary or follicular thyroid carcinoma, regardless of PD-L1 status	Pembrolizumab monotherapy	ORR 6.8%; median duration of response 18.4 months; responses independent of PD-L1 status; ~50% alive at 3 years	Durable benefit in a small minority; PD-L1 alone does not predict response, highlighting the need for better biomarkers
Capdevila et al., spartalizumab (PDR001) (59)	Phase 2 cohort of a phase 1/2 study	42 patients with locally advanced or metastatic anaplastic thyroid carcinoma	Anti-PD-1 monotherapy, 400 mg every 4 weeks	ORR 19% (3 complete, 5 partial responses); all responses in PD-L1-positive tumors, with response rate rising with PD-L1 level	First trial to show responsiveness of ATC to PD-1 blockade; supports PD-L1-guided selection in this subtype
Sehgal et al., nivolumab plus ipilimumab (33)	Phase 2, nonrandomized, single center	32 RAI-refractory DTC (primary cohort), 7 MTC and 10 ATC (exploratory cohorts)	Dual checkpoint blockade (anti-PD-1 plus anti-CTLA-4)	ORR 9.4% in RAI-refractory DTC (primary endpoint not met); ORR 30% in ATC; no responses in MTC; NRAS alterations linked to worse outcome	Does not support dual blockade in unselected DTC or MTC; the ATC signal merits further evaluation
Dierks et al., lenvatinib plus pembrolizumab (67)	Retrospective series	Patients with ATC and PDTC	Anti-PD-1 therapy combined with a VEGFR-targeting multikinase inhibitor	Complete and long-lasting remissions in the retrospective series	Demonstrates the potential of combining immune modulation with antiangiogenic therapy in aggressive thyroid cancer
Dierks et al., ATLEP (lenvatinib plus pembrolizumab) (68)	Prospective phase 2 trial	27 patients with ATC and 8 with PDTC	Anti-PD-1 therapy combined with a VEGFR-targeting multikinase inhibitor	Primary endpoint met, with an ORR of 34.3% at 3 months	Provides prospective evidence for the combination in aggressive thyroid cancer
Cabanillas et al., atezolizumab plus mutation-matched targeted therapy (65)	Phase 2, nonrandomized, single center	42 patients with unresectable or metastatic anaplastic thyroid carcinoma, assigned by genotype	Atezolizumab with vemurafenib/cobimetinib (BRAF V600E), cobimetinib (RAS or NF1/2) or bevacizumab (other)	Median OS 18.2 months overall and 43.2 months in the BRAF V600E cohort, against a historical benchmark of ~5 months	Longest overall survival published to date for systemic therapy in ATC; establishes genotype-directed therapy plus PD-L1 blockade as a leading strategy
Chintakuntlawar et al., pembrolizumab with chemoradiotherapy (63)	Phase 2	3 patients with newly diagnosed ATC	Pembrolizumab added to concurrent chemoradiotherapy as initial treatment	Initial locoregional responses occurred, but all 3 patients died within 6 months, including 2 with unexpected fatal pulmonary complications; the study was closed	Does not support routine first-line integration of the tested regimen
Iyer et al., salvage pembrolizumab (64)	Retrospective, single center	Patients with anaplastic thyroid carcinoma progressing on kinase inhibitors	Pembrolizumab added to ongoing kinase inhibitor therapy at progression	Median overall survival of 6.9 months from addition of pembrolizumab, with clinical benefit in a subset	Suggests a salvage role for checkpoint blockade and motivated prospective front-line combination trials
Hamidi et al., dabrafenib/trametinib with or without checkpoint inhibitor (66)	Retrospective cohort	Patients with BRAF V600E-mutated anaplastic thyroid carcinoma	Dabrafenib plus trametinib, with or without an added anti-PD-1 agent, with or without subsequent surgery	Improved outcomes with the addition of checkpoint inhibition; further benefit from resection of the primary tumor in selected patients	Supports combining BRAF/MEK-directed therapy with immunotherapy; requires prospective confirmation

[a] Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ATC, anaplastic thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor.

separate retrospective cohort reported the effectiveness of the same combination as first-line systemic therapy for metastatic ATC (69). The biological rationale includes inhibition of tumor angiogenesis, reduction of immunosuppressive myeloid cells, enhanced T-cell infiltration, and improved immune recognition of tumor cells.

7.5.2. Combination with BRAF- and MEK-Directed Therapy

For BRAF V600E-mutated ATC, dabrafenib plus trametinib is the standard of care, but resistance ultimately develops. Preclinical models showed that adding an anti-PD-1 or anti-PD-L1 antibody to BRAF inhibition dramatically improved survival and remodeled

Table 4. Mechanisms of Resistance to PD-1/PD-L1 Blockade and Potential Therapeutic Strategies in Thyroid Cancer [a]

Type of Resistance	Biological Mechanism	Relevance to Thyroid Cancer	Potential Strategies to Overcome Resistance
Primary: immune-excluded tumor phenotype	Lack of effective infiltration of CD8+ cytotoxic T cells despite the presence of tumor antigens.	Some differentiated thyroid cancers exhibit limited immune cell infiltration and poor response to checkpoint blockade.	Combination with radiotherapy, antiangiogenic therapy or agents promoting immune cell recruitment.
Primary: low tumor immunogenicity	Low neoantigen production and limited tumor-specific immune recognition.	Most thyroid cancers have relatively low tumor mutational burden compared with highly immunogenic cancers; ATC is a partial exception.	Combination therapies that enhance antigen presentation or increase tumor immunogenicity.
Primary: defective antigen presentation	Loss of MHC class I expression, beta-2-microglobulin alterations or impaired interferon signaling reduce T-cell recognition.	MHC class I loss has been documented in papillary thyroid cancer and was reversible in vitro with interferon or MEK inhibition.	Restoration of antigen presentation pathways, MEK inhibition and combination immunotherapy.
Primary: immunosuppressive tumor microenvironment	Increased regulatory T cells, tumor-associated macrophages, MDSCs and immunosuppressive cytokines.	Particularly relevant in aggressive thyroid cancers including PDTC and ATC; lenvatinib expands PMN-MDSCs, an effect reversed by anti-PD-1 therapy.	Targeting TAMs, MDSCs, Tregs or cytokine pathways in combination with PD-1/PD-L1 inhibitors.
Acquired: loss of interferon signaling	Mutations or dysfunction in JAK1/JAK2 and downstream IFN-gamma signaling reduce immune-mediated tumor killing.	May explain disease progression after an initial response.	Combination approaches targeting alternative immune pathways.
Acquired: alternative checkpoint activation	Upregulation of inhibitory molecules such as LAG-3, TIM-3, TIGIT and VISTA after PD-1 inhibition.	Potential mechanism of resistance in patients receiving long-term checkpoint therapy.	Dual or multi-checkpoint inhibition strategies.
Acquired: tumor evolution and heterogeneity	Selection of resistant tumor clones with reduced antigenicity or enhanced immune escape properties.	A common challenge in advanced metastatic thyroid cancer, where clonal evolution is rapid.	Serial molecular profiling and adaptive treatment strategies.
Stroma-related resistance	Cancer-associated fibroblasts and extracellular matrix components restrict immune cell migration and activity.	May contribute to immune exclusion in aggressive thyroid tumors.	Stromal-targeting approaches combined with immunotherapy.
Angiogenesis-related resistance	Abnormal tumor vasculature limits immune cell trafficking and promotes immunosuppression.	Relevant in advanced RAI-refractory thyroid cancers and in ATC.	Combination of checkpoint inhibitors with VEGFR-targeting TKIs such as lenvatinib.

[a] Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ATC, anaplastic thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; MHC, major histocompatibility complex; MDSCs, myeloid-derived suppressor cells; PMN-MDSCs, polymorphonuclear myeloid-derived suppressor cells; TAMs, tumor-associated macrophages; Tregs, regulatory T cells; RAI, radioactive iodine; VEGFR, vascular endothelial growth factor receptor; TKIs, tyrosine kinase inhibitors.

the immune microenvironment (51). Clinically, both the atezolizumab plus vemurafenib/cobimetinib regimen (65) and the addition of a checkpoint inhibitor to dabrafenib/trametinib (66) have been associated with prolonged survival in BRAF-mutated ATC, making this the best-supported combination in thyroid oncology to date.

7.5.3. Combination with Radiotherapy and Multimodal Treatment

Radiotherapy has traditionally been regarded as a local modality; however, radiation can enhance tumor antigen release, promote dendritic cell activation, and increase immune recognition, potentially improving responses to checkpoint blockade. In ATC, a phase 2 study of pembrolizumab with concurrent chemoradiotherapy produced initial locoregional responses, but all 3 patients died within 6 months, including 2 with unexpected fatal pulmonary complications, prompting study closure (63). Although such strategies aim to convert immunologically cold tumors into more immune-responsive tumors, this study does not support routine first-line integration of the tested regimen.

7.5.4. Dual Checkpoint Blockade and Emerging Targets

Simultaneous inhibition of PD-1 and CTLA-4 produced an ORR of 30% in the exploratory ATC cohort of a phase 2 trial, with clinical benefit in half of the patients. The trial did not meet its primary endpoint in RAI-refractory DTC, and no objective responses were observed in MTC (33). Combinations targeting other checkpoints, including LAG-3, TIGIT, and TIM-3, may provide further opportunities for patients who develop resistance to PD-1/PD-L1 blockade (13).

7.6. Safety Considerations

Across thyroid cancer trials, the toxicity profile of PD-1/PD-L1 blockade has been consistent with that observed in other tumor types, comprising predominantly immune-related adverse events such as pruritus, rash, diarrhea, fatigue, and elevations of lipase and liver enzymes (33). Two considerations are specific to this setting. First, patients with ATC frequently have bulky, invasive cervical disease, and combinations that include antiangiogenic agents carry a risk of fistula formation, bleeding, and infectious

complications (67). Second, because checkpoint inhibitors can themselves induce thyroid dysfunction, hypothyroidism and thyroiditis require particular attention in a population that is often already receiving thyroid hormone replacement.

7.7. Summary of the Current Therapeutic Position

Current evidence indicates that PD-1/PD-L1 blockade has substantial therapeutic potential in anaplastic thyroid carcinoma, where high PD-L1 expression, inflammatory signaling, and the lack of effective conventional treatment options converge. In radioactive iodine-refractory differentiated thyroid cancer, particularly after progression on targeted therapy, a small minority of patients derive durable benefit. The greatest potential appears to lie in combination regimens, especially checkpoint inhibitors combined with mutation-matched targeted therapy or multikinase inhibitors, in which modification of the tumor microenvironment appears to amplify the immune response. The evidence also demonstrates that PD-L1 positivity alone is insufficient to predict response. Future trials should prospectively incorporate molecular and immune profiling.

8. Challenges, Resistance Mechanisms and Future Perspectives

8.1. Challenges in Clinical Application

Although checkpoint inhibitors have introduced a new therapeutic paradigm in oncology, their use in thyroid cancer remains constrained. Thyroid cancers are heterogeneous in their immune profiles, molecular characteristics, and treatment responsiveness, and only a subset of patients derives meaningful and durable benefit (70).

The principal challenge is the absence of validated predictive biomarkers. As discussed in Section 6, the dynamic nature of PD-L1 expression, variability in immunohistochemical assessment, and incomplete representation of the tumor immune microenvironment limit its accuracy as a single marker. A comprehensive strategy integrating tumor genomics, immune profiling, and microenvironmental characteristics is required to optimize patient selection (Table 4).

8.2. Primary Resistance

Primary resistance refers to the failure of tumors to respond to checkpoint inhibition despite appropriate treatment. Several mechanisms contribute to primary resistance in thyroid cancer.

8.2.1. Lack of Immune Infiltration and Immune Exclusion

An effective response requires activated tumor-specific T cells that can be reactivated after checkpoint inhibition. Some thyroid cancers exhibit an immune-excluded phenotype characterized by limited infiltration of cytotoxic lymphocytes despite the presence of tumor antigens. This phenotype results from abnormal vasculature, extracellular matrix barriers, chemokine dysregulation, and stromal-mediated suppression (71).

8.2.2. Defective Antigen Presentation

Recognition of tumor cells by T lymphocytes depends on efficient antigen processing and presentation through MHC molecules. Loss or downregulation of the antigen presentation machinery prevents immune recognition and causes resistance despite PD-1/PD-L1 inhibition. Alterations affecting beta-2-microglobulin, MHC class I expression, and interferon signaling have been implicated in multiple cancers (72). MHC class I loss has also been documented specifically in papillary thyroid cancer, and this loss was reversible in vitro with interferon or MEK inhibition (28).

8.2.3. Low Tumor Immunogenicity

Tumor mutational burden reflects the number of alterations that can generate neoantigens. Compared with melanoma or lung cancer, most thyroid cancers exhibit relatively low TMB, which may partly explain the modest response rates observed with single-agent PD-1/PD-L1 inhibition (60). ATC is a partial exception, with higher mutational burden and genomic instability than differentiated tumors.

8.3. Acquired Resistance

A separate group of mechanisms explains progression after an initial response. Loss-of-function mutations in JAK1 or JAK2 abrogate IFN-gamma signaling, rendering tumor cells insensitive to interferon-mediated growth arrest and antigen presentation; this is a well-documented route to both primary and acquired resistance (72, 73). Compensatory upregulation of alternative inhibitory receptors, such as LAG-3, TIM-3, TIGIT, and VISTA, may restore T-cell suppression despite continued PD-1 blockade (13). Finally, immune editing selects tumor subclones with reduced antigenicity or enhanced escape capacity, a process particularly relevant in the rapidly evolving genomic landscape of advanced thyroid cancer (57). Serial molecular and immune profiling during therapy is therefore likely to be necessary to guide adaptive treatment strategies.

9. Conclusions and Future Directions

Thyroid cancer is a biologically heterogeneous group of malignancies whose progression is determined not only by intrinsic genetic alterations but also by complex interactions between cancer cells and the immune microenvironment (74). The PD-1/PD-L1 checkpoint has emerged as a central mechanism of immune escape and a promising therapeutic target in this setting.

PD-L1 is expressed across thyroid cancer subtypes, but its biological and clinical significance varies. Differentiated thyroid cancers generally show lower checkpoint activation, whereas poorly differentiated and anaplastic carcinomas display a more immunosuppressive phenotype, with higher PD-L1 expression, immune cell dysfunction, and multiple escape mechanisms (61). This provides a strong rationale for checkpoint blockade, particularly in advanced or treatment-refractory disease.

Clinical results show a clear gradient. Single-agent PD-1 blockade produces objective responses in fewer than 1 in 10 patients with advanced differentiated thyroid cancer, although these responses can be durable (58). In anaplastic thyroid carcinoma, single-agent PD-1 blockade achieves an objective response rate of approximately 19% (59). Combining checkpoint inhibition with genotype-directed targeted therapy has extended median overall survival to 18 months overall and 43 months in BRAF V600E-mutated disease, the best systemic therapy outcomes yet reported in ATC (65). Immunotherapy has therefore moved from an experimental option to a component of standard multimodal management in anaplastic disease, while remaining investigational in differentiated and medullary carcinoma.

Several challenges persist. PD-L1 expression alone has insufficient predictive accuracy, and its interpretation is complicated by immunohistochemical variability, tumor heterogeneity, and dynamic regulation (26). Progress will depend on integrated biomarker approaches that combine tumor genomics, immune cell composition, spatial immune architecture, inflammatory signatures, and circulating biomarkers (75).

Future research should also clarify the mechanisms of primary and acquired resistance and evaluate alternative immunosuppressive pathways, including LAG-3, TIGIT, and TIM-3, as combination partners. In parallel, advances in single-cell sequencing, spatial transcriptomics, and computational tumor profiling offer new opportunities to characterize the immune landscape of thyroid cancer at high resolution.

In conclusion, the PD-1/PD-L1 pathway represents a critical interface between tumor biology and immune regulation in thyroid cancer. Its therapeutic use is already established in anaplastic carcinoma and remains promising, although unproven, in other advanced subtypes. Further progress will depend on moving from a generalized immunotherapy approach toward precision immuno-oncology, in which treatment decisions are guided by comprehensive molecular and immune profiling and supported by well-designed thyroid-specific clinical trials.

Footnotes

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