Signaling pathways and targeted therapy in high-risk refractory thyroid cancer: From bench to bedside (Review)

JIAN WANG[1], ZHI LIU[2], QING ZHANG[2] and WEI SUN[1]

[1]Department of Thyroid and Breast Surgery, Ma'anshan People's Hospital, Ma'anshan, Anhui 243000, P.R. China;
[2]Department of Pathology, Ma'anshan People's Hospital, Ma'anshan, Anhui 243000, P.R. China

Received April 2, 2026; Accepted July 24, 2026

DOI: 10.3892/ijo.2026.5927

Abstract. Thyroid cancer is the most common endocrine malignancy worldwide, with its incidence increasing markedly over the past several decades, while mortality trends have shown complex patterns. High-risk refractory thyroid cancers (including radioactive iodine-refractory differentiated thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid carcinoma, progressive medullary thyroid carcinoma and locally advanced disease) pose major challenges in clinical management. The present review systematically reviewed recent epidemiological trends in thyroid cancer and provided an in-depth exploration of the molecular regulatory mechanisms of key signaling pathways, including MAPK, PI3K/AKT, Janus kinase/STAT, WNT/β-catenin and NF-κB, along with their roles in the pathogenesis and progression of thyroid cancer. Based on this, the latest clinical research advances in targeted therapies for high-risk, refractory thyroid cancer are elaborated on, covering multikinase inhibitors, B-Raf proto-oncogene, serine/threonine kinase/mitogen-activated protein kinase kinase inhibitors, immunotherapy combinations, innovative targeted strategies and redifferentiation approaches. Finally, future directions are discussed based on the 'total treatment' paradigm and strategies to overcome drug resistance, aiming to provide a systematic reference for basic research and clinical translation in thyroid cancer.

Contents

Correspondence to: Dr Wei Sun, Department of Thyroid and Breast Surgery, Ma'anshan People's Hospital, 45 Hubei Road, Ma'anshan, Anhui 243000, P.R. China
E-mail: sunwei9241@163.com

Key words: high-risk refractory thyroid cancer, signal pathway, targeted therapy, immunotherapy

1. Introduction

Epidemiological shifts in thyroid cancer and the urgency of the precision medicine era. Thyroid cancer is one of the fastest-rising malignancies in incidence worldwide. According to statistics from the American Cancer Society (1), an estimated 44,020 new cases are projected in the United States in 2025, with women accounting for >71% and a median age at diagnosis of 51 years, markedly younger than that of most solid tumors. In China, thyroid cancer has become the most common malignancy among women and ranks fifth among men (2). A population-based study using Chinese cancer registry data reported that between 2013 and 2017, the number of newly diagnosed cases reached 37,862 in men and 117,979 in women, with age-standardized incidence rates of 6.9 and 21.1 per 100,000 population, respectively. The incidence has shown a marked upward trend, with the rate of increase far exceeding that observed in most countries worldwide (3). Between 2003 and 2017, the average annual increase in thyroid cancer incidence among Chinese adolescents and young adults (aged 15-39 years) exceeded 20%, placing China among the highest globally (4). Nevertheless, the overall prognosis of thyroid cancer remains favorable, with ~95% of cases being differentiated thyroid cancer and a 5-year relative survival rate of 98.4% (2). An analysis based on a large-sample registry of 55,343 patients at Fudan University Shanghai Cancer Center further demonstrated a 10-year overall survival rate of 95.81% for thyroid cancer patients, reaching 97.99% for those with stage I disease but declining to 62.95% for stage IV patients (5). Between 1990 and 2021, the mortality rate of thyroid cancer among women in China exhibited a clear downward trend, whereas the mortality rate among men has tended to stabilize (6,7).

However, these optimistic figures mask the clinical challenges posed by rising incidence and tumor heterogeneity. With the sharp increase in incidence, a projection study estimates that the number of thyroid cancer mortalities in China will increase from 14,366 to 32,644 between 2025 and 2034 (8). The true bottleneck in clinical management lies in

high-risk, refractory and recurrent thyroid cancers, which pose a substantial threat to patient survival time and quality of life. Data from the Swedish national cancer registry reveal notable differences in survival across histological subtypes. Among female patients with thyroid cancer in Sweden between 1999 and 2018, the 5-year relative survival rates were 100.0% for follicular thyroid cancer (FTC), 93.4% for papillary thyroid carcinoma (PTC), 89.7% for medullary thyroid carcinoma (MTC) and 6.1% for anaplastic thyroid carcinoma (ATC). Among male patients, the rates were 87.2% for FTC, 92.6% for PTC, 84.4% for MTC and 5.4% for ATC (9). ATC, including those arising from dedifferentiation of PTC and FTC, still accounts for ~40% of thyroid cancer-related mortalities, with respiratory failure being the most common direct cause of death (10).

In the present review, the term 'high-risk refractory thyroid cancer' was used to designate a group of thyroid malignancies that share poor prognosis, resistance to conventional therapies (including radioactive iodine) and high mortality. This category explicitly includes the following five subtypes: i) Radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC) (11-13); ii) poorly differentiated thyroid cancer (PDTC) (14,15); iii) ATC (9,10); iv) progressive or high-risk MTC (5,16); and v) locally advanced thyroid cancer that is not amenable to curative surgery (17-19). These five entities collectively define the scope of this review and represent the primary targets of the precision therapies discussed in the present study.

In light of these clinical challenges, a deeper understanding of the molecular drivers of thyroid cancer has become critical for overcoming therapeutic bottlenecks. A study published in *Cell* demonstrated that the MAPK pathway is a key signaling axis driving thyroid carcinogenesis (20). The BRAF V600E mutation is present in 78-95% of recurrent PTC cases (21). In PDTC and ATC, the mutational burden is greater, involving genes such as TP53, telomerase reverse transcriptase (TERT) promoter, effectors of the PI3K/AKT/mTOR pathway, SWItch/sucrose non-fermentable (SWI/SNF) complex subunits and histone methyltransferases. DNA mismatch repair deficiency and apolipoprotein B mRNA editing enzyme, catalytic polypeptide cytidine deaminase activity are considered mechanisms associated with high mutational burden in subsets of DTC and ATC (22). These driver genes not only regulate cell proliferation and survival through canonical signaling pathways but also influence therapeutic responses via metabolic reprogramming and remodeling of the tumor immune microenvironment (23).

In recent years, considerable progress has been made in the development of drugs targeting these molecular alterations. Multikinase inhibitors (MKIs) such as sorafenib and lenvatinib have been approved for RAI-R DTC (24,25), while the dabrafenib plus trametinib regimen targeting BRAF V600E has shown encouraging efficacy in ATC (26). However, primary and acquired resistance have become increasingly prominent, driving the exploration of combination therapies and novel drug strategies (27,28). The substantial disease burden and unique epidemiological characteristics of thyroid cancer in China underscore the necessity and urgency of strengthening basic research on signaling pathways and clinical translation of targeted therapies.

2. Progress in research on key signaling pathways in thyroid cancer

The development and progression of thyroid cancer are closely associated with the aberrant activation of multiple signaling pathways, including MAPK, PI3K, AKT and NOTCH. These pathways not only regulate tumor cell proliferation, survival, metabolism and migration but also influence therapeutic responses through complex interaction networks (29-31). An overview of these pathways and their interactions are presented in Fig. 1.

MAPK signaling pathway: Driving core and mechanisms of resistance. The BRAF V600E mutation was first identified in thyroid cancer in 2003 and subsequent studies rapidly established its role as a hallmark genetic event in various types of thyroid cancer (32,33). The BRAF V600E mutation is present in 23-83% of PTC, with a generally higher prevalence in Asian populations, often >70% (34). BRAF is a key regulator of the MAPK signaling pathway; the mutant BRAF V600E can function as a monomer, constitutively activating the MAPK pathway and serving a fundamental and dominant role in the initiation and progression of thyroid cancers harboring this mutation (33,35). As research on the BRAF V600E mutation in thyroid cancer has advanced, an integrative genomic analysis of 496 PTC cases systematically mapped the genomic landscape of PTC. The Cancer Genome Atlas (TCGA) Research Network performed an integrative genomic analysis of 496 PTC cases and confirmed that ~97% of PTCs harbor a genetic driver event, with MAPK pathway drivers, predominantly BRAF V600E and RAS mutations, being dominant and mutually exclusive (20). The Cancer Genome Atlas (TCGA) Research Network, for the first time, proposed that BRAF V600E-mutant thyroid tumors are not a single entity but can be classified into molecular subtypes with distinct degrees of differentiation based on gene expression profiles, and innovatively introduced the concept of the Thyroid Differentiation Score (TDS) (20). Subsequent studies further characterized these subtypes based on TDS stratification (36). The study innovatively introduced the concept of the Thyroid Differentiation Score (TDS), quantifying a continuous PTC spectrum ranging from well-differentiated (RAS-like) to poorly differentiated (BRAF-like), thereby greatly reshaping the understanding of the molecular basis of thyroid cancer (20,36). As the dedifferentiation process of thyroid cancer cells progressively intensifies, certain genetic alterations cooperate with other molecular changes, leading to continuously enhanced MAPK and PI3K/Akt signaling. Consequently, PTC may gradually transform into PDTC and ATC (14,15). Importantly, TERT promoter mutations frequently co-occur with BRAF V600E mutations in advanced thyroid cancer and this co-occurrence is associated with more aggressive tumor behavior, higher rates of recurrence and worse patient survival compared with BRAF mutations alone (14,22). The transcriptional activation of TERT depends on E26 transformation-specific (ETS) transcription factors, whose activity is co-regulated by both the MAPK and PI3K/AKT pathways, establishing a feed-forward regulatory loop that drives malignant progression (14).

Constitutive activation of the MAPK pathway suppresses the expression of thyroid-specific genes such as sodium/iodide

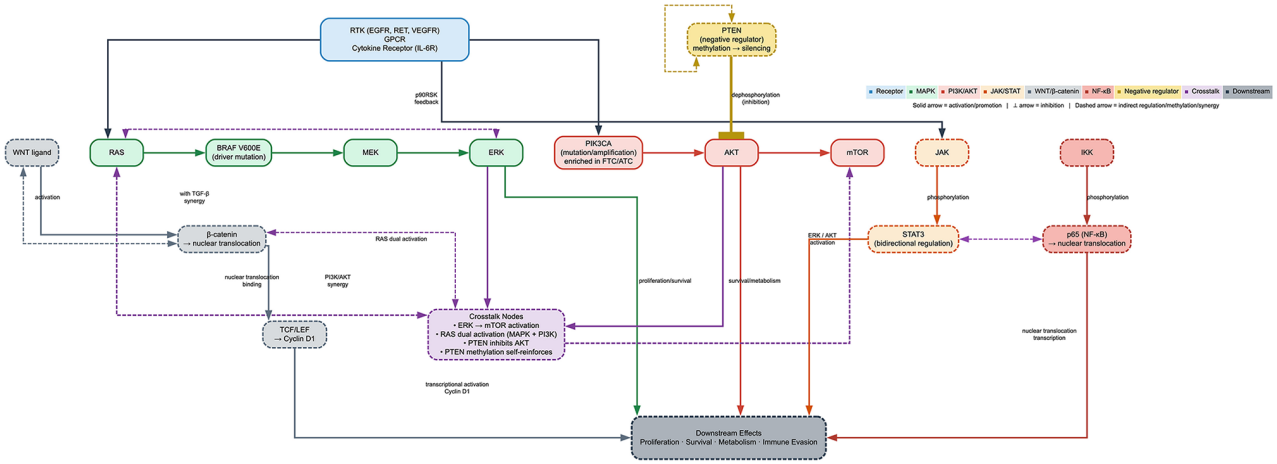

Figure 1. Major signaling pathways and their crosstalk in thyroid cancer. Schematic of five key pathways (MAPK, PI3K/AKT, JAK/STAT, WNT/β-catenin, NF-κB) involved in thyroid cancer. RTKs, GPCRs and cytokine receptors activate downstream cascades. The MAPK pathway (RAS-BRAF-MEK-ERK) is a core driver, with BRAF V600E as a prevalent mutation (13,19,27,29). RAS also engages PI3K/AKT signaling through dual pathway activation (50). The PI3K/AKT cascade (PIK3CA-AKT-mTOR) is frequently altered in FTC and ATC (13,21,41) and is negatively regulated by PTEN, whose methylation-driven silencing reinforces pathway activity (13,47). JAK/STAT (JAK-STAT3) mediates inflammatory signaling and immune modulation, with context-dependent functions (52,54). WNT/β-catenin promotes EMT, stemness and therapy resistance, with crosstalk to TGF-β and PI3K/AKT (62,63). NF-κB (IKK-p65) links inflammation to progression and cooperates with STAT3 (68,70) Key crosstalk nodes include ERK-mediated mTOR activation, RAS dual engagement, PTEN loss and p90RSK feedback (47,50). Solid arrows, activation; blunt arrow (⊥), inhibition; dashed arrows, indirect regulation or synergy. AKT, protein kinase B; ATC, anaplastic thyroid carcinoma; BRAF, B-Raf proto-oncogene, serine/threonine kinase; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; FTC, follicular thyroid carcinoma; GPCR, G protein-coupled receptor; IKK, IκB kinase; IL-6R, interleukin-6 receptor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RAS, rat sarcoma virus oncogene; RTK, receptor tyrosine kinase; STAT3, signal transducer and activator of transcription 3; TCF, T-cell factor; TGF-β, transforming growth factor-beta; WNT, wingless-related integration site.

cotransporter (NIS), thyroglobulin and thyroid stimulating hormone receptor, leading to loss of cellular differentiation and reduced iodine uptake, which is a key mechanism underlying RAI-R status (37,38). Research on resistance mechanisms to B-Raf proto-oncogene, serine/threonine kinase/mitogen-activated protein kinase kinase (BRAF/MEK) inhibitors (such as dabrafenib and trametinib) has also progressed. One study reported that 4 patients with thyroid cancer (2 with PTC and 2 with ATC) treated with BRAF inhibitors all acquired new RAS mutations (KRAS G12V, NRAS Q61K, NRAS G13D) while retaining the original BRAF V600E mutation, suggesting that RAS mutation may be a common cross-tumor resistance pathway (39). Another real-world clinical study in 2023 identified a pathogenic NRAS mutation in one out of nine patients with BRAF-mutant ATC who progressed following treatment with dabrafenib plus trametinib, further validating the clinical relevance of this mechanism (40).

Simultaneously, the multidimensional network of resistance mechanisms is becoming clearer. In a review, Hossain (41) pointed out that acquired resistance to RAF inhibitors mainly involves RAF dimerization, feedback reactivation of the MAPK pathway and paradoxical activation of ERK signaling. BRAF V600E-mutant-driven thyroid cancer exhibits notable transcriptomic and genomic heterogeneity, including differences in TDS, genetic co-alterations and microRNA (miRNA/miR) expression profiles, collectively mediating differential therapeutic responses (42). At the molecular mechanism level, a preprint study (not yet peer-reviewed; preliminary evidence) using CRISPR screening identified tafazzin (TAZ) as a key regulator of BRAF inhibitor resistance, with TAZ deletion enhancing the sensitivity of ATC cells to dabrafenib (43). Secretory leukocyte protease inhibitor is highly expressed in BRAF V600E-mutant PTC and promotes tumor progression while influencing therapeutic sensitivity through activation of the FAK/AKT signaling pathway (44). Further research revealed that growth arrest and DNA-damage-inducible β is markedly downregulated in RAI-R DTC; its overexpression suppresses MAP3K4-mediated MAPK pathway activity and restores expression of iodine metabolism genes, providing a new strategy to overcome RAI resistance (45). Collectively, these mechanisms indicate that resistance to BRAF/MEK inhibitors involves multiple factors, including RAS mutations, RAF dimerization, compensatory activation of bypass pathways, ferroptosis regulation and silencing of iodine metabolism genes, thereby providing a theoretical basis for developing combination targeted strategies (Table I).

PI3K/AKT signaling pathway: from driving mechanisms to metabolic regulation. The PI3K/AKT pathway is the second most critical signaling cascade in thyroid cancer, second only to the MAPK pathway and it serves a dominant role, particularly in FTC and advanced-stage thyroid cancer (46). There are two classic studies on the genetic alteration landscape of dedifferentiated thyroid cancer. Landa *et al* (14) performed genomic profiling of 117 PDTC and ATC cases, while Pozdeyev *et al* (22) conducted a larger comprehensive genomic study comprising 583 advanced DTC and 196 ATC cases, further validating and extending the findings. The authors found that mutations in PIK3CA, which encodes the catalytic subunit of PI3K, occurred markedly more frequently in ATC than in PDTC and PTC. PIK3CA mutations were detected in

Table I. Core molecular regulatory mechanisms and implications of the MAPK signaling pathway.

First author/s, year	Molecular/ mechanism	Regulatory mechanism	Biological impact	(Refs.)
Kimura, 2003	BRAF V600E	Constituent activation of RET/PTC-RAS-BRAF signaling pathway	Promote the occurrence and development of PTC	(32)
Wan *et al*, 2004	BRAF V600E	Mutant BRAF V600E continuously activates downstream MEK/ERK as a monomer	Drive MAPK pathway signal amplification, cell proliferation ↑	(33)
Davies *et al*, Nature. 2002	BRAF V600E	Mutations in kinase domains lead to constitutive kinase activity	Cell transformation and tumorigenesis	(35)
Rashid *et al*, 2020	BRAF V600E	No mechanism involved, for epidemiological analysis	Regional differences in mutation rates	(34)
Cancer Genome Atlas Research Network, 2014	BRAF V600E, RAS	MAPK pathway driven events (BRAF/RAS) dominate and are mutually exclusive	Drive PTC to occur; Divided into different molecular subtypes (TDS) based on gene expression characteristics	(20)
Boucai *et al*, 2022	BRAF V600E	Molecular typing of BRAF mutant PTC based on TDS	High TDS (RAS like) has improved differentiation, while low TDS (BRAF V600E like) has poor differentiation and strong invasiveness	(36)
Landa *et al*, 2016	MAPK, PI3K-Akt, TERT, TP53	MAPK and PI3K Akt signaling enhancement, synergistic TERT/TP53 mutation	Drive PTC to differentiate from PDTC/ATC, invasiveness ↑	(14)
Xing, 2013	BRAF, RAS, RET	The constitutive activation of pathways drives the occurrence of thyroid cancer	Cell proliferation ↑, differentiation ↓	(15)
Aashiq *et al*, 2019	MAPK, NIS	Continuous activation of MAPK inhibits the expression of thyroid specific genes such as NIS, Tg, TSHR, etc	Loss of iodine uptake function, cell differentiation ↓	(37)
Fullmer *et al*, 2021	MAPK, NIS	Activation of MAPK pathway leads to silencing of iodine metabolism genes	Radioactive iodine resistance (RAI-R)	(38)
Cabanillas *et al*, 2020	RAS (KRAS, NRAS)	Under BRAF inhibitor treatment pressure, acquired RAS mutations (KRAS G12V, NRAS Q61K, NRAS G13D) activate bypass pathways	Bypass BRAF inhibition and maintain MAPK signaling	(39)
da Silva *et al*, 2023	NRAS	Acquired NRAS mutation after treatment with dalafenib and trametinib	Activate MAPK pathway, mediate drug resistance	(40)
Hossain, 2025	RAF, MAPK, ERK	RAF inhibitors lead to the formation of RAF dimers and activation of feedback loops	Compensatory activation of signaling pathways leads to drug resistance	(41)
Riesco-Eizaguirre, 2025	BRAF V600E, TDS, miRNA	Transcriptome and genomic heterogeneity (TDS differences, co mutations, miRNA profiles)	Differences in tumor differentiation, invasiveness and treatment response	(42)
Noronha *et al*, 2025 (bioRxiv.)	TAZ	TAZ deficiency can enhance sensitivity to dalafenib	Regulating cell survival signals and mediating drug resistance	(43)
Luo *et al*, 2025	SLPI	SLPI activates the FAK/AKT signaling pathway	Promote tumor progression of BRAF V600E mutant PTC and affect treatment sensitivity	(44)
Jiang *et al*, 2025	Gadd45B, MAP3K4	Downregulation of Gadd45B leads to enhanced MAP3K4 mediated MAPK pathway activity	Inhibition of expression of iodine metabolism genes (NIS, etc.) and RAI resistance	(45)

AKT, protein kinase B; BRAF, B-Raf proto-oncogene, serine/threonine kinase; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; Gadd45B, growth arrest and DNA-damage-inducible beta; MAP3K4, mitogen-activated protein kinase kinase kinase 4; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; miRNA, microRNA; NIS, sodium/iodide symporter; PTC, papillary thyroid carcinoma; RAI-R, radioactive iodine-refractory; RAS, rat sarcoma virus gene family; SLPI, secretory leukocyte protease inhibitor; TAZ, tafazzin (WWTR1); TDS, Thyroid Differentiation Score; Tg, thyroglobulin; TSHR, thyroid stimulating hormone receptor.

16-20% of ATC cases, at lower frequency in PDTC and were extremely rare in TCGA PTC cohort. Meanwhile, inactivation of PTEN, a core negative regulator of the PI3K/AKT pathway, was also confirmed in this study. Some ATC samples exhibited loss of heterozygosity or inactivating mutations of the PTEN gene, leading to loss of its PIP3 dephosphorylation function and consequently disinhibition of AKT signaling. The study further highlighted that TERT promoter mutations are among the most common events in PDTC and ATC (occurring in up to 73% of ATC cases). TP53 mutations are also highly enriched in ATC (occurring in 70-80% of cases) compared with DTC (where they are rare). TP53 inactivation cooperates with MAPK pathway activation to promote dedifferentiation, genomic instability and resistance to both conventional and targeted therapies. The co-occurrence of TP53 mutations with BRAF V600E or TERT promoter mutations is associated with particularly poor prognosis and represents a hallmark of anaplastic transformation (14,22). Their transcriptional activation depends on ETS transcription factors, whose activity is co-regulated by both the MAPK and PI3K/AKT pathways. Thus, a feed-forward regulatory loop involving BRAF/RAS mutations, PIK3CA mutations and TERT promoter mutations cooperatively drives cells toward unlimited proliferative potential (14).

A larger comprehensive genomic study comprising 583 advanced DTC and 196 ATC cases further validated and extended the aforementioned findings, collectively confirming the PI3K/AKT pathway as the second core driver module in ATC. Pozdeyev *et al* (22), in a larger comprehensive genomic study comprising 583 advanced DTC and 196 ATC cases, similarly found that high-frequency enrichment of PIK3CA mutations and widespread inactivation of PTEN in ATC directly and persistently activate PI3K/AKT signaling. Co-occurrence with BRAF V600E or RAS mutations further demonstrated that dual activation of the MAPK and PI3K/AKT pathways is a hallmark of ATC. The study also identified mutations or amplifications of mTOR-related genes (such as MTOR, regulatory associated protein of mTOR complex 1 and DEP domain containing mTOR interacting protein) in a small subset of ATC, suggesting that the assembly and activity of the mTOR complex may be directly regulated in some tumors (22).

Studies on metabolic regulation in thyroid cancer have revealed that the risk of thyroid nodules and thyroid cancer is increased in patients with obesity, metabolic syndrome or type 2 diabetes mellitus and this risk gradually escalates with the severity and duration of metabolic disease. Insulin resistance is an important risk factor contributing to the increased incidence of thyroid diseases (47-49). Chronic hyperinsulinemia occurring in the setting of insulin resistance continuously stimulates the insulin-like growth factor (IGF) axis and downstream targets of the IGF axis can activate the PI3K/AKT/mTOR and RAF/MEK/ERK pathways to mediate oncogenic effects, influencing cell cycle progression, anti-apoptosis and angiogenesis (50,51). Further studies have indicated that dysregulated adipokines such as leptin, adiponectin and visfatin can also promote tumor proliferation and survival through PI3K/AKT, JAK2/STAT3 and ERK signaling and are closely associated with lymph node metastasis, aggressive tumor behavior and radioiodine resistance (50,52).

There is extensive cross-talk between the PI3K/AKT and MAPK pathways; ERK can directly phosphorylate and activate mTOR, while receptor tyrosine kinase (RTK) signals can activate both pathways simultaneously (51). Prete *et al* (53) confirmed that this parallel activation mechanism is an important basis for resistance to targeted therapies. The authors found that pericytes in the tumor microenvironment are core drivers of resistance. Pericytes are cells that cover the outer wall of capillaries; they secrete two key molecules: Thrombospondin-1 (TSP-1) and TGF-β1. Together, these two factors form a positive feedback loop in thyroid cancer cells, leading to synergistic activation of the PI3K/AKT and MAPK pathways, thereby overcoming the cytotoxic effects of targeted therapy. This mechanism provides a theoretical basis for combined blockade of the MAPK and PI3K/AKT pathways in the treatment of refractory thyroid cancer (Table II).

JAK/STAT signaling pathway: Chemokine regulation and immune microenvironment remodeling. The JAK/STAT pathway mediates inflammatory signaling, immune microenvironment remodeling and tumor cell survival in thyroid cancer. IL-6 is markedly upregulated in thyroid cancer tissues, positively correlates with tumor-associated macrophage infiltration and programmed death-ligand 1 (PD-L1) expression and activates the IL-6/JAK/STAT3 pathway to participate in immune microenvironment remodeling (54). In addition, STAT3 can directly bind to the promoter region of PD-L1, upregulating its expression and mediating immune evasion (55,56). Studies have found that the RAF inhibitor vemurafenib (PLX4032) enhances IL-6 secretion, which in turn leads to STAT3 upregulation, ERK signaling activation and reduced sensitivity to BRAF inhibition. Therefore, dual blockade with an IL-6 receptor antibody (tocilizumab) and PLX4032 achieves greater inhibition of cell cycle progression compared with PLX4032 monotherapy (57,58).

CCL17 has been identified as a core chemokine-related biomarker that promotes thyroid cancer progression by regulating the JAK-STAT pathway (59). Mammalian acidic chitinase (CHIA), a member of the chitinase family, is closely associated with the inflammatory microenvironment through its aberrant expression. In thyroid cancer, upregulation of CHIA activates the JAK2/STAT3 signaling pathway, promoting thyroid cancer cell proliferation, migration and invasion (60). Conversely, TLE family member 4, transcriptional corepressor drives tumor progression by downregulating the expression of SOCS1 and activating the JAK/STAT pathway (61). Furthermore, retinoic acid receptor γ can upregulate the expression of CD24 and matrix metalloproteinases by activating the JAK1-STAT3 signaling axis, thereby mediating tumor cell immune evasion and metastasis (62). Collectively, these findings reveal a molecular network through which chemokines and their related regulatory molecules connect inflammatory signaling, immune microenvironment remodeling and tumor cell survival via the JAK/STAT pathway, providing a theoretical basis for therapeutic strategies targeting this pathway (Table III).

WNT/β-catenin signaling pathway: crosstalk network and therapeutic resistance. Aberrant activation of the WNT/β-catenin pathway serves a critical role in the

Table II. Core molecular regulatory mechanisms and implications of the PI3K/AKT signaling pathway.

First author/s, year	Molecular/ mechanism	Regulatory mechanism	Biological impact	(Refs.)
Xing, 2010	PIK3CA, PTEN, AKT1	PTEN inactivation → PIP3 accumulation → AKT sustained activation; PIK3CA mutation → constitutive activation	Cell proliferation ↑, apoptosis ↓, differentiation ↓, associated with follicular carcinoma and advanced thyroid carcinoma	(46)
Cancer Genome Atlas Research Network, 2014	BRAF V600E, RAS MAPK and PI3K/ AKT	MAPK and PI3K/AKT drive events are mutually exclusive in PTC, dominating different molecular subtypes respectively	97% of PTC exhibits MAPK driven events; BRAF mutant tumors exhibit different invasiveness based on their differentiation degree (TDS)	(20)
Landa *et al*, 2016	MAPK, PI3K/AKT, TERT, TP53	PI3K/AKT signal enhancement, synergistic MAPK and TERT/ TP53 mutations	Drive PTC to differentiate from PDTC/ATC, with increased invasiveness and poor prognosis	(14)
Pozdeyev *et al*, 2018	PIK3CA, PTEN, BRAF, RAS, TERT, TP53	PIK3CA mutation and PTEN inactivation markedly increase in ATC → PI3K/AKT pathway highly activated	PI3K/AKT pathway drives highly aggressive phenotype in advanced thyroid cancer (especially ATC)	(22)
Rezzónico *et al*, 2009	Insulin resistance	Insulin/IGF signaling activates PI3K/AKT pathway	Incidence of insulin resistance in DTC patients ↑	(47)
Yeo *et al*, 2014	Diabetes	Hyperinsulinemia, chronic inflammation activate PI3K/AKT and MAPK pathways	Diabetes is markedly and positively correlated with thyroid cancer risk	(48)
Moon *et al*, 2018	Insulin resistance, Metabolic syndrome	Insulin/IGF signaling activates the PI3K/AKT pathway, promoting thyroid cell proliferation	Incidence of thyroid nodules is markedly positively correlated with HOMA-IR	(49)
Manzella *et al*, 2019	IGF axis (IGF1, IGF2, IGF1R)	IGF1R overexpression and ligand activation → sustained stimulation of PI3K/AKT pathway	Cell proliferation ↑, apoptosis ↓ and invasion ↑ are associated with treatment resistance and poor prognosis	(50)
Robbins and Hague, 2016	PI3K/Akt (Endocrine tumors)	Continuous activation of pathways regulates cell survival, proliferation and metabolism	Driving the occurrence of endocrine tumors (including thyroid cancer) with therapeutic targeting potential	(51)
Iuliano *et al*, 2026	Insulin resistance, INSR-A, IGF1R	Chronic hyperinsulinemia activates PI3K/AKT/mTOR and MAPK; INSR-A/IGF1R overexpression amplification signal	Metabolic abnormalities promote thyroid nodules and DTC occurrence through PI3K/AKT activation	(52)
Prete *et al*, 2018	Pericytes, TSP-1/ TGF β1 axis	Pericytes secrete TSP-1 to activate TGF β 1 → bypass activates PI3K/ AKT pathway	Mediating acquired resistance to BRAF inhibitors (vemurafenib) and sorafenib	(53)

AKT, protein kinase B; ATC, anaplastic thyroid carcinoma; BRAF, B-Raf proto-oncogene, serine/threonine kinase; DTC, differentiated thyroid cancer; HOMA-IR, homeostatic model assessment of insulin resistance; IGF, insulin-like growth factor; IGF1R, insulin-like growth factor 1 receptor; INSR-A, insulin receptor isoform A; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; PDTC, poorly differentiated thyroid cancer; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RAS, rat sarcoma virus gene family; TERT, telomerase reverse transcriptase; TGFβ1, transforming growth factor beta 1; TP53, tumor protein p53; TSP-1, thrombospondin-1.

dedifferentiation and invasive progression of thyroid cancer, particularly in the development of ATC. Multiple signaling molecules have been demonstrated to participate in thyroid cancer pathogenesis by regulating this pathway. For example, diaphanous related formin 3 is highly expressed in ATC and cooperates with FOXM1 protein to synergistically activate WNT/β-catenin signaling, thereby promoting ATC cell proliferation and invasion (63). EIF3H is also aberrantly upregulated in ATC; it functions as a deubiquitinase interacting with β-catenin, stabilizes β-catenin protein by

Table III. Core molecular regulatory mechanisms and implications of the JAK/STAT signaling pathway.

First author/s, year	Molecular/ mechanism	Regulatory mechanism	Biological impact	(Refs.)
Cunha LL *et al*, 2021	TAMs, TILs	Differentiation status affects immune cell infiltration and PD-L1/PD-1 expression, indirectly regulating the JAK/STAT pathway	Low differentiated thyroid cancer (PDTC/ATC) presents an immunosuppressive microenvironment associated with JAK/STAT signaling activation	(54)
Shi RL *et al*, 2017	PD-L1	STAT3 directly binds to the PD-L1 promoter region and upregulates its expression	High expression of PD-L1 is associated with increased risk of PTC lymph node metastasis and recurrence	(55)
Ulisse S *et al*, 2019	PD-1/PD-L1	Tumor cells regulate PD-L1 expression through pathways such as STAT3	PD-L1 expression is associated with invasiveness and dedifferentiation in thyroid cancer, suggesting potential targets for immunotherapy	(56)
Notarangelo T *et al*, 2018	IL6/STAT3 axis	BRAF inhibitors induce IL6 secretion and IL6 activates STAT3 through JAK1/2	Mediating acquired resistance to BRAF inhibitor (vemurafenib); Inhibition of IL6/STAT3 can restore sensitivity	(57)
Zhang M *et al*, 2025	CCL17	Activates the JAK-STAT pathway	High expression of CCL17 promotes the progression of thyroid cancer; The constructed chemokine model can predict patient prognosis	(59)
Ma Z *et al*, 2025	CHIA	Activates JAK2/STAT3 signaling pathway	Promote the proliferation, invasion and migration of thyroid cancer cells; Knocking down CHIA can inhibit malignant behavior of tumors	(60)
Lin J *et al*, 2024	TLE4	TLE4 downregulation activates JAK/STAT pathway	Low expression of TLE4 promotes PTC proliferation, migration and invasion, which is associated with poor prognosis	(61)
Zhang FX *et al*, 2023	RARγ	Activates the JAK1-STAT3 axis	Promote invasion and metastasis of thyroid cancer; Regulating downstream CD24 and MMPs expression	(62)

CCL17, C-C motif chemokine ligand 17; CD24, cluster of differentiation 24; CHIA, chitinase, acidic (mammalian); IL-6, interleukin 6; JAK, Janus kinase; MMPs, matrix metalloproteinases; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RARγ, retinoic acid receptor gamma; STAT, signal transducer and activator of transcription; TAMs, tumor-associated macrophages; TILs, tumor-infiltrating lymphocytes; TLE4, transducin-like enhancer protein 4.

removing K48-linked ubiquitin chains and consequently activates WNT/β-catenin signaling to confer resistance to ferroptosis (64).

Regarding the induction of tumor cell dedifferentiation and promotion of epithelial-mesenchymal transition (EMT) and metastasis, Lv *et al* (65) discovered that M2-type tumor-associated macrophages secrete Wnt1 and Wnt3a ligands, which activate the β-catenin pathway in thyroid cancer cells, revealing a key mechanism of crosstalk between immune cells and tumor cells via WNT signaling. semaphorin 3C also activates the WNT pathway by enhancing β-catenin nuclear translocation, thereby promoting stemness maintenance, EMT and metastasis of thyroid cancer cells (66).

Crosstalk between the WNT/β-catenin pathway and other key oncogenic pathways constitutes a core mechanism underlying tumor progression and therapeutic resistance. A study proposed the critical role of the RAS-PI3K/AKT-β-catenin signaling axis in thyroid carcinogenesis: RAS-driven thyroid tumors activate the PI3K/AKT pathway, which induces phosphorylation of β-catenin at Ser552, thereby promoting its nuclear translocation and transcriptional activity, whereas

the BRAF V600E mutation alone does not directly activate β-catenin (67).

The WNT pathway cooperates with TGF-β signaling to drive EMT and maintain cancer stem cell properties, promoting dedifferentiation and invasive progression of thyroid cancer (68). Notably, Zou *et al* (69) elucidated a novel mechanism by which the WNT/β-catenin pathway promotes immune evasion through suppression of innate immune responses. In BRAF V600E-driven thyroid cancer, active β-catenin signaling downregulates the expression of activating natural killer group 2D (NKG2D) receptor ligands and upregulates inhibitory MHC class I molecules, enabling tumor cells to evade natural killer (NK) cell immune surveillance. Upon β-catenin knockout, NKG2D ligand expression is markedly upregulated and tumor cells become highly sensitive to NK cell-mediated killing (69). Furthermore, p21-activated kinases act as signaling hubs that simultaneously regulate the MAPK, PI3K/AKT and WNT/β-catenin pathways, serving an important role in thyroid cancer progression and resistance to targeted therapies (70). In ATC, aberrant activation of the WNT/β-catenin pathway frequently co-occurs with TP53 mutations, TERT promoter mutations and activation of the PI3K/AKT pathway. These synergistic events drive the dedifferentiation of differentiated thyroid cancer toward ATC and are closely associated with resistance to BRAF and MEK inhibitors (69,70). The extensive crosstalk of the WNT/β-catenin pathway with the MAPK, PI3K/AKT, TGF-β and immune regulatory pathways constitutes the molecular basis for aggressive progression and therapeutic resistance in refractory thyroid cancer. Targeting these interaction nodes may represent an effective strategy to overcome drug resistance (Table IV).

NF-κB signaling pathway: inflammatory connection and immune regulation. The NF-κB signaling pathway serves as a key molecular bridge linking the inflammatory microenvironment to thyroid tumorigenesis by mediating chronic inflammatory responses. Xu *et al* (71) found that tumor necrosis factor receptor superfamily member 12A is markedly upregulated in thyroid cancer tissues compared with adjacent normal thyroid tissues. It promotes tumor cell proliferation, inhibits apoptosis and upregulates the expression of pro-inflammatory cytokines IL-1β, IL-6 and IL-8 by activating the MAPK and NF-κB signaling pathways, thereby creating a pro-tumorigenic inflammatory microenvironment. At the level of signaling crosstalk, through systematic analysis of RNA-sequencing data from PTC in TCGA database, researchers confirmed the presence of a characteristic NF-κB activation signature in BRAF V600E-mutant PTC. Among the upstream activators of the canonical and alternative NF-κB pathways, MAP3K14/NIK drives the migration and invasion of tumor cells in BRAF-mutant cell lines by regulating the expression of invasion-related genes such as MMP1, plasminogen activator, urokinase, lipocalin 2 and galectin-3 (72). Under hypoxic conditions, hypoxia inducible factor-1α (HIF-1α) regulates the viability of radioiodine-resistant PTC cells via the pyruvate kinase isozymes M1/M2 (PKM2)/NF-κB signaling pathway; small interfering RNA-HIF-1α effectively inhibits cell proliferation, migration and invasion and alters the protein expression levels of PKM2 and NF-κB p65 (73). Furthermore, Pasquali *et al* (74) showed by immunohistochemical analysis of 80 patients with thyroid cancer that p-NF-κB (p65) is markedly upregulated in tumor cells and is closely associated with aggressive phenotypes and an imbalance of tumor-infiltrating regulatory T cells. Collectively, these studies demonstrate the critical role of NF-κB as a central node in the inflammation-to-cancer transformation axis and provide potential therapeutic targets for refractory thyroid cancer.

The NF-κB signaling pathway also plays a regulatory role in the remodeling of the immune microenvironment in thyroid cancer, affecting antitumor immune responses through multiple mechanisms. Liu *et al* (75) demonstrated that tilianin reduces PD-L1 expression in thyroid cancer cells by inhibiting the Toll-like receptor 4/NF-κB pathway, enhances $CD8^+$ T cell viability and promotes the secretion of IFN-γ, IL-2 and TNF-α, thereby reversing immune evasion and suppressing tumor growth in both *in vitro* and *in vivo* models. At the level of tumor-immune cell crosstalk, the polypeptide N-acetylgalactosaminyltransferase 7 (GALNT7)/NF-κB axis promotes M2 polarization of tumor-associated macrophages and efferocytosis, remodeling the immunosuppressive tumor microenvironment and accelerating the inflammation-to-cancer transition. Kushenol O, as a GALNT7 inhibitor, effectively blocks this process (76). In terms of immune cell infiltration regulation, serum exosomal miR-17-5p is notably enriched in patients with thyroid cancer with lung metastasis. This miRNA activates NF-κB signaling by inhibiting NF-κB repressing factor, promoting the secretion of IL-6 and IL-8 by MRC-5 lung fibroblasts, thereby reshaping the lung microenvironment into a pro-inflammatory niche favorable for thyroid cancer cell colonization and metastasis (77). Regarding treatment response, using patient-derived organoid models, researchers confirmed that NF-κB signaling exhibits a specific activation pattern at different stages of thyroid cancer differentiation. Pharmacological inhibition of NF-κB synergistically enhanced the antitumor efficacy of dasatinib, anti-programmed cell death protein 1 (PD-1) antibody and paclitaxel (with combination indices of 0.58, 0.45 and 0.80, respectively), revealing the great potential of NF-κB as a target to overcome therapeutic resistance (78). As one of the key pathways involved in immune microenvironment remodeling in thyroid cancer, the NF-κB signaling pathway provides a theoretical direction for combining its targeting with immune checkpoint inhibitor therapy (Table V).

3. Advances in targeted therapy for high-risk refractory thyroid cancer

Based on an in-depth understanding of the molecular mechanisms of the aforementioned signaling pathways, various targeted drugs have been investigated in clinical studies for high-risk refractory thyroid cancer and some have been approved for clinical practice. When DTC progresses to the RAI-R state, tumor cells lose their ability to concentrate iodine due to dedifferentiation, the disease behavior often exhibits more aggressive features and the prognosis deteriorates markedly (79). In this context, MKIs such as lenvatinib and sorafenib have become first-line systemic treatment options, while mutation-specific agents targeting particular

Table IV. Core molecular regulatory mechanisms and implications of the WNT/β-catenin signaling pathway.

First author/s, year	Molecular/ mechanism	Regulatory mechanism	Biological impact	(Refs.)
Shi *et al*, 2024	DIAPH3, FOXM1	FOXM1 regulates Wnt/β - catenin signaling through DIAPH3, indirectly affecting the PI3K/AKT axis	Promoting invasive transformation of ATC cells, associated with dedifferentiation and malignant progression	(63)
Zhang *et al*, 2025	EIF3H (m6A modified regulation)	EIF3H stabilizes β - catenin protein, thereby activating downstream signals; There is a synergistic effect with the PI3K/AKT pathway	Promoting ATC progression, mediating iron death resistance and associated with poor prognosis	(64)
Lv *et al*, 2021	Wnt1/Wnt3a derived from M2 macrophages	Secretory Wnt ligands activate the β - catenin pathway, which can interact with PI3K/AKT signaling	Inducing dedifferentiation of thyroid cancer cells, promoting metastasis and reshaping the immune microenvironment	(65)
Li *et al*, 2025	SEMA3C	By activating the Wnt/β - catenin pathway and synergistically promoting tumor progression with PI3K/AKT signaling	Promote proliferation, migration and invasion of thyroid cancer cells	(66)
Sastre-Perona *et al*, 2016	β-catenin	β - catenin signaling is involved in the activation of PI3K pathway in RAS driven thyroid cancer	β - catenin promotes the tumorigenesis of RAS mutant thyroid cancer through PI3K activation	(67)
Li *et al*, 2025	WNT, PI3K/AKT	WNT signal has extensive crosstalk with PI3K/AKT; Epigenetic modifications and non coding RNA involvement in regulation	Drive EMT and cancer stem cell plasticity, mediate RAI/TKI/ICI therapy resistance	(68)
Zou *et al*, 2023	β-catenin, NKG2D	Downregulation of β - catenin affects NKG2D ligand expression and indirectly regulates tumor immune microenvironment	Weakened β - catenin induces BRAF V600E driven immunogenic cell death and tumor regression in thyroid cancer cells	(69)
Bautista *et al*, 2020	P21 activated kinases (PAKs)	PAKs regulate the cytoskeleton and various signaling pathways including MAPK, PI3K/AKT	Mediating proliferation, survival, migration and invasion of thyroid cancer cells, associated with treatment resistance	(70)

AKT, protein kinase B; DIAPH3, diaphanous related formin 3; EIF3H, eukaryotic translation initiation factor 3 subunit H; EMT, epithelial-mesenchymal transition; FOXM1, forkhead box M1; m^6A, N^6-methyladenosine; MAPK, mitogen-activated protein kinase; NKG2D, natural killer group 2D; PAKs, p21-activated kinases; PI3K, phosphatidylinositol 3-kinase; SEMA3C, semaphorin 3C; WNT, Wingless-type MMTV integration site family.

driver genes (for example, the BRAF inhibitor dabrafenib combined with the MEK inhibitor trametinib) offer precision treatment strategies for patients carrying the corresponding molecular markers (80). Real-world studies have shown marked inter-individual variability in patient responses to these drugs. In particular, MKI treatment is often associated with adverse events such as hypertension, proteinuria, fatigue and hand-foot skin reactions, which can partially or severely affect patients' quality of life. Therefore, individualized toxicity management under a multidisciplinary collaboration model is required (81,82).

This section presented clinical evidence from various study designs, each with different levels of evidence quality. Randomized controlled trials (RCTs) and their pooled analyses represent the highest level of evidence (Level I), providing the most reliable assessment of treatment efficacy. Prospective non-randomized trials and large retrospective cohort studies constitute intermediate-level evidence (Level II-III), offering

Table V. Core molecular regulatory mechanisms and implications of the NF-κB signaling pathway.

First author/s, year	Molecular/ mechanism	Regulatory mechanism	Biological impact	(Refs.)
Xu *et al*, 2025	TNFRSF12A	Regulating MAPK and NF-κB pathways	Regulating the proliferation, apoptosis and expression of pro-inflammatory cytokines in thyroid cancer cells	(71)
Cormier *et al*, 2023	MAP3K14/NIK	Activate the non classical pathway of NF-κB	Involved in the occurrence and development of thyroid cancer, related to tumor progression	(72)
Wang *et al*, 2024	HIF-1α, PKM2	HIF-1 α is transmitted through the PKM2/NF-κB signaling axis	Regulating RAIR-DTC cell viability under hypoxic conditions and mediating radioactive iodine resistance	(73)
Pasquali *et al*, 2023	p-NF-κB (p65)	NF-κB p65 phosphorylation	Related to the imbalance of regulatory T cells, shaping the inflammatory microenvironment of tumors	(74)
Liu *et al*, 2025	TLR4	Tilianin inhibits the TLR4/ NF-κB axis	Inhibit the proliferation and invasion of thyroid cancer cells, reshape the immune microenvironment (enhance CD8+T cell function)	(75)
Li *et al*, 2025	GALNT7	Kushenol O regulates NF-κB axis through GALNT7	Regulating M2 polarization and phagocytosis of tumor associated macrophages to inhibit PTC progression	(76)
Gui *et al*, 2025	MiR-17 (derived from extracellular vesicles)	Extracellular vesicle miR-17 activates NF-κB pathway	Drive thyroid cancer lung metastasis	(77)
Gao *et al*, 2026	Microfluidic organoid model	Microfluidic organoids reveal differentiation and maturation driven by NF-κB	Providing a model for precise treatment cancer, NF-κB regulation is associated with of thyroid treatment sensitivity	(78)

$CD8^+$, cluster of differentiation 8-positive T cells; GALNT7, polypeptide N-acetylgalactosaminyltransferase 7; HIF-1α, hypoxia-inducible factor 1-alpha; MAP3K14/NIK, mitogen-activated protein kinase kinase kinase 14/NF-κB-inducing kinase; MAPK, mitogen-activated protein kinase; miR-17, microRNA-17; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PKM2, pyruvate kinase isozyme M2; PTC, papillary thyroid carcinoma; RAIR-DTC, radioactive iodine-refractory differentiated thyroid cancer; TLR4, Toll-like receptor 4; TNFRSF12A, tumor necrosis factor receptor superfamily member 12A.

valuable real-world data but with inherent selection biases. Small retrospective series and case reports (Level IV) can provide important proof-of-concept observations but are hypothesis-generating rather than conclusive. Preclinical studies (*in vitro* and animal models) and preprint articles (not peer-reviewed) are included to illustrate emerging mechanisms and future directions but should be interpreted with caution.

MKIs: From standard therapy to combination exploration. MKIs exert dual antitumor effects by targeting key kinases including vascular endothelial growth factor receptors, platelet-derived growth factor receptors, fibroblast growth factor receptors, RET and c-KIT, thereby inhibiting both tumor angiogenesis and direct tumor cell proliferation (83,84). Based on current clinical trials and expert consensus, MKIs have become the standard systemic treatment option for RAI-R DTC (85,86).

Lenvatinib and sorafenib, as approved tyrosine kinase inhibitors (TKIs) for RAI-R DTC, are supported by evidence from pivotal clinical studies. The international multicenter phase III RCT (Level I evidence) DECISION trial demonstrated that sorafenib markedly prolonged median progression-free survival (PFS) compared with the placebo [10.8 vs. 5.8 months; hazard ratio (HR)=0.59; P<0.0001], with an objective response rate (ORR) of 12.2% (24). Another key phase III RCT (Level I evidence) SELECT trial showed that lenvatinib resulted in a median PFS of 18.3 months, a marked improvement over the 3.6 months observed in the placebo group (HR=0.21; P<0.001) and an ORR as high as 64.8% (25). Notably, the substantial difference in ORR between the two trials (64.8 vs. 12.2%) suggests heterogeneity in efficacy among different TKIs. Real-world retrospective studies (Level II-III evidence) have further confirmed that first-line lenvatinib therapy achieves an ORR of 72.4% and a median PFS of 49.0 months, providing durable disease control for patients with RAI-R DTC (87). Clinical exploration of novel TKIs is ongoing. XL092 (zanzalintinib) is one such novel MKI. Two clinical trials registered on ClinicalTrials.gov (https://clinicaltrials.gov/, NCT06959511 and NCT06959641) are currently conducting phase II studies of XL092 (zanzalintinib) for RAI-R DTC, aiming to evaluate

its efficacy as neoadjuvant or first-line therapy and to explore the immune cell landscape and resistance mechanisms (88,89).

Research on anlotinib monotherapy or its combination with locoregional strategies in refractory thyroid cancer is advancing. Regarding monotherapy, a systematic review by Muntean *et al* (90) comprehensively summarized the efficacy data of anlotinib in thyroid cancer, confirming a neoadjuvant ORR of 76.9%. A prospective single-arm study (Level II evidence) showed that anlotinib monotherapy in progressive RAI-R DTC achieved a median PFS of 22.5 months, an ORR of 47.4% and a disease control rate (DCR) of 89.5% (91). Moreover, a retrospective analysis (Level III evidence) by Sun *et al* (92) of 71 patients with RAI-R DTC found that those with the BRAF V600E mutation had markedly prolonged PFS after MKI treatment (HR=0.296), suggesting that genetic background may influence TKI efficacy. In combination therapy, a retrospective study (Level III evidence) of anlotinib plus ^{125}I seed implantation for RAI-R DTC yielded a median locoregional PFS of 42.2 months and a 6-month ORR of 77%, without additional toxicity (93). A phase II single-arm trial (Level II evidence) evaluating anlotinib combined with ^{131}I therapy for distant metastatic DTC reported an ORR of 55.0% and a DCR of 94.7%, with all patients achieving a biochemical response (94). A retrospective study (Level III evidence) further confirmed that MKIs represented by anlotinib combined with an anti-PD-1 inhibitor as first-line treatment for unresectable ATC achieved an ORR of 61.1% and a median OS of 14.0 months (95). Whether used as monotherapy or in combination with locoregional therapies, anlotinib provides effective treatment options for patients with RAI-R DTC, with combination strategies demonstrating synergistic advantages in enhancing local control and delaying disease progression (Table VI).

BRAF/MEK inhibitors: From ATC expansion to novel strategies for overcoming resistance. Precision therapy targeting the BRAF V600E mutation has achieved breakthroughs in high-risk thyroid cancer, particularly providing an effective treatment option for BRAF-mutant ATC. Based on clinical evidence supporting BRAF V600E as a tumor-agnostic target, the phase II non-randomized basket trial (Level II evidence) Rare Oncology Agnostic Research (ROAR) trial conducted by Subbiah *et al* (96) demonstrated that dabrafenib plus trametinib exhibited durable antitumor activity across BRAF V600E-mutant solid tumors, with an ORR of 56% in ATC. Based on this study and pooled analyses of multiple clinical trials (97,98), the U.S. Food and Drug Administration approved this combination regimen in 2022 for adult and pediatric patients with unresectable or metastatic BRAF V600E-mutant solid tumors, making it the first BRAF/MEK inhibitor combination to receive a tumor-agnostic indication. Regarding optimization of treatment strategies for ATC, in patients with BRAF-mutant ATC, surgical resection of the primary tumor after neoadjuvant therapy should be pursued as a treatment goal, aiming to reduce locoregional complications, improve quality of life and prolong survival (17,18).

However, the long-term efficacy of BRAF inhibitor therapy is often limited by acquired resistance mechanisms. Enrichment of mutations in genes related to the PI3K/AKT/mTOR pathway, MAP/ERK pathway and SWI/SNF chromatin remodeling complex can drive resistance to BRAF inhibitors and tumor dedifferentiation by promoting a switch to alternative cellular states and establishing an immunosuppressive microenvironment (99). This suggests that combining targeted therapy with immunotherapy may represent a novel strategy to overcome resistance.

Although notable progress has been made in the application of BRAF/MEK inhibitors for high-risk refractory thyroid cancer, acquired resistance remains a key challenge limiting long-term efficacy. Recent mechanistic studies have revealed multiple resistance pathways. A study on BRAF-mutant thyroid cancer cell lines uncovered an important resistance mechanism: RNA-sequencing revealed that resistant cells failed to downregulate Aurora kinase B (AURKB) following MEK inhibition and combining an AURKB inhibitor with a MEK inhibitor synergistically suppressed cell growth and induced apoptosis (100). An earlier study on BRAF-mutant ATC cell lines found that SNAI1 mRNA expression increased after BRAF/MEK inhibitor treatment, suggesting that EMT-related pathways may be involved in resistance (101). Tiedje *et al* (102) discovered that epigenetic silencing of MHC class II molecules in BRAF-mutant ATC leads to defects in tumor cell antigen presentation, thereby enabling immune evasion; combining an EZH2 inhibitor restored MHC-II expression and enhanced sensitivity to MAPK inhibitors. Furthermore, studies using mouse models showed that activation of the hepatocyte growth factor/MET signaling pathway in relapsed tumors following BRAF inhibition is an important mechanism of acquired resistance and MET inhibitors effectively suppressed the growth of MET-amplified relapsed tumors (99,103). Collectively, these studies reveal a complex network of resistance mechanisms to BRAF/MEK inhibitors (involving MAPK pathway reactivation, compensatory activation of mitotic kinases, immune microenvironment remodeling and bypass signaling activation) thereby providing diverse target options for developing combination strategies to overcome resistance.

Cabanillas *et al* (104) drew on the successful experience of treating acute lymphoblastic leukemia. The authors proposed a 'Total Therapy' framework for ATC. This framework sequentially integrates targeted therapy, immunotherapy, surgery and radiotherapy. It includes induction, consolidation and maintenance phases. Preliminary evidence is primarily from retrospective studies and case reports (Level III-IV evidence). This evidence suggests that neoadjuvant BRAF/MEK inhibition followed by surgery may improve outcomes in BRAF V600E-mutant ATC (19,105-107). For example, one retrospective study (Level III evidence) reported 12-month OS and PFS rates of 93.6 and 84.4%, respectively. These rates were in patients who underwent surgery after neoadjuvant therapy. By contrast, patients who did not undergo surgery had a 12-month OS rate of 38.5% (105). A prospective single-arm study (Level II evidence) achieved an R0/R1 resection rate of 88.9% after neoadjuvant targeted therapy (107). However, current evidence for this approach remains limited. It consists predominantly of retrospective analyses and case reports. Large-scale prospective or randomized controlled trials are lacking. Nonetheless, the 'Total Therapy' concept represents a promising paradigm shift. It moves toward

Table VI. Clinical trial evidence for MKIs in thyroid cancer.

First author/s, year	Treatment	Target	Research subject	Main efficacy	(Refs.)
Brose *et al*, 2014	Sorafenib	VEGFR, PDGFR, RAF, RET	RAIR-DTC (Phase III DECISION Test)	Median PFS 10.8 months vs. placebo 5.8 months	(24)
Schlumberger *et al*, 2015	Lenvatinib	Ditto.	RAIR-DTC (Phase III SELECT Test)	Median PFS 18.3 months, ORR 64.8%	(25)
Cabanillas *et al*, 2016	Lenvatinib	Ditto.	RAIR-DTC	Role in thyroid cancer and solid tumors	(83)
Worden *et al*, 2024	Lenvatinib	Ditto.	RAIR-DTC (real world studies, USA)	Real world clinical outcomes of first-line monotherapy	(87)
Brose *et al*, 2021	Cabozantinib	VEGFR, MET, AXL, RET	RAIR-DTC (Phase III COSMIC-311 Trial)	Median PFS 11.0 months vs. placebo 1.9 months	(86)
Muntean *et al*, 2025	Anlotinib	VEGFR, FGFR, PDGFR, c- KIT	RAIR-DTC (xystem view)	Good effectiveness and safety	(90)
Sun *et al*, 2025	Anlotinib	Ditto.	Progressive RAIR-DTC (long term results)	Long term follow-up shows effectiveness, PET/CT can predict prognosis	(91)
Sun *et al*, 2025	Anlotinib	VEGFR, FGFR, PDGFR, c-KIT	RAIR-DTC (retrospective analysis)	BRAF V600E mutation patients have improved prognosis	(92)
Chen *et al*, 2025	Anlotinib +^{125}I	Multi target including VEGFR, local radiotherapy	Late RAIR-DTC	Combination therapy for mLPFS 2.2 months, ORR 77%	(93)
Li *et al*, 2025	Anlotinib +^{131}I	Multi target including VEGFR, RAI	Remote transfer DTC (Phase II single arm)	Combination therapy is safe and effective, Some RAIR patients have recovered their iodine intake	(94)
Northwestern University, 2026	XL092 (zanzalintinib)	Multi target TKI	Localized late/ metastatic RAIR-DTC	Clinical trial in progress (Phase II)	(89)
M.D. Anderson Cancer Center, 2026	XL092 (zanzalintinib)	Ditto.	Surgical advanced thyroid cancer (neoadjuvant)	Clinical trial ongoing (preoperative treatment)	(88)
Verburg *et al*, 2021	Clinical practice of TKI	Ditto.	RAIR-DTC (Expert Consensus)	Expert perspective: Issues and controversies in clinical applications	(85)
Song *et al*, 2024	TKI combined with immunotherapy	Multi target TKI+PD-1/ PD-L1	Unresectable ATC (retrospective single center)	Combination therapy is safe and effective and some patients have the opportunity for surgery	(95)

ATC, anaplastic thyroid carcinoma; AXL, AXL receptor tyrosine kinase; c-KIT, KIT proto-oncogene receptor tyrosine kinase; FGFR, fibroblast growth factor receptor; MET, mesenchymal-epithelial transition factor; mL-PFS, median local (locoregional) progression-free survival; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; RAF, RAF proto-oncogene, serine/threonine-protein kinase; RAIR-DTC, radioactive iodine-refractory differentiated thyroid cancer; RET, rearranged during transfection proto-oncogene; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

curative-intent management of this highly lethal malignancy (Table VII). The aforementioned major resistance mechanisms are summarized schematically in Fig. 2.

Immunotherapy combined with targeted therapy: breakthrough clinical advances. The combination of immunotherapy and targeted therapy has achieved breakthrough progress in

Table VII. Advances in the application of BRAF/MEK inhibitors in thyroid cancer.

First author/s, year	Treatment	Target	Research subject	Main efficacy	(Refs.)
Subbiah *et al*, 2023	Dalafenib + Trimetanib	BRAF V600E + MEK	BRAF mutation rare tumor (ROAR test)	ORR 69% (ATC queue), PFS and OS markedly improved	(96)
Salama *et al*, 2020	Dalafenib + Trimetanib	Ditto.	BRAF V600E mutant solid tumor (NCI-MATCH H)	ORR 33.8%, PFS 11.4 months, OS 28.6 months	(97)
Salama *et al*, 2026	Dalafenib + Trimetanib	Ditto.	BRAF V600E mutant solid tumor (NCI-MATCH H update)	Long term follow-up confirms sustained efficacy, with similar response rates across different tumor types	(98)
Wang *et al*, 2019	Dalafenib + Trimetanib (New Assistance)	Ditto.	BRAF mutation ATC (resectability assessment)	Improved complete resection rate and local control after new assistance	(17)
Zhao *et al*, 2023	Dalafenib + Trimetanib (New Assistance)	Ditto.	BRAF mutation ATC	Significant improvement in overall postoperative survival	(105)
Kwiatkowska *et al*, 2025	Dalafenib + Trimetanib (New Assistance)	Ditto.	BRAF mutation ATC	Improve surgical outcomes and increase local control rate	(106)
Bapat *et al*, 2024	Dalafenib + Trimetanib (New Assistance)	Ditto.	BRAF V600E+TERT mutation PTC (unresectable)	Obtain R0 resection to achieve long-term disease-free survival	(19)
Wächter *et al*, 2025	Dalafenib + Trimetanib (New Assistance)	Ditto.	Late BRAF mutation ATC	Convert non resectable ATC to resectable	(107)
Hamidi *et al*, 2024	Dalafenib + Trimetanib + Immune Checkpoint Inhibitors	BRAF V600E + MEK + PD-1/PD-L1	BRAF mutation ATC	Combination therapy improves ORR and surgical conversion rate, prolongs survival	(18)
Hicks *et al*, 2024	Exploration of combination therapy	BRAF + MEK + Aurora kinase	BRAF mutant thyroid cancer	Aurora kinase inhibition enhances MAPK targeted therapy sensitivity	(100)
Kurata *et al*, 2016	Exploration of combination therapy	BRAF + MEK	BRAF mutant thyroid cancer	BRAF/MEK combined inhibition induces growth arrest in ATC cells	(101)

ATC, anaplastic thyroid carcinoma; BRAF, B-Raf proto-oncogene, serine/threonine kinase; MEK, mitogen-activated protein kinase kinase; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PTC, papillary thyroid carcinoma; TERT, telomerase reverse transcriptase.

BRAF-mutant ATC, representing a highly anticipated clinical research advance in recent years. Although BRAF inhibitor monotherapy can rapidly induce tumor regression, the median PFS is only 6 months and the development of resistance is almost inevitable (104). Mechanistic studies have shown that acquired resistance after BRAF inhibition involves multiple genomic alterations; concurrently, tumor cells can shift toward an immunosuppressive state, manifested by increased infiltration of myeloid-derived suppressor cells in the tumor microenvironment and suppression of effector T-cell function (99,108). Further research by Brauner *et al* (109) revealed that PD-L1 expression levels are markedly higher in BRAF V600E-mutant thyroid cancer cells than in BRAF wild-type cells and that MEK inhibitors downregulate PD-L1 expression. The continuously updated understanding of resistance mechanisms has provided a solid molecular foundation for combining targeted therapy with immunotherapy, establishing the 'DTP' regimen (dabrafenib + trametinib + pembrolizumab) as a promising combination strategy for BRAF-mutant ATC, although it is important to note that the supporting evidence for this triple combination is derived primarily from a phase II single-arm trial (110) and real-world retrospective data (18) and further validation in larger prospective studies is warranted.

A landmark parallel-group phase II non-randomized trial (Level II evidence) conducted by Cabanillas *et al* (110) enrolled 43 patients with unresectable ATC, assigning different

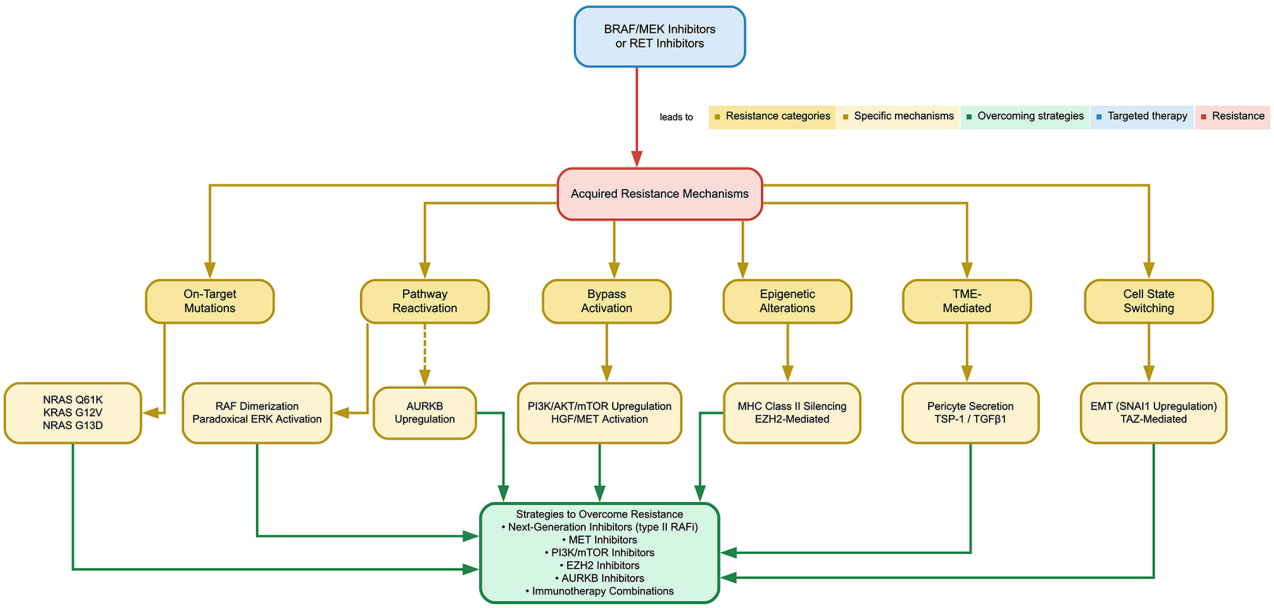

Figure 2. Mechanisms of acquired resistance to targeted therapies in thyroid cancer. Schematic summarizing major resistance mechanisms to BRAF/MEK and RET inhibitors. Resistance categories include: i) On-target mutations (secondary NRAS/KRAS mutations) (34,38,39); ii) pathway reactivation (RAF dimerization, paradoxical ERK activation) (36,40); iii) bypass activation (PI3K/AKT/mTOR upregulation, HGF/MET activation) (97,101,103); iv) epigenetic alterations (MHC class II silencing via EZH2) (100); v) tumor microenvironment-mediated resistance (pericyte-secreted TSP-1/TGFβ1) (49); and vi) cell state switching (EMT, TAZ upregulation) (38,97). AURKB upregulation represents an additional resistance mechanism (98). Potential strategies to overcome resistance include next-generation inhibitors, MET/PI3K/mTOR/AURKB/EZH2 inhibitors and immunotherapy combinations. BRAF, B-Raf proto-oncogene, serine/threonine kinase; MEK, mitogen-activated protein kinase kinase; RET, rearranged during transfection; NRAS, neuroblastoma RAS viral oncogene homolog; KRAS, Kirsten rat sarcoma viral oncogene homolog; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition factor receptor; MHC, major histocompatibility complex; EZH2, enhancer of zeste homolog 2; TSP-1, thrombospondin-1; TGFβ1, transforming growth factor-beta 1; EMT, epithelial-mesenchymal transition; TAZ, transcriptional coactivator with PDZ-binding motif; AURKB, Aurora kinase B; TME, tumor microenvironment.

combination regimens based on mutation status. In the BRAF V600E-mutant cohort receiving vemurafenib, cobimetinib and atezolizumab, the median OS reached 43 months, an ~9-fold improvement over historical data (5 months). This represents the longest median survival ever reported for ATC, confirming the efficacy of combination therapy and offering renewed hope for patients with this malignancy. These clinical data establish the preferred status of targeted-immunotherapy combinations in BRAF-mutant ATC and support the early incorporation of immune checkpoint inhibitors during the induction phase to prevent acquired resistance.

For BRAF wild-type patients, who account for 40-60% of ATC cases (111,112), treatment options remain limited and innovative combination strategies are urgently needed. A retrospective single-center study (Level III evidence) by Hamidi *et al* (113) included 36 patients with BRAF wild-type metastatic ATC who received first-line lenvatinib plus pembrolizumab. The confirmed ORR was 36%, the median OS was 7.7 months and three patients (9%) achieved complete remission, providing an effective treatment option for this difficult-to-treat population. Regarding dual immune checkpoint inhibitor combinations, a phase II non-randomized clinical trial (Level II evidence) evaluated nivolumab plus ipilimumab in aggressive thyroid cancers. In the exploratory ATC cohort, the ORR was 30%, the clinical benefit rate was 50% and the median duration of response was 23.2 months (114). A prospective study in the neoadjuvant setting enrolled 12 patients with advanced ATC who received genotype-guided neoadjuvant therapy. BRAF wild-type patients were treated with lenvatinib plus pembrolizumab and ultimately nine patients successfully underwent surgical resection, demonstrating that the neoadjuvant targeted-immunotherapy combination can convert initially unresectable tumors to a resectable state (107). Another study similarly confirmed that after short-course (4-week) neoadjuvant therapy, BRAF wild-type ATC patients could achieve R0/R1 resection, with postoperative pathology showing >60% tumor necrosis or fibrosis (115). Collectively, these innovative explorations provide multidimensional treatment options for patients with BRAF wild-type ATC, marking a gradual transition for this highly lethal malignancy from palliative to curative-intent strategies (Table VIII).

Redifferentiation strategies. The redifferentiation strategy has garnered increasing attention in recent years. This approach uses transient inhibition of the MAPK pathway to restore NIS expression and iodine uptake in thyroid cancer cells, thereby enabling RAI-R patients to receive radioactive iodine therapy (116,117). Constitutive activation of the MAPK pathway suppresses NIS expression through transcriptional inhibition, which is a core mechanism underlying RAI-R status. BRAF inhibitors block this signal, relieve the suppression of NIS and restore iodine uptake function (37). Short-term MAPK inhibition can restore iodine uptake in a subset of patients, creating an opportunity for repeated radioiodine administration (118).

Clinical evidence for redifferentiation strategies in the treatment of refractory thyroid cancer has been accumulating in recent years. A real-world study demonstrated that after genotype-guided MAPK inhibitor-based redifferentiation

Table VIII. Clinical trial evidence for immunotherapy combined with targeted therapy.

First author/s, year	Treatment	Target	Research subject	Main efficacy	(Refs.)
Cabanillas *et al*, 2025	Total treatment mode (targeted + immune + surgery + radiotherapy)	Multi-target integration	ATC full process management	Induction consolidation maintenance three-stage approach aimed at curative treatment	(104)
Brauner *et al*, 2016	Dalafenib + anti-PD-L1 (preclinical)	BRAF V600E + PD-L1	ATC immune mouse model	Markedly enhance tumor regression and anti-tumor immunity	(109)
Cabanillas *et al*, 2024	Atezolizumab + Vemurafenib + Cobimetinib	PD-L1 + BRAF + MEK	BRAF mutation ATC (stage II non randomized)	ORR 50%, Median PFS 7.9 months, median OS 14.3 months	(110)
Hamidi *et al*, 2026	Lenvatinib + Pembrolizumab	VEGFR + PD-1	BRAF wild-type metastatic ATC (real-world)	Combination therapy is effective and some patients achieve lasting relief	(113)
Sehgal *et al*, 2024	Nivolumab + Ipilimumab	PD-1 + CTLA-4	Invasive thyroid cancer (ATC, PDTC, RAIR - DTC) (stage II)	ORR 9%, Disease control rate of 29%, limited efficacy in ATC subgroup	(114)
Wächter *et al*, 2025	Mutation based neoadjuvant therapy (genotype guidance)	Selection based on driver genes (BRAFi, MEKi)	Late stage ATC (IVB/IVC stage)	Improved surgical conversion rate, achieving R0 resection	(107)

ATC, anaplastic thyroid carcinoma; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; MEK, mitogen-activated protein kinase kinase; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDTC, poorly differentiated thyroid cancer; PFS, progression-free survival; RAIR-DTC, radioactive iodine-refractory differentiated thyroid cancer; VEGFR, vascular endothelial growth factor receptor.

therapy, 10 of 11 (91%) patients with RAI-R DTC regained iodine uptake, with eight (80%) achieving partial response; no grade ≥3 adverse events occurred during a median follow-up of 39 months (117). An expert consensus (Level V evidence) issued by the International Thyroid Oncology Group systematically summarized the clinical evidence for redifferentiation therapy, reporting iodine uptake restoration rates ranging from 33-95% and tumor response rates from 11-80% (119). A retrospective study (Level III evidence) further revealed a notable genotype-dependent association: All 11 patients (100%) with RAS-mutant tumors regained iodine uptake after MEK inhibitor therapy, whereas only 39% (7/18) of BRAF-mutant tumors regained uptake after dabrafenib plus trametinib. A retrospective study by Toro-Tobon *et al* (120) further confirmed a 'two-phase benefit' mechanism of redifferentiation therapy; the targeted agents alone induced ~12% tumor shrinkage and after combined RAI, the total tumor shrinkage rate reached 30% in the successful redifferentiation group (120). Furthermore, progress has been made in redifferentiation therapy for RET fusion-driven thyroid cancer. A case report (Level IV evidence) showed that a patient with metastatic NCOA4::RET fusion-positive PTC received selpercatinib for 3 months followed by RAI, resulting in complete regression of lung metastases, sustained decline in thyroglobulin and PFS exceeding 24 months (121). Although case reports are hypothesis-generating and subject to publication bias, they provide important proof-of-concept observations for rare molecular subtypes. Similarly, NTRK fusions, although rare (occurring in 1-2% of PTC), represent highly actionable driver events in RAI-R DTC. The TRK inhibitors larotrectinib and entrectinib have demonstrated robust and durable responses in NTRK-fusion positive solid tumors, including thyroid cancer, with ORRs >70% (121,122). Furthermore, short-term treatment with TRK inhibitors has been shown to restore iodine avidity in NTRK fusion-positive RAI-R patients, enabling successful redifferentiation therapy and subsequent RAI treatment (122,123). These findings indicate that genotype-guided redifferentiation strategies can safely and effectively restore iodine uptake function in RAI-R patients, creating opportunities for subsequent radioiodine therapy.

In recent years, multiple innovative combination strategies have emerged in the field of redifferentiation therapy for thyroid cancer. Boucai (122) reviewed that following treatment with inhibitors targeting driver genes such as BRAF, RAS, RET and NTRK combined with radioiodine, the structural lesion shrinkage rate reached 33-63% in patients who successfully regained iodine uptake. Short-term selpercatinib therapy enabled a functional 'flip-flop' from high ^{18}F-FDG metabolism to ^{131}I uptake in RET fusion-positive RAI-R patients, creating conditions for repeated RAI therapy and achieving more durable disease control (121,124). A recent review by Zhu *et al* (123) further indicated that components

Table IX. Clinical evidence for redifferentiation strategies.

First author/s, year	Treatment	Target	Research subject	Redifferentiation rate	Follow-up treatment	(Refs.)
Leboulleux *et al*, 2023	Dalafenib + Trimetanib	BRAF V600E + MEK	BRAF V600E mutation metastatic RAIR-DTC (phase II)	12/20 cases (60%) resumed RAI uptake	^{131}I treatment	(116)
Demirkol *et al*, 2026	Dalafenib ± Trimetanib (Genotype guidance)	MEK ± BRAF	RAIR-DTC (Real World)	10/11 cases (91%) restored iodine intake	^{131}I treatment	(117)
Toro-Tobon *et al*, 2024	Dabafenib + Trimetanib ± Pembrolizumab (retrospective analysis)	BRAF + MEK ± PD- 1	RAIR-DTC (clinical retrospective)	Partial patients recover RAI uptake after redifferentiation	^{131}I treatment	(120)
Tarasova *et al*, 2025	Selpercatinib	RET	NCOA4: RET Fusion PTC (case report)	1 patient recovered RAI uptake	^{131}I treatment	(121)
Barbry *et al*, 2025	Selpercatinib	RET	RET Fusion RAIR-DTC (case report)	1 patient recovered RAI uptake	^{131}I treatment	(124)

BRAF, B-Raf proto-oncogene, serine/threonine kinase; MEK, mitogen-activated protein kinase kinase; NCOA4, nuclear receptor coactivator 4; PD-1, programmed cell death protein 1; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; RAI-R, radioactive iodine-refractory; RAIR-DTC, radioactive iodine-refractory differentiated thyroid cancer; RET, rearranged during transfection proto-oncogene.

Table X. Exploration progress of RET inhibitors.

First author/s, year	Treatment	Target	Research subject	Efficacy	(Refs.)
Schöffski *et al*, 2025	BOS172738	RET	RET changes solid tumors (RET fusion NSCLC, RET mutation MTC) (phase I dose escalation/expansion)	Safe and tolerable, RET mutant MTC patients show preliminary anti-tumor activity	(16)
Riya *et al*, 2025	Selpercatinib, Pralsetinib	RET	RET changes thyroid cancer (MTC, PTC) (systematic review and single arm meta- analysis)	ORR 74% (MTC), ORR 86% (RET fused PTC), controllable safety	(127)
Amitani *et al*, 2025	Selpercatinib	RET	CCDC6-RET fusion of thyroid cancer cells (basic research)	AKT mTOR pathway activation mediates acquired resistance to Serpatinib	(128)
Zhou *et al*, 2025	Selpercatinib, Pralsetinib	RET	RET changes thyroid cancer (clinical trial review)	RET inhibitors markedly improve the prognosis of RET mutant MTC and RET fused PTC	(129)

AKT, protein kinase B; mTOR, mechanistic target of rapamycin; MTC, medullary thyroid carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PTC, papillary thyroid carcinoma; RET, rearranged during transfection proto-oncogene.

of the tumor microenvironment, such as tumor-associated macrophages and cancer-associated fibroblasts, influence differentiation status through cytokine secretion and metabolic reprogramming. Targeting these microenvironmental components in combination with MAPK pathway inhibition may represent a novel redifferentiation strategy (123,125).

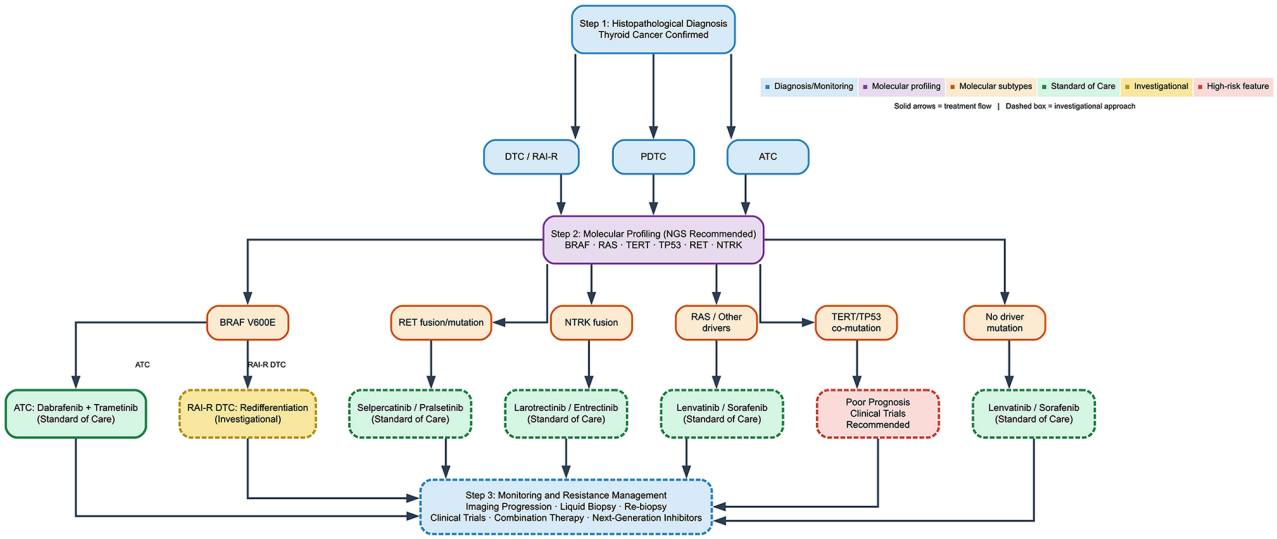

Figure 3. Treatment algorithm for high-risk refractory thyroid cancer based on molecular alterations. Clinical decision-making flowchart integrating molecular profiling results with therapeutic strategies. Steps include histopathological classification (DTC, PDTC, ATC), molecular testing (BRAF, RAS, TERT, TP53, RET, NTRK), treatment selection based on identified alterations and monitoring for resistance. Standard-of-care regimens (solid green boxes) are supported by phase III RCT or registrational trial evidence; investigational approaches (dashed yellow boxes) are supported by phase II trials, retrospective studies, or case reports. TERT/TP53 co-mutations (red box) identify patients with poor prognosis who should be considered for clinical trials (13,21,97). RET fusions/mutations are treated with selpercatinib or pralsetinib (15,123,124), NTRK fusions with larotrectinib or entrectinib (118,119), BRAF V600E-mutant ATC with dabrafenib plus trametinib (90,94) and RAI-R DTC without actionable drivers with lenvatinib or sorafenib (24,25). Treatment decisions should be individualized and made in a multidisciplinary context. ATC, anaplastic thyroid carcinoma; DTC, differentiated thyroid cancer; NGS, next-generation sequencing; PDTC, poorly differentiated thyroid cancer; RAI-R, radioactive iodine-refractory; RCT, randomized controlled trial.

Collectively, these innovative combination approaches depict a new landscape for redifferentiation therapy evolving from 'single-pathway inhibition' to 'genotype-guided, multimodal integration' (Table IX).

RET inhibitors: New advances in precision therapy. The RET proto-oncogene encodes a receptor tyrosine kinase whose mutations or fusions are closely associated with the initiation and progression of thyroid cancer. RET point mutations are found in >60% of sporadic and >90% of hereditary MTC, whereas RET fusions (most commonly CCDC6-RET and NCOA4-RET) occur in 10-20% of PTC cases, particularly in radiation-exposed populations and pediatric patients (16,125). These genetic alterations lead to ligand-independent constitutive activation of the RET kinase domain, driving tumor cell proliferation, survival and migration through downstream pathways including MAPK, PI3K/AKT and JAK-STAT. In addition to its role as a primary driver, RET activation has been implicated in acquired resistance to BRAF inhibitors in BRAF V600E-mutant thyroid cancers, where MAPK pathway feedback reactivation occurs via alternative mechanisms (101,103).

In recent years, the successful development of highly selective RET inhibitors has ushered in a new era of precision medicine for the treatment of high-risk, refractory RET-driven thyroid cancers. First-generation highly selective RET inhibitors, represented by selpercatinib and pralsetinib, have replaced traditional MKIs as the standard of care owing to their superior clinical efficacy and safety profiles. In pivotal phase I/II clinical trials (Level II evidence) such as LIBRETTO-001 and LIBRETTO-531, selpercatinib achieved an ORR >84% in treatment-naïve patients with RET-mutant MTC and an ORR as high as 95% in patients with RET fusion-positive RAI-R DTC, notably delaying disease progression and improving survival (126). A systematic review and meta-analysis (Level I evidence) encompassing 560 patients further confirmed that RET inhibitor therapy for RET-altered thyroid cancers yielded a 1-year PFS rate of 84% (95% confidence interval (CI), 79-88%), an ORR of 69% (95% CI, 65-73%) and a DCR as high as 93% (95% CI, 89-96%). Adverse events were predominantly grade 1-2 and the incidences of grade ≥3 hypertension, diarrhea and elevated liver enzymes were within manageable ranges (127).

Despite the marked initial efficacy of RET inhibitors, acquired resistance remains a major clinical challenge. By establishing selpercatinib-resistant CCDC6-RET fusion-expressing thyroid cancer cell models, Amitani *et al* (128) demonstrated for the first time that the AKT-mTOR pathway is markedly activated in resistant cells, whereas the phosphorylation levels of RET, ERK and EGFR are not correspondingly upregulated. This finding suggests that compensatory activation of the AKT-mTOR pathway is a key off-target mechanism mediating selpercatinib resistance. Combination with the mTOR inhibitor everolimus effectively overcame resistance, providing a novel strategy for clinically reversing RET inhibitor resistance. Furthermore, next-generation RET inhibitors (such as BOS172738 and LOXO-260) and innovative regimens combining RET inhibitors with radioactive iodine or anti-PD-1 antibodies are being actively explored, promising to further expand the application boundaries of precision therapy (16,129) (Table X). A treatment algorithm linking molecular alterations to therapeutic strategies for high-risk refractory thyroid cancer is presented in Fig. 3.

4. Conclusions and future perspectives

Notable progress has been made in the precision therapy of thyroid cancer over the past decade; nevertheless, the aforementioned high-risk refractory subtypes (including RAI-R DTC, PDTC, ATC, progressive MTC and locally advanced thyroid cancer) continue to pose major clinical challenges. Epidemiological data indicate that the high detection rate of thyroid cancer in China may be related to over-examination and there are notable differences between urban and rural areas and different provinces (130,131). Although overall mortality has remained stable, the disease burden of high-risk subtypes such as ATC is extremely heavy, with a mortality risk >12-fold higher than that of PTC (132), underscoring the urgency of strengthening basic research and clinical translation.

At the basic research level, the understanding of signaling pathways in thyroid cancer has expanded from single linear cascades to complex regulatory networks. Zou (58) summarized the central roles of the MAPK and PI3K/AKT pathways. The MAPK pathway acts as a core driver, engaging in compensatory crosstalk with the PI3K/AKT/mTOR pathway (52,53); JAK/STAT mediates inflammation and immunosuppression (133,134); and WNT/β-catenin is involved in tumor dedifferentiation and therapeutic resistance (68). More importantly, these signaling pathways not only regulate cell-intrinsic properties but also shape the tumor ecosystem through metabolic reprogramming and remodeling of the immune microenvironment. This understanding provides a theoretical basis for combination targeted strategies.

At the clinical translation level, MKIs have become the standard of care for RAI-R DTC. The landmark DECISION and SELECT trials established the therapeutic roles of sorafenib and lenvatinib, respectively, in this patient population (24,25). Meanwhile, the combination of dabrafenib and trametinib has shown breakthrough efficacy in BRAF V600E-mutant ATC (96). However, acquired resistance has become increasingly prominent, representing a major bottleneck limiting long-term benefit. Current research directions to overcome resistance mainly include the development of more specific next-generation inhibitors (such as type II RAF inhibitors) (135), exploration of rational combination strategies (such as TKIs combined with locoregional therapy) (93) and implementation of adaptive therapy based on dynamic monitoring. Notably, the redifferentiation strategy, using short-term MAPK inhibition to restore iodine uptake in tumor cells, has re-created opportunities for RAI therapy in RAI-R patients (118), with real-world studies reporting a redifferentiation success rate as high as 91% (117). Collectively, these advances outline a clinical translation landscape evolving from standard targeted therapy toward precise, combined and dynamic treatment paradigms.

The therapeutic value of immunotherapy in thyroid cancer is also being progressively clarified. For metastatic ATC, the combination of kinase inhibitors and immune checkpoint inhibitors has emerged as a promising treatment approach, supported by encouraging results from phase II trials and retrospective series (108). Concurrently, the 'Total Therapy' model has introduced the induction, consolidation and maintenance framework from hematologic oncology into ATC management. This model is currently supported mainly by retrospective data. It represents a conceptual innovation in solid tumor treatment paradigms (104).

A critical limitation of the current literature on high-risk refractory thyroid cancer is the heterogeneity of evidence quality. While phase III randomized controlled trials (Level I evidence) have established the efficacy of MKIs (DECISION and SELECT trials) and systematic reviews/meta-analyses support the use of RET inhibitors, much of the evidence for combination strategies (such as targeted therapy plus immunotherapy) and emerging approaches (such as redifferentiation therapy and 'Total Therapy' model) derives from phase II trials, retrospective studies, case reports and preclinical models (Level II-IV evidence). Future research should prioritize well-designed prospective multicenter trials and, where feasible, randomized controlled designs to validate these promising but preliminary findings. Additionally, real-world registry studies with standardized data collection will help bridge the gap between clinical trials and routine practice, particularly for rare subtypes such as ATC and PDTC.

Looking ahead, precision therapy for high-risk refractory thyroid cancer will advance in several directions: First, multimodal integration based on the 'Total Therapy' concept, aiming for curative outcomes through optimized combinations of targeted therapy, immunotherapy, surgery and radiotherapy; second, adaptive treatment strategies based on dynamic molecular monitoring, using technologies such as liquid biopsy to track the evolution of resistant clones in real time; third, development of next-generation inhibitors to overcome resistance, such as the potential of type II RAF inhibitors; fourth, combination regimens based on signaling pathway crosstalk, such as WNT inhibition combined with RAI sensitization or immunotherapy; fifth, exploration of novel treatment modalities, including antibody-drug conjugates combined with immunotherapy and targeted radionuclide therapy; and sixth, integration of metabolic regulation with targeted therapy, as exemplified by redifferentiation strategies and the use of metabolic agents. The translation from bench to bedside is by no means a one-way linear process. Clinical resistance phenomena feed back to the laboratory, driving the discovery of new mechanisms such as MAPK reactivation and proliferation of immunosuppressive macrophages, while the proposal of the 'Total Therapy' model translates the concept of multimodal integration into clinical practice. This bidirectional interaction will continue to deepen the understanding of thyroid cancer biology and ultimately translate into survival benefits for patients. Confronting the challenge of high-risk refractory thyroid cancer, integrating multi-omics data, designing innovative clinical trials and developing rational combination regimens constitute the essential path toward the future of precision therapy.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Anhui Province Higher Education Scientific Research Project (grant

no. 2025AHGXZK30887) and the Ma'anshan City Science and Technology Foundation (grant no. YL-2024-04).

Availability of data and materials

Not applicable.

Authors' contributions

ZL and QZ consulted and preliminarily summarized the literature required for the manuscript. JW was the major contributor in writing the manuscript. WS approved the final version of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Kratzer TB, Giaquinto AN, Sung H and Jemal A: Cancer statistics, 2025. CA Cancer J Clin 75: 10-45, 2025.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
3. Zhu Q, Liu J, Hu J and Zhang Y: The epidemiological landscape of thyroid cancer and estimates of overdiagnosis in China: A population-based study. Thyroid 35: 307-320, 2025.
4. Li M, Dal Maso L, Pizzato M, Rumgay H and Vaccarella S: Thyroid cancer in adolescents and young adults: A population-based study in 185 countries worldwide. Lancet Diabetes Endocrinol 14: 112-122, 2026.
5. Shen J, Liu W, Wang Z, Mu S, Mo M, Zhou C, Yuan J, Wang Y, Zheng Y and Ji Q: Survival and cause-of-death analysis of 55 thousand thyroid cancer cases in China from a large single institution hospital-based cancer registry database. China Oncology 35: 68-76, 2025. https://www.china-oncology.com/thesisDetails#10.19401/j.cnki.1007-3639.2025.01.008&lang=en
6. Yin Y and Zhang X: A comprehensive analysis and comparative study of the trends in thyroid cancer burden in China and globally from 1990 to 2021, with projections for the next 15 Years. Front Oncol 15: 1505728, 2025.
7. Huang K, Huang X, Qian S, Cai Y, Wu F and Luo D: Temporal trends of thyroid cancer in China and globally from 1990 to 2021: An analysis of the global burden of disease study 2021. Sci Rep 14: 25538, 2024.
8. Sun PY, Yao WJ, Fu RY, Huang H, Ma XQ, Hu ZL, Wu MY, Yan Q, Lin YB, Jiang XY, *et al*: Prediction of economic burden caused by thyroid cancer in China, 2025-2034. Zhonghua Liu Xing Bing Xue Za Zhi 47: 119-126, 2026 (In Chinese).
9. Zitricky F, Koskinen A, Sundquist K, Sundquist J, Liska V, Försti A, Hemminki A and Hemminki K: Survival in thyroid cancer in sweden from 1999 to 2018. Clin Epidemiol 16: 659-671, 2024.
10. Yamazaki H, Sugino K, Inoue K, Katoh R, Matsuzu K, Kitagawa W, Nagahama M, Saito A and Ito K: Analysis of immediate 503 thyroid carcinoma deaths: Trend of single institution in 2005-2024. Eur Thyroid J 14: e240368, 2025.
11. Lin YS, Wang RF, Huang R, Wen Q, Cao W, Chen LB, Guo Y, Hou XR, Li L, Li XY, *et al*: Chinese management guidelines for radioactive iodine-refractory differentiated thyroid cancer (2025 edition). Eur J Nucl Med Mol Imaging 52: 3859-3876, 2025.
12. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, Caillou B, Ricard M, Lumbroso JD, De Vathaire F and Schlumberger M: Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma. J Clin Endocrinol Metab 91: 2892-2899, 2006.
13. Bogdanova T, Rogounovitch TI, Zurnadzhy L, Mitsutake N, Tronko M, Ito M, Bolgov M, Chernyshov S, Gulevatyi S, Masiuk S, *et al*: Characteristics and immune checkpoint status of radioiodine-refractory recurrent papillary thyroid carcinomas from Ukrainian Chornobyl Tissue Bank donors. Front Endocrinol (Lausanne) 14: 1343848, 2024.
14. Landa I, Ibrahimpasic T, Boucai L, Sinha R, Knauf JA, Shah RH, Dogan S, Ricarte-Filho JC, Krishnamoorthy GP, Xu B, *et al*: Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J Clin Invest 126: 1052-1066, 2016.
15. Xing M: Molecular pathogenesis and mechanisms of thyroid cancer. Nat Rev Cancer 13: 184-199, 2013.
16. Schöffski P, Gazzah A, Trigo J, Italiano A, Gougis P, Subbiah V, Shih JY, Loong HH, Doger B, Keegan M, *et al*: BOS172738, a selective RET inhibitor, for the treatment of patients with RET-altered tumors including RET-fusion-positive non-small-cell lung cancer and RET-mutant medullary thyroid cancer: A phase I dose-escalation/expansion multicenter study. ESMO Open 10: 105543, 2025.
17. Wang JR, Zafereo ME, Dadu R, Ferrarotto R, Busaidy NL, Lu C, Ahmed S, Gule-Monroe MK, Williams MD, Sturgis EM, *et al*: Complete surgical resection following neoadjuvant dabrafenib plus trametinib in BRAFV600E-Mutated anaplastic thyroid carcinoma. Thyroid 29: 1036-1043, 2019.
18. Hamidi S, Iyer PC, Dadu R, Gule-Monroe MK, Maniakas A, Zafereo ME, Wang JR, Busaidy NL and Cabanillas ME: Checkpoint inhibition in addition to dabrafenib/trametinib for BRAFV600E-Mutated anaplastic thyroid carcinoma. Thyroid 34: 336-346, 2024.
19. Bapat N, Ferraro T, Esper L, Joshi AS, Haroun F and Baldwin CK: Treatment of unresectable BRAF V600E, TERT-Mutated differentiated papillary thyroid cancer with dabrafenib and trametinib. JCEM Case Rep 2: luae112, 2024.
20. Cancer Genome Atlas Research Network: Integrated genomic characterization of papillary thyroid carcinoma. Cell 159: 676-690, 2014.
21. Xing M, Haugen BR and Schlumberger M: Progress in molecular-based management of differentiated thyroid cancer. Lancet 381: 1058-1069, 2013.
22. Pozdeyev N, Gay LM, Sokol ES, Hartmaier R, Deaver KE, Davis S, French JD, Borre PV, LaBarbera DV, Tan AC, *et al*: Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. Clin Cancer Res 24: 3059-3068, 2018.
23. Zhang T, Han H, Zhang T, Zhang Y, Ma L, Yang Z and Zhao YX: Oncogenic mutation-driven metabolism-immunity regulatory axis: Potential prospects for thyroid cancer precision therapy. Biochim Biophys Acta Rev Cancer 1880: 189459, 2025.
24. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, *et al*: Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. Lancet 384: 319-328, 2014.
25. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, *et al*: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 372: 621-630, 2015.
26. Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, Wen PY, Zielinski CC, Cabanillas ME, Boran A, *et al*: Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: Updated analysis from the phase II ROAR basket study. Ann Oncol 33: 406-415, 2022.
27. Papuc M, Metzger R, Milas K, Nsar C, Edmond A, Camou M and Niu J: Avoiding surgical resection of recurrent BRAF V600E-mutated iodine-refractory papillary thyroid cancer involving trachea/thyroid cartilage via resensitization with dabrafenib and trametinib: Report of 3 cases. Am J Manag Care 31(Spec. No. 11): SP756-SP758, 2025.
28. Zhang X, Lu H, Lv Y, Gao H and Jin H: Combination therapy of TKIs and ICIs for the treatment of anaplastic thyroid carcinoma. Front Oncol 15: 1564865, 2025.
29. Huang D, Xie Z, Zhang S, Su Y, Liu C and Chen W: M6A methylation in thyroid cancer: Functions, mechanisms, and clinical significance. Cancer Genet 302-303: 27-39, 2026.
30. Zhang T, Han H, Zhang Y, Zhang T, Ma L, Yang Z and Zhao YX: The molecular mechanisms and potential therapeutic implications of the crosstalk between DNA methylation and metabolic reprogramming in thyroid cancer. Cell Death Discov 12: 110, 2026.

31. Liu L and Wei F: Mutation interactions of BRAF and TP53 define novel prognostic stratification and therapeutic implications in papillary thyroid carcinoma. Front Endocrinol (Lausanne) 16: 1584618, 2025.
32. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE and Fagin JA: High prevalence of BRAF mutations in thyroid cancer: Genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 63: 1454-1457, 2003.
33. Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, Jones CM, Marshall CJ, Springer CJ, Barford D, *et al*: Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 116: 855-867, 2004.
34. Rashid FA, Munkhdelger J, Fukuoka J and Bychkov A: Prevalence of BRAFV600E mutation in Asian series of papillary thyroid carcinoma-a contemporary systematic review. Gland Surg 9: 1878-1900, 2020.
35. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, *et al*: Mutations of the BRAF gene in human cancer. Nature 417: 949-954, 2002.
36. Boucai L, Seshan V, Williams M, Knauf JA, Saqcena M, Ghossein RA and Fagin JA: Characterization of subtypes of BRAF-Mutant papillary thyroid cancer defined by their thyroid differentiation score. J Clin Endocrinol Metab 107: 1030-1039, 2022.
37. Aashiq M, Silverman DA, Na'ara S, Takahashi H and Amit M: Radioiodine-refractory thyroid cancer: molecular basis of redifferentiation therapies, management, and novel therapies. Cancers (Basel) 11: 1382, 2019.
38. Fullmer T, Cabanillas ME and Zafereo M: Novel therapeutics in radioactive iodine-resistant thyroid cancer. Front Endocrinol (Lausanne) 12: 720723, 2021.
39. Cabanillas ME, Dadu R, Iyer P, Wanland KB, Busaidy NL, Ying A, Gule-Monroe M, Wang JR, Zafereo M and Hofmann MC: Acquired secondary RAS mutation in BRAFV600E-Mutated thyroid cancer patients treated with BRAF Inhibitors. Thyroid 30: 1288-1296, 2020.
40. da Silva TN, Rodrigues R, Saramago A, Pires C, Rito M, Horta M, Martins C, Leite V and Cavaco BM: Target therapy for BRAF mutated anaplastic thyroid cancer: A clinical and molecular study. Eur J Endocrinol 188: lvac011, 2023.
41. Hossain MA: A comprehensive review of targeting RAF kinase in cancer. Eur J Pharmacol 986: 177142, 2025.
42. Riesco-Eizaguirre G: BRAF V600E in thyroid cancer: Navigating prognostic uncertainty and therapeutic opportunity. Eur Thyroid J 14: e250225, 2025.
43. Noronha S, Liu Y, Geneti G, Li H, Wu X, Sun D, Gujar V, Furusawa T, Lobanov A, Cam M, *et al*: CRISPR-Based gene dependency screens reveal mechanism of BRAF inhibitor resistance in anaplastic thyroid cancer. Preprint. bioRxiv [Preprint] 2025.06.26.661609, 2025.
44. Luo W, Ji X, Tan XY, Li YT, Zhang ZQ and Zeng CM: SLPI as a dedifferentiation biomarker in BRAFV600E-mutant papillary thyroid cancer. Endocr Connect 14: e250349, 2025.
45. Jiang S, Hong Z, Wu Q, A R, Wang Z, Guan X, Wang X, Kassardjian AA, Cui Y and Ma T: Gadd45B deficiency drives radio-resistance in BRAFV600E-Mutated differentiated thyroid cancer by disrupting iodine metabolic genes. Cancers (Basel) 17: 3201, 2025.
46. Xing M: Genetic alterations in the phosphatidylinositol-3 kinase/Akt pathway in thyroid cancer. Thyroid 20: 697-706, 2010.
47. Rezzónico JN, Rezzónico M, Pusiol E, Pitoia F and Niepomniszcze H: Increased prevalence of insulin resistance in patients with differentiated thyroid carcinoma. Metab Syndr Relat Disord 7: 375-380, 2009.
48. Yeo Y, Ma SH, Hwang Y, Horn-Ross PL, Hsing A, Lee KE, Park YJ, Park DJ, Yoo KY and Park SK: Diabetes mellitus and risk of thyroid cancer: A meta-analysis. PLoS One 9: e98135, 2014.
49. Moon JH, Hyun MK, Lee JY, Shim JI, Kim TH, Choi HS, Ahn HY, Kim KW, Park DJ, Park YJ and Yi KH: Prevalence of thyroid nodules and their associated clinical parameters: A large-scale, multicenter-based health checkup study. Korean J Intern Med 33: 753-762, 2018.
50. Manzella L, Massimino M, Stella S, Tirrò E, Pennisi MS, Martorana F, Motta G, Vitale SR, Puma A, Romano C, *et al*: Activation of the IGF Axis in thyroid cancer: Implications for tumorigenesis and treatment. Int J Mol Sci 20: 3258, 2019.
51. Robbins HL and Hague A: The PI3K/Akt pathway in tumors of endocrine tissues. Front Endocrinol (Lausanne) 6: 188, 2016.
52. Iuliano S, Mirabelli M, Giuliano S and Brunetti A: Insulin resistance and metabolic dysfunction in thyroid nodules and differentiated thyroid cancer. Curr Opin Oncol 38: 1-10, 2026.
53. Prete A, Lo AS, Sadow PM, Bhasin SS, Antonello ZA, Vodopivec DM, Ullas S, Sims JN, Clohessy J, Dvorak AM, *et al*: Pericytes elicit resistance to vemurafenib and sorafenib therapy in thyroid carcinoma via the TSP-1/TGFβ1 axis. Clin Cancer Res 24: 6078-6097, 2018.
54. Cunha LL, Domingues GAB, Morari EC, Soares FA, Vassallo J and Ward LS: The immune landscape of the microenvironment of thyroid cancer is closely related to differentiation status. Cancer Cell Int 21: 387, 2021.
55. Shi RL, Qu N, Luo TX, Xiang J, Liao T, Sun GH, Wang Y, Wang YL, Huang CP and Ji QH: Programmed death-ligand 1 expression in papillary thyroid cancer and its correlation with clinicopathologic factors and recurrence. Thyroid 27: 537-545, 2017.
56. Ulisse S, Tuccilli C, Sorrenti S, Antonelli A, Fallahi P, D'Armiento E, Catania A, Tartaglia F, Amabile MI, Giacomelli L, *et al*: PD-1 ligand expression in epithelial thyroid cancers: Potential clinical implications. Int J Mol Sci 20: 1405, 2019.
57. Notarangelo T, Sisinni L, Trino S, Calice G, Simeon V and Landriscina M: IL6/STAT3 axis mediates resistance to BRAF inhibitors in thyroid carcinoma cells. Cancer Lett 433: 147-155, 2018.
58. Zou Z and Zhong L: Anaplastic thyroid cancer: Genetic roles, targeted therapy, and immunotherapy. Genes Dis 12: 101403, 2024.
59. Zhang M, Zou B, Li Q, Zhao Y and He Y: Constructing a chemokine-based model and identifying CCL17 as a core biomarker associated with immune infiltrates in thyroid cancer. Transl Cancer Res 14: 5720-5744, 2025.
60. Ma Z, Mu R, Zhou Z, Hu Z, Shen M, Lu C, Wang H, Zhang C, Zhang M, Yi Z, *et al*: The mammalian acid chitinase promotes oncogenic properties of thyroid cancer cells through the JAK2/STAT3 pathway. Eur Thyroid J 14: e240311, 2025.
61. Lin J, Cai B, Lin Q, Lin X, Wang B and Chen X: TLE4 downregulation identified by WGCNA and machine learning algorithm promotes papillary thyroid carcinoma progression via activating JAK/STAT pathway. J Cancer 15: 4759-4776, 2024.
62. Zhang FX, Xu P, Zhang LJ, Fan R, Zhang HX, Liu DH, Liu K and Shen DY: RARγ promotes the invasion and metastasis of thyroid carcinoma by activating the JAK1-STAT3-CD24/MMPs axis. Int Immunopharmacol 125 (Pt A): 111129, 2023.
63. Shi P, Fang H, Fu K, Zhao Z, Yang F and Liu Y: The functional DIAPH3-FOXM1 interaction modulates the aggressive transformation of anaplastic thyroid carcinoma cells and Wnt/β-catenin signalling. Endokrynol Pol 75: 501-509, 2024.
64. Zhang Z, Zhou D, Qiu X, Xia F and Li X: N6-methyladenosine-mediated EIF3H promotes anaplastic thyroid cancer progression and ferroptosis resistance by stabilizing β-catenin. Free Radic Biol Med 231: 38-47, 2025.
65. Lv J, Feng ZP, Chen FK, Liu C, Jia L, Liu PJ, Yang CZ, Hou F and Deng ZY: M2-like tumor-associated macrophages-secreted Wnt1 and Wnt3a promotes dedifferentiation and metastasis via activating β-catenin pathway in thyroid cancer. Mol Carcinog 60: 25-37, 2021.
66. Li S, Cheng Y, Gao C, Yuan Q and Lu X: SEMA3C promotes thyroid cancer via the Wnt/β-catenin pathway. Exp Cell Res 444: 114378, 2025.
67. Sastre-Perona A, Riesco-Eizaguirre G, Zaballos MA and Santisteban P: β-catenin signaling is required for RAS-driven thyroid cancer through PI3K activation. Oncotarget 7: 49435-49449, 2016.
68. Li Z, Lv D, Niu L, Wan Y and Li J: The role of WNT signaling in papillary thyroid cancer: Mechanisms, epigenetic regulation, therapeutic resistance, and emerging clinical strategies. Pathol Res Pract 275: 156231, 2025.
69. Zou M, Al-Yahya S, Al-Alwan M, BinEssa HA, Khabar KSA, Almohanna F, Assiri AM, Altaweel A, Qattan A, Meyer BF, *et al*: β-catenin attenuation leads to up-regulation of activating NKG2D ligands and tumor regression in BrafV600E-driven thyroid cancer cells. Front Immunol 14: 1171816, 2023.
70. Bautista L, Knippler CM and Ringel MD: p21-Activated kinases in thyroid cancer. Endocrinology 161: bqaa105, 2020.
71. Xu Q, Fan G and Shao S: Role of TNFRSF12A in cell proliferation, apoptosis, and proinflammatory cytokine expression by regulating the MAPK and NF-κB pathways in thyroid cancer cells. Cytokine 186: 156841, 2025.

72. Cormier F, Housni S, Dumont F, Villard M, Cochand-Priollet B, Mercier-Nomé F, Perlemoine K, Bertherat J and Groussin L: NF-κB signaling activation and roles in thyroid cancers: Implication of MAP3K14/NIK. Oncogenesis 12: 55, 2023.
73. Wang D, Liu X, Li M and Ning J: HIF-1α regulates the cell viability in radioiodine-resistant papillary thyroid carcinoma cells induced by hypoxia through PKM2/NF-κB signaling pathway. Mol Carcinog 63: 238-252, 2024.
74. Pasquali D, Giacomelli L, Pedicillo MC, Conzo G, Gentile G, De Stefano IS, Angelillis F, Santoro A, Miele F, Digitale Selvaggio L, *et al*: Tumor inflammatory microenvironment of the thyroid cancer: Relationship between Regulatory T-Cell Imbalance, and p-NFKB (p65) Expression-A preliminary study. J Clin Med 12: 6817, 2023.
75. Liu J, Zhu Z, Dong Y, Shi D, Ding Y and Zheng F: Tilianin regulates the proliferation, invasion and tumor immune microenvironment of thyroid cancer cells through the TLR4/NF-κB axis. Int Immunopharmacol 158: 114783, 2025.
76. Li Y, Miao J, Liu C, Tao J, Zhou S, Song X, Zou Y, Huang Y and Zhong L: Kushenol O Regulates GALNT7/NF-κB axis-Mediated macrophage M2 polarization and efferocytosis in papillary thyroid carcinoma. Phytomedicine 138: 156373, 2025.
77. Gui Y, Pan W, Dong Z, Hu D, Guo Y, Wen X, Zhang H, Jiang Z, Zheng X, Gao M and Wang J: Exosomal miR-17 drives thyroid cancer lung metastasis via NF-κB activation. Oncol Res 33: 3991-4011, 2025.
78. Gao H, Lin J, Chen X, Su Y, Huang Y, Zhang Y, Zhang J, Xu N and Dai X: Microfluidic-based patient-derived organoids recapitulate thyroid cancer heterogeneity and reveal NF-κB-driven maturation for precision therapy. J Transl Med 24: 467, 2026.
79. Díaz Vico T, Martínez-Amores Martínez B, Mihic Góngora L, Jiménez-Fonseca P, Peinado Martín P, Grao Torrente I, García Muñoz-Nájar A and Durán-Poveda M: Systemic therapeutic options in radioiodine-refractory differentiated thyroid cancer: Current indications and optimal timing. Cancers (Basel) 17: 1800, 2025.
80. Patel DC, Azaryan I and Konda B: Approach and challenges for patients with advanced radioiodine-refractory differentiated thyroid cancer. Endocr Pract 32: 268-279, 2026.
81. Jerkovich F, Capalbo S, Abelleira E and Pitoia F: Ten years' real-life experience on the use of multikinase inhibitors in patients with advanced differentiated thyroid cancer. Endocrine 85: 817-826, 2024.
82. Li L, Bai J, Wen X and Zeng X: Adverse reactions of four multi-targeted tyrosine kinase inhibitors: A descriptive analysis of the WHO-VigiAccess database. Front Pharmacol 16: 1585862, 2025.
83. Cabanillas ME and Habra MA: Lenvatinib: Role in thyroid cancer and other solid tumors. Cancer Treat Rev 42: 47-55, 2016.
84. Dunn L and Fagin JA: Therapy: Lenvatinib and radioiodine-refractory thyroid cancers. Nat Rev Endocrinol 11: 325-327, 2015.
85. Verburg FA, Amthauer H, Binse I, Brink I, Buck A, Darr A, Dierks C, Koch C, König U, Kreissl MC, *et al*: Questions and controversies in the clinical application of tyrosine kinase inhibitors to treat patients with radioiodine-refractory differentiated thyroid carcinoma: Expert perspectives. Horm Metab Res 53: 149-160, 2021.
86. Brose MS, Robinson B, Sherman SI, Krajewska J, Lin CC, Vaisman F, Hoff AO, Hitre E, Bowles DW, Hernando J, *et al*: Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 22: 1126-1138, 2021.
87. Worden F, Rajkovic-Hooley O, Reynolds N, Milligan G and Zhang J: Real-world treatment patterns and clinical outcomes in patients with radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) treated with first line lenvatinib monotherapy in the United States. Endocrine 84: 663-669, 2024.
88. National Library of Medicine: Zanzalintinib for the Treatment of Advanced Thyroid Cancer Before Surgery. ClinicalTrials.gov Identifier: NCT06959511. https://clinicaltrials.gov/study/NCT06959511.
89. National Library of Medicine: XL092 for the Treatment of Locally Advanced or Metastatic Radioiodine Refractory Differentiated Thyroid Cancer. ClinicalTrials.gov Identifier: NCT06959641. https://clinicaltrials.gov/study/NCT06959641?cond=Follicular%20thyroid%20cancer&aggFilters=status:not%20rec%20ava&viewType=Table&rank=10.
90. Muntean C, Solomon A, Cipaian RC, Vonica RC, Butuca A, Gaborean V, Faur IF and Feier CVI: The efficacy and safety of anlotinib in the treatment of thyroid cancer: A systematic review. J Clin Med 14: 338, 2025.
91. Sun D, Zhang X, Zhang Y, Shi C, Jin X, Sun Y, Liang J and Lin Y: Anlotinib in progressive RAI-refractory differentiated thyroid cancer: Long-term results and PET/CT prognostic markers. Endocr Relat Cancer 32: e250027, 2025.
92. Sun D, Zhang X, Jin X, Shi C, Sun Y, Zhang Y, Liang J and Lin Y: BRAFV600E mutation is associated with better prognoses in radioactive iodine refractory thyroid cancer patients treated with multi-kinase inhibitors: A retrospective analysis of registered clinical trials. Thyroid Res 18: 5, 2025.
93. Chen Z, Tang X, Tan L, Su Y, Wang W and Wu Z: Efficacy and safety of anlotinib combined with 125I seed implantation for iodine-refractory thyroid cancer. Front Endocrinol (Lausanne) 16: 1587412, 2025.
94. Li Y, Liu J, Su Q, Liu X, Yang Z, Yang Z, Fu J, Zhang Y, Tong L, Yang F and Dai D: Efficacy and safety of anlotinib in combination with 131I therapy in the treatment of distant metastatic differentiated thyroid cancer: A single-arm, phase II study. Front Oncol 15: 1622676, 2025.
95. Song Y, Zhang Y, Bai Y, Wang T, Xu G, Ma X, Fei K and Zhang B: Combination kinase inhibitors and immunotherapy for unresectable anaplastic thyroid carcinoma: A retrospective single-center study. Oral Oncol 159: 107067, 2024.
96. Subbiah V, Kreitman RJ, Wainberg ZA, Gazzah A, Lassen U, Stein A, Wen PY, Dietrich S, de Jonge MJA, Blay JY, *et al*: Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: The phase 2 ROAR trial. Nat Med 29: 1103-1112, 2023.
97. Salama AKS, Li S, Macrae ER, Park JI, Mitchell EP, Zwiebel JA, Chen HX, Gray RJ, McShane LM, Rubinstein LV, *et al*: Dabrafenib and trametinib in patients with tumors with BRAFV600E mutations: Results of the NCI-MATCH trial subprotocol H. J Clin Oncol 38: 3895-3904, 2020.
98. Salama AKS, Wang V, Macrae ER, Park JI, Chen HX, Gray RJ, McShane LM, Rubinstein LV, Patton D, Williams PM, *et al*: Phase II study of dabrafenib and trametinib in patients with tumors With BRAFV600E mutations: Updated results from NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol H. JCO Precis Oncol 10: e2500338, 2026.
99. Lee M and Morris LG: Genetic alterations in thyroid cancer mediating both resistance to BRAF inhibition and anaplastic transformation. Oncotarget 15: 36-48, 2024.
100. Hicks HM, Nassar VL, Lund J, Rose MM and Schweppe RE: The effects of Aurora Kinase inhibition on thyroid cancer growth and sensitivity to MAPK-directed therapies. Cancer Biol Ther 25: 2332000, 2024.
101. Kurata K, Onoda N, Noda S, Kashiwagi S, Asano Y, Hirakawa K and Ohira M: Growth arrest by activated BRAF and MEK inhibition in human anaplastic thyroid cancer cells. Int J Oncol 49: 2303-2308, 2016.
102. Tiedje V, Greenberg J, Qin T, Im SY, Krishnamoorthy GP, Boucai L, Xu B, French JD, Sherman EJ, Ho AL, *et al*: Loss of tumor cell MHC class II drives MAPK inhibitor insensitivity of BRAF-mutant anaplastic thyroid cancers. J Clin Invest 135: e191781, 2025.
103. Knauf JA, Luckett KA, Chen KY, Voza F, Socci ND, Ghossein R and Fagin JA: Hgf/Met activation mediates resistance to BRAF inhibition in murine anaplastic thyroid cancers. J Clin Invest 128: 4086-4097, 2018.
104. Cabanillas ME, Akhave N, Banuchi V, Busaidy N, Dadu R, Ferrarotto R, Gunn GB, Hamidi S, Hofmann MC, Hosseini SM, *et al*: Reimagining the therapeutic approach for anaplastic thyroid cancer: The roadmap to a cure. Thyroid 35: 462-470, 2025.
105. Zhao X, Wang JR, Dadu R, Busaidy NL, Xu L, Learned KO, Chasen NN, Vu T, Maniakas A, Eguia AA, *et al*: Surgery After BRAF-Directed therapy is associated with improved survival in BRAFV600E mutant anaplastic thyroid cancer: A single-center retrospective cohort study. Thyroid 33: 484-491, 2023.
106. Kwiatkowska N, Nieto C, Cirera A, Chabla J, Arroyo N, Pañella C, Iglesias C, Ciscar A, Zafon C and Vilallonga R: Improving outcomes in anaplastic thyroid carcinoma: Surgical strategies and neoadjuvant therapy. Endokrynol Pol 76: 124-125, 2025.
107. Wächter S, Bartsch DK, Knorrenschild JR, Pehl A, Eilsberger F, Pfestroff A, Luster M, Holzer K, Neubauer A and Maurer E: Mutation-based, neoadjuvant treatment for advanced anaplastic thyroid carcinoma. Front Endocrinol (Lausanne) 16: 1619875, 2025.

108. Hamidi S, Maniakas A and Cabanillas ME: Advances in anaplastic thyroid cancer treatment. Endocrinol Metab Clin North Am 54: 361-375, 2025.
109. Brauner E, Gunda V, Vanden Borre P, Zurakowski D, Kim YS, Dennett KV, Amin S, Freeman GJ and Parangi S: Combining BRAF inhibitor and anti PD-L1 antibody dramatically improves tumor regression and anti tumor immunity in an immunocompetent murine model of anaplastic thyroid cancer. Oncotarget 7: 17194-17211, 2016.
110. Cabanillas ME, Dadu R, Ferrarotto R, Gule-Monroe M, Liu S, Fellman B, Williams MD, Zafereo M, Wang JR, Lu C, *et al*: Anti-Programmed death ligand 1 plus targeted therapy in anaplastic thyroid carcinoma: A nonrandomized clinical trial. JAMA Oncol 10: 1672-1680, 2024.
111. Saito Y, Kage H, Kobayashi K, Kamogashira T, Fukuoka O, Yamamura K, Yamashita S, Tanabe M, Oda K and Kondo K: Comprehensive genomic profiling from C-CAT database unveiled over 80% presence of oncogenic drivers in anaplastic thyroid carcinoma including BRAF, RAS family, NF1, and FGFR1. Clin Endocrinol (Oxf) 101: 170-179, 2024.
112. Wang JR, Montierth M, Xu L, Goswami M, Zhao X, Cote G, Wang W, Iyer P, Dadu R, Busaidy NL, *et al*: Impact of somatic mutations on survival outcomes in patients with anaplastic thyroid carcinoma. JCO Precis Oncol 6: e2100504, 2022.
113. Hamidi S, Vodopivec DM, Busaidy NL, Gule-Monroe M, Akhave NS, Banuchi VE, Ferraroto R, Fournier I, Gunn GB, Iyer PC, *et al*: Real-World experience with lenvatinib plus pembrolizumab in metastatic BRAF wild-type anaplastic thyroid carcinoma. Thyroid 36: 153-161, 2026.
114. Sehgal K, Pappa T, Shin KY, Schiantarelli J, Liu M, Ricker C, Besson NR, Jones SM, Welsh EL, Pfaff KL, *et al*: Dual immune checkpoint inhibition in patients with aggressive thyroid carcinoma: A phase 2 nonrandomized clinical trial. JAMA Oncol 10: 1663-1671, 2024.
115. Maurer E, Eilsberger F, Wächter S, Riera Knorrenschild J, Pehl A, Holzer K, Neubauer A, Luster M and Bartsch DK: Mutation-based, short-term 'neoadjuvant' treatment allows resectability in stage IVB and C anaplastic thyroid cancer. Eur Arch Otorhinolaryngol 280: 1509-1518, 2023.
116. Leboulleux S, Do Cao C, Zerdoud S, Attard M, Bournaud C, Lacroix L, Benisvy D, Taïeb D, Bardet S, Terroir-Cassou-Mounat M, *et al*: A Phase II redifferentiation trial with dabrafenib-trametinib and 131I in metastatic radioactive iodine refractory BRAF p.V600E-Mutated differentiated thyroid cancer. Clin Cancer Res 29: 2401-2409, 2023.
117. Demirkol MO, Kaya G, Seymen H, Alagol F and Selcukbiricik F: Restoring radioiodine avidity in radioiodine-refractory differentiated thyroid cancer with genotype-guided MAPK inhibition and dosimetry-guided radioiodine. Clin Nucl Med 51: e293-e300, 2026.
118. Arawker MH, Habibullah F, Fu L, Baral S and Qiu X: Theranostic and radionuclide-based treatment approaches for radioiodine-refractory thyroid cancer: From biology to clinical application. Mol Imaging Biol 28: 212-226, 2026.
119. Leboulleux S, Boucai L, Busaidy N, Durante C, Fagin JA, Fazeli S, Gianoukakis AG, Haugen BR, Kang H, Konda B, *et al*: Redifferentiation therapy in unresectable or metastatic radioactive iodine refractory thyroid cancer: An International Thyroid Oncology Group statement. Lancet Diabetes Endocrinol 13: 516-527, 2025.
120. Toro-Tobon D, Morris JC, Hilger C, Peskey C, Durski JM and Ryder M: Clinical outcomes of radioactive iodine redifferentiation therapy in previously iodine refractory differentiated thyroid cancers. Thyroid 34: 70-81, 2024.
121. Tarasova VD, Chung CH and Agosto Salgado S: Durable response to redifferentiation in a patient with metastatic NCOA4::RET fusion-driven papillary thyroid cancer. JCEM Case Rep 3: luaf054, 2025.
122. Boucai L: An update on redifferentiation therapy for radioiodine refractory thyroid cancer. Endocrinol Metab Clin North Am 54: 419-431, 2025.
123. Zhu L, Jing X and Ahn BC: Turning tumor microenvironmental foes to friends: A new opportunity for thyroid cancer therapy and redifferentiation. Oral Oncol 168: 107513, 2025.
124. Barbry F, Chevalier B, Beron A, Lion G, Boury S, Marciniak C, Baillet C, Do Cao C and Jannin A: Redifferentiation of a RET-Fusion, radioiodine-refractory, differentiated thyroid cancer with selpercatinib: flip-flop between (18F)FDG PET/CT and 131I posttreatment scanning. J Nucl Med 66: 330, 2025.
125. Pappa T and Wirth L: An update on redifferentiation strategies for radioactive iodine-refractory differentiated thyroid carcinoma. Endocrine 87: 1-10, 2025.
126. Gauduchon T, Varnier R and Cassier PA: Selpercatinib in the treatment of thyroid cancer. Future Oncol 21: 2585-2592, 2025.
127. Riya IJ, Piya IJ, Priantti JN, Lee CL, Barman L and Altobi A: Efficacy and safety of RET-kinase inhibitors in RET-altered thyroid cancers: A systematic review and single-arm meta-analysis. Endocr Relat Cancer 32: e240219, 2025.
128. Amitani M, Shimizu T, Oba T, Kawamura M and Ito KI: Activation of the AKT-mTOR pathway confers selpercatinib resistance in thyroid cancer cells harboring the CCDC6-RET fusion gene. Biochem Biophys Rep 43: 102136, 2025.
129. Zhou Y, Cao J, Zhang S, Sun M, Zhang Y, Li S, Luo Z, Wang P and Xie J: Review and analysis of clinical trials of selective RET inhibitors for the treatment of thyroid cancer. Front Oncol 15: 1683624, 2025.
130. Li M, Zheng R, Dal Maso L, Zhang S, Wei W and Vaccarella S: Mapping overdiagnosis of thyroid cancer in China. Lancet Diabetes Endocrinol 9: 330-332, 2021.
131. Regmi S, Farazi PA, Lyden E, Kotwal A, Ganti AK and Goldner W: Disparities in thyroid cancer diagnosis based on residence and distance from medical facility. J Endocr Soc 8: bvae033, 2024.
132. Du B, Wang F, Wu L, Wang Z, Zhang D, Huang Z, Gao L, Li Y, Liang C, Li P and Yao R: Cause-specific mortality after diagnosis of thyroid cancer: A large population-based study. Endocrine 72: 179-189, 2021.
133. Carnazza M, Yang N, Tiwari RK, Geliebter J and Li XM: Natural compounds targeting MAPK, PI3K/Akt, and JAK/STAT signaling in papillary thyroid cancer. Int J Mol Sci 26: 10498, 2025.
134. Zhang B, Zheng XY, Tai XH, Shen Y and Cao JH: Identification of potential molecular targets for thyroid cancer using multiple-omics analysis and machine learning. Ann Med Surg (Lond) 87: 8229-8244, 2025.
135. Karimi AH, Zeng PY, Cecchini M, Barrett JW, Pan H, Ying S, Le N, Mymryk JS, Ailles LE and Nichols AC: Novel insights in advanced thyroid carinoma: From mechanisms to treatments: Molecular insights into the origin, biology, and treatment of anaplastic thyroid carcinoma. Eur Thyroid J 14: e250057, 2025.