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*Review Article*

# Leveraging molecular targeted drugs and immune checkpoint inhibitors treat advanced thyroid carcinoma to achieve thyroid carcinoma redifferentiation

Jing-Yang Su[1,2*], Ting Huang[1*], Jia-Lin Zhang[1*], Jin-Hua Lu[1*], Meng-Lei Wang[1], Jiang Yan[1], Ren-Bin Lin[1], Sheng-You Lin[3], Jue Wang[1]

*[1]Hangzhou Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, Hangzhou 310007, Zhejiang, China; [2]Tongde Hospital of Zhejiang Province, Hangzhou 310012, Zhejiang, China; [3]Department of Oncology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310000, Zhejiang, China. [*]Equal contributors.*

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**Abstract:** Thyroid cancer can be classified into three different types based on the degree of differentiation: well-differentiated, poorly differentiated, and anaplastic thyroid carcinoma. Well-differentiated thyroid cancer refers to cancer cells that closely resemble normal thyroid cells, while poorly differentiated and anaplastic thyroid carcinoma are characterized by cells that have lost their resemblance to normal thyroid cells. Advanced thyroid carcinoma, regardless of its degree of differentiation, is known to have a higher likelihood of disease progression and is generally associated with a poor prognosis. However, the process through which well-differentiated thyroid carcinoma transforms into anaplastic thyroid carcinoma, also known as "dedifferentiation", has been a subject of intensive research. In recent years, there have been significant breakthroughs in the treatment of refractory advanced thyroid cancer. Clinical studies have been conducted to evaluate the efficacy and safety of molecular targeted drugs and immune checkpoint inhibitors in the treatment of dedifferentiated thyroid cancer. These drugs work by targeting specific molecules or proteins in cancer cells to inhibit their growth or by enhancing the body's immune response against the cancer cells. This article aims to explore some of the possible mechanisms behind the dedifferentiation process in well-differentiated thyroid carcinoma. It also discusses the clinical effects of molecular targeted drugs and immune checkpoint inhibitors in thyroid cancer patients with different degrees of differentiation. Furthermore, it offers insights into the future trends in the treatment of advanced thyroid cancer, highlighting the potential for improved outcomes and better patient care.

**Keywords:** Thyroid carcinoma, sodium iodide symporter, tyrosine kinase inhibitors, immune checkpoint inhibitors, redifferentiation

## Introduction

Thyroid carcinoma (TC) accounts for 3.1% of the global incidence rate and 0.4% of the global death rate among 36 cancers in 185 countries, with an estimated 567233 new patients in 2018 [1]. TC can be classified into three main types based on the degree of histological differentiation: well-differentiated thyroid carcinoma (WDTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic thyroid carcinoma (ATC). DTC is the most common type, accounting for more than 90% of cases, while PDTC and ATC are less common but more aggressive forms of the disease [2, 3]. ATC is particularly concerning, as it occurs in only around 2% of TC cases but is responsible for 14% to 39% of all TC-related deaths. Unfortunately, the prognosis for patients with ATC is very poor, with most patients surviving less than six months after diagnosis [4-7].

In some cases of DTC, the cancer does not respond to treatment with radioactive iodine (RAI), or the disease continues to progress despite RAI therapy. These patients are diagnosed with radioiodine-refractory differentiated thyroid cancer (RAI-rDTC) [8]. The decrease in expression or targeting of the sodium iodide symporter (NIS) protein, which plays a crucial

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role in capturing iodine and allowing it to be taken up by thyroid cells, can cause DTC to progress into more advanced stages [9-11]. There is also evidence suggesting that PDTC and ATC may arise from pre-existing DTC. This process, known as "dedifferentiation", involves the loss of characteristics that make the tumor cells resemble normal thyroid cells [12-14]. It has been linked to gene mutations, such as the BRAF gene mutation, as well as decreased expression of the β-catenin protein and changes in the tumor microenvironment [13, 15-17]. To improve the treatment outcomes for patients with advanced TC, including RAI-rDTC, PDTC, and ATC, tyrosine kinase inhibitors (TKIs) have become an important therapeutic option. These drugs work by either enhancing NIS expression or inhibiting tumor-related angiogenesis through the inhibition of the phosphoinositide 3-kinase (PI3K)/AKT/mTOR and RET/RAS/RAF/mitogen-activated protein kinase (MAPK) pathway, which is the formation of new blood vessels that supply nutrients to the tumor.

TKIs such as sorafenib, lenvatinib, and cabozantinib have been approved by the Food and Drug Administration (FDA) for the treatment of RAI-rDTC, as they have been shown to significantly prolong the median progression-free survival (PFS) of patients [18-20]. In addition to TKIs, immune checkpoint inhibitors (ICIs) have also shown promise in the treatment of TC. These drugs, which target specific molecules involved in regulating the immune response, have produced preliminary results in clinical trials. PD-1/PD-L1 inhibitors and CTLA-4 inhibitors are being studied for their potential in treating TC [21]. This review aims to explore the mechanisms underlying the dedifferentiation of WDTC into more advanced stages and discuss the results of molecular targeted drugs and ICIs therapy for TC with varying degrees of differentiation. The findings can serve as a reference for clinicians in deciding the most appropriate treatment options for their patients.

## Dedifferentiated process underlying the well-differentiated thyroid carcinoma

### *Pathological evolution of well-differentiated thyroid carcinoma into anaplastic thyroid carcinoma*

In 1993, Laan et al. [22] conducted biopsies on TC specimens and discovered similar cell features in different types of tissues. Based on the co-occurrence of differentiated tissues in the same tumor specimen, which led them to believe that most advanced thyroid cancers, such as PDTC and ATC, originated from WDTC [23, 24] and that PDTC serves as a bridge between WDTC and ATC [25, 26]. However, approximately 50% of ATC specimens can coexist histologically with WDTC [27], the conversion rate from WDTC to PDTC was estimated to be less than 1% [28]. WDTC mainly includes papillary thyroid carcinoma (PTC) with typical papillary/follicular solid structure and follicular thyroid carcinoma (FTC) characterized by follicular cell differentiation but lacking the diagnostic features of papillary carcinoma [29, 30]. PDTC, in contrast, has lost the structural features of WDTC but shows specific characteristics such as convoluted nuclei, mitotic activity (≥3×10 high-power fields), and necrosis [31, 32]. A retrospective study found that patients with poorly differentiated areas of DTC had a similar prognosis to those with PDTC, indicating a close relationship for both [33].

ATC exhibits diverse pathological features and is considered the most aggressive type of thyroid cancer. It typically consists of a mixture of spindle, epithelioid, and pleomorphic giant cells. Spindle cell patterns are the most common (about 50%), followed by pleomorphic giant cell patterns (30%-40%), and squamous cell patterns (<20%) are less common [7]. ATC is characterized by a high mitotic index, necrosis, hemorrhage, and vascular invasion, reflecting the further dedifferentiation of WDTC or PDTC [34]. Two approaches have been used to define ATC and DTC. One approach is based on the volume of undifferentiated TC tissue, where if the volume exceeds 10%, it is classified as ATC, and if it is less than 10%, it is considered DTC [35]. This indirectly highlights the importance of well-differentiated thyroid cancer tissue. The other approach involves immunohistochemical staining, which has confirmed the continuum theory from well-differentiated tumors to PDTC and then to ATC. Both ATC and PDTC exhibit local aggressiveness and have poor survival rates [7]. However, compared to ATC, PDTC has more homogenous cell populations, with single-cell populations and less obvious nuclear pleomorphism or heteromorphism. Additionally, PDTC often does not show obvious necrosis and has a better prognosis than ATC. It is also suggested that PDTC is an

intermediate pathological morphology in the evolution of WDTC to ATC.

*Pathogenesis of anaplastic thyroid carcinoma: from molecular targets and immune checkpoints*

The process of WDCT transfering into ATC not only changes at the macroscopic level of pathology, but also changes at the microscopic level such as molecular targets. NIS (sodium iodide symporter) is located on the surface of thyroid follicular epithelial cells, mediating the transport of active iodine to the thyroid and other tissues [36, 37]. Due to the NIS dysfunction or NIS expression deficiency, tissue uptake of radioiodine is reduced and thyroid cancer gradually dedifferentiates. Approximately 20% of DTC patients have local recurrence and 10% of DTC patients have distant metastases, and the 10-year survival rate is less than 10% [10, 11]. Gene mutations, particularly the $BRAF^{V600E}$ mutation, play a significant role in the dedifferentiation and progression of DTC. This mutation primarily affects two signaling pathways, the PI3K/AKT/mTOR pathway and the RET/RAS/RAF/MAPK pathway, leading to resistance against the NIS [9, 38]. Hayes et al. proposed that DTC patients with $BRAF^{V600E}$ mutation may experience preferential benefits [39]. The $BRAF^{V600E}$ mutation promotes the aggressive behavior and malignant transformation of tumors. Thus, silencing the BRAF gene can reverse RET gene rearrangements, such as ERK phosphorylation, thereby promoting redifferentiation [40, 41]. Numerous studies have shown that $BRAF^{V600E}$ inhibitors can restore NIS activity and expression [42, 43]. Additionally, BRAF inhibitors not only activate the MAPK pathway but also negatively regulate the PI3K/AKT/mTOR pathway, which is controlled by the tumor suppressor gene PTEN. This inhibition consequently restricts the proliferation and migration of various cancer cells, thereby enhancing iodine uptake in TC [44-46].

NIS has the ability to enhance the immune response specifically against tumor antigens in DNA vaccines for tumors. It can also induce stronger responses of chemokines and cytokines by ingesting iodide [47, 48]. P53 positivity is common in advanced TC (dedifferentiated thyroid cancer) [37]. The P53 gene can activate PD-1 expression by linking acetyltransferase cofactor [49], and the NIS expression is influenced by PD-1 expression level [50]. Furthermore, TC cell lines and tumor samples from patients with $BRAF^{V600E}$ mutated tumors had higher PD-L1 levels than wild-type BRAF tumors or normal thyroid tissue [51]. A cellular study demonstrated that MEK inhibitors can restore the expression of NIS, improve the efficacy of radioactive iodine, and consistently reduce the levels of PD-L1 and protein *in vitro* [52, 53]. This suggests that TKIs are closely linked to the expression of PD-1. However, it has been observed that TKIs alone are less effective in treating ATC [7, 54], possibly because these targeted drugs cannot counteract the immunosuppressive effect caused by the tumor microenvironment in ATC patients. Clinical studies are currently being conducted to investigate the combination of TKIs and immune checkpoint inhibitors (ICIs) for the treatment of dedifferentiated TC. Some progress has been made in this area, suggesting that this combination therapy may hold promise for improving treatment outcomes [53, 55, 56].

PD-1 (B7-1) is a glycoprotein expressed by macrophages and T cells that inhibits T-cell immunity by binding to its ligand (PD-L1/PD-L2) [57]. Typically, PD-L1 is not present in normal thyroid tissue and WDTC. However, in cases of ATC, there is a high density of tumor-associated macrophages (TAMs) in the tumor microenvironment, which is associated with the highly expression of PD-L1 [58]. When testing for PD-L1 expression in ATC cases, the majority of tests showed positive results. In fact, the average PD-L1 expression in ATC was significantly higher (TPS 30%) compared to PDTC (5%) and normal thyroid tissue (0%) [54]. This suggests that positive PD-L1 expression is more common in advanced TC and high PD-L1 expression usually has a poor prognosis [59]. Meanwhile, guidelines recommend PD-L1 testing for patients with advanced ATC, and those with high PD-L1 expression can use ICIs to prolong survival [60]. In addition to restoring anti-cancer immunity, the PD-1 pathway can directly promote hypoxia and apoptosis of tumor cells, limiting their growth by inhibiting the MAPK signaling pathway [61].

## Redifferentiation therapy underlying the advanced thyroid carcinoma

*Molecular targeted therapy in advanced thyroid carcinoma*

Molecular targeted drugs inhibit tumor cell growth through RET/RAS/RAF/MEK/ERK and

**Table 1.** Targeted therapy for thyroid carcinoma

| No. | Type | Drugs | ORR | The most common adverse events | Trial number and/or reference |
|---|---|---|---|---|---|
| 1 | TC | Dabrafenib Trametinib | / | / | NCT0518293 |
| 2 | TC | Dabrafenib Trametinib | / | / | NCT04619316 |
| 3 | TC | Anlotinib | 10/13 | Hypertension 77%, proteinuria 54%, hypercholesterolemia 69% | NCT04309136 |
| 4 | TC | Lenvatinib Denosumab | / | / | NCT03732495 |
| 5 | TC | Lenvatinib | / | / | NCT03573960 |
| 6 | TC | Apatinib | / | / | NCT03300765 |
| 7 | TC | Apatinib | / | / | NCT03199677 |
| 8 | TC | Lenvatinib Everolimus | / | / | NCT03139747 |
| 9 | TC | KTN3379 Vemurafenib | 2/7 | Maculopapular rash 71%, nausea 57%, diarrhea and arthralgia 43% | NCT02456701 |
| 10 | TC | Selumetinib | / | Fatigue 71%, acneiform rash 50%, maculopapular rash and diarrhea 46% | NCT02393690 |
| 11 | TC | Sorafenib Everolimus | / | Hypertension 91%, fatigue 88%, diarrhea and anemia 82% | NCT02143726 |
| 12 | TC | Sorafenib | / | / | NCT02084732 |
| 13 | TC | Dovitinib | / | / | NCT01947023 |
| 14 | TC | Pazopanib | Q1: 25/50 Q2: 20/50 | Diarrhea 76%, asthenia 64%, hypertension 56% | NCT01813136 |
| 15 | TC | Lenvatinib | 23/51 | Hypertension 90%, decreased appetite 78%, HFSR 77% | NCT01728623 |
| 16 | TC | Dabrafenib Trametinib | / | / | NCT01723202 |
| 17 | TC | Vemurafenib | / | / | NCT01709292 |
| 18 | TC | Everolimus | 2/38 | Mucositis 84%, anorexia 44%, AST/ALT elevation 26% | NCT01164176 |
| 19 | TC | Sorafenib Everolimus | / | / | NCT01141309 |
| 20 | TC | Everolimus | / | Fatigue 80%, cough 62%, hypercholesterolemia 58% | NCT00936858 |
| 21 | TC | Sorafenib | 8/32 | HFSR 66%, weight loss 56%, diarrhea 50% | NCT00887107 |
| 22 | TC | Sorafenib | 19/59 | HFSR 78%, rash 75%, diarrhea 53% | NCT00654238 |
| 23 | TC | Pazopanib | 22/60 | Fatigue 78%, diarrhea 75%, hypertension 72% | NCT00625846 |
| 24 | TC | Vandetanib | 6/72 | Diarrhea 74%, hypertension 34%, acne 27% | NCT00537095 |
| 25 | TC | Sunitinib | / | / | NCT00510640 |
| 26 | TC | Axitinib | 18/52 | Diarrhea 60%, hypertension 54%, fatigue 48% | NCT00389441 |
| 27 | TC | Imatinib | 2/8 | Myalgia/arthralgia and lymphopenia 91%, electrolyte abnormality 82% | NCT00115739 |
| 28 | TC | Axitinib | 18/60 | Fatigue 50%, diarrhea 48%, nausea 33% | NCT00094055 |
| 29 | TC | Sorafenib | 7/30 | HFSR 93%, diarrhea and rash 80% | [131] |
| 30 | TC | Sorafenib | 6/41 | Dry skin 84%, fatigue 82%, diarrhea 75% | [132] |
| 31 | TC | Sunitinib | 11/35 | Neutropenia 34%, leukopenia 31%, fatigue, HFSR and diarrhea 26% | [133] |
| 32 | TC | Sorafenib | 5/34 | HFSR 79%, diarrhea 77%, fatigue 59% | [134] |
| 33 | TC | Everolimus | 0/28 | Anemia and cough 64%, stomatitis and hyperglycemia 61% | NCT01118065 |
| 34 | TC | Cabozantinib | / | / | NCT02041260 |
| 35 | TC | Everolimus Pasireotide | / | / | NCT01270321 |
| 36 | TC | Sorafenib | / | / | NCT00095693 |
| 37 | TC | Dovitinib | / | / | NCT01964144 |
| 38 | TC | Sorafenib | 2/18 | HFSR 44%, hypophosphatemia, proteinuria and maculopapular rash 11% | NCT02114658 |

| | | | | | |
|---|---|---|---|---|---|
| 39 | TC | VEGF Trap | 0/40 | / | [135] |
| 40 | DTC | Sorafenib Tipifarnib | 6/35 | Fatigue 49%, diarrhea 43%, rash 40% | [136] |
| 41 | DTC | Anlotinib | / | / | NCT05007093 |
| 42 | DTC | Dabrafenib Trametinib | / | / | NCT04940052 |
| 43 | DTC | Lenvatinib | / | / | NCT04321954 |
| 44 | DTC | Apatinib | / | / | NCT04180007 |
| 45 | DTC | Donafenib | / | / | NCT03602495 |
| 46 | DTC | Imatinib | / | / | NCT03469011 |
| 47 | DTC | Apatinib | / | / | NCT03167385 |
| 48 | DTC | Anlotinib | 67/113 | Hypertension 84%, HFSR 74% | NCT02586337 |
| 49 | DTC | Vandetanib | / | Diarrhea 67%, hypertension 40%, rash 34% | NCT01876784 |
| 50 | DTC | Selumetinib | / | Diarrhea and dermatitis acneiform 44%, nausea and fatigue 29% | NCT01843062 |
| 51 | DTC | Sorafenib Everolimus | / | / | NCT01263951 |
| 52 | DTC | Pazopanib | / | Fatigue 100%, anorexia 83%, diarrhea, hypertension and HFSR 67% | [137] |
| 53 | RAI-rDTC | Apatinib | 25/46 | Hypertension 87%, HFSR 87%, proteinuria 76% | NCT03048877 |
| 54 | RAI-rDTC | Sunitinib | 6/23 | Leukopenia 83%, neutropenia 65%, thrombocytopenia 57% | NCT00668811 |
| 55 | RAI-rDTC | Selumetinib | 1/32 | Rash 77%, fatigue and diarrhea 49% | NCT00559949 |
| 56 | RAI-rDTC | Motesanib | 13/93 | Diarrhea 59%, hypertension 56%, fatigue 46% | NCT00121628 |
| 57 | RAI-rDTC | Vemurafenib | 16/48 | Fatigue, asthenia or malaise 71%, rash 69%, weight decrease 53% | NCT01286753 |
| 58 | RAI-rDTC | Dabrafenib Trametinib | / | / | NCT04554680 |
| 59 | RAI-rDTC | Vemurafenib Copanlisib | / | / | NCT04462471 |
| 60 | RAI-rDTC | Cabozantinib | 8/15 | Diarrhea 51%, HFSR 45%, hypertension 28% | NCT03690388 |
| 61 | RAI-rDTC | Dabrafenib Trametinib | / | / | NCT03244956 |
| 62 | RAI-rDTC | Sirolimus Cytoxan | / | / | NCT03099356 |
| 63 | RAI-rDTC | Lenvatinib | 72/103 | Hypertension 82%, proteinuria 81%, HFSR 58% | NCT02966093 |
| 64 | RAI-rDTC | Donafenib | 4/35 | HFSR 83%, alopecia 71%, hypertension 46% | NCT02870569 |
| 65 | RAI-rDTC | Apatinib | Q1: 9/10 Q2: 7/10 | HFSR 95%, proteinuria 80%, fatigue and AST elevation 75% | NCT02731352 |
| 66 | RAI-rDTC | Lenvatinib | Q1: 31/77 Q2: 43/75 | Hypertension 55%, diarrhea 54%, weight loss 40% | NCT02702388 |
| 67 | RAI-rDTC | Surufatinib | 13/59 | Proteinuria 73%, hypertension 51%, hypertriglyceridemia 39% | NCT02614495 |
| 68 | RAI-rDTC | Vemurafenib | 33 | Maculopapular rash 75%, fatigue 67%, HFSR 58% | NCT02145143 |
| 69 | RAI-rDTC | Cabozantinib | 10/25 | Liver transaminase elevation 80%, HFSR 76%, fatigue 76% | NCT01811212 |
| 70 | RAI-rDTC | Lenvatinib | 169/261 | Hypertension 68%, diarrhea 59%, fatigue or asthenia 59% | NCT01321554 |
| 71 | RAI-rDTC | Sorafenib Temsirolimus | 8/36 | / | NCT01025453 |
| 72 | RAI-rDTC | Sorafenib | 24/207 | HFSR 76%, diarrhea 69%, alopecia 67% | NCT00984282 |
| 73 | RAI-rDTC | Selumetinib | 5/20 | Rash 90%, fatigue 80%, hepatic enzymes increased 70% | NCT00970359 |
| 74 | RAI-rDTC | Lenvatinib | / | Hypertension 76%, weight loss 69%, diarrhea 67% | NCT00784303 |
| 75 | RAI-rDTC | Sunitinib | / | Fatigue 87%, neutropenia 79%, anemia 76% | NCT00381641 |
| 76 | ATC | HLX208 | / | / | NCT05102292 |
| 77 | ATC | Dabrafenib Trametinib | / | / | NCT04739566 |
| 78 | ATC | Dabrafenib Trametinib | / | / | NCT03975231 |

| | | | | | |
|---|---|---|---|---|---|
| 79 | ATC | Sorafenib | / | / | NCT03565536 |
| 80 | ATC | Trametinib Paclitaxel | / | / | NCT03085056 |
| 81 | ATC | Lenvatinib | / | / | NCT02726503 |
| 82 | ATC | Lenvatinib | 1/34 | Hypertension 56%, anorexia, fatigue and stomatitis 29% | NCT02657369 |
| 83 | ATC | Sapanisertib | / | / | NCT02244463 |
| 84 | ATC | Sorafenib | 2/20 | Rash/desquamation 65%, fatigue 60, weight loss 60% | NCT00126568 |
| 85 | ATC | Dabrafenib Trametinib | 11/16 | Fatigue 44%, pyrexia 31%, nausea 31% | [90] |
| 86 | ATC | Dabrafenib Trametinib | 20/36 | / | [138] |

TC, thyroid carcinoma; DTC, differentiated thyroid carcinoma; RAI-rDTC, radioiodine-refractory differentiated thyroid carcinoma; ORR, objective response rate; ATC, anaplastic thyroid carcinoma; AST, aspartate transaminase; ALT, alanine transaminase; HFSR, hand-foot skin reaction; Q1, Queue1; Q2, Queue2.

PI3K/AKT/mTOR signaling pathways to treat advanced thyroid cancer. We searched and summarized the results of molecular targeted drugs in treating TC patients of Pubmed database and the website of *https://www.clinicaltrials.gov* by July 2023, as demonstrated in **Table 1**. The search strategy is detailed in **Appendix 1**. As mentioned earlier, decreased NIS expression is strongly associated with thyroid cancer dedifferentiation, approximately 15% of DTC patients progress to RAI-rDTC, PDTC or ATC due to insensitivity to radioactive iodine therapy. Molecular targeted drugs in treating patients with early radioiodine-insensitive DTC mainly inhibit the growth and progression of tumor cells by enhancing the rate of iodine uptake. Selumetinib (MEK inhibitor) may be able to redifferentiate by increasing the rate of iodine uptake in advanced TC. In one study, out of 20 patients with radioiodine-refractory differentiated thyroid cancer (RAI-rDTC), 12 patients experienced improved radioiodine uptake in the lesion, and 5 patients showed partial response [62]. Besides, the study of selumetinib plus lenvatinib in ATC reduced tumor proliferation and increased apoptosis through the AKT and ERK signaling pathways *in vitro* and *in vivo* [63], without significant side effects. Therefore, Selumetinib has also been considered to be an effective redifferentiation agent for TC, which can enhance NIS expression and promote the reconstruction of iodine uptake ability of TC cells, restore their normal thyroid-like characteristics, and respond to iodine-based therapy [64]. In addition to selumetinib, TKIs and ICIs can also promote thyroid cancer redifferentiation. This finding holds great promise for the treatment of thyroid cancer, as it offers a potential means of enhancing the effectiveness of existing treatments and improving patient outcomes.

Randomized controlled clinical trials of TKIs in the treatment of RAI-rDTC have yielded promising results. Our previous meta-analysis showed that treatment with TKIs significantly improved the median PFS (HR 0.30, 95% CI: 0.18-0.50, *P<0.00001*) and overall survival (OS) (HR 0.70, 95% CI: 0.57-0.88, *P=0.002*) [65]. In more detail, our another study revealed that RAI-rDTC patients responded best to anti-vascular endothelial growth factor receptor (VEGFR) inhibitors, medullary thyroid carcinoma (MTC) patients benefited from RET gene inhibitors, and ATC patients were primarily treated with TKIs combined with ICIs [66]. The results of our study showed that the median PFS in DTC was [HR 0.30, (95% CI: 0.18, 0.50), *P<0.00001*] and in MTC was [HR 0.39, (95% CI: 0.27, 0.58), *P<0.00001*]. The drugs used in the treatment of MTC are specifically designed to inhibit the RET gene, including vandetanib and cabozantinib. As a result, the FDA has approved vandetanib for treating MTC [67]. In fact, in the phase II trial of vandetanib for RAI-rDTC, the median PFS in the treatment group was only 5.2 months longer than in the control group, and there was no statistical difference in OS (*P=0.42*). However, in the phase III randomized trial of vandetanib for MTC, PFS was significantly prolonged (HR 0.46, 95% CI: 0.31-0.69, *P<0.001*) [68]. This difference in efficacy may be attributed to the lower selectivity of vandetanib for VEGFR and higher selectivity for RET inhibition and therefore less effective for RAI-rDTC redifferentiation.

During the Sorafenib's phase III trial, PFS was 10.8 months in the treatment group and 5.8

months in the placebo group. In contrast, the two phase III trials of lenvatinib showed a median PFS of 18.3 vs. 3.6 months (HR 0.21, 99% CI: 0.14-0.31) and 23.9 vs. 3.7 months (HR 0.16, 95% CI: 0.10-0.26), respectively [19, 69]. Through indirect comparison of the SELECT and DECISION trials, the improvement of PFS in the lenvatinib group was significantly better than in the sorafenib group, even though the basic conditions of patients were worse in the lenvatinib group [24]. Aside from the improvement in PFS, lenvatinib also exhibited higher OS and objective response rate (ORR), along with manageable side effects [18, 19, 70-72]. This led to lenvatinib being listed as the top recommended treatment for RAI-rDTC. Besides, at least 40% of patients show meaningful redifferentiation of TC with new RAI uptake after short-term lenvatinib therapy, then followed by I-131 therapy [73]. Interestingly, cabozantinib still achieved good PFS in patients with progression who had previously failed treatment with sorafenib or lenvatinib (HR 0.22, 96% CI: 0.13-0.36, *P<0.0001*) [20]. This may be related to cabozantinib increasing the MET and AXL action sites, thereby improving the insensitivity of the VEGF inhibitory pathway [74-76]. Both selumetinib and cabozantinib are MET inhibitors, but cabozantinib has more targets, so it can better achieve thyroid cancer redifferentiation. Regardless of the efficacy, vandetanib, sorafenib, lenvatinib and cabotinib can activate the sensitivity of RAI by inhibiting BRAF gene in patients with advanced TC to achieve redifferentiation of thyroid cancer [77].

Apatinib, developed in China, extended the median PFS in RAI-RDTC patients by 12.6 months compared with the sorafenib study (DECISION trial). The $IC_{50}$ (1 nM) of apatinib's VEGFR-2 *in vitro was* significantly lower than the $IC_{50}$ values of sorafenib and lenvatinib [78], resulting in higher selective VEGFR-2 inhibition and stronger redifferentiation. Moreover, apart from apatinib, other drugs have also been utilized in patients with RAI-RDTC to achieve redifferentiation and improve outcomes. These include sunitinib, pazopanib, dovitinib, motesanib, axitinib and surufatinib. The median PFS achieved with these drugs ranged from 5.4 to 11.7 months, suggesting their potential in managing RAI-RDTC [79-84]. Overall, these findings highlight the remarkable progress of TKI-targeted therapy in patients with dedifferentiated thyroid cancer, with particularly promising results in prolonging progression-free survival and promoting redifferentiation.

Patients with RAI-rDTC are highly susceptible to relapse and metastasis. These negative outcomes are often attributed to gene fusion and mutations, such as the $BRAF^{V600E}$ mutation. Recent studies have shown that approximately 25% of patients with RAI-rDTC have achieved objective remission through the use of BRAF inhibitors like vemurafenib or dabrafenib [85, 86]. ATC (advanced dedifferentiated thyroid cancer) was poorly treated with antiangiogenic drugs, with the best ORR of only 10% in three published studies [87-89]. However, a significant breakthrough has been made with the combination therapy of trametinib and dabrafenib [90]. This remarkable response rate may be attributable to the fact that the transformation of ATC primarily occurs from TC with the BRAF mutation. Therefore, the focus of treatment should be directed towards inhibiting this particular mutant gene. A recent discovery by Dunn and colleagues has shed light on the potential of vemurafenib in reestablishing RAI avidity in BRAF-mutated RAI-refractory thyroid cancer [91]. The most common genetic alteration in TC is the BRAF mutation, found in nearly 45% of sporadic PTC [92]. Naturally, BRAF has evolved as a target of therapeutic interest. In particular, inhibiting BRAF directly using BRAF inhibitors or targeting downstream MAPK kinase (MEK) with MEK inhibitors has shown promise in restoring iodine concentration in thyroid tumor cells [36, 62, 93]. Investigations into the use of MEK1/2 inhibitors like selumetinib and BRAF inhibitors like dabrafenib have yielded positive outcomes, allowing for the induction of RAI sensitivity in a relatively short treatment duration. This approach permits additional treatment with radioactive iodine (131I) while minimizing drug exposure and associated adverse effects [62, 93]. In a case report, Groussin et al. 33 also found that treatment with the selective NTRK inhibitor larotrectinib reestablished RAI uptake on diagnostic imaging that was not previously evident [94].

There are many other targeted agents that can also achieve thyroid cancer redifferentiation. The targets and mechanisms of targeted drugs are displayed in **Table 2** and **Figure 1**. We analyzed the data and found that out of the 86

**Table 2.** The targets of molecular targeted drugs

| No. | Drugs | Targets |
|---|---|---|
| 1 | Apatinib | VEGFR |
| 2 | Anlotinib | VEGFR, FGFR, PDGFR, c-KIT |
| 3 | Axitinib | VEGFR, FGFR, c-KIT, RET |
| 4 | Cabozantinib | VEGFR, MET, c-KIT, RET, FLT-3 |
| 5 | Copanlisib | PI3K, mTOR |
| 6 | Dabrafenib | BRAF |
| 7 | Dovitinib | VEGFR, FGFR, RET, c-KIT, FLT-3 |
| 8 | Everolimus | mTOR |
| 9 | HLX208 | BRAF |
| 10 | Imatinib | PDGFR, c-KIT |
| 11 | Lenvatinib | VEGFR, FGFR, PDGFR, c-KIT, RET |
| 12 | Motesanib | VEGFR, PDGFR, c-KIT, RET |
| 13 | Pazopanib | VEGFR, PDGFR, c-KIT |
| 14 | Sapanisertib | mTOR |
| 15 | Selumetinib | MEK |
| 16 | Sirolimus | mTOR |
| 17 | Sorafenib | VEGFR, PDGFR, c-KIT, RET, BRAF |
| 18 | Sunitinib | VEGFR, PDGFR, c-KIT, RET, FLT-3 |
| 19 | Surufatinib | VEGFR, FGFR |
| 20 | Temsirolimus | mTOR |
| 21 | Tipifarnib | RAS |
| 22 | Trametinib | MEK |
| 23 | Vandetanib | VEGFR, EGFR, RET |
| 24 | Vemurafenib | BRAF |

studies examined, 47 studies provided detailed descriptions of adverse events related to the drugs. Among these adverse events, diarrhea was the most commonly reported, appearing in 26 studies (55% of the total). Hypertension and fatigue or asthenia were also frequently observed, being reported in 51% of the studies each. Other commonly reported adverse events included hand-foot skin reaction (HFSR) (36%), and rash (28%). Hypertension and HFSR are the most common drug-related adverse events in studies of lenvatinib and sorafenib, respectively, which can be reduced by monitoring blood pressure and moisturizing topical ointment, respectively. While it is crucial to prolong the survival period of patients, it is equally important to enhance their quality of life. Therefore, it is essential to prevent and control adverse reactions related to drug treatment. Traditional Chinese Medicine (TCM) offers unique characteristics in this regard. For example, the Shouzu Ning decoction has been found to relieve symptoms of HFSR according to a study [95]. However, it is important to note that the prevention and treatment of adverse events using TCM require more stringent trials and accurate evaluation criteria to verify their efficacy.

*Immune checkpoint inhibitors in advanced thyroid carcinoma*

Although vandetanib, sorafenib, lenvatinib, and cabozantinib have been approved by the FDA for the treatment of RAI-rDTC, they lack strong cytotoxic effects in patients with more aggressive advanced ATC and are prone to discontinue treatment due to drug resistance or more adverse reactions [96]. Several studies have shown that ATC patients with a higher density of TAMs tend to have a lower survival rate. This can be attributed to the elevated expression of PD-L1 in these patients. [97-99]. In fact, PD-1 and its ligand PD-L1 are highly expressed in ATC, and redifferentiation of thyroid cancer by inhibiting PD-1/PD-L1 expression becomes another promising treatment [100].

TAM can be divided into two categories: alternation activated macrophages (M2) and classical activated macrophages (M1), among which the M2 macrophages have been found to have a dominant role in inhibiting anti-tumor functional T cells and B cells by expressing inhibitory ligands of PD-L1/L2 and CD80/86 [101-103]. TAM (mainly M2 macrophages) upregulates or directly affects PD-1 related genes, promotes PD-1 binding to PD-L1, activates downstream pathways (such as PI3K/AKT/mTOR) to regulate immune cells and promote tumor failure [57, 104, 105]. Therefore, PD-1/PD-L1 inhibitors can block the tumor effect induced by TAM, enhance the immune activity of effector T cells, and limit tumor invasion progression [106, 107], as demonstrated in **Figure 2**.

Landa et al. conducted a study and concluded that ATC was enriched by TAM [23]. Data from the study showed that M2 macrophages infiltrated ATC tissues and played a role in promoting the metastasis of ATC cells. This could be attributed to the activation of the PI3K/AKT/mTOR signaling pathway mediated by M2 macrophages [108]. As mentioned, only targeted therapy for ATC patients often had a poor prog-

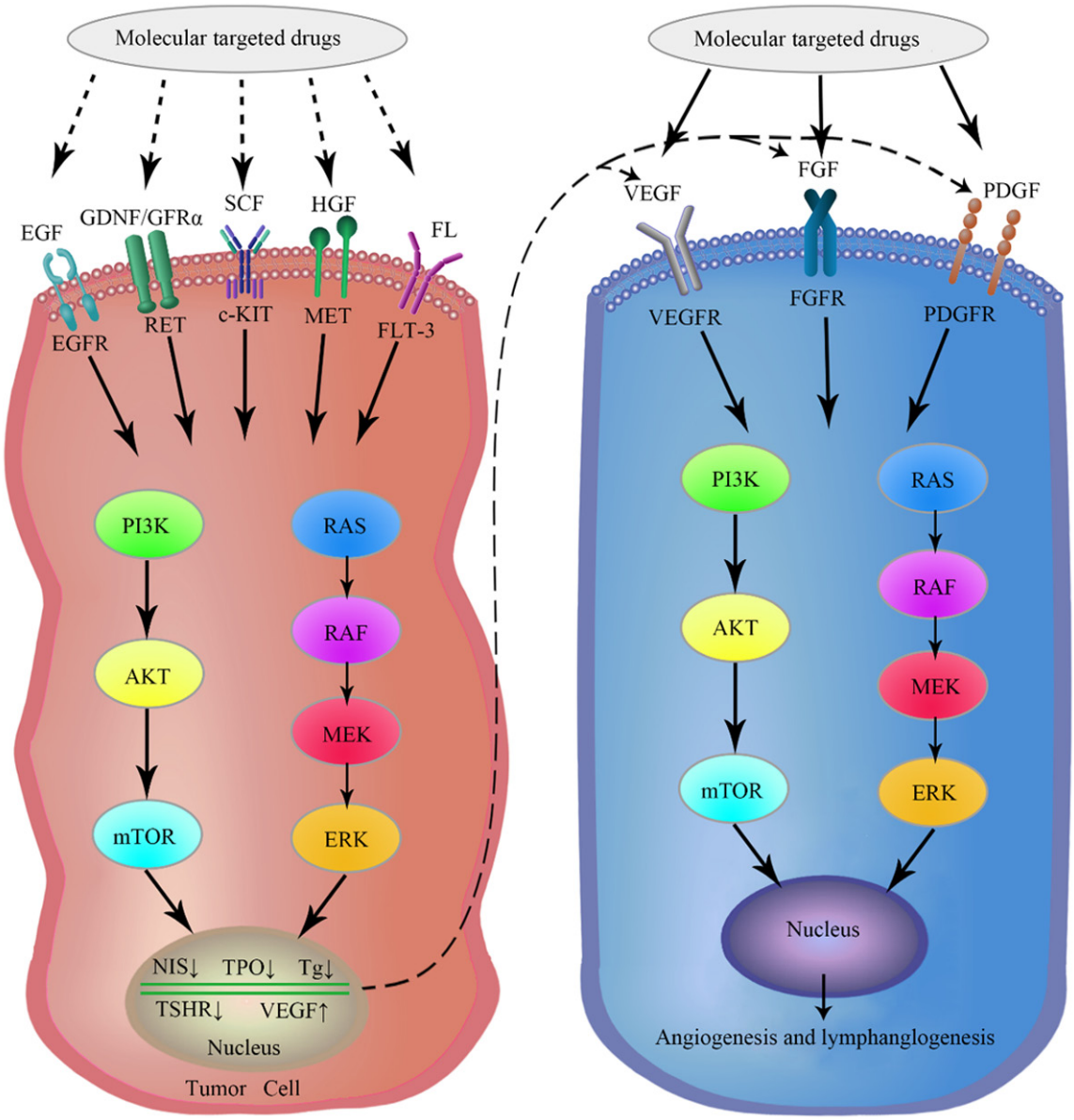


**Figure 1.** The major signaling pathways of molecular targeted drugs. FL, FLT-3 ligand; FLT-3, FMS-like tyrosine kinase-3; GDNF, glial cell-derived neurotrophic factor; GFRα, GDNF family receptor α; RET, rearranged during transfection; HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition factor; SCF, stem cell factor; c-KIT, proto-oncogene proteins c-kit; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; PI3K (phosphatidylinositol-3 kinase)/AKT/mammalian target of rapamycin (mTOR) signaling pathway; RAS/RAF/MEK/ERK signaling pathway.

nosis. Generally, the expression of PD-L1 and PD-L2 are usually positively correlated. An increased positive expression of PD-L1/PD-L2 indicates that TC patients may have the $BRAF^{V600E}$ mutation, experience poor survival, or have a higher risk of disease recurrence [59, 109]. Several studies have reported elevated macrophage scores and increased expression of CTLA-4 and PD-L1 in patients with thyroid dedifferentiation or the presence of the $BRAF^{V600E}$ mutation [110-113]. Giannini et al. also confirmed that ATC predominantly expressed inhibitory immune checkpoint mediators such as PD-L1/PD-L2 and PD-1, CD86,

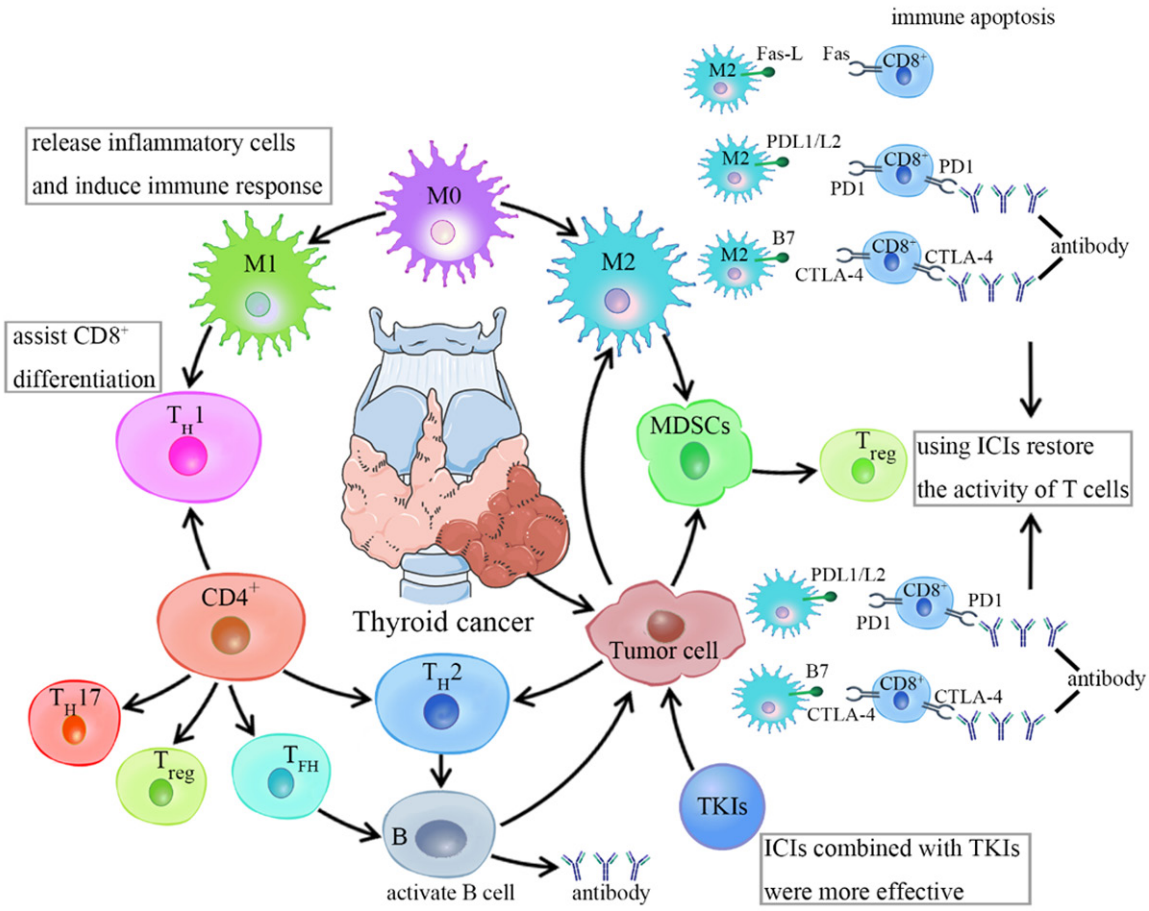


**Figure 2.** The mechanism of immune checkpoint inhibitors in thyroid carcinoma. ICIs, immune checkpoint inhibitors; TKIs, tyrosine kinase inhibitors; MDSCs, myeloid-derived suppressor cells; Treg, regulatory T cell; $CD8^+$, cytotoxic T cell; $CD4^+$, helper T cell.

and CTLA-4 [114]. And PCR analysis revealed that ATC samples had the highest expression of PD-L1 (>30%), while in WDTC samples had lower expression of PD-L1 (<10%) [115].

The differentiation degree of TC can also be quantified by thyroid differentiation score (TDS). The thyroid differentiation score was worse, and the TDS value was lower [110, 116]. One study conducted a gene expression analysis on a database of 505 TC patients. The results showed that the thyroid differentiation score (TDS) was negatively correlated with immunosuppressive markers like CTLA-4 (r=-0.47, *P< 0.001*) and PD-L1 (R=-0.33, *P<0.001*) [113, 117]. This suggests that patients with poorly differentiated TC, indicated by a lower TDS value, may be more suitable candidates for ICIs therapy.

Furthermore, a NanoString analysis revealed that ATC is generally considered as "hot" tumors with high T cell inflammation and immune scores. This finding indicates that the tumor microenvironment of ATC is characterized by immune cell infiltration [114]. Therefore, using ICIs such as PD-1 or CTLA-4 inhibitors can activate the existing immune cells to recognize and eradicate the cancer cells. ALL of these data indicate that the more poorly differentiated the thyroid cancer, the higher the PD-1/PD-L1 or CD86/CTLA-4 expression, and the more need for ICIs treatment, and also indicate that ATC patients need to use ICIs-based treatment methods to achieve thyroid cancer redifferentiation.

The first ICI (pembrolizumab) study for advanced DTC had a disease control rate of 68%, all patients were well tolerated, but only two patients had a partial response (9%) [118]. Although the study of spartalizumab demonstrated a promising objective response rate (19%) and disease control rate (31%) in patients

**Table 3.** Immune checkpoint inhibitors therapy for thyroid carcinoma

| No. | Type | Drugs | ORR | The most common adverse events | Trial number and/or reference |
|---|---|---|---|---|---|
| 1 | TC | Pembrolizumab<br>Lenvatinib<br>Chemotherapy | / | / | NCT04731740 |
| 2 | TC | Nivolumab<br>Ipilimumab | / | / | NCT03246958 |
| 3 | TC | Nivolumab<br>Ipilimumab<br>Cabozantinib | / | / | NCT03914300 |
| 4 | TC | Atezolizumab<br>Bevacizumab<br>Nab-paclitaxel<br>Paclitaxel<br>Cobimetinib<br>Vemurafenib | / | / | NCT03181100 |
| 5 | TC | Durvalumab | / | / | NCT03215095 |
| 6 | TC | Pembrolizumab<br>Lenvatinib | / | / | NCT04171622 |
| 7 | TC | Encorafenib<br>Binimetinib<br>Nivolumab | / | / | NCT04061980 |
| 8 | TC | Apatinib<br>Camrelizumab | / | / | NCT04612894 |
| 9 | TC | Toripalimab<br>Surufatinib | / | / | NCT04524884 |
| 10 | TC | Dabrafenib<br>Trametinib<br>Spartalizumab | / | / | NCT04544111 |
| 11 | TC | Durvalumab<br>Tremelimumab | / | / | [139] |
| 12 | TC | Nivolumab<br>Ipilimumab | 2/17 | Fatigue 41%, elevated lipase 29% | [120] |
| 13 | TC | Pembrolizumab<br>Lenvatinib | 8/20 | / | [124] |
| 14 | TC | Nivolumab<br>Ipilimumab | 6/32 | / | [121] |
| 15 | TC | Pembrolizumab<br>Lenvatinib | 6/8 | Hypertension 63%, anorexia 50%, fatigue 38% | [127] |
| 16 | TC | Camrelizumab<br>Famitinib | 20/37 | Hypertension 40%, fatigue 33%, HFSR 30% | NCT04521348 |
| 17 | TC | Pembrolizumab | 6/43 | / | [122] |
| 18 | DTC | Durvalumab<br>Tremelimumab | / | / | NCT03753919 |
| 19 | DTC | Anlotinib<br>Pembrolizumab | / | / | NCT04952493 |
| 20 | DTC | Pembrolizumab | 2/22 | Diarrhea 32%, fatigue 18%, pruritus 14% | NCT02054806 |
| 21 | RAI-rDTC | Pembrolizumab<br>Lenvatinib | 18/29 | / | [125] |
| 22 | RAI-rDTC | Pembrolizumab<br>Lenvatinib | 3/20 | / | NCT02973997 |
| 23 | ATC | Pembrolizumab | / | / | NCT05119296 |

| | | | | | |
|---|---|---|---|---|---|
| 24 | ATC | Pembrolizumab | 3/5 | Hypertension and fatigue 100%, shortness of breath 83% | NCT02688608 |
| 25 | ATC | Durvalumab Tremelimumab | / | / | NCT03122496 |
| 26 | ATC | Dabrafenib Trametinib Pembrolizumab | / | / | NCT04675710 |
| 27 | ATC | Docetaxel Doxorubicin Pembrolizumab | / | Pneumonitis 67%, nausea 33%, respiratory failure 67% | NCT03211117 |
| 28 | ATC | Pembrolizumab | / | / | NCT05059470 |
| 29 | ATC | Spartalizumab | 8/42 | Diarrhea and pruritus 12%, fatigue and pyrexia 7% | NCT02404441 |
| 30 | ATC | Pembrolizumab TKI | 5/12 | Fatigue 92%, anemia 83%, hypertension and dry mouth 67% | [140] |

TC, thyroid carcinoma; DTC, differentiated thyroid carcinoma; RAI-rDTC, radioiodine-refractory differentiated thyroid carcinoma; ORR, objective response rate; HFSR, hand-foot skin reaction.

with ATC [119], several studies demonstrated no improvement in combination immunotherapy (PD-1 and CTLA-4 inhibitors) with objective response rates of less than 20% [120, 121]. Leboulleux and colleagues conducted a phase II trial (NCT03012620) evaluating the use of pembrolizumab in RAI-r DTC. They observed a median overall survival of 12.7 months and a median progression-free survival of 2.6 months. Six months into the trial, the overall survival rate was 73.3%, and the progression-free survival rate was 16.9% [122].

Interestingly, the combination of TKI-targeting therapy with ICIs has shown superior prognostic outcomes in the treatment of patients with advanced TC. In a study conducted on animals, it was found that the use of anti-PD-L1 antibody combined with BRAF inhibitor significantly reduced tumor volume by 81% ($P<0.001$) and 66% ($P=0.023$) compared to anti-PD-L1 antibody and BRAF inhibitor alone, respectively [53]. In a prospective multiarm trial, there were three cohorts, including the anti-PD-L1 atezolizumab in combination with either vemurafenib or cobimetinib in patients with BRAF mutations (cohort 1), cobimetinib alone in patients with RAS and NF1 mutations (cohort 2), and bevacizumab in patients without mutations (cohort 3) [123]. The median OS of cohort 1, 2, and 3 were not reached, 18.23 and 6.21 months, respectively. The response rate was 71% in cohort 1 and 7% in cohort 2. Based on these findings, it can be concluded that the combination of ICIs with targeted therapy holds great promise for the treatment of patients with ATC and specific molecular alterations. This approach could potentially lead to improved prognosis and survival rates in ATC patients.

In studies examining the use of multiple TKIs combined with ICIs in treating patients with TC, it was found that the highest ORR was 62%, and most results showed ORR above 40% [124-126], as demonstrated in **Table 3**. In a retrospective study conducted by Diercks et al., six patients with metastatic ATC were treated with a combination of lenvatinib and pembrolizumab. Remarkably, 66% of these patients achieved a complete response, meaning that their cancer disappeared entirely. The median PFS for these patients was 16.8 months, and the OS was 17.3 months [127]. These findings provide further evidence for the effectiveness of combining TKIs with ICIs in the treatment of ATC patients. Looking ahead, it is possible that the preferred treatment for dedifferentiated advanced thyroid cancer (particularly PDTC or ATC) will involve a combination of molecular targeted therapy and immunotherapy. By combining these two approaches, it may be possible to achieve even greater efficacy in treating advanced forms of TC. However, it is crucial to ensure that patients do not experience severe grade 3 drug-related adverse reactions, as these can significantly impact overall prognosis. PD-1 immunotherapy can cause various endocrine toxicity, including thyroid dysfunction, adrenal insufficiency, type 1 diabetes, etc. [128, 129]. The prevention and treatment of

adverse reactions after immunotherapy should be further studied. Therefore, in addition to improving treatment effectiveness, efforts should also be made to minimize the occurrence of such adverse reactions in order to improve patient outcomes.

## Conclusion and future directions

ATC oncogenesis may be a multistep process with biological transformation from DTC to ATC. The presence of a concomitant DTC tumor component or a history of DTC was prevalent in 58% to 90% of cases, thus indicating this hypothesis [130]. The process of dedifferentiation of WDTC into ATC involves the decrease of NIS expression, the activation of TKIS-mediated signaling pathway and the increase of immunosuppressive factors. This review focuses on the mechanism of TC dedifferentiation and NIS expression, BARF gene mutation mediated signaling pathway and immune checkpoint activation. The pathological changes of DTC dedifferentiation into ATC were described from the macroscopic level, and the changes of molecular expression levels involved in this process were introduced from the microscopic level. Based on these findings, it is concluded that the expression of NIS interacts with TKI-mediated signaling pathways and immune checkpoint-mediated immune responses. This suggests that targeting these factors may be a potential strategy for redifferentiation of thyroid cancer. The treatment options for thyroid cancer vary based on the degree of differentiation. In patients with RAI-rDTC, TKIs are often used to increase NIS expression, enhance iodination, or inhibit tumor-related angiogenesis, aiming to achieve redifferentiation. On the other hand, for patients with advanced forms of TC such as poorly differentiated or ATC, a combination of ICIs and TKIs should be considered for redifferentiation. Although there is a lack of extensive experimental evidence specifically for ATC, the review provides insights into the clinical efficacy of targeted drugs and ICIs for the treatment of advanced ATC. Ongoing clinical studies are anticipated to further elucidate the role of these therapies in TC redifferentiation. It is also necessary to monitor the changes in the expression values of signaling pathway related targets and immune-related indicators before and after treatment of advanced thyroid cancer to achieve more accurate redifferentiation of thyroid cancer. We look forward to more positive outcomes and treatment options for TC redifferentiation in the future.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Jue Wang, Department of Oncology, Hangzhou Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, Hangzhou 310007, Zhejiang, China. E-mail: starmoon7@163.com

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# Appendix 1

**1. Targeted therapy for thyroid cancer**

**PICOS**

**P:**

**MeSH terms: Thyroid Neoplasms**

**Free terms:** (Thyroid Carcinoma) OR (Thyroid Cancer) OR (Thyroid Adenoma) OR (Thyroid Neoplasm)

**I:** (Apatinib OR Anlotinib OR Axitinib OR Bortezomib OR Cabozantinib OR Copanlisib OR Dabrafenib OR Dovitinib OR Everolimus OR Imatinib OR Lenvatinib OR Motesanib OR Pazopanib OR Pralsetinib OR Sapanisertib OR Selpercatinib OR Selumetinib OR Sirolimus OR Sorafenib OR Sunitinib OR Surufatinib OR Temsirolimus OR Tipifarnib OR Trametinib OR Vandetanib OR Vemurafenib)

**C:**

**O:**

**S:**

**2. Immune checkpoint inhibitors therapy for thyroid cancer**

**PICOS**

**P:**

**MeSH terms: Thyroid Neoplasms**

**Free terms:** (Thyroid Carcinoma) OR (Thyroid Cancer) OR (Thyroid Adenoma) OR (Thyroid Neoplasm)

**I:**

**MeSH terms: Immune Checkpoint Inhibitors**

**Free terms:** (nivolumab OR BMS-963558 OR pembrolizumab OR MK-3475 OR ipilimumab OR MDX-010 OR avelumab OR durvalumab OR tremelimumab OR atezolizumab OR MPDL3280A OR Spartalizumab OR programmed cell death OR Cytotoxic T Lymphocyte Associated Protein 4 OR Programmed Death Ligand 1 OR immunotherapy OR PD1 OR PD-1 OR PDL1 OR PDL2 OR PD-L2 OR PDCD1 OR PD-L1 OR CTLA-4 OR immune checkpoint OR checkpoint blockade OR immune checkpoint inhibitors OR ICI OR ICIs OR immune checkpoint blockers OR ICB OR B7 H1 OR CD279 OR CD274)

**C:**

**O:**

**S:**