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Review

# Molecular basis and targeted therapy in thyroid cancer: Progress and opportunities

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ABSTRACT

Thyroid cancer (TC) is the most prevalent endocrine malignant tumor. Surgery, chemotherapy, radiotherapy, and radioactive iodine (RAI) therapy are the standard TC treatment modalities. However, recurrence or tumor metastasis remains the main challenge in the management of anaplastic thyroid cancer (ATC) and radioiodine (RAI) radioactive iodine-refractory differentiated thyroid cancer (RR-DTC). Several multi-tyrosine kinase inhibitors (MKIs), or immune checkpoint inhibitors in combination with MKIs, have emerged as novel therapies for controlling the progression of DTC, medullary thyroid cancer (MTC), and ATC. Here, we discuss and summarize the molecular basis of TC, review molecularly targeted therapeutic drugs in clinical research, and explore potentially novel molecular therapeutic targets. We focused on the evaluation of current and recently emerging tyrosine kinase inhibitors approved for systemic therapy for TC, including lenvatinib, sorafenib and cabozantinib in DTC, vandetanib, cabozantinib, and RET-specific inhibitor (selpercatinib and pralsetinib) in MTC, combination dabrafenib with trametinib in ATC. In addition, we also discuss promising treatments that are in clinical trials and may be incorporated into clinical practice in the future, briefly describe the resistance mechanisms of targeted therapies, emphasizing that personalized medicine is critical to the design of second-line therapies.

## 1. Introduction

Thyroid cancer (TC) is the most common endocrine malignancy globally. Its incidence has sharply increased since 2000. According to American Cancer Society data, there were 44,280 new cases and 2200 deaths from TC in 2021 in the United States [1]. This increase in the incidence of TC is attributable to the overdiagnosis of differentiated thyroid cancer (DTC). The incidence rates of medullary thyroid cancer (MTC), follicular thyroid cancer (FTC), and anaplastic thyroid cancer (ATC) remained stable during the same period [2].

DTC is a common subtype of TC, including papillary thyroid carcinoma (PTC) and FTC, accounting for about 85% and 10% of all TCs, respectively [3,4]. In particular, DTC tumors are classified as poorly differentiated thyroid carcinoma (PDTC) when they exhibit high pathological features, such as elevated mitotic index and the presence of tumor necrosis associated with an aggressive clinical course [5]. The

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incidence of PDTC is 2% to 15% of all TCs and is the leading cause of mortality in non-anaplastic follicular cell derived thyroid carcinoma. Treatment of PDTC has not been standardized due to strong heterogeneity and rarity. Treatment decisions for PDTC are mainly based on the treatment experience of DTC [6]. Surgery, radiotherapy, and radioactive iodine (RAI) therapy are effective for most DTC patients [7]. However, the iodine uptake capacity of cancer cells in some DTC patients (specially PDTC) may be lost, and the patients no longer respond to $^{131}I$ therapy, namely the radioiodine (RAI)-refractory DTC (RR-DTC), with a 10-year survival rate of only 10% from the time of discovery of metastasis [8,9]. Systemic therapy is warranted for lesions approaching 1 cm in diameter with a doubling time < 1 year and for DTC tumors larger than 1.5–2.0 cm with a doubling time < 1–4 years [3]. MTC (<5%) are less common in TCs. For patients with advanced MTC with large tumor load and multiple metastatic sites, and with rapid tumor progression (<12–14 months), systemic tumors should be applied according to Response Evaluation Criteria in Solid Tumors (RECIST) standards and clinical judgment [10].

ATC is undifferentiated carcinoma, with an incidence rate of <2% of all TCs, but it is refractory to standard treatments, the median survival is only 6 months [4,11]. Unsurprisingly, ATC is one of the most aggressive and deadly malignancies, with 98–99% cancer-specific mortality, and it is estimated to be the major cause of annual TC-related mortality [12]. Currently, there are no effective treatment options for ATC, and new treatments are urgently being developed [11]. Postoperative recurrence, tumor metastasis, RR-DTC, and more mutation-laden ATC are the main challenge associated with TC [13]. Based on genetic abnormalities in the tumor subtype, as a therapeutic entry point, additional therapeutic options are required, including tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors (ICIs).

Genetic researchers have gradually identified the TC signature "oncogenes" or "tumor suppressors" that can serve as diagnostic tools or therapeutic targets. For example, abnormal amplification and copy number increase of genes encoding receptor tyrosine kinases (RTKs) are one of the common pathogeneses of TC. The development of TKIs has achieved the targeted treatment of such patients. TKIs compete with adenosine triphosphate (ATP) for ATP binding site, disrupting kinase phosphorylation and thus, inhibiting the transduction and proliferation of cancer cells [14]. Before a new drug can be used in the "real world", a large number of clinical studies are conducted to evaluate its safety and efficacy in TC treatment, and official approval is required before it can be used in the clinic. At present, numerous targeting mutation-driven kinase inhibitors, including multi-kinase inhibitors (MKIs), have undergone preclinical and clinical trials [13].

In recent years, studies on ICIs based on the activation of the mechanism of T cells to improve the body's natural anti-tumor defense ability, thereby changing the cancer treatment mode, have increased [15]. In addition, more attention has been paid to the efficacy of ICIs alone and in combination with TKIs in TC. At present, antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab), programmed cell death protein-1 (PD-1) (cemiplimab, nivolumab, and pembrolizumab), and programmed death ligand-1 (PD-L1) (atezolizumab, avelumab, and duralumab) have been approved by the Food and Drug Administration (FDA) for human tumor treatment.

In this review, we summarize common genetic alterations and corresponding inhibitors targeted for TC treatment either in the preclinical or clinical phase. Moreover, we highlight advances in the application of MKIs in clinical studies and systematically summarized the results of clinical studies on the safety and efficacy of these drugs in the treatment of TCs. Finally, we briefly described the resistance mechanisms of targeted therapies and summarized the potential TC treatment technologies.

## 2. Common genetic alterations in TC

Currently, the occurrence and development of TC are related to various genetic changes, mainly including gene amplifications and copy-number gains, somatic mutation, chromosomal rearrangement, epigenetic changes dominated by DNA methylation, and imbalance of non-coding RNAs (ncRNAs), and other molecular events [16,17] (Fig. 1). Among them, gene amplifications and copy-number gains, somatic mutation, chromosomal rearrangement are classic tumor drivers.

(I) Gene amplifications and copy-number gain

Oncogene amplification or copy number increase is an important genetic mechanism of thyroid tumorigenesis, especially the genes encoding RTKs, including epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), KIT and MET [16]. The phosphoinositide 3-kinase (PI3K) pathway-related functional regulation genes, including phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), PI3K catalytic subunit beta (PIK3CB), inosine 3-phosphate dependent protein kinase 1 (PDK1), serine/threonine-protein kinase 1 (AKT1), and AKT2, are also commonly detected to have increased copy numbers in TC [18,19].

Abnormal copies of these genes are found more frequently in ATC than in DTC. The mechanism of their promotion of thyroid tumorigenesis and development is through the increase of protein expression and subsequent abnormal activation of PI3K/AKT, mitogen-activated protein kinase (MAPK), and other related signal pathways [19]. In addition, some other abnormal gene amplifications have been of great concern. For example, IQ-motif-containing GTPase-activating protein 1 (IQGAP1) is highly expressed in invasive TC, Cyclin D1 is highly expressed in ATC, and mucin 1 (MUC1) is related to the invasiveness of PTC [20–22].

(II) Somatic mutation

*BRAF-V600E mutant.* The expression of the BRAF-V600E mutant protein caused by T1799A cross-point mutation and the structural activation of this AKT is one of the most classic examples of somatic mutation [23]. BRAF-V600E mutations occur in about 45% of PTCs and partial PTC-derived ATCs but are not observed in MTC and FTC [24]. The specificity and high frequency of BRAF mutation indicate that the mutation may play a key role in the development of PTC tumors and drive the formation of ATC [24]. Some convincing evidence shows that targeted expression of BRAF-V600E in thyroid-like cells of transgenic mice can induce PTC to transform into undifferentiated carcinoma, and BRAF-V600E is closely related to poor clinical treatment and pathological results of PTC [25]. Thyroid cancer genome mapping studies have shown that the classification of adult PTC into two molecular defined RAS-like and BRAF-like categories can more accurately reflect cell signaling, cell differentiation, and clinical behavior [26].

*RAS mutation.* RAS mutation is also a common carcinogenic driver of TC. It is a classic dual activator of MAPK and PI3K/AKT pathways. The activation of RAS may play a role in early FTA, and its mutation is related to the pathological process from FTA to FTC [27]. RAS mutations usually occur in various TCs, including FTC (40–50%), PTC (10–20%), and ATC (20–40%) [17,28]. Moreover, the incidence of RAS mutations in sporadic MTC ranges from 0 to 43.3%, usually occurring in rearranged during transfection (RET) mutation-negative MTC [29]. Recently, targeted sequencing showed that RAS mutation is present in up to 24.3% of sporadic MTC cases, and is the second main driver of an oncogene in sporadic MTC, especially HRAS and KRAS genes [30].

*RET mutation.* RET germline mutations occur in up to 95%–98% of familial MTC, and 25–50% of sporadic MTC harbored RET somatic mutations [31]. Targeted next-generation sequencing data of 181 patients with sporadic MTC showed that 55.8% of cases harbored RET gene mutation, further confirming that RET, particularly the M918T mutation (occurring in codon M918 within exon 16), is the main driving oncogene of sporadic MTC [30].

*Others.* In addition, multiple mutations of effector genes related to the PI3K/AKT pathway, such as phosphatase and tensin homolog (PTEN), PIK3CA, and AKT1 mutations, are frequently detected in FTC [32]. Telomerase reverse transcriptase (TERT) promoter mutations, catenin beta 1 (CTNNB1) mutations, TP53 mutations, neurotrophic

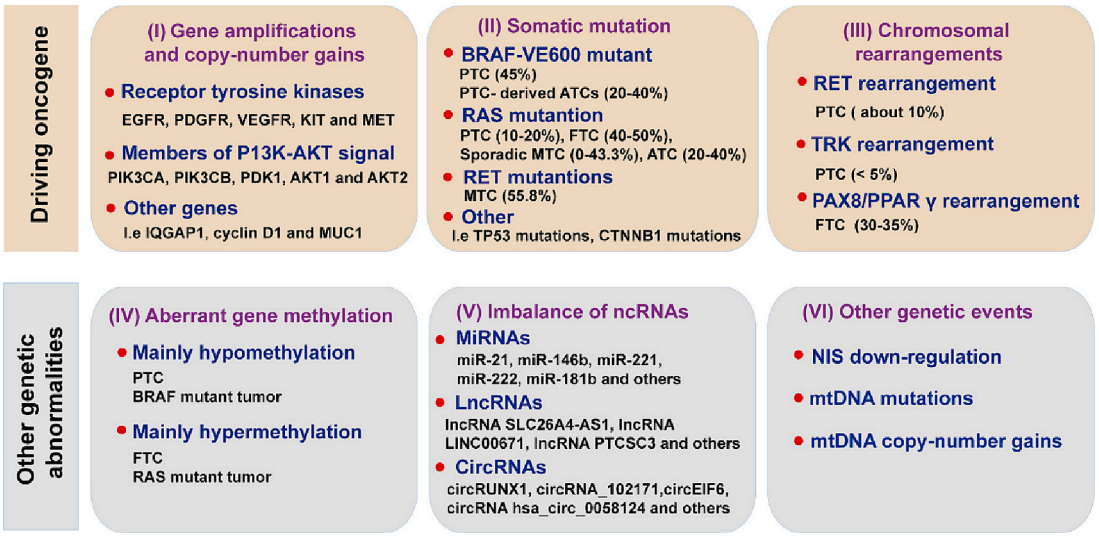


**Fig. 1.** Genetic alterations in TC. Common molecular mechanisms in TC are gene amplifications and copy-number gains, somatic point mutation, chromosomal rearrangement, epigenetic changes dominated by DNA methylation, and imbalance of noncoding RNAs and other molecular events.

receptor tyrosine kinase (NTRK), and analytical lymphoma kinase (ALK) variances occur first in poorly differentiated TC and ATC [33], indicating that these mutations and rearrangements may be related to the degree of differentiation of TC and disease progression.

(III) Chromosomal rearrangements

Gene fusion is positive in about 15% of TCs. RET/PTC, tropomyosin receptor kinase (TRK), and paired Box 8 (PAX8)/peroxisome proliferator-activated receptor gamma (PPAR γ) rearrangements are common chromosomal rearrangements with high frequency in TC. The PAX8/PPAR rearrangement usually occurs in up to 35% of FTC [34]. RET/PTC was detected in PTC (10–20%), and the incidence of NTRK1 chromosome rearrangements, also known as TRK rearrangements, in PTC is significantly lower than RET/PTC rearrangements (<5%) [17]. RTK fusion genes NTRK and RET are rare (about 10%) in PTC [26].

(IV) Aberrant gene methylation

The epigenetic difference between PTC and ATC indicates that the mutation frequency of PTC is one of the lowest in solid tumors, while the mutation frequency of ATC is the opposite. Histologically relevant DNA methylation characteristics indicate that compared with normal thyroid tissues, PTC is characterized by a higher number of hypomethylation than hypermethylation, while compared with PTC, FTC shows more hypermethylation than hypomethylation. Importantly, BRAF-mutated tumors have more hypomethylation (this mutation is almost only detected in PTC), whereas RAS-mutated tumors have more hypermethylation (mutations mainly occur in FTC) [35,36]. The expression of thyroid-stimulating hormone receptor (TSHR) is also inhibited by abnormal methylation of the gene promoter. Galrao et al. found a remote enhancer highly methylated in DTC-regulated sodium/iodide symporter (NIS) expression [37]. Although there is no substantial conclusion on the relationship between gene mutation and methylation of these genes, these studies provide a basis for epigenetic regulation and treatment of TC.

(V) Imbalance of ncRNAs

Functional gene products are not limited to proteins but include unique ncRNAs [38]. Studies have revealed the roles of various ncRNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) in TC, some of which are used in the clinical setting [16]. Imbalanced expression of ncRNAs, including abnormal miRNAs, lncRNAs, and circRNAs, are potential diagnostic markers or therapeutic targets for cancers [39]. Recent studies have shown that some regulatory ncRNAs participate in the occurrence and development of TC, including predisposition, tumor growth, and prognosis [39].

(VI) Other genetic events

The functional expression of NIS that exists on the thyroid cell membrane to promote the inflow of iodine ions will be lost due to cell dedifferentiation, which seriously affects the iodine radiotherapy of TC. NIS gene expression is frequently down-regulated in TC. About 10–20% of differentiated TC does not express NIS, and it is almost completely silent in poorly differentiated and anaplastic TC [40]. The decreased expression of NIS, the decreased membrane targeting of NIS, or both are mainly caused by genetic and epigenetic changes and signal pathway disorders [41].

With the development of sequencing technology, changes in molecular spectra of different subtypes of TC are becoming more detailed. Gene changes extending to the mitochondria — mitochondrial DNA (mtDNA) mutations in TC cells — such as the G3842A mutation, accelerate tumorigenicity through the reactive oxygen species (ROS)/extracellular signal-regulated kinase (ERK) pathway [42]. Moreover, Zheng et al. found that the content of leukocyte mtDNA copy number was positively correlated with the increased risk of TC (especially PTC and FTC) [43]. All these genetic events are of great significance for better pathogenesis, treatment, and diagnosis of TC.

## 3. MKIs in TC

Disruption of the MAPK pathway induced by mutations in oncogenic BRAF, RAS, and RET fusions dominate the genomic landscape in PTC, ATC, and RET-mutated MTC [44]. Thus, overexpression of kinase caused by these mutations and activated RAS/MAPK pathways are at the core of TC pathogenesis and progression [11]. Regulatory mechanisms of pathways and targets related to TKIs in the development of TC are illustrated in Fig. 2. These small molecule inhibitors can specifically target hyperactive or mutant extracellular surface-binding receptors, such as VEGFR, EGFR, fibroblast growth factor receptor (FGFR), RET, PDGFR, etc., block the activity of protein kinases, suppressing tumor angiogenesis, invasiveness, and local and distant metastases [4,13]. TKIs can also directly inhibit constitutively active mutant protein kinases or induce RAI-refractory disease (RAIRD) redifferentiation by restoring RAI sensitivity [13]. Currently, targeted inhibitors, mainly MKIs, are the standard of care for RR-DTC, ATC, and metastatic MTC [13].

### 3.1. MKIs and DTC

$^{131}$I therapy is one of the most important treatment modalities for patients with distant metastatic DTC. However, MKIs are a major treatment option when the patient develops iodine resistance and does

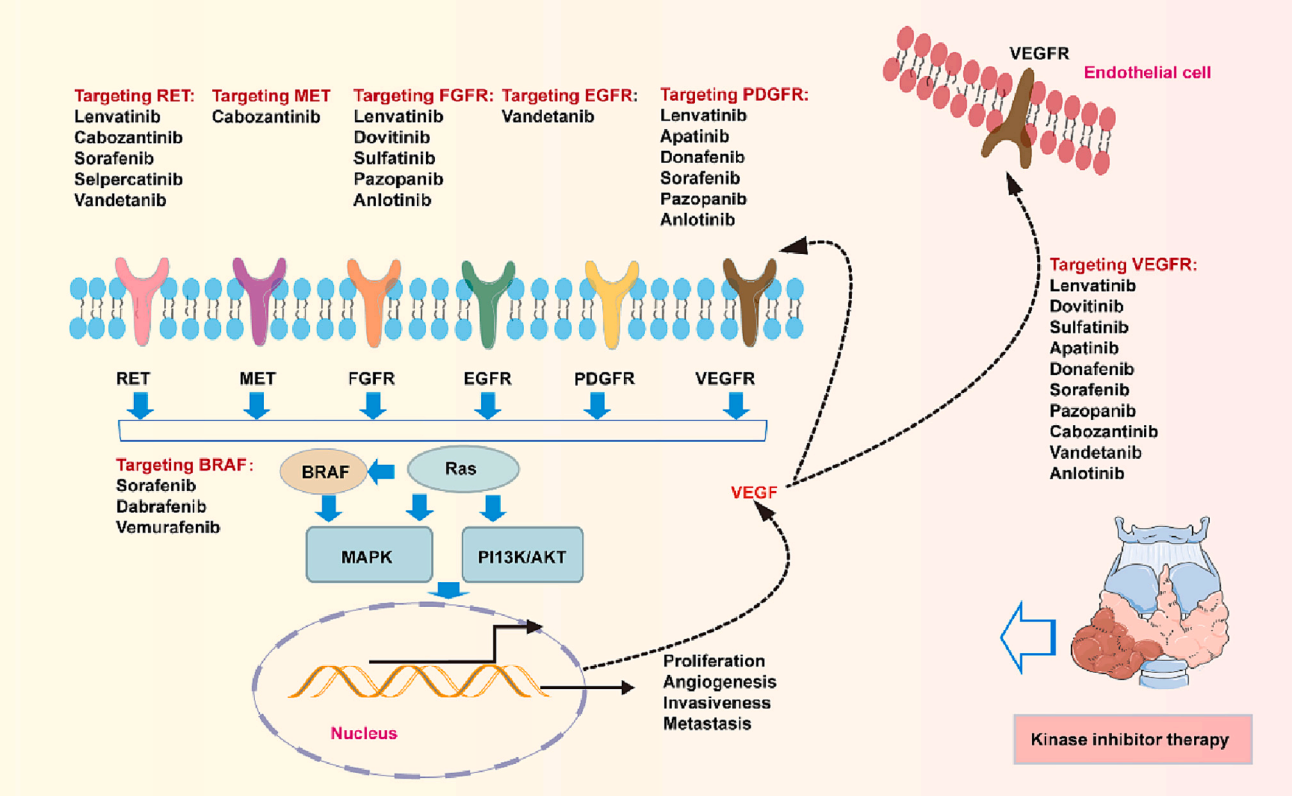


**Fig. 2.** The regulation mechanisms and tyrosine kinase inhibitor (TKI)-related targets that participate in the development of Thyroid tumor. TC cells are regulated by various growth factors, which disrupt the proliferation, angiogenesis, invasion, and metastasis of cancer cells by regulating MAPK and PI3K/AKT pathways. Deregulated receptor tyrosine kinases (RTKs) on these tumor cells are also therapeutic targets for TKIs. For example, lenvatinib, cabozanitinib, sorafenib, selpercatinib, and vandetanib inhibit RET, cabozanitinib inhibits MET, vandetanib inhibits EGFR, lenvatinib, dovitinib, sulfatinib, pazopanib, and anlotinib inhibit FGFR, lenvatinib, apatinib, donafenib, sorafenib, pazopanib, and anlotinib inhibit PDGFR, lenvatinib, dovitinib, sulfatinib, apatinib, donafenib, sorafenib, pazopanib, cabozanitinib, vandetanib, and anlotinib inhibit VEGFR to inhibit tumor angiogenesis. Sorafenib, dabrafenib, and vemureafenib target BRAF. The selectivity of these TKIs includes broad-spectrum multi-kinase inhibitors of most RTKs as well as individual-specific inhibitors.

not respond to $^{131}$I treatment [8]. To date, lenvatinib, sorafenib, and cabozantinib have received regulatory approval for the treatment of RR-DTC (Table 1). Lenvatinib, a multi-targeted MKI with VEGFR1-3, FGFR1-4, PDGFR, RET, and KIT proto-oncogene (c-kit) showed a 69.9% response rate in a randomized RAIRD III clinical trial with a median progression-free survival (PFS) of 23.9 months compared with 3.7 months in placebo-treated patients. The most common adverse events experienced by all patients were hypertension and proteinuria, and most of these events could be managed with dose adjustment and medication [45]. Lenvatinib showed optimal objective response rate (ORR) and median PFS. Clinical studies showed that lenvatinib at an initial dose of 18 mg/day did not reduce efficacy compared with a starting dose of 24 mg/day and that lowering the dose reduced the incidence of grade $\geq$ 3 adverse events. These results indicate that lenvatinib can be used as a first-line clinical agent in the treatment of RR-DTC patients [46].

Sorafenib — a kinase inhibitor of VEGFR1-3, PDGFR, RET, c-kit, and BRAF — prolongs median PFS in TC. In a phase III study of RR-DTC therapy, sorafenib significantly increased the median PFS (10.8 months) compared with the placebo (5.8 months). The ORR was 12.2% in the sorafenib treatment group, but adverse events occurred in 98.6% of patients. The safety is consistent with the known sorafenib safety profile and is not associated with unique, adverse safety events. The FDA has approved the clinical use of sorafenib for RR-DTC treatment [47]. A systematic study evaluated the cost-effectiveness of lenvatinib and sorafenib in patients with RR-DTC, the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) for lenvatinib versus best supportive care (BSC) was £65,872, the ICER per QALY of sorafenib versus BSC was £85,644, and the ICER for both treatments was higher than £50,000/QALY [48].

Cabozantinib is a recently FDA-approved MKI for the treatment of adults and children aged 12 years and older with locally advanced or metastatic DTC. Cabozantinib showed a significant improvement over a median of 1.9 months of PFS in the placebo group with an ORR of 15% and can be used as a second-line treatment agent after lenvatinib [46,49,50].

Apatinib — an oral TKI that has multiple targets such as VEGFR2, PDGFRβ, c-kit, and SRC — exhibits potent antitumor angiogenesis effects and has been approved for gastric cancer treatment [51]. A recent phase II clinical study showed that patients with RAIRD exhibited an 80% ORR and 95% disease control rate (DCR) to apatinib treatment. In addition, the overall median PFS and overall survival (OS) of RAIRD patients were 18.4 and 51.6 months, respectively. Patients with BRAF-V600E mutation have a longer PFS. Treatment-related adverse events were predominantly grade 1–2 and could be minimized by dose reduction [52]. In a recent Phase III clinical study, the median PFS in the apatinib group was 22.2 months, ORR was 54.3%, DCR was 95.7%, and the median OS was not reached, which was consistent with the Phase II clinical results. Apatinib has shown significant clinical benefit in patients with locally advanced or metastatic RR-DTC with a manageable safety profile [53]. Apatinib and lenvatinib have shown clinical efficacy in the first-line treatment of advanced RR-DTC in China. A cost-effectiveness analysis of the selection showed that the risk ratio of apatinib to lenvatinib and the cost of the targeted drug had a significant impact on the model. Sensitivity analysis showed that apatinib was more cost-effective in China [54]. Therefore, apatinib is a promising

**Table 1**
TKIs have been approved for TC treatment.

| Approved Drugs | Phase | Targets | Cancer | Number of patients | Response Rate | The median PFS | Reference | Common adverse events |
|---|---|---|---|---|---|---|---|---|
| Lenvatinib | III | VEGFR1-3, FGFR1-6, PDGFR, RET, c-kit | RR-DTC | 151 | 69.90% | 23.9 months | [45] | Hypertension and proteinuria |
| Sorafenib | III | VEGFR1-4, PDGFR, RET, c-kit, BRAF | RR-DTC | 417 | 12·2% | 10.8 months | [47] | Hand-foot skin reaction, diarrhea, alopecia, and rash or desquamation |
| Cabozantinib | III | VEGFR2, MET, FLT4, RET, c-kit | RR-DTC | 187 | 15% | Not reached | [50] | Palmar-plantar erythrodysaesthesia hypertension and fatigue |
| Vandetanib | III | EGFR, VEGFR2/3, RET | MTC | 331 | 45% | Not reached | [62] | Hypertension, Diarrhea |
| Cabozantinib | III | VEGFR2, MET, FLT4, RET, c-kit | MTC | 330 | 28% | 11.2 months | [63] | Diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue |
| Selpercatinib | I/II | RET | MTC | 162 | 69% | RET-Mutant MTC: 1-year progression-free survival was 92%; RET fusion-positive thyroid cancer: 1-year progression-free survival was 64% | [55] | Hypertension, increased alanine aminotransferase level, increased aspartate aminotransferase level, hyponatremia, and diarrhea |
| Pralsetinib | I/II (ARROW) | VEGFR2, RET | MTC | 142 | 71% (Participants had never been treated with MKIs); 60% (Participants had been treated with MKIs); 89% (RET fusion-positive TC) | ND | [64] | Hypertension, neutropenia , lymphopenia, and anemia |
| Anlotinib | IIB | VEGFR, PDGFR, FGFR, and c-kit | MTC | 91 | 48.40% | 20.7 months | [65] | Palmar-plantar erythrodysesthesia syndrome, proteinuria, and hypertriglyceridemia. |
| Dabrafenib and trametinib | II | Dabrafenib: BRAF V600E; Trametinib: MEK1, MEK2 | ATC | 16 | 69% | Not reached | [66] | Anemia, Fatigue, diarrhea, and hyperglycemia |

treatment option for RAIRD patients due to its therapeutic efficacy, cost-effectiveness, and tolerable safety profile.

Meanwhile, MKIs such as donafenib, pazopanib and sulfatinib has been evaluated in preclinical studies and clinical trials (https://clinicaltrials.gov/) and have exhibited promising results in RR-DTC therapy (Table 2). The ORR, median PFS, and common adverse events occurred in TC patients receiving TKIs are summarized in Table 2.

Somatic BRAF-V600E mutations involved in tumor aggressiveness occur in approximately 37–50% of patients with PTC, predominantly with classic or high cellularity [24,55]. For RR-DTC, ongoing studies using the BRAF enzyme inhibitor are generally conducted through two regiments: (I) a long-term treatment with an anti-tumor objective; (II) recovery of radioactive iodine uptake through a short-term redifferentiation regimen in conjunction with the RAI therapy.

Vemurafenib is a BRAF enzyme inhibitor approved for the treatment of melanoma with BRAF mutation [59]. In the phase II clinical study, the ORR of vemurafenib was 38.5% and 27% for the VEGFR inhibitor-naïve individual group and those with a history of VEGFR inhibitor treatment group, respectively, whereas their median PFS was 18.3 and 12.0, respectively. However, the main disadvantage of vemurafenib is that it can trigger squamous cell carcinoma or lead to an anaplastic transformation of DTC [56]. A Phase II clinical study in patients with BRAF-mutated RAI refractory progressive DTC showed that with long-acting therapy, ORR was not significantly better in the dalafenib + trametinib group (48%) than in the dabrafenib group (42%) [57].

In a study of vemurafenib redifferentiation in RR-DTC patients with a BRAF-V600e mutation, 4 of 10 patients with an evaluable BRAF mutation had a thyrotropin-stimulated iodine-124 response to vemurafenib and treatment with $^{131}I$, resulting in tumor regression after 6 months. Further analysis showed that vemurafenib's inhibition of the MAPK pathway was associated with increased thyroid gene expression and RAI uptake [58]. In a recent pilot clinical trial, a combination of vemurafenib and anti-ErbB3 monoclonal antibody (mAb) CDX-3379 improved RAI safety and efficacy [59]. In addition, selective BRAF inhibitor dabrafenib stimulated iodine uptake in 60% of patients with unresectable or metastatic RR-DTC and BRAF-V600E mutation [60]. These findings indicate that BRAF-V600E inhibitors can potentially improve the treatment outcomes of RR-DTC patients with BRAF-V600E mutations.

In addition to somatic BRAF-V600E mutations, RET fusion, TRK fusion, and ALK fusion occur in some rare patients with advanced DTC. Specific inhibitors are a beneficial strategy for these patients. For example, a clinical phase I/II study found that treatment of TRK fusion-positive advanced disease requiring systemic therapy with larotrectinib, a highly selective inhibitor of TRK, resulted in an ORR of up to 86% in PTC/FTC patients, demonstrating rapid and durable disease control and a good safety profile [61]. Selecting specific inhibitors that target genetic changes in patients seems promising.

Generally, MKI inhibitors showed certain efficacy on RR-DTC, especially lenvatinib and apatinib. BRAF-V600E inhibitors also improve the ORR of BRAF V600E mutant RR-DTC. However, they cannot solve all the problems faced by RR-DTC, such as serious side effects. An increase in the donafenib dosage does not increase the therapeutic effect, or even reduce PFS, which may also be attributable to adverse events. The balance between adverse events and therapeutic efficacy is also one of the common difficulties of MKIs. In addition, most of the participants included in the study were few, with the lowest being

**Table 2**
Results of clinical trials of targeted kinase inhibitors starting within the study period 2012 to 2022 (Source: https://clinicaltrials.gov/).

| Drug | Phase | Targets | Cancer | Number of patients | Response Rate | The median Progression free survival | Reference | Common adverse events |
|---|---|---|---|---|---|---|---|---|
| Lenvatinib | II | VEGFR1-3, FGFR1-4, PDGFR, RET, c-kit | RR-DTC, MTC, ATC | 51 | RR-DTC: 68%; MTC: 22%; ATC: 24%. | RR-DTC: 25.8 months; MTC: 9.2 months; ATC: 7.4 months | [78] | Hypertension, decreased appetite, palmar-plantar erythrodysesthesia, fatigue and proteinuria |
| Dovitinib | II | FGFRs, VEGFR, c-kit, and FMS-like tyrosine kinase 3 (FLT3) | PTC, MTC and FTC | 40 | 20.50% | 5.4 months | [83] | Diarrhea, anorexia, vomiting, fatigue and nausea |
| Sulfatinib | II | VEGFR1, 2, and 3, FGFR 1, and CSF-1R | RR-DTC and MTC | 59 | 23.2% | 11.1 months (DTC1 and MTC cohorts), DTC2 cohort: not reached | [84] | Hypertension, proteinuria, and elevated blood pressure, hypertriglyceridemia and pulmonary inflammation |
| Apatinib | II | VEGFR 2, PDGFRβ, c-kit, SRC | RR-DTC | 20 | 80% | 18.4 months and BRAFV600E mutation not reached | [52] | Palmar-plantar erythrodysesthesia syndrome, proteinuria, and hypertension (16/20) |
| Donafenib | II | VEGFR, PDGFR | RR-DTC | 48 | 12.5% (200 mg) 13.33% (300 mg) | 14.98 months (200 mg) 9.44 months (300 mg) | [85] | Palmar-plantar erythrodysesthesia and hypertension |
| Pazopanib | II | VEGFR-1, −2 and − 3, PDGFR-α, and -β, c-kit, FGFR-1 | RR-DTC | 168 | 35.6% | intermittent pazopanib:5.7 continuous pazopanib: 9.2 months | [86] | Gastrointestinal disorders, increased ALT, AST and vascular disorders including hypertension |
| Cabozantinib | II | VEGFR2, MET, FLT3, RET, c-kit | MTC | 25 | 20% | 12.7 months | [87] | Fatigue, weight loss, diarrhea, palmar-plantar erythrodysesthesia, and hypertension |
| Dabrafenib | ND | BRAF | BRAFV600E-mutant RR-DTC | 10 | 60% (developed new radioiodine uptake) | ND | [88] | Squamous cell carcinoma of the skin,lymphopenia, increased γ-glutamyltransferase |
| Vemurafenib | II | BRAF | BRAFV600E-mutant RR-DTC | 51 | 38·5% (Participants had never been treated with a VEGFR inhibitor); 27·3% (Participants had been treated with a VEGFR inhibitor) | 18·8 months (Participants had never been treated with a VEGFR inhibitor); 12·0 months (Participants had been treated with a VEGFR inhibitor) | [56] | Rash, fatigue, weight loss, taste alteration, and alopecia |
| Dabrafenib and trametinib | II | Dabrafenib: BRAF V600E; Trametinib: MEK1, MEK2 | BRAF V600E-mutant RR-DTC | 53 | Dabrafenib group: 42% Dabrafenib + trametinib group: 48% | Not reached | [57] | Fever, nausea, chills and fatigue |
| Vemurafenib + CDX-3379 | I | Vemurafenib: BRAF; CDX-3379: ErbB3 | BRAFV600E-Mutant DTC | 7 | 83.30% | ND | [59] | Maculopapular rash, nausea and diarrhea |
| Lenvatinib | II | VEGFR1-3, FGFR1-5, PDGFR, RET, c-kit | ATC | 17 | 24% | 7.4 months | [79] | Decreased appetite, hypertension, fatigue, nausea, and proteinuria |
| Sorafenib | II | VEGFR1-3, PDGFR, RET, c-kit, BRAF | ATC | 20 | 10% | 1.9 months | [82] | gastrointestinal perforation |
| Anlotinib | IIB | VEGFR, PDGFR, FGFR, and c-kit | MTC | 91 | 48.40% | 20.7 months | [65] | Palmar-plantar erythrodysesthesia syndrome (62.9%), proteinuria (61.3%), and hypertriglyceridemia (48.4%). |

only 7, which also reduced the persuasiveness of some clinical results. MKIs are still a potential auxiliary drug tool for RR-DTC. Dose management and combined drug use can be used to reduce adverse events.

### 3.2. MKIs and MTC

MTC originates from neural crista-derived parafolicular c cells and accounts for about 3–5% of all thyroid cancers, either hereditary (25%) or sporadic (75%) [67,68]. MTCs are a class of highly vascularized tumors which overexpress VEGFA and VEGFRs [69]. Due to its limited level of differentiation, it is more severe compared with both papillary carcinoma and follicular carcinoma. With current interventions such as surgical excision and ionizing radiation, the 10-year survival rate for patients with MTC is >70%, with 30% of cases resistant to existing treatments [30,67].

RET mutation is present in almost all hereditary MTC and many sporadic patients, and the mutations occur in 70% of MTC [55,70]. Therefore, MKIs targeting VEGFR and RET, such as vandetanib and cabozantinib, approved by the FDA, are the classical medicines for MTC treatment [62,63]. Cabozantinib phase III clinical trials, the ORR and

median PFS of MTC patients were 28% and 12.3 months, respectively [63]. In vandetanib phase III trial, the ORR of vandetanib was 45%, and the drug significantly prolonged the PFS of MTC patients (30.5 months) compared to the placebo (19.3 months) [62]. To evaluate the efficacy and safety of vandetanib in patients with progressive and symptomatic MTC, a post hoc analysis of the Phase III clinical trial of vandetanib involving patients with advanced MTC, vandetanib treatment increased PFS and ORR was 37% in the treatment group [71]. However, these two multi-kinase inhibitors often induce unintended side effects, which restrict their utility for patients with RET-related malignancies, such as RET-mutated MTC. showed frequently off-target side effects, which limit their application in patients with RET-driven cancers, including RET-mutated MTC [62,63]. Economic analysis showed that the ICER of cabozantinib and vandetanib was £138,000 per added QALY in symptomatic and progressive MTC. For patients doubling times of CEA/CTN $\leq$ 24 months, vandetanib's ICER is expected to receive $>$ £66,000 per QALY [72].

Selpercatinib, a RET-specific inhibitor, has a stronger inhibitory effect on the common RET activating mutations M918T and KIF5B-RET (−/+V804L/M) than cabozantinib and vandetanib in vitro. The inhibition efficiency of selpercatinib against KIF5B-RET(−/+V804L/M) was 60 to 1300 times that of cabozantinib and vandetanib [73]. And selpercatinib has demonstrated significant efficacy in phase I/II clinical trials in RET-mutant medullary TC. The response rate for patients with RET-mutant medullary TC previously treated with van dertanib and/or carbozanib is 69%, while that of treatment-naïve patients is 73%. The response rate in TC patients with RET fusion and previously treated with vandetanib or cabozantinib is 79%. The 1-year progression-free survival rate of the three groups of patients is significantly longer, and only about 2% of the patients were discontinued from treatment due to selpercatinib -related adverse reactions. The high activity and controllable toxicity imply that selpercatinib has the potential to become the first-line regimen for the treatment of RET-positive patients [55]. In May 2020, the FDA approved selpercatinib for the treatment of thyroid cancer patients with RET alteration [74]. In December 2020, the EMA approved the drug for use in patients with advanced MTC aged $\geq$12 years, but only after prior treatment with cabozantinib or vandetanib, or both [75].

Pralsetinib, another strong RET inhibitor, was 8 to 28 times more effective against wild-type RET kinase domains than cabozantinib and vandetanib [76]. In the ARROW study (NCT03037385), the ORR of pralsetinib in naive RET-mutant MTC patients, patients previously treated with cabozantinib or vandetanib, or both, RET fusion positive TC patients were 71%, 60%, and 89%, respectively. The most frequent severe (grade 3 or higher) adverse events caused by this treatment are hypertension, neutropenia, lymphocytopenia, and anemia. Serious treatment-related adverse events occurred in 15% of patients, and 4% discontinued treatment due to treatment-related events. In December 2020, the FDA approved pralsetinib for use in patients $\geq$12 years of age with advanced or metastatic RET mutant MTC and in patients with advanced or metastatic RET fusion positive RR-DTC [64].

In addition, anlotinib, which selectively targets VEGFR, PDGFR, FGFR, and c-kit signaling, achieved a response rate of 48.8% in MTC, and this drug has been approved by the China National Medical Products Administration in 2018 [65]. In terms of effectiveness, the median PFS in the amlotinib group was 20.7 months, nearly double that in the placebo group, which was comparable to cabozantinib [63,65]. Unlike vandetanib and cabozantinib, whose efficacy is affected by RET changes, amlotinib mainly targets tumor angiogenesis and c-kit, and its survival benefit may be independent of RET M918T mutations. From a safety perspective, the application of vandetanib to treat patients with cardiac conduction disorders, and the high incidence of bleeding after treatment of cabozantinib limits its use in patients at higher risk of bleeding and fistula formation. The incidence of these two serious adverse events was lower in the amlotinib treatment group, which indicated that amlotinib was effective for more patients [62,63,65].

The current clinical results show that the RET specific inhibitors have high ORR. Currently approved RET specific inhibitors, including selpercatinib and pralsetinib, must be performed after prior treatment with cabozantinib or vandetanib or both, and the efficacy is satisfactory. However, the clinical outcome of cabozantinib or vandetanib following selpercatinib or pralsetinib is unknown. Therefore, RET-specific inhibitors are not yet available as first-line agents for MTC treatment [77]. In the future, it is worth comparing the efficacy of selpercatinib, pralsetinib or anlotinib alone, or two combinations, or in combination with vandetanib or cabozantinib, for treating MTC.

### 3.3. MKIs and ATC

RAF/MAPK signaling is one of the major contributors to ATC progression, and the application of multi-kinase inhibitors, such as lenvatinib, has shown promising therapeutic effects [26]. A phase II clinical study demonstrated that lenvatinib had 68%, 22%, and 24% ORRs for RR-DTC, MTC, and ATC, respectively [78]. In ATC patients, lenvatinib exhibited a median PFS and OS of 7.4 and 10.6 months in a phase II clinical trial in Japanese, with patients displaying manageable toxicities [79]. Paradoxically, an open-label, multicenter, international Phase II study of lenvatinib treatment in ATC patients with $\geq$1 measurable target lesion was discontinued due to ineffectiveness, however, the interim analysis did not reach the minimum score ORR threshold [80]. One reason why the results were inconsistent could be that the earlier Japanese study had an inadequate sample size (only 17 cases). A recent Phase II study in Japan with an expanded sample number (42 patients) further explored the efficacy and safety of lenvatinib in ATC, with an overall 1-year survival rate of 11.9%, including 9 patients (21.4%) with persistent and stable disease, an objective response rate of 11.9%, and a disease control rate of 73.8% [81]. These results further indicate that lenvatinib is less than satisfactory in patients with unresectable ATC. The response rate is not ideal, but the response is durable, suggesting that lenvatinib is only effective in a select group of patients, for reasons that need further investigation and verification. Furthermore, the activity of sorafenib on ATC is limited, and the ORR (10%) and median PFS (1.9 months) are very low [82]. However, dabrafenib combined with trametinib is the first regimen shown to have high clinical activity (69% ORR) and manageable toxicity in $BRAF^{V600E}$-mutated anaplastic TC. The FDA approved a dabrafenib and trametinib combination for treating patients with $BRAF^{V600E}$ mutation-positive, locally advanced, or metastatic ATC with no access to standard local treatment options [66]. In contrast to the low response rates of lenvatinib and sorafenib, the combination of specific driver mutation inhibitors (dabrafenib + trametinib) showed high response rates in BRAF-mutated ATC. For ATC patients with specific mutations, inhibitors of these mutated genes may be considered as first-line agents. These data demonstrated the effective activity of the combination of MKI inhibitors and some specific driving mutation inhibitors on ATC and also inspired exploration of the combination of MKI inhibitors or the combination of MKI inhibitors and other targeted drugs for the treatment of ATC.

In addition to these completed MKIs with clinical results, a new set of kinase inhibitors or a combination of drugs are also under clinical trial (Table 3). The main categories for kinase inhibitors include single kinase drugs, a combination of two kinase inhibitors, and a combination of kinase inhibitors with monoclonal antibody drugs. A combination of dabrafenib and trametinib is highly efficacious against ATC with $BRAF^{V600E}$ mutation, and a number of clinical studies on this combination in the treatment of refractory ATC have been carried out (Table 3). Based on the present clinical research, even though various MKIs exhibit varying response rates and objective remission rates for diverse forms of TC, they have an overall therapeutic benefit. Adverse events are unavoidable, but in most cases the side effects are manageable according to standard clinical practice alone or in combination with dose reductions.

**Table 3**
Ongoing clinical trials of targeted inhibitors in TC (as on July 16, 2022), listed from (Source: https://clinicaltrials.gov/).

| Recruiting | Phase | Target | ClinicalTrials.gov Identifier: | Cancers |
|---|---|---|---|---|
| Regorafenib | II | VEGFR1-3, TIE2, PDGFR-β, FGFR and oncogenic receptor tyrosine kinases (c-kit, RET, and RAF) | NCT02657551 | Metastatic MTC |
| Selpercatinib | III | RET | NCT04211337<br>NCT03157128<br>NCT03899792 | RET-Mutant MTC |
| Dabrafenib and trametinib | II | Dabrafenib: BRAF;<br>Trametinib: MEK1, MEK2 | NCT03753919<br>NCT04554680 | Refractory Advanced TC |
| Cemiplimab combined with Dabrafenib and Trametinib | II | Dabrafenib: BRAF;<br>Trametinib: MEK1, MEK2;<br>Cemiplimab: PD-1 | NCT04238624 | BRAF-Mutant ATC |
| Dabrafenib and Trametinib | III | Dabrafenib: BRAF;<br>Trametinib: MEK1, MEK2 | NCT04940052 | Locally advanced or metastatic BRAFV600E mutation-positive DTC |
| Imatinib | I | PDGFRα | NCT03469011 | Advanced TC |
| Trametinib | II | MEK1, MEK2 | NCT04619316 | Metastatic TC |
| Lenvatinib | II | VEGFR1-3, FGFR1-4, PDGFR, RET, c-kit | NCT04321954 | Locally Advanced Invasive TC |
| Camrelizumab + Apatinib | II | Camrelizumab: PD-1;<br>Apatinib: VEGFR2, PDGFRβ, c-kit, SRC | NCT04560127 | RR-DTC |
| Anlotinib hydrochloride | II | VEGFR, PDGFR, FGFR, and c-kit | NCT05007093 | DTC |
| Lenvatinib + Denosumab | II | Lenvatinib: VEGFR1-3, FGFR1-4, PDGFR, RET, c-kit<br>Denosumab: receptor activator of NF-kB ligand | NCT03732495 | Predominant Bone Metastatic RR-DTC |
| Vemurafenib + Copanlisib | I | Vemurafenib: BRAFV600E<br>Copanlisib: PI3K | NCT04462471 | RR-DTC |
| HA121-28 Tablets | II | EGFR/RET | NCT04787328 | MTC |
| Spartalizumab combined with either trametinib or dabrafenib | II | Spartalizumab: PD-1;<br>Dabrafenib: BRAF;<br>Trametinib: MEK1, MEK2 | NCT04544111 | RR-DTC |
| Encorafenib and Binimetinib with or without Nivolumab | II | Encorafenib: BRAF;<br>Binimetinib: MEK1 and MEK2;<br>Nivolumab: PD-1 | NCT04061980 | Metastatic Radioiodine Refractory BRAFV600E Mutant TC |
| Dabrafenib and Trametinib | II | Dabrafenib: BRAFV600E;<br>Trametinib: MEK1, MEK2 | NCT04739566 | BRAF-positive ATC |
| Pembrolizumab + (Dabrafenib and Trametinib) | II | Dabrafenib: BRAFV600E;<br>Trametinib: MEK1, MEK2<br>Pembrolizumab: PD-1 | NCT04675710 | BRAF-Mutated ATC |
| TPX-0046 | I/II | RET | NCT04161391 | MTC Harboring RET Fusions or Mutations |
| Cabozantinib + Atezolizumab | II | Cabozantinib: VEGFR2, MET, FLT4, RET, c-kit;<br>Atezolizumab: PD-L1 | NCT04400474 | ATC |
| Nivolumab + Ipilimumab | II | Nivolumab: PD-1;<br>Ipilimumab: CTLA-4 | NCT03246958 | TC |
| Atezolizumab With Chemotherapy | II | Atezolizumab: PD-L1 | NCT03181100 | ATC or Poorly Differentiated TC |

### *3.4. Resistance mechanisms of targeted MKIs therapy*

Resistance mechanisms are usually identified in preclinical and clinical studies and later overcome with the discovery of new drugs [89]. Understanding the resistance mechanism of targeted therapy is meaningful for optimizing further treatment strategies. Acquired resistance to MKI inhibitors occurs through two common mechanisms: (I) Target modification (RET-dependent resistance mechanism); (II) Bypass signaling.

(I) *Targeted modification.* RET V804M/L mutations occur primarily in hereditary and sporadic medullary thyroid carcinoma, where they cause intrinsic resistance to several MKIs (such as vandetanib and cabozantinib) by increasing adenosine triphosphate affinity and steric hindrance [90]. Whereas selpercatinib and pralsetinib are highly selective for RET, bind differently to RET and MKIs, and have shown clinical activity in patients with medullary thyroid carcinoma containing RET V804M "gatekeeper" mutations in clinical trials [73]. Therefore, selpercatinib can be used as an alternative treatment strategy for MTC treatment with RET V804M mutation. In the presence of the non-caretaker solvent frontier mutation RETG810S/R/C, glycine is substituted with cysteine, serine, or arginine, and patients develop resistance to the selective RET inhibitors selpercatinib and pralsetinib. In addition, hinge area Y806C/N and β2 chain V738A mutations were also resistant to these two selective RET inhibitors [91].

(II) *Activation of Bypass signaling.* The variability of the treatment response is not influenced by pre-treatment genomics, but manifests as alternative pathways of carcinogenesis or up-regulation of various downstream pathways to develop drug-escaping receptor inhibition. For example, Rosen et al.'s study showed that the key mechanism of primary and acquired Selpercatinib resistance is focused on MAPK pathway activation. To extend the far-reaching clinical benefit of selpercatinib therapy, it may be necessary to combine it with MAPK inhibitors [92]. RAS bypass mutations associated with MTC patients produce resistance to vandetanib or cabozantinib [93]. In patients with MET amplification, selpercatinib resistance was overcome and phosphorylated Ret and phosphorylated MET levels were reduced by the combination of selpercatinib and MET/ALK/ROS1 inhibitor crizotinib alone [94].

Furthermore, the impact of molecular targeted therapy is also influenced by the tumor microenvironment and immune cell infiltration, which includes cancer-associated fibroblasts (CAFs) and macrophages that are present within the tumor. Production of chemokines and lack of oxygen in tumor microenvironment, such as micro environmental factors of innate and adaptive immune cells create an immunosuppression microenvironment, is also one of the key factors of drug resistance [95]. Therefore, multiple clinical studies of MKIs in combination with immune checkpoint inhibitors are under way as a potential strategy for addressing drug resistance and enhancing therapeutic efficacy.

## 4. Immune checkpoint inhibitors in TC

Immune checkpoint inhibitors regulate T cell-mediated antitumor immunity by targeting inhibiting cytotoxic T lymphocyte antigen 4 (CTLA-4) or programmed cell death-1 (PD-1) and its ligand PD-L1 [96]. Fig. 3 shows two T cell activation or exhaustion signaling pathways mediated by immune checkpoint inhibitors. CTLA-4 is homologous to the T cell costimulatory protein CD28 and competes with CD28 for CD80 and CD86 binding sites on antigen-presenting cells. However, CTLA-4 has a greater binding affinity to CD80 and CD86 than CD28, delivering inhibitory signals to T cells, which increase tumor cell proliferation. CTLA-4 monoclonal antibodies, such as ipilimumab and tremelimumab, releases the "brake" on T cell activation and allow CD28 to engage smoothly [96]. Furthermore, when PD-1 on the T cell surface binds to the corresponding ligand PD-L1 on the tumor cell surface, it mediates the suppression of T cell activation and activates the T cell exhaustion pathway. A "PD1-PDL1" interaction blockade is critical for relieving T cell immunosuppression and restoring T cell activity [96,97].

ATC and DTC present PD1/PD-L1 signaling, but PD-L1 expression in MTC tumor cells are extremely low [98]. In a clinical phase Ib study of PD-1 antibody pembrolizumab in patients with PTC or FTC, the ORR and median PFS were only 9% and 7 months [99]. The inadequate objective response rate (ORR) could be attributed to the insufficient expression of PD-L1 in the tumors. Based on preclinical investigations, BRAF-mutated thyroid tumor cells showed a substantial increase in PD-L1 expression compared to thyroid tumor cells with wild-type BRAF. The corresponding ATC animal model showed that combining BRAF inhibitor and PD-1 (mAb) inhibited tumor growth [100]. Additionally, preclinical studies revealed that combining MKI lenvatinib and PD-1 mAb increased $CD8^+$ T-cells and decreased the proportion of polymorphonuclear myeloid-derived suppressor cells compared with lenvatinib monotherapy, effectively improving the antitumor effect of Lenvatinib [101]. Clinically, combining pembrolizumab with MKIs (dabrafenib + trametinib, lenvatinib, or trametinib alone) treatment was beneficial to a subset of ATC patients [102]. For example, in patients with metastatic ATC and two patients with PDTC, lenvatinib and pembrolizumab combined therapy yielded optimal overall response of 66% complete response. The median progression-free survival of ATCs was 16.5 months. These results preliminarily suggest that the combination of lenvatinib and pembrolizumab may be safe and effective in patients with ATC/PDTC, and more systematic phase II trials should be performed to verify this [103]. Li et al. reported a case of RR-DTC in which a patient who had developed resistance to donafenil benefited from combination apatinib and camrelizumab therapy and gradually reduced the focus after treatment, suggesting that combination immunotherapy also has promise as a treatment option for some resistant patients [104]. Further clinical studies are advocated to determine whether the antitumor activity of PD-1/PD-L1 mAbs in vivo is positively correlated with the expression of PD-L1 in thyroid tumors.

Moreover, several clinical trials combining MKIs with PD-1/PD-L1 mAb, including combining cemiplimab with dabrafenib and trametinib (NCT04238624), pembrolizumab with dabrafenib and trametinib (NCT04675710), camrelizumab with apatinib (NCT04560127), spartalizumab with either trametinib or dabrafenib (NCT04544111), encorafenib and binimetinib with nivolumab (NCT04061980), and cabozantinib with atezolizumab (NCT04400474) in patients with TC are currently ongoing. Trials for PD-1 mAb in combination with CTLA-4 antibody (ipilimumab) or as an adjuvant of chemotherapy/radiotherapy are also underway (Table 3). In clinical practice, combining two or more drugs seems to be an attractive option, and strategies to reduce adverse events through drug dose control or drug intervention should be developed. Importantly, the expression of PD-1 or PD-L1 in tumors may be one of the main factors affecting drug efficacy, and they may have individual differences in expression in different patients. It is meaningful to determine personalized detection and drug regimen. In other words, whether these immune checkpoint inhibitors are suitable for treating TC, the suitable thyroid therapy and the most appropriate treatment plan needs further investigation.

Tumor mutation load (TMB) was low in both DTC and MTC, which was associated with a low response rate to immunotherapy. However, aggressive DTCs usually exhibit a higher density of infiltrating T cells and hence have higher PD-L1 expression (especially in the BRAFV600E mutant DTCs). Studies have high an anti-tumor $CD8^+$ T cell response in advanced DTC patients, and immunotherapy may enhance anti-tumor efficacy [98]. Similarly, T cell infiltration is increased in some advanced MTC tumors. This demonstrates that immunotherapy can be an effective interventions for advanced MTC and DTC, but further research is needed [95]. Unlike DTC and MTC, the cancer genome of ATC exhibits the consequences of genomic instability, characterized by a significantly higher mutation burden [95]. ATC tumors showed infiltration of $CD8^+$ T cells and Treg cells. In the ATC mouse model, BRAFV600E inhibitor promoted the increase of immune cells and the up-regulation of PD-L1 in the tumor, and BRAFV600E inhibitor combined with anti-PD-L1 treatment significantly inhibited tumor growth compared with single drug [98]. In the future, BRAF inhibitors and immunotherapy may be encouraged to enhance anti-tumor effects in combination therapy with BRAFV600E mutant ATC or DTC, and further studies are needed to support validation.

## 5. Prospect

In recent years, the development of targeted drugs based on MKIs and immune checkpoint inhibitors has been of great interest for researchers. The suboptimal efficacy and serious adverse events of some

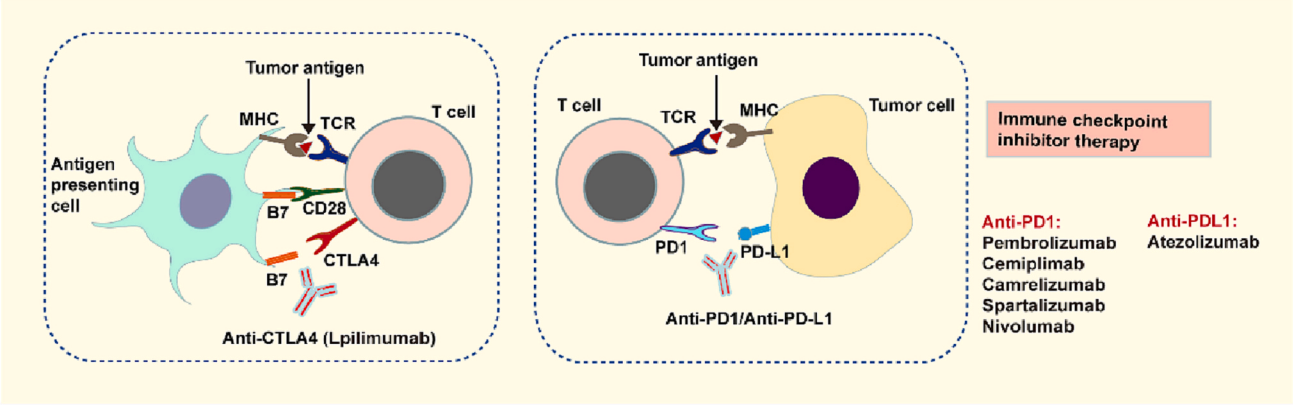


**Fig. 3.** Immune checkpoint inhibition for treating TC. Immune checkpoint inhibition kills TC tumor cells by blocking CLTA-4 (lpilimumab), PD-1 (pembrolizumab, cemiplimab, camrelizumab, spartailzumab or nivolumab), or PD-L1 (atezolizumab) pathways to mediate T cells activation and anti-exhaustion.

MKIs and checkpoint inhibitors have limited their clinical application. Therefore, developing novel targets, such as ncRNAs, and novel targeting drugs remains crucial to TC management. Currently, research on these ncRNAs in TC is still in the preclinical stage, and the development of mature ncRNAs targeting drugs and clinical trials need to be expedited.

Moreover, there has been interdisciplinary research focused on the diagnosis and management of TC, with nanoscience being a particularly beneficial aspect for individuals with resistant forms of TC. For example, Liu et al. constructed a nano-delivery system to deliver siRNA that inhibits the expression of BRAF, which significantly inhibited tumor growth and metastasis in an orthotopic ATC mouse model [105]. Rajendran et al. restored the iodine sensitivity of radioactive iodine-refractory TC cells using extracellular vesicle (EV) delivery of TKIs. Based on these studies, it is also necessary to elucidate whether the application of mature nano-platforms, targeted delivery of MKIs, ncRNAs or mRNAs for precise release at tumor sites can help reduce adverse events and improve drug efficacy.

## Ethics approval and consent to participate

Not applicable.

## Availability of data and materials

Not applicable; all information in this review can be found in the reference list.

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## Authors' contributions

#L.Z. and Q.F. contributed equally to this work. L.Z. and Q.F. contributed to the conception of the study and wrote the initial draft. M. G. reviewed the manuscript and provided suggestions for revision. Z.T. and Q.L. helped perform the analysis with constructive discussions. All authors read and approved the final manuscript.

## Declaration of Competing Interest

The authors declare that they have no competing interests.

## Data availability

No data was used for the research described in the article.

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