Review

Novel Inhibitor-Based Therapies for Thyroid Cancer—An Update

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Abstract: Thyroid cancers (TCs) are the most common tumors of the endocrine system and a constant rise in the number of TC cases has been observed for the past few decades. TCs are one of the most frequent tumors in younger adults, especially in women, therefore early diagnosis and effective therapy are especially important. Ultrasonography examination followed by fine needle biopsy have become the gold standard for diagnosis of TCs, as these strategies allow for early-stage detection and aid accurate qualification for further procedures, including surgical treatment. Despite all the advancements in detection and treatment of TCs, constant mortality levels are still observed. Therefore, a novel generation line of targeted treatment strategies is being developed, including personalized therapies with kinase inhibitors. Recent molecular studies on TCs demonstrate that kinase inhibitor-based therapies might be considered as the most promising. In the past decade, new kinase inhibitors with different mechanisms of action have been reported and approved for clinical trials. This review presents an up-to-date picture of new approaches and challenges of inhibitor-based therapies in treatment of TCs, focusing on the latest findings reported over the past two years.

Keywords: thyroid cancer; targeted therapies; kinase inhibitors; RAI-refractory

1. Introduction
1.1. Thyroid Cancer: Origins and Classification

The thyroid gland consists of two types of cells: thyocytes (epithelial, follicular cells) and C cells (parafollicular cells). Thyrocytes form thyroid follicles, which are the structural and functional units of the mature thyroid gland. Thyroid hormones (THs), which are involved in regulation of metabolism, are synthetized and stored in the follicular lumen. Production and secretion of THs is controlled by the thyroid-stimulating hormone (TSH) [1]. C cells are located adjacent to thyroid follicles and are responsible for production of various biologically-active substances, such as calcitonin, carcinoembryonic antigen, prostaglandins and serotonin [2].

Classification of thyroid cancer is based on the histological type of thyroid cells. Differentiated thyroid cancer (DTC) and de-differentiated thyroid cancer (DeTC) arise from follicular cells. DTC is subclassified into papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and Hürthle cell carcinoma (HCC) [3]. HCC, which was previously recognized as FTC, is now classified as a subtype of DTC [3,4]. The rarest, but most aggressive forms of TC, anaplastic thyroid carcinoma (ATC) and poorly differentiated thyroid carcinoma (PDTC) are classified as DeTCs. PDTCs are a subset of thyroid tumors intermediate between DTCs and ATCs. Medullary thyroid cancer (MTC) is classified as the forth main type of TC and in contrast to DTC and DeTC, is a neuroendocrine tumor originating from parafollicular C cells. The Cancer Genome Atlas (TCGA) Research
Network [5] data and other subsequent studies [6–8] underlined the need for reclassification of thyroid cancers into molecular- and genotype-based subtypes that would predict their prognosis and be helpful in administration of treatment strategies. Therefore, molecular and genetic aberrations were additionally considered and implemented to the World Health Organization (WHO) Classification of Tumours of Endocrine Organs that was published in 2017 [3].

1.2. Thyroid Cancer Epidemiology

Thyroid cancers (TCs) account for ~3% of all malignancies worldwide. Among cancers of the endocrine system, TCs are the most common (approximately 95% of all cases). For the past several decades, a substantial increase in cancer morbidity has been observed and the same tendency has been found for TCs. According to GLOBOCAN 2020, the WHO cancer statistics for 185 countries worldwide, 586,202 new TC cases were reported with mortality of all cancer types reaching 0.4% [9]. This ranks TCs in the 11th place for all cancer incidences. Until 2020, the morbidity of TCs was the most rapidly increasing among all cancers in the United States. In 2021, in the USA alone, the number of TCs was estimated to be about 44,280 cases and ~2200 patients were expected to die [10].

DTCs account for more than 90% of all TC cases, where ~84% of incidences are PTCs, while diagnoses of FTCs and HCCs stand for approximately 2% each. ATC also represents ~2% of thyroid malignancies, and as the most aggressive thyroid tumor, is responsible for 50% of annual thyroid cancer deaths. ATC generally affects 60–70 year-old patients. PDTC is a relatively rare disease, accounting for slightly more than 2% of all new cases of TCs each year. MTC accounts for about 4–5% of thyroid cancers. Most MTCs (70–80%) are observed in 50 to 60 year-old patients and result from sporadic mutations. Over 50 different point mutations have been linked with development of MTC [11]. A hereditary pattern of MTC is present in 20–30% of cases, transmitted as an autosomal dominant trait, while a mutation in the RET gene at codon 634 is responsible for development of familial MTC in 85% of patients. MTC is associated with multiple endocrine neoplasia (MEN) type IIA and IIB syndrome. Approximately 35% of patients with MTC have lymph node metastases at the time of diagnosis, while about 20% have distant metastases [3,12,13].

1.3. Thyroid Cancer: Risk Factors

Incidences of TC are most common among younger adults [14,15]. Women are three times more likely to develop TC than men [10,16]. This sex-dependent disparity is mostly observed for PTCs and FTCs [17]. The possible relationship between female hormonal and reproductive processes (menstrual cycle, pregnancy, menopause and hormone replacement therapy) has been studied, but no direct correlation with higher risk of developing thyroid cancer was established [18,19]. According to the American Thyroid Association (ATA), a high-risk factors for TC are: (i) history of TC in one or more first degree relatives, (ii) exposure to external beam radiation in the childhood, (iii) exposure to ionizing radiation in the childhood or adolescence, (iv) prior hemithyroidectomy with discovery of TC, (v) 18F-fluoro-2-deoxy-D-glucose (18FDG) avidity on positron emission tomography (PET) scanning in thyroid nodule, (vi) calcitonin blood level more than 100 pg/mL [20]. Moreover, there are several genetic syndromes predisposing to TC development, like multiple endocrine neoplasia type 2 (MEN2), familial adenomatous polyposis (FAP), Cowden disease, Carney complex and Werner syndrome/progeria [20,21]. Thyroid dysfunctions, especially hypothyroidism, are postulated as factors associated with increased incidence of TC [22,23]. The association between elevated body mass index (BMI) and aggressive clinicopathologic features of PTC has also been reported [24].

1.4. Role of Genetic Factors in Pathogenesis of TC

Progression of TC relies on both phenotypic diversity and genetic alterations. DNA sequencing studies of TC have revealed that most tumors harbor genetic aberrations affecting the mitogen-activated protein kinase (MAPK) or phosphatidylinositol 3-kinase
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Progression of TC relies on both phenotypic diversity and genetic alterations. DNA sequencing studies of TC have revealed that most tumors harbor genetic aberrations [27,29,30]. Further accumulation of epigenetic and genetic alterations, as well as infiltration of the thyroid gland by immune cells, seem to be the major triggers of ATC (Figure 1) [31].

Pathogenesis of TC can also be associated with mutations of receptor tyrosine kinases (RTKs) and other less commonly reported pathways, including Wnt/β-catenin, FOXO3 and NF-kB [25,26]. Genetic dysfunctions of components of these pathways, accompanied by epigenetic modifications, lead to progression of normal thyroid follicular cells to PTC or FTC [27]. The so-called “early” molecular driver alterations, BRAF V600E or RAS, are the most common [28]. Co-occurrence of other mutations and/or rearrangements with increased signaling of the MAPK and/or PI3K/AKT pathways likely promotes progression to PDTC [27,29,30]. Further accumulation of epigenetic and genetic alterations, as well as infiltration of the thyroid gland by immune cells, seem to be the major triggers of ATC (Figure 1) [31].

Figure 1. Schematic representation of TC progression showing critical genes and factors involved in de-differentiation. Modified from [29]. ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; PDCT, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma.

1.4.1. MAPK Pathway

The MAPK pathway connects extracellular signals to intracellular transduction cascades that play a central role in regulation of cell growth. The major processes governed by the MAPK signaling chain include: proliferation, migration, apoptosis, cytoskeletal integrity, survival and cellular differentiation. In TCs, particularly in PTC, MAPK stimuli play a crucial role, as MAPK-activating mutations in genes encoding for both B-Raf proto-oncogene (BRAF) kinase and RAS kinase, or RET/PTC rearrangements, are frequently observed [32,33].

Substitution of valine with glutamic acid in codon 600 (V600E) of the BRAF gene encoding the BRAF serine/threonine kinase results from a thymine-to-adenine point mutation at position 1799 (T1799A). Oncogenic BRAF is the most frequently mutated gene in TCs and presence of the V600E alteration is reported in up to 80% of PTC cases, as well as 20–30% of ATCs [34–36]. The BRAF V600E-mutated kinase acts as the constitutive trigger of signal transmission in the MAPK pathway, independent of its upstream target, RAS, ultimately leading to increased activation of ERK kinases (Figure 2). Hyeractivation
of signaling pathways, mediated by the BRAF V600E allele, causes impaired expression of sodium iodide symporter (NIS) and plays a key role in the radioiodine refractory (RAIR) phenomenon [37–39]. Some studies associate BRAF V600E with development of more aggressive and resistant forms of TCs [30,40]. The BRAF V600E allele is a useful prognostic marker determining tumor malignancy, especially in countries with a high prevalence of this genetic aberration [41,42].

**Figure 2.** Schematic representation of major molecular targets in kinase inhibition-based therapies for thyroid cancer. RTK, receptor tyrosine kinase.

### 1.4.2. PI3K/AKT Pathway

PI3K/AKT is another signaling pathway that plays major and diverse roles in regulation of cell growth, proliferation, apoptosis, metabolism, motility, angiogenesis and resistance to treatment. Genetic alterations affecting signal transduction in this pathway involve: (i) mutations in RAS isoform-encoding genes, (ii) mutations or amplifications in the alpha catalytic subunit of PIK3CA, (iii) mutations in the AKT gene and (iv) mutations in the phosphatase and tensin homolog phosphatase PTEN [28,43]. Genetic changes in RAS family genes are considered as “early” alterations and are characteristic for DTCs, especially for FTC. However, mutations of downstream effectors of the pathway are also commonly identified in less-differentiated TCs [30,44].

The RAS family of cell membrane-anchored GTPases (HRAS, NRAS and KRAS) activates downstream proteins (e.g., PI3K and BRAF kinases) when bound to guanosine triphosphate (GTP). Constitutively activated (mutated) GTP-bound RAS isoforms stimulate downstream effector pathways, even in the absence of extracellular stimuli (Figure 2) [45,46]. The utility of RAS mutations as a diagnostic tool is rather low [44]. RAS mutations occur, on average, in 30–40% of FTCs, 30–45% of the follicular variant of PTCs (FVPTCs), in approximately 25% of ATCs and PDTCs, in 15% of HCCs and in 10–45% of MTCs. Rare cases of mutations in the classical variant of PTC have also been reported [47–50].

PTEN is a tumor suppressor that decreases the cellular levels of phosphatidylinositol 3-phosphate (PIP3) to down-regulate the activity of the PI3K/AKT pathway. PTEN loss through gene deletion, mutations and epigenetic modifications results in dysregulation of the PI3K/AKT pathway, leading to uncontrolled cell proliferation, motility and protein synthesis. PTEN alterations have been described in FTC (14%), PDTC (4%), ATC (15%), PTC (2%) and HCC (5%) [4,5,50–52].

Activating (missense) mutations in PIK3CA or copy number gains lead to increased PIK3CA expression. Nevertheless, its role in carcinogenesis is still not well-defined. PIK3CA genetic alterations are common in de-differentiated TCs, like ATCs (18%), and less frequent in FTCs (1%) and PDTCs (2%) [53,54].
The AKT kinase family is comprised of three highly homologous isoforms: AKT1, AKT2 and AKT3. Activating mutations in genes encoding these protein kinases have been detected in FTCs, PDTCs and ATCs [53,55,56]. Murine TC model-based studies have shown that AKT1 is the primary promoter of TC development and local invasion, while vascular invasion and metastatic progression are dependent predominantly on AKT1 and AKT3, and to a lesser extent, on AKT2 [57,58].

1.4.3. Molecular Alterations in Receptor Tyrosine Kinases

RTKs are key regulators of cellular processes that are controlled by a variety of positive and negative feedback loops [59]. Various alterations may lead to their constant activation and triggering of signaling cascades, including MAPK and PI3K/AKT pathways, that might contribute to carcinogenesis [29,50]. The RTK family encompasses single-pass transmembrane proteins, such as RET, TRK, VEGFR and ALK. The most frequent and well-described genetic aberrations in RTK genes include rearrangements, duplications and point mutations in RET, ALK and NTRK [60].

RET is a transforming proto-oncogene. RET fusions or point mutations are potent oncogenic drivers in TCs. Up to a quarter of PTCs harbor RET fusions, where RET/PTC1 and RET/PTC3 rearrangements are most common. It has been reported that their prevalence is increased in patients previously exposed to high-dose radiation. RET fusions are also found in PDTCs and rarely in ATCs. In about 20–30% of all MTCs, germline mutations of the RET gene lead to hereditary MTC in the course of MEN2, whereas somatic RET mutations are mainly associated with sporadic MTC (approximately 50% of cases). The RET alteration determines distinct phenotypes of MTC that may differ in terms of age of disease onset and aggressiveness. For example, malignancies harboring the RET M918T somatic mutation that is the most frequent genetic change in sporadic MTCs, are related to a more aggressive MTC course and worse survival [61,62].

The anaplastic lymphoma kinase (ALK) is a transmembrane tyrosine kinase of the insulin receptor family that, upon ligand binding to its extracellular domain, promotes activation of multiple downstream signaling pathways, such as MAPK, PI3K/AKT and JAK/STAT. ALK gene activation, driven by mutations/rearrangements and gene fusions, is predominantly reported in PDTCs, ATCs and less frequently in PTCs and is linked with disease progression and aggressiveness [54,63–65].

Tropomyosin receptor kinases A, B and C (TRKA, TRKB and TRKC) are a group of receptor tyrosine kinases that play a crucial role in control and promotion of cell proliferation, survival and differentiation through the MAPK, PI3K/AKT and phospholipase C (PLC-γ) pathways. Activating DNA rearrangements that affect genes encoding TRKs (NTRK1, NTRK2 and NTRK3) as oncogenic drivers were reported in PTCs, PDTCs and ATCs [66–69]. Recently, determination of the NTRK activation status has gained great clinical utility since the emergence of targeted inhibitor therapy, as discussed below.

1.4.4. Other Molecular Alterations

PAX8-PPARγ, a nuclear transcription factor enhancing apoptosis, is the product of a gene fusion between paired box 8 (PAX8) and peroxisome proliferator activated receptor γ (PPARγ). It is suggested that the PAX8-PPARγ protein exerts a dominant negative effect on endogenous PPARγ and/or leads to the activation of subsets of PPARγ and PAX8 inducible genes. The fusion gene is detected in approximately 30% of FTCs and approximately 5% of FVPTCs, and rarely in PDTCs, HCCs and benign follicular adenoma [5,70–72].

TP53 is a suppressor gene controlling the cell cycle and apoptosis, and its mutations promote tumor development and progression. TP53 mutations are found in more than half of ATCs and in a small fraction of well-differentiated cancers [50,73,74].

The telomerase reverse transcriptase (TERT) gene encodes the catalytic subunit of telomerase, the enzyme responsible for adding tandem arrays of simple-sequence repeats to the ends of chromosomes and thereby preventing replicative senescence. Activating mutations in the promoter of TERT are believed to represent a “late” driver molecular event
in the development of well-differentiated TCs. These genetic alterations are associated with tumor aggressiveness and poor outcomes in TC patients. The frequency of TERT mutations is 40–70% in ATCs, 40% in PDTCs, 32% in aggressive forms of HCCs, 20% in FTCs and 10% in PTCs [51,75,76]. It has been observed that enhanced activity of mutant TERT, which acts as an oncoprotein, accelerates further progression of cancer cells and tumor development, especially when BRAF V600E is already present [77]. Moreover, co-occurrence of TERT and BRAF mutations leads to failure of MAPK-targeted therapies [78].

The EIF1AX gene encodes for an eukaryotic translation initiation factor 1A (eIF1A), which is responsible for assembly of the ribosomal pre-initiation complex, mRNA binding, scanning and ribosomal subunit joining. Mutations in EIF1AX have been detected in 11% of PDCBs, 9% of ATCs and 1–2% of PTCs [5,79]. It seems that different EIF1AX mutations correspond to distinct phenotypes in thyroid cancer and, when they co-occur with RAS in advanced TCs, are related to higher tumor aggressiveness [80,81].

Aberrant activation of the Wnt/β-catenin signaling pathway, commonly observed during PTC initiation and progression, contributes to therapeutic resistance in cancer cells via increased expression of resistance-related genes. Among these targets of the Wnt/β-catenin signaling pathway, proteins functioning as extrusion pumps are found, such as P-glycoprotein encoded by the ABCB1 gene [82,83]. Upregulation of the pathway confers resistance to vemurafenib, a MEK inhibitor [83]. Mutations of components of the Wnt/β-catenin signaling cascade, like β-catenin (CTNNB1), adenomatous polyposis coli (APC) or axis inhibition protein 1 (AXIN1), are common in less-differentiated TCs, i.e., in 60–65% of ATCs and 25% of PTCs [82,84].

Functionally, isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) play a key role within the Krebs cycle and produce α-ketoglutarate by catalyzing the oxidative decarboxylation of isocitrate. Mutations in IDH1-encoding genes are present in 16% of TCs, in particular in ATCs (11%) and FTCs (5%), whereas IDH2 mutations have been identified in only 3% of ATCs [85–87]. Unlike in other tumors, IDH1 and BRAF (or RAS) mutations in TCs are not mutually exclusive. Until now, no association between the IDH mutational status and clinical characteristics has been reported [86].

2. Current Diagnostic and Treatment Strategies

Diagnosis of TC is required when a patient presents symptoms, like palpable thyroid lesions, enlargement of the thyroid gland (especially in a short period of time), exposure to ionizing factors in childhood or a history of thyroid disease (adenoma, goiter or thyroiditis) [12,88].

In most TC incidents it is advised to perform surgical thyroidectomy and dissection of local metastases, if present, in the shortest possible time from diagnosis. After surgery, the extent of spread of cancer is assessed using the TNM Classification of Malignant Tumors. Recommendations of surgical intervention depend on the TC type and are discussed in the next subsection. Additionally, based on the TC type, various adjuvant therapies can be applied. For ATC and MTC, complementary chemotherapy and/or radiotherapy can be performed, as well as new targeted therapies, which strictly rely on the type of molecular alterations. In patients with DTC and PDTC, the recommended adjuvant therapy is radioactive iodine/radioiodine (RAI) treatment [12,13,88].

2.1. Diagnosis of TC: Ultrasonography (USG) and Fine-Needle Aspiration Biopsy (FNAB)

Palpation is the first line examination of the thyroid gland, while the best tool for the diagnosis of thyroid disorders is ultrasonography examination. The frequency of diagnosed nodules in palpation is 2–6%, while USG can detect thyroid nodules even in 19–68% of randomly selected individuals [89,90]. Thyroid nodules are found in 8–65% of autopsy specimens [91]. Among the nodules detected by palpation or USG, approximately 5–15% are malignant [92,93].

USG scan is recommended as the first-line thyroid imagining technique, preceding computer tomography (CT), magnetic resonance imaging (MRI) and others. USG enables
identification of features, such as shape (taller than wide), echogenity, echostructure, margin and microcalcifications, that aid differentiation between benign and malignant thyroid nodules [94]. Nevertheless, there is a need to create a pattern of thyroid cancer USG images that will enable better TC risk stratification and decrease the rate of fine-needle aspiration biopsy.

Since 2009, when Horvath published the Thyroid Imaging Reporting and Data System (TIRADS) [95], other classifications of thyroid nodules have been published, including the ATA guideline in 2015 [20], the Korean Thyroid Association (K-TIRADS) guideline in 2016 [96], the European Thyroid Association (EU-TIRADS) guideline in 2017 [97], the American College of Radiology (ACR-TIRADS) guideline in 2017 and the Chinese (C-TIRADS) guideline in 2020 [98].

Indication to FNAB is made based on the clinical and USG examination. The material obtained during FNAB is analyzed and the risk of malignancy is estimated using The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [99]. Also, depending on the result of FNAB, the decision of surgical thyroid excision is made.

2.2. Surgical Treatment of TC

Although DTC patients have a more favorable prognosis than most other cancers, with an overall survival (OS) rate of 98.3% at 5 years for the majority of cases, local recurrence occurs in about 20% of cases and distant metastases are found in approximately 10% of patients [100]. PDTC has a higher risk of persistence and mortality [101,102]. According to recent guidelines [20], surgical treatment is the gold standard in TC therapy. Before cervical surgery, a detailed USG of the neck with evaluation of lymph nodes should be performed. If any suspicious lymph nodes are recognized, they should be removed simultaneously with the gland. The range of surgery depends on the type of TC and on the stratification of recurrence risk. DTC patients with low risk of recurrence can be treated with total thyroidectomy or lobectomy with isthmusectomy. DTC and PDTC patients with intermediate or high risk of recurrent disease undergo total thyroidectomy and therapeutic neck dissection with or without prophylactic central neck dissection. Patients with intermediate or high risk of recurrence or with distant metastases should be treated with radioiodine [13].

ATC is an undifferentiated subtype of TCs that is resistant to therapy with the iodine-131 radioisotope. Due to an inauspicious prognosis, TNM classification for ATC only provides stage IV, which is subdivided into three classes: IVA, IVB and IVC. Surgery, followed by chemotherapy and radiotherapy, is recommended as the first choice of intervention for management of ATC, provided that a full resection of the tumor can be obtained and no distant metastases are identified (stage IVA). Patients with unresectable ATCs or with local invasion and small-volume metastases confirmed in the neck (IVB) should be treated with radiation therapy and adjuvant chemotherapy, without surgical intervention. Furthermore, systemic therapies with or without palliative radiotherapy should be considered for patients with large-volume or distant metastases. Recent ATA Guidelines for Management of Patients with ATC, which were released in March 2021, incorporate targeted therapies with kinase inhibitors in their recommendations [103], as discussed below.

Patients with MTC have poor prognosis, with a 10-year survival rate at approximately 50% and distant metastases observed in 7–23% of cases at the moment of recognition. The first-choice treatment is surgical thyroidectomy and central compartment neck dissection, but it is curative only for localized MTCs. In case of widespread regional or metastatic disease, surgical interventions are not associated with a higher cure rate, therefore, less aggressive local treatment procedures should be preferred. Systemic therapy is employed in multi-metastatic and rapidly progressing malignancies [61,104,105].
2.3. RAI Treatment

The thyroid gland has the unique ability to uptake and concentrate iodide, which is a critical step in biosynthesis of TH. Iodide is actively transported from the blood through the basolateral plasma membrane by the NIS protein, whereas the anion transporter pendrin and other proteins mediate iodide efflux to the follicular lumen. Thyroid peroxidase (TPO) attaches oxidized iodide to tyrosine residues of thyroglobulin (Tg) producing monoiodotyrosine (MIT) and diiodotyrosine (DIT). Subsequently, TPO couples a MIT and a DIT residue to form triiodothyronine (T3) or two DIT residues to form thyroxine (T4) [1,106].

The ability to uptake the iodine-131 radioisotope is preserved in most cases of DTC, therefore RAI has become a basic treatment modality in DTC. The accumulated radioiodine predominantly emits β-particles, which penetrate a short distance of only a few millimeters causing death of cancer cells. RAI is recommended as remnant ablation for patients with intermediate-risk DTC and as an adjuvant therapy for patients with high-risk DTC. For patients with low-risk DTC, who have undergone less than total thyroidectomy, RAI is not recommended [13,20,107].

De-differentiated TCs, like ATC and some PDTCs, lose their functional ability to transport and accumulate iodine due to several alterations. The same phenomenon occurs in 5–15% of DTC incidents [108], while approximately 50% of metastatic DTCs are refractory to RAI treatment [109,110].

DTCs that are metastatic or locally advanced and have one or more metastatic sites without any radioiodine uptake, or for which significant progression of the disease is observed during the year after radioiodine treatment, are considered as RAIR. RAIR-DTC significantly reduces the mean life expectancy by 3–5 years [111].

The other molecular mechanism harming iodine uptake is an underpinning dysfunction of NIS, which occurs predominantly in BRAF-mutated tissue. However, other aberrant activations of MAPK and PI3K/AKT pathways are also associated with this phenomenon. Much effort has been made to identify small molecule inhibitors that would be able to restore and enhance NIS protein expression and its physiological functions [112,113]. It seems that BRAF/MEK inhibitors are the most promising agents for selected DTCs, nevertheless, prospective multicenter trials are required to evaluate the efficacy and safety of iodine uptake restoration on a larger cohort of patients [37,39].

3. Currently Used and Investigated Targeted Therapies in TCs

Although most TC cases can be cured by combined surgical and RAI treatment, all ATCs and MTCs, as well as some DTC incidents, require further therapy. Standard chemotherapy, if recommended, is used in ATC treatment, whereas in DTC, only doxorubicin has been approved for RAIR-DTC patients. Further treatment of MTC relies on removal of metastases (e.g., external beam radiation therapy, EBRT) and no systemic chemotherapy is recommended. Due to numerous adverse events and lack of survival rate enhancement, standard chemotherapy is insufficient in treatment of TCs. Over the last decade, knowledge about the molecular basis of TC carcinogenesis has led to the development of kinase inhibition-based therapies, which allow for targeting of tumor cells and are thus considered as a novel tool for personalized medicine [43].

Kinase inhibitors (KIs) are small molecular compounds. Most of the Food and Drug Administration (FDA)-approved inhibitors for DTC, ATC and MTC competitively block the ATP-binding pocket of protein kinase(s), thereby inhibiting cell signaling and proliferation. First generation KIs, such as lenvatinib, sorafenib, vandetanib and cabozantinib, present a broad-spectrum of activity and are known as multi-kinase inhibitors (MKIs). Due to their low selectivity, MKIs have more off-target side effects leading to certain adverse events (AEs). The higher selectivity of the second generation of specific kinase inhibitors (SKIs) that target individual protein kinases, e.g., BRAF-specific inhibitors, makes those drugs more tolerable and less AEs-triggering [114–116].

Ten years have passed since the first targeted kinase inhibitor, vandetanib, was approved and registered for treatment of symptomatic or progressive MTCs. Since then, other
MKIs, such as sorafenib, lenvatinib, vandetanib and cabozantinib, were approved for TC treatment by both the FDA and the European Medical Agency (EMA). Lenvatinib and sorafenib are used for treatment of advanced RAIR-DTC, while vandetanib and cabozantinib are administered in MTC therapy. Apart from the approved indications, MKIs are used in other subtypes of TCs with variable effect [28,114,115].

Larotrectinib, entrectinib and selpercatinib represent selective FDA- and EMA-approved inhibitors. Pralsetinib (BLU-667), a selective inhibitor targeting mutated and fused forms of RET, has been approved by the FDA and is under evaluation by the EMA [115]. Combinatory therapy using dabrafenib and trametinib, which are selective inhibitors of MEK and BRAF, respectively, has been approved by the FDA for ATC treatment in patients with locally advanced or metastasized disease [103]. Kinase inhibitors that have been approved for TC therapy are summarized in Table 1. The clinical and preclinical approaches from the last two years regarding the use of kinase inhibitors in the treatment of TCs are discussed below.

**Table 1.** Kinase inhibitors currently approved for thyroid cancer (TC) treatment.

| Cancer Type | Agent (Brand Name(s)) | Time of Approval | Point of Action | Indication |
|-------------|------------------------|------------------|----------------|-----------|
| DTC         | Entrectinib (Rozlytrek) | FDA 2019 EMA 2020| NTRK | Solid tumors with a NTRK gene fusion without a drug-resistance mutation in certain TRK proteins |
|             | Larotrectinib (Vitrakvi)| FDA 2018 EMA 2019| NTRK | Solid tumors with a NTRK gene fusion without a drug-resistance mutation in certain TRK proteins |
|             | Lenvatinib (Lenvima)    | FDA 2015 EMA 2014| MKI  | Progressive, recurrent or metastatic RAIR-DTC |
|             | Pralsetinib (Gavreto)   | FDA 2020         | RET  | Metastatic or advanced TCs with a RET fusion gene |
|             | Selpercatinib (Retevmo, Retsevmo) | FDA 2020 EMA 2021 | RET  | FDA: metastatic or advanced RAIR-DTC patients aged 12 years with a RET fusion gene; EMA: advanced DTC patients with changes in RET gene previously treated with sorafenib and/or lenvatinib |
|             | Cabozantinib (Cabometyx, Cometriq) | FDA 2021 | MKI  | Advanced or metastatic RAIR-DTC that has progressed following prior VEGFR-targeted therapy |
|             | Sorafenib (Nexavar)     | FDA 2005 EMA 2006| MKI  | Progressive, recurrent or metastatic RAIR-TC |
| ATC         | Dabrafenib (Tafinlar)   | FDA 2018         | BRAF | Locally advanced or metastasized ATC that cannot receive local treatment; Therapy in combination with trametinib |
|             | Entrectinib (Rozlytrek) | FDA 2019 EMA 2020| NTRK | Solid tumors with a NTRK gene fusion without a drug-resistance mutation in certain TRK proteins |
|             | Larotrectinib (Vitrakvi)| FDA 2018 EMA 2019| NTRK | Solid tumors with a NTRK gene fusion without a drug-resistance mutation in certain TRK proteins |
|             | Pralsetinib (Gavreto)   | FDA 2020         | RET  | Metastatic or advanced TCs with a RET fusion gene |
|             | Selpercatinib (Retevmo, Retsevmo) | FDA 2020 EMA 2021 | RET  | FDA: metastatic or advanced ATC patients aged 12 years with a RET fusion gene; EMA: advanced ATC patients with changes in RET gene previously treated with sorafenib and/or lenvatinib |
Table 1. Cont.

| Cancer Type | Agent (Brand Name(s)) | Time of Approval | Point of Action | Indication |
|-------------|-----------------------|------------------|----------------|------------|
| MTC         | Trametinib (Mekinist) | FDA 2018         | MEK            | Locally advanced or metastasized ATC that cannot receive local treatment; Therapy in combination with dabrafenib |
|             | Cabozantinib (Cabometyx, Cometriq) | FDA 2012 EMA 2014 | MKI | Progressive or metastasized MTC |
|             | Pralsetinib (Gavreto) | FDA 2020         | RET            | Advanced or metastatic MTC with a mutation in the RET gene |
|             | Selpercatinib (Retevmo, Retsevmo) | FDA 2020 EMA 2021 | RET | FDA: advanced or metastatic MTC aged ≥ 12 years with a mutation in the RET gene; EMA: advanced MTC patients aged ≥ 12 years with changes in RET gene previously treated with cabozantinib and/or vandetanib |
|             | Vandetanib (Caprelsa) | FDA 2011 EMA 2013 | MKI | Locally advanced or metastasized MTC |

ATC, anaplastic thyroid carcinoma; DTC, differentiated thyroid carcinoma; EMA, European Medical Agency; FDA, Food and Drug Administration; MKI, multikinase inhibitor; MTC, medullary thyroid carcinoma; RAIR, radioiodine refractory.

3.1. Targeted Therapies for DTC Treatment

Guidelines for DTC treatment that were developed in 2015 [20], include recommendations for KI usage in metastatic, rapidly progressive and symptomatic RAIR-DTC cases. A variety of novel agents and combinatory treatments are being tested as candidate clinical approaches in DTC and progressive metastatic RAIR-DTC (summarized in Table 2). Special attention is paid to inhibitors directed against BRAF, RET, MEK and TRK kinases, which will “re-sensitize” DTC and RAI-refractory tumors.

Table 2. Kinase inhibitors currently investigated in clinical trials for DTC treatment (registered under ClinicalTrials.gov and clinicaltrialsregister.eu).

| Agent (Drug Name) | Alternative/Control Treatment | Study Phase | Specific Inclusion Criteria | Study Start/Estimated Completion Date | Status | Trial Number |
|-------------------|-------------------------------|-------------|-----------------------------|---------------------------------------|--------|--------------|
|                   |                               |             |                             |                                       |        | MKIs         |
| Anlotinib         | ND                            | II          | ND                          | 01.12.2020/07.12.2022                 | Recruiting | NCT05007093 |
| Apatinib          | ND                            | II          | VEGFR2                      | 10.04.2019/30.05.2020                 | Recruiting | NCT04180007 (APT-01) |
| Apatinib          | Placebo                       | III         | VEGFR2                      | 12.2016/06.2022                      | Active, not recruiting | NCT03048877 |
| Cabozantinib      | ND                            | II          | ND                          | 01.2014/05.2022                      | Active, not recruiting | NCT02041260 |
| Cabozantinib      | Placebo                       | III         | ND                          | 05.10.2018/12.2022                   | Active, not recruiting | NCT03690388 |
| Donafenib         | Placebo                       | III         | ND                          | 29.04.2018/12.2021                   | Recruiting | NCT03602495 |
| Lenvatinib        | ND                            | I/II        | FTC, PTC                    | 29.12.2014/31.03.2022                | Active, not recruiting | NCT02432274 (in Cohort 2A) |
| Lenvatinib        | ND                            | II          | ND                          | 01.05.2021/01.05.2021                | Not yet recruiting | NCT04858867 |
| Lenvatinib        | ND                            | III         | ND                          | 11.01.2017/30.10.2021                | Active, not recruiting | NCT02966093 |
Table 2. Cont.

| Agent (Drug Name)           | Alternative/Control Treatment | Study Phase | Specific Inclusion Criteria | Study Start/Estimated Completion Date | Status                  | Trial Number  |
|------------------------------|-------------------------------|-------------|-----------------------------|--------------------------------------|-------------------------|---------------|
| Entrectinib ND II            | NTRK, ROS1 or ALK PTC         | II          | 01.12.2022/02.12.2024        | Recruiting                          | NCT02568267 (STARTRK-2) |
| Imatinib ND I PTC           | PTC                           | I           | 18.09.2018/30.12.2021        | Recruiting                          | NCT03469011 |
| Vandetanib Placebo II FTC, PTC | FTC, PTC                     | II          | 29.09.2007/12.2021           | Active, not recruiting              | NCT00537095 |
| Vandetanib Placebo III ND   | FTC, PTC                      | III         | 17.09.2013/31.12.2021        | Active, not recruiting              | NCT01876784 |
| Larotrectinib ND II NTRK    | NTRK                          | II          | 30.09.2015/30.09.2025        | Recruiting                          | NCT02576431 (NAVIGATE) |
| Alectinib ND II ALK-mutant PTC | ALK, ROS1 or NTRK rearrangements | II          | 24.05.2021/01.12.2025        | Recruiting                          | NCT04644315 |
| Repotrectinib ND I ALK      | ALK-mutant PTC                | I           | 27.02.2017/12.2022           | Recruiting                          | NCT03093116 (TRIDENT-1) |
| Cobimetinib/ABM-1310        | BRAF V600E                    | I           | 16.06.2020/12.2021           | Recruiting                          | NCT04190628 |
| Encorafenib/ Binimetinib/ Encorafenib/  | BRAF V600E/M                  | II          | 30.10.2020/01.08.2024        | Recruiting                          | NCT04061980 |
| Trametinib/T [131]          | RAS-mutant or RAS/BRAF wt     | II          | 14.08.2014/31.12.2021        | Active, not recruiting              | NCT02152995 |
| Dabrafenib/Tematinib        | BRAF V600E or RAS BRAF wt     | II          | 27.12.2017/12.2022           | Recruiting                          | NCT03244956 (MERAIODE) |
| Trametinib Trametinib/Dabrafenib | BRAF V600E (Trametinib) and  | II          | 05.02.2018/30.06.2022        | Recruiting                          | NCT04619316 (ERRITI) |
| Dabrafenib/Tematinib        | BRAF V600E or RAS BRAF wt     | II          | 30.12.2020/04.2022           | Recruiting                          | NCT04554680 |
| Trametinib Trametinib/Dabrafenib | BRAF V600E (Trametinib) and  | I (pilot study) | ND                            | Ongoing                             | 2016-002941-4 (ERRITI) |
| Dabrafenib/Tematinib        | BRAF V600E (Trametinib) and   | III         | 01.10.2021/30.10.2026        | Not yet recruiting                  | NCT04940052 |
| Vemurafenib ND II PTC       | PTC                           | II          | 07.11.2012/30.11.2020        | Active, not recruiting              | NCT01709292 |
| Agent (Drug Name) | Alternative/Control Treatment | Study Phase | Specific Inclusion Criteria | Study Start/Estimated Completion Date | Status | Trial Number |
|------------------|-------------------------------|-------------|-----------------------------|---------------------------------------|--------|--------------|
| Anlotinib/I131   | ND                            | II          | ND                          | 15.08.2021/20.07.2024                 | Not yet recruiting | NCT04952493 |
| Apatinib/ Camrelizumab 1 | ND                             | II          | ND                          | 23.09.2020/30.06.2023                 | Recruiting     | NCT04560127 |
| Cabozantinib/ Nivolumab 1 / Ipilimumab 2 | ND                             | II          | ND                          | 15.07.2019/15.01.2022                 | Recruiting     | NCT03914300 |
| Cabozantinib/ Atezolizumab 1 | ND                             | I           | ND                          | 05.09.2017/12.2022                   | Recruiting     | NCT03170960 |
| Lenvatinib/ I131 | ND                            | II          | ND                          | 08.10.2021/30.09.2022                | Recruiting     | NCT02973997 |
| Pembroliuzumab 1 | ND                            | I           | BRAF                        | 29.08.2013/01.07.2022                | Active, not recruiting | NCT01947023 |
| Lapatinib/ Dabrafenib | ND                             | II          | BRAF                        | 26.07.2019/15.06.2022                | Recruiting     | NCT03732495 (LENOVS) |
| Lenvatinib/ Denosumab 3 | ND                             | II          | TC                          | 06.2010/06.2022                    | Active, not recruiting | NCT01141309 |
| Sorafenib/ Everolimus 4 | ND                             | II          | DTC progressed on monotherapy with Sorafenib | 10.2010/03.2021            | Active, not recruiting | NCT01263951 |
| Sorafenib/ Everolimus 4 | ND                             | II          | ND                          | 04.05.2018/05.2022                  | Recruiting     | NCT03475953 (REGOMUNE) |
| Selumetinib      | Sorafenib alone                | II          | RAIR-HCC                    | 01.10.2014/28.01.2021                | Active, not recruiting | NCT02143726 |
| Selumetinib      | Selumetinib/I131               | II          | ND                          | 04.05.2015/20.02.2022                | Active, not recruiting | NCT02393690 |
| Sorafenib/ Toripalimab 1 | ND                             | II          | ND                          | 01.10.2020/30.09.2022                | Not yet recruiting | NCT04524884 |
| Dabrafenib       | Dabrafenib/ Lenvatinib         | II          | BRAF                        | 07.11.2012/31.12.2021               | Active, not recruiting | NCT01723202 |
| Trametinib/I131  | Trametinib/ Dabrafenib/I131   | ND          | ND                          | ND                                  | Ongoing         | NCT03244956 (MERAIODE) |
| PDR001 1 / Trametinib (Cohort A) or Dabrafenib (Cohort B) | ND                             | II          | BRAF                        | 02.09.2020/02.09.2022                | Recruiting     | NCT04544111 |
| Vemurafenib/ Copanlisib 5 | ND                             | I           | BRAF V600E                  | 26.06.2020/06.2022                 | Recruiting     | NCT04462471 |

1 Anti-PD-1 monoclonal antibody; 2 anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody; 3 anti-receptor activator of nuclear factor κB ligand (RANKL) monoclonal antibody; 4 mTOR inhibitor; 5 phosphatidylinositol 3-kinase (PI3K) inhibitor; wt, wild type; ND, not defined.
3.1.1. MKI-Based Therapies of DTC

Recent studies on the use of MKIs in RAIR-DTCs showed that treatment with lenvatinib or sorafenib results in an improvement of progression-free survival (PFS) [117], objective tumor response rate and OS. However, during treatment, dose modifications are required to reduce AEs [118]. A long-term evaluation of apatinib-based therapy in a phase II trial for progressive RAIR-DTC displayed sustainable efficacy and a tolerable safety profile, therefore, it can be considered as a promising treatment option [119]. The benefit from apatinib therapy may result from the effective inhibition of proliferation and migration of PTC cells, as well as from induction of apoptosis, cell cycle arrest and autophagy, as was recently demonstrated in an in vitro study [120]. Donafenib tested in a randomized, open-label, multicenter phase II trial of progressive locally advanced or metastatic RAIR-DTC, demonstrated improvement in PFS, partial response (PR) and the overall response rate (ORR). That effect was dose-dependent and effective for both used regimens, but a higher rate of AEs was reported in the higher dose group [121]. In a randomized, double-blind, placebo-controlled phase III trial, treatment with cabozantinib (an agent already approved for MTC therapy) prolonged PFS in RAIR-DTC patients, but at the same time accounted for a relatively high rate of AEs [122].

The results of Real-World Studies (RWS) showed that treatment with lenvatinib, sorafenib and pazopanib, followed or accompanied by another therapy, may improve the clinical outcome (i.e., higher PFS) of patients with RAIR-DTC [123–125]. However, the observed AEs, most frequently fatigue, asthenia and hypertension (HT), forced to reduce the MKI dose. Despite that, a dose reduction likely did not abrogate the apparent efficacy of therapy [126]. A recently published report, comparing sorafenib and lenvatinib for RAIR-DTC treatment, showed that in the group treated with lenvatinib, PR to treatment was significantly increased, and was accompanied by a drop in serum Tg levels [127]. Even though MKIs are considered as a promising treatment for RAIR-DTC, the use of them should be cautious due to a high frequency of AEs [128].

There is increasing interest in MKI-based therapies in combination with immunotherapy (e.g., NCT04560127, NCT03732495), MAPK- or PI3K/AKT-SKIs (e.g., NCT02143726, NCT01947023) or radioiodine (NCT04952493). In the recently reported preliminary studies on a small, randomized, multi-institutional phase II study (NCT0143726), where everolimus (mTOR inhibitor) and sorafenib co-therapy was applied for patients with RAI refractory HCC, improved PFS was observed [129]. Similarly, in a preclinical study, DTC cells treated with a combined therapy, including lenvatinib and radiation, synergistically induced apoptosis and G2/M phase arrest, as well as inhibited colony formation in vitro (cell lines) and tumor growth in nude mice [130].

3.1.2. Single Kinase-Targeted Therapies of DTC

Since MAPK activation, mediated by a BRAF single-nucleotide mutation, is one of the most critical events in DTC development, there are ongoing efforts to investigate BRAF-specific SKIs either in monotherapy or in combination with other agents. For example, a recent in vitro study performed on BRAF V600E-positive TC cell lines indicated antiproliferative and re-differentiative effects of dabrafenib and vemurafenib [131]. Moreover, vemurafenib-treated BRAF V600E-positive PTC cells exhibited an increased apoptosis level [132], whereas ascorbic acid (vitamin C) was found to sensitize BRAF V600E-positive thyroid cancer cells to this agent [133]. Recent reports suggest, that co-therapy based on dabrafenib and trametinib may lead to durable disease control and prolonged benefit in patients with a BRAF-mutated PTC [134]. This combination of drugs is currently under investigation in a panel of clinical trials, such as NCT03244956, NCT04619316 and NCT04554680 (Table 2). Simultaneous treatment with BRAF and MEK inhibitors upregulates NIS expression, suggesting it may improve RAI responsiveness [135]. According to preclinical data, this effect may be amplified when either dabrafenib or vemurafenib is used in combination with follistatin or vactosertib, SMAD pathway inhibitors [136]. A prospective, multicentric, open-label phase II trial (MERAIODE, NCT03244956) evaluating
the efficacy and tolerance of trametinib and dabrafenib treatment followed by administration of RAI in patients with metastatic DTC provided promising results. The therapy restored radioiodine accumulation in *BRAF*-mutated patients and led to tumor control in 90% of cases [137].

In a phase I, open label study of lifirafenib (BGB-283), a RAF family kinase inhibitor targeting *BRAF* V600E, EGFR and RAS proteins, four patients with *BRAF* V600E-positive TCs were enrolled, including one in the dose-escalation phase and three in the dose-expansion phase. Lifirafenib demonstrated antitumor activity with PR and an acceptable risk benefit profile in *BRAF* V600E-positive solid tumors [138]. Recently, enrollment for a phase I/II trial for assessment of the safety and efficacy of lifirafenib in combination with a MEK inhibitor (mirdametinib) in patients with *BRAF*- and *RAS*-mutated tumors was commenced (NCT03905148).

The utility of therapies based on inhibitors specific for tropomyosin receptor kinases in *NTRK* gene fusion-positive solid tumors was also investigated. Entrectinib (RXDX-101), a potent inhibitor of TRKA, TRKB and TRKC, was reported to induce durable and clinically meaningful responses in patients with *NTRK* fusion-positive solid tumors [139]. A phase I study recruitment of patients with PTC (STARTRK-1, NCT02097810) was completed in June 2021 and a phase II trial (STARTRK-2, NCT02568267) is still recruiting. Another TRK inhibitor, larotrectinib, was found to restore radioiodine avidity in PTC-pediatric patients, leading to inhibition of tumor growth [140].

The common activating *RET* alterations in PTC cases encouraged researchers to use *RET* kinase inhibitors for PTC therapy. The results of selpercatinib treatment in two independent case reports of patients with *RET*-altered PTC (*NCOA4-RET* and *CCDC6-RET* fusions) showed restored radioiodine avidity and a re-differentiation effect suppressing Tg after six months of treatment [140,141].

A report on ALK-targeted therapy in RAIR-PTC patients harboring an *EML4-ALK* gene fusion variant 3 has just been released. In the experimental approach, the authors established a cell line derived from a PTC patient to select the most potent ALK-specific inhibitor in vitro. Tumor cell line data showed that lorlatinib (3rd generation ALK TKI) was a more potent drug than the previously administered crizotinib (1st generation ALK TKI). After lorlatinib therapy, the patient exhibited a significant decrease in Tg levels, a partial drop in PR, with a decrease in the sum of the target lesions [142].

### 3.2. Targeted Therapies for ATC Treatment

Recent ATA guidelines for management of ATC patients with grade IVB and IVC recommends mutation-guided individualized targeted therapeutic strategies based on KIs. Therefore, extended molecular profiling of ATC cases is strongly recommended, as it may reveal promising possibilities for target-specific therapies [143]. If it is possible, patient participation in clinical trials should be taken under consideration [103]. The list of on-going clinical trials for treatment of ATC is provided in Table 3.

**Table 3.** Kinase inhibitors currently investigated in clinical trials for ATC treatment (registered under ClinicalTrials.gov and clinicaltrialsregister.eu).

| Agent (Drug Name) | Alternative/Control Treatment | Study Phase | Specific Inclusion Criteria | Study Start/Estimated Completion Date | Status | Trial Number |
|-------------------|-------------------------------|-------------|----------------------------|--------------------------------------|--------|--------------|
| Dabrafenib/Trametinib | ND | II | Mutated *BRAF* | 22.01.2021/01.2026 | Recruiting | NCT04739566 (ANAPLAST-NEO) |
| Dabrafenib/Trametinib | ND | I | *BRAF* V600E | 04.05.2020/30.04.2025 | Recruiting | NCT03975231 |
| Cobimetinib/ABM-1310 | ABM-1310 | I | *BRAF* V600E | 16.06.2020/12.2021 | Recruiting | NCT04190628 |
Table 3. Cont.

| Agent (Drug Name) | Alternative/Control Treatment | Study Phase | Specific Inclusion Criteria | Study Start/Estimated Completion Date | Status | Trial Number |
|-------------------|-------------------------------|-------------|-----------------------------|--------------------------------------|--------|--------------|
| RET inhibitors    |                               |             |                             |                                      |        |              |
| Selpercatinib     | ND                            | II          | Mutated RET                 | 26.02.2021/10.09.2024                 | Recruiting | NCT04759911 |
| TRK inhibitors    |                               |             |                             |                                      |        |              |
| Larotrectinib     | ND                            | II          | NTRK                        | 30.09.2015/30.09.2025                 | Recruiting | NCT02576431 (NAVIGATE) |
| MKIs in combination with other agents | | | | | | |
| Cabozaatinib/Atezolizumab | ND | II | ND | 07.10.2020/03.2024 | Recruiting | NCT04400474 (CABETEN) |
| Lenvatinib/Pembrolizumab | ND | II | ND | 02.03.2021/31.08.2022 | Not yet recruiting | NCT04171622 |
| Pazopanib/Paclitaxel 2/IMRT | Placebo/Paclitaxel 2/IMRT | II | ND | 28.10.2010/lack of data | Active, not recruiting | NCT01236547 |
| SKIs in combination with other agents | | | | | | |
| Repotrectinib     | ND                            | I           | ALK, ROS1, NTRK rearrangements | 27.02.2017/12.2022                  | Recruiting | NCT03093116 (TRIDENT-1) |
| Cobimetinib/Atezolizumab | ND | II | Mutated BRAF (Cohort A) vs. RAS, NF1, NF2 and MAPK pathway proteins at or above Mek mutations (Cohort B) | 27.07.2017/27.07.2023 | Recruiting | NCT03181100 |
| Dabrafenib/Trametinib/Cemiplimab | ND | II | BRAF V600E | 20.01.2020/20.06.2022 | Recruiting | NCT04238624 |
| Trametinib/Dabrafenib/Pembrolizumab | ND | II | Mutated BRAF | 24.06.2021/30.06.2024 | Recruiting | NCT04675710 |
| Trametinib/Paclitaxel 2 | ND | I (pilot study) | ND | 03.2017/09.2023 | Recruiting | NCT03085056 |

1 Anti-PD-1 monoclonal antibody; 2 taxan; IMRT, intensity-modulated radiation therapy.

3.2.1. MKI-Based Therapies of ATC

Over the last two years, a few studies have reported the results of MKI-based approaches in ATC treatment. Lenvatinib, an oral multitarget inhibitor, has been used in adjuvant therapy after thyroidectomy with neck dissection and postoperative chemoradiotherapy. Therapy extended the time to progression, but some AEs, like HT fatigue, anorexia and severe drug-induced hepatitis, forced investigators to taper the drug dose \cite{144,145}. Results of treatment of ATC patients with lenvatinib (phase II trial) confirmed tumor size reduction (in more than half of evaluated patients), PR to treatment ($n = 1$) and $>30\%$
reduction in the total size of the target lesion. Nevertheless, lack of efficacy per prespecified criteria in interim analysis led to end the study at the enrolment stage. The authors suggested that lenvatinib, when used alone, may not be an effective treatment for ATC [146]. Another preclinical study demonstrated that combination of lenvatinib with the MEK inhibitor selumetinib (AZD6244) enhanced the antitumor effects of monotherapy in vitro and in an ATC mouse model. These effects may occur through the PI3K/AKT and MAPK signaling pathways [147]. Sorafenib, an oral MKI, exerts activity against ATC cells, especially in combination with other drugs. Simultaneous administration of sorafenib and an agent restoring molecular function of the p53 protein (CP-31398) was reported to decrease viability of ATC-derived cells (SW579) [148]. Another study showed that combination of \( N\)-hydroxy-7-(2-naphthylthio) heptanamide (HNHA), sorafenib and radiation was effective in inducing apoptosis and cell cycle arrest, leading to significant suppression of tumor growth in a mouse xenograft model and may be considered as a potential approach to ATC treatment [149].

3.2.2. Single Kinase-Targeted Therapies of ATC

Since AEs are a significant limitation of the currently available MKI-based therapies, identification of novel molecule inhibitors for ATC management is needed. CTOM-DHP is a promising SKI specifically inhibiting both MAPK and PI3K/AKT signaling pathways. Administration of this compound to the ATC-originated cell line and tumor xenograft mice model led to increased NIS promotor expression, RAI avidity (both \( ^{124}I \) and \( ^{131}I \) uptake) and cytotoxicity. Therefore, CTOM-DHP may be considered as a potent compound for restoring RAI avidity in ATC [112]. Furthermore, it is postulated that combinatorial approaches, rather than single inhibitor-based therapies, may provide more benefits for patients. As already mentioned above, co-administration of selective BRAF and MEK inhibitors (dabrafenib and trametinib, respectively) has received FDA approval for treatment of locally advanced and metastatic \( \text{BRAF} \text{V600E} \)-positive ATCs [103]. A retrospective study on such combinatorial treatment showed prolonged survival of \( \text{BRAF} \)-mutant ATC patients [150]. Additionally, a recently released case report demonstrated a good rapid response in a patient treated with dabrafenib and trametinib who had already received other BRAF-targeted inhibitors [151]. Moreover, co-administration of BRAF-directed agents with other drugs, like check point inhibitors (pembrolizumab), may prolong survival of patients [152]. In in vitro studies, exposure of \( \text{BRAF} \text{V600E} \)-positive ATC cell lines to dabrafenib and metlatonin showed synergistic inhibition of hTERT, and in consequence, cell arrest in the G1 phase and decreased cell viability [153]. Similarly, usage of another SKI, vemurafenib with a STAT3 pathway inhibitor on ATC-derived cell lines (sphere and monolayer) and mouse xenografts resulted in decreased viability and increased rate of cell apoptosis. These results indicate that inhibition of other pathways, like STAT3, could enhance the sensitivity of kinase inhibitors in ATC cells [154].

3.3. Targeted Therapies for MTC Treatment

Due to their origins, MTCs are unable to accumulate radioiodine, thus only surgical- and systemic-based treatments may be applicable in clinical practice. Most MTCs occur sporadically, but in approximately one-fifth of cases, they are familial and caused by germline mutations of the \( \text{RET} \) proto-oncogene. Somatic \( \text{RET} \) mutations are found in approximately half of patients with sporadic MTCs. \( \text{RAS} \) gene mutations, and less often \( \text{ALK} \) fusions, are alternative genetic events spotted in sporadic MTCs. Apart from these alterations of the proto-oncogene, overexpression of vascular endothelial growth factor (VEGF) receptors is often detected in the disease. The advent of targeted small-molecule KIs has revolutionized medical treatment of MTCs. As already mentioned, current guidelines on management of MTC patients recommend cabozantinib and vandetanib as the first-line single-agent systemic therapy in patients with advanced progressive MTC, based on their documented ability to improve PFS (Table 1). Both drugs inhibit RET kinase activity to some extent, however, their major anticancer effect is due to their strong inhibition of
angiogenesis [13,61,105,155]. The list of on-going clinical trials for treatment of MTC is provided in Table 4.

**Table 4.** Kinase inhibitors currently investigated in clinical trials for MTC treatment (registered under ClinicalTrials.gov and clinicaltrialsregister.eu).

| Agent (Drug Name) | Alternative/Control Treatment | Study Phase | Specific Inclusion Criteria | Study Start/Estimated Completion Date | Status | Trial Number |
|-------------------|--------------------------------|-------------|-----------------------------|---------------------------------------|--------|--------------|
| **MKIs**          |                                |             |                             |                                       |        |              |
| Anlotinib         | ND                             | II          | ND                          | 01.01.2019/01.06.2022                 | Active, not recruiting | NCT04309136 |
| Cabozantinib      | ND                             | II          | Pediatric MTC               | 08.05.2017/01.07.2022                | Active, not recruiting | NCT02867592 |
| Cabozantinib      | Cabozantinib 140 mg            | IV          | ND                          | 12.2014/12.2022                      | Active, not recruiting | NCT01896479 |
| Ponatinib         | ND                             | II          | ND                          | 26.07.2019/06.2022                  | Recruiting | NCT03838692 |
| Regorafenib       | ND                             | II          | ND                          | 01.2016/10.2022                     | Recruiting | NCT02657551 |
| Sorafenib         | ND                             | II          | Hereditary vs. sporadic MTC | 05.10.2006/30.01.2017               | Active, not recruiting | NCT00390325 |
| Sunitinib         | ND                             | II          | ND                          | 08.08.2006/31.12.2016               | Recruiting | NCT00381641 |
| Vandetanib        | Placebo                        | III         | ND                          | 30.11.2016/30.12.2021               | Recruiting | NCT00410761 |
| Vandetanib        | Vandetanib 300 mg              | IV          | ND                          | 06.2014/30.12.2020                  | Recruiting | NCT01496313 |
| **SKIs**          |                                |             |                             |                                       |        |              |
| BOS172738         | ND                             | I           | RET; MTC                    | 12.12.2018/06.2022                  | Active, not recruiting | NCT03780517 |
| Pralsetinib       | ND                             | I/II        | RET; MTC and PTC            | 17.03.2017/29.02.2024               | Recruiting | NCT03037385 (ARROW) |
| TPX-0046          | ND                             | I/II        | RET; MTC and other TCs      | 16.12.2019/03.2025                  | Recruiting | NCT04161391 |
| Selpercatinib     | ND                             | II          | RET; MTC and other TCs      | 16.03.2020/20.10.2025               | Active, not recruiting | NCT04280081 (LIBRETTO-321) |
| Selpercatinib     | ND                             | I/II        | RET; MTC and other TCs      | 02.05.2017/21.11.2023               | Recruiting | NCT03157128 (LIBRETTO-001) |
| Selpercatinib     | ND                             | II          | RET; MTC                    | 26.02.2021/10.09.2024               | Recruiting | 2017-000800-59 |

Kinase inhibitors in combination with other agents

| MKIs (not precised)/ Anti-PD-1 antibody (not precised) | ND | II | Arm B: MTC | 30.12.2019/30.06.2023 | Recruiting | NCT04521348 |
Table 4. Cont.

| Agent (Drug Name) | Alternative/Control Treatment | Study Phase | Specific Inclusion Criteria | Study Start/Estimated Completion Date | Status | Trial Number |
|-------------------|--------------------------------|-------------|-----------------------------|---------------------------------------|--------|--------------|
| Apatinib/Camrelizumab ¹ | ND | ND | 01.12.2020/31.12.2023 | Not yet recruiting | NCT04612894 |
| SKIs vs. MKIs | Pralsetinib | Cabozantinib or Vandetanib | III | Mutated RET | 01.09.2021/15.04.2028 | Not yet recruiting | NCT04760288 (AcceleRET-MTC) |
| | Selpercatinib | Cabozantinib or Vandetanib | III | Mutated RET | 30.12.2019/30.06.2023 | Recruiting | NCT04211337 (LIBRETTO-531) 2019-001978-28 |

¹ Anti-PD-1 monoclonal antibody.

3.3.1. MKI-Based Therapies of MTC

In 2021, the results of a comprehensive retrospective study, which aimed to identify whether approval of MKIs for MTC is associated with changes in systemic therapy administration or changes in overall survival, was published [156]. The clinicopathologic comparisons were conducted between pre-multikinase (2005–2010) and post-multikinase inhibitor (2011–2016) approval groups. A total of 2891 patients were enrolled, including 1265 cases in the pre-MKI and 1626 cases in the post-MKI approval group. The results showed that after approval of MKIs, the rate of systemic treatment administration significantly increased (8.3% and 11.3% in pre-MKI and post-MKI, respectively). Nevertheless, no improvements in OS were detected between those two groups of patients. In 2020, a post hoc analysis phase III trial (ZETA trial) involving patients with advanced MTCs treated with vandetanib demonstrated increased PFS and improved ORR compared to a placebo; however, OS did not significantly differ between vandetanib- and placebo-treated patients. In contrast, time to worsening of pain, which was predefined as an endpoint to assess symptomatic benefits of the trial, was found to be extended in the vandetanib group [157]. According to recent reports [158,159], one in four patients treated with vandetanib or cabozantinib developed AEs, which required withdrawal of the drug, or exhibited drug resistance. Therefore, extensive efforts are made to broaden the panel of MKI-based therapies for MTC patients. For example, Matrone et al. (2021) evaluated the impact of the off-label use of lenvatinib in a group of ten patients affected by locally advanced, non-resectable, metastatic MTCs with previous failure of other TKIs [160]. Lenvatinib induced substantial stabilization of metastatic lesions and disease control. The observed AEs were consistent with other studies and could be managed by personalization of the initial dose and one or more prompt dose reductions. It seems that this agent could be effective as salvage therapy in cases, where no other treatment strategies are available. Moreover, due to the absence of cross-resistance between vandetanib and lenvatinib, second- and third-line kinase inhibitor treatment should always be considered [160]. A multicenter, randomized, double-blind, placebo-controlled phase IIB study investigated the usefulness of a novel MKI, anlotinib, in the therapy of locally advanced or metastatic MTCs. Drug treatment, compared to placebo, significantly improved the median PFS and ORR, with no significant difference in OS between the tested groups [161].

3.3.2. Single Kinase-Targeted Therapies of MTC

Since the release of the MTC management guidelines [105] in 2020, the FDA has approved two new, highly potent RET-selective tyrosine kinase inhibitors, pralsetinib and selpercatinib. Both agents are destined for individuals 12 years or older with advanced, metastatic RET-mutant MTCs or other RET fusion-positive TCs, which require systemic therapy. Selpercatinib has also been approved by the EMA for patients aged ≥ 12 years,
who were previously treated with cabozantinib and/or vandetanib, while pralsetinib is still awaiting a positive opinion. Pralsetinib and selpercatinib recommendations were based on multicenter, open label, multi-cohort clinical trials, ARROW, NCT03037385 [162] and LIBRETTO-001, NCT03157128, respectively, that investigated their efficacy in MTC patients with RET gene alterations. These potent inhibitors not only improved ORR, but also higher PFS and OS, with a lower rate of AEs was observed [162,163]. Unfortunately, in a number of cases, there were no improvements after treatment and resistance-associated mutations were identified [62,163,164]. Several recent studies have shown that both pralsetinib and selpercatinib are inefficient in MTC patients with RET non-gate mutations at the front and at the hinge of the receptor. However, strong pralsetinib-resistant L730V/I mutations, located at the roof of the solvent front of the RET ATP-binding site, remained sensitive to selpercatinib in the preclinical study [165]. These findings highlight the need to develop a next-generation of drugs covering both gatekeeper and non-gatekeeper mutations for on-target resistance, in addition to deciphering patterns of off-target resistance by alternative mechanisms for combinatory therapies [62,164].

4. Treatment-Related Toxicities

MKI-related toxicities (listed in Table 5) are very common and likely reflect target-binding affinities specific to each drug [62,166–169]. Among the AEs observed during treatment, HT appears to be the most frequent and is managed using standard antihypertensive drugs. Early diagnosis of HT may help avoid serious complications and prevent premature termination of MKI-based therapies in patients [38,168]. Administration of MKIs is also frequently associated with an increased risk of palmar-plantar erythrodysesthesia syndrome (PPES), characterized by tingling and tenderness, with more serious symptoms including symmetrical redness, swelling and pain on the palms and soles. The etiology of PPES is still unclear and its management is predominantly symptomatic with dose reduction or interruption for severe cases. Other reported muco-cutaneous AEs, such as rash, alopecia and oral stomatitis, are specifically related to inhibition of the VEGFR/EGFR pathway [162,168]. Proteinuria is a common renal side effect of antiangiogenic MKIs [166]. All MKI treatments evaluated in TCs are related to increased risk of gastrointestinal toxicities, including nausea, vomiting, diarrhoea, mucositis, weight loss and hepatic impairment [122,166]. Fatigue, also defined as asthenia, can arise as a common AE during treatment with MKIs [168]. Recently, Monti et al. (2021) suggested that adrenal insufficiency may be responsible for lenvatinib-associated fatigue (especially in patients experiencing extreme fatigue) [170]. Preliminary findings suggest that early diagnosis of primary adrenal insufficiency is important, since cortisone acetate replacement therapy can improve fatigue in patients without the need of dose reduction of MKIs [170]. Thyroid function and thyroid hormone metabolism are the most commonly reported endocrine toxicities caused by MKIs, especially those targeting VEGFR [171]. The majority of severe side effects occur early in the course of treatment, and if managed, patients may experience persistent long-term disease control [172]. Side effects occur more frequently in older patients and may differ according to the patient’s ethnicity [169].
Table 5. Most common adverse events (AEs) reported for kinase inhibitors in TC treatment over the past two years.

| Research          | Study Phase | Agent (Dose or Group) | No of Patients: Total/ Dropouts due to AEs | Dose Reduction (No of Patients) | ORR   | DCR   | CR    | PR    | SD    | PD    | OS (Months) | PFS (Months) | All-Grade Most Common AEs (%) |
|-------------------|-------------|-----------------------|--------------------------------------------|---------------------------------|-------|-------|-------|-------|-------|-------|-------------|--------------|-----------------------------|
| Li et al. [161]   | IIB         | Anlotinib vs. placebo vs. open label | 62 vs. 29 vs. 12 | 10 vs. 1 vs. 1 | 48% vs. 0% vs. 33% | 89% vs. 86% vs. 83% | ND | ND | ND | ND | 50 vs. ND | 21 vs. 19 vs. 11 | ND | Proteinuria (63% vs. 10% vs. ND) |
| Lin et al. [119]  | II          | Apatinib (500 mg vs. 750 mg) | 10 vs. 10 | 5 vs. 9 | 70% vs. 90% | 90% vs. 100% | 0% vs. 0% | 70% vs. 90% | 20% vs. ND | ND | 34 vs. 52 | 14 vs. 15 | ND | PPES (63% vs. 10% vs. ND) |
| Brose et al. [122]| III         | Cabozantinib vs. placebo | 125/6 vs. 62/0 | 70 vs. 3 | 35% vs. 2% | 43% vs. 16% | 0% vs. 0% | 9% vs. 0% | 61% vs. 34% | ND | 6 vs. 2 | ND | ND | Proteinuria (90%) |
| Lin et al. [121]  | II          | Donafenib (200 mg vs. 300 mg) | 17/1 vs. 18/3 | 8 vs. 13 | 13% vs. 13% | 100% vs. 100% | ND | 13% vs. 13% | 88% vs. ND | ND | 9 vs. 15 | ND | ND | PPES (88% vs. 78%) |
| Wirth et al. [146]| II          | Lenvatinib | 34/6 | 14 | 3% | 53% | 0% | 3% | 50% | 27% | 3 | 3 | ND | ND | Decreased appetite (29%) |
| Takahashi et al. [124]| ND         | Lenvatinib (DTC or ATC or MTC) | 442 or 124 or 28 | 105 or 37 or 6 | 59% or 44% or 45% | 92% or 76% or 100% | 3% or 3% or 5% | 57% or 41% or 40% | 33% vs. 41% | ND or ND or ND | ND | ND | PPES (39% or 26% or 39%) |
| Song et al. [126]| ND         | Lenvatinib | 43/6 | 30 | ND | 98% | ND | 65% | 56% | 2% | ND | 22 | ND | ND | Fatigue or asthenia (72%) |

MKIs

- Proteinuria (61% vs. 10% vs. ND)
- Hypertriglyceridermia (48% vs. 24% vs. ND)
- Hypertension (56% vs. 57% vs. ND)
- Decreased appetite (29%)
- Fatigue (29%)
- Stomatitis (29%)
- Proteinuria (43% or 30% or 39%)
- PPES (39% or 26% or 39%)
- Fatigue or asthenia (72%)
- Diarrhoea (67%)
- HT (65%)
- Proteinuria (58%)
| Research          | Study Phase | Agent (Dose or Group) | No of Patients: Total/Dropouts due to AEs | Dose Reduction (No of Patients) | ORR | DCR | CR | PR | SD | PD | OS (Months) | PFS (Months) | All-Grade Most Common AEs (%) |
|-------------------|-------------|----------------------|------------------------------------------|----------------------------------|-----|-----|----|----|----|----|------------|--------------|-----------------------------|
| Porcelli et al.   | ND          | Lenvatinib           | 23/3                                     | 23                               | ND  | ND  | ND | ND | ND | 26%| 61% | 4% | 46 | 25 | HT (78%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Fatigue (74%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Weight loss (65%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Asthenia (50%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Nausea (40%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Diarrhoea (30%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Weight loss (30%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | PPES (81% vs. 39%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | HT (19% vs. 94%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Thrombocytopenia (ND vs. 50%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Hypocalcemia (38% vs. ND) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Proteinuria (33% vs 33%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Loss of appetite/weight (46% vs. 49% vs. 25%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Diarrhoea (43% vs. 44% vs. 42%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Fatigue (ND vs. 44% vs. 29%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Hypothyroidism (92% vs. 100%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Rash (28% vs. 48%) |
|                   |             |                      |                                          |                                  |     |     |    |    |    |     |    |    |    | Diarrhoea (12% vs. 39%) |
| Matrone et al.    | ND          | Lenvatinib           | 9                                        | 7                                |    | 36% | 80% | ND | 11% | 89% | ND | ND | ND | ND | ND |
| Ito et al.        | ND          | Sorafenib vs. Lenvatinib | 21 vs. 18                             | ND                               | ND  | ND  | ND | ND | 22% vs. 62% | 72% vs. 24% | 6% vs. 2% | ND | ND | ND |
| Koehler et al.    | ND          | Sorafenib vs. Lenvatinib vs. Pazopanib | 33/14 vs. 53/23 vs. 15/4 | 16 vs. 34 vs. 6 | 18% vs. 70% vs. 60% | ND | 68% vs. 53% | 21% vs. 9% | ND | 37 vs. 47 vs. 34 | 9 vs. 12 vs. 12 | ND | ND | ND |
| Valerio et al.    | ND          | Vandetanib (short-term vs. long-term treatment) | 25 vs. 54 | ND | ND | ND | ND | 26% vs. 72% | ND | ND | ND | 47 vs. 87 | ND | ND | ND |

Table 5. Cont.
| Research            | Study Phase | Agent (Dose or Group)                                                                 | No of Patients: Total/Dropouts due to AEs | Dose Reduction (No of Patients) | ORR  | DCR  | CR   | PR   | SD  | PD  | OS (Months) | PFS (Months) | All-Grade Most Common AEs (%) |
|---------------------|-------------|-------------------------------------------------------------------------------------|------------------------------------------|----------------------------------|------|------|------|------|-----|-----|------------|--------------|-----------------------------|
| Salama et al. [134] | II          | Dabrafenib and Trametinib                                                          | 29                                       | ND                              | 38%  | 76%  | ND   | 38%  | 38% | 7%  | 29          | 11           | Fatigue (74%) Nausea (57%) Chills (54%) Dysgeusia (47%) Fatigue (35%) Constipation (28%) Fatigue (69% vs. 49%) Acneiform dermatitis (43% vs. 18%) Decreased appetite (40% vs. 36%) Constipation (40% vs. 27%) |
| Doebele et al. [139] | I /II       | Entrectinib                                                                          | 68/3                                     | 27                              | 57%  | ND   | 7%   | 50%  | 17% | 7%  | 21          | 11           |                                                                           |
| Desai et al. [138]  | I           | Lifirafenib (dose escalation vs. dose expansion)                                    | 35/5 vs. 96/19                          | ND                              | ND   | ND   | ND   | ND   | ND  | ND  | ND          | ND           | Fatigue (69%) vs. 49% Acneiform dermatitis (43% vs. 18%) Decreased appetite (40% vs. 36%) Constipation (40% vs. 27%) |
| Subbiah et al. [162]| I /II       | Pralsetinib (RET<sup>m</sup> MTC previously treated or RET<sup>m</sup> MTC with no previous treatment or RET<sup>f</sup> TC) | 55 or 21 or 9 (and 8 deaths)           | 5 (and 8 deaths)                | 60%  | 93%  | 2%   | 58%  | 33% | 4%  | 17 or 19     | 15 or 13     | Neutropenia (34%) Decreased WBC count (34%) Increased AST level (34%) |
Table 5. Cont.

| Research     | Study Phase | Agent (Dose or Group)                                                                                                                                                                                                 | No of Patients: Total/Dropouts due to AEs | Dose Reduction (No of Patients) | ORR | DCR | CR | PR | SD | PD | OS (Months) | PFS (Months) | All-Grade Most Common AEs (%) |
|--------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|-------------------------------|-----|-----|----|----|----|----|-------------|---------------|-------------------------------|
| Wirth et al. | I/II        | Selpercatinib (RETm MTC previously treated or RETm MTC with no previous treatment or RETf TC previously treated)                                                                                                         | 55 or 88 or 19                          | ND                            | 62% or 71% or 58% | 69% or 67% or 58% | 5% or 3% or 0% | 56% or 67% or 58% | 29% vs. 27% vs. 37% | 5% vs. 0% vs. 0% | ND           | 27 or 24 or ND       | Dry mouth (46%) HT (43%) Diarrhoea (38%) Fatigue (38%) |

AST, aspartate aminotransferase; CR, complete response; DCR, disease control rate; HT, hypertension; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PPES, palmar-plantar erythrodysesthesia syndrome; PR, partial response; RETf, RET fusion-positive; RETm, RET mutation-positive; SD, stable disease; WBC, white blood cell.
The most frequent AEs in BRAF- and MEK-targeted therapies are fatigue, fever, diarrhoea, HT and hyperproliferative cutaneous events [38,173]. Most are grade 1 and 2 and are consistent with those reported for BRAF or MEK inhibitors alone [173]. The incidence of AEs in combinatory therapy with dabrafenib and trametinib is highest during the initial six months of treatment and declines thereafter [173]. These findings emphasize the need for proper management of AEs during early treatment, similarly to MKI-based therapies, to avoid poor adherence and early discontinuation from the treatment [166,167,173]. RET-targeted therapies, based on selpercatinib and pralsetinib, seem to exhibit lower side effects than other FDA-approved treatments (Table 5). The majority of patients tolerate these drugs well, while only a few percent of patients discontinue the therapy due to treatment-related AEs [62,162,163]. The most commonly observed AEs of selpercatinib are HT, diarrhoea, fatigue and dry mouth [163], whereas pralsetinib administration is associated with increased risk of neutropenia and liver impairment as well as decreased white blood cells (WBCs) count [162]. Overall, comprehensive education of patients to increase their awareness of signs and symptoms of possible side effects and continued monitoring is critical.

5. Conclusions and Future Perspectives

Novel tyrosine kinase inhibitor-based approaches have been studied, alone or in combination, to improve the inauspicious prognosis of TC patients. The results of recent studies highlight new treatment opportunities for RAIR-DTC, ATC and MTC patients. Prolonged progression-free and overall survival are possible with targeted therapeutic agents. Prospectively, information on molecular aberrations will be more important than the histological type of TC and will be crucial for clinical decision-making.

Implementation of kinase inhibitors promotes approaches, which are related to the individual needs of patients. Such personalized, low-risk therapies, in which the administered selective KIs target certain specific aberrations, are possible due to the increasing availability of advanced molecular tests that allow for rapid mutational analysis of TCs. Moreover, therapy of TCs will be based upon selection of chemotherapeutics previously used in other cancer types, while the aim of treatment will focus on the point of action, i.e., place and type of mutation.

Despite remarkable progress, there continue to be two broad categories of barriers in clinical usage of targeted therapeutics in TCs, i.e., limiting adverse effects and development of resistance. Targeted agents usually have less severe and long-term AEs than conventional chemotherapy. However, they should be considered as chronic approaches, and appropriately managed to prolong treatment duration in patients exhibiting a clinical benefit [38]. The acquired drug-resistance phenomenon, which results from systemic therapies, remains a concern. For example, up to half of patients treated with BRAF-targeted SKIs eventually develop resistance. It is typically mediated through reactivation of the MAPK pathway and can occur through several mechanisms, including upstream activating mutations (e.g., mutations in RAS-encoding genes), downstream MAPK pathway alterations (e.g., MEK and ERK mutations), activation of parallel signaling pathways (e.g., PI3K/AKT), increase in the expression level of RTKs (e.g., EGFR) and BRAF gene amplification and alternative splicing. The failure of targeted therapies could also result from overexpression of ATP binding cassette (ABC) drug efflux pumps [173,174]. Recent studies demonstrated that overexpression of ABCB1 is sufficient to confer resistance of cancer cells to kinase inhibitors [175,176]. The phenomenon of multidrug resistance requires use of combinatory therapies that are composed of drugs with differing molecular targets, mechanisms of action and various signaling pathways. Thus, both non-selective and selective kinase inhibitors, as well as immunomodulatory drugs, check-point inhibitors and agents that influence other signaling pathways will be implemented in management and therapy of TCs.
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Abbreviations

AEs adverse events
ALK anaplastic lymphoma kinase
AST aspartate aminotransferase
ATA American Thyroid Association
ATC anaplastic thyroid cancer
BMI body mass index
BRAF B-Raf proto-oncogene
CT computer tomography
CTLA-4 cytotoxic T-lymphocyte antigen-4
DeTC dedifferentiated thyroid cancer
DIT diiodotyrosine
DTC differentiated thyroid cancer
EBRT external beam radiation therapy
eIF1A eukaryotic translation initiation factor 1A
EMA European Medical Agency
FAP familial adenomatous polyposis
FDA Food and Drug Administration
\(^{18}\)FDG \(^{18}\)-fluoro-2-deoxy-D-glucose
FNAB fine-needle aspiration biopsy
FTC follicular thyroid carcinoma
FVPTC follicular variant of PTC
GTP guanosine triphosphate
HCC Hürthle cell carcinoma
HNHA N-hydroxy-7-(2-naphthylthio) heptanamide
HT hypertension
IDH1 isocitrate dehydrogenase 1
IDH2 isocitrate dehydrogenase 2
IMRT intensity-modulated radiation therapy
KIs kinase inhibitors
MAPK mitogen-activated protein kinase
MEN multiple endocrine neoplasia
MEN2 multiple endocrine neoplasia type 2
MIT monoiodotyrosine
MKIs multi-kinase inhibitors
MRI magnetic resonance imaging
MTC medullary thyroid cancer
ND not defined
NIS sodium iodide symporter
ORR overall response rate
OS overall survival
PAX8 paired box 8
PD progressive disease
PDCT poorly differentiated thyroid carcinoma
PET positron emission tomography
PFS progression-free survival
PI3K phosphatidylinositol 3-kinase
PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase
PLC-γ phospholipase C
PPARγ peroxisome proliferator activated receptor γ
PPES palmar-plantar erythrodysesthesia syndrome
PR partial response
PTC papillary thyroid carcinoma
RAI radioactive iodine; radioiodine
RAIR radioactive iodine refractory; radioiodine refractory
RANKL receptor activator of nuclear factor κB ligand
RETf RET fusion-positive
RETr RET mutation-positive
RTK receptor tyrosine kinase
RWS Real-Word Studies
SD stable disease
SKIs specific kinase inhibitors
T3 triiodothyronine
T4 thyroxine
TBSRTC The Bethesda System for Reporting Thyroid Cytopathology
TC thyroid cancer
TCGA The Cancer Genome Atlas
TERT telomerase reverse transcriptase
Tg thyroglobulin
THs thyroid hormones
TPO thyroid peroxidase
TRK tropomyosin receptor kinase
TSH thyroid-stimulating hormone
USG ultrasonography
WBC white blood cell
WHO World Health Organization
wt wild type

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