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**Chapter**

# Thyroid Cancer: From Genes to Treatment—Recent Developments

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## Abstract

Thyroid cancer carries a good prognosis in most cases and is treated by thyroid-ectomy, radioiodine administration thereafter, thyroxine treatment. Although, most cases of thyroid cancer are curable, if thyroid cancer loses the ability to concentrate iodine and thus becomes refractory to radioiodine, and if thyroid cancer becomes a progressive disease, the need for targeted treatment becomes necessary. Research in the area of the biology of thyroid cancer and in particular the discovery of somatic genetic mutations involved in the pathophysiology of thyroid cancer as well as research in the treatment of other cancer types with tyrosine kinase inhibitors have led to the application of tyrosine kinase and angiogenetic factor inhibitors in the treatment of thyroid cancer. The application of tyrosine kinase inhibitors in other tumor types led to the discovery that they target the thyroid. Thus, tyrosine kinase inhibitors entered the field of radioactive iodine refractory and advanced thyroid cancer treatment. Multi-kinase and angiogenetic factor inhibitors have provided a novel method that targets thyroid tumors and have revolutionized the treatment of radioiodine refractory and advanced thyroid cancer.

**Keywords:** tyrosine kinase inhibitors, multi-kinase and angiogenetic factor inhibitors, advanced thyroid cancer, iodine refractory thyroid cancer, differentiated thyroid cancer, medullary thyroid carcinoma

## 1. Introduction

Thyroid cancer represents 90% of malignant tumors of the endocrine system and is the cause of 0.5% of all deaths from cancer in man [1–3]. Thyroid cancer is quite frequent, as in adults in autopsy findings it has been observed with a frequency ranging from 4 to 36% [4]. In the clinical setting, thyroid cancer is found in 6–10% of thyroid nodules [5]. Thyroid cancer is observed with greater prevalence in female as compared to male patients with a rate of 2–3/1 [6]. The incidence of thyroid cancer was rising until recently in the USA; however, its incidence now has leveled off. The main types of thyroid cancer are the two types of differentiated follicular thyroid carcinoma, namely papillary and follicular, representing 70–80% and 15–20%, respectively, and medullary and anaplastic thyroid carcinomas with a frequency of 5–8% and 3–5%, respectively (**Figure 1**) [7]. The etiology of thyroid cancer includes genetic mutations, head and neck irradiation, and iodine deficiency [8]. The diagnosis is
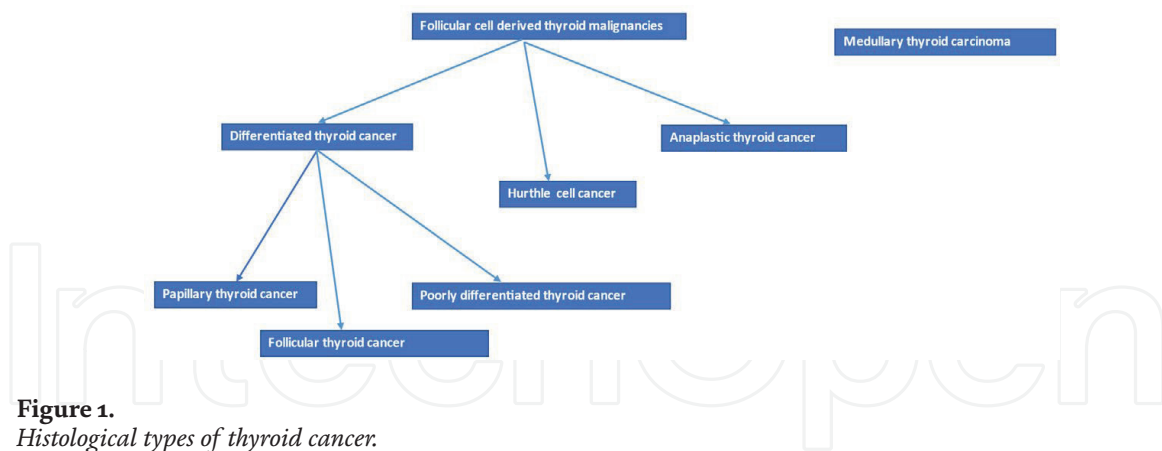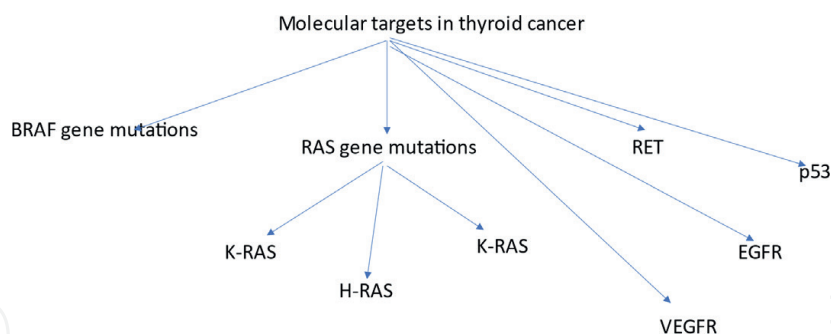
**Figure 1.**
*Histological types of thyroid cancer.*

based on history, clinical examination, biochemical and imaging examination, and fine needle aspiration biopsy [9]. Treatment of differentiated and medullary thyroid carcinoma is total or near total thyroidectomy, including lymph node dissection [10, 11]. In differentiated thyroid carcinoma, radioactive iodine is administered for the destruction of thyroid remnants [12]. In anaplastic thyroid carcinoma, an effort is made for resection of as much as possible of the tumor. In all cases, thyroxine treatment is administered [13]. The prognosis of differentiated thyroid cancer is good and 10-year prognosis in papillary thyroid cancer is 93%, in follicular thyroid cancer is 85%, in medullary thyroid cancer 75%, and in anaplastic thyroid cancer 2–6 months, while rarely more than a year [14].

Although, most cases of thyroid cancer are curable, if thyroid cancer loses the ability to concentrate iodine and thus becomes refractory to radioiodine and if thyroid cancer becomes a progressive disease the need for targeted treatment becomes necessary [15]. Novel treatment methods for the management of advanced thyroid cancer have emerged after extensive research efforts, which have revolutionized thyroid cancer treatment [16–22]. Research in the area of the biology of thyroid cancer and in particular the discovery of somatic genetic mutations [23, 24] involved in the pathophysiology of thyroid cancer as well as research in the treatment of other cancer types with tyrosine kinase inhibitors [25] have led to the application of tyrosine kinase and angiogenetic factor inhibitors in the treatment of thyroid cancer [26]. In cases of renal cancer, the application of tyrosine kinase inhibitors led to the appearance of hypothyroidism due to the destruction of the thyroid gland [27, 28]. Thus, tyrosine kinase entered the field of radioactive iodine refractory and advanced thyroid cancer [29]. Multi-kinase and angiogenetic factor inhibitors have revolutionized the treatment of radioiodine refractory and advanced thyroid cancer [29]. The need for genetic mutation testing before treatment is initiated [30, 31] has been recognized in patients with radioiodine refractory and advanced thyroid cancer to enable targeted treatment.

## 2. Molecular genetics in the etiology of thyroid cancer

The etiology of thyroid cancer is not known, although there are factors known to induce its development, such as ionizing radiation and iodine deficiency. Recent progress in molecular genetics has shown that thyroid cancer is due to genetic mutations either germline or somatic (**Figure 2**) [32]. These mutations lead to the inactivation of

**Figure 2.**
*Molecular targets in thyroid cancer.*

onco-suppressor genes, which inhibit the formation of cancer or to the activation of oncogenes, which act on normal cells and lead to cancer development.

Papillary thyroid carcinoma is the most common thyroid cancer and represents approximately 80% of cases. Papillary thyroid carcinomas frequently harbor genetic changes leading to the activation of the mitogen-activated protein kinase (MAPK) signaling pathway [33]. These genetic alterations are mainly the RET/PTC rearrangement and point mutations of the BRAF and RAS genes. Mutations involving the above-mentioned genes are observed in more than 70% of papillary carcinomas and are mutually exclusive, meaning that if one mutation is found the other is not observed [32]. Genetic changes observed in follicular carcinomas, which represent the second in frequency type of thyroid cancer, are RAS mutations and PAX8-PPARγ rearrangement [33]. The discovery of these mutations led to extensive research and the discovery of therapeutic agents for the successful management of iodine refractory or advanced thyroid cancer.

In papillary thyroid cancer, the most common genetic mutation which has been observed is the gene rearrangement of the RET gene, which leads to increased expression of tyrosine kinase [34]. Thus, the thyroid cell is led to increased growth and multiplication and finally to tumor formation.

Follicular thyroid cancer presents with mutations in RAS oncogenes, which cause cell growth and multiplication [33]. The presence of RAS mutations is also observed in papillary carcinomas with follicular differentiation. Ionizing radiation is a known etiologic factor for thyroid cancer. It appears that small energy sources are transferred with radiation to the cells, leading subsequently to RAS gene mutations.

Anaplastic thyroid carcinoma has mutations in p53 gene [35, 36]. The p53 gene is a translational factor that is involved in the regulation of apoptosis and the cell cycle. It appears that this is the final step in the formation of thyroid cancer with the most malignant phenotype, which is added to the already existing genetic changes.

Medullary thyroid cancer presents with mutations in RET oncogene [37]. There has been progress in the pathogenesis of medullary thyroid carcinoma both in the hereditary and sporadic medullary thyroid carcinoma. The RET gene is involved in the pathogenesis of hereditary and sporadic medullary thyroid carcinoma. Mutations observed in the germ cells are detected in all the cells of the organism and their detection in the DNA of blood leucocytes forms the basis of finding carriers of the MEN2 syndrome. The MEN2 syndrome diagnosis is based on finding medullary thyroid cancer, pheochromocytoma, and parathyroid adenoma. In 97% of patients mutations in the RET gene have been observed in the DNA of blood leucocytes. In sporadic

medullary thyroid carcinoma, somatic RET mutations at the level of the thyroid tumor have been observed.

## 3. Genetic mutations and thyroid cancer

### 3.1 BRAF

The most studied point mutation in thyroid cancer is that of the BRAF gene [33, 34]. The BRAF$^{v600E}$ somatic mutation is involved in approximately 45% of papillary thyroid cancer and tall cell variant and in 25% of anaplastic thyroid cancer. This somatic mutation of thyroid cells is related to the substitution of valine with glutamate and leads to the activation of BRAF kinase, which phosphorylates several targets and in particular mitogen-activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK) [38]. The BRAF$^{v600E}$ mutation is associated with tumor aggressiveness and a poor prognosis, as it leads to higher tumor size and metastasis, either lymph node or distant metastasis.

### 3.2 RET/PTC

The RET proto-oncogene codes for a cell membrane receptor tyrosine kinase. Within the thyroid, RET is expressed in parafollicular C cells, within which it can be activated by chromosomal rearrangement. In RET/PTC the 3′ portion of the RET gene is fused to the 5′ portion of various unrelated genes [39]. The RET/PTC1 and RET/PTC3 account for most of the rearrangements observed in papillary carcinomas. RET/PTC is tumorigenic in thyroid follicular cells and is detected in approximately 20% of papillary thyroid carcinomas. Papillary thyroid carcinomas with RET/PTC rearrangement present at a younger age, have lymph node metastases and may have a favorable prognosis.

### 3.3 RAS

Another frequent driver of somatic mutation involved in the pathogenesis of thyroid cancer is that of the RAS gene [40], which lies upstream of BRAF. N-RAS, H-RAS, and K-RAS are members of the RAS family and those most commonly involved in thyroid cancer are the N-RAS and H-RAS and can constitutively activate the MAPK and PI3K/AKT pathways. RAS somatic mutations are present in 40–50% of follicular thyroid cancer, 15% of papillary thyroid cancer, follicular variant thyroid cancer, and 50% of anaplastic thyroid cancer. The K-RAS mutation is considered an activator of the MAPK pathway as compared to N-RAS mutation, which is an activator of the PI3K-AKT pathway. In papillary thyroid cancer genetic mutations of the RAS gene are mutually exclusive with the mutations of the BRAF gene.

### 3.4 RET point mutations

In medullary thyroid carcinomas, RET is activated by point mutations, as compared to its activation by chromosomal rearrangement in papillary thyroid cancer. Germline mutations are observed in MEN2A, MEN2B, and familial medullary thyroid

carcinoma [41]. In MEN2A most mutations affect codon 634, whereas in MEN2B germline mutations affect codon 918, whereas in sporadic medullary thyroid carcinomas, somatic mutations of RET are observed [42].

### 3.5 VEGF

Angiogenesis has a key role in tumor initiation and progression and lymphangiogenesis is crucial for metastasis formation. Thus, angiogenesis and lymphangiogenesis are targets of cancer treatment. Angiogenesis involves the activation of VEGFR2, a tyrosine kinase receptor that is expressed in vascular endothelial cells. The expression of VEGFR2, a tyrosine kinase receptor is induced by VEGF-A produced by neoplastic and immune cells within the tumor.

Hypoxia within the tumor induces the activation of transcriptional factor hypoxia-inducible factor-1 alpha (HIF-1$\alpha$), which leads to expression of VEGF-A. HIF-1$\alpha$ is expressed mainly in anaplastic thyroid cancer cells.

Thyroid cancer aggressiveness is associated with increased angiogenesis and the expression of VEGF/VEGFR, PDGF/PDGFR, and EGF/EGFR [43, 44]. In differentiated thyroid cancer, VEGFR and VEGFR-2 are overexpressed and contribute to tumor progression and aggressiveness. In particular, in papillary thyroid cancer, VEGF expression is related to local and distant metastatic disease.

### 3.6 EGFR

The EGFR cell surface protein is a member of the ErbB family of receptors. In epithelial carcinoma, EGFR mutations have been observed. EGFR has been found to be related to thyroid cancer progression and invasiveness and its overexpression has been observed in anaplastic thyroid cancer [45].

### 3.7 Tumor suppressor genes

The gene tumor protein P53 (TP53) encodes the tumor suppressor gene p53. The loss of its expression leads to a loss of control of cell growth and cell apoptosis. The p53 gene is mutated in anaplastic thyroid cancer and is involved in its pathogenesis [35, 46].

## 4. Multi-kinase and angiogenetic factor inhibitors

The successful application of multi-kinase and angiogenetic factor inhibitors in the treatment of various types of cancer [25] has led to observations that multiple kinase and angiogenetic factor inhibitors attack the thyroid cells and may lead to hypothyroidism and in some cases eradication of the thyroid gland [27, 28, 47]. These observations led to the application of multi-kinase and angiogenetic factor inhibitors in the treatment of radioactive iodine refractory and advanced thyroid cancer (**Table 1**) [37]. Multi-kinase and angiogenetic factor inhibitors interfere with some of the pathogenetic pathways involved in the pathogenesis of thyroid cancer and in tumor growth and the development of metastatic disease [10]. This application has led to a revolution in the treatment of advanced thyroid cancer.

| Drug | Target—mode of action | Indications by histology of thyroid cancer |
|---|---|---|
| Axitinib | TKI VEGFR1–3 | DTC, MTC, ATC |
| Cabozantinib | TKI, VEGFR2, MET, FLT3, RET, c-kit | MTC, DTC |
| Dabrafenib | STKI, BRAF$^{V600E}$ | DTC |
| Dabrafenib with trametinib | STKI, BRAF$^{V600E}$, MEK1/2 | DTC |
| Entrectinib | TrkI, NTRK fusions | DTC |
| Larotrectinib | TrkI, NTRK fusions | NTRK-fusion thyroid carcinoma |
| Pazopanib | TKI, VEGFR1–3 PDGFR, FGFR1/2, c-kit | MTC, DTC, ATC |
| Sorafenib | TKI, VEGFR1–3, PDGFR, RET, c-kit, CSF-1R, Flt-3 | DTC, MTC, ATC |
| Sunitinib | TKI: VEGFR1–3, PDGFR, RET, c-kit, CSF-1R, Flt-3 | MTC |
| Vandetanib | TKI, VEGFR2/3, EGFR, RET | MTC, DTC |
| Vemurafenib | STKI, BRAF$^{V600E}$ | DTC |

*TKI—tyrosine kinase inhibitor, STKI—serine-threonine kinase inhibitor, DTC—differentiated thyroid cancer, MTC—medullary thyroid cancer, ATC—anaplastic thyroid cancer.*

**Table 1.**
*Drugs applied in the treatment of advanced thyroid cancer.*

## 4.1 Sunitinib

Sunitinib is a small molecule and is a multi-kinase and angiogenetic factor inhibitor that inhibits RET/PTC subtypes 1 and 3, VEGFR1, VEGFR-2, VGEFR-3, KIT, and PDGFR kinases [48]. The drug was initially approved by the FDA for gastrointestinal stromal tumor and clear cell renal carcinoma [49]. The drug is currently under investigation for the treatment of several human tumors. The most common adverse events are hand-foot syndrome, fatigue, neutropenia, diarrhea, hypothyroidism, and hypertension [50].

Sunitinib was found in preclinical studies to inhibit *in vitro* RET/PTC oncoproteins. It has been studied in various studies in differentiated thyroid cancer and medullary thyroid cancer patients and either partial response or stable disease was observed [51, 52]. In a study with metastatic radioiodine-refractory thyroid cancer partial response was observed. In the phase II trial of sunitinib (THYSU), the drug was tested in patients with advanced or metastatic differentiated/anaplastic or medullary thyroid cancer with improvement in progression-free survival and overall survival [53, 54]. In the phase II trial of sunitinib in progressive medullary thyroid cancer patients, the drug was found to be effective in progressive medullary thyroid cancer. In an open-label phase II study, sunitinib was found to induce complete response in some patients with metastatic medullary thyroid cancer and differentiated thyroid cancer. In an anaplastic thyroid cancer patient, sunitinib was administered with a good clinical response [55].

### 4.2 Sorafenib

Sorafenib is a multi-kinase inhibitor that inhibits RAF, VEGFR2, VEGFR3, PDGFR, RET, and KIT kinases [56, 57]. It exerts anti-neoplasmatic effects in preclinical models of cancer and thyroid cancer cell lines. Sorafenib inhibits thyroid cancer growth by acting with antiproliferative and antiangiogenic mechanisms [57]. The FDA has approved its use in hepatocellular and renal cell carcinoma and metastatic differentiated thyroid carcinoma [58]. Sorafenib is administered orally at 400 mg twice daily and is usually well tolerated. Sorafenib has been administered to patients with metastatic radioiodine refractory thyroid cancer for about 27 weeks and it was found to induce a partial response, improve progression-free survival and have clinical benefits [59]. In another study, sorafenib was administered to patients with metastatic papillary thyroid cancer chemotherapy-naive and in patients with papillary thyroid cancer who had already received chemotherapy and other subtypes of thyroid cancer and it was found to induce partial response in 6 of 22 patients and to induce disease stabilization which lasted more than 6 months in 23 patients [59, 60]. Sorafenib was administered to radioactive iodine refractory papillary and follicular thyroid cancer with a remission rate of 20% [59]. In these patients with metastatic thyroid cancer, the response of metastatic disease differed depending on the site of metastasis. Bone lesions had a minimal response, whereas a better effect was observed in lung metastatic disease. Thyroglobulin was considered a positive biomarker of response to treatment. In a double-blind phase III trial, the clinical activity of sorafenib as compared to placebo was assessed in patients with radioactive iodine refractory locally advanced or metastatic differentiated thyroid carcinoma [17]. In patients treated with sorafenib, the progress-free survival increased in all subgroups regardless of mutation status. This study demonstrated the efficacy of sorafenib in radioactive–iodine refractory differentiated thyroid cancer. Other studies demonstrated the efficacy of sorafenib in progressive metastatic differentiated thyroid cancer. A meta-analysis involving 15 studies evaluated the safety and efficacy of sorafenib in radioactive iodine refractory differentiated thyroid carcinoma [59]. Sorafenib improved progression-free survival in patients with radioactive iodine refractory differentiated thyroid carcinoma patients. The most frequent adverse effects were hand-foot syndrome, diarrhea, fatigue, alopecia, weight loss, and rash. The study focused on the efficacy of sorafenib in improving progression-free survival in differentiated thyroid cancer as compared to placebo. Although sorafenib was observed in combination with metformin to inhibit anaplastic thyroid cancer cells [61], the drug was not effective *in vivo* in an anaplastic thyroid cancer patient [36].

Sorafenib is associated with an increase in progression-free survival and disease stabilization. Sorafenib administration and acquired resistance to it may be associated with the induction of autophagy [62]. In this context, several substances have been applied to limit autophagy and the related resistance of cancer to treatment [62, 63]. The administration of agents to inhibit autophagy may sensitize a tumor to the multi-kinase inhibitor linifanib [64].

### 4.3 Vandetanib

Vandetanib is a potent inhibitor of VEGFR-2, VEGFR-3, RET, and EGFR kinases [65]. Vandetanib has been approved by FDA and EMA for use in patients with

metastatic or progressive medullary thyroid cancer [66]. In an international randomized trial, the therapeutic efficacy of vandetanib was shown in patients with advanced medullary thyroid cancer as it showed a significant prolongation of progression-free survival as compared to placebo [67]. In a double-blind phase II study, vandetanib was shown to prolong progression-free survival in patients with locally advanced or metastatic differentiated thyroid carcinoma patients [68]. Recently, a meta-analysis and systematic review, through standardized RECIST criteria as endpoints, investigated vandetanib efficacy in medullary thyroid carcinoma. The study included only original studies in which the drug was used as a single agent. Ten (eight observational longitudinal studies and two randomized controlled trials) were included among the 487 screened articles. The results obtained through the RECIST criteria did not provide clear evidence of the efficacy of vandetanib [69]. Nonetheless, vandetanib is considered a new-generation treatment in advanced medullary thyroid carcinoma.

Vandetanib has been evaluated in patients with symptomatic or progressive medullary thyroid cancer in various starting doses, 150 or 300 mg daily, and was found to have a good response with a better response at the dose of 300 mg [70]. Adverse effects of vandetanib were QTc prolongation, hypocalcemia, asthenia, diarrhea, keratopathy, and hypokalemia. In a systematic review, the cost-effectiveness of cabozantinib and vandetanib were compared [71]. Both drugs improved progress-free survival although no significant overall survival benefits were observed. Vandetanib is considered a new-generation treatment for advanced medullary thyroid cancer.

## 4.4 Lenvatinib

Lenvatinib inhibits FGFR-1, FGFR-2, FGFR-3, FGFR-4, PGGFRβ, VEGFR-1, VEGFR-2, VEGFR-3, RET, and KIT kinases [72]. Lenvatinib has been approved by FDA and EMA for the treatment of advanced radioactive iodine refractory differentiated thyroid cancer [73]. Lenvatinib was administered to patients with advanced radioiodine refractory differentiated thyroid cancer that had progressed during the earlier 12 months. After a follow-up of 14 months, the overall response rate was 50%, the median time to relapse was 3.6 months, the median progression-free survival was 12.6 months and the median response duration was 12.7 months. Lenvatinib was administered to patients with unresectable progressive medullary thyroid cancer and was found to be effective [74]. In a double-blind randomized study, lenvatinib was administered to 261 patients with progressive radioiodine refractory thyroid carcinoma [16]. The study included a placebo group of 131 patients. Median progression-free survival was longer in the lenvatinib group as compared to placebo. The response rate was 64.8%. However, side effects were observed. In a randomized study examining the effect of lenvatinib on tumor size, it was shown to improve tumor size rapidly at the beginning of the study and to induce continued shrinkage thereafter [75]. A phase II study evaluated lenvatinib in 51 patients with radioactive iodine refractory differentiated thyroid carcinoma, medullary thyroid carcinoma, and anaplastic thyroid cancer with a median progression-free survival of 25.8 months, 9.2 months, and 7.4 months, respectively [76]. The safety profile of the drug was manageable, and an antitumor efficacy was observed in radioactive iodine refractory thyroid cancer and promising efficacy in medullary thyroid cancer and anaplastic thyroid cancer. Lenvatinib was also evaluated postoperatively in anaplastic thyroid cancer patients and was shown to have a response rate of 17.4% [77]. Hypertension was the most frequent adverse effect.

### 4.5 Cabozantinib

Cabozantinib inhibits Tie-2, c-MET, KIT, VEGFR-1, VEGFR-2, and RET kinases [78]. In a phase I trial, cabozantinib was administered to patients with advanced solid tumors, including 37 patients with advanced medullary thyroid cancer, and was found to have efficacy and a good safety profile in medullary thyroid cancer as it induced tumor shrinkage of >30% in some medullary thyroid cancer patients with measurable disease [79]. Cabozantinib was also evaluated in 15 radioiodine refractory differentiated thyroid cancer patients who had progressed on conventional treatment and had measurable disease [80]. FDA-approved cabozantinib for the treatment of metastatic medullary thyroid cancer. Cabozantinib was also evaluated in patients with advanced radioiodine refractory differentiated thyroid cancer who had already received another VEGFR-targeted treatment and was found to be clinically effective [81]. In a double-blind phase III trial, cabozantinib was found to be effective in improving progression-free survival in patients with progressive medullary thyroid cancer [82].

### 4.6 Dabrafenib and trametinib

Dabrafenib (also known as GSK2118436) is a BRAF kinase inhibitor, which has been tested *in vitro* and has demonstrated antiproliferative effects in human colon cancer xenografts and BRAF$^{V600E}$ positive melanoma [83]. It has also been tested in clinical trials in BRAF-positive cancers. In this case, BRAF-positive cancers become resistant to dabrafenib in 6–7 months. To prevent this therapeutic failure dabrafenib was administered with trametinib, a MEK inhibitor, and this combination was approved by the FDA for the treatment of BRAF$^{V600E}$ positive metastatic melanoma. Dabrafenib and trametinib were administered to anaplastic cancer patients with BRAF$^{V600E}$ mutation with promising results [55, 84–87].

### 4.7 Pazopanib

Pazopanib has been tested for advanced thyroid cancer and RET-mutant medullary thyroid cancer [88]. It can be used to treat advanced papillary or follicular thyroid cancer if they express RET gene changes. Pazopanib is an oral small-molecule multi-kinase inhibitor that primarily inhibits vascular endothelial growth factor receptor-1, -2, and -3, platelet endothelial growth factor receptor-α, and -β, and the stem-cell factor receptor c-kit [89]. Pazopanib was introduced as a treatment against various tumors and it has been approved in several countries for advanced soft-tissue sarcoma and renal cell carcinoma. Large clinical trials with pazopanib in patients having soft-tissue sarcoma and renal cell carcinoma have shown beneficial effects. Adverse events include liver dysfunction and hypertension but are generally manageable. Pazopanib has also been used in patients with advanced thyroid cancer [90].

### 4.8 Selpercatinib

Selpercatinib is a receptor tyrosine kinase RET (rearranged during transfection) inhibitor developed for the treatment of cancers harboring RET alterations [22]. Selpercatinib was approved by the FDA for the treatment of RET fusion-positive non-small cell lung cancer, RET fusion-positive thyroid.

### 4.9 Larotrectinib

Larotrectinib is a selective and specific inhibitor of tropomyosin receptor kinase A (TRKA), TRKB, and TRKC approved for use in Europe and the USA, which is used in the therapy of solid tumors harboring NTRK gene fusions. NTRK gene fusions involving either NTRK1, NTRK2, or NTRK3 (encoding the neurotrophin receptors TRKA, TRKB, and TRKC, respectively) are oncogenic drivers of various adult and pediatric tumor types. It has been applied in thyroid tumors thought to harbor NTRK gene fusions [91] and has been approved by the FDA for tumor agnostic indications.

### 4.10 Entrectinib

Entrectinib is another inhibitor of TRKA, TRKB, and TRKC. It has been applied in the treatment of NTRK fusion-positive cancers, including thyroid cancer [92]. Thyroid cancer-specific data are not yet available for entrectinib.

### 4.11 Vemurafenib

Vemurafenib was developed as a low-molecular-weight molecule for the inhibition of the mutated serine-threonine kinase BRAF, and it selectively binds to the ATP-binding site of BRAF$^{v600E}$ kinase and inhibits its activity [93]. It has potential to be applied in papillary thyroid carcinoma, which harbors a BRAF mutation.

## 5. Mutational testing in thyroid cancer

Most thyroid cancer cases carry a good prognosis. However, 15% of differentiated thyroid cancer cases present with locally advanced disease, and in radioiodine refractory thyroid cancer 10-year survival drops below 50%. Patients with advanced thyroid cancer and radioiodine refractory thyroid cancer should undergo somatic mutational screening [94], as novel drugs are available to treat them. These drugs are the novel multiple kinase and angiogenetic factor inhibitors, which have offered patients and physicians a new option for the treatment of advanced thyroid cancer and have revolutionized the treatment of advanced thyroid cancer patients.

## 6. Conclusion

The application of multi-kinase and angiogenetic factor inhibitors in the treatment of radioiodine refractory and advanced thyroid cancer has enabled the successful management of the disease and has revolutionized the management of radioiodine refractory and advanced thyroid cancer. As the application of these multi-kinase and angiogenetic factor inhibitors is related with an increase in progression-free survival and disease stabilization, further research is needed to identify the mechanisms involved in the acquired resistance to these agents and the ways to manage this resistance. Mutational testing in thyroid cancer may contribute to the application of targeted treatment.

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