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REVIEW

Overview of management and therapeutic advances in medullary thyroid cancer

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Abstract

Medullary thyroid carcinoma (MTC) is a rare cancer of the thyroid's calcitonin-producing C cells. This review covers recent advances in MTC treatment, emphasizing surgical and systemic therapies. For localized MTC, surgery remains the primary and most effective treatment, with total thyroidectomy and lymph node dissection providing the highest potential for cure. However, prognosis worsens significantly with local and distant metastases, underscoring the importance of early diagnosis and intervention. MTC can be sporadic or hereditary, with the latter associated with germline *RET* proto-oncogene mutations linked to multiple endocrine neoplasia types 2A and 2B. Genetic discoveries have enabled preventive measures such as prophylactic thyroidectomy, increasing the cure rate of hereditary cases. Since 2011, systemic treatment options have expanded with multikinase inhibitors (MKIs), such as vandetanib and cabozantinib, and selective RET inhibitors such as selpercatinib and pralsetinib. MKIs extend progression-free survival in advanced cases by targeting tumor growth and angiogenesis but can cause off-target effects. RET inhibitors offer precision treatment for *RET*-mutated tumors, showing high efficacy and fewer side effects, though resistance to these inhibitors has emerged, and current research focuses on developing next-generation inhibitors to overcome these barriers. Effective MTC management, particularly given its rarity, benefits from specialized high-volume centers. Precision medicine, standardized therapy selection and ongoing research are essential for improving outcomes in both *RET*-positive and *RET*-negative MTC patients.

Keywords: medullary thyroid carcinoma; RET

Overview of medullary thyroid carcinoma treatment

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor originating from the parafollicular cells (C cells) of the thyroid, which secrete calcitonin (Ctn) and carcinoembryonic antigen (CEA), both valuable tumor markers for diagnosing and managing MTC (Wells *et al.* 2015). Surgical resection remains the primary and most effective treatment, offering the highest chance of cure when the tumor is localized to the thyroid. However, prognosis worsens significantly once the disease metastasizes to the cervical lymph nodes, reducing the cure rate to around 30%. Lymph node involvement at diagnosis is a key prognostic factor (Weber *et al.* 2001, Machens *et al.* 2005).

Before 2011, no effective systemic treatments were available for advanced MTC. However, the past 14 years have witnessed remarkable advancements, notably with the introduction of multikinase inhibitors (MKIs) that target metastatic disease (Wells *et al.* 2012, Schlumberger *et al.* 2017, Kreissl *et al.* 2020).

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In the last 5 years, even more promising therapeutic developments have been made, including the approval of selective RET inhibitors, offering renewed hope for patients with advanced or metastatic MTC (Subbiah *et al.* 2018*a*,*b*, 2021*b*, 2024, Wirth *et al.* 2020, Hadoux *et al.* 2023).

Although MTC is a rare malignancy, accounting for only 5% of thyroid cancers, it is associated with considerable morbidity and mortality, corresponding to 13.4% of deaths from thyroid cancer (Kebebew *et al.* 2000). When treated according to current guidelines, patient survival and quality of life can improve significantly. This highlights the importance of adhering to current treatment guidelines, as 25% of MTC cases are still not being managed in accordance with best practices, which can negatively affect patient outcomes (McMullin *et al.* 2023, Szabo Yamashita & Grubbs 2024). This review will focus on the current therapeutic approaches for MTC.

Epidemiology and prevalence in adults and young patients: hereditary and sporadic forms

MTC can occur in two forms: sporadic and hereditary. The hereditary form is associated with pathogenic gain-of-function germline variants in the *RET* proto-oncogene and is linked to an autosomal dominant genetic syndrome known as multiple endocrine neoplasia type 2 (MEN2) (Wells *et al.* 2015). MTC is the predominant clinical manifestation of MEN2, occurring in over 95% of individuals carrying pathogenic *RET* variants, generally in the first two decades of life. MEN2 syndromes are characterized by a combination of endocrine tumors and non-endocrine manifestations and are classified into two subtypes: MEN type 2A (MEN 2A) and MEN type 2B (MEN 2B). MEN 2A is characterized by the development of MTC, pheochromocytoma and primary hyperparathyroidism. MEN 2B is associated with a distinctive phenotype that includes a marfanoid habitus, mucosal and gastrointestinal ganglioneuromas and ocular abnormalities, along with MTC and pheochromocytoma (Wells *et al.* 2015).

In adults, approximately 75% of MTC cases are sporadic, while the remaining 25% or more are hereditary. The increasing detection of hereditary cases is largely attributed to the widespread implementation of routine genetic screening within families (Wells *et al.* 2015). This rare cancer is even more uncommon in individuals under the age of 20, accounting for only 5% of all MTC cases (Zhao *et al.* 2020). Among this younger population, hereditary cases make up 86%, while sporadic cases represent just 14%.

In young patients with sporadic MTC, the *RET* gene is the primary driver, found in 80–93% of cases (Vanden Borre *et al.* 2017, Castroneves *et al.* 2024). Two recent studies of young patients with sporadic MTC demonstrated similarly aggressive disease profiles to those observed in MEN 2B patients, with a high prevalence of somatic *RET* variants, particularly the p.Met918Thr variant (Castroneves *et al.* 2024, Hensley *et al.* 2024).

Genetic and molecular basis of hereditary and sporadic forms

The *RET* proto-oncogene, located on the long arm of chromosome 10 (10q11.2), encodes a receptor tyrosine kinase critical for cell proliferation, differentiation and survival (Wells *et al.* 2015, Romei *et al.* 2016*b*, Salvatore *et al.* 2021). Germline *RET* variants account for over 95% of MEN2 cases, and the identification of these variants in 1993 revolutionized the diagnosis and management of affected individuals (Donis-Keller *et al.* 1993, Mulligan *et al.* 1993).

A significant genotype–phenotype correlation exists within MEN2, particularly regarding the aggressiveness of MTC based on the earliest reported age of onset and the risk of developing other endocrine tumors (Machens *et al.* 2003). This correlation has enabled the classification of *RET* variants into highest-, high- and moderate-risk categories, which are essential for determining the appropriate timing of prophylactic thyroidectomy, initiating surveillance for pheochromocytoma and primary hyperparathyroidism, and identifying non-carriers who do not require follow-up (Table 1) (Wells *et al.* 2015, Elisei *et al.* 2019*a*, Machens *et al.* 2003).

Multiple endocrine neoplasia type 2B (MEN 2B) represents the most aggressive form of MTC. In 95% of MEN 2B cases, a pathogenic variant in exon 16 of the *RET* gene (p.Met918Thr) is identified. Tumor development in MEN 2B patients typically occurs early, with prophylactic thyroidectomy recommended within the first year of life. However, many cases arise from *de novo* pathogenic variants, with no family history, leading to delayed diagnosis. As a result, these cases are often detected at more advanced or metastatic stages (Wells *et al.* 2015, Elisei *et al.* 2019*b*).

Sporadic MTC generally occurs later in life compared to most hereditary forms, typically between the fourth and sixth decades of life. Approximately 7–10% of patients with apparently sporadic MTC, who have no family history of the disease, are found to carry germline *RET* variants (Wiench *et al.* 2001, Romei *et al.* 2011). Consequently, it is recommended that all MTC patients undergo *RET* germline testing, regardless of family history or age at diagnosis (Wells *et al.* 2015).

The *RET* gene also plays a pivotal role in the somatic development of sporadic MTC. Studies show that somatic

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Table 1 Recommended age for prophylactic thyroidectomy, indications for central neck dissection, and initiation of pheochromocytoma and hyperparathyroidism screening based on the consensus classification of RET variant risk (modified from Wells *et al.* (2015)).

Risk category	*RET* codon	Recommended age for prophylactic thyroidectomy	Central neck dissection	Initial age for pheochromocytoma screening	Initial age for hyperparathyroidism screening
Highest	918	<1 year	If suspicion of metastases Prophylactic only if the parathyroids are visible	11 years	---------
High	634 883	<5 years	Calcitonin > 40 pg/mL or suspicion of lymph node metastases	11 years	11 years
Moderate	533 609 611 618 620 630 631 666 786 790 804 891 912	Before or after 5 years # Elevated calcitonin (basal or after stimulus) # Consider aggressiveness of MTC in the family # No consensus / no extensive experience to define most appropriate age	Calcitonin > 40 pg/mL or suspicion of lymph node metastases	16 years	16 years

RET variants are present in 40–50% of sporadic MTC cases, with a prevalence of up to 90% in patients with more aggressive disease forms. The presence of a pathogenic *RET* variant in the tumor is associated with a more aggressive disease course, characterized by a higher incidence of distant metastases and a poorer prognosis (Elisei *et al.* 2008, Moura *et al.* 2009, Romei *et al.* 2012, 2016*a*).

In addition to *RET*, variants in the *H-RAS* and *K-RAS* genes have been identified in 6–28% of sporadic *RET*-negative MTC tumors (Moura *et al.* 2011, Boichard *et al.* 2012, Agrawal *et al.* 2013, Ciampi *et al.* 2013, 2019, Oczko-Wojciechowska *et al.* 2015, Heilmann *et al.* 2016, Chang *et al.* 2018, Shirali *et al.* 2024). These *RAS* variants are mutually exclusive with *RET* variants. Recent somatic analyses of four sporadic MTC patients negative for *RET* and *RAS* variants revealed biallelic inactivation of *NF1*, a tumor suppressor gene associated with neurofibromatosis type 1 (Shi *et al.* 2022, Ciampi *et al.* 2023, Castroneves *et al.* 2024). In these cases, *NF1* loss of heterozygosity leads to the loss of functional neurofibromin, a negative regulator of the RAS signaling pathway. This results in the constitutive activation of the pathway, promoting cell proliferation and survival, which is critical for tumor development. This discovery highlights *NF1* as a novel driver gene for MTC (Elisei *et al.* 2008, Steinmann *et al.* 2009, Laycock-Van Spyk *et al.* 2011).

Rearrangements of the anaplastic lymphoma kinase (ALK) gene have also been detected in sporadic MTC, with ALK fusions identified in two adult patients from a cohort of 98 individuals, as well as in one pediatric patient (Ji *et al.* 2015, Hillier *et al.* 2019).

Other genetic alterations, whose roles in tumor progression remain uncertain, have been identified in genes such as *MET*, *MDC1*, *ATM*, *BRAF*, *TSHR*, *ITGA10* and *PDE4DIP*. However, these alterations have not yet been observed in a significant number of MTC patients (Agrawal *et al.* 2013, Simbolo *et al.* 2014, Ji *et al.* 2015, Heilmann *et al.* 2016, Chang *et al.* 2018, Ciampi *et al.* 2019, Shi *et al.* 2022). In addition, variants in the *FAT1* or *FAT4* genes were found in 18 Chinese patients with MTC, with somatic variants present in 22.2% of cases and germline variants in 38.8% (Qu *et al.* 2020). A substantial proportion of sporadic MTC cases lack a clear, identifiable driver gene, with recent research suggesting this proportion may be around 18–20% (Ciampi *et al.* 2023).

Identifying somatic drivers in sporadic MTC, particularly *RET* variants, is crucial for guiding targeted treatments. Both non-selective MKIs and selective RET inhibitors have shown significant potential in improving progression-free and overall survival (OS) in patients with metastatic MTC (Wells *et al.* 2012, Elisei *et al.* 2013, Wirth *et al.* 2020, Hadoux *et al.* 2023, Subbiah *et al.* 2024).

Diagnostic approaches

Thyroid nodule evaluation is primarily performed using ultrasound (US), with fine-needle aspiration cytology (FNAC) conducted when US features

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suggest malignancy (Haugen *et al.* 2016). Most studies on US features predicting malignancy focus on papillary thyroid cancer due to its higher prevalence. MTC nodules are typically solid, hypoechoic and have regular margins, with approximately half showing calcifications, although microcalcifications are less frequent. Few MTC nodules exhibit a 'taller-than-wide' shape, and only 7.9% of MTC nodules demonstrate at least four simultaneous US features suggestive of malignancy. Studies highlight the limited performance of neck US in identifying MTC, often leading to its underdiagnosis and missed FNAC evaluations (Trimboli *et al.* 2012, Matrone *et al.* 2021*b*).

Classic cytological features of MTC on FNAC include plasmacytoid and polygonal cells, multinucleation, dispersed cell arrangement, salt-and-pepper chromatin and the presence of amyloid (Geddie *et al.* 1984, Pusztaszeri *et al.* 2014). However, these findings are uncommon, and FNAC sensitivity is variable. A systematic review reported a sensitivity of 56.4% (95% confidence interval (CI): 52.6–60.1), with FNAC often yielding benign, indeterminate or nondiagnostic results. MTC is frequently misinterpreted as other tumors, such as oncocytic or follicular neoplasms, corresponding to Bethesda categories II to V (Essig *et al.* 2013, Trimboli *et al.* 2015, Suzuki *et al.* 2017, Workman *et al.* 2021).

In cases with a high suspicion of MTC, diagnostic accuracy can be enhanced by measuring Ctn levels in the fine-needle aspiration (FNA) washout fluid and/or by using immunocytochemical staining for markers such as Ctn, chromogranin and CEA (Wells *et al.* 2015, Trimboli *et al.* 2016, Liu *et al.* 2021).

Routine serum Ctn measurement for all patients with thyroid nodules or before thyroid surgery remains controversial, as only 1 in 200 screened individuals is likely to have MTC (Wells *et al.* 2015, Durante *et al.* 2023). While early diagnosis via Ctn screening can potentially improve prognosis (Elisei *et al.* 2004, Elisei 2008), limitations include the lack of randomized trials, variability in Ctn assay accuracy, limited availability of pentagastrin stimulation tests and cost-effectiveness concerns.

Nevertheless, studies suggest that universal Ctn screening in patients with non-highly suspicious thyroid nodules can be cost-effective, particularly when using a Ctn threshold of >50 pg/mL to define a positive test (Cheung *et al.* 2008, Al-Qurayshi *et al.* 2020). Although not without limitations, Ctn screening is a cost-effective tool for identifying MTC before thyroid lobectomy or during the follow-up of benign nodules. It is particularly recommended for patients with suspicious nodules, those scheduled for surgery, or with indeterminate FNAC results (Bethesda III–V), as it enhances preoperative detection of MTC (Sencar *et al.* 2022, Durante *et al.* 2023).

In addition, calcitonin testing should be prioritized in individuals with a personal or family history of MTC or MEN2 (Wells *et al.* 2015, Durante *et al.* 2023).

For patients with confirmed MTC, preoperative evaluation should include imaging to assess the extent of the disease. Basal Ctn levels can guide the selection of appropriate imaging tests. In patients with Ctn levels below 500 pg/mL, the disease is typically localized (Machens & Dralle 2010, Wells *et al.* 2015), and US and/or computed tomography (CT) of the neck are recommended to evaluate the cervical lymph nodes. For patients with basal Ctn levels exceeding 500 pg/mL, the risk of distant metastasis significantly increases. Therefore, additional imaging is recommended, such as contrast-enhanced chest CT, magnetic resonance imaging (MRI) of the abdomen and pelvis, triphasic abdominal CT, bone scintigraphy and spinal MRI (Machens & Dralle 2010, Wells *et al.* 2015).

Currently, no positron emission tomography (PET) imaging modality offers optimal whole-body diagnostic assessment for patients with biochemical or metastatic MTC. However, ^{18}F-DOPA PET has shown the highest accuracy in detecting recurrent MTC (Lee *et al.* 2020). In addition, ^{68}Ga-DOTATATE PET/CT is particularly effective in identifying bone lesions, offering detection rates superior to those of bone scintigraphy and comparable to a combination of bone scans and spine MRI (Castroneves *et al.* 2018).

Testing for the germline *RET* proto-oncogene is recommended in the following situations: i) genetic testing should be performed for all cases of MTC, even in the absence of a family history (Wells *et al.* 2015, Elisei *et al.* 2019*a*); ii) testing is also recommended for first-degree relatives of individuals confirmed to carry MTC and pathogenic *RET* variants (Wells *et al.* 2015, Elisei *et al.* 2019*a*).

Since the results of germline *RET* testing may take several weeks, it is important to perform preoperative screening for pheochromocytoma and hyperparathyroidism. This applies to both cases without a confirmed genetic diagnosis and known hereditary cases. Proper screening helps prevent hypertensive crises during surgery and avoids the need for a second neck surgery to treat primary hyperparathyroidism (Wells *et al.* 2015, Viola & Elisei 2019).

Annual screening for pheochromocytoma, including plasma metanephrines and normetanephrines or 24-h urinary metanephrines and normetanephrines, is recommended for patients with MEN 2A, along with screening for hyperparathyroidism through serum calcium and parathyroid hormone (PTH) levels. For patients with MEN 2B, annual screening for pheochromocytoma is advised. The appropriate age to begin screening depends on the risk classification associated with specific *RET* gene variants (Table 1) (Wells *et al.* 2015).

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Surgical management of MTC

Surgery is the only definitive treatment for MTC, and optimal outcomes are more likely when performed by experienced high-volume neck surgeons (Machens & Dralle 2010, McMullin *et al.* 2023, Szabo Yamashita & Grubbs 2024). A thorough preoperative evaluation is essential, with neck ultrasound and/or CT scans being important to identify nodal disease before surgery. Proper imaging ensures precise surgical planning and execution. The chance of a cure significantly drops if there are lymph node metastases at the time of diagnosis, which makes early detection critical (Wells *et al.* 2015).

The standard surgical treatment for both hereditary and sporadic MTC is total thyroidectomy with central neck compartment dissection for all patients (Wells *et al.* 2015). However, in hereditary cases identified through family screening, central neck dissection can be avoided if specific criteria are met: serum Ctn level is below 40 pg/mL, the thyroid nodule is smaller than 5 mm, and there is no evidence of lymph node metastases. In such cases, only a prophylactic thyroidectomy is performed (Machens & Dralle 2010, Wells *et al.* 2015, Viola & Elisei 2019). The recommended age for this procedure, according to the risk category of the *RET* variant, is detailed in Table 1 (Wells *et al.* 2015).

If preoperative imaging indicates nodal disease in the neck or mediastinum, a compartmental dissection of the affected region is required. Confirmation of metastasis should be achieved through FNA, with cytology and/or Ctn measurements in the needle wash. This protocol applies to both central and lateral neck compartments (Wells *et al.* 2015).

For patients with serum Ctn levels between 50 and 200 pg/mL, which typically correlate with ipsilateral N1b disease (Machens & Dralle 2010), elective neck dissection may only be considered if metastatic disease is confirmed through FNAC. In cases where serum Ctn levels exceed 200 pg/mL, contralateral N1b disease or mediastinal involvement becomes more likely (Machens & Dralle 2010), necessitating preoperative confirmation of metastatic disease before undertaking dissection (Wells *et al.* 2015).

If MTC is unexpectedly diagnosed following a thyroid lobectomy, the decision to proceed with a completion thyroidectomy should be guided by the presence of a germline *RET* variant. If a pathogenic *RET* variant is identified, a total thyroidectomy with central neck dissection is recommended. However, if no *RET* variant is detected and postoperative Ctn levels are undetectable, a more conservative approach may be taken, involving regular follow-ups with tumor marker assessments and cervical ultrasounds (Wells *et al.* 2015).

In cases where primary hyperparathyroidism is diagnosed, thyroid surgery should be accompanied by parathyroidectomy after accurate localization of the parathyroid disease. For patients with pheochromocytoma, an adrenalectomy must always precede thyroidectomy to prevent adrenal crises during surgery (Wells *et al.* 2015).

Follow-up and management after primary surgery

Post-surgical follow-up is crucial for evaluating the response to initial treatment. While patients with MTC require thyroid hormone replacement, TSH suppression is not necessary. The postoperative normalization of Ctn levels is the most significant predictor of prognosis. Ctn and CEA levels should be measured no earlier than 3 months after surgery to assess for any persistent disease (Wells *et al.* 2015, Viola & Elisei 2019).

Patients with undetectable tumor markers and a normal neck US after surgery are considered to have an excellent response to the initial treatment. These patients should undergo follow-up monitoring with neck US and tumor marker tests every 6 months for the first 2 years and then annually thereafter.

Residual disease is common in MTC, with retrospective studies showing that 24–90% of patients have detectable Ctn levels after initial surgery, indicating either biochemical or structural residual disease (Hoff & Hoff 2007, Prete *et al.* 2023). Ctn levels up to 150 pg/mL are often associated with metastatic disease localized to the neck or with biochemical disease and should be evaluated alongside tumor markers (Ctn and CEA) and neck US (Machens & Dralle 2010).

Data from a large cohort of patients with sporadic MTC showed that individuals with a biochemical incomplete response after initial treatment have a 50% risk of developing structural disease within 10 years, most commonly in cervical lymph nodes. Predictive factors for the development of structural disease include elevated Ctn levels (≥50 pg/mL and advanced tumor stage (IVA or IVB). During follow-up, a shorter Ctn doubling time (≤24 months) was also identified as a significant predictor. Patients with these risk factors require closer monitoring and stricter follow-up protocols. In contrast, patients with Ctn levels below 50 pg/mL and earlier tumor stages (I–III) can be safely monitored every 9–12 months using cervical US and tumor markers, without requiring additional imaging unless tumor markers show a significant increase (Prete *et al.* 2023).

Locally recurrent disease may be managed through either observation or surgical intervention, depending on the risk of tumor involvement with vital structures and other patient-specific factors (Wells *et al.* 2015). For patients whose initial surgical intervention was incomplete, reoperation with central (level VI) and

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bilateral neck compartment (levels II–V) dissection may be considered if metastatic disease is confirmed by FNAC.

Calcitonin levels exceeding 150 pg/mL can be associated with distant metastases (Machens & Dralle 2010). Staging of the primary metastatic sites – including the neck, mediastinum, lungs, liver and bones – is recommended through neck US, chest CT, MRI of the abdomen and pelvis, or triple-phase abdominal CT, along with bone scintigraphy and spinal MRI. The frequency of follow-up depends on the stability or rise in tumor markers, with intervals ranging from every 3–12 months (Wells *et al.* 2015).

Although CEA is not a specific marker for MTC, it remains valuable for monitoring disease progression. Significant increases in CEA, particularly when Ctn levels remain stable or decrease, may suggest poorly differentiated MTC, which is associated with a worse prognosis. Calculating the doubling times of Ctn and CEA is a useful prognostic tool, correlating with 5- and 10-year survival rates. For accurate results, at least four measurements over a 2-year period are recommended. Doubling times can be determined using the American Thyroid Association's online calculator (https://www.thyroid.org/professionals/calculators/thyroid-cancer-carcinoma/) (Miyauchi *et al.* 1984, Barbet *et al.* 2005, Wells *et al.* 2015). This information helps determine the frequency of imaging exams and follow-up evaluations.

Management of advanced and metastatic disease

Distant metastatic disease is present at diagnosis in approximately 15–20% of patients. Retrospective studies report a 10-year survival rate of 20–40% from the time of initial metastasis, highlighting the challenges associated with this advanced stage of the disease (Roman *et al.* 2006). While surgical resection remains the primary treatment for localized MTC, advanced or metastatic disease poses significant therapeutic challenges.

Given the complexity of managing patients with metastatic MTC, a multidisciplinary team approach is highly beneficial. Such a team typically includes endocrinologists, oncologists, surgeons, radiotherapists, interventional radiologists, dermatologists, cardiologists, psychologists and nutritionists.

The primary goal of treating advanced MTC is to manage life-threatening or symptomatic tumors. This is often achieved through surgical resection or localized therapies such as ablation or radiotherapy, particularly for isolated metastatic lesions that are growing or located in problematic areas. For solitary or localized disease, particularly in the bone or in the liver, local treatment options include surgery, cryoablation, chemoembolization or radiation therapy.

Metastatic MTC is often associated with the secretion of peptides such as serotonin, vasoactive intestinal peptide, histamine and kinins. These substances can cause clinical symptoms such as flushing and diarrhea, which may significantly impact the patient's quality of life. The decision to initiate systemic therapy is primarily guided by the presence of symptomatic disease, high-volume metastases or progressive disease. This is particularly important when the disease involves vital structures, presents with a high tumor burden, or shows rapid progression on radiologic imaging. For patients with high-volume, progressive or symptomatic metastatic disease, systemic therapy is recommended (Wells *et al.* 2015).

Conventional chemotherapy, including dacarbazine, 5-fluorouracil and anthracyclines, has shown poor efficacy in metastatic MTC, with response rates (RR) ranging between 10 and 20% (Nocera *et al.* 2000). As a result, chemotherapy is no longer recommended for metastatic MTC due to its limited effectiveness.

Advances in understanding the molecular biology of MTC have paved the way for targeted therapies, particularly with anti-angiogenic MKIs and RET inhibitors, which will be discussed in detail in this review.

Recent studies have identified a subset of MTC patients who lack *RET* and *RAS* variants but instead display biallelic NF1 inactivation (Shi *et al.* 2022, Ciampi *et al.* 2023, Castroneves *et al.* 2024). However, treatment options for these metastatic cases are still limited, with current therapeutic choices including vandetanib and cabozantinib. Notably, patients with neurofibromatosis type 1 (NF1) who develop unresectable plexiform neurofibromas – benign peripheral nerve sheath tumors – often face significant symptoms such as pain, disfigurement and motor dysfunction. Recent advancements in targeted therapies, particularly with the MEK inhibitor selumetinib, have shown promising efficacy, leading to its approval for treating symptomatic, inoperable plexiform neurofibromas in pediatric patients in both the US and Europe. Ongoing research is evaluating the effectiveness of MEK inhibitors in other NF1-associated tumors, including cutaneous neurofibromas and low-grade gliomas. However, clinical experience with the treatment of metastatic MTC cases harboring *NF1* variants remains absent (Fangusaro *et al.* 2019, Armstrong *et al.* 2023, Church *et al.* 2024).

Figure 1 outlines a standardized approach for selecting the most effective systemic therapy for each patient, tailored to their unique molecular biology. In addition, the following sections will provide a detailed discussion of approved drugs and emerging therapies for MTC.

Nonselective multi-kinase inhibitors (MKIs)

In thyroid cancers, there are several signaling pathways that are upregulated, promoting disease growth and

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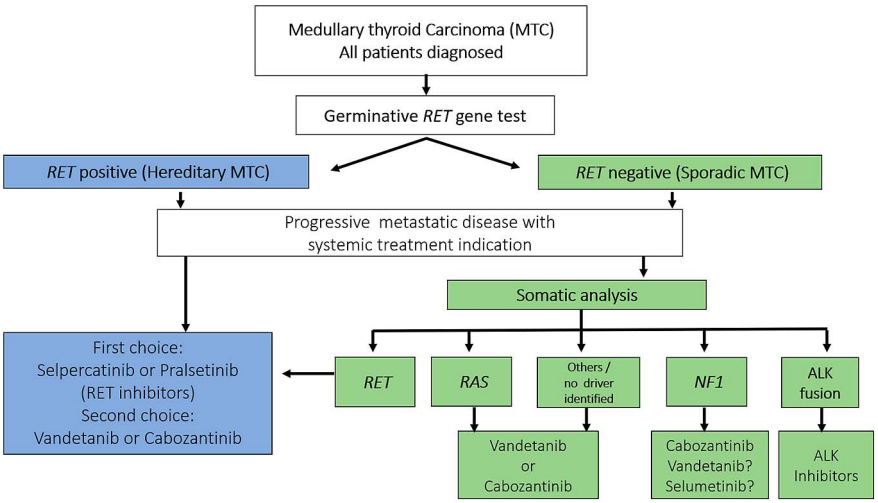


Figure 1

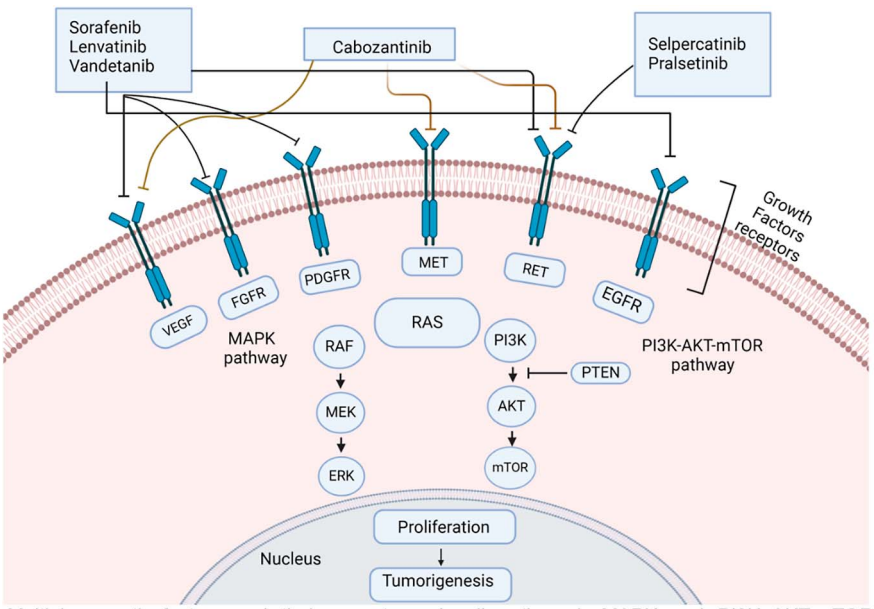
Treatment flowchart for MTC.

progression. These include RET, the hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptor 2 (VEGFR2) (Trovato *et al.* 1998, Capp *et al.* 2010). The primary therapeutic target of MKIs is VEGFR2 to inhibit angiogenesis. Inhibition of VEGFR2 is associated with adverse events (AEs), including hypertension, an increased risk of bleeding and impaired wound healing, leading to dose reductions, treatment interruptions and, in some cases, drug discontinuation, which limit their efficacy (Fig. 2) (Liu *et al.* 2016, Zhang *et al.* 2016).

Sorafenib

The MKIs approved by the U.S. Food and Drug Administration (FDA) for the treatment of progressive, radioactive-refractory, differentiated metastatic thyroid carcinoma are the broad-spectrum kinase inhibitors sorafenib and lenvatinib. These were approved based on phase III clinical trials (Brose *et al.* 2014, Schlumberger *et al.* 2015).

Sorafenib demonstrates potent activity by inhibiting downstream Raf serine/threonine kinase activity and blocking several tyrosine kinase receptors, including VEGFR2, VEGFR3, PDGFR, RET and c-Kit. In a phase II clinical trial for patients with metastatic MTC, sorafenib showed a median PFS of 17.9 months in the sporadic MTC group, with most patients achieving stable disease (Lam *et al.* 2010). In addition, a retrospective study by Castroneves *et al.* on patients with metastatic MTC reported that it is well tolerated and provides a durable clinical response, with 75% of patients



Multiple growth factors and their receptors signaling through MAPK and PI3K–AKT-mTOR pathway regulate the thyroid cell proliferation and represent therapeutic targets for non-selective MKIs and selective RET inhibitors

Figure 2

Key targets of multikinase and RET inhibitors in thyroid cancer tumorigenesis.

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Table 2 AEs related to MKIs (Wells *et al.* 2012, Elisei *et al.* 2013, Brose *et al.* 2014, Schlumberger *et al.* 2015).

Vandetanib	Cabozantinib	Sorafenib	Lenvatinib
Diarrhea (57%)	Diarrhea (63.1)	Hand foot skin (76%)	Hypertension (67.8%)
Rash (45%)	Palmar-plantar erythrodysesthesia (50%)	Diarrhea (69%)	Diarrhea (59.4%)
Nausea (33%)	Decreased weight (47.7%)	Alopecia (67%)	Fatigue (59%)
Hypertension (32%)	Decreased appetite (45.8)	Rash/desquamation (50%)	Anorexia (50.2%)
Fatigue (24%)	Nausea (43%)	Fatigue (50%)	Weight loss (50%)
Headache (26%)	Fatigue (40.7%)	Weight loss (47%)	Nausea (41%)
Decrease appetite (21%)	Dysgeusia (34.1%)	Hypertension (41%)	Stomatitis (35.6%)
Acne (20%)	Hair color changes (33.6%)	Anorexia (32%)	Palmar plantar erythrodysesthesia (31.8%)

AEs, adverse events; MKIs, multikinase inhibitors.

experiencing stable disease for at least 6 months and a PFS of 9 months among those treated with sorafenib (Fig. 2) (De Castroneves *et al.* 2016).

Lenvatinib

Lenvatinib is an inhibitor of multiple tyrosine kinases, including VEGFR1-3, FGFR1-4, PDGFRα, RET and Kit. In a phase II clinical trial involving 59 patients with unresectable, progressive metastatic MTC, lenvatinib demonstrated an overall response rate of 36% (95% CI: 24–49%). The response rate was similar between patients with or without prior exposure to anti-vascular endothelial growth factor (VEGF) therapy. All responses were partial, and no correlation was observed between *RET* tumor status and clinical outcomes. Lenvatinib exhibited a manageable safety profile, with a disease control rate of 80% (95% CI: 67–89%). Among responders, the median time to response was 3.5 months (95% CI: 1.9–3.7 months), and the median PFS was 9.0 months (95% CI: 7.0 months–not evaluable) (Schlumberger *et al.* 2016).

In real-world clinical practice, ten patients with advanced, progressive metastatic MTC and a large tumor burden – each previously treated with a TKI – achieved disease stabilization and control with lenvatinib, with a median time to response of 3 months. Although AEs were notable, they remained manageable. These findings suggest that lenvatinib could be a viable treatment option, especially for patients who are *RET*-negative and lack access to newer targeted therapies (Matrone *et al.* 2021*a*).

Vandetanib

Vandetanib and cabozantinib are MKIs approved by the FDA for the treatment of metastatic MTC. They are the first-line systemic treatments for progressive MTC in patients with negative RET mutational status.

Vandetanib is a multi-targeted TKI that inhibits RET, VEGFR and EGFR (Valerio *et al.* 2017). It was FDA-approved based on the results of the phase III ZETA trial (NCT00410761) (Wells *et al.* 2012). This trial showed an increase in PFS of 11.2 months compared to placebo, with an objective response rate (ORR) of 45% (Wells *et al.* 2012). Subgroup analysis of PFS by *RET* M918T mutation status suggested that patients with a positive mutation exhibited a higher response rate to vandetanib compared to those with a negative mutation status (Wells *et al.* 2012). In Europe, since the activity of vandetanib, based on available data, is considered insufficient in patients with no identified *RET* mutation, treatment with vandetanib is strongly recommended only in patients harboring a *RET* (germline or somatic) positive mutation, and the presence of a *RET* mutation should be determined by a validated test before initiation of the treatment (https://www.ema.europa.eu/en/documents/product-information/caprelsa-epar-product-information_en.pdf).

The rate of treatment discontinuation because of toxicity was 12%. The most prevalent AEs included diarrhea, rash, nausea and hypertension, affecting more than 30% of patients (Table 2). Clinically significant QTc prolongation occurred in 8% of patients, and nearly half of those on vandetanib required an increase in their thyroid hormone replacement dose (Wells *et al.* 2012). The IC50 against RET kinase domain mutations is 1.83 (1.57–2.08) (Fig. 2) (Liu *et al.* 2018).

Cabozantinib

Cabozantinib is a potent inhibitor of VEGFR2 that also inhibits RET and, unlike vandetanib, targets mesenchymal epithelial transition factor (MET). It was FDA-approved for the treatment of unresectable, progressive metastatic MTC, regardless of tumor mutational status, based on the results of the EXAM trial (NCT00704730). This trial showed a median PFS of 7.2 months for cabozantinib versus 4.0 months for placebo, an ORR of 28%, and a median estimated duration of response (DoR) of 14.6 months (Elisei *et al.* 2013). Responses were independent of mutational status, with prolonged PFS observed across all subgroups, including by age and prior TKI treatment (Elisei *et al.* 2013). The IC50 against RET kinase domain mutations is 1.57 (1.41–1.74) (Liu *et al.* 2018). The most frequently reported AEs were diarrhea, palmar-plantar

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erythrodysesthesia, weight loss, nausea, fatigue and hypertension (Table 2) (Elisei *et al.* 2013).

It is important to note that the ZETA and EXAM trials are not directly comparable, given their differences in inclusion criteria and trial design. Notably, the EXAM trial required participants to meet RECIST criteria for radiologic progression before enrollment, which likely resulted in a cohort with more advanced disease, whereas the ZETA trial did not have this requirement (Fig. 2) (Wells *et al.* 2012, Elisei *et al.* 2013).

Mechanism of resistance to MKIs

In addition to off-target side effects, secondary *RET* mutations that confer resistance to MKIs during therapy have been described. Examples include the V804L and V804M gatekeeper mutations, which reduce the ability of drugs such as cabozantinib and vandetanib to effectively bind to the RET kinase's ATP-binding site, potentially allowing the RET kinase to bind more tightly to ATP, reducing the effectiveness of these drugs (Drilon *et al.* 2018). Here, we can consider the RET kinase as a two-compartment lock, with one compartment devoted to the action of the gate (the V804 residue). MKIs act such as keys that fit on either side of the gate and bind to both compartments, locking the molecular machine in a nonfunctional state. However, these mutations switch the amino acid in the gate from valine (V) to leucine (L) or methionine (M) – two much bulkier amino acids – making it much harder for the MKIs 'key' to fit through and reach the compartments on either side of the gate, rendering the key less effective at binding to the gate and reducing the drug's effectiveness. RET gatekeeper mutations, such as V804M and V804L, have been reported in non-small cell lung carcinoma and MTC (Carlomagno *et al.* 2004, Wirth *et al.* 2019, Liu *et al.* 2018).

Selective RET inhibitors

With the advent of comprehensive next-generation sequencing of tumors, the identification of molecular drivers of tumorigenesis has led to the development of targeted therapies with greater efficacy and reduced potential for off-target AEs. Two specific RET inhibitors have been approved for the management of MTC.

Selpercatinib

This highly selective, ATP-competitive small-molecule RET inhibitor effectively targets RET with minimal effects on other proteins and can cross the blood–brain barrier (Subbiah *et al.* 2018*a*). The drug was approved by the FDA in May 2020 for the treatment of *RET* fusion-positive non-small-cell lung cancer (NSCLC) and *RET* fusion-positive thyroid cancers, as well as *RET*-mutant MTC in patients ≥12 years of age. Approval was based on the phase I/II LIBRETTO-001 trial, which included 55 *RET*-mutant MTC previously treated with vandetanib or cabozantinib, 88 treatment-naïve *RET*-mutant MTC patients, and 19 previously treated *RET* fusion-positive thyroid cancer patients (Wirth *et al.* 2020, Subbiah *et al.* 2022). Among patients with MTC previously treated with vandetanib or cabozantinib, the ORR was 69%, regardless of the number of prior therapies or specific *RET* mutations. Treatment-naïve patients showed a 73% ORR (Table 3), with biochemical response rates of 91% for Ctn and 66% for CEA. Selpercatinib demonstrated efficacy regardless of the number of previous MKI therapies or specific *RET* mutations, including the resistance-associated mutation *RET* V804M (Table 3) (Wirth *et al.* 2020).

Table 3 Efficacy of selective RET inhibitors in clinical trials (Hadoux *et al.* 2023, Subbiah *et al.* 2024).

Agent	Cancer type	ORR (%)	CR (%)
Selpercatinib	RET + MTC (previously treated)	69%	9%
	RET + MTC (treatment naive)	73%	11%
	RET fusion + thyroid cancer	79%	5%
Pralsetinib	RET + MTC (previously treated)	60%	2%
	RET + MTC (treatment naive)	71%	5%
	RET fusion + thyroid cancer	89%	0%

In the post-hoc analysis of LIBRETTO-001, with a median treatment duration of 30.1 months (range: 0.1–66.8), the most common treatment-related AEs occurring in over 20% of patients included diarrhea, dry mouth, hypertension, fatigue, elevated AST/ALT, peripheral edema, constipation, nausea, headache, abdominal pain, increased blood creatinine, vomiting, cough, rash, arthralgia, dyspnea, back pain, decreased appetite and QT prolongation. Severe grade 3–4 AEs included hypertension (19.4%), ALT elevation (11.8%), hyponatremia (9.2%), lymphopenia (5.9%) and diarrhea (5.9%) (Table 4). Only 4.3% of patients discontinued due to treatment-related AEs (Raez *et al.* 2024).

Although generally well tolerated compared to other MKIs, after wider use, selpercatinib has been associated with specific AEs. Gastrointestinal symptoms, small-bowel edema and ascites have been

Table 4 Common AEs related to selective RET inhibitors (Subbiah *et al.* 2021*b*, Raez *et al.* 2024).

Selpercatinib	Pralsetinib
Diarrhea ++++	Leukopenia ++++
Dry mouth ++++	Increased AST ++++
Hypertension ++++	Neutropenia ++++
Increased AST +++	Hypertension ++++
Increased ALT +++	Anemia +++
Increased ALT +++	Constipation +++
Peripheral edema +++	Increased ALT +++

Interpretation: ++++: >40% +++: 20–30%. AEs, adverse events.

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reported, presenting with abdominal pain and bloating that typically resolve with dose interruption or reduction (Tsang *et al.* 2022). Effusions, often chylous, developed in 80% of patients in one study, with dose reduction significantly improving symptoms (Prete *et al.* 2022). Weight gain was more frequent in patients with prior TKI treatment compared to TKI-naïve patients (Gouda *et al.* 2023).

Erectile dysfunction (ED) was reported in 90% of male patients with normal sexual function before treatment, with higher prevalence when actively assessed. Improvement was observed in 90% of cases treated with phosphodiesterase-5 inhibitors (Matrone *et al.* 2024).

Rare events included fluctuating obliterative bronchiolitis, managed with active surveillance due to mild clinical features (Gambale *et al.* 2024), and Langerhans cell histiocytosis (LCH) driven by a somatic BRAF mutation, which improved with inhaled corticosteroids. RET blockade may have activated a downstream BRAF mutation in this case (Wu *et al.* 2024).

Long-term outcomes and rare complications of selpercatinib remain under investigation. Understanding its full AE profile is essential for optimizing prevention and management strategies to prolong treatment duration.

LIBRETTO-531 (NCT04211337) is a large, multicenter, open-label, randomized, controlled, phase III trial comparing selpercatinib with physicians' choice of cabozantinib or vandetanib in patients with advanced metastatic *RET*-mutant MTC who had not previously received MKIs (Wirth *et al.* 2022). The primary endpoint was PFS, with treatment failure-free survival also evaluated as a secondary endpoint. Crossover to selpercatinib was permitted among patients in the control group after disease progression. Patients were randomly assigned in a 2:1 ratio to receive either selpercatinib (160 mg twice daily) or the physician's choice of cabozantinib (140 mg once daily) or vandetanib (300 mg once daily) (Hadoux *et al.* 2023). The study enrolled 291 patients with progressive *RET*-mutant MTC, with *RET* M918T as the most common mutation in both groups. At 12 months, PFS was 86.8% in the selpercatinib group compared to 65.7% in the control. Median PFS was not reached in the selpercatinib group and was 16.8 months in the control group (vandetanib or cabozantinib), which indicates a significant better PFS in the selpercatinib group. The median treatment failure–free survival was not reached in the selpercatinib group but was 13.9 months in the control group (Hadoux *et al.* 2023).

The recommended starting dose of selpercatinib is 160 mg twice daily for patients weighing over 50 kg and 120 mg twice daily for those weighing under 50 kg.

Pralsetinib

This highly selective RET inhibitor targets RET-altered kinases, including V804L/M gatekeeper mutations. FDA approval was based on the ARROW trial (NCT03037385), a phase 1/2 open-label study of *RET*-altered, locally advanced or metastatic *RET*-mutant MTC with disease progression within 14 months before enrollment and *RET* fusion-positive thyroid cancers (Subbiah *et al.* 2021*b*). The phase I study evaluated pralsetinib dose escalation, establishing a recommended dose of 400 mg daily for the phase II study (Subbiah *et al.* 2021*b*). The phase II primary endpoints were ORR per RECIST version 1.1 and safety, enrolling patients with *RET*-mutant MTC and *RET* fusion-positive thyroid cancer.

The study included 84 individuals with *RET*-mutant MTC, mostly with sporadic disease. Among them, 55 were evaluated for response, with most having prior treatment with vandetanib or cabozantinib, while 21 were treatment-naïve (Subbiah *et al.* 2021*b*). In previously treated patients, the ORR was 60% (33/55), with a complete response (CR) rate of 2% (1/55). The median time to first response was 3.7 months, and the median DoR was not reached after a median follow-up of 11.2 months. At a median follow-up of 14.9 months, the estimated 1-year PFS was 75%, and the estimated 1-year OS was 89%. In treatment-naïve patients, the ORR was 71% (15/21), with a CR rate of 5% (1/21) (Table 2) and an estimated 1-year PFS of 81% at a median follow-up of 15.1 months. Responses were observed irrespective of the *RET* mutation, including V804L/M gatekeeper mutations (Subbiah *et al.* 2021*b*).

The most common side effects were anemia, muscle and bone pain, constipation, elevated liver enzymes and hypertension. More serious side effects (Grade 3) were hypertension and reduced white cell counts (neutropenia and lymphopenia) (Table 4) (Subbiah *et al.* 2021*b*).

Pralsetinib was FDA-approved in December 2020 for adults and pediatric patients ≥12 years old with advanced or metastatic *RET*-mutant MTC requiring systemic therapy. However, its accelerated approval was voluntarily withdrawn for the treatment of advanced or metastatic *RET*-mutant MTC in the United States on July 20, 2023 (Fig. 2).

Mechanisms of resistance to RET inhibitors

Selective RET inhibitors were designed to overcome gatekeeper mutations. Both selpercatinib and pralsetinib bind to the RET kinase in a distinctive manner, different from MKIs. They fill both the front and back pockets, avoiding the usual gate formed by the amino acids V804 and K758. In this way, gatekeeper mutations do not disrupt their binding mode. However, these inhibitors remain susceptible to

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several known non-gatekeeper mutations. These include mutations in *RET* located at the solvent front (*RET* G810C/S/R), the hinge region (*RET* Y806C/N) and the β2 strand (*RET* V738A), which confer resistance to both selpercatinib and pralsetinib (Subbiah *et al.* 2018*b*, 2021*a*). The solvent front mutations (SFMs) were first described by Solomon *et al.* in five patients with *RET* fusion-positive NSCLC and *RET*-mutant MTC, with progressing tumors and measurable levels of circulating tumor DNA for G810R/S/C mutations (Solomon *et al.* 2020).

Emergent therapies are currently under investigation to develop drugs capable to overcome this mechanism of resistance.

Emerging therapies

TPX-0046

TPX-0046 is a potent RET and SRC inhibitor that spares VEGFR2. Its rigid, macrocyclic structure enhances its potency against *RET* mutations, including those associated with resistance, such as *RET* G810. TPX-0046 demonstrated antitumor properties in both cell line and patient-derived xenograft models of *RET*-driven tumors. While effective against SFMs, it does not target V804 gatekeeper mutations (Drilon *et al.* 2019). The drug was evaluated in a phase 1/2 clinical trial involving adults with advanced solid tumors harboring *RET* fusions or mutations. However, this study was terminated due to side effects that altered the risk-benefit profile (http://clinicaltrials.gov/show/NCT04161391, accessed 01.05.2025).

Vepafestinib

Vepafestinib (TAS0953/HM0) is a novel, highly selective, ATP-competitive RET inhibitor designed to overcome SFMs. It shows strong selectivity for RET and efficacy against common on-target resistance mutations (RETL730, RETV804 and RETG810). Moreover, vepafestinib improved blood-brain barrier penetration and distribution compared to approved RET inhibitors (Miyazaki *et al.* 2023). The phase 1/2 margaRET trial will assess its safety and efficacy in solid tumors with Ret alterations (https://clinicaltrials.gov/study/NCT04683250, accessed 01.05.2025).

BOS172738

BOS172738 is a highly potent and selective RET inhibitor. Preclinically, it has exhibited potency against several oncogenic *RET* mutations, including wild-type RET, M918T, V804L, V804M and *RET* fusions. BOS172738 is evaluated in patients with advanced NSCLC and MTC (NCT03780517) (Keegan *et al.* 2019, Schoffski *et al.* 2019).

Conclusion

Due to the rarity and complexity of MTC, it is highly recommended that patients receive care at specialized high-volume centers with expertise in the management of this disease. The development of more selective RET inhibitors has marked a new era in the treatment of *RET*-positive tumors, providing targeted and highly effective therapeutic options. For *RET*-negative cases, MKIs such as cabozantinib remain valuable treatment options, while vandetanib may exhibit lower efficacy.

The increasing emphasis on precision medicine underscores the importance of identifying additional actionable genetic alterations to further refine and personalize treatment strategies. Furthermore, disparities in the availability of therapeutic agents globally remain a significant concern. In many countries, certain therapies are either unavailable, not approved as first-line options or not covered by national health systems. These limitations present challenges for patients and highlight the importance of improving global access to effective therapies for MTC.

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