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State of the art and future directions in the systemic treatment of medullary thyroid cancer

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Purpose of review
Systemic treatment is the only therapeutic option for patients with progressive, metastatic medullary thyroid cancer (MTC). Since the discovery of the rearranged during transfection (RET) proto-oncogene (100% hereditary, 60–90% sporadic MTC), research has focused on finding effective systemic therapies to target this mutation. This review surveys recent findings.

Recent findings
Multikinase inhibitors are systemic agents targeting angiogenesis, inhibiting growth of tumor cells and cells in the tumor environment and healthy endothelium. In the phase III EXAM and ZETA trials, cabozantinib and vandetanib showed progression-free survival benefit, without evidence of prolonged overall survival. Selpercatinib and pralsetinib are kinase inhibitors with high specificity for RET; phase I and II studies showed overall response rates of 73% and 71% in first line, and 69% and 60% in second line treatment, respectively. Although resistance mechanisms to mutation-driven therapy will be a challenge in the future, phase III studies are ongoing and neo-adjuvant therapy with selpercatinib is being studied.

Summary
The development of selective RET-inhibitors has expanded the therapeutic arsenal to control tumor growth in progressive MTC, with fewer adverse effects than multikinase inhibitors. Future studies should confirm their effectiveness, study neo-adjuvant strategies, and tackle resistance to these inhibitors, ultimately to improve patient outcomes.

Keywords
medullary thyroid cancer, multikinase inhibitors, resistance, rearranged during transfection inhibitors, systemic therapy

GENERAL INTRODUCTION

Medullary thyroid cancer (MTC) is a rare neuroendocrine disease, encompassing about 5% of all thyroid cancers [1], occurring sporadically in 75%, and as part of the Multiple Endocrine Neoplasia type 2 (MEN2) syndrome in 25% of cases [2]. MEN2A (80% of MEN2) has a 100% MTC penetrance and is characterized by pheochromocytoma(s) (10–60%) and primary hyperparathyroidism (10–30%). MEN2B (10% of MEN2) includes pheochromocytoma(s) and extra-endocrine characteristics (ganglioneuromas, gastrointestinal diseases, marfanoid habitus) [3,4]. Familial MTC (FMTC) is considered a variant of MEN2A where only MTC occurs within a family (10%) [5].

In sporadic MTC, at least 45% of patients present with lymph node metastases and 10% with distant metastasis at diagnosis [6–9]. Patients with metastatic disease often have systemic symptoms such as diarrhea (especially in the presence of liver metastases), flushing, or (bone) pain [6,10]. Patients with a hereditary syndrome are often treated with a prophylactic thyroidectomy [3,6,11]. In one series, 66% of MEN2A patients and 54% of sporadic MTC patients were cured after surgery [12].

PROGNOSIS AND MARKERS FOR DISEASE PROGRESSION

MTC localized to the thyroid has an almost 100% 10-year survival rate; with distant metastases (most

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KEY POINTS

- Systemic therapy is the only option in patients with progressive systemic medullary thyroid cancer.
- The exact moment of systemic treatment initiation is difficult to establish.
- Rearranged during transfection-specific tyrosine kinase inhibitors provide better efficacy and fewer adverse events than nonspecific multiple kinase inhibitors.
- Primary and acquired resistance mechanisms will be a future challenge.

often in lung, liver and bone) this decreases to 40% [13–15]. Locoregional lymph node metastases are often confined to the central cervical compartment (level VI) (48%) but also spread ipsilaterally or contralaterally to the jugular vein and carotid artery (levels II–V) in 48% and 24% of patients [8]. With regional lymph node metastases present, the 10-year survival rate is 76% [15]. Contralateral lymph node metastases and extra-thyroidal growth increase the risk of distant metastases [14,16].

Calcitonin and carcinoembryonic antigen (CEA) are secreted by MTC, and therefore used as tumor markers during initial work-up and follow-up to assess tumor load and monitor tumor progression [17,18].

IMAGING

Molecular and conventional imaging modalities assess disease extent and guide treatment decisions. Ultrasonography combined with a fine needle aspirate (FNA) is often used as first imaging modality for a thyroid nodule or lymphadenopathy [19,20]. Whole-body imaging may be required, especially when locoregional or distant metastases are suspected. F-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT has an overall sensitivity of 62–76%, with higher uptake in patients with aggressive tumors (calcitonin-doubling times <9 months) [21,22]. The scarcely available and more expensive ^{18}F-dihydroxyphenylanaline PET/CT (^{18}F-DOPA-PET) is most exact for tumors with calcitonin doubling times of >12 months, uptake therefore suggests more indolently growing tumors [23,24]. Data on somatostatin receptor scintigraphy (SST-R) with ^{68}Ga-labeled compounds is limited. ^{68}Ga-DOTATATE PET/CT is superior to conventional imaging but limited compared to ^{18}F-FDG-PET and ^{18}F-DOPA-PET in whole-body lesion detection [20,25,26]. Conventional imaging (CT, MRI) can be used in preparation for extensive bilateral lymph node dissection [20]. RECIST (Response Evaluation Criteria in Solid Tumor) criteria help to objectively define tumor progression, and evaluate when to start systemic therapy in patients with progressive systemic disease [27].

TREATMENT IN DISEASE CONFINED TO THE NECK

Surgery is the preferred, and only, treatment to achieve cure of MTC [5]. Because MTC disseminates to locoregional lymph nodes relatively early in the disease, a total thyroidectomy, and at least a central cervical lymph node dissection (level VI) (CLND), is recommended [5,8,9]. Although consensus is lacking about standard dissection of the contralateral cervical compartment, an ipsilateral CLND is often followed by a contralateral CLND. A bilateral CLND carries greater risk of morbidity – temporary or even permanent hypoparathyroidism, injury to the recurrent laryngeal nerve, bleeding – but re-operating may induce even more morbidity [28]. Recent advances in (molecular) imaging seem to have eliminated the need to perform prophylactic bilateral CLNDs to keep tumor markers at an acceptable level; most decisions to perform CLNDs are now based on preoperative imaging.

After thyroid and/or lymph node surgery, external beam radiotherapy (EBRT) may be applied to improve locoregional control in high-risk patients [29,30]. A recent study of 297 patients illustrated that factors like T4, positive nodal disease, extranodal growth and postoperative residual disease characterize patients who may benefit from EBRT [31].

TREATMENT MODALITIES FOR OLIGOMETASTASIS

For patients with extensive local disease (large MTC tumor or extensive lymphadenopathy), a debulking thyroidectomy or even lymphadenectomy may be considered (even in the presence of distant metastases) to achieve symptomatic control, without curative intent. For patients with distant metastases confined to a single organ (oligometastasis), local treatment can reduce disease-related symptoms [10].

In patients with bone metastases, EBRT is used mainly to maintain function, reduce pain or prevent spinal injury (skeletal-related events) [32]. Percutaneous techniques like thermal ablation or cementoplasty, possibly effective, have not been evaluated in MTC. Antiresorptive therapy in MTC patients with bone metastases reduces rates of skeletal-related events [33,34]. Percutaneous or intraoperative radiofrequency ablations can be applied for liver metastases to improve symptomatic control with a low risk of side-effects [35,36]. Similarly,

transarterial embolization can be used for liver metastases [37–39]. Lung metastases are often multiple and combined with mediastinal lymph node metastases [14,40–42]. EBRT, surgery or stenting may be considered in case of bleeding or compression of the airways [43–45].

SYSTEMIC THERAPY

MTC is known for its indolent growth rate, remaining stable for relatively long periods in a considerable number of patients, even those with distant metastases. When disease progresses (based on clinical or biochemical findings), imaging modalities can be used to objectify the rate of progression. However, even after establishing the latter, determining exactly when to initiate systemic treatment remains difficult. A specialized multidisciplinary team should, in consultation with the patient, balance various factors and only initiate systemic therapy when the expected delay of disease progression is in balance with maintenance or improvement of quality of life. Current available systemic therapies for MTC have been shown to improve progression-free survival (PFS), but without increasing overall survival (OS) (see Table 1) and with numerous side effects.

Chemotherapy

Although various chemotherapy regimens for MTC were studied, none yielded promising results [5,10,46,47]. Chemotherapy is thus inappropriate in MTC treatment.

Rearranged during transfection as an oncogene

A breakthrough in the treatment of MTC has been the insight into genetic alterations and signaling pathways in tumor cells, resulting in molecular medicine specifically targeting driver mutations. Over 25 years ago, inherited receptor tyrosine kinase rearranged during transfection (RET) mutations were identified as the cause of MEN2A and MEN2B [48,49]. Although RET plays an important role in the development of normal kidney and nervous system tissue, when mutated it acts as an oncogene [50]. RET fusions are seen in only 1–2% of nonsmall cell lung cancers, and in 10–20% of papillary thyroid cancers. In contrast, an activating RET mutation is seen in the majority of MTCs: 60–90% in sporadic MTC and 100% in hereditary MTC [50,51].

Tyrosine kinases (TKs) are enzymes supporting signal transduction cascades that activate numerous proteins by phosphorylation. They significantly affect proliferation, differentiation and survival of cells. As a result of oncogenic mutations, tyrosine kinases like RET are constitutively phosphorylated, leading to activation of PI3K-AKT and RAS-MAPK signaling pathways, thereby stimulating cancer cell proliferation. The most frequent mutation in MEN2A substitutes the cysteine at position 634 of the extracellular cysteine-rich domains (CRD) of the RET protein, and less frequently at positions 609, 611, 618, 620 and 630. Mutations that substitute several amino acids within the intracellular kinase domain (mostly M918T and less frequently A883F) underlie MEN2B. FMTC mutations, V804M and V804L, are also cysteine mutations localized in the CRD of the intracellular kinase domain. In sporadic MTCs, the most frequent somatic RET mutations are C634R, V804M/L, A883F and M918T [52–55].

Multikinase inhibitors

TK inhibitors (TKIs) are drugs that inhibit tyrosine kinases, thereby inhibiting signal transduction cascades. TKIs work by blocking the ATP pocket of the TK receptor, thereby inhibiting autophosphorylation. Because TKIs target several different tyrosine kinase receptors, they are also known as multikinase inhibitors (MKIs). RET is one of the kinases targeted by several MKIs (see Fig. 1) [56].

A number of MKIs have been tested in MTC. Vandetanib especially blocks signaling of the tyrosine kinases vascular endothelial growth factor receptor-2 (VEGFR-2), RET, and epidermal growth factor receptor (EGFR). Cabozantinib targets VEGFR-2, RET, and hepatocyte growth factor receptor (MET). Both MKIs are approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

The phase III registration study of vandetanib versus placebo in MTC (ZETA trial) showed a statistically significant benefit in median progression-free survival (PFS) of 11 months for vandetanib (median PFS 30.5 versus 19.3 months, hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.31–0.69, $P < 0.001$), with an objective response rate (ORR) of 45% and 13% in the vandetanib and placebo groups (odds ratio [OR] 5.48, 95% CI 2.99–10.79, $P < 0.001$), respectively [57] (see Table 1). Final OS analysis showed no statistically significant difference (median OS 81.6 versus 80.4 months, HR 0.99, 95% CI 0.72–1.38, $P = 0.975$) [58]. However, 79% of patients first treated in the placebo-arm received vandetanib after progression; this cross-over hampers interpretation of the OS-results.

For cabozantinib, the phase III study (EXAM trial) showed a significant benefit in median PFS of 7 months versus placebo (median PFS 11.2 versus

Table 1. Efficacy and safety of cabozantinib, vandetanib, pralsetinib and selpercatinib

Trial		EXAM			ZETA		ARROW*		LIBRETTO-001*	
Population	Progression <14m			Stable + progressive disease, calcitonin >500			RETm first line	RETm second line	RETm first line	RETm second line
Primary endpoint	PFS			PFS				ORR		ORR
Treatment		Cabozantinib	Placebo		Vandetanib	Placebo	Pralsetinib	Pralsetinib	Selpercatinib	Selpercatinib
Patients (*n*)		219	111		231	100	21	55	88	55
Efficacy										
PFS (months)		11.2	4.0		30.5**	19.3	1y-PFS 81%	1y-PFS 75%	1y-PFS 92%	1y-PFS 82%
OS (months)		26.6	21.1		81.6	80.4[a]				
ORR		28%	0%		45%	13%	71%	60%	73%	69%
Median DOR (months)					22.0**		Not reached	Not reached	22.0	Not reached
Safety[b] – overall TRAEs										
Patients (*n*)		214	109		231	99	142[c]		162[c]	
	Diarrhea	70%	36%	Diarrhea	56%	26%	Decreased white blood cell count	35%	Dry mouth	39%
	Weight decreased	58%	11%	Rash	45%	11%	Increased AST	35%	Hypertension	30%
	PPES	53%	2%	Nausea	33%	16%	Hypertension	33%	Increased AST	28%
TRAEs ≥ grade 3										
	Diarrhea	22%	2%	Diarrhea	11%	2%	Hypertension	17%	Hypertension	12%
	PPES	13%	0%	Hyper-tension	9%	0%	Neutropenia	13%	Increased ALT	10%
	Hypo-calcemia	11%	0%	QT-prolonged	8%	1%	Lymphopenia	12%	Increased AST	8%
Dose reductions		82%			35%	3%	46%			30%[d]
Treatment discontinuation		22%	9%		12%	3%	4%			2%[d]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PPES, palmar-plantar erythrodysesthesia syndrome; RETm, RET-mutant medullary thyroid cancer; TRAEs, treatment-related adverse events.

*Efficacy was only assessed in patients with measurable disease at baseline.

**Estimated using Weibull model.

[a]crossover from placebo to vandetanib in 79%.

[b]only data of the three most common TRAEs (for the treatment group) is shown.

[c]TRAEs were calculated over patients with RET mutant medullary thyroid cancer and RET fusion positive thyroid cancer combined.

[d]Of all 531 patients who received selpercatinib in phase I + II combined.

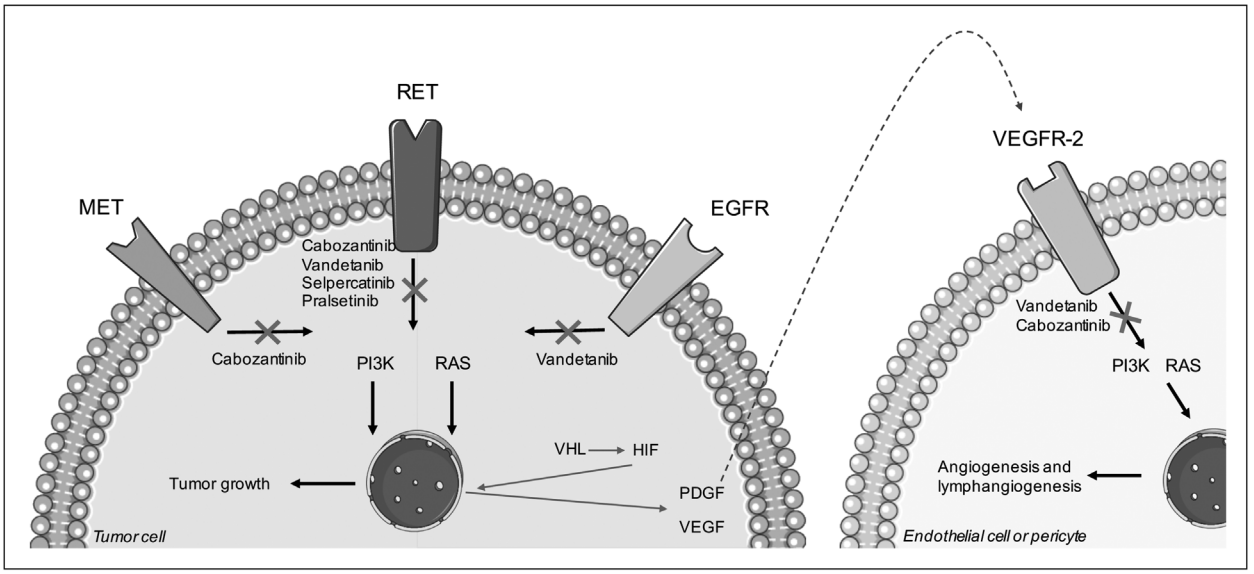

FIGURE 1. Inhibitory mechanisms of cabozantinib, vandetanib, selpercatinib and pralsetinib on tumor cells and healthy endothelium. The multiple kinase inhibitors (MKI) cabozantinib and vandetanib block several tyrosine kinases (MET, RET/RET, EGFR). This reduces activation of intracellular pathways that normally stimulate tumor growth and angiogenesis. Apart from their direct inhibitory effect on VEGFR, MKIs have an additional effect on endothelial cells and pericytes, because downregulation of VHL and HIF lowers stimulation of VEGFR-2 via VEGF and PDGF (56). The RET-specific TKIs, selpercatinib and pralsetinib, prevent only the phosphorylation of RET thus selectively inhibiting proliferation of the tumor cell. EGFR, epidermal growth factor receptor; HIF, hypoxia-inducible factor; MET, hepatocyte growth factor receptor; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; RAS, rat sarcoma protein; RET, re-arranged during transfection; VEGF(R), vascular endothelial growth factor (receptor); VHL, von Hippel-Lindau tumor suppressor. Source: original.

4.0 months, HR 0.28, 95% CI 0.19–0.40, $P < 0.001$), with ORRs of 28% and 0% in the cabozantinib and placebo groups, respectively [59]. Final OS analysis showed no statistically significant difference between the treatment and placebo groups (median OS 26.6 versus 21.1 months, stratified HR 0.85, 95% CI 0.64–1.12, $P = 0.24$). No cross-over occurred in this trial. In a subgroup analysis of only the 126 patients with a confirmed RET-mutation (M918T), OS was longer for patients treated with cabozantinib versus placebo (median OS 44.3 versus 18.9 months; HR 0.60, 95% CI 0.38–0.94). However, as no correction for multiple testing was applied, this subgroup analysis is considered exploratory.

The efficacy results of the two trials cannot be compared directly because the study populations differed. The EXAM trial included patients after confirmed progression; this was not required in the ZETA trial. The shorter survival of patients in the placebo arm of the EXAM trial suggests worse prognosis of these patients at baseline. Therefore, cross-study comparison of PFS and OS data is inadequate.

In both trials, adverse events (AEs) were common, resulting in dose reduction in 35% of the vandetanib and 82% of the cabozantinib treated patients, and discontinuation of therapy in 12% and 22% of patients, respectively (see Table 1). The high rates of AEs may be due to the unspecific effect of MKIs on multiple tyrosine kinases, not only on tumor cells but also on normal cells (see Fig. 1). The efficacy of vandetanib and cabozantinib is probably the result of their antiangiogenic activity, rather than their effects on mutant oncoproteins; this could also explain the numerous side-effects.

Selective rearranged during transfection inhibitors

The recent development of selective inhibitors targeting driver alterations in the RET gene in MTC is an example of successful precision oncology. The highly selective inhibition of RET in RET dependent cancers results in effective control of tumor growth, and in lower toxicity due to fewer off-target side-effects compared to MKIs. Efficacy and safety results for the two currently approved selective RET-inhibitors, selpercatinib and pralsetinib (the latter registered in the United States only), have recently been published (see Table 1).

Selpercatinib was studied in the phase I-II Libretto-001 trial including 143 patients with MTC with a confirmed RET mutation [60▪]. For the 88 patients treated in first line, the overall response rate (ORR) was 73%, with 10/88 (11%) complete responses (CR) and 54/88 (61%) partial responses (PR). In the 55 patients pretreated with vandetanib or cabozantinib, ORR was 69%, with 5/55 (9%) CR and 33/55 (60%) PR. The median duration of response (DOR) was 22 months (95% CI could not be estimated) in the first line setting, and was not reached (after a median follow-up duration of 14 months) in the previously treated patients. The most common treatment-related adverse events (TRAEs) of grade 3 or higher (hypertension (12%), increased alanine aminotransferase (10%) or aspartate aminotransferase (8%) and diarrhea (3%)) were treatable and resolved. TRAEs resulted in drug discontinuation in only 2% of patients.

Pralsetinib had been studied in a phase I-II trial (ARROW trial) [61▪]. The phase II included 122 patients with proven RET-mutant MTC. ORR was assessed in MTC patients with measurable disease ($n = 76$). For the 21 patients treated in first line, the ORR was 71%, with one CR. The estimated probability of ongoing response at 12 months was 84% (95% CI 63–100). Of the 55 patients previously treated with cabozantinib and/or vandetanib, the ORR was 60%, with one CR. The estimated probability of ongoing response at 12 months was 92% (95% CI 90–100). The median DOR was not reached in both groups, after median follow-up of about 11 months. The most common treatment-related adverse events (grade 3 or higher) were hypertension (17%), neutropenia (13%), lymphopenia (12%) and anemia (10%). Drug discontinuation due to TRAE was reported in 4% of patients. Disease-related diarrhea resolved in 93% of affected patients after two treatment cycles, highlighting how treatment can affect quality of life.

The high response rate in metastatic MTC has led to evaluation in the neo-adjuvant setting. For example, a patient with a primarily irresectable MTC underwent a complete surgical resection after a more than 50% RECIST-assessed response to neo-adjuvant treatment with selpercatinib [62▪]. To further evaluate neo-adjuvant treatment with selpercatinib in patients with RET-altered thyroid cancer, a phase II trial is currently ongoing [63].

Resistance to rearranged during transfection inhibitors

Because vandetanib and cabozantinib are MKIs with anti-RET, but also antiangiogenic activity, occurrence of new mutations in both pathways may lead to resistance. Moreover, primary and acquired resistance mechanisms may be present. Preclinical studies have shown that mutations of the RET gatekeeper residue V804L cause resistance to cabozantinib, and that the same mutation as well as an S904F mutation, confers resistance to vandetanib [64]. The selective RET inhibitors selpercatinib and pralsetanib were therefore designed to exhibit activity against gatekeeper mutations like RET V804M and S904F. Recently, two patients with nonsmall cell lung cancer (NSCLC), extensively pretreated with chemotherapy and MKIs and having an initial response to selpercatinib, finally developed resistance to this drug. Structural and functional studies in tumor tissue showed that the most likely mechanism was the occurrence of acquired RET solvent front mutations, resulting in interference of the mutated residue with drug-target binding [65,66▪]. Moreover, in-vitro studies confirmed that cabozantinib, vandetanib, selpercatinib and pralsetinib all lost inhibitory effect against nongatekeeper mutations RET G810S, G810R and G810C, whereas for selpercatinib and pralsetinib the inhibitor activity against RET V804and S904F gatekeeper mutations was maintained [65]. The nongatekeeper mutations at the solvent front and hinge led to cross-resistance for selpercatinib and pralsetinib [66▪].

Studies in NSCLC indicate that in RET-rearranged tumors, other mechanisms can induce an escape from RET inhibition, like reactivation of the RAS/MAPK pathway, or retained activation in EGFR or AXL signaling [67▪]. Whether these mechanisms also affect resistance to selective RET inhibition in MTC is unknown.

Novel developments in rearranged during transfection inhibition

Several next-generation RET inhibitors with different molecular properties are being developed (for an extensive overview see Fancelli 2021, reference 67). Currently, three clinical studies are ongoing: with the selective RET/SRC inhibitor TPX-0046 developed against solvent front mutations [68]; with BOS172738, a selective RET inhibitor with a 330-fold selectivity against VEGFR2 [69]; and with TAS0953/HM06, also a selective RET inhibitor [70]. Preclinical studies explored different strategies to overcome treatment resistance, such as combinations of mTOR inhibitor everolimus with vandetanib, selpercatinib with crizotinib – a MET/ALK/ROS1 inhibitor, – and the MKI sorafenib with the MEK-inhibitor selumetinib [71–74]. Combinations of different TKIs, or sequential application of targeted drugs based on acquired mutation resistance patterns, are soon expected to create new treatment

possibilities. Preclinical studies are also assessing new molecules selectively designed against RET, like NPA-101.3 and hSN608 [75,76].

Alternative strategies

There is limited experience with peptide receptor radionuclide therapy (PRRT) in patients with metastatic MTC. Recently, a systematic review evaluated 220 patients treated with PRRT (90Y-DOTATOC, 177Lu-DOTA-TATE, 111_Indium-based agent or unknown agent) and found objective responses in 10.6% of the patients [77]. Another new systemic treatment approach uses 177Lu-DOTA-(d-Glu)6-Ala-Tyr-Gly-Trp-Nle-Asp-PheNH2 (177Lu-PP-F11N), a radiolabeled mini-gastrin analog targeting the cholecystokinin 2 receptor. A recently published pilot study in six MTC patients showed accumulation of this agent in MTC tissue, stomach and kidneys, with low acute toxicity to the latter. Further studies to establish tolerated dose and evaluate therapeutic efficacy and safety are awaited [78].

CONCLUSION

The discovery of RET mutations in MTC, and the development of RET inhibitors with increasingly selective inhibition of RET, have expanded the therapeutic arsenal for effective control of tumor growth in progressive, distant metastasized MTC. Although preventing resistance to these selective RET inhibitors is a new challenge, growing knowledge of the molecular basis for such resistance promises further improvement of patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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