

Multikinase Inhibitors for the Treatment of Progressive, Metastatic Medullary Thyroid Cancer – An Evolving Paradigm

Barbara Jarzab¹ and Jolanta Krajewska²

1. Head of Nuclear Medicine and Endocrine Oncology Department; 2. Research Assistant, Nuclear Medicine and Endocrine Oncology Department, M. Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland

Abstract

Medullary thyroid cancer (MTC) is an uncommon type of thyroid cancer, representing around 4 % of the all thyroid cancers, and is a challenging malignancy. So far, surgery has been the only curative treatment and until recently there have been no effective medications. Within the past 5 years, multi-targeted kinase inhibitors have emerged that have shown convincing efficacy against such tumours. These drugs have changed the landscape in MTC treatment by providing effective medication for the first time. The modes of action of these drugs differ, but most target RET, a tyrosine kinase shown to play an important role in the pathobiology of MTC, as well as other receptors including vascular endothelial growth factor receptors (VEGFRs), epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor MET. Two agents in this class, vandetanib and cabozantinib, have demonstrated efficacy and safety in phase III trials and have consequently received regulatory approval. Other therapies for MTC treatment, including some with similar modes of action, are also in early development.

Keywords

Cabozantinib, medullary thyroid cancer, tyrosine kinase inhibitors, vandetanib

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Correspondence: Barbara Jarzab, Nuclear Medicine and Endocrine Oncology Department, M. Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Wybrzeże AK 15, 44-101 Gliwice, Poland E: bjarzab@io.gliwice.pl

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Thyroid cancer is the most common endocrine malignancy, being responsible for approximately 95 % of endocrine cases and 1.5 % of all cancers.¹ Its incidence has increased substantially in recent decades and has been rising by 6.4 % per year over the past 10 years.¹ This is due to a combination of an apparent increase resulting from more sensitive diagnostic procedures and of a true increase, a possible consequence of increased population exposure to radiation and to other still unrecognised carcinogens.² In Europe there were approximately 52,900 new cases of thyroid cancer in 2012 (approximately 40,700 in women; 12,300 in men).³

Medullary thyroid cancer (MTC) is an uncommon type of thyroid cancer, representing around 4 % of thyroid cancers.⁴ It is also a challenging malignancy, since until recently surgery was the only effective therapeutic option. There is therefore a need for novel treatment options, especially for patients for whom surgery is unsuitable and with metastatic disease. This article aims to consider the current state of treatments, the efficacy and safety evidence from clinical trials supporting the tyrosine kinase inhibitors (TKIs) cabozantinib and vandetanib and their prospects for future use in this disease.

Prognosis, Clinical Presentation and Diagnosis

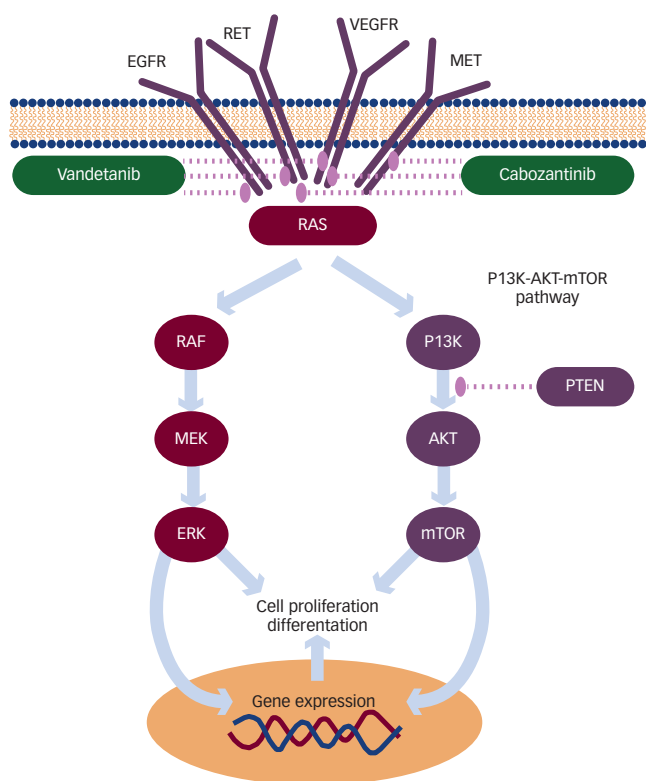
Thyroid cancers are classified into three groups. Differentiated thyroid carcinoma (DTC) represents 94 % of all thyroid cancers and includes three

subtypes: papillary (80 %), follicular (11 %) and Hurthle cell carcinoma (3 %). Anaplastic (undifferentiated) thyroid carcinoma (ATC) represents 2 % of all thyroid cancers.⁴ And, as previously mentioned, MTC accounts for 4 % of the total cases.

MTC originates from the parafollicular C cells that produce calcitonin. MTC is generally more aggressive than follicular cell-derived thyroid cancer and is responsible for a large proportion of thyroid cancer-related mortality. The overall 5-year survival rate is 80–86 %, and the 10-year survival rate is 75 %.^{5,6} In patients with unresectable or metastatic MTC, the disease course is heterogeneous, ranging from disease progression during a period of months, to slowly progressing disease over many years. Patients with metastatic MTC have a poor prognosis, and they may experience symptoms such as pain from bone metastasis and diarrhoea. Progressive metastatic MTC is the main cause of medullary thyroid cancer-related morbidity and mortality; patients with distant metastases at diagnosis have only 40 % survival at 10 years.⁷

Although MTC is generally regarded as an indolent disease, patients with radiographic evidence of progressive MTC can have a substantial disease burden and high incidence of disease-related symptoms.⁸ Patients typically do not present with a characteristic pattern of symptoms but may report one or more of the following: a lump at the base of the neck, which may interfere with swallowing, hoarseness and diarrhoea.

Figure 1: Kinase Signaling Cascade Involved in the Targeted MTC Treatment



AKT = protein kinase B; EGFR = epidermal growth factor receptor; ERK = extracellular signal regulated kinases; MAPK = mitogen-activated protein kinase; MEK = mitogen-activated protein kinase kinase; MTC = medullary thyroid cancer; mTOR = mammalian target of rapamycin; PTEN = phosphatase and tensin homologue; RET = REarranged during Transfection tyrosine kinase; VEGFR = vascular endothelial growth factor receptor Source: Wells et al. 2012.⁴⁰

Several diagnostic techniques for MTC are used routinely,^{9,10} among them thyroid fine-needle aspiration cytology (FNAC),^{11,12} although certain thyroid pathologies have similar cytology, making diagnosis difficult. The serum calcitonin level should also be measured: calcitonin is the main biochemical marker in MTC and can inform staging, postoperative management and prognosis.^{9,13} Calcitonin doubling time is an independent predictor of survival in MTC and may be superior to clinical staging.^{5,14,15} Carcinoembryonic antigen (CEA) is also a useful biomarker. In addition, CEA doubling time is a strong prognostic indicator for disease recurrence and death.¹⁴ If MTC is diagnosed or suspected on the basis of FNAC findings or calcitonin levels, ultrasonography should be undertaken to help confirm the diagnosis and to detect lymph node metastases.^{12,16} However, this often fails to locate metastatic disease and fluorine-labelled dihydroxyphenylalanine ((¹⁸F)-DOPA) or (¹⁸F)-FDG positron-emission tomography/computed tomography (PET/CT) may be used.¹⁷

Genetic testing is an important component of the diagnostic workup and is recommended in family members following a diagnosis of MTC.^{9,18} Up to 25 % of all MTCs are familial and carry a specific germline mutation in the REarranged during Transfection tyrosine kinase (RET) proto-oncogene.¹⁸ Even in apparently sporadic MTC the frequency of inherited disease ranges between 6.5–10 %.^{19,20} Molecular analyses show that approximately 55 % of MTC tumours have activating mutations in RET, including inherited and sporadic cases.²¹ These RET mutations in tumours, especially RET-M918T, have a strong negative prognostic impact. RET is targeted by most agents assessed in recent systemic therapy trials of MTC, along with vascular endothelial growth factor receptors (VEGFRs).²¹

Current Treatment Options for Medullary Thyroid Cancer

Treatment of MTC is based on evidence-based recommendations from the American Thyroid Association,^{9,22} although in practice different patterns exist in terms of diagnosis, treatment and long-term management.²³ During the meeting of the European Thyroid Association [ETA] in 2009 some controversies arose.²⁴ The most controversies were related to basal and stimulated serum calcitonin measurements, the extent of lymph node surgery, the extent of RET diagnosis and the management of inherited MTC.²⁴

Surgical treatment of MTC is currently the only curative treatment modality and aims to provide local control of the cancer while maintaining laryngoesophageal function. Treatment involves total thyroidectomy, central neck dissection and autograft of an inferior parathyroid gland.²⁵ Prophylactic surgery should be considered in inherited disease. Ipsilateral lateral neck dissection may also be performed if the primary tumour is >1 cm in size or there is evidence of positive nodes in the central neck. A contralateral lateral neck dissection may be considered in patients with bilateral tumours or extensive lateral adenopathy on the side of the primary tumour.²⁶

Radiation therapy also plays a role in the treatment of MTC: external beam radiotherapy is an option for patients with locally advanced MTC to optimise locoregional control.²⁶ Calcitonin and CEA are useful to monitor disease status after surgery; however, a minority of patients with nodal disease at the time of surgery have undetectable calcitonin levels postoperatively.²⁵ Systemic chemotherapy and radiation therapy have limited benefit in disseminated MTC.²⁷ There is variation among practitioners regarding when to initiate therapy in metastatic MTC. ETA guidelines are informative in this context.²²

In 2009, a paradigm for targeted therapy in MTC was proposed following the discovery of genetic abnormalities in tumours, in particular mutations in the RET/PTC-RAS-RAF-mitogen-activated protein kinase (MAPK) axis and the phosphatidylinositol-3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway.^{28,29} RET is the most studied of these potential therapeutic targets, and is able to activate a variety of signaling cascades, including MAPK and PI3K-AKT (see Figure 1).³⁰

TKIs have been associated with limited or transient benefit arising from drug resistance.^{31,32} As a result, drug development has focused on agents capable of targeting several tyrosine kinases as well as other oncogenic pathways. Vandetanib (Caprelsa[®], AstraZeneca) and cabozantinib (Cometriq[®], Exelixis) are multitargeted TKIs with distinct but overlapping mechanisms of action that act to differing extents against multiple receptors including RET kinase, VEGFRs, epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor MET.³³ Both agents have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA): cabozantinib was approved in the US in 2012 and in Europe in 2014; vandetanib was approved in the US in 2011 and in Europe in 2012.

Cabozantinib has been shown to inhibit the activity of receptor tyrosine kinases including MET, RET and VEGFR2.³⁴ In preclinical studies, cabozantinib showed significant antiangiogenic and antitumour activity in a broad range of tumour models, including a model of MTC with an activating RET mutation.³⁵ It also resulted in decreased tumour invasiveness and decreased metastasis compared with agents

targeting VEGF signalling without MET inhibition. Vandetanib also inhibits RET and VEGFR2, but in addition also targets EGFR.^{36,37}

Vandetanib

Following evidence of antitumour activity in patients with hereditary MTC,³⁸ and demonstration of durable partial objective responses and disease control in a phase II study,³⁹ vandetanib was investigated in the Zactima Efficacy in Thyroid Cancer Assessment (ZETA) phase III clinical trial.⁴⁰ This study randomised 331 patients with unresectable locally advanced or metastatic MTC (2:1) to vandetanib 300 mg/day or placebo. In the event of objective disease progression, patients could elect to receive open-label vandetanib. At a median follow-up of 24 months the response rate (RR) was 45 % for vandetanib versus 13 % in placebo. (One per cent for placebo arm patients who had a response while on placebo, as opposed to after crossover to vandetanib). The median progression-free survival (PFS) was 19.3 months for vandetanib and this endpoint had not been reached for placebo at study completion, but a Weibull model indicated a predicted median of 30.5 months. The long PFS in placebo-treated patients reflects the inclusion criteria that did not require radiographic evidence of progressive disease within a specified time period prior to study entry; therefore, patients with slowly progressing disease could be included in the trial. However, patients were required to have a serum calcitonin level ≥ 500 pg/ml. The study met its primary objective of PFS prolongation with vandetanib versus placebo (hazard ratio [HR] 0.46; $p < 0.001$). The improvement in PFS for vandetanib over placebo was also seen in all subgroups analysed including gender, race, World Health Organization (WHO) performance status ≥ 1 or $=0$, hereditary mutation, presence of metastatic cancer and prior therapy history. Overall survival data were immature at data cutoff (HR 0.89; 95 % confidence interval [CI] 0.48–1.65).

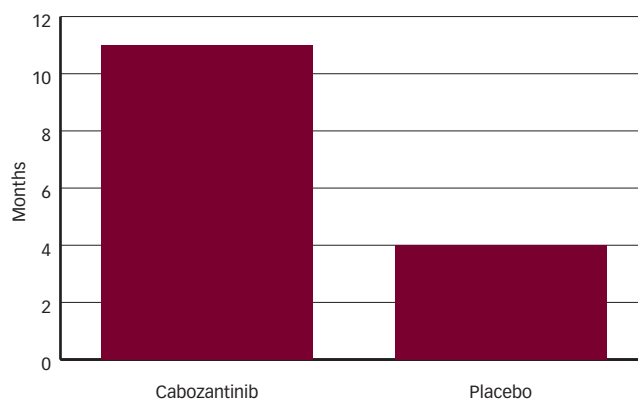
Common adverse events (AEs; any grade) occurred more frequently with vandetanib compared with placebo, including diarrhoea (56 % versus 26 %), rash (45 % versus 11 %), nausea (33 % versus 16 %), hypertension (32 % versus 5 %) and headache (26 % versus 9 %). The AE of most concern was corrected QT interval prolongation, a potential risk factor for torsades de pointes, particularly in view of the long terminal elimination half-life of the drug.

Cabozantinib

In a phase I study, ($n=85$, including 37 with MTC), 29 % of patients with MTC and measurable disease had a confirmed partial response. Overall, 49 % of the MTC patients with measurable disease experienced tumour shrinkage of 30 % or more. In addition, 41 % of the patients with MTC had stable disease for at least 6 months.⁴¹ Long-term disease control exceeding 2 years has now been demonstrated in these patients.⁴²

Cabozantinib was subsequently investigated in the Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer (EXAM) phase III clinical trial.⁴³ Following the vandetanib phase III trial, it was suggested that subsequent studies should include patients with more aggressive disease. This study therefore recruited 330 patients with unresectable locally advanced or metastatic MTC with radiographic disease progression per modified Response Evaluation Criteria in Solid Tumors (mRECIST) at screening compared with tumour measurements obtained within the previous 14 months. Patients were randomised 2:1 to receive cabozantinib (140 mg per day) or placebo. The estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (HR 0.28; $p < 0.001$) (See Figure 2). The short PFS in placebo-treated patients reflected the inclusion criteria specifying only patients with radiographic evidence of progressive disease were eligible. The

Figure 2: Progression-free Survival in the EXAM Phase III Trial of Cabozantinib versus Placebo in Medullary Thyroid Cancer



Source: Elisei et al. 2013.⁴³

study found prolonged PFS with cabozantinib across all subgroups including by age, prior TKI treatment and RET mutation status (hereditary or sporadic). The RR was 28 % and responses were seen regardless of RET mutation status. Kaplan-Meier estimates of patients alive and progression free at 1 year were 47.3 % for cabozantinib and 7.2 % for placebo.

Subgroup analysis of the EXAM trial PFS data found that patients with mutations in genes encoding RET (pre-specified analysis) or RAS proteins (post-hoc analysis) experienced a significantly higher benefit than patients without those mutations.⁴⁴ The RET status was determined in 65 % of the study participants; of these, 79 % had an activating mutation and 21 % were RET wild type. All RET mutation subgroups showed PFS benefit from cabozantinib treatment (although the confidence interval for the RET mutation-negative subgroup crossed 1.0), and demonstrated RRs between 22 % and 32 %. Patients harbouring a RET mutation had longer median PFS on cabozantinib (60 weeks) than patients with wild type RET (25 weeks; $p=0.0001$). The PFS benefit was slightly greater in patients with RET M918T, the most common RET mutation that is associated with poor prognosis⁴⁵ (median of 61 weeks versus 36 weeks with another RET mutation; $p=0.009$). Patients with hereditary MTC had similar PFS to those with sporadic disease, and the presence of the common RET polymorphism G691S had no effect on either PFS or RR.

Since RAS gene mutations have been identified in some patients who lack a RET mutation, potential RAS gene mutations in the RET-wild type and RET status unknown arm were investigated and 16 patients were found to have a RAS gene mutation.⁴⁴ Patients with a RAS gene mutation had a similar RR (31 %) and median PFS (47 weeks) to those with RET mutations (32 % and 60 weeks). The study concluded that the benefit observed in patients with an unknown RET mutation status might have been due to undetected RET or RAS gene mutations. Currently, the standard of care for MTC does not involve testing for these mutations in tumours.

Common cabozantinib-associated AEs included diarrhoea (63.1 % versus 33.0 %), palmar-plantar erythrodysesthesia (50.0 % versus 1.8 %), decreased weight (47.7 % versus 10.1 %), decreased appetite (45.8 % versus 15.6 %) nausea (43.0 % versus 21.1 %) and fatigue (40.7 % versus 28.4 %). Regarding to cardiac toxicity no clinically significant QT prolongation was observed in the trial. However, rare but

Table 1: Summary of Clinical Studies Investigating Targeted Therapies for Medullary Thyroid Cancer

Drug	Trial Design	Results	Reference
Axitinib	Phase II, n=52, MTC/DTC	ORR = 35 %; SD in 35 %; PFS = 16.1 months; OS = 27.2 months	50
Cabozantinib	Phase III, n=330, MTC	ORR = 28 % versus 0 %; PFS = 11.2 months versus 4.0 months	43
Lenvatinib	Phase II, n=59, MTC	ORR = 35 %; PFS = 9 months; 22 % withdrawn due to toxicity	51
Motesanib	Phase II, n=91, 48 weeks, MTC	ORR = 2 %; SD in 81 %; PFS = 48 weeks	46
Pazopanib	Phase II, n=35, MTC	ORR = 14 %; PFS = 9.4 months; OS = 19.0 months	52
Sorafenib	Phase II, metastatic MTC, n=16	ORR = 6.3 %; SD in 87.5 %; PFS = 17.9 months	49
Sorafenib	Phase II, n=34 (15 MTC, 19 DTC), 6 months	ORR = 15 %; SD in 74 %; PFS and OS not reached at 19 months	48
Sunitinib	Phase II, n=25, MTC, 11 months	ORR = 35 %; SD in 57 %; PFS = 7 months	47
Vandetanib	Phase III, n=331, MTC, median follow-up 22 months	ORR = 45 % versus 13 %; PFS = 30.5 months* versus 19.3 %	40

*Predicted value, progression-free survival (PFS) not reached at study completion.

DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; PFS = progression-free survival; ORR = overall response rate; OS = overall survival.

Table 2: Comparison of the ZETA and EXAM Clinical Trials

	ZETA	EXAM
Inclusion criteria	Measurable, unresectable locally advanced or metastatic, hereditary or sporadic MTC. WHO performance status of 0 to 2 and serum calcitonin level 500 pg/ml	Locally advanced or metastatic MTC that showed radiographic disease progression per mRECIST at screening compared with tumour measurements obtained within the previous 14 months
Outcomes	Median PFS was 19.3 months in the placebo group and, not reached for the vandetanib group, (Weibull model indicated predicted median of 30.5 months). (HR 0.46, 95 % CI 0.31 to 0.69; p<0.001)	Median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (HR 0.28, 95 % CI 0.19 to 0.40; p<0.001)
Adverse effects	AEs led to treatment discontinuation in 12 % receiving vandetanib and 3 % receiving placebo. AEs such as diarrhoea, rash, nausea and hypertension occurred in more than 30 % of patients receiving vandetanib; AEs leading to discontinuation of vandetanib reported in more than 1 % of patients were asthenia (1.7 %) and rash (1.3 %) Dose reduction required in 35 % of treatment group	AEs led to treatment discontinuation in 16 % of cabozantinib-treated patients and in 8 % of placebo-treated patients. Common AEs included diarrhoea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea and fatigue. Dose reduction required in 79 % of treatment group
Reference	Wells et al. 2012 ⁴⁰	Elisei et al. ⁴³

AE = adverse event; CI = confidence interval; EXAM = Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer; HR = hazard ratio; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MTC = medullary thyroid cancer; PFS = progression-free survival; WHO = World Health Organization; ZETA = Zactima Efficacy in Thyroid Cancer Assessment.

potentially life-threatening AEs including gastrointestinal perforations, fistula development and haemorrhage were observed. Hypertension was reported in 32.7 % of patients with cabozantinib versus 4.6 % with placebo. AEs led to treatment discontinuation in 16 % of cabozantinib-treated patients and in 8 % of placebo-treated patients. The toxicity was considered significant but manageable.

Other Multikinase Inhibitors

Other promising multikinase inhibitors that have been investigated in MTC are summarised in *Table 1* and include motesanib: a highly selective inhibitor of VEGFR, platelet-derived growth factor receptor (PDGFR) and KIT.⁴⁶ Other kinase inhibitors include sunitinib⁴⁷ and sorafenib,^{48,49} and axitinib.⁵⁰ Lenvatinib, an oral multiple receptor tyrosine kinase (RTK) inhibitor targeting VEGFR-1 and -3, fibroblast growth factor receptor-1 and -4, RET, KIT and PDGFR, has received considerable attention as a promising therapeutic option,^{30,51} as has pazopanib.⁵² In preclinical studies, ponatinib has been shown to be a highly potent inhibitor of activated variants of RET found in MTC.⁵³ Ongoing phase II trials in patients with MTC are investigating ponatinib,⁵⁴ imatinib,⁵⁵ nintedanib⁵⁶ and anlotinib.⁵⁷

Other Therapeutic Options

Expression of somatostatin receptor subtypes sst1, sst2 and/or sst5 have been shown in the majority (~80 %) of patients with MTC,⁵⁸ leading to the investigation of somatostatin analogues in the treatment of MTCs. Pasireotide is currently being investigated alone and in combination with the mTOR inhibitor everolimus.⁵⁹ Yeast-CEA (GI-6207), a therapeutic cancer vaccine genetically modified to express recombinant CEA, is

also in early-stage clinical development.⁶⁰ Radiopharmaceuticals are also available for the palliative treatment of advanced MTC: these include agents that target of the specific expression of receptors, such as ¹¹¹In-octreotide, hormone transporters (radiolabelled meta-iodobenzylguanidine [MIBG]) or molecular targets (radiolabelled anti-CEA monoclonal antibodies).⁶¹

Incorporating New Tyrosine Kinase Inhibitors into Current Treatment Paradigms

The availability of new targeted therapies requires a reconsideration of current treatment approaches for MTC. However, there is a need to identify a patient population most likely to benefit from these agents. These include patients with progressive distant metastases, patients without contraindications such as certain cardiac arrhythmias and patients in whom non-durable partial responses are expected to increase life expectancy. Patients with stable disease in whom the calcitonin or CEA doubling time are slow and those with multiple comorbidities may not be good candidates for multikinase inhibitors.

In terms of comparisons between vandetanib and cabozantinib, there are important differences in between the ZETA and EXAM trials (see *Table 2*). Among the inclusion criteria for EXAM trial was radiographic disease progression per mRECIST at screening compared with tumour measurements obtained within the previous 14 months, which was not an entry criterion in ZETA. The EXAM study population had rapidly progressive disease, reflected by a 4.0 month median PFS in the placebo group compared with 19.3 months median PFS for the placebo

group in the ZETA trial. The EXAM study population also had advanced disease at baseline, reflected in the high level of baseline symptoms including pain and fatigue.^{43,62} To our knowledge, similar baseline data from the ZETA trial have not yet been published. In the EXAM trial, patients previously treated with TKIs (21 %) showed a significant benefit from cabozantinib, whereas the ZETA trial did not report data on previous TKI therapy. Both agents produced objective responses and both required dose reduction (35 % with vandetanib; 79 % with cabozantinib). The high percentage of dose reduction of the latter can be explained by the fact that the drug passed from phase I to stage III testing without a phase II trial. It is possible that a lower dose may be as effective, with improved tolerability and lower rates of dose reduction and/or discontinuation. The US Food and Drug Administration (FDA) has requested a postmarketing clinical trial to evaluate the safety and efficacy of a lower cabozantinib dose.⁶³

Another important area for future study is the impact of cabozantinib in bone, one of the most common and early metastases seen in MTC.⁶⁴ In a phase II study in advanced prostate cancer, cabozantinib had a substantial effect on disease in the bone, with an improvement in bone pain reported in 67 % of evaluable patients.⁶⁵ Further clinical investigation is required to determine the effect of cabozantinib on bone metastases in patients with MTC.

Physicians treating patients with MTC now have a choice of two effective treatment options, but there are no data comparing these agents in the same study and patient population. For now, the choice of agent should be individualised.⁶⁶ Cabozantinib might be preferred in patients with bone metastases, in those who are already receiving drugs to prolong the QT interval or who have significant electrolyte imbalances, although this needs further study. On the other hand, vandetanib seems to be better tolerated as dose reduction was required in only 35 % of patients in the ZETA study compared with 79 % receiving cabozantinib under the EXAM trial. However, the direct comparison of these drugs is necessary to confirm this hypothesis. Physicians should be familiar with the toxicity profiles of both drugs so that AEs relating to treatment can be identified at an early stage and prompt dose reductions can be implemented. Moreover, despite AEs related to drug toxicity, patients may complain of symptoms related to hormonally active metastases. The last ETA guidelines for metastatic MTC involved recommendation for these patients.²²

It is important to remember that MTC is often an indolent condition, for which immediate therapy may not be required. There is a need

to apply clinical judgement before initiating treatment. A calcitonin doubling-time of more than 2 years is a prognostic indicator of indolent disease and, in these patients, a 'watch and wait' strategy may be more appropriate.⁴ Conversely, symptomatic disease, where diarrhoea and pain are reported, can be a prompt to initiate therapy. There is a need to examine quality of life (QoL) measures in patients who are likely to be taking these therapies over a long period of time. There is also a need to investigate combined or sequenced therapeutic strategies. Monotherapy with vandetanib or cabozantinib affects only limited molecular targets and is unlikely to be curative because multiple signalling pathways and molecular mechanisms may be involved in disease progression. Combined approaches are likely to result in a broader range of AEs. However, since the toxicity associated with these agents has been reported as manageable, there is a rationale for investigating combined therapy and strategies for sequencing therapies.

In order to achieve clinical benefit and preserve QoL, it is important to identify patients who will benefit the most from these therapies. The role of RET and RAS gene mutations should be addressed in future studies of cabozantinib and vandetanib.⁶⁷ The extent of benefit may depend in part on RET genotype.⁶⁸ Both the EXAM and ZETA studies showed a PFS advantage in patients with RET mutation-positive tumours, including patients with the poor-prognosis mutation M918T.^{40,43,68}

Summary and Concluding Remarks

There is a lack of effective therapy for patients with MTC, for which survival is currently worse than in differentiated thyroid cancer, and new treatment options are urgently needed. The multikinase inhibitors represent a paradigm shift in the treatment of MTC and have achieved prolonged responses and improved PFS. Vandetanib and cabozantinib have been approved for the treatment of advanced MTC, with several other agents in clinical development. However, MTC can be a slow-growing disease and there remains a need for long-term data to determine the benefits of these agents in terms of overall survival and QoL. There is a need for updated guidelines related to the treatment of advanced MTC.

It is likely that the number of treatment options for this patient population will continue to grow, but there are at present limited data to inform choices of which drug should be used first. There is a need to define the patient population at risk so that patients with indolent disease are not exposed to toxic agents prematurely when survival is not affected. In conclusion, multikinase inhibitors represent a significant landmark in the treatment of MTC. ■

- American Cancer Society, What are the key statistics about thyroid cancer?, 2013. Available at: <http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-key-statistics> (accessed 21 August 2014).
- Pellegriti G, Frasca F, Regalbutto C, et al., Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors, *J Cancer Epidemiol*, 2013;2013:965212.
- Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al., Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012, *Eur J Cancer*, 2013;49:1374–403.
- NCCN, National Comprehensive Cancer Network. Thyroid Carcinoma (version 2.2013). Available at: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf (accessed 26 June 2014).
- Barbet J, Campion L, Kraeber-Bodere F, et al., Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma, *J Clin Endocrinol Metab*, 2005;90:6077–84.
- Grünwald F, Biersack HJ, Grünwald F, National Cancer Database in the US (eds.), *Thyroid cancer*, Berlin: Springer, 2005.
- Roman S, Lin R, Sosa JA, Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases, *Cancer*, 2006;107:2134–42.
- Schoffski P, Cohen, E.E.W., Bentzien, F et al., Baseline disease characteristics and symptoms among patients with metastatic medullary thyroid cancer enrolled in the EXAM trial. Presented at the 2nd World Congress on Thyroid Cancer, 10–14 July 2013, Toronto, Canada. Abstract no 106.
- American Thyroid Association Guidelines Task F, Kloos RT, Eng C, et al., Medullary thyroid cancer: management guidelines of the American Thyroid Association, *Thyroid*, 2009;19:565–612.
- Ahmed SR, Ball DW, Clinical review: Incidentally discovered medullary thyroid cancer: diagnostic strategies and treatment, *J Clin Endocrinol Metab*, 2011;96:1237–45.
- Chang TC, Wu SL, Hsiao YL, Medullary thyroid carcinoma: pitfalls in diagnosis by fine needle aspiration cytology and relationship of cytomorphology to RET proto-oncogene mutations, *Acta Cytol*, 2005;49:477–82.
- Cobin RH, Gharib H, Bergman DA, et al., AAACE/AAES medical/surgical guidelines for clinical practice: management of thyroid carcinoma. American Association of Clinical Endocrinologists. American College of Endocrinology, *Endocr Pract*, 2001;7:202–20.
- Eielsei R, Bottici V, Luchetti F, et al., Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders, *J Clin Endocrinol Metab*, 2004;89:163–8.
- Meijer JA, le Cessie S, van den Hout WB, et al., Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis, *Clin Endocrinol (Oxf)*, 2010;72:534–42.
- Gawlik T, d'Amico A, Szpak-Ulczok S, et al., The prognostic value of tumor markers doubling times in medullary thyroid carcinoma – preliminary report, *Thyroid Res*, 2010;3:10.
- Machens A, Ukkat J, Hauptmann S, et al., Abnormal carcinoembryonic antigen levels and medullary thyroid cancer progression: a multivariate analysis, *Arch Surg*, 2007;142:289–93; discussion 94.
- Kauhanen S, Schalin-Jantti C, Seppanen M, et al., Complementary roles of 18F-DOPA PET/CT and 18F-FDG PET/CT in medullary thyroid cancer, *J Nucl Med*, 2011;52:1855–63.
- Roy M, Chen H, Sippel RS, Current understanding and management of medullary thyroid cancer, *Oncologist*, 2013;18:1093–100.
- Wiench M, Wygoda Z, Gubala E, et al., Estimation of risk of inherited medullary thyroid carcinoma in apparent sporadic patients, *J Clin Oncol*, 2001;19:1374–80.
- Romei C, Cosci B, Renzini G, et al., RET genetic screening of sporadic medullary thyroid cancer (MTC) allows the preclinical

- diagnosis of unsuspected gene carriers and the identification of a relevant percentage of hidden familial MTC (FMTC), *Clin Endocrinol (Oxf)*, 2011;74:241–7.
21. Ball DW, Management of medullary thyroid cancer, *Minerva Endocrinol*, 2011;36:87–98.
 22. Schlumberger M, Bastholt L, Dralle H, et al., 2012 European thyroid association guidelines for metastatic medullary thyroid cancer, *Eur Thyroid J*, 2012;1:5–14.
 23. Panigrahi B, Roman SA, Sosa JA, Medullary thyroid cancer: are practice patterns in the United States discordant from American Thyroid Association guidelines?, *Ann Surg Oncol*, 2010;17:1490–8.
 24. Feldt-Rasmussen U, Soderstrom F, Results and summary of voting among the audience during presentation and discussion of Medullary Thyroid Carcinoma clinical guidelines prepared by American Thyroid Association Thyroid Research, 2013;6(Suppl. 1):S12.
 25. Mazeh H, Sippel RS, Surgical management of medullary thyroid cancer, *Minerva Endocrinol*, 2012;37:329–34.
 26. Terezakis SA, Lee NY, The role of radiation therapy in the treatment of medullary thyroid cancer, *J Natl Compr Canc Netw*, 2010;8:532–40; quiz 41.
 27. Sherman SI, Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers, *J Clin Endocrinol Metab*, 2009;94:1493–9.
 28. Ye L, Santaripa L, Gagel RF, Targeted therapy for endocrine cancer: the medullary thyroid carcinoma paradigm, *Endocr Pract*, 2009;15:597–604.
 29. Carlomagno F, Santoro M, Identification of RET kinase inhibitors as potential new treatment for sporadic and inherited thyroid cancer, *J Chemother*, 2004;16 Suppl. 4:49–51.
 30. Stjepanovic N, Capdevila J, Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib, *Biologics*, 2014;8:129–39.
 31. Bergers G, Hanahan D, Modes of resistance to anti-angiogenic therapy, *Nat Rev Cancer*, 2008;8:592–603.
 32. Chen, Y-F and Fu, L-W, Mechanisms of acquired resistance to tyrosine kinase inhibitors, *Acta Pharmaceutica Sinica B*, 2011;1:191–207.
 33. Sherman SI, Lessons learned and questions unanswered from use of multitargeted kinase inhibitors in medullary thyroid cancer, *Oral Oncol*, 2013;49:707–10.
 34. Houvras Y, Wirth LJ, Cabozantinib in medullary thyroid carcinoma: time to focus the spotlight on this rare disease, *J Clin Oncol*, 2011;29:2616–8.
 35. Sennino B, Naylor RM, Tabruyn SP, et al., Reduction of tumor invasiveness and metastasis and prolongation of survival of RIP-Tag2 mice after inhibition of VEGFR plus c-Met by XL184, *Mol Cancer Ther*, 2009;8(Suppl. 12):A13.
 36. Morabito A, Piccirillo MC, Falasconi F, et al., Vandetanib (ZD6474), a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) tyrosine kinases: current status and future directions, *Oncologist*, 2009;14:378–90.
 37. Carlomagno F, Vitagliano D, Guida T, et al., ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases, *Cancer Res*, 2002;62:7284–90.
 38. Robinson BG, Paz-Ares L, Krebs A, et al., Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer, *J Clin Endocrinol Metab*, 2010;95:2664–71.
 39. Wells SA, Jr., Gosnell JE, Gagel RF, et al., Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer, *J Clin Oncol*, 2010;28:767–72.
 40. Wells SA, Jr., Robinson BG, Gagel RF, et al., Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial, *J Clin Oncol*, 2012;30:134–41.
 41. Kurzrock R, Sherman SI, Ball DW, et al., Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer, *J Clin Oncol*, 2011;29:2660–6.
 42. Cohen EEW, Hong DG, Salgia R, et al., Long-term disease control of ≥2 years achieved with cabozantinib in subjects with metastatic medullary thyroid carcinoma on a phase I study, *J Clin Oncol*, 2013;31(Suppl); abstr 6090.
 43. Elisei R, Schlumberger MJ, Muller SP, et al., Cabozantinib in progressive medullary thyroid cancer, *J Clin Oncol*, 2013;31:3639–46.
 44. Sherman SI, Cohen EEW, Schoffski P, et al., Efficacy of cabozantinib (Caboz) in medullary thyroid cancer (MTC) patients with RAS or RET mutations: Results from a phase III study, *J Clin Oncol*, 2013;31(Suppl. abstr 6000).
 45. Elisei R, Cosci B, Romei C, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *J Clin Endocrinol Metab*. 2008 Mar;93(3):682–7
 46. Schlumberger MJ, Elisei R, Bastholt L, et al., Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer, *J Clin Oncol*, 2009;27:3794–801.
 47. de Souza JA, Busaidy N, Zimrin A, et al., Phase II trial of sunitinib in medullary thyroid cancer (MTC), *J Clin Oncol*, 2010;28(15 Suppl.):5504.
 48. Ahmed M, Barbachano Y, Riddell A, et al., Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: a phase II study in a UK based population, *Eur J Endocrinol*, 2011;165:315–22.
 49. Lam ET, Ringel MD, Kloos RT, et al., Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer, *J Clin Oncol*, 2010;28:2323–30.
 50. Locati LD, Licitra L, Agate L, et al., Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments, *Cancer*, 2014; [Epub ahead of print].
 51. Schlumberger M, Jarzab B, Cabanillas M, et al., A phase II trial of the multitargeted kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer (MTC), *J Clin Oncol*, 2012;30 (Suppl.); abstract 5591.
 52. Bible KC, Suman VJ, Molina JR, et al., A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H, *J Clin Endocrinol Metab*, 2014;99:1687–93.
 53. Gozgit JM, Chen T-H, Clackson Y, et al., Ponatinib is a highly potent inhibitor of activated variants of RET found in MTC and NSCLC. *Cancer Research*: April 15, 2013; Volume 73, Issue 8, Supplement 1; abstract 2084, 2013;.
 54. clinicaltrials.gov, Ponatinib for Advanced Medullary Thyroid Cancer. Available at: <https://clinicaltrials.gov/ct2/show/NCT01838642> (accessed 26 June 2014).
 55. Imatinib in Combination With Dacarbazine and Capecitabine in Medullary Thyroid Carcinoma. Available at: <http://clinicaltrials.gov/show/NCT00354523> (accessed 7 July 2014).
 56. Nintedanib (BIBF1120) in thyroid cancer. Available at: <http://clinicaltrials.gov/ct2/show/NCT01788982?term=NCT01788982&rank=1> (accessed 7 July 2014).
 57. A phase II study of anlotinib hydrochloric capsule in MTC patients (ALTN/MTC). Available at: <http://clinicaltrials.gov/ct2/show/NCT01874873?term=NCT01874873&rank=1> (accessed 7 July 2014).
 58. Mato E, Matias-Guiu X, Chico A, et al., Somatostatin and somatostatin receptor subtype gene expression in medullary thyroid carcinoma, *J Clin Endocrinol Metab*, 1998;83:2417–20.
 59. Faggiano A, Colao A, The antiproliferative effect of pasireotide LAR alone and in combination with everolimus (RAD001) in patients with progressive medullary thyroid cancer (MTC): A single-center, open-label, phase II, proof-of-concept study, *J Clin Oncol*, 2010;28:15 Suppl.; abstr TPS219.
 60. Bilusic M, Heery CR, Arlen PM, et al., Phase I trial of a recombinant yeast-CEA vaccine (GI-6207) in adults with metastatic CEA-expressing carcinoma, *Cancer Immunol Immunother*, 2014;63:225–34.
 61. Ruffini V, Castaldi P, Treglia G, et al., Nuclear medicine procedures in the diagnosis and therapy of medullary thyroid carcinoma, *Biomed Pharmacother*, 2008;62:139–46.
 62. Schoffski P, Cohen E, Bentzien F, et al., Progressive, metastatic medullary thyroid cancer: Baseline symptoms and disease characteristics among patients enrolled in the EXAM trial Abstract 3154 (oral), European cancer Congress – European Society for Medical Oncology (ECCO-ESMO), 2013.
 63. Yang J, Mehrotra N, Zhao H, et al., Characterization of the exposure-response relationship leading to recommendations for dosing optimization in a new drug application review, *J Clin Oncol*, 2013;31(Suppl.):143s, abstr 2510.
 64. Wu K, Hou SM, Huang TS, et al., Thyroid carcinoma with bone metastases: a prognostic factor study, *Clin Med Oncol*, 2008;2:129–34.
 65. Smith DC, Smith MR, Sweeney C, et al., Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial, *J Clin Oncol*, 2013;31:412–9.
 66. Haddad RI, How to incorporate new tyrosine kinase inhibitors in the treatment of patients with medullary thyroid cancer, *J Clin Oncol*, 2013;31:3618–20.
 67. Agrawal N, Jiao Y, Sausen M, et al., Exomic sequencing of medullary thyroid cancer reveals dominant and mutually exclusive oncogenic mutations in RET and RAS, *J Clin Endocrinol Metab*, 2013;98:E364–9.
 68. Sherman SI, Cohen EEW, Schoffski P, et al., Efficacy of cabozantinib (Caboz) in medullary thyroid cancer (MTC) patients with RAS or RET mutations: Results from a phase III study, *J Clin Oncol*, 2013;31(Suppl.):363s, abstr. 6000.