REVIEW

Recent advances in the biology and therapy of medullary thyroid carcinoma [version 1; referees: 2 approved]

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Abstract

Medullary thyroid cancer (MTC) is a relatively uncommon yet prognostically significant thyroid cancer. Several recent advances in the biology and current or potential treatment of MTC are notable. These include a new understanding of the developmental biology of the thyroid C cell, which heretofore was thought to develop from the neural crest. RET, encoded by the most common driver gene in MTC, has been shown to be a dual function kinase, thus expanding its potential substrate repertoire. Promising new therapeutic developments are occurring; many have recently progressed to clinical development. There are new insights into RET inhibitor therapy for MTC. New strategies are being developed to inhibit the RAS proteins, which are potential therapeutic targets in MTC. Potential emerging immunotherapies for MTC are discussed. However, gaps in our knowledge of the basic biology of the C cell, its transformation to MTC, and the mechanisms of resistance to therapy impede progress; further research in these areas would have a substantial impact on the field.

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Introduction

Medullary thyroid cancer (MTC) is a relatively uncommon (about 1,400 new cases per year in the US) cancer of the thyroid C cells, yet accounts for a substantial fraction of thyroid cancer mortality. Excellent comprehensive reviews of the biology, genetics, and management of MTC have been published[1–9]. Briefly, in 25% of MTC cases, the disease is hereditary, occurring as part of the MEN 2 syndromes (MEN 2A, MEN 2B, and familial medullary thyroid cancer) due to germline activating mutations of the *RET* receptor tyrosine kinase gene. *RET* is also mutated in about 50% of sporadic cases of MTC; in both hereditary and sporadic cases, specific mutations are correlated with phenotype and prognosis[4,6]. MTC is resistant to cytotoxic chemotherapy. RET inhibitors have provided significant clinical benefit; two RET inhibitors, vandetanib and cabozantinib, are US Food and Drug Administration (FDA)-approved for the treatment of advanced MTC[10–12]. In this short and necessarily selective review, I discuss some recent advances in MTC and in related areas that are likely to affect MTC. I have tried to point out some other areas in which MTC research might be productively focused.

Biology of medullary thyroid cancer

Medullary thyroid cancer is not derived from the neural crest

For almost half a century, thyroid C cells have been thought to be derived from the neural crest. This hypothesis was based largely on chick-quail xenotransplantation studies by Le Douarin *et al.*[13,14], which revealed that avian calcitonin-producing ultimobranchial bodies were derived from the neural crest. This model was extrapolated to mammalian species, in which the ultimobranchial bodies are derived from the fourth pharyngeal pouch and invade the thyroid during development, differentiating into C cells. The neural crest derivation of mammalian ultimobranchial bodies and thyroid C cells was challenged by Kameda *et al.*[15], who showed by cell-lineage tracing that mouse ultimobranchial bodies were not derived from neural crest cells. Recently, Johansson *et al.*[16] used an elegant lineage-tracing scheme to confirm that mouse ultimobranchial bodies and thyroid C cells are not derived from neural crest cells but rather from pharyngeal endoderm. Nevertheless, C-cell development is significantly influenced by neural crest-derived cells[17]. These findings may have an impact on our understanding of the biology of mixed histology tumors, as discussed by DeLellis and Mangray[8]. While many of these are likely to be "collision tumors", the endodermal origin of both C cells and follicular cells strengthens the possibility that some of these tumors arise from a single progenitor cell.

Understanding RET

A potential dramatic change in our understanding of RET kinase function is underway. Bagheri-Yarmand *et al.*[18] reported that RET is not only a membrane-bound receptor tyrosine kinase, but also is localized to the nucleus. There, one of its functions is to inhibit the pro-apoptotic transcription factor ATF4. This antagonism of ATF4 activity provides a potential mechanism for the anti-apoptotic function of RET[19]. Remarkably, Bagheri-Yarmand *et al.*[18] showed that RET appears to accomplish this inhibition by *threonine* phosphorylation of ATF4, marking it for proteolytic degradation; thus, RET is a dual specificity tyrosine-threonine kinase. Plaza-Menacho *et al.*[20] recently confirmed and extended this finding of dual specificity, showing that RET is autophosphorylated at serine 909 in the activation domain. While they show that this phosphorylation has no effect on RET enzymatic activity *in vitro*, they showed that it affects RET signaling in an *in vivo* model. In the *Drosophila* Ret2B model of MEN 2B, *dRet* M955T mutation, analogous to human *RET* M918T, results in a rough eye phenotype[21]. When a further *dRet* S946A mutation (analogous to human S909A) was introduced, the rough eye phenotype was rescued. Plaza-Menacho *et al.*[20] speculate that RET pS909 may function in docking of downstream effector proteins. This expanded specificity has the potential to expand the universe of substrates of RET; in any case, important RET effector substrate proteins still await identification.

Under-researched area: biology of C-cell transformation

Thus far, relatively little is known regarding the molecular steps of C-cell transformation leading to MTC[22]. This is due in large part to the rarity of C cells in the normal human and mouse thyroid, limiting their study to *in situ* methods. Cell-sorting methods applied to thyroid glands[23–25] suggest that isolation of small numbers of normal or early dysplastic C cells may be feasible; functional and "omics" studies on such cell populations could sharply address our dearth of knowledge in this important area.

Genomics of medullary thyroid cancer

MTC cases typically have few mutations[26]. As mentioned, about 50% of sporadic cases have an activating point mutation in the *RET* gene. The only other common mutations identified in sporadic MTC are *KRAS* and *HRAS*; *NRAS* mutations are infrequent[26–31]. Recent reports have described *ALK* and *RET* gene rearrangements in sporadic MTC[32,33]. While these rearrangements are infrequent, they indicate the potential for targeted therapy in specific cases; perhaps even more importantly, they suggest the important role that these and other rearrangements may play in MTC. Rearrangements would not likely have been detected in whole exome sequencing studies of MTC[26] and can play a dominant driver role in cancer development[34–36].

Treatment of medullary thyroid cancer

RET inhibitors: fulfilling the promise

Introduction. Vandetanib and cabozantinib have changed the face of MTC systemic therapy, offering an effective targeted treatment. Nevertheless, both drugs are effective in less than half of patients with MTC and have significant adverse effects, and (even in responsive cases) resistance develops, typically within a few years.

Adverse effects. It is not clear which effects are off-target (non-RET) and which are on-target (due to RET inhibition). Since both vandetanib and cabozantinib are multikinase inhibitors, there is some thought that more specific inhibitors may alleviate these effects. However, it is necessary to consider the possibility that the inhibition of some of the other kinases

targeted by these drugs contributes to their efficacy. The response of *RET* wild-type (wt) tumors may suggest that this occurs; the ability of both vandetanib and cabozantinib to inhibit VEGFR2 suggests it as a potential candidate target, in which case VEGFR2-dependent adverse effects may be inseparable from efficacy.

Resistance. As mentioned above, MTC commonly exhibits intrinsic resistance to RET inhibitors, and even those cases that are initially sensitive to RET inhibitors almost always develop acquired resistance, resulting in disease progression. A critical need in the field is an understanding of the mechanisms of intrinsic and acquired resistance to RET inhibitors in MTC. Numerous mechanisms for resistance to tyrosine kinase inhibitors (TKIs) have been described, including feedback signaling response, secondary mutations, or gene amplification in the TKI, bypass activation of other signaling or survival pathways, and pharmacokinetic/pharmacodynamic (PK/PD) issues; several resistance mechanisms can coexist in a single resistant tumor[37]. Mathematical modeling of resistance in other cancers has shown that even apparently acquired resistance may exist intrinsically as subclonal cell populations within the tumor, and such resistant cells can be selected by treatment[38–40]. That an understanding of the mechanisms of resistance can direct subsequent effective therapeutic strategies is not only intuitive; it has been demonstrated dramatically in many instances for TKIs and other targeted therapeutics[41–46].

Some information regarding resistance to vandetanib and cabozantinib is available, but much further study is urgently needed. Both inhibitors perform poorly on *RET* mutants with V804M or V804L mutations[47,48]; these mutations are orthologous to the *BCR-ABL* T315I "gatekeeper" mutation which confers resistance to imatinib in chronic myelogenous leukemia[49]. A recent article identified *RET* I788N as another mutation conferring resistance to cabozantinib and vandetanib[50]; I788 is an ortholog of the V654 residue in c-*KIT*, mutation of which confers resistance to imatinib[51]. PK studies of vandetanib and cabozantinib have been extensive. There is limited bioavailability *in vivo* and this is due in part to substantial plasma protein binding (92–94% for vandetanib[52] and more than 99.7% for cabozantinib[53,54]). This suggests that resistance may be due in part to limited drug exposure within the tumor. Unfortunately, PD studies in patients treated with these compounds, pivotal for our understanding, have not been reported.

Remarkably, changes in MTC seen on progression after TKI therapy have not yet been reported. Such studies have been uniquely informative in identifying mechanisms of resistance to other therapeutics[41–46]. In such studies, progression biopsies are compared with pretreatment samples by using next-generation sequencing to look for secondary mutations, amplifications, and other genomic changes, transcriptomic studies such as RNA-seq, or proteomic studies to look for potential gene expression changes and pathway activation that may account for acquired resistance. Given the experience with disease progression on current TKIs and the facile availability of these technologies, one would hope that these elucidating correlative studies soon become standard.

Cabozantinib: who benefits? In the Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer (EXAM) phase 3 clinical trial of cabozantinib[12], MTC patients receiving the drug had a significantly longer progression-free survival (PFS) than patients receiving the placebo control (median PFS 49 versus 17 weeks; hazard ratio [HR] = 0.28, p <0.0001). Recent correlative subgroup analysis indicated that patients with a *RET* M918T mutation significantly benefited from cabozantinib treatment[55,56]. All other mutational subgroups (*RET* non-M918T mutation, RAS mutation, RAS wt, *RET* and RAS wt, *RET* unknown status, and *RET* mutation of unknown significance) also exhibited decreased HR in response to cabozantinib treatment; the PFS differences in these subgroups did not reach statistical significance, although in some cases this was likely due to the small size of the subgroups. As the authors note, the effects of cabozantinib in these smaller subgroups will need to be resolved in future prospective studies. Notably, the M918T subgroup was the only group to exhibit a significant increase in overall survival (OS) (44.3 versus 18.9 months; HR = 0.60, p <0.03). Thus, it is clear that cabozantinib is effective for MTC patients with the *RET* M918T mutation, but in no case is it yet possible to exclude patients from cabozantinib treatment on the basis of mutation status, especially given the paucity of effective MTC treatments other than RET multikinase inhibitors.

If, as suggested by the correlative data in the EXAM trial, MTC with *RET* M918T mutations derives more clinical benefit from cabozantinib than do other MTC subgroups, what might be the mechanism? Here, our understanding is impeded by our limited knowledge of the biology of *RET* mutations. A few transcriptomic studies have compared MTC cases with *RET* M918T mutations versus other *RET* mutations[57–60], but further work is necessary, since some of the studies were underpowered and consensus among other studies was lacking. One potentially important difference between M918T and other *RET* mutations is in substrate specificity. RET M918T has a relaxed and altered substrate preference[61]. This is due to destabilization of the substrate recognition domain, which also leads to increased kinase activity[62–64]. Speculatively, this altered kinase activity could lead to greater oncogene addiction, which would result in augmented clinical activity of RET inhibitors.

By what mechanism might cabozantinib provide benefit to MTC cases without RET mutations? The potential for other kinase targets of cabozantinib (including VEGFR2, MET, TIE2, RON, and others)[65] to contribute to angiogenesis[65], malignant transformation[66], or other MTC functions has been discussed[55]. The possibility also exists that wt RET is important in the biology of MTC.

New RET inhibitors. Several new RET inhibitors have been reported[67]. Some of these compounds have been designed for increased potency, increased specificity (especially as compared with KDR inhibition), improved PKs, or the ability to inhibit RET gatekeeper mutants. The following four interesting compounds are currently in clinical trials.

Alectinib (Roche) is an ALK inhibitor approved for ALK-rearranged non-small cell lung cancer. It is highly specific, inhibiting little other than ALK and RET (concentration resulting in inhibition of 50% of activity [IC_{50}] for RET = 4.8 nM)[68]. At somewhat higher concentrations, alectinib also effectively targets the RET gatekeeper mutants, V804L (32 nM) and V804M (53 nM). While alectinib effectively reduced phospho-RET levels in MTC cell (TT) xenografts, it had little effect on MTC xenograft growth[68]. This suggests that another target, in addition to RET, may serve to maintain growth in MTC cells. Whether this intrinsic resistance will be seen clinically in MTC is unknown but should be determined shortly; a phase 1 trial for alectinib in MTC and other RET-driven thyroid and lung cancers (NCT03131206) is ongoing.

BLU-667 (Blueprint Medicines) inhibits RET at subnanomolar concentrations[69]. It efficiently inhibits the RET V804M gatekeeper mutant at similar concentrations and has 70-fold specificity versus KDR. It is in a phase 1 clinical trial (NCT03037385) for cancers with activating *RET* gene alterations, including MTC.

LOXO-292 (Loxo Oncology) inhibits RET at nanomolar concentrations[70]. It also inhibits the RET gatekeeper mutant at similar concentrations. Importantly, LOXO-292 has been shown to be very specific for RET in kinase assays. Its efficacy in inhibiting the growth of MTC cell xenografts further confirms that targeting RET alone is a viable therapeutic strategy in MTC. LOXO-292 is in a phase 1 clinical trial (NCT03157128) for cancers with activating *RET* gene alterations, including MTC.

RXDX-105 (Ignyta) was originally developed as a BRAF inhibitor (IC_{50} = 14 nM)[71]. It also efficiently inhibits wt RET (IC_{50} = 1.5 nM)[71]. This suggests the potential for RXDX-105 to act as a combination treatment, targeting RET and the RAF-MEK-ERK pathway, a combination which may be synergistic in MTC cells (72 and unpublished results). RXDX-105 is reported to have 96–100% bioavailability[71], a substantial improvement over other RET inhibitors. However, while RXDX-105 does not inhibit KDR, it is a broad-specificity inhibitor[71], so it may have significant adverse effects. Moreover, since it does not have activity against CRAF, one can envision "paradoxical activation" of the RAF-MEK-ERK pathway[73–75]. Nevertheless, in an ongoing phase 1 trial of RXDX-105 for RET-driven solid tumors (NCT01877811), a partial response was noted in a lung adenocarcinoma patient with a RET gene rearrangement[76].

RAS as a therapeutic target in medullary thyroid cancer

The discovery of RAS mutations in MTC[26–31] highlighted the possibility of targeting RAS therapeutically in some cases of MTC; since RET signaling functions in part through RAS activation[77], RAS inhibition also may be a potential therapeutic strategy in MTC with RET mutations. However, RAS has a long history as an intractable target[78–80]. It was realized early that targeting RAS-guanosine triphosphate (RAS-GTP) interaction would be difficult since GTP has picomolar affinity for RAS while GTP is present at millimolar concentrations in cells[81]. A substantial effort to block RAS attachment to the cell membrane by blocking farnesyltransferase was unsuccessful because of alternative cellular mechanisms (geranylgeranylation) of membrane attachment[78,79,82–84]. Blocking RAS downstream signaling has been attractive but has commonly suffered from ineffectiveness of blocking one pathway and toxicity of blocking multiple pathways[85]. In recent years, with advances in drug and protein biochemistry, there has been renewed interest and preclinical success in directly inhibiting RAS via a multitude of novel strategies, including small-molecule binding, inhibition of protein interactions, and antisense approaches[86–111]. A review of this rapidly advancing field, other than the several examples below, is outside the scope of this review, and the reader is directed to the cited references. In addition, it must be noted that some of the promising therapeutic approaches target specific RAS mutations; at least one of these targeted mutations, KRAS G12C[87,91,92,95,100], is rarely found in MTC[31].

PDE6δ inhibitors. The prenyl-binding chaperone protein PDE6δ is necessary for RAS membrane localization[111]. Early PDE6δ inhibitors, including deltarasin and deltazinone, had low nanomolar affinity for PDE6δ but required micromolar concentrations for RAS inhibitory activity in intact cells[88,99]. This discrepancy was recently reported to be due to inhibitor release mediated by the release factor Arl2[104]. Newly designed PDE6δ inhibitors with subnanomolar affinity have been shown to be effective in cells and can block KRAS-dependent cell proliferation[104]. A third generation of highly specific PDE6δ inhibitors covalently binds the active site of PDE6δ, rendering these compounds refractory to Arl2-mediated release[105].

Farnesyltransferase inhibition. As mentioned above, the farnesyltransferase inhibitors (FTIs) failed because of alternative prenylation of RAS proteins. However, *HRAS*, the most commonly mutated RAS gene in MTC, cannot employ this alternative prenylation strategy and is dependent upon farnesyltransferase for activity. Thus, HRAS-driven cancers should be sensitive to FTIs. This hypothesis is being tested in a phase 2 study of the FTI tipifarnib for HRAS mutant thyroid or head and neck cancers (NCT02383927). Interestingly, a phase 1 clinical trial of a combination of the FTI tipifarnib and the multikinase (including RET) inhibitor sorafenib showed significant activity for MTC with or without RET mutations; HRAS mutation status was not evaluated[112]. While the response rate was greater than that seen in another trial employing sorafenib alone[113], the trials were not powered for statistical comparison. If this combination is effective, it may be due to additional targets of tipifarnib[112], or to synergistic pathway inhibition by tipifarnib and sorafenib, similar to the synergy reported in studies of sorafenib and the MEK inhibitor selumetinib in MTC cells *in vitro*[72].

Farnesyltransferase-mediated delivery of covalent RAS inhibitors. In this recently reported, very novel approach, endogenous farnesyltransferase activity was hijacked to mislocalize KRAS by blocking normal prenylation mediated by both farnesyltransferase and geranylgeranyltransferase[106]. Thus, a farnesyltransferase neosubstrate was designed that binds covalently to the RAS CAAX moiety yet does not promote membrane

localization. In cell culture, treatment with this neosubstrate resulted in decreased RAS signaling. The effects were modest, and specificity for transformed cells and efficacy *in vivo* were not addressed. Nevertheless, this report represents the first step in the development of a promising strategy to overcome the ability of KRAS to evade the therapeutic effects of prenylation inhibitors.

Inhibition of RAS-effector interaction. RAS activates its downstream effectors by interaction with their RAS-binding domains (RBDs). Many of the small-molecule RAS direct inhibitors in development appear to work by disrupting these interactions[97,98,103]. Notably, rigosertib, a kinase inhibitor already in phase 3 clinical development for myelodysplastic syndrome, was recently shown to be a RAS mimetic, binding to the RBDs of RAF, PI3K, and RAL-GEF, preventing interaction with RAS and pathway activation[94]. Rigosertib was shown to inhibit tumorigenesis in several RAS-driven xenograft models.

Antisense oligonucleotides. While therapeutic antisense technology has been hampered by delivery issues, a recent article showed that KRAS expression can be efficiently silenced *in vivo* by systemic treatment with modified 2',4'-constrained ethyl antisense oligonucleotides[107]; toxicity was not seen, and xenograft growth inhibition was demonstrated. If successful in further studies, such an approach may also be applicable to *KRAS*, *HRAS*, and *RET* mutations in MTC.

Immunotherapy for medullary thyroid cancer

Exciting recent advances have been made in immunotherapy for a variety of cancers[114–118]. The current state of immunotherapy for thyroid cancer, including MTC, was reviewed recently[119]. While effective immunotherapy has not yet reached MTC, there are several points of interest.

Immune checkpoint therapy. It is not clear whether immune checkpoint therapy has promise in MTC. As noted, MTC has a low mutation burden[26]. MTC also has very low expression of the immune checkpoint ligand PD-L1[120]; both of these correlate with poor response to checkpoint blockade[118,121,122]. Nevertheless, in early preclinical and clinical studies, MTC cell or calcitonin vaccines elicited a T-cell response, with apparent antitumor activity[123–126], suggesting the possibility that checkpoint blockade, perhaps in combination with a vaccine, may be effective. A phase 2 clinical trial (NCT03072160) employing the PD-1 checkpoint-blocking antibody pembrolizumab for MTC will begin to explore this potential therapeutic strategy.

Adoptive cell therapies: tumor-infiltrating lymphocyte, T-cell receptor, and chimeric antigen receptor transfer[127–130]. The low mutation burden of MTC renders these exciting strategies somewhat challenging. Analysis of the most common RET mutations (M918T, C634 mutations) using NetMHC 3.4 software[131] failed to identify neoepitopes for avid major histocompatibility complex (MHC) binding in the most common serotypes (unpublished data). Wild-type (and mutated) RET have several epitopes predicted to bind avidly to common MHC alleles; while these could be targeted as potential tumor-associated antigens, the expression of RET in normal cells throughout the body[132,133] raises significant safety concerns of off-tumor toxicity[134,135].

Wang *et al*. reported recently that peptides surrounding the commonly mutated KRAS G12 position are avidly bound and presented by the HLA-A11*01 serotype[136], facilitating recognition of these KRAS neoepitopes by T-cell receptors. Wang *et al*. demonstrated that KRAS G12V and KRAS G12D could be recognized by T cells. They isolated high-affinity T-cell receptors specific for these neoepitopes and showed that adoptive transfer of peripheral blood lymphocytes transduced with these KRAS-specific T-cell receptors could effect an antitumor immune response against xenografts harboring the cognate KRAS mutation. While this epitope is not presented by most other common MHC serotypes, Wang *et al*. note that HLA-A11*01 is present in 14% of the U.S. Caucasian population and in 40% of residents of southern China. Moreover, HRAS and NRAS are identical with KRAS in this region, so this strategy could be effective for all RAS isoforms. A phase 1 clinical trial has been opened for HLA-A11*01-positive patients with tumors harboring a KRAS G12V mutation (NCT03190941); this trial is open to MTC patients.

Antibody-drug conjugates. MTC and other neuroendocrine tumors commonly express DLL3, a Notch ligand, on their cell surface[137,138]. A DLL3 antibody linked to a DNA crosslinker warhead (Rovalpituzumab tesirine; Rova-T) was shown to efficiently inhibit the growth of DLL3-expressing xenografts; notably, tumor-initiating cells were also targeted. A phase 1 trial of Rova-T in small cell lung cancer showed significant clinical activity, almost exclusively in DLL3-highly expressing tumors[139]. A phase 2 trial of Rova-T in DLL3-expressing solid tumors, including a cohort for MTC, is now open (NCT02709889).

Intracellular antibodies. In general, antibody targeting of intracellular targets has been challenging. However, a recent report describes the construction and preclinical use of a monoclonal antibody that penetrates the cytoplasm and targets activated RAS[140]. The antibody was modified to achieve cellular uptake by endocytosis, followed by endosomal escape into the cytosol. By binding activated RAS, the antibody disrupted downstream signaling pathways and interfered with cell growth. While activity *in vivo* was modest, several strategies were discussed to increase *in vivo* activity. If successful, this promising, albeit nascent, strategy may be applicable not only for RAS but also for targeting other intracellular targets, including RET M918T in MTC.

Peptide receptor radionuclide therapy

Neuroendocrine cancers, including MTC, frequently express somatostatin receptors (SSTRs), and the potential use of somatostatin analogs for imaging, therapy, or therapeutic targeting has been a common focus for many years. In a recently reported phase 3 trial, midgut neuroendocrine tumors were successfully treated by using peptide receptor radionuclide therapy (*PRRT*)[141]. Tumors were stratified by ^{111}In-DOTATATE scintigraphy for SSTR expression; in SSTR-positive midgut neuroendocrine tumors (NETs), ^{177}Lu-DOTATATE (Lutathera) treatment resulted

in highly significant prolongation of PFS and OS and modestly increased objective response rate (ORR). These results have led to European approval of Lutathera for the treatment of midgut NETs; a new drug application has been submitted to the FDA. Could this PRRT strategy work in MTC? In five small studies in MTC, using either ^{90}Y- or ^{177}Lu- somatostatin analogs[142–146] (reviewed in[147]), a modest ORR and frequent stable disease were seen. One might envision PRRT as a salvage therapy, stratifying MTC patients with ^{68}Ga-SST analog positron emission tomography (PET) (^{68}Ga-SST analog PET is more sensitive than ^{111}In-DOTATATE scintigraphy and detects lesions in about 70% of MTC patients with advanced or recurrent disease[147–151]). One concern regarding the potential use of PRRT for MTC is that SSTR expression in MTC has been reported to be focal rather than uniform[151,152]; this tumor heterogeneity could significantly limit efficacy.

Conclusions

The array of exciting directions for advancing our understanding of MTC, and especially for achieving more effective therapies, has never been more promising. Nevertheless, it must be emphasized that further advances will require careful design of basic, translational, and clinical research. Preclinical resources, including cell lines, animal models, and patient-derived xenografts, are currently very limited. A better understanding of the biology of the C cell and its transformation to MTC is critical. As discussed above, it is imperative to understand the mechanisms of MTC progression on therapy, and this will require extensive analysis of progression biopsies. The recent and future advances in the field validate the tireless and ingenious effort that so many researchers have devoted.

Abbreviations

EXAM, Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer; FDA, US Food and Drug Administration; FTI, farnesyltransferase inhibitor; GTP, guanosine triphosphate; HR, hazard ratio; IC_{50}, concentration resulting in inhibition of 50% of activity; MEN, multiple endocrine neoplasia; MHC, major histocompatibility complex; MTC, medullary thyroid cancer; NET, neuroendocrine tumor; ORR, objective response rate; OS, overall survival; PD, pharmacodynamic; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetic; PRRT, peptide receptor radionuclide therapy; RBD, RAS-binding domain; SST, somatostatin; SSTR, somatostatin receptor; TKI, tyrosine kinase inhibitor; wt, wild-type.

Competing interests

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The referees who approved this article are:

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