State-of-the-Art Strategies for Targeting *RET*-Dependent Cancers

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ABSTRACT

Activating receptor tyrosine kinase RET (rarranged during transfection) gene alterations have been identified as oncogenic in multiple malignancies. RET gene rearrangements retaining the kinase domain are oncogenic drivers in papillary thyroid cancer, non–small-cell lung cancer, and multiple other cancers. Activating RET mutations are associated with different phenotypes of multiple endocrine neoplasia type 2 as well as sporadic medullary thyroid cancer. RET is thus an attractive therapeutic target in patients with oncogenic RET alterations. Multikinase inhibitors with RET inhibitor activity, such as cabozantinib and vandetanib, have been explored in the clinic for tumors with activating RET gene alterations with modest clinical efficacy. As a result of the nonselective nature of these multikinase inhibitors, patients had off-target adverse effects, such as hypertension, rash, and diarrhea. This resulted in a narrow therapeutic index of these drugs, limiting ability to dose for clinically effective RET inhibition. In contrast, the recent discovery and clinical validation of highly potent selective RET inhibitors (pralsetinib, selpercatinib) demonstrating improved efficacy and a more favorable toxicity profile are poised to alter the landscape of RET-dependent cancers. These drugs appear to have broad activity across tumors with activating RET alterations. The mechanisms of resistance to these next-generation highly selective RET inhibitors is an area of active research. This review summarizes the current understanding of RET alterations and the state-of-the-art treatment strategies in RET-dependent cancers.

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INTRODUCTION

The receptor tyrosine kinase RET (rearranged during transfection) plays an important role in the development of the kidney and nervous system. When aberrantly activated, it can act as an oncogene in multiple malignancies. *RET* fusions retaining the kinase domain are drivers of papillary thyroid cancer (PTC), non–small-cell lung cancer (NSCLC), and other cancers. Activating *RET* mutations are associated with different phenotypes of multiple endocrine neoplasia type 2 (MEN2) as well as sporadic medullary thyroid cancer (MTC). RET is thus an attractive therapeutic target in patients with oncogenic *RET* alterations. Multikinase inhibitors (MKIs) with ancillary RET inhibitor activity, such cabozantinib and vandetanib, have been explored in the clinic for RET-driven cancers. The off-target adverse effects, such as hypertension and diarrhea, have restricted the dosing that patients can tolerate. In contrast, the recent discovery and clinical validation of next-generation highly potent selective RET inhibitors (pralsetinib/BLU667, selpercatinib/LOXO-292) demonstrating improved efficacy and a more favorable toxicity profile in registrational clinical trials are poised to alter the landscape of RET-altered cancers.[1,2] This review summarizes the current understanding of *RET* alterations and the state-of-the-art treatment strategies in *RET*-aberrant cancers.

THE FUNCTION AND BIOLOGY OF RET

The proto-oncogene *RET* was identified in 1985 by Takahashi et al[3] as a transforming gene that was derived by DNA rearrangement during transfection of mouse NIH3T3 cells with human lymphoma DNA. Therefore, it was designated RET. The *RET* gene encodes a receptor tyrosine kinase (RTK) that contains a large extracellular domain, a transmembrane domain, and an intracellular tyrosine kinase domain (Fig 1).[4] Studies from molecular modeling,[5] electron microscopy, and small-angle x-ray scattering[6] revealed the structure of the RET extracellular domain, including four cadherin-like domains (CLD1-4), a calcium-binding side between CLD2 and CLD3, and a conserved cysteine-rich domain. After the transmembrane domain, a juxtamembrane segment lies at the beginning of the intracellular portion of RET and immediately adjacent to the kinase domain. The C-terminal tail of RET has two major forms, which diverge after residue G1063 because of alternative splicing—a short 9–amino acid one (RET9) and a long 51–amino acid one (RET51). Although the two isoforms share a largely common sequence and are coexpressed in many tissues, numerous studies have demonstrated differences in their temporal and spatial regulation of expression, cellular localization and trafficking, and biologic functions. It has been suggested that RET51 is the more prominent isoform in tumors. RET51 is more effective than RET9 at promoting cell proliferation, migration, and anchorage-independent

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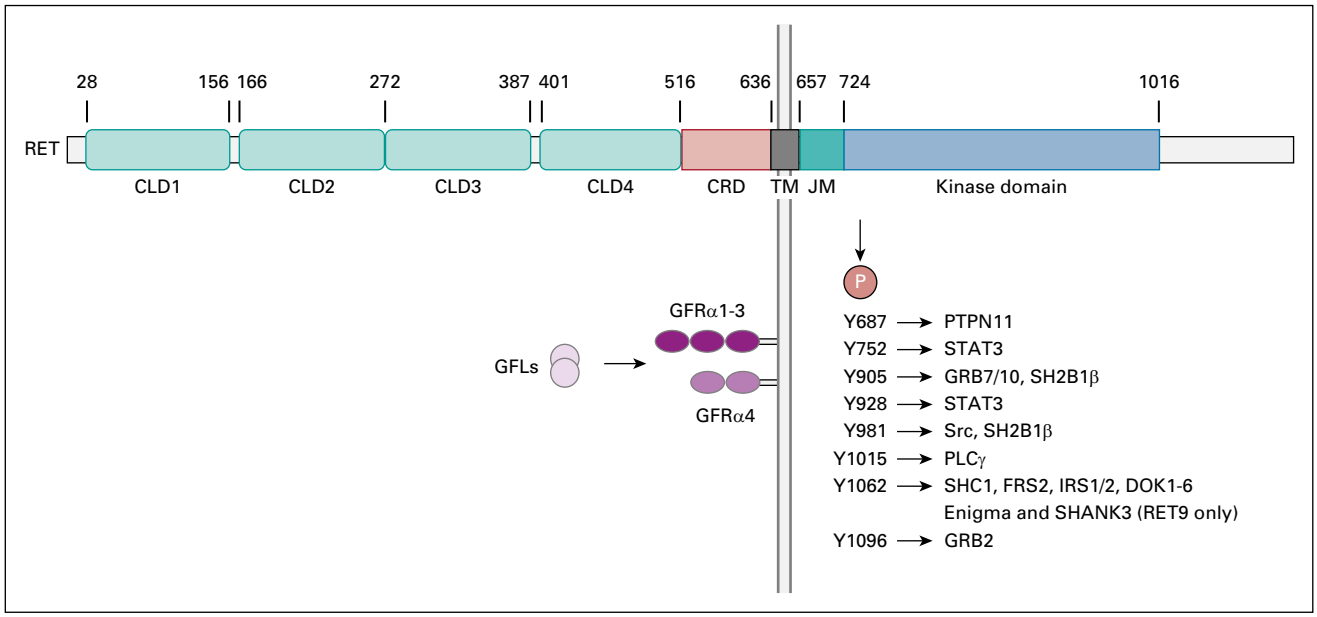


FIG 1. Schematic illustration of RET protein, its ligands, receptors, and signaling pathways. The numbers above the RET domains indicate amino acid positions. The main RET phosphorylation sites are listed together with their binding proteins. CLD, cadherin-like domain; CRD, cysteine-rich domain; GFLs, GDNF-family ligands; GFRα, GDNF-family receptor-α; JM, juxtamembrane; TM, transmembrane domain.

growth.[7,8] In addition, the transcripts of RET51 are more abundant than those of RET9 in some MEN2 tumors.[9] In breast cancer cells, estrogen upregulates RET51 at a much greater level compared with RET9.[10] RET51 expression is increased in 4 out of 5 stage IIB pancreatic tumors.[11]

The RET ligands include glial cell line–derived neurotrophic factor (GDNF), neurturin, artemin, and persephin, all belonging to the GDNF family ligands (GFLs).[12] These GFLs do not directly bind to RET and instead bind to GDNF family receptor-α (GFRα) coreceptors, which in turn recruit RET for dimerization.[6,13] Subsequently, autophosphorylation on intracellular tyrosine residues of RET creates docking sites for downstream signaling adaptors, leading to the activation of multiple pathways (Fig 1).[12] Phosphorylated Y1062 is the key docking site for several adaptor proteins, which can activate pathways such as Ras/MAPK, PI3K/AKT, and JNK.[14,15] Autophosphorylation of Y1096 on the RET51 isoform (and not on RET9) also contributes to the activation of Ras/MAPK and PI3K/AKT pathways.[14,16] Among other autophosphorylation sites, Y1015 is involved in the activation of protein kinase C signaling through binding of phospholipase Cγ (PLCγ).[17] Y752 and Y928 are STAT3 docking sites.[18] Phosphorylated Y687 and Y981 bind to tyrosine phosphatase Shp2 and Src kinase, respectively.[19,20]

In addition, RET plays important roles in the development of the kidney and nervous system. Studies in mouse models have shown that RET and the phosphorylation of its docking sites are critical for the growth and branching morphogenesis of ureteric bud cells from the metanephric mesenchyme.[21,22] RET is expressed in neural crest cells and required for the proliferation, differentiation, and survival of these cells.[21,23] RET is also involved in motoneuron survival and connectivity.[24,25] In addition, RET signaling contributes to the regulation and function of hematopoietic cells and spermatogenesis.[26,27] Loss-of-function RET mutations in humans have been linked to Hirschsprung disease, congenital anomalies of kidney or urinary tract, and congenital central hypoventilation syndrome.[28]

ONCOGENIC ACTIVATION OF *RET*

RET is activated in cancer mainly through chromosomal rearrangements that generate fusion genes containing the kinase domain of RET (Fig 2) and gain-of-function missense mutations in both the extracellular and cytoplasmic regions of RET protein (Fig 3). Apart from these mechanisms, the increased expression level of wild-type RET has been linked to the pathogenesis of several cancer types.[28]

RET REARRANGEMENTS

Somatically occurring *RET* rearrangements involve the 3′ sequence of *RET* that encodes the kinase domain and the 5′ sequence of other partner genes. The chromosomal breakpoints of *RET* often occur within intron 11 and lead to fusions with only the cytoplasmic portion of RET. Occasionally, some breakpoints occur within introns 7 and 10, creating chimeric proteins containing the RET transmembrane domain (Fig 2).[29] To date, more than 35 genes have been reported to form fusion genes with *RET* (Fig 2). These partner genes can contribute dimerization domains to the fusion proteins, such as the coiled-coil domain,[30] the Lis1 homology (LisH) domain,[31] and the sterile α motif (SAM) domain.[32]

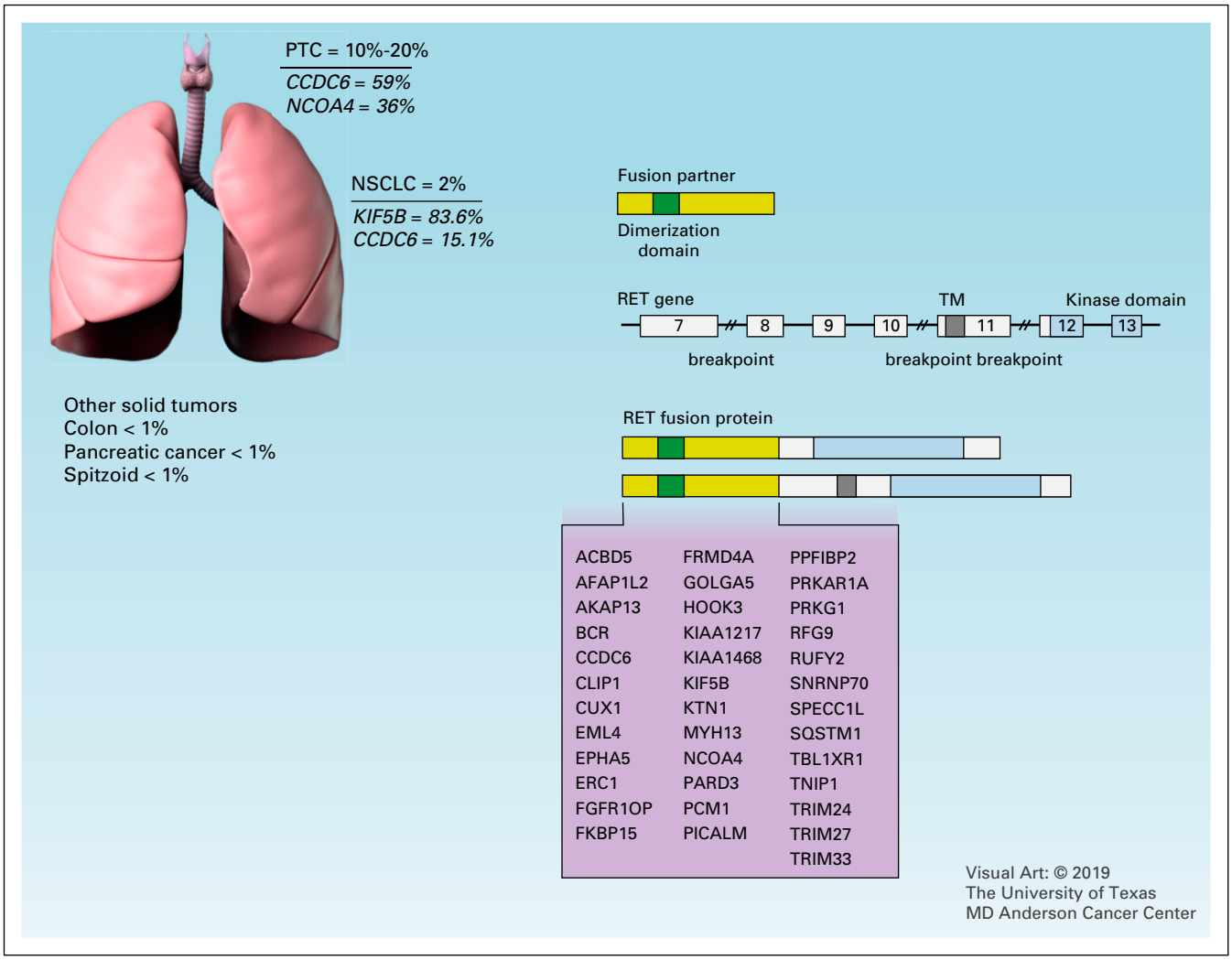
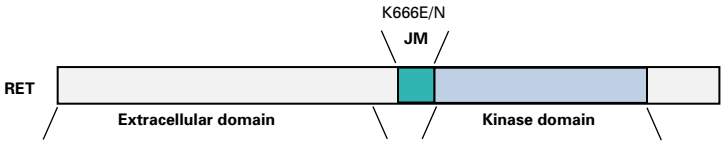


FIG 2. RET fusion. The chromosomal breakpoints of the RET gene often happen within intron 11 and occasionally in introns 7 and 10. The numbers indicate exons in RET gene. The resulted fusion protein contains the dimerization domain (green) from the fusion partner and the kinase domain (blue) of RET, or both the transmembrane (TM) domain (dark gray) and the kinase domain of RET. Reported fusion partner genes are listed in the figure. Frequencies are derived from COSMIC database. NSCLC, non–small-cell lung cancer; PTC, papillary thyroid cancer.

RET fusions can activate downstream pathways through multiple means. By fusing to the kinase domain of RET, dimerization domains can mediate ligand-independent constitutive activation of the RET kinase[33,34] (Fig 4). *RET* fusions can increase the expression of RET, as illustrated by Kohno et al,[35] who showed that KIF5B-RET resulted in 2- to 30-fold higher transcription of *RET* than normal lung tissues. Altered function of the fusion partner may be another factor. One such partner, *PRKAR1A*, is a tumor suppressor gene that is inactivated in patients with Carney complex, an autosomal dominant syndrome with an increased risk of developing several types of tumors.[36] PRKAR1A-RET fusion may not only activate RET but also inactivate PRKAR1A.

The molecular mechanism responsible for *RET* rearrangements is believed to be the unfaithful repair of DNA double-strand breaks through nonhomologous end joining, break-induced replication, and other complex rearrangements.[29,37] Various noncellular and cellular causes can result in double-strand breaks, such as ionizing radiation and fragile site induction by genotoxic chemicals or stress factors (for instance, hypoxia and replication stress).[38,39]

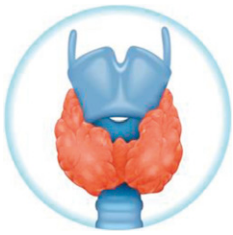
In human cancers, *RET* rearrangement was initially identified in PTC in 1987.[40] Recent clinical data suggest that *RET* rearrangements occur in up to 10%-20% of PTCs. The prevalence of *RET* rearrangements is much higher in radiation-induced PTCs. As an example, these alterations have been reported in approximately 50%-80% of patients with PTC who were previously exposed to the Chernobyl radioactive fallout or the atomic bomb in Japan.[41-44] These rearrangements are more frequently identified in children than in adults with PTC, at least partially because of the high proliferation rate of thyroid follicular cells in children and consequently the increased susceptibility of these cells



V292M
E505_G506del
A510V
E511K
C515S/W
C531R
G533C
K603Q
Y606C
C609R/S/W/Y
C611W/Y
E616Q
C618G/R/S/Y
C620R/S/Y
L629_D631delinsH
C630F/R/Y
D631_R635delinsG
D631Y
E632_L633del
L633_C634dup
C634_R635insHELC
C634F/G/L/R/S/W/Y
T636M
E734A
E768D
V804L/M
E805K
Y806C
R833C
M848T
I852M
A883F/T
R886W
S891A
S904F
R912A/P
M918T
A919P

Somatic RET mutations in sporadic MTC

RET mutation	Frequency among somatic RET mutations in MTC (%, n = 850)
M918T	70.5
C634R	4.8
A883F	2.2
C634Y	2.1
C634W	1.9
C630R	1.5
E632_L633del	1.4
D898_E901del	1.4
C620R	0.6
S891A	0.6



MTC

***RET* mutations among different MEN2 phenotypes**

Codon	Frequency of families with RET mutations (%)		
	MEN2A (n = 196)	MEN2B (n = 37)	FMTC (n = 265)
C515			0.4
C609	2.6		2.3
C611	0.5		1.1
C618	4.1		8.7
C620	5.6		7.2
C630			3.0
E632			0.4
C634	84.2		12.5
V648			0.8
K666			0.8
E768	0.5		4.9
L790			6.0
Y791			1.1
V804	1.5		30.6
R833			0.4
M848			0.8
A883			1.1
S891			12.5
S904			0.8
M918		97.3	1.1

FIG 3. RET mutation. Somatic *RET* mutations in sporadic medullary thyroid cancer (MTC) and among different multiple endocrine neoplasia type 2 (MEN2) phenotypes are shown. The frequencies of somatic mutations are derived from the COSMIC database. The frequencies of mutations in MEN2 are derived from published studies.[44a-d] FMTC, familial medullary thyroid carcinoma.

to DNA damage compared with adult cells. Among patients with PTC, CCDC6-RET and NCOA4-RET are the most common *RET* rearrangements,[30] which are generated via reciprocal or nonreciprocal paracentric inversion on the long arm of chromosomal 10.[45,46] *RET* rearrangements and BRAF mutations are largely mutually exclusive in PTCs.[47,48] In addition to PTC, *RET* rearrangements have been identified at much lower prevalence in other types of thyroid cancer, such as anaplastic thyroid carcinoma, follicular thyroid carcinoma, and medullary thyroid carcinoma.[49-51]

During the past decades, *RET* rearrangements have been reported in a number of other cancer types, including, but not limited to, NSCLC,[52] Spitz tumors and spitzoid melanomas,[53] chronic myelomonocytic leukemia,[54] colorectal cancer,[55] and breast cancer.[56] *RET* rearrangements are detected in approximately 1%-2% of NSCLCs, particularly adenocarcinoma.[57,58] The patients with NSCLC with these rearrangements have shown unique clinicopathologic characteristics: they were relatively younger (≤ 60 years), had more poorly differentiated tumors, and had minimal or no prior history of smoking.[59,60] RET fusions have been reported as a mechanism of acquired resistance to osimertinib in *EGFR*-mutant NSCLC.[61] It has been shown clinically that this bypass track can be overcome by combining RET inhibitor to EGFR inhibitor. Interestingly, patients with *RET*-rearranged lung cancer generally showed low levels of PD-L1 expression and low tumor mutational burden and had poor outcome on immunotherapies.[62] Another study demonstrated that *RET*-altered patients had shorter median time to progression with immune checkpoint inhibitors (ICIs) compared with non-ICI therapies.[63]

Despite that there is no universally accepted standard to detect *RET* rearrangements, several methods are used in the clinic. In general, immunohistochemistry is not reliable for the detection of *RET* rearrangement. Reverse transcription polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) are both sensitive and effective approaches. However, RT-PCR is insufficient to detect novel fusion partners or isoforms. FISH with dual color break-apart probe is unable to identify the specific fusion partner. Furthermore, it has been shown that next-generation sequencing (NGS) can simultaneously detect both gene fusions and somatic mutations in tumor samples. Targeted RNAseq is also complementary to DNA-based sequencing, as demonstrated by its ability to identify actionable alterations that were missed by DNA-based sequencing.[64]

ACTIVATING MUTATIONS OF *RET*

More than 60 activating *RET* mutations have been reported to date. Heritable activating mutations have been extensively

TABLE 1. Mechanisms of Acquired Resistance to Multikinase Inhibitors and Selective RET Inhibitors

Mechanism	Alteration/Pathway	Source	Resistant to	Sensitive to
Secondary RET alterations	RET S904F	Patient sample	Vandetanib	—
	RET I788N	Preclinical model	AD80, cabozantinib	Ponatinib
	RET V804L/M	Preclinical model	Cabozantinib, vandetanib	BLU-667, LOXO-292
		Patient sample		
	RET G810A	Preclinical model	Vandetanib	Ponatinib, lenvatinib
	RET G810S and G810R	Preclinical model	BLU-667, LOXO-292	TPX-0046
Acquired non-RET alterations	MDM2 amplification	Patient sample	Cabozantinib	AMG232, RG7388; AMG232 + cabozantinib (all preclinical)
	NRAS Q61K	Preclinical model	Ponatinib	trametinib
Activation of bypass signaling	Activation of MAPK	Preclinical model	AD80	AD80 + trametinib
	Activation of EGFR	Preclinical model	Sunitinib, E7080, vandetanib (partial), sorafenib (partial)	Gefitinib or cetuximab + sunitinib, E7080, vandetanib, or sorafenib
	Activation of EGFR and AXL	Preclinical model	Ponatinib, cabozantinib, alectinib	Afatinib, gefitinib; afatinib + cabozantinib or foretinib

studied in the MEN2 syndrome, an autosomal dominant multitumor syndrome that is characterized by a high risk of developing MTC (Fig 3).[65] With novel detection technologies, especially NGS, somatic activating mutations of *RET* have been discovered in multiple other cancer types.[66] These studies are outlined and discussed in the following sections.

GERMLINE MUTATIONS

Germline activating *RET* mutations are pathognomonic in MEN2 (Table 3), which can be classified into three subtypes depending on clinical features—MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC). MEN2A is the most common subtype and affects 60%-90% of MEN2 families. MEN2A is characterized by MTC in all patients, pheochromocytoma in approximately 50% of patients, and hyperparathyroidism and/or lichen planus amyloidosis in up to one-third of patients.[67,68] MEN2B makes up 5% of MEN2 cases. It is the most aggressive subtype and has a very early onset of MTC.[69] In addition to MTC (100% of cases) and pheochromocytoma (50% of cases), patients with this subtype have no hyperparathyroidism but present with extraendocrine features, including intestinal and mucosal ganglioneuromatosis, marfanoid habitus, skeletal abnormalities, and delayed puberty.[70,71] FMTC is the most indolent subtype of MEN2 and is characterized by a later onset and MTC being the only consistent clinical feature.[69] It has been proposed that FMTC should be considered a variant of MEN2A.[72] Notably, prophylactic thyroidectomy on the basis of genetic screening of germline *RET* mutations has shown significant impact on MEN2 families.[73,74]

Mutation hotspots in patients with MEN2A cluster within the cysteine-rich domain of RET extracellular region. Substitutions at these cysteines (codons 609, 611, 618, and 620 in exon 10, and 630 and 634 in exon 11) occur in > 95% of patients with the MEN2A subtype. Particularly,

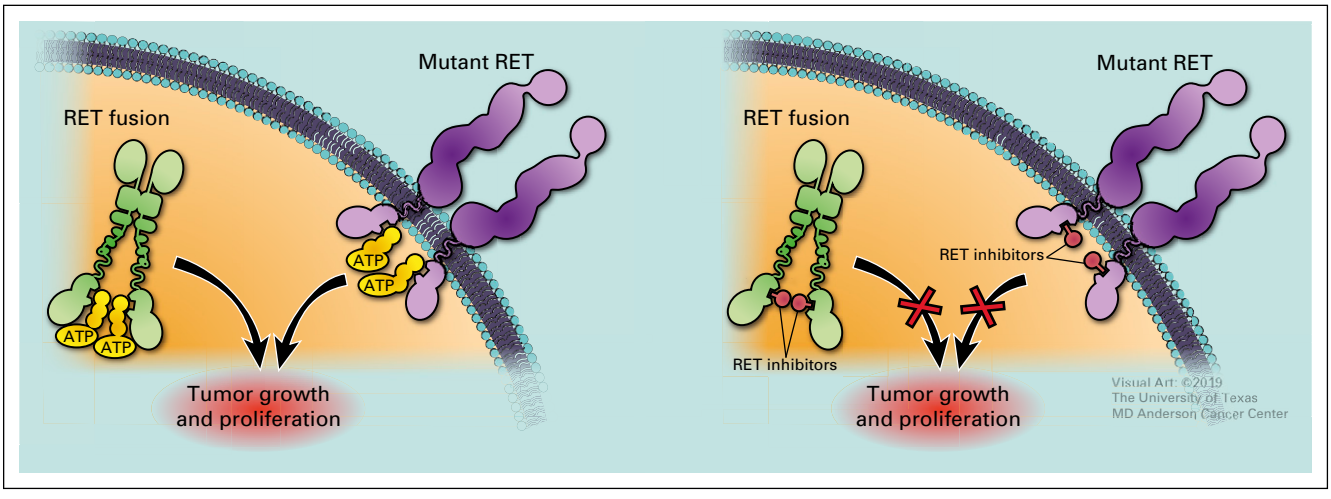


FIG 4. Oncogenic RET signaling and RET inhibitors.

TABLE 2. Preclinical and Clinical Activity, IC50, and Efficacy of Multikinase Versus Selective RET Inhibitors

	IC50, nM						ORR (%)	
	RET							
Drug	WT	M918T	V804L	V804M	CCDC6-RET	VEGFR2	Thyroid	NSCLC
Vandetanib	4	7	3,597	726	20	4	45 (MTC)	18, 53 (Japan)
Cabozantinib	11	8	45	162	34	2	28 (MTC)	28
LOXO-292	0.4	0.7	—	0.8	—	100	62 (RET fusion-positive thyroid)	68
							56 (MTC)	
BLU-667	0.4	0.4	0.3	0.4	0.4	35	56 (MTC)	58

Abbreviations: IC50, half maximal inhibitory concentration; MTC, medullary thyroid cancer; NSCLC, non–small-cell lung cancer; ORR, objective response rates; WT, wild type.

patients with C634 mutations account for approximately 85% of the population.[75,76] These mutations replace cysteines with other amino acids and decrease the formation of intramolecular disulfide bonds, promoting the formation of RET homodimer through intermolecular disulfide bonds between RET monomers. This results in ligand-independent constitutive activation of RET.[77,78]

The MEN2B subtype is associated with the kinase domain mutation M918T in > 95% of cases.[75,79] Other mutations identified in patients with MEN2B include A883F, which is also located in the kinase domain of RET,[79] and co-occurring *RET* mutations involving V804M.[80] These mutations can change protein conformation, increase ATP binding affinity, and decrease autoinhibition.[77,81] A883F is linked with less-aggressive phenotypes compared with M918T.[82]

Mutations of FMTC are found at not only the cysteine residues but also other noncysteine residues in both the extracellular and intracellular regions, such as G533, E768, L790, V804, and S891.[83,84] In addition, cysteine substitutions occur at different frequencies in FMTC, with a much lower frequency of C634 substitutions and higher frequencies of substitutions from other cysteines.[75] Furthermore, many of the noncysteine mutations are also identified in patients with MEN2A.[85]

However, these genotype-phenotype correlations can be confounded in some cases. For example, the polymorphism RET G691S, a modifying variant, enhances the oncogenic activity of RET S891A in vitro. Patients with FMTC harboring both variants demonstrated a trend toward an earlier age of diagnosis.[86] G691S is associated with earlier onset of sporadic MTC.[87] Several tandem mutations involving V804M, such as V804M and Q781R, are found in patients with an MEN2B phenotype instead of FMTC and MEN2A.[80] Although two homozygous carriers were diagnosed with MTC, other family members bearing heterozygous A883T were not affected.[88] Moreover, a few cysteine variants at codons 609, 611, 618, and 620 can cause both gain-of-function and loss-of-function in different tissues, thereby resulting in cosegregation of Hirschsprung disease and MEN2 in some families.[89-91]

SOMATIC MUTATIONS

Point mutations, small deletions, and/or insertions involving *RET* have been reported in both sporadic and familial MTC. Somatic *RET* mutation is a hallmark of sporadic MTC.[92,93] Among these alterations, M918T is the most frequently reported mutation (Table 4). Other less-common somatic mutations occur at residues C634, A883, C630, and others.[94] *RET* mutations have been found to be mutually exclusive with HRAS and KRAS mutations in sporadic MTC, indicating RAS activation as a driver pathway in MTC.[95,96] A recent study used NGS to identify *RET* mutations in tumors from 4,871 patients.[66] The result showed that somatic *RET* point mutations exist in a variety of cancer types, such as breast carcinoma (C634R), colorectal adenocarcinoma (V804M), GI stromal tumor (V804M), Merkel cell carcinoma (E511K), and paraganglioma (M918T). However, the functional effect of *RET* mutations on tumorigenesis in these tumors remains to be elucidated.

TARGETED THERAPIES FOR RET

MKIs

As a tyrosine kinase receptor, RET shares similarities in the sequence and structure of the kinase domain with other tyrosine kinases.[65,97] Many MKIs have demonstrated activity against RET, such as cabozantinib, lenvatinib, sorafenib, vandetanib, ponatinib, sunitinib, and alectinib.[28,98] Among them, cabozantinib and vandetanib are approved for advanced MTC by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), although *RET* mutation is not required as a selective biomarker. Data from the phase III trial of vandetanib in advanced MTC (ZETA; ClinicalTrials.gov identifier: NCT00410761)[99] showed a predicted median progression-free survival (PFS) of 30.5 months by the Weibull model in the treatment group and a median PFS of 19.3 months in the placebo group. The objective response rates (ORRs) were 45% in the treatment group and 13% in the placebo group. Although the subgroup analysis based on *RET* mutation status is inconclusive, the patients whose cancers harbored a *RET* M918T mutation had a higher ORR with

vandetanib than M918T-negative patients. In the phase III trial of cabozantinib (EXAM; ClinicalTrials.gov identifier: NCT00704730), the median PFS/ORR for cabozantinib and placebo are 11.2 months/28% and 4 months/0%, respectively.[100] Retrospective analysis of the EXAM trial demonstrated that cabozantinib had increased benefit in patients with *RET* M918T than in patients without this mutation in term of PFS, ORR, and overall survival (OS).[101,102] However, cabozantinib was favored for both OS and PFS regardless of *RET* mutation status.[102] The clinical benefits were also not associated with *RET* mutation status in a phase II trial of lenvatinib in MTC.[103] The ongoing observation study evaluating vandetanib in patients with MTC with or without *RET* mutations (ClincalTrials.gov identifier: NCT01945762), as well as future RET-directed prospective trials, will further shed light on this matter.

Despite the fact that lenvatinib and sorafenib are approved for radioactive iodine-refractory differentiated thyroid cancer (DTC) by the FDA and EMA, neither phase III trial that led to their approval investigated the correlation between *RET* rearrangement and the efficacy of the drugs.[104,105] Several phase II trials involving sunitinib,[106] dovitinib,[107] and vandetanib[108] in DTC did not explore this drug-biomarker relationship.

Nevertheless, insights have been provided by an array of clinical studies in *RET*-rearranged NSCLC. A phase II trial evaluating cabozantinib was conducted in patients with NSCLC with *RET* rearrangement. The ORR, median PFS, and OS among 25 patients were 28%, 5.5 months, and 9.9 months.[109] Vandetanib was subsequently assessed in a Japanese phase II trial (LURET) and a Korean phase II trial on NSCLC with *RET* rearrangements. The analysis of the LURET trial showed 53% ORR, median PFS of 4.7 months, and median OS of 11.1 months.[110] Even though the 18% ORR of a separate South Korean phase II trial was lower than that in LURET, the median PFS (4.5 months) and median OS (11.6 months) were comparable with LURET trial.[111] In another phase II trial testing lenvatinib, the ORR was 16% and the median PFS was 7.3 months.[112] In addition, a global registry of RET-rearranged NSCLC (GLORY) retrospectively reported 53 patients who were treated with one or more MKIs. Within these patients, the ORRs for cabozantinib, vandetanib, and sunitinib were 37%, 18%, and 22%, respectively. The median PFS and median OS were 2.3 months and 6.8 months.[113] A recent phase I/Ib trial with RXDX-105 in *RET* fusion-positive NSCLC showed that the ORR with RXDX-105 was 19%.[114] Interestingly, what was observed was a striking divergence in response to RXDX-105 dependent on the gene fusion partner, as responses were observed only in non-KIF5B upstream partners.[114] The analysis of fusion partner in the aforementioned trials of cabozantinib, vandetanib, and RXDX-105 suggested a tendency toward worse clinical outcomes (ORR and PFS) in cancers with KIF5B-RET compared with cancers with other known *RET* fusion.[109-111,115] Additional investigation is needed, considering that the sample sizes were small in these trials, and the results of GLORY study showed no significantly different clinical outcomes in patients bearing different *RET* fusions.[113]

Although the data of MKIs have demonstrated their clinical utility in RET-driven cancers, the ORRs (16%-53%) and median PFSs (2.3-7.3 months) in *RET*-rearranged NSCLCs are lower than those seen in other patients with oncogene-driven NSCLC receiving targeted tyrosine kinase inhibitors. As an example, patients with NSCLC with *EGFR* mutation, *ALK* rearrangement, or *ROS1* rearrangement have ORRs of 56%-85% and median PFS of 8-34.8 months with targeted therapies.[116-119] The retrospective analysis of the EXAM trial showed no difference of OS between cabozantinib and placebo.[102] The achievement of complete response was also rarely reported in all clinical trials mentioned previously. The limited efficacy of MKIs on RET-driven cancers can be at least partially attributed to the off-target activity of these inhibitors. MKIs can usually target a wide spectrum of kinases besides RET. Particularly, because of the high homology of the kinase domain between RET and VEGFR2, many VEGFR2 inhibitors can also target RET with a lower affinity, such as cabozantinib, vandetanib, and lenvatinib.[85,120-122] The off-target effect contributes to inferior inhibition of RET, as well as drug-related toxicities, which can in turn result in drug discontinuation and dose reduction, further compromising the efficacy of these drugs. Moreover, an inhibitor may have different efficacies against various *RET* mutations and RET rearrangements with different fusion partners. For instance, cabozantinib and vandetanib can effectively block the activity of *RET* M918T but fail to inhibit the gatekeeper mutations *RET* V804M and V804L.[123,124] The two gatekeeper mutations and other mutations like S904F, G810R, and I788N may emerge as mechanisms of acquired resistance to the MKIs.[125-127] In addition, acquired genomic changes in other genes, such as NRAS Q61K or MDM2 amplification, can lead to resistance to these inhibitors.[128,129] Another mechanism of acquired resistance is through the activation of bypass signaling, including MAPK, EGFR, and AXL pathways.[125,128,130]

The complexity of genomic changes in RET-driven cancers also underlines the need for combination therapies. Activation or genomic alterations of other pathways can co-occur with *RET* rearrangement. For example, concomitant activating BRAF, KRAS, and NRAS mutations have been identified in some *RET*-rearranged PTCs.[131,132] AKT2 amplification was found to coexist with *RET* rearrangement in a patient with lung adenocarcinoma, who responded to the combination of vandetanib and everolimus with a decrease in the intracranial disease burden.[133] This combination is being tested in a phase I trial (ClincalTrials.gov identifier: NCT01582191) and has demonstrated antitumor activity in patients with both *RET* fusions and mutations.[134,135] In the aforementioned treatment-activated bypass signaling, preclinical data have shown that the

resistant cells remain sensitive to strategies combining MKIs and MEK or EGFR inhibitors.[125,128,130]

Selective RET Inhibitors

In recent years, selective RET inhibitors have been developed to achieve higher potency and less toxicity. Two such next-generation small molecular inhibitors, namely pralsetinib (BLU-667) and selpercatinib (LOXO-292), have been rapidly translated to clinic[1,2] (Table 1). The functional studies using various in vitro and in vivo models showed that both inhibitors are capable of inhibiting a wide spectrum of *RET* alterations, including M918T, C634W, gatekeeper mutations V804L and V804M, KIF5B-RET, and CCDC6-RET (Table 1).[1,2] Importantly, LOXO-292 and BLU-667 have much less activity against VEGFR2 relative to *RET* alterations, potentially reducing toxicity.

The preliminary results from early-phase trials have demonstrated such superior activity and tolerability with these agents compared with MKIs that these agents have received US FDA breakthrough designation and are on track for registration (Table 1). In the recent update of the ARROW trial (ClincalTrials.gov identifier: NCT03037385), pralsetinib showed an ORR of 56% in *RET*-mutated MTC[136,137] and 58% in *RET* fusion-positive NSCLC.[138] Among these patients, the ORRs were 60% in patients with post-platinum RET-fusion NSCLC and 63% in patients with RET-mutant MTC previously treated with MKIs treated at the 400-mg daily dosing. According to the registrational dataset analysis of a phase I/II LIBRETTO-001 trial (ClincalTrials.gov identifier: NCT03157128), selpercatinib showed an ORR of 68% in *RET* fusion-positive NSCLC (85% in treatment-naïve patients), 62% in *RET* fusion-positive thyroid cancer, and 56% in *RET*-mutant MTC (59% in cabozantinib/vandetanib-naïve patients).[2,139-141] The median duration of response (DOR) and PFS were 20.3 months and 18.4 months in patients with *RET* fusion-positive NSCLC but not reached in treatment-naïve patients with NSCLC.[140] The median DOR and PFS were not reached in *RET*-mutant MTC and *RET* fusion-positive thyroid cancer.[141] In the both trials, most adverse events were grade 1 or 2, and only a few patients had treatment discontinued because of treatment-related adverse events (1.7% in NCT03157128, 2.9% in NCT03037385).[136,138,140,141] This favorably compares with other MKIs such as vandetanib, cabozantinib, or lenvatinib that showed a drug discontinuation rate of 21%, 8%, and 20%, respectively. Notably, antitumor activity was observed in patients with brain metastases for both the selective RET inhibitors.[139-142]

The "RET+ all-comer basket arms" of these clinical trials are in active recruitment, and results from these arms may inform tissue-agnostic development potential. Beyond lung cancers and thyroid cancers, clinical activity of selective RET inhibitors has been seen in patients with GI cancers (pancreatic cancer and intrahepatic bile duct carcinoma)[138,139] as well as in pediatric patients with *RET*-altered cancers (PTC, MEN2A MTC, infantile myofibroma, congenital mesoblastic nephroma, infantile fibrosarcoma, and lipofibromatosis).[143]

Newer Selective RET Inhibitors and Acquired Mechanisms of Resistance

Several other selective RET inhibitors, BOS172738, TPX-0046, and TAS0953/HM06, are also in early stages of development.[144,145] In addition to the RET V804M gatekeeper mutation, several other acquired resistance mechanisms to MKIs have been reported (Table 2). Resistance mechanisms to selective RET remains an active area of research. A preclinical study has shown that novel solvent front mutation KIF5B-RET G810R may develop as on-target resistance to selpercatinib and pralsetinib but remains sensitive to another selective RET inhibitor, TPX-0046, designed with a macrocyclic structure targeting active RET confirmation (Table 2).[145]

In conclusion, the role of *RET* activating mutations and rearrangements in tumorigenesis has been established during the past three decades. There is considerable excitement in the RET field with the advent of highly selective RET inhibitors. The next-generation selective RET inhibitors selpercatinib and pralsetinib have demonstrated remarkable clinical efficacy and safety in preliminary phase I/II trials. Both agents have received US FDA breakthrough designations. Unanswered questions remain as to what the PFS, DOR, and OS with these agents would be; if all RET-aberrant cancers respond similarly for a tissue-agnostic indication; and what the acquired resistance mechanisms to the potent RET inhibitors would be. In addition, combination therapies exploring the concurrent inhibition of RET and related pathways will provide insight into the clinical utility of such strategies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

State-of-The-Art Strategies for Targeting *RET*-Dependent Cancers

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