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## Precision therapy for *RET*-altered cancers with RET inhibitors

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### Abstract

Rearranged during transfection (*RET*) is involved in the physiological development of some organ systems. Activating *RET* alterations via either gene fusions or point mutations are potent oncogenic drivers in non-small cell lung cancer, thyroid cancer, and in multiple diverse cancers. *RET*-altered cancers were initially treated with multikinase inhibitors (MKIs). The efficacy of MKIs was modest at the expense of notable toxicities from their off-target activity. Recently, highly potent and *RET*-specific inhibitors selpercatinib and pralsetinib were successfully translated to the clinic and FDA approved. We summarize the current state-of-the-art therapeutics with preclinical and clinical insights of these novel *RET* inhibitors, acquired resistance mechanisms, and future outlooks.

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## Introduction

*RET* is the transforming proto-oncogene that encodes a receptor tyrosine kinase and was accidentally discovered in a patient with T cell lymphoma upon transfecting human tumor DNA with rearrangement by Takahashi *et al.* about three and a half decades ago [1]. While the receptor tyrosine kinase RET is involved in the fetal development of nervous, hematopoietic, gastrointestinal, and genitourinary systems, activating *RET* aberration is a potent oncogenic driver in many cancer types [2–7]. *RET* proto-oncogene can be activated aberrantly by two major mechanisms: gene fusion and point mutation. *RET* gene fusions or rearrangements are the principal aberrations occurring in 1–2% of non-small cell lung cancer (NSCLC) and 10–20% of papillary thyroid carcinoma (PTC). By contrast, *RET* mutations are the major activating alteration in sporadic medullary thyroid cancer (MTC) and as germline mutation in multiple endocrine neoplasia syndrome (MEN) [8–14]. Advances in **next generation sequencing** (see Glossary) combined with precision oncology have uncovered *RET* alterations in several other malignancies, albeit rarely [6,15–20].

Researchers have tried to tackle *RET*-driven cancers with different approaches and therapeutics. Despite the past decade of effort utilizing various multikinase inhibitors (MKI) with RET inhibitory activity, their efficacy was modest at the expense of noteworthy toxicities and significant impact on health-related quality of life, ultimately leading to their discontinuation due to off-target side effects [21]. Hence, developing RET-specific therapeutics has become paramount. The recent FDA approvals of highly potent and selective RET inhibitors selpercatinib and pralsetinib have stimulated the field of *RET*-aberrant cancer research. We summarize the utility of precision medicine in addressing *RET*-driven tumors and depicting the mechanistic insight of the novel selective RET inhibitors, including emerging resistance mechanisms.

## **RET alterations in cancers**

### **The structure of RET and its fundamentals**

The transmembrane receptor tyrosine kinase RET, which is encoded by the proto-oncogene *RET* located on chromosome 10, plays a role in the early development of kidneys and the enteric nervous system [2–4]. The RET protein comprises an extracellular domain, a transmembrane domain, and an intracellular tyrosine kinase domain [22]. The extracellular domain contains four cadherin-like domains (CLD1–4), a calcium binding site, and a cysteine-rich domain. The intracellular region contains a tyrosine kinase domain and tyrosine phosphorylation sites located next to the C terminal region, where two major isoforms, *RET9* and *RET51*, are positioned due to alternative splicing [23,24]. The latter isoform has stronger tumorigenic activity [14], although both isoforms are coexpressed in many tissues. There are six known RET ligands; artemin, differentiation factor 15 (GDF15), glial cell line-derived neurotrophic factor (GDNF), GDNF receptor  $\alpha$  (GFR $\alpha$ )-like protein (GFRAL), neurturin, and persephin, and coreceptors called GDNF family receptor- $\alpha$  (GFR $\alpha$ 1–4) [7,25–29]. RET homodimerization, mediated by a ligand-coreceptor complex, leads to the activation of several downstream pathways, including RAS/MAPK, PI3K/AKT, JAK/STAT, PKA, and PKC pathways (Figure 1) [30–34]. Although *Y1062* is the important docking site of major pathways, autophosphorylation of certain docking sites specifically

gives rise to separate downstream pathways; such as *Y1096* leading to RAS/MAPK and PI3K/AKT pathways, *Y1015* conferring PLC $\gamma$ , *Y752* and *Y928* to JAK/STAT pathway, and *Y687* and *Y981* binding to Shp2 and Src kinases, respectively [33,35–40].

## RET fusions

NSCLC and PTC are the most common cancer types harboring *RET* fusions [10,11,14,41–43]. Adenocarcinomas are the most frequent histology to carry *RET* rearrangements, followed by adenosquamous, squamous cell, and neuroendocrine cancers. About 2% of patients with NSCLC harbor *RET* fusions and they tend to occur in relatively younger (<60 years of age), never- or light-smokers, which are similar to those carrying *ALK* or *ROS* rearrangements [14,42,44,45]. Meanwhile, 5–10% of PTC carry *RET* fusions, in which the prevalence is further heightened in patients who had previous radiation exposure [46–54]. Like other common drivers, such as sensitizing *EGFR* mutations and *ALK* or *ROS1* rearrangements, *RET* fusions tend to occur in a mutually exclusive fashion, yet they might be acquired in some patients who become resistant to EGFR therapies in *EGFR*-mutant NSCLC [55,56]. Kinesin family member 5B (*KIF5B*) from the pericentric inversion of chromosome 10 is the most common somatic rearrangement identified in lung cancer [10,11]. Coiled-coil domain containing 6 (*CCDC6*)-*RET*/*RET*/*PTC1*) fusion contributes to 10–25% of *RET* fusions. Other uncommon fusions in lung cancer include *NCOA4-RET*, *TRIM33-RET*, *ZNF477P-RET*, *ERCC1-RET*, *HTR4-RET*, *CLIP1-RET*, *FRMD4-RET*, and *WAC-RET* [15,57]. *CCDC6-RET* and nuclear receptor coactivator 4 (*NCOA4*)-*RET* (*RET*/*PTC3*) account for the majority (>90%) of rearrangements in PTC [46,58]. More than ten other *RET* fusions have been reported in PTC, including *RET*/*PTC2*, *RET*/*PTC4* through *RET*/*PTC9*, *ELKS-RET*, *PCMI-RET*, *RFP-RET*, and *HOOK3-RET* [57]. *RET* fusions occur in less than 1% in pancreatic cancer, salivary gland cancer, spitz tumors, colorectal cancer, ovarian cancer, and others [6,16–20]. To date, more than 35 different ***RET* fusion genes** have been reported [15]. These fusion partners permit RET kinase expression in cell types in which RET or its coreceptors are not normally expressed and cause dimerization that aberrantly activates the RET kinase [7].

## RET point mutations

In contrast to PTC, most MTC carry *RET* mutations, although a few cases of *RET* fusions have been reported in MTC [59]. *RET* point mutations, which occur as germline or somatic mutations, are found in families with **multiple endocrine neoplasia type 2 (MEN 2) syndrome**. MEN 2 is an inherited cancer syndrome, comprising MTC, pheochromocytoma, and parathyroid hyperplasia and it has three subtypes: MEN 2A, MEN 2B, and familial medullary thyroid cancer (FMTC). Mutations contributing to MEN 2 are clustered in the cysteine-rich domain in exon 10, 11, and the tyrosine kinase domains in exons 13 to 16 of *RET* [8,12]. *RET*<sup>M918T</sup> is the most common and most aggressive mutation out of more than 60 activating *RET* mutations discovered [15]. *RET*<sup>M918T</sup> is located in the kinase domain and has higher ATP-binding affinity and altered *RET* autophosphorylation trajectory [60].

## Treating *RET*-altered cancers

### Response to immunotherapy and chemotherapy

Like patients with NSCLC harboring *ALK* or *ROS1* rearrangements, *RET*-rearranged lung cancers can respond to pemetrexed-based doublet chemotherapy with an **objective response rate (ORR)** of 45% and median **progression-free survival (PFS)** of 19 months [61]. There is emerging data on the response to immunotherapy in *RET*-altered cancers [62–64]. A study of 74 patients with *RET*-rearranged lung cancers who were treated with immune checkpoint inhibitors (ICI) either as single- or dual-agent immunotherapy [63] (Table 1) revealed that *RET*-rearranged lung cancers have low levels of PD-L1 expression and low tumor mutation burden in the majority of patients and poorer responses to immunotherapy. In the MD Anderson Cancer Center cohort, the median time to progression was shorter in patients with *RET*-aberrant cancers who received ICI compared with non-ICI therapies [62] (Table 1). Retrospective studies including real-world data on ICI in *RET*-altered cancers are depicted in Table 1. While prospective data on immunotherapy in *RET*-altered cancers is lacking, the retrospective evidence points to poor response to immunotherapy. *RET*<sup>+</sup> NSCLC seem to be biologically ‘cold’ tumors with low tumor mutational burden (TMB) and low PDL1 expression. *RET*<sup>+</sup> NSCLC usually occurs in patients with a history of no tobacco use or minimal smokers, which could be the link to lower TMB. This lower TMB renders them as ‘cold tumors’ that have an immune-poor microenvironment, rich in regulatory T cells, and poor in activated T cells, responding less to checkpoint inhibitors [65]. However, TMB and tumor microenvironment (TME) are dynamic as T cell-inflamed TME seems to positively correlate with responsiveness to ICIs and adoptive cell therapy. Therefore, future studies should look into opportunities to convert these ‘cold’ oncogene-driven tumors to hot tumors [65].

### Tackling *RET* proto-oncogene with nonspecific MKIs

The utilization of MKI is one strategy to target *RET*. Several FDA-approved protein tyrosine kinase inhibitors, including cabozantinib, vandetanib, lenvatinib, sorafenib, and sunitinib, cross-inhibit *RET* and have been trialed in *RET*-altered cancers [15,21]. Across different studies, NSCLC patients with *RET* rearrangements who were treated with cabozantinib, vandetanib, or lenvatinib achieved a modest ORR (16–47%), median PFS (4.9–11.6 months), and median overall survival (OS) (4.9–11.6 months) [66–69] (Table 2). However, ~70% of patients experienced grade 3 and above adverse events (G3AEs), leading to dose reduction in the majority of trial participants and discontinuation in some. In contrast to the *RET*-rearranged NSCLC, some MKIs have been approved in thyroid cancers. Cabozantinib and vandetanib were approved in MTC by the US FDA and the European Medicines Agency (EMA) after the landmark EXAM and ZETA trials showed positive results [70,71] (Table 2). In the EXAM trial, cabozantinib contributed to ORR of 28% and median PFS of 11.2 months compared with ORR/PFS of 0%/4 months in the placebo arm and the activity of cabozantinib was noted regardless of *RET* mutation status [71,72]. Similar to the study in NSCLC, dose reduction occurred in 79%, while 16% had stopped the trial medication. In the ZETA trial employing vandetanib, the ORR/PFS was 45%/30.5 months in the treatment group versus 13%/19.3 months in the placebo arm [70]. Notably, vandetanib gave rise to greater ORR in *M918T*-mutant MTC. The pivotal DECISION and SELECT trials led

to the approval of sorafenib and lenvatinib in patients with differentiated thyroid cancer (DTC), who were refractory to radioactive iodine [73,74]. Although these MKIs conferred higher ORR and survival benefits in thyroid cancers and modest benefits in NSCLC, they underscored the tolerability issues impacting health-related quality of life from ‘off-target’ toxicities. It is believed that an underlying cause of toxicity is attributed to inhibition of VEGFR1/FLT and VEGFR2/KDR [21].

RXDX-105 was developed as a VEGFR1/2-sparing dual *RET* and *BRAF* MKI [75,76]. In a clinical study, RXDX-105 was efficacious only in non-*KIF5B* fusion partners [76]. As the clinical virtue has been sparse in patients with NSCLC harboring *KIF5B-RET* fusion, which remains the most common subtype, more novel approaches and therapeutics are needed. It is unclear why *KIF5B-RET* fusion-positive NSCLC were nonresponsive to RXDX-105. In a fruit fly model of oncogenic RET activity, *KIF5B-RET*, but not *CCDC6-RET* or *NCOA4-RET*, activated *EGFR* and *FGFR* strongly via the kinesin motor domain and RAB GTPase [77]. *KIF5B-RET*-induced *EGFR* and *FGFR* phosphorylation required RET kinase activity. Although *KIF5B-RET* may have stronger oncogenic activity because of activating multiple signaling hubs, RET kinase activity is a prerequisite; thus, inhibiting RET kinase activity alone is sufficient to silence oncogenic activity. In patient-derived xenograft (PDX) tumor growth experiments, both *KIF5B-RET*-positive NSCLC PDX and *CCDC6-RET*-positive PDX responded similarly to RXDX-105 [75]. However, in RET fusion kinase-dependent BaF3 cell models, the RXDX-105 IC<sub>50</sub> in BaF3/*KIF5B-RET* cells was approximately twofold higher than those in BaF3/*CCDC6-RET* and BaF3/*NCOA4-RET* cells. The difference in the IC<sub>50</sub>s could be caused by either different expression levels of the RET fusion kinases or different signaling mechanisms. In the *RET* fusion-positive NSCLC, the expression level of the *RET* fusion genes are most likely dictated by the fusion partners located on the 5′ side. Because the mRNA expression data of the RET fusion genes in NSCLC are not available, we examined the mRNA expression levels of *KIF5B* and the three non-*KIF5B* fusion partner genes (*CCDC6*, *EML4*, *PARD3*) in lung adenocarcinoma from the TCGA PanCancer Atlas dataset. *KIF5B* mRNA is expressed at a significantly higher level ( $P < 0.0001$ ) than the other three genes that are the non-*KIF5B RET* fusion partners in the clinical study of RXDX-105 (Figure S1 in the supplemental information online) [76], raising the possibility that *KIF5B-RET* fusion is expressed at a higher level than the other three non-*KIF5B-RET* fusions reported in the RXDX-105 clinical trial of NSCLC [76]. The higher level of *KIF5B-RET* would be predicted to generate greater signaling strength and require more drug to inhibit it. This is important because the suboptimal *in vivo* levels of multikinase RET inhibitors, including RXDX-105 [76], may not be able to adequately suppress the *KIF5B-RET* kinase activity in NSCLC, resulting in no objective response in *KIF5B-RET* fusion NSCLC.

While RXDX-105 has potent RET protein kinase inhibitor (TKI) activity and lower VEGFR2/KDR-mediated AEs than other RET MKIs, like cabozantinib and vandetanib [78,79], RXDX-105 was unable to inhibit *RET*<sup>V804M/L</sup> gatekeeper mutants [75,80]. Consequently, tumors with *RET*<sup>V804M</sup> progressed on RXDX-105 treatment [81]. Structurally, these MKIs bind to the RET kinase domain in a manner that occupies both front and back clefts of the active site by going through the gate that separates these two clefts, which is formed by the gatekeeper V804 and the invariable gate wall K758 residues

(Figure 2A) [75,82]. Gatekeeper *V804V/M* mutants cause steric hindrance that interferes with the binding of these drugs [75,80].

### RET-specific, gatekeeper mutant-sensitive TKIs

Recently, two RET-specific, gatekeeper mutant-effective TKIs (pralsetinib and selpercatinib) were approved by the US FDA for the treatment of *RET*-altered NSCLC and thyroid cancers.

Pralsetinib (BLU-667) is an orally bioavailable selective RET inhibitor that is more potent than other RET TKIs. Pralsetinib inhibits the *RET<sup>V804M/L</sup>* gatekeeper mutants with a similar potency to RET and *RET<sup>M918T</sup>* in an *in vitro* kinase activity assay [80]. The X-ray crystal structure of the RET-pralsetinib complex reveals that pralsetinib binds to the RET kinase by occupying both the front and back clefts without passing through the gate like vandetanib (Figure 2A). Instead, pralsetinib wraps outside the K758 gatewall residue to access both the front and back clefts (Figure 2B,C) [83]. This binding avoids the interference of gatekeeper mutations while allowing high-affinity binding.

Pralsetinib is also highly selective against VEGFR2 [80], ultimately lessening ‘off-target’ AEs caused by blocking VEGFR2 activity. The findings from the Phase I/II, global, multicenter, registrational ARROW trial ([ClinicalTrials.gov Identifier: NCT03037385](https://clinicaltrials.gov/ct2/show/study/NCT03037385)) (Table 3) revealed that the majority of patients tolerated pralsetinib well, resulting in 4% treatment discontinuation due to treatment-related adverse events (TRAE), and the most common any grade TRAEs were elevated AST (34%), anemia (24%), elevated ALT (23%), and hypertension (22%).

Recently, the FDA approved pralsetinib in patients with *RET*-altered thyroid cancers [84]. The AcceleRET Lung study of pralsetinib in patients with previously untreated *RET* fusion-positive NSCLC was recently launched [85]. Concurrently, the preliminary activity of pralsetinib in patients with other *RET* fusion-positive solid tumors was reported [86]. The cohort included 29 patients: 16 PTC, one undifferentiated thyroid cancer, two cholangiocarcinoma, three pancreatic, three colorectal cancers, and four others. In 11 evaluable patients with thyroid cancer, the ORR was 91%, with all achieving partial response (PR) and the **disease control rate (DCR)** was 100%. In other *RET* fusion-positive solid tumors, six out of 12 obtained PR, contributing to an ORR of 50%, whereas the DCR was 92%. Remarkably, all five patients with cholangiocarcinoma and pancreatic cancer (*CCDC6-RET* fusion, *TRIM33-RET* and *JMJD1C-RET* fusions) achieved PR. In a patient with intrahepatic bile duct carcinoma with *NCOA4-RET* fusion, who progressed after three prior lines of therapy (cisplatin/gemcitabine/nab-paclitaxel, erlotinib/bevacizumab, and osimertinib), showed a deep and durable PR with 64% shrinkage at 20 months of treatment.

Selpercatinib (LOXO-292) is another orally bioavailable, potent RET-specific TKI capable of inhibiting the *RET<sup>V804M/L</sup>* gatekeeper mutants [81,83]. Like pralsetinib, selpercatinib docks one end of the ATP-binding pocket without inserting into the gate and wraps outside the K758 gatewall residue to access the back cleft (Figure 2D). In various cell culture models, selpercatinib was >20-fold more potent than cabozantinib, vandetanib, or lenvatinib [78,81,83]. The pivotal multicenter, dose escalation, Phase I/II registrational

LIBRETTO-001 trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03157128) Identifier: [NCT03157128](https://clinicaltrials.gov/ct2/show/study/NCT03157128)) demonstrated the efficacy of selpercatinib [87,88] (Table 3). The most observed high-grade AEs were hypertension (14–21%), elevated ALT (11–12%), and elevated AST (9–10%). The majority of patients tolerated selpercatinib well, while only 2% had treatment discontinuation due to TRAE. With these promising results, selpercatinib secured FDA approval in patients with *RET*-altered lung and thyroid cancers in May 2020 [89]. Recently, two randomized Phase III LIBRETTO-431 and LIBRETTO-531 studies in patients with treatment-naïve advanced *RET* fusion-positive NSCLC and treatment-naïve *RET*-mutant MTC were launched [90,91].

Both selpercatinib and pralsetinib have been approved for the same indications in *RET*-aberrant NSCLC and thyroid cancers. Both agents were approved in the treatment-naïve and treatment refractory settings and offer options for patients in the clinic as different drugs have different clinical properties, patient access mechanisms, and coverage. Although mechanism of action and clinical trial results are similar, the trials enrolled different populations with varied entry criteria and eligibility; hence, it may not be appropriate to make cross-trial comparisons. Selpercatinib is dosed orally twice daily, while pralsetinib is given orally once a day. Regarding safety profile, grade 3 or greater QT prolongation and hypersensitivity are safety warnings for selpercatinib, but are not safety warnings for pralsetinib. Pneumonitis, seen in 2% of patients on pralsetinib, is not a safety issue with selpercatinib. Hypertension rates were similar with both drugs [87,88,92,93].

Although *RET* inhibitors have been approved in *RET*-altered lung and thyroid cancers, clinical trials for tissue-agnostic and pediatric indication continue and data are emerging. Despite the rare prevalence, the selective *RET* inhibitors showed robust activity in other *RET* alteration-positive solid tumors and pediatric populations. The early data from the studies show that *RET* fusions are oncogenic in multiple tumor types and can be targeted by selective *RET* inhibition. However, the **duration of response** and **acquired resistance** in non-lung and non-thyroid tumors remains unknown. Since *RET* plays a crucial role in the development of the nervous system and kidney, and in spermatogenesis, the clinical implications of long-term *RET* inhibition in young children remains to be known. The first experience with selpercatinib in five pediatric patients under institutional review board-approved single patient protocols reported [94] that four out of the five pediatric patients with *RET*-altered cancers treated with selpercatinib at a starting dose of 90 mg/m<sup>2</sup> twice daily (BID) had achieved PR and another patient had stable disease. They included different tumor types, namely PTC (*CCDC6-RET*), infantile myofibroma/hemangiopericytoma (*MYH10-RET*), congenital mesoblastic nephroma/infantile fibrosarcoma (*SPECCIL-RET*), lipofibromatosis (*NCOA4-RET*), and MTC (*RET* codon 918 mutation, MEN2B). A Phase I/II LIBRETTO-121 enrolling pediatric patients with *RET*-altered advanced solid or primary central nervous system (CNS) tumors is currently underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03899792) Identifier: [NCT03899792](https://clinicaltrials.gov/ct2/show/study/NCT03899792)).

### Preclinical and clinical intracranial response data of selective *RET* inhibitors

A global *RET* registry depicted that brain metastases could be found in ~50% of *RET*-aberrant NSCLC where MKIs conferred suboptimal CNS activity [95]. Hence, it is important that *RET*-specific inhibitors have CNS coverage. Selpercatinib and pralsetinib

have demonstrated intracranial activity in preclinical models. Pralsetinib showed intracranial tumor target engagement in a *CCDC6-RET* fusion-driven preclinical model, and human DUSP6/SPRY4 transcripts decreased >90% with 10 or 30 mg/kg pralsetinib at 4 hours and indicated full pathway inhibition at doses demonstrating antitumor activity [96]. The negative control, human GSK3B expression was not inhibited with pralsetinib treatment. In the case of selpercatinib, intracranial activity was demonstrated in *CCDC6-RET* fusion-positive PDX tumor suspensions and treated orally with vehicle, ponatinib (40 mg/kg daily) or selpercatinib (30 mg/kg twice daily) and survival was compared with Kaplan–Meier analysis before and after dose reduction by tenfold on day 52. At proportionately reduced doses, selpercatinib significantly prolonged survival (median not reached) compared with ponatinib (median 18.5 days) [81]. Both selective RET inhibitors cross the blood–brain barrier and demonstrate clinical intracranial responses. In the LIBRETTO-001 trial, intracranial ORR was 82% [95% confidence interval (CI), 60–95], including 23% with complete responses among 22 patients with measurable intracranial efficacy evaluable disease at baseline [97]. In the ARROW trial with pralsetinib, shrinkage of intracranial metastases was seen in all patients with measurable intracranial metastases at baseline and at least one post-baseline intracranial response assessment. Five of nine (56%) patients had an intracranial response, including three with complete response (CR) [92]. Moreover, recent cases have demonstrated the efficacy of RET-specific inhibitor in parenchymal disease and leptomeningeal metastases [98,99]. The case depicted the robust activity of selpercatinib in a patient with *RET* fusion-positive lung cancer, resulting in a reduction in 65% from baseline at 21 weeks of treatment and subsequent scans showed resolution of leptomeningeal enhancement. A recent anecdotal case report showed subsequent clinical response to selpercatinib in a patient with *RET* fusion-positive NSCLC, who had a durable extracranial response to pralsetinib, but had leptomeningeal progression [100]. It will be interesting to see if these agents can be used sequentially, especially in these special situations, potentially opening up more options for patients. These RET-specific inhibitors have expanded treatment options where limited options are available and remain an area in dire need of therapeutic innovation. Future studies should explore further clinical CNS activity of both these agents.

### **TPX-0046, BOS172738, and other RET inhibitors in development**

TPX-0046 is a novel orally bioavailable RET/SRC kinase inhibitor and has strong potency on the wild type and *RET*<sup>G810C/S/R</sup> solvent-front *RET* mutants [101]. In addition to RET, TPX-0046 inhibits several other protein tyrosine kinases, such as the SRC family kinases [102] and the clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04161391) Identifier: [NCT04161391](https://clinicaltrials.gov/ct2/show/study/NCT04161391)) employing TPX-0046 is underway. BOS172738 (DS-5010) is another novel RET inhibitor with nanomolar potency against RET. BOS172738 showed exquisite potency for the wild type *RET*, *RET*<sup>V804M/L</sup> gatekeeper mutants, and the most common oncogenic *RET* mutation *M918T* and had high selectivity against VEGFR2 [103]. The clinical study of BOS172738 is now enrolling patients with *RET*-altered tumors ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03780517) Identifier: [NCT03780517](https://clinicaltrials.gov/ct2/show/study/NCT03780517)). TAS0953/HM06 is another RET TKI currently in preclinical development. Early nonclinical studies with BiDAC™ (bifunctional degradation activating compounds) RET inhibitor from C4 therapeutics, and second generation selective RET



inhibitors from KinaRx and LOXO Oncology (LOX-18228 and LOX-19260) are also ongoing.

### Mechanisms of resistance to RET-targeted therapy

**De novo resistance** and acquired resistance to RET TKIs have been observed in the clinic. The response rates to MKI RET inhibitors such as cabozantinib and vandetanib are low, likely in part to the incomplete suppression of the oncogenic RET kinase. Because off-target AEs, dose-reduction was necessary in 35–79% of MTC patients treated with vandetanib and cabozantinib [21]. Therefore, it is difficult to achieve optimal drug concentrations for RET inhibition with these MKIs [21]. While the more potent pralsetinib and selpercatinib have improved response rates [87,88], over 30% of *RET*-altered NSCLC and thyroid cancers do not achieve PR to these drugs. Co-occurrence of **driver oncogenes**, such as RAS and EGFR mutations and MET amplification, are observed in *RET*-altered cancers [6,104] and as acquired mutations in the laboratory [105]. Conceivably, co-occurrence of other driver oncogenes could by-pass the requirement of the *RET* oncogene, rendering RET TKIs ineffective. A combination of the MET/ALK/ROS1 TKI crizotinib with selpercatinib in patients who had *RET* fusion-positive and MET amplification NSCLC resulted in a response of the selpercatinib-resistant tumors to the combinational therapy [106].

Like other protein tyrosine kinase-targeted therapy, acquired secondary *RET* mutations that cause resistance to multikinase or specific RET TKIs have been identified in preclinical experiments and in patients whose tumors acquire TKI resistance (Figure 1). The gatekeeper *RET*<sup>V804M/L</sup> mutants are resistant to vandetanib, cabozantinib, lenvatinib, RXDX-105, and other MKIs used to inhibit RET [21,78,79,107–109]. Other MKI-resistant mutations are located in the hinge Y806, C-lobe solvent front G810, and N-lobe solvent front L730 (also called the roof) sites [78,110,111]. *L730V/I* roof mutations are resistant to pralsetinib but remain sensitive to selpercatinib in preclinical experiments [110,111], raising the possibility that selpercatinib could be used as a secondary drug when RET roof mutations cause pralsetinib resistance. However, this use has yet to be validated clinically. Mutations located outside the drug binding pockets of the RET kinase domain could cause resistance to RET TKIs [78]. For instance, *RET*<sup>S904F</sup>, located in the activating loop of the kinase domain, was found as a secondary mutation in a *CCDC6-RET*-positive NSCLC patient after the tumors developed vandetanib resistance [112].

Specific RET TKIs, selpercatinib and pralsetinib, circumvent the resistance mechanism of gatekeeper mutations. However, they face new challenges of resistance caused by mutations at non-gatekeeper sites. In a laboratory screening of selpercatinib resistance, *G810C/S/R* mutations at the C-lobe solvent front, *Y806C/N* mutations at the hinge, and the *V738A* mutation at the  $\beta$ 2 strand were identified [83]. All five selpercatinib-resistant *RET* mutants are cross-resistant to pralsetinib. The most substantial resistance is at the C-lobe solvent front *G810* site. Co-crystal structures of RET-selpercatinib and RET-pralsetinib show that *Y806* and *V738* are involved in the binding of these drugs (Figure 2D) and substitution of glycine with an amino acid with a bulky side chain would cause steric clash with these drugs [83].

Substitution of the Gly-810 solvent front residue with Lys, Ser, Cys, or Val was first reported in tissue biopsies and cell-free (cf)DNA from a *KIF5B-RET* fusion-positive and a *CCDC6-RET* fusion-positive NSCLC patients, who acquired resistance to selpercatinib after initially responding to the drug [113]. Three of four recurrent tumors in *CCDC6-RET* PDxS had *G810S* mutation after treatment with a low dose (3 mg/kg, BID) of selpercatinib.

Tissue and plasma biopsies obtained from patients with *RET* fusion-positive NSCLC treated with selpercatinib, pralsetinib, or both [111] revealed that some *CCDC6-RET* fusion-positive NSCLC patients (10%) had acquired *G810C/S* solvent front mutations during selpercatinib treatment, whereas acquired *MET* amplification without identifiable *RET* resistance alterations was observed in three cases (15%). Acquired *KRAS* amplification was also observed, proposing *MET* and *KRAS* amplifications as a more common resistance mechanism in this population. In another report [83], acquired *G810C/S* and *Y806C/N* *RET* mutations were detected in the cfDNA of a patient who had *RET*<sup>M918T+V804M/L</sup> MTC, whose liver metastases progressed following initial response to selpercatinib. In addition, acquired *G810C* mutation was observed in a *CCDC6-RET* fusion-positive NSCLC, who developed acquired resistance to selpercatinib. Tumor biopsy of another patient with *RET*<sup>M918T</sup>-positive metastatic MTC and treated sequentially with vandetanib (2 months), cabozantinib (8 months), selpercatinib (12 months), and pralsetinib (6 weeks) had *RET*<sup>M918T+V804M+G810S</sup> mutations at progression on selpercatinib [114]. *KHDRBS1-NTRK3* fusion (*K8;N14*) as an acquired resistance mechanism to selpercatinib in a *KIF5B-RET* fusion (*K15;R12*) positive lung cancer and acquired tertiary *MET* resistance (*MET* D1228N + *LSM8-MET* fusion) to selpercatinib and *MET* inhibitor capmatinib in *KIF5B-RET*-positive NSCLC with secondary *MET* amplification as initial resistance to selpercatinib have also been recently reported [115,116]

## Concluding remarks

*RET*-altered cancers occur frequently in MTC and PTC in the forms of oncogenic mutations and gene fusions, respectively. Besides PTC, more than 35 different *RET* fusion oncogenes have been observed in diverse cancers, which occur most frequently in lung adenocarcinoma. The high response rates of these *RET*-altered cancers to the highly specific RET TKIs pralsetinib and selpercatinib unequivocally established the oncogenic RET kinase as the therapeutic target in *RET*-altered cancer. However, several critical issues remain to be addressed, including the incomplete response and relative resistance to selpercatinib and pralsetinib in approximately one-third of *RET*-altered cancers, and the emergence of acquired resistance to these RET TKIs by secondary on-target mutations and/or acquisition of alternative driver oncogenes. (see Outstanding questions). A combination treatment of amplified *MET* with crizotinib has illustrated the clinical efficacy of this approach to circumvent co-aberrant oncogenes. The solvent front *G810* mutations is emerging as a predominant on-target resistant mechanism to selpercatinib and pralsetinib. A new generation of RET TKI capable of inhibiting *G810* solvent front mutants among other on-target resistance mechanisms are needed. Several RET TKIs like TPX-0046, BOS172738, and TAS0953/HM06 have started human clinical studies. Early nonclinical studies with BiDAC™ RET inhibitor from C4 therapeutics and second generation RET inhibitors from KinaRx and LOXO Oncology are in progress.

The initial results of the global multicenter registrational ARROW and LIBRETTO-001 trials employing the selective RET therapeutics such as LOXO-292 (selpercatinib) and BLU-667 (pralsetinib) are promising. Both agents have received accelerated approval from the FDA. The Phase III randomized trials versus standard of care have been launched.

Postulating and validating the resistance mechanisms is the subject of ongoing studies and second generation RET inhibitors are in clinical development. Furthermore, the intracranial activity of these RET-specific agents has drawn much attention where steering the CNS metastases in the NSCLC remains an arduous therapeutic challenge. Researchers should remain vigilant upon the resurgence of the resistance mechanisms.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Declaration of interests

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## Glossary

### Acquired resistance:

resistance to therapy that emerges after some length of time after a patient was given a specific therapy. It may include the acquisition of new alterations in the tumor or the expansion of some low level clones that had the plasticity to expand in the face of therapy.

### *De novo* resistance:

intrinsic (pre-existent) primary resistance where no initial response is observed to a drug in treatment-naïve patients.

### Disease control rate (DCR):

the proportion of patients whose tumors have responded to the therapy and achieved complete response, partial response, and stable disease.

### Driver oncogenes:

genes that promote tumorigenesis when altered by mutations or rearrangements.

**Duration of response (DOR):**

the length of time from initial response to subsequent disease progression or relapse or death.

**Fusion genes:**

genes that become hybridized and fused from two previously independent genes either via translocation, deletion, or chromosomal inversion.

**Multiple endocrine neoplasia type 2 (MEN 2) syndrome:**

an inherited cancer syndrome that comprises medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia.

**Next generation sequencing:**

a high-throughput parallel deep sequencing method to identify the nucleotide sequence, targeted regions of a genome, or even a whole genome.

**Objective response rate (ORR):**

the proportion of patients whose tumors have responded to the therapy either by partial or complete response.

**Progression-free survival (PFS):**

the time from randomization of clinical participant to progression of disease or death from any cause.

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### Highlights

Rearranged during transfection (*RET*) is an oncogenic driver activated by either *RET* fusions or mutations. *RET* fusions occur predominantly in 2% of lung cancers and 10–20% of thyroid cancers and in low frequency in an increasing number of diverse cancers.

Various nonselective multikinase inhibitors with ancillary *RET* inhibitory activity have been used in the clinic, despite having modest activity and notable off-target toxicities.

Recently, highly potent and *RET*-specific inhibitors selpercatinib and pralsetinib have been successfully translated to the clinic and are FDA approved.

Data on acquired resistance to *RET*-specific inhibitors are rapidly emerging but not fully understood. However recent studies have suggested on-target mutations at non-gatekeeper sites or emergence of off-target alterations such as *MET* amplification or *NTRK* fusion as mechanisms of acquired resistance.

### Outstanding questions

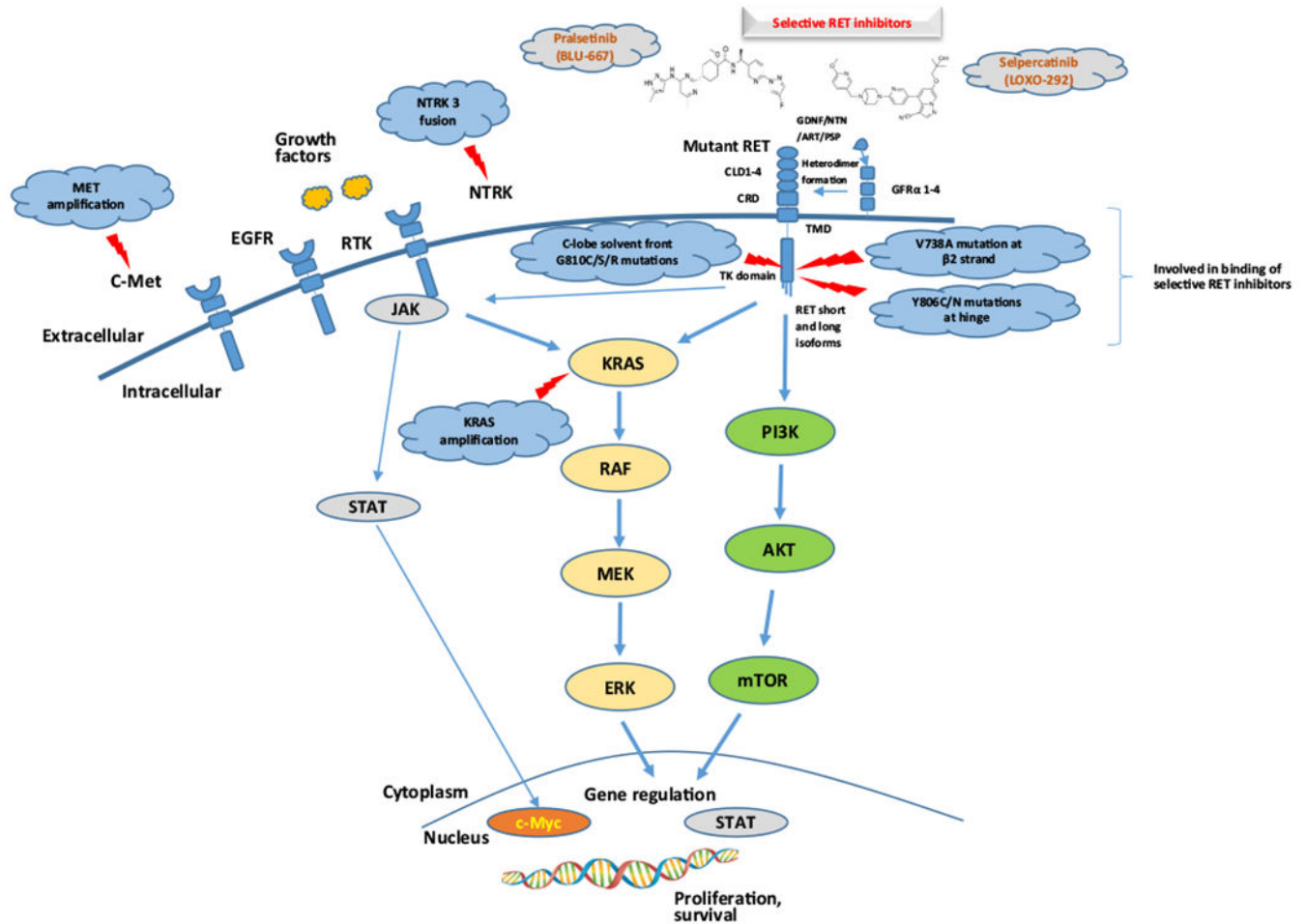
As patients with NSCLC are at high risk of CNS metastases, can we sustain durable CNS activity from selective *RET* inhibitors?

Since *RET* plays a crucial role in the development of the nervous system and kidney, and in spermatogenesis, what would be the clinical implications of long-term *RET* inhibition in very young children?

What will be the impact of selective *RET* inhibitors in other *RET*-altered non-thyroid, non-NSCLC solid tumors and in pediatric population? Although selective *RET* inhibitors render some promising preliminary activity in other solid tumors, would those *RET*-specific inhibitors become the next tumor-agnostic indication? The duration of response and acquired resistance in non-lung and non-thyroid tumors is unknown.

In light of new challenge of resistance caused by mutations at non-gatekeeper sites or co-occurrence of other oncogenic drivers, how can we overcome resistance to those newer *RET*-specific inhibitors? Which combinatorial strategies could be warranted?

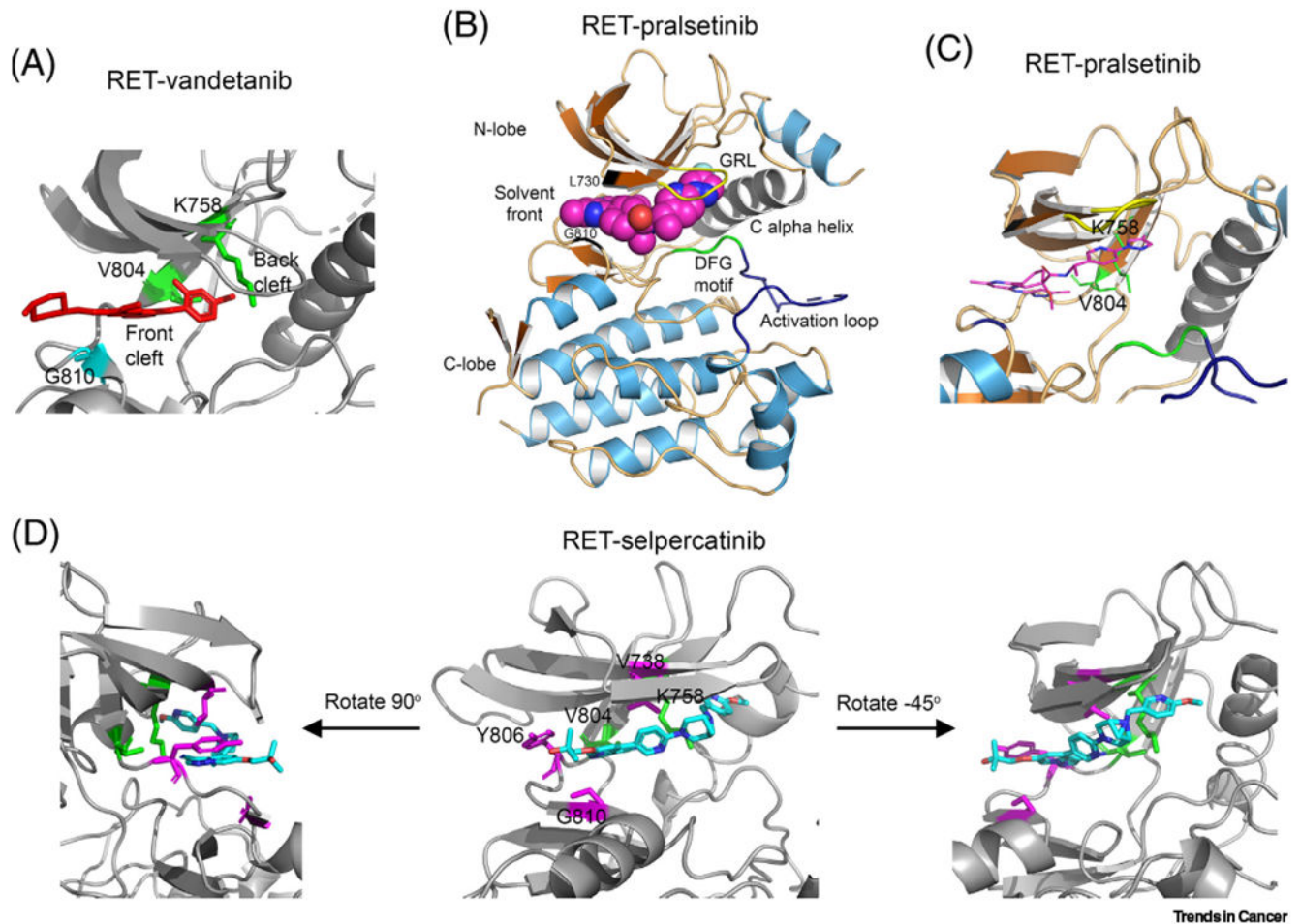
Can we achieve more durable and better response with combinatorial approaches utilizing selective *RET* inhibitors?



Trends In Cancer

**Figure 1. Rearranged during transfection (RET) pathway and acquired resistance mechanisms (red arrow) to selective RET inhibitors in RET-aberrant cancers.**

Abbreviations: AKT, protein kinase B; ART, artemin; c-Met, mesenchymal epithelial transition factor; c-Myc, avian myelocytomatosis virus oncogene cellular homolog; CLD 1–4, cadherin-like domain 1–4; CRD, cysteine-rich domain; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; GDNF, glial derived neurotrophic factor family ligands; GFR $\alpha$  1–4, GDNF family alpha receptors 1–4; JAK, Janus kinase; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; MAPK pathway (RAF/MEK/ERK), mitogen-activated protein kinase pathway; MEK, MAPK/ERK kinase; mTOR, mammalian target of rapamycin; NTN, neurturin; NTRK, neurotrophic tyrosine receptor kinase; PI3K, phosphatidylinositol 3-kinase; PSP, persephin; RAF, rapidly accelerated fibrosarcoma; RTK, receptor tyrosine kinase; STAT, signal transducer and activator of transcription; TK, tyrosine kinase; TM, transmembrane.



**Figure 2. Co-crystal structure of rearranged during transfection (RET)- tyrosine kinase inhibitor (TKI) complex.**

(A) RET-vandetanib complex [Protein Data Bank (PDB): 2IVU] [82]. Red, vandetanib; green, *V804* gatekeeper residue and *K758* gatewall residue; cyan, *G810* solvent front residue. (B,C) Co-crystal structure of RET-pralsetinib complex (PDB: 7JU5) [83]. (D) Co-crystal structure of RET-selpercatinib complex (PDB: 7JU6) [83]. Gatekeeper *V804* and gatewall *K758* are in green. Magentas denotes residues where selpercatinib-resistant mutations have been identified. Abbreviation: GRL, Gly-rich loop.

**Table 1.**

Immune checkpoint inhibitors (ICI) in *RET*-altered cancers<sup>a</sup>

Study	MSKCC retrospective study [63]	MDACC retrospective study [62]	Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic database (CGD) and Guardant Health database (GHD) [64]
Number of patients	74	70	29 in CGD, 40 in GHD
Tumor types	<i>RET</i> -rearranged lung cancers	<i>RET</i> -altered solid tumors; NSCLC ( <i>n</i> = 29), MTC ( <i>n</i> = 32), DTC and other cancers ( <i>n</i> = 9)	<i>RET</i> fusion-positive NSCLC
Smoking history	31% tobacco exposure	29% tobacco exposure	12/29 tobacco exposure
<i>RET</i> fusion partner	<i>KIF5B</i> (58%) <i>CCDC6</i> (16%)	Fusion (49%) - <i>KIF5B</i> (41%) Mutation (51%) - <i>M918T</i> (67%)	<i>KIF5B</i> (74%) <i>CCDC6</i> (14%)
Immune phenotype findings in available population	PD-L1 expression: zero (58%), 1–49% (23%) Tumor mutational burden (TMB) - <i>RET</i> -rearranged (1.75 Mut/Mb) versus <i>RET</i> wild-type (5.27 Mut/Mb) ( <i>P</i> < 0.0001)	PD-L1 expression: weak (<1%) (56%), 1–49% (22%) Tumor mutational burden (TMB) - All 15 patients have TMB low ( 5 Mut/Mb)	PD-L1 expression: <1% (7/13), 1% (6/13), others missing Tumor mutational burden (TMB) - <6 Mut/Mb (11/14) - 6 Mut/Mb (3/14) - Others missing
Response in evaluable patients	Response was not observed ( <i>n</i> = 13) - SD 3/13 (23%), PD 8/13 (62%), mPFS 3.4 months	Time to treatment discontinuation (TTD) - Non-ICI group (18 months) versus ICI group (5.2 months) ( <i>P</i> = 0.00045)	Median real-world PFS of 4.2 months and OS of 19.1 months (CGD)

<sup>a</sup> Abbreviations: DTC, differentiated thyroid cancer; MDACC, MD Anderson Cancer Center; mPFS, median progression-free survival; MSKCC, Memorial Sloan-Kettering Cancer Center; MTC, medullary thyroid cancer; Mut/Mb, mutations per mega base; NA, not available; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; SD, stable disease.

**Table 2.** Safety and efficacy of nonspecific multikinase inhibitors (MKIs) in RET-aberrant malignancies<sup>a</sup>

	<b>Cabozantinib</b>	<b>Vandetanib</b>	<b>Lenvatinib</b>	<b>Others</b>
Efficacy and safety in patients with NSCLC	RET + NSCLC (MSKCC study) ( <i>n</i> = 26) - ORR = 28%, mPFS = 5.5 months, OS = 9.9 months - G3AEs = 69%, - 73% dose-reduced, - 8% discontinued	RET + NSCLC (Japan LURET trial) ( <i>n</i> = 19) - ORR = 47%, mPFS = 4.7 months, mOS = 11.1 months - 53% dose-reduced, - 21% discontinued RET + NSCLC (Korea trial) ( <i>n</i> = 18) - ORR = 18%, - PFS = 4.5 months, - OS = 11.6 months - 27% dose-reduced	RET + NSCLC (Phase II study) ( <i>n</i> = 25) - ORR = 16%, - mPFS = 7.3 months - 64% dose-reduced, 20% discontinued	GLORY RET registry Cabozantinib in RET + NSCLC ( <i>n</i> = 19) - ORR = 37%, - mPFS = 3.6 months, - mOS = 4.9 months Vandetanib in RET + NSCLC ( <i>n</i> = 11) - ORR = 18%, - mPFS = 2.9 months, - mOS = 10.2 months Sunitinib in RET + NSCLC ( <i>n</i> = 9) - ORR = 22%, - mPFS = 2.2 months - mOS = 6.8 months
Efficacy and safety in patients with thyroid cancers	MTC (EXAM trial) - ORR = 32%, - PFS = 14 months, - OS = 44.3 months - G3AEs = 69%, 79% dose-reduced, - 16% discontinued	MTC (ZETA trial) - ORR = 45%, - PFS 30.5 months, - OS NA - G3AEs = 69%, 35% dose-reduced, - 12% discontinued	MTC (Phase II study) ( <i>n</i> = 59) - ORR = 36%, - mPFS = 9.0 months, - mOS = 16.6 months - 59% dose-reduced, 24% discontinued	
FDA approval timeline	Cabozantinib in metastatic MTC (November 2012)	Vandetanib in metastatic MTC (April 2011)	Lenvatinib in progressive, RAI-refractory DTC (February 2015)	Sorafenib in progressive, RAI-refractory DTC (November 2013)

<sup>a</sup> Abbreviations: G3AEs, grade 3 and above adverse events; mOS, median overall survival; mPFS, median progression-free survival; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not available; NSCLC, non-small cell lung cancer; ORR, objective response rate; RAI, radioactive iodine.

**Table 3.**

Published clinical data of specific RET inhibitors in various stages of development<sup>a,b</sup>

	<b>Selpercatinib (LOXO-292)</b>		
Clinical trial	LIBRETTO-001 (NCT03157128)		
Trial setting	Multicenter, multicohort, Phase I/II		
RP2D	160 mg orally twice daily		
Published preliminary efficacy in patients with NSCLC and thyroid cancers	<i>RET</i> + NSCLC [88]	<i>RET</i> + NSCLC [92]	
	1. Previously treated ( <i>n</i> = 105): ORR 64%, CR 2%, mDOR 17.5 months, mPFS 16.5 months, 1-year PFS 66% 2. Treatment naïve ( <i>n</i> = 39): ORR 85%, CR 0%, mDOR NE, mPFS NE, 1-year PFS 75%	1. Previously treated ( <i>n</i> = 87): ORR 61%, CR 6%, mDOR NR, mPFS 17.1 months 2. Treatment naïve ( <i>n</i> = 27): ORR 70%, CR 11%, mDOR 9 months, mPFS 9.1 months	
Activity in <i>RET</i> + tumors beyond NSCLC and thyroid	<i>RET</i> + thyroid cancers [87]	<i>RET</i> + thyroid cancers [93]	
	1. Previously treated <i>RET</i> -mutant MTC ( <i>n</i> = 55): ORR 69%, CR 9%, mDOR NE, mPFS NE, 1-year PFS 82% 2. Treatment naïve <i>RET</i> -mutant MTC ( <i>n</i> = 88): ORR 73%, CR 11%, mDOR 22 months, mPFS 23.6, 1-year PFS 92% 3. Previously treated <i>RET</i> fusion-positive thyroid cancer ( <i>n</i> = 19): ORR 79%, CR 5%, mDOR 18.4, mPFS 20.1, 1-year PFS 64%	1. Previously treated <i>RET</i> -mutant MTC ( <i>n</i> = 55): ORR 60%, CR 2%, mDOR NR, mPFS NR 2. Treatment naïve <i>RET</i> -mutant MTC ( <i>n</i> = 21): ORR 71%, CR 5%, mDOR NR, mPFS NR 3. Previously treated <i>RET</i> fusion-positive thyroid cancer ( <i>n</i> = 9): ORR 89%, CR 0%, mDOR NR, mPFS NR	
CNS activity	AACR 2021 data <a href="https://cancerres.aacrjournals.org/content/81/13_Supplement/CT011">https://cancerres.aacrjournals.org/content/81/13_Supplement/CT011</a>	ASCO 2021 data <a href="https://meeting.library.asco.org/record/197581/abstract">https://meeting.library.asco.org/record/197581/abstract</a>	
FDA approval timeline	May 8, 2020 1. Adult patients with metastatic <i>RET</i> fusion-positive NSCLC; 2. Adult and pediatric patients 12 years of age with advanced or metastatic <i>RET</i> -MTC who require systemic therapy; 3. Adult and pediatric patients 12 years of age with advanced or metastatic <i>RET</i> fusion-positive thyroid cancer who require systemic therapy and who are RAI-refractory	Pre-clinical and clinical data +++ / ++++	Pre-clinical and clinical data +++ / ++++

<sup>a</sup> Clinical trials with TPX-0046 (NCT04161391), BOS 172738 (NCT03780517), and TAS0953/HM06 (NCT04683250) are ongoing. Early nonclinical studies with *BIDAC*<sup>TM</sup> *RET* inhibitors from C4 therapeutics and KimaRx are ongoing.

<sup>b</sup> Abbreviations: BID, twice daily; G3, grade 3; G4, Grade 4; mDOR, median duration of response; mPFS, median progression-free survival; NCT, National Clinical Trial; NE, could not be evaluated; NR, not reached; RP2D, recommended Phase II dose; TRAE, treatment-related adverse events.