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Tumour Review

RET fusions in solid tumors

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ABSTRACT

The *RET* proto-oncogene has been well-studied. *RET* is involved in many different physiological and developmental functions. When altered, *RET* mutations influence disease in a variety of organ systems from Hirschsprung's disease and multiple endocrine neoplasia 2 (MEN2) to papillary thyroid carcinoma (PTC) and non-small cell lung cancer (NSCLC). Changes in *RET* expression have been discovered in 30–70% of invasive breast cancers and 50–60% of pancreatic ductal adenocarcinomas in addition to colorectal adenocarcinoma, melanoma, small cell lung cancer, neuroblastoma, and small intestine neuroendocrine tumors. *RET* mutations have been associated with tumor proliferation, invasion, and migration. *RET* fusions or rearrangements are somatic juxtapositions of 5′ sequences from other genes with 3′ *RET* sequences encoding tyrosine kinase. *RET* rearrangements occur in approximately 2.5–73% of sporadic PTC and 1–3% of NSCLC patients. The most common *RET* fusions are *CDCC6-RET* and *NCOA4-RET* in PTC and *KIF5B-RET* in NSCLC. Tyrosine kinase inhibitors are drugs that target kinases such as *RET* in *RET*-driven (*RET*-mutation or *RET*-fusion-positive) disease. Multikinase inhibitors (MKI) target various kinases and other receptors. Several MKIs are FDA-approved for cancer therapy (sunitinib, sorafenib, vandetanib, cabozantinib, regorafenib, ponatinib, lenvatinib, alectinib) and non-oncologic disease (nintedanib). Selective *RET* inhibitor drugs LOXO-292 (selpercatinib) and BLU-667 (pralsetinib) are also undergoing phase I/II and I clinical trials, respectively, with preliminary results demonstrating partial response and low incidence of serious adverse events. *RET* fusions provide a viable therapeutic target for oncologic treatment, and further study is warranted into the prevalence and pathogenesis of *RET* fusions as well as development of current and new tyrosine kinase inhibitors.

RET Proto-Oncogene pathway

The *RET* (REarranged during Transfection) gene derives its name from its discovery via transfection of NIH/3T3 cells with human lymphoma DNA. *RET* codes for a transmembrane receptor tyrosine kinase (RTK) with proto-oncogene properties [1]. *RET* binds with the ligand-co-receptor complex of glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs) consisting of GDNF, neurturin (NRTN), artemin (ARTN), or persephin (PSPN) and one of four GDNF family receptor-α (GFRα). The *RET*-bound complex is then incorporated into cholesterol-rich transmembrane subdomains known as lipid rafts, where adaptor and signaling proteins bind to *RET* intracellular tyrosine kinase residues that have undergone dimerization and autophosphorylation [2–6] (Fig. 1). These signaling proteins then bind to docking sites, primarily phosphotyrosine 1062 (pY1062) and pY1096, leading to activation of signaling pathways such as RAS/mitogen activated protein kinase (MAPK), RAS/extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K)/AKT, and c-Jun N-terminal kinase (JNK) [7–12]. *RET* signaling is vital for renal morphogenesis, neural and neuroendocrine tissue development, and spermatogonial stem cell maintenance [8,13,14].

RET (REarranged during Transfection) forms a heterodimeric complex with GDNF (glial cell line-derived neurotrophic factor) family ligands GDNF, NRTN (Neurturin), ARTN (Artemin), PSPN (Persephin) and GDNF family co-receptors GFRα1-4. This leads to autophosphorylation of the intracellular tyrosine kinase domain, leading to downstream signaling pathway activation.

Given its prominent involvement in multi-system tissue development, *RET* mutations have similarly been implicated in the progression of several different disorders. Germline nonsense and/or missense

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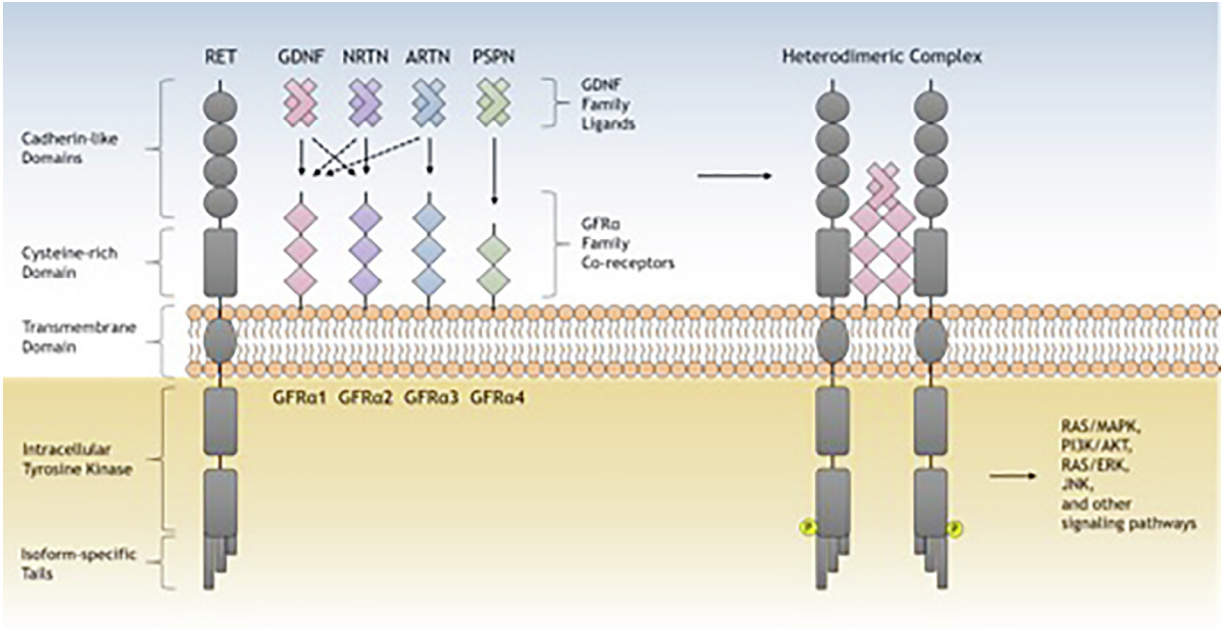

Fig. 1.

mutations decrease the amount of functional *RET* receptors on developing gut tissue, leading to the failure of neuroblast migration and enteric nervous system development seen in Hirschsprung's disease [15–17]. Reduced or loss of function *RET* mutations have also been associated with congenital anomalies of the kidney and urinary tract (CAKUT) and renal agenesis [18]. Aberrant activation of the *RET* receptor through gain of function mutations primarily by single amino acid substitution have been associated with multiple endocrine neoplasia 2 (MEN 2), an autosomal dominant cancer predisposition syndrome consisting of subtypes Familial MTC (FMTC), MEN2A, and MEN2B. MEN2 consists of three primary tumor types: medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia or adenoma [19–22] *RET* germline mutations have also been identified in nonsyndromic pheochromocytomas [23].

RET expression in solid tumors

Variations in *RET* expression have been discovered in several different solid tumor types. *RET* has been found to be expressed in 30–70% of invasive breast cancers, and more frequently expressed in ER+, HER2+, and a subset of ER- breast cancers [24–28]. Both *RET* and *GFRA1* have been found to be upregulated and linked to cellular proliferation, survival, and scattering [25,29,30]. *RET* expression is associated with tamoxifen and aromatase inhibitor resistance in ER+ breast cancers [24,31]. Targeting *RET* with the multikinase inhibitor vandetanib potentiated the effect of tamoxifen (selective estrogen receptor modulator), demonstrating greater reduction in tumor growth compared to single agent therapy in estrogen-receptor alpha (ERα) positive breast cancer cells [31]. *RET* inhibitor NVP-AST487 in combination with aromatase inhibitor letrozole was effective in inhibiting breast cell line motility and growth [32].

Frequent aberrant methylation of *RET* is found in colon adenomas and adenocarcinomas, and is associated with decreased *RET* expression, potentially leading to inhibition of *RET*-induced apoptosis of colon cancer cells [33]. *RET* G533C variant was found to promote increased cellular proliferation and migration in colon cancer. *In vitro* studies demonstrated that vandetanib induced a dose-dependent reduction in *RET* G533C mutant cell number [34].

In pancreatic cancer, *RET* expression was linked to lymphatic invasion, and found to be significantly higher in patients with lymph node metastasis. *RET* was found to be expressed in 50–65% of pancreatic ductal adenocarcinomas [35,36]. *In vitro* studies demonstrated significantly lower neural invasion index and invasion severity score of *RET* knockdown tumors compared with controls, suggesting involvement of *RET* upregulation in pancreatic ductal adenocarcinoma nerve invasion [37].

Positive *RET* expression is associated with low Fuhrman nuclear grade in papillary renal cell carcinoma [38]. Cytoplasmic and nuclear expression of *RET* in renal clear cell carcinoma were demonstrated to be strong negative predictors of survival, with high expression correlating with shorter median progression-free survival (PFS) and overall survival (OS). High *RET* nuclear expression was also found to be an independent predictor of distant and postoperative metastasis in clear cell carcinoma [39]. In prostate cancer, moderately to poorly differentiated tumors (Gleason scores greater than 2) displayed overexpression of *RET*. Cytoplasmic *RET* expression was increased in all variants of prostatic intraepithelial neoplasia [40]. *In vitro* knockdown of *RET* in prostate cancer cell lines reduced cellular proliferation, invasion, and colony formation. *In vivo RET* knockdown was associated with decreased tumor growth. Lenvatinib (multikinase inhibitor including *RET*) also inhibited invasion and soft agar colony formation *in vivo*. Furthermore, *RET* was strongly expressed in small-cell neuroendocrine prostate cancer [41].

The *RET* G691S polymorphism (*RET*p) was present in high frequency in desmoplastic melanoma, and was shown to interact with GDNF to promote proliferation, migration, and invasion [42,43]. Increased RFP-*RET* protein, c-*RET*, *GFRα1,* and *GDNF* levels were noted in malignant murine melanomas compared with benign melanocytic tumors [44]. *RET* was also found to be highly expressed in neuroblastoma and small-cell lung cancer (SCLC). One *RET* mutation was associated with increased *ERK* activation, *MYC* expression, and cellular proliferation in two SCLC cell lines [45]. Tyrosine kinase inhibitors with RET inhibitory activity cabozantinib, regorafenib, sunitinib, and sorafenib inhibited cell growth of GOT1 metastatic small intestinal neuroendocrine tumor cells [46]. No longer isolated to the MEN2 syndrome of malignancies, *RET* is becoming increasingly recognized as an oncogenic contributor to disease and potential therapeutic target.

Detection of *RET* fusions

RET fusions or rearrangements are a type of somatic mutation leading to formation of distinct *RET* oncoproteins. *RET* fusions occur when 5′ sequences from another gene encoding protein dimerization domains juxtapose with *RET* 3′ sequences that encode the intracellular tyrosine kinase domain via chromosomal inversion or translocation [22]. RET somatic mutations have been increasingly identified in multiple tumor types, and are a focus of study in regards to tumorigenesis, progression, prognosis, therapy, and therapeutic response. Fluorescence in situ hybridization (FISH) can be used to detect gene fusions, however is limited in single gene assays and is unable to consistently identify fusion partners. Real-time PCR assays can detect both fusion drivers and partners, but possesses the same limitation in detecting a limited quantity of genes at a time and cannot identify novel fusion partners. Immunohistochemistry (IHC) was found to be limited in detecting *RET* rearrangements due to variable staining patterns and weak reactivity [47,48].

The introduction of high-throughput next generation sequencing (NGS) of whole genomes or transcriptomes offered simultaneous sequencing analyses of multiple genes, resulting in high-sensitivity detection of multiple mutations including gene fusions and variant allele frequencies. Unfortunately, NGS of whole genomes comes at a high per-sample cost. Targeted NGS addresses this issue by sequencing a selected subset of clinically relevant genes. The gene detection sensitivity of targeted sequencing has been found to meet or exceed that of FISH [49–55]. Several different targeted NGS methodologies have been created to assess gene fusions [56–58]. The recent FDA authorizations of NGS panels provides increasing accessibility to engage in individualized, precision oncology practice and research [59]. The use of RNA sequencing can allow a more comprehensive detection of actionable gene rearrangements compared with DNA sequencing only and might be considered as a complementary option in apparently driver-negative cases by DNA sequencing [60]. Some gene fusions in fact arise from rearrangements in very long introns or in introns that harbor repetitive sequence elements also present elsewhere in the genome, making difficult their assessment with DNA sequencing. In addition, RNA sequencing can allow direct evidence that the rearrangement produces a fusion expressed at the mRNA level, overcoming the limits of DNA sequencing when rearrangements appear non-canonical at the genomic DNA level [60].

Liquid biopsy has emerged as a new powerful tool for tumor genotyping to guide the clinical management of advanced solid tumors, including NSCLC [61]. Multiple NGS platforms are now widely available and can allow the identification of less common, but potentially targetable alterations such as activating RET alterations [62]. The identification of gene fusions in plasma is feasible using hybrid capture-based technologies, although differences in hybrid capture techniques and bioinformatic calling may be sources of variations in sensitivity among the different assays available [63].

RET fusions in thyroid cancer

There are at least 13 different *RET* fusions in PTC, the two most prevalent being coiled-coil domain containing 6 (*CCDC6*)-*RET* (also known as *RET/PTC1*) and nuclear receptor co-activator 4 (*NCOA4*)-*RET* (also known as *RET/PTC3*), which account for > 90% of all rearrangements [64–69]. Other *RET* fusions seen in PTC include *RET/PTC2, RET/PTC4* through *RET/PTC9*, *ELKS-RET*, *PCM1-RET*, *RFP-RET*, and *HOOK3-RET* [68], (Fig. 2). Although sparse, *RET* fusions in MTC have been reported in the literature [70,71]. A targeted 244 cancer-related gene and 20 fusion gene paralleled sequencing assay detected *RET* fusions in 4.35% of papillary thyroid carcinoma (PTC) samples [72]. Integrated multiplatform analyses performed through The Cancer Genome Atlas (TCGA) network yielded *RET* fusions in 6.8% of PTC samples [73]. Other studies have shown somatic *RET* locus rearrangements at chromosome 10q11.2 presenting in 2.5–73% of sporadic PTC and 22–87% of post-Chernobyl PTC, occurring more frequently in childhood than adulthood thyroid cancer.

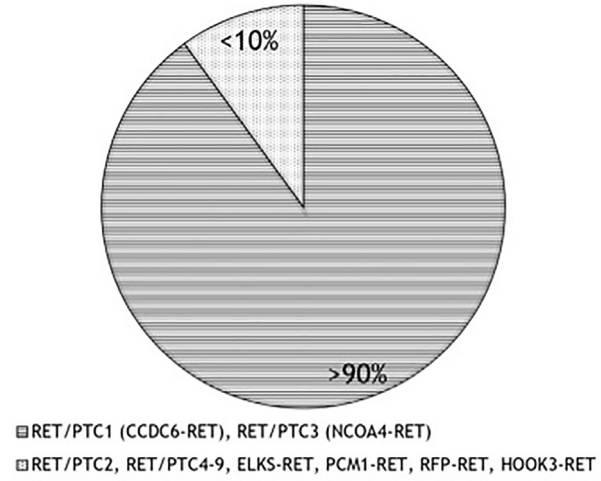

Fig. 2.

RET fusions are more prevalent in radiation-exposed populations. *RET* rearrangements were present in 84% of PTC and 45% of follicular adenomas from patients exposed to external thyroid radiation, with *RET/PTC1* being most common followed by *RET/PTC3* [74]. *RET/PTC* rearrangement was found in 22% of PTC patients exposed to radiation from the Hiroshima or Nagasaki atomic bombings. *RET* fusions occurred in higher frequency of 50% in patients with high dose (> 0.5 Gy) exposure, and novel rearrangements have been found in this group [75,76]. *RET* fusion mutations were detected in 35–69% of Ukranian patients with PTC living in Chernobyl-contamined areas at the time of the accident [77,78]. One Chernobyl patient with spontaneous medullary thyroid carcinoma (MTC) was found to have *RET* rearrangement of p.Met918Thr alteration, suggesting that radiation exposure is not associated with *RET* fusions in MTC compared to PTC [79].

There are conflicting reports regarding the clinical significance of *RET* rearrangements in PTC. *RET/PTC* fusions have been associated with advanced stage disease, more aggressive phenotype, and extra-thyroid extension at diagnosis [80–84]. In contrast, another study found no significant correlation of *RET/PTC* with clinical aggressiveness [85]. *RET/PTC1* was shown to be associated with a more benign clinical course while *RET/PTC3* was associated with more aggressive tumor behavior [67]. Multiple genetico-clinical analyses performed on PTC samples have demonstrated no association between *RET/PTC* expression and clinico-pathological and prognostic features such as age, sex, thyroid function, lifestyle, tumor size, pT, pN, number of tumor foci, histological subtype, high grade cancers, solid follicular or classic papillary variants [64,86–93]. The important prognostic significance of RET rearrangements remains unclear and represents an unmet area of medical study.

RET fusions in lung cancer

RET mutations, albeit rare, but not *RET* fusions have been found in neuroendocrine small cell lung cancers (SCLC) [94]. Chimeric *RET* rearrangements have been identified in 1–3% of non-small cell lung cancers (NSCLC) in various ethnic populations, and were found to have significantly higher frequencies in younger (< 60 years of age), female, non-smoking, and patients with lung adenocarcinoma histology (LADC) [95–101]. *RET* fusions in LADC were also associated with poor differentiation, solid subtype, smaller T stage (≤3 cm) with N2 disease [102]. The most common *RET* fusions in lung cancer are kinesin family

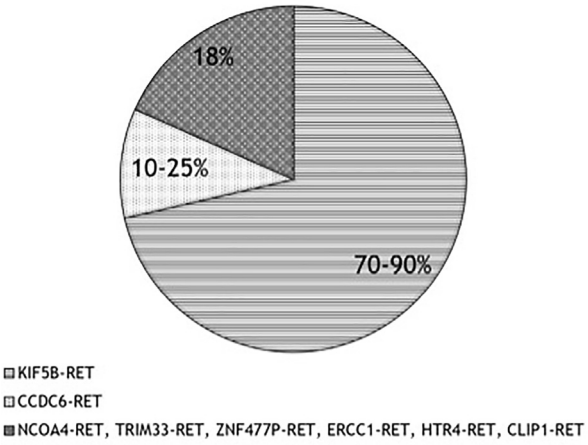

Fig. 3.

member 5B (*KIF5B*)-*RET* (70–90%) and *CCDC6-RET* (10–25%), followed by *NCOA4-RET*, *TRIM33-RET*, *ZNF477P-RET*, *ERCC1-RET, HTR4-RET*, *CLIP1-RET* (18%) [23,103–105] (Fig. 3).

The *RET* tyrosine kinase is preserved across all fusions despite the breakpoint, promoting ligand-independent dimerization, phosphorylation, and constitutive *RET* activation with resultant intact downstream intracellular kinase activity. Exogenous *KIF5B-RET* expression was found to confer interleukin-3 (IL-3) independent growth in Ba/F3 cells and induce morphological transformation and anchorage-independent growth in NIH/3T3 fibroblasts. The coiled-coil domain of *KIF5B* induces homodimerization and activates the *RET* tyrosine kinase domain by autophosphorylation. Drosophila models demonstrated *CCDC6-RET* and *NCOA4-RET*-directed cellular migration, delamination, and epithelial-mesenchymal transition ultimately leading to death when broadly expressed [106]. LADCs positive for *KIF5B-RET* were shown to possess two to thirty-fold higher *RET* expression compared with benign lung tissue, suggesting *RET*-driven carcinogenesis [95,97,98,103,107,108].

Clinically, both *KIF5b-RET* and *CCDC6-RET* rearrangements have been found to co-exist with activated epidermal growth factor receptor (*EGFR*) mutations in *EGFR*-mutated NSCLC patients who had progressed on first or second generation *EGFR* TKI (tyrosine kinase inhibitors) [109]. EGF (epidermal growth factor) decreased the sensitivity of *CCDC6-RET*-positive LADC cells, and transduced bypass signaling through extracellular signal-regulated kinases (*ERK*) and protein kinase B (*AKT*) leading to development of resistance to tyrosine kinase inhibitors sunitinib, lenvatinib, vandetanib, and sorafenib [110]. *CCDC6-RET* fusion expression was associated with conferring *EGFR* TKI resistance in *EGFR*-mutant NSCLC cell lines via continuing cellular proliferation as well as *RET* phosphorylation in *CCDC6-RET* cell lines when treated with osimertinib or afatinib [111]. Some retrospective studies have evaluated the activity of conventional approved therapies in these patients. RET rearranged NSCLCs show durable benefits with pemetrexed-based therapies, similarly to other rearranged lung cancers (ALK and ROS1) [112]. Furthermore, RET translocated NSCLCs have an immunophenotype “cold” that is associated with low response to immune checkpoint inhibition (PD-1/PD-L1 +/− CTLA-4 inhibitors), due to low PD-L1 expression and low tumor mutation burden (TMB), consistent with other oncogene-addicted NSCLCs [113].

RET fusions in other solid tumors

RET fusions are not as extensively studies in solid tumors aside from thyroid and lung cancer. One review notes *RET* fusion expression in small cohorts of lung carcinosarcoma (16.7%), ovarian epithelial carcinoma (1.9%), salivary gland adenocarcinoma (3.2%), pancreatic ductal carcinoma (0.6%), and carcinoma of unknown primary (0.7%) [101]. *RET/PTC3* has been detected in human malignant pleural mesothelioma cell line EHMES-10 [114]. *RET* rearrangements *CCDC6-RET, NCOA4-RET,* and *KIF5B-RET* were discovered in 0.2–1.6% of colorectal carcinomas [115,116], defying a new subgroup of patients (RAS/BRAF wild type, right-sided, MSI-high) at poor prognosis with conventional therapeutic strategies [117]. *RET* rearrangements including *CCDC6-RET, NCOA4-RET,* and *RASGEF1A-RET* were detected in 0.16% of breast cancers. Similar to PTC and NSCLC studies, the *NCOA4-RET* fusion detected in this study encoded the characteristic coiled-coil domain and *RET* exons encoding the kinase domain. Expression of *NCOA4-RET* and *RASGEF1A-RET* along with *RET* amplification in NIH/3T3 fibroblasts and MCF10A mammary cells resulted in increased growth capacity and clonogenic expansion, demonstrating constitutive kinase activation. NIH/3T3 cells transduced with *NCOA4-RET* formed tumors within 2 weeks [118].

RET tyrosine kinase inhibitors

Studies involving *RET*-targeted therapy primarily involve thyroid cancer and NSCLC. Pyrazolopyrimidine, a *RET* kinase inhibitor with sedative, anxiolytic, and pesticidal properties, was shown to inhibit *RET/PTC1* at IC(50) in the nanomolar range, preventing growth in *RET/PTC1*-fusion-positive NIH/3T3 fibroblasts and two human PTC cell lines harboring *RET/PTC1* [119]. AUY922 is a heat shock protein 90 (HSP90) inhibitor that was found to inhibit downstream *RET* signaling targets in *RET/PTC1* cell lines [120]. Several multikinase inhibitors (MKI) are FDA-approved for cancer therapy (sunitinib, sorafenib, vandetanib, cabozantinib, regorafenib, ponatinib, lenvatinib, alectinib) and non-oncologic diseases (nintedanib), and are being evaluated in clinical trials for a variety tumor types. Several drugs are undergoing clinical trials in *RET*-fusion-positive malignancies (Table 1). Importantly, a phase I/Ib trial is currently underway for RXDX-105, a *VEGFR*-sparing *RET* and *BRAF* inhibitor [121]. Selective *RET* inhibitor drugs LOXO-292 (selpercatinib) and BLU-667 (pralsetinib) are also in phase I/II and I clinical trials, respectively [122,123].

Table 1
Studies on Therapies directed towards *RET*-rearranged Cancers.

Drug	Cancer	Study Type
Alectinib	NSCLC, Thyroid Cancer	Phase I/II (NCT03131206)
Alectinib	NSCLC	Phase II (NCT03445000)
Alectinib	NSCLC	Phase II (NCT02314481)
Apatinib	NSCLC	Phase II (NCT02540824)
AUY922	NSCLC	Phase II (NCT01922583)
BLU-667	NSCLC, MTC, PTC, Colon Cancer, and other Solid Tumors	Phase I (NCT03037385)
BOS172738	NSCLC	Phase I (NCT03780517)
Cabozantinib	NSCLC	Phase II (NCT01639508)
Cabozantinib	NSCLC	Phase II (NCT03468985)
Dasatinib	Salivary Gland Cancer	Phase II (NCT00859937)
Dovitinib	Solid and Hematological Malignancies	Phase II (NCT01831726)
Lenvatinib	LADC	Phase II (NCT01877083)
LOXO-292	NSCLC, MTC, PTC, Colon Cancer, other Solid Tumors	Phase I/II (NCT03157128)
Ponatinib	NSCLC	Phase II (NCT01813734)
Regorafenib	Melanoma	Phase II (NCT02587650)
RXDX-105	NSCLC	Expanded Access (NCT03784378)
Sunitinib	Solid Tumors	Pilot Study (NCT02450123)
Sunitinib	Solid Tumors	Pilot Study (NCT02691793)
Sunitinib	MTC, PTC, FTC, Hurthle Cell Carcinoma	Phase II (NCT00381641)
Vandetanib	NSCLC	Phase II (NCT01823068)

RET, rearranged during transfection, LADC, lung adenocarcinoma, NSCLC, non-small cell lung cancer, MTC, medullary thyroid carcinoma, PTC, papillary thyroid carcinoma, FTC, follicular thyroid carcinoma.

There are several preclinical studies on multikinase inhibitors in *RET*-fusion-positive cell lines. Ba/F3 cells harboring the *KIF5B-RET* fusions common in *RET*-fusion-positive NSCLC were found to be sensitive to sorafenib [124]. LADC cell line LC-2/ad harboring *RET*-fusions were sensitive to vandetanib, regorafenib, ponatinib and lenvatinib treatment [115,125,126]. *CCDC6-RET*-expressing cell lines were sensitive to combined therapy of BLU-667 (selective *RET* inhibitor) or cabozantinib (multikinase inhibitor with *RET* activity) and either afatinib or osimertinib (EGFR inhibitors), suggesting that acquired *EGFR* TKI resistance from *CCDC6-RET* fusion can be overcome with dual *EGFR* and *RET* inhibition [111]. Cabozantinib and vandetanib inhibited the colony-forming abilities of *RET* fusion cell lines and lead to colony reduction, causing rapid tumor regression in mouse models with *NCOA4-RET* xenografts [118]. Vandetanib was shown to potently inhibit AKT and ERK phosphorylation in metastatic colon cancer patient-derived cells expressing *NCOA4-RET* fusion [116]. Lenvatinib inhibited autophosphorylation of *KIF5B-RET, CCDC6-RET,* and *NCOA4-RET*, suppressed *CCDC6-RET*-positive human lung and thyroid cancer cell lines, and suppressed tumorigenicity and anchorage-independent growth of *RET*-fusion harboring NIH/3T3 cells [127]. Sunitinib suppressed *RET/PTC*-fusion-positive PTC cell growth *in vitro* and *in vivo* via inhibition of *MEK/ERK* pathway and G1 arrest [128]. Alectinib demonstrated antitumor activity *in vivo* of *RET*-fusion-positive mouse models [129]. RXDX-105 inhibited *in vitro* cell lines harboring *CCDC6-RET, NCOA4-RET* and *PRKAR1A-RET,* and also inhibited the *in vivo* tumor growth of patient-derived xenografts harboring *CCDC6-RET, NCOA4-RET* and *KIF5B-RET* [130].

Ongoing clinical trials elaborate on *RET*-directed therapy efficacy and safety. A prospective phase II trial of 25 *RET*-rearranged NSCLC patients treated with cabozantinib yielded overall response rate (ORR) of 28%, median progression-free survival (mPFS) of 5.5 months and median overall survival (mOS) of 9.9 months [131]. A phase II trial of 25 *RET*-rearranged NSCLC patients treated with levantinib resulted in ORR of 16%, mPFS of 7.3 months and non-evaluable mOS [132]. A phase II trial of 17 *RET*-fusion-positive NSCLC patients treated with vandetanib showed ORR of 18%, mPFS of 4.5 months, and mOS of 11.6 months [133]. A phase II trial of 19 *RET*-fusion-positive, *EGFR*-negative NSCLC patients treated with vandetanib resulted in ORR of 47%, mPFS of 6.5 months, and mOS of 13.5 months [134,135]. Of note, the ORR was lower in *KIF5B-RET* rearranged patients in the two aforementioned trials compared to other *RET* fusions, and no objective response was observed in *KIF5B-RET* patients in another trial. Taken together, these four clinical trials [Table 2] show an average ORR of 24,25%, average mPFS of 5.96 months, and average mOS of 11.7 months. Similar trials are currently underway, such as a phase I/II clinical trial of alectinib treatment in *RET*-rearranged NSCLC in Japan [136].

RET-specific inhibitors

Multikinase inhibitors target several other receptors, and thus are associated with a variety of treatment-emergent adverse events (TEAE) [121]. Resistance to MKIs has been found through development of gatekeeper position mutations that sterically hinder inhibitor binding. It is hypothesized that *RET*-specific antagonists may produce improved clinical outcomes with potentially less adverse events compared to MKIs [139]. Experimental selective *RET* inhibitors LOXO-292 (LIBRETTO-001 Clinical Trial, Phase I/II, NCT03157128) and BLU-667 (ARROW Clinical Trial, Phase I, NCT03037385) seek to address this issue (Table 3). BLU-667 and LOXO-292 have recently received FDA breakthrough therapy designation for *RET*-fusion-positive NSCLC after progressing to platinum-based chemotherapy, *RET*-mutant MTC, and *RET*-fusion-positive thyroid cancer in patients who require systemic therapy, progressed on prior treatment, or have no other acceptable alternative treatment options [122,123]. Early results show that these two selective *RET* antagonists are well-tolerated (Table 4). The *RET* inhibitor BOS172738 is currently undergoing Phase I clinical trial (NCT03780517) with *RET* fusion-positive NSCLC, *RET* mutant MTC, and *RET* gene-altered NSCLC/MTC with prior specific *RET* gene-targeted therapy. GSK3352589 and GSK3179106 are *RET*-specific inhibitors with recently completed Phase I clinical trials designed for irritable bowel syndrome with potential applications for MEN2 and other *RET*-positive malignancies [140,141].

LOXO-292 was found to be 60 to 1300-fold more effective in inhibiting *KIF5B-RET* in engineered cells compared to other targets inhibited by MKIs. LOXO-292 caused significant tumor regression in *RET*-fusion-positive mouse models compared to cabozantinib which only caused mild regression. Additionally, intrathecal LOXO-292 caused significantly prolonged survival in intracranial *CCDC6-RET*-fusion-positive mouse models compared to ponatinib. One patient with metastatic *RET*-fusion-positive MTC treated with LOXO-292 experienced dramatic decreases in serum carcinoembryonic antigen (CEA) and calcitonin levels, symptom resolution, and RECIST tumor response of 54% after 6.9 months of treatment. Another patient with metastatic *RET*-fusion-positive NSCLC treated with LOXO-292 had symptom resolution, RECIST tumor response of 57%, and RANO-BM brain metastases shrinkage or resolution of 89% after 2 months of treatment. LOXO-292 was well-tolerated in both patients and was associated with Grade 1 TEAEs such as fatigue, dyspnea, joint pain, insomnia, and aspartate aminotransferase elevation [137]. Preliminary results from the LIBRETTO-001 trial of *RET*-fusion-positive NSCLC patients treated with LOXO-292 (selpercatinib) were recently presented at the 2019 Internal Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer and the 2019 European Society for Medical Oncology (ESMO) Annual Meeting. Selpercatinib was associated with an impressive activity in RET fusion-positive NSCLCs, reporting an ORR of 68% in the primary analysis set (PAS), including 105 patients who had received previous platinum-based chemotherapy, and 85% in treatment-naïve patients (n = 39). Responses were durable (median duration of response of 20.3 months in the PAS and not reached in treatment-naïve patients) with a median PFS of 18.4 months (95% CI, 12.9–24.9) and not reached (95% CI, 9.2-NE) for the PAS and treatment-naïve population, respectively [122]. LOXO-292 was overall well-tolerated with mostly Grade 1–2 TEAEs, with only a 1.7% discontinuation rate [122]. Similar activity was also reported in the *RET*-mutant MTC and *RET* fusion-positive thyroid cancer cohorts, with an ORR of 56–59% in *RET*-mutant MTC pretreated with cabozantinib/vandetanib and treatment-naïve, respectively, and 62% in *RET* fusion-positive thyroid cancer [145]. LOXO-292 showed activity also against RET gatekeeper mutations, such as RET V804M and RET V804L, which are responsible of acquired resistance to MKI [122,145]. Based on these impressive results, a new drug application has been submitted to the FDA and two randomized phase III trials versus platinum-pemetrexed ± pembrolizumab in the upfront setting in *RET* fusion-positive NSCLC and versus cabozantinib/vandetanib in TKI-naïve *RET*-mutant MTC have been planned.

BLU-667 was found to be 8 to 28-fold more potent against wild-type *RET* compared with vandetanib, cabozantinib, and RXDX-105, and also displayed greater potency against *RET* V804L/M, *RET* M918T, and *CCDC6-RET* compared with MKIs. BLU-667 also possessed potency against RET^{V804L}, RET^{V804M}, and RET^{V804E}, gatekeeper mutations that can confer MKI resistance, suppressing proliferation *in vitro*. BLU-667 was found to be at least 100-fold more selective for *RET* over 96% of tested MKIs, and demonstrated at least 10 times more potency than vandetanib, cabozantinib, and RXDX-105 in inhibiting *RET* autophosphorylation in Ba/F3 cells harboring *KIF5B-RET* fusion. BLU-667 retained this antitumor activity and *RET* selectivity *in vivo*. Two patients with MTC treated with BLU-667 showed over 90% reduction in serum calcitonin, and 57–75% decrease in CEA with 19% reduction in target lesion size after 8 weeks, a confirmed partial response of 47% maximal reduction at 10 months in one patient and 35% radiographic response by RECIST after 8 weeks in another. Two patients with NSCLC treated

Table 2
Activity of RET inhibitors in RET fusion positive NSCLCs in phase I/II studies.

Study	n	Drug	RET detection method (s)	RET Fusion partners	ORR	PFS	OS
Drilon, 2016 [131]	26	Cabozantinib	FISH, hybrid-capture NGS	KIF5B-RET 62% CCDC6-RET 4% Unknown 23%	28% (95% CI 12–49).	5.5 months (95% CI 3.8–8.4).	9.9 months (95% CI 8.1–NR)
Yoh, 2017 & 2018 [134,135]	19	Vandetanib	RT-PCR and FISH	KIF5B-RET 53% CCDC6-RET 31% Unknown 16%	47% (95% CI 24–71)	6.5 months (95% CI 2.8–8.5)	13.5 months (95% CI 9.8–28.1)
Lee, 2017 [133]	18	Vandetanib	FISH (10/18 confirmed with other methods)	KIF5B-RET 28% CCDC6-RET 11% Unknown 55%	18%	4.54 months	11.63 months
Velcheti, 2016 [132]	25*	Lenvatinib	Not reported	KIF5B-RET 52% Others 48%	16%	7.3 (95% CI 3.6–10.2)	NR (5.8–NR)
Oxnard, 2018 [122]	38**	LOXO-292	Not reported	KIF5B-RET 60.5% CCDC6-RET 26.3% Unknown 7.9%	68% (95% CI 51–83)	Not reported	Not reported
Subbiah, 2018 [137]	19	BLU-667	Not reported	Not reported	50%	Not reported	Not reported
Drilon, 2017 [138]	40*** (22 treatment-naïve, evaluable)	RXDX-105	Not reported	KIF5B-RET 50% CCDC6-RET 15% Unknown 5%	27% (treatment-naïve) 75% (non-KIF5B fusions)	Not reported	Not reported

Legend. RN, not reached; FISH, fluorescent in situ hybridization; NGS, next generation sequencing; RT-PCR, real-time polymerase chain reaction; IHC, immunohistochemistry.

* 28% had previously received a RET-targeted therapy.

** 55% had previously received ≥ 1 multi-target inhibitors.

*** 22.5% had previously received a RET-targeted therapy.

with BLU-667 developed 25–34% tumor reduction followed by partial response. All four patients tolerated the treatment well with Grade 1 TEAEs of nausea, constipation, dry skin, rash, leukopenia, and hyperphosphatemia [137]. Two patients in a separate study with *EGFR*-mutant NSCLC and acquired *CCDC6-RET* fusion developed RECIST tumor shrinkage of 78% after concurrent osimertinib and BLU-667 treatment [111]. Preliminary results from the ARROW trial of BLU-667 treatment of *RET*-driven (*RET* mutation or *RET* fusion) cancers were presented at the 2018 American Association for Cancer Research (AACR) Annual Meeting (Abstract CT043) and at the 2019 ASCO annual meeting. Over 90% of PTC and MTC patients with measurable target lesions achieved radiographic tumor reduction. The preliminary ORR 60% (DCR 100%) in *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy, 63% (94% DCR) in *RET*-mutated MTC pretreated with cabozantinib or vandetanib, and 83% in *RET* fusion-positive papillary thyroid cancer. The majority of TEAEs were Grade 1–2 and Grade 3 TEAEs of anemia, hypertension, diarrhea, leukopenia, neutropenia, and increased alanine aminotransferase [123,142,143].

Preliminary data were also reported with the selective RET inhibitor RXDX-105. Based on analysis of safety, efficacy and pharmacokinetics across multiple doses in a phase 1/1b study, 275 mg fed, administered orally once daily, was selected as the RP2D. An expansion cohort of the phase 1b portion of the study enrolled 47 RET fusion positive patients, including 40 NSCLCs. In treatment-naïve patients (22 patients evaluable), receiving RXDX-105 at 275 mg or 350 mg/daily, an ORR of 27% was reported, with a differential activity between KIF5B-RET fusions (ORR 0%, albeit 21.4% experienced a SD lasting ≥ 6 months) and non-KIF5B-RET fusions (ORR 75%) [138] (Table 2), further confirming the lower sensitivity of KIF5B-RET fusions to RET-targeted inhibition. RXDX-105 demonstrated a manageable safety profile, with the majority of TEAEs of grade ≤2 and the most frequent AEs of grade ≥3 were rash (10%), hypophosphatemia (7%), increase of ALT/AST (7% and 4%, respectively), and diarrhea (4%) [138].

Discussion

From its discovery of *RET* rearrangement over two decades ago to the development of selective *RET* inhibitors, the *RET* gene has undergone extensive study in the field of oncology [1,22]. No longer known solely as the source of germline mutations involved in Hirschsprung's disease and MEN2, *RET* has become increasingly recognized as a key driver of tumorigenesis and prognostic indicator or treatment response. *RET* mutations and *RET* fusions occur in an abundance of tumor types from papillary thyroid carcinoma to non-small cell lung cancer. *RET* fusions such as *KIF5B-RET, CDCC6-RET,* and *NCOA4-RET* are now being studied in the laboratory and clinical trials in a variety of different

Table 3
Selective *RET* Inhibitors.

Drug	Clinical Trial	FDA-Approved Indications
LOXO-292	Phase I/II (NCT03157128)	Breakthrough therapy designation for *RET*-fusion-positive NSCLC, *RET*-mutant MTC, *RET*-fusion-positive thyroid cancer requiring systemic therapy, progressed on prior treatment, or without acceptable alternative treatment options
BLU-667	Phase I (NCT03037385)	N/A
BOS172738	Phase I (NCT03780517)	N/A
GSK3352589	Phase I (NCT03154086)	N/A
GSK3179106	Phase I (NCT02798991, NCT02727283)	N/A

RET, rearranged during transfection, NSCLC, non-small cell lung cancer, MTC, medullary thyroid carcinoma.

Table 4
Treatment-Emergent Adverse Events of Selective and non-selective *RET* Inhibitors.

Drug	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Ref.
LOXO-292 (selpercatinib)	Diarrhea (21%), Fatigue (15%), Dry Mouth (29%), Constipation (19%), Headache (15%), Nausea (15%), Hypertension (4%), Increased AST (17%), Increased ALT (13%), Peripheral edema (16%), Increased creatinine (14%)	Diarrhea (8%), Fatigue (9%), Constipation (3%), Headache (4%), Nausea (4%), Dry mouth (4%), Hypertension (11%), Increased AST (5%), Increased ALT (4%), Peripheral edema (4%), Increased creatinine (4%)	Diarrhea (2%), Fatigue (1%), Constipation (< 1%), Headache (1%), Nausea (< 1%), Hypertension (14%), Increased AST (6%), Increased ALT (7%), Peripheral edema (< 1%)	Hypertension (< 1%), Increased AST (1%), Increased ALT (1%), Increased creatinine (< 1%)	None	[122,145]
BLU-667 (pralsetinib)	Decreased WBC (10%), Neutropenia (7%), Anemia (12%), Increased blood Creatinine (28%), Increased ALT (23%), Increased AST (29%), Hypertension (7%), Constipation (32%), Diarrhea (16%), Fatigue (13%), Headache (13%)	Decreased WBC (15%), Neutropenia (7%), Anemia (10%), Increased blood Creatinine (1%), Increased AST (4%), Hypertension (7%), Constipation (3%), Diarrhea (4%), Fatigue (4%), Headache (3%)	Decreased WBC (4%), Neutropenia (9%), Anemia (9%), Increased ALT (1%), Hypertension (16%), Diarrhea (7%), Fatigue (1%), Headache (1%)	Neutropenia (4%)	None	[143]
Vandetanib	Diarrhea (26–33%), Rash acneiform (16–39%), Dry skin (21–22%), Prolonged QT corrected interval (0–11%), Anorexia (5–21%), Increased creatinine (21%), Vomiting (5–21%), Paronychia (16–17%), Oral mucositis (21%), Nausea (5–11%), Liver dysfunction (16%), Hypoalbuminemia (5%), Photosensitivity (11%), Pruritus (16%)	Hypertension (26–39%), Diarrhea (5–42%), Rash acneiform (11–32%), Dry skin (0–16%), Prolonged QT corrected interval (21%), Anorexia (5%), Increased creatinine (11%), Vomiting (5%), Paronychia (11%), Proteinuria (21%), Nausea (0–5%), Liver dysfunction (5%), Hypoalbuminemia (16%), Photosensitivity (5%)	Hypertension (17–58%), Diarrhea (0–11%), Rash acneiform (0–16%), Dry skin (0–5%), Prolonged QT corrected interval (5–11%), Anorexia (0–5%), Proteinuria (5%), Nausea (0–5%), Photosensitivity (5%)	Prolonged QT corrected interval (5%),	None	[133,134]
Cabozantinib	ALT increased (81%), AST increased (62%), Hypothyroidism (15%), Diarrhea (46%), Palmar-plantar erythrodysaesthesia (35%), Thrombocytopenia (31%), Fatigue (15%), Oral mucositis (42%), Lipase increased (12%), Nausea (19%), Dysgeusia (23%), Amylase increased (19%), Anorexia (4%), Dry skin (19%)	ALT increased (8%), AST increased (4%), Hypothyroidism (54%), Diarrhea (15%), Palmar-plantar erythrodysaesthesia (23%), Skin hypopigmentation (50%), Thrombocytopenia (12%), Fatigue (27%), Lipase increased (8%), Nausea (12%), Dysgeusia (8%), Amylase increased (8%), Anorexia (15%), Hypertension (15%)	ALT increased (8%), AST increased (8%), Palmar-plantar erythrodysaesthesia (4%), Thrombocytopenia (8%), Fatigue (4%), Oral mucositis (4%), Lipase increased (15%), Hypertension (4%)		None	[131]
Lenvatinib	Hypertension (12%), Nausea (48%), Anorexia (52%), Diarrhea (44%), Proteinuria (32%), Vomiting (36%), Headache (40%), Fatigue (28%), Thrombocytopenia (24%), ALT increased (20%), AST increased (24%), Constipation (24%), Cough (24%), Peripheral edema (20%), Hyponatremia (4%)		Hypertension (56%), Nausea (12%), Diarrhea (8%), Proteinuria (16%), Vomiting (8%), Fatigue (8%), Thrombocytopenia (4%), Hyponatremia (12%)	Hyponatremia (8%)	None	[132]

Treatment-Emergent Adverse Events were assessed via CTCAE, Common Terminology Criteria for Adverse Events. Grade 1, mild, Grade 2, moderate, Grade 3, severe, Grade 4, life-threatening, Grade 5, death, ALT, alanine aminotransferase, AST, aspartate aminotransferase, WBC, white blood cell.

cancers as potential therapeutic targets. Early clinical trial results in NSCLC show encouraging results in treating *RET*-fusion-positive malignancy with MKIs [131–135]. The majority of TKIs are already FDA-approved for a diverse array of cancers such as GIST, CRC, RCC, HCC, pNET, DTC, MTC, NSCLC, CML and ALL and are well-tolerated, while others such as apatinib and LOXO-292 have received orphan drug and breakthrough therapy designations, respectively by the FDA. Selective TKIs LOXO-292 and BLU-667 have been shown to be efficacious and well tolerated due to their selectivity compared to MKIs in preliminary Phase I clinical trial data and early studies [111,122,123,137,142]. Moreover, the excellent intracranial activity of LOXO-292 and BLU-667 seen in these preliminary clinical trials provides a further advantage compared with MKIs that were associated with low CNS activity in RET fusion positive NSCLCs, but are associated with a high cumulative incidence of brain metastases during the course of their disease (46% lifetime prevalence in stage IV disease) [121]. The widespread use and accessibility of NGS allow for increasingly targeted therapies tailored to each individual patient, holding promise for the field of precision oncology [59].

There are vast opportunities for further research into *RET* fusions from bench to bedside. Novel *RET* rearrangements continue to be discovered in solid tumors. More studies are necessary into the pathogenesis of *RET* fusions and clinic-pathological correlations. One experiment induced the *KIF5B-RET* fusion in 201T human lung cells using 1 Gy of γ radiation [144]. Further study is warranted to investigate the relationship between *RET* fusions and radiation exposure, especially with the frequent use of gamma radiation via computed tomography and nuclear imaging in modern medicine [144]. Multikinase inhibitors have been FDA-approved for over a decade, yet much more work remains to be done in terms of efficacy and safety in current Phase IV trials as well as breaking new ground in TKI therapy of *RET* fusions in rarely studied and unstudied tumors such as pancreatic cancer, melanomatous and non-melanomatous skin cancers, head and neck malignancies, soft tissue tumors, and bone malignancies. More research into selective *RET* inhibitors LOXO-292 and BLU-667 will be conducted, eventually progressing to Phase II-IV clinical trials and potential FDA approval. Studies into *RET* fusions at every level from risk factors and genetic understanding to clinical presentation and therapeutic response have great potential to impact patients across all spectrum of cancers.

Declaration of Competing Interest

Dr. Rolfo reports personal fees from Novartis, personal fees from MSD, non-financial support from OncoDNA, personal fees and non-financial support from GuardantHealth, institutional grant from Biomark inc., outside the submitted work. All other authors have no conflicts of interest to report.

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