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Review Article

The Efficacy and Safety of *RET*-selective Inhibitors for Cancer Patients

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Abstract

The rearrangement during transfection (*RET*) encodes a receptor tyrosine kinase (RTK), which is involved in the development of various tissues and cells. The rearrangements and mutations of *RET* contribute to the development of a variety of human malignancies. Therefore, *RET* alterations are novel therapeutic targets. Inhibitors for *RET* and other kinases have been approved for the treatment of *RET*-altered tumors and have demonstrated their benefits for some types of cancer patients in clinics. However, due to off-target effects, these inhibitors have some adverse effects and dose-limiting toxicity. Therefore, long-term treatment with these inhibitors has potential limitations. Novel highly selective inhibitors (pralsetinib and selpercatinib) that target the *RET* pathway are well tolerated and have significant and long-lasting antitumor activity. They have been accelerated for approval by the FDA. This article will focus on the role of highly selective inhibitors targeting the *RET* and their efficacy and safety in therapy for *RET*-associated cancers.

Introduction

Rearrangements in the rearrangement during transfection (*RET*) genes that encode transmembrane receptor tyrosine kinases (RTK) are associated with tumorigenesis. The RET protein forms a heterodimer complex after it is engaged by a ligand in the glial cell line-derived neurotropic factor (GDNF) family that causes autophosphorylation of the tyrosine kinase domain in the cells and activates downstream signaling, regulating the processes of cell differentiation, cell migration, and proliferation.[1–4] *RET* can regulate the development of multiorgans, cell survival, death, and migration and its mutations or gene fusion can promote spontaneous tumor proliferation, activation, and migration.

Alterations in the *RET* gene are associated with the pathogenesis of many human diseases, including multiple endocrine neoplasia type 2 (MAN-2), papillary thyroid cancer, Hirschsprung's disease, colon adenocarcinoma, invasive breast cancer, non-small cell lung cancer (NSCLC), and others.[5] *CDCC6-RET* and *KIF5B-RET*, two *RET* fusions are common in papillary thyroid carcinoma and NSCLC, respectively. A germline mutation in the *RET* can cause MAN-2 syndrome.[6] Germline-activated *RET* mutations are found in 95–98% of hereditary medullary thyroid cancer (MTC) and somatic *RET* mutations are found in 25–40% of sporadic MTC. In addition, *RET* mutations are associated with the aggressiveness of MTC, such as distant metastasis.[7] The *RET* fusions are detected in 1–2% of NSCLC,[8] particularly for lung adenocarcinoma and *RET* rearrangements, are found in other histological types of NSCLC, including malignant neuroendocrine tumor and squamous cell carcinoma.[9] It was found that the *RET* fusion genes were detected in lung cancer, thyroid cancer, colon adenocarcinoma (*CCDC6-RET*) and invasive breast cancer (*ERC1-RET*).[10]

The biology and function of *RET*

The *RET*, a transforming gene, was first discovered in mouse em-

Keywords: Efficacy; Pralsetinib; Rearrangement during transfection alteration; Safety; Selpercatinib; Tyrosine kinase inhibitor.

Abbreviations: *RET*, rearrangement during transfection; MAN-2, multiple endocrine neoplasia type 2; NSCLC, non-small cell lung cancer; MTC, medullary thyroid cancer; NIH, National Institutes of Health (USA); RTK, receptor tyrosine kinase; CNS, central nervous system; GDNF, glial cell line-derived neurotrophic factor; GFL, GDNF Family Ligands; GFRα, growth factor receptor-alfa; MKI, multi-kinase inhibitors; PFS, progression-free survival; ORR, overall response rate; DOR, duration of response; FDA, Food and Drug Administration.

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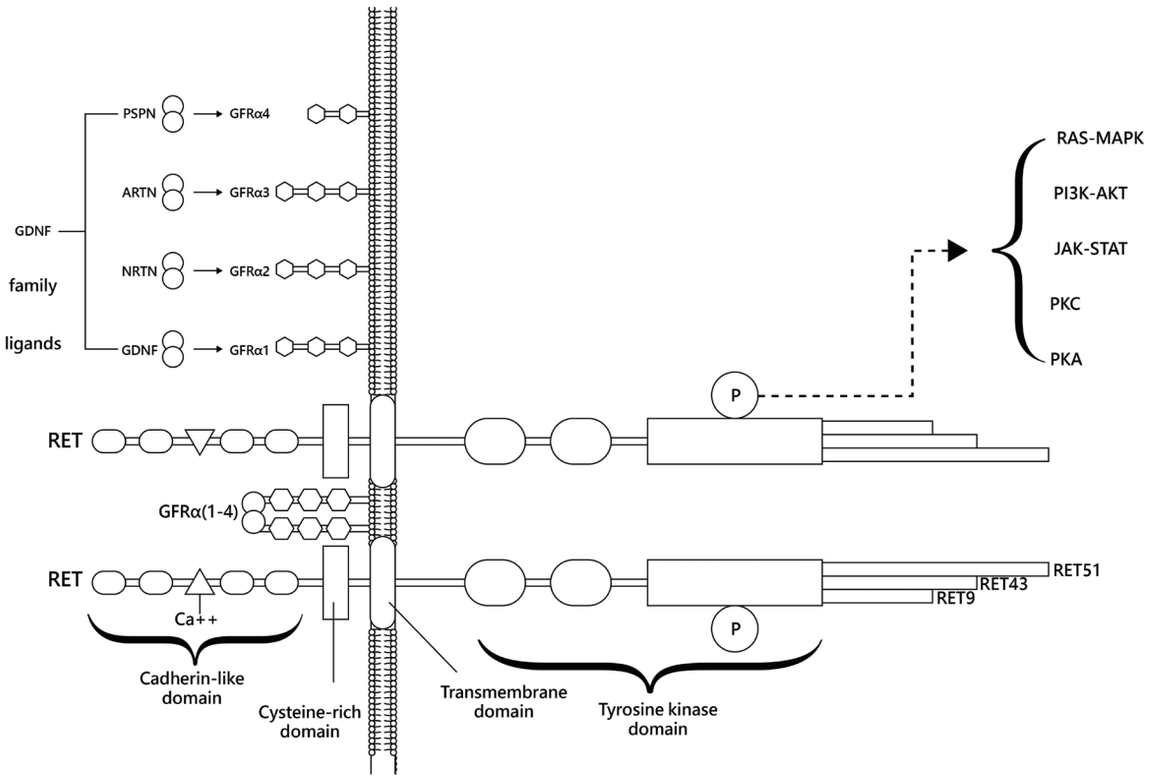

Fig. 1. The RET structure and signaling network. RET, rearrangement during transfection; GDNF, glial cell line-derived neurotrophic factor; GFRα, growth factor receptor-alfa; ART, artemin; NTN, neurturin; PSP, persephin; Ca++, calcium ion.

bryonic fibroblast cells that were established by the National Institutes of Health (NIH) transfected with DNA from human T cell lymphoma.[11] The *RET* gene is located at 10q11.2 and contains 21 exons.[12] The *RET* encodes an RTK, a type of transmembrane glycoprotein, which mediates signal transduction during various processes, such as cell migration, proliferation, and differentiation. It is required for the development and maturation of various organs and cells.[13] Studies have confirmed that *RET* is crucial for the formation and development of the kidneys and nervous system. In addition, the *RET* supports the survival of hematopoietic stem cells and early spermatogenesis.[14,15] Structurally, *RET* contains three domains; an extracellular domain, a transmembrane domain, and an intracellular domain that contains the tyrosine kinase domain adjacent to the transmembrane region. The large extracellular region contains a domain of four cadherin-like repeats, a calcium-binding site, and a conserved cysteine-rich portion at the proximal end of the membrane.[16] The C-terminal of *RET* has two main forms, which are formed by alternate splicing of G1063 residue to exon 3. There are 9 or 51 amino acids at the end of the C-terminal, respectively called *RET* 9 and *RET* 51.[17] Unlike other RTKs, RET protein does not directly transmit signals after it is engaged by its ligand. The ligands of RET are members of the GDNF family, which include neuroturin, artemin, and persephin.[2] These GDNF family ligands (GFLs) can bind to four types of GDNF family growth factor receptor-alfa (GFR-α) to form a coreceptor. This GFL-GFR-α binary complex can bind to the intracellular tyrosine kinase domain of RET and induce dimerization of RET.[18] The formation of a homodimer between two RET will cause transphosphorylation of intracellular tyrosine residues of RET and create a docking site for the signal adapter molecule. The phosphorylated RET will then recruit key signal adapter molecules and activate a variety of cellular signal cascades, including the MAPK, PI3K, JAK-STAT, PKA, and PKC pathways.[3,16] (Fig. 1)

Multikinase inhibitors

Multikinase inhibitors for thyroid cancer

Multikinase inhibitors (MKIs) that target the *RET* pathway have been tested for their antitumor activity in patients with thyroid cancer. Some drugs have shown clinical efficacy, such as vandetanib, cabozantinib, lenvatinib, alectinib, and sorafenib.[19] Between them, cabozantinib and vandetanib have been approved for the treatment of locally advanced or metastatic MTC. Vandetanib, an oral *RET* kinase inhibitor, has shown therapeutic potential in a Phase III trial (ZETA, ClinicalTrials.gov number NCT00410761) in patients that have locally advanced or metastatic MTC. The results of the ZETA study indicated that treatment with vandetanib significantly prolonged the progression-free survival (PFS) in patients that had locally advanced or metastatic MTC (30.5 versus 19.3 months for patients with placebo).[20] Similarly, treatment with cabozantinib significantly prolonged the PFS (11.2 versus 4.0 months) of MTC patients in a Phase III trial (EXAM, NCT00704730) with a higher objective response rate [ORR (28% versus 0%)].[21] The retrospective analysis of the EXAM trial in two studies revealed that treatment with cabozantinib for MTC patients with the *RET* M918T mutation achieved a better median PFS (61 versus 17 weeks).[22,23]

MKIs for NSCLC

MKIs have made some progress in the treatment of *RET*-associated NSCLC. A multicenter Phase II clinical trial (LURET, UMIN-CTR, UMIN000010095) revealed that treatment with vandetanib achieved an ORR of 53% [95 confidence interval (CI)% 28–77], and a median PFS of 4.7 months (95% CI 2.8–8.5) in previously treated NSCLC patients that harbored *RET* rearrangements. Further subgroup analysis indicated that treatment with vandetanib resulted in ORRs of 83% and 20% in patients with *CCDC6-RET* and *KIF5B-RET* fusion genes, respectively.[24] Furthermore, a Phase II clinical trial (NCT01639508) reported that treatment with cabozantinib led to an ORR of 28% (95% CI 12–49) with a median PFS of 5.5 months (95% CI 3.8–8.4) in NSCLC patients.[25] This data indicated that MKIs are effective for NSCLC patients with *RET* fusion, particularly for the common *CCDC6-RET* and *KIF5B-RET* fusions. However, whether the efficacy of MKIs is a result of their inhibition of these specific biomarkers needs to be further explored.

Limitations of MKIs

MKIs are usually not selective for targeting *RET*, and they can target other kinases, such as EGFR, VEGFR-2, KIT, and MET.[26] In particular, because the domain of VEGFR-2 kinase has a high degree of homology with *RET,* several tyrosine kinase inhibitors that target VEGFR-2 (*e.g.*, cabozantinib, vandetanib, and lenvatinib) have shown therapeutic potential for cancer patients with *RET* alterations to a certain extent.[8,27–29] Due to the off-target effect, the inhibitory effect of these MKIs specifically on *RET* might be limited. Moreover, these MKIs have drug-related toxicity, and increase the dose-reduction rates and treatment-discontinuation rates of drugs, further reducing their clinical applications.[17] In addition, these MKIs have developed intrinsic resistance that has limited their clinical application in targeted therapy for *RET*-altered cancers. The intrinsic resistance might be caused by the fusion between the upstream partner gene *KIF5B* and *RET*.[16,30] Treatment with MKIs had less efficacy in NSCLC patients that carried *KIF5B-RET* fusion genes than those without the *KIF5B-RET* fusion in the LURET study and the Phase I/Ib trail of RXDX-105.[31] The acquired resistance to MKIs is probably from specific *RET* alterations, which result in gatekeeper mutations V804M and V804L on *RET*.[32,33] Particularly, cabozantinib and vandetanib are not effective for NSCLC patients with V804M and V804L mutations.[34,35]

Selective RET inhibitors

Because traditional MKIs have limitations, including off-target effects, treatment-related toxicity, and acquired resistance new and potent inhibitors that selectively inhibit *RET* have recently been developed and approved for clinical applications for some types of cancers. For example, selpercatinib (RETEVMO or LOXO-292) and pralsetinib (BLU-667) are two small molecule inhibitors with highly selective inhibition of *RET* and have been approved by the FDA.[36,37]

Selpercatinib (RETEVMO or LOXO-292)

Compared with MKIs, preclinical studies have shown that LOXO-292 can selectively target the *RET* mutants, including gatekeeper resistance mutations and *RET* fusions compared with MKIs; LOXO-292 exhibits lower toxicity and has low activity against non-*RET* gene alterations (*i.e.*, VEGFR-2).[37] Several clinical studies have been carried out on the treatment of cancer patients.

Selpercatinib for thyroid cancer

Selpercatinib was approved for the treatment of NSCLC and MTC patients with *RET*-alteration by the FDA on 8 May 2020.[38] The multicohort, Phase I/II clinical trial (LIBRETTO-001, NCT03157128) reported that selpercatinib had a significant and long-lasting antitumor activity with an ORR of 69% (n = 38, 95% CI 55–81) and low-grade toxicity in advanced thyroid cancer patients with *RET* alterations, including patients with *RET*-mutant MTC resistant to vandetanib or cabozantinib (Table 1). Of interest, some patients with *RET* mutations or gatekeeper resistance responded to selpercatinib although they were resistant to one or two MKIs previously. Treatment with selpercatinib for the patients with MTCs that harbored *RET*-alteration without previous MKI treatment achieved an ORR of 73% (n = 64, 95% CI 62–83), the median duration of response (DOR) of 22 months (95% CI Not-Estimable NE–NE) and a PFS of 23.6 months (95% CI NE–NE). Furthermore, treatment with selpercatinib for patients with thyroid cancer bearing the *RET* fusion observed an ORR of 79% (95% CI 54–94), median DOR of 18.4 months (95% CI 7.6–NE) and a PFS of 20.1 months (95% CI 9.4–NE). Of interest, treatment with selpercatinib for patients with newly diagnosed thyroid cancer without previous systemic treatment resulted in an ORR of 100% (95% CI 63–100).[39,40] Selpercatinib appeared to be safe for humans and there was only grade 1 and 2 of treatment-related adverse effect in a population of 162 patients. There were few cases with a low adverse effect or discontinuer event following selpercatinib treatment.[39] The low adverse effect of selpercatinib might be attributed to its high selectivity against the *RET.*

Selpercatinib for NSCLC

In the Phase I/II clinical trial, LIBRETTO-001 (NCT03157128), the therapeutic efficacy of selpercatinib in patients with NSCLC bearing advanced *RET* fusion was evaluated (Table 1).[41] Treatment with selpercatinib 105 NSCLC patients with previous platinum-based chemotherapy obtained an ORR of 64% (n = 67, 95% CI 54–73), median DOR of 17.5 months (95% CI 12.0–NE) and a PFS of 16.5 months (95% CI 13.7–NE). In addition, treatment with selpercatinib benefited 55% of NSCLC patients who received immunotherapy and 56% of NSCLC patients who had received ≥3 systemic therapies. Of note, 38 out of 105 patients had brain metastases, and 11 of them had measurable lesions. The intracranial ORR was 91% (n = 10, 95% CI 95–100), and the median central nervous system (CNS) DOR was 10.1 months (95% CI 6.7–NE). Treatment with selpercatinib obtained an ORR of 85% (n = 33, 95% CI 70–89) in 39 patients with newly diagnosed NSCLC.[41] Selpercatinib has a higher therapeutic efficacy in newly diagnosed NSCLC patients than in those with NSCLC refractory common therapies.

Similar to thyroid cancer, selpercatinib treatment resulted in grade 1 and 2 drug-related adverse effects in NSCLC patients. There were a few patients that needed to reduce drug doses or treatment termination.[41] Because the most common grade 3 adverse reactions are reversible after dose adjustment, long-term

Table 1. Key Clinical trials of selpercatinib and pralsetinib

Agent	Condition	Phase	Status	Locations	NCT no.
selpercatinib	*RET* fusion-positive solid tumors, MTC, and other tumors with *RET* activation	II	Active	China	NCT04280081
selpercatinib	Advanced solid tumors, lymphomas, or histiocytic disorders with *RET* activation in pediatric patients(a pediatric MATCH treatment trial)	II	Recruiting	US	NCT04320888
selpercatinib, cabozantinib, vandetanib	*RET*-mutant MTC	III	Recruiting	Multiple countries	NCT04211337
selpercatinib	*RET* fusion-positive solid tumors, MTC, and other tumors with *RET* activation	I/II	Recruiting	Multiple countries	NCT03157128
selpercatinib, carboplatin, cisplatin, pemetrexed, pembrolizumab	Advanced or metastatic *RET* fusion-positive NSCLC	III	Recruiting	Multiple countries	NCT04194944
selpercatinib	*RET* fusion-positive advanced NSCLC	II	Recruiting	US	NCT04268550
selpercatinib	Solid tumors with *RET* activation (expanded access)	N/A	Available	Multiple countries	NCT03906331
selpercatinib	Advanced solid or primary CNS tumors in pediatric patients	I/II	Recruiting	US	NCT03899792
selpercatinib,osimertinib,savolitinib,gefitinib,necitumumab,durvalumab,carboplatin,pemetrexed,alectinib	Advanced NSCLC	II	Recruiting	Multiple countries	NCT03944772
pralsetinib	Thyroid cancer, NSCLC, and other advanced solid tumors	I/II	Recruiting	Multiple countries	NCT03037385
pralsetinib	Unresectable or metastatic MTC or NSCLC	N/A	Available	N/A	NCT04204928
pralsetinib,carboplatin,cisplatin,pemetrexed,pembrolizumab, gemcitabin	Advanced NSCLC	III	Recruiting	Multiple countries	NCT04222972

N/A, not applicable; CNS, central nervous system; MTC, medullary thyroid carcinoma; NSCLC, non-small cell lung cancer; NCT, National Clinical Trials

treatment with selpercatinib is feasible. Further analysis of selpercatinib safety supported that selpercatinib was relatively safe in a population of 531 patients with NSCLC and thyroid cancer. The most common adverse events during selpercatinib treatment were at grade 1–2, where 30% (n = 160) of patients reduced the drug dose, and 2% (n = 12) discontinued treatment.

Selpercatinib for other cancers with *RET*-alteration

Preliminary studies have shown that selpercatinib benefits pediatric cancer patients bearing *RET*-alterations. A study reported that treatment with selpercatinib for 1–2 cycles achieved a partial response in four pediatric patients with cancers harboring *RET* fusions (including papillary thyroid cancer and soft-tissue sarcomas).[42] Similarly, treatment with selpercatinib resulted in a partial response in four out of five pediatric cancer patients and the remaining one achieved stable disease. Several clinical trials are ongoing, for example, LIBRETTO-431 (NCT04194944), LIBRETTO-121 (NCT03899792), and LIBRETTO-321 (NCT04280081), and might extend selpercatinib to other types of cancers that have *RET* alterations (Table 1).

Pralsetinib (BLU-667)

A preclinical study has shown that BLU-667 can selectively target *RET* with higher efficiency.[36] The Phase I/II study (ARROW study) (ClinicalTrials.gov number NCT03037385) indicated that BLU-667 has better therapeutic efficacy than other MKIs in advanced thyroid cancer and NSCLC.[43,44] Pralsetinib was approved by the FDA for the treatment of NSCLC with *RET* fusion on 4 September 2020.[45]

Pralsetinib for thyroid cancer

According to the available data from the ARROW study, treatment with pralsetinib achieved an ORR of 65% (95% CI 53–75) in 79 MTC patients with *RET* mutations. Similarly, pralsetinib treatment resulted in an ORR of 60% (95% CI 46–74), 71% (95% CI 58–85) with 18 month PFS and 90% (95% CI 77–100) with DOR in 53 MTC patient's resistant to cabozantinib, or vandetanib, or both. Furthermore, treatment with pralsetinib resulted in 74% (95% CI 49–91) of patients with ORR, 85% with 18-month PFS, and 86%

with DOR in patients newly diagnosed MTC.[46] Finally, 9 out of 12 patients with thyroid cancer achieved ORR and a median DOR of 14.5 months following pralsetinib treatment.[47]

Pralsetinib for lung cancer

In the ARROW trial, pralsetinib treatment was effective for patients with NSCLC bearing *RET* fusion, including an ORR of 57% (95% CI 46–68) in patients with previous cisplatin chemotherapy. Furthermore, treatment with pralsetinib achieved an ORR of 59% (95% CI 42–74) in a cohort of 39 patients without anti-PD-1 or anti-PD-L1 treatment. Similarly, pralsetinib treatment resulted in an ORR of 70% (95% CI 50–86), a median DOR of 9.0 months (95% CI 6.3–NE) in the untreated cohort (n = 2 7). After 8 weeks of treatment with pralsetinib, 90% of NSCLC patients eliminated plasma ctDNA of the *RET* variant and 90% of them reduced plasma ctDNA levels by ≥50%.[48]

Pralsetinib for other solid tumors with *RET*-alteration

In addition to thyroid cancer and NSCLC, pralsetinib has been used for the treatment of other solid tumors with *RET* alterations. Following pralsetinib treatment, three out of five patients responded, including two advanced pancreatic cancer patients with a partial response and a DOR of 5.5 months; two colon cancer patients with stable disease; an intrahepatic bile duct carcinoma patient with a DOR of 7.5 months.[47] Several clinical trials, such as the ARROW trial and AcceleRET Lung study (NCT04222972), are ongoing to test the therapeutic efficacy and safety of pralsetinib. The analysis of 438 patients that received pralsetinib showed that the treatment-related adverse effects of pralsetinib were in grades 1–2, and only 4% of patients discontinued treatment, similar to that of selpercatinib.[46]

Future directions

Several problems need to be solved urgently. The emergence of potent and highly selective *RET* inhibitors has led to the development of acquired resistance. The mechanisms underlying the resistance of these inhibitors need to be explored. Precise therapy for cancers that harbor *RET* alterations requires accurate diagnosis. Therefore, the detection of *RET* alterations in tumors faster and accurately (including *RET* structural variants of unknown significance and uncommon *RET*-alteration) is a challenge for future research. In addition, the exploration of the next-generation of selective *RET* inhibitors and the combination of existing *RET* inhibitors and agents that target other pathways might provide new strategies for the clinical treatment of *RET*-altered tumors.

Conclusions

In the last few decades, the role of *RET* proto-oncogene mutations and rearrangements in the development of several malignancies have been clarified. Treatment with MKIs has achieved certain efficacy in tumor patients with *RET* alterations. However, due to their off-target effects, the inhibition of non-*RET* targets, including the VEGFR-2, leads to significant dose toxicity, limiting their long-term administration. Selpercatinib and pralsetinib are new selective *RET* inhibitors, which are well tolerated and have reproducible and significant antitumor activity. Therefore, these drugs have been approved for clinical application.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

All the listed authors made substantial contributions to: conception and design, and/or acquisition of data, and/or analysis and interpretation of data; and all the authors gave final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content. The details are listed as follows: study concept and design and obtained funding (LYZ); draft manuscript and analysis and interpretation of data (FBZ, QHG).

References

[1] Amoresano A, Incoronato M, Monti G, Pucci P, de Franciscis V, Cerchia L. Direct interactions among Ret, GDNF and GFRalpha1 molecules reveal new insights into the assembly of a functional three-protein complex. Cell Signal 2005;17(6):717–727. doi:10.1016/j.cellsig.2004.10.012.

[2] Wang X. Structural studies of GDNF family ligands with their receptors-Insights into ligand recognition and activation of receptor tyrosine kinase RET. Biochim Biophys Acta 2013;1834(10):2205–2212. doi:10.1016/j.bbapap.2012.10.008.

[3] Arighi E, Borrello MG, Sariola H. RET tyrosine kinase signaling in development and cancer. Cytokine Growth Factor Rev 2005;16(4-5):441–467. doi:10.1016/j.cytogfr.2005.05.010.

[4] Tansey MG, Baloh RH, Milbrandt J, Johnson EM Jr. GFRalpha-mediated localization of RET to lipid rafts is required for effective downstream signaling, differentiation, and neuronal survival. Neuron 2000;25(3):611–623. doi:10.1016/s0896-6273(00)81064-8.

[5] Li AY, McCusker MG, Russo A, Scilla KA, Gittens A, Arensmeyer K, *et al*. RET fusions in solid tumors. Cancer Treat Rev 2019;81:101911. doi:10.1016/j.ctrv.2019.101911.

[6] Gertner ME, Kebebew E. Multiple endocrine neoplasia type 2. Curr Treat Options Oncol 2004;5(4):315–325. doi:10.1007/s11864-004-0022-6.

[7] Ciampi R, Romei C, Ramone T, Prete A, Tacito A, Cappagli V, *et al*. Genetic Landscape of Somatic Mutations in a Large Cohort of Sporadic Medullary Thyroid Carcinomas Studied by Next-Generation Targeted Sequencing. iScience 2019;20:324–336. doi:10.1016/j.isci.2019.09.030.

[8] Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat Rev Endocrinol 2016;12(4):192–202. doi:10.1038/nrendo.2016.11.

[9] Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. RET Aberrations in Diverse Cancers: Next-Generation Sequencing of 4,871 Patients. Clin Cancer Res 2017;23(8):1988–1997. doi:10.1158/1078-0432.Ccr-16-1679.
[10] Stransky N, Cerami E, Schalm S, Kim JL, Lengauer C. The landscape of kinase fusions in cancer. Nat Commun 2014;5:4846. doi:10.1038/ncomms5846.
[11] Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell 1985;42(2):581–588. doi:10.1016/0092-8674(85)90115-1.
[12] Ishizaka Y, Itoh F, Tahira T, Ikeda I, Sugimura T, Tucker J, *et al*. Human ret proto-oncogene mapped to chromosome 10q11.2. Oncogene 1989;4(12):1519–1521.
[13] Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer 2014;14(3):173–186. doi:10.1038/nrc3680.
[14] Jain S, Naughton CK, Yang M, Strickland A, Vij K, Encinas M, *et al*. Mice expressing a dominant-negative Ret mutation phenocopy human Hirschsprung disease and delineate a direct role of Ret in spermatogenesis. Development 2004;131(21):5503–5513. doi:10.1242/dev.01421.
[15] Fonseca-Pereira D, Arroz-Madeira S, Rodrigues-Campos M, Barbosa IA, Domingues RG, Bento T, *et al*. The neurotrophic factor receptor RET drives haematopoietic stem cell survival and function. Nature 2014;514(7520):98–101. doi:10.1038/nature13498.
[16] Kohno T, Tabata J, Nakaoku T. REToma: a cancer subtype with a shared driver oncogene. Carcinogenesis 2020;41(2):123–129. doi:10.1093/carcin/bgz184.
[17] Subbiah V, Yang D, Velcheti V, Drilon A, Meric-Bernstam F. State-of-the-Art Strategies for Targeting RET-Dependent Cancers. J Clin Oncol 2020;38(11):1209–1221. doi:10.1200/jco.19.02551.
[18] Goodman KM, Kjær S, Beuron F, Knowles PP, Nawrotek A, Burns EM, *et al*. RET recognition of GDNF-GFRα1 ligand by a composite binding site promotes membrane-proximal self-association. Cell Rep 2014;8(6):1894–1904. doi:10.1016/j.celrep.2014.08.040.
[19] Wells SA Jr. Advances in the management of MEN2: from improved surgical and medical treatment to novel kinase inhibitors. Endocr Relat Cancer 2018;25(2):T1–t13. doi:10.1530/erc-17-0325.
[20] Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, *et al*. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30(2):134–141. doi:10.1200/jco.2011.35.5040.
[21] Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, *et al*. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31(29):3639–3646. doi:10.1200/jco.2012.48.4659.
[22] Sherman SI, Clary DO, Elisei R, Schlumberger MJ, Cohen EE, Schöffski P, *et al*. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer 2016;122(24):3856–3864. doi:10.1002/cncr.30252.
[23] Schlumberger M, Elisei R, Müller S, Schöffski P, Brose M, Shah M, *et al*. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol 2017;28(11):2813–2819. doi:10.1093/annonc/mdx479.
[24] Yoh K, Seto T, Satouchi M, Nishio M, Yamamoto N, Murakami H, *et al*. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. Lancet Respir Med 2017;5(1):42–50. doi:10.1016/s2213-2600(16)30322-8.
[25] Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M, *et al*. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol 2016;17(12):1653–1660. doi:10.1016/s1470-2045(16)30562-9.
[26] Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol 2018;15(3):151–167. doi:10.1038/nrclinonc.2017.175.
[27] Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, *et al*. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther 2011;10(12):2298–2308. doi:10.1158/1535-7163.Mct-11-0264.
[28] Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, *et al*. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. Cancer Res 2002;62(24):7284–7290.
[29] Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, *et al*. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 2002;62(16):4645–4655.
[30] Das TK, Cagan RL. KIF5B-RET Oncoprotein Signals through a Multi-kinase Signaling Hub. Cell Rep 2017;20(10):2368–2383. doi:10.1016/j.celrep.2017.08.037.
[31] Drilon A, Fu S, Patel MR, Fakih M, Wang D, Olszanski AJ, *et al*. A Phase I/Ib Trial of the VEGFR-Sparing Multikinase RET Inhibitor RXDX-105. Cancer Discov 2019;9(3):384–395. doi:10.1158/2159-8290.Cd-18-0839.
[32] Wirth LJ, Kohno T, Udagawa H, Matsumoto S, Ishii G, Ebata K, *et al*. Emergence and Targeting of Acquired and Hereditary Resistance to Multikinase RET Inhibition in Patients With RET-Altered Cancer. JCO Precis Oncol 2019;3:doi:10.1200/po.19.00189.
[33] Dagogo-Jack I, Stevens SE, Lin JJ, Nagy R, Ferris L, Shaw AT, *et al*. Emergence of a RET V804M Gatekeeper Mutation During Treatment With Vandetanib in RET-Rearranged NSCLC. J Thorac Oncol 2018;13(11):e226–e227. doi:10.1016/j.jtho.2018.06.021.
[34] Mologni L, Redaelli S, Morandi A, Plaza-Menacho I, Gambacorti-Passerini C. Ponatinib is a potent inhibitor of wild-type and drug-resistant gatekeeper mutant RET kinase. Mol Cell Endocrinol 2013;377(1-2):1–6. doi:10.1016/j.mce.2013.06.025.
[35] Carlomagno F, Guida T, Anaganti S, Vecchio G, Fusco A, Ryan AJ, *et al*. Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. Oncogene 2004;23(36):6056–6063. doi:10.1038/sj.onc.1207810.
[36] Subbiah V, Gainor JF, Rahal R, Brubaker JD, Kim JL, Maynard M, *et al*. Precision Targeted Therapy with BLU-667 for RET-Driven Cancers. Cancer Discov 2018;8(7):836–849. doi:10.1158/2159-8290.Cd-18-0338.
[37] Subbiah V, Velcheti V, Tuch BB, Ebata K, Busaidy NL, Cabanillas ME, *et al*. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol 2018;29(8):1869–1876. doi:10.1093/annonc/mdy137.
[38] Markham A. Selpercatinib: First Approval. Drugs 2020;80(11):1119–1124. doi:10.1007/s40265-020-01343-7.
[39] Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, *et al*. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. N Engl J Med 2020;383(9):825–835. doi:10.1056/NEJMoa2005651.
[40] Mendes Oliveira D, Grillone K, Mignogna C, De Falco V, Laudanna C, Biamonte F, *et al*. Next-generation sequencing analysis of receptor-type tyrosine kinase genes in surgically resected colon cancer: identification of gain-of-function mutations in the RET proto-oncogene. J Exp Clin Cancer Res 2018;37(1):84. doi:10.1186/s13046-018-0746-y.
[41] Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, *et al*. Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2020;383(9):813–824. doi:10.1056/NEJMoa2005653.
[42] Gerdemann U, Lee YA, Henry D, Smith S, Ortiz MV, Rothenberg SM, *et al*. First experience of LOXO-292 in the management of pediatric patients with RET-altered cancers. J Clin Oncol 2019;37(15 Suppl):10045. doi:10.1200/JCO.2019.37.15_suppl.10045.
[43] Gainor JF, Lee DH, Curigliano G, Doebele RC, Kim DW, Baik CS, *et al*. Clinical activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients (pts) with advanced RET-fusion+ non-small cell lung cancer (NSCLC). J Clin Oncol 2019;37(15 Suppl):9008. doi:10.1200/JCO.2019.37.15_suppl.9008.
[44] Taylor MH, Gainor JF, Hu MIN, Zhu VW, Lopes G, Leboulleux S, *et al*. Activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients with advanced RET-altered thyroid cancers. J Clin Oncol 2019;37(15 Suppl):6018. doi:10.1200/JCO.2019.37.15_suppl.6018.
[45] Markham A. Pralsetinib: First Approval. Drugs 2020;80(17):1865–1870. doi:10.1007/s40265-020-01427-4.
[46] Hu M, Subbiah V, Wirth LJ, Schuler M, Mansfield AS, Brose MS, *et al*. Results from the registrational phase I/II ARROW trial of pral-

setinib (BLU-667) in patients (pts) with advanced RET mutation-positive medullary thyroid cancer (RET+ MTC). Ann Oncol 2020(Suppl 4):S1084. doi:10.1016/j.annonc.2020.08.1401.

[47] Subbiah V, Hu MIN, Gainor JF, Mansfield AS, Alonso G, Taylor MH, *et al*. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion + solid tumors. J Clin Oncol 2020;38(15 Suppl):109. doi:10.1200/JCO.2020.38.15_suppl.109.

[48] Curigliano G, Subbiah V, Gainor JF, Lee DH, Taylor MH, Zhu VW, *et al*. Treatment With Pralsetinib (BLU-667), a Potent and Selective RET Inhibitor, Provides Rapid Clearance of ctDNA in Patients With RET-Altered Non-Small Cell Lung Cancer (NSCLC) and Thyroid Cancer. Ann Oncol 2019;30(5):v790. doi:10.1093/annonc/mdz268.093.