REVIEW ARTICLE

RET Fusion: Joining the Ranks of Targetable Molecular Drivers in NSCLC

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ABSTRACT

The era of precision medicine has resulted in the identification of a number of genomic alterations that can be targeted with novel therapies. In lung adenocarcinomas, a histology structure that accounts for nearly 50% of all cases of lung cancer, and a number of genomic targets have been linked with effective targeted therapies. For patients with advanced-stage lung adenocarcinomas, molecular testing is now a standard part of diagnostic workup; for patients that have specific driver molecular events, targeted therapies have resulted in substantial improvement in efficacy without excessive toxicity. *RET* gene fusions are present in approximately 1% to 2% of NSCLC. It is emerging as a new targetable driver for this population. Despite sensitivity to platinum-based chemotherapy and conflicting small reports regarding the efficacy of immune checkpoint inhibitors, there have been limited treatment approaches for this subset of patients. Multiple nonselective RET tyrosine kinase inhibitors exhibited modest anti-*RET* activity with an increased off-target toxicity profile that often required dose interruption, reduction, or treatment cessation. Recently, novel selective RET inhibitors pralsetinib (BLU-667) and selpercatinib (LOXO-292) have exhibited promising clinical activity with low adverse effect profile in early clinical trials. These new agents are poised to represent a new hope for this special subgroup with unmet needs.

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Keywords: Lung cancer; Precision oncology; Pralsetinib; RET fusion; Selpercatinib; Targeted Therapy

Introduction

Targeted therapy has reshaped the care of patients with lung cancer with a specific molecular driver. Sensitizing *EGFR* [1] and *BRAF* V600E [2] mutations, *ALK*,[3] *ROS1*,[4], and *NTRK* [5,6] gene rearrangements have emerged as targetable molecular drivers in patients with lung cancer. The use of novel targeted therapies provides a robust response rate and progression-free survival (PFS). In the case of EGFR-targeted therapy, an improvement in overall survival (OS) has recently been reported with a third-generation tyrosine kinase inhibitor.[1] Similarly, for patients with *ALK* gene rearrangement, second-generation ALK inhibitors are associated with a median PFS of longer tan 2 years.[3,7] These agents are also associated with marked anticancer activity against brain metastasis, which is common in these molecular subsets of NSCLC. Consequently, a number of agents are being developed for various targets observed in patients with NSCLC. Among these, promising results have been observed with novel agents targeting *RET* fusion, *MET* exon 14 alteration,[8] and *KRAS* G12C mutation[9-11] in lung cancer.

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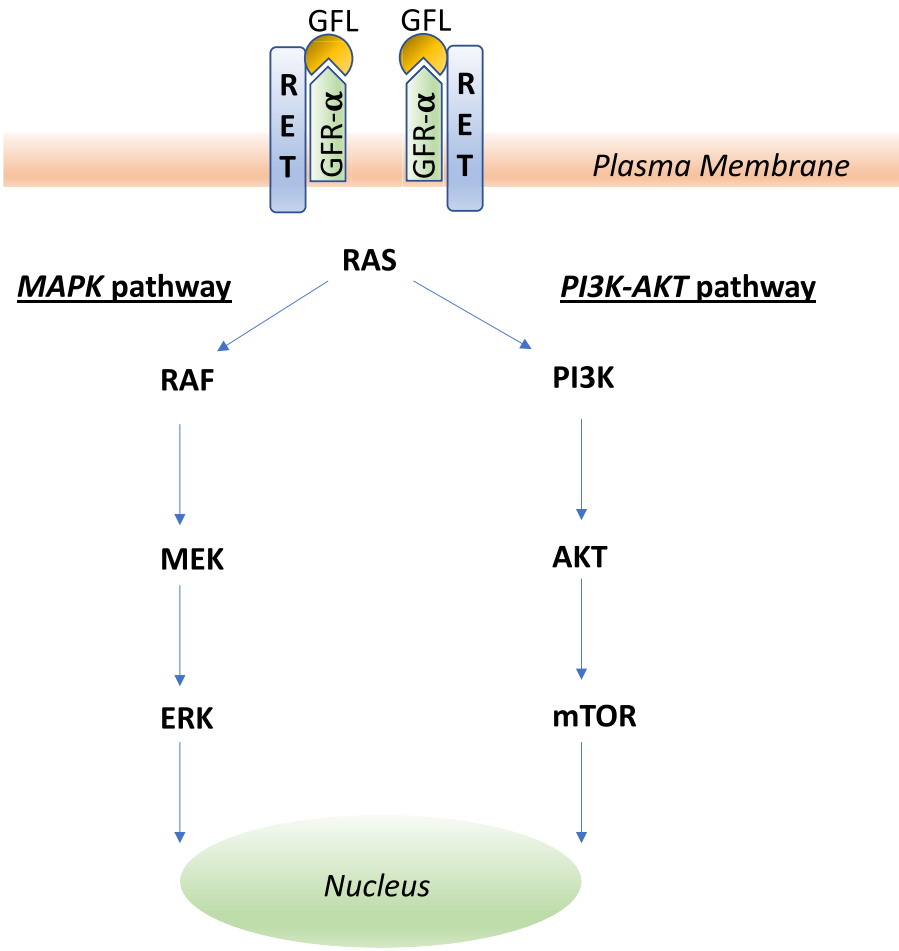

Figure 1. RET signaling diagram. GFL, glial cell line-derived neurotrophic factor family ligands; GFR-α, glycosyl-phosphatidylinositol-anchored coreceptor.

The *RET*-activating gene was originally identified in 1985.[12] It encodes the transmembrane RET kinase; RET is activated when the glial cell line-derived neurotrophic factor family ligands binds to the RET coreceptor, glycosyl-phosphatidylinositol–anchored coreceptor (GFR-α).[13] This leads to a signaling cascade that triggers the activation of downstream signals including MAPK and PI3K-AKT pathways (Fig. 1) and promotes cancer initiation and progression.[14] In normal cells, RET kinase signaling is well-controlled. In cells with activating alterations of the *RET* gene, aberrant signaling leads to uncontrolled cell growth that eventually results in malignant transformation.[15] RET is activated by two major mechanisms in cancer: *RET* fusions and *RET* point mutations. In *RET* fusions, owing to aberrant DNA repair processes, the *RET* gene is fused to another unrelated gene. *KIF5B* and *CCDC6* are the most frequently reported *RET* fusion partners in patients with NSCLCs.[16] These fusion partners can encode proteins that contain the coiled-coil domain, which causes *RET* fusion protein to dimerize allowing for constitutive ligand-independent RET activation. In addition to *RET* fusions, activating *RET* point mutations can also lead to constitutive ligand-independent RET signaling.

RET gene fusions have been reported in 1% to 2% of NSCLC and in 10% to 20% of sporadic papillary thyroid cancer.[16-20] Other cancer types like breast cancer, colorectal cancer, and pancreatic cancer are also known to harbor activating *RET* fusions at a lower frequency (<1%). In addition, approximately 60% sporadic medullary thyroid cancer (MTC) and greater than 90% of hereditary MTC harbor an activating intracellular or extracellular *RET* mutation.

Although no therapy that selectively targets RET in NSCLC is currently approved, clinical trials that focus on *RET*-altered cancers are ongoing. In this review, we discuss the biology, clinical characteristics, emerging treatment options, and mechanisms for acquired resistance for patients with *RET*-positive NSCLC.

Characteristics of Patients With *RET* Fusion-Positive NSCLC

The characteristics and outcomes of patients with *RET* fusion–positive NSCLC were presented by Gautschi et al.[16] from the Global Multicenter RET Registry (GLORY), the largest and international registry of 165 patients identified by a global network of thoracic oncologists. *RET* rearrangements were identified by reverse transcriptase–polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or next-generation sequencing (NGS). The median age of patients was 61 years (range, 29–89), and most patients were never-smokers (63%), with lung adenocarcinomas (98%). Most patients had the advanced-stage disease (stage III-IV) (91%). The most frequent rearrangements were *KIF5B-RET* (72%) and *CCDC6-RET* (23%). *NCOA4* (2%), *EPHA4* (1%), and *PICALM* (1%) were uncommon partners. It is not known whether there are any biological differences in downstream signaling on the basis of the *RET* fusion partner. Most patients were from the United States and Europe (86%) with a modest representation of Asian patients (16%). A total of 53 patients (32%) with *RET*-rearranged lung cancers received a RET inhibitor during the course of their therapy. All patients had advanced disease (stage III or IV). Apart from staging ($p = 0.004$), their clinical characteristics were similar to patients who were not treated with a RET inhibitor.

RET-Directed Therapies in Lung Cancer

RET-positive NSCLC seems to be sensitive to platinum-based chemotherapy. There are limited data on the role of cytotoxic therapy in patients with *RET*-positive NSCLC. Gautschi et al.[16] described a cohort of 108 patients treated with first-line chemotherapy for advanced-stage disease. In this posthoc analysis, the median PFS was 6.6 months (95% confidence interval [CI]: 5.1–9.3), median OS was 23.6 months (95% CI: 13.6–30.8), and the best response rate was 52% (95% CI: 39.8–64.4). Out of the 108 patients, 54 were treated with platinum-doublet chemotherapy. These results were comparable with the outcome with systemic chemotherapy in other oncogene-addicted NSCLC subsets.[21,22] Therefore, platinum-based chemotherapy is a rational treatment approach for *RET*-positive NSCLC; before the emergence of selective RET inhibitors, systemic chemotherapy has remained the standard first-line therapy for this subset of patients. In a multicenter retrospective study of stage IIIB or IV patients with *RET* fusion–positive NCSLC adenocarcinomas, Shen et al.[23] found an increase of median PFS in patients who received pemetrexed-based chemotherapy compared with those who received other regimens in the first-line setting (N = 40; 9.2 versus 5.2 mo; $p = 0.007$). There was no statistical difference in PFS between patients with *KIF5B* and non-*KIF5B* fusions. Drilon et al.[24] found that similar patients achieved an overall response rate (ORR) of 45%, and a median PFS of 19 months with pemetrexed-based chemotherapy (N = 18).

The potential efficacy of immune checkpoint inhibitors (ICIs) in this population has not been tested prospectively. With the aim to address immune therapy efficacy in the context of driver mutation in a retrospective study (IMMUNOTARGET registry), Mazieres et al.[25] found that 16 patients with *RET* fusion–positive NSCLC had a lower response rate and shorter PFS than 271 patients with *KRAS* mutation (6% versus 26% and 2.1 versus 3.2 mo, respectively). In another retrospective study, Hegde et al.[26] found that 12 patients positive with *RET* fusion cancer treated with ICI had a shorter time to progression than 21 patients positive with *RET* fusion cancer treated with non-ICI (3 versus 8.3 mo, respectively; hazard ratio 1.73 [0.70, 4.26], $p = 0.25$). In a series of 74 patients with *RET* fusion–positive NSCLC, Offin et al.[27] found that most of these patients (81%) had low programmed death ligand-1 (less than 50%) and a low tumor mutation burden score (median 1.75 mutations/Mb). The median PFS was 3.4 months (95% CI: 2.1–5.6). There was no association between PFS and programmed death ligand-1 or tumor mutation burden. No response to ICI was observed. In contrast, Guisier et al.[28] reported that ICIs used beyond the first line was effective in nine patients with *RET*-positive NSCLC with a response rate of 37.5%, disease control rate (DCR) of 62.5%, median PFS of 7.6 months (95% CI: 2.3–not reached [NR]), and the 12-month OS rate of 88.9% (95% CI: 70.6–100%). The low number of therapies before ICI (median 1), and the local evaluation of tumor response, which might lead to overestimation, could explain why Guisier's study had better outcomes compared with others. From these limited experiences, it does not seem that immune checkpoint inhibition is an effective therapy for *RET*-positive NSCLC. Future studies combining chemotherapy and ICI are warranted.

When the first reports of *RET* fusions in NSCLC emerged in 2012,[15,19,29,30] clinical trials were launched with multikinase inhibitors such as cabozantinib,[17] vandetanib,[31-33] lenvatinib,[34] and sunitinib[16] that also inhibit RET. These agents have revealed modest anti-RET activity with an increased off-target toxicity profile that often required dose interruption, reduction, or treatment cessation. The increased toxicity is because of stronger inhibition of other targets such as VEGFR and EGFR inhibition and unfavorable pharmacokinetic profile for use in this setting (Table 1). However, the emergence of a new generation of highly selective RET inhibitors has revealed robust clinical results with favorable toxicity profiles (Table 2).

Table 1. Summary of Studies With MKI for the Treatment of Patients With *RET* Fusion-Positive NSCLC

Author	MKI	N	Detection Method (Tissue)	ORR, % (n; 95% CI)	PFS (Range)	OS (Range)	Grade 3-4 TRAE, %
Retrospective study							
Gautschi et al.2017[16]	Cabozantinib	21	FISH, PCR, NGS	37 (7; 16.3-61.5)	3.6 (1.3-7.0)	4.9 (1.9-14.3)	Nr
	Vandetanib	11		18 (2; 2.3-51.8)	2.9 (1.0-6.4)	10.2 (2.4-NR)	
	Sunitinib	10		22 (2; 2.8-60.0)	2.2 (0.7-5.0)	6.8 (1.1- NR)	
Prospective studies—phase 2							
Drilon et al.2016[17]	Cabozantinib	26	FISH, NGS	28 (7; 12-49)	5.5 (3.8- 8.4)	9.9 (8.1-NR)	69
Lee et al.2017[31]	Vandetanib	18	FISH, PCR, NGS	18 (3; Nr)	4.5	11.6	28
Yoh et al.2017[32]	Vandetanib	19	FISH, PCR	47 (9; 28-77)	4.7 (2.8- 8.5)	11.1 (9.4-NR)	>58
Hida et al.2019[34]	Lenvatinib	25	NGS	16 (4; 4.5-36.1)	7.3 (3.6- 10.2)	NR	92
PROSPECTIVE STUDIES - Phase 1b							
Drilon et al.2019[36]	RXDX-105	31	NGS	19 (6; 8-38)	Nr	Nr	Nr

CI, confidence interval; FISH, fluorescence in situ hybridization; MKI, multikinase inhibitor; NGS, next-generation sequencing; NR, not reached; Nr, not reported; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; TRAE, treatment-related adverse event.

Nonselective Multikinase Inhibitors

In the retrospective study of the GLORY registry (Table 1),[16] 53 patients (32%) with *RET*-positive advanced NSCLC were treated with one or more multikinase inhibitors: cabozantinib (21 patients), vandetanib (11 patients), sunitinib (10 patients), sorafenib (2 patients), alectinib (2 patients), lenvatinib (2 patients), nintedanib (2 patients), ponatinib (2 patients), and regorafenib (1 patient). The ORR to cabozantinib, vandetanib, and sunitinib were 37%, 18%, and 22%, respectively. Objective responses were also observed with lenvantinib and nintedanib. However, the median PFS was relatively modest at 2.3 months (95% CI: 1.6–5.0), and the median OS was only 6.8 months (95% CI: 3.9–14.3).

Cabozantinib. Cabozantinib inhibits RET, VEGFR2, ROS1, MET, AXL, TIE2, and KIT; it is approved for the treatment of renal cell carcinoma and thyroid cancers. It has also revealed clinical activity in patients with advanced NSCLC.[35] It is administered orally at a standard dose of 60 mg/day for renal cancer and 140 mg/day for MTC. Dose reduction is often necessary to manage adverse events associated with cabozantinib.

In a phase 2 clinical trial, Drilon et al.[17,31] evaluated the efficacy of cabozantinib in 26 patients with *RET* fusion–positive NSCLC. The median age was 59 years; most participants were women (58%) and never-smokers (65%); 32% had brain metastases. Among 25 patients evaluable for efficacy, seven had a partial response (PR) (ORR 28%, primary end point). The median PFS was 5.5 months (95% CI: 3.8–8.4), and the median OS was 9.9 months (95% CI: 8.1–NR). Although responses were observed in 20% of patients with *KIF5B-RET*, none was observed in patients with *CCDC6-RET*. Dose reduction for cabozantinib was done for 73% of patients; the most common treatment-related adverse events (TRAEs) were grade 1 or 2 in severity. The most common grade 3 TRAE included asymptomatic elevation of serum lipase (15%), the elevation of alanine aminotransferase (ALT) (8%) and aspartate aminotransferase (AST) (8%), thrombocytopenia (4%), and hypophosphatemia (4%). No grade 4 or 5 TRAE was reported. Cabozantinib was discontinued in 8% of patients for retroperitoneal hemorrhage (4%) and thrombocytopenia (4%).

Vandetanib. Vandetanib inhibits RET, EGFR, and VEGFR; it is administered orally at a dose of 300 mg/day. In a phase 2 clinical trial, Lee et al.[31] evaluated the efficacy of vandetanib in 18 patients with *RET* fusion–positive NSCLC (selected by FISH assay) who had received previous platinum-doublet chemotherapy. The median age was

Table 2. Summary of Phase 2 Clinical Trials With Selective *RET* Kinase Inhibitor for the Treatment of Patients with *RET* Fusion-Positive NSCLC

Author	*RET* Inhibitor	N	Platinum Exposed, N (%)	Detection Method (tissue)	ORR, % (95% CI; n)	PFS (Range)	DCR, %	Grade 3-4 TRAE, %
Gainor et al.2019[40]	Pralsetinib	57	30 (53)	Nr	56 (32; -)	Nr	91	28
Drilon et al.2019[41]	Selpercatinib	105	105 (100)	PCR, NGS	68 (71; 58-76)	18.4 (Nr)	94	Nr

CI, confidence interval; DCR, disease control rate; NGS, next-generation sequencing; Nr, not reported; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; PCR, polymerase chain reaction; TRAE, treatment-related adverse event.

56 years, with a higher proportion of men (67%) and never-smokers (61%). Among 17 evaluable patients, three had PR (ORR 18%, primary end point), eight had stable disease (SD) (DCR 65%); clinical benefit beyond 6 months was observed in eight patients (73%). The median PFS was 4.5 months (6-mo PFS rate 44%), and the median OS was 11.6 months (12-mo OS rate was 33%). The most common TRAE included hypertension (89%), rash (72%), diarrhea (44%), acne (28%), and xerosis (22%). No grade 4 or 5 TRAEs were reported.

In another multicenter phase 2 clinical trial of 19 patients with previously treated *RET*-rearranged NSCLC (LURET), Yoh et al.[32] observed objective responses in nine of the 19 intention-to-treat patients with vandetanib (47%); the median PFS was 4.7 months (95% CI: 2.8–8.5) and the median OS was 11.1 months. *RET* was detected by RT-PCR and confirmed with the FISH assay. In a subset of six patients with *CCDC6-RET* fusion, ORR, the median PFS, 12-month OS were more favorable (83%, 8.3 mo, 67%, respectively) than the 10-patient subgroup with *KIF5B-RET* fusion (20%, 2.9 mo, 42%, respectively).

Lenvatinib. Lenvatinib, an inhibitor of RET, VEGFR, and FGFR, is approved for the treatment of thyroid cancer, renal cell cancer, and hepatocellular carcinoma. It is administered orally at a standard dose of 24 mg/day. In a phase 2 clinical trial, Hida et al.[34] evaluated the efficacy of lenvatinib in 25 patients with *RET* fusion–positive NSCLC. The median age was 63 years; most patients were women (72%), never-smokers (56%), and had received previous chemotherapy (92%). *KIF5B-RET* was present in 52% of the patients. The ORR was relatively modest at 16% (95% CI: 4.5–36.5). The median PFS was 7.3 months (95% CI: 3.6–10.2), and the median OS was not reached. The response rate, median PFS, and 12-month OS were more favorable in patients (N = 12) with *CCDC6-RET* fusion (16.7%, 9.1 mo, 66.7%, respectively) than patients (N = 13) with *KIF5B-RET* fusion (15.4%, 3.6 mo, 40.4%, respectively). Grade 3 and 4 TRAEs were observed in 92% of patients: hypertension (56%), hyponatremia (20%), pneumonia (16%), nausea (12%), vomiting (8%) diarrhea (8%), fatigue (8%), and proteinuria (16%). One patient had a grade 5 TRAE (pneumonia).

RXDX-105. In a phase 1b cohort with 31 *RET* fusion–positive, RET inhibitor–naive NSCLC,[36] RXDX-105, a VEGFR-sparing potent RET and BRAF inhibitor, revealed activity in non–*KIF5B-RET* (ORR 67%, n = 6 of 9) but not in *KIF5* (ORR 0%, n = 0 of 20) *RET* fusion partner. RXDX-105 had a manageable safety profile. The most common severe grade TRAEs were hypophosphatemia (9%), elevated ALT (8%), maculopapular rash (7%), elevated AST (5%), and diarrhea (5%). No update on this agent's future development plan.

Alectinib. Alectinib is currently used for the treatment of *ALK*-positive NSCLC; it has a good tolerability profile and high central nervous system activity. In addition to ALK inhibition, alectinib also inhibits RET. The anticancer effects of alectinib in *RET*-positive NSCLC have been reported in xenograft models. In a small cohort of six patients with *RET* fusion–positive NSCLC, two objective responses were observed.[16,37] The ALERT-lung is an ongoing single-arm, phase 2 trial investigating the efficacy of alectinib in patients with advanced-stage *RET*-positive NSCLC treated with at least one platinum-based chemotherapy (Clinicaltrials.gov identifier: NCT03445000). Alectinib was also active in resistant *RET* gatekeeper mutations (*RET* V804L and V804M).[38] A list of ongoing clinical trials targeting *RET*-positive NSCLC is summarized in Table 3.

The lower activity seen with nonselective RET inhibitors is possibly owing to high half-maximal inhibitory concentration leading to suboptimal RET kinase inhibition; inhibition of concomitant targets such as VEGFR also contributes to toxicity, limiting their long-term use.

Another reason for the lower efficacy of nonselective RET inhibitors is that most studies included heavily-treated patients. Their tumors were more likely to develop mechanisms of resistance to RET inhibition by multikinase inhibitors that remained not well understood. Preclinical studies[38,39] revealed that *RET* gatekeeper mutations and EGFR/VEGFR pathway activation may drive this resistance that may require combination therapy to improve outcomes. Future trials with tissue sampling and liquid biopsy before and after RET therapy are needed to understand the mechanisms of resistance to RET inhibition. Combination therapies that build on selective RET inhibitors may provide a more tolerable option to improve the clinical outcomes of these patients.

New Selective RET-Targeted Therapies (Table 2)

New selective RET-targeted therapies are summarized in Table 2.

Pralsetinib (BLU-667). Pralsetinib, a highly selective and potent oral RET inhibitor, is currently under investigation in patients with *RET*-positive NSCLC. A global phase 1/2 clinical trial (ARROW) is evaluating the safety and efficacy of pralsetinib for the treatment of patients with *RET* fusion–positive refractory solid tumors.[40] In the dose-escalation phase (phase 1), the recommended phase 2 dose (RP2D) was established at 400 mg/day. In

Table 3. Summary of Ongoing Clinical Trials With RET Kinase Inhibitor for the Treatment of Patients With *RET* Fusion-Positive NSCLC[a]

Trials	Status	RET Inhibitor	ClinicalTrials.gov Identifier
AcceleRET lung study of pralsetinib for the first-line *RET* fusion-positive, metastatic NSCLC (phase 3)	Recruiting	Pralsetinib (BLU-667)	NCT04268550
Phase 1/2 study of the highly selective *RET* inhibitor, pralsetinib (BLU-667), in patients with thyroid cancer, NSCLC, and other advanced solid tumors	Recruiting	Pralsetinib (BLU-667)	NCT04222972
Phase 1/2 study of the highly selective RET inhibitor, pralsetinib (BLU-667), in patients with thyroid cancer, NSCLC, and other advanced solid tumors	Recruiting	Pralsetinib (BLU-667)	NCT03037385
Targeted treatment for *RET* fusion-positive advanced NSCLC cancer (a LUNG-MAP treatment trial)	Recruiting	Selpercatinib (LOXO-292)	NCT03037385
Phase 1/2 study of LOXO-292 in patients with advanced solid tumors, RET fusion-positive solid tumors, and MTC	Recruiting	Selpercatinib (LOXO-292)	NCT03157128
A study of Selpercatinib (LY3527723) in participants with advanced or metastatic RET fusion-positive NSCLC (LIBRETTO-431; phase 3)	Recruiting	Selpercatinib (LOXO-292)	NCT04194944
Study of TPX-0046, A RET/SRC inhibitor in adult subjects with advanced solid tumors harboring RET fusions or mutations	Recruiting	TPX-0046	NCT04161391
ALEctinib for the treatment of pretreated RET-rearranged advanced NSCLC	Recruiting	Alectinib	NCT03445000

[a]Details of this table were accessed on April 28, 2020.
MTC, medullary thyroid cancer.

the expansion phase (phase 2), patients were enrolled in cohorts on the basis of tumor type, previous therapies, and *RET* alterations with response rate and safety as primary end points.

The primary analysis of the registrational data included the 79 enrolled patients with *RET* fusion–positive NSCLC: 21 in the dose-escalation and 58 in the dose-expansion. The most common fusion partners were *KIF5B* (56%) and *CCDC6* (20%). Approximately 40% of the patients had brain metastases. Patients had received a median of two previous treatment regimens for their disease and 41% were previously treated with ICI; nearly 30% had previously received a multikinase inhibitor.

Among 57 patients evaluable for response, the objective response rate was 56% (95% CI: 42%–69%): six patients (19%) had achieved response duration longer than or equal to 6 months; 26% had SD; the overall DCR was 91%. Over 90% of the 32 responding patients remain on treatment (December 2018). Among the 30 platinum-exposed patients treated at RP2D, the response rate was 60% with 18 PR. Objective responses were also noted in the brain of seven of nine patients (78%) with measurable brain disease, providing evidence of activity against brain metastases. Responses did not differ on the basis of previous therapy, fusion partner, or brain metastases.

Pralsetinib was tolerated well with most adverse events of grade 1 or 2 in severity; 28% of the patients experienced greater than or equal to grade 3 toxicity. The most common all-grade TRAE included elevation of AST (22%), hypertension (18%), elevation of ALT (17%), constipation (17%), fatigue (15%), and neutropenia (15%); severe grade hypertension (10%). Only 7% of patients with NSCLC discontinued therapy owing to treatment-related toxicity at the RP2D. Pralsetinib was granted breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) in 2018 after initial data from the ARROW study revealed broad and durable antitumor activity and was well tolerated in patients with *RET* fusion–positive NSCLC that progressed after platinum-based chemotherapy.

Pralsetinib is to be compared with the combination of platinum and pemetrexed with or without pembrolizumab in LIBRETTO-431, a randomized phase 3 trial in patients with treatment-naive *RET* fusion–positive NSCLC with PFS as the primary end point (Table 3).

Selpercatinib (LOXO-292). Selpercatinib is another highly selective RET inhibitor that has revealed promising activity in RET-positive NSCLC. Drilon et al.[41] presented data from the clinical trial "LOXO-292 investigated to block *RET*-altered tumors" (LIBRETTO-001) at the 2019 World Conference on Lung Cancer (2019). In the dose-escalation phase (phase 1), the RP2D was established at 160 mg given orally twice daily. In the expansion phase (phase 2), patients were enrolled in various cohorts on the basis of tumor type, previous therapies, and *RET* alterations. The primary end point was objective response rate; the duration of response (DOR), PFS, and safety were secondary end points.

The primary analysis of the registrational data included the first 105 enrolled patients with *RET* fusion–positive NSCLC previously treated with platinum-based

Table 4. Incidence Comparison of Some Important All-Grade TRAEs Among Different RET Inhibitors

	Cabozantinib (N = 26), %	Vandetanib (N = 18), %	Lenvatinib (N = 25), %	RXDX-105 (N = 31), %	Pralsetinib (N = 57), %	Selpercatinib (N = 105), %
Nausea	31	6	60	8	Nr	19
Diarrhea	62	44	52	18	Nr	31
Fatigue	46	11	36	22	15	24
Hypertension	19	89	68	Nr	18	29
Neutropenia	Nr	Nr	Nr	Nr	15	Nr
Elevated ALT	96	6	20	16	17	26
Elevated AST	73	6	24	16	22	28

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Nr, not reported. TRAE, treatment-related adverse event.

therapy. The median age was 61 years, 59% were women, and 35% had brain metastases. The median number of previous systemic therapies was three (1–5). Most patients (55%) had previously received treatment with an ICI; 48% had previously received one or more multikinase inhibitor therapy.

The response rate was 68% (95% CI: 58%–76%); 26% had SD, and DCR was 94%. Only 2% had progressive disease as best response, and the remaining were not evaluable for response. Responses did not differ on the basis of the type or number of previous therapies, or the fusion partner. In the subset of 11 patients with measurable brain metastases at baseline, 10 patients (91%) had an intracranial objective response (95% CI: 59%–100%), with a DCR of 100%. One patient with heavily pretreated brain metastases achieved a clinical response within the first week of selpercatinib for her leptomeningeal metastases followed by a resolution on imaging at week 8.[42] With a median follow-up of 8 months, the median DOR, and PFS were 20.3 months (95% CI: 13.8–24) and 18.4 months (95% CI: 12.9–24.9), respectively. In patients (N = 39) who received selpercatinib as first-line therapy, the response rate was 85% (95% CI: 69–91), and 9% had SD (DCR 94%). Median DOR and PFS were not reached (follow-up duration 4.8 and 3.7 mo, respectively). For both groups combined, the most common fusion partners were *KIF5B* (53%) and *CCDC6* (22%).

Selpercatinib was tolerated well; only nine patients (8.5%) discontinued therapy owing to treatment-related toxicity. The most common all-grade treatment-emergent adverse events in the primary analysis set were: dry mouth (32%), diarrhea (31%), hypertension (29%), increased AST (28%), increased ALT (26%), fatigue (24%), constipation (22%), headache (20%), nausea (19%), peripheral edema (19%), and increased creatinine (18%). The most common grade 3 to 4 was hypertension (14%). No other severe grade treatment-emergent adverse event occurred in more than 8% of patients.

Selpercatinib was granted breakthrough therapy designation by the FDA in 2018 after initial data from the clinical trial LIBRETTO-001, which revealed robust antitumor activity against several diverse *RET* fusions and brain metastases and also strong evidence of durability in a population with an unmet need, which are patients with *RET* fusion–positive NSCLC.

Selpercatinib will be compared with the first line to platinum-based chemotherapy in AcceleRET lung, a randomized phase 3 trial in patients with RET fusion–positive NSCLC with PFS as the primary end point (Table 3).

Comparing RET inhibitors' safety profile (Table 4), hypertension is reported but less frequently with the selective RET inhibitors compared with the other RET multikinase inhibitors. This is likely owing to the high degree of similarity between RET and VEGR kinases, which renders avoiding VEGFR inhibition challenging. In addition, neutropenia reported with pralsetinib but not with selpercatinib explains that selpercatinib is likely to be selectively cytotoxic to *RET*-altered cells.

Currently, there are no FDA-approved options for this patient subpopulation. The potential approval of the two selective RET inhibitors on the basis of phase 2 data would represent a major step forward in providing the first effective targeted therapy for patients positive with *RET* fusion with NSCLC.

Detection of *RET* Fusion

Given the robust efficacy with selective RET inhibitors, *RET* rearrangement should now be considered as a targetable driver mutation in NSCLC similar to *EGFR* mutations and *ALK* and *ROS1* rearrangements. Therefore, it is very important to screen patients with NSCLC for *RET* rearrangements at the time of diagnosis. Because there are no specific clinical features of this subset of NSCLC, clinical selection cannot be used to determine whether a given patient should be screened for *RET*. Multiple methods have been used for RET analysis: NGS, FISH, immunohistochemistry, and RT-PCR. NGS is currently the most sensitive method for *RET* analysis.[43] NGS also provides comprehensive molecular profiling

to identify upstream gene partners and concurrent genomic aberration that may predict treatment response.[17] In addition, it will allow for a better selection of patients for referral to matched clinical trials targeting *RET*. DNA-based NGS offers a comprehensive tool to detect genomic alterations. However, it may not detect gene fusions in samples with low tumor purity (<20%) or suboptimal DNA quality or quantity. One consideration would be to perform an RNA-based NGS to uncover targetable *RET* fusions that were not detected by DNA-based NGS.[44] RT-PCR is successful to detect most common *RET* fusion partners but not the less common ones.[45] *RET* FISH has a high positive rate owing to the narrow spacing between the split probe signals. It has a sensitivity of 100% and a suboptimal specificity of 45% to 60% and a false-positive of 39% to 55%.[45] Screening for *RET* using FISH after RT-PCR might have decreased the detection of patients with false-positive in the study by Yoh et al.[32]; this allowed a better selection of patients and could explain the increased ORR with vandetanib compared with the study by Lee et al.[31] RET immunohistochemistry (anti-RET antibody ab134100, Abcam, Cambridge, United Kingdom) does not have strong corroborating evidence to warrant clinical use because of low sensitivity 55% to 65% and variable specificity 40% to 85%.[45]

Most of the clinical studies included *RET* with different fusion partners. There is no strong preclinical and clinical data to our knowledge to support the sensitivity of different fusion partners to *RET* inhibition. Therefore, future studies are needed to determine the predictive and prognostic value of the *RET* fusion partner.

RET Emergence as a Mechanism of Acquired Resistance to EGFR Inhibition

Few reports reported that an actionable driver oncogene (*RET*) can develop as a mechanism of acquired resistance to another actionable driver mutation (*EGFR*) during therapy with EGFR inhibition and that targeting both drivers is a promising therapeutic strategy for these patients. In a comprehensive review, Zhu et al.[46] reported the distribution of receptor tyrosine kinase fusions detected in tissue or blood at the time of acquired resistance to EGFR inhibition in NSCLC. *RET* fusion was detected in 55%, 27%, 40%, and 42% at the time of acquired resistance to first-, second-, and third-generation EGFR inhibition, and also after osimertinib use in *T790* mutation, respectively. Most *RET* fusions were *CCDC6* (58%) and *NCOA4* (26%).

CCDC6-RET fusion has emerged as a potential acquired mechanism of resistance to osimertinib, an EGFR inhibitor used in metastatic, recurrent NSCLC with *EGFR* exon 19 deletion, exon 21 L858R, or T790 mutations.[47,48] The combination of second-line osimertinib with a selective RET inhibitor, pralsetinib, led to a decrease in cell viability in vitro; it was well tolerated and led to an impressive response with 78% tumor shrinkage at 8 weeks in two patients with *EGFR* exon 19 deletions: one with *CCDC6-RET* fusion identified on MGH Solid Fusion Assay 18 months after progression on second-line osimertinib; and another with *NCOA4-RET* fusion identified on NGS 2 years after progression on the combination afatinib and cetuximab.[49] Other reports described the fusion *KIF5B-RET* found on tissue[50] or liquid[51] biopsy as a potential mechanism of acquired resistance in patients with NSCLC with *EGFR* exon 19 deletions who progressed on EGFR inhibition with erlotinib[52] or icotinib.[51] The patient who progressed after 11 months of treatment with icotinib, had an SD for 2 months with the addition of cabozantinib.

NCOA4-RET is a rare fusion reported as a potential mechanism of resistance to a patient with *EGFR* mutation L858R NSCLC treated with afatinib for 20 months and responded to the addition of cabozantinib with 7-month of SD.[52]

Mechanism of Resistance to RET Inhibition

Knowledge regarding the biological mechanisms that mediate acquired resistance to RET inhibitors is emerging; bypass pathways that are not blocked by current RET multikinase inhibitors are likely to be among the most common mechanisms.

Preclinical studies found that activation of the EGFR, VEGFR, and downstream mTOR pathways may drive the resistance to RET inhibition; the combination of everolimus, an mTOR inhibitor, and vandetanib, a RET/VEGFR/EGFR inhibitor, was able to overcome resistance. On the basis of this rationale, the combination has been studied in *RET*-positive NSCLC.[53,54] Among 13 patients, seven objective responses, and a median PFS of 4.4 months (95% CI: 3.4–NR) were observed. In patients with *RET* fusion–positive by NGS, the response rate was 70%, and the median PFS was 8 months (95% CI: 3.4–NR). No response was seen in the three patients with FISH-positive NGS-negative *RET* fusion. Severe toxicities included diarrhea (21%), thrombocytopenia (16%), QTc prolongation (5%), and rash (5%). Most patients (89%) required dose modifications after one cycle owing to toxicity.

Solvent mutations sterically hinder the binding of RET inhibitor leading to the loss of RET activity in selective and multikinase RET inhibitors. Preclinical studies reported the emergence of *RET* G810R solvent mutation as acquired resistance to selective RET

inhibitors such as selpercatinib and pralsetinib. However, solvent mutations remained sensitive to another potent and selective next-generation RET/SRC oral kinase inhibitor, TPX-0046, that lacks activity against RET V804M gatekeeper mutation. TPX-0046 is VEGFR2 sparing and is currently being tested in phase 1/2 clinical trial for patients with advanced solid tumors harboring *RET* fusions or mutations (NCT04161391). Of note, *RET* V804M mutation has been reported to confer resistance to vandetanib (and *RET* S904F mutation) and can be overcome with selpercatinib but not TPX-0046.[55-58]

Recently, Solomon et al.[56] described the first mechanism of "on-target" resistance to selpercatinib with the detection of *RET* solvent front mutations G810R, G810S, and G810C on circulating tumor DNA few months before the emergence of clinical resistance in five patients who had a dramatic initial response to selpercatinib, three of them with NSCLC. At autopsy, plasma and tumor biopsies confirmed G810 mutations at multiple sites of metastatic disease for the same patient. These important observations will allow for developing strategies to overcome acquired resistance.

Conclusions

With the emergence of selective RET inhibitors, patients with advanced-stage NSCLC should have their tumors tested routinely for *RET* fusion using NGS. Enrollment of patients with *RET* fusion–positive metastatic NSCLC in clinical trials should be highly encouraged. Otherwise, given *RET* fusion–positive NSCLC sensitivity to platinum-based chemotherapy and the low activity of RET multikinase inhibitors, it is reasonable to treat these patients first with platinum-doublet chemotherapy, then consider a RET multikinase inhibitor as their next line of therapy until FDA approval of the selective inhibitors.

It is hoped that the selective RET inhibitors will be available for routine clinical practice in the near future. With a response rate of approximately 60% to 70% and a median PFS of approximately 18 months, RET inhibition should be considered as first-line therapy for patients with *RET* fusion. Knowledge regarding mechanisms of acquired resistance to RET inhibition is beginning to emerge; this will pave the way for the development of novel approaches to overcome acquired resistance and promote long-term efficacy.

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