Clinical development of RET inhibitors in RET-rearranged non-small cell lung cancer: Update

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Abstract

Precision oncology is now the evidence-based standard of care for the management of many advanced non-small cell lung cancers (NSCLC). Notably, new molecular profiling technologies have permitted dynamic growth in the identification of actionable driver oncogenes including *RET* rearrangements. *RET* oncogenes cannot be adequately detected by immunohistochemistry, although fluorescence *in situ* hybridization, reverse transcriptase polymerase chain reaction and next-generation sequencing are complementary diagnostic tools. In the clinical setting, the benefit of the most developed RET inhibitors, *i.e.*, cabozantinib, vandetanib and lenvatinb, in terms of response and median progression-free survival has been demonstrated. The absence of striking clinical results of RET inhibitors underscores the clear need for development of more selective and potent RET inhibitors. This paper reviews the clinical data available on RET inhibitors in RET-associated NSCLC.

Introduction

In NSCLC, the main potentially targetable chromosome rearrangements involve the *ALK, ROS1, NTRK* and *RET* (rearranged during transfection) genes. However, these chromosomal rearrangements are present only in a small percentage of patients with lung cancer (3%-7%,[1] 1%-2%,[2] 3.3%[3] and ~1%-2%,[4] respectively). Oncogenic gene rearrangements in NSCLC can lead to the expression of oncogenic fusion proteins that retain the kinase domain of the proto-oncogene, and the downstream signaling directs cells to proliferation and survival in a ligand-independent manner. Inhibition of the oncogenic fusion proteins can result in potent cancer growth inhibition and regression of tumors in patients. To date, the drugs for NSCLC approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have been targeted to ALK and ROS1 rearrangements only. The activity of many multi-kinase inhibitors has been explored in *RET*-rearranged NSCLC, and novel RET-specific inhibitors have recently transitioned to clinical development. Based on initial results obtained with the multi-kinase inhibitors in RET-rearranged NSCLC, the National Comprehensive Cancer Center Network (NCCN) 2017 guidelines recommend the use of cabozantinib and vadentanib outside the context of a clinical trial. In this paper, we review the current available clinical data on RET inhibitors, reasons for their resistance, and emerging treatment approaches in RET-rearranged NSCLC.

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RET rearrangements in NSCLC

RET is a 150 KDa membrane-bound receptor tyrosine kinase that is expressed in a variety of neuronal and endocrine tumors.[5] The RET transmembrane protein is encoded by proto-oncogene *RET* located on chromosome 10q11.2.[6] Activation of RET leads to auto-phosphorylation on intracellular tyrosine residues and initiation of Ras/MAP kinase, PI3K/AKT, and phospholipase C pathways that signal cell proliferation and survival. Oncogene activation of *RET* can occur by somatic or germline alterations. Germline mutations of *RET* lead to type 2 multiple endocrine neoplasia, whereas somatic mutations lead to sporadic medullary thyroid carcinoma. Somatic *RET* rearrangements induce formation of the RET fusion protein kinases that localize in the cytosol and have transforming and oncogenic properties.[7] Fusion proteins resulting from the chromosomal rearrangement of *RET* were first identified in papillary thyroid carcinoma (PTC).[8,9] In 2012, four independent research groups identified *RET* fusions in NSCLC.[10-13] Collectively, these studies concluded that *RET* fusions occur in approximately 1% to 2% of NSCLCs and that *RET* rearrangements tend to be mutually exclusive with other major lung-cancer drivers such as *EGFR, KRAS* mutations and *ALK* or *ROS1* rearrangements.[14] In NSCLC, at least 12 fusion *RET* partner genes have been identified to date. The recent global registry of patients with *RET*-rearranged NSCLC reported that among 81 cases with identifiable fusion partners, 72% involved the kinesin family *5B* gene (*KIF5B).* The second most common fusion partner is *CCDC6* (23%), followed by *NCOA4* (2%), *EPHA5* (1%) and *PICALM* (1%).[15] *RET* rearrangements were observed in males and females in equal proportions. As per the global registry, 63% were never smokers, 24% were former smokers, and 10% were current smokers. Histologically, most *RET* rearrangements were identified in adenocarcinoma. At present, there is no gold-standard method for the identification of *RET* rearrangements. Although immuno-

histochemistry (IHC) is an effective screening tool to detect ALK- and *ROS1*-positive NSCLC, the utility of IHC for the detection of *RET* fusions has been limited because of variable staining patterns and weak reactivity.[16] Reverse transcriptase polymerase chain reaction (RT-PCR) is both sensitive and specific for the detection of known fusions, but it is not reliable for the detection of new fusion partners. Fluorescence *in situ* hybridization (FISH) and next-generation sequencing (NGS) are effective techniques for the detection of *RET* fusions, but their high costs and technical expertise for interpretation made them usually available only in larger reference centers.[17] Therefore, in most screening studies for *RET* rearrangements, RT-PCR was typically combined with FISH, suggesting that they are complementary.

Clinical trial results with RET inhibitors for *RET* rearrangements in NSCLC

The main clinical data on the most developed multi-kinase inhibitors in RET-rearranged NSCLC are summarized in Tables 1 and 2. The clinical activity of RET-directed therapy was first reported in 2013 by Drillon et al., when three patients with *RET*-rearranged NSCLC were treated with cabozantinib.[18] Two of these patients experienced partial responses by RECIST 1.1 criteria, and the third had prolonged stable disease. Based on this early experience, a phase 2 trial was conducted to assess the activity of cabozantinib 60 mg/d in 26 patients with *RET*-rearranged NSCLC screened by FISH or NGS. Of these patients, 62% had a *KIF5B-RET* rearrangement. Among 25 patients who were assessable for response, there were seven partial responses [overall response rate (ORR) 28%]. The median progression-free survival (mPFS) was 5.5 months, and the median overall survival (mOS) was 9.9 months.[19] The ORR in patients with *KIF5B-RET*-rearranged NSCLC was 20%, and it was 50% in patients with different known *RET* fusion genes. Twenty-six patients treated were evaluable for toxicity. Treatment-related adverse events were predominantly grade 1 or grade 2, and one or more drug-related toxicities of any grade were observed in 25 patients (overall toxicity rate of 96.2%). The most common treatment-related adverse events of any grade were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hypothyroidism, diarrhea, palmar plantar erythrodysesthesia, and skin hypopigmentation. The most common grade 3 treatment-related adverse events were lipase elevation in four patients (15%), increased ALT in two patients (8%), decreased platelet count in two patients (8%), and hypophosphatemia in two patients (8%). Patients in whom these toxicities were observed were asymptomatic. Nineteen patients (73%) required a cabozantinib dose reduction due to intolerable grade 2 or grade 3 drug-related toxicities. The most common reasons for dose reduction included palmar plantar erythrodysesthesia in seven patients (37%), fatigue in three patients (16%), and diarrhea in two patients (11%).

In selected patients with NSCLC, vandetanib (300 mg/d) was tested in two different trials. A Japanese phase II (LURET) study included 1,536 patients with *EGFR*-negative NSCLC, who were screened by multiplex transcriptase PCR and FISH break-apart assay.[20] Among the patients who were screened, 34 (2%) were *RET* positive, and 19 were enrolled in the study and treated with 300 mg of vandetanib daily. Among 17 patients with evaluable data included in primary analysis, the ORR was 53%, and the median PFS was 4.7 months. The OS rate at 12 months was 47%, and the median OS was 11.1 months. The treatment response and survival outcome were much higher in patients with the *CCDC6-RET* fusion subtype, with 83% ORR and mPFS of 8.3 months compared with 20% and 2.9 months, respectively, for patients with the *KIF5B-RET* fusion variant. In another similar study design, a Korean phase II trial evaluated vandetanib (300 mg/d) in 18 patients with RET-rearranged NSCLC; 28% of them had *KIF5B-RET* rearrangement, 11% were *CCDC6-RET*-positive, 56% had an unknown *RET* fusion gene, and one patient (5%) displayed a novel *MYO5C-RET* rearrangement. Among the 17 patients with evaluable results, the ORR was 18% (three patients with partial responses), the mPFS was 4.5 months, the mOS was 11.6 months and the 1-year OS rate was 33%.[21] Overall, the treatment was well tolerated. Hypertension (16.89%), rash (13.72%), diarrhea (8.44%), acne

Table 1. Clinical data on single-agent RET inhibitors in advanced pre-treated *RET*-rearranged NSCLC.

Type of Study (Identifier)	RET inhibitor	Screening techniques	# patients	ORR	mPFS (months)	mOS (months)
Phase II single arm (NCT01639508)[19]	Cabozantinib 60 mg/d	FISH or NGS	26	28%	5.5	9.9
Phase II single arm - Japan (UMIN000010095)[20]	Vandetanib 300 mg/d	RT-PCR and FISH	19	53%	4.7	11.1
Phase II single arm (NCT01823068)[21]	Vandetanib 300 mg/d	FISH	18	18%	4.5	11.6
Phase II single arm (NCT01877083)[22]	Lenvatinib 24 mg/d	NA	25	16%	7.3	NR

NSCLC, non-small cell lung cancer; RET, rearranged during transfection; *RET,* rearranged during transfection gene; FISH, fluorescence *in situ* hybridization; NGS, next-generation sequencing; RT-PCR, reverse-transcriptase polymerase chain reaction; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; NA, not available.

Table 2. The most common treatment-emergent adverse events (TEAEs) of the most developed RET inhibitors in NSCLC.

Cabozatinib (n = 26)	Vandetanib (*n* = 18)	Lenvatinib (*n* = 25)
ALT increased (96%)	Hypertension (89%)	Hypertension (68%)
AST increased (73%)	Rash (72%)	Nausea (60%)
Hypothyroidism (69%)	Diarrhea (44%)	Decreased appetite (52%)
Diarrhea (62%)	Acne (28%)	Diarrhea (52%)
Palmar plantar erythrodysesthesia (58%)	Xerosis (22%)	Proteinuria (48%)
Skin hypopigmentation (50%)	Abdominal discomfort (17%)	Vomiting (44%)
Dose reduction (73%)	Dose reduction (28%)	Dose reduction (64%)

NSCLC, non-small cell lung cancer; RET, rearranged during transfection; ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, number of subjects.

(5.28%), xerosis (4.22%), and abdominal discomfort (3.17%) were the most frequent adverse events in the study patients (Table 2). Five patients experienced adverse events of grade 3: hypertension (3, 18%), asymptomatic QTc prolongation in electrocardiography (2, 12%), and elevated serum level of aminotransferases (1, 6%). Among these, four patients underwent dose reduction (28%).

In another phase II trial, lenvatinib (24 mg/d) was tested in 25 patients with RET-rearranged NSCLC. The results were presented at the 2016 European Society for Medical Oncology (ESMO) Congress. Of them, 52% had a *KIF5B-RET* rearrangement and 48% had different unknown RET fusions genes determined by NGS. The ORR was 16% (four patients with partial responses) and the mPFS was 7.3 months.[22] In seven patients who had received previous RET therapy, ORR with lenvatinib was 14% with a mPFS lower than other knowns fusion variants (3.6 *versus* 9.1 months). Grade ≥3 treatment emergent adverse events (TEAEs) occurred in 23 (92%) patients. Of three fatal AEs, one (pneumonia) was possibly related to lenvatinib. TEAEs requiring dose reduction occurred in 16 (64%) patients. The most common TEAEs included hypertension (17.68%), nausea (15.60%), decreased appetite (13.52%), diarrhea (13.52%), proteinuria (48%), and vomiting (11.44%).

Other multi-target kinase inhibitors have also been tested in *RET*-rearrangement NSCLC, including sunitinib,[23] sorafenib,[24] alectinib,[25] nintedanib, ponatinib and regorafenib.[26] Data on these agents are generally limited to case reports. No direct comparison of RET inhibitors has been performed. Therefore, it is not possible to identify the most active RET inhibitor based on the currently available clinical data.

Mechanisms of RET-inhibitor resistance and emerging therapeutic approach

The activity of multi-kinase inhibitors in patients with *RET*-rearranged NSCLC (ORR 16%-53% and mPFS 4.5-7.3) is clearly inferior to the responses and survival outcomes seen with selective TKIs in other oncogene-associated NSLC models. In fact, the ORR of 56%-85% and mPFS duration 9.2-13.7 months was achieved with targeted TKIs in patients with EGFR mutant,[27] the ORR of 60%-95% and mPFS 8-11 months was achieved in patients with *ALK*-rearranged NSCLC,[28] and the ORR of 65%-85% and mPFS 9.3-19.3 months was achieved in patients with ROS1-rearragend NSCLC.[29] One possible explanation for the limited efficacy of multi-kinase RET inhibitors relates to the inhibition of non-RET kinases rather than RET-specific blocking. As such, the use of multi-kinase RET inhibitors is often associated with high rate of toxicities (hypertension, proteinuria, palmar plantar erythodysesthesia) that are mostly due to the activity against VEGFR kinases, or diarrhea due to activities related to *EGFR* inhibition, which lead to dose reductions in up to 73% of the patients (Table 2) and achieving suboptimal RET-inhibitory plasma concentrations consequently. It is therefore possible that other intrinsic mechanisms play a role in the resistance.

The mechanisms of acquired resistance to RET inhibitors in the patients are currently poorly understood. In fact, the Japanese phase II study of vandetanib showed a lower ORR and shorter mPFS duration among patients with tumors harboring the KIF5B-RET-positive fusion versus those with tumors harboring the CCDC6-RET fusion type.[20] Recent molecular studies have identified MDM2 proto-oncogene (*MDM2*) amplification in pretreatment biopsy specimens from 8 of 16 NSCLC who developed resistance to cabozantinib.[30] Metastasis to the central nervous system (CNS) also represents an important clinical challenge in RET-rearranged NSCLC. Vandetanib is thought to have a limited blood-

Table 3. Ongoing clinical trials of known and novel *RET* inhibitors in RET-rearranged NSCLC.

Agent	Manufacturer	Anti-RET (IC_{50}, nM)	Other major targets	Phase	NSCLC population (Identifier)
Alectinib	Roche	4.8	ALK, LTK, CHEK2, FLT3, PHKG2	I/II	*RET*-rearranged NSCLC – Japan (UMIN000020628)
Alectinib	Roche	4.8	ALK, LTK, CHEK2, FLT3, PHKG2	I/II	*RET*-rearranged NSCLC (NCT03131206)
Apatinib	Jiangsu Hengrui/ LSK BioPharma	13	VEGFR2, KIT, SRC	II	*RET*-rearranged NSCLC (NCT02540824)
BLU-667	Blueprint Medicines	0.4	VEGFR2	I/II	*RET*-rearranged NSCLC prior or not prior to TKI that inhibits RET (NCT03037385)
Lenvatinib	Eisai	1.5	VEGFR1-3, FGFR1-4, PDGFR, KIT	II	*KIF5B-RET*-positive and other confirmed RET translocations lung adenocarcinoma (NCT01877083)
Ponatinib	Ariad	25.8	BCR-ABL, SRC, VEGFR, PDGFR, FGFR, FLT3, KIT	II	*RET*-rearranged NSCLC (NCT01935336)
Sunitinib	Pfizer	220-1300	VEGFR1-2, PDGFRβ, FLT3, KIT	II	*RET*-positive lung adenocarcinoma (NCT01829217)
Sitravatinib	Mirati Therapeutics	44	VEGFR, PDGFRα, MET, AXL, TRK, DDR1-2, FLT3, KIT, EPHA2-4, EPHB2/4, MER, MST1R	I/IB	NSCLC with genetic alterations in *MET, AXL, RET, TRK, DDR2, KDR, PDGFRa, KIT* or *CBL* (NCT02219711)
BLU-667	Blueprint Medicines	0.4	RET-specific inhibitor	I/II	*RET*-rearranged NSCLC prior or not prior to TKI that inhibits RET (NCT03037385)
LOXO-292	Loxo Oncology	NA	RET-specific inhibitor	I	*RET*-fusion NSCLC (NCT03157128)

NSCLC, non-small cell lung cancer; RET, rearranged during transfection; RET, rearranged during transfection gene, IC50, half maximal inhibitory concentration; VEGFR, vascular endothelial growth factor receptor; MET, MET proto-oncogene, receptor tyrosine kinase; AXL, AXL receptor tyrosine kinase; FLT3, FMS-like tyrosine kinase; KIT, KIT proto-oncogene, receptor tyrosine kinase; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; BCR-ABL, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1; SRC, SRC proto-oncogene, non-receptor tyrosine kinase; DDR, discoidin domain receptor; EPHA, ephrin receptor A; EPHB, ephrin receptor B; MST1R, macrophage-stimulating protein receptor 1; PDGRF, platelet-derived growth factor receptor; *PDGRFa*, platelet-derived growth factor receptor alpha gene; *P*DGFR*b* , platelet-derived growth factor receptor beta gene; KIT, KIT proto-oncogene receptor tyrosine kinase gene; ALK, anaplastic lymphoma kinase; LTK, leukocyte receptor tyrosine kinase; CHEK2, checkpoint kinase 2; PHKG2, phosporylase kinase gamma 2; MER, MER tyrosine kinase receptor; MST1R, macrophage stimulating 1 receptor; TRK, tropomyosin receptor kinase; KDR, kinase insert domain receptor; CBL, Casitas B-lineage Lymphoma.

brain barrier penetration, which may be improved by modulation of P-gp/Abcb1- and Bcrpl/Abcg2-mediated efflux through the use of mTOR inhibitor.[31,32] Therefore, a phase I trial (NCT01582191) testing the antitumor activity of vandetanib (100 mg/d) in combination with everolimus (m-TOR inhibitor) at 2.5 mg/d in patients who have refractory solid tumors, including those with *RET*-rearranged NSCLC, was initiated. Preliminary results indicate that the combination of vandetanib and everolimus is well tolerated. The most common treatment-related AEs are diarrhea, fatigue, mucositis, and rash. The combination produced significant antitumor activity in patients with *RET*-rearranged NSCLC.[33] This study is active and recruiting patients; updated results about a larger cohort of patients with *RET*-rearranged NSCLC are eagerly awaited.

Currently, there are several ongoing clinical trials testing the safety and efficacy of known and novel RET inhibitors in RET-rearranged NSCLC (Table 3). The difference in the relative potency of RET inhibitors restricts the therapeutic window as high levels of these drugs may cause toxicity related to other targets before reaching optimum RET inhibition levels. Therefore, novel and potent inhibitors have been developed to selectively target the RET kinase. Two of these novel RET-specific inhibitors, BLU-667 and LOXO-292,[34,35] have broad preclinical activity against various RET rearrangements. BLU-667 is being studied in a phase I trial (NCT03037385) enrolling medullar thyroid carcinoma (MTC), NSCLC and other tumors displaying RET activation. The trial has a target enrollment of 115 patients. Preliminary data from the trial is expected in Q1 2018. LOXO-292 is currently being studied in a phase I trial (NCT03157128) enrolling advanced tumors with RET drivers, including NSCLC with RET fusions. The trial is seeking to enroll 180 patients, and an early update from the trial was presented at the International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer 2017 in Yokohama, Japan. The abstract describes the first two patients with RET-fusion lung cancer with and without brain metastases treated with LOXO-292. Both patients had disease progression while receiving prior multi-kinase inhibitors. On LOXO-292, both patients achieved partial responses and the therapy has been well-tolerated with no adverse events attributed to it. A more robust data of the trial is expected in 2018.

Conclusions

At present, the use of the few investigated RET inhibitors in RET-rearranged NSCLC has not shown striking clinical benefits compared with what has been seen with other targeted agents in other gene rearrangement types. The mechanisms of resistance to them are not well understood. Furthermore, RET inhibitors showed high rates of severe toxicities, leading to frequent dose reduction. No definitive conclusions can be done on the rather confounding data about the potential different impact of anti-RET therapies according the RET-rearrangement or fusion variants generated from small subgroups analysis. *RET*-rearrangement remains a challenging target, and the biology behind these drivers in NSCLC will require further exploration of the most potent and selective RET inhibitors and CNS activity. The *RET* rearrangements are rather rare, so that it may not be possible to conduct randomized trials to compare the activity of traditional chemotherapy or immunotherapy or the impact on different fusion variants. To conduct prospective trials with larger sample sizes, collaboration between various investigators and centers around the globe is crucial. Combination therapies and novel RET-specific inhibitors in NSCLC patients harboring RET rearrangements are being explored to boost the activity observed with the existing multi-kinase RET inhibitors in the clinic. Further research in the field of RET-inhibitors in RET-rearranged NSCLC is encouraged.

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