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 lenvatinib, 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%–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 vandetanib 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.

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. The RET transmembrane protein is encoded by proto-oncogene RET located on chromosome 10q11.2. 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. Fusion proteins resulting from the chromosomal rearrangement of RET were first identified in papillary thyroid carcinoma (PTC). In 2012, four independent research groups identified RET fusions in NSCLC. 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. 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%). 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-
hypothesis (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. 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. 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. 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. 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. 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%. 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 (NCT01635958) | Cabozantinib 60 mg/d | FISH or NGS | 26 | 28% | 5.5 | 9.9 |
| Phase II single arm - Japan (UMIN000010095) | Vandetanib 300 mg/d | RT-PCR and FISH | 19 | 53% | 4.7 | 11.1 |
| Phase II single arm (NCT01823068) | Vandetanib 300 mg/d | FISH | 18 | 18% | 4.5 | 11.6 |
| Phase II single arm (NCT01871083) | Lenvatinib 24 mg/d | NA | 25 | 10% | 7.3 | NR |

NSCLC, non-small cell lung cancer; RET, rearranged during transfection; 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.

|                  | Cabozantinib (n = 26) | Vandetanib (n = 18) | Lenvatinib (n = 25) |
|------------------|-----------------------|---------------------|---------------------|
| ALT increased   | Hypertension (89%)    | Hypertension (68%)  |                     |
| AST increased   | Rash (72%)            |                     | Nausea (60%)        |
| Hypothyroidism  | Diarrhea (44%)        |                     | Decreased appetite (52%) |
| Diarrhea        | Acne (28%)            |                     | Diarrhea (52%)      |
| Palmar plantar erythrodysesthesia | Xerosis (22%)       | Proteinuria (48%)   |                     |
| Skin hypopigmentation | Abdominal discomfort (17%) | Vomiting (44%) |                     |
| Dose reduction  | Dose reduction (28%)  |                     | Dose reduction (54%) |

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. In seven patients who had received previous RET therapy, ORR with lenvatinib was 14% with a mPFS lower than other known 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 (15.52%), proteinuria (48%), and vomiting (11.44%).

Other multi-target kinase inhibitors have also been tested in RET-rearrangement NSCLC, including sunitinib, sorafenib, alectinib, nintedanib, ponatinib and regorafenib. 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 NSCLC 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, the ORR of 60%-95% and mPFS 8-11 months was achieved in patients with ALK-rearranged NSCLC, and the ORR of 65%-85% and mPFS 9.3-19.3 months was achieved in patients with ROS1-rearranged NSCLC. 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 erythrodysesthesia) that are mostly due to the activity against VEGF receptors, 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. Recent molecular studies have identified MDM2 proto-oncogene (MDM2) amplification in pretreatment biopsy specimens from 8 of 16 NSCLC who developed resistance to vandetanib. 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-
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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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