Editorial

The importance of RET-directed therapy in patients with *RET*-rearranged non-small cell lung cancer

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Non-small cell lung cancer (NSCLC) has been recognized as a heterogeneous set of diseases according to oncogenic gene alterations level, such as sensitizing *EGFR* mutations, *ALK* rearrangements, or *ROS1* rearrangements (1). Specific molecularly targeted therapies are effective in NSCLC patients harboring sensitizing *EGFR* mutations, *ALK* or *ROS1* rearrangements, with response rates of approximately 60% and median progression-free survival of over 10 months (2-4). *RET* is a proto-oncogene that codes for a transmembrane protein belonging to the receptor tyrosine kinases family (5). In 2012, *RET* rearrangements were identified as new oncogenic alterations occurring in 1% to 2% of patients with NSCLC (6-9). It is reported that *RET* rearrangements has tumor-driving activity *in vitro* and *in vivo*. *RET* can partner with different genes in NSCLC, and *KIF5B* is the most common fusion partner in NSCLC. To date, several other genes including *CCDC6*, *NCOA*, *TRIM33*, *CUX1*, *KIAA1468*, *KIAA1217*, and *FRMD4A*, have been identified as other fusion partners of *RET* in NSCLC patients. *RET* rearrangements tend to be found in younger patients, female, never or former light smokers, and in patients with lung adenocarcinomas (10). A few case reports reported that cabozantinib and vandetanib, which are multi-targeted tyrosine kinase inhibitor exhibiting RET kinase activity, have antitumor activity in patients with *RET*-rearranged NSCLC (11-13).

The Global, Multicenter RET Registry (GLORY) is the largest single database of patients with *RET*-rearranged NSCLC. In a recent paper by Gautschi *et al.* (14), GLORY presented the results of independent retrospective and prospective series that described clinicopathologic features of *RET*-rearranged NSCLC and collected real-world data on the use of RET-directed, targeted therapy outside of clinical protocols. From June 2015 to April 2016, 165 patients with *RET*-rearranged NSCLC from 29 centers in 12 countries across Europe, Asia, and the United States were accrued in GLORY. Median age was 61 years (range, 29 to 89 years) and the percentage of males and females was balanced. The majority of patients were never smokers (63%) and the predominant histology was lung adenocarcinoma (98%). Most patients (72%) had stage IV disease at diagnosis. Molecular testing for *RET* was performed locally via fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), and real-time polymerase chain reaction (RT-PCR). The fusion partners were identified in 81 (49%) of 165 patients. *KIF5B* was the most common partner and was found in 58 patients (72%), followed by *CCDC6* in 19 patients (23%), *NCOA4* in two patients (2%), *EPHA5* in one patient (1%), and *PICALM* in one patient (1%).

Fifty-three (33%) of 162 patients with *RET*-rearranged NSCLC received a RET inhibitor during the course of therapy. RET inhibitors included cabozantinib in 21 patients, vandetanib in 11 patients, sunitinib in 10 patients, sorafenib in two patients, alectinib in two patients, lenvatinib in two patients, nintedanib in two patients, ponatinib in two patients, and regorafenib in one patient. Among the 50 assessable patients by RECIST version 1.1, the best response was complete response in 2 patients (4%), partial response in 11 patients (22%), stable disease in 16 patients (32%), progressive disease in 20 patients (40%), and not evaluable in 1 patient (2%). Responses were observed with cabozantinib, vandetanib, sunitinib, lenvatinib, and nintedanib, but not with sorafenib, alectinib, ponatinib, or regorafenib. Median progression-free survival (PFS) was 2.3 months (95% CI, 1.6

Table 1 Summary of phase 2 trials to investigate the activity of single-agent RET inhibitors in patients with *RET*-rearranged NSCLC

Item	Study		
	Drilon *et al.* (15)	Yoh *et al.* (16)	Lee *et al.* (17)
RET inhibitors	Cabozantinib	Vandetanib	Vandetanib
Enrolled patients	26	19	18
Age (years)			
Median [range]	59 [54–67]	59 [41–80]	56 [36–72]
Sex			
Female/male	15/11	14/5	6/12
Smoking history			
Never/ever	17/9	13/6	11/7
Number of prior systemic regimens			
0/1/2 or more	6/13/7	0/7/12	0/5/13
Assessable patients	25	17	17
ORR (%)	28	53	18
Median PFS (months)	5.5	4.7	4.5
Median OS (months)	9.9	11.1	11.6

NSCLC, non-small-cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

to 5.0 months). Median overall survival (OS) was 6.8 months (95% CI, 3.9 to 14.3 months). Analysis of the efficacy according to RET inhibitors was performed. In 19 patients who were treated with cabozantinib, the response rate was 37% and median PFS was 3.6 months. In 11 patients who were treated with vandetanib, the response rate was 18% and median PFS was 2.9 months. In 9 patients who were treated with sunitinib, the response rate was 22% and median PFS was 2.2 months. GLORY indicated that available multi-targeted tyrosine kinase inhibitors had limited activity of patients with *RET*-rearranged NSCLC.

Several phase 2 trials were performed to investigate the activity of single-agent RET inhibitors in patients with *RET*-rearranged NSCLC. The summary is listed in *Table 1*. Drilon *et al.* (15) reported the results of a phase II trial to evaluate the activity of cabozantinib in 26 patients with *RET*-rearranged NSCLC. The objective response rate (ORR) in the 25 assessable patients was 28% [95% CI (12%, 49%)]. 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, not reached)]. We reported the results of a phase II trial to evaluate the activity of vandetanib in 19 patients with *RET*-rearranged NSCLC (16). Among 17 eligible patients included in primary analysis, the ORR was 53% [95% CI (28%, 77%)]. The median PFS was 4.7 months [95% CI (2.8, 8.5)], and the median OS was 11.1 months [95% CI (9.4, not reached)]. Lee *et al.* (17) reported the results of a phase II trial to evaluate the activity of vandetanib in 18 Korean patients with *RET*-rearranged NSCLC. Among 17 eligible patients, the ORR was 18%, the median PFS was 4.5 months, and the median OS was 11.6 months.

The efficacy of single-agent RET inhibitors in these clinical trials was more promising than the response rates of 10% to 20% reported for second-line therapy in molecularly unselected NSCLC patients. However, this efficacy was lower than that of targeted therapy in NSCLC patients harboring sensitizing *EGFR* mutations, *ALK* or *ROS1* rearrangements. The results of GLORY are also consistent with findings from clinical trials. The reasons for this are considered to be as follows. One is that the identification of *RET* rearrangements is various by each study. Now, there is no gold-standard method for the identification of *RET* rearrangements. Available methods for *RET* testing have FISH, RT-PCR, or NGS. Consequently, some false *RET*-positive NSCLC patients might be included in previous studies, which led to the lower efficacy of RET inhibitors. Another is that the used targeted therapy is not selective RET inhibitor but multi-targeted RET inhibitors. Multi-targeted RET inhibitors may be not clinically enough *RET* kinase activity for patients with *RET*-rearranged NSCLC. Also, in-vitro experiments have proposed a signal switch as well as secondary *RET* mutations as possible mechanisms of resistance to RET inhibitors (18,19). Highly selective RET inhibitor and other therapeutic combinations with a RET inhibitor might help to improve clinical outcomes.

RET-rearranged NSCLC patients are rarely encountered. To identify clinicopathologic features and collect clinical data in a real-world setting of such patients, the global, multicenter registry such as GLORY is very useful. On the based the results of GLORY and several clinical trials, multi-targeted RET inhibitors have shown clinical antitumor activity in patients with *RET*-rearranged NSCLC. This results define RET rearrangement as a new molecular subgroup of NSCLC suitable for targeted therapy.

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Footnote

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