Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry


ABSTRACT

Purpose
In addition to prospective trials for non–small-cell lung cancers (NSCLCs) that are driven by less common genomic alterations, registries provide complementary information on patient response to targeted therapies. Here, we present the results of an international registry of patients with RET-rearranged NSCLCs, providing the largest data set, to our knowledge, on outcomes of RET-directed therapy thus far.

Methods
A global, multicenter network of thoracic oncologists identified patients with pathologically confirmed NSCLC that harbored a RET rearrangement. Molecular profiling was performed locally by reverse transcriptase polymerase chain reaction, fluorescence in situ hybridization, or next-generation sequencing. Anonymized data—clinical, pathologic, and molecular features—were collected centrally and analyzed by an independent statistician. Best response to RET tyrosine kinase inhibition administered outside of a clinical trial was determined by RECIST v1.1.

Results
By April 2016, 165 patients with RET-rearranged NSCLC from 29 centers across Europe, Asia, and the United States were accrued. Median age was 61 years (range, 29 to 89 years). The majority of patients were never smokers (63%) with lung adenocarcinomas (98%) and advanced disease (91%). The most frequent rearrangement was KIF5B-RET (72%). Of those patients, 53 received one or more RET tyrosine kinase inhibitors in sequence: cabozantinib (21 patients), vandetanib (11 patients), sunitinib (10 patients), sorafenib (two patients), alectinib (two patients), lenvatinib (two patients), nintedanib (two patients), ponatinib (two patients), and regorafenib (one patient). The rate of any complete or partial response to cabozantinib, vandetanib, and sunitinib was 37%, 18%, and 22%, respectively. Further responses were observed with lenvatinib and nintedanib. Median progression-free survival was 2.3 months (95% CI, 1.6 to 5.0 months), and median overall survival was 6.8 months (95% CI, 3.9 to 14.3 months).

Conclusion
Available multikinase inhibitors had limited activity in patients with RET-rearranged NSCLC in this retrospective study. Further investigation of the biology of RET-rearranged lung cancers and identification of new targeted therapeutics will be required to improve outcomes for these patients.

INTRODUCTION

The use of targeted therapy is a standard of care for subgroups of patients with advanced non–small-cell lung cancer (NSCLC), including those whose tumors harbor sensitizing EGFR mutations and ALK or ROS1 rearrangements.1 As the molecular landscape of NSCLC unfolds—largely secondary to improvements in comprehensive molecular profiling—rare but clinically actionable drivers continue to emerge.2 For less common driver mutations, it has become increasingly difficult to mount and complete prospective trials
within a time frame that generates data that help guide clinical decisions.

To complement ongoing prospective investigations, cohort studies generated by multicenter registries provide information on clinicopathologic and molecular features as well as outcomes with targeted therapy,\(^3\) as evidenced by works we previously published for patients with ROS1-rearranged, BRAF-mutant, and ERBB2-mutant lung cancers.\(^4-7\) Our registries demonstrate that clinicians are inclined to test for less common genomic alterations and to treat patients whose tumors harbor these drivers.

The rearranged during transfection, or RET gene, is a known proto-oncogene.\(^8-11\) Oncogenic activation can occur via mutation or rearrangement. RET rearrangement was first detected in NIH-3T3 cells that were transfected with lymphoma DNA\(^12\) and subsequently identified in papillary thyroid cancers.\(^13,14\) In NSCLCs, RET rearrangements occur in 1% to 2% of unselected cases. These are commonly found in adenocarcinomas from patients who are never smokers or who have minimal history of tobacco exposure.\(^15\) In contrast to thyroid cancer where CCDC6 and NCOA4 are more common upstream partner genes, KIF5B is the most common upstream fusion partner of RET in NSCLCs.\(^16-21\)

Independent investigators have demonstrated that multikinase RET inhibitors, such as cabozantinib and vandetanib, are active in vitro and in vivo against various RET-rearranged lung cancer models.\(^22-24\) Furthermore, Drilon et al\(^25\) previously reported the activity of cabozantinib in patients with RET-rearranged lung cancers in a phase II trial. Subsequent data on the activity of vandetanib on two separate molecularly enriched phase II trials have likewise been published.\(^26,27\)

On the basis of these results as well as inclusion of some of these data in the National Comprehensive Cancer Center Network guidelines, clinicians who practice in a variety of settings have treated patients with RET-rearranged lung cancer outside the context of a clinical trial with different RET inhibitors.\(^28-33\) These therapies include cabozantinib, vandetanib, sorafenib, and levantinib, which are approved for treatment of advanced thyroid cancers, and ponatinib, alecinib, and sunitinib, which are approved for other indications.

We set out to systematically gather and analyze these data by launching the Global, Multicenter RET Registry (GLORY) in 2015. In this article, we present the results of this collective experience with a focus on outcomes with multikinase RET inhibitor therapy in patients with RET-rearranged lung cancers.

### METHODS

#### Study Objectives

The aims of this study were to describe the clinicopathologic characteristics of patients with RET-rearranged lung cancers and to document the outcomes of patients with advanced disease who were treated with systemic therapy, focusing on multikinase inhibitors that target the RET kinase.

#### Patient Selection

A global, multicenter network of thoracic oncologists accrued patients with RET-rearranged lung cancers to this registry. Investigators were identified via ongoing collaboration that was established by our prior registry efforts in other subsets of driver-positive lung cancer.\(^4-7\) Eligible patients had a pathologic diagnosis of NSCLC of any stage (I to IV) and RET rearrangement by a validated test that was performed in an accredited local laboratory. Accepted test methods were fluorescence in situ hybridization, reverse transcriptase polymerase chain reaction, and next-generation sequencing. Validation of test results by a second method was not mandatory. Investigators administered multikinase inhibitors cabozantinib, vandetanib, sunitinib, sorafenib, alecinib, levantinib, nintedanib, ponatinib, and regorafenib according to the approved initial starting dose of these drugs in their respective approved cancer indications—data on dose interruption and modification were not collected. Participating centers were responsible for patient consent and institutional approval. All contributors were trained in good clinical practice. The study was purely an academic collaboration and was not funded by industry.

#### Data Collection and Response Assessment

Anonymized clinical data—age, gender, RET upstream fusion partner, tumor stage, date of diagnosis, initiation and completion of RET inhibitor therapy, progression, and death—were recorded. Anonymous data were collected centrally at the University of Toulouse. The registry was opened in June 2015 and data cutoff was on April 15, 2016. Patients who were treated with a RET inhibitor outside of the context of a clinical trial were eligible for analysis of efficacy of RET inhibitor therapy. RET inhibitor therapy was defined as treatment with any drug that is known to inhibit RET kinase at clinically relevant concentrations.\(^28-37\) Best response to systemic therapies, defined as a complete or partial response achieved at least once during the course of therapy, was assessed locally by each investigator using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).\(^38\) As a result of the limits of this registry and the lack of a formal response assessment plan for each patient, response confirmation could not be assessed and overall response rate could not be calculated. Patients who were treated with RET inhibitor therapy in a clinical trial were not included in an analysis of efficacy of RET inhibitor therapy.

#### Statistical Methods

Data were summarized according to frequency and percentage for qualitative variables as well as by medians and ranges for quantitative variables. Comparisons between groups were performed by using the \(\chi^2\) test or Fisher’s exact test for qualitative variable test, and by the Mann-Whitney test for quantitative variables. Progression-free survival was measured as the time from the first administration of RET inhibitor therapy to progression defined by RECIST v1.1 or death from any cause. Patients who were alive without having experienced progression at the time of analysis were censored at their last follow-up. Overall survival was measured as the time from the first administration of RET inhibitor therapy to death from any cause. Patients who were alive at the time of analysis were censored at their last follow-up. Survival rates were estimated by using the Kaplan-Meier method. Statistical analyses were carried out by using STATA software (version 13.0; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).

### RESULTS

#### Clinicopathologic and Molecular Features

From June 2015 to April 2016, 29 different centers from 12 countries in Europe, Asia, and the United States contributed a total of 165 patients (Table 1). Median age was 61 years (range, 29 to 89 years) and the percentage of males and females was balanced. The majority of patients (103 of 165 patients; 63%) were never smokers. Lung adenocarcinoma was the predominant histology (158 of 162 patients; 98%). Most patients (117 of 165 patients; 72%) had stage IV disease at diagnosis. Molecular testing for RET was performed locally via fluorescence in situ hybridization,
next-generation sequencing, and real-time polymerase chain reaction. Upstream fusion partners were identified in 81 tumor samples. 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%).

Outcomes With RET Inhibitor Therapy in Tyrosine Kinase Inhibitor–Naïve Patients

Fifty-three tyrosine kinase inhibitor (TKI)–naïve patients with RET-rearranged lung cancers received a RET inhibitor during the course of therapy. All patients had advanced (stage III and IV) disease. Apart from stage, clinical characteristics did not differ from patients who were not treated with a RET inhibitor (Table 1). All patients received their first RET inhibitor as a single agent. TKIs administered 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. The median line of systemic therapy of the first RET TKI administered was as third line (range, first to eighth line). Median time from initial diagnosis to the start of RET inhibitor therapy was 12.0 months (range, 0.1 to 92.0 months).

Of 53 patients, data on response to therapy by RECIST v1.1 was available in 50 patients. The best response to single-agent RET inhibition of any kind was complete response in two patients (4%), partial response in 11 patients (22%), stable disease in 16 patients (32%), progressive disease in 20 patients (40%), and not evaluable in one patient (2%). Responses were observed with cabozantinib, vandetanib, sunitinib, lenvatinib, and nintedanib, but not with sorafenib, alectinib, ponatinib, or regorafenib (Table 2). There were no statistically significant differences in terms of best response and progression-free or overall survival with RET inhibitor therapy by upstream fusion partner (KIF5B vs other partner) in 24 patients in whom the gene partner was known. Response to therapy was noted in three patients with non-KIF5B fusion partners, including two with CCDC6-RET and one with EPHA5-RET.

A swimmer’s plot outlining the duration of RET inhibitor therapy for each of the 53 patients is shown in Fig 1. Median duration of RET inhibitor therapy was 1.8 months (range, 0.5 to 12 months). At the data cutoff, eight patients (15%) remained on RET inhibitor therapy, and 45 patients (85%) had discontinued treatment. Median progression-free survival was 2.3 months (95% CI, 1.6 to 5.0 months). Twenty-one patients (40%) were alive at the time of the analysis. Median overall survival was 6.8 months (95% CI, 3.9 to 14.3 months). Kaplan–Meier survival curves are shown in Fig 2.

Table 1. Clinicopathologic Features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 165)</th>
<th>Patients not Treated With a RET Inhibitor (n = 112)</th>
<th>Patients Treated With a RET Inhibitor (n = 53)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>61 (28-89)</td>
<td>62 (29-89)</td>
<td>57 (28-83)</td>
<td>.166</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>126 (76)</td>
<td>82 (79)</td>
<td>44 (83)</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>39 (24)</td>
<td>30 (27)</td>
<td>9 (17)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>79 (48)</td>
<td>57 (51)</td>
<td>22 (42)</td>
<td>.260</td>
</tr>
<tr>
<td>Female</td>
<td>86 (52)</td>
<td>55 (49)</td>
<td>31 (59)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>103 (63)</td>
<td>69 (62)</td>
<td>34 (65)</td>
<td>.110</td>
</tr>
<tr>
<td>Former</td>
<td>45 (27)</td>
<td>35 (31)</td>
<td>10 (19)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>16 (10)</td>
<td>8 (7)</td>
<td>8 (15)</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tumor histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>158 (98)</td>
<td>108 (98)</td>
<td>50 (96)</td>
<td>.487</td>
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<tr>
<td>Squamous</td>
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<td>0</td>
<td>1 (2)</td>
<td></td>
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<tr>
<td>NSCLC NOS</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>1 (2)</td>
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<tr>
<td>Unknown</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RET fusion gene partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIF5B</td>
<td>58 (72)</td>
<td>39 (68)</td>
<td>19 (79)</td>
<td>.327</td>
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<tr>
<td>Other</td>
<td>23 (28)</td>
<td>18 (32)</td>
<td>5 (21)</td>
<td></td>
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<td>Unknown</td>
<td>84</td>
<td>55</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II</td>
<td>14 (8)</td>
<td>14 (13)</td>
<td>0</td>
<td>.004</td>
</tr>
<tr>
<td>III</td>
<td>31 (19)</td>
<td>24 (22)</td>
<td>7 (14)</td>
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<td>IV</td>
<td>117 (72)</td>
<td>73 (66)</td>
<td>44 (86)</td>
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<td>2</td>
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</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>68 (41.2)</td>
<td>48 (42.9)</td>
<td>20 (37.7)</td>
<td>.3103</td>
</tr>
<tr>
<td>Europe and Israel</td>
<td>71 (43.0)</td>
<td>44 (39.3)</td>
<td>27 (50.9)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>26 (15.8)</td>
<td>20 (17.9)</td>
<td>6 (11.3)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are given as No. (%) unless otherwise noted. Clinicopathologic features of 165 patients with RET-rearranged lung cancers are summarized. In addition, the clinicopathologic features of 53 patients with advanced RET-rearranged lung cancers who received a RET inhibitor during the course of treatment are summarized and compared with 112 patients who did not receive a RET inhibitor. Abbreviations: NOS, not otherwise specified; NSCLC, non–small-cell lung cancer.

* Fisher’s exact and χ² tests.
Outcomes With Specific RET Inhibitors in TKI-Naïve Patients

Analysis of the efficacy of individual RET TKIs was performed if each drug was administered to at least 10 RET TKI-naïve patients with RET-rearranged NSCLC (Table 3). The best response to cabozantinib was complete response in one patient (5%), partial response in six patients (32%), stable disease in five patients (26%), and disease progression in seven patients (37%). Median progression-free survival was 2.9 months (95% CI, 1.3 to 7.0 months) and median overall survival was 4.9 months (95% CI, 1.9 to 14.3 months).

The best response to vandetanib was partial response in two patients (18%), stable disease in three patients (27%), and disease progression in six patients (55%). No complete responses were observed. Median progression-free survival was 2.9 months (95% CI, 1.0 to 6.4 months) and median overall survival was 10.2 months (95% CI, 2.4 months to not reached).

The best response to sunitinib was partial response in two patients (18%), stable disease in three patients (27%), and disease progression in six patients (55%). No complete responses were observed. Median progression-free survival was 7.8 months (95% CI, 5.3 to 10.2 months) and median overall survival was 10.2 months (95% CI, 2.4 months to not reached).

Outcomes With Chemotherapy

Eighty-four patients with advanced disease at initial diagnosis and RET-rearranged lung cancers received platinum-based chemotherapy in the first-line setting (Table 4). In these patients, a best response of complete or partial response was achieved in 33 (51%; 95% CI, 38.1 to 63.4) of 65 response-evaluable patients. Median progression-free survival was 7.8 months (95% CI, 5.3 to 10.2 months) and median overall survival was 24.8 months (95% CI, 13.6 to 32.3 months) in 70 patients with survival data.

Of 84 patients who received a platinum doublet in the first-line setting, 66 patients received a platinum agent and pemetrexed. In these patients, a best response of complete or partial response was achieved in 27 (49%; 95% CI, 35.4 to 62.9) of 55 response-evaluable patients. Median progression-free survival was 6.4 months (95% CI, 4.3 to 8.8 months) and median overall survival was 23.6 months (95% CI, 13.4 to 33.2 months) in 57 patients with survival data.

### Table 2. Best Response to RET Inhibitor Therapy

<table>
<thead>
<tr>
<th>RET Inhibitor</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Disease Progression</th>
<th>Not Evaluable</th>
<th>Missing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>All agents (n = 53)</td>
<td>2 (4%)</td>
<td>11 (22%)</td>
<td>16 (32%)</td>
<td>20 (40%)</td>
<td>1 (2%)</td>
<td>3</td>
</tr>
<tr>
<td>Cabozantinib (n = 21)</td>
<td>1 (5%)</td>
<td>6 (32%)</td>
<td>5 (26%)</td>
<td>7 (37%)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vandetanib (n = 11)</td>
<td>0</td>
<td>2 (18%)</td>
<td>3 (27%)</td>
<td>6 (55%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sunitinib (n = 10)</td>
<td>0</td>
<td>2 (22%)</td>
<td>3 (33%)</td>
<td>3 (33%)</td>
<td>1 (11%)</td>
<td>1</td>
</tr>
<tr>
<td>Sorafenib (n = 2)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alectinib (n = 2)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Lenvatinib (n = 2)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nintedanib (n = 2)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Regorafenib (n = 1)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. The best response to a multikinase inhibitor with activity against RET is summarized for 53 patients with advanced RET-rearranged lung cancers.

Discussion

To the best of our knowledge, GLORY represents the largest single database of patients with RET-rearranged lung cancers. This global, multicenter registry was organized independently of industry support, and with limited academic resources, generated meaningful clinical data within a short time period. The number of contributions and participating centers exceeded our expectations, which demonstrated the interest of the community in less common driver mutations as well as the feasibility of international academic
projects of this nature. Whereas our study has several limitations, including reporting bias, lack of central molecular and radiologic assessment, variable scanning intervals, and the inability to analyze dose modifications and interruptions, we were able to confirm the results of independent retrospective and prospective series that described clinicopathologic features of RET-rearranged lung cancers and collected real-world data on the use of RET-directed, targeted therapy outside of clinical protocols.

Our data are consistent with previous studies that have shown that RET rearrangements are identified predominantly in adenocarcinomas from patients with a minimal to no history of tobacco exposure. In our registry, RET rearrangements were also identified, albeit at a lower frequency, in smokers and in patients with NSCLCs not otherwise specified. Future efforts should focus on systematically assessing potential risk factors for the development of RET rearrangement in NSCLC, including radiation and occupational exposures.

Whereas overall outcomes were disappointing compared with the activity of targeted therapy in other genomic subsets of lung cancer, we observed that multikinase RET inhibitors induced sustained responses in a subset of patients with RET-rearranged lung cancers. Whereas nine RET inhibitors were used in this registry, which provided a unique opportunity to explore the clinical activity of different agents, these results must be interpreted with caution. Although our registry was retrospective and drug dosage was not controlled, the activity of cabozantinib in our series was comparable to that reported for an ongoing phase II clinical trial of the drug in RET-rearranged lung cancers (n = 26; overall response rate [ORR], 28%; median progression-free survival [PFS], 5.5 months). Likewise, the activity of vandetanib in our

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**Fig 2.** Survival with RET inhibitor therapy. (A and B) Kaplan-Meier curves of progression-free survival (PFS) are shown for patients with RET-rearranged lung cancers who received (A) any multikinase inhibitor with activity against RET, and (B) cabozantinib, vandetanib, or sunitinib. (C and D) Kaplan-Meier curves of overall survival (OS) are shown for patients with RET-rearranged lung cancers who received (C) any multikinase inhibitor with activity against RET and (D) cabozantinib, vandetanib, or sunitinib.
result in toxicities that may limit chronic dosing. In this respect, like VEGFR2, are inhibited much more potently than RET and available RET inhibitors target a variety of kinases, some of which, RET kinase is suboptimal at clinically deliverable doses. Currently be responsible for this difference. It is possible that inhibition of the lower than that observed with targeted therapy in important to point out that the activity of these drugs is markedly and

<table>
<thead>
<tr>
<th>RET Inhibitor</th>
<th>Best Response (%; 95% CI)</th>
<th>Median DoT (range)</th>
<th>Median PFS (95% CI)</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>7 of 19 evaluable (37%; 16.3 to 61.6)</td>
<td>1.6 months (0.5 to 12.2 months)</td>
<td>3.6 months (1.3 to 7.0 months)</td>
<td>4.9 months (1.9 to 14.3 months)</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>2 of 11 evaluable (18%; 2.3 to 51.8)</td>
<td>2.9 months (0.8 to 7.1 months)</td>
<td>2.9 months (1.0 to 6.4 months)</td>
<td>10.2 months (2.4 months to NR)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2 of 9 evaluable (22%; 2.8 to 60.0)</td>
<td>2.2 months (0.7 to 6.6 months)</td>
<td>2.2 months (0.7 to 5.0 months)</td>
<td>6.8 months (1.1 months to NR)</td>
</tr>
</tbody>
</table>

NOTE. The percentage of patients who achieved a complete or partial response as their best response, and the median DoT, median PFS, and median OS with cabozantinib, vandetanib, and sunitinib are summarized. 

Abbreviations: DoT, duration of treatment; NR, not reached; OS, overall survival; PFS, progression-free survival.

series was comparable to results of an ongoing phase II trial of the drug in Korean patients (n = 19; ORR, 18%; median PFS, 4.5 months), but less than that observed in a separate phase II trial of the same drug in Japanese patients (n = 19; ORR, 53%; median PFS, 4.7 months). The reasons for discrepant response rates between the latter two trials remains unclear. More recently, preliminary results of a trial with lenvatinib were presented (n = 25; ORR, 16%; median PFS, 7.3 months). Whereas the activity of RET inhibition is documented in some patients with RET-rearranged lung cancers, and the ORR exceeds the historical response rate of single-agent chemotherapy in this setting (< 10% with docetaxel in the second-line setting), it is important to point out that the activity of these drugs is markedly lower than that observed with targeted therapy in EGFR-mutant and ALK/ROS1-rearranged lung cancers. A number of factors may be responsible for this difference. It is possible that inhibition of the RET kinase is suboptimal at clinically deliverable doses. Currently available RET inhibitors target a variety of kinases, some of which, like VEGFR2, are inhibited much more potently than RET and result in toxicities that may limit chronic dosing. In this respect, we look forward to the introduction of highly selective RET inhibitors in the clinic. These drugs are likely to result in more potent inhibition of RET and less off-target toxicities. Combination therapy represents a second approach to maximizing efficacy, although the potential for increased toxicity will have to be taken into account.

Other explanations for the relatively low activity of multikinase inhibitors include molecular heterogeneity and the presence of concomitant alterations. It has been speculated that the type of fusion partner (KIF5B v CCDC6 v other partners) may play a role in determining response to treatment. In our exploratory analysis of response and survival by fusion type, no statistically significant differences in clinical outcomes were observed. RET-rearranged lung cancers may also harbor concurrent genomic alterations that decrease the likelihood of response to therapy.

Given the combined results of our series where a limited number of patients derived meaningful clinical benefit from multikinase inhibition, the published prospective clinical trial data on outcomes with targeted therapy in RET-rearranged lung cancers, and the emerging strategies for this genomic subset of patients, our personal preference is to screen for RET rearrangements in patients with advanced nonsquamous NSCLC whenever possible. Doing so will allow patients to be enrolled in prospective trials of novel strategies for RET-rearranged lung cancers, with the intent of eventually improving outcomes for these patients.

Finally, we demonstrate that RET-rearranged lung cancers seem to be sensitive to platinum-based chemotherapy. Given the low activity of currently available multikinase inhibitors, a possible treatment strategy for patients with RET-rearranged lung cancer would be to begin first-line chemotherapy and, outside the confines of a clinical trial, to consider a RET TKI as a second line of therapy; however, as mentioned above, enrollment of patients in clinical trials of novel targeted therapy strategies is encouraged. Whereas one previous series described the potential sensitivity of RET-rearranged lung cancers to pemetrexed-based chemotherapy, the activity of pemetrexed could not be validated in our registry and requires additional work. The potential efficacy of programmed death-ligand 1 (PD-L1) checkpoint inhibitors in this population has not been tested thus far. Whereas PD-L1 expression was found in RET-rearranged lung cancers, the sequencing of RET inhibitors and PD-L1 checkpoint inhibitors in patients remains to be established.

RET rearrangement remains a challenging target, and the biology behind these drivers in lung cancer will require further exploration. Despite its many limitations, systemically examining the activity of multikinase inhibitors with activity against RET has led to progress over the last few years and created options for patients whose tumors harbor these targets. To conduct prospective trials with larger sample sizes, collaboration between various investigators and centers around the globe will be crucial. As a means of

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Chemotherapy Agents (n = 108)</th>
<th>Platinum Doublet (n = 84)</th>
<th>Platinum + Pemetrexed (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response (95% CI)</td>
<td>52% (39.9 to 64.4)</td>
<td>51% (38.1 to 63.4)</td>
<td>49% (35.4 to 62.9)</td>
</tr>
<tr>
<td>Disease control rate (95% CI)</td>
<td>75% (63.3 to 85.1)</td>
<td>75% (63.1 to 85.1)</td>
<td>75% (61.0 to 85.3)</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>6.8 months (5.1 to 9.3)</td>
<td>7.8 months (5.3 to 10.2)</td>
<td>6.4 months (4.3 to 8.8)</td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>23.6 months (13.6 to 30.8)</td>
<td>24.8 months (13.6 to 32.3)</td>
<td>23.6 months (13.4 to 33.2)</td>
</tr>
</tbody>
</table>

NOTE. The best response, disease control rate, median PFS, and median OS of patients with advanced non–small-cell lung cancer and first-line chemotherapy are summarized. 

Abbreviations: OS, overall survival; PFS, progression-free survival.
complementing these efforts, international academic registries, such as GLORY, that explore the efficacy of systemic therapies in real-world settings can generate meaningful results and networks.

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Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry

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