The advent of precision lung cancer medicine, involving the treatment of tumors with EGFR and ALK oncogene aberrations with drugs that inhibit EGFR and ALK kinase activities, respectively, is potentially transformative for lung cancer patients. In 2012, oncogenic fusion of the RET gene, a driver of thyroid carcinogenesis, was re-discovered in a small subset of lung cancer by several groups (1-3). In-flame fusion of the RET tyrosine kinase gene with kinesin family member 5B (KIF5B) or coiled-coil domain containing 6 (CCDC6) genes, resulting in constitutive activation of the RET oncogene product, was identified as a novel oncogenic aberration in 1–2% of non-small cell carcinomas (NSCLCs), mainly in those with a histology of lung adenocarcinoma (LADC). These and a subsequent study demonstrated that the RET fusion gene has tumor-driving activity in vitro and in vivo (1-4). Up to now, a few other genes, including nuclear-receptor coactivator 4 (NCOA), tripartite-motif containing 33 (TRIM33), cutlike homeobox 1 (CUX1), KIAA1468 and KIAA1217 [also known as SKT, the human homolog of murine Skt (Sickle tail)], have been identified as other fusion partners of RET in NSCLC patients (5,6). In all these RET fusions, the coiled-coil domains of the partner proteins induce dimerization of the RET fusion protein, resulting in constitutive activation of RET kinase. The KIF5B-RET fusion is specific to lung cancer, while the CCDC6-RET fusion or the NCOA-RET fusion is common to both lung and thyroid cancers. RET fusions tend to be detected in young, female, and/or never/light-smoker patients with NSCLC (2,3,7-9).

It is noteworthy that the growth of RET fusion-positive tumor cells in vitro and in vivo can be suppressed by existing tyrosine kinase inhibitors (TKIs) that target RET protein, such as vandetanib, caboazatinib, and alectinib (4,7,10-13). Therefore, targeting the RET fusion with these agents holds promise for the treatment of NSCLC with RET kinase gene fusions, following the success for NSCLC with ALK kinase gene fusions (14). Our recent exome sequencing study indicated that lung cancers with RET or ALK fusions develop with exclusive dependence on oncogene fusions (15), suggesting that it is worthwhile examining the efficacy of RET-TKI monotherapy in lung cancer patients. Unfortunately, RET fusion-positive cases constitute only a small subset of all NSCLC cases. Positive tumors often show well- or moderately-differentiated histological features, similar to those carrying EGFR mutations, while, in some cases, such as those with the CCDC6-RET fusion, mucinous cribriform features similar to those of ALK fusion-positive tumors are observed (2,7-9). In addition, immune-histochemical staining of RET protein does not allow us to distinguish RET fusion-positive cases from others (3). Therefore, histological and immune-histological methods cannot be used for diagnosis. Thus, genetic tests, including fluorescence in situ hybridization, reverse transcription-PCR, and next-generation sequencing, are needed to identify RET fusion-positive NSCLC.

In a recent paper by Falchook et al. (16), vandetanib, a RET-TKI approved for the treatment of medullary thyroid carcinoma by the US Food and Drug Administration (FDA), was used to treat a patient with CCDC6-RET fusion-positive LADC. The patient was a 36-year-old, never-smoking woman, which is a characteristic of patients with this type of cancer up until now (2,3,7-9). She had widely metastatic lung cancer and was positive for the RET fusion as diagnosed by next-generation sequencing of a
neck lymph node tumor sample by Foundation Medicine (Cambridge, MA, USA), one of the groups who discovered the RET fusion in lung cancer (1). The results of the study strongly indicated that vandetanib is a promising TKI for the treatment of this type of tumor. A Computed Tomography (CT) scan after 6 weeks of treatment demonstrated a dramatic response in the size of a large tumor mass in the left supraclavicular fossa, and CT scans at 11 weeks demonstrated a 76% decrease in tumor size as measured by RECIST version 1.1.

Currently, at least seven clinical trials are ongoing worldwide to examine the therapeutic utility of RET-TKIs against RET fusion-positive NSCLC (Table 1). All the studies have single-arm open-label designs, with the response rate as the primary endpoint; only RET fusion-positive NSCLC patients have been enrolled and all are being treated only with RET-TKIs. The trials are coupled with genetic screening, as exemplified by the Japanese study “LURET (UMIN000010095)”, which is coupled to the nation-wide screening program “SCRUM-Japan” (11,17). Preliminary results of one of the trials (NCT01639508 in Table 1) have been published. Cabozantinib, another FDA-approved RET-TKI, was found to have antitumor activity in all of the three patients participating in the study (18). Falchook’s case report (16), as well as another previous case report (19), indicated that not only cabozantinib but also vandetanib has potential for the treatment of RET fusion-positive NSCLC. In fact, vandetanib is being tested in two of the eight clinical trials (UMIN000010095 and NCT01823068 in Table 1) and promising results were reported (20). Taken together, these studies suggest that precision lung cancer medicine will be vastly improved by the addition of vandetanib as a therapeutic modality for patients with RET fusion-positive LADC.

**Acknowledgements**

*Funding:* The author received a grant from Japan Agency for Medical Research and Development (16ck0106012h0003).

**Footnote**

*Provenance:* This is a Guest Editorial commissioned by Section Editor Wei Xu (Division of Respiratory Disease, Department of Geriatrics, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Comment on:* Falchook GS, Ordóñez NG, Bastida CC, et al. Effect of the RET Inhibitor Vandetanib in a Patient With RET Fusion-Positive Metastatic Non-Small-Cell Lung

---

**Table 1** Clinical trials of the therapeutic effects of RET-TKIs against RET fusion-positive NSCLCs

<table>
<thead>
<tr>
<th>Clinical trial number</th>
<th>Country: principal institution</th>
<th>Drug</th>
<th>Number of enrolled patients</th>
<th>Primary endpoint</th>
<th>Start year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01639508</td>
<td>USA: Memorial Sloan Kettering Cancer Center</td>
<td>Cabozantinib</td>
<td>25</td>
<td>Response rate</td>
<td>2012</td>
</tr>
<tr>
<td>UMIN000010095</td>
<td>Japan: National Cancer Center</td>
<td>Vandetanib</td>
<td>17</td>
<td>Response rate</td>
<td>2013</td>
</tr>
<tr>
<td>NCT01823068</td>
<td>Korea: Seoul National University Hospital</td>
<td>Vandetanib</td>
<td>17</td>
<td>Response rate</td>
<td>2013</td>
</tr>
<tr>
<td>NCT01877083</td>
<td>Global: Eisai</td>
<td>Lenvatinib</td>
<td>20</td>
<td>Response rate</td>
<td>2013</td>
</tr>
<tr>
<td>NCT01813734</td>
<td>USA: Massachusetts General Hospital</td>
<td>Ponatinib</td>
<td>20</td>
<td>Response rate</td>
<td>2013</td>
</tr>
<tr>
<td>NCT02540824</td>
<td>China: Tongji University</td>
<td>Apatinib</td>
<td>40</td>
<td>Response rate</td>
<td>2015</td>
</tr>
<tr>
<td>UMIN000020628</td>
<td>Japan: Kanazawa University</td>
<td>Alectinib</td>
<td>27</td>
<td>Response rate</td>
<td>2016</td>
</tr>
</tbody>
</table>

NSCLCs, non-small cell carcinomas.

References