Editorial

Promise of vandetanib, a FDA-approved RET kinase inhibitor, for the treatment of *RET* fusion-positive lung adenocarcinoma

Takashi Kohno

Division of Genome Biology, National Cancer Center Research Institute, Tokyo, Japan

Correspondence to: Takashi Kohno, Division of Genome Biology, National Cancer Center Research Institute, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Email: tkkohno@ncc.go.jp.

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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, cabozantinib, 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

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

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

NSCLCs, non-small cell carcinomas.

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.

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