IN THE SPOTLIGHT

The New Kid on the Block: RET in Lung Cancer

Justin F. Gainor and Alice T. Shaw

Summary: RET has recently been identified as a potential new oncogenic driver in a subset of patients with non–small cell lung cancer (NSCLC). In this issue of Cancer Discovery, Drilon and colleagues report preliminary trial data with a RET inhibitor in RET fusion-positive NSCLC, validating RET as a therapeutic target in lung cancer.

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See related article by Drilon et al., p. 630 (12).

The therapeutic landscape for patients with non–small cell lung cancer (NSCLC) has been transformed in recent years by the identification of new molecular targets, defined by genetic alterations in driver oncogenes. Cancers harboring these alterations are often dependent on single oncogenic pathways for cell growth and survival, thus providing a rationale for therapeutic inhibition of these pathways. The 2004 discovery that activating mutations in EGFR confer sensitivity to the EGFR inhibitor gefitinib provided early validation of this treatment paradigm and spurred efforts to identify additional oncogenic drivers (1, 2). More recently, chromosomal rearrangements involving ALK and ROS1 have been identified in NSCLC (3, 4). These rearrangements lead to the formation of chimeric fusion kinases capable of oncogenic transformation. Like EGFR mutations, ALK and ROS1 rearrangements are associated with unique clinical and pathologic features and confer marked sensitivity to specific tyrosine kinase inhibitors (TKI) such as crizotinib (5, 6).

Since the initial descriptions of ALK and ROS1 rearrangements in NSCLC (3, 4), subsequent gene discovery efforts have focused on finding additional novel oncogenic fusions. In this setting, chromosomal rearrangements involving the RET proto-oncogene have recently been identified in NSCLC (7–10). RET encodes a receptor tyrosine kinase normally expressed in tissues derived from the neural crest. Although RET point mutations and fusions have long been recognized in medullary and papillary thyroid cancers, respectively, RET rearrangements in NSCLC were only recently discovered in 2011. In this early report, Ju and colleagues (7) used whole-genome and transcriptome sequencing to identify a novel fusion gene involving KIF5B (kinesin family member 5B) and RET in a 33 year-old never-smoker with lung adenocarcinoma. This fusion gene arises through a pericentric inversion in chromosome 10 that juxtaposes the 5′ portion of KIF5B with the 3′ end of RET. The latter encodes the entire RET tyrosine kinase domain. Several independent sets of investigators subsequently reported similar RET fusions in NSCLC and confirmed the ability of these rearrangements to induce oncogenic transformation (8–10). As in the case of RET rearrangements in papillary thyroid cancer, alternative RET fusion partners (CCDC6 and NCOA4) have since been described (11). Importantly, all of these fusion partners contain coiled-coil domains that are believed to mediate ligand-independent dimerization and constitutive activation of RET.

In early screening studies, RET rearrangements were identified in approximately 1% to 2% of unselected patients with NSCLC (8–10). Like ALK and ROS1 rearrangements, RET fusions are associated with specific clinicopathologic features, such as lack of smoking history and adenocarcinoma histology (11). Wang and colleagues (11) also recently reported that RET fusions are more commonly found among younger patients (age ≤60 years) and those with more poorly differentiated tumors. In addition, RET rearrangements are largely mutually exclusive with genetic alterations in other oncogenic drivers, such as EGFR, KRAS, ALK, and ROS1 (8–11). Altogether, these features suggest that RET rearrangements define a new, distinct molecular subset of NSCLC.

In this issue of Cancer Discovery, Drilon and colleagues (12) report preliminary findings from a prospective phase II trial for patients with advanced NSCLC harboring RET rearrangements (ClinicalTrials.gov number NCT01639508). The authors used FISH as the primary technique for detection of RET rearrangements, screening a population composed of never-smokers with nonsquamous histology who were otherwise “pan-negative” for alterations in driver oncogenes (EGFR, KRAS, NRAS, BRAF, HER2, PIK3CA, MEK1, AKT, ALK, and ROS1). Through this enrichment strategy, the authors identified RET rearrangements in 16% (5/31) of patients, a marked increase in the 1% to 2% prevalence identified in prior studies among unselected populations (8–11). The success of this approach provides support for similar enrichment strategies to identify otherwise rare molecularly defined cohorts. Such efforts are particularly important to facilitate the timely completion of clinical trials examining genotype-directed therapies in these rare populations.
Preclinical data suggest that RET rearrangements may be viable therapeutic targets in NSCLC (8–10). For example, exogenous expression of RET fusion transcripts in NIH3T3 cells leads to anchorage-independent growth in culture and formation of subcutaneous tumors when these cells are injected into nude mice (8, 9). Similarly, expression of RET fusions in Ba/F3 cells results in oncogenic transformation, as determined by interleukin-3 (IL-3)-independent growth (8, 10). Treatment of these cells with TKIs possessing anti-RET activity results in growth inhibition, confirming the central role of RET signaling in these cells. Informed by these preclinical models, Drilon and colleagues (12) recently initiated a phase II trial of cabozantinib (XL-184), a multitargeted TKI with anti-RET activity, in patients with advanced NSCLC harboring RET rearrangements; the authors present preliminary efficacy results from the first 3 patients enrolled on trial. All 3 patients harbored RET rearrangements, including a novel TRIM33–RET fusion in one patient. Notably, confirmed partial responses (defined as ≥30% tumor shrinkage) were observed in 2 of 3 patients treated with cabozantinib. Both of these patients also experienced improvements in cancer-related symptoms. The third patient treated with cabozantinib has experienced prolonged stable disease for 31 weeks. All 3 patients remain on therapy at the time of reporting.

These findings are noteworthy in that they show early proof-of-principle that RET rearrangements are likely oncogenic drivers in NSCLC. Furthermore, the partial responses reported in 2 of 3 RET-positive patients treated with cabozantinib provide preliminary signals that these genetic alterations may confer sensitivity to RET-directed therapies, consistent with the oncogene-addiction paradigm in NSCLC. In addition, the observation that a third RET-positive patient treated with cabozantinib has had prolonged stable disease for nearly 8 months should not be minimized, as the median progression-free survival following treatment with standard second-line chemotherapy in NSCLC is approximately 3 months (13). Although these initial findings are promising, long-term follow-up from this ongoing trial is clearly necessary to confirm that RET rearrangements are viable therapeutic targets responsive to targeted therapies. Extended follow-up will also be important to establish the durability of responses to cabozantinib. In total, 25 patients harboring RET rearrangements will be enrolled in this trial.

This report also raises several questions. The median overall survival from time of diagnosis for patients harboring RET rearrangements in this series was 27 months, with 4 of 5 patients still alive at the time of reporting. This finding, together with observations that all of the RET-positive patients treated with cabozantinib had low baseline burdens of disease, raises the question of whether RET rearrangements are associated with a more indolent phenotype. In evaluating the responses to cabozantinib described by Drilon and colleagues (12), one also questions whether RET inhibition alone accounts for the observed antitumor activity. Cabozantinib is a multitargeted TKI with activity against a number of kinases, including MET and VEGFR2. The authors do note that testing for genetic alterations in MET was negative in 1 patient. Still, additional genotyping that focuses on MET may be informative in future participants in this study. Trials of other RET inhibitors with different kinase selectivity profiles may also provide additional insights.

One particularly striking aspect of this report is the short time interval between target identification and initial target validation. As noted earlier, the first description of RET rearrangements in NSCLC was published in December 2011 (7). Shortly thereafter, several independent investigators showed that RET rearrangements confer sensitivity to RET inhibition in vitro (8–10). Impressively, in less than 6 months after publication of these reports, Drilon and colleagues (12) were able to initiate a prospective trial directed at this rare population. To do so required the development of a diagnostic screening assay (14), identification of RET-positive patients, and formulation of a clinical protocol. Now, just over 1 year since the original description of RET rearrangements in NSCLC (Fig. 1), these authors report their preliminary clinical experience with cabozantinib, providing early clinical validation of RET as a potential therapeutic target. This serves as yet another illustrative example of how drug development can be facilitated by the rapid translation of preclinical discoveries.

At the same time, efforts to target ever smaller, molecularly defined subpopulations of NSCLC also raise new questions for drug development and clinical investigation. For example, the ongoing trial described by Drilon and colleagues (12) is a single-arm study with response rate as the primary endpoint. If a high response rate is confirmed in a larger cohort of RET-positive patients, will this measure of efficacy be sufficient to meet regulatory requirements and change practice patterns? If not, will randomized trials comparing targeted therapies and systemic chemotherapy be necessary? If such a determination is made, will randomized studies actually be feasible given the low frequency of RET rearrangements in NSCLC? Moreover, will such studies be ethical, given the preponderance of data supporting the superiority of targeted therapies over chemotherapy in the setting of oncogene addiction? The answers to these questions will have important implications for clinical trial design and drug development, particularly as advances in tumor genotyping reveal new molecular subsets of patients.

Finally, as is the case in other subsets of oncogene-driven NSCLC, resistance to RET inhibition is likely to emerge. It will therefore be necessary to evaluate RET-positive patients for possible mechanisms of resistance at the time of progression on cabozantinib. Indeed, Drilon and colleagues (12) recently amended their study protocol to permit repeat biopsies in such patients. Insights into the mechanisms of resistance may in turn guide the development of subsequent treatment strategies. One such strategy may involve the use of alternative TKIs with anti-RET activity, such as sorafenib, sunitinib, vandetanib, and ponatinib (8–10, 15), as has been done in ALK-positive NSCLC. Additional studies will be necessary to determine the clinical activity of these agents in patients harboring RET rearrangements. Such studies, along with additional updates from the ongoing trial of cabozantinib in RET-positive patients, are eagerly awaited.
Timelines for Targeting ALK and RET Rearrangements

- Initial report of EML4-ALK in NSCLC
- First report of activity of crizotinib
- FDA approves crizotinib for ALK+ NSCLC

2007  2008  2009  2010  2011  2012  2013

- Phase I trial of crizotinib initiated
- First ALK+ patient treated with crizotinib
- Phase III trial of crizotinib initiated

- Initial description of RET rearrangements in NSCLC
- Preliminary report of activity of cabozantinib in RET+ NSCLC
- Phase II trial of cabozantinib in RET+ NSCLC initiated

**Figure 1.** Depiction of the timelines from target discovery to target validation for ALK and RET fusions in NSCLC. The short interval (4 years) from the discovery of ALK fusions in NSCLC to U.S. Food and Drug Administration approval of the first ALK inhibitor has served as a model for drug development and has informed subsequent approaches to newly identified targets, such as RET. In this issue of Cancer Discovery, Drilon and colleagues (12) report preliminary activity of a RET inhibitor in RET-positive patients. This report comes just over 1 year from the initial discovery of RET rearrangements in NSCLC.

**Disclosure of Potential Conflicts of Interest**

A.T. Shaw is a consultant/advisory board member of Ariad, Pfizer, Novartis, Daiichi-sankyo, and Chugai. No potential conflicts of interest were disclosed by the other author.

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