Editorial

About rearranged during transfection in non-small cell lung cancer

Cesare Gridelli[1], **Tania Losanno**[2]

[1]Division of Medical Oncology, S.G. Moscati Hospital, Avellino, Italy; [2]Division of Medical Oncology, Azienda Ospedaliera San Camillo Forlanini, Roma, Italy

Correspondence to: Cesare Gridelli, MD. Division of Medical Oncology, "S.G. Moscati" Hospital, Città Ospedaliera, Contrada Amoretta 8, 83100 Avellino, Italy. Email: cgridelli@libero.it.

Comment on: Gautschi O, Milia J, Filleron T, *et al*. Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET registry. J Clin Oncol 2017;35:1403-10.

Submitted Aug 28, 2017. Accepted for publication Sep 11, 2017
doi: 10.21037/tcr.2017.09.21
View this article at: http://dx.doi.org/10.21037/tcr.2017.09.21

Lung cancers represent a more large landscape than well-known histological categories including lung adenocarcinoma (45% of cases), squamous cell carcinoma (25%), large cell carcinoma (10%) and small cell lung carcinoma (20%). Since 2004, when epidermal growth factor receptor (EGFR) mutations were discovered to give sensitivity to tyrosine kinase inhibitors (TKIs) in lung adenocarcinomas, developments had showed that lung cancer are molecularly distinct with different therapeutic vulnerabilities (1).

Increasingly molecular profiles are detected to determine the best treatment option for each lung cancer patient. Actually, there is large scenery of rarer drug gable gene mutations among non-small-cell lung cancer (NSCLC) subgroups. Targeted therapy is now a standard of care for patients with a NSCLC harbouring EGFR mutations, and anaplastic lymphoma kinase (ALK) rearrangements (2). In addition to ALK-rearrangements, other gene fusions had been discovered involving the tyrosine kinases ROS1 and RET.

The RET (REaranged during Transfection) proto-oncogene, situated on chromosome sub-band 10q11.2, encodes a receptor tyrosine kinase expressed in tissues and tumors derived from neural crest. RET is a receptor tyrosine kinase involved in cell proliferation, neuronal navigation, cell migration, and cell differentiation. Oncogenic activation can occur via mutation or rearrangement. Germline mutations in RET cause multiple endocrine neoplasia type 2 (MEN 2), an inherited cancer syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. Somatic RET mutations have been found in a proportion of sporadic medullary thyroid carcinomas and pheochromocytomas, and are associated with sporadic and radiation-induced papillary thyroid cancer (3-6).

Recently novel gene fusions involving the RET tyrosine kinase gene were described in lung adenocarcinomas: *KIF5B*, *CCDC6*, and *NCOA4* . These fusions are generated by an inversion of the short and long arms of chromosome 10. All the proteins encoded by *KIF5B-RET*, *CCDC6-RET*, and *NCOA4-RET* have coiled-coil domains, inducing constitutive dimerization of the oncoprotein, with abnormal activation of RET kinase function, similarly to the ALK fusions (7,8). RET alterations are found in about 1–2% of unselected lung adenocarcinomas patients, reaching a frequency of about 6% among never-smokers patients, with tumors not-harbouring other known driver mutations (9-11). While the functional consequences and the clinical relevance of RET fusions in lung adenocarcinoma are not fully understood, they are oncogenic *in vitro* and *in vivo*.

Ju and colleagues reported for the first time a case of RET fusion in lung cancer in 2011 (12). Since then several groups found RET fusions, detecting a new molecular subset of NSCLC. Wang *et al.* examined 936 Chinese patients with surgically resected NSCLC to study the distribution of mutations among NSCLC, including RET fusion gene (13). This was found only in 13 patients, with adenocarcinomas or adenosquamous cell carcinomas of the lung. These patients seem to be a discernible clinicopathologic pattern, characterized by younger age, never-smokers status, smaller primary lesion, early lymph node metastases, poor differentiation, a solid-predominant subtype, and a shorter relapse-free survival.

Because the growth of these tumors is strongly

depending on RET activity, suppression of RET could be a potent therapeutic treatment. TKIs commonly used in clinical practice, as vandetanib, sunitinib or sorafenib, in *in vitro* models target RET kinase activity, suggesting that patients with NSCLC harbouring a RET alteration could be treatable with a TKI (9,11). There are limited retrospective and prospective data correlating the presence of RET fusions and the response to any particular therapy.

A clinical trial currently ongoing in RET fusion positive NSCLC shows preliminary data suggesting that these tumors may also be responsive to cabozantinib, a TKI with multiple targets including also vascular endothelial growth factor (VEGF) receptor 2, that can inhibit RET (NCT01639508) (14). Among a total of 31 patients with pan-negative lung adenocarcinoma, RET fusions were found in five patients. Three of them were eligible for treatment with cabozantinib, reporting two cases of partial response (PR) and one case of stable disease (SD).

However, given that RET fusions are uncommon genomic alterations, prospective trials may be difficult to implement.

In this context, data from the Global Multicenter RET Registry (GLORY) could be very useful, especially considering that clinicians tend to investigate uncommon genomic alterations to treat patients whit tumors harbouring these driver mutations (15).

The aim of the study of Gautschi *et al.* colleagues was to illustrate the clinicopathologic characteristics of patients with advanced RET-rearranged lung cancers, reporting the outcomes of the patients treated with the different therapies, focusing on multi-TKIs. This global multicenter registry involved a multicenter network of thoracic oncologists including 165 patients with a diagnosis of NSCLC from first to advanced stage. RET rearrangement was performed in an accredited local laboratory. Patients received a multi-TKI among alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorafenib, sorafenib, sunitinib, and vandetanib, at the dosage of these drugs as registered and currently used in their respective cancer indications. Patients were enrolled in the period between June 2015 and April 2016, in Europe, Asia, and USA. Median age of the patients was 61 years (range, 29 to 89 years), with a good balance between male and female patients. Sixty-three percent of patients were never-smokers. The most frequent histology was adenocarcinoma (98%), and the 72% of patients had an advanced disease at diagnosis. Molecular testing for RET was carried out locally by fluorescence *in situ* hybridization, next-generation sequencing, and real-time polymerase chain reaction. RET fusions were identified in 49% of cases. The most frequent fusion was *KIF5B* and was detected in 58 patients (72%), then *CCDC6* in 19 patients (23%), *NCOA4* in 2 patients (2%), *EPHA5* and *PICALM* each in 1 patient (1%).

The median line of therapy with multi-TKI was third line setting (range first to eight lines). Among the 53 patients treated, 21 of them received cabozantinib, 11 patients received vandetanib, 10 sunitinib. Sorafenib, alectinib, lenvatinib, nintedanib and ponatinib were administered each to 2 patients, while only 1 patient received regorafenib. Responses to therapy were reported with cabozantinib, vandetanib, sunitinib, lenvatinib, and nintedanib. Objective response (OR) rate was observed in 13 (26%) of cases. Complete response (CR) was reported in 2 patients (4%), one with cabozantinib and one with nintedanib, respectively. PR was reported in 11 patients (22%), SD in 16 patients (32%), while 40% of patients progressed during single-agent RET inhibition therapy. Median progression free survival (PFS) was 2.3 months (95% CI: 1.6–5.0 months), and median overall survival (OS) was 6.8 months (95% CI: 3.9–14.3 months). The longer median PFS was reported with cabozantinib (3.6 months, 95% CI: 1.3–7.0 months), while the longer median OS was reported with vandetanib (10.2 months, 95% CI: 2.4–not reached). Regarding the various RET fusions, there were no statistically significant differences regarding PFS or OS.

Despite all the limits of retrospective data and uncontrolled drug dosage, the activity of cabozantinib reported in the present study is comparable to that reported for patients with RET fusions positive NSCLC in the ongoing phase 2 study of Drilon and colleagues, whose primary endpoint was overall response rate (ORR) (16). In this study, 26 patients received cabozantinib at 60 mg daily dosage, but 19 of them (73%) reduced the dose for drug-related adverse events (AEs). Response-assessable patients were 25, and 7 of them showed a confirmed PR (ORR 28%; 95% CI: 12–49). Median PFS was 5.5 months. The most frequently reported grade 3 treatment-related AEs were lipase elevation in 4 (15%) patients, and increased alanine aminotransferase and aspartate aminotransferase, decreased platelet count, and hypophosphatemia each one in 2 (8%) patients. Similarly, the findings reported with vandetanib are comparable with those from a study conducted in Korean patients (17) but inferior than results from another study conducted among Japanese patients (18). However data derived from all these studies should be considered with caution, because of the rarity of RET fusions and the consequent small number of patients with

these alterations and eligible to a multi-TKI treatment. Moreover, the wide spectrum of toxicity of the multi-TKIs should be considered.

From the global RET registry (15), we learn that among the 84 patients who received a platinum based chemotherapy as first-line treatment, 65 were evaluable and 33 of them reported an OR (51%; 95% CI: 38.1–63.4). Median PFS was 7.8 months (95% CI: 5.3–10.2 months) and median OS was 24.8 months (95% CI: 13.6–32.3 months). Among 84 patients receiving chemotherapy, 66 of them received chemotherapy with platinum and pemetrexed.

The probable durable benefit with pemetrexed-based chemotherapy in NSCLC with RET rearrangements was already demonstrated in a retrospective review regarding patients treated at a single oncologic centre between 2007 and 2014. This analysis has some limitations as the fact that there was no standardized schedule of tumor assessments and patients with select driver-positive NSCLCs were taken as control groups that may not be representative of the overall of patients whose carcinomas are negative for RET rearrangements (19). However, the authors reported an ORR of 45% compared to an attested response rate of 30% with other platinum-based chemotherapy. Disease control was durable, with a median PFS of 19 months (95% CI: 12–not reached), and time to treatment discontinuation was prolonged.

Several elements should be taken into account to explain the efficacy of pemetrexed reported in this group of RET-rearranged NSCLC, as the fact that prolonged survival may reflect the natural history of these tumors, and that benefit due to pemetrexed-based chemotherapy may be reflective of the benefit with chemotherapy in general. Moreover, while the sensitivity of ALK-rearranged NSCLC to pemetrexed has previously been attributed to lower levels of thymidylate synthase compared to tumors without ALK fusions (20), we do not know yet the biologic explanation in support of the hypothesis of the probable increased activity of pemetrexed-based chemotherapy in RET-rearranged NSCLC. Future investigation is warranted.

In conclusion, we are facing lung cancer with RET rearrangement as a set of "rare tumors". It is getting harder to conduct perspective trials with larger sample size, with at least two consequent questions: if for tumor subgroups, clinical trial should be conducted similar to those for frequent tumors, and how much and what evidence is needed to introduce a new treatment in clinical practice.

Although data from the present study (15) can have many limitations, on the other hand systematically examining the activity of multi-tyrosine inhibitors helped to better investigate a therapeutic option for patients with a RET-rearranged NSCLC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Shaohua Cui (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.09.21). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Politi K, Herbst RS. Lung cancer in the era of precision medicine. Clin Cancer Res 2015;21:2213-20.
2. Masters G, Temin S, Hanna N, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33:3488-515.
3. Eng C. RET proto-oncogene in the development of human cancer. J Clin Oncol 1999;17:380-93.
4. Grieco M, Santoro M, Berlingieri MT, et al. PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary

carcinomas. Cell 1990;60:557-63.
5. Santoro M, Dathan NA, Berlingieri MT, et al. Molecular characterization of RET/PTC3; a novel rearranged version of the RET proto-oncogene in a human thyroid papillary carcinoma. Oncogene 1994;9:509-16.
6. Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. Nat Rev Endocrinol 2011;7:569-80.
7. Soda M, Choi TL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
8. Takeuchi K, Choi YL, Togashi Y, et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res 2009;15:3143-9.
9. Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med 2012;18:375-7.
10. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med 2012;18:378-81.
11. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 2012;18:382-4.
12. Ju YS, Lee WC, Shin JY, et al. A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. Genome Res 2012;22:436-45.
13. Wang R, Hu H, Pan Y, et al. RET fusion define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol 2012;30:4352-9.
14. Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013;3:630-5.
15. Gautschi O, Milia J, Filleron T, et al. Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET registry. J Clin Oncol 2017;35:1403-10.
16. Drilon A, Rekhman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol 2016;17:1653-60.
17. Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. Ann Oncol 2017;28:292-7.
18. Yoh K, Seto T, Satouchi M, et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. Lancet Respir Med 2017;5:42-50.
19. Drilon A, Bergagnini I, Delasos L, et al. Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. Ann Oncol 2016;1286-91.
20. Shaw AT, Varghese AM, Solomon BJ, et al. Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. Ann Oncol 2013;24:59-66.

Cite this article as: Gridelli C, Losanno T. About rearranged during transfection in non-small cell lung cancer. Transl Cancer Res 2017;6(Suppl 7):S1169-S1172. doi: 10.21037/tcr.2017.09.21

