Editorial

Alectinib in RET-rearranged non-small cell lung cancer—Another progress in precision medicine?

Robert Pirker, Martin Filipits

Department of Medicine I, Medical University of Vienna, 1090 Vienna, Austria
Correspondence to: Prof. Dr. Robert Pirker. Department of Medicine I, Währinger Gürtel 18-20, 1090 Vienna, Austria.
Email: robert.pirker@meduniwien.ac.at.

Abstract: RET fusions have been recognized as potential therapeutic targets in advanced non-small cell lung cancer. RET fusion proteins are detected in about 2% of lung adenocarcinomas. Alectinib, a second generation ALK inhibitor, was shown to block growth of cells with RET fusions. Thus alectinib should be further evaluated within clinical trials in patients with RET fusion-positive adenocarcinomas of the lung.

Keywords: Alectinib; biomarker; RET; targeted therapy; tyrosine kinase inhibitor

Submitted Mar 09, 2015. Accepted for publication Mar 16, 2015.
doi: 10.3978/j.issn.2218-6751.2015.03.08
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.03.08

Introduction

Precision medicine or personalized medicine based on molecular tumor features has offered new opportunities for the treatment of patients with advanced non-small cell lung cancer (NSCLC) (1). Growth factor receptors and angiogenesis have preferentially been studied as potential therapeutic targets.

The epidermal growth factor receptor (EGFR) has been of major interest as a therapeutic target because it is often deregulated in cancers. EGFR-directed tyrosine kinase inhibitors have shown better efficacy in terms of progression-free survival and quality of life compared to first-line platinum-based chemotherapy in phase III trials in patients with advanced EGFR mutation-positive NSCLC (2). Based on these results, afatinib, erlotinib and gefitinib have been approved for first-line therapy of patients with advanced EGFR mutation-positive NSCLC. Novel EGFR tyrosine kinase inhibitors specifically targeting EGFR mutations and sparing the wild-type are currently evaluated in phase III trials.

Anti-EGFR monoclonal antibodies have also been studied in combination with chemotherapy in patients with advanced NSCLC (3). The First-Line ErbituX (FLEX) in lung cancer trial demonstrated improved overall survival for the addition of cetuximab to chemotherapy in patients with advanced NSCLC and this benefit was limited to patients with high EGFR expression in their tumors (4,5). The SQUIRE trial demonstrated a survival benefit for necitumumab combined with cisplatin plus gemcitabine in patients with squamous cell NSCLC compared to chemotherapy alone (3).

EML4-ALK is another clinically relevant therapeutic target in approximately 3%-5% of NSCLC (6). Crizotinib has shown efficacy in patients with ALK-positive NSCLC in patients who have previously been treated with chemotherapy and, more recently, also in chemo-naive patients (6). However, patients will eventually develop resistance to crizotinib and often also brain metastases at the time of disease progression. Second generation ALK inhibitors are in clinical development and offer the advantage of overcoming crizotinib resistance and of penetrating more easily into the central nervous system (6).

Alectinib

Alectinib is an oral, second generation and highly selective ALK inhibitor. In preclinical models, alectinib may overcome crizotinib resistance as it has been shown to be active against the resistance mutation L1196M (7). Alectinib was also shown to be active against tumors implanted into the brain (8). Alectinib is metabolized by the cytochrome

P450 3A4 enzyme and excreted in the faeces.

Alectinib has been evaluated within clinical trials in patients with ALK-positive NSCLC (9,10). A Japanese study evaluated alectinib in a phase I-II study in crizotinib-naive patients with advanced ALK-positive NSCLC (9). Alectinib was administered at 20-300 mg twice daily in the phase I portion. Because no dose-limiting toxicities had been observed, 46 patients received alectinib 300 mg twice daily in the phase II portion of the trial. The response rate was 93% and included complete responses in 4% of the patients. Fifteen patients had brain metastases at the time of enrolment (12 patients with previous radiation for brain metastases, and 3 patients with stable and asymptomatic brain metastases) but none of these patients did progress during treatment with alectinib. Consistent with preclinical results, these data suggest that alectinib may penetrate into the central nervous system and, thereby, act against brain metastases. Serious adverse events occurred in 11% of the patients and included brain edema, radius fracture, tumor hemorrhage, sclerosing cholangitis and allergic alveolitis. Grade 3 treatment-related adverse events were seen in 26% of the patients but no grade 4 adverse events did occur.

Another Japanese phase 1/2 study aimed at establishing both the recommended dose for phase 2 trials and determining the activity of alectinib in patients resistant or intolerant to crizotinib (10). A total of 47 patients were enrolled. Overall, alectinib was well tolerated. Most patients experienced some toxicity but the grade of toxicity was usually mild. The most common adverse events were fatigue in 30%, myalgia in 17% and peripheral edema in 15% of the patients. The most common grade 3-4 adverse events were increased levels of gamma-glutamyl transpetidase in 4%, neutropenia in 4% and hypophosphatemia in 4% of the patients. In three patients, four serious adverse events grade 4 (acute renal failure, pleural and pericardial effusions, and brain metastasis) did occur but were deemed unrelated to alectinib. At the dose level of 900 mg twice daily, headache grade 3 and neutropenia grade 3 were determined as dose-limiting toxicities. Objective responses were seen in 55% of 44 patients evaluable for response. Twenty-one patients had brain metastasis at baseline and 52% did respond. Based on their results, the authors recommended a dose of 600 mg twice daily for further study in the phase 2 portion of their study.

Based on its high efficacy and good tolerance, alectinib administered orally at 300 mg twice daily has been approved in Japan for patients with ALK-positive unresectable, advanced or recurrent NSCLC.

RET proto-oncogene

The rearranged during transfection (*RET*) proto-oncogene encodes a receptor tyrosine kinase that plays a crucial role in cell growth and differentiation. Mutations in *RET* have been shown to be associated with cancer predisposition syndromes and developmental disorders (11). *RET* gain-of-function mutations can lead to a constitutively active receptor tyrosine kinase and predispose to multiple endocrine neoplasia type 2 (medullary thyroid cancer, phaeochromocytoma, and hyperparathyroidism) (11). In contrast, loss-of-function mutations predispose to developmental disorders such as Hirschsprung disease or aganglionosis of the gut (11).

As with other receptor tyrosine kinases, RET is inactive when present as a monomer. Binding of the RET ligand glial cell derived neurotrophic factor (GDNF) to the receptor leads to dimerization and activation by autophosphorylation of the tyrosine kinase domain (12). RET can also be activated by chromosomal rearrangements leading to a *RET* fusion gene (13). Fusion partner genes of *RET* include *CCDC6* (coiled-coil domain containing 6), *NCOA4* (nuclear receptor coactivator 4), and *KIF5B* (kinesin family member 5B). Activation of these *RET* fusion genes involves ligand-independent dimerization of the oncoprotein (13-18). A coiled-coil domain that comes from the fusion partners, functions as a dimerization unit, inducing homodimerization and activation.

These RET fusions also have the potential to transform cells. In Ba/F3 cells, an interleukin-3 dependent murine B cell line, exogenous expression of KIF5B-RET confers growth independent of interleukin-3 (15). Similarly, the exogenous expression of a RET fusion protein leads to cell proliferation in mouse embryonic fibroblast NIH 3T3 cells (14).

Chromosomal rearrangements involving *RET*, such as *CCDC6-RET* and *NCOA4-RET*, are often detected in sporadic and irradiation-induced papillary thyroid carcinoma (17).

Recently, *KIF5B-RET*, *CCDC6-RET*, and *NCOA4-RET* fusion genes were identified as driver oncogenes in 2% of lung adenocarcinomas or adenosquamous carcinomas (18). Patients who harbor these molecular alterations in their tumors had more poorly differentiated tumors with a solid subtype, were of younger age and were more often never-smokers than smokers.

RET as a novel target for alectinib

Clinically available tyrosine kinase inhibitors such as

sunitinib, sorafenib, vandetanib and cabozantinib target RET kinase activity, suggesting that this subset of NSCLC may be treatable with a kinase inhibitor (19,20).

Most recently, Kodama *et al*. demonstrated the antitumor activity of alectinib against RET-rearranged NSCLC (21). These investigators explored whether alectinib may be suitable also for treatment of non-ALK-positive cancers and found that alectinib has activity against RET-arranged NSCLC (21). In this study, kinase inhibitory assays were used to study the activity of alectinib against the following kinases: RET, ROS1, RON, EGFR, KDR, PDGFRbeta, FGFR2, KIT, SRC, HER2, MET, RAF1 and MEK1. The authors found that alectinib inhibited RET kinase and the growth of RET fusion-positive cells. In contrast to crizotinib and ceritinib, alectinib had only low activity against ROS1 kinase. The activity of alectinib against RET was then further confirmed in a mouse model. Importantly, alectinib inhibited RET gatekeeper mutations and tumors driven by KIF5B-RET V804L and V804M. In contrast to other multikinase inhibitors, alectinib only slightly affected KDR activity. Thus alectinib will not result in KDR inhibition-associated toxicities such as hypertension which is frequently observed in patients treated with multikinase inhibitors. Therefore, the lack of KDR inhibition may be advantageous in patients.

In summary, alectinib lends itself as a potential novel drug against RET-driven NSCLC. Thus clinical studies determining the efficacy of alectinib in patients with RET fusion-positive advanced NSCLC are warranted. It is hoped that these studies will further advance precision medicine by establishing a novel drug against RET fusion-positive NSCLC.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Associate Editor-in-Chief Wenzhao Zhong (Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China).

Conflicts of Interest: Robert Pirker has received speaker's fees and/or honoraria for advisory boards from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Roche, Pfizer and Synta. Martin Filipits has received speaker's fees and/or honoraria for advisory boards from Astra Zeneca, Eli Lilly, Novartis, Pfizer, Pierre Fabre Pharma SA, and Roche.

Comment on: Kodama T, Tsukaguchi T, Satoh Y, *et al*. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. Mol Cancer Ther 2014;13:2910-8.

References

1. Pirker R, Filipits M. Targeted therapies in lung cancer. Curr Pharm Des 2009;15:188-206.
2. Soria JC, Mok TS, Cappuzzo F, et al. EGFR-mutated oncogene-addicted non-small cell lung cancer: current trends and future prospects. Cancer Treat Rev 2012;38:416-30.
3. Pirker R. Epidermal growth factor receptor-directed monoclonal antibodies in nonsmall cell lung cancer: an update. Curr Opin Oncol 2015;27:87-93.
4. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-31.
5. Pirker R, Pereira JR, von Pawel J, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol 2012;13:33-42.
6. Pall G. The next-generation ALK inhibitors. Curr Opin Oncol 2015;27:118-24.
7. Sakamoto H, Tsukaguchi T, Hiroshima S, et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. Cancer Cell 2011;19:679-90.
8. Kodama T, Hasegawa M, Takanashi K, et al. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. Cancer Chemother Pharmacol 2014;74:1023-8.
9. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. Lancet Oncol 2013;14:590-8.
10. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014;15:1119-28.

11. Zbuk KM, Eng C. Cancer phenomics: RET and PTEN as illustrative models. Nat Rev Cancer 2007;7:35-45.
12. Jing S, Wen D, Yu Y, et al. GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF. Cell 1996;85:1113-24.
13. Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell 1985;42:581-8.
14. Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med 2012;18:375-7.
15. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med 2012;18:378-81.
16. 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.
17. 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.
18. Wang R, Hu H, Pan Y, et al. RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol 2012;30:4352-9.
19. Gautschi O, Zander T, Keller FA, et al. A patient with lung adenocarcinoma and RET fusion treated with vandetanib. J Thorac Oncol 2013;8:e43-4.
20. 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.
21. Kodama T, Tsukaguchi T, Satoh Y, et al. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. Mol Cancer Ther 2014;13:2910-8.

Cite this article as: Pirker R, Filipits M. Alectinib in RET-rearranged non-small cell lung cancer—Another progress in precision medicine? Transl Lung Cancer Res 2015;4(6):797-800. doi: 10.3978/j.issn.2218-6751.2015.03.08

